The Directed Remote Metalation - Carbamoyl Migration Reaction. Total Syntheses of the Defucogilvocarcins and Arnottin I and Synthesis of Heteroarylfused Benzopyranones

by

Clint A. James

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Abstract

Total synthesis of the naturally occurring 6*H*-naptho[1,2-*b*]benzo[*d*]pyran-6-one defucogilvocarcin V **149d** has been accomplished in 9 steps and 14% overall yield. A high yielding Suzuki coupling reaction allows the preparation of the key biaryl carbamate for the DreM - carbamoyl migration process. Investigation of several protecting groups (TBS, *i*-Pr and MOM) allowed a determination of the stability of these groups to the DreM conditions. Preparation of the required AB ring coupling partner was carried out in two ways; a detailed investigation of benzyne chemistry provided one route to the desired *O*-naphthylcarbamate. A more efficient route based on the selective carbamoylation of juglone derivatives was adopted. From a common triflate, introduction of substituents required for the preparation of defucogilvocarcins M and E was accomplished, using Pd(0) catalyzed cross coupling chemistry.

Total synthesis of the naturally occurring arnottin I **158** was accomplished using DreM - carbamoyl migration methodology combined with D*o*M and cross coupling. The methylenedioxy group was found to be unstable to the DreM conditions and several alternative groups for protection of catechols were investigated (*i*-Pr, MOM). Efficient synthesis of the AB coupling partner **306** was accomplished *via* an aryne based route. The total synthesis was accomplished in 11 steps and 1.8% overall yield.

The synthesis of four thieno[3,2-*c*]benzo[*e*]pyran-4-ones **499a-d** was accomplished using the DreM - carbamoyl migration strategy combined with D*o*M and cross coupling. The 2-heteroarylcarbamates were prepared by either the Negishi or Suzuki reaction. In general, the Suzuki coupling proved more efficacious; however, the coupling reactions invariably were more efficient when the heteroaryl coupling partner contained the metal species. In a similar manner, several other classes of heteroarylbenzopyranones were prepared including 6*H*-thianaphtheno[2,3-*c*]benzo[*e*]pyran-6-one, a previously unknown ring system.

Acknowledgements

I would like to thank Professor Victor Snieckus for his guidance, support and patience throughout the course of this work. Thanks, Vic, for believing in me when few others did and also for not giving up on me. Special thanks to Anne Snieckus who helped make my transition from Nova Scotia to Ontario an easy one.

Special thanks are extended to Mr. Matt Gevaert and Mr. Pat Forgione who pioneered the work on the heteroarylbenzopyranones.

I would like to thank all the members of the VS Group that I have met over the years, of which there are too many to list, for making my time here interesting and providing such an enjoyable atmosphere in the lab. Special thanks to Brian Chapell, Dr. David Roe, Dr. Paul Bury, Dr. Claude Quesnelle, Dr. Mike Campbell, Dr. Ed Griffen, Dr. Francis Beaulieu, Dr. Masao Tsukazaki, Dr. Brian McKibben, Professor Neville Emslie, Steve MacNeil, Brian Chauder, Aaron Kinsman, Dr. Alex Kalinen, Dr. Stephen Houldsworth, Mr. Rob Milburn, Ms. Claire Jackson, Mr. Pete Sampson, Mr. Randy Frank and Mr. Alexander Keith for useful discussions both in and out of the lab, and for their friendship.

To the members of my advisory committee, Professors Morris Tchir, Don MacKay and Adrian Schwan, my most sincere appreciation for their suggestions and helpful discussions.

I would like to thank my parents and my sister Carol for their support and encouragement during my University career as well as my Grandparents who, somehow, had the foresight to prepare for this twenty-nine years ago.

For Mom and Dad, Carol, Nanny and Granddad Isnor, Nanny James and in loving memory of Granddad James.

"Just because I don't care doesn't mean I don't understand"

Homer J. Simpson

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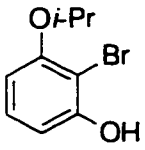

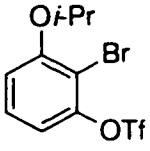

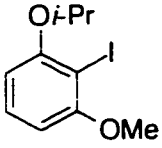

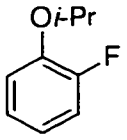

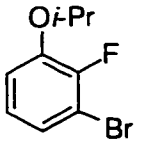

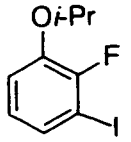

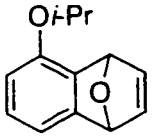

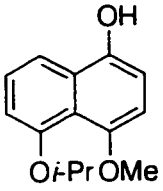

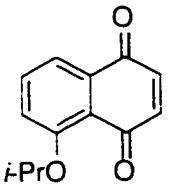

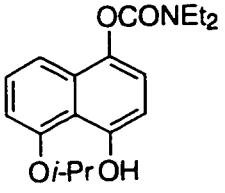

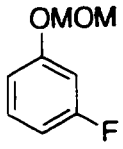

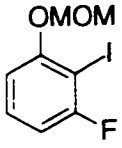

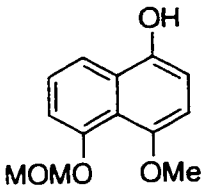

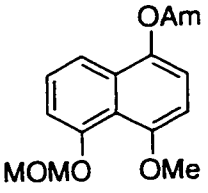

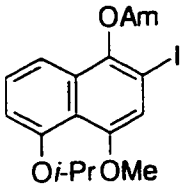

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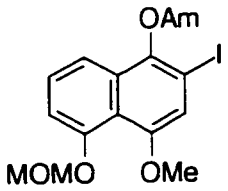

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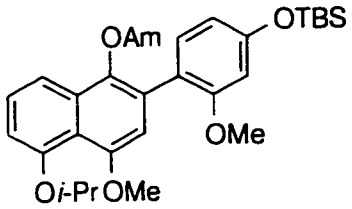

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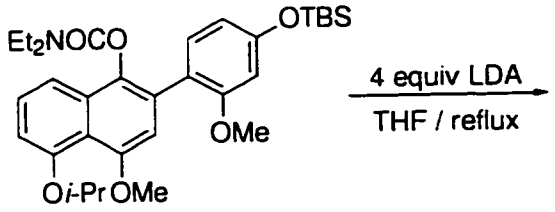

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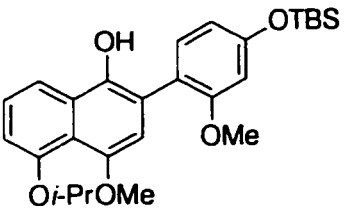

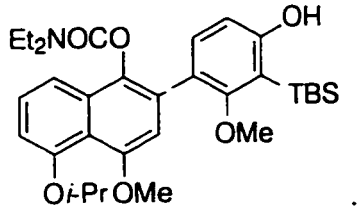

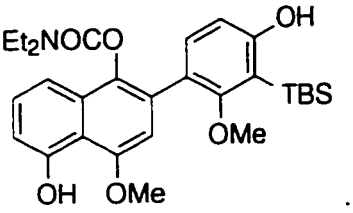

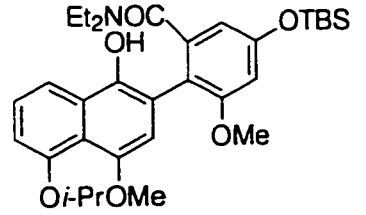

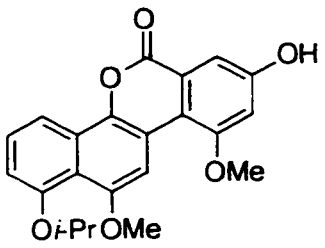

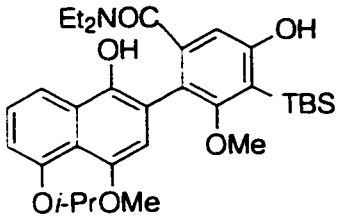

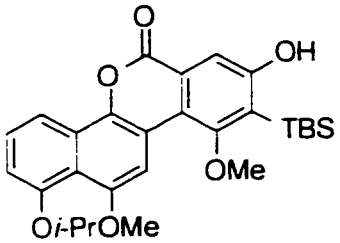

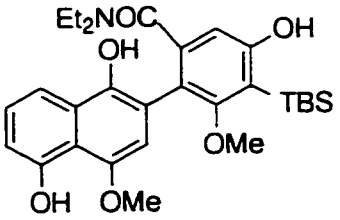

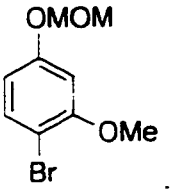

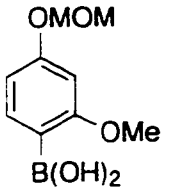

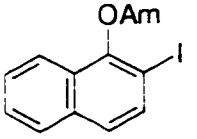

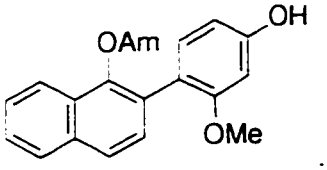

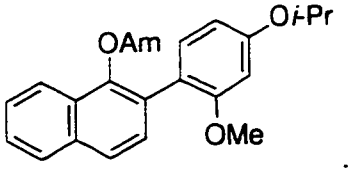

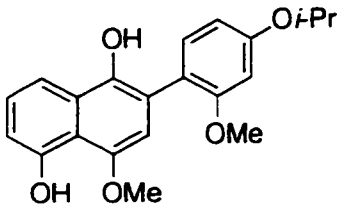

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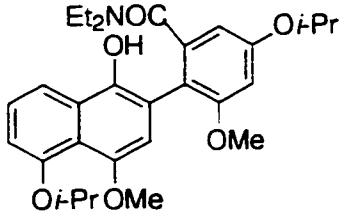

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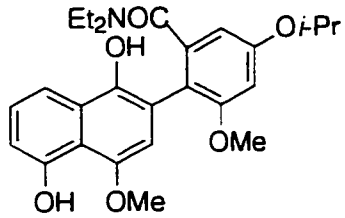
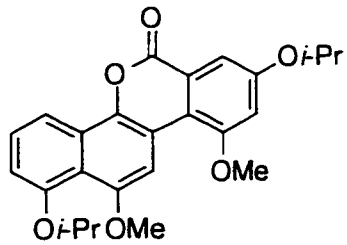
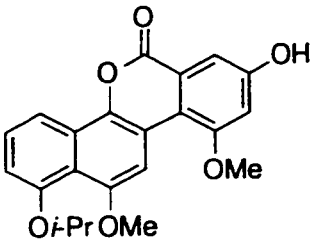
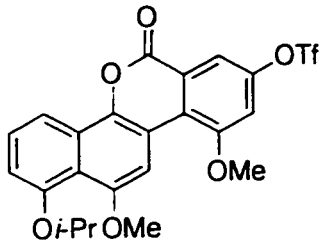
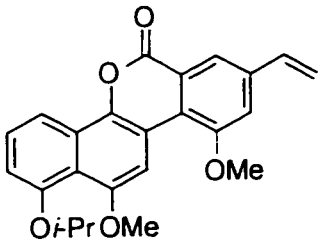


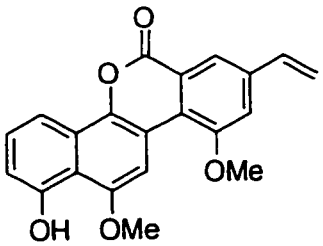
1,8-Diisopropoxy-10,12-dimethoxy-6*H*-naphtho[1,2-*b*]-benzo[*d*]pyran-6-one (282)

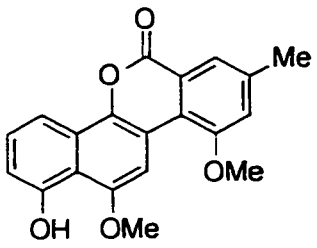




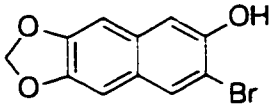




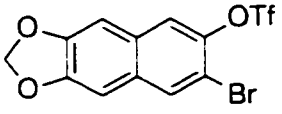




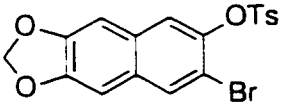
3-Bromo-6,7-methylenedioxy-2-naphthol (295)



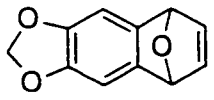
3-Bromo-6,7-methylenedioxy-2-naphthyltrifluoromethanesulfonate (296a)



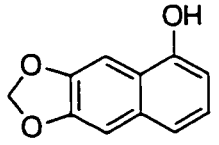
3-Bromo-6,7-methylenedioxy-2-naphthyl *p*-toluensulfonate (296b)

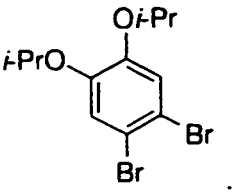


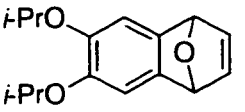
1,4-Dihydro-6,7-methlenedioxy-1,4-epoxynaphthalene (292)

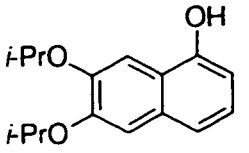


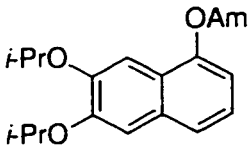
6,7-Methylenedioxy-1-naphthol (291)

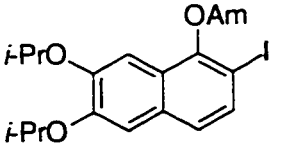


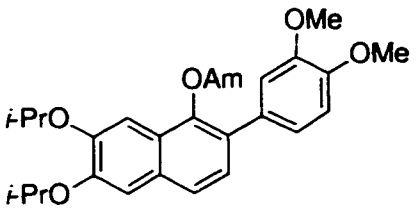






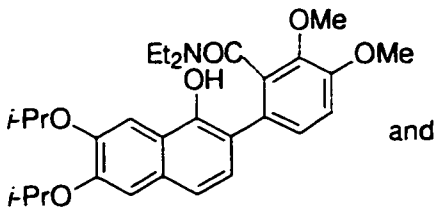






..... 206

N,*N*-Diethyl 2-(6,7-diisopropoxy-1-hydroxy-2-naphthyl)-5,6-dimethoxyphenyl benzamide (309) and 6,7-diisopropoxy-2-(3,4-dimethoxyphenyl) -1-naphthol (310)..... 207



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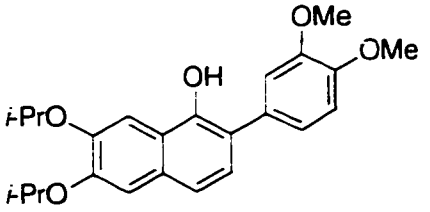
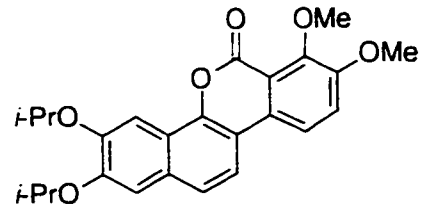


..... 207

3,4-Diisopropoxy-7,8-dimethoxy-6*H*-naphtho[1,2-*b*]benzo[*d*] pyran-6-one (311)..... 209



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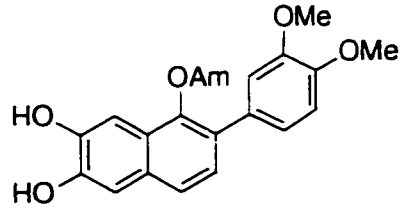
N,*N*-Diethyl *O*-[6,7-dihydroxy-2-(3,4-dimethoxy-phenyl)]-1-naphthyl carbamate (312)..... 209



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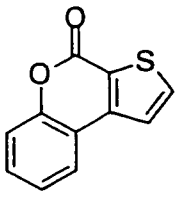

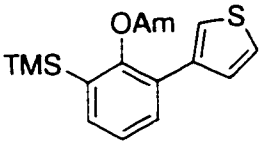

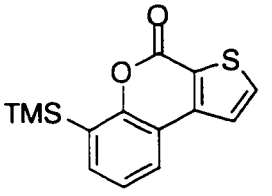

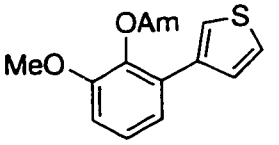

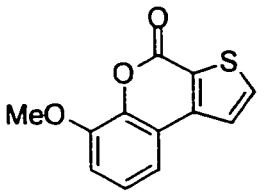

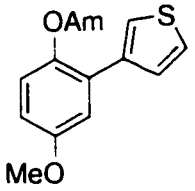

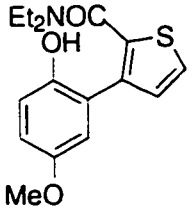

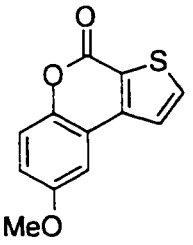

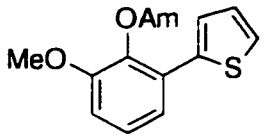

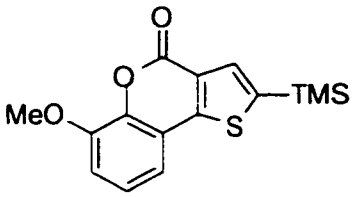

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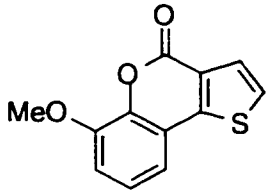

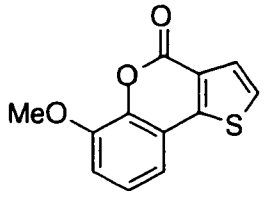

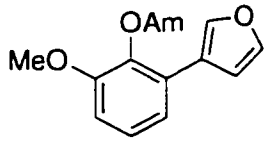

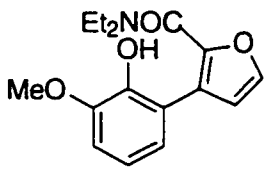

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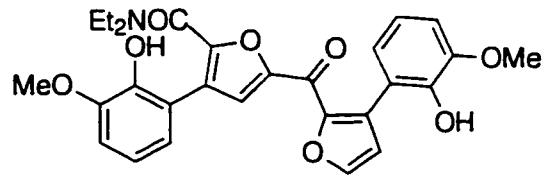
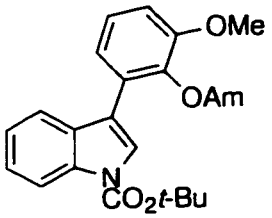
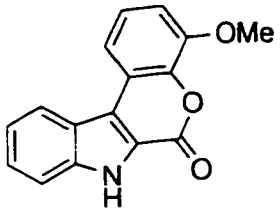






List of Tables

Abbreviations

Ac	acetyl
acac	acetonylacetonate
AIBN	2,2′-azobis(isobutyronitrile)
Ar	aryl
app	apparent
br	broad
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
t-Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
CIPE	complex induced proximity effect
d	doublet
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFGE	defucogilvocarcin E
DFGM	defucogilvocarcin M
DFGV	defucogilvocarcin V
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMG	directed metalation group
DMSO	dimethylsulfoxide
DoM	directed *ortho* metalation

dppf	diphenylphosphinoferrocene
dppp	diphenylphosphinopropane
DreM	directed remote metalation
E^+	electrophile
EI	electron impact
equiv	equivalent(s)
exch	exchangeable
Et	ethyl
FAB	fast atom bombardment
g	gram
GC	gas chromatography
h	hour
HOESY	Heteronuclear Overhauser Enhancement Spectroscopy
HRMS	high resolution mass spectrum
Hz	Hertz
IR	infra-red
L	ligand
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidide
m	multiplet
Me	methyl
MHEX	metal - halogen exchange
mmol	millimole
MOM	methoxymethyl
MS	mass spectrum
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectrscopy
PG	protecting group
Ph	phenyl
PPA	polyphosphoric acid
ppt	precipitate
Py	pyridine
q	quartet
rt	room temperature
s	singlet
SAR	structure activity relationship
sept	septet
t	triplet
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMEDA	*N.N.N'.N'*-tetramethylethylenediamine
Ts	*p*-toluenesulfonyl

1. DoM, DreM and Cross Coupling in Synthesis

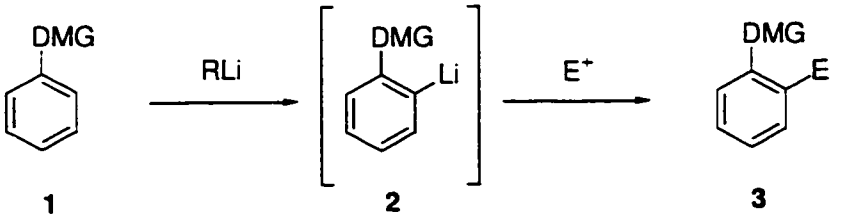
1.1 Introduction

The regiospecific synthesis of aromatic and heteroaromatic compounds is an ongoing challenge for synthetic chemists. The need to prepare such compounds stems from the fact that many important pharmaceuticals[1] and compounds for material science are aromatic or contain some aromatic structural subunit. Several strategies have been developed to address this issue but the most common method of functionalization of aromatic compounds is the electrophilic aromatic substitution reaction.[2] Although useful in its own right, the reaction often suffers from harsh reaction conditions and poor regiochemical selectivity making the preparation of contiguously substituted aromatics difficult.

1.2 The Directed *ortho*-Metalation Reaction

The directed *ortho*-lithiation of anisole was discovered independently by Gilman[3] and Wittig.[4] The deprotonation of aromatic species bearing a heteroatom containing Directed Metalation Group (DMG) has now become a valuable process in organic synthesis. The reaction involves treatment of DMG bearing aromatic compounds **1** **(Scheme 1)** with strong base, typically alkyllithium reagents in ethereal or hydrocarbon solvents, to regioselectively afford the 2-lithioaromatics **2**. Treatment of these

Scheme 1

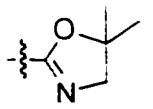


compounds with appropriate electrophiles generates the 1,2-disubstituted aromatics **3**. The reaction is now very general and has been extensively reviewed.[5]

1.2.1 Directed Metalation Groups

Since the initial discovery of the methoxy group as a DMG, a large number of functional groups have been shown to be effective at directing aromatic lithiation. These are broadly broken into two groups, carbon-based and heteroatom-based DMGs, referring to the atom at the point of attachment of the functional group to the aromatic ring. Several examples of common DMGs are collected in **Table 1**. Of the directing

Table 1. Common Directed Metalation Groups

Carbon-Based	ref	Heteroatom-based	ref
CH_2NR_2	5b	NR_2	5b
CF_3	5b	OMe	3,4
CONHR	5b, 6	NHCOR	7
$CONR_2$	5e, 8	$NHCO_2R$	9, 10
CO_2H	11	OCH_2OMe	12, 13
CH_2OH	14	OTHP	5b
	15	OH	16
		$OCONR_2$	5e, 17
C=NR	18	$OPO(NR_2)_2$	19
		F, Cl	20, 21
		SO_2NR_2, SO_2-*t*-Bu	5b
		P(O)-*t*-Bu_2	22

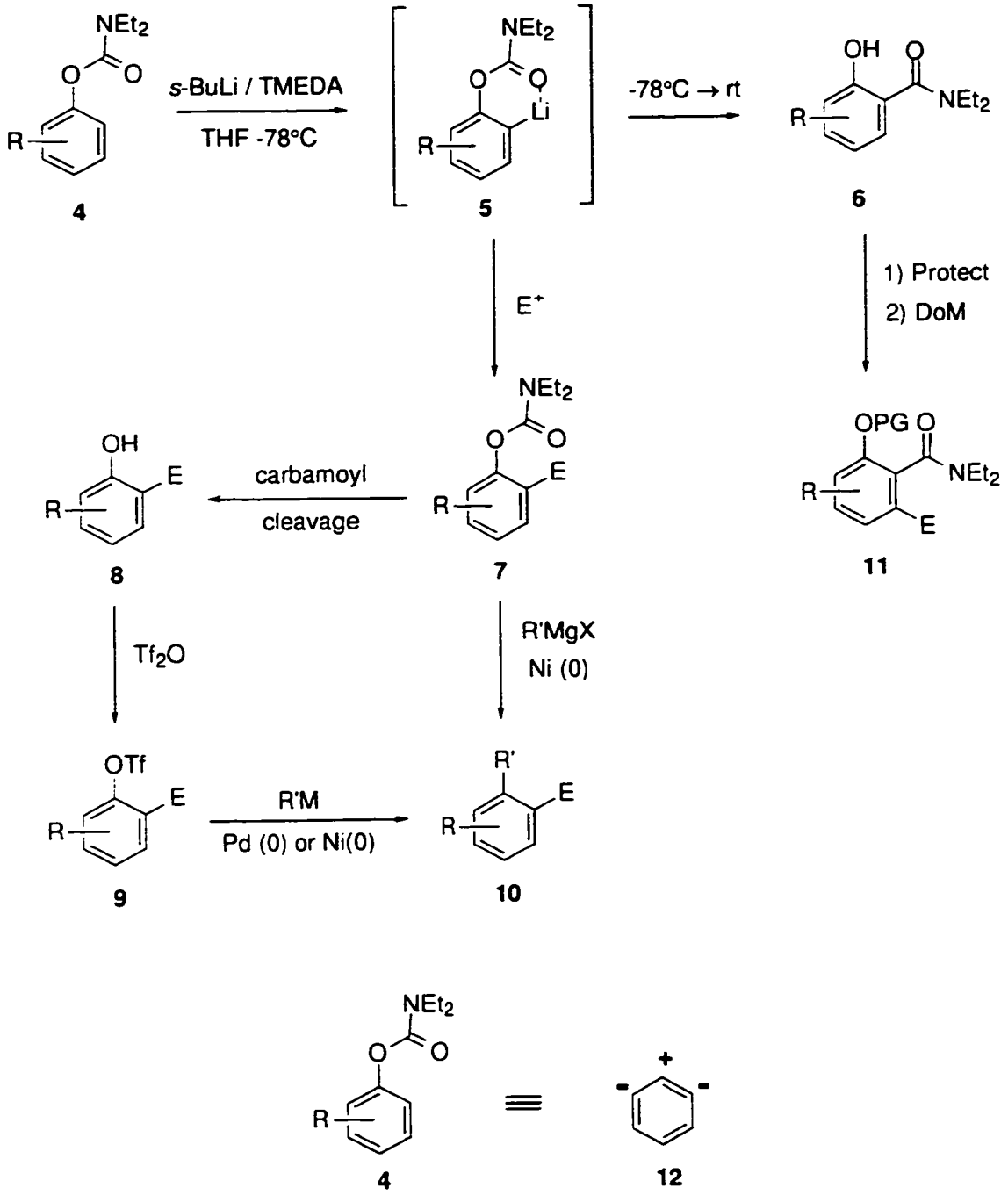
groups listed, those which have been exploited to the greatest extent are the oxazoline by Meyers,[15] the tertiary amides ($CONEt_2$, $CON(i\text{-}Pr_2)_2$) by Beak[8] and Snieckus,[5e] and the

tertiary diethyl carbamate ($OCONR_2$) by Snieckus.[17] Transformations of this latter DMG will be the focus of this work and therefore the scope and utility of this DMG warrants further discussion.

1.2.2 The Carbamoyloxy Directing Group

In 1983 Sibi and Snieckus demonstrated that the carbamoyloxy group is a powerful DMG and evaluated its scope and utility through the preparation[17] of a wide variety of 1,2-disubstituted compounds **(Scheme 2)**. Thus, treatment of aryl carbamates **4** with *s*- BuLi / TMEDA affords *o*-lithiocarbamate **5** which on treatment with electrophiles affords *ortho*-substituted carbamates **7** in good to excellent yields. The synthetic utility of these compounds can be further demonstrated *via* removal of the carbamoyl function using basic hydrolysis (NaOMe), strong nucleophiles (MeLi) or reductive cleavage ($LiAlH_4$) allowing regioselective preparation of 1,2-disubstituted phenols **8**. The carbamoyl group thus serves as a masked phenol derivative allowing preparation of *ortho*-substituted phenols with higher selectivity than classical electrophilic methods.[2] These phenols may then be further transformed by conversion to the triflate and subsequently subjected to cross coupling conditions with organometallic reagents and Pd(0) or Ni(0) catalysis. Common examples are Grignard,[23] organozinc,[24] organotin,[25] and organoboron reagents.[26] Recently in this laboratory it was demonstrated that the carbamoyl group itself can act as a leaving group in the Ni(0) catalyzed cross coupling reaction,[27] allowing a shortened synthesis of substituted biaryls **10**. Thus, aryl carbamates can be considered as a reagent for the tripolar synthon **12**.

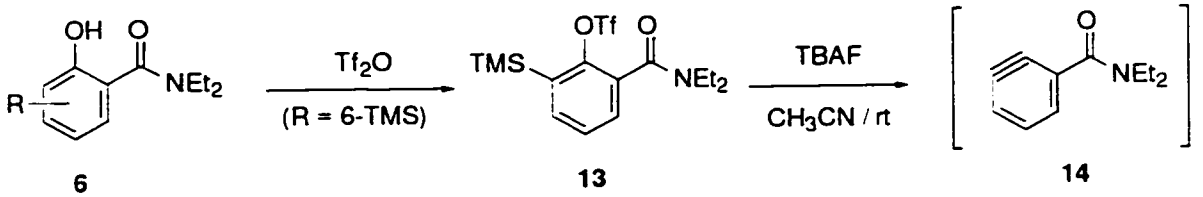
Scheme 2



Another aspect of the utility of the carbamate DMG is illustrated in the absence of an electrophile. On warming **5** to room temperature, a 1,5-O → C carbamoyl migration occurs affording salicylamides **6**. This migration process is formally an anionic equivalent of the *ortho*-Fries rearrangement. The synthetic utility of this process is

twofold. First, if the phenol moiety of **6** is masked with a suitable protecting group, the aromatic ring may be further functionalized using metalation with the tertiary amide as the DMG, thus establishing a synthetic link between the carbamate and the amide DMGs. Second, in the specific case for **6** (R = 6-TMS) **(Scheme 3)** conversion of the phenol to the triflate **13**, allows utilization of the mild conditions for aryne formation established by Koybayashi[28] to give reactive intermediate **14** which may be trapped in synthetically useful processes.[29] The applicability of the carbamate has also been demonstrated in the synthesis of natural products. Snieckus has used it in the synthesis of Ochratoxins A and B[30] and Danishefsky has employed it in the early stages of a synthesis of Pancratistatin.[31]

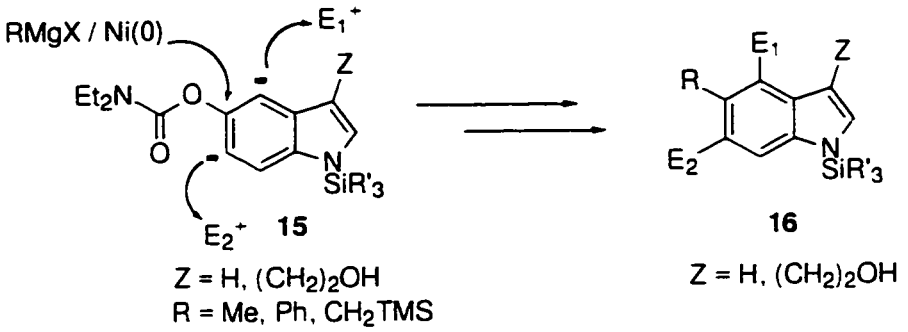
Scheme 3



6 **13** **14**

Recently a combination of carbamate D*o*M, anionic *ortho*-Fries rearrangement, and Ni(0) catalyzed cross coupling has been shown to be effective for the functionalization of the indole benzenoid ring[32] **(Scheme 4)**. Indole 5-carbamate **15** can be lithiated selectively in the 4 or 6 positions and a wide variety of electrophiles introduced. Furthermore, since the carbamate may act as a cross coupling partner with Grignard reagents under Ni(0) catalyzed coupling conditions, functionalization of the 5-position is feasible. This methodology was also carried out on tryptophol derivatives and is the first D*o*M approach to the functionalization of the benzenoid ring of indole.

Scheme 4



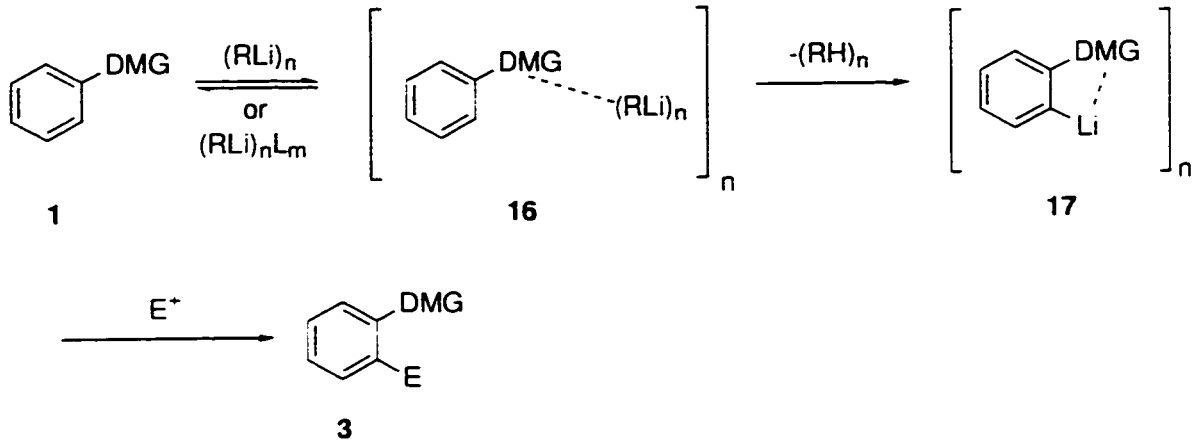
1.2.3 Mechanistic Aspects of the Directed *ortho* Metalation Reaction

In perhaps the first proposal regarding the mechanism of D*o*M, Roberts and Curtin[33] postulated complexation of the organolithium reagent with the heteroatom of the DMG (oxygen for anisole) which acted in concert with the inductive effect of the heteroatom to increase the acidity of the *ortho* protons leading subsequently to deprotonation. Though there was no experimental evidence, this concept was generally accepted and it was believed[5a] that two separate mechanistic extremes may be in operation depending on the DMG. The first is the so called "coordination only" mechanism for which DMG = CH_2NR_2 is a good example. The second occurs if the DMG has limited or no ability for complexation, for example DMG = F ("acid-base" mechanism). Certain cases would, of course, warrant invoking some compromise between these two extremes.

The direct observation by Beak[34] of the coordination of an organolithium reagent to the carbonyl of a tertiary benzamide by stopped flow IR spectroscopy served to furnish concrete evidence supporting Curtin and Roberts postulate. The new proposal incorporated a preequilibrium between the organolithium aggregate and **1** affording a complex of type **16 (Scheme 5)**. This initial coordination brings the base into close

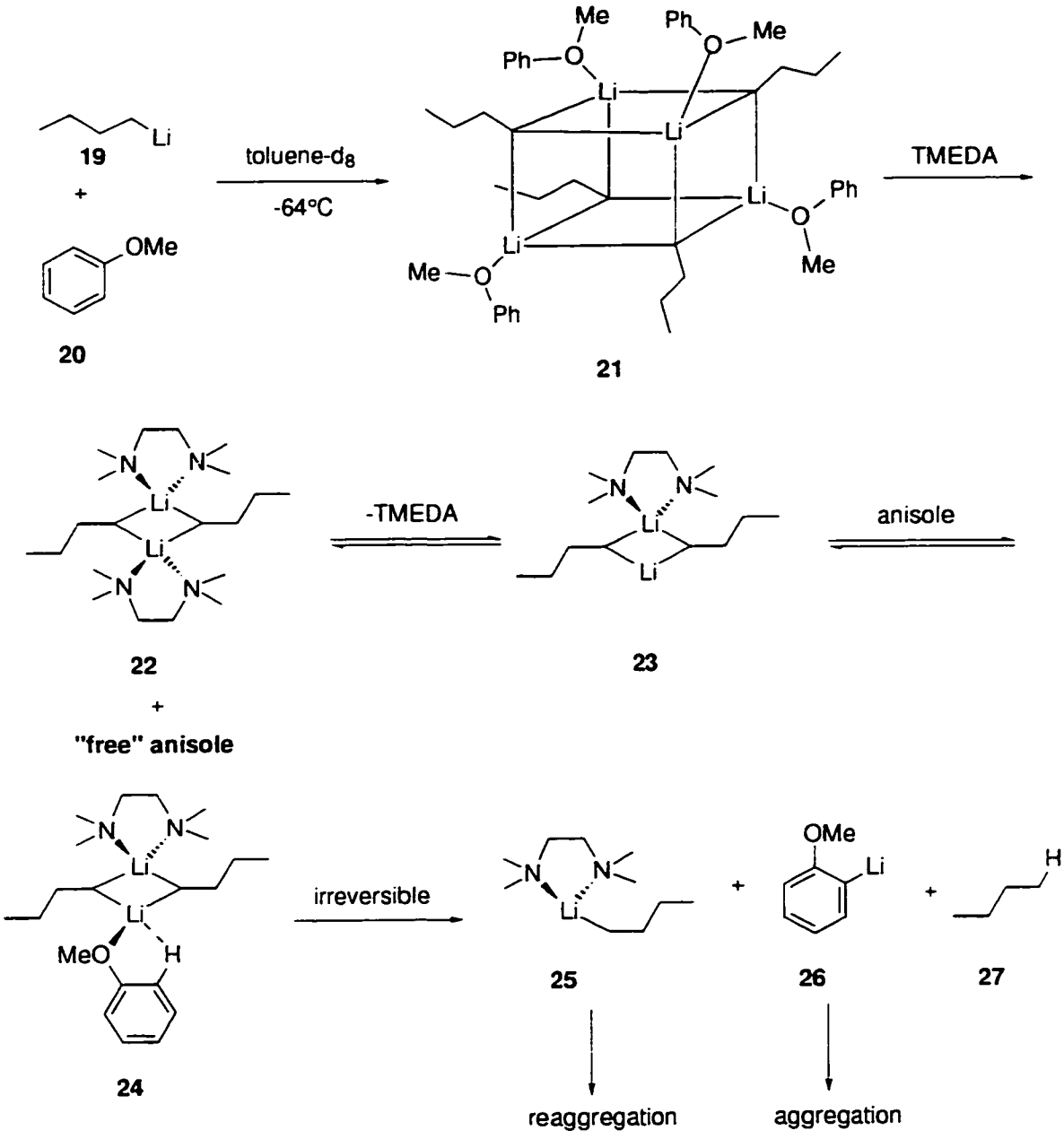
proximity to the *ortho* protons allowing facile irreversible proton abstraction affording the intramolecularly complexed lithio species **17**. Reaction of this intermediate with electrophiles then produces the disubstituted aromatics **3**. The initial coordination termed the Complex Induced Proximity Effect (CIPE) brings conceptually together a variety of observations with a kinetic commonality which overrides thermodynamically driven events.[35,36] It is now a valuable concept in the mechanistic considerations of the DoM reaction.[37]

Scheme 5



Studies by Schleyer[38] and co-workers have also provided evidence supporting the formation of a complex. They studied the lithiation of anisole with *n*-BuLi in toluene-d_8 using ^{6}Li, ^{1}H HOESY NMR and observed a tetramerically aggregated complex of *n*-BuLi which was peripherally ligated with anisole in the cubic structure **21** shown in **Scheme 6**. Even though the HOESY data provided evidence for close Li-H contacts, no ortho-lithiation was observed even at rt. Addition of one equivalent of *N.N.N'.N'*-tetramethylethylenediamine (TMEDA) disrupted the anisole - *n*-BuLi complex giving free anisole and the dimeric *n*-BuLi - TMEDA complex **22**. At this stage lithiation occurred quickly giving the expected 2-lithioanisole. Loss of one ligated TMEDA gives **23** having a coordinatively unsaturated lithium which can incorporate free anisole to give the

Scheme 6



reactive complex **24**. Irreversible deprotonation occurs generating lithioanisole which aggregates until further reaction, and **25** which also reaggregates and undergoes further metalation cycles. Thus, Schleyer and co-workers suggest that the dimeric alkyllithium intermediate **23** which has two or more available coordination sites is the reactive species, not the NMR observable tetrameric complexes such as **21**. Schleyer has also

proposed that in **24**, further acidification of the C-H bond is provided by Li - H agostic interactions. This has been supported by MNDO[38] and *ab initio*[39] calculations of model transition states. Similar calculations have been performed for substituted anisoles,[40] phenolic compounds[41] and substituted toluenes.[42] Recently, Saá and co-workers[43] have applied ^{7}Li - ^{1}H HOESY NMR techniques to a study of the metalation of 1-naphthol, suggesting a mechanism analogous to that proposed by Schleyer.

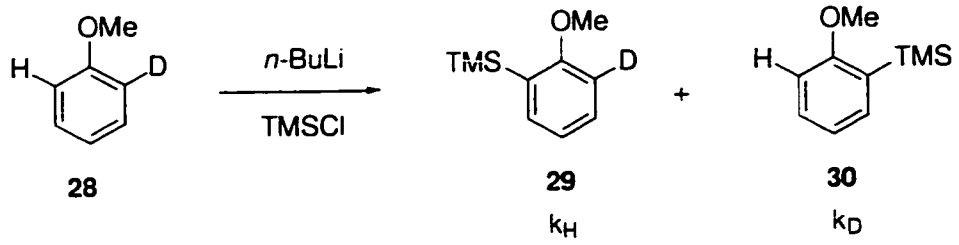
Recent *ab initio* calculations by Schleyer[44] also suggest that the initial complex between *n*-BuLi and anisole may not be necessary for lithiation to occur. By considering LiH as a model for alkyllithium reagents Schleyer has shown that in the metalation of phenol (as a model for anisole) and fluorobenzene the energy of the transition state is calculated to be lower than that for the initially formed complex and suggests that this lowering of the energy of the transition state enhances the rate of the reaction. These results are in disagreement with the CIPE theory which relies on the initially formed complex to explain the facile nature of the reaction. Thus, Schleyer has termed the process "kinetically enhanced metalation".

Slocum and co-workers[45] have proposed a different rationalization for the DoM of anisole. They agree that for DMGs containing a heteroatom directly bound to the aromatic ring, there must be initial coordination of the alkyllithium reagent. In the case of anisole, however, they suggest that ground state resonance depletes electron density on the heteroatom rendering it a less effective coordinator. Therefore, at room temperature in the absence of TMEDA the initial coordination is slow and no metalation is observed. In the presence of TMEDA, the rate of lithiation increases dramatically. This is accounted for by considering an "overriding base" theory where the *n*-BuLi - TMEDA complex effects fast deprotonation of anisole without prior complexation. This model has been used to understand the lithiation of *p*-fluoroanisole,[46] *p*-methylanisole[47] and dimethoxybenzenes.[48]

Very recently, Stratakis[49] has reported a study of isotope effects in lithiation of anisole in Et_2O in the absence and presence of TMEDA (**Scheme 7**). From the observations of identical inter and intramolecular isotope effect ratios Stratakis concluded

Scheme 7

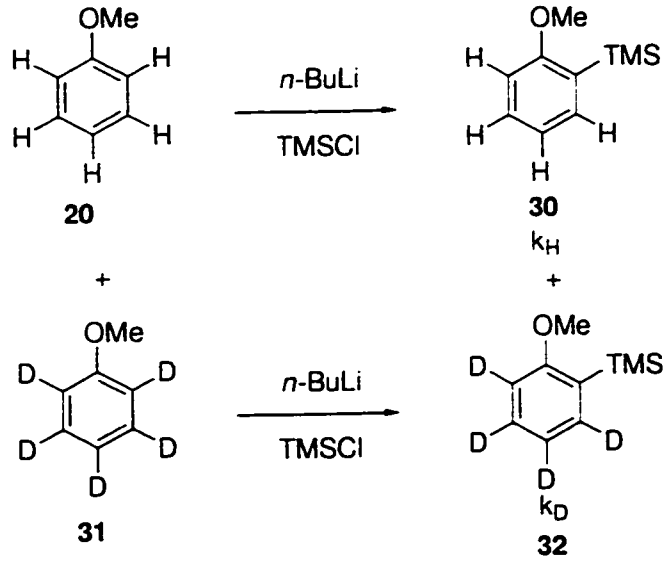
Intramolecular:



28 **29** k_H **30** k_D

Et_2O	Et_2O / TMEDA
$k_H/k_D = 2.3 \pm 0.1$	$k_H/k_D = 3.1 \pm 0.1$

Intermolecular:



20 **30** k_H + **31** **32** k_D

Et_2O	Et_2O / TMEDA
$k_H/k_D = 2.5 \pm 0.2$	$k_H/k_D = 3.2 \pm 0.2$

that the abstraction of the *ortho*-proton occurs in the rate limiting step, consistent with the studies of Schleyer. Unfortunately, comparison of the isotope effect data with and

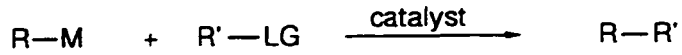
without TMEDA gave no insight into the nature of the structure or aggregation state of the reactive intermediates.

Most recently, Collum and co-workers[50] have reported a kinetic study of the metalation of anisole. By examining the dependence of the reaction on the concentration of TMEDA and *n*-BuLi the rate law was established as -d[anisole]/dt = k[anisole][TMEDA]^0[(*n*-BuLi)$_2$(TMEDA)$_2$] where (*n*-BuLi)$_2$(TMEDA)$_2$ is the dimeric *n*-BuLi - TMEDA aggregate. From this it is suggested that the transition state consists of the stoichiometry [(*n*-BuLi)$_2$(TMEDA)$_2$•anisole]‡. However, the exact structure of the reactive intermediate could not be determined. The results are discussed in terms of a dimer based structure but are not consistent with the coordinatively unsaturated intermediate proposed by Schleyer (e.g. **24**, **Scheme 6**). Thus, in spite of the abundant mechanistic information regarding the D*o*M reaction, it is still relatively poorly understood.

1.3 The Transition Metal Catalyzed Cross Coupling Reaction

The transition metal catalyzed cross coupling[51] is a relatively new but very useful process for the construction of C-C bonds. Outlined in **Scheme 8**, the reaction consists of an organometallic species, an organic fragment bearing a leaving group, and a transition metal catalyst. Most commonly, the metal of R-M is magnesium, tin, zinc or boron and the catalyst is typically from the nickel triad (Ni, Pd, Pt), although others have been used including Ag, Cu, Co, and Fe.[52] Recently, independent contributions from Buchwald and Hartwig have detailed methods for the Pd catalyzed coupling of heteroatom based (Ar-NH$_2$, ArOH) substrates to allow preparation of diarylamines[53,54]

Scheme 8



R = alkyl, alkenyl, alkynyl, aryl,
R' = alkyl, alkenyl, aryl, acyl,
catalyst = Ni, Pd.
LG = I, Br, Cl, OTf, $OCONEt_2$, $SCONR_2$

M	Reaction	ref
MgX	Corriu - Kumada - Tamao	55
SnR_3	Stille	56
ZnX	Negishi	57
$B(OR)_2$	Suzuki - Miyaura	58

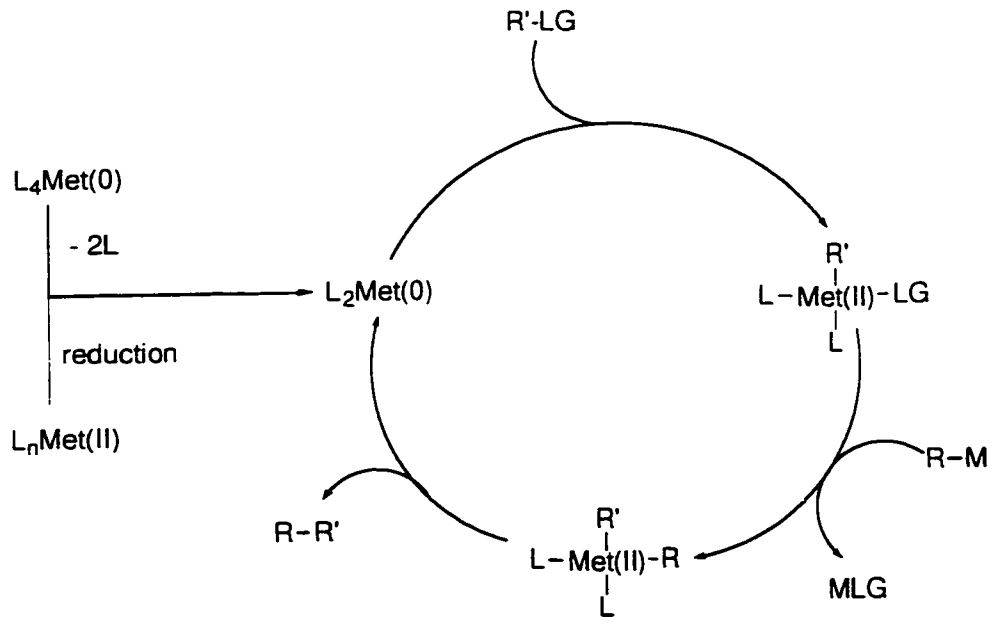
and ethers[59] under mild conditions. Common leaving groups include halogens (I, Br, and to a lesser extent Cl), oxygen based derivatives such as triflates[23,26c,60] and other sulfonates,[61,62] the *N,N*-diethyl *S*-arylthiocarbamate, and as discussed in Section **1.2.2**, the *N,N*-diethyl *O*-arylcarbamate.

Historically the Ni(0) catalyzed reaction of Grignard reagents with aryl halides was the first cross coupling process to be discovered. The reaction is limited to substrates which bear no functionality, such as esters, which are sensitive to strong nucleophiles. The wide availability of Grignard reagents as well as leaving groups which are reactive to Grignard reagents under Ni(0) catalysis (e.g. OMe,[63] $OP(O)(OEt)_2$,[64] SR,[65] and SO_2R[66]) have helped to dramatically increase the scope of the reaction. The Stille reaction suffers from the disadvantage that the tin side - products are toxic and often problematic to remove. However, the ease of preparation and stability of the stannanes as well as the mild reaction conditions have made this a useful process. Recently, Farina[67] has extended the scope, optimized the reaction conditions and provided mechanistic information through a systematic investigation of kinetics and ligand and catalyst effects. The Negishi reaction overcomes the nucleophilicity concern of the Grignard reaction as the corresponding organozinc reagents are not strongly

nucleophilic and therefore functional groups such as esters, aldehydes, nitriles and nitro groups are tolerated and protection - deprotection sequences are not required. Unfortunately, like the Grignard reagents, the organozinc compounds are moisture sensitive and therefore careful drying of reaction vessels is required. The Suzuki - Miyaura coupling of aryl boronic acids with halides and triflates is advantageous in that boronic acid reagents are stable to air and moisture and are non-toxic. Similarly, these reagents may be easily prepared from the corresponding aryllithium or Grignard reagent by treatment with trialkyl borate reagents. Through a study of the effects of bases on the Suzuki - Miyaura reaction, Campbell[68] demonstrated that the reaction requires a weak base to generate the boronate species which is the actual reagent which participates in the reaction. It was also shown that bases such as $Ba(OH)_2$ and Cs_2CO_3 dramatically accelerate the reaction.

The currently accepted mechanism of the cross coupling reaction is shown in **Scheme 9**. The first step is generation of the active zero - valent metal catalyst. This

Scheme 9



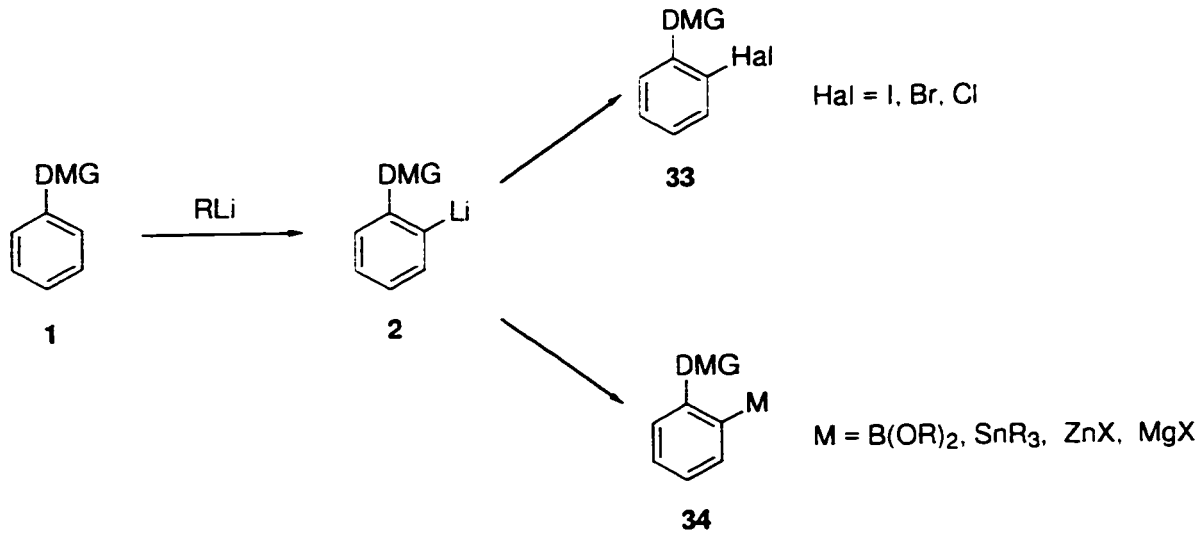
may occur by ligand dissociation (e.g. $Pd(PPh_3)_4$) or by *in situ* reduction of a Pd(II) or Ni(II) catalyst. The next step is oxidative addition of the Met(0) catalyst to the carbon - heteroatom bond of ArLG to give the Met(II) intermediate. Transmetalation by the organometallic reagent is followed by elimination of metal halide. The diorganometallic species may now undergo reductive elimination to generate the new carbon - carbon bond and regenerate the active catalyst which re-enters the catalytic cycle.

1.4 The Directed *ortho*-Metalation - Cross Coupling Connection

A valuable advantage of the DoM reaction is that it allows regioselective introduction of the required functionality for cross coupling chemistry. Initial *ortho*-lithiation of DMG bearing aromatics followed by treatment with suitable electrophiles allows direct generation of a wide variety of cross coupling partners **(Scheme 10)**. The aromatic lithio species may serve as the organometallic coupling partner **34** *via* treatment with suitable electrophilic metal derivatives, alternatively it may be used to prepare the halide coupling partner. The use of OH^- sources allows access to oxygen based leaving groups. Similarly, as was described in **Section 1.2.2**, if the DMG in **Scheme 10** is carbamate, then the *ortho*-Fries rearrangement allows connection to the cross coupling protocol *via* the triflate leaving group. Complex substitution patterns can be generated through the use of initial DoM processes to functionalize the precursors. Several examples of the diversity of this connection, first demonstrated by Sharp,[69] include the synthesis of polyphenyls,[70] dibenzopyranones,[71] phenanthridines[72] and phenanthridinones.[73]

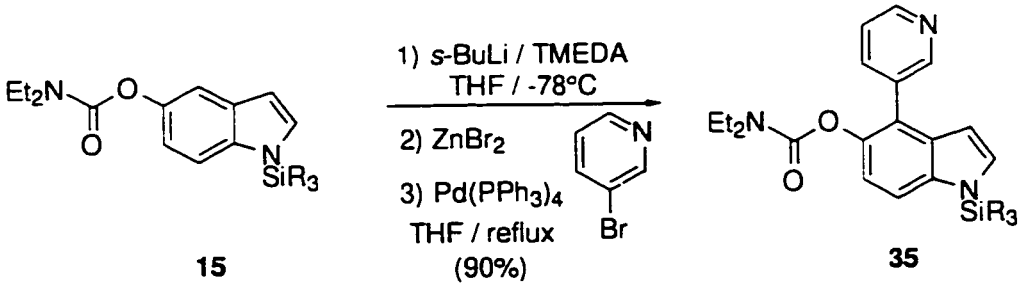
An example of the DoM - Negishi cross coupling protocol was demonstrated by Griffen, Roe and Snieckus.[32] Indole carbamate **15** was treated with *s*-BuLi / TMEDA at

Scheme 10



low temperature affording the corresponding 4-lithioindole which was transmetalated with $ZnBr_2$ to give the corresponding zinc reagent. Negishi coupling with 3-bromopyridine using $Pd(PPh_3)_4$ afforded the interesting biaryl **35** in excellent yield **(Scheme 11)**.

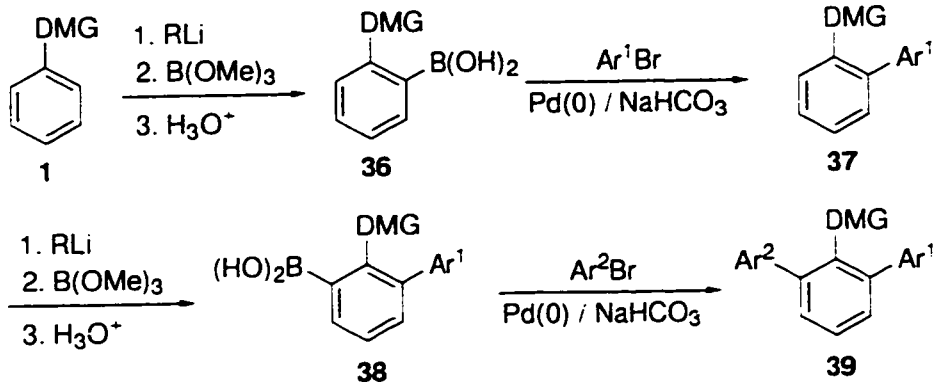
Scheme 11



The connection of DoM to cross coupling also has the potential to allow further functionalization of the newly formed biaryl ring. Treatment with base can allow a

second metalation to introduce electrophiles, which may be used for introduction of simple functional groups or for further cross coupling processes. This was demonstrated

Scheme 12

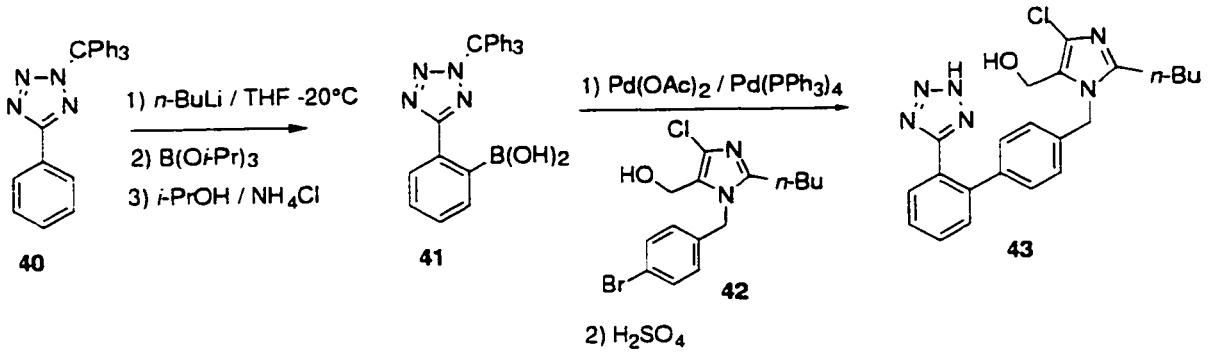


DMG = a: CON(*i*-Pr)$_2$, b: OCONEt$_2$, c: OMOM, d: NHCO$_2$*t*-Bu

via the synthesis of DMG bearing teraryls[74] **(Scheme 12)**. Biaryl **37**, generated by an initial D*o*M - cross coupling sequence is further transformed by metalation to allow preparation of boronic acids **38**. A second Suzuki cross coupling reaction allowed the preparation of a wide variety of unsymmetrical teraryls **39**.

A final example which illustrates not only the significance of the D*o*M - cross coupling connection but also the applicability of the individual methods to industry, is the efficient DuPont - Merck synthesis[75,76] of the Angiotensin II receptor antagonist[77] Losartan **43 (Scheme 13)**. *N*-Tritylated phenyltetrazole **49** was sequentially metalated and treated with triisopropyl borate to afford the boronic acid **41**. This material was coupled with bromide **42** which, after acid mediated cleavage of the triphenylmethyl protecting group, afforded Losartan. This process is currently carried out on multi - kilogram scale to produce this clinical drug for treatment of hypertension.[77c]

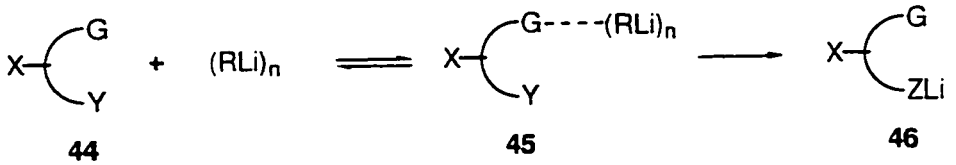
Scheme 13



1.5 The Directed Remote Metalation (DReM) Reaction

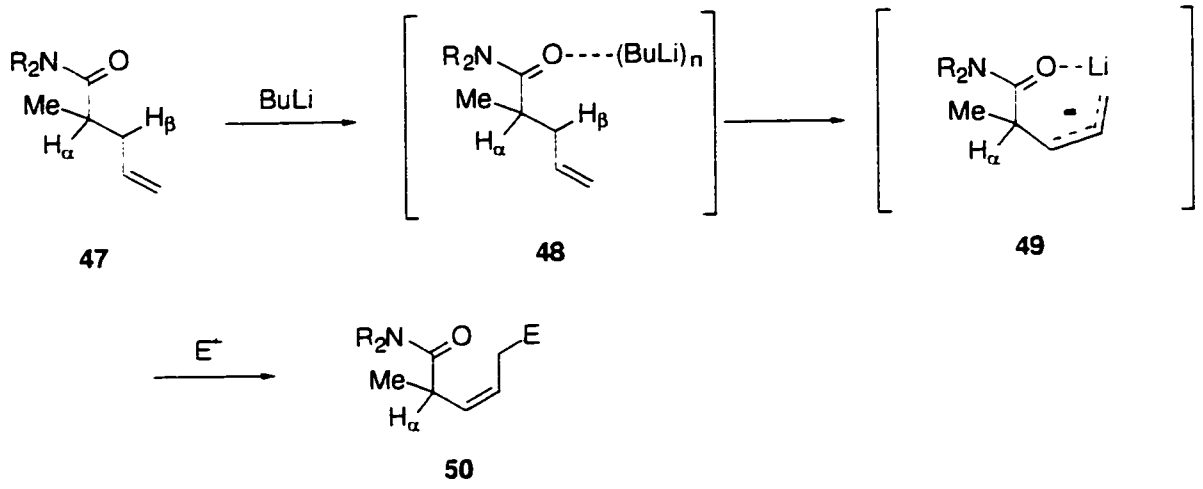
The concept of remote metalation is an extension of the D*o*M process whereby a conventionally non-acidic proton is influenced by a distal functional group to render it reactive. This idea is not a new one and has been exploited in aliphatic chemistry for many years due largely to the efforts of Beak[35] and Klumpp.[36] A useful mechanistic guideline for this process is derived from the CIPE **(Scheme 14)** where initial coordination of RLi to a functional group G generates a prelithiation complex **45** in which the alkyllithium reagent and one of several possible reactive functional groups (X, Y) are proximal. The process is now intramolecular and therefore entropically favored and reaction occurs *via* the kinetically more favorable transition state giving rise to kinetic products rather than the expected thermodynamic alternatives.

Scheme 14



An example is the lithiation of γ,δ-unsaturated amide **47** **(Scheme 15)**. Treatment of this material with *s*-BuLi led only to δ-substituted products on treatment with electrophiles. Clearly H_α is more acidic (ca. 10 orders of magnitude) yet reaction only occurs *via* deprotonation of H_β, suggesting that coordination of the alkyllithium reagent to the carbonyl favors kinetic deprotonation at H_β rather than the thermodynamically favored H_α.

Scheme 15



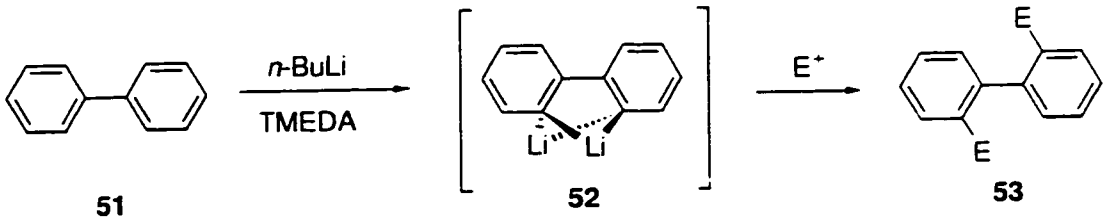
47 **48** **49** **50**

One of the simplest examples of remote metalation in aromatic systems is lithiation of 1-methoxynaphthalene.[78] Treatment with *t*-BuLi in cyclohexane affords, almost exclusively, remote metalation in the 8-position as proven by isolation of the corresponding acid on quenching with CO_2. Changing the base to *n*-BuLi in the presence of TMEDA afforded predominantly the 2-substituted acid. Similar results have been demonstrated with 1-dimethylamino- and 1-dimethylaminomethylnaphthalenes.[79,80]

Schleyer[81] has shown that on treatment with two equivalents of *n*-BuLi and TMEDA, biphenyl **(51)** undergoes dilithiation in the 2,2′-positions to give **52** on

quenching with electrophilies affording the disubstituted biphenyls **53 (Scheme 16)**. According to MNDO calculations, the dilithio intermediate is a bridged type structure **52** in which each lithium atom is involved in a 3-center-2-electron bond. This methodology was adapted to dilithiation of triphenylene and other polycyclic aromatic hydrocarbons.[82] For example, treatment of triphenylene **54** with 5 equivalents of *n*-BuLi / TMEDA generated the dilithio species which was treated with SCl_2 affording the heterocycle **55 (Scheme 17)**. Further studies by Schleyer[83,84] on 1-lithionaphthalene and other

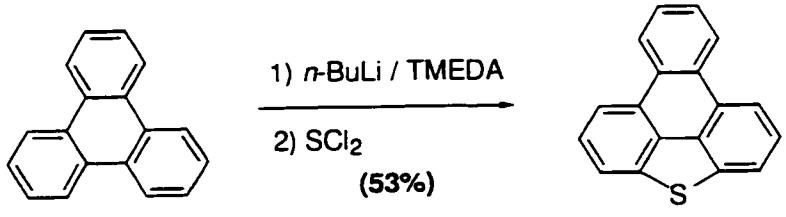
Scheme 16



51 **52** **53**

aromatic lithio compounds again by ^6Li, ^1H-HOESY and MNDO calculations suggest that the presence of the initial C-Li bond influences the second metalation *via* short Li - H distances (agostic interactions) in the complex between the monolithio species and the alkyllithium reagent.

Scheme 17

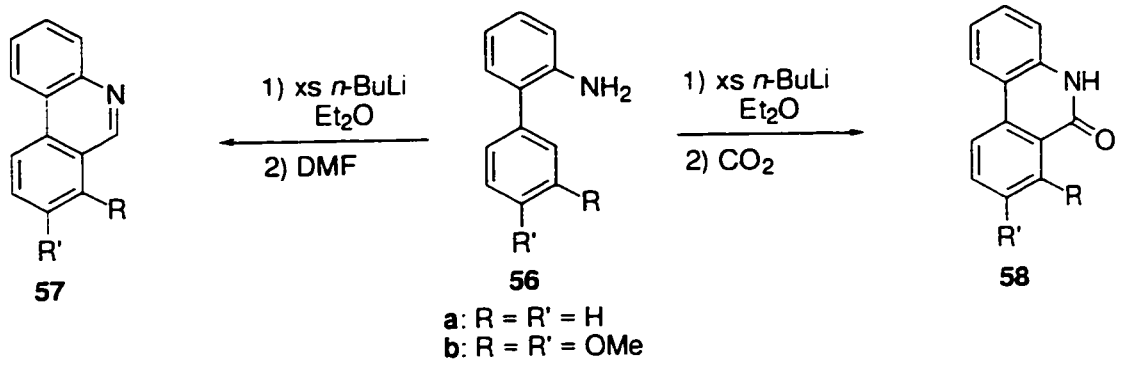


54 **55**

To the best of our knowledge, Narasimhan[85,86] was the first to show that a heteroatom can direct alternate - ring lithiation in the 2-aminobiphenyl case. Thus,

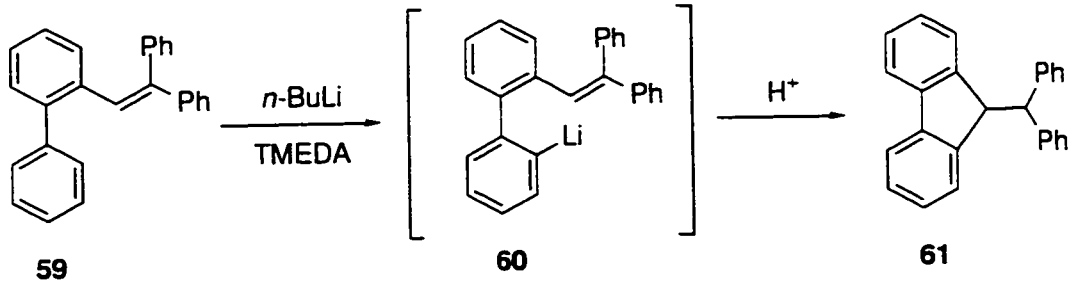
treatment of **56a, b** with excess *n*-BuLi effects deprotonation of the aniline which in turn directs metalation regioselectively to the 2′-position. Treatment of the reaction mixture with CO_2 yields phenanthridinones **58** while use of DMF as the electrophile generates phenanthridines **57** **(Scheme 18)**. The reaction is regioselective and no products derived from *ortho*-lithiation are observed.

Scheme 18



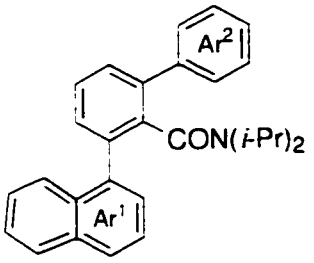
During the course of mechanistic studies of [1,2] anionic rearrangements of metalated aromatic hydrocarbons, Eisch[87] and co-workers observed remote anion - mediated cyclization of 2-(2-biphenylyl)-1,1-diphenylethene **(59)** **(Scheme 19)**. Initial 2′-lithiation **59** → **60** was followed by intramolecular addition of the lithio species to the diphenylethenyl group to furnish, after protic workup, the substituted flourene **61**.

Scheme 19

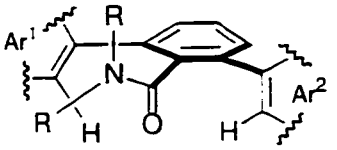


1.5.1 The Remote Metalation Concept for Amides

In the course of generalization of the D*o*M - cross coupling connection (Section 1.4) the diisopropyl amide **62** was prepared whose x-ray structure showed that the carbonyl was approximately orthogonal to the central aromatic ring. Thus, at least in the solid state, the carbonyl oxygen was positioned in close proximity to the *ortho*-hydrogens of the aromatic ring in the 2 and 6 positions as depicted in **63**. These



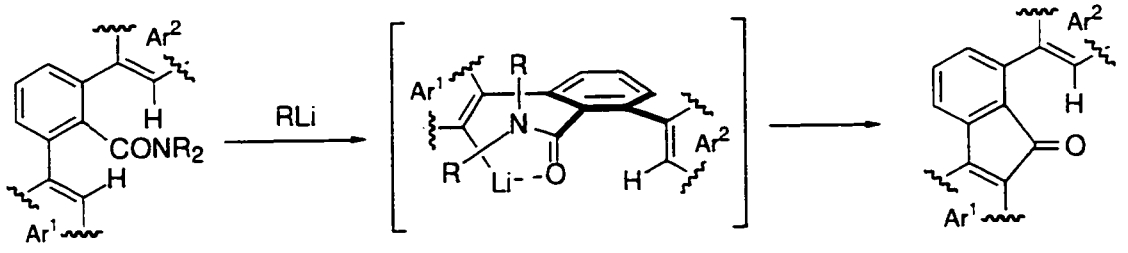
62



63

observations, in conjunction with consideration of the CIPE[35,36] led to the question of whether treatment of **62** with strong base might lead to *remote* deprotonation of the 2′ or 2″ proton induced *via* prior coordination of the strong base to the carbonyl oxygen.

Scheme 20

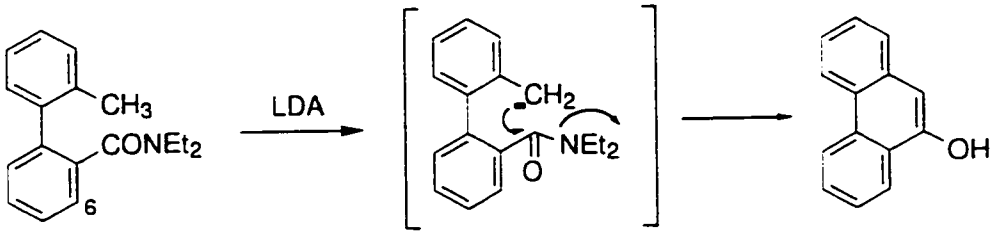


64 **65** **66**

Initial experiments[88] demonstrated that this was indeed the case. Thus, treatment of amides **64** with *t*-BuLi or LDA **(Scheme 20)** effects lithiation followed by cyclization to give the corresponding fluorenones **66**. Subsequently, this method was generalized through the preparation of a series of condensed fluorenones[89] including the natural product dengibsinin[90] and the interesting alkaloid natural product imeluteine.[91]

An interesting variation of the amide remote metalation is observed for the 2′-methyl substituted biaryl amide **67**. The methyl protons are thermodynamically more acidic than that in the 6-position and deprotonation occurs exclusively at this former site. The corresponding anion undergoes condensation with the amide function to generate phenanthrols[92] **69 (Scheme 21)**. This methodology has been exploited extensively in our laboratories for the preparation of a range of compounds including polycyclic aromatic hydrocarbons[93], *o*-quinones[94] and natural products.[95]

Scheme 21

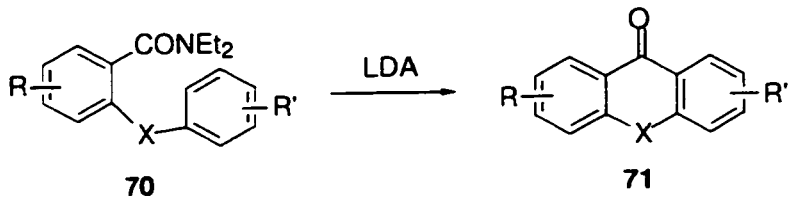


67 **68** **69**

Further modification of this theme is possible by introduction of a heteroatom linking the biaryl system. Several examples of this useful process have been investigated in our laboratories **(Scheme 22)**. Bridging groups include phenylsulphonyl, phenylphosphinoxide, oxygen, and *N*-methyl furnishing thioxanthenonedioixides,[96]

dibenzophosphinones,[97] xanthones[98] and acridones[99] respectively on LDA mediated cyclization.

Scheme 22



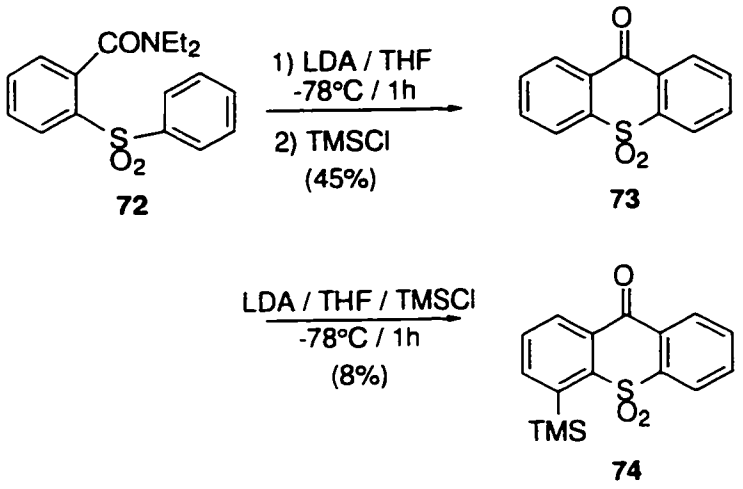
70 **71**

X = SO_2Ph, P(O)Ph, O, NMe

Similarly, in the acridone case, introduction of a methyl substituent in the 2'-position appears to be a promising method for synthesis of dibenzazepinones.[99]

In the phenylsulphonyl case, the operation of the CIPE was probed. Subjection of carboxamidodiaryl sulphone **72** to kinetic metalation conditions (*s*-BuLi / TMEDA / THF) at -78°C or -100°C for 5 min or 1 h afforded only recovery of starting material or an intractable mixture respectively and none of the desired cyclized product. Sequential treatment with LDA followed by TMSCl afforded the thioxanthenone dioxide **73** as the only isolable product. Using LDA with TMSCl as an *in situ* electrophile afforded the 4-silylated product **74** in low yield, which was shown not be formed from **73** by control

Scheme 23



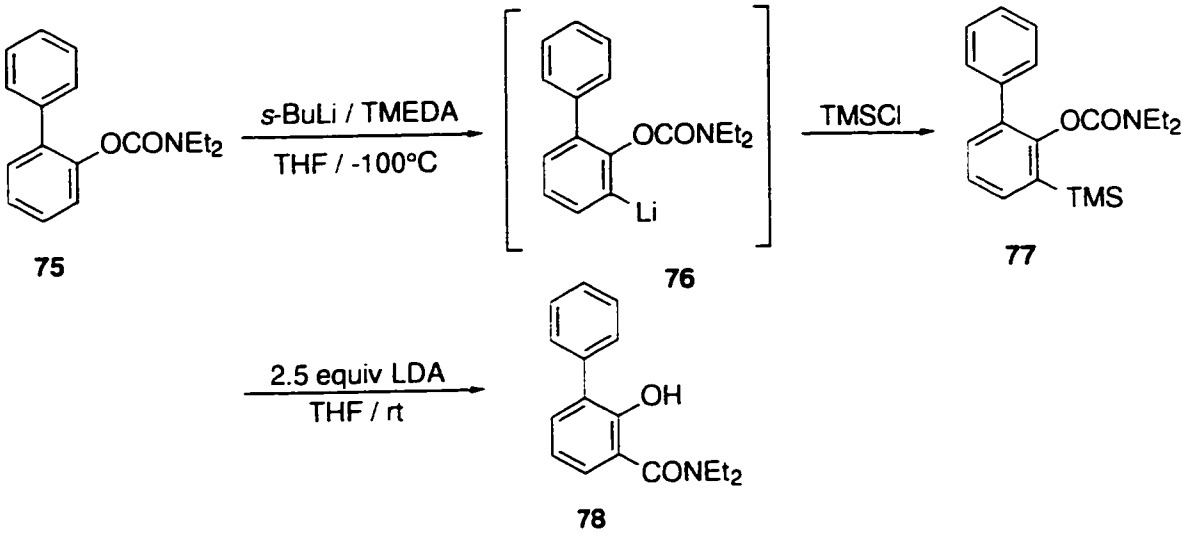
experiments. Similarly, metalation of diphenyl sulfone *via* sequential treatment with LDA (THF / 0°C / 1 h) and then TMSCl, to mimic the cyclization conditions, afforded only 26% of 2-trimethylsilyldiphenyl sulfone suggesting that the sulfone does not act as a strong DMG under the cyclization conditions. It is therefore reasonable to assume that metalation of **72** occurs in the 2′ position but that the sulfone does not extensively contribute to anion formation *via* *Do*M. This implies that the carboxamide plays an important role, perhaps through the CIPE, in the overall anionic transformation.

1.5.2 The Remote Metalation Concept for Biaryl-*O*-Carbamates

Encouraged by the results obtained with biaryl amides, the analogous biaryl-*O*-carbamate system **75** was considered as a logical extension of the DreM process. Early experiments by Sharp demonstrated the necessity for a protecting group in the 2 position due to its high kinetic acidity as evidenced during the preparation of **77** **(Scheme 24).**[74] That the 2-position was also thermodynamically more acidic was established by conversion of carbamate **75** to salicylamide **78**. These experiments showed the intermediacy of the *ortho*-lithio species **76** and therefore demonstrated a need to

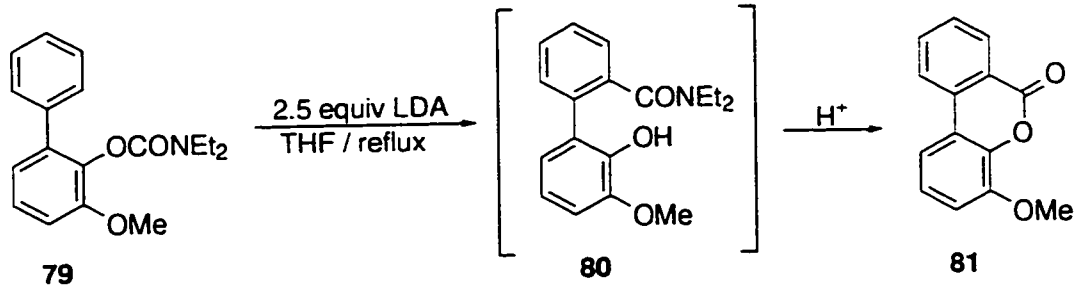
introduce a protecting group to avoid the unwanted *ortho*-anionic Fries rearrangement. In early investigations, Fu tested methoxycarbamate **79** and showed that on treatment with LDA, carbamoyl migration occurred and the corresponding dibenzopyranone was isolated in 68% overall yield after acidic workup **(Scheme 25)**. Although the methoxy group provided the desired result, it severely limited the scope of the process and another protecting group was necessary. Previous work in our laboratory indicated that trimethylsilyl is a suitable latent protecting group due to the fact

Scheme 24



75 **76** **77** **78**

Scheme 25

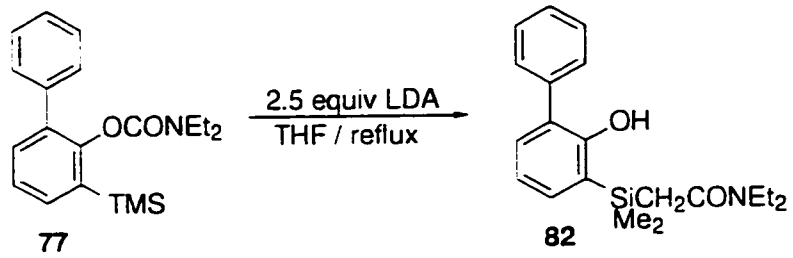


79 **80** **81**

that it can be easily introduced *via* D*o*M, is readily removed by fluoride mediated processes and can be further modified by ipso chemistry.[100] To this end, silylcarbamate

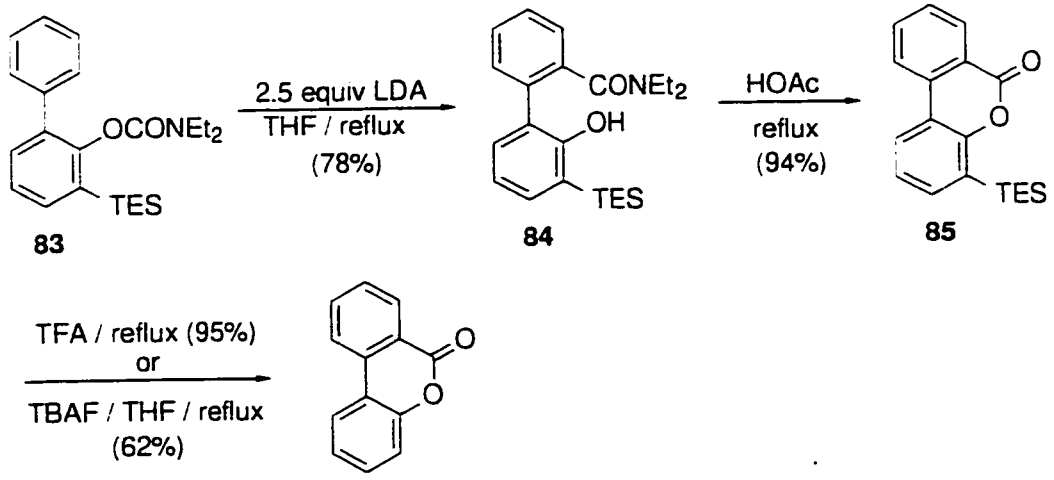
77 was treated with LDA in refluxing THF; unexpectedly, deprotonation occurred at the silyl methyl group followed by carbamoyl migration to give the α-silylacetamide **82** **(Scheme 26)**. In order to avoid this unwanted migration the more bulky triethylsilyl group was chosen and on treatment of **83** with LDA, the desired carbamoyl migration occurred giving hydroxy amide **84**, which could be cyclized under acidic conditions and the silyl group subsequently removed on treatment with TBAF or TFA **(Scheme 27)**.

Scheme 26



77 82

Scheme 27

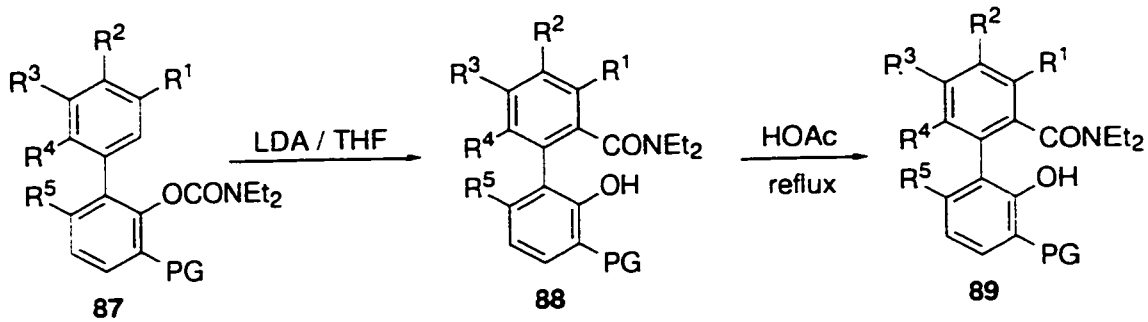


83 84 85 86

With a suitable protecting group in place, Wang[101] investigated the scope of this process through the preparation of sterically hindered biaryl amides and substituted dibenzopyranones **(Scheme 28)**. Clearly it can be seen that the yields of this process

are generally good and various substitution patterns are possible. If the 2′-position is activated by the presence of a 3′-DMG (e.g. **87f** and **87g** R^1 = $CONEt_2$ and OMe respectively) the enhanced acidity allows the reaction to be carried out at room temperature and the protecting group may then be trimethylsilyl.

Scheme 28



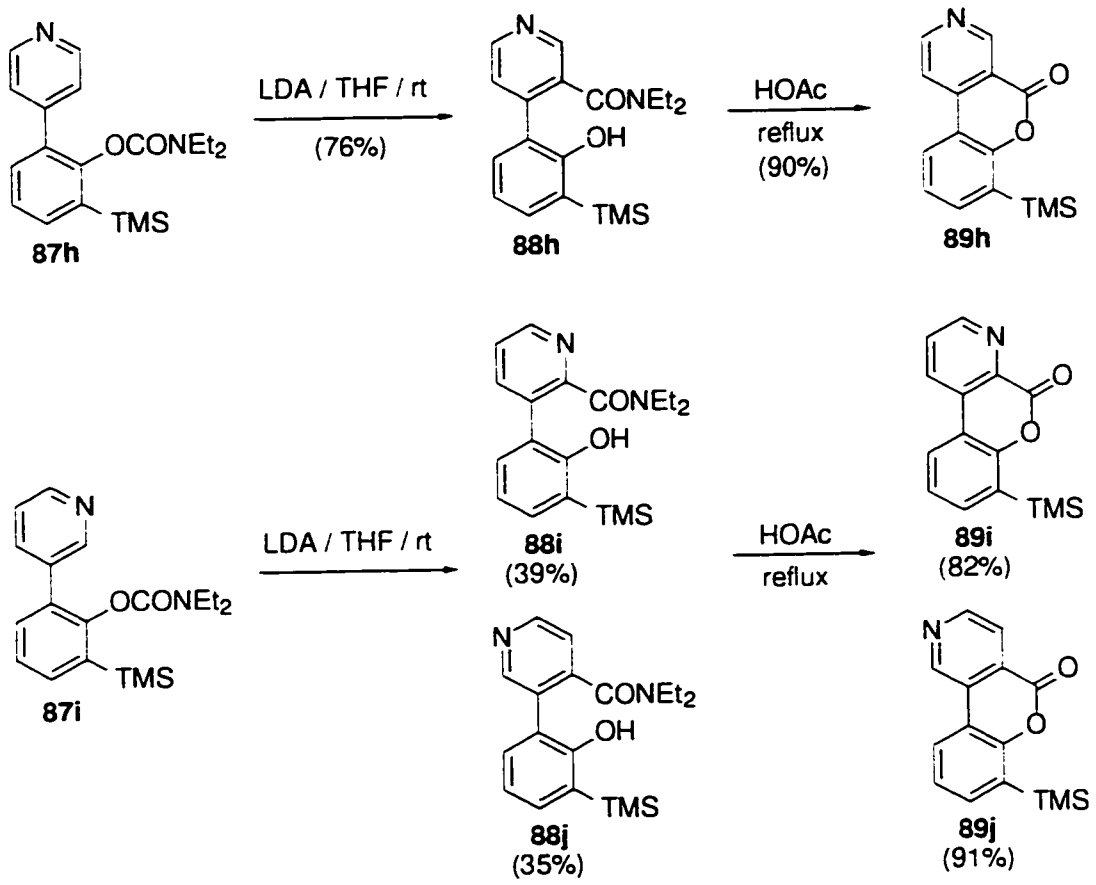
87 **88** **89**

87	PG	R^1	R^2	R^3	R^4	R^5	Yld, % **88**	Yld, % **89**
a	TES	H	H	H	OMe	H	78	89
b	TES	H	OMe	H	H	H	84	90
c	TES	H	OMe	OMe	OMe	H	80	93
d	TES	H	H	H	OMe	OMe	36	84
e	OMe	OMe	H	H	H	H	-	67 (2 steps)
f	OMe	$CONEt_2$	H	H	H	H	96	94
g	TMS	OMe	H	H	H	H	74	91

Access to heterobiaryl amides was also shown to be possible as demonstrated by the pyridyl substrates **87h** and **87i** **(Scheme 29)**. In these instances the inherently higher acidity of the pyridyl protons allowed the reactions to be carried out under mild

conditions. Similarly, the use of trimethylsilyl as the protecting group is also feasible. In the case of the unsymmetrical **87i**, there are two possible sites of metalation and both products were observed in a 1:1 ratio. In both heterobiaryl cases cyclization occurred smoothly to afford the condensed dibenzopyranones **89h-j**.

Scheme 29

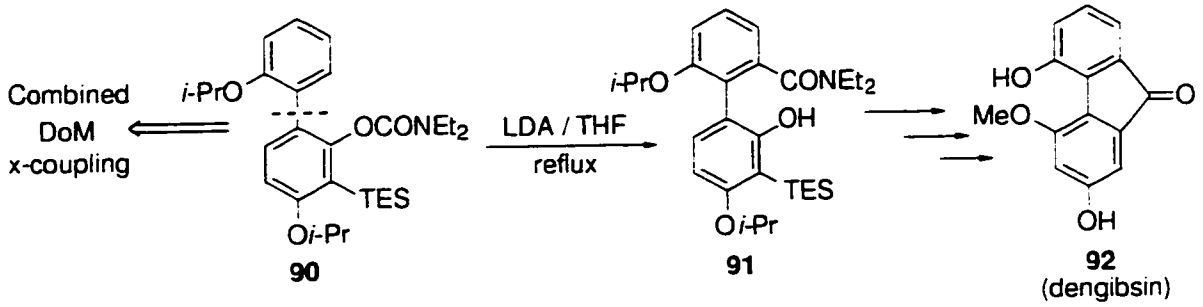


Wang demonstrated the application of this methodology in the total synthesis of the naturally occurring fluorenone dengibsin **(Scheme 30)**.[101] DoM combined with cross coupling methodology was used for the synthesis of the migration precursor and carbamate translocation *via* the key remote anionic Fries rearrangement allowed construction of the intermediate trisubstituted biaryl amide **91**. Completion of the total

synthesis utilized DReM to generate the fluorenone moiety **(Section 1.5.1)** required in the natural product.

An important advantage of the remote anionic Fries tactic is that it allows the preparation of highly substituted biaryl amides *via* translocation of the carbamoyl

Scheme 30



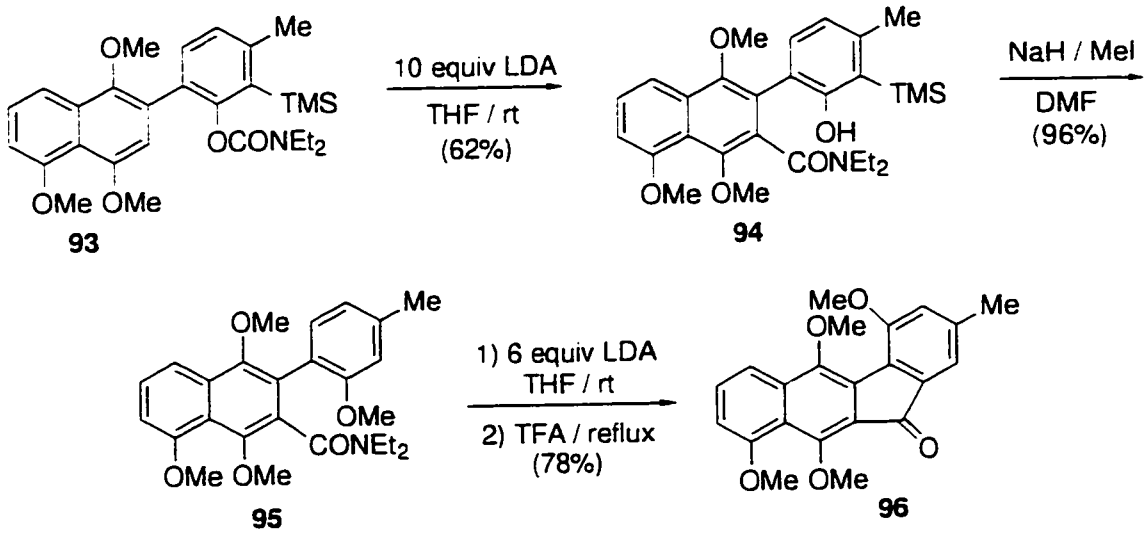
function *after* formation of the biaryl bond. In general, cross coupling reactions suffer from steric hindrance in cases where both coupling partners have *ortho* substituents. Thus 2,2',6- and 2,2',6,6'-substituted biaryls are produced in low yield or not at all by standard cross coupling protocols. Amide **87d** exemplifies this advantage allowing preparation of the highly hindered tetrasubstituted biaryl amide **88d**. Although the yield of this reaction is low, this substitution pattern would not be accessible by cross coupling alone.

The Directed Remote Metalation (DreM) - carbamoyl migration technology has recently been used in our laboratories[102] as the key step in a synthesis of kinobscurinone dimethylether **96**, a derivative of kinobscurinone, a putative intermediate[103] in the biosynthesis of the kinamycin family of antitumor compounds isolated from *Streptomyces murayamaensis*.[104] Thus, treatment of biaryl **93 (Scheme 31)**, derived from Suzuki cross coupling, with excess LDA effected carbamoyl migration to give the

highly hindered biaryl **94**. Protection of the phenol as the methyl ether followed by LDA mediated cyclization afforded the corresponding fluorenone. The synthesis was concluded with protodesilylation to afford **96** the corresponding demethylated quinone of which had previously been converted to kinobscurinone by Gould and co-workers.[104]

Thus, it is apparent that the Directed Remote Metalation (DReM) - carbamoyl migration process of biaryl carbamates is a useful strategy for the synthesis of hindered biaryls and condensed heterocycles. The applicability of the D*o*M - cross coupling connection for the synthesis of the required biaryl 2-*O*-carbamates renders this tactic a very powerful one.

Scheme 31

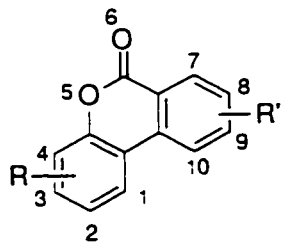


2. Dibenzopyranone Natural Products

2.1 Occurrence and Biological Properties

Compounds containing the interesting dibenzopyranone structure **106** occur in nature and are isolated mainly from microbes[105] and plant sources.[106] Some examples are shown in **Table 2**. Alternariol **(106a)** was isolated from certain species of the *Dematiaceae* family of molds[107] and has been shown to have general cytotoxicity as well as activity against certain murine tumors.[108] Both autumnariol and autumnariniol **(106b and 106c)** were obtained from the ethanol extracts of the bulbs of various types of lily,[109] and altenuisol from the fungus *Alternaria tenuis*[110] whose biological activity has not been reported in the literature to date. The unnamed derivative **106g** was isolated from the deposits of certain herbivore organs including the Canadian beaver.[111] Compounds **106g-i** have been isolated from the oriental panacea medicine Shilajit, originating from exudation of steep rock.[106]

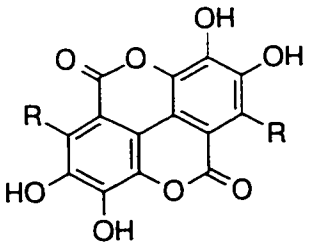
Table 2. Common Dibenzopyranone Natural Products



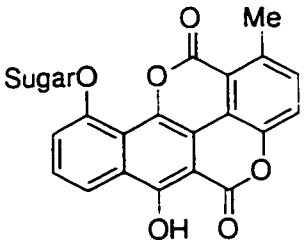
106

106	R	R'	
a:	1-Me, 3-OH	7-OH, 9-OH	alternariol
b:	1-Me, 3-OH	7-OH	autumnariol
c:	1-Me, 3-OH, 4-OMe	7-OH	autumnariniol
d:	2-OH, 3-OMe	7-OH, 9-OH	altenuisol
e:	3-OH, 4-OH	7-OH, 8-OH	
f:		7-OH, 8-OH	
g:	3-OH	8-OH	
h:	3-OH		
i:	3-OMe		

More complex derivatives of **106** are also known. For example, ellagic acid **107a**, as well as the related coruleoellagic acid[112] **107b**, have been isolated from a wide variety of dicotyledonous plants.[113] Ellagic acid may commonly be found as the free molecule but is also isolated in the form of ellagitannins (e.g. **109a** and **109b**) combined with a sugar moiety through *O*-glycoside bonds to give tannins of varying complexity.[114] These compounds have important biological properties such as anti HIV,[115] antitumor[116,117] and anti-topoisomerase;[118] consequently, they have recently attracted synthetic interest.[119] Alkylated derivatives of ellagic acid are less common in nature than the free phenol, however, in 1979 several *O*-methylated derivatives were isolated from *Shorea worthingtonii* and *Vatica obscura*.[120] Previously, isolation of these derivatives was studied in several plant species and the relative distribution of ellagic acid derived polyphenols constituted a definite taxonomic characterization.[121] Studies on ellagic acid have shown that it is an effective inhibitor of the mutagenicity of (+)-7β,8α-dihydroxy-9α-10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene, which is thought to be the ultimate carcinogenic metabolite of benzo[*a*]pyrene.



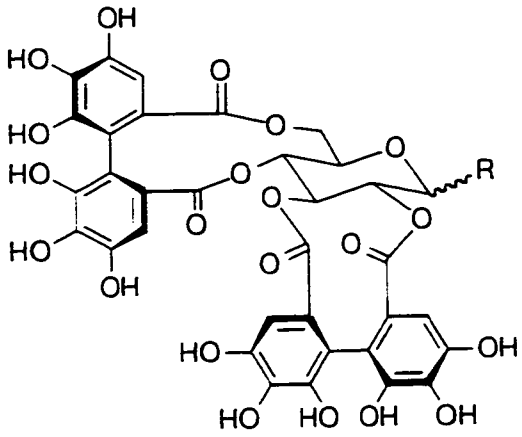
107a: R = H ellagic acid
107b: R = OH coruleoellagic acid



108: Chartreusin

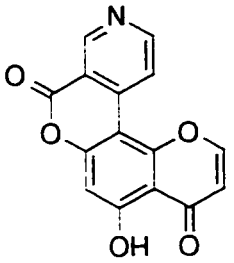
Chartreusin **(108)** has also been known for many years, having first been isolated in 1953 by Leach and co-workers from *Streptomyces chartreusis*.[122] Biological screens demonstrated that this molecule possessed significant anticancer activity but the

compound was rapidly eliminated through the bile rendering it useless as a drug candidate.[123] Subsequently, several derivatives of chartreusin, differing only in the structure of the *O*-glycoside portion, were isolated which showed similar activity and much higher bioavailability.[124,125] Perhaps for this reason, there have been two reported syntheses of the aglycone of chartreusin.[126,127]

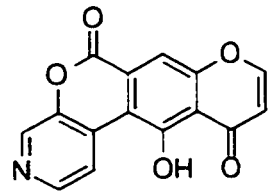


109a: R = OH Pedunculagin
109b: R = β-O-glucose Cascuarictin

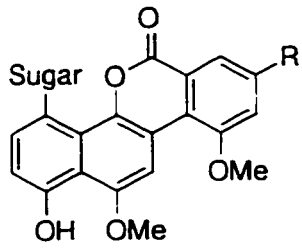
The chromone alkaloids schumanniophytine **(110)** and isoschumanniophytine **(111)** are representative of the relatively few examples of azadibenzopyranones that have been isolated from natural sources. The compounds were isolated independently by Schittler[128] in 1978 and Houghton[129] in 1985 from root bark and stem extracts of *Schumanniphytin magnificum*, and are of interest due to the use of this plant in folklore medicine. In Cameroon the bark is used as a treatment for dysentery[130] as an enema, while in Nigeria the stem juice is used against snakebite and the roots are used to treat madness![131] The gilvocarcins and related antibiotics **112** contain the naphthobenzopyranone structure and their structures and synthesis will be discussed in detail in **Section 2.3.**



110: Schumanniophytine



111: Isoschumanniophytine



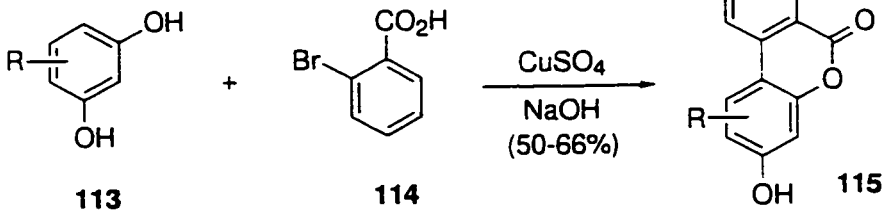
112: R = Me, Et, Vinyl

2.2 Synthesis of Dibenzopyranones

Due to the interesting structural features and biological properties of dibenzopyranones there have been numerous efforts towards the construction of the ring system. An excellent review by Darbarwar and Sundaramurthy[132] collects the efforts to 1982. Newer examples or those that are of general synthetic utility will be presented briefly.

Chronologically, the first synthesis of the dibenzopyranone ring system was reported in 1929 by Hurtley.[133] Condensation of several phenols **113**, with *o*-bromobenzoic acid **(114)** in the presence of copper sulfate in alkaline medium gave the dibenzopyranones in a single step, although in modest yields **(Scheme 32)**. Yields have been improved by the use of CuOAc in ethanol[134] and this method has been used in

Scheme 32

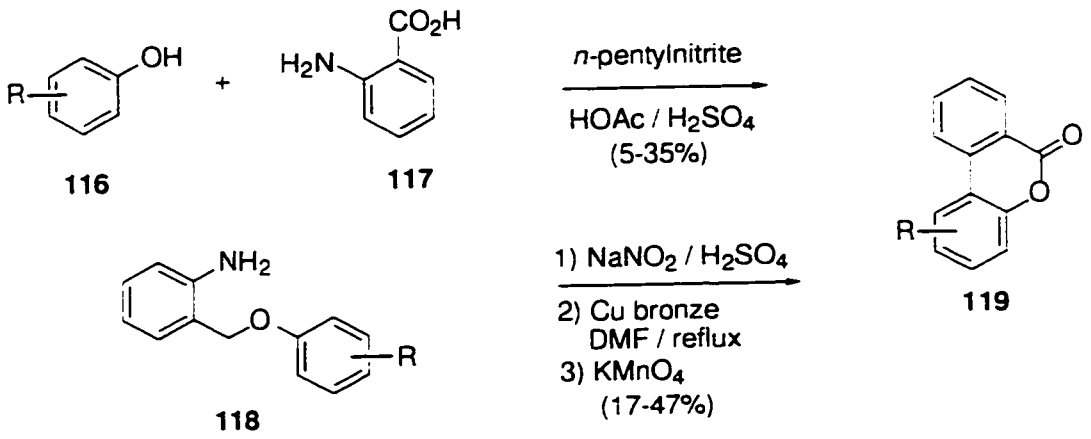


113 **114** **115**

the total synthesis of autumnariol **(106b)** and autumnariniol[135] **(106c)**, and also **(106g)**.[136] Although useful, the reaction is limited by the requirement of highly active resorcinols **113**.

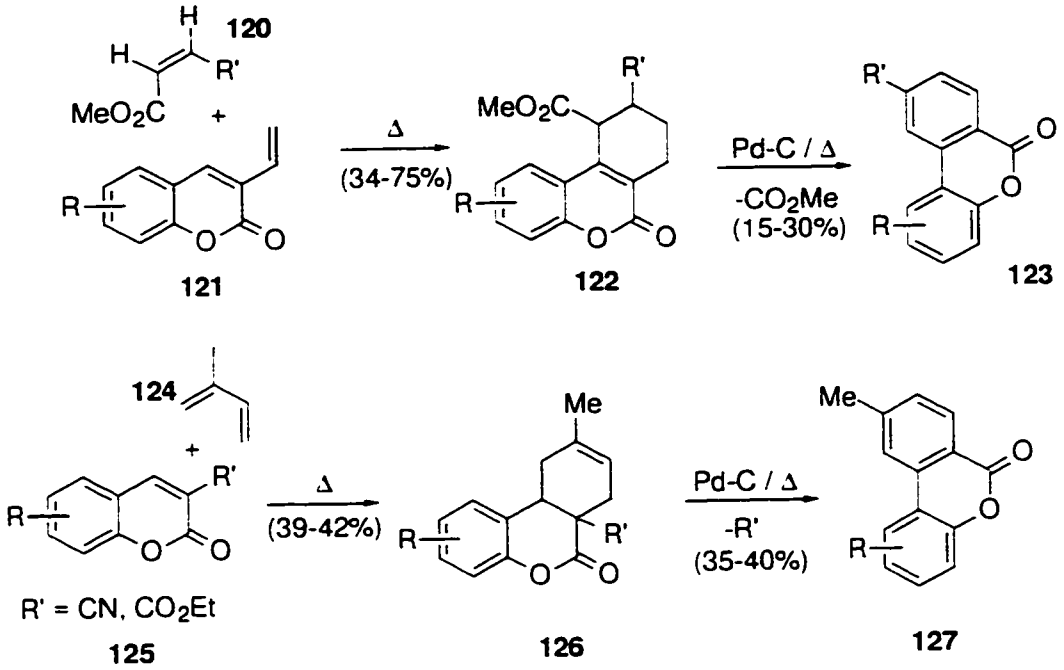
Variations on the diazotisation of anthranilic acids have also been used. In general, attack by the aromatic ring of phenol **116** on the diazonium salt derived from **117** generates the biaryl bond followed by intramolecular lactonization.[137] Similarly, benzylethers **118** can be used, allowing intramolecular coupling of the diazonium species[138] **(Scheme 33)**. However, this process requires an extra step to oxidize the intermediate pyran to the pyranone.

Scheme 33



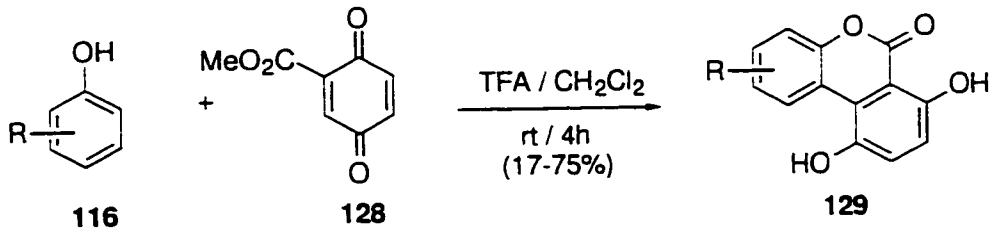
Minami[139] and co-workers have effected Diels-Alder reactions of substituted alkenes **120** with 3-vinylcoumarins **121** to generate tetrahydrodibenzopyranones **122** **(Scheme 34)**. These compounds are then dehydrogenated to afford the desired products. Similarly, Strojny[140] and Adams[141] have used coumarins **125** as the dienophile in reactions with isoprene to afford methyl substituted dibenzopyranones **127**. Interestingly, this methodology has been applied to the preparation of cannabinol derivatives by Razdan.[142]

Scheme 34



Eugster[143] has described the acid catalyzed addition of phenols to activated quinones **128 (Scheme 35)** as a method for the preparation of dibenzopyranones with hydroxyl groups in the 7- and 10-positions. The reaction proceeds under mild conditions and both electron donating and withdrawing groups in the phenol are tolerated. The

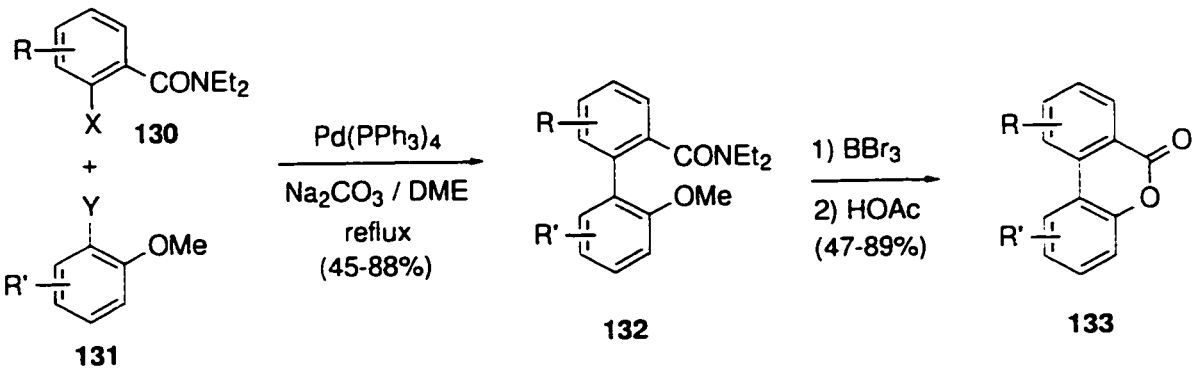
Scheme 35



yields are modest to good, however activated quinones are required which limits the scope of the reaction.

Snieckus and co-workers[71] have developed a regioselective and efficient synthesis of dibenzopyranones based on the D*o*M - cross coupling strategy. The use of the Suzuki cross coupling reaction allows facile generation of biaryls **132** **(Scheme**

Scheme 36

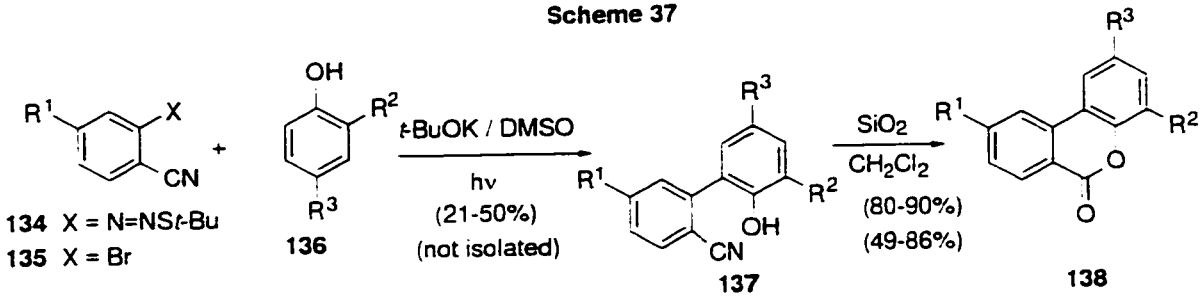


36). Deprotection of the methyl ether followed by acidic cyclization affords the dibenzopyranones **133**. The utility of this method is derived from the D*o*M reaction. The tertiary amide DMG allows selective introduction of the cross coupling functionality in the *ortho*-position, enabling the preparation of a wide variety of coupling precursors. Similarly, the coupling substituents (X and Y) may be interchanged, allowing further flexibility in the synthesis. The yields in these reactions are generally excellent; however, functional groups are limited to those which are stable to the conditions of the D*o*M reaction.

Two groups have independently investigated the preparation of dibenzopyranones *via* the photoactivated $S_{RN}1$ reaction **(Scheme 37)**. Petrillo[144] and co-workers have used *o*-cyano substituted azosulfides **134** to give hydroxybiaryls **137** whereas Bois-Choussy[145] utilized the bromo derivatives **135**. In each case, the photoactivated $S_{RN}1$ process was used to generate the biaryl bond of **137** followed by mild cyclization

conditions. In Petrillo's study the yields were generally lower than those of Bois-Choussy; however, a wider range of substitution patterns were examined in the former investigation. In both cases the scope of the reaction was severely limited by the need for substitution in the 4-position (R^3 of **136**). Without this substituent, competing substitution at the 4-position occurs, drastically lowering the yields.

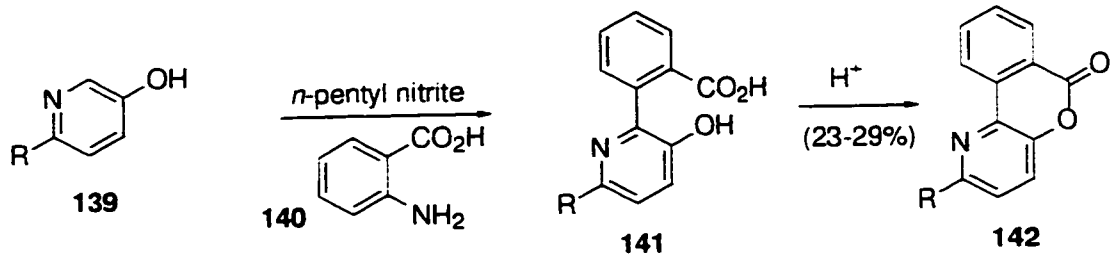
Scheme 37



Other less utilized reactions for the synthesis of dibenzopyranones include: the exhaustive ozonolysis of phenanthrene by Griesbaum[146] which gave dibenzopyranones in non-synthetically useful yields; the Baeyer-Villiger oxidation of fluorenone,[147] which has not been carried out on unsymmetrical cases; as well as a relatively recent report by Yokayama and co-workers[148] on the oxidative cyclization of 2-phenylbenzoic acid with hypervalent iodine reagents. Although excellent yields were obtained by the last method, the reaction was again limited to the unsubstituted derivative.

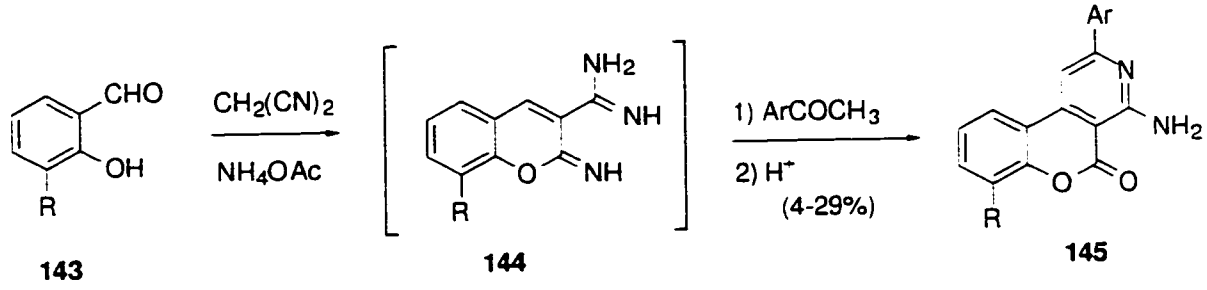
In contrast, there are relatively few methods available for the synthesis of azadibenzopyranones. Katritzky[149] has modified the intermolecular diazotisation process (cf. **Scheme 33**) to include hydroxypyridines **139**, which couple with diazotised anthranilic acids, affording biaryl hydroxy acids **141** which then cyclize generating azadibenzopyranones **142 (Scheme 38)**.

Scheme 38



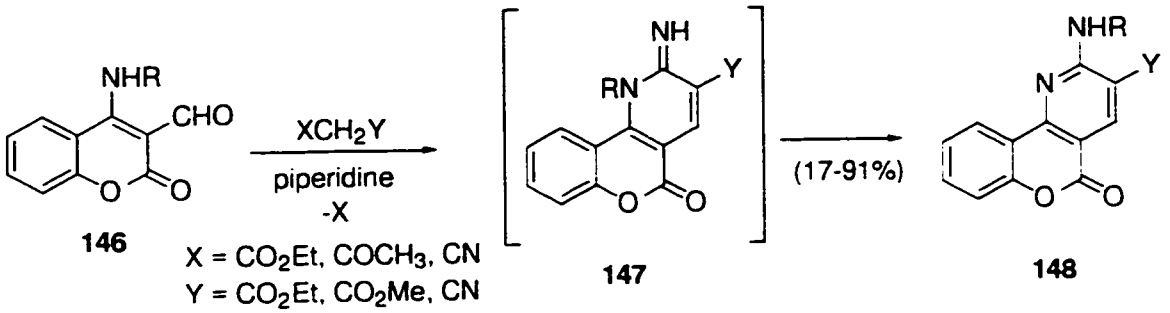
Sakurai[150] has developed a method based on the condensation of malononitrile with salicylaldehydes **143** **(Scheme 39)**. The derived imino coumarin **144** is not isolated but condensed directly with acetophenones which, after hydrolysis, afford the substituted azadibenzopyranones **145**. The yields of this reaction are typically low, ranging from 4-29%. Ivanov[151] has used a similar method based on formylated

Scheme 39



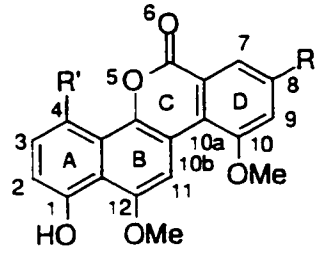
coumarins **146** **(Scheme 40)**. Knoevenagel condensation of **146** with malonate derivatives affords the azadibenzopyranones **148** in somewhat better yields. In this case the intermediate iminolactone **147** is converted to the azadibenzopyranone accompanied by an alkyl group shift. Although the yields of this method are slightly better than that of Sakurai, the latter process has been studied in more detail and has greater generality. Reynolds[152] and co-workers have utilized a similar method based on the addition of malononitrile to the carbonyl of substituted chromone derivatives. Finally, Kahn[153] has utilized the Skraup reaction of 3-aminocoumarin to give an azadibenzopyranone.

Scheme 40

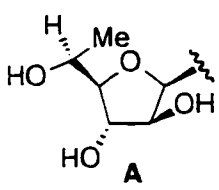


2.3 The Gilvocarcins and Related Antibiotics

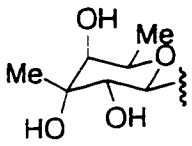
The group of dibenzopyranones containing the naphtho[*b*,*d*]benzopyranone substructure **149** are a relatively small family of antibiotic natural products which have been isolated from various strains of *Streptomyces*. **Table 3** shows the naturally occurring members of this group and indicates the organism(s) from which they have been isolated. Structural variations include the sugar moiety at the C-4 position joined through a C-glycoside bond as well as minor variations at the C-8 position where there may be a methyl, ethyl or a vinyl group. Gilvocarcins V and M were originally isolated from *Streptomyces gilvotanareus* in the early 1980s by Ito and co-workers. The discovery of the same antibiotics from multiple sources by different groups **(Table 3)** has led to some confusion in the naming of the different sub-groups. The gilvocarcins have therefore been called toromycins as well as anandimycins depending on the *Streptomyces* species by which they are produced. Similarly, virenomycins V and M are sometimes referred to as chrysomycins A and B, respectively. Relatively recently, two new compounds related to gilvocarcin M have been isolated from *Streptomyces rutgerensis*[154] subsp *castelarensis*.



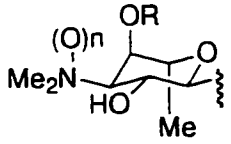
149



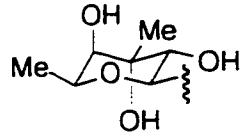
A



B



C R = Ac, n= 0
D R = H, n = 1
E R = H, n = 0

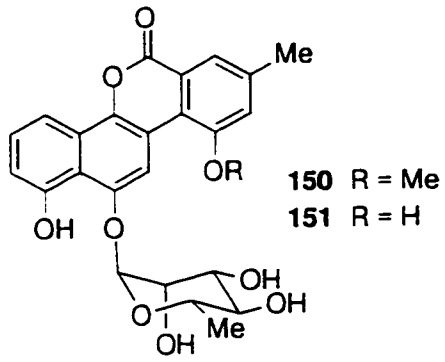


F

Table 3. Naturally Occurring Naphtho[*b*,*d*]benzopyranones

Name	**149**	R	R`	*Streptomyces* Source	Ref
gilvocarcin M	**a**	Me	A	*gilvotanareus*	155
				anandii	156
gilvocarcin V	**b**	vinyl	A	*gilvotanareus*	155
				anandii	156
				arenae	157
				collinus	158
gilvocarcin E	**c**	ethyl	A	*anandii*	156
defucogilvocarcin V	**d**	vinyl	-	*arenae*	159
virenomycin M	**e**	methyl	B	*A-419*	160
virenomycin V	**f**	vinyl	B	*A-419*	160
ravidomycin	**g**	vinyl	C	*ravidus*	161
albacarcin M	**h**	methyl	F	*albaduncas*	162
albacarcin V	**i**	vinyl	F	*albaduncas*	162
deacetylravidomycin	**j**	vinyl	E	*ravidus*	163
deacetylravidomycin-*N*-oxide	**k**	vinyl	D	*ravidus*	163

These derivatives, called BE-12406A and BE-12406B (**150** and **151** respectively) differ in the fact that the sugar is attached at C-12 of the naphthopyranone system through an *O*-glycoside bond. Also, these structures do not possess a methyl group at the C-10 phenol as in the parent structures.



150 R = Me
151 R = H

Elucidation of the structures of the naphtho[*b*,*d*]benzopyranone class of compounds has been carried out largely by Findlay[164] at the University of New Brunswick. Careful examination of ^{1}H and ^{13}C NMR data for ravidomycin and its diacetate as well as chemical degradation studies led to structure **149g**. Independently, Takahashi and co-workers[165] applied similar tactics to solve the structures of gilvocarcins V and M. Confirmation of these efforts came in the form of an x-ray structure[166] for gilvocarcin M, firmly establishing the nature of the ring system and the substitution pattern.

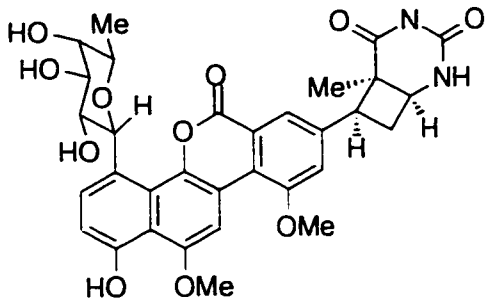
The biological properties of the gilvocarcins and related antibiotics have been well studied. Gilvocarcin V shows strong activity against Gram-positive bacteria but essentially none against Gram-negative ones. At concentrations of 0.5 μg/mL or higher, bactericidal properties are observed.[167] Other *in vitro* tests by the same group showed the ability of the antibiotic to inhibit the synthesis of DNA, and to a lesser extent RNA. Tomita and co-workers have shown potent activity against a variety of murine tumors.[168] Forty percent of mice infected with *Ehrlich ascites* carcinoma survived 60 days longer

than control animals when treated intraperitoneally with gilvocarcin V. Tomita also demonstrated that the activity of the drug occurred at low concentrations and that the toxic dose to mice was high having an LD_{50} greater than 1,000 mg/Kg (single intraperitoneal dose).[167] Gilvocarcin M, on the other hand, was shown to be almost devoid of antitumor activity, suggesting the necessity of the vinyl group in its mode of action.

Subsequent studies have shown that the cytotoxicity of gilvocarcin V only occurs in the presence of ultra-violet or visible light.[169] Greenstein[170] demonstrated the photocytotoxicity of ravidomycin through a study of the inhibition of the enzyme β-galactosidase, a measure of the ability of a chemical to damage DNA. Enzyme inhibition, as well as bactericidal activity, showed a marked increase in the presence of light of wavelength 362 nm and 497 nm. Similarly, photoactivated ravidomycin showed potent activity against human colon carcinoma. Bockstahler and co-workers have also shown activity in human cell lines, demonstrating that gilvocarcin V has the ability to inhibit *Herpes virus* plaquing in human fibroblasts.[171]

Studies on the mechanism of action of gilvocarcin V and gilvocarcin M have shown that both have the ability to intercalate DNA in the absence of light.[172] On irradiation, however, only gilvocarcin V produces chemical changes. Gasparro[173] and co-workers have supplemented these findings by determining the binding constant of gilvocarcin V to calf DNA ($6.6 \times 10^5\ M^{-1}$). Elespuru[174] has investigated the nature of the DNA modification in human P3 carcinoma cells. It was shown that photoactivated gilvocarcin V induced single strand breaks as well as DNA to protein covalent bond cross links. This DNA damage was shown to occur at very low concentrations of the drug (7.5×10^{-9} M) as well as under low fluences of radiation (100 kJ/m^2), indicating potential for use in photochemotherapy. Similarly, Elespuru[169] has shown that gilvocarcin V is 10^5 times more active in a lysogenic induction assay than 8-

methoxypsoralen, a drug used in photochemotherapy of psoriasis[175] and cutaneous T cell lyphoma.[176] Solid chemical evidence regarding the mechanism of gilvocarcin induced cell damage was finally provided by McGee and Misra who isolated and characterized the photoadduct of the drug with DNA.[177] On consideration of the structure of **152**, it was rationalized that the vinyl group undergoes a [2+2] photoinduced cycloaddition reaction with a thymine residue. The strongly acidic conditions used for the isolation of the adduct caused isomerization of the gilvocarcin V furanoside to the pyranoside shown.



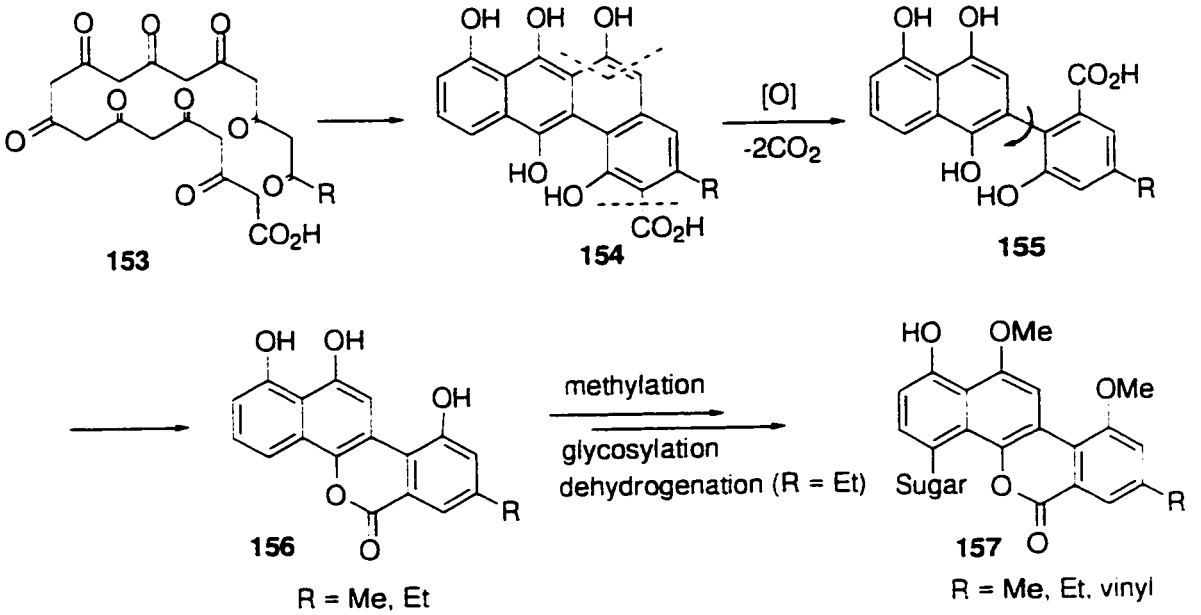
152

2.4 On the Biosynthesis of the Naphtho[*b*,*d*]benzopyranones

Several groups have investigated the biosynthesis of the chromophoric naphthobenzopyranone unit of several of the gilvocarcins and related natural products. All of these studies indicate that the aromatic tetracycle is of polyketide origin based on incorporation of labeled precursors into culture broths. Carter has proposed biogenetic pathways to ravidomycin[178] **(149g)** and virenomycins M and V[179] **(149e** and **149f** respectively). Incorporation of [1-^{13}C]propionate, [1-^{13}C]acetate, [2-^{13}C]acetate, and [1,2-^{13}C]acetate led to the proposed biosynthestic pathway shown in **Scheme 41**. Ketide precursor **153** yields tetracycle **154** on cyclization. This compound must lose a carbon atom, generating the corresponding hydroxy acid **155**, which then undergoes cyclization after bond rotation to give the requisite lactone **156**. This intermediate might then undergo selective methylation and glycosylation giving the natural products. The

labeling experiments suggested that for gilvocarcin M, and related compounds, the starting unit is acetate (**153** R = Me). This process would give rise to the C-8 methyl derivatives. For the vinyl substituted compounds the starting unit is proposed to be propionate based on incorporation of [2-] and [3-^{13}C]propionate at the α- and β-vinyl positions respectively.

Scheme 41

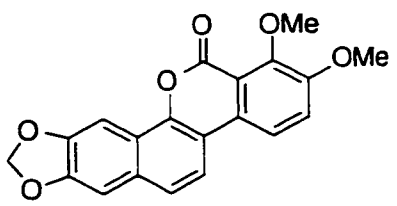


Tomita[180] has observed incorporation of [2-^{13}C]acetate as well as [1-^{13}C]propionate in the vinyl carbons of gilvocarcin V. From this observation he proposed that the vinyl substituent is introduced intermolecularly from incorporation of a separate propionate unit *after* construction of the tetracyclic framework. However, the experiments performed by both workers were insufficient to distinguish between these pathways.

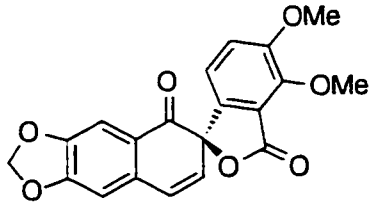
Kingston[181] has established the stereochemistry of hydrogen loss in the formation of the vinyl group for ravidomycin. Feeding stereospecifically deuterated propionic acids to a ravidomycin-producing strain of *Streptomyces* allowed the isolation of the antibiotic with or without label. When the organism was treated with *(R)*-CH_3CHDCO_2Na, the ravidomycin isolated contained no deuterium. On the other hand, when the *(S)* isomer was fed, the label was retained thus establishing that it is the pro-*R* hydrogen that is lost on formation of the vinyl group. Unfortunately, there is no experimental evidence to indicate the exact mechanism of this process.

2.5 Arnottin I and Related Natural Products

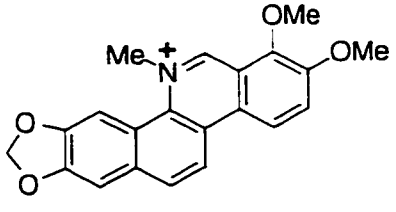
Arnottin I **(158)** is a naptho[*b*,*d*]benzopyranone natural product isolated by Ishikawa and co-workers as a minor constituent from the bark of *Xanthoxylum arnottianum*.[182] Along with this material arnottin II **(159)** as well as the benzophenanthridine alkaloid chelerythrine[183] **(160)** were isolated. Although initially isolated in 1977, the elucidation of the structure of arnottin I was not published[184] until 1993 due, in part, to the fact that the producing plant yielded only small quantities of the material. The biological activity of the arnottins is unknown; however, compounds related to **160** have been known for some time and have been shown to have significant



158



159



160

antileukemic properties[185] as well as activity against certain murine tumors.[186] Ishikawa has indicated some significance of Arnottin I through the suggestion[184] that it is a potential intermediate in the biosynthesis of chelerythrine. The structural similarity to the gilvocarcins and related antibiotics **(Section 2.3)** also suggests the possibility of similar biological properties.

3. Previous Synthetic Efforts

3.1 Previous Syntheses of Gilvocarcin and Related Compounds

The naphtho[*b*,*d*]benzopyranone and related natural products are interesting synthetic targets due to their potent antitumor activity at exceptionally low concentrations. Synthetically challenging structural features such as the differentially protected trioxygenated naphthalene portion amplify this interest. As a result, there has been a great deal of effort towards the synthesis of these and related natural products as well as the naphtho[*b*,*d*]benzopyranone ring system in general. The synthesis of the gilvocarcins and related antibiotics have been comprehensively reviewed by Hua and Saha[187] to 1995. Until the preparation of this thesis, no further efforts had appeared in the literature.

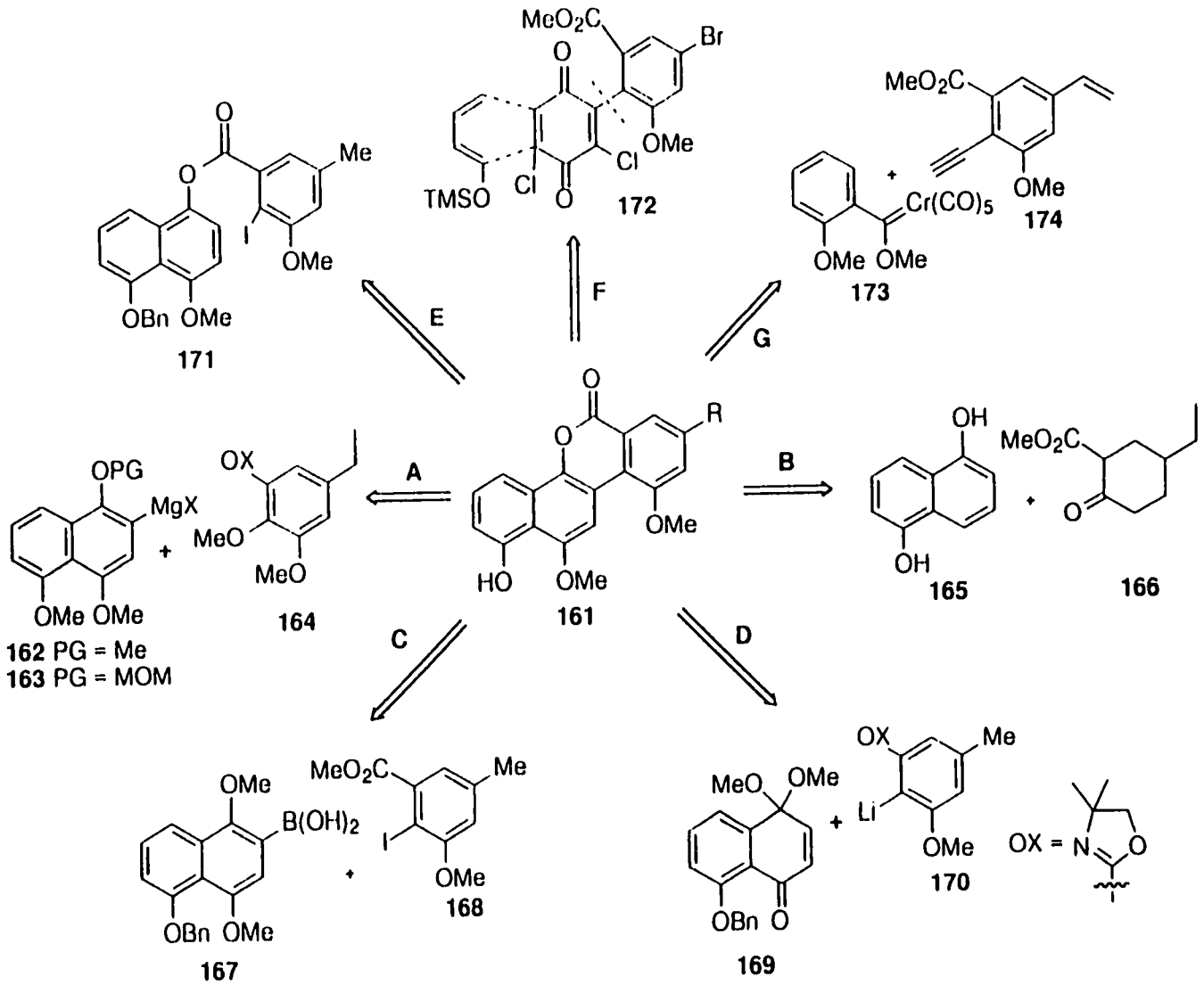
In general, the key steps in the previous syntheses involve the formation of the C10a-C10b biaryl bond followed by lactonization. These methods are presented in the form of a retrosynthetic analysis in **Scheme 42**. In the interest of brevity, these sequences will not be analyzed in detail. Findlay[188] in 1987 and then Danishefsky[189] in 1988 have utilized the Meyers coupling of oxazolines with methoxyarenes[190] (Path A) to form the required biaryl bond in total syntheses of defucogilvocarcin V (DFGV). The two syntheses differed only in the protecting group used in the naphthalene portion (**162**

vs. **163**) and in the fact that Danishefsky's route introduced the vinyl group required for the natural product directly, whereas the Findlay route involved modification of an existing ethyl group. For this latter reason, the synthesis of Danishefsky is slightly more convergent.

In a very convergent approach, McGee[191] has used the Pechmann condensation[192] (Path B) to construct the entire tetracyclic ring system of DFGV in one step. Unfortunately this strategy was rendered inefficient due to a low yielding and non-selective oxidation to introduce the C-10 and C-12 oxygen substituents. Hua[193] has also used this approach in a synthesis of the C-1 methyl ether of defucogilvocarcin E (DFGE), modifying it to incorporate the C-12 oxygenation but still requiring a difficult oxidation of the C-10 position. Despite the convergence of these syntheses, the problematic modifications of the tetracyclic condensation product caused them to be lengthy and inefficient.

Jung and Jung[194] have reported a method which utilizes a Suzuki cross coupling reaction to form the biaryl bond (Path C). Coupling of boronic acid **167** with hindered iodide **168** gave the corresponding biaryl in 61% yield; however, the synthesis was lengthened considerably by a necessary oxidative methyl ether cleavage - reductive cyclization - reprotection sequence. By this route, the preparation of defucogilvocarcin M (DFGM) was accomplished in 10 steps and 17% overall yield.

In 1989 Hart[195] and Merriman reported an efficient synthesis of DFGM based on the MAD-mediated[196] addition of lithiated oxazoline **170** to naphthoquinone monoketal **169** to generate the crucial C10a-C10b bond (Path D) [MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)]. Further modification of this key intermediate proceeded without difficulty resulting in one of the more efficient syntheses, affording DFGM in 9 steps and 31% overall yield.

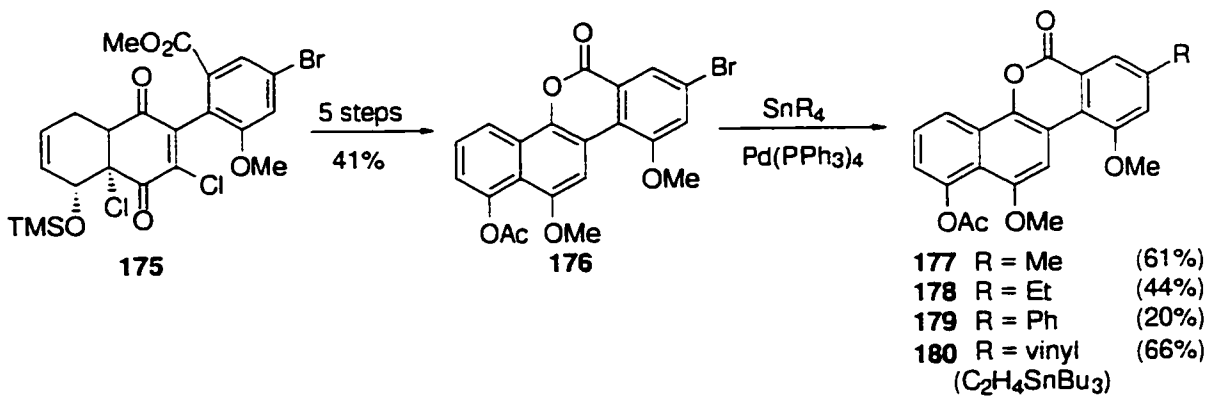

MeO2C
Br
O
TMSO
Cl
Cl
OMe
O
172
MeO2C
OMe
Cr(CO)5
OMe
OMe
173
174
O
Me
O
I
OMe
OBn
OMe
171
E
F
G
R
O
O
OMe
HO
OMe
OH
MeO2C
O
OH
165
166
A
B
OPG
MgX
OX
MeO
MeO
OMe
OMe
162 PG = Me
163 PG = MOM
164
161
C
D
OMe
B(OH)2
MeO2C
Me
I
OMe
OBn
OMe
167
168
MeO
OMe
OX
Me
Li
OMe
OBn
O
169
170
OX =
N
O

Scheme 42

A variation of the initial C10a-C10b bond formation strategy has been achieved by Martin.[197] Lactonization was carried out first, followed by Pd(II) catalyzed intramolecular cyclization of iodide **171** (Path E), in contrast to the standard initial generation of this bond in the previous efforts. This protocol was used in a synthesis of both DFGM and DFGE.

The Meerwein arylation reaction[198] was the key step in the synthesis of McKenzie.[199,200] Aryl diazonium salt coupling with 2,6-dichlorobenzoquinone generated the key biaryl bond affording **172**, and completion of the AB ring system was effected *via* regioselective Diels-Alder cycloaddition of the Meerwein adduct with 1-trimethylsiloxybutadiene (Path F). The chlorines in **172** were necessary to assist in directing the cycloaddition; however, they proved difficult to remove rendering the synthesis rather long. This strategy was first used by McKenzie in a synthesis of DFGM[199a] and later, in an interesting variation,[200] to prepare a common intermediate which allowed preparation of defucogilvocarcin analogues. The application of this strategy is outlined in **Scheme 43**. The Diels-Alder adduct **175** was converted in 5 steps and 41% overall yield to the lactone **176**. Stille coupling of this

Scheme 43



175

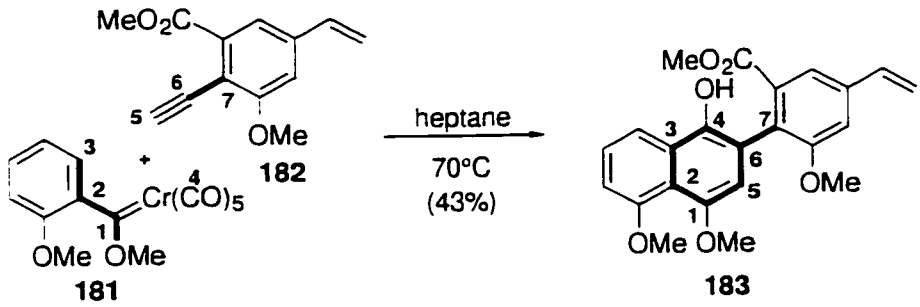
176

177 R = Me (61%)
178 R = Et (44%)
179 R = Ph (20%)
180 R = vinyl (66%)
($C_2H_4SnBu_3$)

intermediate with the requisite stannane reagents allowed preparation of the acetates of defucogilvocarcins M, E, V and the unnatural phenyl derivative **179**. This strategy constitutes the first use of a common intermediate to allow introduction of the various substituents at the C-8 position present in the natural products.

The approach of Parker[201] and co-workers makes use of the coupling of carbene **181** with arylacetylene **182** for ring B annulation. Again, this strategy deviates slightly from the standard biaryl bond formation strategy. Although very convergent, this method resulted in a low yielding synthesis of DFGV C-1 methyl ether and not the natural product. **Scheme 44** indicates the key synthetic step and serves to clarify the process.

Scheme 44

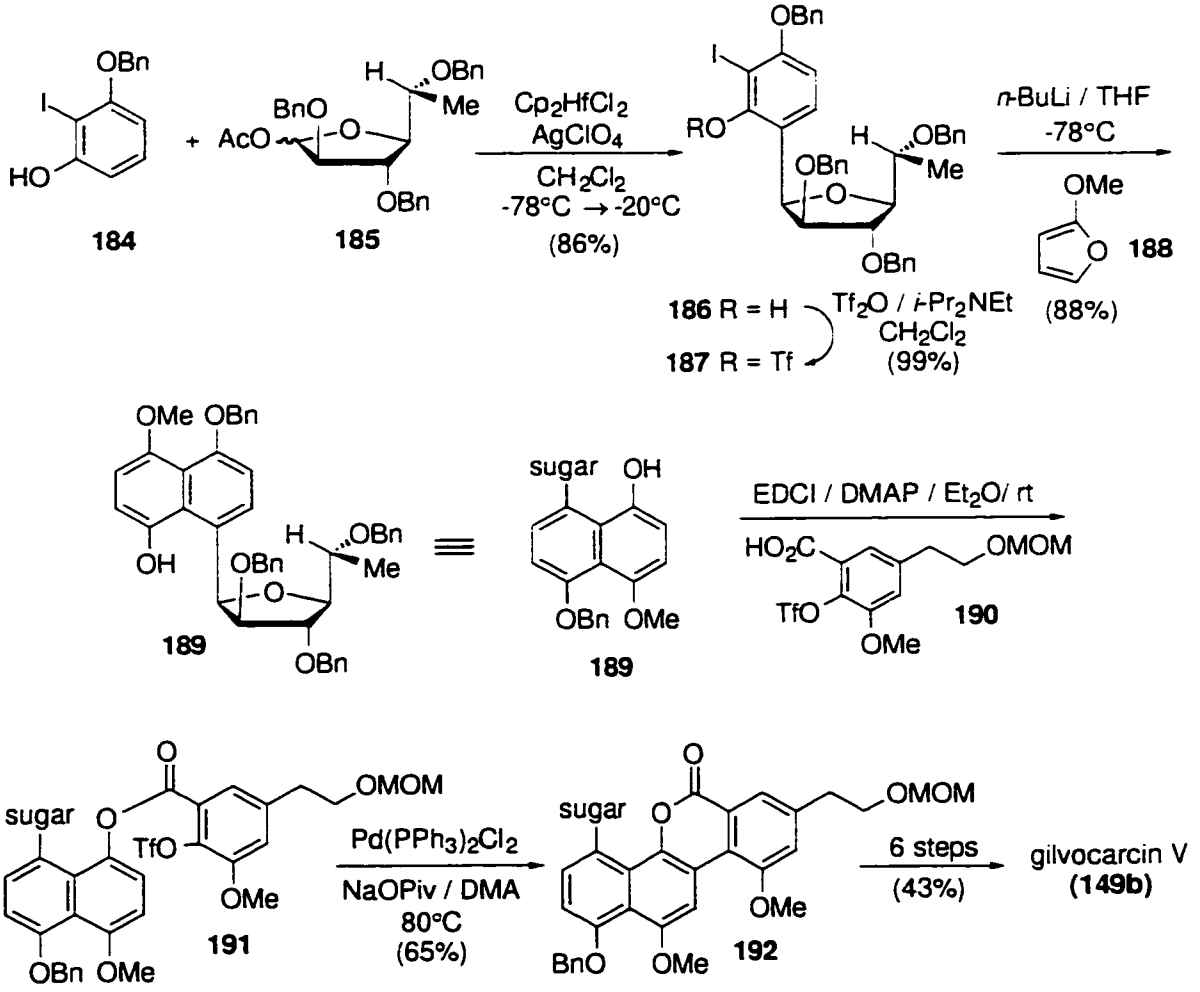


Suzuki and co-workers reported a modified version of the intramolecular palladium catalyzed protocol developed by Martin[197] for the formation of the key biaryl bond. Considerable effort was expended in the incorporation of the sugar moiety and this allowed a preparation of gilvocarcins M[202] and V.[203]

Thus, as outlined in **Scheme 45**, iodophenol **184** was coupled with furanose **185** using a hafnium complex affording the C-glycosylated arene in good yield (86%,

8.2:1 α:β anomeric ratio). Conversion of the phenol to the triflate with triflic anhydride was followed by treatment with *n*-BuLi at low temperature in the presence of 2-methoxyfuran (**188**). These conditions[204] served to effect iodine - lithium exchange triggering the elimination of LiOTf to give the corresponding aryne which was trapped in a [4+2] cycloaddition with furan **188**. In this manner, the AB portion of the ring system was quickly and regioselectively assembled with all of the required oxygenation in place. Acylation of naphthol **189** with carboxylic acid **190** afforded the ester and set the stage for the intramolecular coupling. To this end, treatment of triflate **191** with $Pd(PPh_3)_2Cl_2$ effected the desired coupling in 66% yield, generating the C10a-C10b bond, and

Scheme 45



completing the construction of the tetracyclic framework required for the natural product. Conversion of the two carbon unit in the C-8 position to the required vinyl group and completion of the total synthesis was carried out using standard chemistry in 6 steps and 43% yield after removal of the benzyl groups and reprotection as the acetates. This impressive synthetic effort constitutes the only reported synthesis of any of the gilvocarcins.

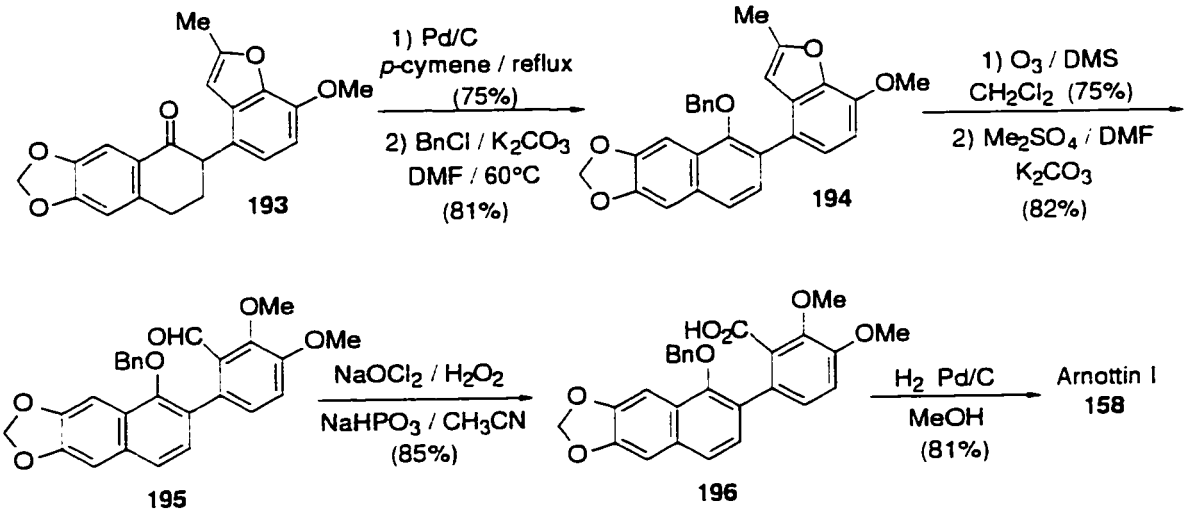
Other methods for C-glycosylation of aryl derivatives have been investigated for the preparation of compounds related to the gilvocarcins. Along with the hafnium promoted method illustrated above, other Lewis acid mediated processes are known. For example, $SnCl_2$[205] and $BF_3 \cdot Et_2O$[206] have been used for the coupling of glycosyl acetates with activated arenes. The Heck reaction has also proved useful and several accounts of the use of Pd(II) catalyzed coupling of dihydrofuran derivatives with aryl iodides have appeared.[207] Similarly the Stille reaction has been utilized.[208,209] Model studies towards gilvocarcin related C-glycosides have also been investigated using cuprate addition to epoxy sugars[210] as well as reductive aromatization of quinone ketals.[211,212] These methods have been exhaustively reviewed[187] and therefore do not warrant further elaboration here.

3.2 Previous Syntheses of Arnottin I

To date, there have been but two total syntheses of arnottin I. The first, by Ishii,[213] relies on the oxidative cleavage of a benzofuran derivative to generate the 2,2′-hydroxy acid required for lactonization. Thus, ketone **193** is first subjected to conditions of forceful aromatization followed by benzylation **(Scheme 46)**. The furan ring is then cleaved by ozonolysis to give the salicylaldehyde which upon treatment with

Me_2SO_4 provides methyl ether **195**. Treatment of **195** with sodium chlorite - hydrogen peroxide completes the oxidation to provide the lactone precursor. Hydrogenolysis allows simultaneous cleavage of the benzyl ether and cyclization to give arnottin I. The precursor **193** was also used in a synthesis[214] of chelerythrine **(160)** and was prepared[215] from isovanillin in 8 steps through classical and rather inefficient chemistry.

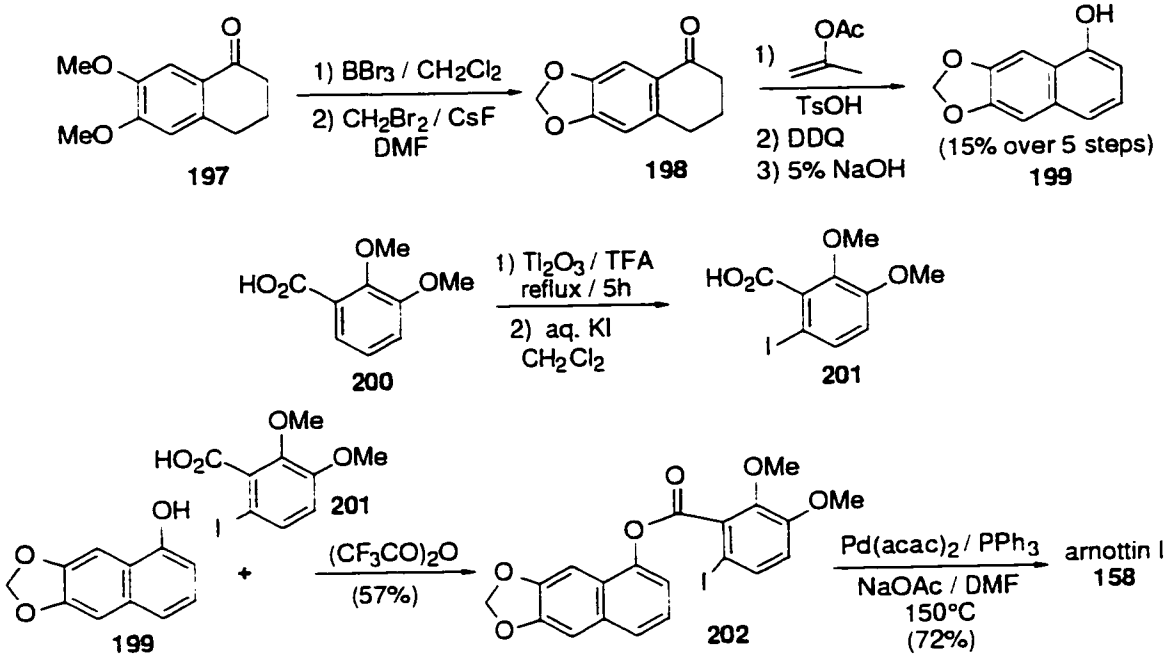
Scheme 46



Recently, Harayama[216] has reported a convergent synthesis of arnottin I based on the intramolecular Pd(II) catalyzed coupling of aryl iodides, similar to that used by Martin[197] **(Section 3.1)**. Demethylation of tetralone **197** **(Scheme 47)** with BBr_3 was followed by CsF-mediated introduction of the required methylenedioxy group. Aromatization was accomplished by treatment of the ketone **198** with isopropenyl acetate followed by oxidation of the intermediate enol acetate with DDQ and hydrolysis of the resulting ester affording naphthol **199** in 15% yield over five steps. The iodide **201** was prepared from 2,3-dimethoxybenzoic acid in a single step (yield not given) using the thallation procedure of McKillop.[217] Ester formation was then accomplished *via* the mixed anhydride to afford coupling precursor **202**. Conditions to effect the formation of the key biaryl bond were investigated in some detail both in model cases and the desired

substrate. Optimum conditions were determined to be 10 mol% $Pd(acac)_2$ in the presence of PPh_3 as a ligand. The coupling reaction occurred smoothly affording the natural product **158** in good yield. Although convergent, the synthesis requires quite lengthy routes to starting materials.

Scheme 47



4. Proposal

4.1 Introduction

The exceptional biological activity of gilvocarcin V in conjunction with the synthetically challenging tetracyclic ring system makes it an attractive synthetic target. This is demonstrated through the extensive and diverse synthetic efforts that have been expended on these molecules to date (see Section 3.1). Similarly, arnottin I is a naphtho[*b*,*d*]benzopyranone which is the first such natural product to be isolated from a plant source. Although its biological properties are unknown, the interesting structural features make an efficient synthesis an attractive goal.

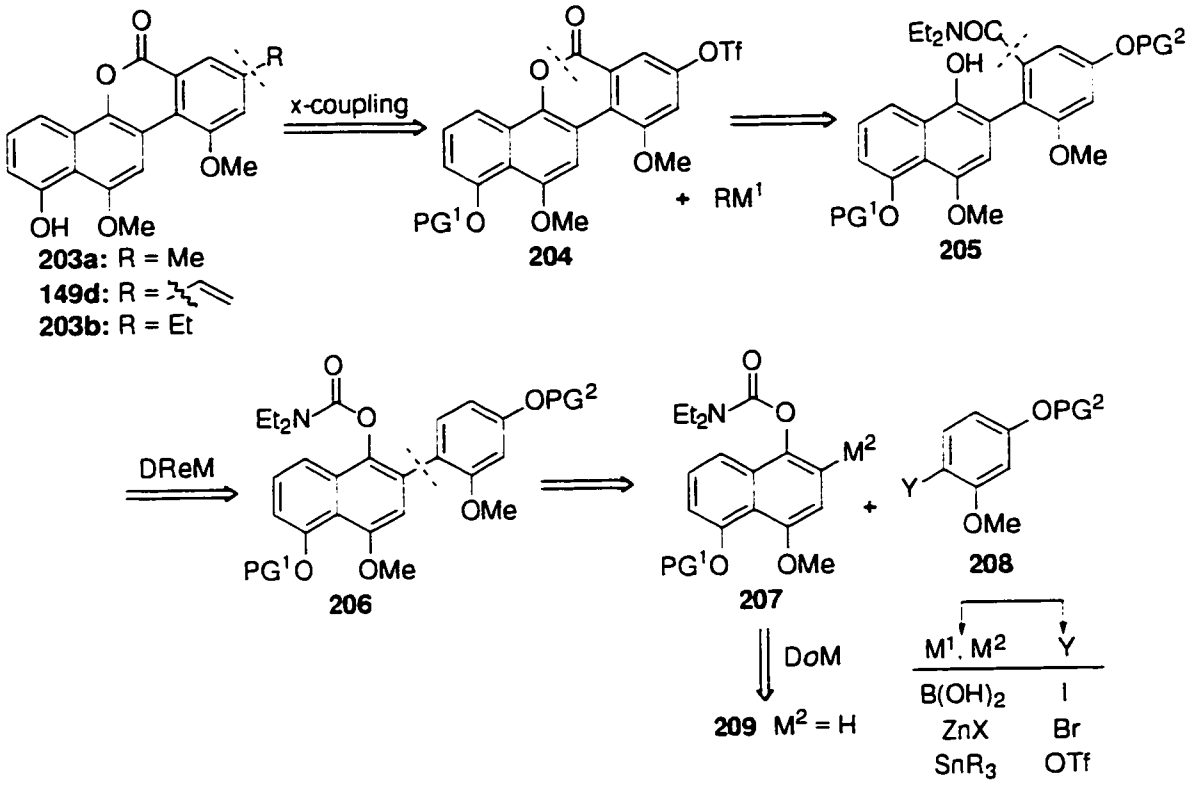
The focus of this work is to apply the DreM strategy demonstrated by Wang and Snieckus[101] for the synthesis of dibenzopyranones in conjunction with the combined cross coupling - directed metalation tactics to establish total syntheses of these naturally occurring dibenzopyranones. Initial inspection of the structures reveals the common tetracyclic aromatic ring system, suggesting the same strategy for both compounds.

4.2 Retrosynthetic Analysis of the Gilvocarcins

Since there has been extensive effort expended in the area of glycosylation of arenes for the synthesis of gilvocarcins and related structures, as well as the fact that the sugar moiety is not necessary for the antitumor activity, it is the goal of this work to focus on the construction of the aglycones of the gilvocarcins. **Scheme 48** illustrates a retrosynthetic analysis. The initial disconnection involves removing the C-8 substituent *via* a cross coupling retron similar to that used by McKenzie and Hassen.[200] This would allow the selective introduction of the required substituents at C-8 through transition metal catalyzed cross coupling chemistry. Opening of the lactone ring reveals biaryl

hydroxy amide **205** which can be further disconnected *via* the key remote metalation - carbamoyl migration protocol. The corresponding carbamate may be disconnected at the crucial C10a-C10b biaryl bond giving the *O*-naphthylcarbamate **207** and the trisubstituted arene **208** as cross coupling partners. Finally, disconnection by DoM gives the highly oxygenated *O*-arylcarbamate **209**.

Scheme 48

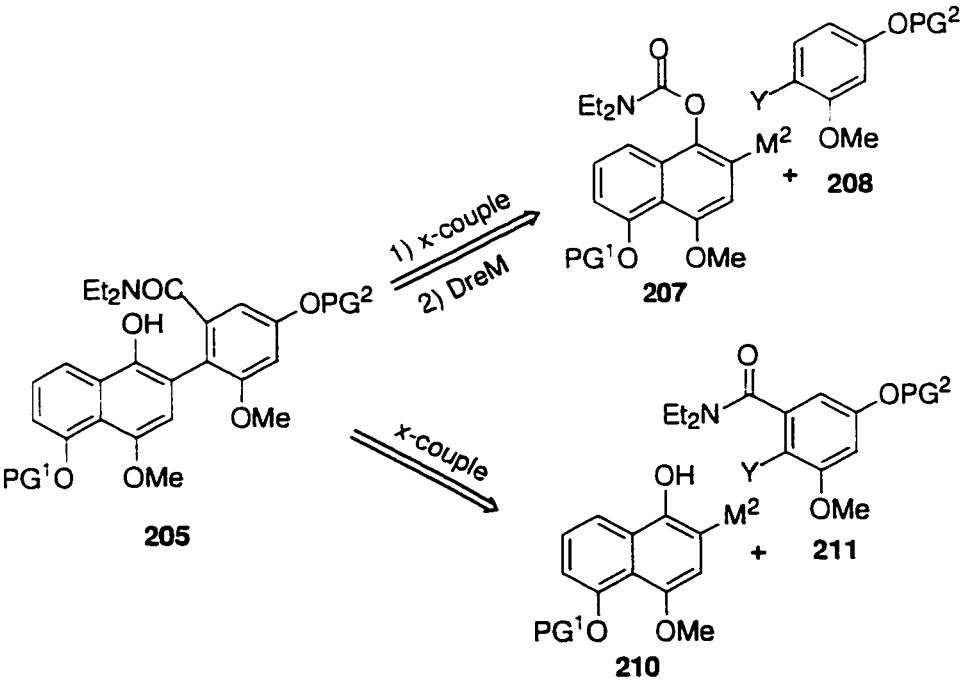


Several concerns arise on consideration of the required cross coupling partners **207** and **208**. The choice of protecting groups (PG^1 and PG^2) is crucial. They must be able to withstand both the cross coupling conditions chosen, as well as those required for the remote metalation - carbamoyl migration step. They must also be easily removed in the presence of a methoxy group. Secondly, the synthesis of the *O*-naphthylcarbamate with the desired differentially protected trioxygenation pattern has been shown to be

difficult in previous syntheses.[194,197] Finally, an efficient synthesis of the D ring coupling partner **208** will be required.

The proposed synthetic strategy offers several possible advantages. First, the remote metalation - carbamoyl migration protocol facilitates the cross coupling step by allowing the use of less hindered coupling partners. Thus the carboxamide functionality, required in one of the *ortho* positions for pyranone ring formation, is introduced at a late stage in the sequence and consequently offers decreased steric bulk in the cross coupling reaction **(207 + 208** vs **210 + 211, Scheme 49)**. Furthermore, the wide variety of choices of organometallic reagent and leaving group for biaryl cross coupling reactions allows several choices for the formation of this key bond. Similarly the use of the tertiary carbamate of **209** as a DMG should allow regioselective introduction of the required functionality for the cross coupling *via* metalation.

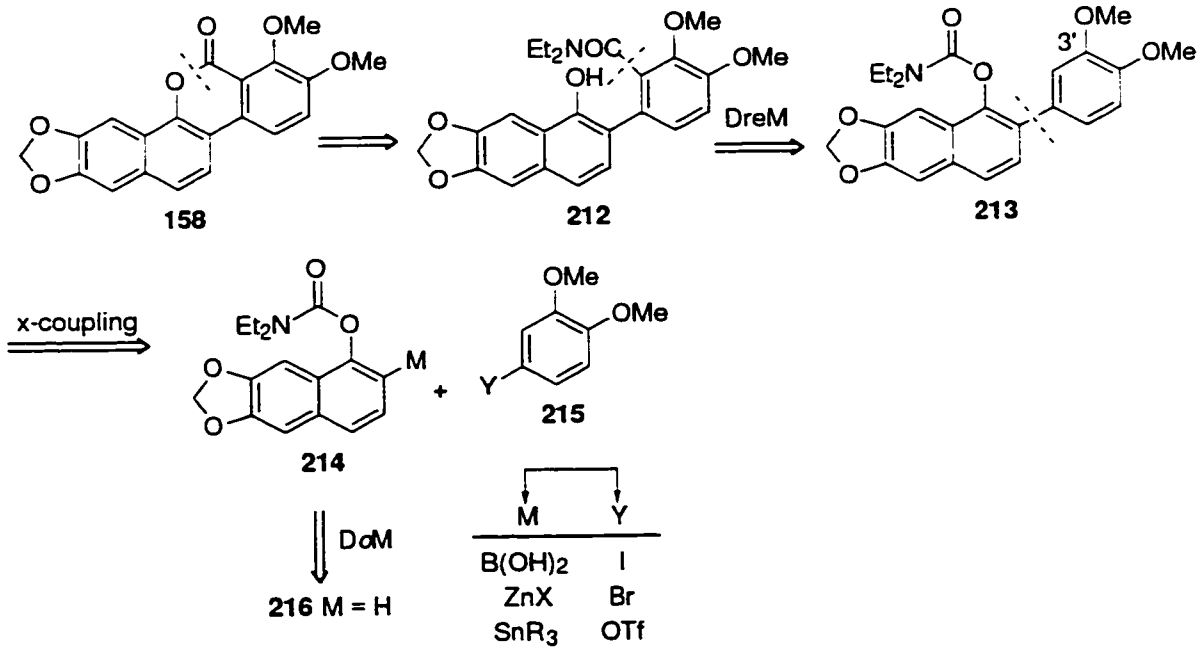
Scheme 49



4.3 Retrosynthesis of Arnottin I

Application of the same retrosynthetic analysis to arnottin I is shown in **Scheme 50**. The DreM - carbamoyl migration protocol may provide the *O*-biarylcarbamate which is again suitable for scission of the biaryl bond as the second key retrosynthetic step. Naphthylcarbamate **214**, along with substituted veratrole **215**, are revealed as the required coupling partners. Again, the cross coupling diversity and the regioselectivity of the *Do*M reaction should prove advantageous in the preparation of **213**. A clear advantage of the strategy is inherent in the presence of the 3'-methoxy group. This substituent will serve as a DMG and thus facilitate the DreM process allowing the reaction to proceed under milder conditions.[101] Efficient syntheses of the required coupling partners **214** and **215** is the remaining challenge.

Scheme 50



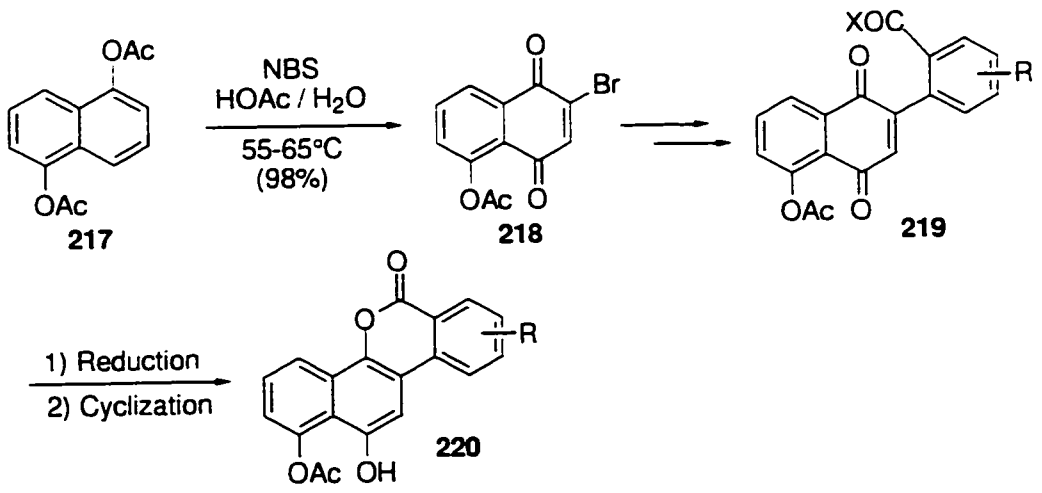
5. Results and Discussion

5.1 Total Synthesis of the Defucogilvocarcins

5.1.1 Preparation of the AB-Ring Coupling Partner

Examination of **Scheme 48** indicates that the AB-ring coupling partner **207** requires differential protection of the oxygen substituents. Previous methods for the synthesis of such ring systems have involved lengthy and inefficient sequences. The oxidative bromination of diacetoxynaphthalene **217** affords bromojuglone derivative **218** in high yield **(Scheme 51)**. Differentiation of the oxygen substituents is then effected by coupling of the D ring portion bearing a carboxylic acid or the equivalent, followed by reduction and cyclization. This strategy has been used in Jung's synthesis of defucogilvocarcin M (DFGM)[194] as well as by Findlay[188] and Danishefsky[189] in syntheses of DFGV.

Scheme 51

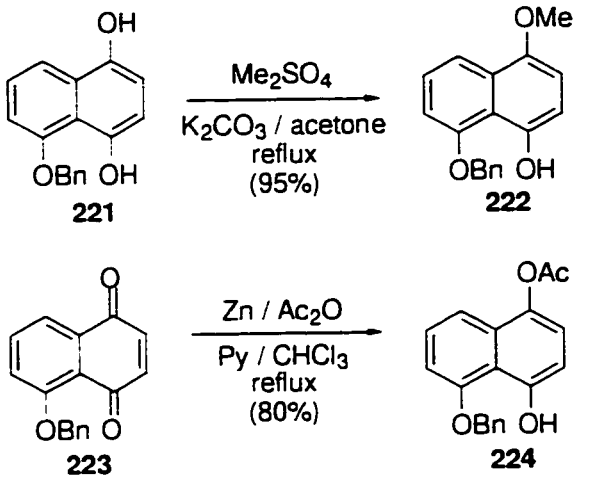


Methods have also been developed for the selective alkylation or acylation of hydroquinone derivatives. Thus, Hart[195] has selectively methylated benzyl ether **221**

using Me_2SO_4 in excellent yield **(Scheme 52)**, and this has been applied in a synthesis of DFGM. Similarly, Martin[197] has used the selective reductive acylation of juglone derivatives originally developed by Giles,[218] to prepare acetate **224**. Although the key steps in these processes are generally high yielding, they constitute rather lengthy synthetic routes from readily available starting materials. A short convenient route to **209** is therefore desirable.

Consideration of readily available protecting groups for the phenol moeity led to the isopropyl substituent for protection of C-5 due to its known stability under the DreM conditions.[101] Similarly, the availability of mild conditions to allow selective cleavage of this group in the presence of methoxy ethers made it an attractive possibility.[98]

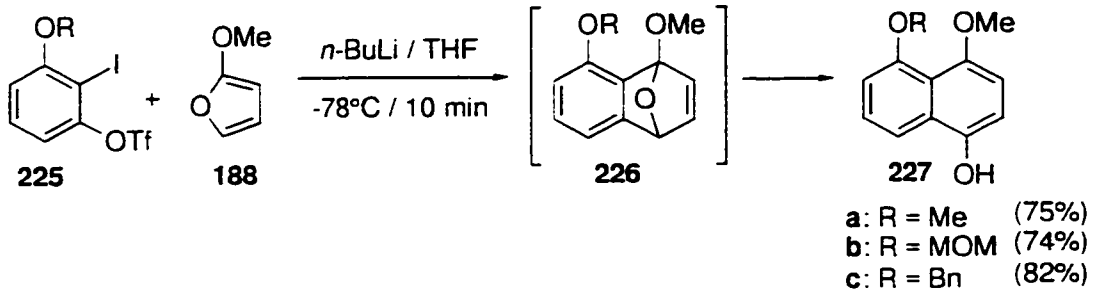
Scheme 52



In 1991, Suzuki and co-workers[204] reported an efficient and regioselective synthesis of differentially protected trioxygenated naphthalenes based on the cycloaddition of 3-substituted arynes with 2-methoxyfuran **(Scheme 53)**. Treatment of iodoaryltriflate **225** with *n*-BuLi effected lithium-halogen exchange which triggered elimination of LiOTf. The corresponding aryne was trapped in a [4+2] cycloaddition to give adduct **226** which underwent ketal opening under the reaction conditions to afford

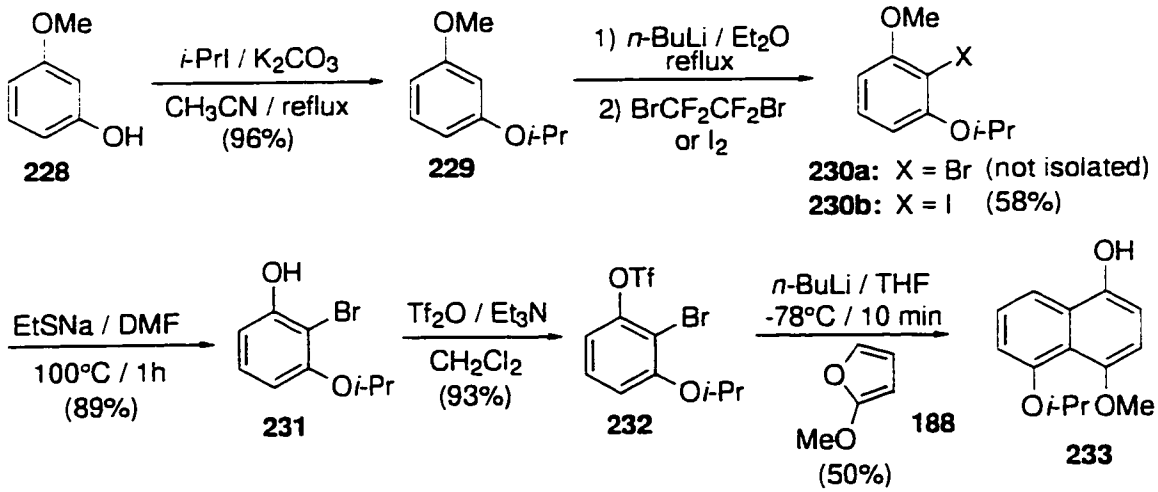
the naphthols **227** in good yield. For our purposes, it was hoped that modification of this method incorporating the desired isopropoxy protecting group would prove fruitful.

Scheme 53



Synthesis of the required naphthol **233** was achieved based on this method as outlined in **Scheme 54**. Introduction of the isopropoxy protecting group was followed by metalation of ether **229** and quench with $BrCF_2CF_2Br$ as a source of electrophilic bromine. Selective demethylation was effected using the conditions of Feutrill[219]

Scheme 54

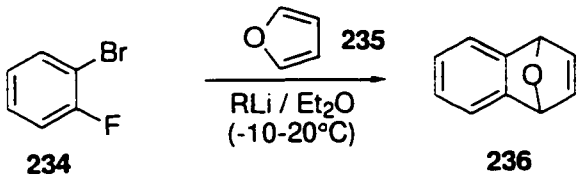


affording the corresponding phenol. Unfortunately, introduction of the bromine substituent in **230** did not occur cleanly and the ether was contaminated with ca. 5-10%

of an unidentifiable impurity as determined by ^{1}H NMR. In general, it proved practical to carry out the demethylation process on the crude material and a reasonable yield of the desired phenol was obtained (89% over two steps). Using the same method with I_2 as electrophile, the pure iodide **230b** was isolated in 58% yield; however, the material was unstable and all attempts at demethylation afforded complex mixtures. Therefore, the bromide **230a** was transformed into the triflate **232** in 93% yield for the purpose of incorporating the leaving group for the benzyne formation. To this end, treatment of **232** with *n*-BuLi in the presence of 2-methoxyfuran **(188)** gave the desired naphthol **233** in 50% yield in which all three oxygen substituents are differentiated. Due to the problems associated with the metalation of **229** as well as the low yield in the cycloaddition step, this method to the AB-ring system was abandoned.

An alternate synthesis of the requisite aryne was proposed based on studies by Gilman,[220] who showed that the reaction of *o*-fluorobromobenzene **(234)** with alkyllithium reagents in the presence of furan affords the corresponding cycloadduct **236** in good yield **(Scheme 55)**.

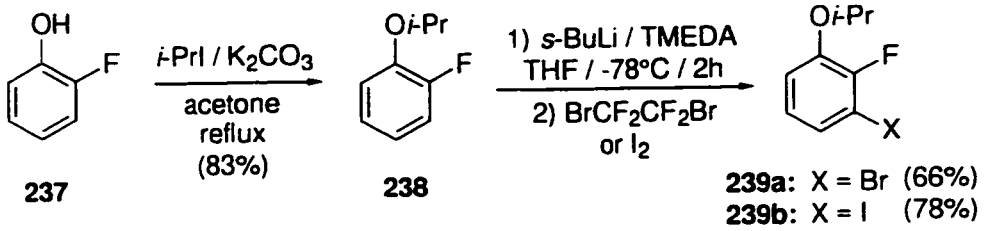
Scheme 55



R	Yld%, **236**
Me	84
n-Bu	68
Ph	71

With this precedent in mind, synthesis of the required aryne precursor was simplified as shown in **Scheme 56**. Isopropylation of commercially available

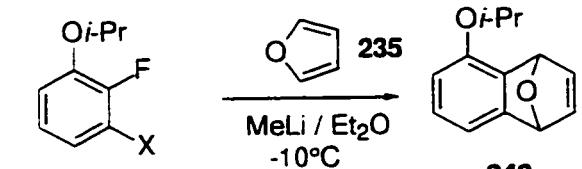
Scheme 56



237 **238** **239a:** X = Br (66%) **239b:** X = I (78%)

2-fluorophenol **(237)** proceeded smoothly to give ether **238**. Introduction of the requisite halogen as the trigger for the aryne formation was accomplished *via* *Do*M using the fluoro substituent as the DMG.[221] Thus, metalation with *s*-BuLi in the presence of TMEDA followed by treatment with either $BrCF_2CF_2Br$ or I_2 allowed incorporation of bromo or iodo substituents, in 66% and 78% yields respectively. This constituted a rapid and efficient route to the requisite benzyne precursors.

In an effort to investigate the applicability of **239b** in the synthesis of **233**, as well as to limit the use of expensive 2-methoxyfuran, a model study was undertaken **(Table 4)**. Conditions were chosen to approximate those of Gilman, using Et_2O as the solvent at -10°C. An initial attempt based on metalation of **238** (entry 1) proved unsuccessful affording only a complicated product mixture from which none of the cycloadduct could be isolated. The yield of the reaction was essentially constant in the vicinity of 50% but was observed to increase on increasing the scale of the reaction. Thus, the desired 1,4-epoxynaphthalene **240** was isolated in 70% yield when the scale was increased to 25 mmol. Presumably the increase in scale effectively reduced the rate of addition of the alkyllithium reagent into the reaction mixture. After investigating the conditions in the model case, the reaction was carried out using the required 2-methoxyfuran **(188)** **(Scheme 57)**. The reaction gave low and variable yields; however, and altering the conditions did not improve these results. For example, changing the solvent to THF decreased the yield dramatically (10-28% yield) in accordance with the findings of Gilman.[220]



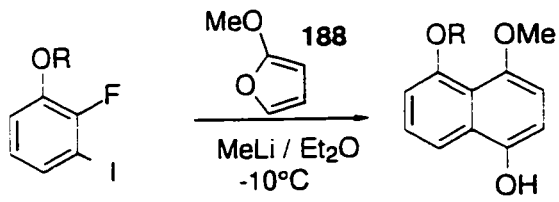
238: X = H
239a: X = Br
239b: X = I

240

Table 4. Model Cycloaddition Study to 240

Entry	R	X	Yld, % 240	Scale, mmol
1	*s*-Bu	H	0	1.74
2	*n*-Bu	I	44	0.6
3	Me	Br	47	0.9
4	Me	I	58	1.0
5	Me	I	70	25

Scheme 57



239b: R = *i*-Pr
241: R = MOM

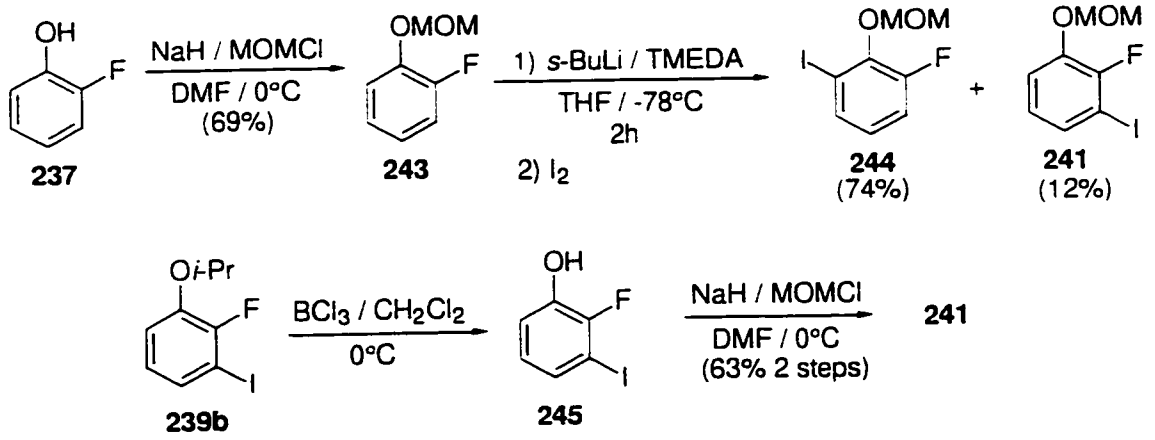
233: R = *i*-Pr (25-50%)
242: R = MOM (40-50%)

The spectral data obtained for **233** did not match those reported in the literature (see Experimental Section), and although the method of Suzuki provided some precedent for the indicated regiochemistry, the conditions of the two reactions were substantially different. Thus, the regiochemistry of the cycloaddition was uncertain but was later proven to be correct by x-ray crystallography (*vide infra*).

In an attempt to investigate if the isopropoxy group was too sterically demanding and consequently resulting in low yields, the PG was changed to the methoxymethyl (MOM) ether **241**. In the event, the yield of the desired naphthol was shown to be more

reproducible although not improved, at an average of 45%. The preparation of the MOM substituted precursor was effected in two ways. Initially, the metalation route (**243** → **244** + **241**) was attempted **(Scheme 58)**; however, the desired ether **241** was isolated in only 12% yield accompanied by the undesired 2,6-derivative as the major isomer in 74% yield. Differentiation of these compounds was not straightforward by ^{1}H NMR. However, in the ^{13}C NMR spectrum of **244** and **241**, the aromatic carbons bearing an iodine are strongly shielded and are thus easily distinguished from the others. In the two compounds in question, the coupling to the fluorine atom provided the necessary distinction. Typical values for $^{3}J_{F\text{-}C}$ are small (0-5 Hz) whereas $^{2}J_{F\text{-}C}$ values are larger (10-25 Hz).[222] Thus, in **241** the carbon bearing the iodine appears as a doublet (δ 82.0 J = 23 Hz) whereas in **244** it is a singlet (δ 92.3). Thus, spectroscopic differentiation of the two compounds was possible. This assignment was confirmed by chemical means.

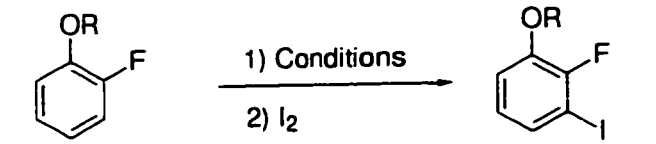
Scheme 58



Treating **244** and **241** separately with *n*-BuLi in the presence of 2-methoxyfuran afforded only MOM ether **243** from iodide **244**; however, **241** gave naphthol **242** **(Scheme 57)** as established qualitatively by TLC.

Alternatively, the desired isomer **241** was obtained by the more indirect but reliable deprotection - reprotection route shown (**239b** → **245** → **241**, **Scheme 58**). Thus, isopropyl cleavage followed by introduction of the MOM group afforded **241** in 63% over two steps. Although this route afforded the desired **241**, it relied on the preparation of the corresponding isopropoxy compound **246** as a starting material, rendering it inconvenient. Thus, a more efficient method based on the metalation of fluorophenol derivatives was investigated (**Table 5**). Metalation of 2-fluorophenol (**237**) using standard conditions for metalation of fluoroarenes[221] followed by I_2 quench provided none of the desired iodophenol **245** (entry 1). Isolation of **245** was possible by a stepwise procedure (entry 2). Initial deprotonation using *n*-BuLi followed by TMSCl quench allowed *in situ* protection of the phenol as the trimethylsilyl ether. Subsequent treatment with *s*-BuLi at low temperature followed by quench with iodine afforded **245** but not in synthetically useful yields (30%). Attempted metalation of MOM ether **243** using LDA (entries 3 and 4) failed resulting only in complex reaction mixtures. Presumably at low temperature LDA is of insufficient strength to deprotonate the substrate and metalation can only occur at higher temperatures which may promote benzyne formation[223] and complicated reaction mixtures. Finally, compound **241** was isolated in synthetically useful yields by treatment of **243** with Schlosser's base[224] at -78°C for 2 h. None of the corresponding 2,6-substituted regioisomer could be detected in the reaction mixture.

As a more thorough investigation for access of naphthol **242**, the effect of the orientation of the iodine and fluorine substituents on the cycloaddition reaction was examined. Inversion of these two groups was carried out as shown in **Scheme 59**. Commercially available 3-fluorophenol (**246**) was protected as the MOM ether using the previously established conditions. Metalation of **247** with *t*-BuLi followed by treatment



237 R = H
243 R = MOM

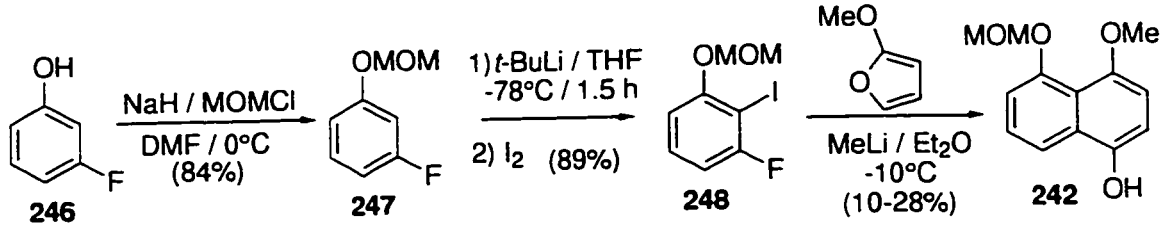
245 R = H
241 R = MOM

Table 5. Metalation of Compounds 237 and 243.

Entry	R	Conditions	Comments
1	H	2.5 equiv *s*-BuLi / TMEDA / THF / -78°C 2 h	intractable mixture
2	H	a) 1 equiv *n*-BuLi / THF / -78°C b) 1 equiv TMSCl c) *s*-BuLi / TMEDA / 2 h	30% yield
3	MOM	1 equiv LDA / THF / -78°C / 2 h	intractable mixture
4	MOM	2.5 equiv LDA / THF / -78°C / 2 h	intractable mixture
5	MOM	1 equiv *n*-BuLi / *t*-BuOK / THF / -78°C / 2 h	71% yield

with iodine afforded **248** in 89% yield. Treatment of **248** under the standard conditions employed for the cycloaddition reaction afforded the naphthol **242** in low and irreproducible yield. Presumably, coordination of the lithium to the MOM group in the intermediate is possible. This might serve to slow the elimination of LiF consequently increasing the concentration of the aryllithium species present in the reaction mixture allowing side reactions to occur, for example, biaryl formation.[225]

Scheme 59

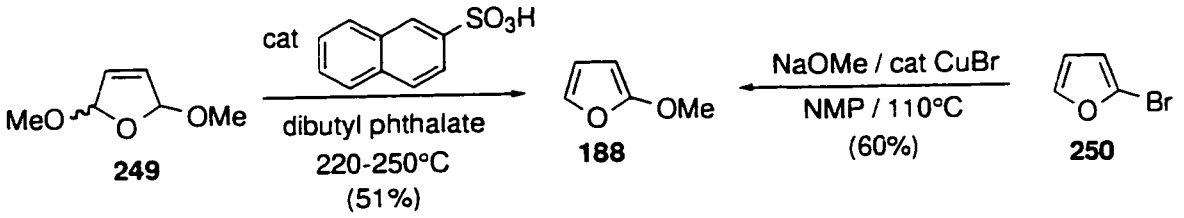


246 **247** **248** **242**

To summarize, application of aryne chemistry has allowed the development of efficient routes to the desired naphthol bearing isopropoxy or MOM protecting groups at

C-1. An issue which detracts from the synthetic utility of the method is the expense of the commercially available 2-methoxyfuran. This problem was addressed through attempted syntheses of this material. Unfortunately, reported methods, pyrolysis of 2,5-dihydro-2,5-dimethoxyfuran reported by D'Alelio and co-workers[226] and the CuBr catalyzed method for etherification of aryl halides by Brandsma[227] were found to be irreproducible in this laboratory **(Scheme 60)**. The pyrolysis reaction afforded the desired compound; however, the yield was invariably low and irreproducible, often accompanied by polymeric material. Brandsma's method was not synthetically useful due to the difficulty encountered in preparation of the required 2-bromofuran. Both the metalation[228] and electrophilic[229] processes reported for the preparation of **250** by Brandsma failed to provide the desired compound reproducibly. Thus the commercial material was used in all experiments.

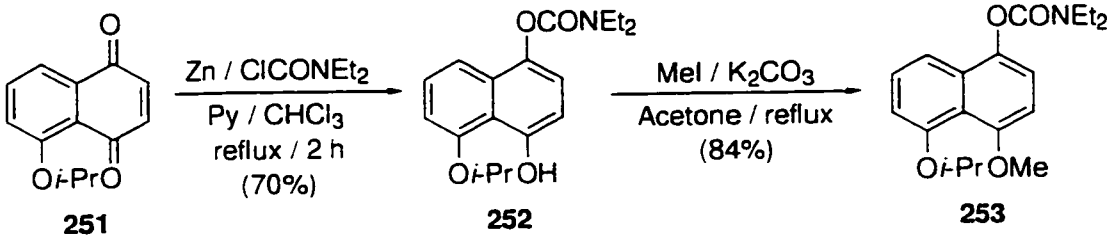
Scheme 60



A significant improvement in the synthesis of naphthyl carbamate **253** was achieved using a modification of the selective reductive - acylation of alkylated juglone derivatives established by Giles.[218] Isopropoxyjuglone **251**, prepared by the method of Laatsch[230] in 76% yield, was treated with $ClCONEt_2$ in the presence of Zn dust affording the *O*-naphthylcarbamate **252** in 70% yield **(Scheme 61)**. Methylation under standard alkylation conditions afforded the key carbamate **253** in good yield. This method allows direct introduction of the requisite carbamoyl group and avoids the deacetylation - reprotection steps necessary in Giles' procedure. Synthesis of **253** is thus achieved in

three steps and 45% yield compared with four steps and 30% yield for the method based on the isopropylfluoride **239b (Scheme 57)**.

Scheme 61

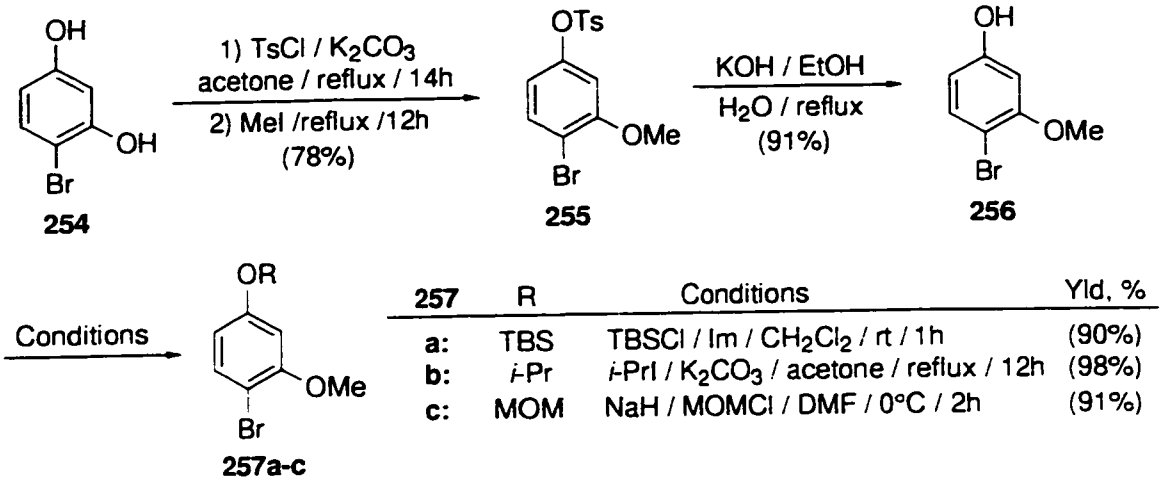


251 **252** **253**

5.1.2 Preparation of the D Ring Coupling Partner

During the course of studies concerning the reactions of aryl chromium carbene complexes with alkynes, Bos and co-workers[231] prepared phenol **256**. This method allowed the preparation of ethers **257a-c** as D ring coupling partners. Thus, sequential treatment of 4-bromoresorcinol with TsCl and MeI allowed selective formation of **255**. Hydrolysis of the tosylate afforded phenol **256** in excellent yield which was then converted into the TBS, isopropoxy, and MOM ethers, **257a-c** respectively **(Scheme 62)**. The yields obtained in the preparation of **256** were comparable to those obtained by Bos; however, a substantial improvement came on scaling the reaction to 50 mmol, as chromatography was avoided and a single recrystallization afforded pure **256**.

Scheme 62



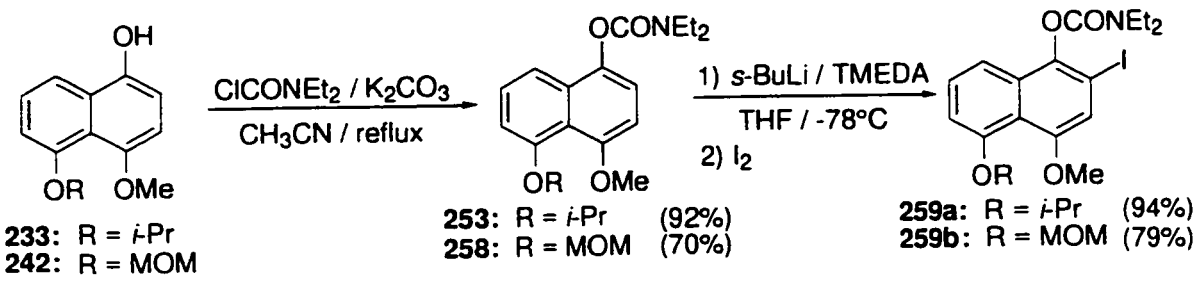
257	R	Conditions	Yld, %
a:	TBS	TBSCl / Im / CH_2Cl_2 / rt / 1h	(90%)
b:	*i*-Pr	*i*-PrI / K_2CO_3 / acetone / reflux / 12h	(98%)
c:	MOM	NaH / MOMCl / DMF / 0°C / 2h	(91%)

5.1.3 Formation of the Biaryl Bond *via* Cross Coupling

5.1.3.1 C-8 Protection by the TBDMS Group

The *O*-carbamates **253** and **258** required for cross coupling were obtained in high yields from naphthols **233** and **242** by standard methods **(Scheme 63)**. Standard *O*-arylcarbamate metalation conditions (*s*-BuLi / TMEDA / -78°C) followed by quench with iodine gave the corresponding iodides in good yield providing the cross coupling handle. Initially, C-8 TBS ether protection was chosen due to its ease of cleavage in the presence of methoxy and isopropoxy ethers under mild conditions.[232] Negishi cross coupling conditions were chosen for the coupling of the carbamates with the D ring fragment **(Table 6)**. In the initial attempt, cross coupling of the arylzinc bromide derived from *ortho*-metalation / transmetalation of **253** (X = H → Li → ZnBr) with arylbromide **257a** in the presence of Pd(0) catalyst afforded the desired biaryl in only 45% yield. Reversal of the coupling substituents gave a much better result. Thus,

Scheme 63



reaction of iodide **259a** with the arylzinc bromide **257a** (Y = ZnBr) derived from metal halogen exchange (MHEX) / transmetalation (X = Br → Li → ZnBr), afforded the desired biaryl **260a** in excellent yield. Having established the necessary orientation of the halogen and zinc substituents, coupling of iodide **259b** with **257a** afforded the corresponding C-1 MOM substituted biaryl **260** in 90% yield.

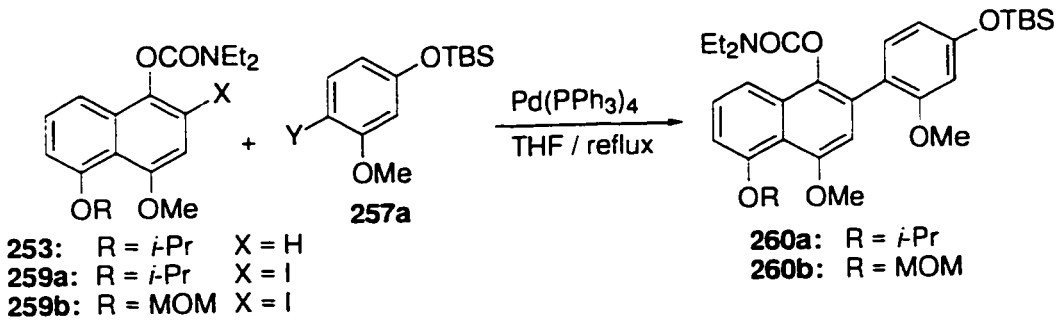


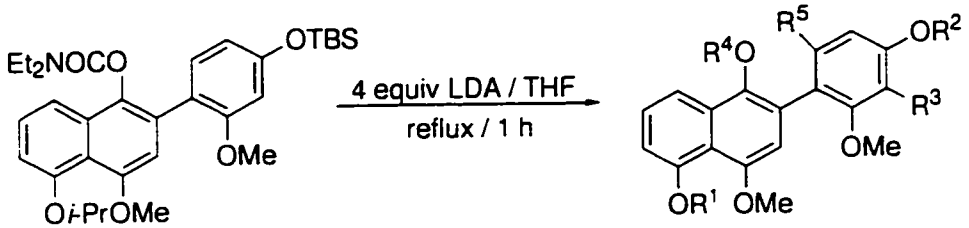
Table 6. Negishi Cross Coupling Route to 260a,b

Entry	Cmpd	X	R	Y	Yld, %
1	**253**	ZnBr	*i*-Pr	Br	45
2	**259a**	I	*i*-Pr	ZnBr	90
3	**259b**	I	MOM	ZnBr	90

With the biaryl-*O*-carbamates **260a,b** in hand, the LDA induced DreM metalation - carbamoyl migration process was tested (**Table 7**). Unfortunately, the results were not straightforward as six compounds were isolated. Phenol **261a**, derived from

carbamoyl cleavage which often accompanies the carbamoyl migration reaction,[101] was isolated in low yield. The major product, phenol **261b**, is the result of an unexpected silyl migration to C-3′. Cleavage of the isopropyl protecting group under the reaction conditions was also observed demonstrated by isolation of triphenol **261c**. Products **261e-f** are combinations of these processes, isolated in 21 and 13% yields respectively along with the desired carbamoyl migration product **261d** in only 4% yield.

Identification of these products was not straightforward. The ^{1}H NMR spectra of compounds **261b,c and 261e,f** which had undergone silyl migration displayed unusual features. In these cases, the methoxy group at C-2′ (δ 3.30 ppm) was shielded and substantially broadened relative to that in the starting material (δ 3.70 ppm), and in

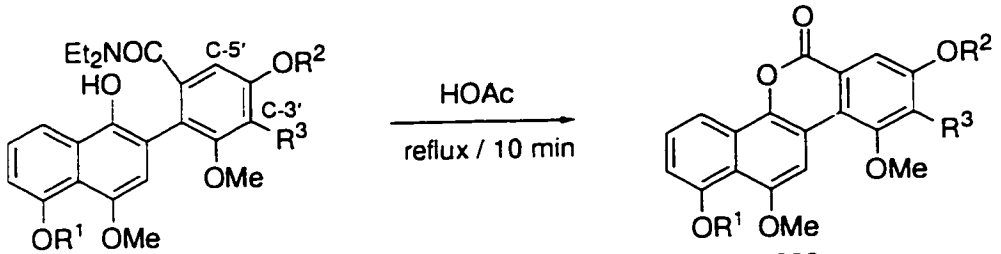


260a **261a-f**

Table 7. DreM Reactions of Carbamate 260a

261	R^1	R^2	R^3	R^4	R^5	Yld, %
a	*i*-Pr	TBS	H	H	H	4
b	*i*-Pr	H	TBS	$CONEt_2$	H	27
c	H	H	TBS	H	H	16
d	*i*-Pr	TBS	H	H	$CONEt_2$	4
e	*i*-Pr	H	TBS	H	$CONEt_2$	21
f	H	H	TBS	H	$CONEt_2$	13

some cases was almost buried in the broad signal of the methylene protons (δ 3.2-3.6 ppm) of the amide or carbamate. Determination of the location of the silyl groups in **261b-f** was effected by both chemical and spectroscopic means. First, compounds **261d-f** were subjected to lactonization using HOAc, conditions under which the TBS aryl ether is labile. Of the isolated lactones **262d-f (Table 8)** only **262a** showed loss of the TBS group by ^{1}H NMR. Lactones **262b,c** retained the TBS group indicating that it was attached at either C-3′ or C-5′ of the hydroxyamide. This distinction was made based on the NOESY spectra of compounds **261b** and **262e,f**. Examination of these spectra showed NOE cross peaks between the methoxy group and the dimethyl portion of the silyl substituent, locating the silyl group at C-3′ in these compounds. Based on these results the structure of **261c** was assigned by analogy. Direct ^{1}H NMR spectral examination was sufficient to assign the structure of **261a**.



261d-f **262a-c**

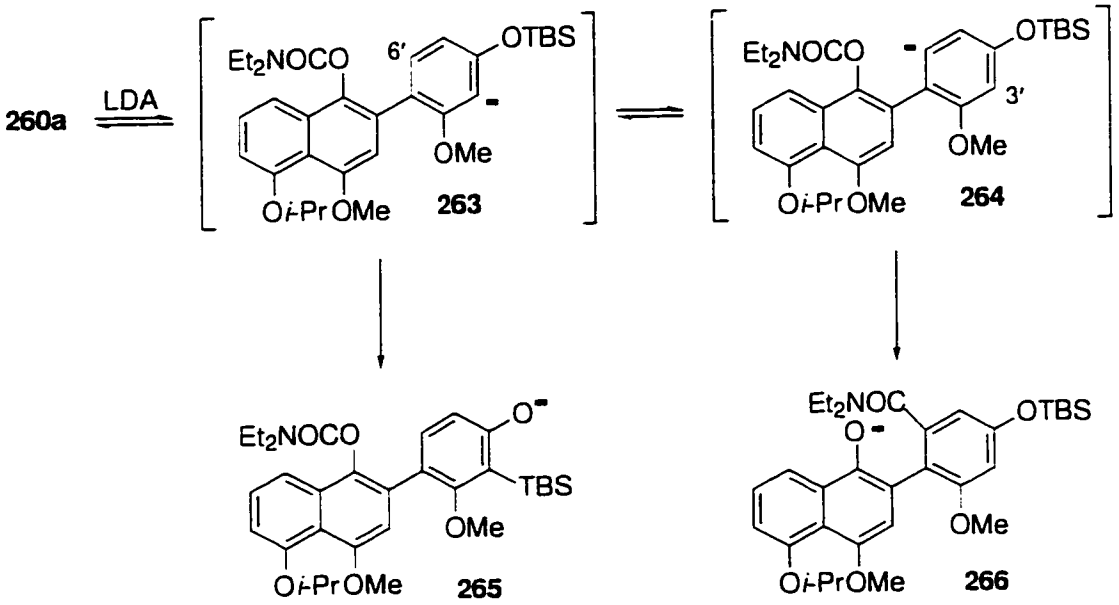
Table 8. Cyclization of Hydroxy Amides 261d-f

261	R^1	R^2	R^3	262	Yld, %
d	*i*-Pr	H	H	**a**	91
e	*i*-Pr	H	TBS	**b**	89
f	H	H	TBS	**c**	91

Presumably, under the reaction conditions, reversible thermodynamic deprotonation occurs at C-3′ to give **263 (Scheme 64)** which is in equilibrium with the C-6′ anion **264**. These intermediates may undergo irreversible silyl or carbamoyl

migration to afford **265** and **266** respectively. Formation of **261e,f** in which both migrations have occurred may be rationalized as taking place in a stepwise manner; however, under the rather forcing conditions, dianion formation should not be discounted. The 1,3 O → C migration of a silyl group has been demonstrated previously[233] in the case of *o*-lithiosiloxyarenes generated by MHEX. Cleavage of the isopropoxy group under the reaction conditions probably occurs *via* LDA induced E_2 elimination *(vide infra)*. That **261b**, derived only from silyl migration (**263** → **265**),

Scheme 64



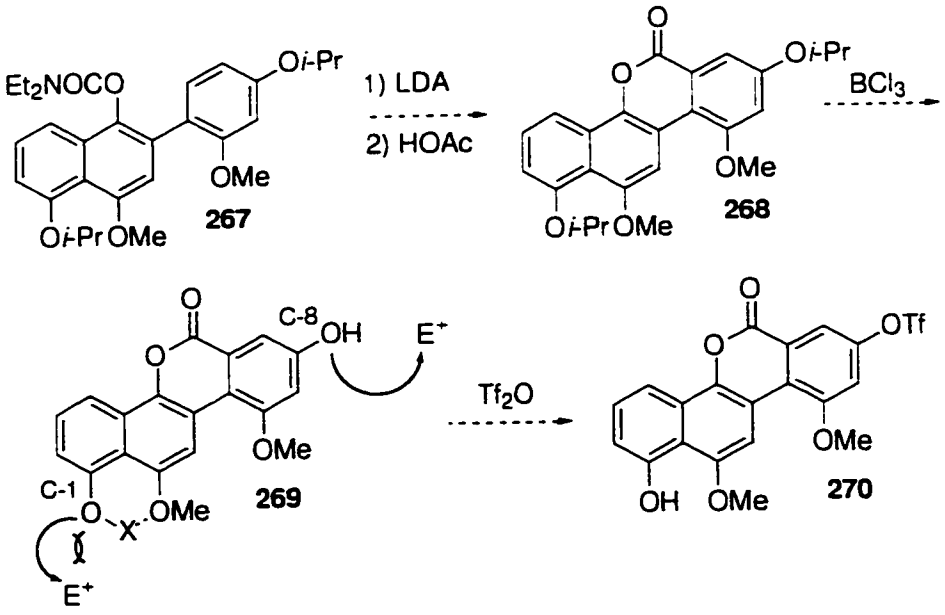
was isolated as the major product suggests that this process is faster under the reaction conditions than the desired carbamoyl migration (**264** → **266**). Thus, a more robust C-4′ phenol protecting group is required. When the MOM substituted carbamate **260b** was subjected to the migration conditions the reaction was somewhat more complex and isolation of products was difficult. Analysis of several chromatographic fractions

suggested similar reactivity; however, cleavage of the MOM ether appered to have occurred to a greater extent.

5.1.3.2 C-8 Protection by the Isopropoxy Group

Results achieved by Wang during the total synthesis of the naturally occurring fluorenone dengibsin **(92)**, suggested that an isopropyl ether would be stable to the conditions of the LDA induced carbamoyl migration process.[101] Thus, the concept of C-4′ phenol protection by isopropylation was entertained. Application of this tactic would necessitate re-evaluation of the PG strategy as both phenol substituents of **268** would bear the same group. Thus, after subjecting **267** to carbamoyl migration and cyclization conditions **(Scheme 65)**, the expected product **268** would require selective deprotection at C-8. It was envisioned that the C-12 methoxy group may serve as a coordinating group to allow steric differentiation of the two phenols. This may occur

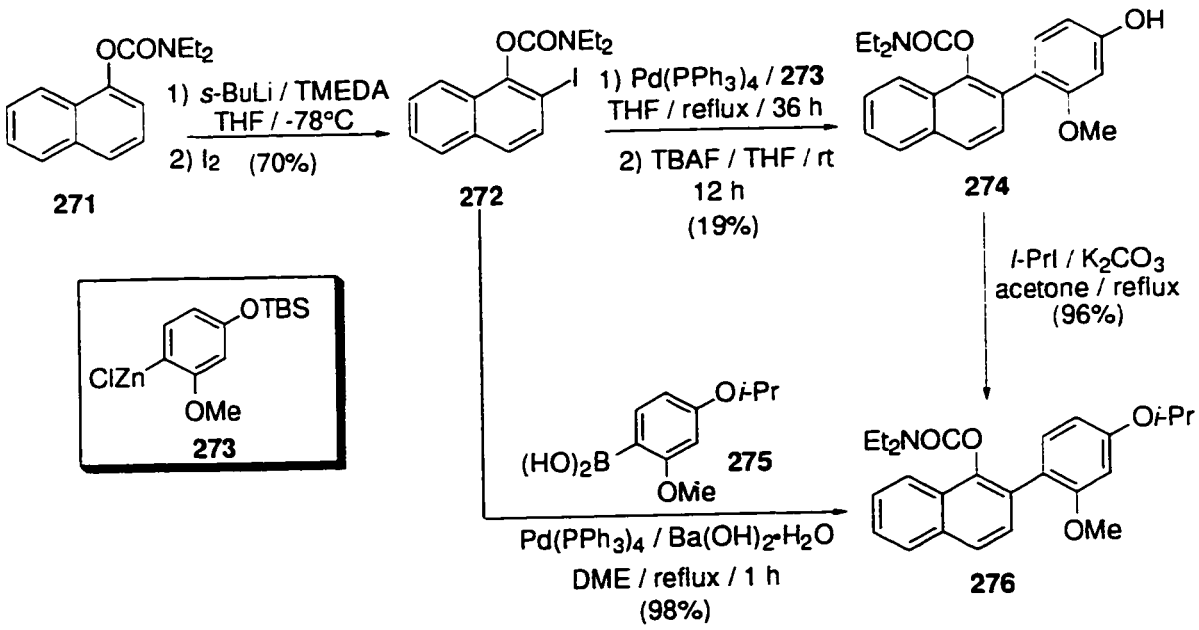
Scheme 65



through hydrogen bonding (**269** X = H) or *via* coordination of a metallic reagent such as $B(OAc)_3$ or $ZnCl_2$. Triacetoxyborane has been used in an analagous manner for the selective acetylation of xanthone derivatives.[234] If **269** could be thereby obtained, selective introduction of the triflate would lead to **270** which could then be protected or directly subjected to cross coupling conditions.

In order to test the feasibility of the *i*-Pr protecting group, a model substrate **(276)** was prepared by two different routes **(Scheme 66)**. Metalation of **271** followed by introduction of iodine afforded **272**. Negishi cross coupling of iodide **272** with arylzinc chloride **273** followed by direct cleavage of the silyl protecting group gave phenol **274** in 19% yield over two steps. Isopropylation of the phenol with *i*-PrI under standard conditions afforded the desired ether **276** (96%). Alternatively, Suzuki cross

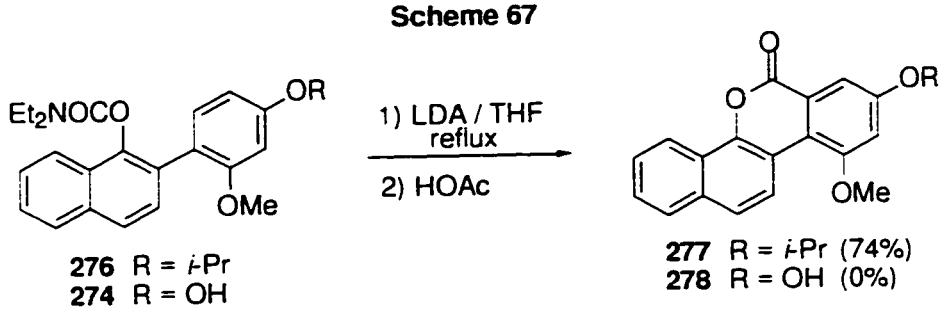
Scheme 66



coupling of **272** with boronic acid **275** in the presence of Pd(0) catalyst gave carbamate **276** in excellent yield in a single step.

To investigate the stability of the isopropoxy group to the DreM conditions, the model substrate **276** was subjected to the standard LDA reaction conditions (**Scheme 67**). Gratifyingly, after direct acid catalyzed cyclization, the desired lactone **277** was isolated with no evidence for the cleavage of the isopropoxy group. Phenol **274** was subjected to the same conditions to determine if the protecting group could be circumvented, an advantage which would increase the scope of the DreM - carbamoyl migration protocol. Unfortunately, after heating **274** with 3.5 equiv of LDA and column chromatography only several unidentifiable compounds were obtained in low yield. Analysis by ^{1}H NMR spectroscopy suggested the cleavage of the carbamoyl group but the identity of the compounds could not be firmly established.

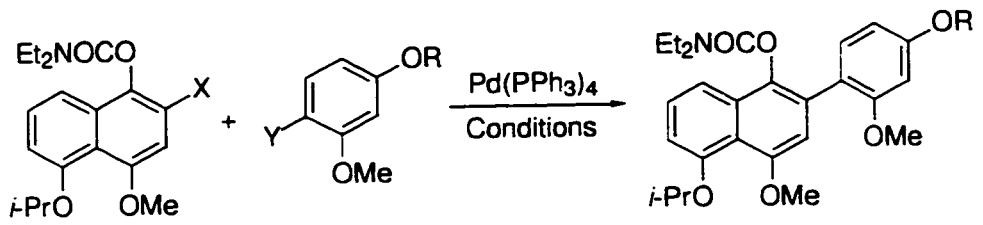
Scheme 67



276 R = *i*-Pr
274 R = OH

277 R = *i*-Pr (74%)
278 R = OH (0%)

Encouraged by the results of the above model study, the synthesis of the desired diisopropoxy ether **267** was undertaken (**Table 9**). Metalation of carbamate **253** and transmetalation of the lithio species to the corresponding arylzinc chloride followed by coupling with bromide **257b** under Negishi conditions failed to give the desired **267**. Reversal of the halogen and zinc functional groups (entry 2) in **259a** and **257b** respectively provided the desired compound in only 21% yield. Switching to the boronic



253: X = H
259a: X = I

267: R = *i*-Pr
279: R = MOM

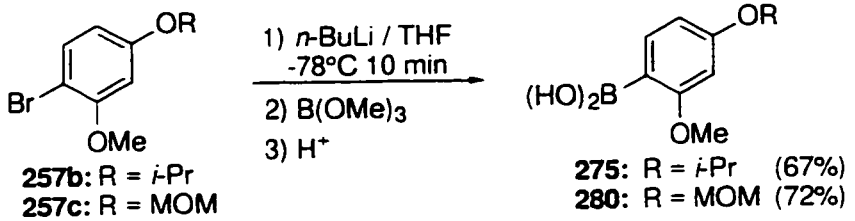
Table 9. Cross Coupling Route to 267 and 279

Entry	X	Cmpd	Y	R	Conditions	Yld, %
1	ZnCl	**257b**	Br	*i*-Pr	THF / reflux / 12 h	0
2	I	**257b**	ZnCl	*i*-Pr	THF / reflux / 48 h	21
3	I	**275**	$B(OH)_2$	*i*-Pr	aq Na_2CO_3 / DME / reflux / 12 h	28
4	I	**275**	$B(OH)_2$	*i*-Pr	aq $Ba(OH)_2$ / DME / reflux / 12 h	92
5	I	**280**	$B(OH)_2$	MOM	aq $Ba(OH)_2$ / DME / reflux / 1 h	99

acid **275** failed to produce substantial improvement in coupling with **259a** when Na_2CO_3 was used as the base. However when $Ba(OH)_2$ was employed, the yield increased dramatically affording the desired biaryl carbamate **267** in 92% yield. Similarly the MOM substituted derivative **279** was prepared in almost quantitative yield. Campbell[68] has semi-quantitatively demonstrated the accelerating effect of $Ba(OH)_2$ on the Suzuki-Miyaura reaction and others[235] have qualitatively observed this effect; however, a rationalization has not been given. Preparation of the required boronic acids was accomplished *via* MHEX followed by treatment with $B(OMe)_3$ and acidic workup to afford **275** and **280** as stable solids in 67 and 72% yields, respectively **(Scheme 68)**.

Having prepared biaryl **267** by the modified Suzuki cross coupling route, the LDA mediated migration reaction **267** → **281c** was tested **(Table 10)**. As expected

Scheme 68



the C-4′ isopropyl PG was stable; however, that at C-5 proved labile giving **281b,d** which accounted for 39% of the reaction mixture. Interestingly, treatment of **281c** separately under the DreM reaction conditions afforded **281d** in 90% yield; however, similar treatment of **281d** failed to effect cleavage of the remaining isopropyl group, returning starting material quantitatively. In a separate experiment with 3 equiv of LDA, lactone **282** was isolated in 54% after direct cyclization (**Scheme 69**). The location of the cleaved protecting group was established by cyclization (HOAc / reflux) of the hydroxyamide **281d** affording the corresponding lactone **283**. An NOE difference experiment established a strong NOE between H_a and the isopropyl methine and no NOE with H_c (**Scheme 69, 283a**). Differentiation of H_c and H_a was easily accomplished

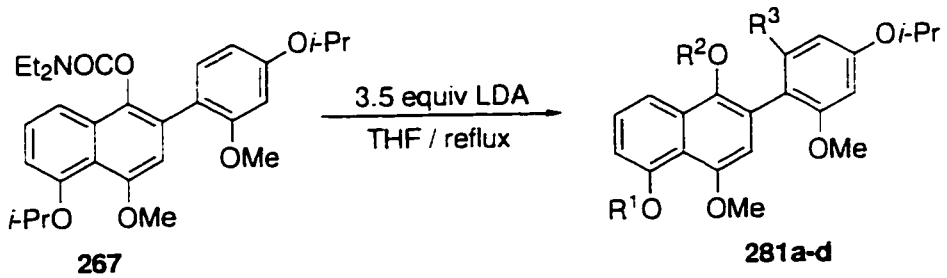
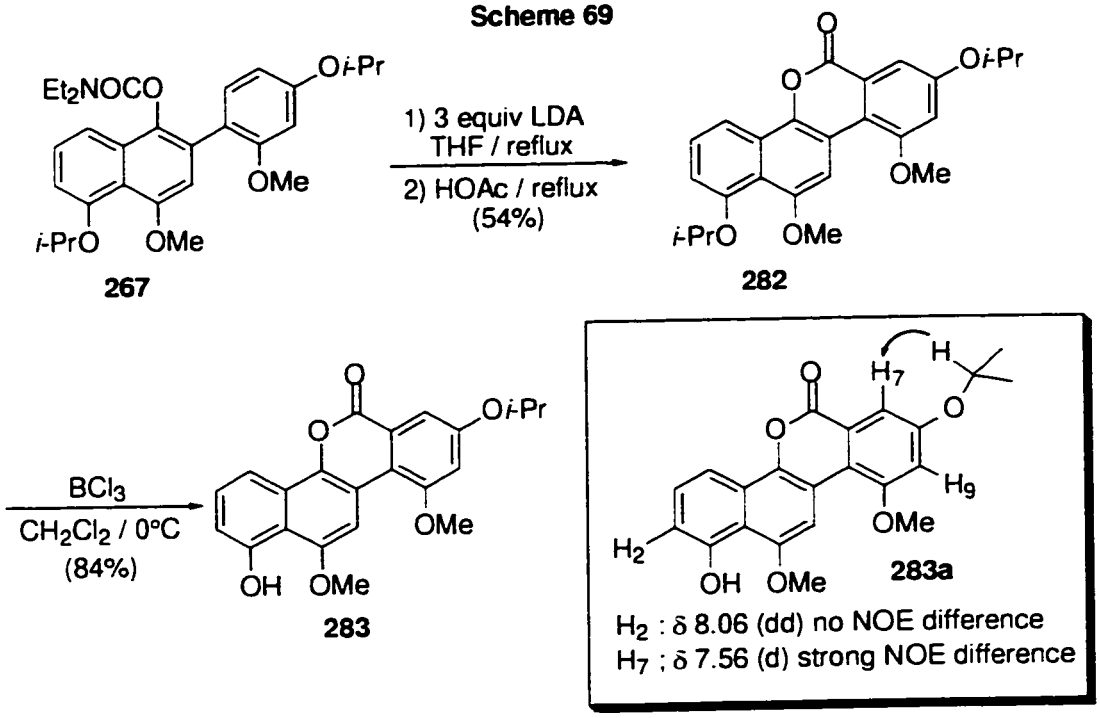


Table 10. DreM Reaction of 267

R^1	R^2	R^3	**281**	Yld, %
i-Pr	H	H	**a**	13
H	H	H	**b**	9
i-Pr	H	$CONEt_2$	**c**	41
H	H	$CONEt_2$	**d**	30

Scheme 69

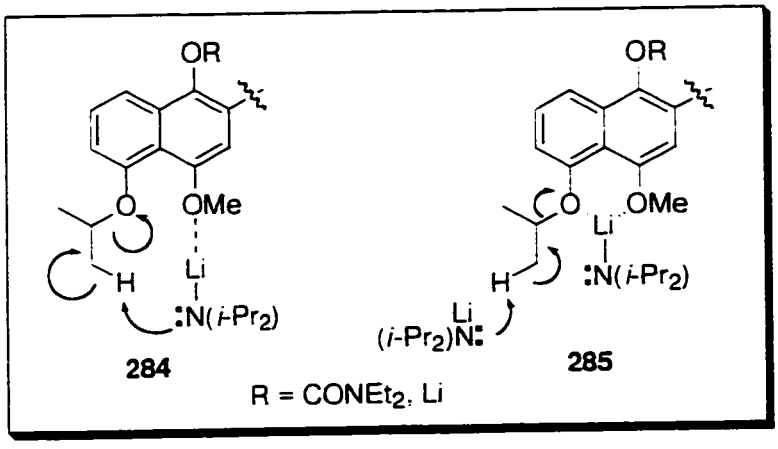


based on their relative multiplicities (H_2 δ 8.06, dd vs H_7 δ 7.56 d). Attempted cleavage of both isopropyl groups of **282** was unsuccessful. Treatment with BCl_3 at 0°C afforded a compound in 84% yield which by ^1H NMR had retained one isopropyl group and an NOE difference experiment again confirmed the regiochemistry of deisopropylation. Treatment with $TiCl_4$ afforded the same material in 77% yield. Similarly, subjection of **283** to BCl_3 (0°C → rt) afforded only starting material. The structure of **282** was proven by x-ray crystallography (see Appendix 1), confirming the naphtho[1,2-*b*]benzo[*d*]pyranone structure derived from the DreM - carbamoyl migration - cyclization sequence. Also, this structure firmly established the position of the A ring isopropyl PG which, as discussed in Section 5.1.1, was uncertain.

Selective cleavage of the C-5 isopropoxy group under the DreM conditions suggests the participation of the C-4 methoxy substituent. Presumably coordination of

LDA to the oxygen allows an E_2 elimination to occur **(Figure 1)**. Alternatively, one lithium atom may bridge both oxygens, weakening the O-C bond of the isopropoxy group facilitating an intermolecular E_2 elimination by a second molecule of LDA. Differentiation of these two mechanisms might be feasible based on kinetic studies of the

Figure 1



process. First order kinetics with respect to LDA would suggest a mechanism proceeding *via* **284** whereas second order would implicate **285**.

5.1.3.3 C-8 Protection by the Methoxymethoxy Group

The relatively inert nature of the C-4′ isopropoxy group suggested an alternate more labile group would be necessary to achieve the desired selectivity. Consideration of the facile cleavage of the C-5 isopropyl group under the DreM conditions suggested that the MOM group in this position of **260b (Section 5.1.3.1)** was cleaved by a similar coordinative assistance. Therefore, it may be reasonable to assume that a C-4′ MOM ether might be stable to the carbamoyl migration conditions in the absence of such a cleavage mechanism. Also, it was hoped that the MOM PG would undergo cleavage to

the corresponding phenol under the cyclization conditions. In order to test these possibilities, carbamate **279**, prepared by Suzuki coupling **(Table 9)**, was subjected to the standard LDA mediated acid catalyzed cyclization sequence **(Scheme 70, Table 11)**. Initial results (entry 1) gave the desired lactone **287** in only 40% yield, in addition to the MOM ether **287b** in small amounts, suggesting that cleavage of the C-8 PG was relatively slow under the cyclization conditions. Treatment of **279** under the standard migration conditions without direct cylization, afforded the hydroxy amide **286** in only 28% yield. The cleavage of the C-5 isopropyl group was thought to be the competing process contributing to the low yield of **286**, and although a compound of similar R_f to that expected for isopropyl cleavage was detected by TLC, it could not be isolated. In

Scheme 70

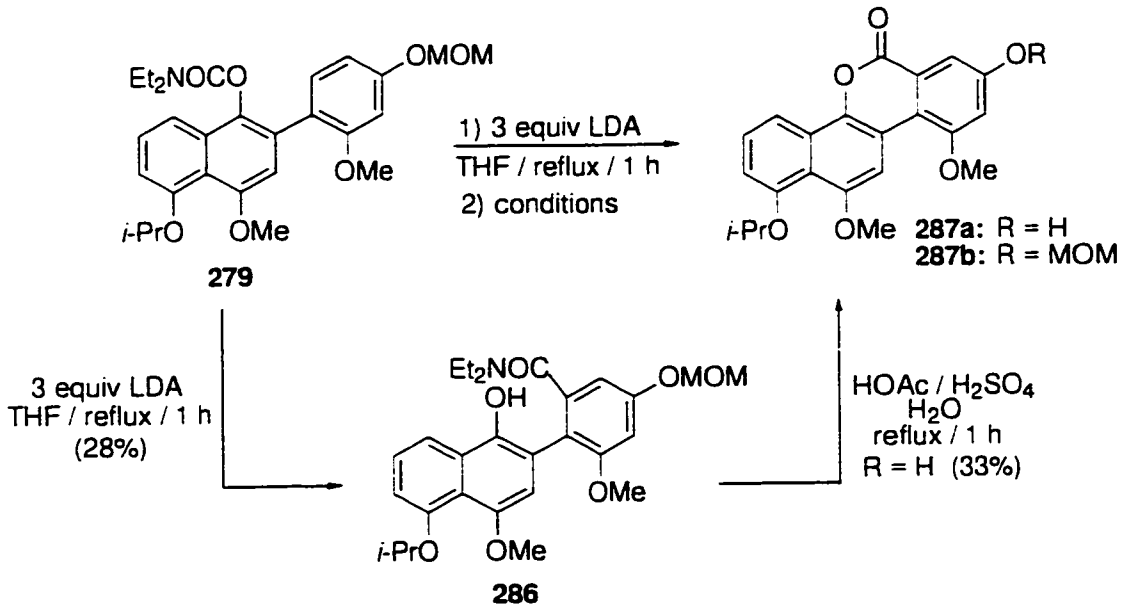


Table 11. DreM Reaction of 279

Entry	[279], mol/L	conditions	Yld **288**, %
1	0.075	HOAc / reflux	40
2	0.071	HOAc / cat H_2SO_4 / H_2O / reflux	39
3	0.050	HOAc / H_2O (1:1) / reflux	70

order to test the possibility that the simple cyclization conditions were too mild, more forcing conditions for MOM cleavage were employed (entry 2). Isolation of **287a** resulted in only 39% over two steps. Cyclization of hydroxy amide **286** under the same conditions resulted in isolation of 287a in 33% yield confirming that these cinditions were too severe, resulting in degredation of the product, presumably *via* cleavage of the C-4 isopropoxy group. A substantial improvement occurred on modification of the migration and cyclization conditions (entry 3). Introduction of LDA in two portions (1.3 equiv and then 1.3 equiv after 1 h), followed by cyclization of the reaction mixture with 1:1 HOAc:H_2O afforded the desired compound in 70% yield. Presumably, introduction of the base in two portions serves to keep the concentration of LDA low during the reaction, suppressing the base induced cleavage of the isopropoxy group as well as the nucleophilic displacement of the carbamoyl group.

5.1.4 Introduction of the C-8 Substituents: Completion of the Total Synthesis

Completion of the syntheses of DFGV, DFGM, And DFGE is shown in **Scheme 71**. Phenol **287** was first converted to the corresponding triflate **288**. Initial experiments using CH_2Cl_2 and stoichiometric Et_3N or pyridine failed due to the low solubility of **287**. Utilization of pyridine as the solvent,[236] in which **287** is freely soluble allowed complete dissolution of the starting phenol in CH_2Cl_2. An initial attempt under these conditions resulted in a complex reaction mixture from which **288** was isolated in low yield (<10%). Substantial improvement was achieved by performing and quenching the reaction with sat $NaHCO_3$ at -78°C allowing isolation of **288** in 81% yield.

Cross coupling tactics were then utilized to introduce the various substituents present in the natural products **(Table 12)**. Treatment of **288** with BEt_3 under Suzuki conditions[237] afforded 1-isopropoxydefucogilvocarcin E **289a** in 75% yield. Negishi - Quesnelle coupling of MeZnBr[237,24d] with **288** afforded 1-isopropoxydefucogilvocarcin M **289b** in 59% yield. Modified[238] Stille conditions using the vinylstannane reagent allowed introduction of the required C-8 vinyl substituent to give **289c**. Finally, cleavage of the C-1 isopropoxy protecting groups proceeded smoothly affording DFGV in 95% yield completing the synthesis of the natural product which was shown to be identical with the natural product by comparison of physical and spectroscopic data. Similar deprotection of **289a** and **289b** afforded DFGE **(290a)** and DFGM **(290b)** in 86 and 83% yields respectively.

Scheme 71

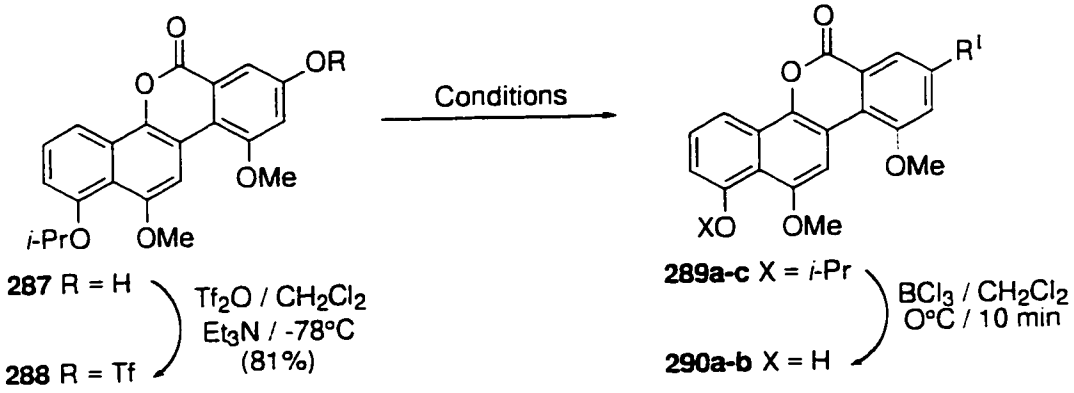


Table 12. Introduction of C-8 Substituents

Conditions	R^1	**289**	Yld, %	**290**	Yld, %
BEt_3 / $PdCl_2$ (dppf) K_3PO_4 / THF / reflux	Et	**a**	75	**a**	86
MeZnCl / $NiCl_2$(dppp) THF / reflux	Me	**b**	59	**b**	83
$C_2H_3SnBu_3$ Pd_2dba_3 / NMP / LiCl (2-furyl)$_3$P	vinyl	**c**	69	**149d**	95

5.1.5 Conclusions

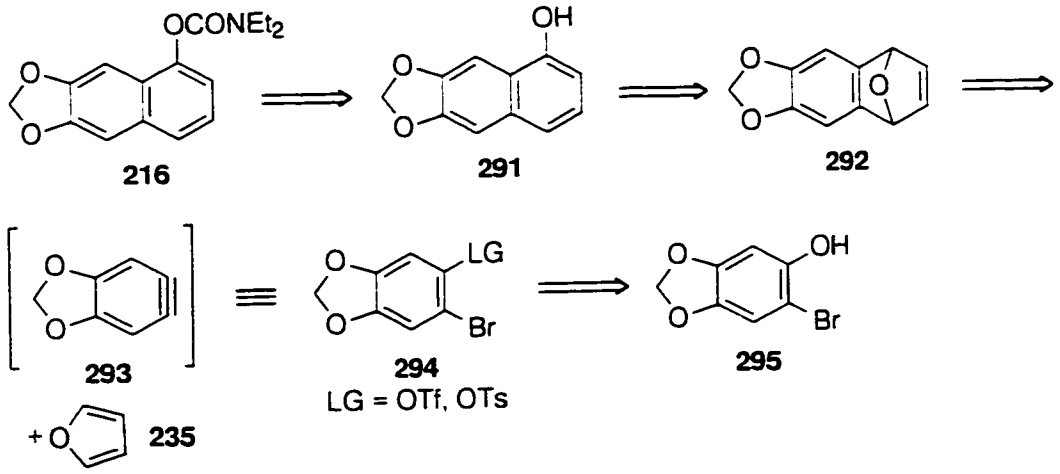
Total synthesis of defucogilvocarcin V **149d** was achieved in 9 steps and 14% overall yield starting from commercially available juglone. Diverse cross coupling strategies allowed introduction of the three different substituents present in the natural products, (DFGV **149d**, DFGE **290a** and DFGM **290b**). The DreM - carbamoyl migration protocol was shown to be an effective method for the construction of the naphtho[1,2-*b*]benzo[*d*]pyran-6-one framework. Modification of the conditions allowed significant improvement in the LDA mediated DreM reaction **(Scheme 70, Table 11)**. Suzuki cross coupling produced the key biaryl **279** in excellent yield and allowed facile preparation of intermediates for the detailed study of C-8 protecting groups. The TBS protecting group was found to be unsuitable for DreM - carbamoyl sequence due to a competing O $\rightarrow$ C anionic silyl migration. Finally, two methods were established for the construction of the trioxygenated naphthalene **253** based on aryl - furan cycloaddition **(Scheme 57)** and reductive acylation of isopropoxy juglone **(Scheme 61)**.

6. Total Synthesis of Arnottin I

6.1 Methylenedioxy Protecting Group

According to the retrosynthetic analysis of arnottin I (**Scheme 48 Section 4.3**), the key carbamate **216** was required. Its derivation *via* an aryne route was contemplated as shown in **Scheme 72**. Thus, naphthol **291** may be disconnected to the 1,4-epoxynaphthalene derivative **292**. Realization of the cycloaddition disconnection reveals symmetrical aryne **293**, containing no substituents *ortho* to the reactive sites. *ortho*-Bromosulfonates **294** were considered to be suitable precursors for benzyne **293**, derived from readily available 5-bromosesamol **(295)**.

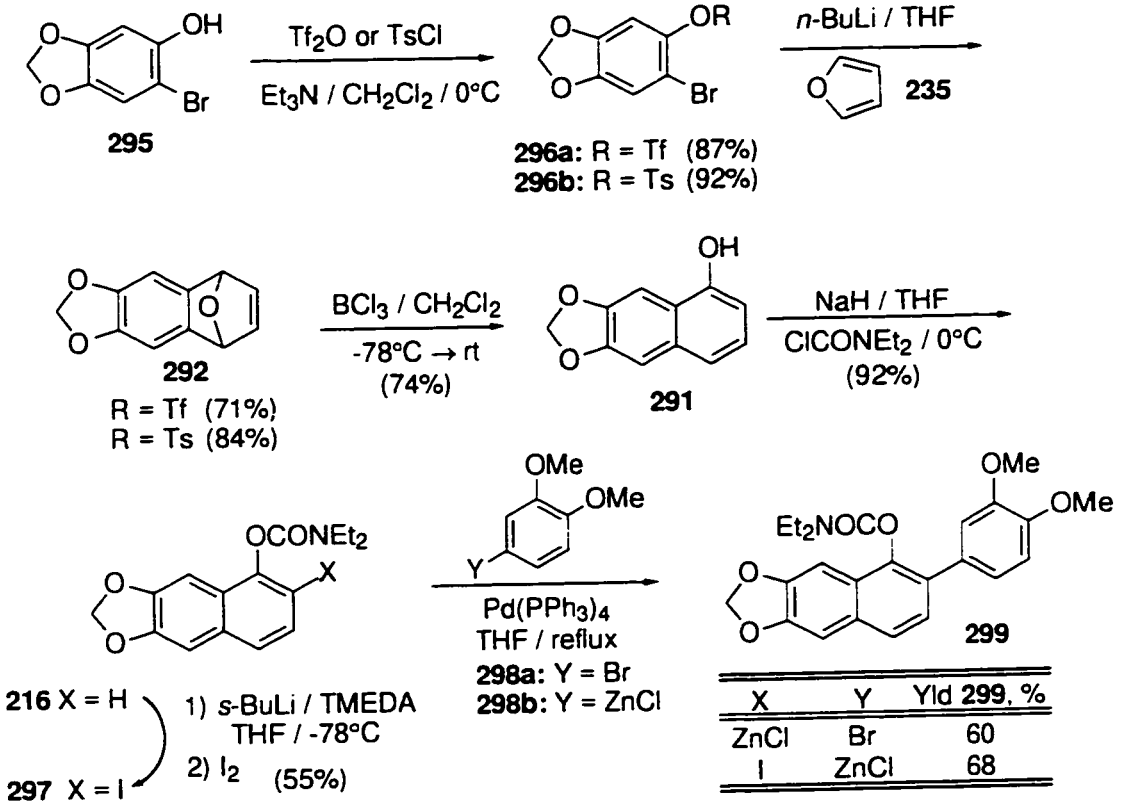
Scheme 72



Construction of the naphthalene framework **216** commenced from bromosesamol **295** which was prepared by the method of Alexander[239] in 84% yield **(Scheme 73)**. Synthesis of triflate **296a** and tosylate **296b** occurred smoothly under similar conditions in 87% and 92% yields respectively. Treatment of **296a** with *n*-BuLi at -78°C in the presence of furan afforded the corrseponding cycloadduct in 71% yield. The tosylate under similar conditions (-100°C) afforded **292** in excellent yield. Altering the

conditions did not improve the yield, in fact, substitution of Et_2O for THF as solvent for the cycloaddition of triflate **296a** with **235** afforded **292** in only 31% yield. Ring opening and aromatization of epoxynaphthalene **292** was accomplished using BCl_3 at low temperature. Other Lewis acids such as 9-BBN-Br gave comparable yields. Milder sources of acid such as HOAc at rt or reflux or anhydrous HCl in Et_2O proved

Scheme 73



ineffective. Introduction of the carbamoyl function occurred smoothly using NaH to afford **216** in excellent yield. Standard metalation - iodination conditions were employed to introduce iodine at C-2 of **297** in modest yield. Negishi coupling was found to be satisfactory to furnish biaryl **299**. Metalation of **216** followed by transmetalation to the arylzinc species (X = H → Li → ZnCl) followed by coupling with arylbromide **298a** afforded **299** in 60% yield. Alternatively, preparation of iodide **297** under standard

conditions followed by coupling with the arylzinc reagent derived by MHEX of **298a** (X = Br → Li → ZnCl) afforded carbamate **299** in only slightly improved yield.

Attempts at carbamoyl migration of **299** are shown in **Table 13**. Standard conditions (entry 1) afforded none of the desired product but gave the methylenedioxy cleaved derivative **300** in 40% yield, presumably the result of nucleophilic attack of LDA on the methylenedioxy group of **299**. Switching to the bulkier LiTMP (entry 2) resulted in a decreased amount of **300**; however none of the desired material was detected. In an attempt to investigate the nature of the anionic intermediates formed under the reaction conditions, the *in situ* method of Martin was attempted.[240] On warming **299** in the presence of LDA / TMSCl only SM could be detected. More forcing conditions (entry 4) produced 2 compounds which were inseparable and therefore could not be identified. Examination of the ^{1}H NMR spectrum

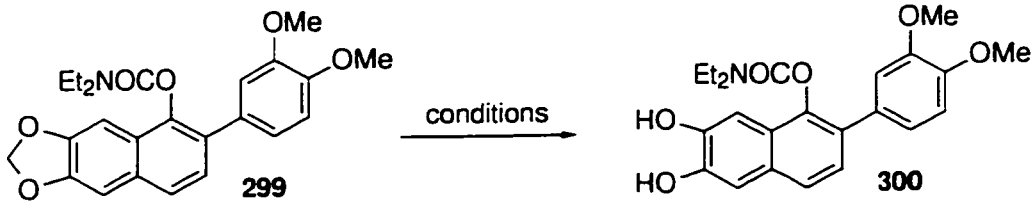


Table 13. DreM Reaction of 299

Entry	Conditions	Products (Yld, %)
1	2.5 equiv LDA / THF / 0°C → rt	**300** (43%)
2	2.5 equiv LiTMP / THF / 0°C → rt	**300** (26%)
3	2 equiv TMSCl / 5 equiv LDA / THF / -78°C → rt	**SM** (70%)
4	10 equiv TMSCl / 10 equiv LDA / THF / -78°C → rt	2 inseparable compounds
5	2 equiv *t*-BuLi / THF / -20°C → rt	**SM** (37%), **300** (22%)
6	2.5 equiv (*i*-Pr$_2$)NMgBr / THF / 0°C → rt	**SM** (quant)
7	2.5 equiv (*i*-Pr$_2$)NMgBr / THF / reflux	**SM** (quant)

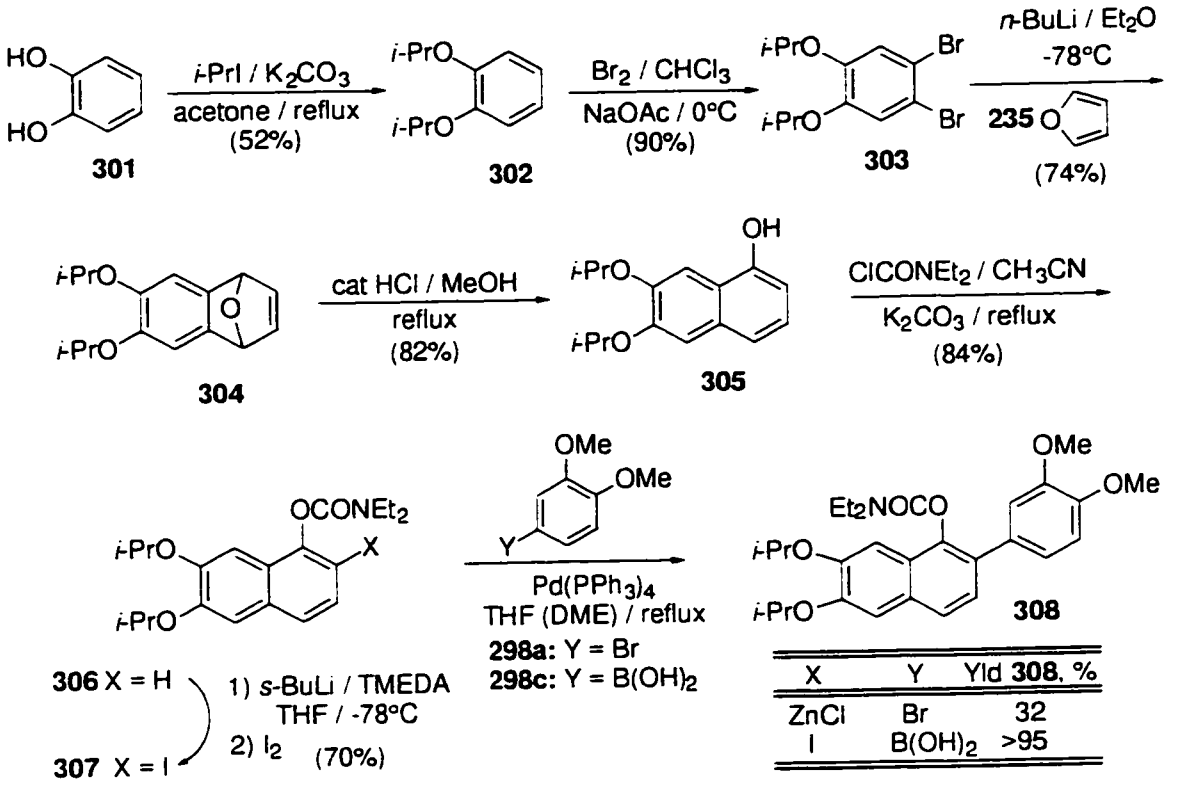
of the mixture of products showed the incorporation of TMS; however, the location of the silyl groups could not be determined. The use of alkyllithium base (entry 5) in an attempt to use the methoxy group as a DMG afforded SM accompanied by methylenedioxy cleavage. Finally, bromomagnesiumdiisopropylamide[241] was used as a less nucleophilic base. Unfortunately, only SM was recovered from reactions carried out both at rt and reflux. Clearly, the methylenedioxy group is unsuitable as a catechol PG under any DreM conditions and is therefore of no use in the total synthesis of arnottin I.

6.2 C-6, C-7 Isopropoxy Protection

The stability of the isopropoxy group to the DreM conditions **(Section 5)** suggested that its application to the synthesis of arnottin I may be feasible. To this end, the synthesis of the naphthyl carbamate was reconsidered based on the use of isopropyl groups to protect the catechol moiety **(Scheme 74)**. Protection of catechol **(301)** followed by double isopropylation and bromination proceeded without event to afford dibromide **303**. In both cases, the isolation of products was effected *via* distillation eliminating the need for chromatography. Generation of the corresponding aryne of **303** was carried out *via* metal halogen exchange and *in situ* trapping with furan afforded cycloadduct **304** in good yield. Optimization of the reaction conditions demonstrated that addition of the SM to a solution of alkyllithium reagent and furan (inverse addition) was necessary, normal addition afforded **304** in only 45% yield. Ring opening was easily accomplished *via* treatment with cat HCl. Conversion of the naphthol **305** to the corresponding carbamate **306** occurred smoothly under standard conditions. Negishi coupling of the arylzinc reagent (**306** X = H → Li → ZnCl) gave the biaryl **308** in low yield. The success of the modified Suzuki conditions ($Pd(PPh_3)_4$ / $Ba(OH)_2 \cdot 8H_2O$ / DME reflux / 1 h) in the synthesis of the gilvocarcins **(Section 5)** prompted their

application to this coupling. Gratifyingly, these conditions were found to be equally efficient, affording **308** in almost quantitative yield. Synthesis of the required boronic acid **298c** was accomplished from **298a** [1) *n*-BuLi / THF / -78°C 2) $B(OMe)_3$ 3) H^+].

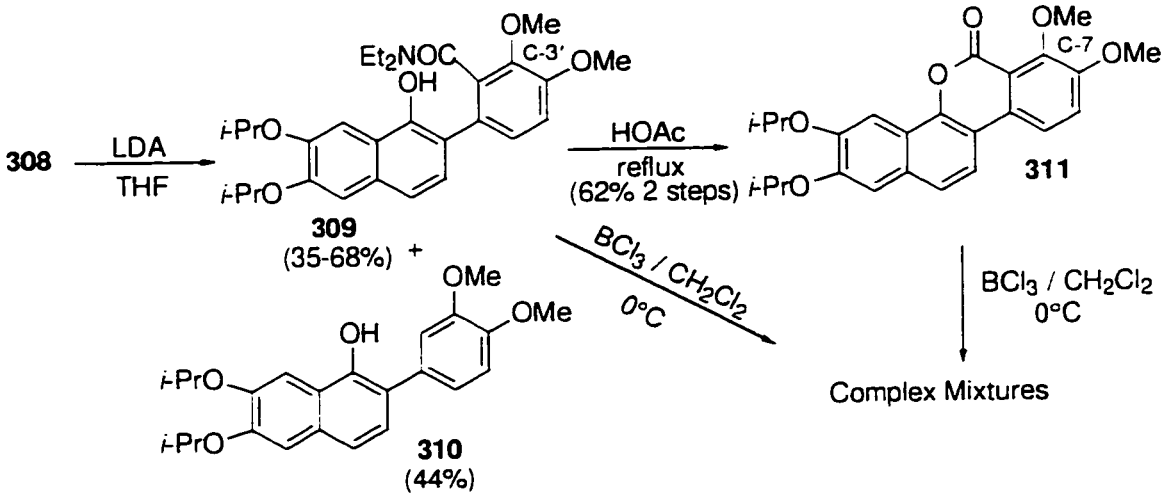
Scheme 74



In an initial migration experiment, **308** was treated with 2.5 equiv LDA furnishing **309** with no evidence of isopropyl cleavage **(Scheme 75)**. ^{1}H NMR spectral examination of the crude hydroxy amide **309** failed to clearly establish the regiochemistry of the migration reaction. For this purpose, **309** was cyclized to afford lactone **311** in 62% yield over two steps whose ^{1}H NMR spectrum clearly indicated 2 singlets and 4 doublets as required for the regiochemistry shown. Although the yield of the process was reasonable, a significant amount of SM was detected as evidenced from ^{1}H NMR analysis of the crude reaction mixture. Thus, more forcing conditions were employed. Treatment of **308** with 3.5 equiv LDA at reflux afforded the desired product

in 60% yield, comparable to the initial attempt. Treatment of **308** with 10 equiv of LDA at rt afforded **309** in decreased yield (35%) and carbamoyl cleavage occurred, giving **310** in 44% yield. The optimum yield was achieved by application of the modified conditions described in **Section 5**. Thus, sequential treatment with two portions of LDA (2.5 equiv each, separated by 6 h) at rt afforded **309** in 68% yield. Having established satisfactory migration conditions, the cleavage of the isopropoxy groups was investigated. Treatment of **311** with with BCl_3 afforded complex reaction mixtures from which products were difficult to isolate due to their insolubility. Presumably, initial complexation of the boron reagent to the carbonyl facilitates cleavage of the C-7 methoxy

Scheme 75

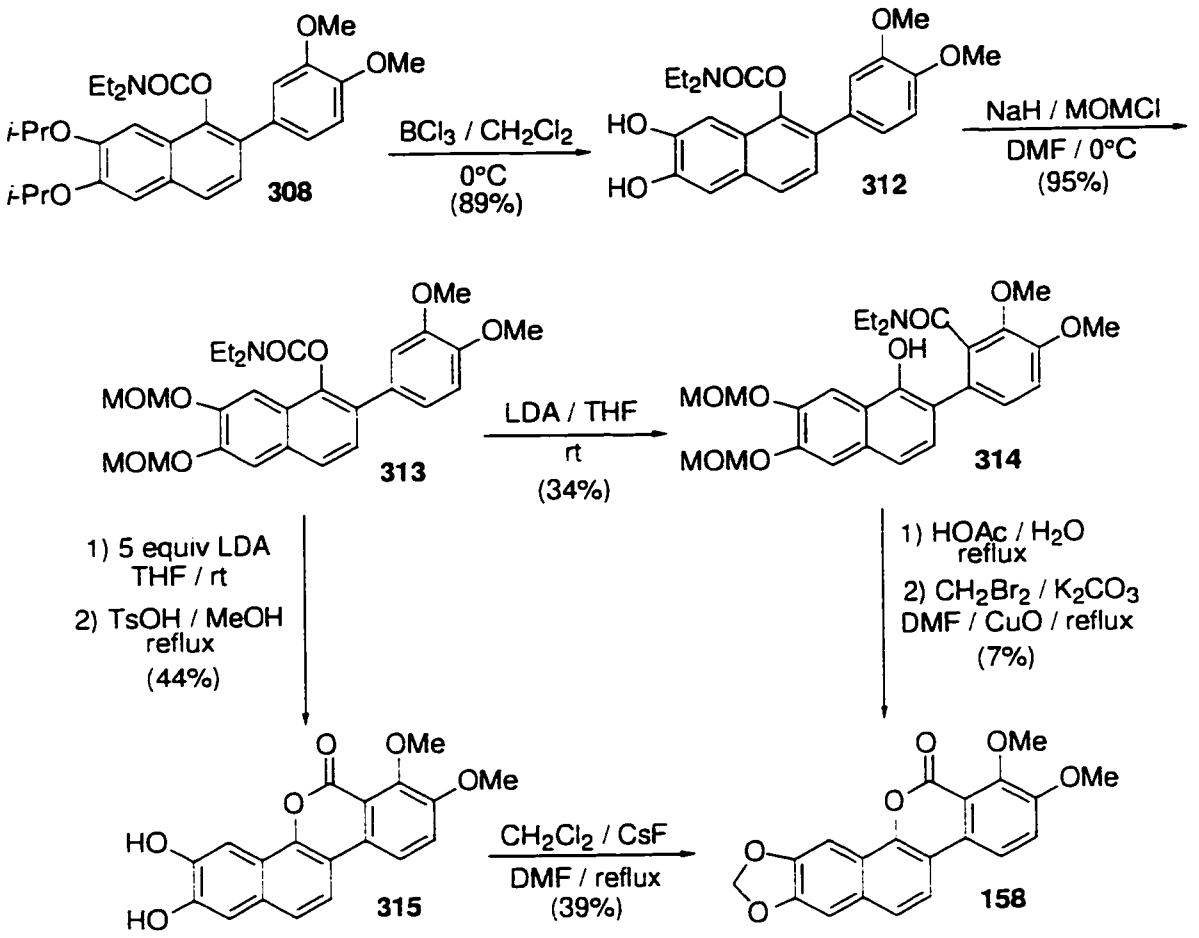


group which competed with deisopropylation. In an attempt to circumvent this problem, direct treatment of the hydroxyamide **309** with BCl_3 was considered. It was hoped that coordination of the boron reagent to the amide carbonyl would be negligible due to steric restrictions. In the event, only complicated mixtures were obtained. ^1H NMR analysis of crude reaction mixtures suggested the loss of isopropyl groups; however, demethylation at C-3′ appeared to be competitive.

6.3 C-6, C-7 MOM Protection. Completion of the Total Synthesis of Arnottin I

The difficulties associated with cleavage of the isopropyl groups in **309** necessitated a further modification of the PG strategy. Although the use of the MOM group proved quite successful in the synthesis of the gilvocarcins **(Section 5.1.3.3)**, it was initially discounted in favour of the isopropyl groups due to the insolubility of hydroxynaphtho[1,2-*b*]benzo[*d*]pyran-6-ones **287a** previously prepared by direct MOM cleavage **(Scheme 70)**. However, it was hoped that altering the cyclization conditions may allow isolation of **315 (Scheme 76)**. To this end, **308** was converted to the catechol **312** in good yield. Protection as the bis MOM ether was effected to furnish **313** in 95% yield. Initial migration attempts using standard conditions (6 equiv LDA / THF / rt) provided the desired hydroxyamide **314** in low yield. Application of the modified DreM conditions resulted in only a minor improvement in the yield. Thus, sequential treatment of **313** with three portions of LDA (2 equiv each separated by 2 h) afforded **314** in 34% yield. As expected, attempts at simultaneous cyclization - MOM cleavage resulted in formation of a non-isolable product. Similarly, subjection of the crude cyclization mixture to conditions of methylenedioxy formation[242] afforded arnottin I **158** in very low yield, establishing the presence of **315** in the reaction mixture. Unfortunately, this reaction was irreproducible and the yields were always low. Thus, alternative cyclization conditions were investigated. Treatment of **313** with LDA followed by direct cyclization with TsOH in MeOH allowed isolation of the desired catechol **315**. In this case, the product conveniently precipitated from the reaction mixture, allowing its isolation in 44% yield. As expected the catechol was extremely insoluble in the common organic solvents. Treatment of **315** with CsF in the presence of CH_2Cl_2 afforded the natural product arnottin I **158** reproducibly in 39% yield. The

Scheme 76



conditions of Clark[243] (**316** → **158**) were chosen over the CuO mediated process[242] (**315** → **158**) for this transformation based on a literature survey which suggested that the fomer method was the most reliable. Finally, synthetic arnottin I was shown to be identical to the natural product by comparison of physical and spectral data (See Experimental section).

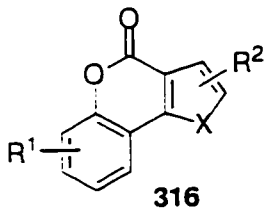
6.4 Conclusions

The DreM - carbamoyl migration strategy served as the key step in the synthesis of a naphtho[1,2-*b*]benzo[*d*]pyran-6-one **315** as an intermediate in a total synthesis of arnottin I **(Scheme 76)**. Preparation of the required biaryl was accomplished *via* the Suzuki cross coupling reaction **(Scheme 74)**. The methylenedioxy group was shown to be incompatible with the DreM conditions and the MOM group was employed leading to a total synthesis of arnittin I **158** in 11 steps and 1.8% overall yield.

7. DreM - Based General Synthesis of Heteroaromatic Fused Dibenzopyranones

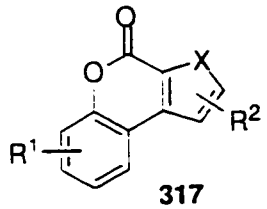
7.1 Introduction

Heteroaromatic analogues of dibenzopyranones **316** - **319** constitute large and diverse classes of natural and synthetic products which are of biological and medicinal interest. For this reason, and in conjunction with their structural similarity to coumarins[244] (**320 and 321**), which possess a wide range of biological activity, these



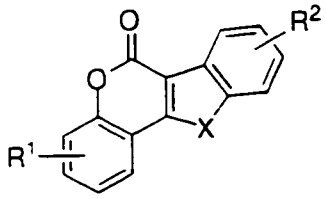
316

X = O furo[3,2-c]coumarins
X = S thieno[3,2-c]coumarins
X = NR pyrrolo[3,2-c]coumarins



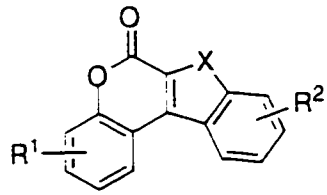
317

X = O furo[2,3-c]coumarins
X = S thieno[2,3-c]coumarins
X = NR pyrrolo[2,3-c]coumarins



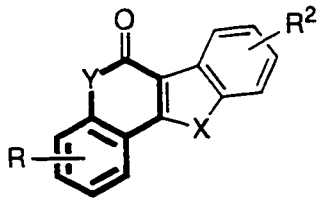
318

X = O coumestans
X = S thiocoumestans
X = NR azacoumestans



319

X = O isocoumestans
X = S isothiocoumestans
X = NR isoazacoumestans



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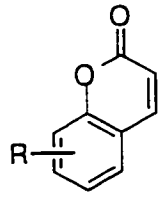


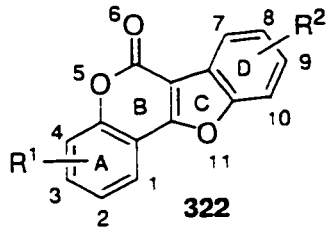
321

compounds have attracted considerable synthetic attention. This section presents a review of the chemistry and synthesis of these classes of molecules preceeding the description of a general synthesis of certain members based on the DreM - carbamoyl migration protocol.

7.2 Coumestans

7.2.1 Occurrence and Biological Activity

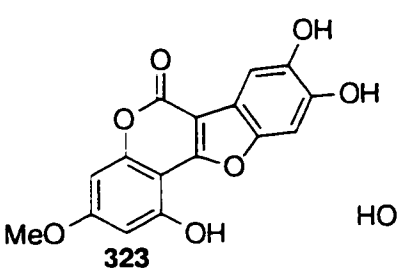
Compounds with the trivial name coumestans **(322)** or 6*H*-benzofuro[3,2-*c*]benzo[*e*]pyran-6-ones are a relatively large class of natural products isolated mainly from the families *Leguminosae*, *Papilionacae* and *Compositae*.[244] Naturally occurring coumestans are characterized by the predominance of oxygen substituents in the C-3 and C-9 positions as hydroxy and methoxy groups or fused pyran and furan ring systems. The unsubstituted parent system, coumestan **(322)** ($R^1 = R^2 = H$) does not occur in



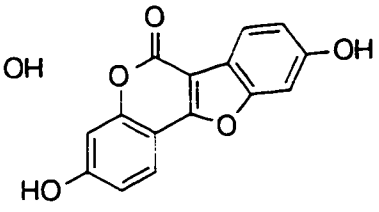
322

nature. Representative examples include wedelolactone **(323)**, the first isolated coumestan, from the leaves of *Wedelia caledulacae*,[245] as well as the simple derivative, coumestrol **(324)**, which was isolated from ladino clover[246] and alfalfa.[247] Chakravarti and co-workers[248] isolated psoralidin **(325)**, containing a C-2 isopentenyl group, from the seeds of *Psoralea corylifolia*. The methylenedioxy containing medicagol **(326)** was also isolated from alfalfa (*Medicago sativa*) by Livingston.[249] Erosnin **(327)**, containing

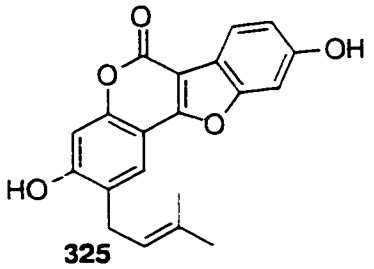
a furan fused at the 2,3-positions was isolated by Eisenbeiss[250] from the seeds of yam beans (*Pachyrrhizus erosus*) and the interesting chromene containing plicadin **(328)** was recently isolated from the sub-tropical herb *Psoralea plicata* by Rasool and co-workers.[251]



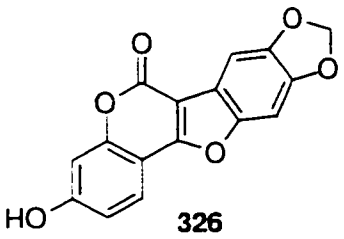
323



324



325



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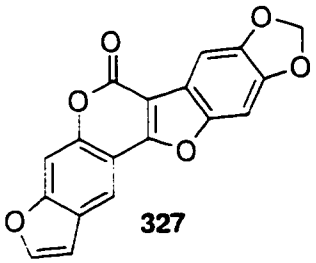
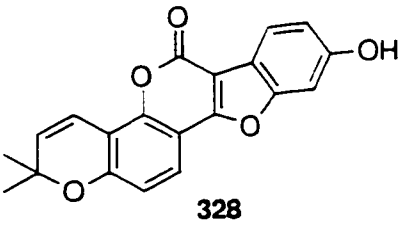
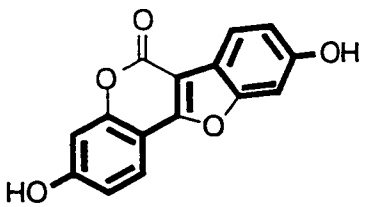


327

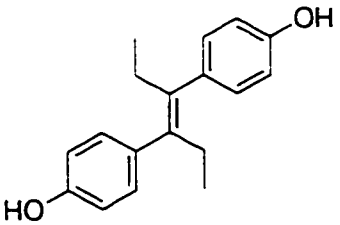


328

The biological properties of coumestans are diverse. Coumestrol has been shown to display potent estrogenic activity which is thought[252] to arise from the stilbene-like substructure **329** similar to that found in the potent estrogen diethylstilbestrol **(330)**. In fact, the related tamoxifen **(331)**, is a therapeutic agent for the treatment of breast cancer.[253] Structure activity relationship (SAR) studies investigated this activity based on



329



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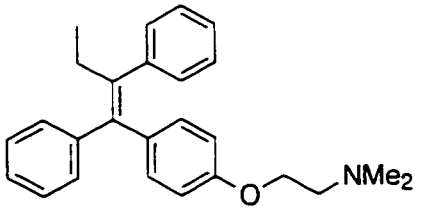


331

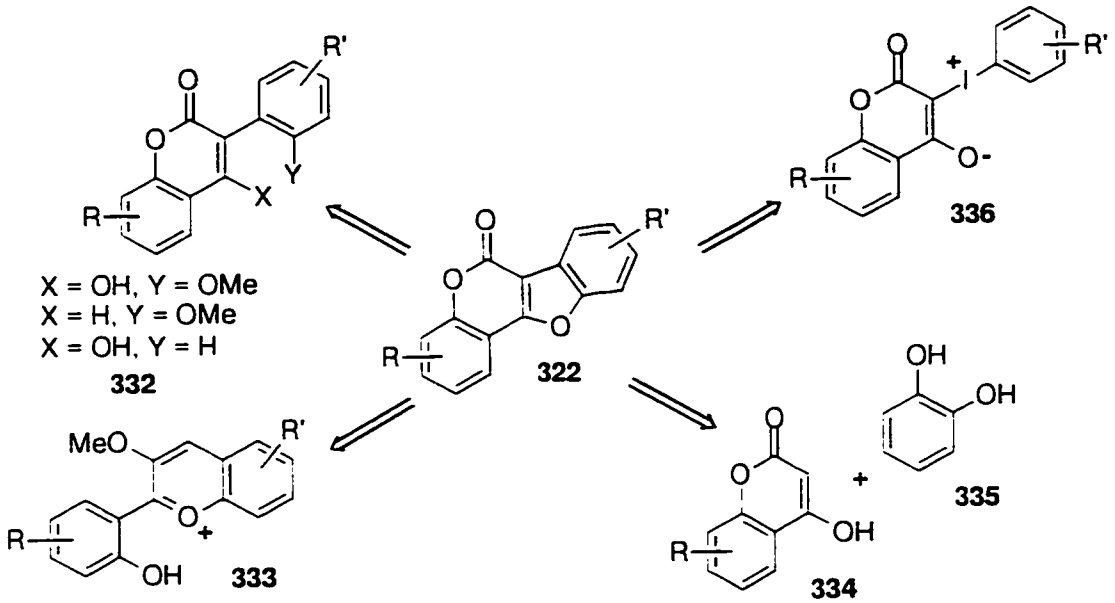
oral administration of several coumestan derivatives to immature mice.[254,255] It was determined that the presence of the hydroxyl groups in the 3- and 9-positions was essential for activity and that the presence of other hydroxyl functions decreased the observed activity. Similarly, etherification of the C-3 and C-9 hydroxyls reduced the activity to almost nil. Recently a synthetic derivative of coumestrol was shown to be a potent estrogen antagonist as well as being a hypercholesteremic agent.[256]

In general, coumestans display antibiotic activity[257] and an important aspect of their biological properties is accumulation in plants in response to injury or infection. Such agents are known as phytoalexins, and it is believed that these increases in antibiotic concentration constitute part of the mechanism for disease resistance in some plants.[258] Thus, levels of coumestrol in clover were shown to be much higher in virus-infected plants than in control specimens.[258] Other properties of some coumestans include insecticidal activity[259] as well as toxicity to fish.[260]

7.2.2 Synthesis of Coumestans

The literature regarding the synthesis of coumestans is vast; fortunately, several excellent reviews[261] have been compiled. Synthetic methods to prepare the coumestan ring system consist of four types as illustrated retrosynthetically **(Scheme 77)**. Cyclization of 3-arylcoumarins **332** can be effected by acid catalysis,[262] oxidative methods,[263] or palladium catalyzed tactics.[264] Flavyllium salts **333** can be converted to coumestans based on the method of Jurd.[265] Wanzlick's oxidative coupling[266] of catechol **(335)** with coumarins **333** is an efficient method, and finally, iodonium ylides **336** may be converted to coumestans *via* thermal rearrangement followed by photoinduced or transition metal catalyzed cyclization.[267]

Scheme 77

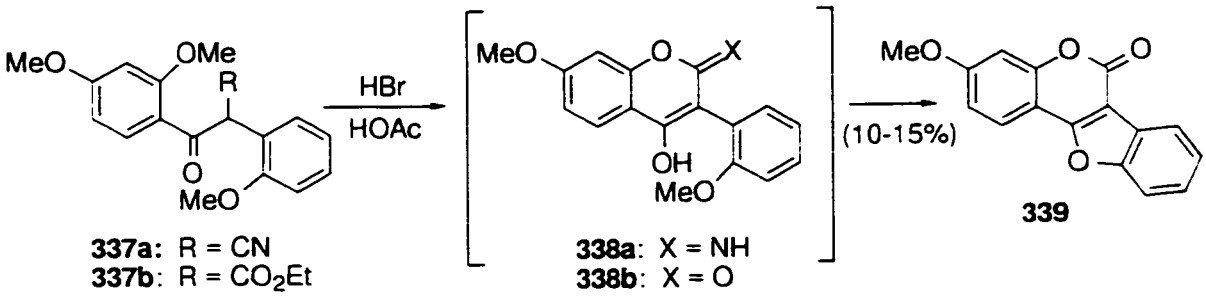


7.2.2.1 Cyclization of 3-Arylcoumarins

Chatterjea[236] and Kawase[268] were the first to demonstrate the acid mediated cyclization of 3-arylcoumarins. Thus, treatment of nitrile **337a** and ester **337b** with HBr in glacial acetic acid afforded coumestan **339** *via* the imino coumarin **338a** and coumarin **338b** respectively, as intermediates **(Scheme 78)**. This method, although convenient, encounters difficulty as it relies on two successive selective demethylations of the 2- and 2′-methoxy groups. This method does not differentiate methyl ether cleavage elsewhere in the molecule, which may occur competitively, resulting in complex reaction mixtures. Other reagents that have been used to effect this type of cyclization include other mineral acids[269] (e.g. HI, HCl), $AlCl_3$,[268] and pyridine hydrochloride.[270] Variations of this method are possible[271] and these often involve preparation of the appropriately substituted 3-aryl-4-hydroxycoumarins of type **338b**, as starting materials. In spite of the selectivity problems and the lengthy preparation of starting materials, this

method has been used for the synthesis of several naturally occurring coumestans, for example wedelolactone[272] **(323)** and coumestrol[269] **(324)**.

Scheme 78



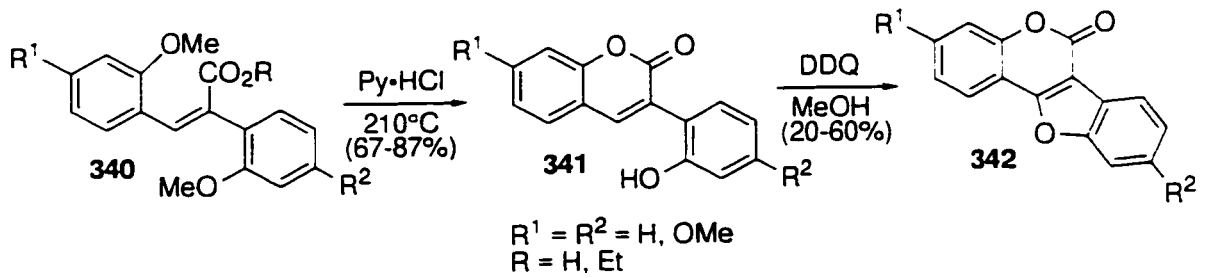
337a: R = CN
337b: R = CO_2Et

338a: X = NH
338b: X = O

339

The oxidative cyclization of hydroxycoumarin derivatives **341** to substituted coumestans **342 (Scheme 79)** is a relatively recent method demonstrated independently by Pandit[263] and Mali.[273] Both studies involve the preparation of cinnamic acid derivatives **340** by different (and lengthy) methods. Cyclization to the coumarin was then accomplished using pyridine hydrochloride. Subjection of **341** to DDQ furnished

Scheme 79



340

341

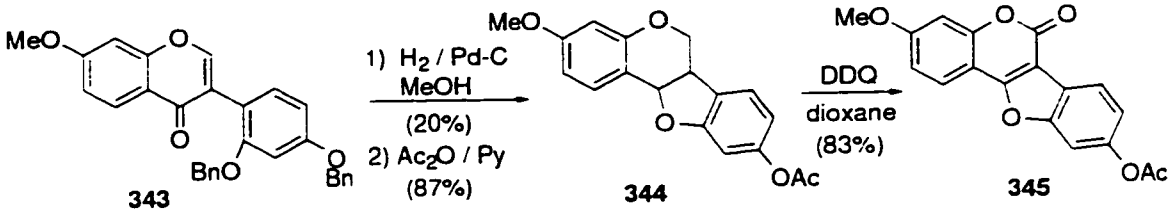
342

$R^1 = R^2 = H$, OMe
R = H, Et

the corresponding coumestans **342** in moderate yields (20-60%). The use of DDQ as the oxidizing agent represents an improvement over the seminal study by Kurosawa[274] who used $Pb(OAc)_4$ giving poor yields (10-20%).

Related methods which make use of oxidative processes as a key step are also known. Prasad and co-workers[275] have shown that isoflavone **343** may be converted to the corresponding pterocarpan **344** by reductive cyclization. After acetylation, conversion to the coumestan **345** was effected *via* DDQ mediated oxidation **(Scheme 80)**. Although the yield of the oxidation step is high, the reductive cyclization is inefficient. An advantage of this method is the availability of the required isoflavones by the method of Farkas.[276]

Scheme 80

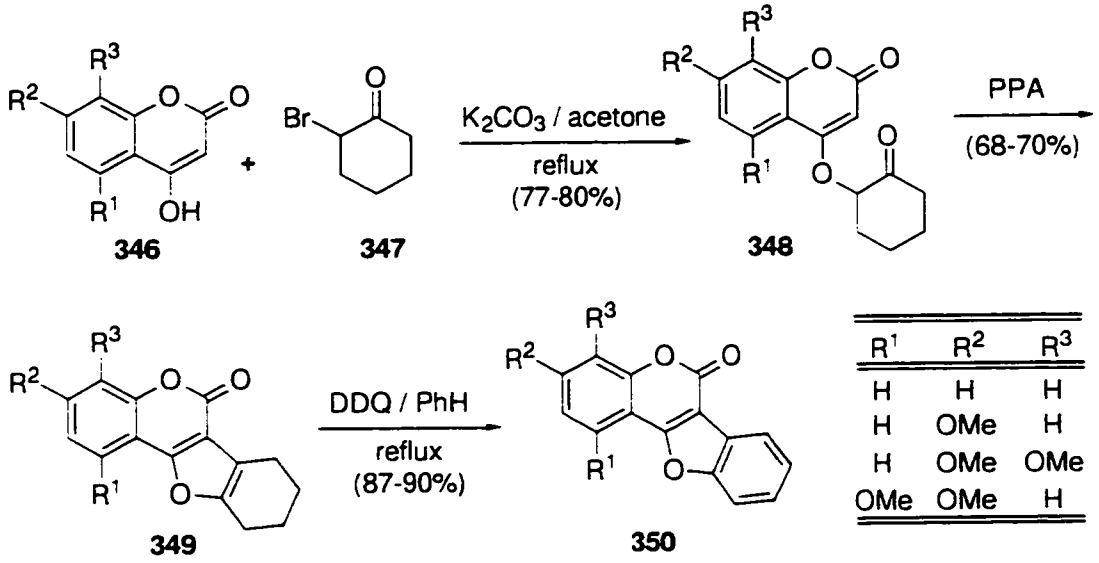


In a modification of the original procedure by Subba Rao,[277] Singh[278] has shown that the condensation of hydroxycoumarins **346** with 2-bromocyclohexanone **(347)** produced ethers **348** which, on cyclization with PPA, afforded the tetrahydrocoumestan derivatives **349**. Aromatization with DDQ then furnished the coumestans **350** **(Scheme 81)**. The yields in this sequence are generally good, affording the coumestans in 60-63% yield over the cyclization and dehydrogenation steps; however, no cases were examined which included substituents in the cyclohexanone moiety.

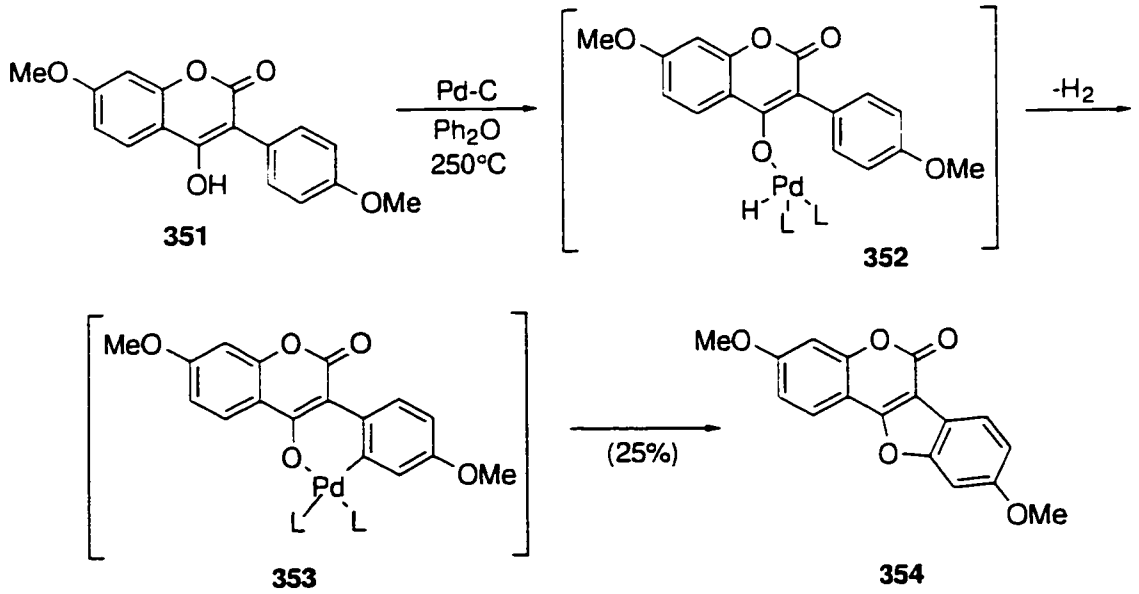
The palladium mediated cyclodehydrogenation of coumarin **351** has been used by Kappe[264] **(Scheme 82)**. Presumably this reaction occurs *via* initial oxidative addition of Pd(0) to the hydroxy group to give an intermediate such as **352**. Insertion of Pd into the remote C-H bond of the neighboring phenyl ring produces metallocycle **353**. Reductive elimination results in ring closure to afford coumestan **354**. Using this

method, Kappe prepared coumestrol, coumestrol dimethyl ether[264] and several azacoumestans.[279,280]

Scheme 81



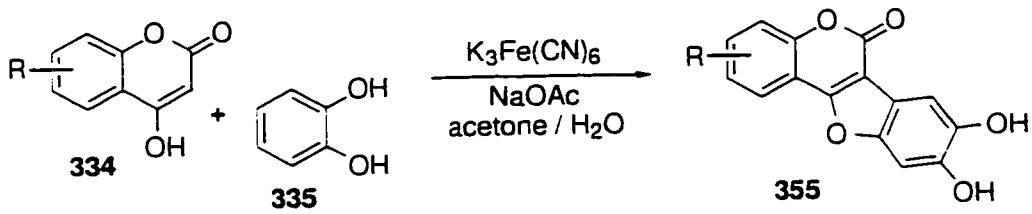
Scheme 82



7.2.2.2 Wanzlick Oxidative Coupling

The elegant procedure developed by Wanzlick[266] involves the reaction of catechol (**335**) with coumarins **334** in the presence of potassium ferricyanide to afford coumestans **355** in a single step (**Scheme 83**). The reaction is high yielding, occurs under mild conditions and has been used for the synthesis of many naturally occurring coumestans, including wedelolactone (**324**). Unfortunately, the process is somewhat limited in scope in that only 8,9-dioxygenated coumestan derivatives are available. In a modification of this procedure, Tabakovic[281] used electrochemical oxidation as an alternative method for oxidation. The yields in the process are high (90-95%); however, the reaction requires high dilution and is therefore of limited synthetic value. Similarly, enzymatic oxidation using mushroom tyrosinase has been employed by Bhalerao and co-workers[282,283] in a suggested biomimetic approach to coumestans.

Scheme 83

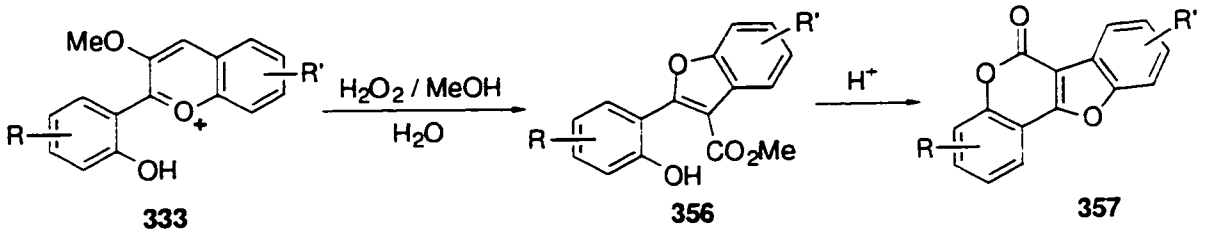


7.2.2.3 Jurd Oxidation of Flavyllium Salts

Jurd[265] has demonstrated that the hydrogen peroxide mediated oxidation of flavyllium salts **333** occurs smoothly to generate hydroxy esters **356** (**Scheme 84**). Cyclization with mild acid leads to **357**, a transformation which often occurs under the reaction conditions. The reaction sequence is high yielding and many substitution

patterns are tolerated affording an advantage over the Wanzlick method. A further advantage of this method is the wide availability of flavyllium salts.[284]

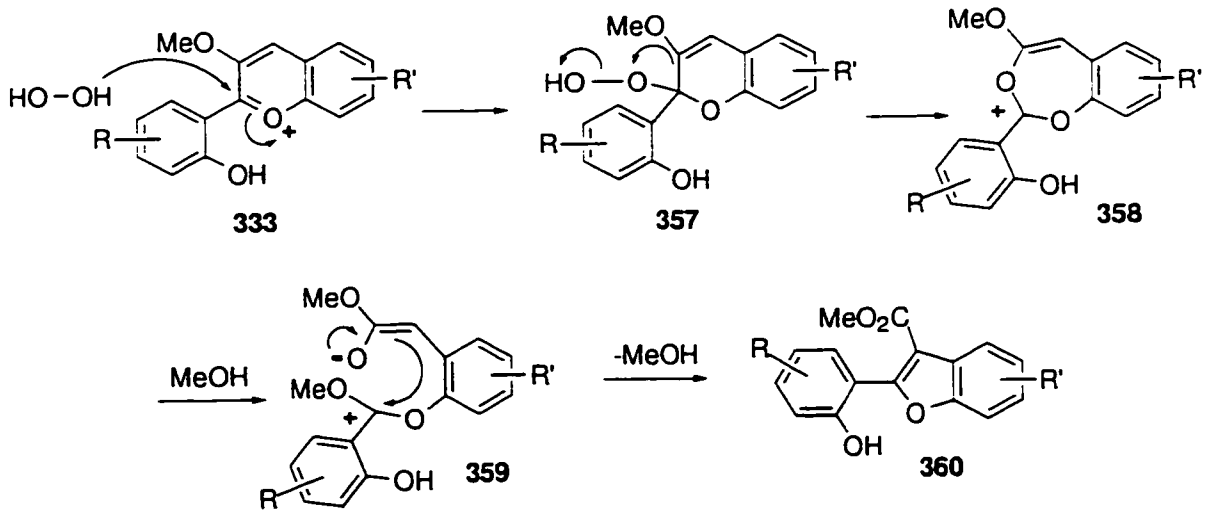
Scheme 84



333 **356** **357**

The mechanism[284] of the reaction is believed to involve H_2O_2 addition to **333** followed by a Baeyer-Villiger type migration to afford cation **358 (Scheme 85)** which rearranges to give substituted benzofurans **360** after elimination of MeOH. Through the use of the Jurd method, syntheses of several naturally occurring coumestans have been effected including trifoliol,[285] coumestrol[286] and several highly oxygenated derivatives of coumestrol.[287]

Scheme 85

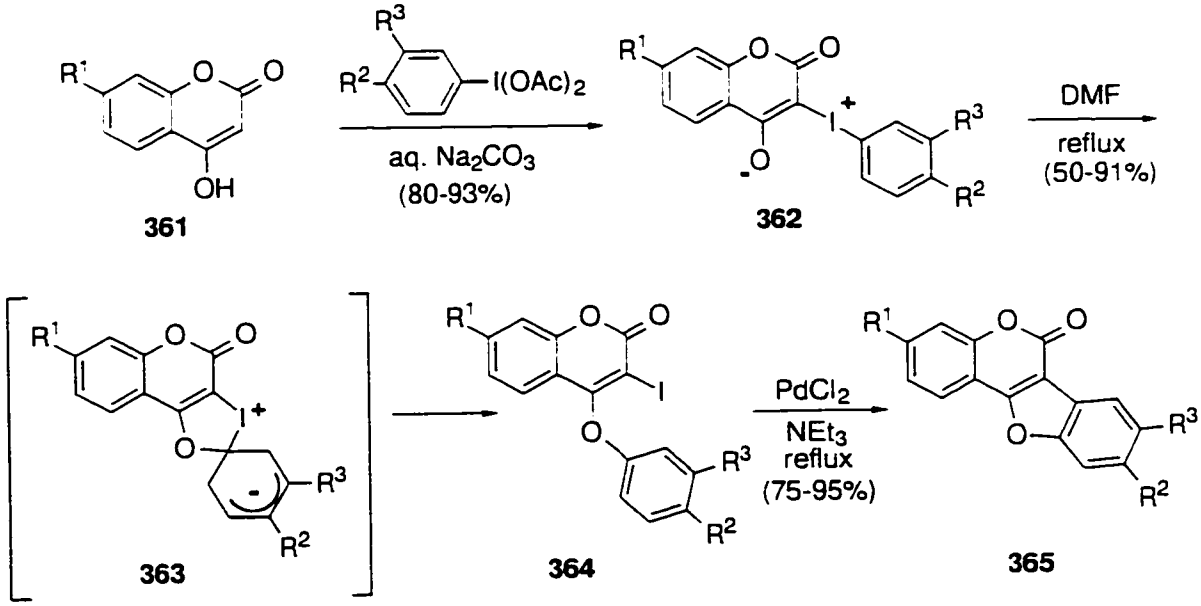


333 **357** **358** **359** **360**

7.2.2.4 Synthesis of Coumestans *via* Iodonium Ylides

Kappe[267, 288] has shown that coumestans can be prepared from iodonium ylides **362 (Scheme 86)**. Thus, treatment of coumarins **361** with iodosyl arenes, prepared *in situ* from diacetoxyiodoarenes, afforded the corresponding ylides **362** in good yields. Thermal rearrangement to the iodocoumarins **364** is thought to occur *via* the spiro intermediate **363** in a variation of the Smiles rearrangement.[289] Intramolecular Pd(II) - catalyzed coupling afforded the corresponding coumestans **365** in good yields (75-95%). Alternate conditions for the formation of the key bond were studied and it was found that methods based on the Ullmann reaction using copper and copper salts failed whereas photocylization was successful albeit in very low yields.

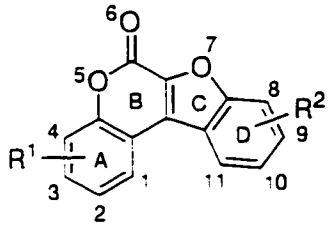
Scheme 86



R^1, R^2, R^3 = H, OMe,

7.3 Isocoumestans

Compounds containing the 6*H*-benzofuro[2,3-*c*]benzopyran-6-one or isocoumestan ring system **366** have not yet been found in nature. However, their structural similarity to the coumestans has resulted in considerable attention to the synthesis of this class of heterocycles. The first synthesis of this substructure **369** was reported by King and co-workers[290] in 1948 *via* the sulfuric acid - mediated Pechmann condensation of resorcinol derivatives **(367)** with ester **368** in 87% yield **(Scheme 87)**.

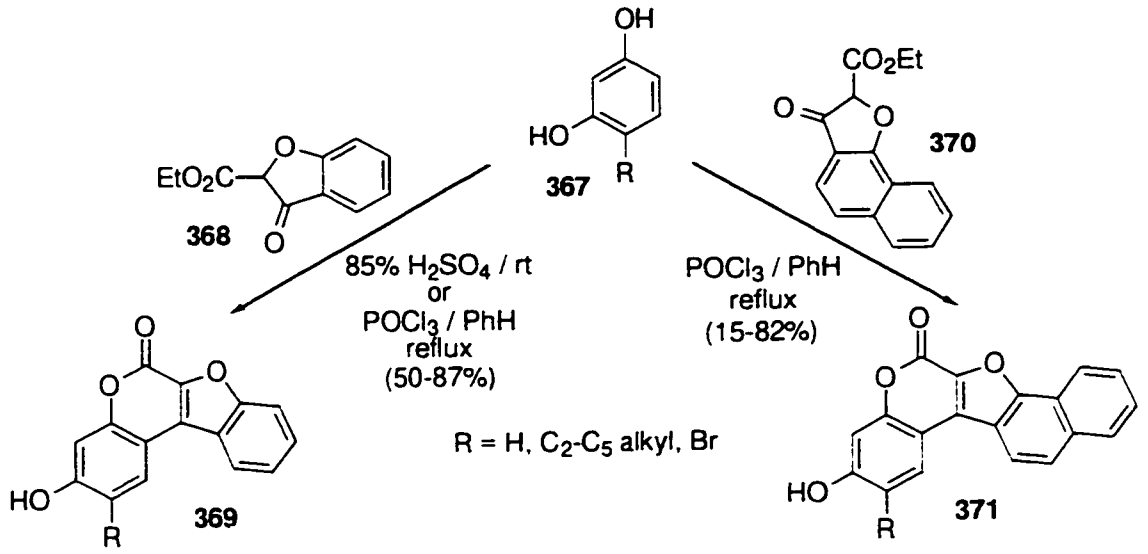


366

During the course of studies toward the preparation of analogues of cannabinoids,[291] Mahesh[292,293] adopted the Pechmann method for the preparation of a number of alkyl substituted isocoumestans **371 (Scheme 87, 367 → 371)**. In this case, $POCl_3$ instead of mineral acid was used for the reaction. The yields are variable (15-82%), and the benzofused ester **370** was the only variation which allowed substitution of the D ring. Recently, Soman and Trivedi have applied this methodolgy in conjunction with the Claisen rearrangement to a synthesis of pyrano[294] and furo[295] fused isocoumestan derivatives.

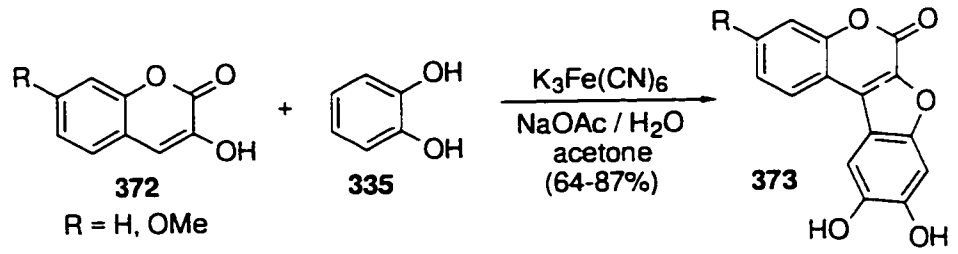
The versatile Wanzlick oxidative coupling of catechol with coumarins has been modified by Chatterjea[296,297] to include 3-hydroxycoumarins **372 (Scheme 88)**. As in

Scheme 87



the original method for the synthesis of coumestans, the yields of the reaction are good (64-78%); however, the scope of the reaction is limited due to the use of catechol derivatives as starting materials and only 9,10-dihydroxyisocoumestan derivatives are produced. In 1977, Sundaramurthy[298] showed that *p*-benzoquinone reacts with 3-hydroxycoumarin in a Wanzlick type oxidation to give 10-hydroxyisocoumestan in good yield.

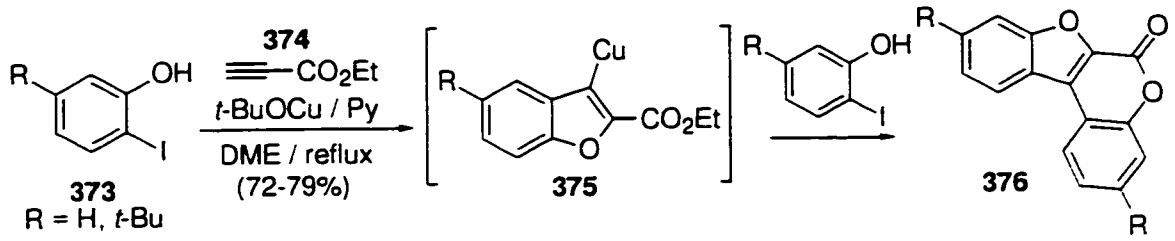
Scheme 88



Recently, Nilsson[299] and co-workers have utilized an extension of the Castro[300] synthesis of benzofurans to prepare isocoumestans. Treatment of *o*-iodophenols **373** **(Scheme 89)** with *t*-BuOCu[301] in the presence of ester **374** affords isocoumestans **376** in good yield in a single step. The cuprated benzofuran **375** was proposed as an

intermediate which presumably undergoes coupling with a second iodophenol followed by lactonization to afford the product. The scope of this highly convergent method was not investigated, and only two compounds have been prepared (R = H, R = *t*-Bu). Other, less efficient methods for the preparation of the bare isocoumestan ring system include the condensation of 2,2'-dihydroxyacetophenone with diethyl bromomalonate[302] or with *N,N*-diethylchloroacetamide in the presence of $POCl_3$[303] to give isocoumestan in a single step. Furthermore the scope of these classical processes has not been investigated.

Scheme 89

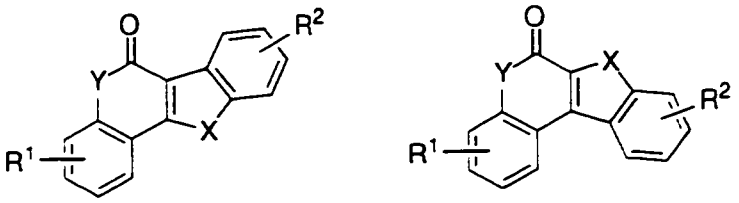


7.4 Azacoumestans

7.4.1 Introduction

Azacoumestans, or indolocoumarins **(377 and 378)** are known with both possible indole ring fusions. Diazacoumestans **(377c** and **378c)** are the most well known in the family of compounds. None of these ring systems have ben found in nature, however, interest in the synthesis of these compounds arises from their coumarin substructure **(320, Section 7.1)**, as well as the finding that certain azacoumestan derivatives of type **377a** possess antiosteoporotic activity.[304] A comprehensive review by Kappe[261d] encompasses diazacoumestans **(377c, 378c)** as well as azacoumestans of

type **377a** and **378a** which are beyond the scope of the this discussion. This section will only present the syntheses of 6*H*-indolo[2,3-*c*]benzo[*e*]pyran-6-ones **(377b)** and 6*H*-indolo[3,2-*c*]benzo[*e*]pyran-6-ones **(378b)**.



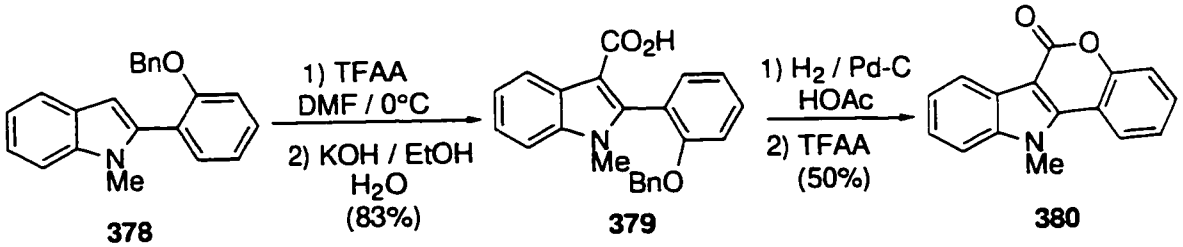
377 **378**

a: X = O Y = NR
b: X = NR Y = O
c: X = NR Y = NR

7.4.2 6*H*-Indolo[3,2-*c*]benzo[*e*]pyran-6-ones

Bourdais[305] reported the first synthesis of azacoumestan **380** by a rather lengthy route **(Scheme 90)**. Benzylation of *N*-methyl-2-(2′-hydroxyphenyl)indole, prepared by the Fischer indole synthesis, afforded ether **378**. Treatment of **378** with TFAA followed by alkaline hydrolysis gave the carboxylic acid **379** necessary for cyclization. Hydrogenolysis of the benzyl ether followed by cyclization *via* the mixed anhydride afforded indolocoumarin **380** in 10% overall yield. A more efficient method, also using

Scheme 90

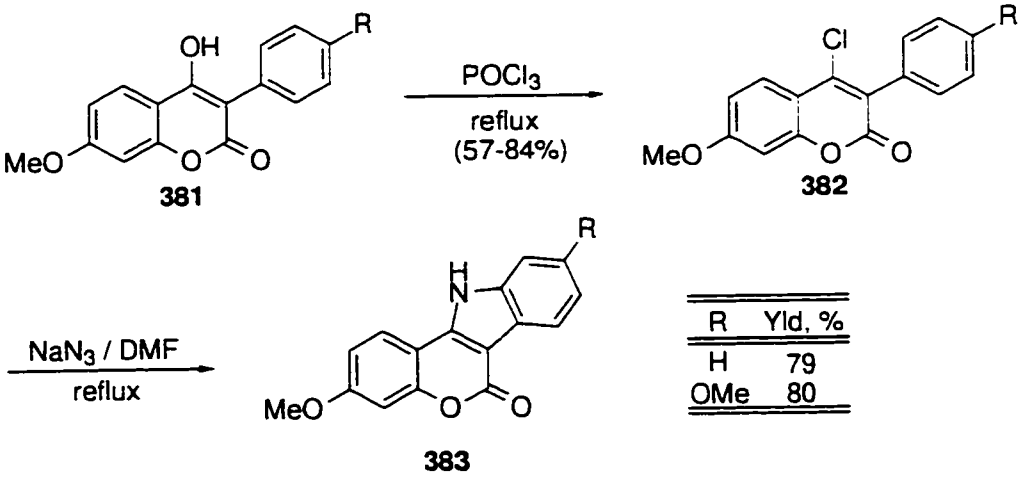


378 **379** **380**

N-methyl-2-(2′-hydroxyphenyl)indole as the starting material, was reported by Bergmann.[306] Reaction of this hydroxyindole with phosgene in dioxane afforded **380** in a single step in 83% yield. In the reactions of both Bourdais and Bergmann only the parent compound was prepared, and therefore the reactions are of unknown scope.

Kappe[307] has offered the only other contribution to the synthesis of indolo[2,3-*c*]coumarins **(Scheme 91)**. Conversion of 4-hydroxyl-3-arylcoumarins **381** into the corresponding chlorides **381** was easily achieved using $POCl_3$. Treatment of the chloride with sodium azide in DMF at reflux afforded the azacoumestans **383** in high yield. The expected intermediate azide derived from **382** was isolated when the reaction was performed at rt. Similarly, Kappe has also shown that cyclization of the azide isolated in this way may be carried out thermally or photolytically to give **383**.[308] This method offers the advantage that the 4-hydroxy-3-arylcoumarins required as starting materials are available by the cyclization methods described for coumestan synthesis **(Section 7.2.2.1)**.

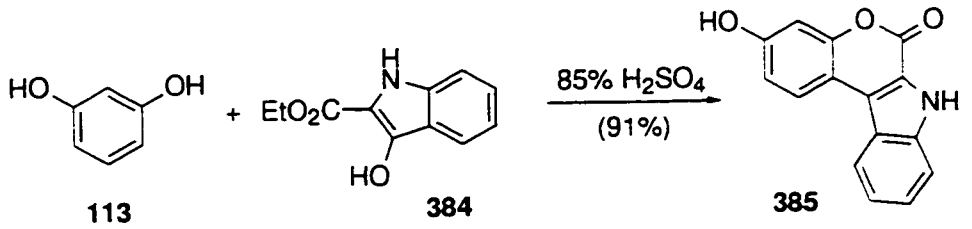
Scheme 91



7.4.3 6*H*-Indolo[2,3-*c*]benzo[*e*]pyran-6-ones

Relatively few methods are available for the preparation 6*H*-indolo[3,2-*c*]benzo[*e*]pyran-6-ones (isoazacoumestans) **385**. The first[290] was a modification of King's method for the synthesis of 3-hydroxyisocoumestans based on the Pechmann condensation.[192] Thus, treatment of hydroxyindole **384** and resorcinol in the presence of sulfuric acid afforded the indolocoumarin **385** in excellent yield **(Scheme 92)**. Only 3-hydroxyindolocoumarin **385** was prepared and therefore the scope of the reaction is unknown.

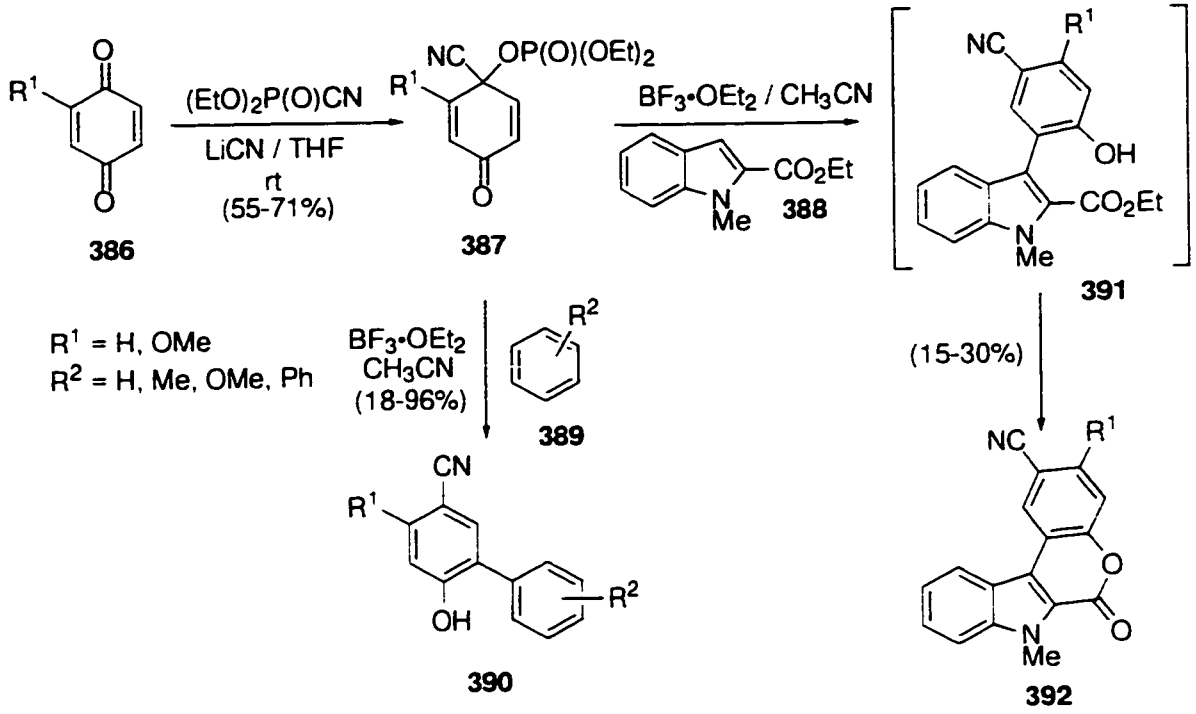
Scheme 92



113 **384** **385**

The only other report on the synthesis of indolo[3,2-*c*]benzo[*e*]pyran-6-ones appeared in 1987 by Kurihara and co-workers.[309] During the course of studies towards the Meerwein-like arylation of cyanophosphonate **387** **(Scheme 93)** for the synthesis of a series of biaryls **390**, it was shown that, in the reaction of **387** with indole **388**, intermediate hydroxyester **391** was generated which spontaneously cyclized affording indolocoumarins **392**. The authors suggested that the reaction proceeds by initial coordination of the Lewis acid to the phosphonyl oxygen followed by S_N2' attack by the arene **388** or **389** to generate the corresponding biaryls. The yields of the reaction of **388** with **390** are generally poor to good; however, those for the synthesis of **392** were lower (15-30%).

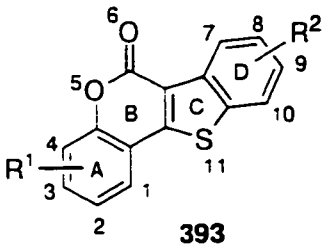
Scheme 93



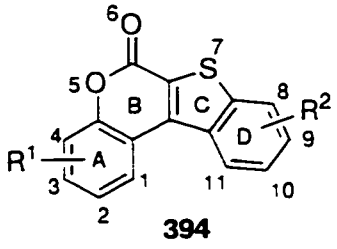
7.5 Thiacoumestans

There exists but one method for the synthesis of thiacoumestans or 6*H*-benzothieno[3,2-*c*]benzo[*e*]pyran-6-ones (**393**). At the time of the preparation of this thesis, the corresponding isothiocoumestan **394** was an unknown ring system. Heindel and co-workers[310,311] established an effective synthesis of thiacoumestans based on the condensation of thianaphthen-2-one **396** with salicylaldehydes **395a-g (Scheme 94)** *via* the intermediate dihydrothianaphthenylcoumarins **398a-g (Table 14)**. Dehydrogenation with DDQ provided the corresponding unsaturated derivatives **397a-g**. In the case of the nitro aldehyde **395f**, none of the desired dihydrothiacoumestan was isolated. The initial condensation product was intercepted by the solvent, affording the

corresponding ethyl ester. Switching reaction solvents to the less nucleophilic *t*-BuOH generated the desired product **398f**. Recently, Meegan[312] and co-workers have used this method to prepare a series of compounds of type **393** as intermediates for the preparation of 2-aryl-3-hydroxymethylbenzothiophenes, by LAH reduction, for testing as antifungal agents.



393



394

Scheme 94

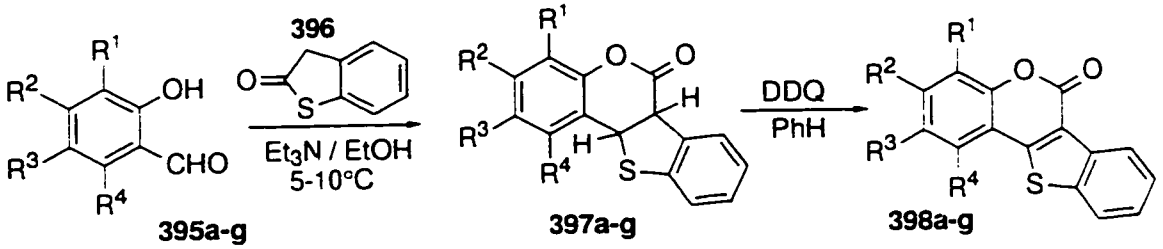


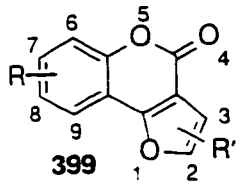
Table 14. Preparation of 6*H*-Thianaphthenyl[3,2-*c*]benzo[*e*]pyran-6-ones (398a-g)

395	R^1	R^2	R^3	R^4	Yld %, 397	Yld %, 398
a:	H	H	H	H	79	75
b:	OMe	H	H	H	80	66
c:	H	OMe	H	H	82	66
d:	H	H	OMe	H	71	57
e:	Cl	H	H	H	34	59
f:	NO_2	H	H	H	0	55
g:	H	H	benzo		76	72

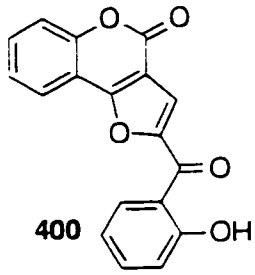
7.6 Furocoumarins

7.6.1 4*H*-Furo[3,2-*c*]benzo[*e*]pyran-4-ones

Initially, interest in the synthesis of furo[3,2-*c*]coumarins **399** arose as a result of their structural relationship to compounds with anticoagulant properties. For example, 2-benzoyl substituted furocoumarin **400** was prepared, and shown to have potent long lasting anticoagulant activity without hemorrhaging properties.[313] The structural similarity of this type of furocoumarins to the coumestans has also fueled this synthetic interest.



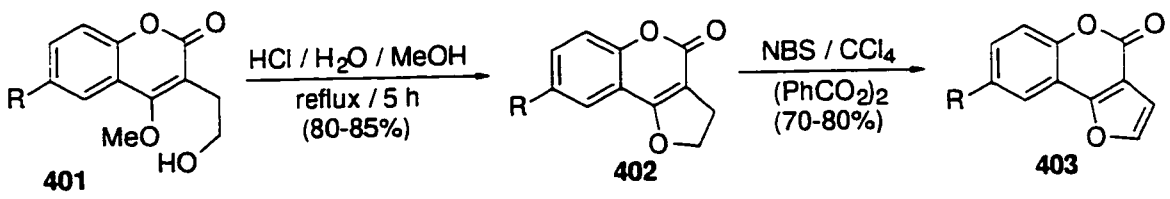
399



400

In the first synthesis of furo[3,2-*c*]coumarins, Kobayashi and co-workers[314] effected cyclization of 4-methoxy-3-hydroxyethylcoumarins **401** under acidic conditions

Scheme 95



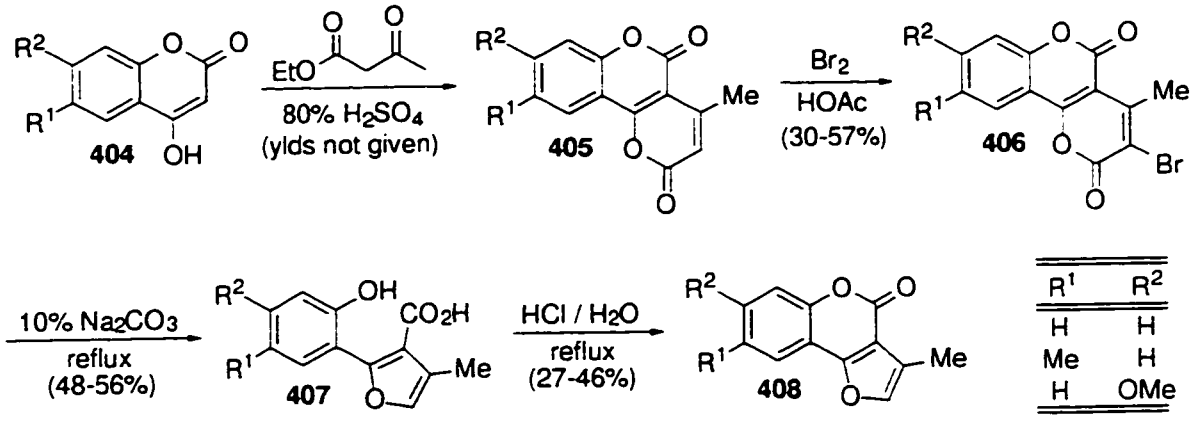
401 **402** **403**

R = H, Br, NO_2

to afford the dihydro derivatives **402** in good yield **(Scheme 95)**. Dehydrogenation was accomplished *via* radical initiated bromination and *in situ* elimination of HBr to give **403**. Although the yields are good, the scope of the process was not investigated.

Dholakia and Trivedi[315] reported a multistep synthesis of **408 (Scheme 96)** which begins with the Pechmann condensation of ethyl acetoacetate with 4-hydroxycoumarins **404** to yield pyranocoumarins **405** (yields not given). Ring contraction of bromides **406**, obtained from bromination of **405**, was accomplished using aqueous Na_2CO_3. Cyclization of the hydroxy acids **407** occurred in modest yields to afford the furocoumarins **408**.

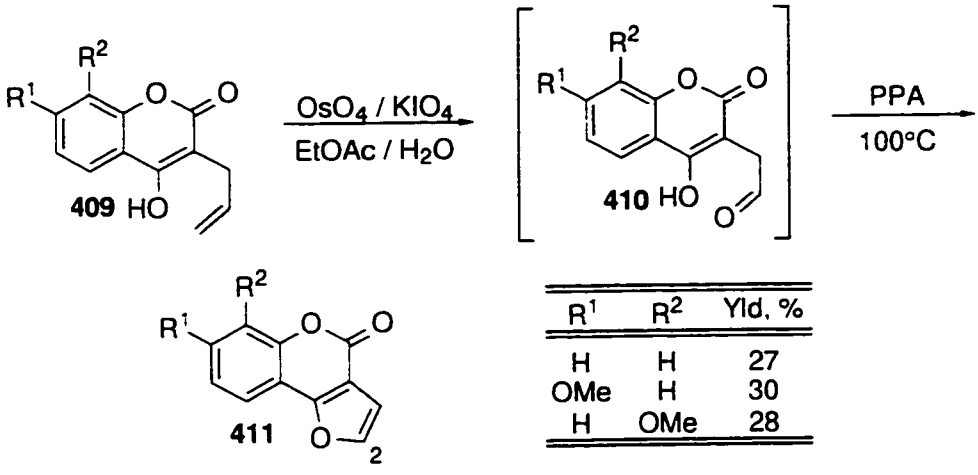
Scheme 96



In a classical method for furocoumarin construction, Ahluwalia and co-workers[316] subjected 4-hydroxy-3-allylcoumarin **409**, to dihydroxylation and periodate cleavage to afford the intermediate aldehyde **410** which was directly cyclized and dehydrated in the presence of PPA to give the furocoumarins **411 (Scheme 97)**. The yields of this process were poor and the scope has not been explored. A similar method was used by Trkovnik[317] to prepare the 2-phenyl derivative of **411** ($R^1 = R^2 = H$).

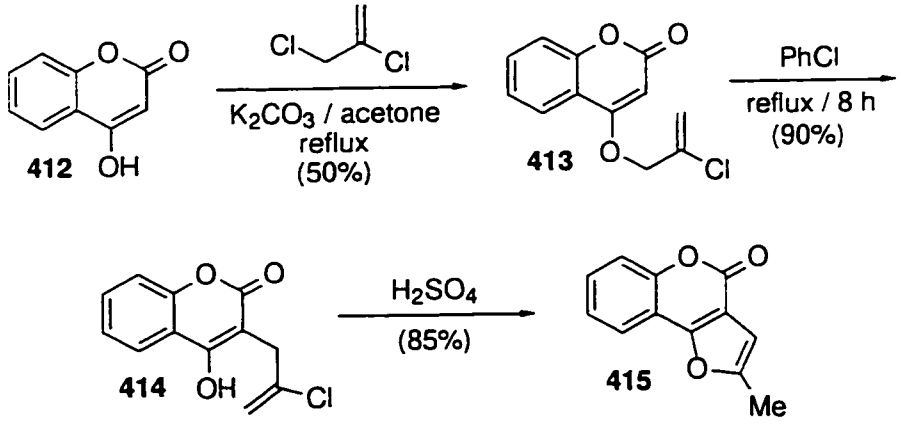
Majumdar[318] described a synthesis of 2-methylfuro[3,2-*c*]coumarin based on the Claisen rearrangement. Allylation of 4-hydroxycoumarin **412** afforded the allyloxy derivative **413** which underwent a [3,3] sigmatropic rearrangement to **414** in excellent yield **(Scheme 98)**. Ring closure afforded the desired methyl derivative **415** in 85% yield. Preparation of **415** could also be accomplished directly by heating **413** in *N,N*-dimethylaniline in 75% yield.

Scheme 97



R^1	R^2	Yld. %
H	H	27
OMe	H	30
H	OMe	28

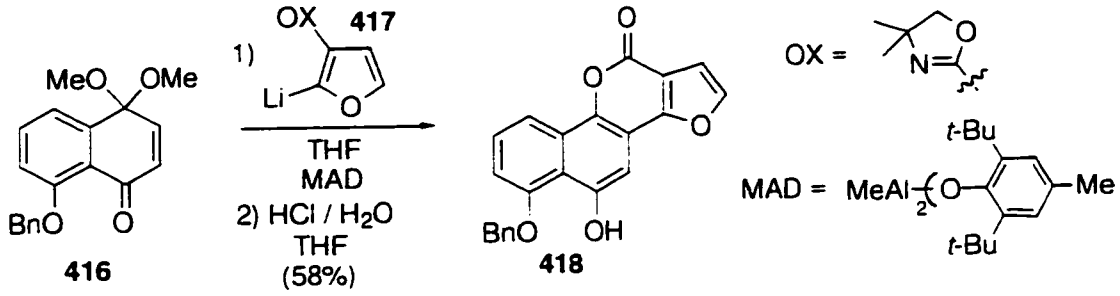
Scheme 98



Recently, during the course of studies towards the synthesis and evaluation of the antitumor activity of some defucogilvocarcin V isosteres, Hart and Mannino[319] prepared furocoumarin **418 (Scheme 99)**. MAD[196] mediated conjugate addition of 3-oxazolino-

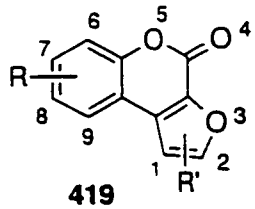
2-lithiofuran to **416** followed by acidic cyclization afforded the pyranone **418** in 58% yield. Unfortunately, the material showed no antitumor activity.

Scheme 99



7.6.2 4*H*-Furo[2,3-*c*]benzo[*e*]pyran-6-ones

The synthesis of furo[2,3-*c*]coumarins **419** is almost invariably achieved from 3-hydroxycoumarin derivatives. Commonly, allyl or propargyl substituents are introduced into the 4-position *via* a Claisen rearrangement and variations occur in the methods used for the formation of the furan ring. Shaikh and Trivedi[320] demonstrated the acid-mediated ring closure of 4-allyl-3-hydroxycoumarin **(421)** followed by dehydrogenation to afford the 2-methyl derivative **423 (Scheme 100, 421 → 423)**. Subsequently, the same group reported[321] a multistep conversion of coumarin **421** to the furocoumarin system **423**. Acetylation followed by bromination of the terminal double bond afforded dibromide **422** in low yield. Cyclization of this intermediate followed by

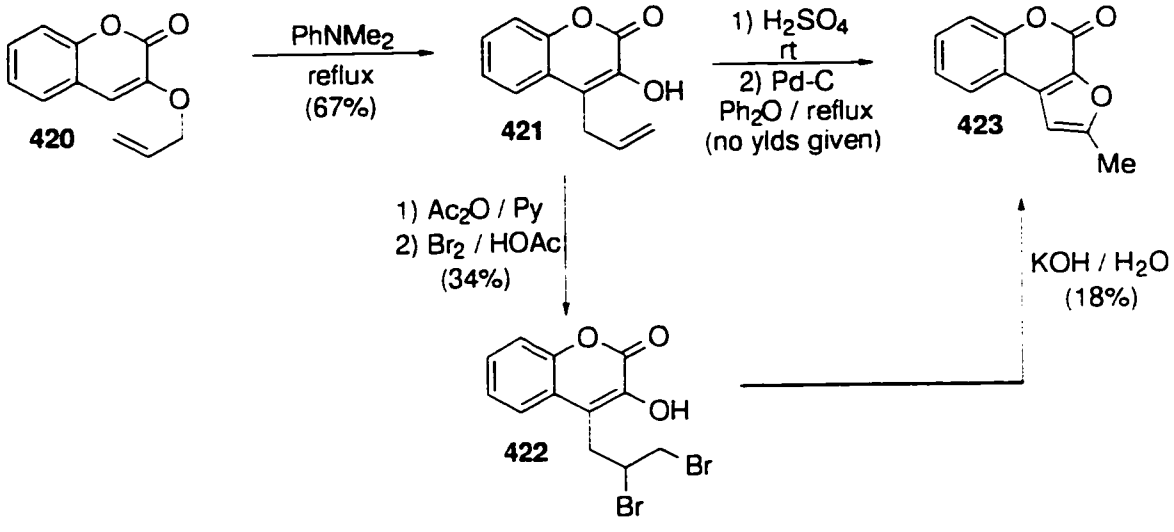


419

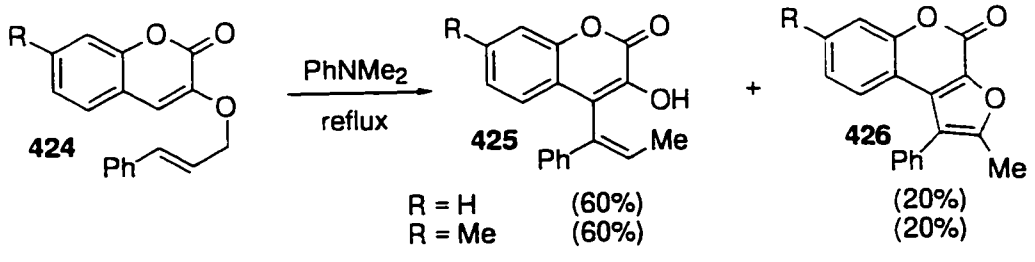
in situ elimination of HBr gave the lactone **423** in 18% yield. The latter cyclization protocol failed when substituents were present in the benzenoid ring.

During the course of studies of the cinnamoylation reaction of 3-hydroxycoumarin derivatives, Ahluwalia and co-workers[322] found that substituted furocoumarins **426** were formed as minor products in the Claisen rearrangement of ethers **424** **(Scheme 101)**. The yields of furocoumarins were low and cyclization of the rearrangement products **425** by other means was not attempted.

Scheme 100

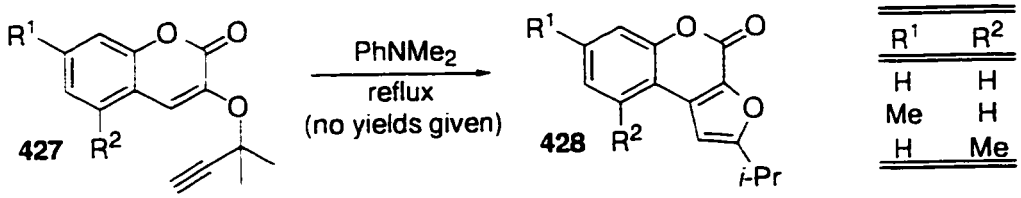


Scheme 101



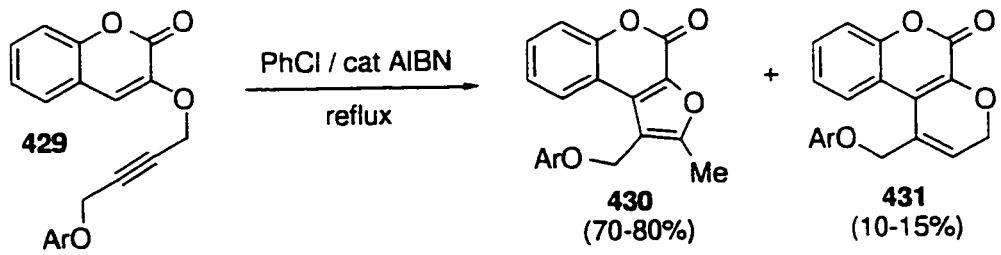
The Claisen rearrangement of propargyl ethers **427 to 428 (Scheme 102)** was studied by Shah and Trivedi.[323] *O*-alkylation was achieved by treatment of 3-hydroxycoumarin with 3-chloro-3-methyl-1-butyne in the presence of K_2CO_3 affording the starting ethers. When heated in dimethylaniline, Claisen rearrangement of **427** occurred followed by *in situ* cyclization to afford the 2-isopropyl substituted furocoumarins **428**. The yields of this sequence were not reported.

Scheme 102



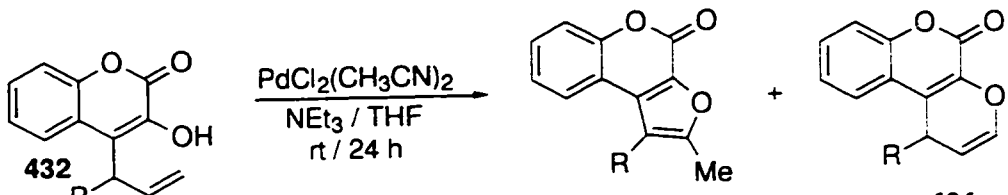
In one of the more detailed studies, Majumdar and co-workers[324] investigated the rearrangement of substituted propargyl ethers **429** in the presence of a radical initiator **(Scheme 103)**. They observed formation of the 2,3-disubstituted furocoumarins **430** as the major products in good yields along with the pyranocoumarins **430** as minor components. The formation of **431** was accounted for by a radical pathway whereas the pyranocoumarins were thought to arise due to a sequence of pericyclic reactions. Although nine cases were examined, only simple variations in the aryloxy portion were investigated and no substrates bearing substituents in the benzenoid ring were prepared.

Scheme 103



Initially discovered[325] during the investigation of Wacker-like oxidation of allyloxycoumarins, Mitra[326] has shown that 4-allyl-3-hydroxycoumarins undergo Pd(II) - mediated cyclization to the corresponding furocoumarins **433 (Scheme 104)**. Again, the starting materials **432** are prepared by Claisen migration of the corresponding allyloxycoumarins. The yields are low due to competing cyclization to the pyranocoumarins **434**. The reaction also suffers from the disadvantage that stoichiometric palladium is used. No attempt was made to make the process catalytic.

Scheme 104



432

R	**433**	**434**
H	40%	0%
Me	32%	30%
Ph	34%	30%

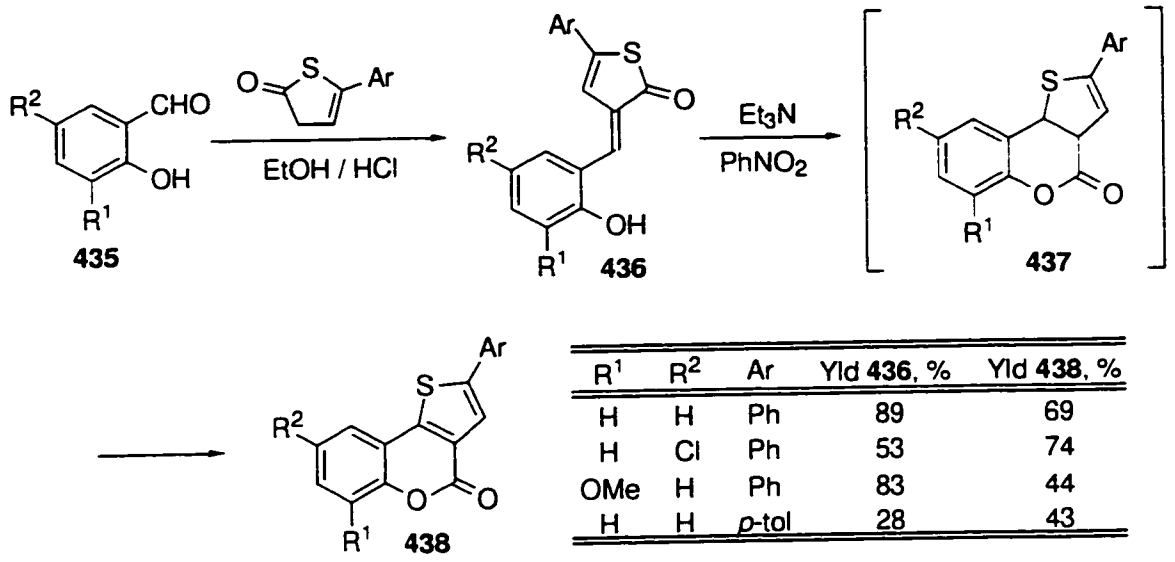
7.7 Thienocoumarins

7.7.1 4*H*-Thieno[3,2-*c*]benzo[*e*]pyran-4-ones

Thieno[3,2-*c*]coumarins have been prepared by a modification of the thiolactone condensation initially demonstrated for thiacoumestans by Heindel and co-workers.[210] Thus, salicylaldehydes **435** are condensed with thiolactones in the presence of HCl gas **(Scheme 105)**.[327] The benzylidene thiolactone products **436**, upon treatment with Et_3N undergo *cis-trans* isomerization and cyclization to afford the dihydrothiophenes **437**. Under the reaction conditions, lactones **437** undergo oxidation to afford the

thienocoumarins **438** in moderate overall yields. The starting 5-arylthiolactones are readily available *via* the method of Kosak.[328]

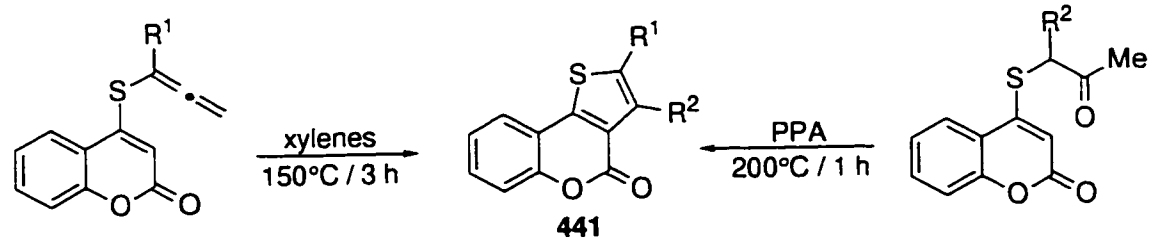
Scheme 105



R^1	R^2	Ar	Yld **436**, %	Yld **438**, %
H	H	Ph	89	69
H	Cl	Ph	53	74
OMe	H	Ph	83	44
H	H	*p*-tol	28	43

Makisumi has reported two different routes to thieno[3,2-*c*]coumarins **441**. In the first route,[329] thermolysis of allenylthiocoumarins **439a** has been shown to lead to thienocoumarins **441a** undoubtedly *via* a Claisen rearrangement as the key step **(Scheme 106)**. In the second method, acid-mediated cyclization of substituted

Scheme 106



439a: R^1 = H, Me

441
a: R^1 = Me, Et R^2 = H
b: R^1 = H, Me R^2 = Me

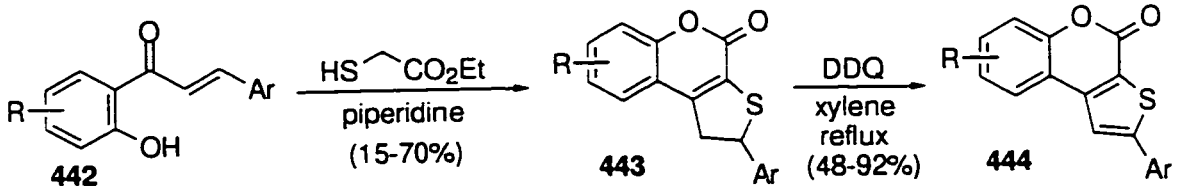
440b: R^2 = H, Me

acetonylthiocoumarins **440b** afforded the desired pyranones **441b**.[330] These compounds were reported to possess antipyretic, antiinflammatory, and antiallergic properties. Finally, Weißenfels[331] has shown that condensation of methyl thioglycolate ($SHCH_2CO_2Me$) with 4-chloro-3-formyl-coumarins, available from 4-hydroxycoumarins under Vilsmeier conditions, affords thienocoumarins in good yields (4 egs, 55-70%).

7.7.2 4*H*-Thieno[2,3-*c*]benzo[*e*]pyran-4-ones

Xicluna and co-workers have undertaken extensive structure activity relationship (SAR) studies on 2-arylsubstituted dihydrothienocoumarins[332] **443** as well as the unsaturated analogues **444**. Thus, condensation of ethyl thioglycolate with various chalcones **442** afforded intermediates **443** whose oxidation to the thienobenzopyranones **444** was accomplished in good yields using DDQ (**Scheme 107**).[333] Biological testing showed that the dihydro derivatives displayed antipyretic and antiinflammatory properties whereas the 4*H*-thieno[2,3-*c*]benzo[*e*]pyran-4-ones **444** did not. The latter class of compounds did however display diuretic properties. This lack of antipyretic and antiinflammatory activity is in contrast to the findings of Makisumi,[330] where 2-alkyl substituted derivatives displayed these properties. These methods constitute the only reports of the synthesis of 4*H*-thieno[2,3-*c*]benzo[*e*]pyran-4-ones **444**.

Scheme 107

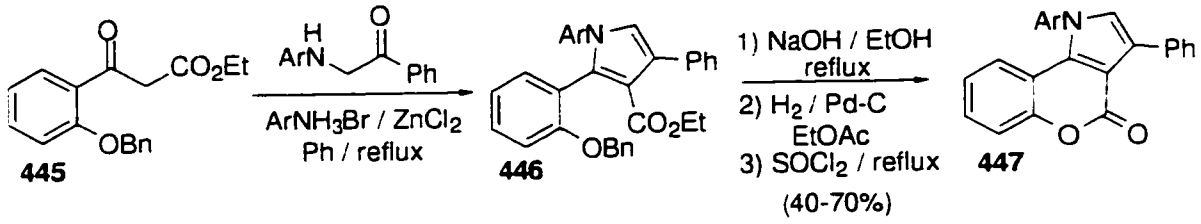


7.8 Pyrrolocoumarins

7.8.1 4*H*-Pyrrolo[3,2-*c*]benzo[*e*]pyran-4-ones

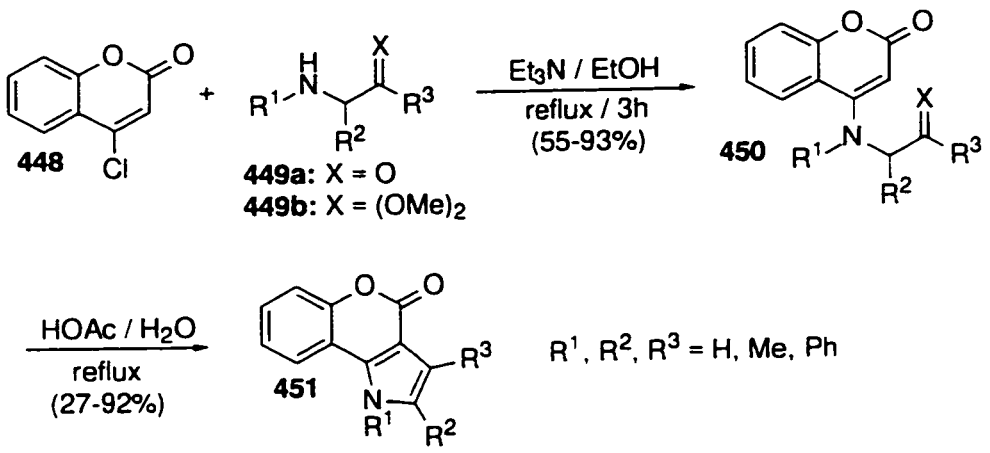
The synthesis of 4*H*-pyrrolo[3,2-*c*]benzo[*e*]pyran-4-ones **447** **(Scheme 108)** has been reported by Colotta and co-workers[334] for SAR studies to investigate their activity as benzodiazepine receptor ligands.[335] Treatment of ketoester **445** with phenacylarylamines in the presence of a catalytic amount of the arylamine hydrobromide and $ZnCl_2$, led to the corresponding pyrrole derivatives **446**. Subsequent ester hydrolysis, debenzylation and lactonization *via* the acid chloride afforded lactones **447** in good yields over four steps. Several substrates were prepared, however, only the *N*-aryl substituent was varied. Some of the derivatives were shown to possess strong affinity for the benzodiazepine receptors.

Scheme 108



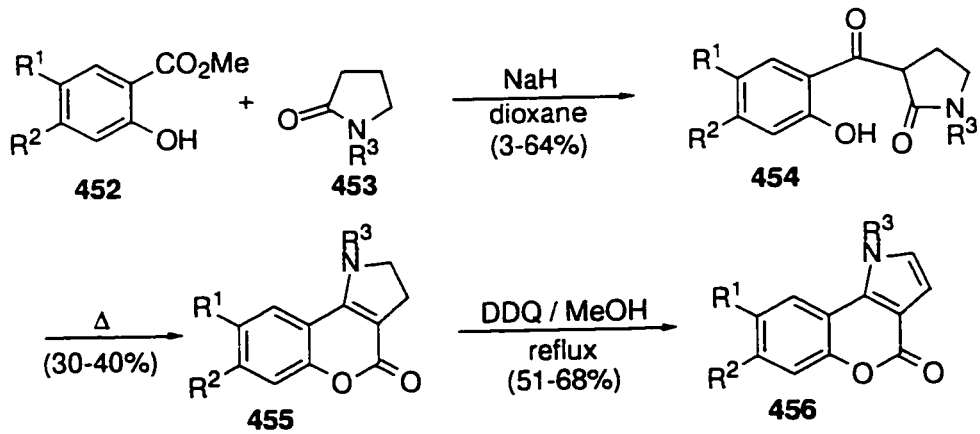
In a related sequence, Alberola[336] has shown that an addition - elimination sequence of amino ketones **449a** or amino acetals **449b** with 4-chlorocoumarin generates vinylogous amides **450** **(Scheme 109)**. Cyclization under acidic conditions affords the 2,3-disubstituted pyrrolocoumarins **451** in poor to excellent yields. Benzene ring substituted derivatives of **451** were not synthesized, limiting the generality of this reaction.

Scheme 109



Claisen condensation of lactams **453** with salicylate esters **452** has been shown to afford substituted pyrrolidinones **454 (Scheme 110)**.[337] Thermolysis of these derivatives generated the dihydropyrroles **455** which were then aromatized with DDQ giving pyrrolocoumarins **456**. The several steps required as well as the low yields in the thermolysis step render this method relatively inefficient. Ahluwalia[338] and Joshi[339] have independently reported the condensation of 4-aminocoumarins with benzoin to afford 2,3-diphenylpyrrolocoumarins. This method affords the desired compounds in good yield but has only been tested on two substrates.

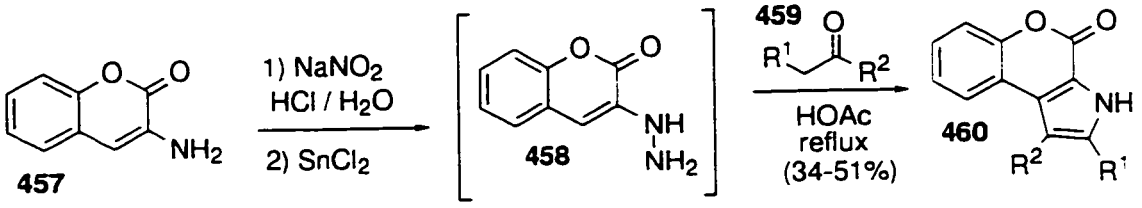
Scheme 110



7.8.2 4*H*-Pyrrolo[2,3-*c*]benzo[*e*]pyran-4-ones

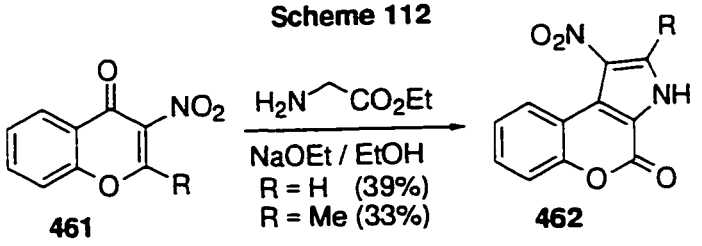
The 4*H*-pyrrolo[2,3-*c*]benzo[*e*]pyran-4-one ring system **460** was unknown in the literature until the report by Khan.[340] In this study, 3-aminocoumarin was converted into the corresponding hydrazine **458** which was not isolated but could be stored and used in solution **(Scheme 111)**. In a modification of the Fischer indole synthesis, heating **458** with ketones and aldehydes in HOAc afforded the pyrrolocoumarins **460** in moderate yields. Although only compounds bearing substituents in the pyrrole ring were prepared, this remains the most general method (7 egs) for the preparation of this ring system. The parent compound (**460**, $R^1 = R^2 = H$) was unavailable by this method.

Scheme 111



Haas and co-workers[341] showed that condensation of 3-nitrochromone **461** with the ethyl ester of glycine under basic conditions affords 3-nitropyrrolocoumarin **462** (R = H) **(Scheme 112)**. The reaction presumably proceeds *via* a conjugate addition - aldol

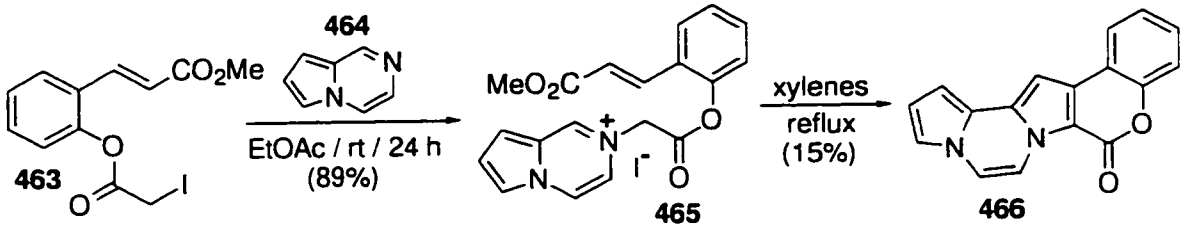
Scheme 112



condensation sequence. This process was later modified by Takagi and co-workers[342] using 3-nitro-4-methylchromone to prepare the nitromethyl derivative **462** (R = Me).

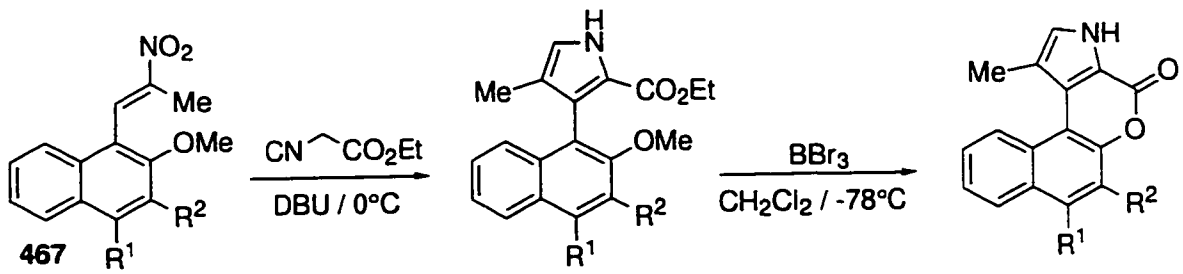
Recently, Mínguez and co-workers[343] demonstrated that the reaction of iodide **463** with **464** generates the ammonium iodide **465** in good yield **(Scheme 113)**. Heating **465** in xylenes generated the unusual pyrrolocoumarin **466** containing the bispyrrole moiety, in low yield. The reaction presumably proceeds *via* an intramolecular [3+2] cycloaddition of the *in situ* generated azomethine ylide of **465**.

Scheme 113



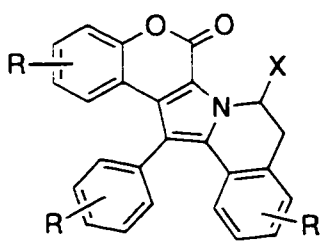
Finally, Furusho[344] has described a synthesis of two pyrrolocoumarins based on the condensation of ethyl isocyanoactetate **468** with nitroalkenes **467 (Scheme 114)**. Cyclization of the intermediate alkoxy esters **469a** using BBr_3 afforded lactone **470a** in good yield. Using this method the anthracenyl derived pyrrolocoumarin was also prepared in moderate yield.

Scheme 114

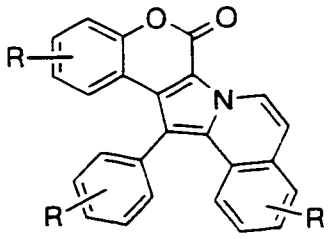


469a: R^1, R^2, = H (83%) **470a:** R^1, R^2, = H (100%)
469b: R^1, R^2, = benzo (77%) **470b:** R^1, R^2, = benzo (58%)

Unlike most of the other heterofused coumarin derivatives, compounds containing the pyrrolo[2,3-*c*]coumarin framework occur in nature. The lamarellins **471** and **472** are a large group of alkaloids isolated[345] originally from molluscs of the *Lamarellia* species and then later from ascidians of the Indian Ocean.[346] Some lamarellins display significant cytotoxicity and immunomodulatory activities[346] and are an unusual modification of the relatively uncommon pyrrolo[2,3-*c*]coumarin framework.



471

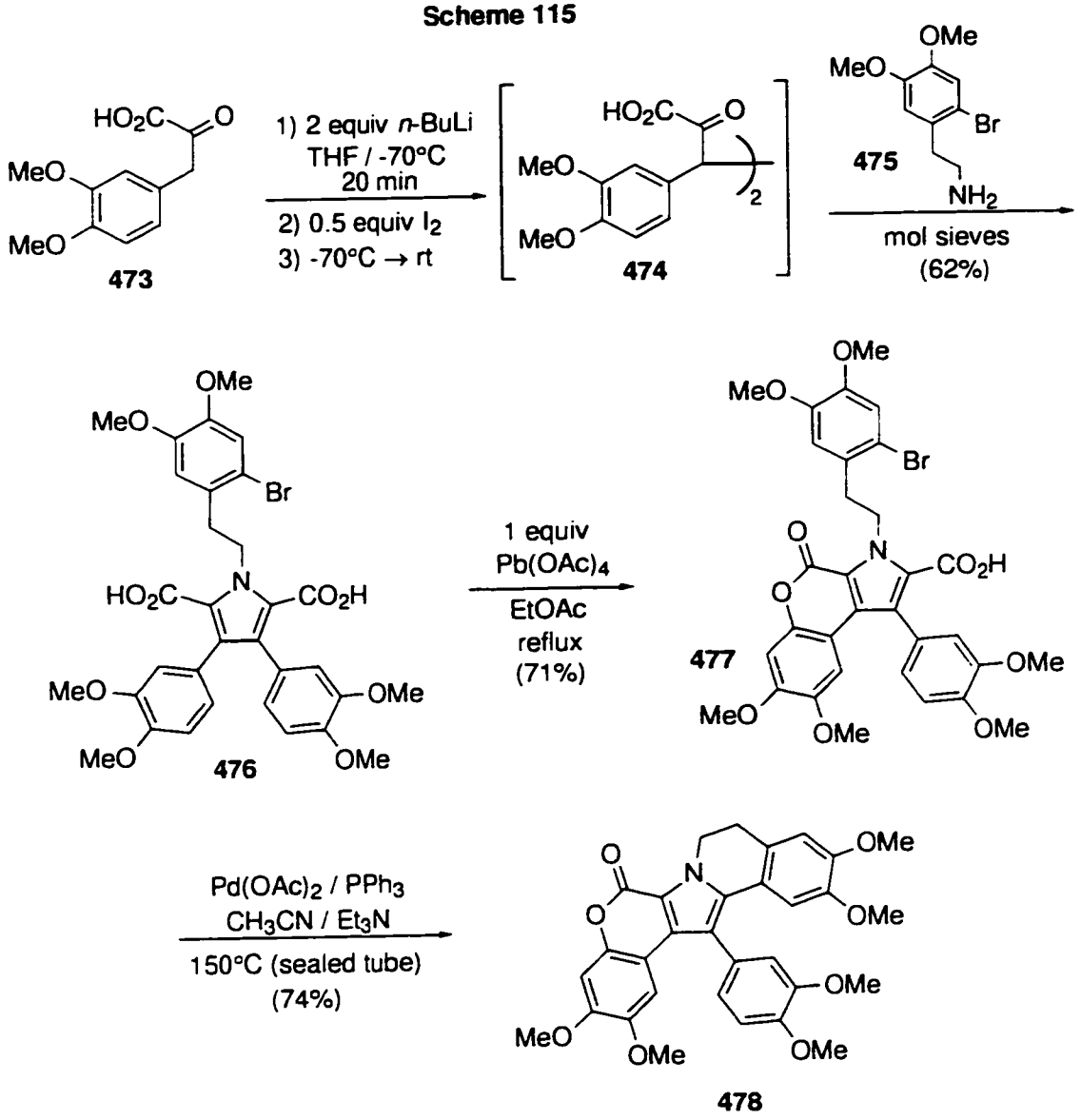


472

R = OH, OMe, OAc,
X = OH, OAc

A proposed biomimetic synthesis of the trimethyl ether of one member of this class of natural products has been accomplished **(Scheme 115)**.[347] Thus, dimerization of ketoacid **473** afforded **474** which was not isolated but treated with phenethylamine **475** giving pyrrole **476** in good yield over two steps. Oxidative cyclization of **476** with 1 equiv of $Pb(OAc)_4$ gave **477** selectively, generating the pyrrolo[2,3-*c*]coumarin framework in good yield. An interesting variation of the Heck reaction **(477 → 478)** afforded lamarellin G trimethyl ether in 74% yield after loss of CO_2.

Scheme 115

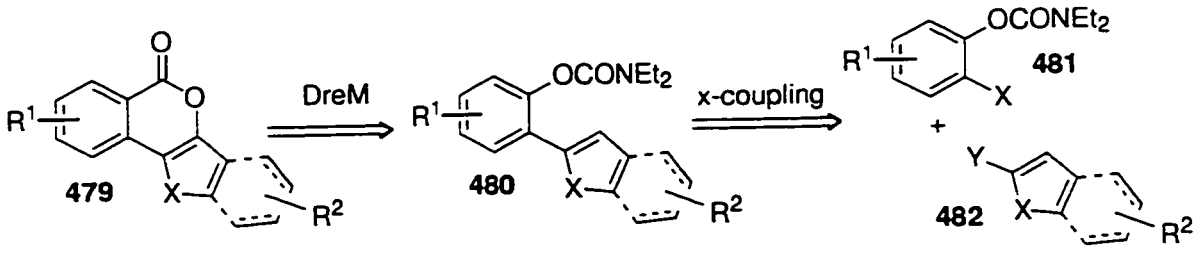

HO2C
O
MeO
MeO
473
1) 2 equiv n-BuLi
THF / -70°C
20 min
2) 0.5 equiv I2
3) -70°C → rt
HO2C
O
MeO
MeO
2
474
OMe
MeO
Br
475
NH2
mol sieves
(62%)
OMe
MeO
Br
HO2C
N
CO2H
MeO
OMe
MeO
OMe
476
1 equiv
Pb(OAc)4
EtOAc
reflux
(71%)
OMe
MeO
Br
O
N
CO2H
O
477
MeO
OMe
OMe
OMe
Pd(OAc)2 / PPh3
CH3CN / Et3N
150°C (sealed tube)
(74%)
O
N
OMe
O
OMe
MeO
OMe
OMe
478

8. Proposed Synthesis of Heteroaryl Fused Benzopyrans

In this section, the application of the DreM - carbamoyl migration protocol **(Section 1.5.2, Scheme 24)** to the synthesis of heteroarylbenzopyranones **(316 - 319, Section 7.1)** is described. As gleaned from the previous sections the existing syntheses are, in many cases, inefficient or limited in scope. The biological properties of the coumestans as well the naturally occurring lamarellins amplify the importance of developing a general synthetic route to these classes of molecules.

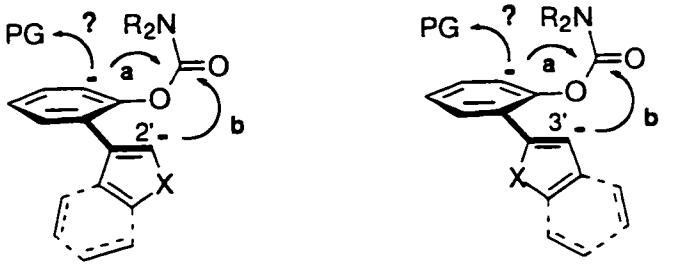
Application of a retrosynthetic analysis to heteroaryl[3,2-*c*]coumarins based on the DreM strategy reveals heterobiarylcarbamate **480** which should be available *via* cross coupling from **481** and **482 (Scheme 116)**. Preparation of the carbamates **481** required for cross coupling *via* DoM is expected to be straightforward, analogous to the methods utilized in the **Sections 5** and **6**. The remainder of the synthesis relies on the availability of suitably functionalized heteroaromatics. A similar retrosynthetic process can be envisioned for the heteroaryl[2,3-*c*]coumarins.

Scheme 116



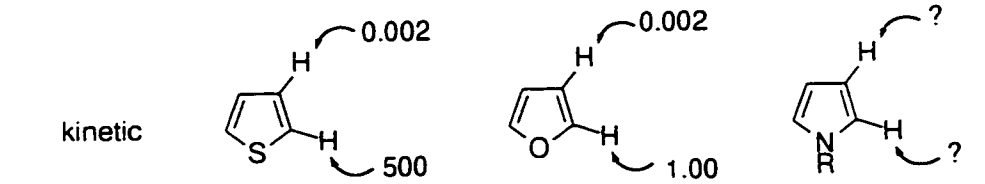
A point which warrants consideration is the acidities of the heteroaryl protons relative to those of a "normal" benzenoid aromatic. For both types of heteroarylcarbamate **483** and **484**, two possible sites of deprotonation exist.

Deprotonation at the C-2′ or C-3′ would lead to the desired carbamoyl migration (path b). C-2 lithiation would, however, produce the undesired salicylamides *via* the anionic *ortho* Fries rearrangement (path a). The enhanced acidity of the heteroaromatic protons may allow selective deprotonation at these positions, eliminating the need for a C-2 protecting group, thus enhancing the scope of the process. The pKa values of simple π-excessive heterocycles are summarized in Figure 2.[348] The thermodynamic values given were measured using the polarographic scale and the relative rates of kinetic deprotonation (C-2 vs C-3) were determined using *t*-BuOK in DMSO.[348]



483 **484**

Figure 2



8.1 Preliminary Results

Preliminary results by Coelho[349] in this laboratory were directed towards the application of the DreM - cross coupling strategies to the synthesis of coumestans

487a,c and thiacoumestans **487b,d**. Suzuki cross coupling of benzofuryl and thianaphthenyl iodides with boronic acids **485**, prepared regioselectively *via* DoM, afforded the heterobiaryl-*O*-carbamates **487a-d** in good yield **(Table 15)**. Toluene was found to be a superior solvent for this reaction as opposed to the normally used[68,72] DME which led to significant amounts of carbamate hydrolysis.

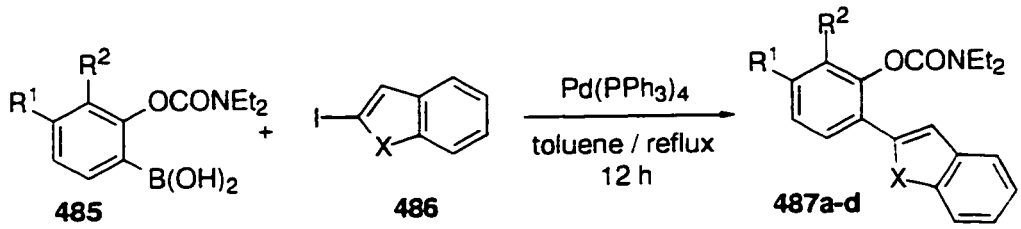


Table 15. Cross Coupling Method to Heterobiaryl-*O*-carbamates 487a-d

Entry	487	R^1	R^2	X	Yld 487, %
1	**a**	H	OMe	O	79
2	**b**	H	OMe	S	79
3	**c**	OMe	OMe	O	94
4	**d**	OMe	OMe	S	93

Coelho found that treatment of carbamates **487** with LDA at 0°C effected the carbamoyl migration reaction to give the corresponding intermediate hydroxy amides which upon cyclization with HOAc afforded the coumestan **489a,c** and thiocoumestan **489b,d** derivatives in excellent yields over two steps **(Table 16)**. The ease of the migration compared to biaryl carbamates **267**, **279 (Section 5.1.3)** is presumably a result of the enhanced acidity of the heteroaromatic 3-hydrogen, allowing the reaction to be carried out under milder conditions. When carbamate **488e**, which bears no protecting group at C-6, was treated under the conditions of the migration reaction, none of the desired coumestan was isolated. The corresponding salicylamide (**488** R^1 = H, R^2 = $CONEt_2$, X = O) was recovered in 59% yield. This result demonstrates the importance of C-6

protection for carbamates of type **484**. The necessity of such a protecting group for 2-(3-heteroaryl)carbamates **483** is, as yet, an unanswered question.

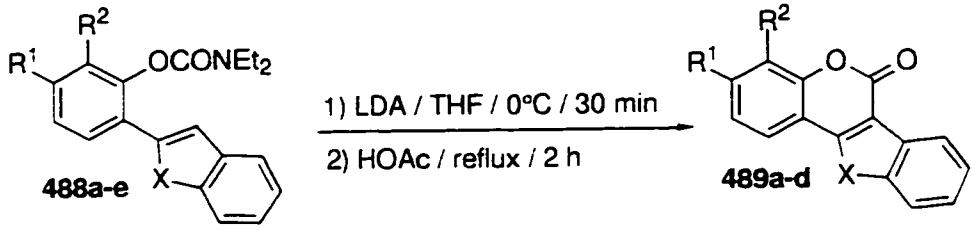
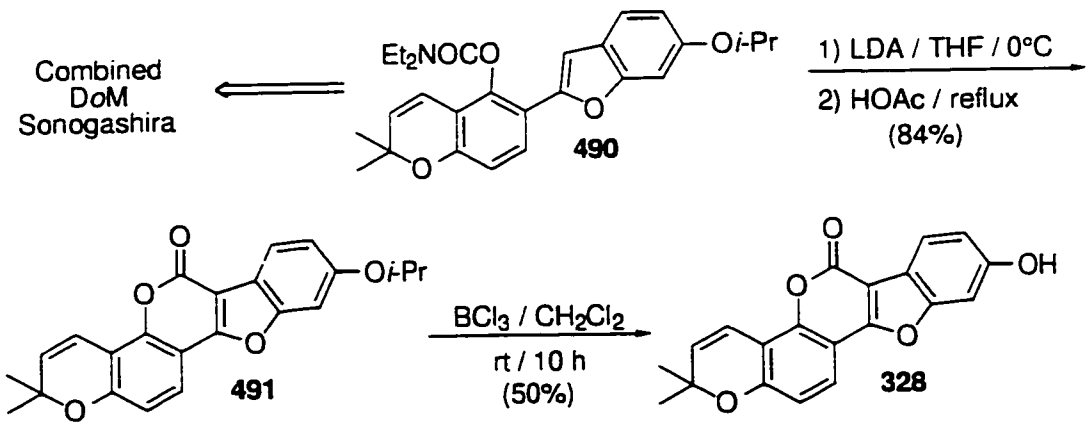


Table 16. DreM Method to Coumestans and Thiacoumestans 489a-d

Entry	488	R^1	R^2	X	Yld 489, %
1	**a**	H	OMe	O	79
2	**b**	H	OMe	S	96
3	**c**	OMe	OMe	O	75
4	**d**	OMe	OMe	S	77
5	-	H	H	O	0

Recently, Chauder[350] has applied this methodology to the total synthesis of plicadin **(328)**, a naturally occurring chromene containing coumestan **(Section 2.1)**. Treatment of carbamate **490** with LDA followed by cyclization afforded coumestan **491** in good yield **(Scheme 117)**. Protecting group cleavage was effected using BCl_3 to afford the natural product **328** in 50% yield.

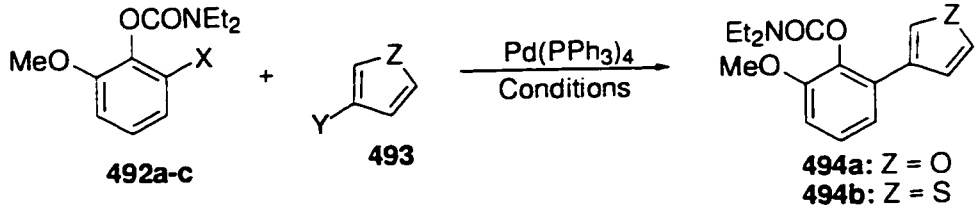
Scheme 117



9. Results and Discussion

9.1 Synthesis and DreM of Heterobiarylcarbamates

Initial studies involved investigation of the optimum location of functional groups required for the cross coupling reaction **(Table 17)**. The Suzuki and Negishi reactions were chosen due to the extensive experience gained with these procedures in the synthesis of the gilvocarcins **(Section 5)** and arnottin I **(Section 6)**. The results presented demonstrate that both the Suzuki and Negishi cross coupling reactions are efficient methods for the preparation of the desired heterobiaryls. Furthermore, the Suzuki reaction is more efficient for the thiophene couplings than is the Negishi protocol (entry 3,4 vs entry 5,6). Comparison of entry 5 and 6 demonstrates that the reaction proceeds more efficiently when the metal substituent is on the heteroaryl coupling partner (Y = $B(OH)_2$). The relative efficiencies of the Suzuki and Negishi coupling protocols in



492a-c **493** **494a:** Z = O **494b:** Z = S

Table 17. Evaluation of Cross Coupling Conditions in the Synthesis of 2-(3-heteroaryl)carbamates (494a,b)

Entry	492	X	Y	Z	Conditions	Yld 494, %
1	**a**	$B(OH)_2$	Br	O	A	16
2	**b**	I	ZnBr	O	B	84
3	**b**	I	ZnBr	S	B	32
4	**c**	ZnCl	Br	S	C	38
5	**a**	$B(OH)_2$	Br	S	A	66
6	**b**	I	$B(OH)_2$	S	A	80

Conditions: A: 2 mol/L Na_2CO_3 / DME / reflux. B: THF / rt. C: THF / reflux

the synthesis of **464a** could not be compared because the inverted Suzuki coupling (**493** Y = $B(OH)_2$, Z = O) was not carried out. The Negishi protocol (entry 2) was shown to be a satisfactory route to **494a**.

That the coupling reactions proceed in higher yields with the metal in the heteroaromatic species is in keeping with the findings of others that high electron density in the coupling partner which bears the leaving group retards the reaction.[68,351] Presumably this is a result of a decrease in the rate oxidative addition.[239,351] In the thieno Negishi couplings of **492c** X = ZnHal, a significant amount of arylcarbamate SM (X = H) was present in the reaction mixture making purification difficult due to its copolarity with the product. The use of Y = $B(OH)_2$ or ZnHal avoided this problem, rendering purification much more facile. In the Negishi coupling route to **494b** (entry 3) the yield was low (32%). The reaction was invariably contaminated with the corresponding 2-(2-thienyl)carbamate as determined by GC injection of an authentic sample, prepared by an independent method (**506, Scheme 120** *vide infra*). Presumably, the formation of this product can be ascribed to the equilibration of 3- and 2-lithiothiophene under the reaction conditions, driven by the higher thermodynamic stability of the 2-lithio species (**Figure 2**). The known stability[352] of 3-lithiothiophene at -78°C suggests that this equilibration is the result of slow reaction of this species with $ZnBr_2$.

Similarly, several other arylcarbamates were prepared as shown in **Table 18**. Thus, synthesis of the 6-silyl derivative **497a** (entry 1) was accomplished using the Suzuki reaction. The presence of the 6-silyl substituent is synthetically valuable in that it may be later removed *via* fluoride or, more importantly, participate in *ipso* electrophilic chemistry[100] to introduce further functionalization into the ring (eg TMS → Br for cross coupling or MHEX). Compounds **497b** and **497c** represent interesting cases as the C-6

positions do not bear a PG, thus allowing a test of the necessity for protection at this position in DreM chemistry.

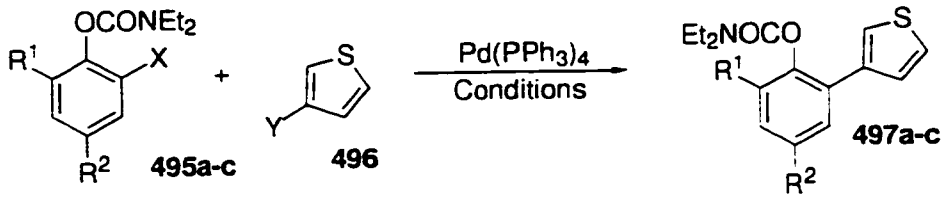


Table 18. Synthesis of Substituted 2-(3-thienyl)-*O*-Arylcarbamates 497a-c

Entry	R^1	R^2	X	Y	Conditions	**497**	Yld, %
1	TMS	H	$B(OH)_2$	Br	A	**a**	47
2	H	OMe	ZnCl	Br	B	**b**	40
3	H	H	Br	$B(OH)_2$	A	**c**	90

Conditions: A: 2 mol/L Na_2CO_3 / DME / reflux. B: THF / reflux.

9.2 DreM - Carbamoyl Migration of 2-Heteroaryl-*O*-carbamates

The available heterobiarylcarbamates **494a,b** and **497a-c** were subjected to standard DreM - induced carbamoyl migration conditions. Typically, the heteroarylcarbamates were treated with 2-3 equiv of LDA in THF at 0°C for 10 min. Results of the migration of the 2-(3-heteroaryl)carbamates to generate the 4*H*-thieno[2.3-*c*]benzo[*e*]pyran-4-ones **499** are collected in **Table 19**. Isolation of the hydroxy amide intermediates **498** was possible but was not generally carried out. Often, cyclization on silica gel occurred to the extent of 5-10% and therefore direct cyclization to the corresponding lactones **499** was more convenient. Yields of the reaction sequence were generally modest; however, no products derived from the suspected anionic *ortho* Fries

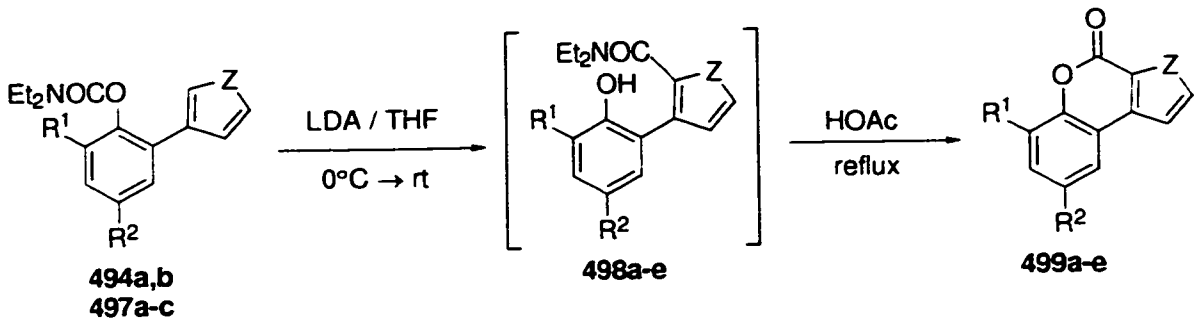


Table 19. DreM of 2-(3-heteroaryl)-*O*-Arylcarbamates

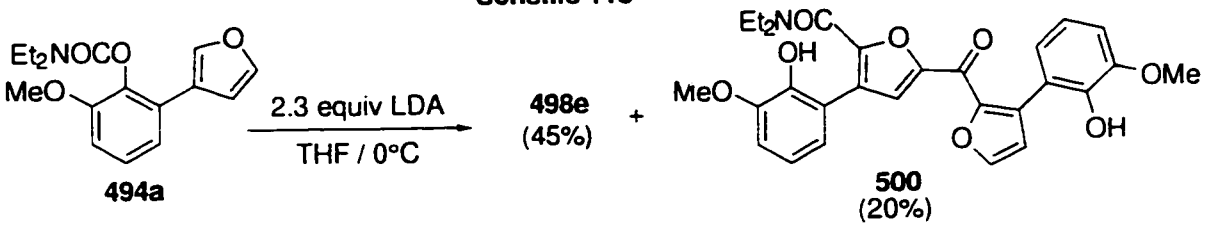
Entry	Cmpd	R^1	R^2	Z	**499**	Yld, %
1	**497a**	TMS	H	S	**a**	62
2	**494b**	OMe	H	S	**b**	38
3	**497b**	H	OMe	S	**c**	48
4	**497c**	H	H	S	**d**	43
5	**494a**	OMe	H	O	**e**	45

rearrangement were detected. Cyclization of the isolated intermediates **498** demonstrated that the yield of this step was generally high, suggesting that there is a competing process in the migration reaction. For example, heating **498e** in HOAc afforded the corresponding lactone in 85% yield (see Experimental Section).

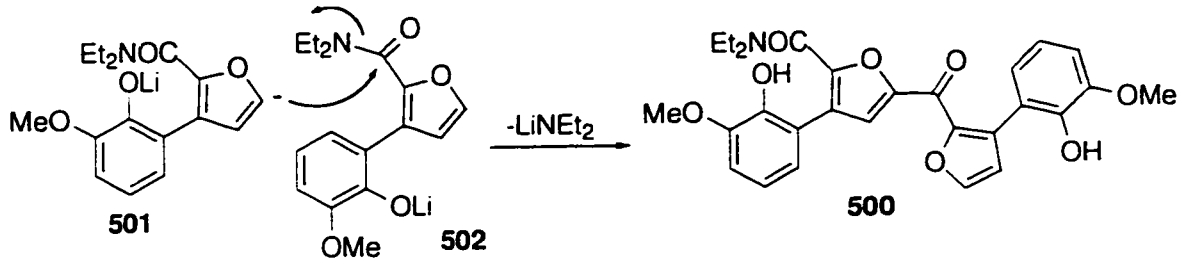
To investigate the cause of the low yields, the migration reaction of 2-(3-furyl)-*O*-carbamate **494a** was investigated in more detail **(Scheme 118)**. Treatment of **494a** with LDA under the normal conditions followed by careful examination of the reaction mixture revealed the expected product **498e** as well as the difuryl ketone **500** in 20% yield. Formation of this product may be rationalized as shown in **Scheme 119**. After initial carbamoyl migration to give **502**, LDA in the reaction mixture mediates C-5 deprotonation to give anion **501** which undergoes intermolecular condensation with **502** to give the observed product. The presence of an electron withdrawing group on the furan ring is known to enhance the acidity of the heteroaryl protons.[353] Thus, the introduction of the carbamoyl group *via* DreM may increase the rate of C-3'

deprotonation relative to C-2′ of **494a**. Consequently formation of the undesired ketone would compete with the DreM - carbamoyl migration sequence. Also, this deprotonation - condensation sequence (**501** + **502** → **500**) may be iterative giving rise to trimers, tetramers, etc thus accounting for the relatively poor mass balance. Other components of higher polarity than dimer **500** were detected in the reaction mixture by TLC but were not isolable.

Scheme 118



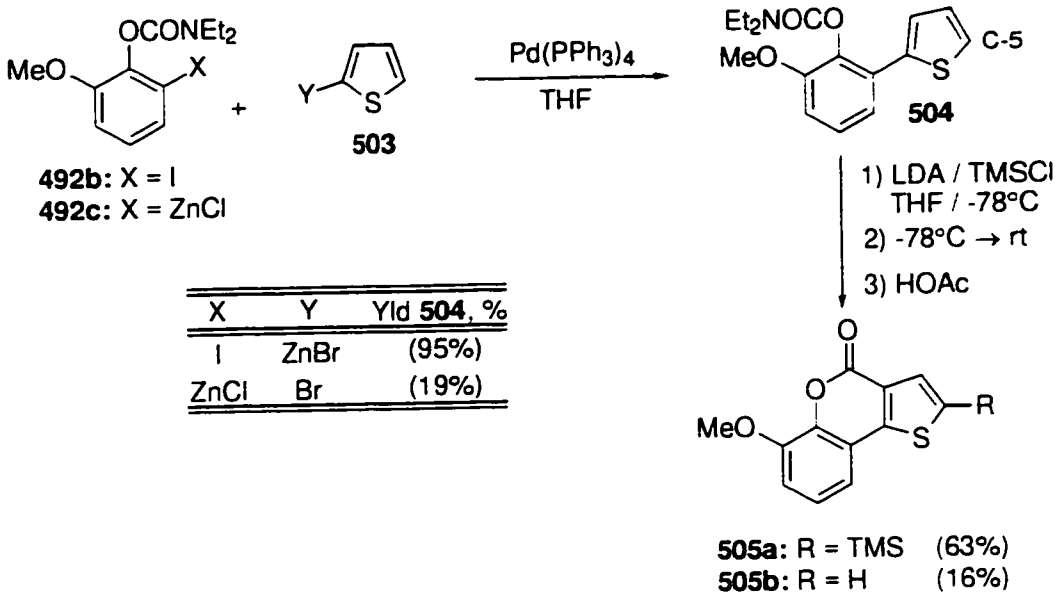
Scheme 119



Next, the synthesis of thieno[3,2-*c*]coumarins was undertaken. Negishi coupling of **492a** and **492c** with thiophene derivatives **503** afforded the 2-(2-thienyl)carbamate **504** **(Scheme 120)**. Optimum yield of thienylcarbamate **504** was obtained *via* coupling of **503** (Y = ZnBr), affording the desired carbamate **504** in 95% yield. The inverted Negishi coupling **503** (Y = Br) afforded **504** in poor yield, consistent with the trend described in **Table 17** (entry 6 vs 5). All attempts to effect DreM - carbamoyl migration of **504** were unsuccessful. Presumably this is a result of the high stability of the C-5 anion. Similarly, subjection of **504** to more forcing conditions, (2-5 equiv of

LDA at rt or reflux) afforded only recovered starting material. This difficulty was circumvented using TMS as an *in situ* generated C-5 protecting group. Thus, treatment of carbamate **504** with 2 equiv TMSCl and 5 equiv LDA at -78°C and allowing the reaction to mixture warm to rt resulted in the desired migration. After acidic cyclization of the resulting crude hydroxy amides, the thieno[3,2-*c*]coumarins **505a** and **505b** were produced. The silyl group of **505a** could easily be cleaved with TBAF to afford **505b** in 50% yield.

Scheme 120

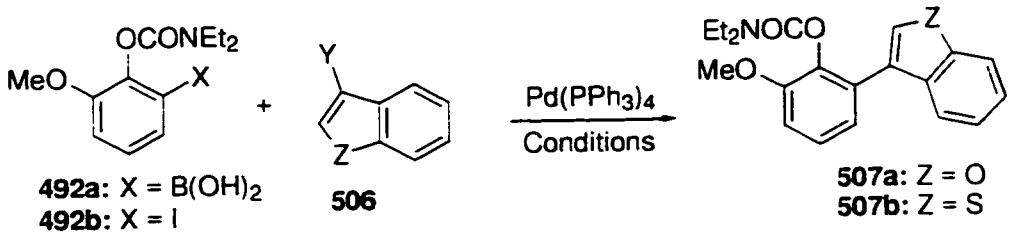


X	Y	Yld **504**, %
I	ZnBr	(95%)
ZnCl	Br	(19%)

9.3 Synthesis of Isocoumestans and their Sulfur and Nitrogen Analogues

Synthesis of the 2-(3-benzofuryl)carbamate **507a** was achieved in low yield by both the Suzuki and Negishi coupling methods **(Table 20)**. The 2-(3-thianaphthenyl)carbamate **507b** was readily available in good yield *via* coupling of 3-bromothianaphthene **506** (Y = Br, Z = S) with arylboronic acid **492a**. Attempted coupling of the thianaphthenylzinc bromide produced the desired compound as part of an

inseparable mixture. Possibly, the initially formed 3-lithiothianaphthene **506** (Y = Li, Z = S) participates in an anionic equilibration of the type proposed for 3-lithiothiophene **(494)** prior to transmetalation (**Table 17**, entry 3).



492a: X = $B(OH)_2$
492b: X = I

506

507a: Z = O
507b: Z = S

Table 20. Cross Coupling Route to Heteroaryl Carbamates 507a,b

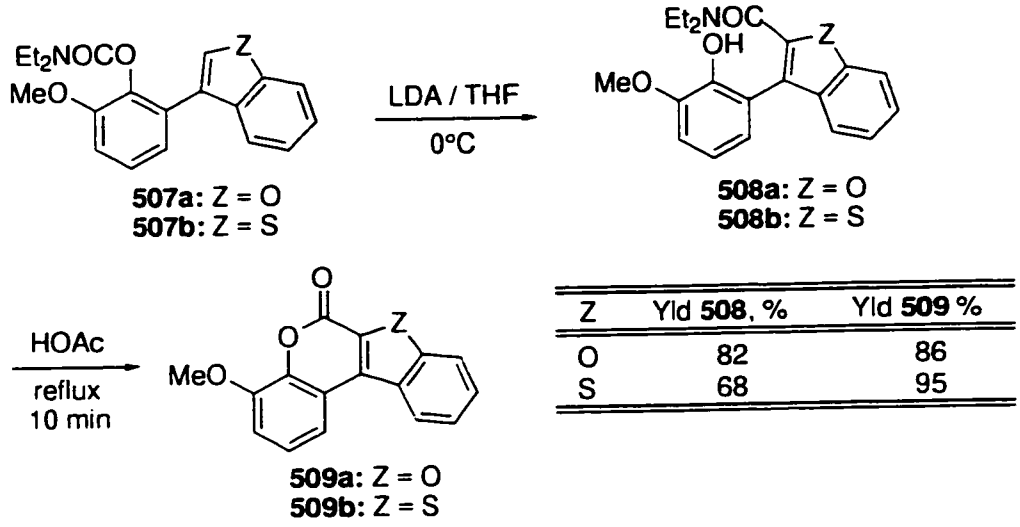
Entry	Z	X	Y	Conditions	**507**	Yld, %
1	O	$B(OH)_2$	Br	A	**a**	34
2	O	I	ZnBr	B	**a**	31
3	S	$B(OH)_2$	Br	A	**b**	86
4	S	I	ZnBr	B	**b**	0[a]

Conditions: A: 2 mol/L Na_2CO_3 / DME / reflux. B: THF / rt.
[a] Inseparable mixture

Migration of carbamates **507a** and **507b** under the standard LDA conditions smoothly afforded the corresponding hydroxy amides **508a**, and **508b** in 82 and 68% yields respectively **(Scheme 121)**. Heating these compounds in HOAc effected cyclization to give the isocoumestan **509a** and the isothiocoumestan **509b** in excellent yield. To the best of our knowledge, the preparation of **509b** constitutes the first synthesis of the 6*H*-thianaphthenyl[2,3-*c*]benzo[*e*]pyran-6-one ring system.

Entry into the azacoumestan and isoazacoumestan systems, **377b** and **378b** respectively, **(Section 7.1)** began with coupling of *N*-*t*-Boc-2-indoleboronic acid **510** with the iodocarbamate **492b (Scheme 122)**. Standard Suzuki conditions afforded the 2-indolylarylcarbamate **511** in mediocre yield. Indoleboronic acid **510** was prepared

Scheme 121



507a: Z = O
507b: Z = S

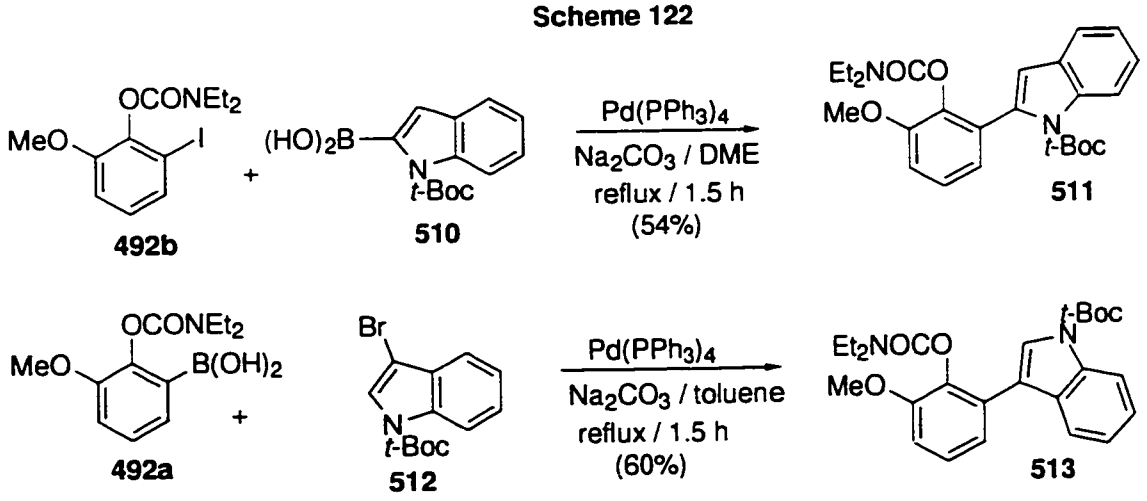
508a: Z = O
508b: Z = S

509a: Z = O
509b: Z = S

Z	Yld **508**, %	Yld **509** %
O	82	86
S	68	95

by metalation of *N*-*t*-butoxycarbonyl indole followed by $B(OMe)_3$ quench and hydrolytic workup. This boronic acid proved to be somewhat unstable and was therefore used directly in the coupling reaction. Coupling of 3-bromoindole (**512**) with aryl boronic acid **492a** in toluene afforded the 3-indolylaryl derivative **513** in 60% yield.

Scheme 122



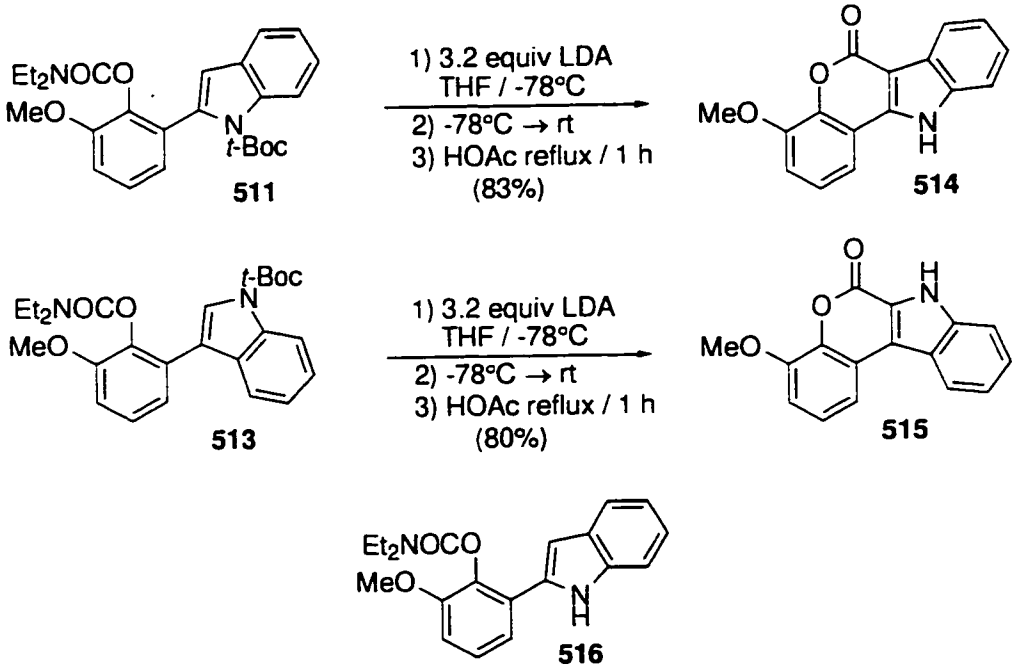
492b + **510** → **511**

492a + **512** → **513**

In an initial migration attempt, treatment of **511** with 2 equiv of LDA under the standard carbamoyl migration conditions followed by heating in HOAc did not afford the

desired azacoumestan **514** but gave, surprisingly, the *N*-Boc cleaved carbamate **516** in 40% yield accompanied by a trace (6%) of the expected **514** **(Scheme 123)**. However, modification of the reaction conditions allowed cleavage of the Boc group *after* the carbamoyl migration reaction had occurred. Treatment of **511** with 3.2 equiv of LDA at -78°C followed by allowing the mixture to warm to rt, and then acidic cyclization, afforded the desired 6*H*-indolo[3,2-*c*]benzo[*e*]pyran-6-one (azacoumestan) **514** in 83% yield. Similarly, reaction of **513** afforded the corresponding 6*H*-indolo[2,3-*c*]benzo[*e*]pyran-6-one (isoazacoumestan) **515** in good yield. Presumably, at some temperature lower than 0°C only metalation occurs and, on warming, carbamoyl migration ensues.

Scheme 123



9.4 Conclusions

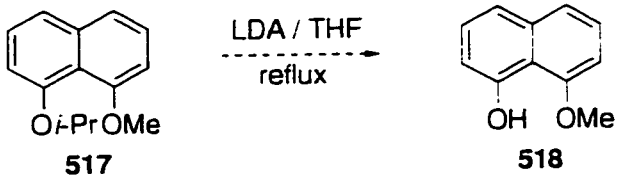
Application of the DreM - carbamoyl migration sequence to 2-(3-thienyl)-arylcarbamates **495a,b** and **497a-c** allowed preparation of a series of substituted 4*H*-thieno[2,3-*c*]benzo[*e*]pyran-4-ones **499a-d**. The required thienylcarbamates were available *via* combined D*o*M - cross coupling strategies. Isolation of difuryl ketone **500** provided a possible rationalization for the moderate yields of the migration of the 2-(3-heteroaryl)carbamates. Using similar methodolgy 4-methoxy-6*H*-benzofuro[2,3-*c*]benzo[*e*]pyran-6-one (4-methoxyisocoumestan) **509a** and 4-methoxy-6*H*-thianaphtheno[2,3-*c*]benzo[*e*]pyran-6-one (4-methoxyisothiacoumestan) **509b** were prepared. The synthesis of **509b** represents the first report of the synthesis of this ring system. Similarly, 4-methoxy-6*H*-indolo[3,2-*c*]benzo[*e*]pyran-6-one (azacoumestan) **514** and 4-methoxy-6*H*-indolo[2,3-*c*]benzo[*e*]pyran-6-one (4-methoxyisoazacoumestan) **515** were prepared in good yield. The preliminary results described should allow the synthesis of a wide variety of members in these classes of compounds.

10. Future Work

10.1 Total Synthesis of the Gilvocarcins

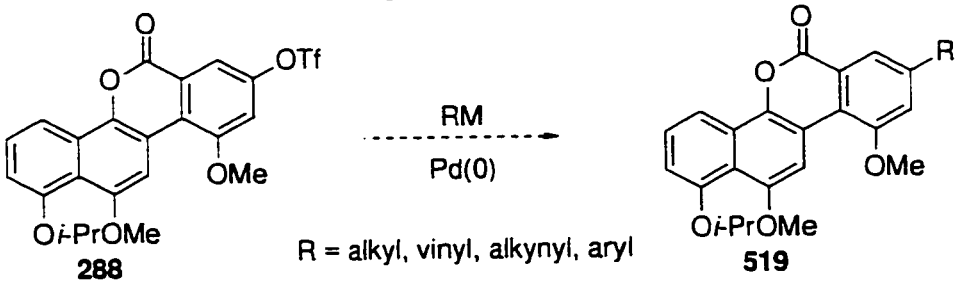
The competing cleavage of the C-5 isopropoxy group under the DreM conditions warrants further study. An understanding of this process may allow further optimization of the reaction conditions to minimize this side reaction. Preparation of **517** **(Scheme 124)** as a model, followed by rigorous investigation of the base induced cleavage might help circumvent this limitation in the total synthesis. Also, the triflate **288** which served as a common intermediate for the coupling of the C-8 substituents **(Scheme 71)**, could be used to prepare synthetic analogues of the gilvocarcins for the purpose of biological testing **(Scheme 125)**.

Scheme 124



517 **518**

Scheme 125

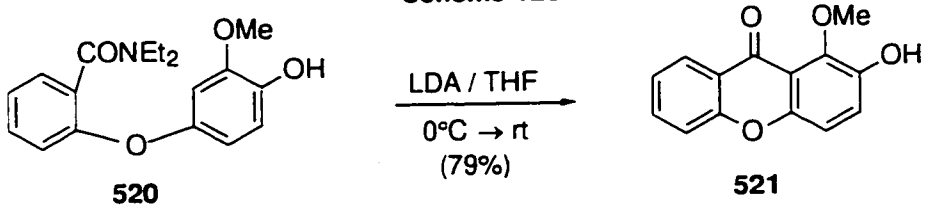


288 R = alkyl, vinyl, alkynyl, aryl **519**

10.2 Total Synthesis of Arnottin I

Protection of the catechol portion of the biarylcarbamate in the total synthesis of arnottin I was problematic. The yield obtained for DreM - carbamoyl migration of MOM ether **313** was invariably poor. Thorough examination of the reaction mixture may elucidate the nature of the competing processes, allowing an improved yield in this step. A general improvement in the DreM of biarylcarbamates would be the successful carbamoyl migration of hydroxy bearing derivatives. In our laboratories, Bower[354] effected xanthone formation from a carboxamido diphenyl ether bearing a hydroxy group **520 → 521 (Scheme 126)**. Although a model case during the gilvocarcin synthesis was unsuccessful **(Scheme 67)**, it was not studied in detail.

Scheme 126

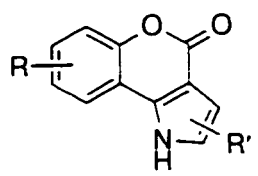


520 **521**

10.3 DreM - Carbamoyl Migration of Heterobiarylcarbamates

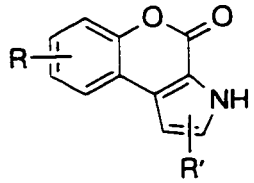
The preliminary results described in Section 9 clearly allow for expansion of the DreM - carbamoyl migration of heterobiarylcarbamates. In the present study, no cases were examined which involved substituents in the heteroaryl ring. Judicious choice of cross coupling partners should allow thorough investigation of the scope of the process. Similarly, no attempts were made to prepare the pyrrolocoumarins **(522** and **523)**. The general retrosynthetic analysis described in **Scheme 116** should be equally applicable based on the analogy of the indolocoumarins prepared **(Scheme 122** and **123)**.

Similarly, synthesis of furo[3,2-*c*]coumarins **399 (Section 7.6.1)** might be attempted using the in situ silyl protection method described in **Scheme 120** for the thieno[3,2-*c*]coumarins.



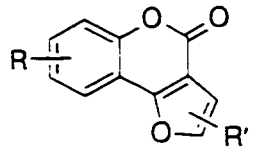
522

pyrrolo[3,2-c]coumarins



523

pyrrolo[2,3-c]coumarins



399

furo[3,2-c]coumarins

11. Experimental

11.1 General Procedures

Melting points were determined using a Büchi SMP-20 or a Fisher-Johns hot stage apparatus and are uncorrected. Infrared spectra were determined on a Bomem FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AM-250 or AC-200, or AMX-500 instrument in $CDCl_3$ with TMS as an internal reference unless otherwise indicated. ^{1}H NMR spectral data is tabulated as follows: chemical shift, multiplicity, coupling constant and number of protons. ^{13}C NMR spectra were obtained using the JMOD pulse sequence unless otherwise stated and are tabulated as follows: chemical shift, multiplicity and coupling constant (in Hz) where appropriate and type of carbon ('o' designates an odd number of protons attached (i.e. CH, CH_3) and 'e' designates an even number (i.e. C, CH_2). For compounds in **Section 9** the JMOD spectra were acquired with the parameter D3 = 0.006 s (default: 0.008 s) to account for the larger (ca. 200 Hz) coupling constant of the C atom directly bound to the heteroatom. Mass spectra were obtained on a Kratos MS 890 spectrometer at the Guelph Center for Mass Spectrometry at the University of Guelph by Dr. H. S. McKinnon or on a VG 70 mass spectrometer by Dr. Jackie Jarvis or Mr. Tim Hoffman at the University of Waterloo. Elemental analyses were performed by either Chemisar Laboratories Guelph, Ontario or MHW Laboratories, Phoenix, Arizona. TLC analysis was carried out using Merck 60F-254 precoated silica sheets and flash column chromatography was carried out using Merck silica gel 60 (0.040 - 0.063 mm).

Tetrahydrofuran (THF), diethyl ether (Et_2O) and 1,2-dimethoxyethane (DME) were freshly distilled from sodium benzophenone ketyl before use. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 before use. $Pd(PPh_3)_4$,[355] $NiCl_2(dppp)$[356] and $PdCl_2(dppf)$[357] were prepared according to literature procedures. Solutions of *s*-BuLi (cyclohexane solution) and *t*-BuLi (pentane solution) were purchased from Aldrich

Chemical Company while *n*-BuLi (hexane solution) was kindly donated by FMC corporation and all alkyllithium reagents were titrated regularly with a standard solution of *s*-butanol with 1,10-phenanthroline as indicator.[358] Reactions carried out at -78°C and -100°C employed CO_2 (dry ice)-acetone and liquid nitrogen-absolute EtOH baths respectively. All reactions requiring anhydrous conditions were carried out using syringe-septum cap techniques in oven or flame dried glassware under an argon atmosphere. Diisopropylamine and *N.N.N'.N'*-tetramethylethylenediamine (TMEDA) were dried over CaH_2 and subsequently distilled under argon and stored in a septum sealed serum bottle over solid KOH. All other commercial reagents were purchased from Aldrich Chemical Co., Lancaster Synthesis Ltd., Fluka, British Drug House Ltd., or Alfa. LDA was prepared by dropwise addition of an equimolar amount of *n*-BuLi to a solution of diisopropylamine in dry THF at 0°C.

The phrase "standard workup" refers to the following: the reaction mixture is quenched with saturated aqueous NH_4Cl followed by extraction with CH_2Cl_2 or Et_2O. The combined organic layers are usually washed with H_2O and brine then dried over anhydrous Na_2SO_4 and the solvent is removed *in vacuo* to afford the crude product. In all cases where I_2 was used as an electrophile standard workup includes washing the combined organic layers with 10% $Na_2S_2O_3$.

11.2 Standard Methods:

General Procedure A: Preparation of aryl-*O*-carbamates. A mixture of phenol (1 mmol), K_2CO_3 (1.3 mmol), and *N,N*-diethylcarbamoyl chloride (1.5 mmol) in acetonitrile was heated at reflux for 12 - 16 h. Standard workup followed by chromatography and distillation or recrystallization afforded the pure products.

The following *O*-arylcarbamates were prepared according to the above procedure. These compounds showed physical and spectral properties consistent with those reported.

***N*,*N*-Diethyl *O*-phenylcarbamate.** (82%) bp 90-95°C / 0.2-0.3 mmHg [lit[359] bp 88-90°C / 0.3 mmHg]

***N*,*N*-Diethyl *O*-(2-methoxy)phenylcarbamate.** (72%) bp 112-114°C / 0.01 mmHg [lit[359] bp 116-122°C / 0.02 mmHg].

***N*,*N*-Diethyl *O*-1-naphthylcarbamate.** (86%) bp 125-131°C / 0.01 mmHg [lit[359] bp 135-140°C / 0.1 mmHg]

General Procedure B: Metalation of *N*,*N*-diethyl-*O*-arylcarbamates. To a solution of aryl carbamate (1 mmol) and TMEDA (1.20 mmol) at -78°C was added dropwise *s*-BuLi (1.20 mmol). After stirring the reaction mixture for a period of time (15 min - 1h) the appropriate electrophile was added by syringe and the resulting solution allowed to warm slowly to room temperature. Standard workup followed by chromatography and distillation or recrystallization afforded the pure products.

General Procedure C1: Remote metalation of biaryl-*O*-carbamates. To a solution of LDA (2 - 5 mmol) in THF (5 mL), prepared as described in the general experimental section, was added a solution of the biarylcarbamate (1.00 mmol) in THF (5 mL) by canula. The solution was then heated at reflux or stirred at rt depending on the substrate until the disappearance of SM by TLC. Standard workup followed by column chromatography afforded the hydroxyamides.

General Procedure C2: Introduction of LDA in Portions. To a solution of LDA (1.00 - 2.00 mmol) in THF (5 mL) was added a solution of biarylcarbamate (1.00 mmol) in THF (1.00 mmol) and the reaction mixture was heated at reflux or stirred at rt

for 1-2 h. A fresh portion of LDA (1.00 - 2.00 mmol) was added by canula and refluxing was continued. This process is repeated as necessary. Standard workup followed by column chromatography afforded the hydroxyamides.

General Procedure D: Cyclization of hydroxyamides. The crude hydroxyamide (1.00 mmol) was dissolved in glacial HOAc (10 mL) and heated at reflux for 10 min and the HOAc was removed *in vacuo*. Standard workup followed by chromatography and distillation or recrystallization afforded the pure products.

General Procedure E: Negishi coupling of aryl halides with arylzinc reagents. 1) Generation of aryl zinc species: To a solution of aryl halide (1.20 mmol) in THF (10 mL) at -78°C was added *n*-BuLi (1.30 mmol) dropwise, the reaction mixture was allowed to stir for 15 min and a solution of flame-dried $ZnCl_2$ or $ZnBr_2$ (1.50 mmol) was added dropwise by canula. The solution was stirred at -78°C (15 - 60 min), the cooling bath removed and the solution warmed to rt over 1h. **2) Coupling of arylzinc with aryl halide**: A separate flask was charged with the aryl halide (1.00 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) in THF (5 mL). The solution of the aryl zinc reagent was then added via canula at rt and the mixture was heated at reflux until disappearance of SM by TLC (3 - 16 h). Standard workup followed by chromatography afforded the biaryl products.

General Procedure F: Negishi coupling of aryl halides with 2-carbamoylarylzinc reagents. 1) Generation of the arylzinc reagent: To a solution of aryl carbamate (1.00 mmol) and TMEDA (1.10 mmol) in THF (10 mL) at -78°C was added *s*-BuLi (1.10 mmol) and the solution was stirred at rt for 3 - 12h. A solution of $ZnCl_2$ (1.20 mmol) in THF or Et_2O was then added and the reaction mixture stirred at -78°C for 15 min and allowed to warm to rt (1h). **2) Coupling of arylzinc reagent with aryl halides**: The solution of the arylzinc reagent was added *via* canula

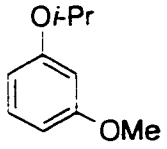
to a flask containing a solution of aryl halide (0.50-0.90 mmol) and Pd catalyst (0.05 mmol) in THF (10 mL). The resulting solution was heated to reflux or stirred at rt, depending on the substrate, until the disappearance of SM by TLC. Standard workup followed by column chromatography afforded the biaryl compounds.

General Procedure G: Suzuki Coupling of arylboronic acids with aryl halides. A mixture of aryl halide (1.00 mmol), Pd catalyst (0.05 mmol), base (aq Na_2CO_3, or $Ba(OH)_2 \cdot 8H_2O$, 2.00 mmol) and arylboronic acid (1.2-1.5 mmol) in DME was heated at reflux for 1 - 12 h. The reaction mixture was filtered through a pad of celite to remove Pd residues and the DME was removed on the rotovap. The residue was then diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography to afford the biaryls.

General Procedure H: Remote metalation of heterobiaryl *O*-carbamates. To a solution of LDA (2 - 4 mmol) in THF (5 mL) at 0°C was added a solution of the heterobiaryl *O*-carbamate (1 mmol) in THF (5 mL). The reaction mixture was stirred for 10 min and quenched with sat NH_4Cl. Standard workup followed by chromatography afforded the crude hydroxy amides. Direct cyclization was carried out according to general procedure D.

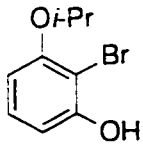
11.3 Specific Experimental Procedures

1-Isopropoxy-3-methoxybenzene (229).



A mixture of *i*-PrI (18.0 mL, 183.3 mmol), K_2CO_3 (25.30 g, 183.1 mmol) and 3-methoxyphenol **(228)** (15.16 g, 122.1 mmol) in acetone (500 mL) was heated at reflux for 14 h. The reaction mixture was cooled to rt and the acetone removed *in vacuo*. The residue was diluted with H_2O (100 mL) and Et_2O (100 mL) and the layers separated. The aqueous phase was extracted twice more with Et_2O (2 X 50 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation affording the title compound as a colorless liquid (19.50 g, 96%). bp 54-60°C / 0.2 mmHg, lit[360] bp 120-121°C / 18 mmHg; ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.15 (m, 1H), 6.50 (m, 3H), 4.54 (sept J = 7 Hz, 1H), 3.75 (s, 3H), 1.32 (d J = 7 Hz, 6H). The NMR spectrum given was consistent with that reported in the literature.[361]

2-Bromo-3-isopropoxyphenol (231).



To a solution of TMEDA (1.51 mL, 10.00 mmol) in THF (10 mL) at 0°C was added *n*-BuLi (5.80 mL, 1.72 mol/L) dropwise. This solution was allowed to stir for 10 min and was then added to a separate flask charged with 3-isopropoxyanisole **(229)** (1.50 g, 9.06 mmol) and THF (20 mL) at rt. The resulting mixture was heated at reflux for 12 h and cooled to rt. To this suspension was added $BrCF_2CF_2Br$ (2.50 mL, 21.0 mmol) and the ppt disappeared after stirring for 1 h. Standard workup followed by column chromatography (10:1 hexane:EtOAc) afforded 1.45 g of the desired bromo derivative **230a** which was contaminated with ca. 5% regioisomer which was not separable by further chromatography (59% yield by nmr).

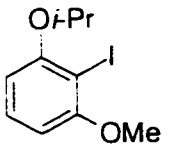
Attempted distillation resulted in decomposition therfore this material was used directly for the next step. To a suspension of NaH (0.538 g, 13.45 mmol) in dry DMF (50 mL) at rt was added EtSH (0.940 mL, 12.90 mmol). After the evolution of hydrogen had ceased the reaction was allowed to stir for 10 min at rt and a solution of the mixture of brominated ethers (1.45 g, 5.92 mmol) in DMF (15 mL) was added *via* canula. The resulting mixture was heated at 100°C for 1 h, cooled to rt and acidified with 10% HCl. The solution was then extracted with Et_2O (3 X 50 mL). The combined organic layers were extracted with 5% KOH (3 X 50 mL) and these were washed with Et_2O and acidified with conc HCl. The acidified aqueous layer was extracted with Et_2O (3 X 50 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (10:1 hexane:EtOAc) affording a colorless oil (0.875 g, 78%). IR (neat) ν (max) 3434 (br), 2978, 2931, 1592, 1471, 1380, 1304, 1159, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.04 (app t J = 8.2 Hz, 1H), 6.63 (d J = 8.1 Hz, 1H), 6.47 (d J = 8.1 Hz, 1H), 5.75 (s, 1H, exch), 4.54 (sept J = 6.0 Hz, 1H), 1.40 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.1 (e), 153.1 (e), 128.4 (o), 108.2 (o), 106.7 (o), 102.7 (e), 72.00 (o), 22.00 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 232 (18), 230 (18), 217190 (100), 188 (100), 172 (16), 170 (16), 161 (8), 159 (8); HRMS (EI (70 eV)) *m/e* calcd for $C_9H_{11}BrO_2$: 229.9942, found 229.9928.

2-Bromo-3-isopropoxyphenyl trifluoromethanesulfonate (232).

To a solution of 2-bromo-3-isopropoxyphenol **(231)** (0.635 g, 2.75 mmol), in CH_2Cl_2 (20 mL) at 0°C was added Et_3N (0.80 mL, 5.74 mmol) followed by Tf_2O (0.70 mL, 4.14 mmol) dropwise over 5 min. The reaction was allowed to warm to rt over 6 h and was then quenched with H_2O. The layers were separated and the aq phase extracted with CH_2Cl_2 (2 X 10 mL) and the

combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (6:1 hexane:EtOAc) giving a colorless liquid (0.925 g, 93%). IR (neat) ν (max) 2983, 2936, 1590, 1439, 1387, 1335, 1279, 1222, 1126, 1045, 1012 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.29 (app t J = 8.4 Hz, 1H), 6.88-6.96 (m, 2H), 4.60 (sept J = 6.0 Hz, 1H), 1.39 (d J = 6.0 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.6 (e), 148.2 (e), 128.5 (o), 118.6 (q J = 320 Hz), 114.1 (o), 114.0 (o), 107.9 (e), 72.72 (o), 21.76 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 364 (M^+, 12), 362 (12), 349 (2), 347 (2), 322 (100), 320 (100), 258 (28), 256 (28), 189 (97), 187 (97), 172 (41), 170 (41), 161 (66), 159 (66), 133 (10), 131 (10); HRMS (EI (70 eV)) *m/e* calcd for $C_{10}H_{10}BrF_3O_4S$: 361.9435, found 361.9415.

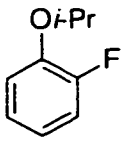
2-Iodo-3-isopropoxyanisole (230b).



To a solution of *n*-BuLi (20.0 mL, 1.72 mol/L) in Et_2O (25 mL) was added a solution of 3-isopropoxyanisole **(229)** (5.238 g, 31.50 mmol) in Et_2O (50 mL) at rt. The reaction mixture was heated at reflux for 8 h, cooled to 0°C and a solution of I_2 (12.90 g, 50.83 mmol) in Et_2O (50 mL) was added. This mixture was allowed to stir for 1h and was then quenched with sat NH_4Cl and diluted with water (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 X 50 mL). The combined organic layers were washed (10% $Na_2S_2O_3$, H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (10:1 hexane:EtOAc) affording the title compound as an unstable dark oil (5.30 g, 58%). IR (neat) ν (max) 2976, 2934, 2836, 1507, 1464, 1379, 1290, 1249, 1116, 1087, 1019 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20 (app t J = 8.0 Hz, 1H), 6.50, (m, 2H), 4.55 (sept J = 6.0 Hz, 1H), 3.90 (s, 3H), 1.39 (d J = 6.0 Hz, 1H); 159.5 (e), 158.1 (e), 129.4 (o), 107.2 (o), 80.21 (e), 71.90 (o), 56.34

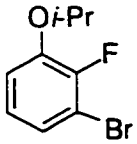
(o), 22.08 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 292 (M^+, 59), 250 (100), 235 (22), 220 (18), 207 (20), 179 (4), 164 (3); HRMS (EI (70 eV)) *m/e* calcd for $C_{10}H_{13}IO_2$: 291.9960, found 291.9936.

2-Fluoroisopropoxybenzene (238).



A mixture of 2-fluorophenol **(237)** (22.18 g, 0.1979 mol), K_2CO_3 (40.00 g, 0.2970 mol) and *i*-PrI (30.0 mL, 0.297 mol) in CH_3CN (300 mL) was heated at reflux for 18 h. The mixture was cooled to rt and diluted with H_2O (200 mL) and the whole extracted with Et_2O (3 X 250 mL). The combined organic layers were washed well with H_2O (5 X 300 mL) and brine. The dry organic layer was concentrated *in vacuo* and the residue purified by distillation affording the title compound as a colorless liquid (25.34 g, 83%) bp 103-100°C / 163-176 mmHg (aspirator). IR (neat) ν (max) 3071, 3044, 2980, 1611, 1589, 1502, 1459, 1385, 1308, 1266, 1206, 1138, 1115, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.80-6.71 (m, 4H), 4.47 (sept J = 6.0 Hz, 1H), 1.33 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.9 (d J = 245 Hz) (e), 145.9 (e), 124.1 (d J = 3.6 Hz) (o), 121.3 (d J = 6.2 Hz) (o), 118.0 (o), 116.3 (d J = 19.0 Hz) (o), 72.30 (o), 21.97 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 154 (M^+, 12), 139 (4), 112 (100), 100 (10), 83 (6), 57 (6); Anal. calcd for $C_9H_{11}FO$: C, 70.11; H, 7.19; found: C, 70.20; H, 7.06.

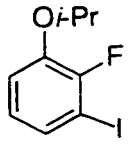
3-Bromo-2-fluoroisopropoxybenzene (239a).



To a solution of 2-fluoroisopropoxybenzene **(238)** (0.405 g, 2.63 mmol) and TMEDA (0.44 mL, 2.89 mmol) in THF (10 mL) at -78°C was added *s*-BuLi and the mixture allowed to stir at -78°C for 2 h. Standard workup followed by column chromatography (15:1 hexane:EtOAc) afforded the title compound

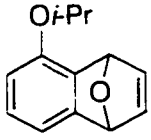
(0.404 g, 66%) as a light yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.91 (m, 2H), 4.53 (sept., J = 6 Hz, 1H), 1.36 (d, J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.9 (d J = 246 Hz) (e), 147.0 (d J = 11.3 Hz) (e), 125.0 (o), 124.5 (d J = 5.2 Hz), 116.7 (e), 109.9 (d J = 18.8 Hz), 72.97 (o), 22.02 (o).

2-Fluoro-3-iodoisopropoxybenzene (239b).



A flame dried 250 mL 2-necked flask equipped with a dropping funnel was charged with THF (100 mL), TMEDA (6.70 mL, 44.5 mmol) and 2-fluoroisopropoxybenzene **(238)** (6.24 g, 40.5 mmol) and the solution was cooled to -78°C. To this solution was added *s*-BuLi (32.0 mL, 1.39 mol/L) dropwise over 20 min and the resulting yellow mixture was allowed to stir at -78°C for 2 h. At this point a solution of I_2 (23.20 g, 91.40 mmol) in THF (50 mL) was added *via* the dropping funnel over a period of 25 min. The reaction mixture was allowed to warm to rt over 4 h, quenched with sat. NH_4Cl and the THF removed *in vacuo*. The residue was extracted with Et_2O (3 X 100 mL) and the combined extracts were washed (10% $Na_2S_2O_3$, H_2O, brine), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (95:2 hexane:EtOAc) affording a colorless oil (8.81 g, 78%). bp 86-87°C / 0.2 mmHg. IR (neat) ν (max) 3024, 2979, 2931, 1589, 1464, 1384, 1375, 1306, 1271, 1224, 1174, 1142, 1109 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28 (ddd J = 7.9, 5.3, 1.5 Hz, 1H), 6.93 (ddd J = 8.2, 8.0, 1.5 Hz, 1H), 6.78 (ddd J = 8.2, 8.0, 1.4 Hz, 1H), 4.50 (sept J = 6.1 Hz, 1H), 1.35 (d J = 6.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.1 (d J = 244 Hz) (e), 146.0 (d J = 12.3 Hz) (e), 130.5 (o), 125.4 (d J = 4.5 Hz) (o), 117.6 (o), 82.2 (d J = 22.9 Hz) (e), 72.7 (o), 21.90 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 280 (100), 238 (100), 152 (2.3), 111 (14.5), 83 (16); HRMS (EI (70 eV)) *m/e* calcd for $C_9H_{10}FIO$: 279.9760, found 279.9781.

1,4-Dihydro-5-isopropoxy-1,4-epoxynaphthalene (240).



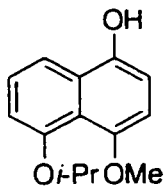
Procedure 1: *From iodo precursor **239b**:* To a solution of aryl iodide **239b** (173.8 mg, 0.6210 mmol) and furan (2.00 mL, 27.5 mmol) in Et_2O (4 mL) at -10°C (internal) was added *n*-BuLi (0.42 mL, 1.63 mol/L) dropwise over 10 min. The solution was allowed to stir for 45 min and then allowed to warm to rt. Standard workup followed by column chromatography (9.5:0.5 hexane:EtOAc) afforded the title compound as a colorless liquid (125.4 mg, 44%). IR (neat) ν (max) 3016, 2977, 1615, 1598, 1469, 1383, 1373, 1280, 1254, 1179, 1117 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (dd J = 5.5, 1.8 Hz, 1H), 7.01 (dd J = 5.5, 1.8 Hz, 1H), 6.91 (m, 2H), 6.57 (dd J = 7.2, 1.8 Hz, 1H), 5.90 (dd J = 1.7, 0.9 Hz, 1H), 5.68 (dd J = 1.8, 0.9 Hz, 1H), 4.44 (sept J = 6.0 Hz, 1H), 1.31 (d J = 6.0 Hz, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$, POWGATE) δ 151.4, 151.4, 142.9, 142.8, 136.6, 126.7, 113.8, 113.7, 82.6, 80.1, 71.3, 22.4, 22.2; MS (EI (70 eV)) *m/e*: (rel intensity) 202 (M^+, 20), 174 (4.4), 160 (36), 132 (100), 115 (4.4), 103 (8,8), 77 (12), 43 (67); HRMS (EI (70 eV)) *m/e* calcd for $C_{13}H_{14}O_2$: 202.0994, found 202.1001.

Procedure 2: *From iodo precursor **239b** (MeLi)*: Repetition of the experiment using aryliodode **239b** (0.2944 g, 1.050 mmol), furan (1.20 mL, 16.7 mmol), MeLi (0.76 mL, 1.35 mol/L in Et_2O) gave **240** (124.0 mg, 58%).

Procedure 3: *From iodo precursor **239b** (MeLi)*: Repetition of the experiment using aryliodide **239b** (7.121 g, 25.44 mmol), furan (31.0 mL, 426 mmol), and MeLi (21.2 mL, 1.25 mol/L in Et_2O) gave **240** (3.60 g, 70%).

Procedure 4: *From bromo precursor **239a** (MeLi)*: Repetition of the experiment using arylbromide **239a** (0.2117 g, 0.9090 mmol), furan (1.10 mL, 15.5 mmol) and MeLi (0.71 mL, 1.35 mol/L in Et_2O) gave **240** (87.0 mg, 47%).

5-Isopropoxy-4-methoxy-1-naphthol (233).

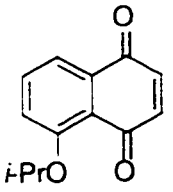


Procedure 1: To a solution of aryliodide **239b** (0.507 g, 1.08 mmol), and 2-methoxyfuran (2.80 mL, 30.4 mmol) in Et_2O (5 mL) at -10°C was added MeLi (1.80 mL, 1.98 mmol in Et_2O) dropwise over 5 min. The solution was allowed to stir for 20 min and standard workup followed by column chromatography (7:3 hexane:Et_2O) and recrystallization (hexane:Et_2O) afforded the title compound as colorless needles (0.194 g, 46%). mp 137-138°C (hexane:Et_2O) lit.[362] mp 101°C; IR (KBr) ν (max) 3370-3060 (br), 3063, 2932, 2828, 1621, 1593, 1519, 1449, 1358, 1261, 1176, 1117, 1049 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd J = 8.4, 1.0 Hz, 1H), 7.38 (dd J = 8.3, 7.7 Hz, 1H), 6.98 (dd J = 7.7, 1.0 Hz, 1H), 6.71 (s, 2H), 5.11 (s, 1H exch), 4.56 (sept J = 6.0 Hz, 1H), 3.88 (s, 3H), 1.41 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$, POWGATE) δ 154.4, 150.8, 151.2, 145.9, 128.0, 125.8, 120.5, 115.1, 113.5, 108.7, 72.87, 57.91, 22.06; MS (EI (70 eV)) *m/e*: (rel intensity) 232 (M^+, 33), 190 (37), 175 (100), 147 (17), 131 (13), 118 (7.6), 103 (12), 91 (6.8); Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; found: C, 72.36, ; H, 6.72.

Procedure 2: *THF as solvent*: Repetition of the experiment using aryliodide (0.5076 g, 1.814 mmol), 2-methoxyfuran (2.80 mL, 30.4 mmol), MeLi (1.80 mL, 2.00 mmol) in THF (5 mL) gave **233** (44.7 mg, 11%).

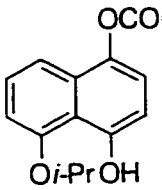
Procedure 3: *From aryltriflate 232*: To a solution of aryltriflate **232** (0.2122 g, 0.5847 mmol) and 2-methoxyfuran (0.12 mL, 1.30 mmol) in THF (5 mL) was added *n*-BuLi (0.42 mL, 1.5 mol/L). The reaction was allowed to stir for 20 min and was then quenched with sat NH_4Cl. Standard workup followed by column chromatography (7:3 hexane:Et_2O) afforded the title compound (73.2 mg, 54%).

5-Isopropoxy-1,4-naphthoquinone (251).



Following a literature[230] procedure, a solution of juglone (2.77g, 15.91mmol), *i*-PrI (3.50 mL, 35.06 mmol) and Ag_2O (20.0 g, 86.30 mmol) in $CHCl_3$ (75 mL) was stirred under argon at rt until disappearance of SM by TLC (CH_2Cl_2, 2h). At this point the reaction mixture was filtered and concentrated *in vacuo*. The residue was recrystallized from hexane:CH_2Cl_2 giving 2.62 g (76%) of the title compound as an orange powder. mp 94-96°C (hexane:CH_2Cl_2), lit[230] mp 96°C (hexane:CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.71 (dd J = 7.6, 1.4 Hz, 1H), 7.60 (app t J = 8.1, 7.6 Hz, 1H), 7.29 (dd J = 8.5, 1.4 Hz, 1H), 6.84 (m, 2H), 4.69 (sept, J = 6 Hz, 1H), 1.45 (d, J = 6 Hz, 6H).

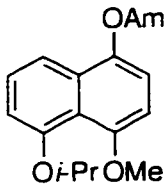
***N,N*-Diethyl *O*-(4-hydroxy-5-isopropoxy)naphthyl-1-carbamate (252).**



A mixture of 5-isopropoxyjuglone **(251)** (0.289 g, 1.34 mmol), $ClCONEt_2$ (0.5 mL, 3.95 mmol), pyridine (0.32 mL, 3.96 mmol), and Zn dust (0.917 g, 14.03 mmol) in $CHCl_3$ (7.0 mL) was heated at reflux until disappearance of SM by TLC (2 h). The reaction mixture was then cooled, diluted with H_2O followed by 10% HCl, and the layers separated. The aqueous layer was extracted twice more with $CHCl_3$ and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexane:EtOAc) and then recrystallized

(EtOH:H_2O) affording the title compound as light brown plates (0.294 g, 70%). mp 66-67°C (EtOH:H_2O). IR (KBr) ν (max) 3374, 3064, 2977, 2934, 1715, 1635, 1393, 1514, 1462, 1404, 1350, 1316, 1267, 1235, 1211, 1154, 1109, 1033 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.69 (s, 1H), (dd J = 8.4, 1.3 Hz, 1H), 7.32 (t J = 7.4, Hz, 1H), 7.12 (d J = 8.4 Hz, 1H), 6.82 (d J = 7.6, 1.0 Hz, 1H), 6.79 (d J = 8.4 Hz, 1H), 4.85 (sept J = 6.1 Hz, 1H), 3.57 (q, br, J = 7.0 Hz, 2H), 3.42 (q, br, J = 7.0 Hz, 2H), 1.49 (d J = 6.1 Hz, 6H), 1.35 (t, br, J = 7.0 Hz, 3H), (t, br, J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.6 (e), 154.3 (e), 152.3 (e), 139.3 (e), 130.2 (e), 126.2 (o), 120.1 (o), 116.3 (e), 115.0 (o), 109.1 (o), 107.0 (o), 72.89 (o), 42.25 (e), 41.89 (e), 21.96 (o), 14.42 (o), 12.61 (o), MS (EI (70 eV)) *m/e*: (rel intensity) 317 (M^+, 25), 260 (0.5), 204 (1.3), 175 (12), 147 (1.6), 100 (100), 72 (27); Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.70; N, 4.41 found: C, 68.26; H, 7.36; N, 4.33.

N,N-Diethyl-5-isopropoxy-4-methoxy-1-naphthyl-O-carbamate (253).

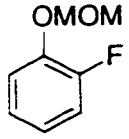


Procedure 1: *From naphthol 233*: According to general procedure A, a mixture of naphthol **233** (2.86 g, 12.32 mmol), K_2CO_3 (2.92 g, 18.5 mmol), $ClCONEt_2$ (2.34 ml, 18.47 mmol) in CH_3CN (100 mL), was heated at reflux for 12 h. Standard workup followed by cloumn chromatography (7:3 hexane:Et_2O) and then recrystallization (hexane:Et_2O) afforded the title compound as colorless plates (3.68 g, 90%). mp 84-85°C (hexane:Et_2O); IR (KBr) ν (max) 3070, 2950, 1722, 1586, 1513, 1323, 1249, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (dd J = 8.4, 1.1 Hz, 1H), 7.36 (dd J = 8.4, 7.6 Hz, 1H), 7.10 (d J = 8.4 Hz, 1H), 6.90 (dd J = 7.6, 1.1 Hz, 1H), 6.80 (d J = 8.4 Hz, 1H), 4.55 (sept J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.61 (q J = 7.0 Hz, 2H), 3.40 (q J = 7.0 Hz, 2H), 1.42 (d J = 6.0 Hz, 6H), 1.36 (t J = 7.0 Hz, 3H), 1.23 (t J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz,

$CDCl_3$) δ 155.2 (e), 154.7 (e), 141.1 (e), 131.2 (e), 126.8 (o), 120.4 (e), 118.4 (o), 114.8 (o), 113.8 (o), 106.2 (o), 73.30 (o), 56.93 (o), 42.39 (e), 42.02 (e), 22.13 (o), 14.56 (o), 13.52 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 331 (M^+, 46), 289 (2), 231 (4), 189 (20), 100 (100), 72 (58); Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23; found: C, 69.00; H, 7.71; N, 4.22.

Procedure 2: *From hydroxycarbamate 252*: A mixture of **252** (1.37 g, 4.35 mmol), K_2CO_3 (3.39 g, 24.53 mmol) and MeI (1.60 mL, 25.7 mmol) in acetone (50 mL) was heated at reflux for 12 h. The reaction was cooled to rt and standard workup followed by column chromatography (silica plug, 2:1 hexane:EtOAc) followed by recrystallization (hexane:Et_2O) afforded the title compound as colorless plates (1.21 g, 84%). mp 86-87°C (hexane:Et_2O). Mixture melting point with a sample prepared by procedure 1: 85-86°C. Spectral properties of the compound were identical with material prepared by procedure 1.

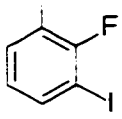
2-Flouromethoxymethoxybenzene (243).



To a suspension of NaH (10.0 g, 0.250 mmol) and MOMCl (6.80 mL, 89.5 mmol) in dry DMF (75 mL) at 0°C was added a solution of 2-fluorophenol **(237)** (5.02 g, 44.8 mmol) in DMF (25 mL). This mixture was allowed to warm to rt over 12 h and was then *slowly* poured portionwise into H_2O (200 mL) containing ice. The mixture was then acidified with 10% HCl (pH 3-4) and the aqueous phase extracted with Et_2O (3 X 200 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (14:1 hexane:EtOAc) followed by distillation giving the title compound as a colorless oil (4.83 g, 69%). bp 172-176°C / 22-23 mmHg, lit[363] bp

100°C / 20 mmHg. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.89-7.84 (m, 4H), 5.20 (s, 2H), 3.52 (s, 3H).

2-Fluoro-3-iodomethoxymethoxybenzene (241).

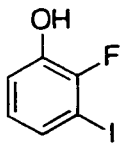


Procedure 1: *Metalation of ether 243*: To a solution of *t*-BuOK (0.212 g, 1.80 mmol) in THF (5 mL) at -78°C was added *n*-BuLi (1.20 mL, 1.53 mol/L) dropwise and the solution was allowed to stir for 10 min. A solution of MOM ether **243** (0.246 g, 1.63 mmol) in THF (3 mL) was added dropwise over 5 min *via* canula and the yellow-orange mixture allowed to stir for a further 2 h. The resulting red solution was treated with a solution of I_2 in THF (5 mL), added dropwise by syringe. The solution was allowed to warm to rt over 12 h. Standard workup followed by column chromatography (12:1 hexane:EtOAc) afforded the title compound (0.327 g, 71%). bp 90-95°C / 0.20 mmHg. IR (neat) ν (max) 2933, 2827, 1593, 1465, 1403, 1310, 1266, 1226, 1155, 1082 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (ddd J = 8.0, 5.3, 1.5 Hz, 1H), 7.16 (ddd J = 8.2, 7.6, 1.5 Hz, 1H), 6.80 (dt J = 8.2, 1.5 Hz, H), 5.20 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.7 (d J = 244 Hz) (e), 145.2 (e), 131.9 (o), 125.6 (d J = 6.0 Hz) (o), 118.1 (o), 95.71 (e), 82.00 (d J = 22.8 Hz) (e), 56.38 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 282 (M^+, 100), 252 (47), 221 (13), 209 (23), 183 (4.7), 110 (9.4), 94 (34), 82 (23), 45 (99); HRMS (EI (70 eV)) *m/e* calcd for $C_8H_8FIO_2$: 281.9553, found 281.9559.

Procedure 2: *Etherification of phenol 245*: To a solution of isopropyl ether **239b** (6.30 g, 22.51 mmol) in CH_2Cl_2 (200 mL) at 0°C was added BCl_3 (30.0 mL, 1.0 mol/L in CH_2Cl_2. The solution was allowed to stir for 12 h and was quenched with sat NH_4Cl. Standard workup afforded the crude phenol **245** which was added to a suspension of

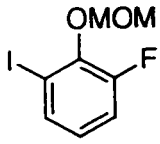
NaH (6.50 g, 0.163 mmol) in dry DMF (75 mL) at 0°C. After evolution of hydrogen ceased (1 h) MOMCl (5.00 mL, 0.0669 mol) was added and the reaction warmed to rt over 2 h. The resulting solution was *slowly* poured into sat NH_4Cl (250 mL) containing ice and the whole extracted with Et_2O (3 X 125 mL). The combined organic layers were washed with H_2O (5 X100 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (20:1 hexane:EtOAc) followed by distillation affording the title compound as a colorless oil (3.98 g, 63%).

2-Fluoro-3-iodophenol (245).



To a solution of 2-fluorophenol **(237)** (0.320 g, 2.85 mmol) in THF (5 mL) at -78°C was added *n*-BuLi (1.80 mL, 1.65 mol/L) and the solution allowed to stir for 5 min. TMSCl (0.38 mL, 3.00 mmol) was added, the reaction mixture was allowed to stir at -78°C for 1 h and at which point the solution was treated with TMEDA (0.52 mL, 3.43 mmol) and *s*-BuLi (2.60 mL, 1.32 mol/L) and stirring was continued for 2 h. A solution of I_2 (1.40 g, 5.70 mmol) in THF (5 mL) was added dropwise *via* syringe over 5 min. The reaction mixture was allowed to warm to rt over 6 h and subsequent standard workup followed by column chromatography (12:1 hexane:EtOAc) afforded the title compound (0.200 g, 30%) as a colorless solid. mp 73-74°C (hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (m, 1H), 6.97 (ddd J = 8.1, 8.0, 1.2 Hz), 6.80 (ddd J = 8.1, 8.0, 1.2 Hz), 5.14 (s, 1H exch).

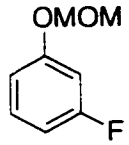
2-Fluoro-6-iodomethoxymethoxybenzene (244).



To a solution of MOM ether **243** (0.497 g, 3.19 mmol) and TMEDA (0.53 mL, 3.50 mmol) in THF (10 mL) was added *s*-BuLi (2.60 mL, 1.33 mol/L) dropwise over 5 min. The reaction mixture was allowed to stir for 2 h and a solution of I_2 (0.970 g, 3.82 mmol) in THF (15 mL) was added. The reaction

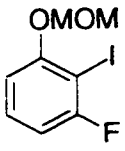
was allowed to stir for 3 h and the cooling bath was removed and the solution warmed to rt (1 h). Standard workup followed by column chromatography (30:1 hexane:Et_2O) afforded the title compound (0.661 g, 74%) along with the corresponding regioisomer **241** (0.108 g, 12%). IR (neat) ν (max) 3073, 2932, 2828, 1573, 1464, 1399, 1262, 1232, 1159, 1084, 1061 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.51-7.55 (m, 1H), 7.02-7.10 (m, 1H), 6.73-6.79 (m, 1H), 5.19 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.5 (e) (d J = 251 Hz), 144.4 (e) (d J = 12 Hz), 134.3 (o), 125.6 (o) (d J = 6.0 Hz), 117.0 (o) (d J = 10 Hz), 98.81 (e) (d J = 6.0 Hz), 92.31 (e), 57.88 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 282 (M^+, 100), 252 (52), 221 (12), 209 (25), 183 (2.0), 110 (40); HRMS (EI (70 eV)) *m/e* calcd for $C_8H_8FIO_2$: 281.9553, found 281.9552.

3-Fluoromethoxymethoxybenzene (247).



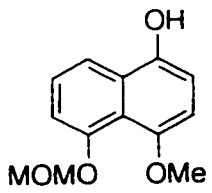
To a suspension of NaH (2.33 g, 58.3 mmol), and MOMCl (2.00 mL, 26.33 mmol) in DMF (10 mL) at 0°C was added a solution of 3-fluorophenol **246** (0.945 g, 8.43 mmol) in DMF (5 mL). The reaction mixture was allowed to warm to rt over 6h and then *slowly* poured into H_2O (100 mL) containing ice. The aqueous mixture was extracted with Et_2O (3 X 20 mL). The combined organic layers were washed (H_2O (5 X 50 mL), brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation affording the title compound as a colorless oil (1.11 g, 84%). bp 127-130°C / 30 mmHg, lit[364] bp 110°C / 0.1 mmHg (Kugelrohr). ^1H NMR (250 MHz, $CDCl_3$) δ 7.18-7.27 (m, 1H), 6.67-6.89 (m, 3H), 5.16 (s, 2H), 3.47 (s, 3H).

3-Fluoro-2-iodomethoxymethoxybenzene (248).



To a solution of MOM ether **247** (0.257 g, 1.65 mmol) in THF (10 mL) at -78°C was added *t*-BuLi (1.20 mL, 1.72 mol/L). The resulting yellow solution was allowed to stir 2 h and a solution of I_2 (0.594 g, 2.34 mmol) in THF (3 mL) was added. The reaction mixture was allowed to warm to rt over 12 h and standard workup followed by column chromatography (15:1 hexane:EtOAc) afforded the title compound as a colorless liquid (0.423 g, 89%). IR (neat) ν (max) 3077, 2957, 2827, 1590, 1462, 1404, 1308, 1269, 1240, 1203, 1155, 1094, 1028 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.22-7.29 (m, 1H), 6.86 (m, 1H), 6.75 (ddd J = 8.5, 7.6, 1.3 Hz, 1H), 5.26 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.2 (e) (d J = 244 Hz), 157.3 (e) (d J = 4.7), 129.9 (o), 109.8 (o) (d J = 24 Hz), 94.77 (e), 75.46 (e), 56.20 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 282 (M^+, 100), 252 (17), 237 (19), 209 (40), 110 (32); HRMS (EI (70 eV)) *m/e* calcd for $C_9H_9FIO_2$: 281.9553, found 281.9550.

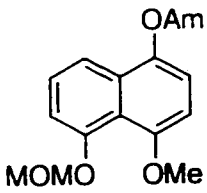
4-Methoxy-5-(methoxymethoxy)-1-naphthol (242).



Procedure 1: *From aryliodide 241:* To a solution of aryl iodide **241** (0.3155 g, 1.120 mmol) and 2-methoxyfuran (2.00 mL, 21.7 mmol) in Et_2O (1.00 mL) at -10°C was added MeLi (0.88 mL, 1.40 mol/l in Et_2O) dropwise over 3 min. The reaction was allowed to stir for 10 min at which point standard workup followed by column chromatography afforded the title compound 0.135 g (51%). mp 109-111 (dec), lit.[365] mp >113 (dec). ^1H NMR (250 MHz, $CDCl_3$) δ 7.87 (dd J = 8.4, 1.1 Hz, 1H), 7.4 (dd J = 8.4, 7.7 Hz, 1H), 7.17 (dd J = 7.7, 1.0 Hz, 1H), 6.73 (m, 2H), 5.26 (s, 2H), 3.91 (s, 3H), 3.61 (s, 3H).

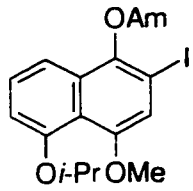
Procedure 2: *From aryliodide 248:* To a solution of aryl iodide **248** (0.360 g, 1.13 mmol) and 2-methoxyfuran (2.00 mL, 21.7 mmol) in Et_2O (1.5 mL) at -10°C was added MeLi (1.10 mL, 1.53 mol/L in Et_2O) dropwise over 5 min. The reaction was allowed to stir for 10 min at which point standard workup followed by column chromatography afforded the title compound 83.0 mg (28%).

***N,N*-Diethyl *O*-[(4-methoxymethoxy)-5-methoxy]naphthyl-1-carbamate (258).**



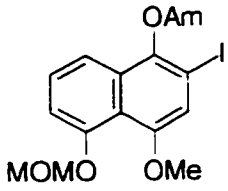
According to general procedure A, a mixture of naphthol **242** (1.15 g, 4.92 mmol), K_2CO_3 (1.19 g, 7.37 mmol) and $ClCONEt_2$ (2.50 mL, 18.44 mmol) in CH_3CN (30 mL) was heated at reflux for 24 h. Standard workup followed by column chromatography (5:2 hexane:EtOAc) afforded 1.14 g (70%) as a yellow oil. IR (neat) ν (max) 2955, 2834, 1718, 1625, 1587, 1463, 1392, 1320, 1262, 1221, 1154, 1083 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.55 (dd J = 8.4, 1.1 Hz, 1H), 7.39, (dd J = 8.4, 7.6 Hz, 1H), 7.16 (d J = 8.4 Hz, 1H), 7.10 (dd J = 7.6, 1.1 Hz, 1H), 6.81 (d J = 8.4 Hz, 1H), 5.25 (s, 2H), 3.95 (s, 3H), 3.60 (s, 3H), 3.46-3.59 (m, 4H), 1.36 (t J = 6.9 Hz, 3H), 1.18-1.25 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.5 (e), 154.3 (e), 154.1 (e), 140.9 (e), 130.9 (e), 126.8 (o), 119.4 (e), 118.5 (o), 115.9 (o), 114.1 (o), 105.7 (o), 96.90 (e), 56.68 (o), 56.38 (o), 42.28 (e), 41.92 (e), 14.47 (o), 13.42 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 333 (M^+, 13), 100 (33), 84 (63), 72 (11), 49 (100); HRMS (EI (70 eV)) *m/e* calcd for $C_{18}H_{23}NO_5$: 333.1577, found 333.1580.

_N,N_-Diethyl O-(2-iodo-5-isopropoxy-4-methoxy)-1-naphthylcarbamate (259a).



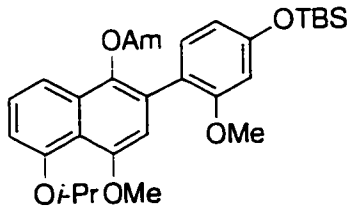
According to general procedure B, a solution of *N,N*-diethyl *O*-(4-methoxy-5-isopropoxy)-1-naphthylcarbamate **(253)** (0.278 g, 0.839 mmol) and TMEDA (0.15 mL, 0.99 mmol) in THF (10 mL) at -78°C was treated with *s*-BuLi (0.79 mL, 1.28 mol/L). The reaction mixture was allowed to stir for 20 min, a solution of I_2 in THF (5 mL) was added and the resulting solution was allowed to warm to rt (6 h). Standard workup followed by column chromatography (4:1 hexane:EtOAc) afforded the title compound (0.383 g, 94%) as a viscous oil. IR (neat) ν (max) 2976, 2983, 1724, 1609, 1575, 1502, 1457, 1424 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.07 (s, 1H), 6.94 (t J = 4.4 Hz, 1H), 4.51 (sept J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.63 (m, 2H), 3.42 (m, 2H), 1.42 (t J = 7.1 Hz, 3H), 1.36 (d J = 6.0 Hz, 6H), 1.25 (t J = 7.1 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.2 (e), 154.9 (e), 152.9 (e), 142.2 (e), 131.2 (e), 127.6 (o), 119.8 (e), 114.9 (o), 114.8 (o), 113.6 (o), 88.16 (e), 73.09 (e), 56.69 (o), 42.36 (e), 42.07 (e), 21.90 (o), 14.51 (o), 13.32 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 457 (M^+; 14), 315 (13), 357 (0.1) 100 (100), 72 (63); HRMS (EI (70 eV)) *m/e* calcd for $C_{19}H_{24}NO_4I$: 457.0750, found 457.0731.

***N*,*N*-Diethyl *O*-[2-iodo-4-(methoxymethoxy)-5-methoxy]-1-naphthyl-carbamate (259b).**



According to general procedure B, a solution of naphthylcarbamate **253** (0.189 g, 0.568 mmol) and TMEDA (0.10 mL, 0.664 mmol) in THF (5 mL) was treated sequentially with *s*-BuLi (0.57 mL, 1.20 mol/L) and I_2 (0.194 g, 0.767 mmol). Standard workup followed by column chromatography (3:1 hexane:EtOAc) afforded 0.261 g (79%) of the title compound as an orange oil. IR (neat) ν (max) 3076, 2972, 2934, 2834, 1724 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 154.4 (e), 154.1 (e), 152.7 (e), 142.0 (e), 130.8 (e), 127.5 (o), 118.8 (e), 115.8 (o), 114.3 (o), 113.8 (o), 96.41 (e), 88.25 (e), 56.47 (o), 56.10 (o), 42.22 (e), 41.93 (e), 14.39 (o), 13.18 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 459 (M^+, 18), 428 (9), 359 (20), 332 (11), 288 (18), 234 (19), 156 (16), 100 (100), 72 (27); HRMS (EI (70 eV)) *m/e* calcd for $C_{18}H_{22}NO_5I$: 459.0544, found 459.0547.

***N*,*N*-Diethyl *O*-[1-isopropoxy-5-methoxy-2-(4-*tert*-butyldimethylsiloxy-2-methoxyphenyl)]naphthyl-1-carbamate (260a).**

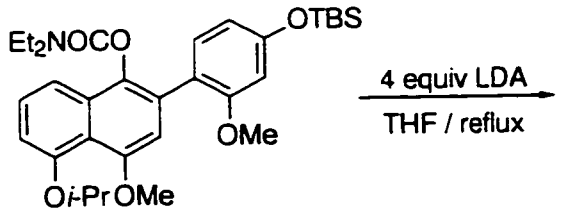


According to general procedure E, a mixture of aryl bromide **257a** was treated sequentially with *n*-BuLi (4.00 mL, 1.67 mol/L) and $ZnBr_2$ (1.64 g, 7.28 mmol) in THF (25 mL), iodide **259a** (0.602 g, 1.32 mmol) and $Pd(PPh_3)_4$ (76.0 mg, 0.0658 mmol) in THF (10 mL). The resulting solution was heated at reflux for 3 h and standard workup followed by column chromatography (4:1 hexane:EtOAc) afforded the title compound as a light yellow viscous oil (675.0 mg, 90%). IR (neat) ν (max) 2948, 2859, 1719, 1604, 1580, 1508, 1460, 1380, 1342,

1293, 1264, 1223, 1203, 1159, 1132, 1076, 1038 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (dd J = 8.4, 1.3 Hz, 1H), 7.36 (dd J = 8.4, 7.6 Hz, 1H), 7.17 (dd J = 6.6, 2.1 Hz, 1H), 6.93 (dd J = 7.6, 1.3 Hz, 1H), 6.76 (s, 1H), 6.47 (m, 2H), 4.53 (sept J = 6.0 Hz, 1H), 3.92 (s, 3H), 3.70 (s, 3H), 3.70 (m, 4H), 1.39 (d J = 6.0 Hz, 6H), 1.02 (m, 6H), 1.01 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.5 (e), 156.1 (e), 154.6 (e), 153.7 (e), 153.5 (e), 138.2 (e), 131.4 (e), 131.2 (o), 128.0 (o), 126.3 (e), 120.1 (e), 119.4 (e), 115.2 (o), 113.2 (o), 111.1 (o), 109.6 (o), 103.5 (o), 72.67 (o), 56.43 (o), 55.17 (o), 41.66 (e), 41.29 (e), 25.42 (o), 21.72 (o), 17.90 (e), 13.78 (o), 12.94 (o), -4.67 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 567 (M^+, 100), 552 (6.1), 525 (11), 467 (93), 425 (55), 410 (16), 353 (27), 337 (21), 262 (29), 100 (67), 72 (63); HRMS (EI (70 eV)) *m/e* calcd for $C_{32}H_{45}NO_6Si$: 567.3016, found 567.3008.

Procedure 2: *Metalation of carbamate **253***: According to general procedure F, a solution of carbamate **253** (0.511 g, 1.54 mmol) in THF (15 mL) at -78°C was sequentially treated with *s*-BuLi (1.80 mL, 1.06 mol/L), a solution of $ZnCl_2$ (1.85 mL, 1.00 mol/L in Et_2O), a solution of arylbromide **257a** (1.0143 g, 3.1984 mmol) and $Pd(PPh_3)_4$ (0.102 g, 0.0883 mmol) in THF (20 mL). The reaction mixture was heated at reflux for 12 h and subsequent standard workup followed by column chromatography (7.5:1.5:1 hexane:CH_2Cl_2:EtOAc) afforded the title compound (0.397 g, 45%).

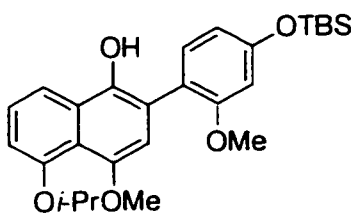
Reaction of 260a with LDA.



According to General Procedure C, a solution of carbamate **260a** (0.673 g, 1.19 mmol) in THF (10 mL) was added to a solution of LDA in THF (10 mL). The reaction mixture

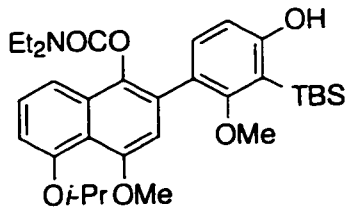
was heated at reflux for 1 h and standard workup followed by column chromatography (4:1 hexane:EtOAc) afforded the products shown below.

5-Isopropoxy-4-methoxy-2-(2-methoxy-4-*t*-butyldimethylsiloxyphenyl)-1-naphthol (261a).



21.3 mg (4%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03 (dd J = 8.4, 1.0 Hz, 1H), 7.40 (dd J = 8.2, 8.0 Hz, 1H), 7.30 - 7.25 (m, 2H), 6.98 (dd J = 6.9, 0.7 Hz, 1H), 6.81 (s, 1H), 6.62 (d J = 8.4 Hz, 1H), 5.49 (s, 1H, exch), 4.60 (sept J = 6.0 Hz, 1H), 3.92 (s, 3H), 3.42 (s, 3H), 1.43 (d J = 6.1 Hz, 6H), 0.97 (s, 9H), 0.43 (s, 6H); MS (EI (70 eV)) *m/e*: (rel intensity) 468 (M^+, 100), 453 (5.9), 426 (18), 411 (8.2), 395 (11), 379 (23), 353 (8.4), 337 (20), 322 (25), 277 (29), 252 (34); HRMS (EI (70 eV)) *m/e* calcd for $C_{27}H_{36}O_5Si$: 468.2332, found 468.2374.

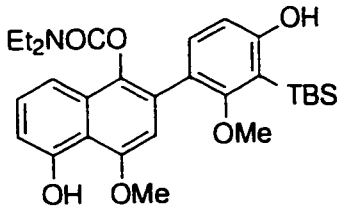
***N*,*N*-Diethyl *O*-[5-isopropoxy-4-methoxy-2-(3-*t*-butyldimethylsilyl-4-hydroxy-2-methoxyphenyl)]-1-naphthylcarbamate (261b).**



182.6 mg (27%) as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.45 - 7.39 (m, 2H), 7.21 (d, br, J = 8.2 Hz, 1H), 6.99 (dd J = 6.5, 2.7 Hz, 1H), 6.89 (s, br, 1H), 6.60 (d, J = 8.2 Hz, 1H), 4.64 (sept, J = 6.0 Hz, 1H), 3.89 (s, 3H), 3.43 - 3.41 (m, br, 2H), 3.30 (s, br, 3H), 3.24 - 3.21 (m, br, 2H), 1.39 (d, J = 6.0 Hz, 6H), 1.05 - 1.02 (m, br, 3H), 0.96 (s, br, 12H), 0.37 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.7 (e), 164.1 (e), 156.1 (e), 155.2 (e), 139.0 (e), 135.1 (o), 133.1 (e), 130.8 (e), 127.6 (o), 126.1 (e), 122.3 (e), 119.9 (e), 115.6 (o), 114.8

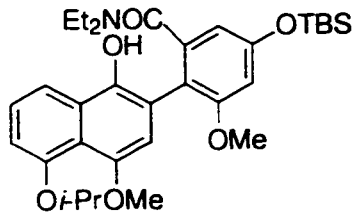
(e), 112.6 (o), 110.7 (o), 110.3 (o), 72.79 (o), 61.00 (o), 57.06 (o), 42.55 (e), 27.83 (o), 22.29 (o), 18.80 (e), 14.67 (o), 13.48 (o), -0.97 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 567 (M^+, 54), 552 (2.8), 525 (2.4), 510 (24), 468 (17), 467 (37), 423 (10), 422 (32), 380 (10), 338 (23), 100 (100), 72 (38); HRMS (EI (70 eV)) *m/e* calcd for $C_{32}H_{45}NO_6Si$: 567.3016, found 567.3028.

***N,N*-Diethyl *O*-[5-hydroxy-4-methoxy-2-(3-*t*-butyldimethylsilyl-4-hydroxy-2-methoxyphenyl)]-1-naphthylcarbamate (261c).**



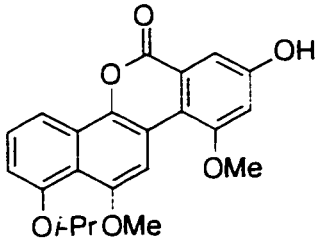
77.3 mg (16%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.39 (dd J = 8.1, 7.8 Hz, 1H), 7.29 (dd J = 8.3, 0.8 Hz, 1H), 7.16 (d, br, J = 8.1 Hz, 1H), 6.90 (d J = 7.5 Hz, 1H), 6.80 (s, br, 1H), 6.34 (d J = 8.2 Hz, 1H), 6.07 (s, br, 1H), 4.02 (s, 3H), 3.40 - 3.28 (m, br, 7H), 1.13 (m, br, 3H), 1.02 (t J= 6.9 Hz, 3H), 0.92 (s, 9H), 0.34 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 164.5 (e), 162.0 (e), 154.7 (e), 153.3 (e), 138.8 (e), 134.2 (o), 131.1 (e), 129.3 (e), 128.4 (o), 121.0 (e), 114.9 (e), 114.8 (e), 112.8 (o), 111.0 (o), 110.2 (o), 106.6 (o), 60.73 (o), 56.37 (o), 42.06 (e), 41.92 (e), 27.17 (o), 18.26 (e), 14.15 (o), 13.18 (o), -1.58 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 525 (M^+, 25), 510 (4.9), 495 (3.5), 468 (37), 453 (3.8), 425 (10), 100 (100), 72 (34); HRMS (EI (70 eV)) *m/e* calcd for $C_{29}H_{39}NO_6Si$: 525.2547, found 525.2571.

***N*,*N*-Diethyl 5-*t*-butyldimethylsiloxy-3-methoxy-2-(1-hydroxy-5-isopropoxy-4-methoxy-2-naphthyl)phenylcarboxamide (261d).**



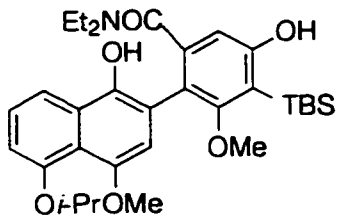
28.7 mg (4%) as a colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd J = 8.4, 0.85 Hz, 1H), 7.76 (s, 1H), 7.32 (dd J = 8.2, 7.9, 1H), 6.96 (dd J = 7.8, 0.8 Hz, 1H), 6.79 (s, br, 1H), 6.57 (s, 1H), 6.22 (s, 1H), 4.55 (sept J = 6.1 Hz, 1H), 3.82 (s, 3H), 3.61 (m, 3H), 3.24 (s, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.51 (m, 1H), 1.40 (d J = 6.1 Hz, 6H), 1.02 - 0.92 (m, 6H), 0.92 (s, 9H), 0.35 (s, 3H), 0.15 (s, 3H).

Cyclization of 261d: 8-hydroxy-1-isopropoxy-10,12-dimethoxy-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (262a).



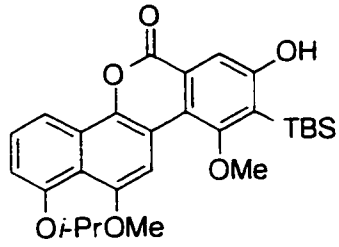
According to general procedure D, hydroxy amide **261d** (28.7 mg, 0.051 mmol) was dissolved in HOAc (5 mL) and heated at reflux for 10 min. Standard workup followed by column chromatography (7:2 hexane:EtOAc) afforded the title compound 20.0 mg (91%), as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.43 (s, 1H), 8.04 (dd J = 8.7, 1.1 Hz, 1H), 7.56 - 7.49 (m, 2H), 7.11 - 7.08 (m, 2H), 4.66 (sept J = 6.0 Hz, 1H), 4.15 (s, 3H), 3.98 (s, 3H), 1.39 (d J = 6.0 Hz, 6H).

***N*,*N*-Diethyl 4-*t*-butyldimethylsilyl-5-hydroxy-3-methoxy-2-(5-hydroxy-1-isopropoxy-4-methoxy-2-naphthyl)phenylcarboxamide (261e).**



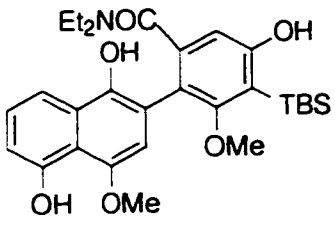
0.139 mg (21%) as a colorless gum. Material cyclized in solution and was therefore directly treated with HOAc according to general procedure D.

Cyclization of 261e: 9-*t*-butyldimethylsilyl-8-hydroxy-1-isopropoxy-10,12-dimethoxy-6*H*-naphtho-[1,2-*b*]benzo[*b*]pyran-6-one (262b).



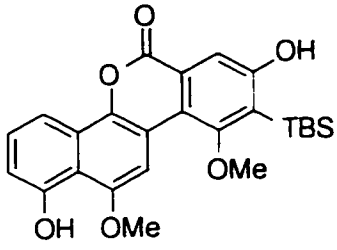
According to general procedure D, hydroxy amide **261e** (49.3 mg, 0.0869 mmol) was dissolved in HOAc (5 mL) and heated at reflux for 10 min. Standard workup followed by column chromatography (7:2 hexane:EtOAc) afforded the title compound 38.2 mg (89%), as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.15 (s, 1H), 8.02 (d J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.52 (dd J = 8.5, 7.8 Hz, 1H), 7.08 (d J = 7.8 Hz, 1H), 4.66 (sept J = 6.0 Hz, 1H), 3.97 (s, 3H), 3.77 (s, 3H), 1.39 (d J = 6.0 Hz, 6H), 0.98 (s, 9H), 0.50 (s, 6H); ^{13}C NMR (62.9 MHz, acetone) δ 166.2 (e), 164.5 (e), 160.9 (e), 155.9 (e), 154.9 (e), 154.6 (e), 140.3 (e), 128.3 (o), 128.0 (e), 126.9 (e), 126.7 (e), 120.3 (e), 119.9 (e), 115.0 (o), 113.8 (e), 113.7 (o), 111.1 (o), 104.2 (o), 72.74 (o), 63.32 (o), 57.25 (o), 27.86 (o), 22.29 (o), 18.85 (e), -1.00 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 494 (M^+, 100), 479 (3.8), 452 (63), 437 (9.4), 407 (10), 396 (54), 365 (21), 312 (68); HRMS (EI (70 eV)) *m/e* calcd for $C_{28}H_{34}O_6Si$: 494.2125, found 494.2118.

***N*,*N*-Diethyl 4-*t*-butyldimethylsilyl-5-hydroxy-3-methoxy-2-(1,5-dihydroxy-4-methoxy-2-naphthyl)-phenylcarboxamide (261f).**



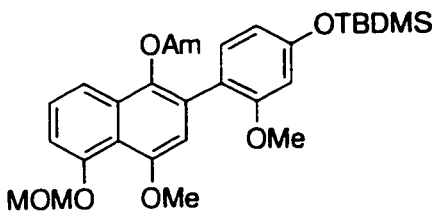
79.4 mg (13%) as a light yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.02 (s, 1H), 9.40 (s, 1H), 7.83 (dd J = 8.2, 0.9 Hz, 1H), 7.40 (dd J = 8.1, 7.9 Hz, 1H), 6.93 (dd J = 7.6, 0.7 Hz, 1H), 6.86 (s, 1H), 6.84 (s, 1H), 6.83 (s, 1H), 4.08 (s, 3H), 3.74 (m, 1H), 3.37 (s, 3H), 2.92 (m, 2H), 2.47 (m, 1H), 0.88 (s, 9H), 0.75 (t J = 7.1 Hz, 3H), 0.71 (t J = 7.1 Hz, 3H), 0.34 (s, 3H), 0.32 (s, 3H).

Cyclization of 261f: 9-*t*-butyldimethylsilyl-1,8-dihydroxy-10,12-dimethoxy-6*H*-naphtho[1,2-*b*]benzo[*b*]pyran-6-one (262c).



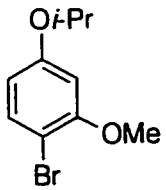
According to general procedure D, hydroxy amide **261f** (79.4 mg, 0.151 mmol) was dissolved in HOAc (5 mL) and heated at reflux for 10 min. Standard workup followed by column chromatography (2:1 hexane:EtOAc) afforded the title compound 64.2 mg (91%), as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.39 (s, 1H), 8.15 (s, 1H), 7.85 (dd J = 8.5, 1.1 Hz, 1H), 7.64 (s, 1H), 7.47 (dd J = 8.3, 7.9, 1H), 6.88 (dd J = 7.8, 0.9 Hz, 1H), 4.19 (s, 3H), 3.78 (s, 3H), 0.99 (s, 9H), 0.51 (s, 6H); MS (EI (70 eV)) *m/e*: (rel intensity) 452 (M^+, 14), 396 (72), 354 (17), 312 (100), 297 (6.6), 274 (9.3); HRMS (EI (70 eV)) *m/e* calcd for $C_{25}H_{28}O_6Si$: 452.1655, found 452.1653.

***N*,*N*-Diethyl *O*-[1-isopropoxy-5-methoxymethoxy-2-(4-*tert*-butyldimethylsiloxy-2-methoxyphenyl)]-1-naphthylcarbamate (260b).**



According to general procedure E, a solution of aryl bromide **257c** (0.314 g, 0.955 mmol) in THF (5 mL) was sequentially treated with *n*-BuLi (0.71 mL, 1.60 mol/L) and $ZnCl_2$ (1.20 mL, 1.0 mol/L in Et_2O). This solution of aryl zinc species was added *via* canula to a flask which was charged with aryliodide **259b** (0.199 g, 0.434 mmol), $Pd(PPh_3)_4$ (35.0 mg, 0.0303 mmol) and THF (5 mL) and the mixture heated at reflux for 16 h. Standard workup followed by column chromatography (4:1 hexane:EtOAc) afforded the title compound as an orange oil (0.226 mg, 90%). IR (neat) ν (max) 2931, 1719 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.52 (dd J = 8.4, 1.0 Hz, 1H), 7.37 (dd J = 8.4, 7.6 Hz, 1H), 7.17 (dd J = 6.9, 2.0 Hz, 1H), 7.08 (dd J = 7.6, 1.0 Hz, 1H), 6.79 (s, 1H), 6.46-6.50 (m, 2H), 5.26 (s, 2H), 3.93 (s, 3H), 3.71 (s, 3H), 3.60 (s, 3H), 3.24-3.33 (m, 4H), 1.03-1.06 (m, 6H), 1.02 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.6 (e), 156.4 (e), 153.9 (e) (X2), 153.4 (e), 138.2 (e), 131.4 (e), 131.3 (o), 128.3 (e), 126.6 (o), 120.0 (e), 118.7 (e), 116.5 (o), 113.9 (o), 111.3 (o), 109.3 (o), 103.6 (o), 96.86 (e), 56.43 (o), 56.13 (o), 55.35 (o), 41.82 (e), 41.44 (e), 25.57 (o), 13.95 (o), 13.09 (o), -4.51 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 569 (M^+, 16), 525 (1.2), 469 (17), 389 (29), 331 (17), 262 (13), 183 (7.0), 100 (100), 72 (54), 45 (39); HRMS (EI (70 eV)) *m/e* calcd for $C_{31}H_{43}NO_7Si$: 569.2810, found 569.2826.

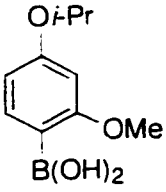
4-Isopropoxy-2-methoxybromobenzene (257b).



A mixture of 4-bromo-3-methoxyphenol[231] **(256)** (2.40 g, 11.88 mmol) *i*-PrI (1.78 mL, 17.82 mmol) and K_2CO_3 (2.46 g, 17.82 mmol) in acetone (30 mL) was heated at reflux under argon for 12 h. The reaction was cooled to rt and most of the acetone removed on the rotary evaporator. The residue was diluted with H_2O and Et_2O and the layers separated. The

aqueous phase was extracted twice more with Et_2O and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation giving the title compound as a colorless liquid (2.86 g, 98%). bp 105-107°C / 0.2 mmHg; IR (neat) ν (max) 3018, 2976, 2935, 1586, 1468, 1408, 1380, 1293, 1200, 1121, 1053, 1022 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38 (d J = 8.7 Hz, 1H), 6.47 (d J = 2.7 Hz, 1H), 6.38 (dd J = 8.7, 2.7 Hz, 1H), 4.51 (sept J = 6.0 Hz, 1H), 3.85 (s, 3H), 1.34 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.5 (e), 156.6 (e), 132.9 (o), 107.9 (o), 102.1 (e), 101.8 (o), 70.3 (o), 56.0 (o), 21.8 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 246 (24), 244 (24), 203 (100), 201 (100), 161 (13), 159 (13); HRMS (EI (70 eV)) *m/e* calcd for $C_{10}H_{13}BrO_2$: 244.0099, found 244.0092.

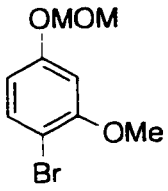
4-Isopropoxy-2-methoxyphenylboronic acid (275).



To a solution of 4-isopropoxy-2-methoxybromobenzene **257b** (1.18 g, 4.82 mmol) in THF (30 mL) at -78°C was added a solution of *n*-BuLi (3.20 mL, 1.82 mol/L) and the resulting solution was allowed to stir for 10 min. A solution of $B(OMe)_3$ (1.60 mL, 14.09 mmol) was added in one portion and the mixture allowed to warm slowly to rt. It was then quenched with sat NH_4Cl and the THF removed on the rotovap. The residue was diluted with H_2O and acidified to ca. pH 5-6 with 10% HCl. The acidic aqueous solution was then extracted with CH_2Cl_2 (3 X 100 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated with hexane to give an off white solid which was purified by recrystallization (hexane:Et_2O) giving colorless plates (0.677 g, 67%). mp 95-98°C (hexane:Et_2O); IR (KBr) ν (max) 3381, 2976, 2941, 1602, 1566, 1451, 1411, 1361, 1335, 1294, 1201, 1157, 1110, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.80 (d J = 8.4 Hz, 1H), 6.75, (s, br, 2H), 6.54 (dd J =

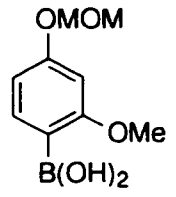
8.4, 2.0 Hz, 1H), 6.44 (d J = 2.0 Hz, 1H), 4.60 (sept J = 6 Hz, 1H), 3.85 (s, 3H), 1.34 (d, J = 6.0 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9 (e), 161.9 (e), 137.9 (o), 106.6 (o), 99.3 (o), 69.7 (o), 55.3 (o), 21.9 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 210 (28, M^+), 168 (74), 124 (100), 96 (59), 94 (63); HRMS (EI (70 eV)) *m/e* calcd for $C_{10}H_{15}BO_4$: 210.1063, found 210.1053.

2-Methoxy-4-methoxymethoxybromobenzene (257c).



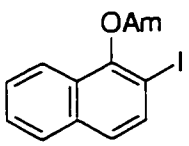
To a suspension of NaH (0.833 g, 60% dispersion in mineral oil, 20.83 mmol), in DMF (20 mL) at 0°C was added a solution of 4-bromo-3-methoxyphenol[231] **(256)** (2.38 g, 11.78 mmol) in DMF (15 mL). The resulting mixture was allowed to stir at 0°C until the evolution of H_2 ceased (30 min). At this point MOMCl (1.50 mL, 19.75 mmol) was added and the reaction mixture allowed to warm to rt over 2 h. The resulting suspension was poured slowly into 150 mL of ice water and the whole extracted with Et_2O (3 x 75 mL). The combined organic layers were washed (H_2O (5 X 100 mL), brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation giving a colorless liquid (2.64 g, 91%). bp 100-105°C / 0.2 mmHg; IR (neat) ν (max) 2935, 2831, 1587, 1471, 1409, 1288, 1215, 1192, 1155, 1079 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.23 (d J = 8.6 Hz, 1H), 6.46 (d J = 2.6 Hz, 1H), 6.39 (dd J = 8.6, 2.4 Hz, 1H), 4.99 (s, 2H), 3.70 (s, 3h), 3.31 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.8 (e) 156.5 (e), 133.2 (o), 108.9 (o), 103.7 (e), 101.6 (o), 94.6 (e), 56.1 (o), 56.0 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 248 (100), 246 (100), 218 (41), 216 (41), 175 (18), 173 (18); HRMS (EI (70 eV)) *m/e* calcd for $C_9H_{11}BrO_3$: 245.9891, found 245.9882.

2-Methoxy-4-methoxymethoxyphenylboronic acid (280).



To a solution of 4-methoxymethoxy-2-methoxybromobenzene **(257c)** (2.13 g, 8.60 mmol) in THF (50 mL) at -78°C was added a solution of *n*-BuLi (1.64 mL, 1.75 mol/L) and the resulting solution was allowed to stir for 10 min. A solution of $B(OMe)_3$ (3.00 mL, 26.42 mmol) was added in one portion and the mixture allowed to warm slowly to rt. The reaction mixture was then quenched with sat NH_4Cl and the THF removed on the rotovap. The residue was diluted with H_2O and acidified to ca. pH 5-6 with 10% HCl. The acidic aqueous solution was then extracted with CH_2Cl_2 (3 X 75 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by recrystallization (hexane:Et_2O) giving colorless plates (1.31 g, 72%). mp 79-81°C (hexane:Et_2O); IR (KBr) ν (max) 3320 (br), 1604, 1572, 1540, 1504, 1455, 1419, 1341, 1306, 1260, 1190, 1149, 1118, 1076 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.76 (d J = 8.2 Hz, 1H), 6.70 (dd J = 8.2, 2.0 Hz, 1H), 6.60 (d J = 2.0 Hz, 1H), 5.86 (s (br), 2H), 5.21 (s, 2H), 3.90 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.8 (e), 161.1 (e), 138.6 (o), 137.9 (o), 108.0 (o), 99.1 (o), 94.1(e), 56.0 (o), 55.4 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 212 (M^+, 11), 182 (5.3), 168 (3.2), 138 (2.7), 69 (5.3), 45 (100); Anal. calcd for $C_9H_{13}BO_5$: C, 50.99; H, 6.18; found: C, 50.90; H, 6.27.

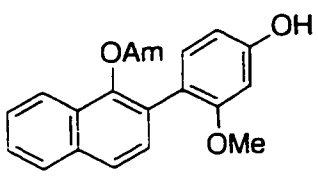
_N,N_-Diethyl _O_-(2-iodo)-1-naphthylcarbamate (272).



According to general procedure B, a solution of *N,N*-diethyl *O*-1-naphthylcarbamate **(271)** (6.83 g, 28.1 mmol) and TMEDA (5.50 mL, 36.5 mmol) in THF (125 mL) at -78°C was sequentially treated with *s*-BuLi (29.0 mL, 1.30 mol/L) and a solution of I_2 (10.68 g, 42.10 mmol) in THF (50 mL). Standard workup followed by column chromatography (9:1 hexane:EtOAc) afforded a yellow oil (7.26 g, 70%). IR (neat) ν (max) 3060, 2975, 2933, 1724, 1582,

1500, 1472, 1424 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.75 (m, 3H), 7.40 (m, 3H), 3.59 (m, br, 2H), 3.42 (m, 2H), 1.38 (m, 3H), 1.23 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.4 (e), 148.2 (e), 134.4 (o), 134.0 (e), 128.4 (e), 127.7 (o), 126.9 (o), 126.8 (o), 126.5 (o), 121.4 (o), 88.53 (e), 42.32 (e), 42.11 (e), 14.47 (o), 13.28 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 369 (21), 270 (8), 242 (24), 181 (27), 100 (100), 72 (100); HRMS (EI (70 eV)) *m/e* calcd for $C_{15}H_{16}O_2NI$: 369.0226, found 369.0242.

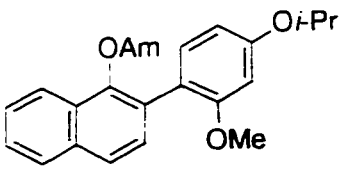
***N,N*-Diethyl *O*-(4-hydroxy-2-methoxyphenyl)-1-naphthylcarbamate (274).**



According to general procedure F, a solution of *N,N*-diethyl *O*-1-naphthylcarbamate **271** (1.08 g, 4.43 mmol) in THF (30 mL) at -78°C was sequentially treated with TMEDA (0.900 mL, 6.00 mmol), *s*-BuLi (5.0 mL, 1.34 mol/L), $ZnCl_2$ (7.00 mL, 1.00 mol/L in Et_2O). This solution was allowed to stir for a further 10 min and subsequently warmed to rt. A separate flask was charged with 4-bromo-3-methoxy-*tert*-butyldimethylsiloxybenzene **257a** (4.27 g, 13.45 mmol) and $Pd(PPh_3)_4$ (0.256 g, 0.220 mmol) and the solution of arylzinc chloride was added by canula. This mixture was heated at reflux for 36 h and standard workup afforded crude silyl ether which was purified by column chromatography (8:1:1 hexane:Et_2O:CH_2Cl_2) giving silyl ether (0.442 g, 21%), which was used directly for the next step. The silyl ether (0.442 g, 0.921 mmol) was dissolved in THF (10 mL), cooled to 0°C and TBAF added (1.20 mL, 1.0 mol/L in THF). The solution was allowed to warm to rt over 12 h. Standard workup followed by purification by passing the residue through a plug of silica gel followed by recrystallization (hexane:CH_2Cl_2) afforded the title compound (0.292 g, 19%) as a colorless powder. mp 159-160°C (hexane:CH_2Cl_2); IR (CH_2Cl_2) ν (max) 3321 (br), 3031, 2948, 1693, 1609, 1514, 1462, 1427, 1368, 1271, 1193 cm^{-1}; ^1H

NMR (250 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.72 (d J = 8.5 Hz, 1H), 7.48 (m, 2H), 7.40 (d J = 8.5 Hz, 1H), 7.14 (d J = 8.1 Hz, 1H), 6.46 (d J = 2.4 Hz, 1H), 6.37 (dd J = 9.1, 2.4 Hz, 1H), 5.23 (s, 1H, exch), 3.68 (s, 3H), 3.48 (m, 4H), 3.32 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ ;157.9 (e), 156.5 (e), 153.9 (e), 144.6 (e), 133.9 (e), 131.9 (o), 129.1 (o), 128.2 (e), 128.1 (e), 127.7 (o), 126.2 (o), 125.8 (o), 124.9 (o), 121.9 (o), 119.4 (e), 106.7 (o), 98.9 (o), 55.5 (o), 41.9 (e), 41.6 (e), 14.0 (o), 13.2 (o); MS (FAB) *m/e*: (rel intensity) 366 (M+H, 74), 336 (8.4), 222 (33), 100 (100), 72 (89); Anal. calcd for $C_{22}H_{23}NO_4$: C, 72.33; H, 6.30; N, 3.84; found: C, 72.57; H, 6.38; N, 3.84.

_N,N_-Diethyl _O_-[2-(4-isopropoxy-2-methoxyphenyl)]-1-naphthylcarbamate (276).

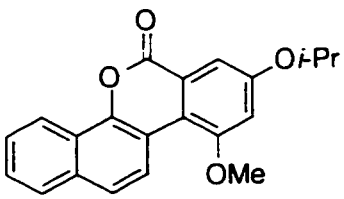


Procedure 1: A mixture of phenol **274** (0.124 g, 0.341 mmol), K_2CO_3 (70.60 mg, 0.511 mmol), and *i*-PrI (0.10 mL, 1.0 mmol) in CH_3CN (20 mL) was heated at reflux for 23 h. Standard workup followed by column chromatography (4:1 hexane:EtOAc) afforded the title compound (0.133 g, 96%) as a gum.

Procedure 2: According to general procedure A, a mixture of *N,N*-diethyl *O*-(2-iodo)-1-naphthylcarbamate **(272)** (0.277 g, 0.749 mmol), 4-isopropoxy-2-methoxyphenylboronic acid **275** (0.191 g, 0.910 mmol), $Pd(PPh_3)_4$ (48.3 mg, 0.0418 mmol) and $Ba(OH)_2$ (0.628 g, 1.99 mmol) in DME (10 mL) containing H_2O (2 mL) was heated at reflux for 1 h. Standard workup followed by column chromatography (4:1 hexane:EtOAc) afforded the title compound (0.300 mg, 98%). IR (neat) ν (max) 2975, 1718, 1609, 1507, 1460 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.72 (d J = 8.5 Hz, 1H),

7.48 (m, 2H), 7.42 (d J = 8.5 Hz, 1H), 7.22 (m, 1H), 6.52 (m, 2H), 4.59 (sept J = 6.0 Hz, 1H), 3.71 (s, 3H), 3.29 (m, 4H), 1.38 (d J = 6.0 Hz, 6H), 1.05 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.8 (e), 158.0 (e), 153.9 (e), 144.8 (e), 133.9 (e), 131.8 (o), 129.2 (o), 128.3 (o), 128.2 (e), 127.8 (o), 126.2 (o), 125.8 (o), 124.8 (o), 122.0 (o), 119.6 (e), 106.2 (o), 100.5 (o), 70.00 (o), 55.56 (o), 41.93 (e), 41.65 (e), 22.08 (o), 14.02 (o), 13.17 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 407(M^+, 19), 265 (3.2), 234 (8.6), 100, (100), 72 (66); HRMS (FAB) *m/e* calcd for $C_{25}H_{30}NO_4$: 408.2175, found 408.2164.

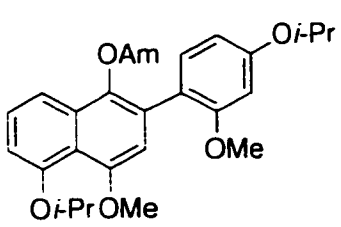
8-Isopropoxy-10-methoxy-6*H*-naphtho[1,2-*b*]benzo[*d*]pyranone (277).



According to general procedure C, a solution of carbamate **276** (0.296 g, 0.727 mmol) in THF (5 mL) was added *via* canula to a solution of LDA (1.74 mmol) in THF (5 mL) at 0°C. The mixture was heated at reflux under Ar for 2.5 h and then cooled to rt. Standard workup afforded the crude hydroxy amide which was cyclized according to General Procedure D (10 mL HOAc). Standard workup followed by purification by column chromatography (6:1 hexane:EtOAc → EtOAc) afforded a colorless solid which was recrystallized (hexane:CH_2Cl_2) affording the title compound (0.179 g, 74%) as colorless needles. mp 210-211°C. IR (KBr) ν (max) 3021, 2976, 1715, 1604, 1560, 1505,1485, 1451 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.80 (d J = 9.2 Hz, 1H), 8.53 (m, 1H), 7.79 (m, 1H), 7.59 (d J = 9.2 Hz, 1H), 7.55 (m, 3H), 6.80 (d J = 2.4 Hz, 1H), 4.75 (sept J = 6.1 Hz, 1H), 3.97 (s, 3H), 1.42 (d J = 6.1 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.3 (e), 158.7 (e), 158.4 (e), 145.1 (e), 132.9 (e), 127.1 (o), 127.0 (o), 126.3 (o), 124.0 (o), 123.7 (e), 123.4 (o), 122.0 (o), 118.3 (e), 113.4 (e), 107.6 (o), 104.7 (o), 70.41 (o), 55.87 (o), 21.92 (o); MS (EI (70 eV))

m/e: (rel intensity) 334 (M^+, 49), 292 (100), 277 (23), 248 (14), 221(12), 192(8), 84 (73); Anal. calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43 ; found: C, 75.18; H, 5.42.

***N,N*-Diethyl *O*-[5-isopropoxy-4-methoxy-2-(4-isopropoxy-2-methoxyphenyl)]-1-naphthylcarbamate (267).**

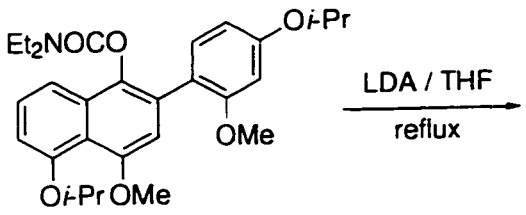


Procedure 1. *From arylboronic acid 275. $Ba(OH)_2$*: According to General Procedure G, a mixture of aryliodide **259a** (3.04 g, 6.65 mmol), arylboronic acid **275** (1.53 g, 7.31 mmol), $Ba(OH)_2 \cdot 8H_2O$ (5.01 g, 15.89 mmol) and $Pd(PPh_3)_4$ (0.117 g, 0.172 mmol) were heated at reflux for 5 h. Standard workup followed by column chromatography (7.5:1:1.5, hexane:CH_2Cl_2:EtOAc) afforded a brown oil which solidified on standing for several days. Recrystallization (hexane:CH_2Cl_2) gave a colorless powder (3.03 g, 92%). mp 99-100°C (hexane:CH_2Cl_2); IR (KBr) ν (max) 2976, 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (dd, J = 8.4, 1.2 Hz, 1H), 7.36 (dd J = 8.4, 7.5 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 6.93 (dd, J = 7.5, 1.2 Hz, 1H), 6.77 (s, 1H), 6.52 (m, 2H), 4.59 (sept J = 6 Hz, 1H) 4.53 (sept J = 6 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 3H), 3.30 (m, 4H), 1.38 (two overlapping d J = 6.0 Hz, 12H), 1.03 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.9 (e), 157.9 (e), 155.0 (e), 154.2 (e), 153,9 (e), 138.1 (e), 131.5 (e), 131.4 (o), 128.1 (e), 126.7 (o), 119.5 (e), 119.3 (e), 115.5 (o), 113.5 (o), 109.6 (o), 106.4 (o), 100.1 (o), 73.3 (o), 69.9 (o), 56.7 (o), 54.9 (o), 41.6 (e), 41.3 (e), 22.0 (o), 13.8 (o), 12.9 (o); MS (EI (70 eV)) *m/e* (relative intensity) 495 (M^+, 18.2), 395 (9.8), 311 (2.3), 280 (2.4), 212 (2.2), 100 (100), 72 (26.9); Anal. calcd for : C, 70.28; H, 7.52; N, 2.83; found: C, 70.15; H, 7.70; N, 2.77.

Procedure 2. *From arylboronic acid 275. Na_2CO_3*: The same procedure using iodide **259a** (0.921 g, 2.016 mmol), arylboronic acid **275** (0.487 g, 2.32 mmol), $Pd(PPh_3)_4$ (0.177 g, 0.153 mmol), Na_2CO_3 (10 mL, 2 mol/L) in DME (40 mL) at reflux for 12 h followed by standard workup and column chromatography (7.5:1:1.5, hexane:CH_2Cl_2:EtOAc) afforded the title compound (0.279 g, 28%).

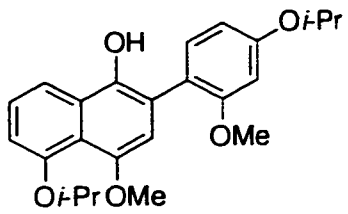
Procedure 3. *From iodide **259a** via Negishi coupling*: According to general procedure E, a solution of aryl bromide **257b** (0.500 g, 2.04 mmol) in THF (10 mL) at -78°C was sequentially treated with *n*-BuLi (1.22 mL, 1.84 mmol), $ZnCl_2$ (2.40 mL, 1.0 mol/L), aryl iodide **259a** (0.354 g, 0.774 mmol), and $Pd(PPh_3)_4$ (56.3 mg, 0.049 mmol). The reaction mixture was heated at reflux for 48 h standard workup and chromatography afforded the title compound (80.7 mg, 21%).

Reaction of 267 with LDA.



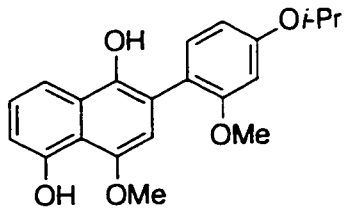
According to general procedure C1, a solution of carbamate **267** (0.277 g, 0.589 mmol) in THF (5 mL) was added to a solution of LDA (1.96 mmol) in THF (5 mL) and the solution was heated at reflux for 1 h. Standard workup followed by column chromatography (3:1 hexane:EtOAc) afforded the products shown below.

5-Isopropoxy-4-methoxy-2-(2-methoxy-4-isopropoxyphenyl)-1-naphthol (281a).



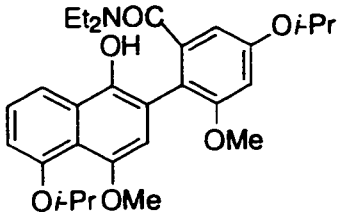
29.4 mg as a gum. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02 (dd J = 8.4, 1.1 Hz, 1H), 7.38 (dd J = 8.4, 7.7 Hz, 1H), 7.31 (d J = 8.4 Hz, 1H), 6.97 (dd J = 8.0, 1.0 Hz, 1H), 6.76 (s, 1H), 6.70-6.63 (m, 2H), 6.51 (s, 1H, exch), 4.62 (sept J = 6.0 Hz, 1H), 4.56 (sept J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.41 (d J = 6.0 Hz, 6H), 1.39 (d J = 6.0 Hz, 6H); MS (EI (70 eV)) *m/e* (relative intensity) 396 (M^+, 12), 354 (5.2), 309 (100); HRMS (EI (70 eV)) *m/e* calcd for $C_{24}H_{28}O_5$: 396.1937, found 396.1949.

5-Hydroxy-4-methoxy-2-(4-isopropoxy-2-methoxyphenyl)-1-naphthol (281b).



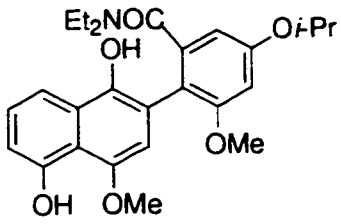
18.2 mg as a gum. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.82 (dd J = 8.4, 1.1 Hz, 1H), 7.39 (dd J = 8.4, 7.8 Hz, 1H), 7.28 (d J = 8.3 Hz, 1H), 6.90 (dd J = 7.7, 1.1 Hz, 1H), 6.69-6.63 (m, 2H), 6.40 (s, 1H), 4.62 (sept J = 6.0 Hz, 1H), 4.02 (s, 3H), 3.89 (s, 3H), 1.39 (d J = 6.0 Hz); MS (EI (70 eV)) *m/e* (relative intensity) 354 (M^+, 69), 339 (43), 312 (100); HRMS (EI (70 eV)) *m/e* calcd for $C_{21}H_{22}O_5$: 354.1467, found 354.1462.

***N,N*-Diethyl 5-isopropoxy-4-methoxy-2-(1-hydroxy-5-isopropoxy-4-methoxy-2-naphthyl)benzamide (281c).**



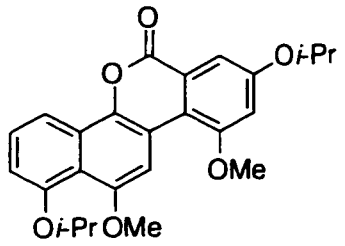
113.6 mg as a gum. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.06 (d J = 8.4 Hz, 1H), 7.32 (dd J = 8.4, 7.8 Hz, 1H), 6.93 (d J = 7.7 Hz, 1H), 6.57 (s, 1H), 6.92-6.64 (m, 2H), 6.40 (d J = 2.1 Hz, 1H), 4.61 (sept J = 6.0 Hz, 1H), 4.50 (sept J = 6.0 Hz, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 3.47-3.21 (m, 2H), 3.19-2.95 (m, 2H), 1.40 (d J = 6.0 Hz, 6H), 1.36 (d J = 6.0 Hz, 6H).

_N,N_-Diethyl 5-isopropoxy-4-methoxy-2-(1,5-dihydroxy-4-methoxy-2-naphthyl)benzamide (281d).



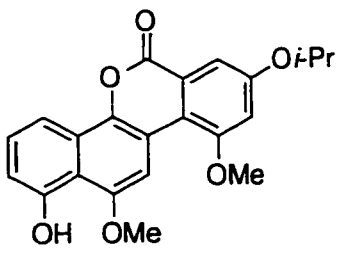
75.3 mg as a colorless solid. Spectral analysis indicated a 1:1 mixture of rotamers. ^{1}H NMR data are listed giving the resonance of one rotamer follwed by the corresponding signal of the other rotamer. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.42 (s, 1H) 9.34 (s, 1H), 7.88 (dd J = 8.4, 1.0 Hz, 1H), 7.79 (dd J = 8.40, 1.0 Hz, 1H), 7.40-7.30 (m, 2H, rotamer signals overlapping), 6.91-6.85 (m, 2H, rotamer signals overlapping), 6.85 (s, 1H) corresponding rotamer signal obscured. 6.64 (s, 1H) 6.47 (s, 1H), 6.57 (d J = 2.3 Hz, 1H) 6.41 (d J = 2.3 Hz), 4.64 (sept J = 6.0 Hz, 1H) 4.60 (sept J = 6.0 Hz, 1H), 3.99 (s, 3H) 3.94 (s, 3H), 3.87 (s, 3H) 3.67 (s, 3H), 3.65-3.61 (m, 1H) 3.43-3.37 (m, 1H), 3.20-3.13 (m, 2H) 3.11-3.00 (m, 2H), 2.86-2.79 (m, 1H) 2.64-2.48 (m, 1H), 1.40 (d J = 6.0 Hz, 6H) 1.39 (d J = 6.0 Hz, 6H); MS (EI (70 eV)) *m/e* (relative intensity) 454 (M^+, 100); HRMS (EI (70 eV)) *m/e* calcd for $C_{26}H_{32}NO_6$: 454.2230, found 454.2234.

1,8-Diisopropoxy-10,12-dimethoxy-6*H*-naphtho[1,2-*b*]-benzo[*d*]pyran-6-one (282).



According to general procedure C1, a mixture of biarylcarbamate **267** (0.199 g, 0.402 mmol) was heated at reflux with LDA (1.26 mmol) for 1.5 h. Standard workup followed by cyclization according to general procedure D (10 mL HOAc) afforded the crude lactone which was purified by column chromatography followed by recrystallisation to give the title compound (91.4 mg, 54%) as fine yellow needles. mp 158-159°C (hexane:Et_2O). IR (KBr) ν (max) 2974, 2931, 1710, 1606, 1587, 1562, 1488, 1468, 1450, 1385, 1365, 1345, 1296, 1239, 1224, 1152, 1132, 1112, 1076 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.34 (s 1H), 8.22 (dd J = 8.4, 1.0 Hz, 1H), 7.56 (d J = 2.5 Hz, 1H), 7.48 (dd J = 8.4, 7.8 Hz, 1H), 7.03 (dd J = 7.8, 1.0 Hz, 1H), 6.80 (d J = 2.5 Hz, 1H), 4.78 (sept J = 6.0 Hz, 1H), 4.59 (sept J = 6.0 Hz, 1H), 4.04 (s, 3H), 4.00 (s, 3H), 1.43 (d J = 6.0 Hz, 6H), 1.42 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.4 (e), 158.8 (e), 158.6 (e), 154.5 (e), 152.4 (e), 140.0 (e), 127.0 (o), 126.8 (e), 124.2 (e), 119.2 (e), 118.3 (e), 115.4 (o), 114.2 (o), 113.6 (e), 107.8 (o), 105.0 (o), 104.8 (o), 73.14 (o), 70.51 (o), 56.90 (o), 56.20 (o), 22.09 (o), 21.96 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 366 (7.4, M+H), 336 (8.4), 222 (33), 100 (100), 72 (89); Anal. calcd for :$C_{25}H_{26}O_6$ C, 71.07; H, 6.20 ; found: C, 71.03; H, 6.27.

1-Hydroxy-8-isopropoxy-10,12-dimethoxy-6*H*-naphtho[1,2-*b*]benzo[*d*] pyran-6-one (283).



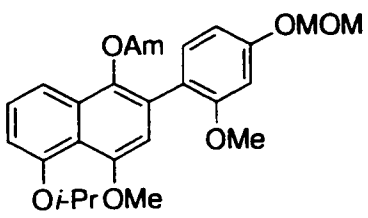
Procedure 1: To a solution of pyranone **282** (28.5 mg, 0.0675 mmol) in CH_2Cl_2 (5 mL) at 0°C was added BCl_3 (0.68 mL, 1.0 mol/L in heptane) dropwise. The reaction was allowed to stir for 15 min and standard workup

followed by column chromatography (6.5:1 hexane *i*-PrOH → 1:1 CH_2Cl_2: *i*-PrOH) afforded the title compound (20.0 mg, 78%) as a bright yellow powder. An analytical sample was obtained by recrystallization from hexane-acetone. mp 239-240°C (hexane:acetone); IR (KBr) ν (max) 3372, 3054, 2984, 1709, 1607, 1563, 1509, 1490, 1443, 1422, 1387, 1347, 1318, 1299, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.34, (s, 1H, exch), 8.23 (s, 1H), 8.03 (dd J = 8.4, 0.6 Hz, 1H), 7.53 (d J = 2.5 Hz, 1H), 7.47 (dd J = 8.1, 8.0 Hz, H), 6.97 (dd J = 7.7, 0.6 Hz, 1H), 6.85 (d J = 2.5 Hz, 1H), 4.87 (sept J = 6.0 Hz, 1H), 4.09 (s 3H), 4.02 (s, 3H), 1.43 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.6 (e), 154.1 (e),151.8 (e), 128.3 (o), 126.1 (e), 124.1 (e), 117.9 (e), 114.2 (e), 113.1 (o), 113.0 (e), 112.1 (o), 107.6 (o), 104.9 (o), 101.4 (o), 70.00 (o), 56.13 (o), 55.93 (o), 21.90 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 380 (100), 338 (16.4), 365 (3.1), 350 (3.1); Anal. calcd for : $C_{22}H_{20}O_6$ C, 69.46; H, 5.29 ; found: C, 69.62; H, 5.05.

Procedure 2: *Titanium Chloride*: To a solution of diisopropyl ether **282** (65.5 mg, 0.155 mmol) in CH_2Cl_2 (5 mL) at 0°C was added $TiCl_4$ (0.80 mL, 1.0 mol/L in CH_2Cl_2) dropwise. The reaction was allowed to stir for 5 min and standard workup followed by column chromatography (10% *i*-PrOH in hexane) afforded the title compound (45.7 mg 77%). Treatment of this material again with $TiCl_4$ (or BCl_3) and warming to rt over several hours afforded only starting phenol.

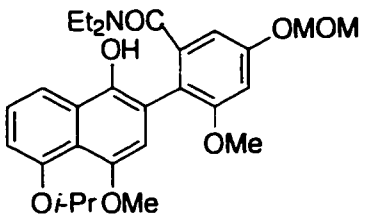
Procedure 3: *Cyclization of **261d***: According to general procedure D, a solution of hydroxyamide **261d** (75.3 mg, 0.166 mmol) in HOAc (5 mL) was heated at reflux for 10 min. Standard workup followed by column chromatography (1:1 hexane:EtOAc) afforded the title compound (63.0 mg, 100%).

***N*,*N*-Diethyl *O*-[4-methoxy-5-isopropoxy-2-(2-methoxy-5-methoxymethoxyphenyl)]-1-naphthylcarbamate (279).**



According to general procedure G, a mixture of naphthyl iodide **259a** (1.00 g, 2.1970 mmol), arylboronic acid **280** (0.677 g, 3.1920 mmol), $Ba(OH)_2 \cdot 8H_2O$ (1.73 g, 5.48 mmol) and $Pd(PPh_3)_4$ (0.140 g, 0.121 mmol) in DME (100 mL) and H_2O (10 mL) was heated at reflux for 3 h. Standard workup followed by column chromatography (2:1 hexane:EtOAc) afforded the title compound as a gum (1.05 g, 99%). IR (neat) ν (max) 2961, 1715, 1581, 1509, 1460, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd J = 8.4,1.3 Hz, 1H), 7.35 (dd J = 8.4, 7.5 Hz, 1H), 7.24 (dd J = 7.5, 1.3 Hz, 1H), 6.93 (dd J = 7.5, 1.3 Hz, 1H), 6.76 (s, 1H), 6.68 (m, 2H), 5.21 (s, 2H), 4.53 (sept J = 6.0 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 3.51 (s, 3H), 2.05 (m, 4H), 1.39 (d J = 6.0 Hz, 6H), 1.03 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.8 (e), 157.5 (e), 154.6 (e), 153.6 (e), 153.5 (e), 138.1 (e), 127.7 (e), 126.3 (o), 120.4 (e), 119.4 (e), 115.1 (o), 113.2 (o), 109.3 (o), 106.8 (o), 99.93 (o), 94.07 (e), 72.67 (o), 56.31 (o), 55.43 (o), 55.13 (o), 41.49 (e), 41.16 (e), 21.65 (o), 13.59 (o), 12.73 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 497 (M^+, 36) 455 (6.2), 397 (32), 331 (10), 271 (8.4), 227 (8.0), 168 (62), 100 (100), 72 (44); HRMS (EI (70 eV)) *m/e* calcd for $C_{28}H_{35}NO_7$: 497.2415, found: 497.2412.

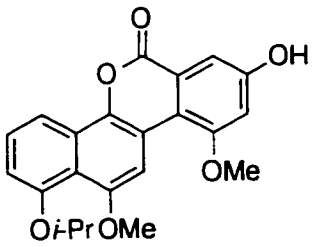
***N*,*N*-Diethyl 3-methoxy-5-methoxymethoxy-2-(4-methoxy-5-isopropoxy-1-hydroxynaphthyl)benzamide (286).**



According to general procedure C1, a solution of carbamate **279** (0.520 g, 0.956 mmol) in THF (8 mL) was added at 0°C to a solution of LDA (3.24 mmol) in THF (5 mL). The cooling bath was removed and the mixture heated to reflux until disappearance of SM by TLC (1h). Standard workup followed by column chromatography (3:2 hexane:EtOAc) afforded the title compound (0.145 mg 28%) as a glassy oil. Spectral analysis indicated a 3:1 mixture of rotamers. IR (neat) ν (max) 3238, 2974, 2935, 1600, 1482, 1455, 1411, 1377, 1325, 1274, 1217, 1187, 1153, 1127, 1078 cm^{-1}; For NMR data the resonance of the major rotamer is given followed by the corresponding peaks for the minor rotamer. ^1H NMR (250 MHz, $CDCl_3$) δ 8.06 (d J = 8.3 Hz, 1H) 7.99 (d J = 8.3 Hz, 1H), 7.32 (t J = 8.0 Hz, 1H) corresponding rotamer peak partially obscured, 6.94 (d J = 7.6 Hz, 1H) 6.98 (d J = 7.6 Hz, 1H), 6.71 (d J = 2.2 Hz, 1H) 6.83 unresolved d 1H, 6.60 (d J = 2.3 Hz, 1H) 6.69 unresolved d 1H, 6.56 (s 1H) 6.87 (s, 1H), 6.00 (s, br, 1H, exch) 7.57 (s, br, 1H, exch), 5.24 (d J = 6.8 Hz, 1H) corresponding rotamer peak partially obscured, 5.17 (d J = 6.8 Hz, 1H) 5.19 (d, J = 6.6 Hz), 4.56, (sept J = 6.0 Hz, 1H) 4.45 (sept J = 6.0 Hz), 3.83 (s, 3H) 3.89 (s), 3.66 (s, 3H) 3.85 (s), 3.50 (s, 3H) rotamer peak obscured, 3.42 (m, 1H) 3.56 (m), 3.20 (m, 1H) 2.83 (m), 3.01 (m, 2H) 2.55 (m), 1.40 (d J = 6.0 Hz, 1H) 1.34 (d J = 6.0 Hz), 0.98 (t J = 7.0 Hz, 3H) 1.24 (t J = 7.0 Hz), 0.62 (t J = 7.0 Hz, 3H) 0.69 (t J = 7.0 Hz, H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.49 (e) 169.25 (e), 158.70 (e) 158.37 (e), 158.13 (e) 156.14 (e), 153.87 (e) 154.44 (e), 149.78 (e) 149.90 (e), 144.10 (e) 142.54 (e), 138.59 (e) 140.57 (e), 130.98 (e) 128.91 (e), 125.16 (o) 125.46 (o), 120.14 (e) 120.01 (e), 118.43 (e) 117.06 (e), 117.43 (e) 116.52 (e), 117.21 (o) 116.64 (o), 113.13 (o) 115.54 (o), 111.93 (o) 109.66 (o), 104.5 (o) 107.92 (o), 100.99 (o) 100.59 (o), 94.38 (e) corresponding rotamer peak obscured, 72.37 (o) 73.88 (o), 57.83 (o) 55.98 (o),

55.89 (o) 56.41 (o), 55.61 (o) 56.21 (o), 42.91 (e) 41.83 (e), 38.74 (e) 38.04 (e), 21.87 (o) 21.92 (o), 13.63 (o) 13.99 (o), 11.55 (o) 11.76 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 497 (5) M^+, 481 (10), 424 (100), 408 (45), 394 (8), 382 (97), 368 (30), 352 (10), 338 (31), 323 (13), 294 (14), 279 (12); HRMS (EI (70 eV)) *m/e* calcd for $C_{28}H_{35}NO_7$: 497.2415, found 497.2409.

8-Hydroxy-1-isopropoxy-10,12-dimethoxy-6*H*-naphtho[1,2-*b*]benzo[*d*] pyran-6-one (287a).

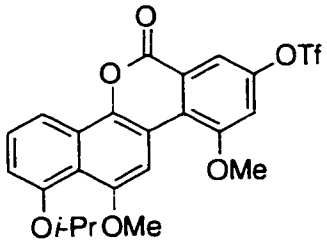


Procedure 1: According to General Procedure C2, a solution of carbamate **279** (1.18 g, 2.38 mmol) in THF (15 mL) was added to a solution of LDA (3.05 mmol) in THF (30 mL) and the mixture heated at reflux for 2 h. At this point a solution of LDA (3.05 mmol) in THF (5 mL) was added. Heating was continued until the disappearance of SM by TLC (1h). Standard workup afforded the crude hydroxyamide which was dissolved in HOAc (10 mL) and heated at reflux for 10 min. At this point an equal volume of H_2O was added and heating continued for 1h. The reaction mixture was then cooled to room temperature and the solvents removed *in vacuo*. The residue was dissolved in acetone and 10 g silica gel added. The acetone was removed on the rotovap and the mixture dry loaded directly onto a flash column. Purification by column chromatography (2:1 hexane:EtOAc → EtOAc) afforded the title compound as a yellow powder (0.641 g, 70%). Due to the insolubility of the material crystallization could not be effected. mp >260°C (dec). IR (KBr) ν (max) 3393, 2956, 1693, 1601, 1487, 1452 cm^{-1}; ^1H NMR (250 MHz, pyridine-d_5) δ 8.56 (s, 1H) 8.29 (d J = 8.5 Hz, 1H), 8.01 (d J = 2.2 Hz, 1H), 7.50 (m, 1H overlapping with solvent), 7.20 (d J = 2.2 Hz, 1H), 7.09 (d J = 7.7 Hz, 1H), 5.50 (s, br, 1H), 4.61 (sept J = 6.0 Hz, 1H), 4.02 (s, 3H), 3.90 (s, 3H), 1.40 (d J = 6.0 Hz, 6H); ^{13}C NMR

(62.9 MHz, $CDCl_3$) δ 161.3 (e), 160.5 (e), 159.7 (e), 155.5 (e), 153.5 (e), 139.8 (e), 127.6 (e), 127.6 (o), 125.0 (e), 119.1 (e), 116.73 (e), 114.9 (o), 114.7 (e), 113.0 (o), 107.9 (o), 107.3 (o), 105.4 (o), 72.44 (o), 56.96 (o), 56.19 (o), 22.17 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 380 (M^+, 74), 338 (100), 323 (29), 295 (25), 252 (7.2), 236 (4.0); HRMS (EI (70 eV)) *m/e* calcd for $C_{22}H_{20}O_6$: 380.1260, found 380.1257.

Procedure 2: A solution of hydroxy amide **286** (0.1438 g, 0.2893 mmol) in HOAc (10 mL) was heated at reflux for 10 min at which point H_2O (5 mL) and H_2SO_4 (conc, 1 drop) were added. The reaction was heated to reflux for 1 h and standard workup and purification as in Procedure 1 afforded the title compound (36.6 mg, 33%).

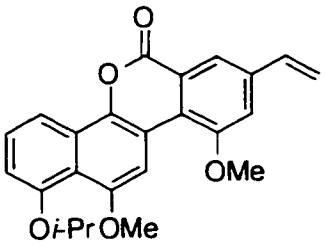
1-Isoprpoxy-10,12-dimethoxy-8-trifluoro-methanesulfonyl-6*H*-naphtho [1,2-*b*]benzo[*d*]pyran-6-one (288).



To a suspension of phenol **287a** (0.699 g, 1.84 mmol) in CH_2Cl_2 (35 mL) at room temperature was added Et_3N (1.50 mL, 10.76 mmol) and the mixture became homogeneous. The yellow solution was cooled to -78°C and Tf_2O (0.40 mL, 2.37 mmol) was added dropwise. The mixture was allowed to stir for 1 h and was then quenched with sat $NaHCO_3$ and the cooling bath removed. Standard workup followed by column chromatography (7:2:1 hexane:CH_2Cl_2:EtOAc) afforded a yellow solid which was recrystallized (hexane:CH_2Cl_2) giving the title compound (0.759 g, 81%) as bright yellow needles. mp 219-221°C (hexane:CH_2Cl_2); IR (CH_2Cl_2) ν (max) 3058, 2982, 1728, 1592, 1462, 1424 1386, 1134 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.20 (dd J = 8.5, 0.8 Hz, 1H), 7.99 (d J = 2.5 Hz, 1H), 7.51 (dd J = 8.2, 8.0 Hz, 1H), 7.17 (d J = 2.5 Hz, 1H), 7.08 (d ,br, J = 7.5 Hz, 1H), 4.62 (sept, J = 6.0 Hz, 1H), 4.13 (s, 3H), 3.99 (s, 3H), 1.45 (d J = 6.0 Hz, 6H);

^{13}C NMR (62.9 MHz, $CDCl_3$) δ 159.6 (e), 158.7 (e), 154.7 (e), 153.2 (e), 148.6 (e), 141.2 (e), 127.4 (e), 126.6 (e), 124.9 (e), 124.3 (e), 119.8 (e), 118.7 (e, q J = 321 Hz), 103.6 (o), 72.91 (o), 56.72 (o), 56.53 (o), 22.03 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 512 (41), 476 (49), 337 (100), 309 (9), 294 (26), 279 (14) Anal. calcd for $C_{23}H_{19}SO_8F_3$: C, 53.91 ; H, 3.74 ; found: C,54.14 ; H, 3.88.

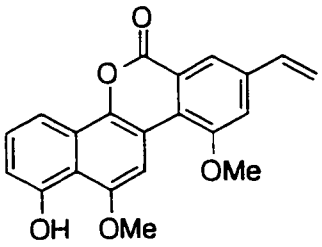
1-Isopropoxy-10,12-dimethoxy-8-vinyl-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (289c).



A solution of triflate **288** (0.102 g, 0.199 mmol), vinyltributyltin (79.8 mg, 0.239 mmol), LiCl (45.0 mg, 1.06 mmol), tri-(2-furyl)phosphine (4.90 mg, 0.201 mmol) and Pd_2dba_3 (9.8 mg, 0.0107 mmol) in anhydrous NMP was stirred at rt under Ar for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the layers separated. The aqueous phase was then extracted twice more with CH_2Cl_2 (10 mL) and the combined organic layers were washed (H_2O, brine) and dried (Na_2SO_4). The solvents were removed under reduced pressure (high vacuum for remaining NMP) and the residue was purified by column chromatography (5:2 hexane:EtOAc) and then recrystallization (CH_2Cl_2:hexane) afforded the title compound (53.4 mg, 69%) as a fine yellow powder. mp 211-213°C (CH_2Cl_2:hexane). IR (CH_2Cl_2) ν (max) 3154, 2984, 1722, 1587, 1422, 1384 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.19 (dd J = 8.4, 1.0 Hz, 1H), 8.07 (d J = 1.5 Hz, 1H), 7.47 (dd J = 7.8, 8.4 Hz, 1H), 7.26 (d overlaps solvent, 1H), 7.05 (dd J = 7.8, 0.8 Hz, 1H), 6.74 (dd J = 10.9, 17.5 Hz, 1H), 5.90 (d J = 17.5 Hz, 1H), 5.04 (d J = 10.9 Hz, 1H), 4.58 (sept J = 6.1 Hz, 1H), 4.05 (s, 3H), 3.97 (s, 3H), 1.43 (d J = 6.1 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 161.2 (e), 157.2 (e), 154.6 (e), 152.7

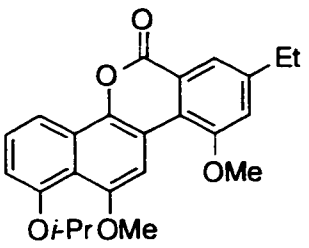
(e), 140.8 (e), 138.3 (e), 135.3 (o), 127.0 (o), 126.7 (e), 123.6 (e), 123.2 (e), 120.3 (o), 119.5 (e), 116.1 (e), 115.5 (o), 114.6 (o), 113.7 (o), 113.2 (e), 104.3 (o), 73.14 (o), 56.43 (o), 55.97 (o), 22.14 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 390 (M^+, 34), 348 (100), 333 (44), 305 (37), 267 (14); Anal. calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.70; found: C, 73.90; H, 5.70.

1-Hydroxy-10,12-dimethoxy-8-vinyl-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (defucogilvocarcin V) (149d).



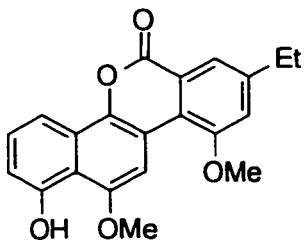
To a solution of isopropyl ether **289c** (33.1 mg, 0.0849 mmol) in CH_2Cl_2 (5 mL) at 0°C was added BCl_3 (0.40 mL, 1.0 mol/L in CH_2Cl_2) dropwise. The solution was allowed to stir for 15 min and was then quenched with H_2O. Standard workup followed by column chromatography (4:1 CH_2Cl_2:hexane) afforded the title compound as a yellow solid (28.4 mg, 95%). mp 259-264°C (dec) lit mp[188] 263-265°C (dec). ^1H NMR (250 MHz, $CDCl_3$) δ 9.34 (s, 1H, exch), 8.29 (s, 1H), 8.13 (d J = 1.7 Hz, 1H), 8.06 (d J = 8.5, 1.0 Hz, 1H), 7.49 (app t J= 8.0 Hz, 1H), 7.32 (d J = 1.7 Hz, 1H), 7.01 (dd J = 7.7, 1.0 Hz, 1H), 6.92 (dd J = 17.6, 10.9 Hz, 1H), 5.94 (d J = 17.6 Hz, 1H), 5.45 (d J = 10.9 Hz, 1H), 4.10 (s, 3H); MS (EI (70 eV)) *m/e*: (rel intensity) 348 (M^+, 100), 333 (19), 319 (4.4), 262 (7.0), 305 (19), 234 (2.9), 205 (3.1), 174 (10), 149 (14); HRMS (EI (70 eV)) *m/e* calcd for $C_{21}H_{16}O_5$: 348.0998, found 348.0992.

1-Isopropoxy-10,12-dimethoxy-8-ethyl-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (289a).



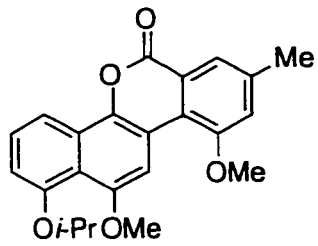
A suspension of K_3PO_4 (0.224 g, 1.05 mmol), $PdCl_2$(dppf) (20.0 mg, 0.0301 mmol) and BEt_3 (0.95 mL, 1.0 mol/L in hexane) in THF (5 mL) under Ar was allowed to stir at room temperature for 10 min and a suspension of triflate **288** (0.231 g, 0.450 mmol) in THF (4 X 5 mL) was added. The reaction mixture was heated at reflux until disappearance of SM by TLC (1h). The reaction was then cooled to rt and treated with 5% NaOH (1.4 mL) and 30% H_2O_2 (0.5 mL), and allowed to stir at rt for 1.5 h. The mixture was then poured into 10% HCl (20 mL) containing ice and extracted with CH_2Cl_2 (3X15 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (7:1:0.5 → 7:2:1 hexane:CH_2Cl_2:EtOAc) and then recrystallization (hexane:CH_2Cl_2) to afford the title compound (0.132 g, 75%) as fine yellow needles. mp 215-216°C. IR (KBr) ν (max) 3055, 2975, 1719, 1610, 1586, 1484, 1448, 1382 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.18 (dd J = 8.4, 0.9 Hz, 1H), 7.85 (d J = 0.6 Hz, 1H), 7.46 (dd J = 8.4, 7.8 Hz, 1H), 7.02 (m, 2H), 4.57 (sept J = 6.0 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 2.69 (q J = 7.6 Hz, 4H), 1.43 (d J = 6.0 Hz, 6H), 1.28 (t J = 7.6 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.4 (e), 157.1 (e), 154.5 (e), 152.6 (e), 145.7 (e), 140.5 (e), 126.8 (e), 126.8 (o), 126.7 (e), 123.0 (e), 122.0 (e), 121.2 (o), 119.3 (e), 116.8 (o), 115.4 (o), 114.3 (o), 113.4 (e), 104.7 (e), 73.03 (o), 56.54 (o), 55.96 (o), 28.75 (e), 22.05 (o), 14.90 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 392 (M^+, 54), 350 (100), 335 (41), 307 (34), 249 (9); Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16; found: C, 73.37; H, 6.06.

1-Hydroxy-10,12-dimethoxy-8-ethyl-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one, (Defucogilvocarcin E) (290a).



To a solution of isopropyl ether **289a** (56.0 mg, 0.143 mmol) in CH_2Cl_2 (10 mL) at 0°C was added BCl_3 (0.72 mL, 1.0 mol/L in CH_2Cl_2) dropwise over 5 min. The solution was allowed to stir for 10 min and was then treated with H_2O. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 X 10 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 CH_2Cl_2:EtOAc) and then recrystallization (CH_2Cl_2:hexane) to afford the title compound as a fine yellow powder (43.2 mg, 86%). mp 255-256°C (CH_2Cl_2:hexane) lit[191] mp 242-244°C ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.29 (s, 1H), 8.06 (dd J = 8.4, 1.0 Hz, 1H), 7.95 (d J = 1.6 Hz, 1H), 7.49 (app t J = 8.1 Hz, 1H), 7.14 (d J = 1.6 Hz, 1H), 6.99 (dd J = 7.7, 1.0 Hz, 1H), 4.09 (s, 3H), 4.07 (s, 3H), 2.79 (q J = 7.6 Hz, 2H), 1.34 (t J = 7.6 Hz, 3H); MS (EI (70 eV)) *m/e*: (rel intensity) 350 (M^+, 100), 335 (25), 307 (30), 292 (5), 249 (9); HRMS (EI (70 eV)) *m/e* calcd for $C_{21}H_{18}O_5$: 350.1154, found 350.1159.

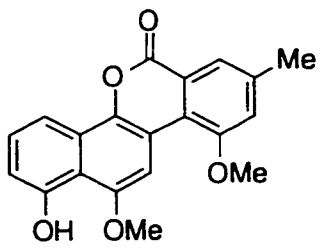
1-Isopropoxy-10,12-dimethoxy-8-methyl-6*H*-naphtho[1,2-*b*]benzo[*d*]-pyran-6-one (289b).



To a solution of MeLi (0.96 mL, 2.20 mol/L in Et_2O) in THF (10mL) at -78°C was added dropwise a solution of flame dried $ZnCl_2$ (0.345 g, 2.53 mmol) in THF (10 mL) over 15 min *via* canula. The solution was maintained at -78°C for 30 min and then allowed to warm to rt over a period of 1 h. This solution was then added *via* canula to a separate flame dried flask which was charged with triflate **288** (0.370 g, 0.722 mmol) and $NiCl_2$(dppp) (43.0 mg, 0.0793 mmol). The resulting solution was then allowed to stir at rt for 2 h at which point standard workup followed by column chromatography (3:1 hexane:EtOAc) afforded a yellow solid which was

recrystallized (hexane:CH_2Cl_2) giving the title compound as fine yellow needles (0.161 g, 59%). mp 232-233°C (hexane:CH_2Cl_2). IR (CH_2Cl_2) ν (max) 3018, 2990, 1722, 1588, 1422, 1385 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.23, (s, 1H), 8.18 (dd J = 7.7, 0.8 Hz, 1H), 7.85 (s, 1H), 7.47 (app t J = 8.1 Hz, 1H), 7.03 (m, 2H), 4.58 (sept J = 6.0 Hz, H), 3.98 (s, 3H), 3.96 (s, 3H), 2.42 (s, 3H), 1.43 (d J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.4 (e), 157.0 (e), 154.5 (e), 152.6 (e), 140.5 (e), 139.6 (o), 126.9 (e), 126.8 (o), 122.5 (e), 121.8 (o), 119.3 (o), 117.9 (e), 115.5 (e), 114.4 (e), 113.4 (o), 73.09 (o), 56.56 (o), 56.02 (o), 21.50 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 378 (M^+, 40), 336 (100), 321 (41), 293, (26),250 (9); Anal. calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86; found: C, 72.58; H, 5.64.

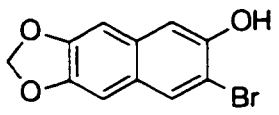
1-Hydroxy-10,12-dimethoxy-8-methyl-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one, (defucogilvocarcin M) (290b).



To a solution of isopropyl ether **289b** (0.113 g, 0.298 mmol) in CH_2Cl_2 (20 mL) at 0°C was added dropwise over 10 min BCl_3 (1.50 mL, 1.0 mol/L in CH_2Cl_2). The solution was allowed to stir for 10 min and was then treated with H_2O. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 X 10 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 CH_2Cl_2:EtOAc) and was recrystallized (CH_2Cl_2:hexane) to give the title compound (83.4 mg, 83%) as a fine yellow powder. mp 271-274°C (dec), (CH_2Cl_2:hexane) lit[366] mp 273-274°C (dec). ^1H NMR (250 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.23 (s, 1H), 8.04 (dd J = 8.4, 0.9 Hz, 1H), 7.89 (s, 1H), 7.48 (app t J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.99 (dd J = 7.7, 0.9 Hz, 1H), 4.07 (s, 3H), 4.04 (s, 3H), 2.48 (s,

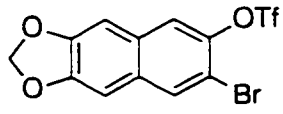
3H); MS (EI (70 eV)) *m/e*: (rel intensity) 336 (M^+, 100), 321 (37), 293 (36), 250 (12); HRMS (EI (70 eV)) *m/e* calcd for $C_{20}H_{16}O_5$: 336.0998, found 336.0991.

3-Bromo-6,7-methylenedioxy-2-naphthol (295).



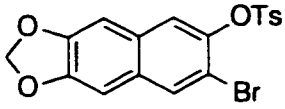
Prepared from a lit[240] procedure. (Yield: 87%) mp 78-80°C (dec). lit[240] mp 84°C.

3-Bromo-6,7-methylenedioxy-2-naphthyltrifluoromethanesulfonate (296a).



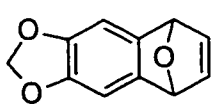
To a solution of phenol **295** (0.645 g, 2.97 mmol) and Et_3N (0.51 mL, 3.86 mmol) in CH_2Cl_2 (25 mL) at 0°C was added Tf_2O (0.63 mL, 3.71 mmol) dropwise. The reaction was allowed to stir for 1 h and was then quenched with H_2O and the layers separated. The aq phase was extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (9:1 hexane:EtOAc) to afford the title compound as a yellow oil (0.901 g, 87%) which crystallized on standing. mp 54-55°C (hexane:Et_2O). IR (KBr) ν (max) 3060, 3004, 2920, 1709, 1616, 1491, 1423, 1387, 1142 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.07 (s, 2H), 6.83 (s, 1H), 7.06 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 148.0 (e), 140.9 (e), 118.6 (q J = 320 Hz) (e), 110.0 (o), 107.2 (e), 104.0 (o), 103.0 (e); Anal. calcd for $C_8H_4BrF_3O_5S$: C, 27.52; H, 1.15; found: C, 27.66; H, 1.14.

3-Bromo-6,7-methylenedioxy-2-naphthyl *p*-toluensulfonate (296b).



A mixture of phenol **295** (0.599 g, 2.76 mmol), TsCl (0.789 g, 4.14 mmol) and Et_3N (0.60 mL, 4.42 mmol) in CH_2Cl_2 (25 mL) was stirred at 0°C for 1 h. The reaction mixture was poured into H_2O (50 mL) and the layers separated. The aq phase was extracted with CH_2Cl_2 (2 X 30 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (7:1 hexane:EtOAc) to afford the title compound as a white solid (0.915 g, 92%). mp 180-180.5°C (hexane:Et_2O). IR (KBr) ν (max) 3055, 2986, 2905, 1599, 1504, 1473, 1425, 1406, 1379, 1307, 1265, 1244, 1212, 1194, 1180, 1157, 1119, 1092 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.79 (d J = 8.2 Hz, 2H), 7.33 (d J = 8.2 Hz, 2H), 6.90 (s, 1H), 6.87 (s, 1H), 6.02 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 147.5 (e), 146.9 (e), 145.7 (e), 141.0 (e), 132.7 (e), 129.8 (o), 128.8 (o), 112.2 (o), 107.4 (e), 105.3 (o), 102.5 (e), 21.72 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 372 (31), 370 (31), 217 (100), 215 (100); Anal. calcd for $C_{14}H_{11}BrO_5S$: C, 45.30; H, 2.99; found: C, 45.46; H, 3.05.

1,4-Dihydro-6,7-methlenedioxy-1,4-epoxynaphthalene (292).

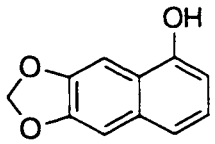


Procedure 1: *From triflate **296a***: To a solution of triflate **296a** (1.67 g, 4.79 mmol) and furan (10.0 mL, 141.5 mmol) in THF (30 mL) at -78°C was added *n*-BuLi (2.80 mL, 1.80 mol/L) dropwise over 10 min. The solution was quenched with sat NH_4Cl and standard workup followed by column chromatography afforded the title compound as a colorless solid (0.636 g, 71%). mp 105-106°C (hexane:Et_2O); IR (KBr) ν (max) 3025, 2896, 1728, 1637, 1616, 1591, 1505, 1485, 1456, 1419, 1395, 1338, 1283, 1201, 1130, 976.0 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.04 (m, 2H), 6.83 (s, 2H), 5.94 (d J = 1.4 Hz, 1H), 5.89 (d J =

1.4 Hz, 1H), 5.64 (s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.4 (e), 143.4 (o), 143.2 (e), 103.4 (o), 101.2 (e), 82.46 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 188 (M^+, 100), 162 (53), 130 (26), 102 (60), 75 (25); Anal. calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29; found: C, 70.18; H, 4.40.

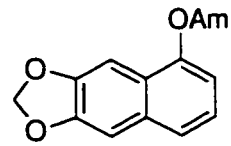
Procedure 2: *From Tosylate **296b***: To a solution of tosylate **296b** (7.00 g, 18.87 mmol) and furan (20 mL, 28.29 mmol) in THF (20 mL) at -95°C (internal) was added *n*-BuLi (11.80 mL, 1.69 mol/L) dropwise over 30 min. The reaction mixture was allowed to stir for 5 min and standard workup followed by column chromatography (5:1 hexane:EtOAc) afforded the title compound (2.997 g, 84%).

6,7-Methylenedioxy-1-naphthol (291).



To a solution of epoxynaphthalene **292** (0.163 g, 0.867 mmol) in CH_2Cl_2 (15 mL) at -78°C was added BCl_3 (0.95 mL, 1.0 mol/L in CH_2Cl_2) dropwise and the reaction allowed to stir for 10 min. The reaction was allowed to warm to rt over 1 h and standard workup followed by column chromatography (5:1 hexane:EtOAc) afforded the title compound (0.121 g, 74%) as colorless plates. mp 129-130°C (hexane:Et_2O); lit[367] mp 133-134°C. ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.26 (m, 1H), 7.17 (app t J = 7.5 Hz, 1H), 7.11 (s, 1H), 6.72 (dd J = 7.5 Hz, 1H), 6.01 (s, 2H), 5.50 (s, 1H, exch)

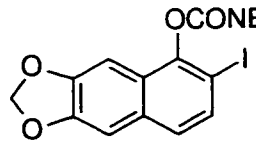
N,*N*-Diethyl *O*-(6,7-methylenedioxy)-1-naphthylcarbamate (216).



To a suspension of NaH (98.2 mg, 2.46 mmol) in THF (5 mL) at 0°C was added a solution of naphthol **291** (0.118 g, 0.627 mmol) in THF (5 mL). After the evolution of H_2 ceased, $ClCONEt_2$ (0.15 mL, 1.00 mmol) was added in one portion. The reaction mixture was allowed to warm to rt over 3 h and was then quenched by pouring *slowly* into sat NH_4Cl (50 mL) containing ice. The

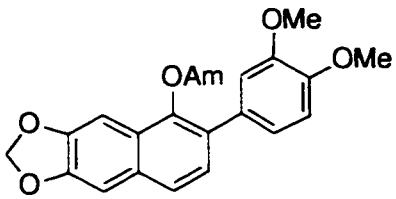
aq phase was extracted with Et_2O (3 X 25 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (6:1 hexane:EtOAc) giving a light yellow oil which solidified on standing (0.165 g, 92%). mp 95.5-96°C (hexane:Et_2O); IR (CH_2Cl_2) ν (max) 2936, 2905, 1715, 1620, 1502, 1464, 1421 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (d J = 8.2 Hz, 1H), 7.28 (app t J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.12 (m, 2H), 6.00 (s, 2H), 3.57 (q J = 7.0 Hz, 2H), 3.42 (q J = 7.0 Hz, 2H), 1.35 (t J = 7.0 Hz, 3H), 1.23 (t J = 7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, POWGATE, $CDCl_3$) δ 154.2, 148.0, 147.9, 132.0, 124.4, 124.4, 124.1, 117.0, 104.0, 101.1, 97.97, 42.33, 41.99, 14.48, 13.42; MS (EI (70 eV)) *m/e*: (rel intensity) 287 (M^+, 23), 187 (4.2), 100 (100), 72 (38); Anal. calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87; found: C, 67.04; H, 6.10; N, 4.86.

_N,N_-Diethyl _O_-(2-iodo-6,7-methylenedioxy)-1-naphthylcarbamate (297).



According to General procedure B, a solution of carbamate **216** (0.621 g, 2.16 mmol) in THF (10 mL) was sequentially treated with *s*-BuLi (1.94 mL, 1.34 mol/L), TMEDA (0.39 mL, 2.6 mmol) and a solution of I_2 (0.751 g, 2.96 mmol) in THF (5 mL). Standard workup followed by recrystallization afforded the title compound (0.522 g, 58%) as colorless plates. ^1H NMR (250 MHz, $CDCl_3$) δ 7.66 (d J = 7.5 Hz, 1H), 7.27 (d J = 7.5 Hz, 1H), 7.08 (s, 2H), 5.93 (s, 2H), 3.87-3.39 (m, 4H), 1.43 (t J = 7.0 Hz, 3H), 1.28 (t J = 7.0 Hz, 3H); MS (EI (70 eV)) *m/e*: (rel intensity) 413 (M^+, 5.0), 313 (1.3), 286 (10), 100 (100), 72 (39); Anal. calcd for $C_{16}H_{16}NO_4I$: C, 46.51; H, 3.90; N, 3.39; found: C, 46.62; H, 3.74; N, 3.35.

***N*,*N*-Diethyl *O*-[2-(3,4-dimethoxyphenyl)-6,7-methylenedioxy]-1-naphthylcarbamate (299).**

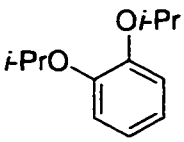


Procedure 1. According to general procedure F, a solution of carbamate **216** (0.333 g, 1.16 mmol) in THF (10 mL) at -78°C was sequentially treated with *s*-BuLi (1.05 mL, 1.35 mol/L), $ZnCl_2$ (1.50 mL, 1.0 mol/L in Et_2O) a solution of 4-bromoveratrole **298a** (0.50 g, 2.30 mmol) and $Pd(PPh_3)_4$ (75.0 mg, 0.0649 mmol) in THF (5 mL). The resulting solution was heated at reflux for 16 h. Standard workup followed by column chromatography (2:1 → 3:2 hexane:EtOAc) afforded the title compound as a colorless powder (0.292 g, 60%). mp 119-120°C (hexane:CH_2Cl_2); IR (CH_2Cl_2) ν (max) 2934, 1715, 1604, 1584, 1520, 1500, 1486, 1419, 1381 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.57 (d J = 8.4 Hz, 1H), 7.32 (d J = 8.4 Hz, 1H), 7.14 (s, 1H), 7.12 (s, 1H), 7.02 (m, 2H), 6.91 (m, 1H), 6.05 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.35 (m, 4H), 1.09 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.1 (e), 153.6 (e), 148.5 (e), 148.2 (e), 147.0 (e), 134.6 (e), 131.4 (e), 129.8 (e), 126.4 (o), 126.0 (o), 125.9 (e), 125.2 (o), 121.6 (o), 112.6 (o), 112.4 (e), 111.0 (o), 103.6 (o), 100.2 (e), 99.58 (o), 56.02 (o), 55.90 (o), 42.08 (e), 41.83 (e), 14.29 (o), 13.32 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 423 (M^+, 21), 350 (2.0), 292 (8.1), 277 (3.5), 209 (1.7), 163 (2.3), 100 (100), 72 (46); Anal. calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31; found: C, 68.01; H, 6.04; N, 3.27.

Procedure 2: According to general procedure E, a solution of 4-bromoveratrole **298a** (0.765 g, 3.55 mmol) in THF (10 mL) was sequentially treated with *n*-BuLi (2.20 mL, 1.75 mol/L), $ZnCl_2$ (4.23 mL, 1.0 mol/L), aryl iodide **297** (0.469 g, 1.14 mmol) and $Pd(PPh_3)_4$ (66 mg, 0.057 mmol). The mixture was heated at reflux for 2.5 h. Standard

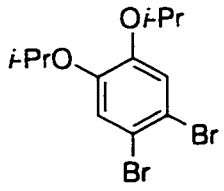
workup followed by column chromatography (3:2 hexane:EtOAc) followed by recrystallization (hexane:acetone) afforded the title compound (0.328 g, 68%) as colorless needles.

1,2-Diisopropoxybenzene (302).



A mixture of resorcinol **301** (27.16 g, 0.247 mol), *i*-PrI (65.0 mL, 0.651 mol) and K_2CO_3 (85.50 g, 0.619 mol) in acetone (500 mL) was heated at reflux for 48 h. Most of the acetone was removed on the rotovap and the resulting slurry was diluted with H_2O (250 mL) and Et_2O (250 mL) and the layers separated. The aq phase was extracted with Et_2O (2 X 200 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation giving the title compound as a colorless oil (24.12 g, 52%). bp 110-112°C / 75 mmHg, lit[368] bp 215°C / 630 mmHg.

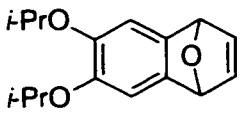
4,5-Dibromo-1,2-diisopropoxybenzene (303).



To a solution of 1,2-diisopropoxybenzene **(302)** (5.02 g, 26.4 mmol) and NaOAc (4.60 g, 55.5 mmol) in $CHCl_3$ (75 mL) at rt was added a solution of Br_2 (2.80 mL, 54.16 mmol) in $CHCl_3$ (18 mL) dropwise over 1 h. After complete addition the reaction mixture was allowed to stir for 1 h and was diluted with enough H_2O to dissolve the inorganic salts and the layers separated. The aq phase was further extracted with $CHCl_3$ (2 X 50 mL) and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation affording the title compound as a light yellow oil (7.41 g, 80%). bp 104-120°C / 0.2 mmHg. IR (neat) ν (max) 3070, 2976, 1578, 1552, 1478, 1384, 1355, 1290, 1138 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.13 (s, 2H), 4.42 (sept J = 6.1 Hz, 1H), 1.30 (d J = 6.1 Hz, 6H); ^{13}C

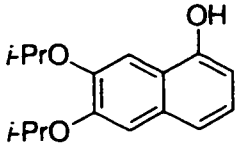
NMR (62.9 MHz, $CDCl_3$) δ 150.0 (e), 122.1 (o), 115.3 (e), 72.66 (o), 21.90 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 354 (37), 352 (65), 350 (39), 312 (9.8), 310 (17), 308 (9.8), 270 (72), 268 (100), 266 (71), 241 (8.7), 239 (17), 237 (17); HRMS (EI (70 eV)) *m/e* calcd for $C_{12}H_{16}Br_2O_2$: 351.9497, found 351.9485.

1,4-Dihydro-6,7-diisopropoxy-1,4-epoxynaphthalene (304).



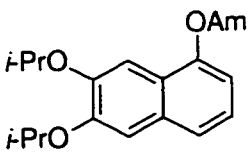
To a solution of furan **235** (72.0 mL, 0.963 mol) and *n*-BuLi (47.0 mL, 1.65 mol/L) in Et_2O (350 mL) at -74°C (internal) was added a solution of dibromide **303** (20.06 g, 57.02 mmol) in Et_2O (100 mL) dropwise *via* a dropping funnel over a period of 1.5 h. During the addition the temperature was not allowed to rise above -70°C (internal). After complete addition the reaction mixture was quenched with sat NH_4Cl at -70°C and was allowed to warm to rt. Standard workup followed by purification by column chromatography (8:1 hexane:EtOAc) and then recrystallization (hexane) afforded the title compound (11.00 g, 74%) as colorless plates. mp 52-52.5°C (hexane); IR (KBr) ν (max) 2930, 1737, 1605, 1466, 1418, 1049 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.99 (d J = 0.6 Hz, 2H), 6.95 (s, 2H), 5.62 (d J = 0.5 Hz, 2H), 4.37 (sept J = 6.0 Hz, 1H), 1.28 (d J = 6.0 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.8 (e), 142.9 (o), 142.3 (e), 113.1 (o), 82.27 (o), 72.73 (o), 72.63 (o), 22.21 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 260 (M^+, 91), 218 (18), 176 (55) 148 (100); Anal. calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; found: C, 73.68; H, 7.60.

6,7-Diisopropoxy-1-naphthol (305).



A solution of epoxynaphthalene **304** (0.253 g, 0.973 mmol) and HCl (1 drop, 12 mol/L) in MeOH (10 mL) was heated at reflux until the disappearance of SM by TLC (45 min). The reaction was cooled and concentrated on the rotovap and the residue dissolved in CH_2Cl_2 (20 mL). The organic layer was washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by recrystallization (hexane:Et_2O) affording the title compound as colorless plates (0.208 g, 82%). mp 121-122°C (hexane:Et_2O). IR (KBr) ν (max) 3402, 3085, 2978, 1629, 1593, 1515, 1470, 1387, 1329, 1282, 1177, 1068 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.21 (d J = 8.2 Hz, 1H), 7.09 (dd J = 8.2, 7.4 Hz, 1H), 6.65 (dd J = 7.4, 0.9 Hz, 1H), 6.37 (s, 1H), 4.65 (sept J = 6.1 Hz, 1H), 1.38 (app t J = 6.1 Hz, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.7 (e), 149.2 (e), 148.3 (e), 131.0 (e), 124.2 (o), 120.2 (e), 118.7 (o), 111.8 (o), 107.4 (o), 106.2 (o), 71.88 (o), 21.92 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 260 (23), 218 (6.9), 176 (100), 147 (37); HRMS (EI (70 eV)) *m/e* calcd for $C_{16}H_{20}O_3$: 260.1412, found 260.1405.

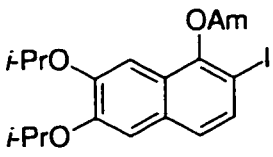
***N,N*-Diethyl *O*-(6,7-diisopropoxy)-1-naphthylcarbamate (306).**



According to general procedure A, a mixture of naphthol **305** (5.04 g, 19.38 mmol) K_2CO_3 (5.40 g, 39.07 mmol) and $ClCONEt_2$ (3.70 mL, 29.07 mmol) in CH_3CN (100 mL) was heated at reflux for 12 h. Standard workup followed by recrystallization (hexane:Et_2O) afforded the title compound as colorless needles (6.96 g, 84%). mp 113.5-114.5°C (hexane:Et_2O). IR (KBr) ν (max) 3056, 2980, 2974, 1715, 1603, 1501, 1470, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (d J = 8.1 Hz, 1H), 7.29 (dd J = 8.1, 7.6 Hz, 1H), 7.23 (s, 1H),

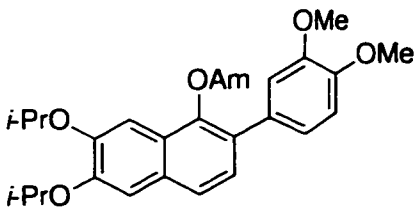
7.20 (s, 1H), 7.13 (dd J = 7.6, 1.2 Hz, 1H), 4.59, (m, 2H), 3.41-3.59 (m, 4H), 1.40 (d J = 6.1, Hz, 6H), 1.39 (d J = 6.1, Hz, 6H), 1.20-1.32 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.1 (e), 149.4 (e), 149.3 (e), 146.3 (e), 130.9 (o), 123.6 (o), 123.5 (o), 123.3 (e), 116.2 (o), 112.3 (o), 105.5 (o), 71.81 (o), 71.70 (o), 42.26 (e), 41.97 (e), 21.90 (o), 14.40 (o), 13.37 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 359 (M^+, 29), 280 (0.26), 260 (0.40), 217 (1.0), 175 (7.0), 147 (11), 100 (100), 72 (45), 44 (11); Anal. calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90; found: C, 70.26; H, 8.27; N, 3.87.

_N,N_-Diethyl _O_-(2-iodo-6,7-diisopropoxy)-1-naphthylcarbamate (307).



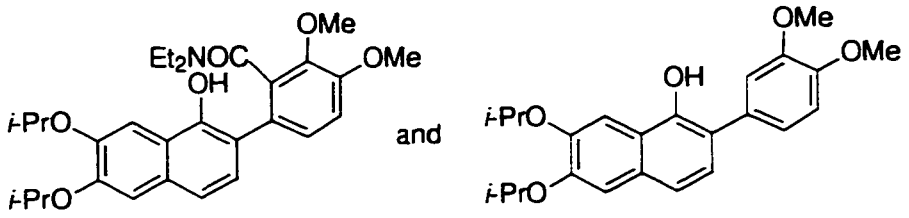
According to general procedure B, carbamate **306** (0.692 g, 1.93 mmol) was treated sequentially with TMEDA (0.28 mL, 1.864 mmol), *s*-BuLi (1.40 mL, 1.41 mol/L) and I_2 (0.552 g, 2.18 mmol). Standard workup followed by column chromatography afforded a light blue solid (0.654 g, 70%). mp 102-103°C (hexane:Et_2O). IR (KBr) ν (max) 2977, 2933, 1723, 1622, 1587, 1496, 1462, 1411 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (d J = 8.6 Hz, 1H), 7.25 (d J = 8.6 Hz, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 4.49-4.61 (m, 2H), 3.57-3.66 (m, br, 2H), 3.43 (q J = 7.1 Hz, 2H), 1.38 (t J = 6.3 Hz, 15H), 1.24 (t J = 7.1 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.4 (e), 149.8 (e), 149.6 (e), 146.8 (e), 132.5 (o), 130.4 (o), 125.3 (o), 124.4 (e), 111.8 (o), 105.5 (o), 86.61 (e), 71.68 (o), 71.58 (o), 42.34 (e), 42.09 (e), 21.80 (o), 21.73 (o), 14.46 (o), 13.26 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 485 (M^+, 15), 358 (5.9), 301 (3.6), 273 (2.6), 174 (4.0), 100 (100), 72 (20); Anal. calcd for $C_{21}H_{28}NO_4I$: C, 51.97; H, 5.81; N, 2.89; found: C, 52.00; H, 5.87; N, 2.84.

***N,N*-Diethyl *O*-[6,7-diisopropoxy-2-(3,4-dimethoxyphenyl)]-1-naphthyl-carbamate (308).**



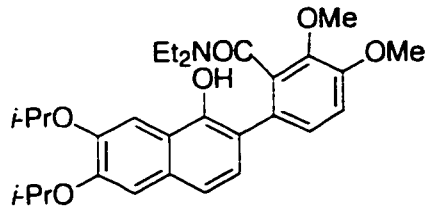
Procedure 1: According to general procedure F, a solution of naphthylcarbamate **306** (1.81 g, 5.04 mmol) in THF (20 mL) was sequentially treated with TMEDA (0.845 mL, 5.61 mmol), *s*-BuLi (4.70 mL, 1.18 mol/L), $ZnCl_2$ (5.60 mL, 1.0 mol/L), a solution of 4-bromoveratrole **(298a)** (2.29 g, 10.55 mmol) in THF (10 mL) and $Pd(PPh_3)_4$ (130 mg, 0.112 mmol). The reaction was heated at reflux for 12 h and standard workup followed by column chromatography afforded the title compound (0.790 g, 32%). IR (neat) ν (max) 2978, 2935, 1712, 1606, 1500, 1469 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.55 (d J = 8.4 Hz, 1H), 7.31 (d J = 8.4 Hz, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 7.04 (m, 2H), 6.92 (d J = 8.0 Hz, 1H), 4.59 (2 overlapping sept J = 6.0 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.40 (q J = 7.0 Hz, 2H), 3.30 (q J = 7.0 Hz, 2H), 1.40 (d J = 6.0 Hz, 12H), 1.17 (t J = 7.0 Hz, 3H), 1.08 (t J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.9 (e), 149.9 (e), 149.3 (e), 148.5 (e), 148.1 (e), 142.8 (e), 131.2 (e), 130.2 (e), 129.7 (e), 126.3 (o), 124.2 (e), 123.9 (o), 121.6 (o), 112.7 (o), 112.6 (o), 111.1 (o), 106.3 (o), 72.03 (o), 71.85 (o), 56.00 (o), 55.80 (o), 42.12 (e), 41.92 (e), 22.05 (o), 22.00 (o), 14.25 (o), 13.28 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 495 (M^+, 26), 453 (1.0), 280 (11), 100 (100), 72 (38); HRMS (EI (70 eV)) *m/e* calcd for $C_{29}H_{37}NO_6$: 495.2622, found 495.2611.

***N,N*-Diethyl 2-(6,7-diisopropoxy-1-hydroxy-2-naphthyl)-5,6-dimethoxyphenylbenzamide) (309) and 6,7-diisopropoxy-2-(3,4-dimethoxyphenyl)-1-naphthol (310).**



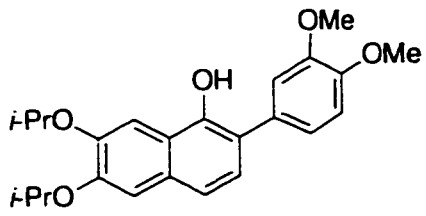
Procedure 1: According to general procedure C1, a solution of carbamate **308** (0.507 g, 1.03 mmol) in THF (10 mL) is treated with a solution of LDA (9.96 mmol) in THF (10 mL) at rt for 6 h. Standard workup followed by column chromatography afforded the desired hydroxyamide as a gum (0.176 g, 35%) along with naphthol **310** (0.177 g, 44%).

Hydroxyamide 309:



IR (neat) ν (max) 3330 (br) 2979, 2938, 1602, 1488 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.67 (s, br, exch, 1H), 7.79 (s, 1H), 7.23 (d J = 8.4 Hz, 1H), 7.14 (s, 1H), 7.00 (m, 3H), 4.64 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H). 3.21 (m, br, 4H), 1.42 (m 12H), 0.90 (t J = 7.1 Hz, 3H), 0.86 (t J = 7.1 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.7 (e), 151.7 (e), 149.5 (e), 148.9 (e), 143.9 (e), 131.5 (e), 130.5 (e), 129.5 (e), 127.7 (o), 126.7 (o), 122.9 (o), 118.5 (o), 113.0 (o), 112.0 (o), 107.8 (o), 71.91 (o), 71.54 (o), 61.56 (o), 55.31 (o), 43.08 (e), 39.08 (e), 22.10 (o), 21.95 (o), 13.50 (o), 11.77 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 495 (11), 422 (100), 380 (29), 338 (60), 274 (24), 100 (16); HRMS (EI (70 eV)) *m/e* calcd for $C_{29}H_{37}NO_6$: 495.2622, found 495.2590.

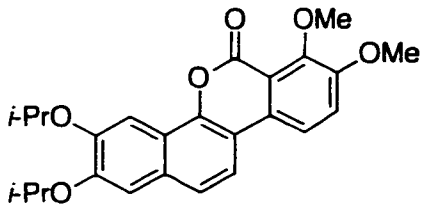
Naphthol 310:



mp 153-154°C (hexane:CH_2Cl_2); IR (KBr) ν (max) 3389, 3055, 2981, 1606, 1582, 1501, 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.29 (d J = 8.5 Hz, 1H), 7.18 (d J = 8.2 Hz, 1H), 7.07 (d J = 8.2 Hz, 1H), 7.07 (d J = 1.7 Hz, 1H), 7.00 (d J = 8.2 Hz, 1H), 5.78 (s, 1H, exch), 4.66 (sept J = 6.0 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 1.41 (d J = 6.0 Hz, 6H), 1.40 (d J = 6.0 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.7 (e), 149.5 (e), 149.0 (e), 148.5 (e), 146.7 (e), 130.0 (e), 130.1 (e), 125.7 (o), 121.2 (o), 119.8 (e), 119.6 (e), 118.4 (o), 112.4 (o), 112.1 (o), 111.9 (o), 106.9 (o), 71.98 (o), 56.10 (o), 22.18 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 396 (M^+, 60), 354 (16), 312 (88), 274 (100), 259 (29), 216 (7.5), 137 (9.6), 115 (6.2), 84 (5.4), 49 (42); HRMS (EI (70 eV)) *m/e* calcd for $C_{24}H_{28}O_5$: 396.1937, found 396.1939.

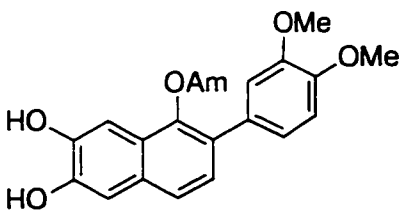
Procedure 2: According to General Procedure C2, a solution of carbamate **308** (0.471 g, 0.951 mmol) in THF (10 mL) was added to a solution of LDA (1.91 mmol) in THF (10 mL). The reaction was allowed to stir at rt for 6 h and a further portion of LDA (0.960 mmol) in THF (5 mL) was added. Stirring was continued until the disappearance of SM by TLC (3h). Standard workup followed by column chromatography (5:1:1 hexane:CH_2Cl_2:EtOAc) afforded hydroxyamide **308** (0.320 g, 68%).

3,4-Diisopropoxy-7,8-dimethoxy-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (311).



According to General Procedure C1, a solution of carbamate **308** (0.241 g, 0.488 mmol), in THF (5 mL) was added to a solution of LDA (1.46 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 3 h and standard workup followed by column chromatography (4:1:1 hexane:CH_2Cl_2:EtOAc) afforded the crude hydroxyamide **309** which was cyclized according to General Procedure D (10 mL HOAc). Standard workup afforded the title compound as a cream colored solid (0.126 g, 62%). IR (KBr) ν (max) 2982, 1729, 1634, 1492 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.89 (d J = 9.0 Hz, 1H), 7.86 (s, 1H), 7.81 (d J = 8.8 Hz, 1H), 7.53 (d J = 8.8 Hz, 1H), 7.44 (d J = 9.0 Hz, 1H), 4.80 (sept J = 6.0 Hz, 1H), 4.66 (sept J = 6.0 Hz, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 1.45 (d J = 6.0 Hz, 6H), 1.43 (d J = 6.0 Hz, 6H); MS (EI (70 eV)) *m/e*: (rel intensity) 422 (M^+, 100), 380 (84), 364 (8.2), 338 (51), 323 (48), 309 (8.2), 294 (26), 279 (12); HRMS (EI (70 eV)) *m/e* calcd for $C_{25}H_{26}O_6$: 422.1729, found 422.1728.

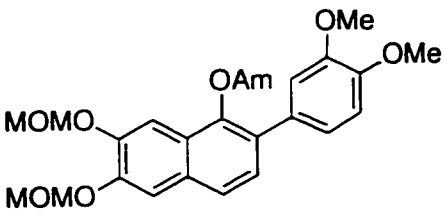
***N*,*N*-Diethyl *O*-[6,7-dihydroxy-2-(3,4-dimethoxy-phenyl)]-1-naphthyl-carbamate (312).**



To a solution of diisopropyl ether **308** (0.197 g, 0.397 mmol) in CH_2Cl_2 (10 mL) at 0°C was added BCl_3 (2.40 mL, 1.0 mol/L in CH_2Cl_2). The reaction was allowed to stir for 1 h and was then quenched with H_2O (20 mL). The layers were separated and the aq phase extracted with CH_2Cl_2 (2 X 20 mL). The combined organic layers were washed (H_2O, brine), dried (Na_2SO_4) and concentrated *in*

vacuo. The residue was purified by recrystallization (hexane:CH_2Cl_2) affording the title compound as colorless plates (0.145 g, 89%). mp 183-184°C (hexane:CH_2Cl_2); IR (KBr) ν (max) 3550-2550 (br), 3052, 2951, 1690, 1638, 1603, 1579, 1514, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.61 (s, 1H, exch), 8.53 (s, 1H, exch), 7.52 (d J = 8.4 Hz, 1H), 7.24 (m, 3H), 7.09 (d J = 1.3 Hz, 1H), 6.95-7.03 (m, 2H), 3.82 (s, 6H), 3.46 (q J = 7.0 Hz, 2H), 3.29 (q J = 7.0 Hz, 2H), 1.15 (t J = 7.0 Hz, 3H), 1.05 (t J = 7.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.6 (e), 149.9 (e), 149.6 (e), 147.8 (e), 147.3 (e), 143.7 (e), 132.5 (e), 130.8 (e), 129.8 (e), 126.3 (o), 125.1 (e), 124.3 (o), 122.4 (o), 114.1 (o), 112.7 (o), 110.5 (o), 105.1 (o), 56.16 (o), 42.51 (e), 14.63 (o), 13.57 (o); MS (EI (70 eV)) *m/e*: (rel intensity); 411 (M^+, 85), 397 (2.0), 340 (1.6), 296 (1.9), 281 (3.6), 237 (1.5), 215 (2.1), 100 (100), 72 (34); Anal. calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.41 found: C, 66.96; H, 6.21, N, 3.38.

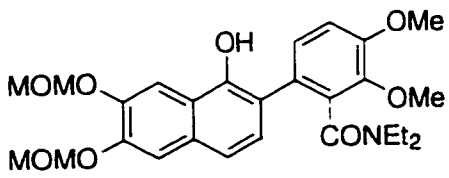
***N,N*-Diethyl *O*-[6,7-dimethoxymethoxy-2-(3,4-methoxyphenyl)]-1-naphthylcarbamate (313).**



To a suspension of NaH (1.20 g, 30.00 mmol) containing MOMCl (1.60 mL, 21.07 mmol) in dry DMF (50 mL) at 0°C was added a solution of catechol **312** in DMF (5 mL) portionwise. After the evolution of hydrogen had ceased the mixture was allowed to warm to rt over 2 h. The reaction was then quenched by pouring *slowly* into 100 mL of H_2O containing ice. The resulting mixture was extracted with Et_2O (3 X 50 mL) and the combined organic layers were washed H_2O (5 X 100 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 hexane:EtOAc) giving the title compound as a colorless glass (1.51 g, 95%). IR (neat) ν (max) 2948, 2833, 1716,

1607, 1584, 1470, 1415 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.60 (d J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.36 (d J = 8.5 Hz, 1H), 7.05-7.09 (m, 2H), 6.92 (d J = 8.1 Hz, 1H), 5.38 (s, 2H), 5.35 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.55 (s, 3H), 3.53 (s, 3H), 3.49 (q J = 6.6 Hz, 2H), 3.30 (q J = 6.6 Hz, 2H), 1.21 (t J = 6.6 Hz, 3H), 1.09 (t J = 6.6 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.7 (e), 148.4 (e), 148.1 (e), 147.3 (e), 142.9 (e), 131.3 (e), 130.2 (e), 130.0 (e), 126.8 (o), 124.3 (e), 124.2 (o), 121.5 (o), 112.4 (o), 111.5 (o), 111.0 (o), 106.0 (o), 95.50 (e), 95.18 (e), 56.11 (o), 56.05 (o), 55.83 (o), 55.71 (o), 42.09 (e), 41.89 (e), 14.09 (o), 13.11 (o); MS (EI (70 eV)) *m/e*: (rel intensity) 499 (M^+, 95), 467 (5.6), 455 (4.6), 437 (3.1), 399 (3.7), 350 (8.0), 336 (9.3), 323 (8.6), 292 (12), 265 (3.7), 165 (2.5), 100 (100), 72 (47); HRMS (EI (70 eV)) *m/e* calcd for $C_{27}H_{33}NO_9$: 499.2206, found 499.2191.

_N,N_-Diethyl 5,6-dimethoxy-2-(1-hydroxy-6,7-bis(methoxymethoxy)-2-naphthyl)benzamide (314).

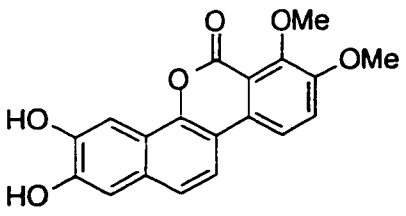


Procedure 1: According to general procedure C1, a solution of carbamate **313** (0.463 g, 0.928 mmol) in THF (5 mL) was added to a solution of LDA (5.60 mmol) in THF (10 mL) at 0°C and the solution allowed to stir at rt for 6 h. Standard workup followed by column chromatography (3:2 hexane:EtOAc) afforded the title compound as a foam (0.114 g, 25%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H, exch), 8.02 (s, 1H), 7.44 (s, 1H), 7.27 (d J = 8.3 Hz, 1H), 7.05 (d J = 8.3 Hz, 1H), 7.00 (d J = 8.6 Hz, 1H), 6.95 (d J = 8.6 Hz, 1H), 5.39 (s, 2H), 5.37 (s, 2H), 3.91 (s 6H), 3.56 (s, 3H), 3.55 (s, 3H), 3.40 (m, 1H), 3.21 (m, 1H), 3.04 (q J = 7.2 Hz, 2H), 0.91-0.84 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.6 (e), 151.6 (e), 148.9 (e),

147.6 (e), 146.6 (e), 143.7 (e), 131.3 (e), 130.7 (e), 129.1 (e), 127.5 (o), 127.3 (o), 123.0 (o), 118.8 (o), 112.8 (o), 110.8 (o), 107.9 (o), 95.28 (e), 95.05 (e), 61.45 (o), 56.18 (o), 56.08 (o), 55.70 (o), 42.96 (e), 38.94 (e), 13.39 (o), 11.75 (o); MS (EI (70 eV)) *m/e* (rel intensity) 499 (M^+, 44), 456 (6.7), 426 (99), 396 (12), 382 (6.8), 365 (7.1), 350 (100), 335 (66), 321 (39), 293 (16), 100 (27), 72 (49); HRMS (EI (70 eV)) *m/e* calcd for $C_{27}H_{33}NO_8$: 499.2206, found 499.2198.

Procedure 2: According to general procedure C2, a solution of carbamate **313** (0.560 g, 2.630 mmol) in THF (10 mL) was added to a solution of LDA (4.53 mmol) in THF (20 mL) at 0°C. The cooling bath was removed and the reaction allowed to stir for 2 h at which point LDA (2.99 mmol, 10 mL THF) was added and stirring continued for 2 h. This process was repeated once more followed by standard workup and column chromatography (3:2 hexane:EtOAc) to afford the title compound as a foam (0.169 g, 34%).

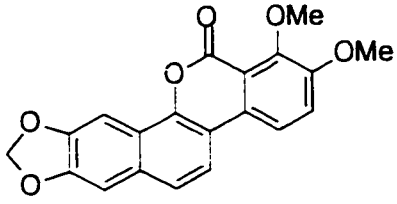
3,4-Dihydroxy-7,8-dimethoxy-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (315).



According to general procedure C1, a mixture of carbamate **313** (0.444 g, 0.890 mmol) in THF (5 mL) was added to a solution of LDA (4.39 mmol) in THF (10 mL) at 0°C. The reaction mixture was allowed to stir at rt for 6 h and standard workup afforded the crude hydroxyamide **314** which was dissolved in MeOH (10 mL) and TsOH (0.850 g, 4.94 mmol) was added. The reaction mixture was heated at reflux for 14 h at which point it was cooled to 0°C and the solid removed by filtration. The filtrate was diluted with 10 mL H_2O and cooled to 0°C and filtered. The precipitate (both crops) was washed with MeOH affording the title compound (0.132 g, 44%) as a light-brown powder. mp 291-294 °C (dec); IR (KBr) ν

(max) 3527, 3432 (br), 2947, 1698, 1634, 1504, 1461 cm^{-1}; ^1H NMR (250 MHz, DMF-d_7) δ 10.02 (s, 2H), 8.18 (d J = 9.0 Hz, 1H), 8.01 (d J = 8.9 Hz, 1H), 7.74 (d J = 8.9 Hz, 1H), 7.75 (s, 1H), 7.59 (d J = 8.9 Hz, 1H), 7.32 (s, 1H), 4.01 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (50 MHz, DMF-d_7) δ 157.6 (e), 153.7 (e), 151.8 (e), 149.4 (e), 148.8 (e), 145.8 (e), 130.7 (e), 130.4 (e), 123.0 (o), 121.0 (o), 119.0 (e), 119.0 (o), 117.6 (o), 115.5 (e), 111.4 (e), 111.0 (o), 104.5 (o), 61.18 (o), 56.74 (o); MS (EI (70 eV)) *m/e* (rel intensity) 338 (M+, 100), 323 (33), 309 (23), 295 (14), 280 (7.4), 265 (5.7), 252 (9.5), 237 (6.1), 196 (15), 139 (8.1); HRMS (EI (70 eV)) *m/e* calcd for $C_{19}H_{14}O_6$: 338.0790, found 338.0804.

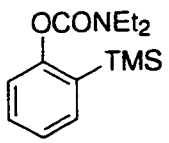
6,7-Dimethoxy-3,4-methylenedioxy-6*H*-naphtho[1,2-*b*]benzo[*d*]pyran-6-one (arnottin I) (158).



Procedure 1: A mixture of catechol **315** (59.2 mg, 0.1751 mmol) and anhydrous CsF (0.310 g, 2.04 mmol) in dry DMF (5 mL) was allowed to stir at rt for 10 min and CH_2Cl_2 (0.1 mL, 1.56 mmol) was added and the mixture heated to 110°C for 24 h. The reaction was quenched with H_2O, the solvents removed *in vacuo*, and the residue diluted with $CHCl_3$ (50 mL) and H_2O (50 mL) and layers separated. The organic phase was washed (brine), dried (Na_2SO_4), concentrated and the residue purified by column chromatography (3:2 hexane:EtOAc → 1:1 hexane: $CHCl_3$) affording the title compound as a fluffy colorless solid (24.0 mg, 39%). mp 301-306°C, lit[182] mp 293-297°C ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d J = 9.1 Hz, 1H), 7.86 (s, 1H), 7.83 (d J = J = 8.8 Hz, 1H), 7.53 (d J = 8.8 Hz, 1H), 7.44 (d J = 8.8 Hz, 1H), 7.14 (s, 1H), 6.10 (s, 2H), 4.04 (s, 3H), 3.99 (s, 3H).

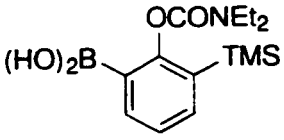
Procedure 2: According to general procedure D, a solution of hydroxy amide **314** (0.169 g, 0.338 mmol) in HOAc (7 mL) was heated at reflux for 20 min and H_2O (7 mL) was added. The reaction was heated at reflux for 1 h and cooled to rt. The resulting precipitate was filtered and washed successively with H_2O, (5 mL) EtOH (5 mL), and Et_2O (10 mL). The solid (81.7 mg) was dissolved in degassed DMF (10 mL) and K_2CO_3 (65.2 mg, 0.4717 mmol), CuO (56.5 mg, 0.710 mmol) and CH_2Br_2 (0.03 mL, 0.427 mmol) were added. The mixture was heated at reflux under Ar for 12 h, the DMF removed in vacuo and the residue diluted with H_2O (50 mL) and $CHCl_3$ (50 mL). The layers were separated and the aq phase extracted twice more with $CHCl_3$ and the combined organic layers were washed, (brine), dried (Na_2SO_4), concentrated and the residue purified by column chromatography (2:1 hexane:EtOAc → 2:2:1 hexane: $CHCl_3$: EtOAc → $CHCl_3$) affording the title compound as a white solid (6.2 mg, 5.2%).

***N,N*-Diethyl *O*-(2-trimethylsilyl)phenylcarbamate.**



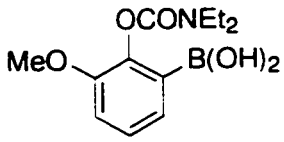
According to general procedure B, a solution of *N,N*-diethyl *O*-phenylcarbamate (12.13 g, 62.9 mmol) and TMEDA (11.4 mL, 75.5 mmol) in THF (200 mL) at -78°C was sequentially treated with *s*-BuLi (56.7 mL, 75.5 mmol) and TMSCl (16.0 mL, 0.126 mmol). Standard workup followed by column chromatography (6:1 hexane:EtOAc) afforded the title compound whose spectral properties were consistent with those reported.[359] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (app dt J = 7.2, 1.8 Hz, 1H), 7.37 - 3.68 (m 1H), 7.17 (app dt J = 7.6 1.1 Hz, 1H), 7.03 (dd J = 8.1, 1.1 Hz, 1H), 3.54 - 3.38 (m, 4H), 1.25 - 1.22 (m, 6H), 0.28 (s, 9H).

2-*N*,*N*-Diethylcarbamato-3-trimethylsilylphenylboronic acid (495a).



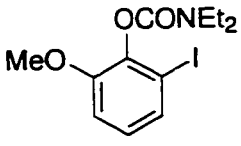
According to general procedure B, a solution of *N*,*N*-diethyl *O*-(2-trimethylsilyl)phenylcarbamate (5.07 g, 19.1 mmol) and TMEDA (3.75 mL, 24.9 mmol) in THF (50 mL) at -78°C was sequentially treated with *s*-BuLi (19.1 mL, 1.30 mol/L) and $B(OMe)_3$ (5.0 mL, 4.00 mmol). Acidification of the reaction mixture with 10% HCl (pH 5-6) followed by standard workup afforded the title compound (5.40 g) as a white solid which was used without further purification.

2-*N*,*N*-Diethylcarbamato-3-methoxyphenylboronic acid (492a).



According to general procedure B, a solution of *N*,*N*-diethyl *O*-(2-methoxy)phenylcarbamate (4.95 g, 22.2 mmol) and TMEDA (3.70 mL, 24.5 mmol) in THF (40 mL) at -78°C was sequentially treated with *s*-BuLi (19.0 mL, 1.35 mol/L) and $B(OMe)_3$ (4.9 mL, 4.30 mmol). Acidification of the reaction mixture with 10% HCl (pH 5-6) followed by standard workup afforded the title compound (5.20 g) as a white solid which was used without further purification.

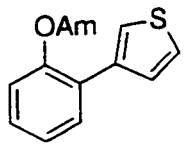
***N*,*N*-Diethyl *O*-(2-iodo-6-methoxy)phenylcarbamate (492b).**



According to general procedure B, a solution of *N*,*N*-diethyl *O*-(2-methoxy)phenylcarbamate (2.52 g, 11.3 mmol) and TMEDA (2.00 mL, 13.3 mmol) in THF (20 mL) at -78°C was sequentially treated with *s*-BuLi (9.80 mL, 1.35 mol/L) and a solution of I_2 (3.60 g, 14.2 mmol) in THF (10 mL). Standard workup followed by column chromatography afforded the title compound as a colorless wax (3.43 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.31

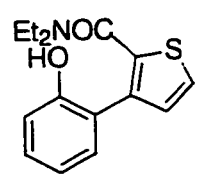
(m, 1H), 6.86-6.84 (m, 2H), 3.74 (s, 3H), 3.48-3.36 (m, 4H), 1.30 (t J = 6.8 Hz, 3H), 1.19 (t J = 6.8 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.1 (e) (X2), 141.0 (e), 129.7 (o), 127.1 (o), 112.1 (o), 92.24 (e), 55.77 (o), 41.97 (e), 41.79 (e), 13.95 (o), 13.02 (o).

_N_,_N_-Diethyl _O_-[2-(3-thienyl)]phenylcarbamate (497c).



According to general procedure G, a mixture of _N_,_N_-diethyl _O_-(2-bromo)phenylcarbamate (1.78 g, 6.55 mmol), 3-thiopheneboronic acid (1.03 g, 8.05 mmol), $Pd(PPh_3)_4$ (0.140 g, 0.121 mmol) and Na_2CO_3 (10.0 mL, 2 mol/L) in DME (100 mL) was heated at reflux for 5 h. Standard workup followed by column chromatography afforded the title compound 1.62 g (90%) as a colorless oil. IR (neat) ν (max) 2976, 2933, 1716, 1686, 1490, 1458, 1418 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 (dd J = 7.5, 1.8 Hz, 1H), 7.36 - 7.16 (m, 6H), 3.33 (m, 4H), 1.11 (t J = 7.2 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.0 (e), 148.5 (e), 138.0 (e), 130.2 (o), 129.9 (e), 128.4 (o), 128.2 (o), 125.2 (o), 124.9 (o), 123.4 (o), 122.8 (o), 41.98 (e), 41.65 (e), 13.99 (o), 13.17 (o); MS (EI (70 eV)) *m/e* (rel intensity) 275 (M^+, 68), 222 (2.9), 176 (8.8), 147 (23), 115 (18), 100 (100), 72 (78); HRMS (EI (70 eV)) *m/e* calcd for $C_{15}H_{17}NO_2S$: 275.0980, found: 275.0982.

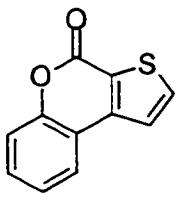
_N_,_N_-Diethyl 3-(2-hydroxyphenyl)thiophene-2-carboxamide (498d).



According to general procedure H, a solution of carbamate **497c** (0.484 g, 1.76 mmol) in THF (10 mL) was added via cannula to a solution of LDA (2.11 mmol) in THF (10mL). After 10 min the reaction mixture was quenched with sat NH_4Cl and subsequent standard workup followed by cloumn chromatography (4:1 hexane:EtOAc) afforded the

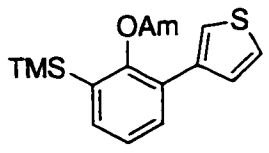
title compound (0.244 g, 50%) as a foam. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.37 (s, 1H, exch), 7.42, (d J = 5.1 Hz, 1H), 7.25 (m, 1H), 7.15 (dd J = 7.6, 1.7 Hz, 1H), 7.02 (dd 8.0, 1.0 Hz, 1H), 6.97 (d J = 5.1 Hz, 1H), 6.92 (app dt J = 7.4, 1.8 Hz, 1H), 3.49 (m, 4H), 1.25 - 1.07 (m, 6H).

4*H*-Thieno[2,3-*c*]benzo[*e*]pyran-4-one (499d).



According to General procedure D, a solution of hydroxy amide **498d** (0.062 g, 0.230 mmol) in HOAc (5 mL) was heated at reflux for 10 min at which point the HOAc was removed in vacuo. Standard workup followed by recrystallization (hexane:Et_2O) afforded the title compound as colorless fine needles (0.039 g, 85%). mp 122-124°C (hexane:Et_2O). IR (KBr) ν (max) 2924, 1722, 1656, 1611, 1589, 1533, 1498, 1452 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (d J = 5.1 Hz, 1H), 7.85 - 7.81 (m, 1H), 7.64 (d J = 5.1, 1H), 7.51 (dd J = 8.4, 1.6 Hz, 1H), 7.46 - 7.27 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ : 157.2 (e), 152.6 (e), 145.0 (e), 136.8 (o), 130.1 (o), 124.5 (o), 123.8 (o), 123.4 (e), 122.3 (o), 117.5 (o), 117.3 (e); MS (EI (70 eV)) *m/e* (rel intensity) 202 (M^+, 100), 174 (29), 145 (15), 120 (3.8), 102 (9.0), 87 (7.1); Anal. calcd for $C_{11}H_6O_2S$: C, 65.33; H, 2.99; S, 15.85; found: C, 65.38; H, 3.01; S, 15.66.

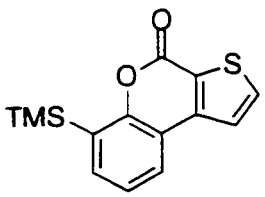
***N*,*N*-Diethyl *O*-[2-(3-thienyl)-6-trimethylsilyl]phenylcarbamate (497a).**



According to general procedure G, a mixture of 2-*N*,*N*-diethylcarbamato-3-trimethylsilylphenylboronic acid **(495a)** (1.89 g, 6.15 mmol), 3-bromothiophene (0.84 g, 4.90 mmol), $Pd(PPh_3)_4$ (0.300 g, 0.260 mmol) and Na_2CO_3 (10 mL, 2.0 mol/L) in DME was heated at reflux for 1 h. Standard workup followed by column chromatography (9:1

hexane:EtOAc) and then recrystallisation (hexane) afforded the title compound (0.796 g, 47%) as colorless plates. mp 60-63°C (hexane); IR (CH_2Cl_2) ν (max) 2977, 1713, 1599, 1522, 1475 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (dd J = 7.2, 1.8 Hz, 1H), 7.39 (dd J = 7.6, 1.8 Hz, 1H), 7.30 - 7.28 (m, 2H), 7.23 (dd J = 7.6, 7.2 Hz, 1H), 7.16 (dd J = 3.9, 2.5, 1H), 3.36 (q J = 7.2 Hz, 2H), 3.17 (m, 2H), 1.09 (t J = 7.2 Hz, 3H), 0.95 (t J = 7.2 Hz, 3H), 0.30 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.4 (e), 136.6 (e), 132.1 (o), 131.1 (e), 129.8 (o), 128.5 (e), 126.6 (o), 123.2 (o), 122.5 (o), 120.6 (o), 39.13 (e), 18.98 (e), 11.69 (o), 10.60 (o); MS (EI (70 eV)) *m/e* (rel intensity) 347 (M^+, 1.4), 332 (15), 217 (3.9), 100 (100), 72 (49); Anal. calcd for $C_{18}H_{25}NO_2SSi$: C, 62.21; H, 7.25; N, 4.03; found: C, 62.19; H, 7.31; N, 4.01.

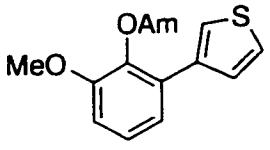
6-Trimehtylsilyl-4*H*-thieno[2,3-*c*]benzo[*e*]pyran-4-one (499a).



According to general procedure H, a solution of aryl carbamate **497a** (0.411 g, 1.18 mmol) in THF (5 mL) was added to a solution of LDA (1.42 mmol) in THF (3 mL) at 0°C and the reaction mixture allowed to warm to rt over 2 h. Standard workup afforded the crude hydroxyamide which was cyclized according to general procedure D. Standard workup followed by column chromatography (6:1 hexane:EtOAc) and then recrystallisation (hexane:Et_2O) afforded the title compound (0.202 g, 62%) as colorless needles. mp 135-136°C (hexane:Et_2O); IR (CH_2Cl_2) ν (max) 3022, 2941, 1719, 1593, 1530, 1453, 1413 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.89 (d J = 5.2 Hz, 1H), 7.85 (dd J = 7.7, 1.6 Hz, 1H), 7.64 (d J = 5.2 Hz, 1H), 7.59 (dd J = 7.2, 1.6 Hz, 1H), 7.33 (app t J = 7.2 Hz, 1H), 0.44 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.1 (e), 145.3 (e), 136.4 (o), 135.7 (o), 129.2 (e), 124.7 (o), 124.4 (e), 124.2 (o), 122.4 (o), 116.6 (e), -0.12 (o); MS (EI (70 eV)) *m/e* (rel intensity) 274 (M^+, 24), 259 (100), 231 (23),

203 (6.3), 187 (3.5), 171 (7.0), 122 (11); Anal. calcd for $C_{14}H_{14}O_2SSi$: C, 61.28; H, 5.14; S, 11.68; found: C, 61.43; H, 5.34; N, 11.72.

_N,N_-Diethyl _O_-[2-(3-thienyl)-6-methoxy)phenylcarbamate (494b).



Procedure 1: According to general procedure G, a mixture of _N,N_-diethyl _O_-(2-iodo-6-methoxy)phenylcarbamate **(492b)** (0.271 g, 0.776 mmol), 3-thiopheneboronic acid (0.151 g, 1.18 mmol), $Pd(PPh_3)_4$ (48.8 mg, 0.042 mmol), and Na_2CO_3 (10 mL) in DME was heated at reflux for 16 h. Standard workup followed by cloumn chromatography (5:1 hexane:EtOAc) and distillation afforded the title compound (0.190 g, 80%) as a colorless oil. bp 155-162°C / 0.15-0.2 mmHg (Kugelrohr); IR (neat) ν (max) 3098, 2974, 2935, 1717, 1608, 1581, 1530, 1467 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38 (dd J = 2.9, 1.3 Hz, 1H), 7.29 (dd J = 5.0, 3.0 Hz, 1H), 7.25 (dd J = 5.0, 1.3 Hz, 1H), 7.15 (app t J = 7.9, 1H), 7.04 (dd J = 7.8, 1.6 Hz, 1H), 6.88 (dd J = 8.0, 1.5 Hz, 1H), 3.81 (s, 3H), 3.35 (m, 4H), 1.13 (t J = 7.1 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.7 (e), 152.3 (e), 137.8 (e), 137.6 (e), 130.9 (e), 128.2 (o), 125.6 (o), 124.7 (o), 122.8 (o), 121.5 (o), 111.1 (o), 55.95 (o), 41.95 (e), 41.78 (e), 13.80 (o), 13.19 (o); MS (EI (70 eV)) *m/e* (rel intensity) 305 (M^+, 41), 290 (4.5), 205 (14), 221 (14), 100 (100), 72 (45); Anal. calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; found: C, 63.14; H, 6.47; N, 4.55.

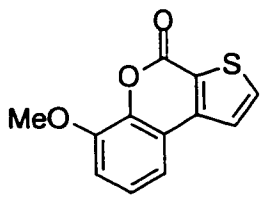
Procedure 2: According to general procedure G, a mixture of arylboronic acid 2-_N,N_-diethylcarbamato-3-methoxyphenylboronic acid **(492a)** (0.640 g, 2.397 mmol), 3-bromothiophene (0.307 g, 1.88 mmol), $Pd(PPh_3)_4$ (0.108 g, 0.094 mmol), and Na_2CO_3 (10 mL) in DME (20 mL) was heated at reflux for 16 h. Standard workup followed by

column chromatography (5:1 hexane:EtOAc) and distillation afforded the title compound as a colorless oil (0.377 g, 66%).

Procedure 3: According to general procedure E, a solution of 3-bromothiophene in THF (10 mL) was sequentially treated with *n*-BuLi (3.30 mL, 1.78 mol/L), a solution of $ZnBr_2$ (1.60 g, 7.11 mmol) in THF (10 mL), *N*,*N*-diethyl *O*-(2-iodo-6-methoxy)phenylcarbamate **(492b)** (0.882 g, 2.53 mmol) and $Pd(PPh_3)_4$ (0.105 g, 0.091 mmol) and the reaction mixture was allowed to stir at rt for 12 h. Standard workup followed by column chromatography and distillation (bp 155-162°C / 0.2 mmHg) afforded the title compound as an inseparable mixture contaminated with the corresponding 2-thienyl isomer as identified by GC. Total mass: 0.678 g; (42% 3-thienyl, 33% 2-thienyl by nmr)

Procedure 4: According to general Procedure F, a solution of *N*,*N*-diethyl *O*-(2-methoxy)phenylcarbamate (1.26 g, 5.64 mmol) in THF (15 mL) was sequentially treated with *s*-BuLi (8.06 mL, 1.05 mol/L), $ZnCl_2$ (8.98 mL, 1.0 mol/L) and a solution of 3-bromothiophene (1.84 g, 11.3 mmol) and $Pd(PPh_3)_4$ (150 mg, 0.130 mmol) in THF (20 mL). The reaction mixture was allowed to heat at reflux for 48 h and standard workup followed by column chromatography afforded the title compound, 0.646 g (38%).

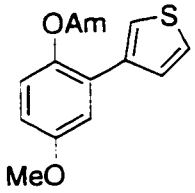
6-Methoxy-4*H*-thieno[2,3-*c*]benzo[*e*]pyran-4-one (499b).



According to general procedure H, a solution of carbamate **494b** (0.232 g, 0.761 mmol) in THF (5 mL) was added to a solution of LDA (1.52 mmol) in THF (5 mL) at 0°C. The reaction mixture was allowed to stir for 10 min and standard workup afforded the crude hydroxy amide which was cyclized according to general procedure D (5 mL HOAc). Standard workup followed by column chromatography (4:1 hexane:EtOAc) and

recrystallisation (EtOH) furnished the title compound (0.0457 g, 27%) as colorless needles. mp 158-160°C (EtOH); IR (KBr) ν (max) 3085, 2975, 2936, 1721, 1605, 1580, 1466, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.91 (d J = 5.3 Hz, 1H), 7.60 (d J = 5.3 Hz, 1H), 7.37 (dd J = 7.9, 1.5 Hz, 1H), 7.25 (dd J = 8.0, 7.9 Hz, 1H), 7.02 (dd J = 8.0, 1.4 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.6 (e), 147.8 (e), 145.1 (e), 142.1 (e), 136.7 (o), 124.4 (o), 122.7 (o), 118.0 (e), 115.2 (o), 112.0 (o), 56.07 (o); MS (EI (70 eV)) *m/e* (rel intensity) 232 (M^+, 100), 217 (13), 203 (4.5), 189 (34), 161 (13), 145 (4.5), 133 (12), 116 (4.5), 89 (16), 63 (10); Anal. calcd for $C_{12}H_9O_3S$: C, 62.06; H, 3.47; found: C, 62.10; H, 3.60.

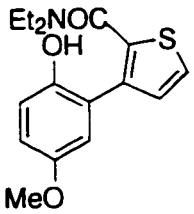
_N,N_-Diethyl _O_-[2-(3-thienyl)-4-methoxy]phenylcarbamate (497b).



According to general procedure F, carbamate *N,N*-diethyl *O*-(4-methoxy)phenylcarbamate (3.04 g, 13.6 mmol) was sequentially treated with *s*-BuLi (11.2 mL, 1.47 mol/L), TMEDA (2.50 mL, 16.36 mmol) a solution of $ZnCl_2$ (16.4 mL, 1.0 mol/L in Et_2O), 3-bromothiophene (2.67 g, 16.4 mmol) and $Pd(PPh_3)_4$ (0.250 g, 0.216 mmol) in THF (40 mL), and the reaction mixture was heated at reflux for 48 h. Standard workup followed by column chromatography (8:1 → 5:1 hexane:EtOAc) and recrystallisation (hexane:Et_2O) afforded the title compound (1.66 g, 40%) as colorless needle-prisms. mp 66-68 ℃ (hexane:Et_2O); IR (KBr) ν (max) 2974, 2935, 2866, 1715, 1609, 1584, 1534, 1499, 1470 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H), 7.22-7.20 (m, 1H), 7.08 (J = 8.8 Hz, 1H), 6.96 (d J = 3.1 Hz, 1H), 6.85 (dd J = 8.8, 3.1 Hz, 1H), 3.80 (s, 3H), 3.30 (m, 4H), 1.10 (t J = 7.1 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.8 (e), 154.4 (e), 142.1 (e), 138.0 (e), 130.6 (e), 128.2 (o), 124.9 (o), 124.0 (o), 122.9 (o),

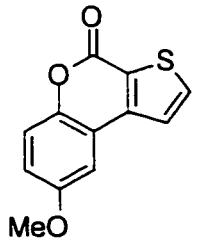
115.1 (o), 113.4 (o), 55.59 (o), 41.94 (e), 41.55 (e), 13.96 (o), 13.18 (o); MS (EI (70 eV)) *m/e* (rel intensity) 305 (M^+, 17), 232 (3.0), 205 (4.1), 177 (3.6), 134 (6.8), 100 (100), 72 (43); Anal. calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; S, 10.50; found: C, 63.17; H, 6.38; N, 4.47; S, 10.61.

_N,N_-Diethyl 3-(2-hydroxy-4-methoxyphenyl)-2-thiophene-carboxamide (498c).



According to general procedure H, a solution of carbamate **497b** (0.270 g, 0.884 mmol) in THF (5 mL) was added to a solution of LDA (2.6 mmol) in THF (10 mL) at 0°C and the mixture allowed to stir for 3 h. Standard workup followed by column chromatography (3:1 hexane:EtOAc) afforded the title compound as a foam (0.159 g, 59%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (d J = 5.0 Hz, 1H), 6.98 (d J = 5.0 Hz, 1H), 6.96 (d J = 8.8 Hz, 1H), 6.83 (dd J = 8.8, 3.0 Hz, 1H), 3.76 (s, 3H), 3.40-3.29 (m, 4H), 1.08 (m, 6H).

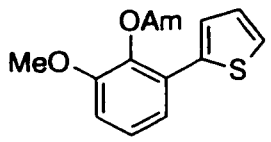
8-Methoxy-4*H*-thieno[2,3-*c*]benzo[*e*]pyran-4-one (499c).



According to general procedure D, a solution of hydroxy amide **498c** (0.0490 g, 0.160 mmol) in HOAc (5 mL) was heated at reflux for 10 min. Standard workup followed by recrystallisation (hexane:Et_2O) afforded the title compound (0.0300 g, 81%) as colorless needles. mp 120-122 °C (hexane:Et_2O); IR (KBr) ν (max) 3020, 1712, 1594, 1536, 1466 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (d J = 5.3 Hz, 1H), 7.62 (d J = 5.3 Hz, 1H), 7.38 (d J = 9.1 Hz, 1H), 7.27 (d J = 2.5 Hz, 1H), 7.07 (dd J = 9.1, 2.5 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.2 (e), 147.0 (e), 144.8 (e), 136.6 (o), 124.8 (e), 122.3 (o), 118.5 (o), 117.8 (e), 117.1 (o), 106.9 (o), 55.86 (o);

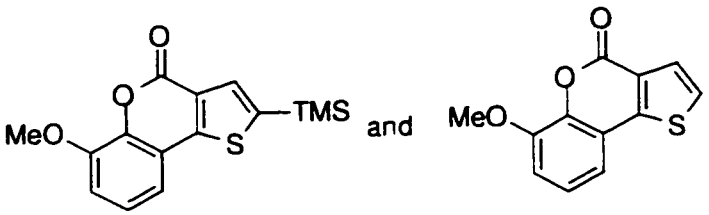
MS (EI (70 eV)) *m/e* (rel intensity) 232 (M^+, 100), 217 (73), 189 (14), 161 (14), 145 (3.3), 133 (10), 116 (5.6), 89 (14), 63 (13); Anal. calcd for $C_{12}H_8O_2S$: C, 62.06; H, 3.47; found: C, 62.20; H, 3.61.

_N,N_-Diethyl _O_-[2-(2-thienyl)-6-methoxy]phenylcarbamate (504).



According to general procedure E, a solution of 2-bromothiophene (1.65 g, 10.1 mmol) in THF (20 mL) was sequentially treated with *n*-BuLi (6.30 mL, 11.2 mmol), $ZnBr_2$ (3.35 g, 14.9 mmol), *N,N*-diethyl *O*-(2-iodo-6-methoxy)phenylcarbamate **(492b)** (1.56 g, 4.46 mmol), and $Pd(PPh_3)_4$ (0.150 g, 0.130 mmol) and the reaction mixture was allowed to stir at rt for 12 h. Standard workup followed by column chromatgraphy (5:1 hexane:EtOAc) and distillation afforded the title compound as a colorless oil. bp 145-150°C / 0.5-0.6 mmHg; IR (neat) ν (max) 2974, 2939, 1722, 1605, 1580, 1526, 1466, 1419 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.23 (dd, J = 8.1, 1.9 Hz, 1H), 7.16 (dd J = 8.1, 7.8 Hz, 1H), 7.05 (dd J = 5.1, 3.7 Hz, 1H), 6.88 (dd J = 7.8, 1.9 Hz, 1H) 3.84 (s, 3H), 3.48-3.36 (m, 4H), 1.21 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.3 (e), 152.5 (e), 138.3 (e), 137.2 (e), 128.8 (e), 126.8 (o), 125.8 (o), 125.7 (o), 120.5 (o), 111.1 (o), 56.02 (o), 42.07 (e), 41.89 (e), 13.90 (o), 13.23 (o); MS (EI (70 eV)) *m/e* (rel intensity) 305 (M^+, 71), 290 (1.6), 262 (15), 223 (46), 205 (6.8), 100 (100), 72 (45); Anal. calcd for $C_{16}H_{19}NO_3S$: C, 62.43; H, 6.27; N, 4.59; found: C, 62.86; H, 6.26; N, 4.51.

6-Methoxy-2-trimethylsilyl-4*H*-thieno[3,2-*c*]benzo[*e*]pyran-4-one (505a) and 6-methoxy-4*H*-thieno[3,2-*c*]benzo[*e*]pyran-4-one (505b).

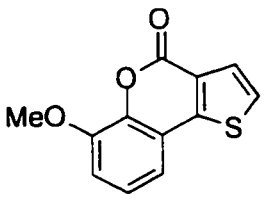


Procedure 1: To a solution of carbamate **504** (0.450 g, 1.33 mmol) and TMSCl (0.18 mL, 1.42 mmol) in THF (10 mL) at -78°C was added a solution of LDA (6.87 mmol) in THF (10 mL) dropwise *via* canula. The reaction mixture was allowed to warm to rt over 12 h. Standard workup followed by cyclization according to general procedure D (20 mL HOAc) afforded the crude cyclized compounds. Standard workup followed by column chromatography (3:1 hexane:EtOAc) afforded the silylated lactone **505a** (0.255 g, 63%) as a colorless oil and the desilylated lactone **505b** (0.493 g, 16%) as colorless plates. Silylated lactone **505a**: IR (neat) ν (max) 2954, 2840, 1733, 1608, 1534, 1487, 1468 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.26 (dd J = 7.9, 1.9 Hz, 1H), 7.20 (app t J = 7.9 Hz, 1H), 7.00 (dd J = 7.9. 1.7 Hz, 1H), 3.97 (s, 3H), 0.39 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.0 (e), 152.5 (e), 147.8 (e), 142.7 (e), 133.5 (o), 126.6 (e), 124.4 (o), 117.8 (e), 115.1 (o), 112.1 (o), 56.17 (o), -0.42 (o); MS (EI (70 eV)) *m/e* (rel intensity) 304 (M^+, 82), 289 (53), 274 (12), 244 (21), 206 (100), 192 (20), 177 (27), 163 (47), 134 (34), 109 (26); HRMS (EI (70 eV)) *m/e* calcd for $C_{15}H_{16}O_3SSi$: 304.0590, found: 304.0598.

Desilylated lactone **505b**: mp 168-169 °C (hexane:CH_2Cl_2); IR (CH_2Cl_2) ν (max) 3029, 2990, 1735, 1592, 1473, 1423 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.64 (d J = 5.3 Hz, 1H), 7.41 (d J = 5.3 Hz, 1H), 7.25 (m, 1H), 7.20 (app t J = 7.9 Hz, 1H), 7.00 (dd J =

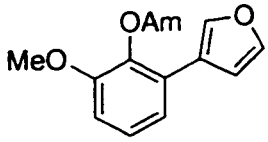
7.1, 2.4 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.6 (e), 148.5 (e), 147.8 (e), 140.9 (e), 126.8 (o), 126.0 (o), 125.4 (e), 124.5 (o), 117.6 (e), 114.8 (o), 112.14 (o), 56.17 (o); MS (EI (70 eV)) *m/e* (rel intensity) 232 (M^+, 91), 217 (8.0), 203 (8.4), 189 (23), 159 (18), 133 (10), 121 (71), 119 (100); Anal. calcd for $C_{12}H_8O_3S$: C, 62.06; H, 3.47; found: C, 62.10; H, 3.29.

6-Methoxy-4*H*-thieno[3,2-*c*]benzo[*e*]pyran-4-one (505b).



Procedure 2: To a solution of silyl lactone **505a** (0.241 g, 0.792 mmol) in THF (10 mL) was added TBAF (1.70 mL, 1.70 mmol in THF) at 0°C and the reaction mixture was allowed to stir for 20 min. Standard workup followed by column chromatography (2:1 hexane:EtOAc) followed by recrystallisation (hexane:CH_2Cl_2) afforded the title compound (0.0915 g, 50%) as colorless fine needles.

***N*,*N*-Diethyl *O*-[2-(3-furyl)-6-methoxy]phenylcarbamate (494a)**

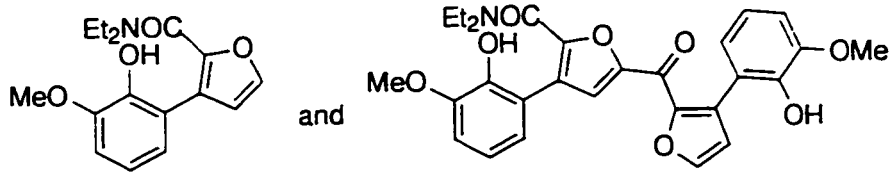


Procedure 1: According to general procedure E, a solution of 3-bromofuran (0.70 mL, 7.79 mol) in THF (15 mL) was sequentially treated with *n*-BuLi (4.60 mL, 1.68 mol/L), a solution of $ZnBr_2$ (2.09 g, 9.27 mmol) in THF (10 mL), *N*,*N*-diethyl *O*-(2-iodo-6-methoxy)phenylcarbamate **(492b)** (1.38 g, 3.95 mmol) and $Pd(PPh_3)_4$ (0.150 g, 0.129 mmol) and the reaction mixture was allowed to stir at rt for 4 h. Standard workup followed by column chromatography (5:1 hexane:EtOAc) and distillation afforded the title compound as a colorless oil (0.958 g, 84%). bp 150-156°C / 1.5 mmHg (Kugelrohr); IR (neat) ν (max) 2974, 2937, 2840, 1719, 1619, 1576, 1468 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.68 (dd J = 1.4, 0.9 Hz, 1H), 7.44 (app t J = 1.7 Hz, 1H),

7.17 (app t J = 7.9 Hz. 1H), 7.06 (dd J = 7.9, 1.6 Hz, 1H), 6.87 (dd J = 7.9, 1.6 Hz, 1H), 6.66 (dd J = 1.7, 0.9 Hz, 1H), 3.83 (s, 3H), 3.82-3.37 (m, 4H), 1.26 (t J = 7.1 Hz, 3H), 1.19 (t J = 7.1 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.5 (e), 152.3 (e), 142.5 (o), 140.2 (o), 137.7 (e), 127.0 (e), 125.7 (o), 121.5 (e), 120.2 (o), 110.7 (o), 110.1 (o), 55.87 (o), 41.99 (e), 41.82 (e), 13.90 (o), 13.22 (o); MS (EI (70 eV)) *m/e* (rel intensity) 289 (M^+, 75), 190 (7.5), 160 (10), 100 (100), 72 (47); Anal. calcd for $C_{16}H_{20}NO_4$: C, 66.36; H, 6.62; N, 4.84; found: C, 66.29; H, 6.71; N, 4.71.

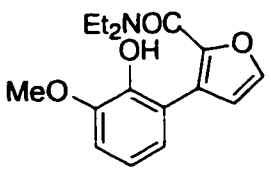
Procedure 2: According to general procedure G, a mixture of 3-bromofuran (0.869 g, 5.914 mmol), (*N,N*-diethylcarbamato-3-trimethylsilyl)phenylboronic acid **(495a)** (2.11 g, 7.91 mmol), $Pd(PPh_3)_4$ (0.137 g, 0.119 mmol) and Na_2CO_3 (20 mL, 2 mol/L) in DME (40 mL) was heated at reflux for 12 h. Standard workup followed by column chromatography (5:1 hexane:EtOAc) afforded the title compound as a colorless oil (0.272 g, 16%).

_N,N_-Diethyl 3-(2-hydroxy-3-methoxyphenyl)furan-2-carboxamide (498e) and ketone (500).



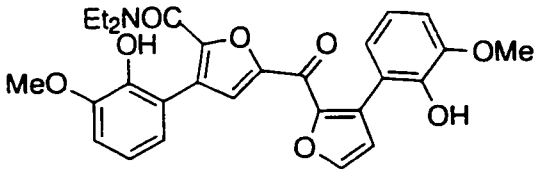
According to general procedure H, a solution of carbamate **494a** (0.127 g, 0.438 mmol) in THF (5 mL) was added to a solution of LDA (0.992 mmol) in THF (5 mL) at 0°C. The reaction mixture was allowed to stir for 15 min at which point standard workup followed by column chromatography (1:1 hexane:EtOAc) afforded the desired product as a foam (57.0 mg, 45%) along with ketone **500** (22.4 mg, 20%) as a gum.

Carboxamide 498e.



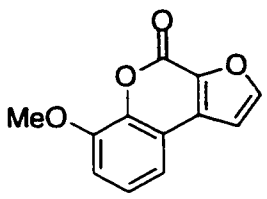
IR (CH_2Cl_2) ν (max) 3584-3038, 2976, 1631, 1605, 1572, 1489, 1440 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.48 (d J = 1.8 Hz, 1H), 6.87 (s, 3H), 6.55 (d J = 1.8 Hz, 1H), 3.90 (s, 3H), 3.48 (q J = 7.3 Hz, 2H), 3.37 (q J = 7.3 Hz, 2H); 1.23-1.25 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.3 (e), 149.5 (e), 144.4 (e), 142.4 (e), 142.1 (o), 126.2 (e), 122.6 (o), 121.2 (e), 119.8 (o), 115.0 (o), 111.1 (o), 56.02 (o), 43.34 (e), 48.82 (e), 14.29 (o), 12.50 (o); MS (EI (70 eV)) *m/e* (rel intensity) 290 (M+H, 100), 217 (48), 202 (19), 173 (4.7), 160 (4.7), 129 (5.9), 95 (22); HRMS (EI (70 eV)) *m/e* calcd for $C_{16}H_{20}NO_4$: 290.1392, found: 290.1385.

Ketone 500.



IR (neat) ν (max) 3520-3126, 2957, 1721, 1632, 1574, 1441 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.68 (d J = 1.8 Hz, 1H), 7.65 (s, 1H), 7.02-6.87 (m, 6H), 6.79 (d J = 1.8 Hz, 1H), 6.56 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.48 (q J = 7.3 Hz, 2H), 3.37 (q J = 7.3 Hz, 2H), 1.29-1.16 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.1 (e), 161.3 (e), 149.3 (e), 149.0 (e), 147.9 (e), 146.4 (e), 146.0 (e), 145.2 (o), 144.1 (e), 143.9 (e), 131.9 (e), 126.7 (e), 124.4 (e), 123.6 (o), 122.9 (o), 122.4 (o), 120.0 (o), 120.0 (o), 119.5 (e), 116.1 (o), 111.4 (o), 111.2 (o), 56.14 (o), 56.08 (o), 43.61 (e), 40.88 (e), 14.32 (o), 12.50 (o); MS (EI (70 eV)) *m/e* (rel intensity) 506 (M^+, 100), 492 (8.3), 434 (18), 386 (18), 371 (36), 316 (22), 293 (17); HRMS (EI (70 eV)) *m/e* calcd for $C_{28}H_{28}NO_8$: 506.1815, found: 506.1768.

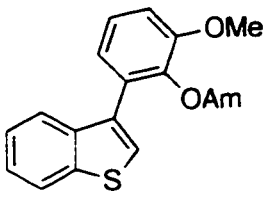
6-Methoxy-4*H*-furano[2,3-*c*]benzo[*e*]pyran-4-one (499e).



Procedure 1: *Direct Cyclization:* According to general procedure H, a solution of carbamate **494a** (0.250 g, 0.864 mmol) in THF (5 mL) was added to a solution of LDA (3.05 mmol) in THF (7 mL) and the reaction mixture allowed to stir for 10 min. Standard workup followed by cyclization of the crude hydroxy amide according to general procedure D (8 mL HOAc) and purification by column chromatography (2:1 hexane:EtOAc) and recrystallisation (hexane:CH_2Cl_2) afforded the title compound as fine colorless plates (36.1 mg, 19%). mp 154.5-155°C (hexane:CH_2Cl_2); IR (KBr) ν (max) 355, 2986, 1746, 1607, 1568, 1488, 1422 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.19 (d J = 1.8 Hz, 1H), 7.47 (dd J = 7.8, 1.4 Hz, 1H), 7.33 (d J = 1.8 Hz, 1H), 7.30 (app t J = 8.0 Hz, 1H), 7.19 (dd J = 8.1, 1.3 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.0 (e), 148.5 (e), 142.6 (e), 138.5 (e), 134.1 (e), 125.5 (o), 117.7 (e), 116.4 (o), 112.8 (o), 108.9 (o), 107.6 (o), 56.35 (o); MS (EI (70 eV)) *m/e* (rel intensity) 216 (100), 210 (34), 188 (5.0), 173 (31), 145 (26), 102 (20); HRMS (EI (70 eV)) *m/e* calcd for $C_{12}H_8O_4$: 216.0423, found: 216.0424.

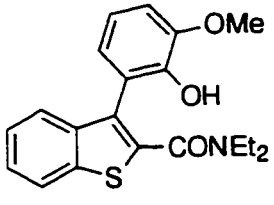
Procedure 2: *Stepwise:* According to general procedure D, a solution of hydroxyamide **498e** (38.0 mg, 0.131 mmol) in HOAc (5 mL) was heated at reflux for 10 min. Standard workup followed by column chromatography afforded the title compound as a colorless solid (26.0 mg, 68%).

***N*,*N*-Diethyl *O*-[2-(3-thianaphthenyl)-6-methoxy]phenylcarbamate (507b).**



According to general procedure G, a mixture of 3-bromothianaphthene[369] (0.560 g, 2.63 mmol), (*N*,*N*-diethylcarbamato-3-methoxy)phenylboronic acid **(492a)** (1.05 g, 3.93 mmol) $Pd(PPh_3)_4$ (0.160 g, 0.139 mmol), and Na_2CO_3 (20 mL, 2 mol/L) was heated at reflux for 12 h. Standard workup followed by column chromatography (5:1 hexane:EtOAc) and distillation afforded the title compound (0.803 g, 86%) as a colorless oil. bp 160-165°C / 0.3 mmHg (Kugelrohr); IR (neat) ν (max) 3066, 2974, 2935, 1718, 1608, 1581, 1469 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ : 7.86 (m, 1H), 7.68 (m, 1H), 7.42 (s, 1H), 7.32 (m, 1H), 7.25 (dd J = 8.0, 7.5 Hz, 1H), 7.04-7-00 (m, 2H), 3.88 (s, 3H), 3.19 (m, 2H), 3.08 (m, 2H), 1.00 (t J = 6.5 Hz, 3H), 0.74 (t J = 6.5 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.5 (e), 152.6 (e), 139.7 (e), 138.7 (e), 133.0 (e), 130.5 (e), 125.7 (o), 124.7 (o), 124.2 (o), 124.2 (o), 124.0 (o), 123.4 (o), 122.7 (o), 122.4 (o), 112.0 (o), 56.14 (o), 41.92 (e), 41.65 (e), 13.29 (o); MS (EI (70 eV)) *m/e* (rel intensity) 355 (M^+, 33), 299 (3.1), 255 (3.2), 227 (5.6), 184 (6.2), 177 (6.2), 100 (100), 72 (36); HRMS (EI (70 eV)) *m/e* calcd for $C_{20}H_{21}NO_3S$: 355.1243, found: 355.1252.

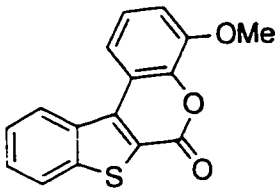
***N*,*N*-Diethyl 3-(2-hydroxy-3-methoxyphenyl)thianaphthene-2-carboxamide (508b):**



According to general procedure H, a solution of carbamate **507b** (0.281 g, 0.792 mmol) in THF (10 mL) was added to a solution of LDA (2.46 mmol) in THF (5 mL) at 0°C. The reaction mixture was allowed to stir for 15 min and standard workup followed by column chromatography (3:2 hexane:EtOAc) afforded the title

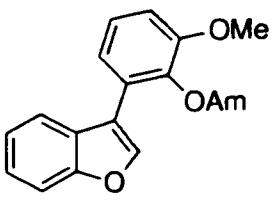
compound (0.190 g, 68%) as a foam. IR (CH_2Cl_2) ν (max) 3329, 2973, 1621, 1538, 1474, 1439 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.87-7.83 (m, 1H), 7.57-7.53 (m, 1H), 7.36 (app dt J = 7.1, 1.7 Hz, 1H), 7.35 (app dt J = 7.0, 1.7 Hz, 1H), 6.97-6.90 (m, 3H), 3.93 (s, 3H), 1.90-1.22 (m, 4H), 1.00-0.98 (m, 3H), 0.94-0.91 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.1 (e), 147.7 (e), 143.6 (e), 138.8 (e), 138.4 (e), 133.5 (e), 131.6 (e), 124.8 (o), 125.1 (o), 124.3 (o), 123.6 (o), 122.3 (o), 122.1 (o), 121.0 (e), 119.9 (o), 111.0 (o), 56.07 (o), 43.09 (e), 39.15 (o), 13.61 (o), 12.01 (o); MS (EI (70 eV)) *m/e* (rel intensity) 356 (M^+, 100), 340 (16), 283 (58), 268 (17), 195 (7.5); HRMS (EI (70 eV)) *m/e* calcd for $C_{20}H_{22}NO_3S$: 356.1321, found: 356.1326.

4-Methoxy-4*H*-thianaphtheno[2,3-*c*]benzo[*e*]pyran-6-one (509b).



According to general procedure D, a solution of hydroxy amide **508b** (0.190 g, 0.536 mmol) in HOAc (10 mL) was heated at reflux for 10 min. Standard workup followed by recrystallisation (CH_2Cl_2:hexane) afforded the title compound (0.143 g, 95%) as light yellow needles. mp 206-207°C (dec) (CH_2Cl_2:hexane); IR (KBr) ν (max) 3013, 2928, 2824, 1720, 1605, 1585, 1449 cm^{-1}; ^1H NMR (500 MHz, DMF-d_7) δ 8.89 (d J = 7.95 Hz, 1H), 8.34-8.29 (m, 2H), 7.78-7.71 (m, 2H), 7.41 (app t J = 8.3 Hz, 1H), 7.39 (d J = 7.4 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (62.9 MHz, DMF-d_7) δ 157.7 (e), 148.6 (e), 143.7 (e), 142.8 (e), 139.4 (e), 135.6 (e), 129.3 (e), 127.1 (e), 126.8 (o), 126.5 (e), 125.6 (o), 124.5 (o), 119.1 (e), 115.9 (o), 113.3 (o), 56.55 (o); MS (EI (70 eV)) *m/e* (rel intensity) 282 (M^+, 100), 239 (26), 224 (3.1), 211 (14), 195 (6.2), 183 (20), 139 (26); Anal. calcd for $C_{16}H_{10}O_3S$: C, 68.07; H, 3.57: found: C, 67.84; H, 3.70;

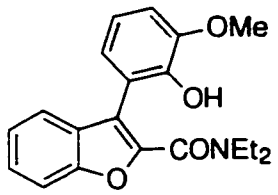
***N*,*N*-Diethyl *O*-[2-(3-benzofuranyl)-6-methoxy]phenylcarbamate (507a).**



Procedure 1: According to general procedure G, a mixture of 3-bromobenzofuran[370] (1.11 g, 5.19 mmol), 2-*N*,*N*-diethylcarbamato-3-methoxyphenylboronic acid **(492a)** (1.82 g, 6.82 mmol) $Pd(PPh_3)_4$ (0.120 g, 0.104 mmol), and Cs_2CO_3 (20 mL, 2 mol/L) was heated at reflux for 12 h. Standard workup followed by purification by column chromatography (5:1 → 4:1 hexane:EtOAc) and distillation afforded the title compound (0.591 g, 34%) as a colorless oil. bp 155-160°C / 0.3 mmHg (Kugelrohr); IR (neat) 3028, 2975, 2936, 2839, 1718, 1611, 1578, 1453, 1417 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.69 (m, 1H), 7.52 (m, 1H), 7.16 (dd J = 7.8, 1.7 Hz, 1H), 6.96 (dd J = 7.8, 1.7 Hz, 1H), 3.85 (s, 3H), 3.27 (q J = 7.3 Hz, 4H), 1.08 (t J = 7.3 Hz, 3H), 0.99 (t J = 7.3 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.1 (e), 153.6 (e), 152.6 (e), 142.7 (o), 138.5 (e), 127.2 (e), 126.4 (e), 125.8 (o), 124.2 (o), 122.7 (o), 121.9 (o), 120.8 (o), 117.3 (e), 111.7 (o), 111.3 (o), 56.04 (o), 41.98 (e), 41.76 (e), 13.65 (o), 13.17 (o); MS (EI (70 eV)) *m/e* (rel intensity) 339 (M^+, 100), 324 (1.9), 285 (1.9), 267 (3.7), 239 (8.6), 239 (9.0), 196 (5.6), 168 (10), 100 (77), 72 (23); HRMS (EI (70 eV)) *m/e* calcd for $C_{20}H_{21}NO_4$: 339.1471, found 339.1484.

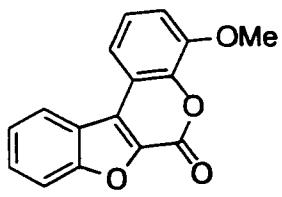
Procedure 2: According to general procedure E, a solution of 3-bromobenzofuran (1.06 g, 5.38 mmol) in THF (20 mL) was sequentially treated with *n*-BuLi (3.6 mL, 1.65 mol/L), a solution of $ZnBr_2$ (1.51 g, 6.71 mmol) in THF (10 mL), iodide **492b** (1.61 g, 4.61 mmol) and $Pd(PPh_3)_4$ (0.112 g, 0.097 mmol). The reaction mixture was allowed to stir at rt for 6 h. Standard workup followed by column chromatography (4:1 hexane:EtOAc) and distillation (Kugelrohr) afforded the title compound (0.488 g, 31%).

***N*,*N*-Diethyl 3-(2-hydroxy-3-methoxyphenyl)benzofuran-2-carboxamide (508a).**



According to general procedure H, a solution of carbamate **507a** (0.280 g, 0.827 mmol) in THF (10 mL) was added to a solution of LDA (2.67 mmol) in THF (5 mL) at 0°C. The reaction mixture was allowed to stir for 15 min and standard workup followed by column chromatography (2:1 hexane:EtOAc) afforded the title compound (0.229 g, 82%) as a foam. IR (CH_2Cl_2) ν (max) 3518, 3057, 292937, 1614, 1573, 1470 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.69 (s, 1H, exch), 7.54-7.59 (m, 2H), 7.38 (ddd J = 8.2, 7.4, 1.2 Hz, 1H), 7.27-7.21 (m, 1H), 7.01-6.90 (m, 3H), 3.89 (s, 3H), 3.49 (q J = 7.1 Hz, 2H), 3.37 (q J = 7.1 Hz, 2H), 1.18 (t J = 7.1 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.5 (e), 153.6 (e), 149.4 (e), 144.4 (e), 144.0 (e), 128.2 (e), 126.2 (o), 123.2 (o), 123.0 (o), 122.4 (o), 121.9 (o), 119.8 (o), 118.9 (e), 111.4 (o), 55.90 (o), 43.25 (e), 40.37 (e), 14.05 (o), 12.35 (o); HRMS (EI (70 eV)) *m/e* calcd for $C_{20}H_{22}NO_4$: 340.1549, found 340.1558.

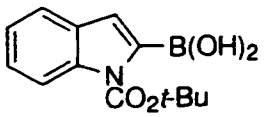
4-Methoxy-6*H*-benzofurano[2,3-*c*]benzo[*e*]pyran-6-one (509a).



According to general procdure D, a solution of hydroxy amide **508a** (0.229 g, 0.676 mmol) in HOAc (10 mL) was heated at reflux for 10 min. Standard workup followed by recrystallisation (CH_2Cl_2:hexane) afforded the title compound (0.154 g, 86%) as a light yellow powder. mp 222-228°C dec (CH_2Cl_2:hexane); IR (KBr) ν (max) 3073, 3011, 2934, 1731, 1614, 1564, 1468, 1444 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 8.60 (d J = 7.9 Hz, 1H), 8.06 (dd J = 8.0, 1.0 Hz, 1H), 7.95 (d J =

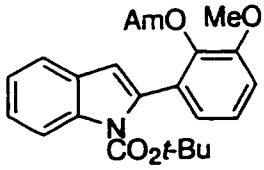
8.5 Hz, 1H), 7.81 (app dt J = 7.9, 1.2 Hz, 1H), 7.64 (app dt J = 7.6 (0.76 Hz, 1H), 7.50 (dd J = 8.2, 8.0 Hz, 1H), 7.39 (dd J = 8.2, 1.0 Hz); ^{13}C NMR (50 MHz, DMF-d_7) δ 157.8 (e), 153.3 (e), 148.4 (e), 142.3 (e), 139.5 (e), 130.8 (o), 128.1 (e), 126.1 (o), 125.8 (o), 124.3 (o), 123.1 (e), 118.0 (e), 116.6 (o), 113.7 (o), 113.2 (o), 56.61 (o); MS (EI (70 eV)) *m/e* (rel intensity) 266 (M+, 18), 223 (8.7), 195 (8.7), 167 (19), 152 (16), 139 (95), 125 (12), 113 (100); Anal. calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79; found: C, 72.33; H, 3.71.

_N_-*t*-Butoxycarbonylindole-2-boronic acid (510).



To a solution of _N_-*t*-butoxycarbonylindole[371] (1.03 g, 4.75 mmol) in THF (20 mL) at -78°C was added *t*-BuLi (4.00 mL, 1.66 mol/L) dropwise over 10 min. The reaction mixture was allowed to stir for 1 h and $B(OMe)_3$ (1.35 mL, 11.9 mmol) was added quickly. The solution was allowed to warm to rt over 6 h, quenched with sat NH_4Cl and subjected to standard workup to afford the crude boronic acid (0.853 g) which was unstable and used without further purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02 (d J = 8.5 Hz, 1H), 7.61 (d J = 7.4 Hz, 1H), 7.50 (s, 1H), 7.42 (s, 2H, exch), 7.36 (app dt J = 7.3, 1.3 Hz, 1H), 7.26 (app dt partially obscured by solvent), 1.74 (s, 9H).

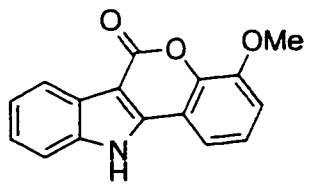
_N_,_N_-Diethyl _O_-[2-(_N_-*t*-butoxycarbonyl-2-indolyl)-6-methoxy]phenylcarbamate (511).



According to general procedure G, a mixture of _N_,_N_-diethyl _O_-(2-iodo-6-methoxy)phenylcarbamate **(492b)** (0.710 g, 2.03 mmol) _N_-*t*-butoxycarbonylindole-2-boronic acid **(510)** (0.6081 g, 2.332 mmol) $Pd(PPh_3)_4$ (0.100 g, 0.0865 mmol) and Na_2CO_3 (10 mL, 2 mol/L) in DME (20 mL) was heated for 1.5 h. Standard workup followed by column

chromatography (5:1 hexane:EtOAc) and recrystallisation (hexane:CH_2Cl_2) afforded the title compound (0.477 g, 54%) as colorless needle-plates. mp 123-124°C (hexane:CH_2Cl_2); IR (CH_2Cl_2) ν (max) 2920, 1727, 1577, 1474, 1418 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.24 (d J = 8.4 Hz, 1H), 7.51 (dd J = 7.0, 0.8 Hz, 1H), 7.29 (ddd J = 8.4, 7.4, 1.5 Hz, 1H), 7.19 (ddd J = 7.6, 7.4, 1.2 Hz, 1H), 7.17 (app t J = 8.0 Hz, 1H), 7.00-6.95 (m, 2H), 6.58 (d J = 0.5 Hz, 1H), 3.82 (s, 3H), 3.19-3.11 (m, 4H), 1.27 (s, 9H), 0.94-0.88 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.7 (e), 151.9 (e), 149.7 (e), 138.6 (e), 136.8 (e), 135.1 (e), 130.1 (e), 128.9 (e), 125.2 (o), 123.9 (o), 122.3 (o), 121.8 (o), 120.3 (o), 114.8 (o), 112.1 (o), 110.2 (o), 82.55 (e), 56.02 (o), 42.10 (e), 41.37 (e), 27.34 (o), 13.39 (o), 12.72 (o); MS (EI (70 eV)) *m/e* (rel intensity) 438 (M^+, 15), 338 (16), 265 (14), 238 (5.0), 195 (3.5), 100 (100), 72 (25); Anal. calcd for $C_{25}H_{30}N_2O_5$: C, 68.63; H, 6.68; N, 6.40; found: C, 68.43; H, 6.86; N, 6.45.

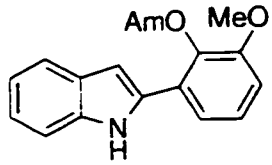
4-Methoxy-6*H*-indolo[3,2-*c*]benzo[*e*]pyran-6-one (514).



To a solution of LDA (0.811 mmol) in THF (5 mL) at -78°C was added a solution of carbamate **511** (0.107 g, 0.244 mmol) in THF (4 mL) *via* canula. The resulting solution was allowed to warm to rt over 12 h and subsequent standard workup afforded the crude hydroxy amide which was cyclised according to general procedure D (10 mL HOAc). After heating at reflux for 1h the cooled solution was diluted with H_2O (10 mL) and cooled in an ice bath. The mixture was filtered and the precipitate washed with cold HOAc-H_2O (1:1) affording the title compound (0.0538 g, 83%). mp 289-296°C dec; IR (KBr) ν (max) 3365, 3070, 2981, 1685, 1623, 1593, 1515, 1465 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 12.98 (s, 1H), 8.03 (d J = 7.6 Hz, 1H), 7.75 (d J = 7.9

Hz, 1H), 7.65 (d J = 8.1 Hz, 1H), 7.42-7.40 (m, 1H), 7.39 (d J = 7.9 Hz, 1H), 7.33 (app t J = 7.6 Hz, 1H), 7.29 (d J = 8.1 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ poor solubility did not allow acquisition of a satisfactory ^{13}C spectrum; MS (EI (70 eV)) *m/e* (rel intensity) 265 (M^+, 100), 222 (14), 194 (6.2), 166 (6.0), 141 (30), 100 (54); HRMS (EI (70 eV)) *m/e* calcd for $C_{16}H_{11}NO_3$: 265.0739, found: 265.0752.

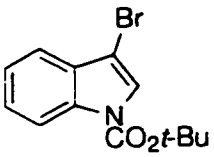
N,N-Diethyl O-[2-(2-indolyl)-6-methoxy]phenylcarbamate (516).



According to general procedure H, a solution of carbamate **511** (0.327 g, 0.748 mmol) in THF (8 mL) was added to a solution of LDA (2.42 mmol) in THF (6 mL) at 0°C and the reaction mixture was allowed to stir for 10 min. Standard workup followed by cyclisation according to general procedure D (10 mL HOAc) afforded crude products. Standard workup afforded an organic soluble fraction which was purified by column chromatography (1:1 hexane:EtOAc) to furnish the title compound (0.121 g, 48%) as well as an organic insoluble fraction which was collected by filtration and washed with cold HOAc-H_2O (1:1, 5 mL) affording lactone **514** (12. 7 mg, 6%).

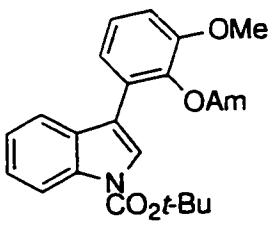
Carbamate **516**: IR (KBr) ν (max) 3584, 3024, 2978, 1759, 1612, 1442 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.55 (dd J = 7.1, 1.0 Hz, 1H), 7.48-7.40 (m, 5H), 7.24 (app t J = 8.1 Hz, 1H), 7.02 (d J = 8.1Hz, 1H), 3.98 (s, 3H), 3.89-3.67 (m, 2H), 3.35-3.27 (m, 2H), 1.43 (t J = 7.1, 3H), 0.99 (t J = 7.1, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.1 (e), 147.6 (e), 133.3 (e), 128.3 (e), 127.6 (e), 126.2 (e), 125.8 (o), 125.7 (o), 125.3 (o), 119.1 (o), 116.2 (o), 115.4 (o), 115.3 (o), 114.2 (e), 112.6 (o), 56.25 (o), 43.35 (e), 39.46 (e), 14.63 (o), 13.00 (o); MS (EI (70 eV)) *m/e* (rel intensity) 338 (M^+, 55), 300 (24), 265 (14), 238 (14), 208 (11), 166 (6.8), 100 (100), 72 (51); HRMS (EI (70 eV)) *m/e* calcd for $C_{20}H_{22}N_2O_3$: 338.1631, found: 338.1627.

_N_-_t_-Butoxycarbonyl-3-bromoindole (512).



A solution of _N_-_t_-butoxycarbonylindole[371] (1.06 g, 4.89 mmol) and NBS (0.920 g, 5.17 mmol) in CH_2Cl_2 (50 mL) was heated at reflux for 2 h and the cooled reaction mixture was diluted with H_2O (50 mL). The layers were separated and the organic phase was washed (10% KOH, H_2O), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (95:5 hexane:Et_2O) affording the title compound (1.41 g, 98%) as a colorless oil which solidified on standing. mp 54-55°C (MeOH); IR (KBr) ν (max) 3063, 2979, 1734, 1681, 1447 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.14 (d J = 7.7 Hz, 1H), 7.63 (s, 1H), 7.53-7.49 (m, 1H), 7.39-7.22 (m, 2H), 1.65 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 148.8 (e), 134.6 (e), 129.3 (e), 125.3 (o), 124.7 (o), 123.2 (o), 119.5 (o), 115.1 (o), 97.89 (e), 84.22 (e), 28.09 (o); MS (EI (70 eV)) *m/e* (rel intensity) 297 (53), 295 (53), 241 (61), 239 (61), 224 (7.5), 222 (7.5), 197 (100), 195 (100), 169 (2.5), 167 (2.5); Anal. calcd for$C_{13}H_{14}NO_2Br$: C, 52.72; H, 4.76; N, 4.73 found: C, 53.00; H, 4.85; N,4.79.

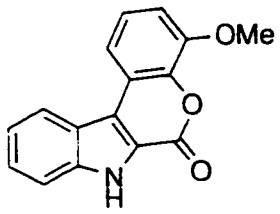
_N_,_N_-Diethyl _O_-[2-(_N_-_t_-butoxycarbonyl-3-indolyl)-6-methoxy]phenylcarbamate (513).



According to general procedure G, a mixture of _N_-_t_-butoxycarbonyl-3-bromoindole **(512)** (0.988 g, 3.34 mmol), 2-_N_,_N_-diethylcarbamato-3-methoxyphenylboronic acid **(492a)** (1.35 g, 5.06 mmol), $Pd(PPh_3)_4$ (0.190 g, 0.164 mmol) and Na_2CO_3 (10 mL, 2 mol/L) in toluene (125 mL) was heated at reflux for 12 h. Standard workup followed by purification by column chromatography afforded the title compound

as a viscous oil (0.883 g, 60%) which solidified on standing. mp 96-97°C (hexane:CH_2Cl_2); IR (KBr) ν (max) 2977, 1725, 1612, 1576, 1458 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.20 (d J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.64 (dd J = 7.0, 1.5 Hz, 1H), 7.32 (ddd J = 7.9, 7.3, 1.5 Hz, 1H), 7.22 (ddd J = 7.6, 7.3, 1.5 Hz, 1H), 7.24 (app t J = 7.9 Hz, 1H), 7.13 (dd J = 7.9, 1.8, 1H), 6.97 (dd J = 7.9, 1.8, 1H), 3.87 (s, 3H), 3.25 (q J = 7.0 Hz, 4H), 1.66 (s, 9H), 1.09-1.02 (m, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 438 (M^+, 7.5), 382 (1.2), 338 (22), 265 (3.1), 238 (3.3), 195 (1.6), 100 (100), 72 (18); Anal. calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39; found: C, 68.60; H,6.85; N, 6.50.

4-Methoxy-6*H*-indolo[2,3-*c*]benzo[*e*]pyran-6-one (515).



To a solution of LDA (0.845 mmol) in THF (5 mL) at -78°C was added a solution of carbamate **513** (0.112 g, 0.255 mmol) in THF (5 mL) dropwise *via* canula and the resulting solution was allowed to warm to rt over 12 h. Standard workup afforded the crude hydroxy amide which was cyclised according to general procedure D (10 mL HOAc). After heating at reflux for 1h the cooled solution was diluted with H_2O (10 mL) and cooled in an ice bath. The mixture was filtered and the precipitate washed with cold HOAc-H_2O (1:1) affording the title compound (54.4 mg, 80%) as a colorless fine solid. mp 274-278°C dec; IR (KBr) ν (max) 3246, 1707, 1539, 1377 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 12.73 (s, 1H), 8.43 (d J = 8.2 Hz, 1H), 8.00 (d J = 8.0 Hz, 1H), 7.66-7.49 (m, 2H), 7.44-7.30 (m, 2H), 7.18 (d J = 8.2 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.0 (e), 147.3 (e), 139.7 (e), 139.5 (e), 127.2 (o), 124.9 (o), 122.6 (o), 121.6 (o), 121.6 (e), 121.3 (e), 120.0 (e), 119.0 (e), 115.1 (o), 113.4

(o), 110.2 (o), 55.94 (o); MS (EI (70 eV)) *m/e* (rel intensity) 265 (M^+, 100), 222 (21), 195 (3.7), 166 (3.1), 133 (5.6); HRMS (EI (70 eV)) *m/e* calcd for $C_{16}H_{11}NO_3$: 265.0739, found: 265.0739.

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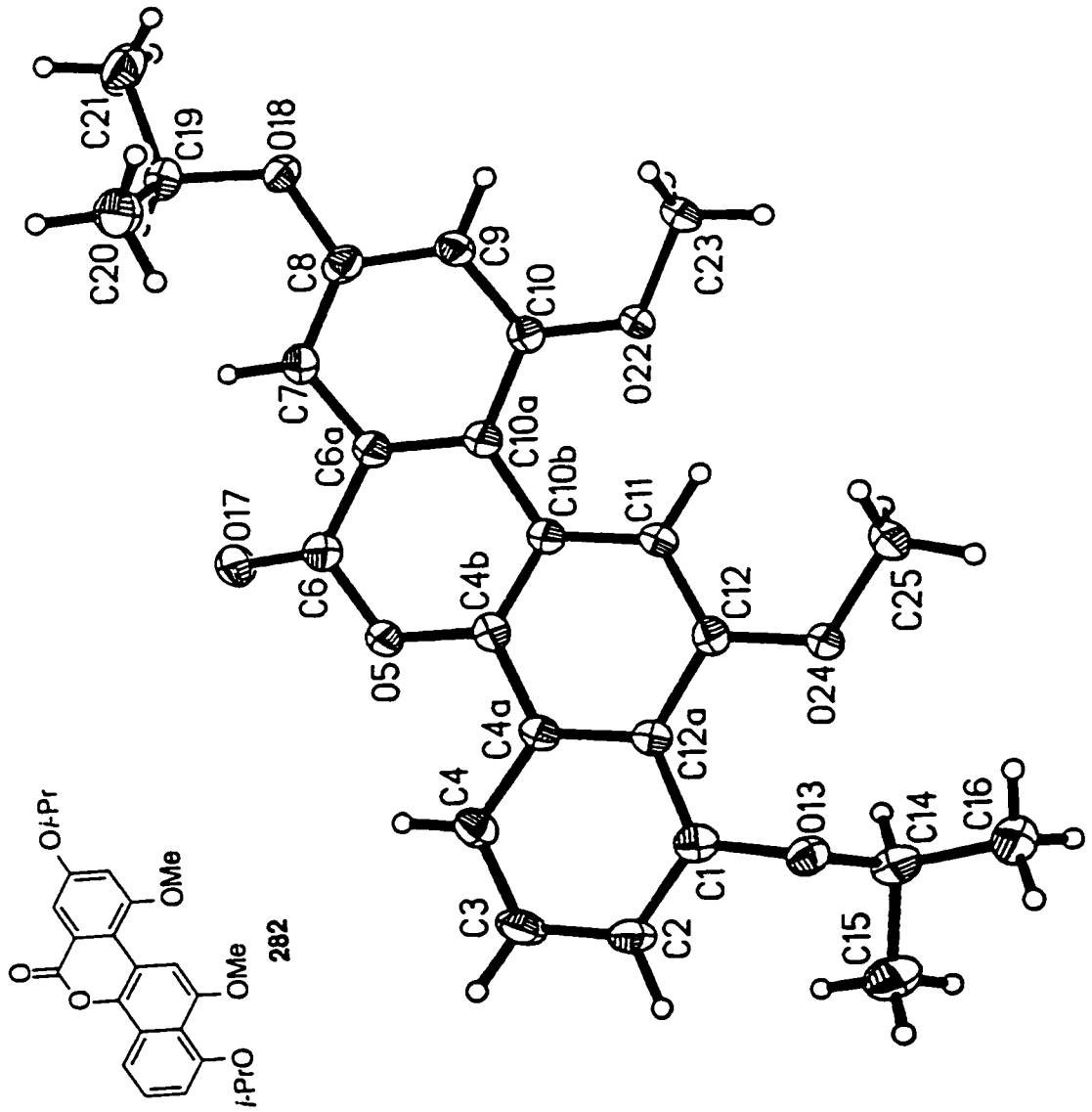
13. Appendices

Appendix 1: X-Ray Crystallographic Data for 282



STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{25}H_{26}O_6$
Color; Habit	Pale yellow needle prism fragment
Crystal Size (mm)	0.40{010}x0.40{0$\bar{1}$1}x0.23{001} x0.50{1$\bar{1}$0}
Crystal System	Triclinic
Space Group	P$\bar{1}$
Unit Cell Dimensions	$\underline{a}$ = 8.3148(8) Å
	$\underline{b}$ = 10.7280(12) Å
	$\underline{c}$ = 13.0079(16) Å
	α = 98.129(9)°
	β = 93.810(7)°
	γ = 112.367(8)°
Volume	1053.03(26) Å^3
Z	2
Formula Weight	422.5
Density(calc.)	1.332 g/cm^3
Absorption Coefficient	0.95 cm^{-1}
F(000)	448

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	160
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 52.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \leq h \leq 10$, $-12 \leq k \leq 12$ $-16 \leq \ell \leq 16$
Reflections Collected	4406
Independent Reflections	4104 (R_{int} = 1.44%)
Observed Reflections	3232 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9604 / 0.9805

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Hydrogen Atoms	Riding model, refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	306
Final R Indices (obs. data)	R = 3.39 %, wR = 3.82 %
(R Indices (all data)	R = 4.16 %, wR = 3.85 %)
Goodness-of-Fit	3.01
Largest and Mean Δ/σ	0.002, 0.000
Data-to-Parameter Ratio	10.6:1
Largest Difference Peak	0.17 $e\text{Å}^{-3}$
Largest Difference Hole	-0.30 $e\text{Å}^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^4$)

	x	y	z	U(eq)
C(1)	3204(2)	5101(2)	1343(1)	234(6)
C(2)	2283(2)	4294(2)	414(1)	296(6)
C(3)	649(2)	3223(2)	385(1)	314(7)
C(4)	-26(2)	2944(2)	1293(1)	259(6)
C(4a)	909(2)	3736(2)	2272(1)	205(6)
C(4b)	268(2)	3396(1)	3224(1)	195(5)
O(5)	-1328(1)	2288(1)	3090.3(7)	227(4)
C(6)	-2070(2)	1738(2)	3910(1)	234(6)
C(6a)	-1065(2)	2331(1)	4957(1)	205(6)
C(7)	-1752(2)	1634(2)	5765(1)	232(6)
C(8)	-860(2)	2145(2)	6763(1)	230(6)
C(9)	599(2)	3378(2)	6968(1)	230(6)
C(10)	1243(2)	4075(1)	6173(1)	199(5)
C(10a)	465(2)	3528(1)	5115(1)	192(5)
C(10b)	1168(2)	4071(1)	4195(1)	190(5)
C(11)	2772(2)	5212(1)	4220(1)	208(5)
C(12)	3423(2)	5609(1)	3333(1)	209(6)
C(12a)	2541(2)	4856(2)	2313(1)	205(6)
O(13)	4861(1)	6074(1)	1325.0(8)	247(4)
C(14)	4968(2)	7448(2)	1265(1)	280(6)
C(15)	4350(2)	7490(2)	151(1)	395(8)
C(16)	6852(2)	8398(2)	1608(1)	367(7)
O(17)	-3486(1)	806(1)	3716.9(8)	348(5)
O(18)	-1300(1)	1539(1)	7616.2(8)	279(4)
C(19)	-2417(2)	90(2)	7443(1)	275(6)
C(20)	-1519(2)	-753(2)	6913(1)	373(7)
C(21)	-2762(3)	-215(2)	8526(1)	514(9)
O(22)	2654(1)	5293(1)	6354.5(7)	248(4)
C(23)	3476(2)	5859(2)	7413(1)	271(6)
O(24)	4941(1)	6722(1)	3357.8(8)	279(4)
C(25)	5820(2)	7509(2)	4357(1)	282(6)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.370(2)	C(1)-C(12a)	1.428(2)
C(1)-O(13)	1.380(2)	C(2)-C(3)	1.400(2)
C(3)-C(4)	1.364(2)	C(4)-C(4a)	1.417(2)
C(4a)-C(4b)	1.420(2)	C(4a)-C(12a)	1.422(2)
C(4b)-O(5)	1.384(1)	C(4b)-C(10b)	1.372(2)
O(5)-C(6)	1.362(2)	C(6)-C(6a)	1.468(2)
C(6)-O(17)	1.201(2)	C(6a)-C(7)	1.402(2)
C(6a)-C(10a)	1.399(2)	C(7)-C(8)	1.377(2)
C(8)-C(9)	1.389(2)	C(8)-O(18)	1.366(2)
C(9)-C(10)	1.379(2)	C(10)-C(10a)	1.422(2)
C(10)-O(22)	1.360(1)	C(10a)-C(10b)	1.464(2)
C(10b)-C(11)	1.421(2)	C(11)-C(12)	1.360(2)
C(12)-C(12a)	1.438(2)	C(12)-O(24)	1.362(2)
O(13)-C(14)	1.456(2)	C(14)-C(15)	1.518(2)
C(14)-C(16)	1.502(2)	O(18)-C(19)	1.450(2)
C(19)-C(20)	1.502(3)	C(19)-C(21)	1.513(3)
O(22)-C(23)	1.433(2)	O(24)-C(25)	1.425(2)

Table 3. Bond angles (°)

C(2)-C(1)-C(12a)	120.9(1)	C(2)-C(1)-O(13)	118.0(1)
C(12a)-C(1)-O(13)	120.8(1)	C(1)-C(2)-C(3)	121.0(1)
C(2)-C(3)-C(4)	120.1(1)	C(3)-C(4)-C(4a)	120.6(1)
C(4)-C(4a)-C(4b)	120.8(1)	C(4)-C(4a)-C(12a)	120.0(1)
C(4b)-C(4a)-C(12a)	119.1(1)	C(4a)-C(4b)-O(5)	114.1(1)
C(4a)-C(4b)-C(10b)	123.4(1)	O(5)-C(4b)-C(10b)	122.5(1)
C(4b)-O(5)-C(6)	122.4(1)	O(5)-C(6)-C(6a)	117.2(1)
O(5)-C(6)-O(17)	117.4(1)	C(6a)-C(6)-O(17)	125.5(1)
C(6)-C(6a)-C(7)	115.8(1)	C(6)-C(6a)-C(10a)	120.8(1)
C(7)-C(6a)-C(10a)	123.4(1)	C(6a)-C(7)-C(8)	118.3(1)
C(7)-C(8)-C(9)	120.2(1)	C(7)-C(8)-O(18)	125.2(1)
C(9)-C(8)-O(18)	114.6(1)	C(8)-C(9)-C(10)	121.0(1)
C(9)-C(10)-C(10a)	120.8(1)	C(9)-C(10)-O(22)	122.2(1)
C(10a)-C(10)-O(22)	117.0(1)	C(6a)-C(10a)-C(10)	115.9(1)
C(6a)-C(10a)-C(10b)	118.3(1)	C(10)-C(10a)-C(10b)	125.7(1)
C(4b)-C(10b)-C(10a)	118.2(1)	C(4b)-C(10b)-C(11)	116.6(1)
C(10a)-C(10b)-C(11)	125.1(1)	C(10b)-C(11)-C(12)	122.4(1)
C(11)-C(12)-C(12a)	121.3(1)	C(11)-C(12)-O(24)	122.4(1)
C(12a)-C(12)-O(24)	116.4(1)	C(1)-C(12a)-C(4a)	117.4(1)
C(1)-C(12a)-C(12)	125.5(1)	C(4a)-C(12a)-C(12)	117.0(1)
C(1)-O(13)-C(14)	115.9(1)	O(13)-C(14)-C(15)	109.3(1)
O(13)-C(14)-C(16)	106.4(2)	C(15)-C(14)-C(16)	112.2(1)
C(8)-O(18)-C(19)	118.3(1)	O(18)-C(19)-C(20)	110.9(1)
O(18)-C(19)-C(21)	104.7(1)	C(20)-C(19)-C(21)	111.4(2)
C(10)-O(22)-C(23)	118.1(1)	C(12)-O(24)-C(25)	117.7(1)

Table 4. Anisotropic displacement coefficients ($Å^2 x 10^4$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	233(8)	278(8)	219(8)	128(7)	39(6)	51(6)
C(2)	321(9)	398(10)	169(8)	145(8)	49(7)	35(7)
C(3)	329(10)	373(10)	177(8)	106(8)	-17(7)	-31(7)
C(4)	231(8)	276(9)	236(8)	84(7)	-4(7)	1(7)
C(4a)	229(8)	224(8)	185(7)	125(7)	8(6)	11(6)
C(4b)	181(8)	184(7)	227(8)	86(6)	13(6)	25(6)
O(5)	214(6)	235(6)	191(5)	56(5)	-1(4)	19(4)
C(6)	229(8)	226(8)	245(8)	89(7)	30(7)	43(6)
C(6a)	217(8)	201(8)	207(8)	101(7)	20(6)	22(6)
C(7)	223(8)	190(8)	265(8)	62(7)	39(7)	36(6)
C(8)	287(9)	216(8)	223(8)	124(7)	84(7)	62(6)
C(9)	277(8)	221(8)	184(8)	101(7)	23(6)	9(6)
C(10)	197(8)	193(8)	211(8)	84(7)	29(6)	25(6)
C(10a)	207(8)	189(7)	205(8)	107(6)	30(6)	26(6)
C(10b)	213(8)	199(8)	185(7)	117(7)	23(6)	19(6)
C(11)	227(8)	220(8)	167(7)	93(7)	0(6)	3(6)
C(12)	194(8)	202(8)	219(8)	70(7)	18(6)	25(6)
C(12a)	221(8)	237(8)	190(7)	130(7)	18(6)	31(6)
O(13)	239(6)	287(6)	231(6)	108(5)	62(5)	68(5)
C(14)	328(9)	315(9)	246(8)	158(8)	92(7)	91(7)
C(15)	459(12)	463(12)	314(10)	199(10)	69(9)	171(8)
C(16)	388(11)	324(10)	355(10)	95(8)	82(8)	70(8)
O(17)	258(6)	354(7)	289(6)	-23(6)	-19(5)	42(5)
O(18)	386(7)	205(6)	212(6)	64(5)	74(5)	58(4)
C(19)	268(9)	220(8)	285(8)	34(7)	48(7)	63(7)
C(20)	499(12)	279(10)	360(10)	185(9)	23(9)	49(8)
C(21)	732(16)	318(11)	382(11)	40(11)	229(11)	125(8)
O(22)	264(6)	229(6)	163(5)	16(5)	-3(4)	11(4)
C(23)	275(9)	280(9)	183(8)	53(8)	-32(7)	-3(6)
O(24)	269(6)	280(6)	181(5)	1(5)	23(5)	21(4)
C(25)	256(9)	269(9)	226(8)	21(7)	2(7)	-10(7)

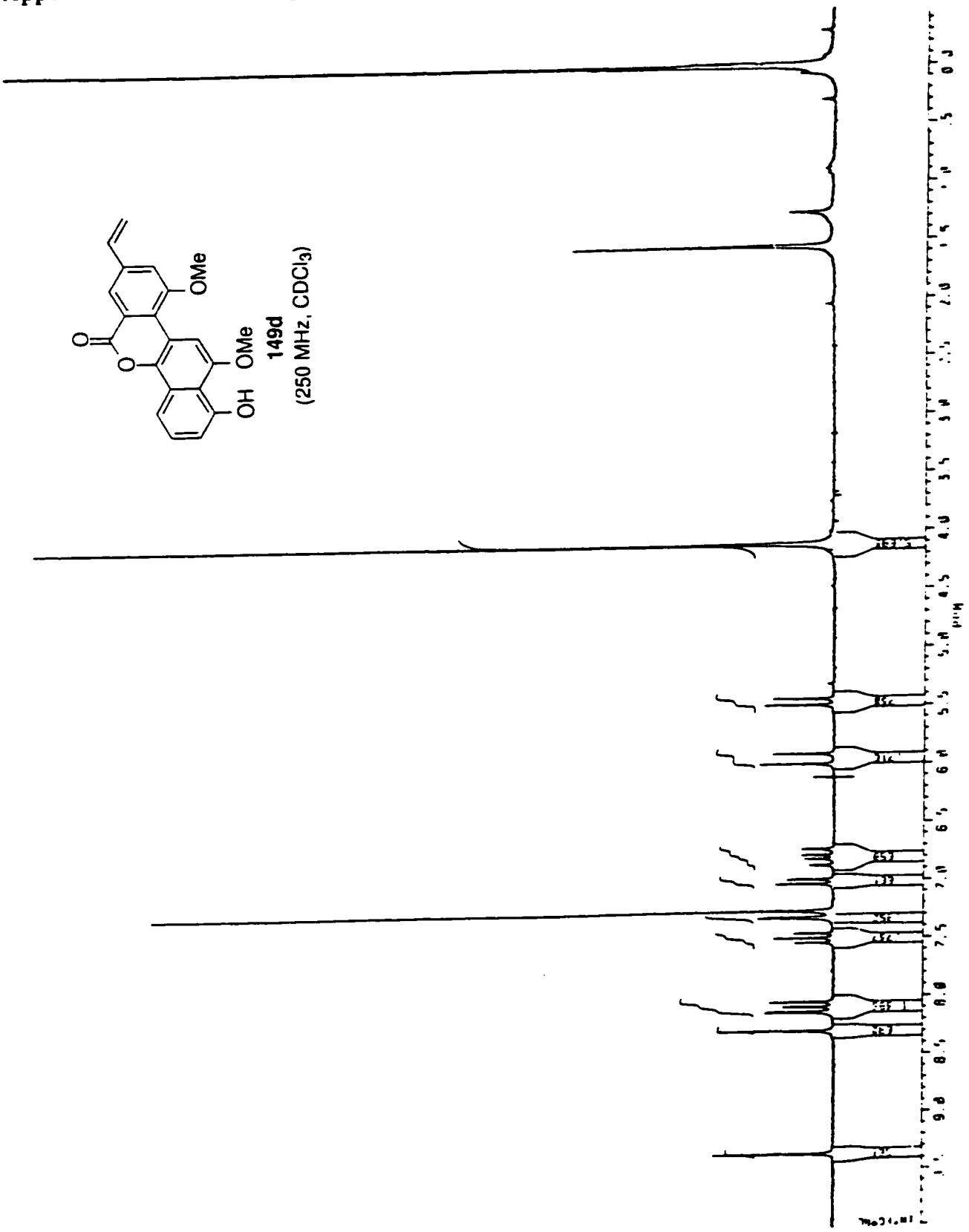
The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

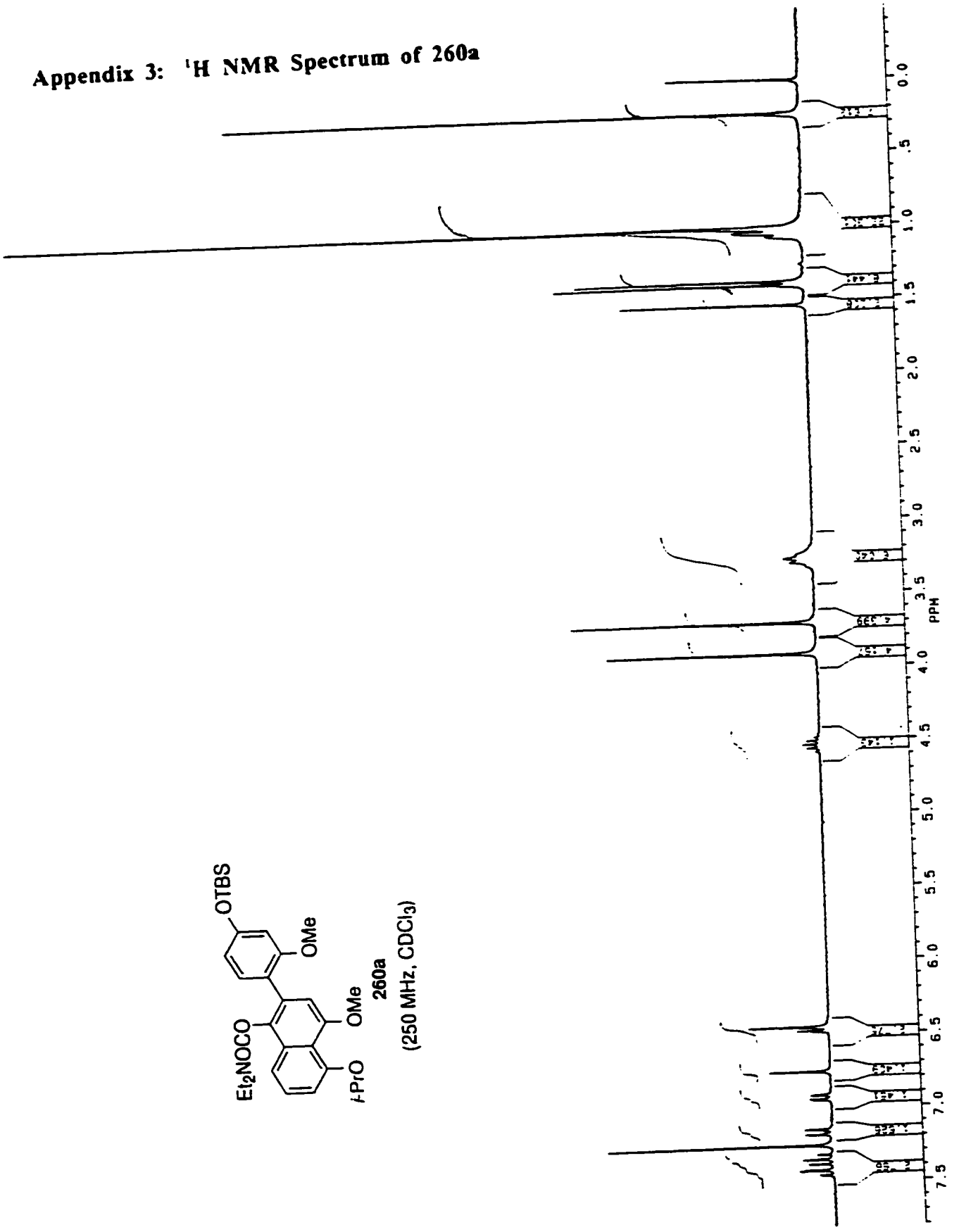
Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(2)	2772	4465	-225	34(5)
H(3)	-2	2689	-275	39(5)
H(4)	-1136	2199	1274	31(4)
H(7)	-2811	818	5622	24(4)
H(9)	1168	3751	7674	23(4)
H(11)	3425	5716	4887	23(4)
H(14)	4243	7687	1733	26(4)
H(15x)	4472	8403	92	48(6)
H(15y)	3144	6872	-45	45(6)
H(15z)	5042	7207	-317	40(5)
H(16x)	6980	9332	1647	50(6)
H(16y)	7559	8195	1109	52(6)
H(16z)	7249	8269	2279	53(6)
H(19)	-3501	-82	7025	24(4)
H(20x)	-519	-661	7378	57(6)
H(20y)	-1149	-445	6277	55(6)
H(20z)	-2313	-1698	6738	52(6)
H(21x)	-1668	-8	8947	81(8)
H(21y)	-3510	-1165	8474	70(7)
H(21z)	-3354	322	8844	75(8)
H(23x)	2640	6026	7826	30(4)
H(23y)	4467	6706	7444	42(5)
H(23z)	3870	5231	7699	28(4)
H(25x)	6139	6942	4767	27(4)
H(25y)	5070	7867	4713	31(5)
H(25z)	6856	8267	4269	40(5)

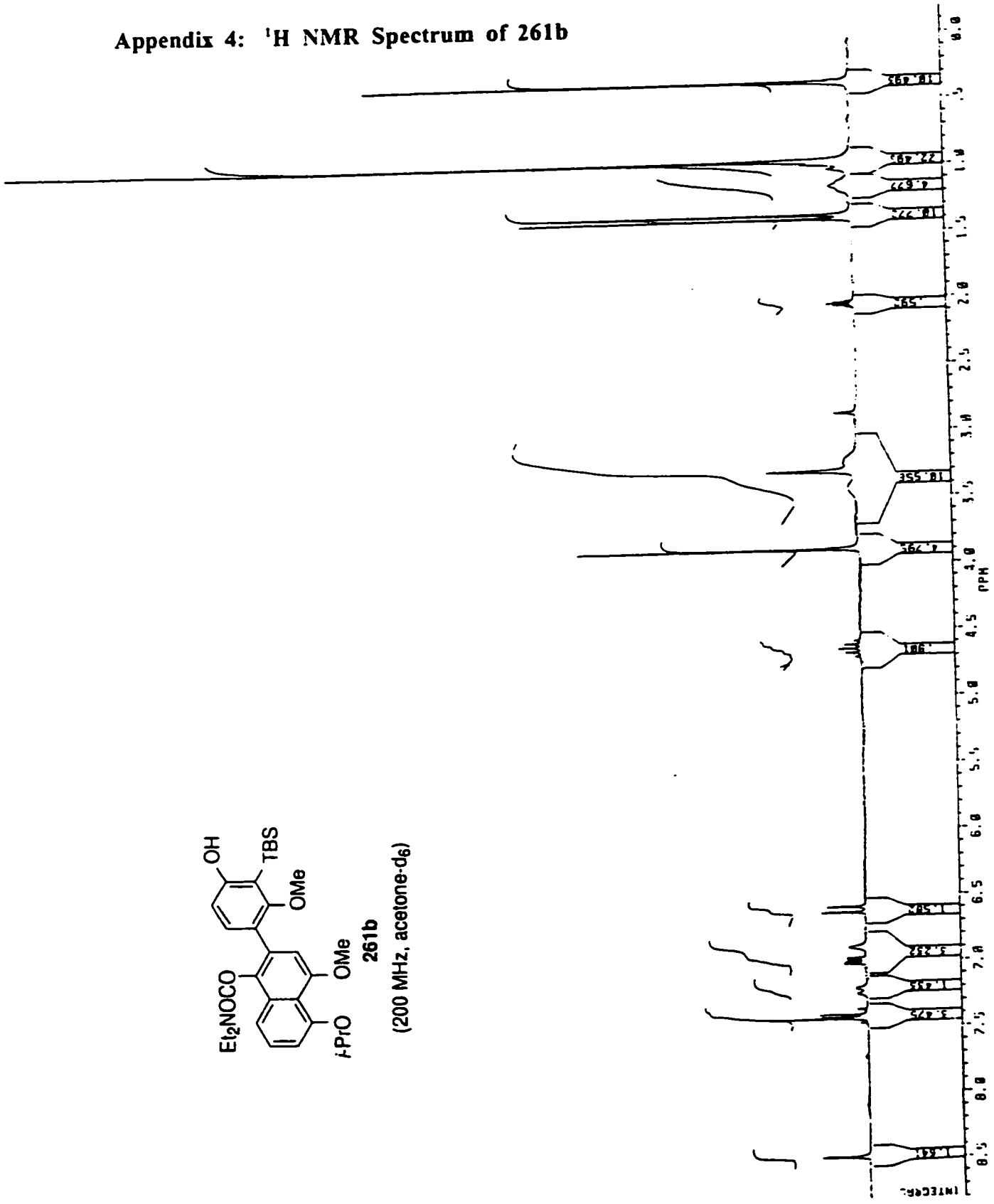
Appendix 2: ^{1}H NMR Spectrum of 149d



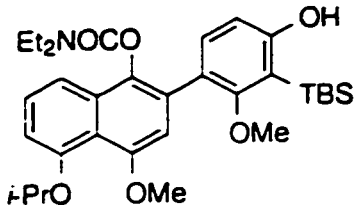
Appendix 3: ^{1}H NMR Spectrum of 260a



Appendix 4: ^{1}H NMR Spectrum of 261b

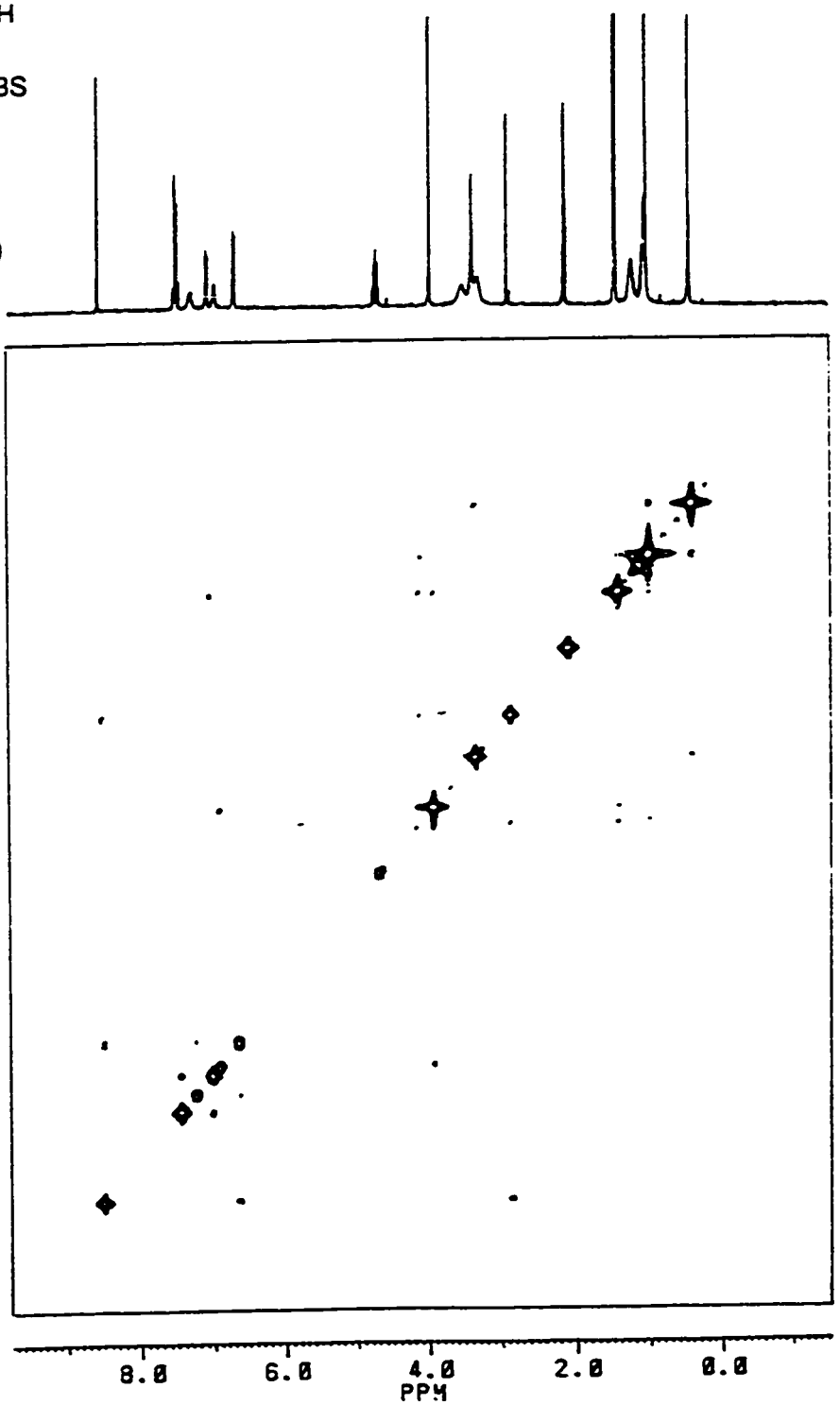


Appendix 5: NOESY Spectrum of 261b

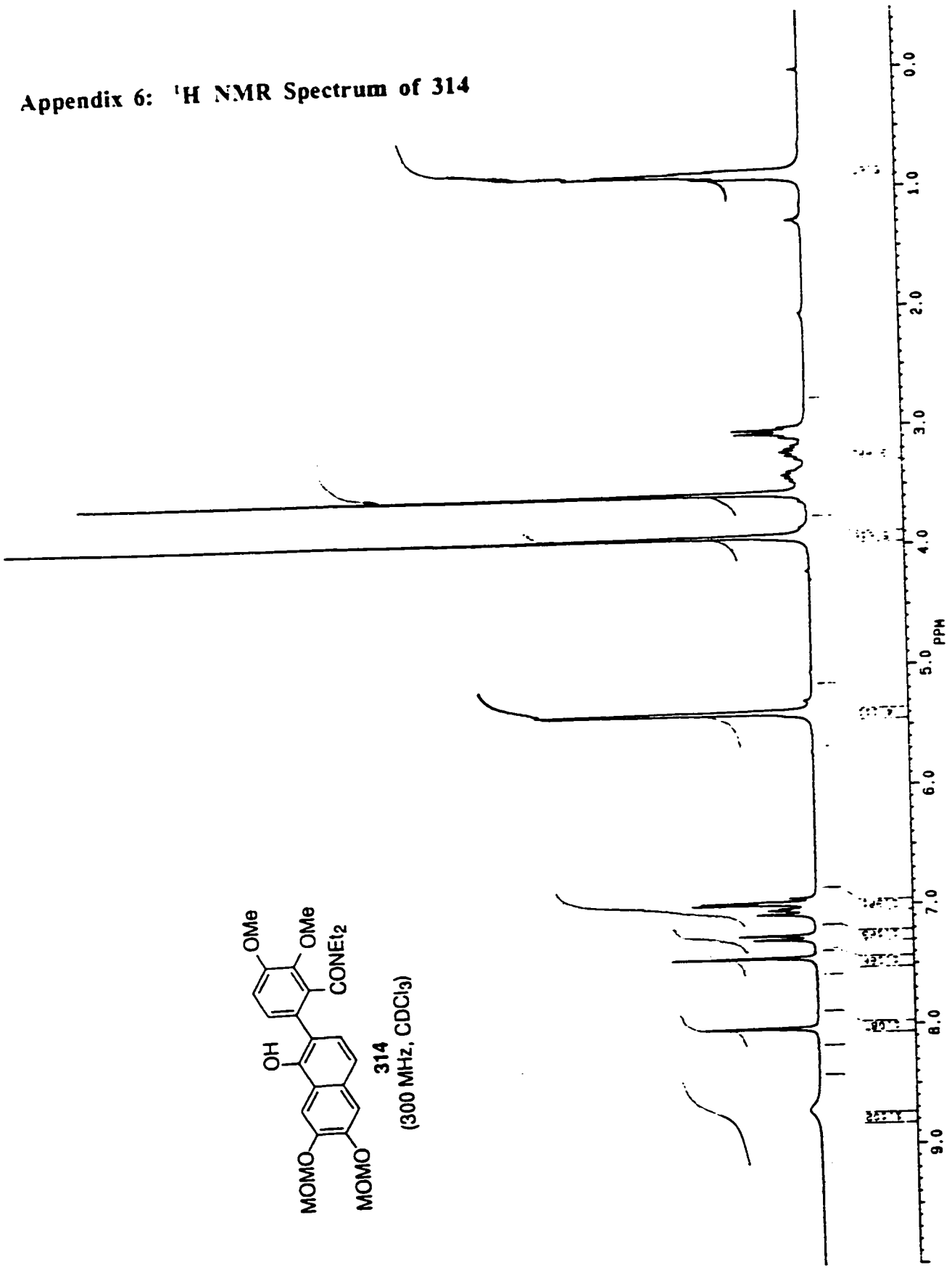


261b

(200 MHz, acetone-d_6)



Appendix 6: ^{1}H NMR Spectrum of 314



Appendix 7: ^{1}H NMR Spectrum of 509b

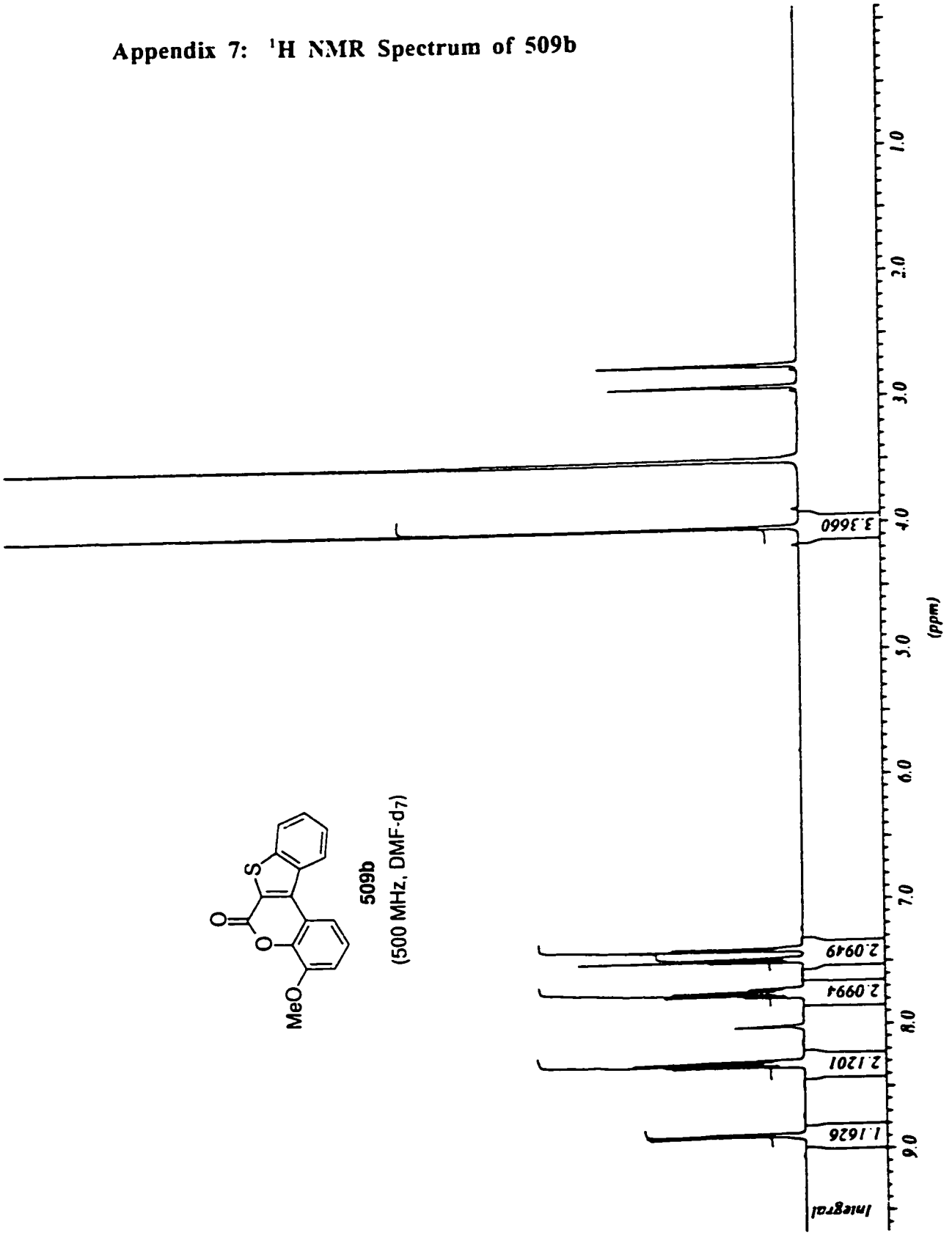
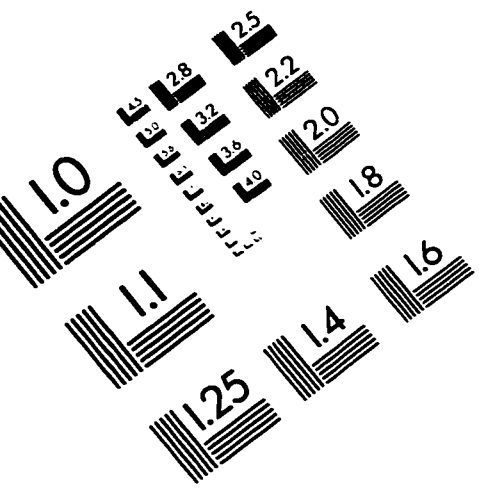
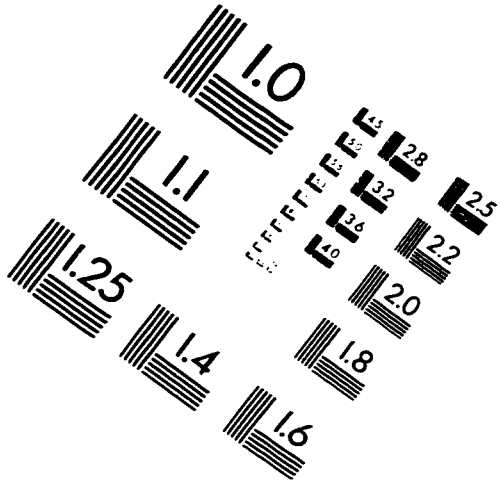
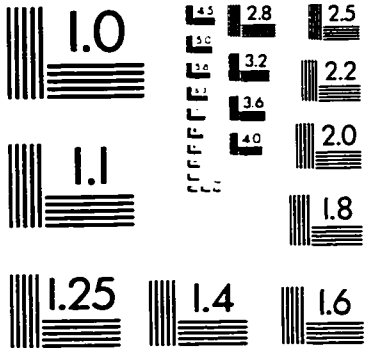
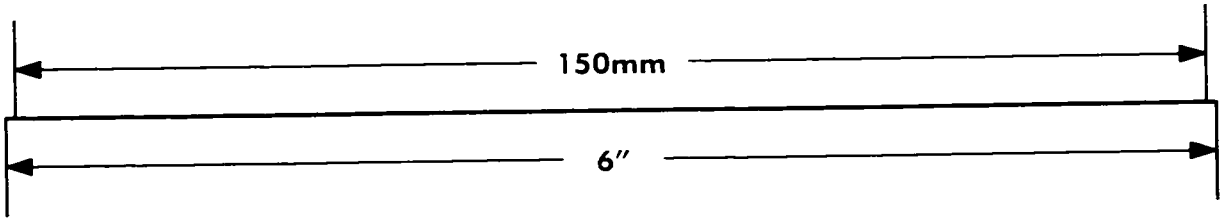


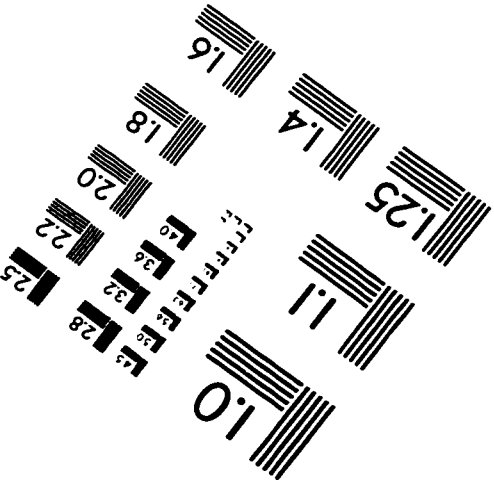
IMAGE EVALUATION
TEST TARGET (QA-3)

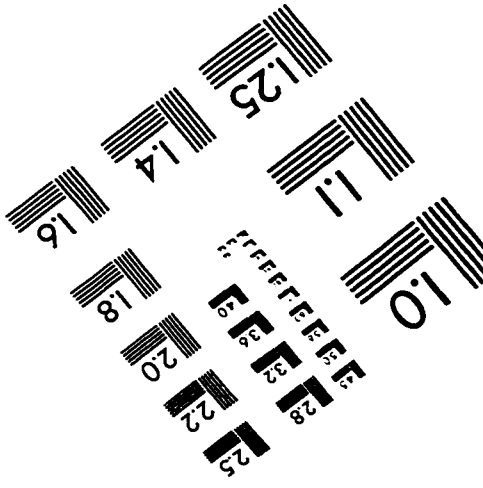












APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989