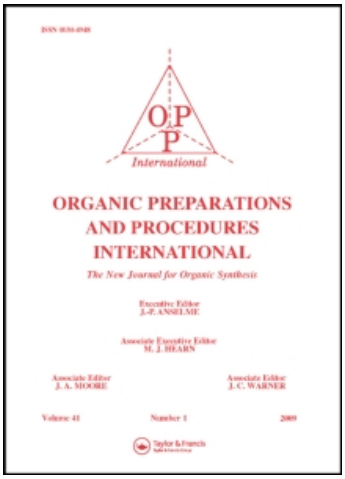

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THE SYNTHESIS OF ISOCOUMARINS OVER THE LAST DECADE. A REVIEW

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Dedicated to Prof. Dieter Seebach on the occasion of his 60th birthday

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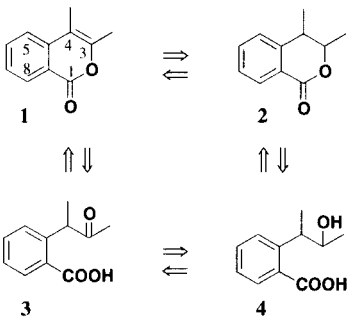
INTRODUCTION

This article reviews the most recent developments in the synthesis of isocoumarins and 3,4-dihydroisocoumarins (isochroman-1-ones), that is, compounds incorporating the substructures **1** or **2**, which are also referred to as 1*H*-2-benzo[c]pyran-1-ones and 3,4-dihydro-1*H*-2-benzo[c]pyran-1-ones, respectively.

Isocoumarins (this term will be used to indicate generically derivatives of either **1** or **2**) were reviewed comprehensively by Barry in 1964.[1] The reasons for interest in this class of compounds have not changed since then. In the more than thirty years elapsed, a conspicuous and still increasing number of new isocoumarins have been found in nature (in prevalence among the products of secondary metabolism of plants and lower microorganisms but also among insect pheromones and venoms) exhibiting a wide structural diversity in dependence of their natural source and their biosynthetic pathway; these findings have been a constant stimulus for synthetic work, which has been undertaken either to confirm novel structures or to provide substantial amounts of material for biochemical and pharmaceutical studies in those cases in which an isocoumarin exibited interesting properties or was suspected of being responsible for the significant properties associated with its natural source. Among the most important isocoumarins, we can mention the AI-77s, endowed of



gastroprotective properties but free of effects on the central nervous system; phyllodulcin, a lead compound in the discovery of novel low calorie sweeteners; and coriandrin, active against HIV. Owing to the general interest of this class of compounds, the synthesis of isocoumarins has become a popular field for testing novel methods of elaboration of aromatic compounds. Finally, isocoumarins have been encountered as intermediates *en route* to other types of compounds.

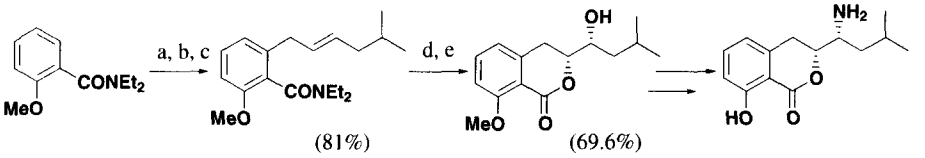
Other reviews on the synthesis of isocoumarins have appeared after the one cited. Narasimhan and Mali have discussed a substantial number of isocoumarin syntheses in the context of a review on the use of heteroatom directed aromatic lithiation in the synthesis of condensed heterocycles.[2] Hill provided an exhaustive list of references to natural isocoumarin syntheses in his compilation on natural isocoumarins.[3] Other sources of information on isocoumarin syntheses are found in the specific sections of general treatises,[4-7] as well as in the introduction of original research articles, among which one by Hauser[8] and one by Snieckus[9] are particularly useful. I will attempt to cover the synthesis of isocoumarins over the last decade in a systematic way. Examples will be preferentially taken from the more recent literature, but references to previous works will be made whenever it is believed to be useful for a comparison with new methods or to trace novel developments and applications.

The problems involved in the synthesis of isocoumarins and 3,4-dihydroisocoumarins are better focused if one considers that these heterocyclic compounds behave in all respects as enol-lactones and lactones, respectively; in fact, the six membered heterocyclic rings can be readily obtained from (or transformed into) the corresponding open chain hydrated derivatives, namely, the aromatic keto and hydroxyacids **3** and **4** respectively. Also, the saturated and the unsaturated heterocycles, as well as the two open chain derivatives, can be interconverted so that substances **1-4** can be considered synthetically equivalent. On the basis of simple rules of bond disconnection, it follows that the synthesis of isocoumarins can be generally related to the obtainment of any benzene derivative bearing a functionalized one-carbon substituent *and* a β-functionalized alkyl chain *ortho* to each other. A target of this type can be reached by elaborating the substituents of a preformed benzene derivative or by generating the substituted benzene ring from a suitable open chain precursor. Section I discusses the syntheses of isocoumarins in which the final carbon framework is obtained from a precursor where the aromatic homocyclic ring is already formed; whithin this section the syntheses are arranged on the basis of the increasing number of carbon atoms of the heterocyclic portion which are already bound to the aromatic homocyclic portion of the precursor. Section II describes the syntheses in which the carbon framework of the isocoumarin system results from the construction of the aromatic homocyclic ring in the last carbon-carbon bond forming step; within this section, the syntheses are organized according to the type of reaction (ionic or pericyclic) adopted for the construction of the aromatic homocyclic ring.

I. ISOCOUMARINS FROM AROMATIC PRECURSORS

1. Syntheses from Aromatic Compounds Featuring Carbon 1

Benzoic acid derivatives are important precursors of isocoumarins; among the methods available for introducing a β-functionalized carbon substituent *ortho* to the carboxyl group, those involving *ortho*-metallation of the benzene ring have enjoyed a great popularity. This approach has been thoroughly reviewed.[2,10] Summarizing the general concepts, carboxylic acids derivatives suitable for promoting *ortho* lithiation are tertiary amides, the (4,4-dimethyl)oxazolin-2-yl group, and secondary amides. Lithiated tertiary amides are readily and generally *ortho*-lithiated using *s*-butyllithium and tetramethylethylenediamine, but their reaction with alkylating agents other than methyl iodide gives low yields because of a poor nucleophilicity. Epoxides, whose reactions would give 3,4-dihydroisocoumarins by simple lactonization, are unfortunately poor electrophiles for *ortho*-metallated tertiary benzamides. Allylation of lithiated tertiary benzamides has however been accomplished in high yields by previous trans-metallation to a magnesium or (better) to a copper derivative; the allyl group thus introduced has been converted to the β-hydroxyalkyl group required to complete the lactone ring in the conditions of the acid hydrolysis of the benzamide, leading to racemic 3,4-dihydroisocoumarins directly, apparently without the possibility of isolating the intermediate allylbenzoic acids; alternatively, asymmetric hydroxylation of the double bond followed by treatment with acids has been used to obtain 3,4-dihydroisocoumarins with a high degree of enantiomeric purity, as demonstrated by the enantioselective synthesis of the isocoumarin portion of AI77B (*Scheme 1*).[11] A

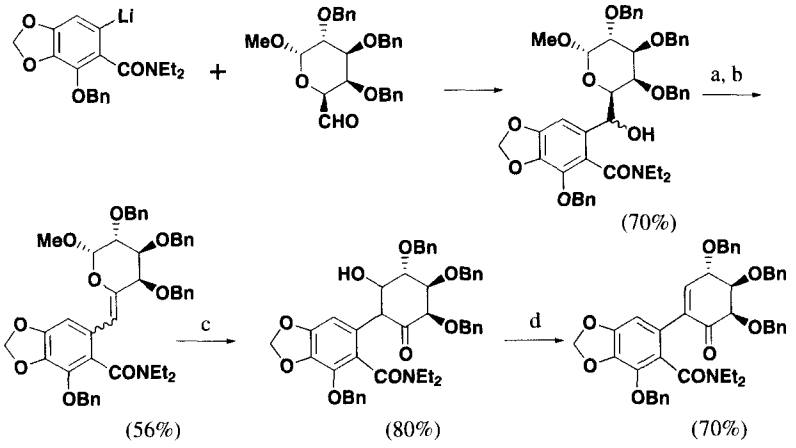


a) Bu^{s}Li, TMEDA; b) $CuCN(LiCl)_2$; c) *e)*-1-bromo-5-methyl-2-hexene; d) Sharpless AD; e) aq NaOH and then HCl

Scheme 1

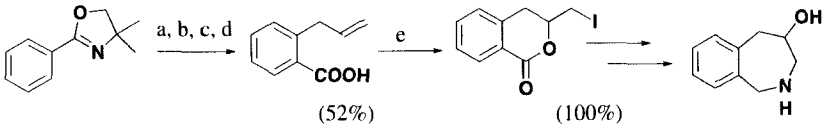
potential use of lithiated benzamides to prepare enantiomerically pure isocoumarins might be their reaction with enantiomerically pure hydroxyaldehydes (sugar derivatives), as suggested by the production of a number of compounds in a model approach to pancratistatin (*Scheme 2*).[12]

The (4,4-dimethyl)oxazolin-2-yl group, which is formed by condensation of carboxylic acids with 2-amino-2-methylpropanol, can promote *ortho*-lithiation employing butyllithium; the allylation of the lithiated intermediate is also in this case better accomplished by prior transmetallation with Cu(I) species; the advantage with respect to benzamides is that allylated products can be hydrolyzed under conditions (methylation at nitrogen followed by treatment with alkali) in which the corresponding allylbenzoic acids can be isolated and subjected to cyclization under more controlled conditions: cyclofunctionalization with iodine can lead to a 3,4-dihydroisocoumarins with 3-iodomethyl substituent capable of further elaboration (*Scheme 3*).[13] Another advantage of lithiated



a) PPh_3Br_2; b) pyridine, Δ; c) $HgCl_2$; d) Ac_2O

Scheme 2

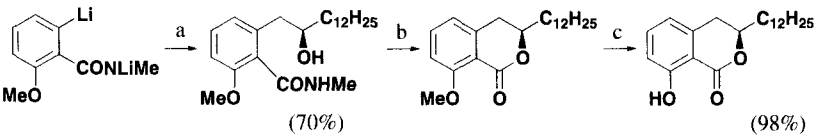


a) Bu^nLi, then CuBr; b) Allyl bromide; c) MeI; d) aq. NaOH then aq. HCl; e) J_2, $NaHCO_3$

Scheme 3

aryloxazolins is their ability to add to epoxides, thus giving in principle the possibility to control the absolute stereochemistry of the final 3,4-dihydroisocoumarins; this possibility has however never been exploited for the synthesis of natural isocoumarins having an alkoxy function at position 8; these syntheses would require 2-(2-alkoxyaryl)oxazolines as starting materials, which tend to undergo nucleophilic aromatic substitution of the alkoxy group when exposed to organolithim reagents.[14]

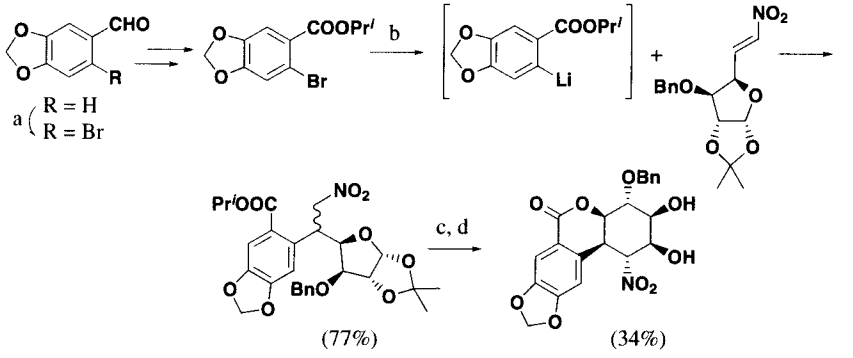
Enantiomerically pure natural 3,4-dihydroisocoumarins have been obtained from lithiated secondary benzamides and homochiral epoxides. Coupling between lithiated secondary benzamides and epoxides belongs to the beginning of the anionic chemistry of aromatic compounds; unfortunately, yields are generally modest and N-alkylation can complicate the reaction.[15] Good yields have occasionally been reported though, as in the synthesis of the allergenic principle of *Gingko biloba* (*Scheme 4*)[16] and of a variety of mellein derivatives.[17]



a) (R)-1,2-epoxytetradecane; b) OH^-, then neutralization; c) BBr_3

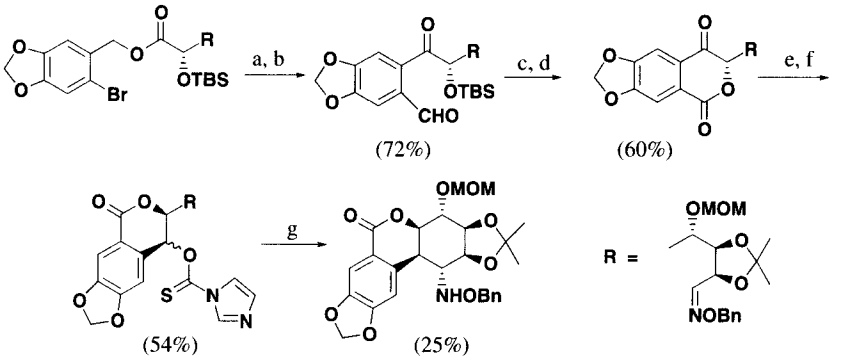
Scheme 4

If the above nitrogen containing benzoic acid derivatives can be metallated directly, the metallation of the position *ortho* to any one-carbon substituent (to mediate the introduction of the β-functionalized alkyl substituent and the subsequent heterocycle formation) can be most generally accomplished by halogen-metal exchange; although this approach has some disadvantages, in that the additional step of ring halogenation is required, it can be convenient owing to the exceedingly high efficiency of the halogen-metal exchange, and even complementary in scope to the direct ring lithiation when the halogen can be placed in a specific position efficiently and regioselectively. These concepts are illustrated in the synthesis of an advanced intermediate in the conversion of glucose to (+)-lycoricidin (*Scheme 5*)[18] and in the synthesis of a number of isocoumarins *en route* to 7-deoxypancratistatin (*Scheme 6*).[19]



a) Br_2; b) Bu^{n}Li -110°, then **1**; c) 50% AcOH; d) Na_2CO_3

Scheme 5

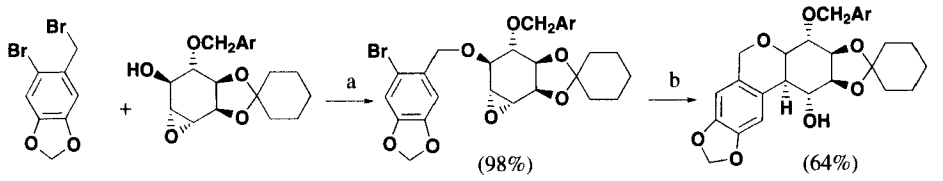


a) Bu^{n}Li; b) tetrapropylammonium perrhutenate and NMO; c) HF-Py; d) Dess-Martin oxidation; e) $NaBH_4$; f) thiocarbonyl diimidazole; g) Bu_3SnH, AIBN

Scheme 6

A possibly interesting route to chiral 3,4-isocoumarins is the intramolecular trapping by an epoxide of a lithiated benzene resulting from halogen-metal exchange, as illustrated in (*Scheme 7*);[20]

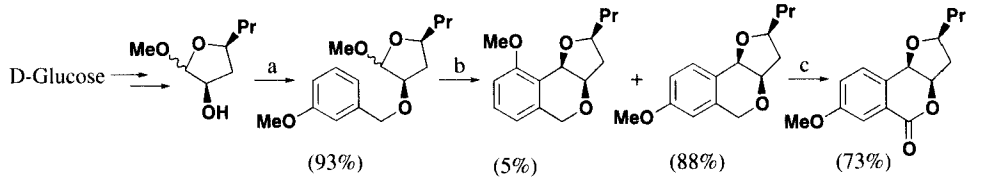
the oxidation of the isochromane, actually produced in this reaction, to an isocoumarin could in fact be accomplished using a variety of reagents (see ref. 32 and 39).



a) NaH, DMF; b) Bu^{n}Li

Scheme 7

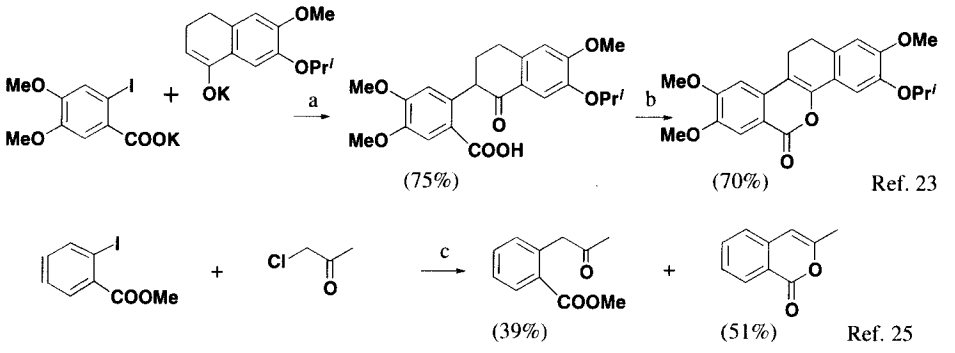
The intramolecular electrophilic substitution of benzoylated or benzylated α-hydroxy carbonyl compounds is another traditional method to elaborate the heterocyclic portion of either isocoumarins and 3,4-dihydroisocoumarins, which have been recently adopted for the synthesis of monocerine analogues (*Scheme 8*)[21] and indanosocoumarins.[22] Yields of the cyclization step appear to be critically dependent upon the substituents present on the aromatic ring.



a) NaH and 3-methoxybenzyl chloride; b) $SnCl_4$; c) CrO_3, Py

Scheme 8

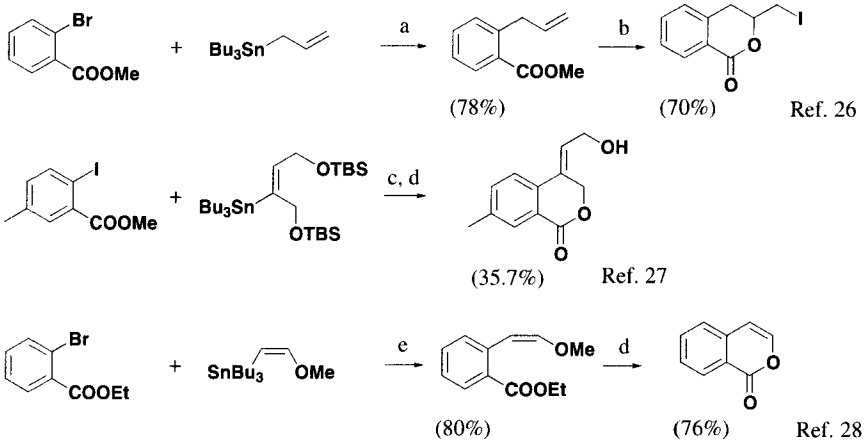
ortho-Halogenated benzoic acid derivatives can participate with functionalized organometallic reagents or with unsaturated compounds under transition metal catalysis in a variety of carbon-carbon forming reactions leading to isocoumarins or dihydroisocoumarins in a more or less direct way, depending on the ease and number of steps required for the conversion of the new carbon substituent of the benzoic acid to a β-oxoalkyl or β-hydroxyalkyl group. The photochemical coupling of *ortho*-iodobenzoic acids with alkali metal enolates ($S_{NR}1$ reaction) is a long known and quite direct method for the preparation of isocoumarins, which has most recently been applied to the preparation of an intermediate *en route* to benzophenantridine alkaloids (*Scheme 9*).[23] Related to the above approach is the coupling of *ortho*-bromobenzoic acid with metallated 1,3-dicarbonyl compounds under Cu(I) catalysis (Hurtley reaction), a useful tool to prepare 4-acylated isocoumarins, which has been subjected to a mechanistic investigation.[24] In this class of transformations we can also include the nickel-catalyzed electrochemical cross-coupling between aryl halides and activated alkyl halides (*Scheme 9*);[25] it should be noted, however, that in this process the aromatic halide is actually involved as the donor rather than the acceptor.



a) hv, then H^+; b) TsOH, benzene; c) Ni cathode, $NiBr_2$bipy

Scheme 9

The Pd(0) catalyzed cross coupling of alkyl *ortho*-iodo or *ortho*-bromobenzoate with unsaturated tin derivatives is an increasingly important reaction to synthesize isocoumarins and 3,4-dihydroisocoumarins, and a few examples are given in *Scheme 10*.[26-28] It is worth remembering here that *ortho*-allylbenzoic acids can be converted to isocoumarins by Pd(II) mediated intramolecular addition of the carboxyl group to the double bond.[29]

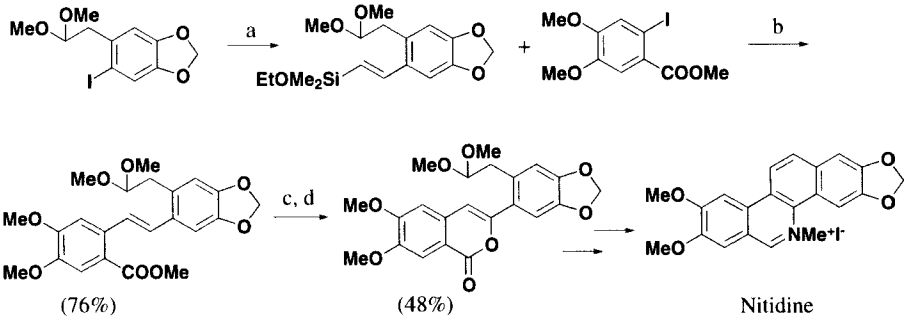


a) $Pd(PPh_3)_4$; b) I_2; c) $Pd(PPh_3)_2Cl_2$, $ZnCl_2$, LiCl; d) HCl; e) $Pd(PPh_3)_2Cl_2$

Scheme 10

2-Halobenzoic acid derivatives are also general precursors to 2-(1-alkenyl)benzoic acids *via* Heck type reactions with monosubstituted olefins;[30,31] the conversion of the resulting open chain unsaturated intermediates to the final heterocycles can be accomplished by Pd catalyzed intramolecular addition of the carboxy group to the double bond or by other types of cyclofunctionalization (for alternative modes of obtainment and cyclization of alkenylbenzoic acids, see section 2). The

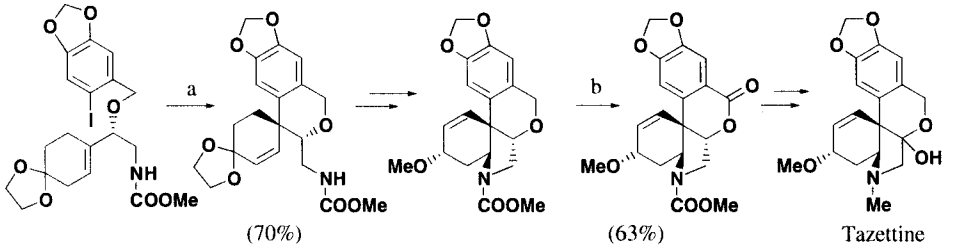
competing cyclization mode to a five memered lactone in the Pd catalyzed annulation step is not a serious side reaction except when the substituent of the olefin is an aryl group bearing an electron-withdrawing *para* substituent. An interesting example of the application of Pd catalysis to the different steps of an isocoumarin synthesis is illustrated in the preparation of the isocoumarin precursor of nitidin (*Scheme 11*).[30a]



a) (ethoxydimethylsilyl)ethylene, $PdCl_2(PPh_3)_2$, Et_3N; b) $[(allyl)PdCl]_2$, $(EtO)_3P$, Bu_4NF; c) hydrolysis; d) $PdCl_2(CH_3CN)_2$

Scheme 11

An efficient construction of complex 3,4-dihydroisocoumarins can be accomplished using the Heck reaction if the aromatic component (an *ortho*-iodobenzylalcohol) and the olefin (such as an allyl alcohol) are tethered to give an ether, as demostrated in the synthesis of an intermediate in the total synthesis of tazettine (*Scheme 12*).[32]



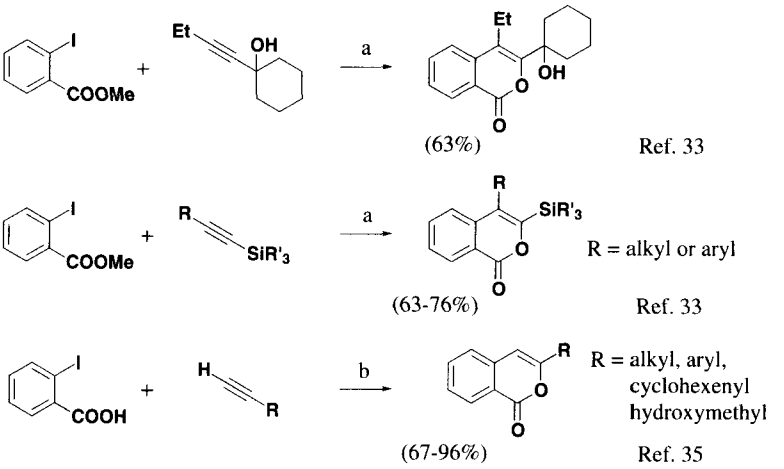
a) $Pd(OAc)_2$, $P(Ph)_3$, Ag_2CO_3; b) CrO_3, 3,5-dimethylpyrazole

Scheme 12

Methyl 2-iodobenzoate gives directly 3,4-substituted isocoumarins by reaction with internal alkynes in the presence of a Pd(0) catalyst; a high degree of regioselectivity is observed with unsymmetrical alkynes, the most hindered group occupying the position 3 in the final isocoumarin (*Scheme 13*).[33]

Also, *ortho*-Halobenzoic acid derivatives can be precursors to isocoumarins by the intermediacy of ethynylbenzoic acids, which are obtained quite efficiently and generally by cross coupling

either with copper acetylides (Castro reaction), or with terminal alkynes in the presence of catalytic amounts of Cu(I) and Pd(0), or in the presence of catalytic CuI and the appropriate phosphine as the ligand.[34] Alkynylbenzoic acids (which can be either preformed by hydrolysis from their esters if the carboxy group is protected as an ester in the coupling step, or generated *in situ* if the halo acid is the substrate of the coupling) can in principle cyclize by intamolecular addition of the carboxy group to the triple bond according to two distinct modes, leading either to a five-membered heterocycle (alkylidene phthalides) or a six-membered heterocycle (isocoumarins). The results depend on the substrate and the reaction conditions. The reaction can be made quite selective in favor of the isocoumarin by using a palladium complex and $ZnCl_2$ as catalysts of the cyclization step (*Scheme 13*).[35]



a) $Pd(AcO)_2$, LiCl, PPh_3; b) $Pd(PPh_3)_4$, $ZnCl_2$, Et_3N

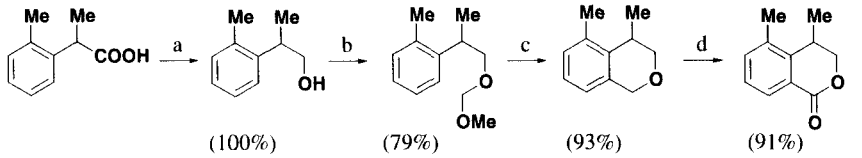
Scheme 13

3-Aryl-4-haloisocoumarins are formed by halolactonization of 2-arylethynylbenzoic acids with N-halosuccinimides.[36] 2-(Phenylethynyl)benzonitrile is converted to 3-phenylisocoumarin by $Ru_3(CO)_{12}$ catalyzed reaction with formic acid, where the latter reagent is the water source for hydration of the triple bond and the nitrile hydrolysis.[37] Besides ionic and transition metal catalyzed reactions, the Claisen rearrangement of allyl ethers of *meta*-hydroxybenzoic acids can be adopted to introduce an allyl group *ortho* to a carboxyl group; such an approach, first reported and developed as a practical tool to obtain isocoumarins in the early eighties, has found some more recent application.[38]

2. Syntheses from Aromatic Compounds Featuring Carbons 3 and 4

Another traditional method to build the carbon framework of isocoumarins is the introduction of the C(1) into a β-arylethanol via electrophilic oxyalkylation or formylation. If generated from formaldehyde or some of its derivatives, the carbon electrophile can be intercepted by the free OH group of the alkyl chain so that its attack on the ring is directed selectively at the *ortho* position; the isochromane resulting from the reaction can be selectively oxidized to a dihydroisocoumarin by a

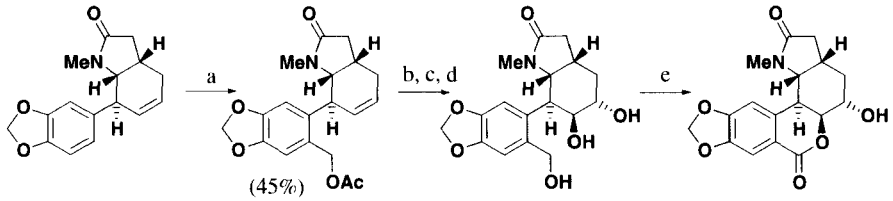
variety of oxidizing agents. A number of isocoumarins including natural compounds have been obtained efficiently by this route in the recent years.[39, 40, 41] Conditions for this two step sequence have been optimized in connection with the synthesis of an isocoumarin intermediate to epianastrephin (*Scheme 14*).[42]



a) $LiAlH_4$; b) $MeOCH_2Cl$, $EtPr^i_2N$; c) $TiCl_4$; d) $KMnO_4$ on alumina.

Scheme 14

When other substituents on the benzene ring are properly located, oxyalkylation can occur regioselectively *ortho* to the alkyl chain even in the absence of the hydroxy group, as demonstrated in the synthesis of racemic hippeastrine (*Scheme 15*)[43] and kigelin.[44] Formylation, which requires the protection of the hydroxy group as an acetyl derivative, can occur at the desired position (*ortho* to the alkyl group) only if other substituents are properly located, as in the case of 3,5-dimethoxyphenyl

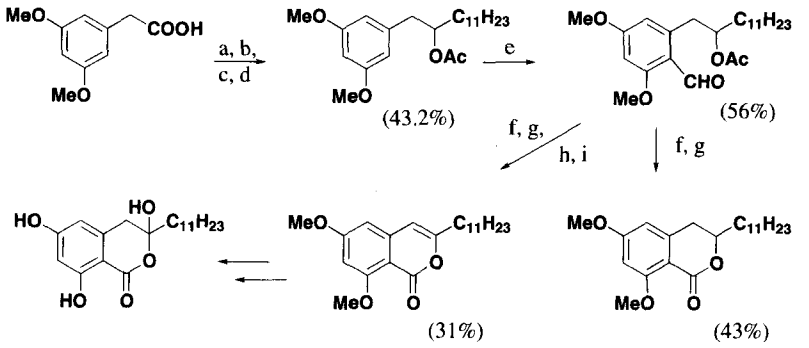


a) CH_3OCH_2Cl, $ZnCl_2$, AcOH; b) MCPBA; c) Ac_2O, AcOH; d) NaOH; e) MnO_2

Scheme 15

alcohols; this reaction has been extensively used in the synthesis of natural 6-methoxy-8-hydroxyisocoumarins (*Scheme 16*).[45] However, when the arylethanol is not symmetrically substituted and the two *ortho* positions are available, mixtures of regioisomers are to be expected in the reaction with carbon electrophiles.[46]

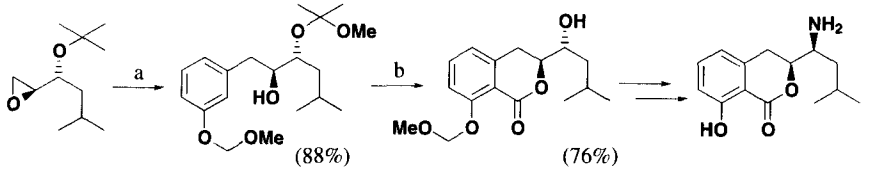
The regioselective introduction of C-1 to build natural isocoumarins and 3,4-dihydroisocoumarins bearing a single oxy-substituent at position 8 is only possible by using the anionic chemistry of benzene. It has been shown that alkyl groups bearing one or two coordinating atoms at the β position (*i.e.*, a hydroxy group, an acetal, an aminal, or an O,N-acetal), which are generally considered poor directors of *ortho* lithiation because of the competing attack of the metallating agent on the benzylic protons, can effectively cooperate with an alkoxy group present in the *meta* position of the benzene ring to promote ring lithiation at the common *ortho* position, thus permitting the regioselective introduction of carbon electrophiles.[47a] Appropriate combinations of groups leading to



a) $SOCl_2$; b) $C_{11}H_{23}MgBr$, $FeCl_3$; c) $NaBH_4$; d) Ac_2O; e) DMF, $POCl_3$; f) $KMnO_4$; g) NaOH, then HCl; h) CrO_3; i) Ac_2O

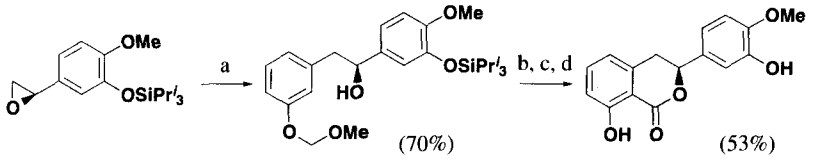
Scheme 16

satisfactory yields in ring metallation have been discussed and applied to the synthesis of racemic hydrangenol,[47b] kigelin,[47c] mellein,[47c] and other 8-oxyisocoumarins.[47d] However, the most generally useful circumstances for ring metallation occur when the ring position is adjacent to a methoxymethyloxy group (CH_3OCH_2O-) *and* a β-hydroxyalkyl or a β-dialkoxyalkyl group; the methoxymethyloxy group, besides behaving as a strong director of the lithiation,[10] permits the use of mild conditions for unmasking the 8-hydroxy function of the final product, which is particularly important to avoid racemization when chiral 3,4-dihydro-8-hydroxyisocoumarins are desired. Based on this concept, enantiomerically pure 3,4-dihydroisocoumarins such as mellein,[47e] the isocoumarin portion of AI77s (*Scheme 17*),[47f] phillodulcin (*Scheme 18*),[47g] as well as oospolactone[47h] have been obtained. If a methoxy group (rather than a methoxymethyloxy group) and a β-hydroxyalkyl group are present on a



a) 3-methoxymethyloxyphenylmagnesium bromide; b) Bu^nLi, then CO_2; c) MeOCOCl, DMF, then HCl

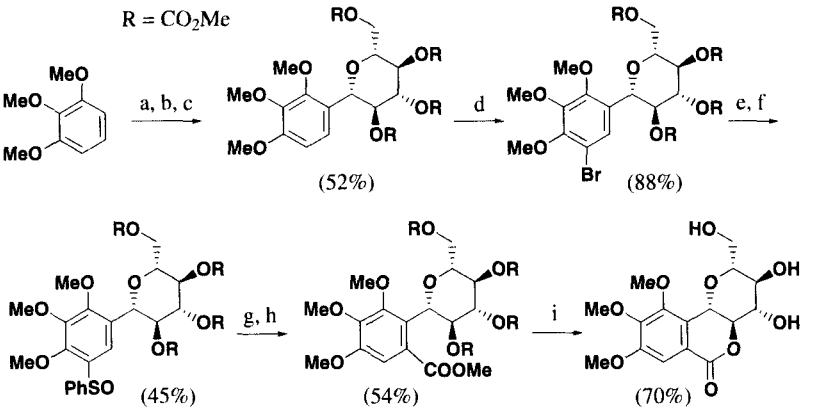
Scheme 17



a) 3-methoxymethyloxyphenylmagnesium bromide; b) Bu^nLi, then CO_2; c) AcO_2, then aq. HCl; d) Bu_4NF

Scheme 18

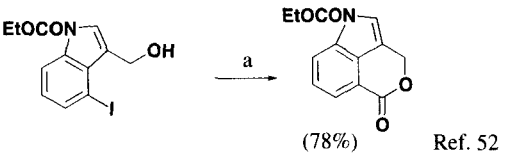
benzene ring *meta* to each other, the metallation of the common *ortho* position is inefficient and not regioselective.[48] Another interesting example of elaboration of a chiral 3,4-dihydroisocoumarin using aryl carbanion chemistry is the synthesis of a bergenin derivative (*Scheme 19*).[49]



a) tetrabenzylglucosyl trifluoroacetate, BF_3•Et_2O; b) H_2, Pd; c) ClCOOMe; d) Br_2; e) Bu^{n}Li, then $(PhS)_2$; f) MCPBA. g) LDA, then $ClCO_2Me$; h) Ni-Raney; i) NaOMe

Scheme 19

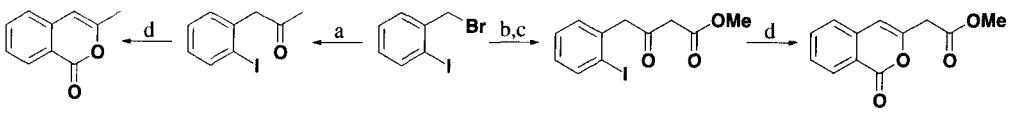
The introduction of a C1 fragment *ortho* to a β-functionalized alkyl group can be accomplished by a number of reactions involving palladium catalyzed carbonylation. Thallium trifluoroacetate can metallate an aromatic ring *ortho* to a β-hydroxyalkyl group (which is likely to direct the attack by coordination); the arylthallium can transmetallate with palladium and the aryl palladium can add carbon dioxide to give dihydroisocoumarins after intramolecular nucleophilic displacement of palladium from the intermediate acylpalladium.[50] Analogous results are obtained when the arylpalladium species is obtained by oxidative addition (*Scheme 20*).[51, 52] The acylpalladium prepared from the



a) $PdCl_2(PPh_3)_2$,CO (600 psi)

Scheme 20

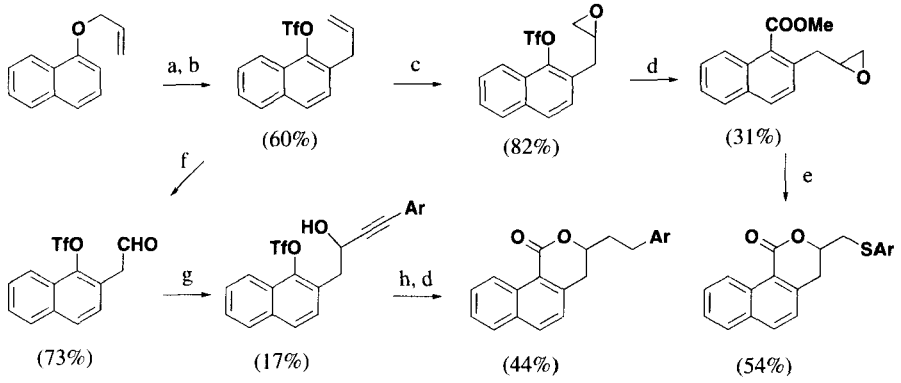
corresponding haloarene can also undergo intramolecular substitution by an enolate, thus giving isocoumarins rather than dihydroisocoumarins (*Scheme 21*).[53] The disadvantages of the above palladium catalyzed reactions are, in one case, the use of the highly toxic thallium metal and, in the other case, the need for an *ortho*-halogen substituted alkyl benzenes. One interesting development of the synthesis of isocoumarins *via* acylpalladiation (*Scheme 22*) starts with an aryl allyl ether which under



a) Lithiated 2-(1-ethoxyethoxy)propionitrile, then hydrolysis; b) NaCN; c) $BrCH_2COOMe$, Zn; d) $PdCl_2(PPh_3)_2$,CO, Et_3N

Scheme 21

goes Claisen rearrangement to an *ortho* allyl phenol selectively (for the regiochemistry of Claisen rearrangement in non symmetrical substrates, see Ref. 38); the phenol is converted into the corresponding triflate and the allyl group is elaborated to give a β-hydroxyalkyl group containing the substituent at C(3) of the final compound; such elaboration can be done either before or after the triflate is converted to a carboxylic derivative *via* the acylpalladium intermediate.[26]



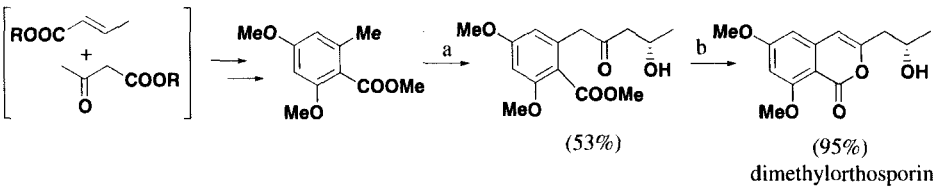
a) 193°; b) Tf_2O; c) MCPBA; d) $Pd(OAc)_2$, dppp, CO, MeOH; e) ArSH; f) O_3, then Me_2S; g) ArC≡CLi; h) H_2/Pd

Scheme 22

3. Syntheses from Aromatic Compounds Featuring Carbons 1 and 4

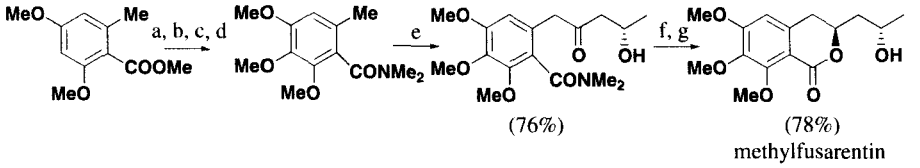
Alkylbenzenes can be metallated with a suitable lithium base either at the ring or at the benzylic (lateral) position depending on the presence of other substituents and on the reaction conditions. Lateral lithiation is particularly easy to accomplish when a carboxylic acid derivative is present *ortho* to the alkyl group, owing to the possibility of an internal solvation of the metal and also to delocalization of the negative charge through a mesomeric effect. Laterally lithiated *ortho*-alkylbenzoic acid derivatives, which can be considered phenylogous of carboxylic acid derivatives enolates, undergo aldol or Claisen type reactions affording the open chain aromatic hydroxy and keto esters, from which the 3,4-dihydroisocoumarins and isocoumarins can be obtained by lactonization. This approach has enjoyed extreme popularity and has been thorougly reviewed recently in connection with the use of lateral lithiation.[54] In summary, an ethyl ester, a nitrile, a carboxamide (either tertiary or a

lithyated secondary amide), and a lithium carboxylate are all suitable for assisting lateral lithiation, which can be generally obtained using hindered amide bases or (limited to less electrophilic amides) with alkyllithiums; sufficiently low temperatures are required in this step in order to avoid self condensation. This is a particularly important side reaction with toluate esters, which are synthetically useful only when a methoxy group is present *ortho* to the carboxyl group to lower its electrophilicity. Addition to aldehydes and ketones can occur with fair to good yields but with scarce diastereoselectivity when chiral hydroxy or amino aldehydes are the electrophiles. Acylation with esters can be accomplished in good yields, provided the amount of base and the reaction conditions allow for the fact that the acylated product is more acidic than the starting toluic acid derivatives; the best general conditions for acylation are perhaps the use of a secondary amide of a toluic acid, the use of alkyllithiums for the metallation and the use of N-methoxy-N-methylcarboxamides (Weinreb amides) as the acylating agents. The examples given here of reactions between lithiated *ortho*-toluic acids derivatives and carbonyl compounds tend to illustrate also the different methods to obtain *ortho*-toluic acids. An example of modern efficiency in isocoumarin construction *via* laterally lithiated alkylbenzoic acids is the synthesis of dimethylorthosporin (*Scheme 23*) [55] and fusarentin (*Scheme 24*);[56a] it is interesting to compare this synthesis of fusarentin with a previous one[56b] in which the



a) LDA, then ethyl (S)-3-hydroxybutyrate; then HCl; b) TsOH, refluxing benzene

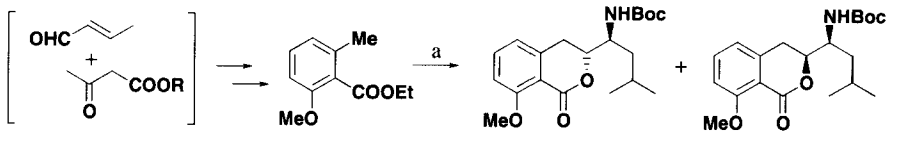
Scheme 23



a) formylation; b) Dakin oxidation; c) methylation; d) Me_3Al, $Me_2HN.HCl$;
e) Bu^sLi, then (S)-3-(*ter*-butyldimethylsilyloxy)-N-Methoxy-N-methylbutanamide;
f) 1% HCl EtOH; g) $Me_4N(OAc)_3BH$; h) 3M HCl; i) BCl_3

Scheme 24

control of the stereochemistry at C3 was entrusted to the diastereoselectivity of the reaction of the lithiated toluic ester with the homochiral β-hydroxyaldehyde. The synthesis of the isocoumarin portion of AI77B (*Scheme 25*) further illustrates problems in the diastereoselectivity of toluate addition to chiral aldehydes.[57]

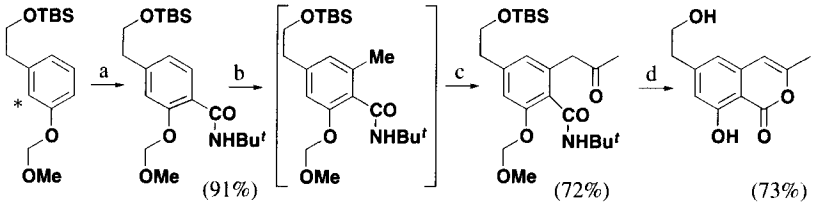


1 : 2.2 (33%)

a) LDA, then N-Boc-leucinal; b) NaOH, then MsCl

Scheme 25

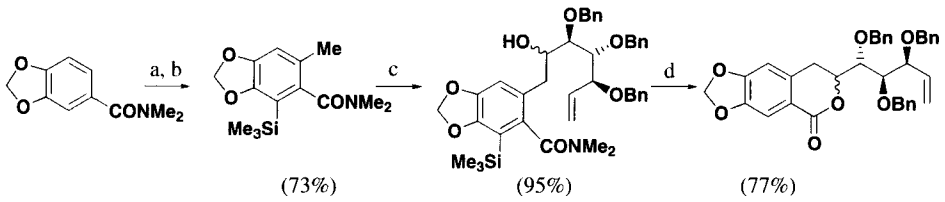
The starting toluic acids in the syntheses outlined in *Schemes 23-25* (derivatives of orsellinic acid and 6-methylsalicilic acid) are available by tandem Michael and intramolecular Claisen (or aldol) condensation of methyl acetoacetate with alkyl crotonate (or crotonaldehyde) followed by aromatization of the six-membered carbocyclic intermediates.[58] The synthesis of the isocoumarin intermediates to cervinomycins (*Scheme 26*) shows, instead, how the anionic chemistry of benzene can be exploited



a) Bu^{s}Li, then Bu^{t}NCO; b) Bu^{t}Li, then MeI; c) Bu^{n}Li, then AcOEt; d) N_2O_4, then HCl, MeOH

Scheme 26

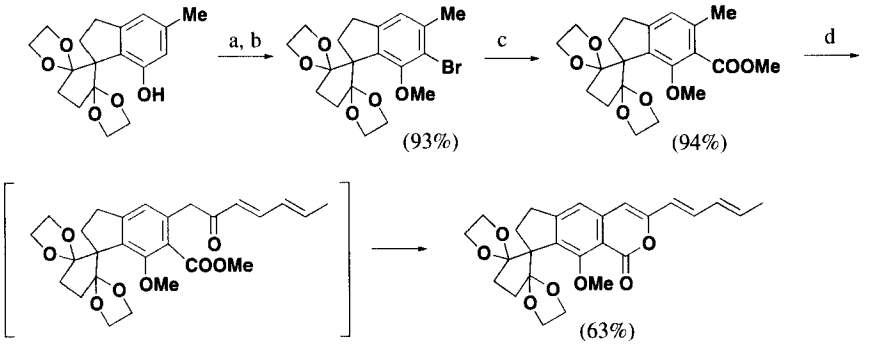
to build an *ortho*-methylbenzamide;[59] it is worth noting that the starting homobenzyl alcohol, under proper conditions, can be lithiated at the alternative position (marked with an asterisk) thus leading to a 8-hydroxyisocoumarin after carbonation and lactonization (see also section 2). The synthesis of the isocoumarin intermediate *en route* to tetrabenzylcorricidin (*Scheme 27*) shows the need for protection of the ring position when ring lithiation can compete with lateral lithiation owing to the presence of other directors of *ortho* metallation such as an alkoxy group.[60]



a) Bu^{s}Li, TMEDA, then Me_3SiCl; b) Bu^{s}Li, TMEDA, then MeI;
c) Bu^{s}Li, then 2,3,4-tribenzyloxy-5-hexenal; d) Bu_4NF; e) H^+

Scheme 27

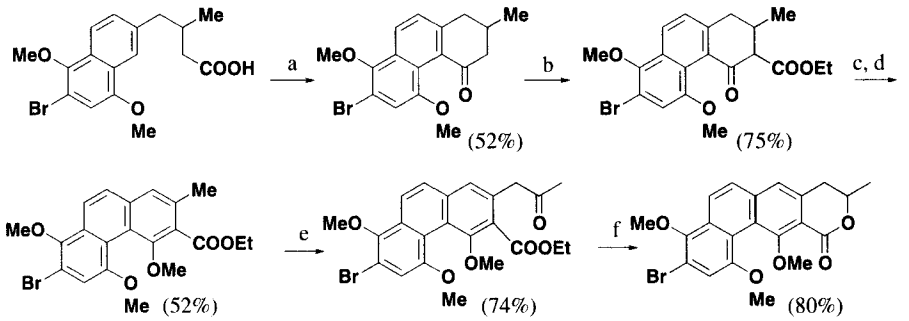
In the preparation of an *ortho*-toluic acid, the carbonation of an *ortho*-lithiated toluene derivative is an alternative to the more common methylation of lithiated benzoic acids derivatives if the corresponding *ortho*-bromotoluene is readily avilable, as observed in a synthesis of fredricamycin A (*Scheme 28*);[61] this synthesis also illustrates the need for a transmetallation with copper (I) of the laterally lithiated alkylbezenes in order to accomplish a clean acylation with 2,4-hexanedioyl chloride.



a) NBS; b) KH, MeI; c) Bu^{n}Li, then ClCOOMe; d) LiTMP, then $CuCN(LiCl)_2$, then sorboyl chloride

Scheme 28

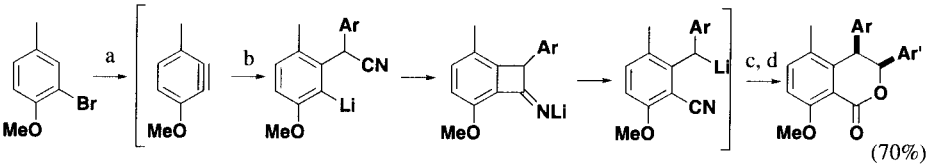
A methyl and a carboxy group can be placed *ortho* to each other on an aromatic ring if they are already present as vicinal substituents on a saturated ring precursor, as demonstrated in the synthesis of the isocoumarin intermediate in an approach to cervinomycins (*Scheme 29*).[62] Other recent studies on isocoumarin synthesis *via* lithiated toluamides[63] and dilithiated toluic acids[64] have



a) PPA; b) NaH, $(EtO)_2CO$, c) $PyHBr_3$, then DBU; d) Me_2SO_4, K_2CO_3;
e) LDA, then N-methoxy-N-methylacetamide; f) $NaBH_4$, then HCl

Scheme 29

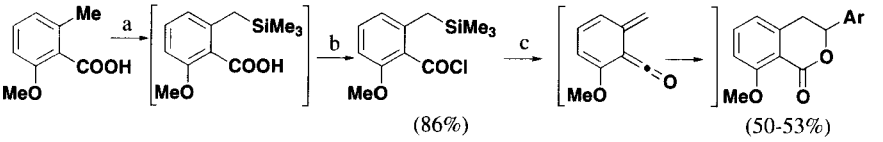
appeared. One interesting method to generate *ortho*-toluic acids (although apparently limited to α aryl-substituted ones) is the reaction of lithiated aryacetonitriles with benzynes in which the first addition product rearranges *via* a lithioiminobenzocyclobutene intermediate to a laterally litiated *ortho*-aralkylbenzonitrile; this, in turn, can add to aromatic aldehydes (*Scheme 30*).[65]



a) LDA; b) ArCHLiCN; c) Ar'CHO; d) H_2O

Scheme 30

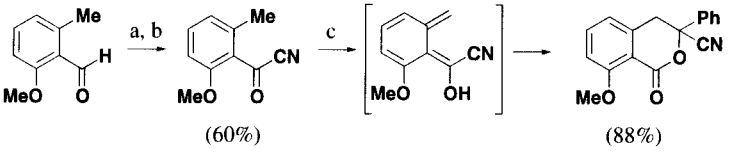
Closely related to lateral lithiation is the desilylation of 2-(trimethylsilylmethyl)benzamides which generates carbanions suitable for additions to aldehydes.[66] 2-(Trimethylsilylmethyl)-benzoyl chlorides also undergo desilylation and addition to aldehydes to give dihydroisocoumarins, through a concerted mechanism involving *ortho*-quinodimethanes rather than carbanions as reactive intermediates (*Scheme 31*).[67] To this class of reactive intermediates belongs the products of UV



a) Bu^{n}Li, then Me_3SiCl; b) $SOCl_2$; c) CsF, ArCHO

Scheme 31

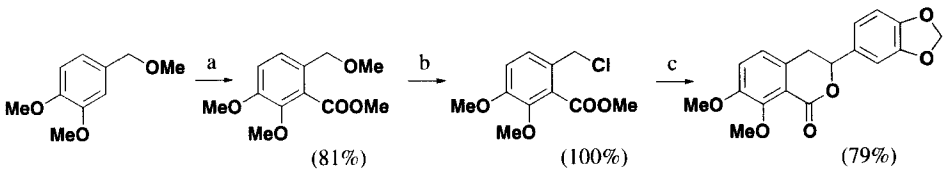
irradiation of *ortho*-toluyl cyanides which add to aliphatic and aromatic acyl cyanides to give 3-cyano-3,4-dihydroisocoumarins which are converted to isocoumarins by treatment with strong bases (*Scheme 32*).[68]



a) Me_3SiCN; b) PCC; c) hv, PhCOCN

Scheme 32

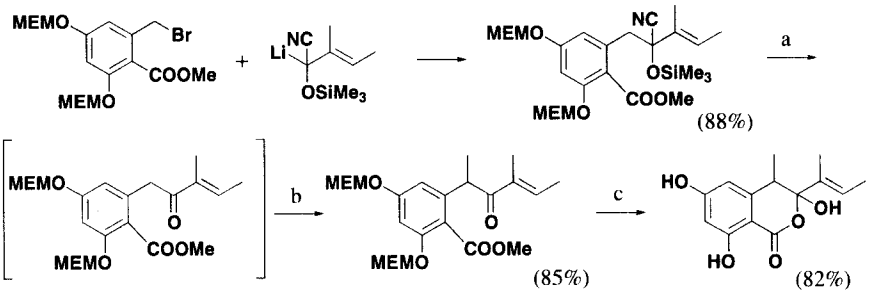
A toluate anion suitable for addition to an aldehyde can also be generated by zinc reduction of the corresponding α–halo derivative, in a process that resembles the Reformatsky reaction; this reaction has some advantages when the chloromethyl derivative is more readily available than the corresponding non halogenated one, as in the case of the isocoumarin intermediate to tetrahydropalmatin (*Scheme 33*).[69] More recently, dihydroisocoumarins have been obtained from bromomethylbenzonitrile *via* a benzyl telluride which undergoes lithium-tellurium exchange yielding ultimately a laterally lithiated toluonitrile suitable for reaction with carbon electrophiles.[70]



a) Bu^nLi, then ClCOOMe; b) AcCl, $ZnCl_2$; c) Zn (Rieke), piperonal

Scheme 33

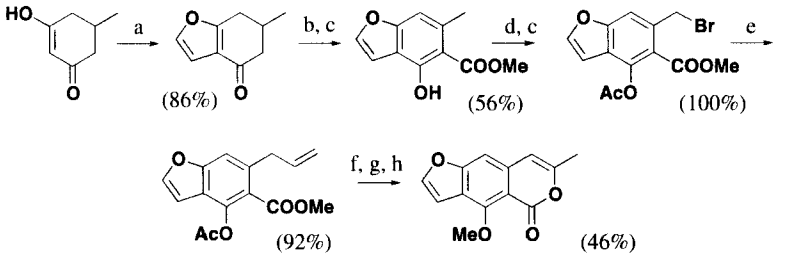
However, alkyl *ortho*-bromomethylbenzoates can participate in carbon-carbon bond formation as acceptors in reactions with acyl anion equivalents leading to benzyl ketones, which are direct precursors to isocoumarins and also suitable intermediates for the introduction of alkyl substituents at C-4 (*Scheme 34*).[71] Coriandrin has been synthesized *via* Pd-catalysed coupling of an *ortho*-



a) Bu_4NF; b) $Bu_4N^+OH^-$, MeI; c) NaOH, then HCl

Scheme 34

bromomethyl toluate and a vinylstannane to yield an allyl derivative which has been lactonized in a second palladium-mediated reaction (*Scheme 35*).[72]

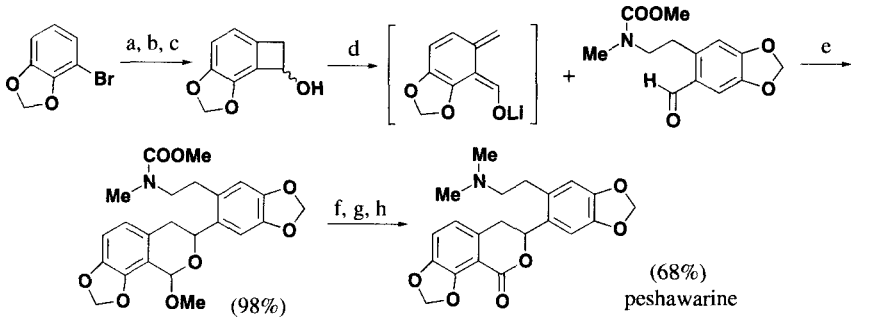


a) $ClCH_2CHO$; b) LDA, then methyl cyanoformate; c) N-bromosuccinimide; d) Ac_2O;
e) $Bu_3SnCH{=}CH_2$, $BnPdCl(PPh_3)_2$; f) LiOH; g) $PdCl_2$; h) DEAD, PPh_3, MeOH

Scheme 35

Parallel to the use of lithiated toluic acid derivatives is the use of *ortho*-tolualdehyde anions, which can be generated by ring opening of benzocyclobuteneoxides; these intermediates add effi-

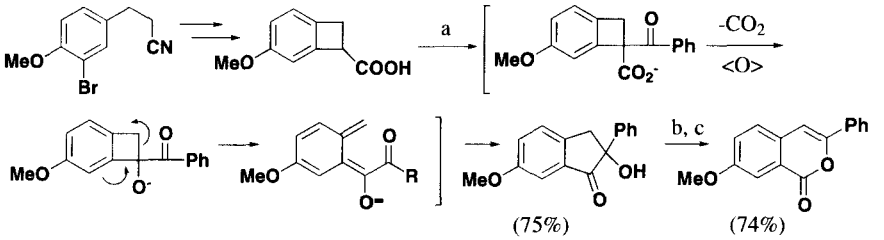
ciently to aromatic aldehydes giving benzopyranols which are easily oxidized to 3-substituted 3,4-dihydroisocoumarins. Such an approach is exemplified in the synthesis of peshawarine (*Scheme 36*).[73] The benzylic carbanion resulting from the opening of a lithiated benzocyclobutenols can be trapped



a) $NaNH_2$, $CH_2=C(OMe)_2$; b) aq HCl; c) $NaBH_4$; d) LiTMP; e) HCl, MeOH; f) $LiAlH_4$; g) HCl-dioxane; h) PCC

Scheme 36

intramolecularly by a carbonyl group, leading to hydroxyindanones, which can be converted to isocoumarins by periodate cleavage and lactonization (*Scheme 37*).[74] The use of dilithiated *ortho*-methylbenzylalcohols, generated by reductive cleavage of phthalans with lithium naphthalenide, have also been successfully used in the synthesis of benzopyrans and 3,4-dihydroisocoumarins.[75]

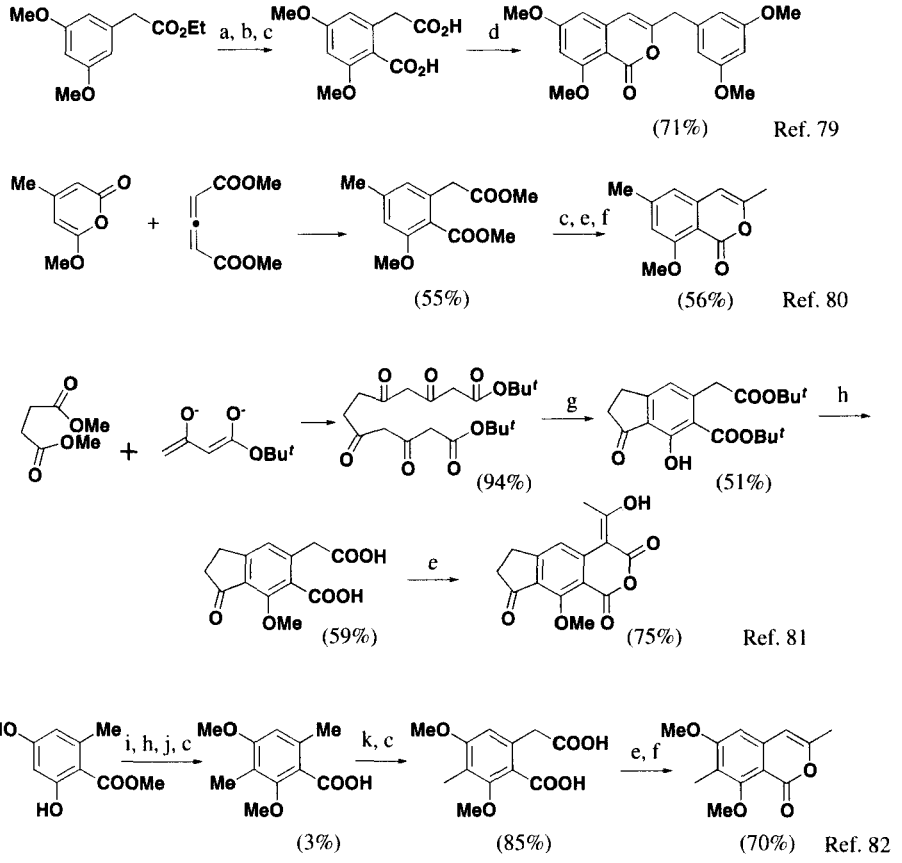


a) LDA, then PhCOOEt, then MoO_5•Py•HMPA; b) H_5IO_6, then $NaBH_4$, then acid

Scheme 37

The benzylic position *ortho* to a carboxy group is much more susceptible to attack by electrophilic reagents if a carboxy group is present. Homophthalic anhydrides and acids have been traditionally acylated by reaction with acid anhydrides and pyridine or, as demonstrated more recently, by simple exposure to acid chlorides, affording adducts which undergo easy decarboxylation and lactonization to a 3-substituted isocoumarins.[76] This approach, which has long been an important entry to isocoumarins, has the disadvantage that one carbon atom is lost (for an alternative use of homophthalic anhydrides in which all the carbon atoms are preserved, see section 4) and that an excess of acylating agent is required, which is inconvenient if it is difficult or expensive to obtain. However, this approach may still be attractive because the two steps have generally high overall yields and

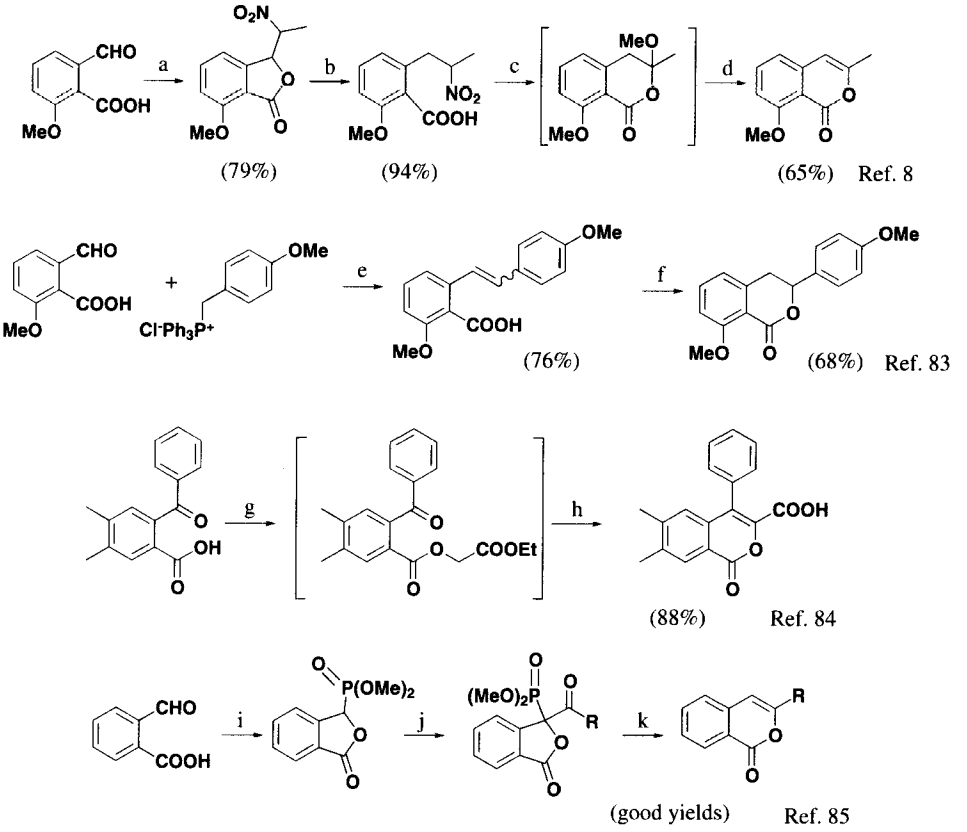
homophthalic acid derivatives are easily accessible materials, available through a number of methods and most directly obtained obtained by reaction of benzynes with the anions of 1,3-dicarbonyl compounds.[77, 78] Even laterally lithiated *ortho*-toluic acid derivatives (which can be acylated directly) have been occasionally acylated in two steps involving carbonation to a homophthalic acid followed by treatment of this intermediate with an excess of acylating agent. The examples given here of isocoumarin synthesis from homophthalic anhydrides also tend to outline the different methods of production of this type of starting material (*Scheme 38*).[79-82]



a) DMF, $POCl_3$; b) $KMnO_4$; c) NaOH, then HCl; d) 3,5-dimethoxyphenylacetyl chloride; e) Ac_2O, pyridine; f) Ac_2O, $HClO_4$; g) NaH; h) MeI, K_2CO_3, then CF_3COOH; i) Br_2; j) Bu^{n}Li, then MeI; k) LDA, then $CO(OMe)_2$

Scheme 38

Phthalaldehydic and *ortho*-benzoylated acids can also serve as precursors to isocoumarins participating in the final carbon-carbon bond forming reaction either as acceptor or umpoled donor reagents (*Scheme 39*).[8,83-85]



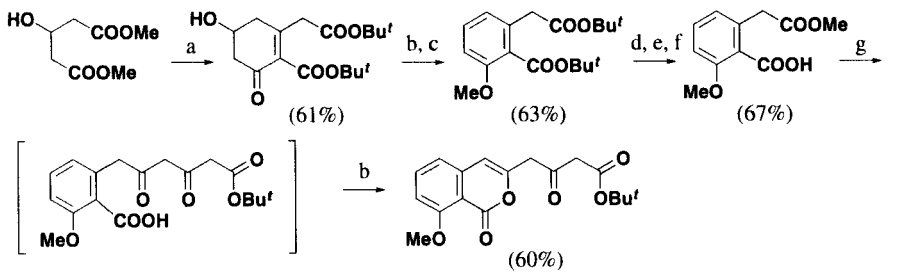
a) $MeCH_2NO_2$, Et_3N; b) $NaBH_4$; c) NaOH, then H_2SO_4, MeOH; d) Ac_2O, $HClO_4$; e) Bu^tOK; f) $AlCl_3$; g) K_2CO_3, $BrCH(COOEt)_2$; h) conc. HCl in AcOH; i) $HPO(OMe)_2$, MeONa, then $MeSO_3H$; j) NaH, then RCOCl; k) Zn, AcOH

Scheme 39

4. Syntheses from Aromatic Compounds Featuring Carbons 1, 3, and 4

Nucleophilic reagents can interact with homophthalic acid derivatives at the carboxy group bound to the methylene, giving homophthalic ketones, which are readily dehydrated to isocoumarins. 3-Arylisocoumarins are obtained classically through this approach by Friedel-Krafts acylation of aromatics with homophthalic anhydrides;[86] 3-ferrocenylisocoumarins have been obtained by reaction of homophthalic acids with ferrocene.[87] 3-Alkylisocoumarins are instead accesible by Claisen condensation of homophthalic esters with esters enolates, as reported in the synthesis of intermediates to urdamicinone,[88a] semivioxantin,[88b] and aklanoic acid (*Scheme 40*).[89]

A homophthalic anhydride can give an isocoumarin with a functionalized substituent at C(3) by reaction with a stabilized phosphorane.[90] Finally, 2-vinylbenzoic acid can be coupled with alkenyl halides or triflates in the presence of Pd(0) to yield predominantly 3-vinyl-3,4-dihydroisocoumarins.[91] A mechanistically related synthesis of isocoumarins from halobenzoic acids and vinyl triflates is described in section 1.



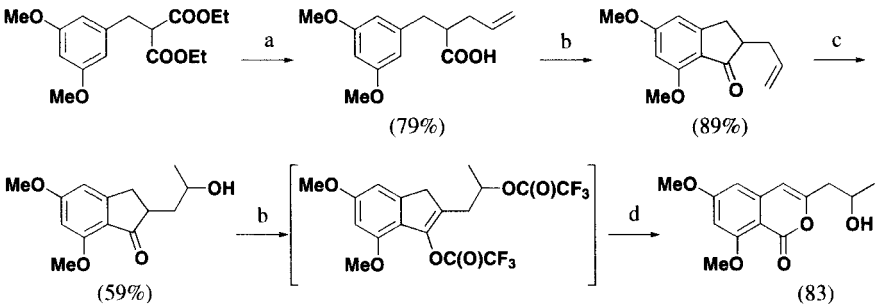
a) $LiCH_2COOBu^t$; b) Ac_2O, then DBU (to aromatize), then K_2CO_3, MeOH (to deacetylate);
c) MeI, K_2CO_3; d) CF_3COOH; e) p-TsOH/PhH/reflux; f) MeOH;
g) dilithium derivative of *t*-butyl acetoacetate

Scheme 40

5. Syntheses by Cleavage of a Carbocycle or a Heterocycle

The oxidative cleavage of 2-indanones has long been known as a valuable approach to isocoumarins, and its application to the synthesis of natural isocoumarins has been systematically investigated by Staunton and his coworkers.[92] Indanones can be made either by cyclization of β-arylpropionic acids or by electrophilic acylation of benzene derivatives, followed by intramolecular electrophilic alkylation employing α,β-unsaturated acid chlorides as ambident electrophiles; the two approaches may be complementary in the obtainment of regioisomerically substituted isosocoumarins.

The approach involving the cyclization of an arylpropionic acid has been more recently adopted for the synthesis of orthosporin (*Scheme 41*)[93] and improved in a synthesis of other phytotoxic fungal metabolites.[94] . The double electrophilic substitution has been adopted for the synthesis of poligonolide (*Scheme 42*).[95]

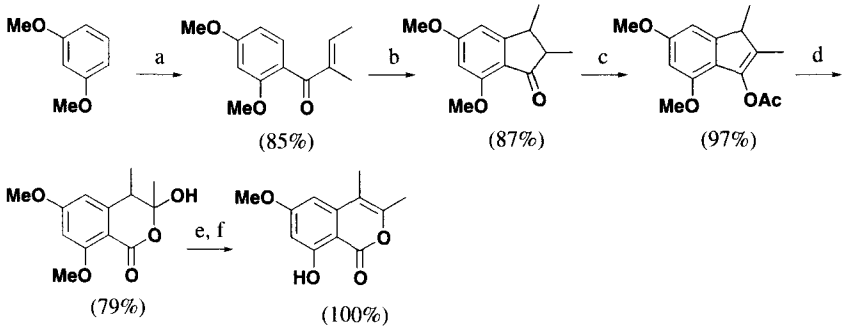


a) NaOEt, allyl bromide, then hydrolysis and decarboxylation; b) $(CF_3CO)_2O$;
c) $Hg(AcO)_2$, then $NaBH_4$; d) $(CF_3CO)_2O$; O_3, then Me_2S

Scheme 41

When trifluoroacetic anhydride is used as condensing agent, the indanone formed from an arene and unsaturated carboxylic acid can undergo autooxidation leading directly to an isocoumarin.[96] 3-Aryl indenones, (which are available by cyclization of hydroxyesters resulting from the Refor-

matsky reaction of bromoesters with benzophenones) are converted to 4-arylisocoumarins by electrochemical oxidation in methanol followed by treatment with acid.[97] Isocoumarins have also been obtained by cleavage of a naphthalene ring[98] or dioxodibenz[b,f]azocine ring[99]. An implementation of the synthesis of indanones has been recently published.[100]



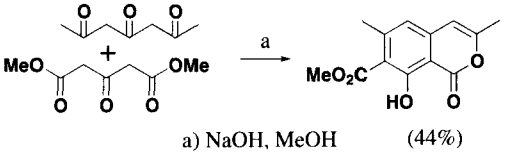
a) 2-methyl-2-butenoyl chloride, $SnCl_4$; b) PPA; c) propenyl acetate, *p*-TsOH; d) O_3, then Me_2S; e) Ac_2O; f) BCl_3

Scheme 42

II. SYNTHESIS FROM NON AROMATIC PRECURSORS.

1. Syntheses by Construction of the Aromatic Ring via Ionic Reactions.

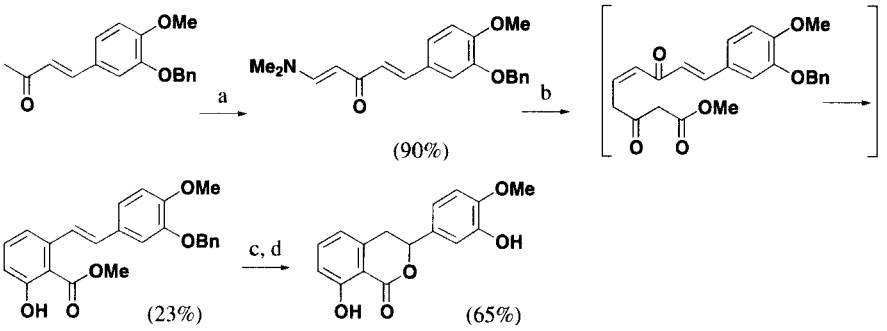
Isocoumarins can be approached by building the homocyclic portion in the last carbon-carbon bond forming step. In biomimetic type synthesis of isocoumarins, the homocyclic portion is obtained by aldol or Claisen condensation of polyketide components,[101] as exemplified by the recent synthesis of an intermediate to fredricamycin (*Scheme 43*),[102] in a synthesis of racemic



a) NaOH, MeOH (44%)

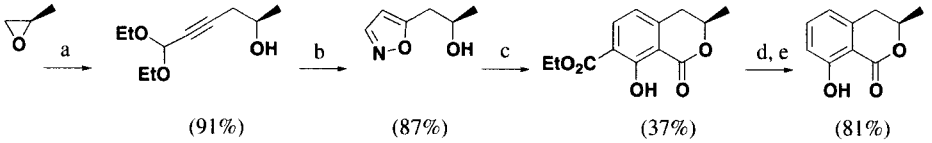
Scheme 43

phyllodulcin (*Scheme 44*),[103] in the enantioselective synthesis of mellein (*Scheme 45*),[104] semivioxantin,[52] and the isocoumarin intermediate to perylenequinone (*Scheme 46*);[105] this last synthesis, giving a benzocondensed 3,4-dihydroisocoumarin, is the evolution of an older approach to benzocondensed isocoumarins.[106]



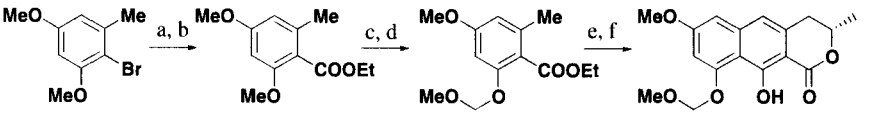
a) *bis*-dimethylaminomethoxymethane; b) dilithiated methyl acetoacetate; c) NaOH; d) conc. HCl

Scheme 44



a) lithiated 2,2-diethoxy-1-propyne; b) $HONH_2$•HCl; c) $Fe_2(CO)_9$, $CO(CH_2CO_2Me)_2$, KF, AcOH; d) NaOH, then HCl; e) 180°

Scheme 45

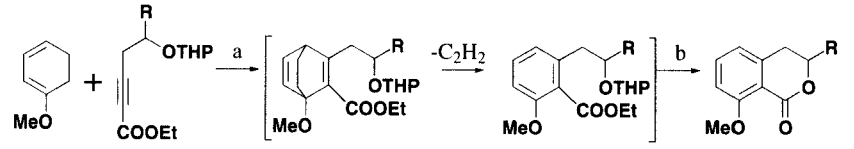


a) Bu^nLi, then CO_2; b) $(COCl)_2$, then EtOH; c) BBr_3; d) $MeOCH_2Cl$, NaH; e) Lithium diisopropylamide, then (*S*)-6-methyl-5,6-dihydropyran-2-one; f) DDQ

Scheme 46

2. Syntheses by Construction of the Aromatic Ring via Pericyclic Reactions

The homocyclic portion of isocoumarins can also be constructed by means of a variety of pericyclic reactions. Mellein,[107] methoxymellein,[107] and phyllodulcin[108] have been obtained by Diels-Alder reaction of 1-methoxy-1,3-cyclohexadiene with the appropriate 5-hydroxy-2-alkynoic acid derivatives (*Scheme 47*).

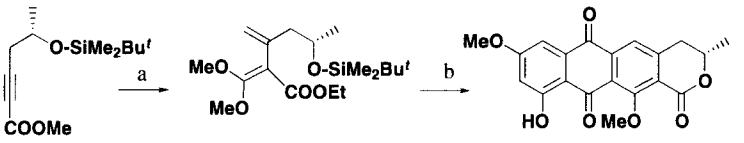


R = methyl or 3-benzyloxy-4-methoxyphenyl (48-52%)

a) 180°; b) NaOH, then HCl

Scheme 47

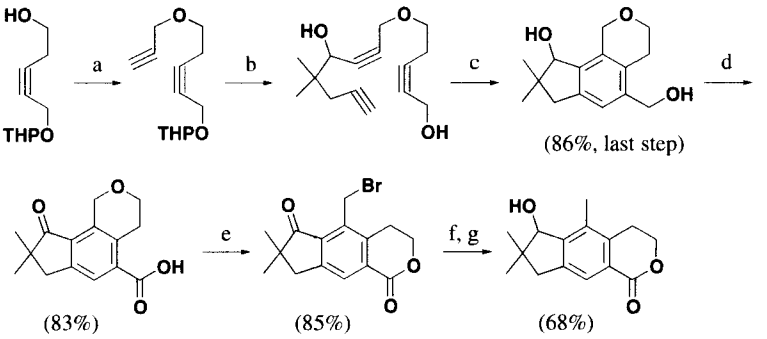
A homochiral 5-hydroxy-2-alkynoic acid derivative has been elaborated into a diene which was converted to dermolactone by regiospecific Diels-Alder reaction with the appropriate chloronaphthoquinone (*Scheme 48*).[109] Calomelanolactone has been obtained by rhodium catalyzed intramolecular



a) ketene dimethyl acetal, 165°; b) 2-chloro-8-hydroxy-6-methoxy-1,4-naphthoquinone, then dil. H_2SO_4

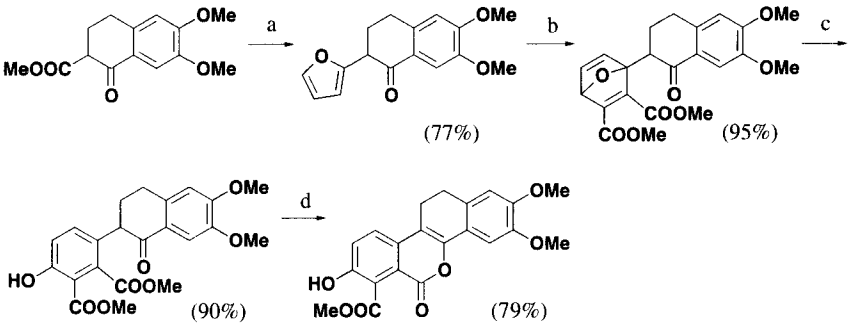
Scheme 48

trimerization of a triyne (*Scheme 49*).[110] A number of isocoumarins used to synthesise the benzo[c]phenantridone ring system have been obtained by cycloaddition of diethyl acethylenedicarboxylate to 2-(2-oxoalkyl)furans (*Scheme 50*).[111] The intramolecular Diels-Alder reaction of an



a) NaOH, propargyl bromide; b) Bu^{n}Li, then 2,2-dimethyl-4-pentynal, then *p*-TsOH in MeOH; c) $RhCl(PPh_3)_3$; d) CrO_3; e) BBr_3; f) Bu_3SnH; g) $NaBH_4$

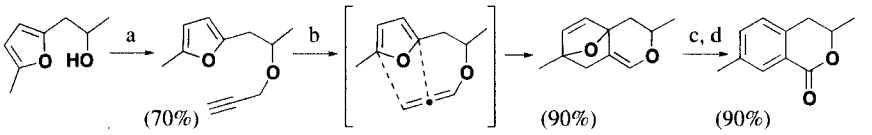
Scheme 49



a) 2,5-dimethoxy-2,5-dihydrofuran, $ZnCl_2$, then LiCl, DMF (decarbomethoxylation); b) DMAD; c) BF_3•Et_2O; d) MeONa, MeOH

Scheme 50

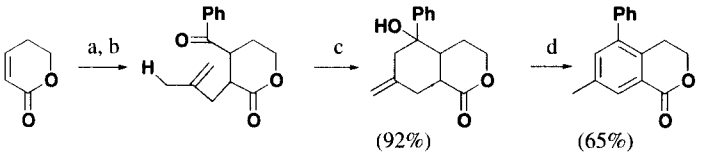
alkyne and a furan has been adopted to generate a polycyclic ethers from which isocoumarins were obtained by rearrangement to aromatic lactols followed by oxydation (*Scheme 51*).[112] Finally, an



a) Bu^{n}Li, propargyl bromide; b) Bu^{t}OK, BuOH; c) *p*-TsOH, H_2O; d) PCC

Scheme 51

isocoumarin has been obtained by aromatization of a bicyclic lactone resulting from an intramolecular carbonyl-ene reaction (*Scheme 52*).[113]



a) lithiated 2-dimethylamino-2-arylacetonitrile, then 2-methyl-allyl bromide;
b) $AgNO_3$; c) TMSTf; d) silica gel

Scheme 52

CONCLUSIONS

Isocoumarins encompass many interesting substances from the natural kingdom as well as useful synthetic intermediates in the synthesis of other classes of compounds. Owing to their borderline position between aromatic and aliphatic compounds, their chemistry is particularly rich and fascinating. The most recent accomplishments in the synthesis of isocoumarins, such as the regioselective synthesis of natural 8-hydroxyisocoumarins, have been possible thanks to the progress in the anionic chemistry of aromatic compounds, which has provided a number of poweful, reliable, and easy to handle synthetic tools. However, more traditional methods of elaboration of the aromatic compounds, based on electrophilic aromatic substitution, may still be able to provide optimal approaches in specific cases, such as 6,8-dioxyisocoumarins. Because of the mild conditions typically required, palladium catalyzed reactions (cross coupling and Heck type reactions) have become increasingly important to build the appropriate carbon framework leading to isocoumarins from simpler aromatic compounds. Finally, less commom used methods of elaboration of aromatic compounds such as those involving the ring synthesis from acyclic components, although less easy to envisage as viable approach to isocoumarins, can be the choice in the case of polysubstituted isocoumarins. We hope that this review reached its goal of enabling the reader to appreciate the above features of isocoumarin synthesis and to provide a practical tool in selecting proper approaches and starting materials when planning a specific isocoumarin synthesis.

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