NATURALLY OCCURRING MELLEIN-TYPE 3,4-DIHYDROISOCOUMARINS AND RELATED LACTONES: SYNTHETIC APPROACHES - A REVIEW

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ABSTRACT

Mellein and its derivatives are the most common 3,4-dihydroisocoumarins and are known to exhibit an array of biological activities such as antibacterial, antifungal, antimalarial, antiallergic, antitumor, anti-inflammatory, antiulcer, pheromonal, plant growth-promoting and antileukemic activities. Other mellein derivatives are recognized phytotoxins, neurotoxins, hepatotoxins, nephrotoxins and teratogens. Consequently, considerable efforts have been directed at studying these natural products. While most of the reported studies have focused on the isolation, characterization and bioassay studies of melleins, a number of synthetic studies have also been reported. This paper focuses on synthetic approaches towards these biologically active and, thus, potentially useful natural products. The aim is to bring together some of the earliest (past) and the more recent (present) and, concurrently, propose prospective (projected) synthetic methodologies. Therefore, this paper provides an overview of the existing and some potential synthetic routes toward melleins and, thus, provides a researcher with ideas and opportunities to choose and apply one or a blend of these synthetic strategies depending on accessible research facilities. Moreover, the projected synthetic strategies focus on the utilization of anacardic acid from Cashew Nut Shell Liquid (CNSL) - a readily available natural resource. Utilization of CNSL, which is considered a waste product, adds value to the cashew crop.

Key words: Melleins, 3,4-dihydroisocoumarins, synthetic methodologies, natural products, CNSL, 3,4-DHICs, lactones

INTRODUCTION

(*R*)-(-)-Mellein (**1**) and (*S*)-(+)-mellein (**1′**) as well as their derivatives such as **2**-**14** [Fig. 1 (a) -(d)] are the most commonly occurring 3,4-dihydroisocoumarins (3,4-DHICs). The common name mellein is derived from *Aspergillus melleus*, the fungus from which compound **1** was first isolated in 1933 (Chacón-Morales *et al*. 2013 and references cited therein). Compound **1** and related fungal metabolites were later isolated from many other different sources including *Aspergillus ochraceus*, a source that led to these compounds to be also commonly named as ochracins in the past.

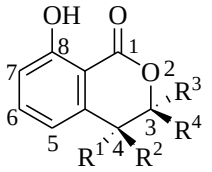
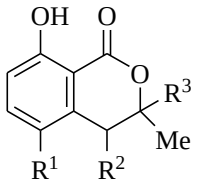
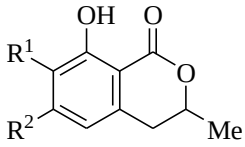
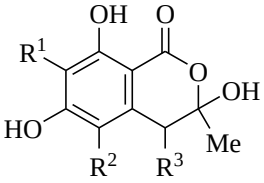
	General Structure	Substituents and Compounds
(a)		Compound R^1 R^2 R^3 R^4 **1** H H CH_3 H **1′** H H H CH_3 **2** OH H CH_3 H **3** H OH CH_3 H
(b)		Compound R^1 R^2 R^3 **4** H H OH **5** Me H H **6** CO_2H H H **7** OH H H
(c)		Compound R^1 R^2 **8** H OMe **9** H OH **10** OH H **11** OMe H
(d)		Compound R^1 R^2 R^3 **12** Me Me Me **13** Me Me H **14** H H H

Figure 1: Structures of (*R*)-(-)-mellein, (*S*)-(+)-mellein, (3*R*,4*R*)-(-)-4-hydroxymellein, (3*R*,4*S*)-(-)-4-hydroxymellein (**1**, **1′**, **2**, and **3**, respectively) and other mellein derivatives (**4-14**)

Based on structural similarities, the 3,4-dihydroisocoumarins can in general be divided into a number of classes; one such class is that of the abovementioned mellein (**1**) and its very close derivatives (the other 3-methyl-3,4-dihydroisocoumarins) illustrated in Figure 1 (a) - (d). The other classes include the 3-alkyl derivatives (apart from the 3-methyl-3,4-dihydroisocoumarins), 3-aryl derivatives (3-phenyl derivatives), aminocoumacins, ochratoxins and cladosporins or asperentins (McInerney and Taylor 1995, Lama *et al.* 2012, Li *et al.* 2012). Some respective members illustrative of each class are depicted in Figure 2 (a) - (e).

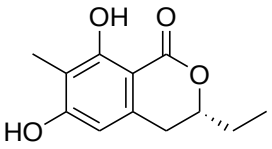
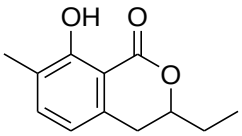
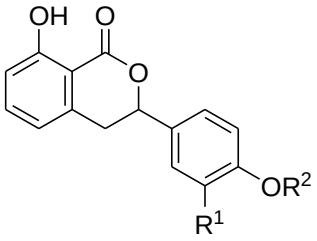
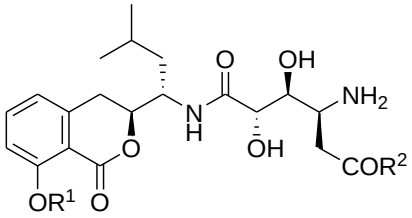
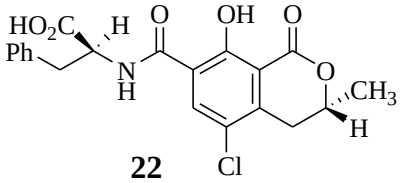
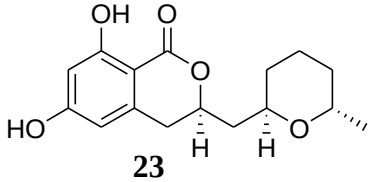
	Class	Examples
(a)	3-Alkyl derivatives	 **15**  **16**
(b)	3-Aryl derivatives	 **17**: $R^1 = R^2 = H$ **18**: $R^1 = OH$, $R^2 = Me$
(c)	Aminocoumacins	 **19**: $R^1 = H$, $R^2 = NH_2$ **20**: $R^1 = H$, $R^2 = OH$ **21**: $R^1 = Me$, $R^2 = OH$
(d)	Ochratoxins	 **22**
(e)	Cladosporins/asperentins	 **23**

Figure 2: Illustrative structures of the different classes of 3,4-dihydroisocoumarins

In addition to the compounds presented in Figures 1 and 2, other examples of known 3,4-DHICs **24**-**40** (sampled from the aforementioned 3,4-DHIC classes) are provided in Figures 3-5 (Çitoğlu *et al*. 2010, Braca *et al.* 2012, Li *et al.* 2012, Tang *et al.*

2014, Heussner and Bingle 2015). Even with these additional compounds, the list only serves to exemplify the diversity of structural types of 3,4-dihydroisocoumarins and it should not be taken as a comprehensive review of the compounds. In a recent review, Braca *et al.* (2012) compiled a total of ninety eight (98) 3,4-DHIC structures. Although the major source of 3,4-DHICs are fungi, these compounds have also been isolated from some plants, insects, bacteria and other living organisms.

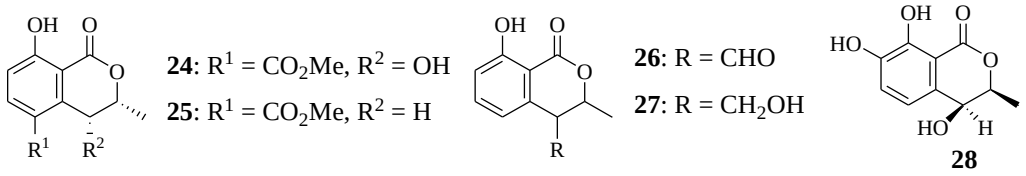


Figure 3: Structures of other mellein-type 3,4-DHICs (**24**-**28**)

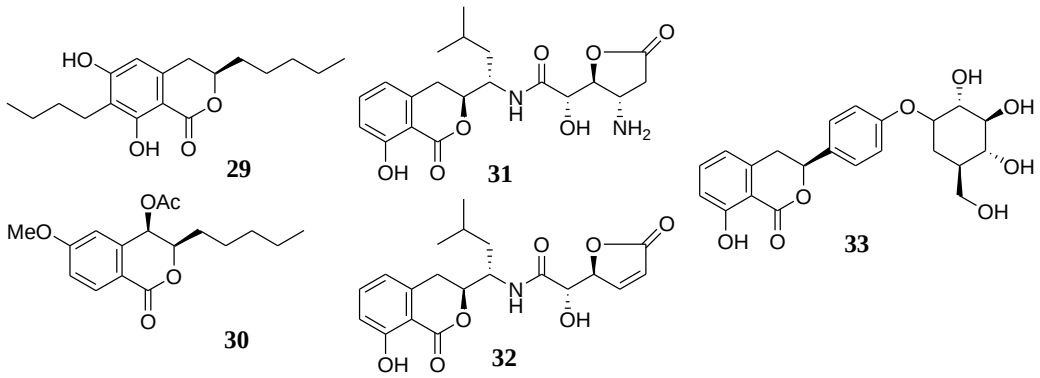


Figure 4: Structures of additional 3-alkyl derivatives, aminocoumacins and a 3-aryl derivative (**29** & **30**, **31** & **32** and **33**, respectively)

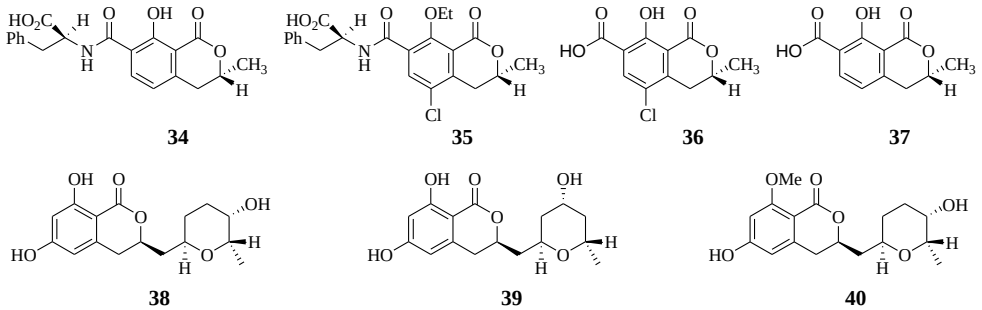
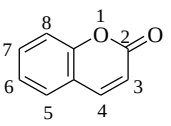
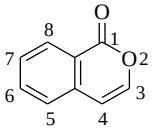


Figure 5: Structures of additional ochratoxins (**34**-**37**) and cladosporins (**38**-**40**)

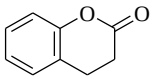
The 3,4-DHICs are often found together with isocoumarins, which are their analogues having a C=C between C-3 and C-4. Figure 6 depicts a comparison between the related coumarin, isocoumarin, dihydrocoumarin (3,4-DHC) and 3,4-dihydroisocoumarin (3,4-DHIC) ring systems. Figure 6 also gives some nomenclature of these related structural types. As it is the case of other classes of the natural products, systematic nomenclature is rarely used for the 3,4-DHICs and related lactones. Thus, almost all naturally occurring isocoumarins and 3,4-dihydroisocoumarins have been given trivial names, which are derived from generic or specific names of source organism; for example mellein (**1**) [*Aspergillus melleus*], hydrangenol (**17**) [*Hydrangea hortensia*], cladosporin (**23**, **38**-**40**) [*Cladosporium* spp.], ochratoxin (**22**, **34**-**37**) [*Aspergillus ochraceus*], etc.



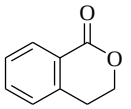
41 = coumarin or 2*H*-chromen-2-one



42 = *iso*coumarin or 1*H*-*iso*chromen-1-one



43 = 3,4-DHC or chroman-2-one



44 = 3,4-DHIC or *iso*chroman-1-one

Figure 6: General structures of coumarin, isocoumarin, dihydrocoumarin and dihydroisocoumarin (**41**, **42**, **43** and **44**, respectively)

Before turning attention to a survey of the existing synthetic methodologies, which is the focus of this review, it is sensible to at least point out the reason why these interesting natural products have captured the attention from synthetic chemists. Essentially, it is because these compounds are known to exhibit a range of biological activities such as antibacterial, antifungal, antimalarial, antiallergic, antitumor, anti-inflammatory, antiulcer, pheromonal, plant growth-promoting and antileukemic activities. Other mellein derivatives are recognized phytotoxins, neurotoxins, hepatotoxins, nephrotoxins and teratogens (Kern and Bestmann 1994, el Khoury and Atoui 2010, Hope and Hope 2012, Chacón-Morales *et al.* 2013). Moreover, these secondary metabolites are known to be involved in the biosynthetic pathways of several other metabolites (McInerney and Taylor 1995).

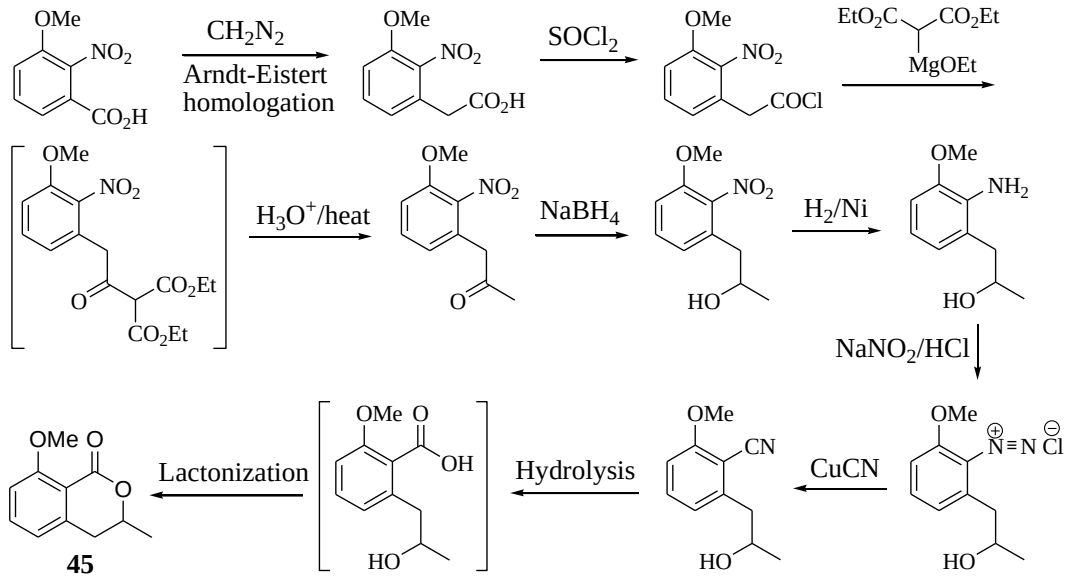
EXISTING SYNTHETIC METHODOLOGIES TOWARD MELLEIN-TYPE 3,4-DHICs AND RELATED LACTONES

According to Braca *et al.* (2012), the first reported isolation of a 3,4-DHIC dates back to 1916 when hydrangenol (**17**), [Fig. 2 (b)] was isolated from the flowers of *Hydrangea hortensia* Smith (Saxifragaceae). Thus, to-date, this class of naturally occurring lactones has existed in the literature for 100 years. Despite this long existence and their important biological activities, the varieties of accessible synthetic strategies have remained limited. In this section of the review the author endeavors to provide an inventory with concise schematic descriptions of some reported major methods in two categories; synthetic strategies that appeared beginning in the 1950s to 2006 (the past) and the ones that

have been developed over the last decade (the present/current).

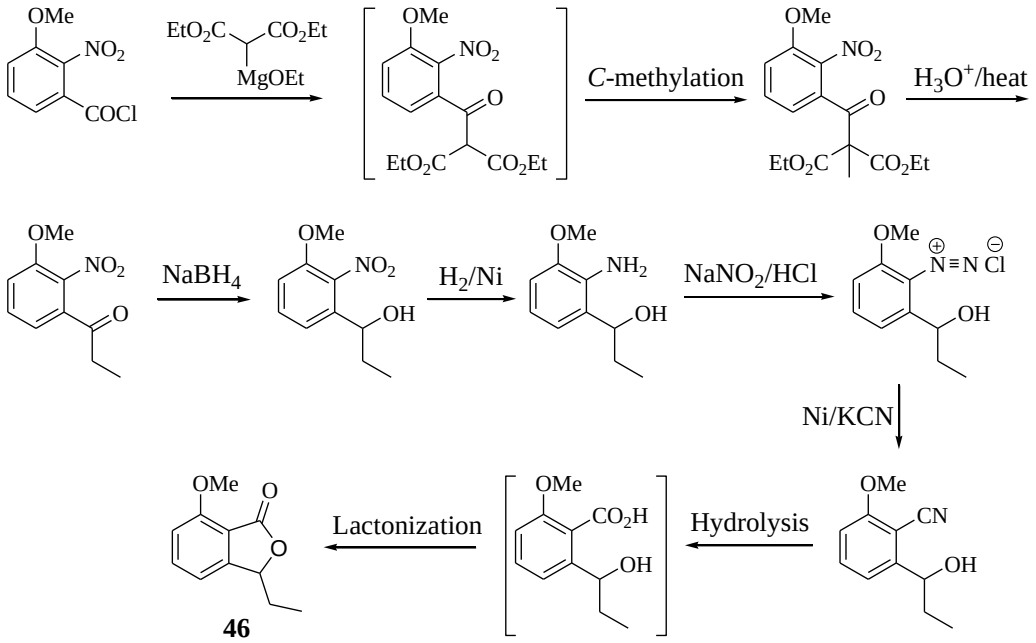
An Overview of the Past Synthetic Approaches (1950s to 2006)

The work of Blair and Newbold (1955) is among the earliest reported direct synthesis of 3-methyl-8-methoxy-3,4-DHIC (**45**), the 8-methoxy derivative of mellein (**1**), which is taken as the parent compound for other simple 3,4-DHICs. Scheme 1 outlines this traditional synthetic approach.



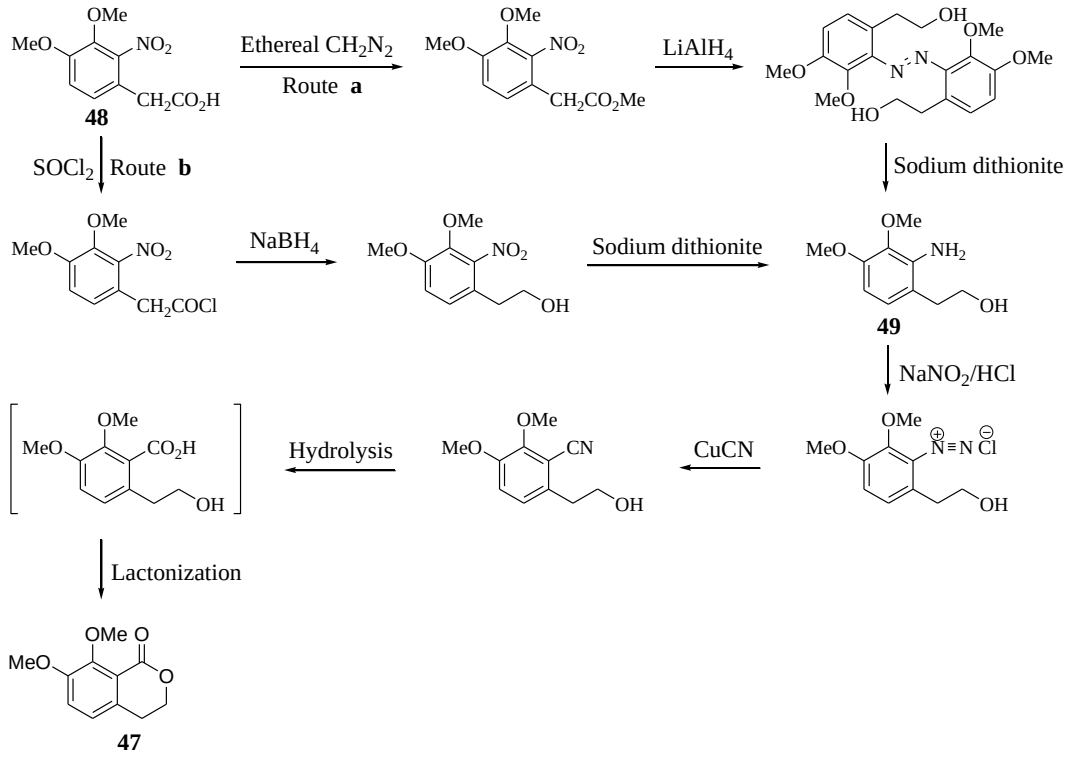
Scheme 1: Synthesis of 3-methyl-8-methoxy-3,4-DHIC (**45**) from 3-methoxy-2-nitrobenzoic acid

In addition to the synthesis of the δ-lactone **45**, Blair and Newbold (1955) were able to synthesize the isomeric γ-lactone **46** (3-ethyl-7-methoxyphthalide) using an approach analogous to the above. This synthesis is summarized in the Scheme 2. 3-Methoxy-2-nitrobenzoyl chloride, which is the starting material in Scheme 2, was obtained from 3-methoxy-2-nitrobenzoic acid by treatment with $SOCl_2$.



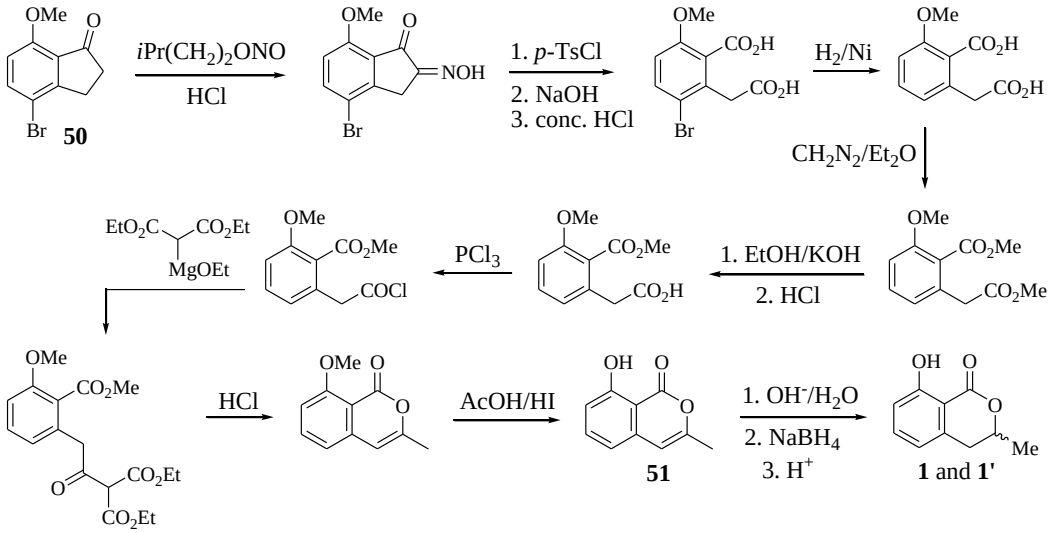
Scheme 2: Synthesis of 3-ethyl-8-methoxyphthalide (**46**) from 3-methoxy-2-nitrobenzoylchloride

Employing a methodology analogous to the one described in Scheme 1, Banerjee and Chaudhury (1961) accomplished the synthesis of 7,8-dimethoxy-3,4-dihydroisocoumarin (**47**) as depicted in Scheme 3. The starting material in this synthesis is 2-(3,4-dimethoxy-2-nitrophenyl)acetic acid (**48**), which was obtained from conversion of 4-acetoxy-3-methoxy-2-nitrobenzaldehyde by adapting a known procedure. Compound **48** was transformed to the amino alcohol **49** by using two different methods (route **a** and **b**). After obtaining compound **49**, these workers essentially followed the Blair and Newbold (1955) steps to finally assemble the 3,4-DHIC **47**. Consequently, diazotization of the amino alcohol **49**, conversion of the resulting arene diazonium salt into the nitrile and subsequent alkaline hydrolysis followed by acidification gave 7,8-dimethoxy-3,4-dihydroisocoumarin (**47**).



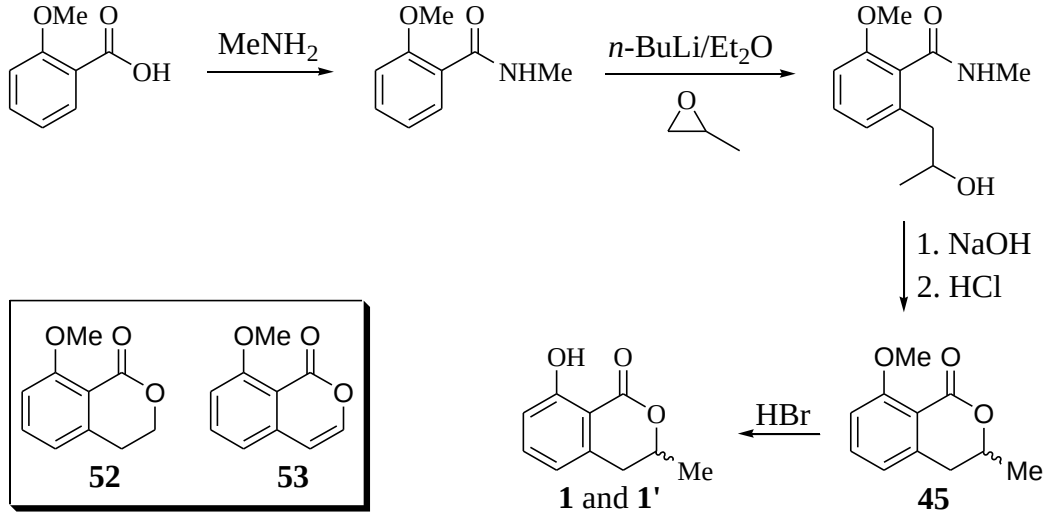
Scheme 3: Synthesis of 7,8-dimethoxy-3,4-DHIC (**47**) from 2-(3,4-dimethoxy-2-nitrophenyl)acetic acid (**48**)

Matsui *et al*. (1964) reported the first direct synthesis of racemic mellein [*i.e.*, a mixture of compounds **1** and **1′**, Fig. 1 (a) and Scheme 4] from 4-bromo-7-methoxy-indanone (**50**) *via* 3-methyl-8-hydroxyisocoumarin (**51**). It is interesting to note that the advanced intermediate **51** in this synthesis is itself a metabolite obtained from *Marasmius ramealis*. This approach, which, like the previous ones described in this section, makes use of traditional organic reactions, is summarized in Scheme 4. It is significant to note that the syntheses reported by Blair and Newbold (1955) and Matsui *et al*. (1964) (Schemes 1 and 4, respectively) remained the only two known syntheses of mellein for more than 35 years from the time it was isolated. These two syntheses are multi-step and linear approaches. However in 1970, Narasimhan and Bhide reported a three-step synthesis of (±)-mellein (**1** and **1′**) from *o*-methoxybenzoic acid; Scheme 5 outlines this synthesis.



Scheme 4: Synthesis of racemicmellein (**1** and **1′**) from 4-bromo-7-methoxy-indanone (**50**) *via* 3-methyl-8-hydroxyisocoumarin (**51**)

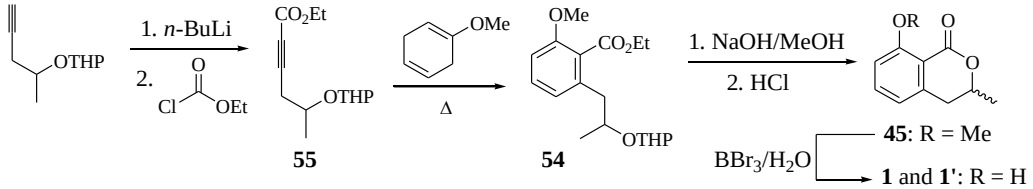
In an approach analogous to the synthesis of (±)-mellein summarized in Scheme 5, Narasimhan and Bhide (1970) also synthesized 8-methoxy-3,4-dihydroisocoumarin (**52**), which was easily converted into 8-methoxyisocoumarin (**53**) in one step. In this case the *ortho* lithiated benzoic acid derivative was treated with ethylene oxide instead of propylene oxide.



Scheme 5: Synthesis of (±)-mellein (**1** and **1′**) from *o*-methoxybenzoic acid by a metallation reaction

In an approach similar to the foregoing, Brahmbhatt and Pandya (2003) synthesized various 3-aryloxymethyl-3,4-DHICs from alkylation of *ortho* lithiated *N*-methyl benzamides with 2-aryloxymethyl oxiranes.

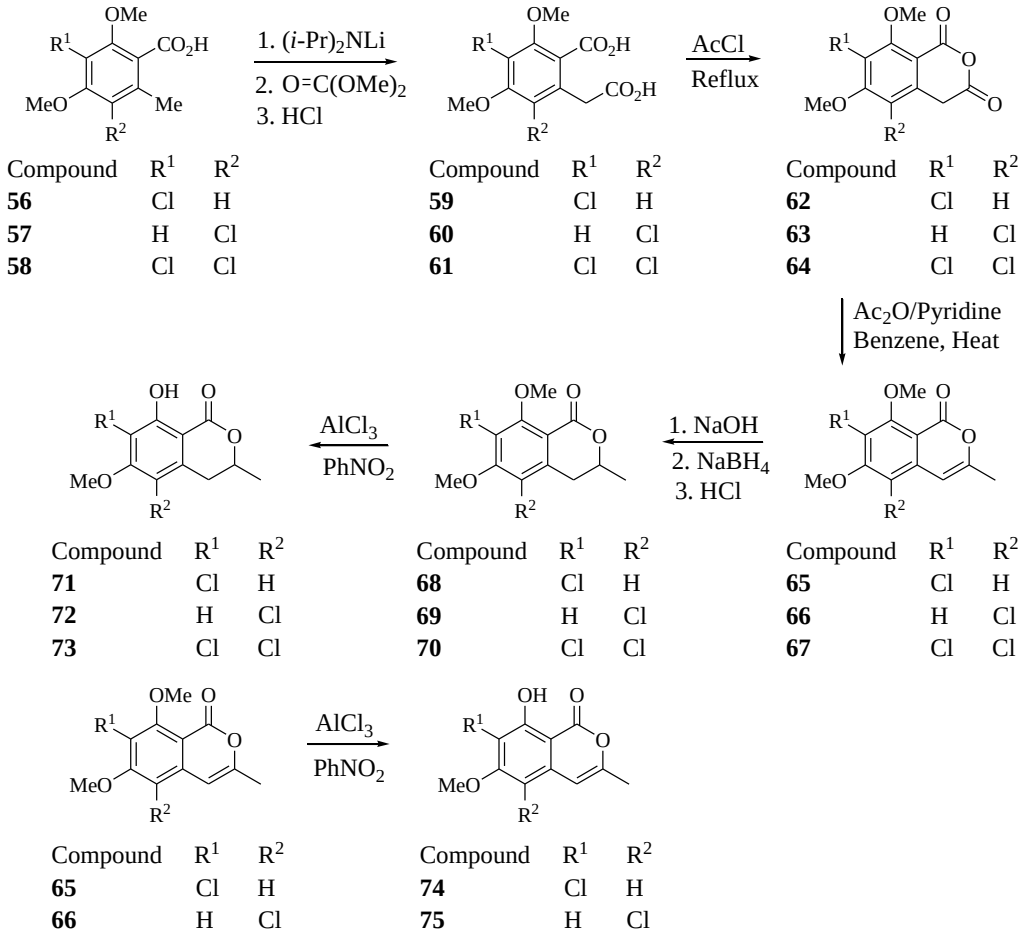
Arai *et al* .(1973) reported a four-step synthesis of (±)-mellein (**1** and **1′**). In this synthetic approach, the Diels-Alder reaction is utilized as a key step in the construction a suitably substituted benzoic acid derivative **54**, which is open to further conversion to the target compounds **1** and **1′** (Scheme 6). Accordingly, compound **54** was prepared by heating a mixture of the acetylenic ester **55** and 1-methoxycyclohexa-1,4-diene at 180 °C for 22 h. Obviously, the above reaction conditions enabled the latter compound to be transformed into 1-methoxycyclohexa-1,3-diene, which is capable of undergoing the Diels-Alder cycloaddition.



Scheme 6: Synthesis of (±)-mellein (**1** and **1′**) by using a Diels-Alder reaction

Henderson and Hill (1982) have reported syntheses of several naturally occurring chlorinated mellein-type 3,4-DHICs (**71-73**) and isocoumarins (**74** and **75**). Their synthetic approach involved carboxylation of the laterally lithiated 3-chloro-, 5-chloro- and 3,5-dichloro-2,4-dimethoxy-6-methylbenzoic acids (**56-58**) resulting in the formation of the corresponding homophthalic acids (**59-61**) as key intermediates. The preparation of latter compounds and their subsequent chemical transformation to the target 3,4-DHICs and isocoumarins (**71-75**) is outlined in Scheme 7.

A paper by Bellinger and co-workers (1982) reports on the syntheses of some 3-aryl-3,4-dihydroisocoumarins (3-aryl-3,4-DHICs) by both acid-catalyzed and thermal ring closure of stilbene-2-carboxylic acids. A number of stilbene-2-carboxylic acids were prepared by employing a variety of ways, although the Wittig reaction was the main approach towards these intermediates. To exemplify the overall approach, Scheme 8 shows how a sample of three isomeric (*cis*/*trans*) pairs of stilbene-2-carboxylic acids (**77-82**), prepared from the Wittig reaction of the phosphonium bromide **76** with benzaldehyde, 3-methoxy- and 4-methoxybenzaldehyde, were chemically transformed to the targeted 3-aryl-3,4-DHICs. Thus, the three 3-aryl-3,4-DHICs **83-85** represent several others that were synthesized in this work.



Compound	R^1	R^2
56	Cl	H
57	H	Cl
58	Cl	Cl

Compound	R^1	R^2
59	Cl	H
60	H	Cl
61	Cl	Cl

Compound	R^1	R^2
62	Cl	H
63	H	Cl
64	Cl	Cl

Compound	R^1	R^2
71	Cl	H
72	H	Cl
73	Cl	Cl

Compound	R^1	R^2
68	Cl	H
69	H	Cl
70	Cl	Cl

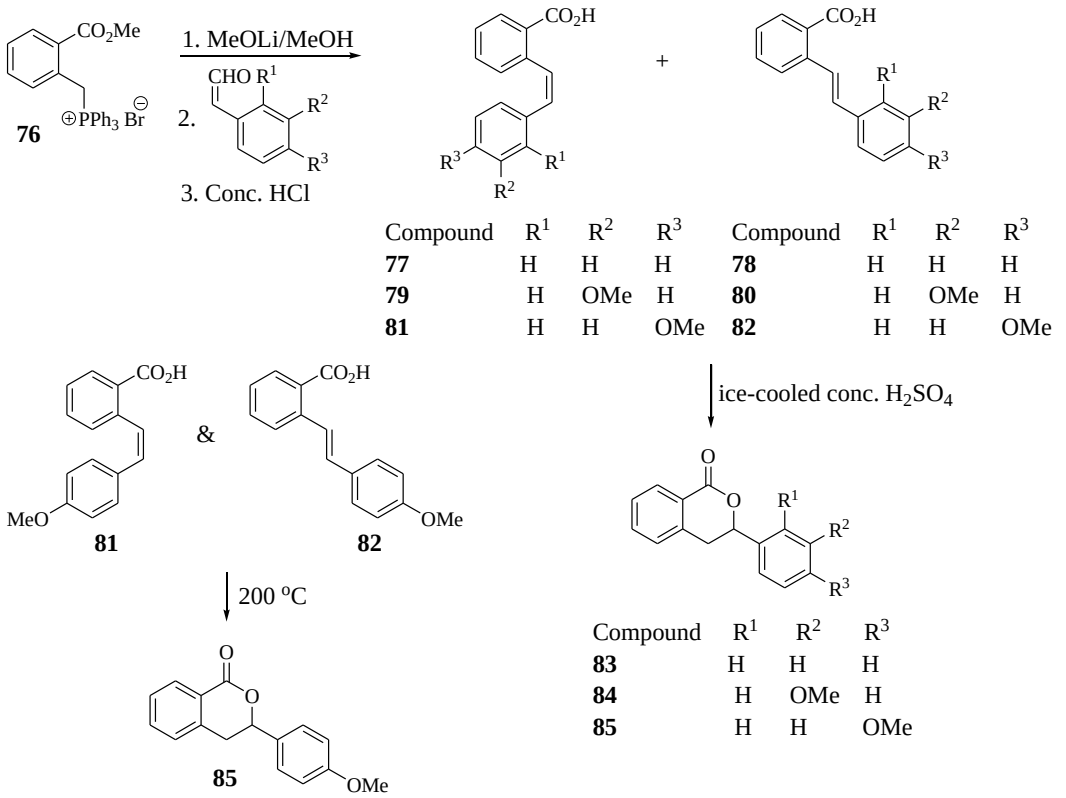
Compound	R^1	R^2
65	Cl	H
66	H	Cl
67	Cl	Cl

Compound	R^1	R^2
65	Cl	H
66	H	Cl

Compound	R^1	R^2
74	Cl	H
75	H	Cl

Scheme 7: Synthesis of chlorinated 3,4-DHICs (**71-73**) and isocoumarins (**74** and **75**) by carboxylation of chlorinated 2,4-dimethoxy-6-methylbenzoic acids (**56-58**)

It must be emphasized that the variety of stilbene-2-carboxylic acids prepared and further transformed to 3-aryl-3,4-DHICs by Bellinger *et al.* (1982) was not limited to compounds **77-82** (Scheme 8). For example, the 2'-methoxy-, 2'-hydroxy- and 4'-hydroxy-substituted stilbene-2-carboxylic acids were also prepared and subjected to both the acid-catalyzed and thermal ring closure reactions. It was observed that only the 2'-hydroxy-, 2'-methoxy-, 4'-hydroxy- and 4'-methoxystilbene-2-carboxylic acids were thermally converted to the corresponding 3-aryl-3,4-DHICs. Guided by these observations, the authors proposed a mechanism for the thermally induced ring closure that possibly involves a reversible protonation of the double bond carbon *ortho* to the $-CO_2H$ group to give a benzyl carbocation, which is resonance-stabilized by a methoxy or hydroxy group in 2' and 4' positions as exemplified by the case of compounds **81** and **82** (Scheme 8).

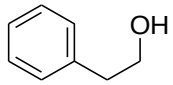
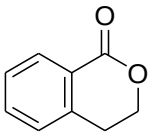
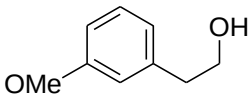
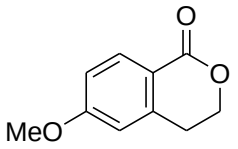
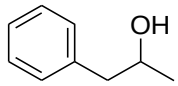
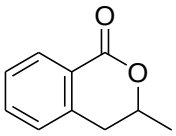
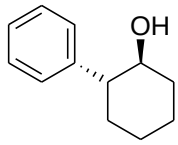
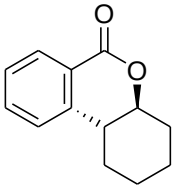
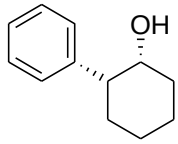
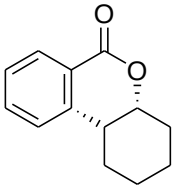


Scheme 8: Synthesis of 3-aryl-3,4-DHICs (**83-85**) by acid-catalyzed and thermal ring closure of stilbene-2-carboxylic acids (**77-82**)

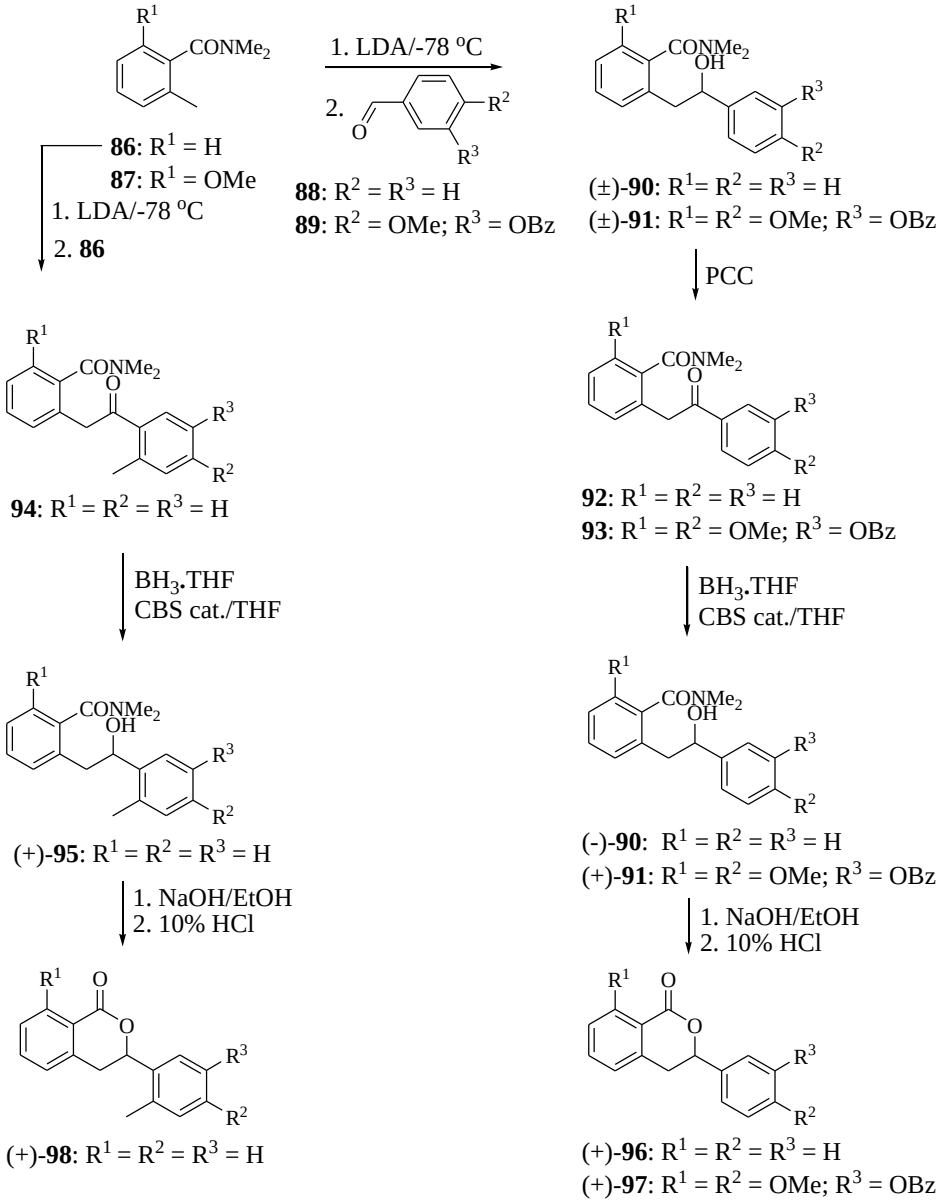
A highly convenient route to 3,4-DHICs by means of *o*-thallation and subsequent carbonylation of β-phenethyl alcohols (2-phenylethyl alcohols) has been reported by Larock and Fellows (1982). Table 1 summarizes the *o*-thallation and carbonylation conditions as well as the 3,4-DHICs produced from selected β-phenethyl alcohols.

For the first time a synthetic approach to optically active 3-aryl-3,4-DHICs was reported in 1992 by Arnoldi and co-workers. In summary, the approach involved the utilization of the Corey-Bashki-Shibata (CBS) catalyst in the enantioselective reduction of aryl 2-carboxybenzyl ketones. The ketones were obtained from oxidation of the corresponding racemic secondary alcohols, which were prepared from the condensation of laterally lithiated *o*-toluamides with aryl aldehydes. Scheme 9 summarizes this approach.

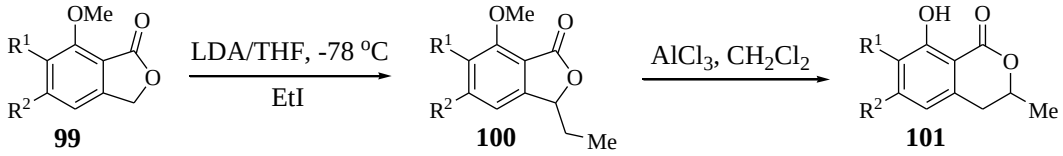
Table 1: Synthesis of 3,4-DHICs from β-Phenethyl Alcohols

Alcohol	Thallation conditions	Carbonylation conditions	Product
	$Tl(OCOCF_3)_3$, TFA, 25 °C, 1 day	0.1 mmol $PdCl_2$, 20 mmol LiCl, 2 mmol MgO or 1 mmol Li_2CO_3, MeOH, CO	
	$Tl(OCOCF_3)_3$, 5:1 THF /TFA, 25 °C, 1 day	As above	
	$Tl(OCOCF_3)_3$, TFA, 25 °C, 1 day	As above	
	$Tl(OCOCF_3)_3$, TFA, 25 °C, 16 h	As above	
	$Tl(OCOCF_3)_3$, TFA, 25 °C, 16 h	As above	

A communication by Mali *et al*. (1992) reported two novel approaches for the syntheses of several naturally occurring (±)-8-hydroxy-3-methyl-3,4-DHICs and other (±)-3-alkyl-3,4-DHICs. The first approach (Scheme 10a) involved the treatment of (±)-3-ethylphthalides **100a-d** with anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature for 1-2 h to give the (±)-8-hydroxy-3-methyl-3,4-DHICs **101a-e**. The (±)-3-ethylphthalides **100a-d** were obtained from the reaction of phthalides **99a-d** with EtI in the presence of LDA. In the second approach (Scheme 10b), a mixture of (*E*)- and (*Z*)-2-(alk-1-enyl)benzoic acids **103** and **104** were treated with $AlCl_3$ in CH_2Cl_2 at room temperature to give the corresponding (±)-8-hydroxy-3-methyl-3,4-DHICs **101a**, **b**, **e** and the (±)-3-alkyl-3,4-DHICs **105a**, **b**, respectively. The (*E*)- and (*Z*)-2-(alk-1-enyl)benzoic acids **103** and **104** were synthesized from phthalaldehydric acids **102** and **102'** using Wittig reaction. The (±)-7,8-dihydroxy-3-methyl-3,4-DHIC **101e**, obtained from both approaches (Scheme 10a and 10b) is a product of demethylation at position 7 of compound **101b**. Moreover, Mali and Babu (2001) employed an approach similar to that outlined in Scheme 10a to synthesize a number of 3-aryl-8-hydroxy-3,4-DHICs.



Scheme 9: Synthesis of optically active 3-aryl-3,4-DHICs (**96-98**) from optically active hydroxyamides **90**, **91** and **95** enantioselectively obtained from ketoamides **92-94**

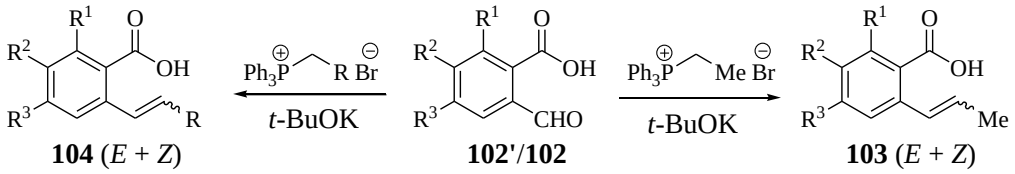


99 **100** **101**

99 and **100a**: $R^1 = R^2 = H$
b: $R^1 = R^2 = OMe$
c: $R^1 = H$; $R^2 = OMe$
d: $R^1 = OMe$; $R^2 = H$

101a: $R^1 = R^2 = H$
b: $R^1 = R^2 = OMe$
c: $R^1 = H$; $R^2 = OMe$
d: $R^1 = OMe$; $R^2 = H$
e: $R^1 = OH$; $R^2 = OMe$

Scheme 10a: Synthesis of 3-methyl-3,4-DHICs **101a-e** by $AlCl_3$-catalyzed reaction of phthalides **100a-d**



104 (*E* + *Z*) **102'**/**102** **103** (*E* + *Z*)

102', **104a**: R = Me; $R^1 = R^2 = R^3 = H$
b: R = Et; $R^1 = R^2 = R^3 = H$

102, **103a**: $R^1 = OMe$; $R^2 = R^3 = H$
b: $R^1 = R^2 = R^3 =$ OMe

105 **101**

105a: R = Me; $R^1 = R^2 = R^3 = H$
b: R = Et; $R^1 = R^2 = R^3 = H$

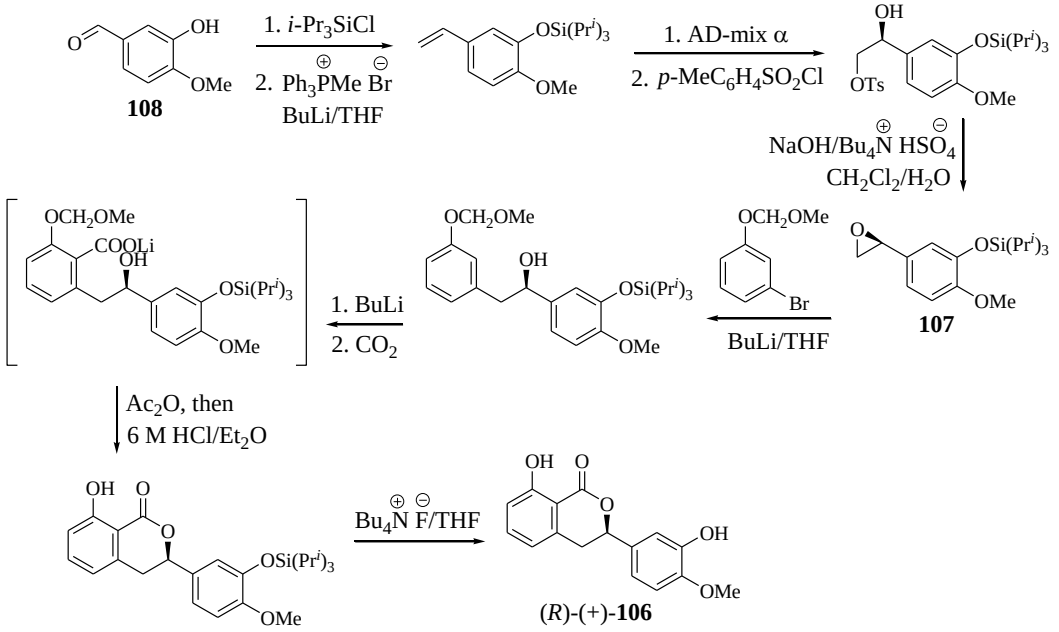
101a: $R^2 = R^3 = H$
b: $R^2 = R^3 =$ OMe
e: $R^2 = OH$; $R^3 =$ OMe

Scheme 10b: Synthesis of 3-alkyl-3,4-DHICs **101a**, **b**, **e** and **105a**, **b** by $AlCl_3$-catalyzed reaction of 2-(alk-1-enyl)benzoic acids **103** and **104**

As was noted earlier (Scheme 9 *vide supra*), the work reported by Arnoldi *et al.* (1992) represents the first synthetic approach to optically active 3-aryl-3,4-DHICs. In this work the 3'-benzyl 8-methyl ether of the naturally occurring (*R*)-(+)-phyllodulcin [compound (+)-**97**, Scheme 9] was obtained in only moderate enantiomeric excess (55% ee). Compound (+)-**98** was obtained in a very low ee of 18%. Although the ee for product (+)-**96** was not reported, its $[\alpha]_D$ was found to be +89°. Thus, further efforts were

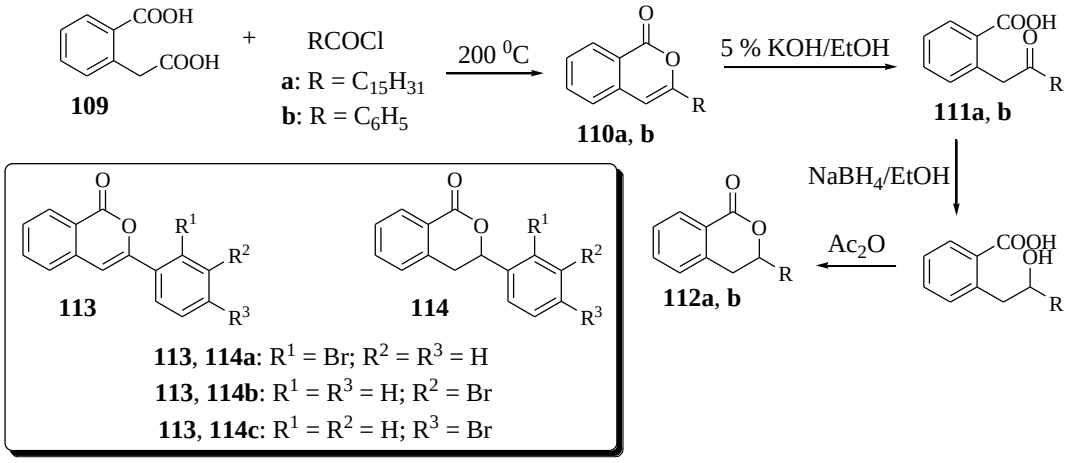
directed towards developing more highly enantioselective approaches to these 3,4-DHICs.

Ramacciotti *et al*. (1996) designed and executed a highly enantioselective synthesis of a naturally occurring 3-aryl-3,4-DHIC phyllodulcin **106**. This approach involved the Sharpless *cis*-dihydroxylation of an olefinic double bond followed by conversion of the *cis*-dihydroxy product to an optically active oxirane (epoxide), namely (*S*)-(4-methoxy-3-triisopropylsilyloxyphenyl)oxirane (**107**) as the intermediate. Scheme 11 outlines this enantioselective synthesis of **106** starting with isovanillin (**108**).



Scheme 11: Enantioselective synthesis of a naturally occurring 3-aryl-3,4-DHIC phyllodulcin **106** starting with isovanillin (**108**) via the oxirane **107.**

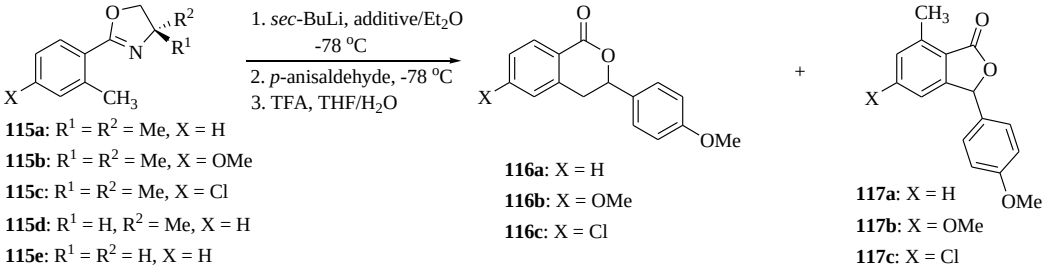
Rama *et al.* (1998) employed the direct condensation of haxadecanoyl and benzoyl chlorides with 2-(carboxymethyl)benzoic acid (**109**) to synthesize 3-pentadecyl- and 3-phenylisocoumarins **110a** and **110b**, respectively. Subsequent alkaline hydrolysis of isocoumarins gave the corresponding keto acids **111a** and **111b**, which were further transformed to the racemic 3,4-DHICs **112a** and **112b** as depicted in Scheme 12. Hussain *et al*. (2001) employed an approach analogous to the foregoing to synthesize 3-(bromophenyl)isocoumarins (**113**) and their corresponding 3-(bromophenyl)-3,4-DHICs (**114**). Furthermore, a series of isocoumarins and corresponding dihydroisocoumarins derivatives have synthesized *via* condensation of homophthalic acid with the acid chlorides of ibuprofen, fluribiprofen, naproxen, valproic acid and 1-naphthoic acid (Hussain *et al*. 2003).



Scheme 12: Synthesis of 3-pentadecyl- and 3-phenylisocoumarins **110a**, **b** and their (*d*,*l*)-3,4-Dihydro Derivatives **112a**, **b**

In a strategy similar to that summarized in Scheme 10a (*vide supra*), Bhide *et al.* (2002) successfully converted some (±)-3-ethyl-3-methyl phthalides to 3,3-dimethyl-3,4-DHICs, including 3-methylmellein.

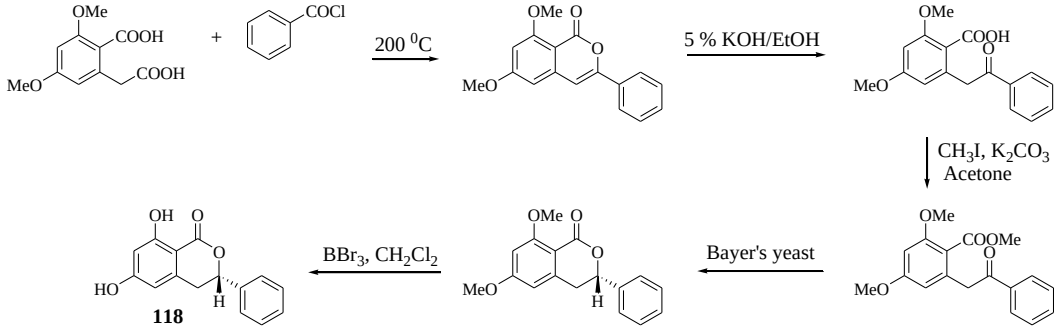
Tactfully, Tahara *et al.* (2002) were able to manipulate reaction conditions so as to predominantly achieve either *ortho* or lateral lithiation of 4,4-dimethyl-2-(*o*-tolyl)oxazolines **115**. Subsequently, the condensation of principally lateral and *ortho* lithiated oxazolines **115** with *p*-anisaldehyde followed by treatment of the crude product with TFA in aqueous THF gave the corresponding 3-aryl-3,4-DHICs **116** and 3-aryl-7-methylphthalide **117** as shown in Scheme 13.



Scheme 13: Synthesis of 3-aryl-3,4-DHICs **116a-c** and 3-aryl-7-methylphthalides **117a-c** by the lateral and *ortho* lithiation of oxazolines **115a-e**, respectively.

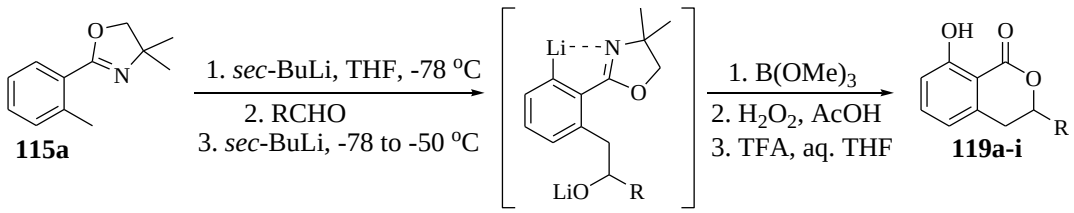
Utilizing a strategy similar to that summarized in Scheme 12, Saeed (2003) accomplished a stereoselective synthesis of the naturally occurring montroumarin [(3*S*)-6,8-dihydroxy-3-phenyl-3,4-dihydroisocoumarin (**118**)]. The starting

materials in this case were 3,5-dimethoxyhomophthalic acid and benzoyl chloride. Scheme 14 provides an outline of this work.



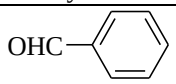
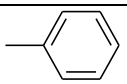
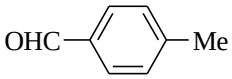
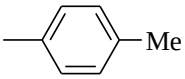
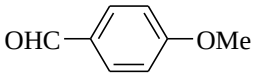
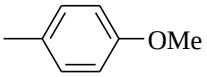
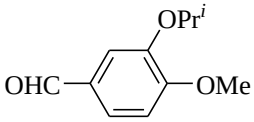
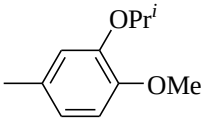
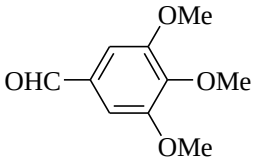
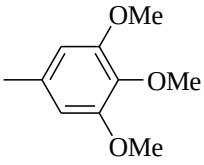
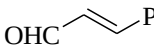
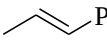
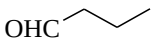
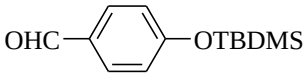
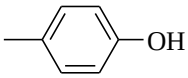
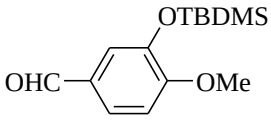
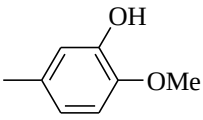
Scheme 14: Stereoselective Synthesis of Montroumarin **118** by direct condensation of benzoyl chloridewith 3,5-dimethoxyhomophthalic acid.

Tahara and collaborators (2004) have successfully modified their previous strategy (Scheme 13, *vide supra*) to synthesize 3-substituted 8-hydroxy-3,4-DHICs in one-pot *via* the initial *sec*-BuLi mediated lateral lithiation of the oxazoline **115a**, followed by addition of aldehyde, then treatment of the condensation product with *sec*-BuLi to effect the second lithiation, which is *ortho* lithiation, and subsequent oxidation to introduce the hydroxy group at position 8. To complete this one-pot synthesis the crude product from the foregoing procedure was treated with TFA in refluxing THF/H_2O give the 3-substituted 8-hydroxy-3,4-DHICs **119a-i** (Scheme 15 and Table 2).

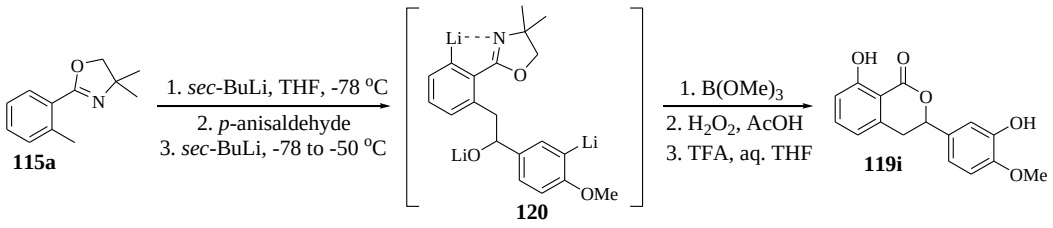


Scheme 15: Synthesis of 3-substituted 8-hydroxy-3,4-DHICs **119a-i** by both lateral and *ortho* lithiation of oxazoline **115a**

Table 2: Synthesis of 3-substituted 8-hydroxy-3,4-DHICs **119a-i** by both lateral and *ortho* lithiation of oxazoline **115a**

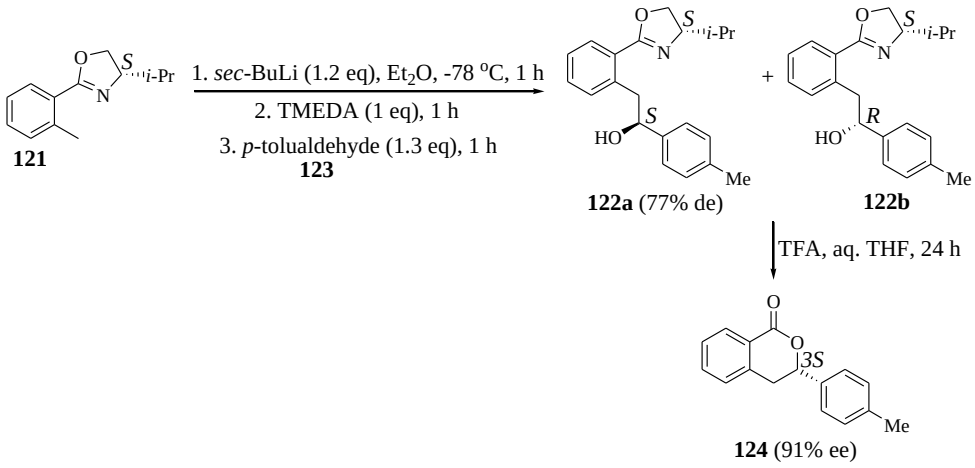
Aldehyde	3,4-DHIC **119**	R
	119a	
	119b	
	119c	
	119d	
	119e	
	119f	
	119g	
	119h	
	119i	

It is worth mentioning that in the last two entries in Table 2, the silyl protecting group was removed during the final TFA treatment to give the naturally occurring (±)-hydrangenol (**119h**) and (±)-phyllodulcin (**119i**). As an extension of the above lithiation-based synthetic strategy, Tahara and co-workers (2004) developed an inexpensive synthesis of (±)-phyllodulcin (**119i**) via the trianion intermediate **120**, a product of successive lateral lithiation and two *ortho* lithiations in one-pot as summarized in Scheme 16.



Scheme 16: Synthesis of (±)-phyllodulcin (**119i**) via the trianion intermediate **120**

An asymmetric synthesis of 3-substituted 3,4-DHICs involving the stereoselective condensation of aldehydes with the laterally lithiated (*S*)-4-isopropyl-2-(o-tolyl)oxazoline (**121**) followed by a diastereomer-selective lactonization of intermediate diastereomers **122a** and **122b** has been reported by Kurosaki *et al.* (2005). Quite a few aldehydes were condensed with the laterally lithiated optically active **121**. Therefore, Scheme 17 depicts the reaction of *p*-tolualdehyde (**123**) with **121** and subsequent transformation of the adducts **122a** and **122b** to the optically active 3-substituted 3,4-DHIC **124** to exemplify the procedure used for a wide range of aldehydes. It is worth mentioning that the (*S*,*S*)-diastereomer **122a** is predominantly formed (77% de) compared to (*S*,*R*)-diastereomer **122b**. Scheme 17 also outlines the reaction conditions (*i.e.*, Et_2O as solvent and TMEDA as the additive, *etc*.) that gave the most satisfactory stereoselectivity of the condensation reaction in favour of the (*S*,*S*) adducts such as **122a**. Moreover, Scheme 17 also illustrates the diastereomer-selective lactonization in which the (*S*,*S*) adducts such as **122a**, reacts faster than the (*S*,*R*) adducts such as **122b** to give the optically enriched (3*S*)-3,4-DHICs such as **124**.



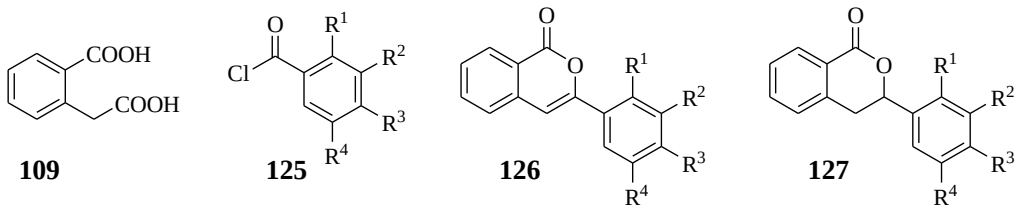
Scheme 17: Synthesis of optically enriched (3*S*)-3,4-DHICs (e.g. **124**) from the optically active oxazoline **121** via the diastereomeric adducts **122a** and **122b**

In the next section of this review, attention is focused on the synthetic approaches that have appeared over the last decade (2007-2016). As it was the case in the preceding section, the synthetic approaches that will be summarized in this section do not constitute an exhaustive catalog of all current syntheses but rather an instructive selection of the currently available methods.

An Overview of the Current Synthetic Approaches (2007-2016)

It is certainly expected that some of the current (2007-2016) synthetic methods may have similarities to those that were reviewed in the preceding section. Consequently, the common characteristics of such methods will not be repeated in this section; however, the reader will be guided so as to access information that has already been provided. The modifications of such overlapping methods or their applications to solve a new synthetic problem will be highlighted.

Qadeer and collaborators (2007) utilized a methodology analogous to those described in the previous section and summarized in Schemes 12 and 14. These researchers successfully synthesized the 3-(dichlorophenyl)isocoumarins (**126a-c**) and their corresponding (±)-3,4-dihydroisocoumarins (**127a-c**) by condensation of homophthalic acid (**109**) with dichlorobenzoyl chlorides **125a-c** (Fig. 7).



125, **126**, **127 a**: $R^1 = R^2 = Br$; $R^3 = R^4 = H$

125, **126**, **127 b**: $R^1 = R^3 = H$; $R^2 = R^4 = Br$

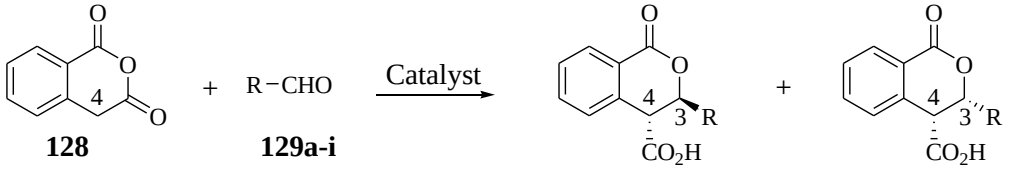
125, **126**, **127 c**: $R^1 = R^4 = Br$; $R^2 = R^3 = Br$

Figure 7: 3-(Dichlorophenyl)isocoumarins (**126a-c**) and (±)-3,4-DHICs (**127a-c**)obtained *via* condensation of homophthalic acid (**109**) with dichlorobenzoyl chlorides **125a-c**

An asymmetric synthesis of 3-substituted 8-hydroxy-3,4-DHICs has been reported by Uchida *et al*. (2007). This approach is very similar to that reported by Kurosaki *et al*. (Scheme 17 *vide supra*). The current approach differs from the previous one in that a methoxy group is incorporated at position 6 of the optically active oxazoline **121** and, thus, setting the stage for the formation of a hydroxy substituent in position 8 of the final 3,4-DHIC products. This method was applied in the synthesis of optically active 3,4-DHIC natural products such as (*R*)-8-hydroxy-3-(1-tridecyl)-3,4-dihydroisocoumarin and (*R*)-(+)-phyllodulcin (**106**; Scheme 11 *vide supra*).

A one-step base-catalyzed condensation of homophthalic anhydride (**128**) with aryl or heteroaryl aldehydes **129** followed by cyclization of the initial condensation adduct to give *cis/trans*-3-aryl(heteroaryl)-3,4-dihydroisocoumarin-4-carboxylic acids **130** has been reported by Bogdanov *etal*. (2007).

The synthesis of these 3-aryl(heteroaryl)-4-carboxy-3,4-DHICs by this methodology is outlined in Scheme 18.



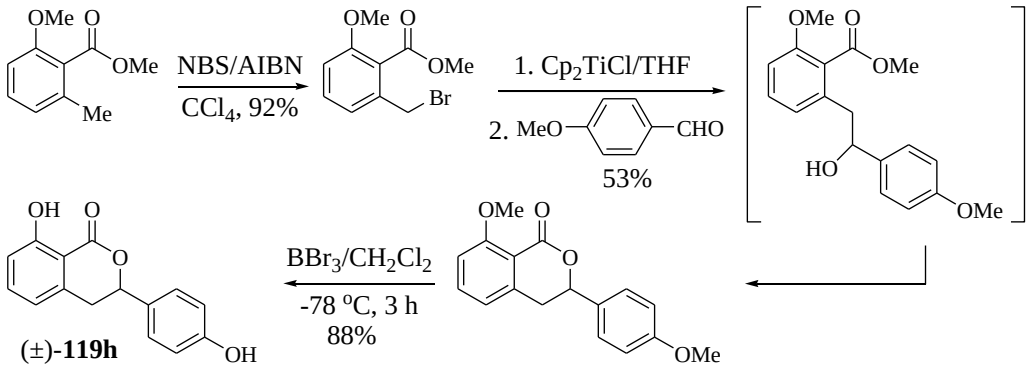
128 **129a-i** ***trans*-130a-f, h, i** ***cis*-130a-c, e, g**

	R = Aryl (Ar)		R = Heteroaryl (HetAr)
a	Phenyl	e	Thiophene-2-yl
b	Benzo[1,3]dioxol-5-yl	f	Furan-2-yl
c	4-Nitrophenyl	g	Pyridin-2-yl
d	N-methylcarbazol-3-yl	h	Pyridin-3-yl
		i	Pyridin-4-yl

Scheme 18: Synthesis of 3-Ar(HetAr)-4-carboxy-3,4-DHICs (**130a-i**) via condensation of homophthalic anhydride (**128**) with aryl or heteroaryl aldehydes **129a-i**

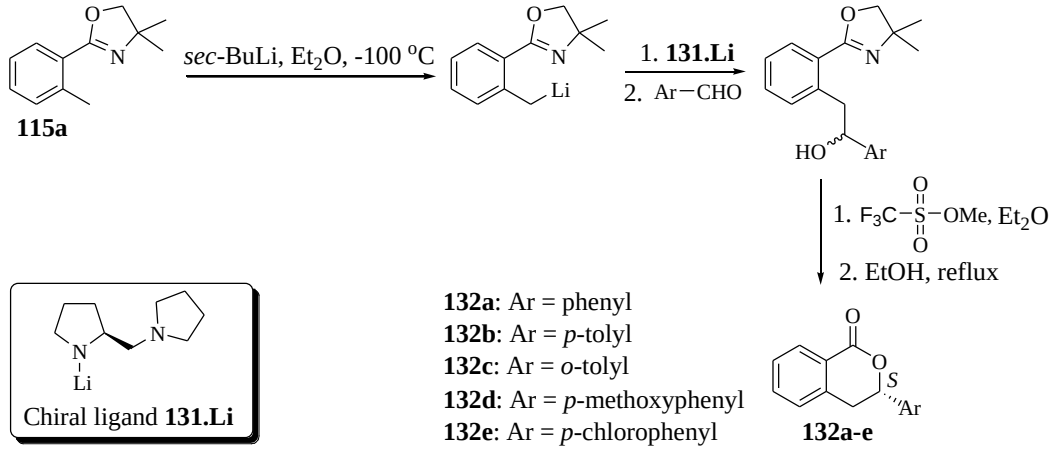
A paper by Mandal and Roy (2007) reports on the utilization of a Cp_2TiCl-catalyzed Barbier-type radical reaction of aryl and alkyl aldehydes with 2-(bromomethyl)benzoates in the synthesis of several 3-substituted 3,4-DHICs. In this reaction, the 2-(2-hydroxyalkyl/aryl)benzoates initially formed undergoes lactonization to furnish the 3-substituted 3,4-DHIC products. To illustrate the synthetic utility of this protocol, Scheme 19 outlines its application in the synthesis of (±)-hydrangenol (**119h**), which is also mentioned in Scheme 15 and Table 2 (*vide supra*).

In an approach parallel to the asymmetric syntheses published by Kurosaki *et al*. (2005) and Uchida *et al*. (2007), Sharma and co-workers (2010) have reported yet another asymmetric synthesis of 3-aryl-3,4-DHICs. Unlike the previous strategies, which used a chiral auxiliary (fixed to the benzoic acid derivative to be laterally and/or *ortho* lithiated), the present strategy employs an external chiral base/ligand as the source of the asymmetric induction. In other words, the two previous approaches involved an intramolecular asymmetric induction whereas Sharma and co-workers' approach involved an intermolecular asymmetric induction.



Scheme 19: Synthesis of the naturally occurring (±)-hydrangenol (**119h**) via a Cp_2TiCl-catalyzed Barbier-type radical reaction

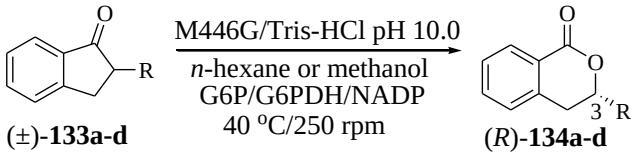
The base/ligand used in this synthetic approach was the lithium amide obtained from (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine (**131.Li**). Accordingly, the reaction sequence of this intermolecularly induced asymmetric synthesis is depicted in Scheme 20. The % ee of the 3-aryl-3,4-DHICs **132** obtained at -100 °C ranged from 53-68%. It is important to mention that the lithium amide **131.Li** was not adequately basic to laterally deprotonate oxazoline **115a**; consequently, **115a** was laterally deprotonated by *sec*-BuLi followed by addition of **131.Li** to play the role of a chiral ligand rather than a chiral base.



Scheme 20: Asymmetric synthesis of 3-aryl-3,4-DHICs **132a-e** by an external chiral ligand **131.Li** as the source of the asymmetric induction

A stereoselective synthesis of the (*R*)-3-alkyl-3,4-DHICs **134a-d**, depicted in Scheme 21, has been reported by Rioz-Martínez *et al*. (2010). This synthetic strategy involved a dynamic kinetic resolution in which the (*R*)-enantiomers of

the *rac*-2-alkyl-1-indanones **133a-d** underwent a fast enzyme catalyzed Baeyer-Villiger oxidation to predominantly form the (*R*)-3-alkyl-3,4-DHICs **134a-d**. The Baeyer-Villiger monooxygenase (BVMO) responsible for these biocatalyzed oxidations was the single mutant of the thermostable phenylacetone monooxygenase (M446G PAMO) from *Thermobifida fusca*. The % yields and enantiomeric excess of the (*R*)-3-alkyl-3,4-DHICs **134a-d** ranged from 50-85% and 50 to ≥97%, respectively. The variations were due changes made in reaction parameters such as solvent and reaction time, which ranged from 48-144 h, as well as the 3-alkyl groups in the substrates **133a-d**.



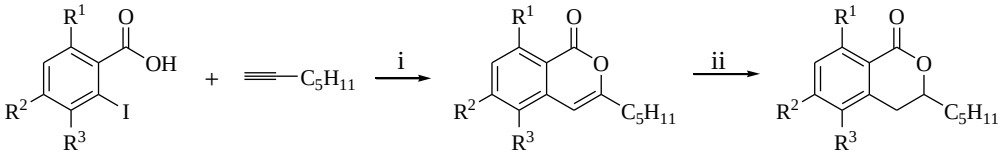
(±)-**133a-d** (*R*)-**134a-d**

a: R = Me; **b**: R = Et; **c**: = *i*-Pr; **d**: R = *n*-Bu

Scheme 21: Asymmetric synthesis of (*R*)-3-akyl-3,4-DHICs **134a-e** by an enzymatic resolution of *rac*-2-alkyl-1-indanones **133a-d** catalyzed by M446G PAMO

Starting with the commercially available 2-iodobenzoic acid derivatives **135a-d** (Scheme 22) and hept-1-yne, a Sonogashira cross coupling reaction in the presence of $ZnCl_2$ was employed by Hampl *et al*. (2011) to synthesize the isocoumarin derivatives **136a-d**. In the presence of $ZnCl_2$, the initially formed 2-(hept-1-ynyl)benzoic acid derivatives were not isolated as they underwent a spontaneous cyclization to give the isocoumarins **136a-d**. On catalytic hydrogenation, the isocoumarins **136a**, **b** and **d** gave the corresponding 5-pentyl-3,4-DHICs **137a**, **b** and **d**.

The work by da Penha *et al*. (2011) applied the Heck-Matsuda reaction as the key step in the construction of both the 3-substituted 3,4-DHIC and 3-substituted phthalide skeletons from the initially produced 2-(alk-1-enyl)benzoic acid derivatives in a selective way. Whether the cyclization of an intermediate 2-(alk-1-enyl)benzoic acid derivative gives a 3,4-DHIC or phthalide, is governed by the electronic nature of the group on the starting olefin. Electron donating groups led to formation of 3,4-DHICs (**139a-e**, Scheme 23a), whereas electron withdrawing groups (EWGs) directed the formation of phthalides (**141a-c,** Scheme 23b).



135a-d **136a-d** **137a**, **b**, **d**

a: $R^1 = R^2 = R^3 = H$ **a**: $R^1 = R^2 = R^3 = H$ **a**: $R^1 = R^2 = R^3 = H$

b: $R^1 = F$; $R^2 = R^3 = H$ **b**: $R^1 = F$; $R^2 = R^3 = H$ **b**: $R^1 = F$; $R^2 = R^3 = H$

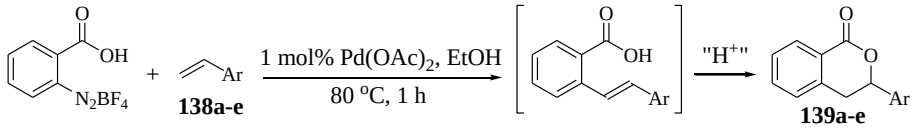
c: $R^1 = R^3 = H$; $R^2 = Cl$ **c**: $R^1 = R^3 = H$; $R^2 = Cl$ **d**: $R^1 = R^2 = H$; $R^3 = Me$

d: $R^1 = R^2 = H$; $R^3 = Me$ **d**: $R^1 = R^2 = H$; $R^3 = Me$

Conditions: i: Triethylamine, $ZnCl_2$, $Pd(PPh_3)_2Cl_2$, DMF, 100 °C, 24 h ;
ii: H_2 Pd/C, methanol, 25 °C, 12 h

Scheme 22: Synthesis of 3-pentyl-3,4-DHICs **137a**, **b**, **d** via the 3-pentylisocoumarins **136a**, **b**, **d** obtained from a Sonogashira reaction as a key step

Consequently, a number of electron rich and electron poor olefins were subjected to the Heck-Matsuda reaction and followed by cyclization to give the 3,4-DHICs and 5-membered phthalides, respectively. As pointed out earlier, Schemes **23a** and **23b** outline this expeditious protocol towards the two ring systems.



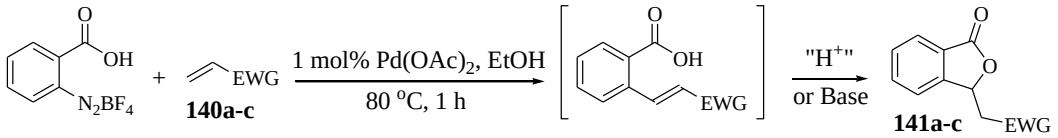
138a-e **139a-e**

a: Ar = phenyl **b**: Ar = 4-acetoxyphenyl **a**: Ar = phenyl **b**: Ar = 4-hydroxyphenyl

c: Ar = 4-methoxyphenyl **d**: Ar = 4-methylphenyl **c**: Ar = 4-methoxyphenyl **d**: Ar = 4-methylphenyl

e: Ar = 4-chlorophenyl **e**: Ar = 4-chlorophenyl

Scheme 23a: Synthesis of 3-aryl-3,4-DHICs **139a-e** from the electron rich olefins **138a-e** by a Heck-Matsuda reaction as a key step



140a-c **141a-c**

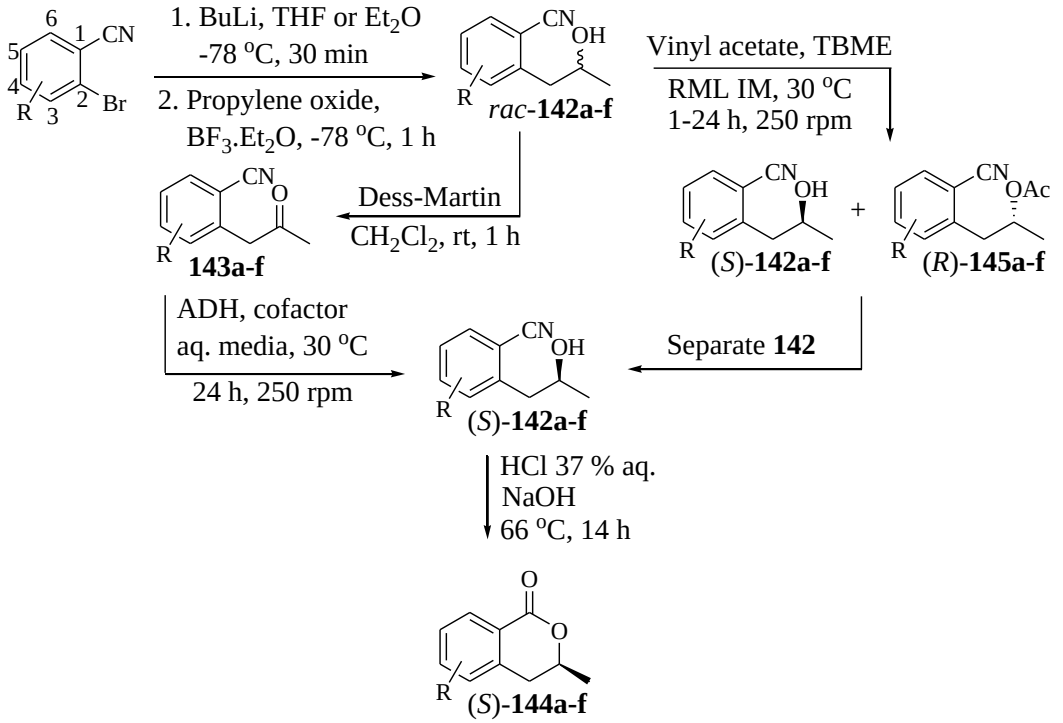
a: EWG = 4-nitrophenyl **a**: EWG = 4-nitrophenyl

b: EWG = acetyl **b**: EWG = acetyl

c: EWG = methoxycarbonyl **c**: EWG = methoxycarbonyl

Scheme 23b: Synthesis of 3-substituted phthalides **1141a-c** from the electron poor olefins **140a-c** by a Heck-Matsuda reaction as a key step

Mangas-Sánchez *et al*. (2012) have reported on two chemoenzymatic asymmetric transformations that led to enantiopure (*S*)-2-(2-hydroxypropyl)benzonitriles **142a-f**, which were key precursors in the synthesis ofthe (*S*)-3-methyl-3,4-DHICs **144a-f** and other structurally similar compounds. The two chemoenzymatic processes involved in this protocol are: a lipase-catalyzed (RML IM-catalyzed) kinetic resolution of *rac*-2-(2-hydroxypropyl)benzonitriles **142a–f** using vinyl acetate as an acyl donor and an alcohol dehydrogenase-catalyzed (ADH-catalyzed) bioreduction of ketones **143a-f**. The initial preparation of the *rac*-2-(2-hydroxypropyl)benzonitriles **142a-f,** the aforementioned chemoenzymatic processes as well as the final cyclization of the enantiopure (*S*)-2-(2-hydroxypropyl)benzonitriles **142a-f** to afford the (*S*)-3-methyl-3,4-DHICs **144a-f** is summarized in Scheme 24.

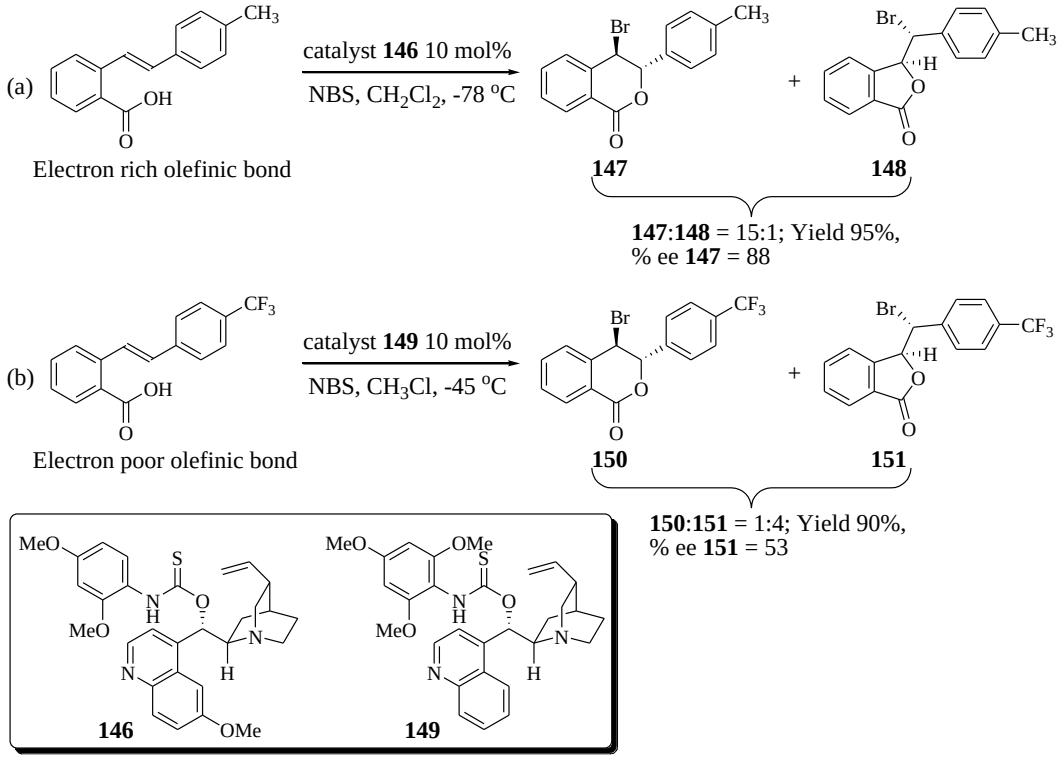


a: R = H; **b**: R = 4-Me; **c**: R = 5-OMe; **d**: R = 5-Me; **e**: R = 3-Me; **f**: R = 4-F

Scheme 24: Synthesis of enantiopure (*S*)-3-methyl-3,4-DHICs **144a-f** *via* chemoenzymatic transformations

As an extension of the above chemoenzymatic method, Mangas-Sánchez *et al*. (2013) have reported a one-pot synthesis of enantiopure 4-alkyl-3-methyl-3,4-DHICs through an *E. coli*/ADH-A-catalyzed dynamic reductive kinetic resolution as a key step.

In this review we already have come across synthetic strategies that make use of cyclization of styrene-type carboxylic acids, which we have also named stilbene-2-carboxylic acids or 2-(alk-1-enyl)benzoic acids (Schemes 8, 10b, 23a and 23b *vide supra*), in the synthesis of a variety of 3-substituted 3,4-DHICs. Disappointingly, none of these approaches were enantioselective and, thus, led to the formation of *rac*-3-substituted 3,4-DHICs. Gratifyingly, however, Chen *et al.* (2012) have utilized these styrene-type carboxylic acids to effect an asymmetric bromocyclization leading to the formation of optically active 4-bromo-3,4-DHICs in good yields and % ees. The asymmetric induction in this method is caused by an amino-thiocarbamate chiral catalyst such as compound **146** and **149** (Scheme 25).



Scheme 25: Enantioselective synthesis of 4-Bromo-3,4-DHICs and phthalides through the Bromocyclization of Styrene-type Carboxylic Acids

By fine-tuning some of the reaction parameters, such as the electronic nature of the olefinic double bond, catalyst, solvent, etc., Chen and co-workers could selectively obtain either the 4-bromo-3,4-DHICs or the equally useful phthalides. More than 20 different styrene-type carboxylic acid substrates were studied in this work; therefore, the two shown in Scheme 25 are chosen to demonstrate the fact that electron

rich olefinic double bonds favoured the formation of the 4-bromo-3,4-DHICs (e.g. **147** *vs* **148**), whereas electron poor olefinic double bonds lead to the formation of phthalides (e.g. **151** *vs* **150**). It is worth mentioning that the 4-bromo-3,4-DHICs provides access to the preparation of other 4-substituted 3,4-DHICs such as the biologically important 4-oxy- and 4-N-substituted 3,4-DHIC systems.

A strategy towards some naturally occurring 4-oxysubstituted 3,4-DHICs has been reported by Fujita *et al*. (2012). This strategy employs a stereoselective oxidative lactonization of *ortho*-alkenylbenzoates in the presence of a chiral hypervalent iodine. The asymmetric induction is caused by the chiral hypervalent iodine reagents ($Ar^*I(OAc)_2$ such as **152** and **153** (Fig. 8).

Starting with the *ortho*-alkenylbenzoates **154a-d**, the asymmetric synthesis of 4-hydroxymellein **156a** and its analogues **156b-d**, as examples of the many 4-oxysubstituted 3,4-DHICs synthesized through this strategy, is outlined in Scheme 26.

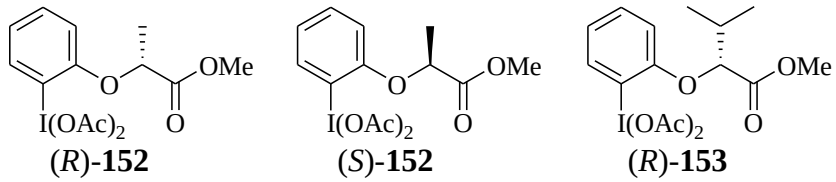
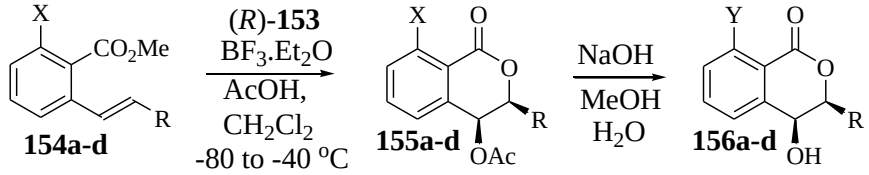


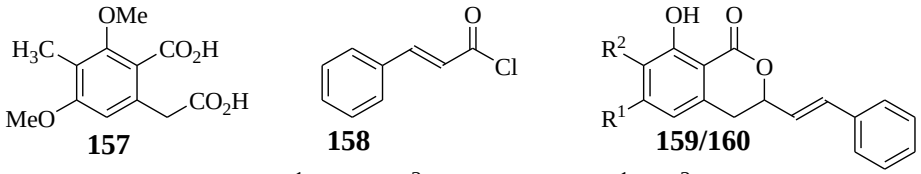
Figure 8: Chiral hypervalent iodine(III) reagents - $Ar^*I(OAc)_2$ (**152**and**153**)



a: R = CH_3, X = OAc, Y = OH
b: R = CH_3, X = Y = H
c: R = *n*-C_5H_{11}, X = OAc, Y = OH
d: R = *n*-C_5H_{11}, X = Y = H

Scheme 26: Stereoselective synthesis of 4-Hydroxymellein **156a** and analogues **156b-d** through the oxidative lactonization of *ortho*-alkenylbenzoates **154a-d**

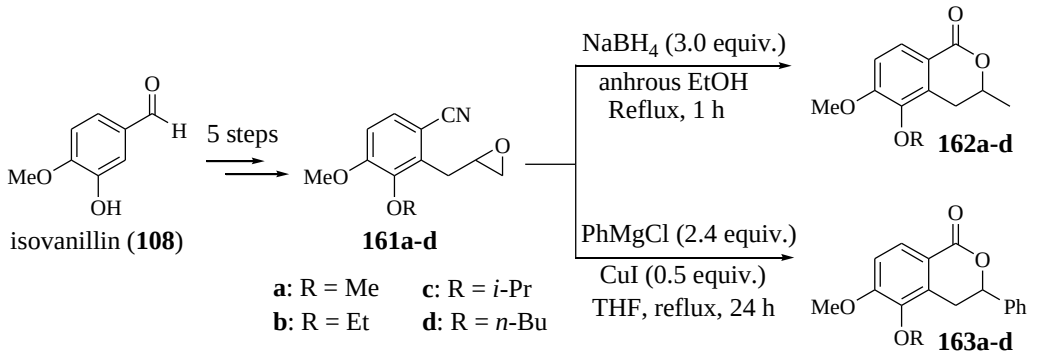
Saeed and collaborators (2013) have used a method analogous to the methods reported by Rama *et al.* (1998) and Saeed (2003), which were summarized in Schemes 12 and 14 (*vide supra*), to synthesize 6,8-dihydroxy-7-methyl-3-styryl-3,4-DHIC (**159**), the analogue of the naturally occurring typharin (**160**). The synthesis was achieved through the initial condensation of the homophthalic acid derivative **157** with cinnamoyl chloride (**158**) (Fig. 9).



159: R^1 = OH, R^2 = CH_3 **160**: R^1 = R^2 = H

Figure 9: 6,8-Dihydroxy-7-methyl-3-styryl-3,4-DHIC (**159**), *via* condensation of homophthalic acid derivative (**157**) with cinnamoyl chloride (**158)**

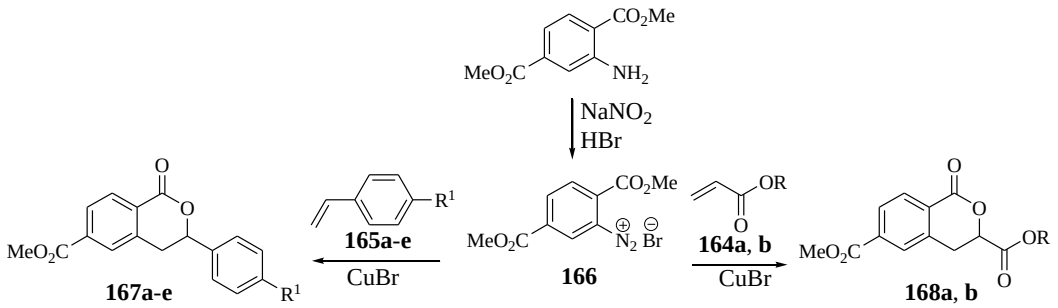
A synthesis of substituted 3-alkyl-3,4-DHICs from the reaction of reaction of *o*-(oxiranylmethyl)benzonitriles **161 a-d** with sodium hydride or Grignard reagent/CuI has been reported by Chen *et al*. (2013). The *o*-(oxiranylmethyl)benzonitrile intermediates were obtained from isovanillin (**108**) in five steps. The epoxide ring of an *o*-(oxiranylmethyl)benzonitrile is opened by a nucleophile ($NaBH_4$ or Grignard reagent/CuI) to give alkoxide anion which attacks the neighboring nitrile to effect an intramolecular cyclization. Subsequent hydrolysis of the resulting isochroman-1-imine intermediates gave the substituted 3-alkyl-3,4-DHICs **162a-d** and **163a-d** as shown in Scheme 27.



a: R = Me **c**: R = *i*-Pr
b: R = Et **d**: R = *n*-Bu

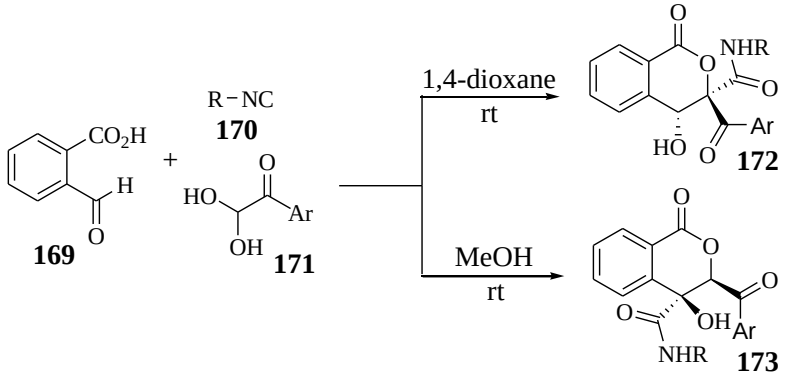
Scheme 27: 3-Alkyl-3,4-DHICs (**162a-d** & **163a-d**) from *o*-(oxiranylmethyl)benzonitriles **161a-d** with $NaBH_4$ and PhMgCl/CuI Nucleophiles

A synthetic strategy involving the Meerwein arylation of alkyl acrylates and styrenes by means of an *ortho*-alkoxycarbonyl arenediazonium bromide with concomitant intramolecular cyclization of the intermediate *ortho*-(alk-1-enyl)benzoates has been reported to yield 3-aryl/alkoxycarbonyl-3,4-DHICs **164a-e** and **165a-b** (Turytsya *et al*. 2014). An outline of this strategy is shown in Scheme 28. The arenediazonium bromide **166** was obtained from the commercially available dimethyl 2-aminoterephthalate.



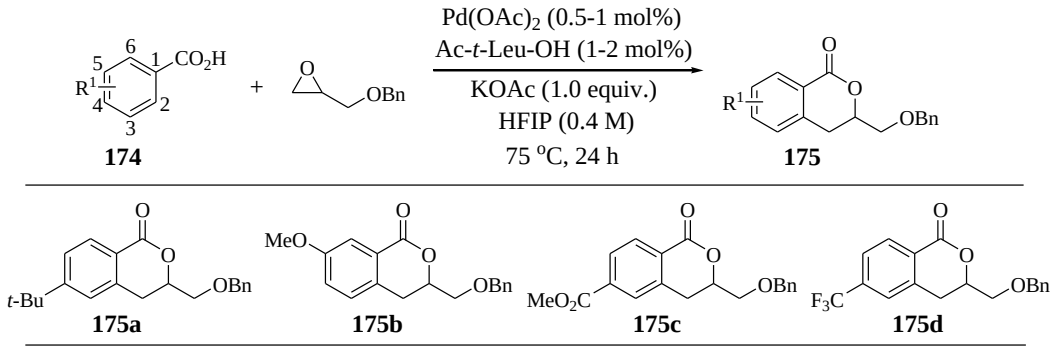
Scheme 28: Synthesis of 3-aryl/alkoxycarbonyl-3,4-DHICs **164a-e** and **165a-b** by Meerwein arylation reaction

A domino strategy incorporating a Passerini 3-component-reaction (P-3CR) and an aldol condensation has been exploited by Ma and co-workers (2014) for the synthesis of 3,4-DHICs with a richly substituted lactone moiety. Two solvent-dependent pathways for this Passerini-aldol sequence leads to differently substituted 3,4-DHICs. When 1,4-dioxane is used as the solvent, the 4-monosubstituted 3,3-disubstituted-3,4-DHICs **172**. On the other hand, using methanol as the solvent leads to formation of the 4,4-disubstituted 3-monosubstituted-3,4-DHICs **173**. The three components (3Cs) required for this domino reaction consist of 2-formylbenzoic acid derivatives **169**, isocyanides **170** and arylglyoxals **171**. Ma and co-workers employed a variety of isocyanides and arylglyoxals to react with 2-formylbenzoic acid. Scheme 29 is a general representation of the solvent-dependent pathways for this Passerini-aldol domino reaction.

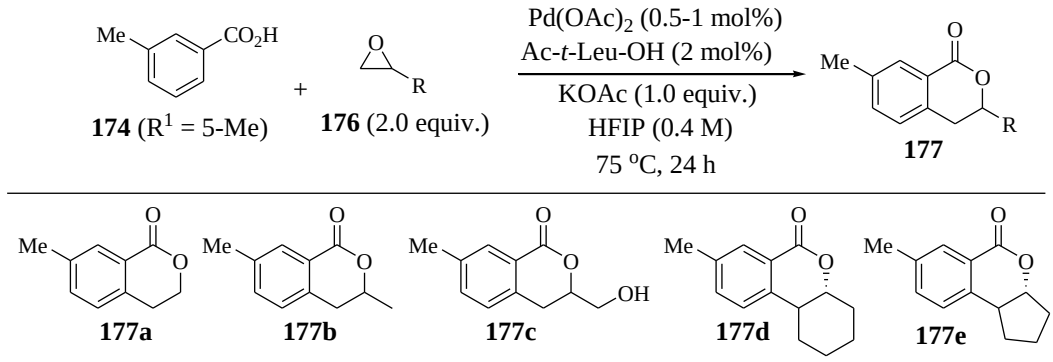


Scheme 29: Synthesis of 3,4-substituted 3,4-DHICs **172** and **173** by Passerini-aldol domino reaction

A very resourceful Pd(II)-catalyzed *ortho* C(sp^2)–H alkylation of benzoic acids with epoxides has been reported by Cheng *et al.* (2015). The C−H alkylation step occurs *via* a redox-neutral S_N2 nucleophilic ring opening process similar to the Grignard reaction. The free alcohol intermediates resulting from alkylation step subsequently undergo lactonization to give 3,4-DHICs in one pot. The range in the variety of both substrates (*i.e.*, the benzoic acid derivatives and epoxides) is very wide and, thus, making this strategy very practical. Both electron donating (e.g. R^1 = *t*-Bu, OMe as in **175a**, **b**) and electron withdrawing groups (e.g. R^1 = CO_2Me, CF_3 as in **175c**, **d**) in the benzoic acid derivatives are well-tolerated in this reaction (Scheme 30a). Moreover, both terminal (as in **177a-c**) and internal epoxides (as in **177d, e**) are also compatible with this reaction (Scheme 30b).



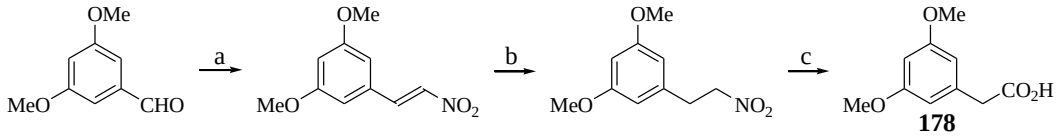
Scheme 30a: Synthesis of 3-substituted 3,4-DHICs **175a-d** by Pd(II)-catalyzed C−H Alkylation: Illustrative Examples of the Benzoic Acid Substrate Scope



Scheme 30b: Synthesis of 3-substituted 3,4-DHICs **177a-e** by Pd(II)-catalyzed C−H Alkylation: Illustrative Examples of the Epoxide Substrate Scope

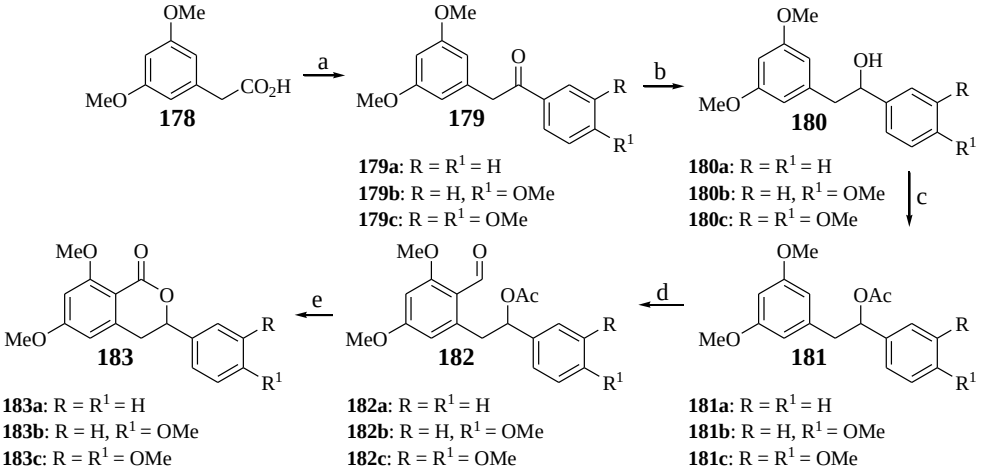
By means of a well thought-out Friedel-Crafts acylation, Vilsmeier-Haack formulation and oxidative cyclization, Limaye *et al.* (2015) have accomplished a convenient synthesis of the *O*-methylated analogues of the naturally occurring 3-aryl-3,4-DHICs montroumarin and thunberginols **C** and **D**. 3,5-Dimethoxyphenyl acetic acid

(**178**), which is the starting material for this synthetic protocol, was obtained from 3,5-dimethoxybenzaldehyde in three steps employing a Nef reaction as a key step.The synthesis of 3,5-Dimethoxyphenyl acetic acid (**178**) and its subsequent conversion to the *O*-methylated analogues of montroumarin (**183a**) and thunberginols **C** (**183b**) and **D** (**183c**) are summarized in Schemes 31 and 32, respectively.



Conditions: **a**: CH_3NO_2, NH_4OAc-AcOH, 80 ^oC, 30 min.; **b**: $NaBH_4$, EtOH-EtOAc 20 ^oC - rt, 2 h; **c**: $NaNO_2$-AcOH, DMSO, 35 ^oC, 2 h

Scheme 31: Synthesis of 3,5-dimethoxyphenyl acetic acid (**178**)

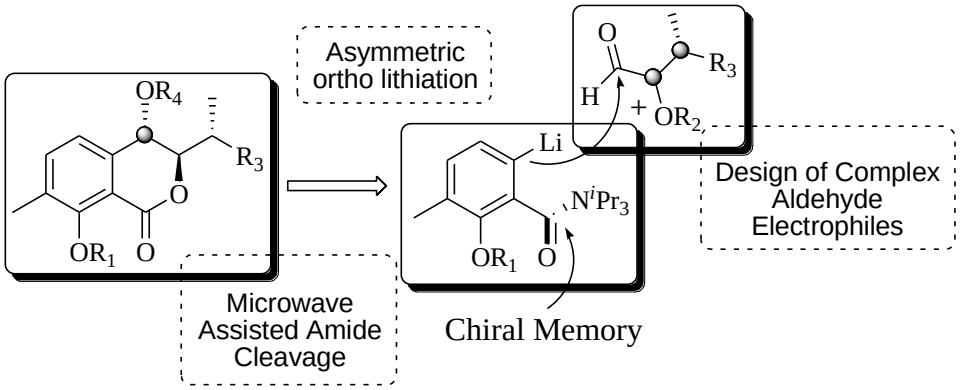


Conditions: **a** (i): $SOCl_2$, reflux, 1 h (ii) Benzene or anisole or 1,2-dimethoxybenzene, $AlCl_3$, rt, 2 h; **b**: $NaBH_4$/MeOH rt, 1 h; **c**: Ac_2O/Pyridine, rt, 1 h; **d**: DMF-$POCl_3$ 0 ^oC-rt, 3 h; **e** (i): $KMnO_4$, dioxane-H_2O, 80 ^oC, 45 min. (ii) conc. HCl, 80 ^oC, 30 min.

Scheme 32: Synthesis of *O*-methylated analogues of montroumarin (**183a**) and thunberginols C (**183b**) and D (**183c).**

Essig and Menche (2016) have reported aninnovative method for the stereoselective synthesis of the 4-hydroxy 3,4-DHIC moiety present in many bioactive natural products including the ajudazols. The method is based on an *ortho* lithiation and asymmetric condensation with aldehyde electrophiles as the key step. The stereocontrol in this condensation reaction is due to the chiral memory of a preoriented atropisomeric

amide axis. The amide with preoriented atropisomeric amide axis (the aromatic reaction partner for the *ortho* lithiation) was obtained from functionalization of 3-methylsalicylic acid. The aldehyde electrophiles developed in this strategy consisted of one or two stereogenic centres and, therefore, allowing access to different stereoisomers of the 4-hydroxyl-3,4-DHICs with up to three adjacent stereocenters; these stereochemical features are present in many bioactive 3,4-DHICs including the ajudazols. In order to achieve the lactonization step, the authors developed efficient procedures for the cleavage of sterically hindered amides; these procedures involve either *O*-alkylation of the amide with MeOTf or the utilization of acetic acid under microwave activation. The design of this conceptually novel approach to the 4-hydroxy-3,4-DHICs is shown in Scheme 33 as a graphical abstract (Essig and Menche 2016).



Scheme 33: Design of a Novel Approach towards the 4-Hydroxy-3,4-DHICs with up to Three Adjacent Stereocentres

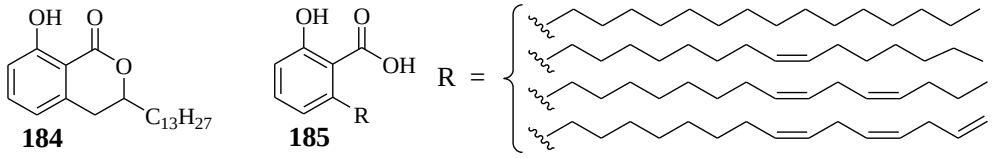
After the appraisal of some past (1950s-2006) and present (2007-2016) synthetic approaches toward the mellein-type 3,4-DHICs and related lactones, the overall state, in terms of the frequently used synthetic strategies, comes into view. Moreover, the commonly employed synthetic intermediates/starting materials have been revealed. In the next section the author strives to describe ways in which some of the synthetic intermediates encountered in the preceding section could be derived from anacardic acid, an inexpensive renewable resource. Therefore, the next section, in conjunction with knowledge of the existing synthetic methodologies described above, presents a researcher with the choice of conceiving a synthetic route towards the title compounds starting from anacardic acid.

PROJECTED SYNTHETIC METHODOLOGIES TOWARD MELLEIN-TYPE 3,4-DHICs AND RELATED LACTONES FROM ANACARDIC ACID

The preceding section of this review has revealed that the existing major synthetic approaches towards the mellein-type 3,4-DHICs have included the traditional multistep syntheses involving benzoic acid, phenylacetic acid and homophthalic acid derivatives, *ortho* and lateral lithiation of benzoic acid derivatives, Diels-Alder

reaction of acetylenic dienophiles with cyclohexa-1,3-dienes, direct thermal condensation of acid chlorides with homophthalic acid and acid-catalyzed or thermal cyclization of *ortho*-(alk-1-enyl)benzoic acid derivatives. In recent years, asymmetric approaches involving chiral auxiliary oxazolines, chiral catalysts and chemoenzymatic protocols have emerged. Moreover, Pd-catalyzed cross coupling reactions (e.g. the Sonogashira and Heck-Matsuda reactions) and C(sp^2)–H alkylation of benzoic acid derivatives have also been employed in recent times. Other metal-catalyzed methods including the CuBr-catalyzed Meerwein arylationof acrylates or styrenes and the Cp_2TiCl-catalyzed Barbier-type radical reactions have also featured among the synthetic methodologies toward the title compounds.

Despite the apparent diversity in synthetic approaches highlighted above, the key synthetic precursors/intermediates have, however, remained limited to primarily benzoic acid derivatives. It is in this light that this section seeks to propose ways on how some of the intermediates encountered in this review can be obtained from anacardic acid, which is a relatively abundant naturally occurring benzoic acid derivative. Precedence is available from the recently published work by Mgaya *et al*. (2015) in which the anacardic acid component of CNSL was utilized as the raw material in the synthesis of 8-hydroxy-3-tridecyl-3,4-dihydroisocoumarin (**184**). Figure 10 shows the structures of compound **184** as well as anacardic acid (**185**).



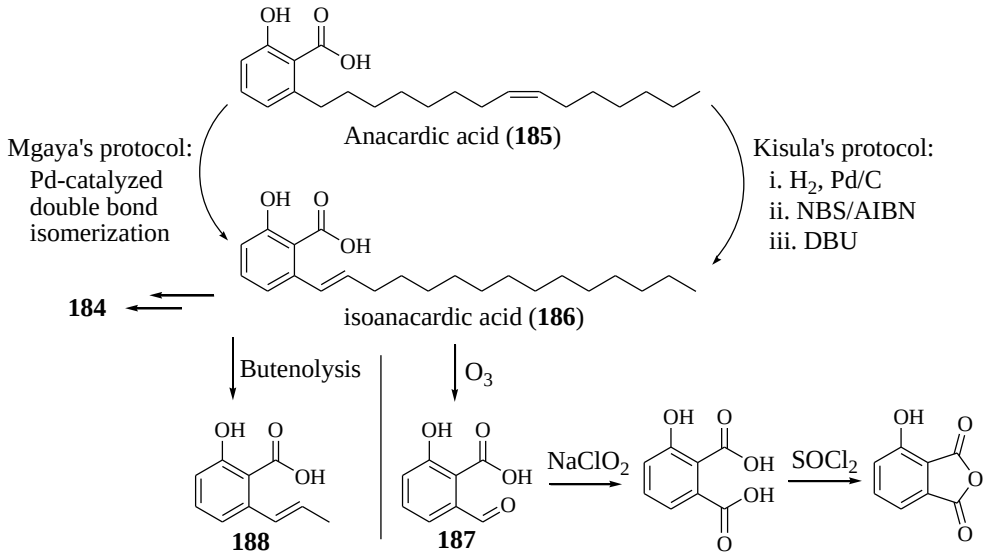
184 **185**

Figure 10: Structure of 8-hydroxy-3-tridecyl-3,4-dihydroisocoumarin (**184**) prepared from anacardic acid (**185**)

Prior to the presentation of the intended schematic description of ways in which anacardic acid (**185**) can chemically be manipulated to afford some synthetic precursors open to further conversion to 3,4-DHICs, it would be prudent to briefly comment on its chemical constitution. As shown in Figure 10, anacardic acid is in essence a salicylic acid derivative. The C_{15} substituent at position 6 occurs as a mixture of a pentadecyl, 8*Z*-pentadecenyl, 8*Z*,11*Z*-pentadecadienyl and 8*Z*,11*Z*,14-pentadecatrienyl carbon chain. However, it is significant to note that the monoenyl (8*Z*-pentadecenyl) side chain constitutes the predominant sub-structure of anacardic acid; consequently, anacardic acid is often formulated as a single compound containing the monoenyl (8*Z*-pentadecenyl) side chain.

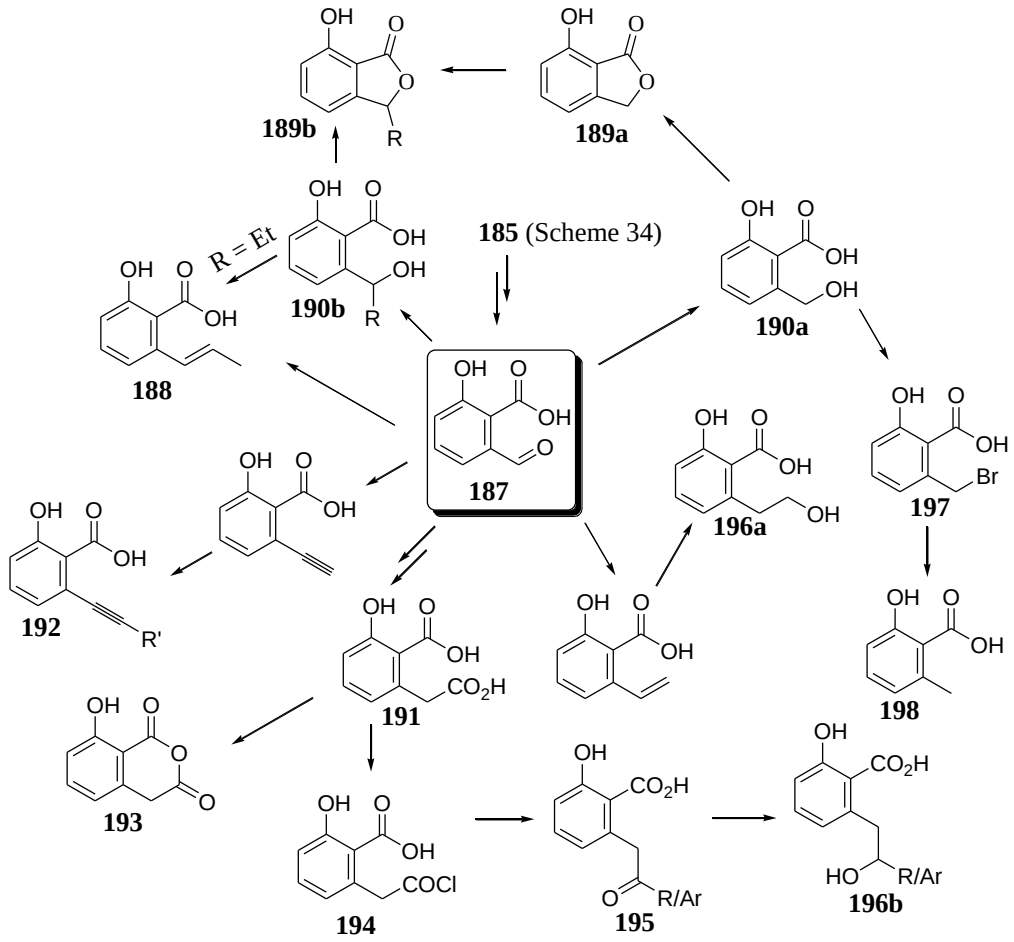
With the foregoing structural clarification in mind, Schemes 34 and 35 graphically summarizes the proposed routes to some of the key intermediates for the synthesis of 3,4-DHICs. The conversion of anacardic acid (**185**) to isoanacardic acid [*i.e.*, (*E*)-2-hydroxy-6-(pentadec-1-enyl)benzoic acid (**186**)] is at the core of these ideas proposed herein. This has already been accomplished by Mgaya *et al*. (2015) and

Kisula (2015) by applying different synthetic protocols as shown in Scheme 34.



Scheme 34: Conversion of anacardic acid (**185**) to isoanacardic acid (**186**) by two different protocols.

As pointed out earlier, Mgaya and co-workers (2015) successfully converted isoanacardic acid (**186**) to 3-tridecanyl-3,4-DHIC **184** (Fig. 10 and Scheme 34). Moreover, compound **188** was obtained from the same source by an alkene metathesis reaction using *cis*-2-butene. In this review we already have encountered the methyl ether (*i.e*, the 2-methoxy derivative **103a**, Scheme 10b) of compound **188**. This imply that isoanacardic acid, obtained from anacardic acid, is a viable source of compound **188**, a key intermediate toward the mellein-type 3,4-DHICs. At this point, the author would like to focus attention on the potential of 6-formyl-2-hydroxybenzoic acid (**187**), obtained from ozonolysis of isoanacardic acid, as a key synthetic precursor towards the title compounds. Earlier in this review we came across the 2-methoxy derivative of compound **187** (*i.e.*, compound **102a** Scheme 10b *vide supra*) as a precursor in the synthesis of a mellein-type 3,4-DHIC. Scheme 35 outlines some routes toward other synthetic precursors utilizing compound **187** as the hub.



Scheme 35: Conversion of aldehyde **187** obtained from anacardic acid (**185**) to diverse synthetic precursors (**188**-**197**)

The phthalides 1**89a**, **b**, benzyl alcohols **190a**, **b**, homophthalic acids **191**, 2-(alk-1-ynyl)benzoic acid derivatives **192**, homophthalic anhydrides **193**, 2-(2-chloro-2-oxoethyl)-6-hydroxybenzoic acid derivatives **194**, keto acids **195**, β-phenethyl alcohols [or 2-(2-hydroxyalkyl/aryl)benzoic acid derivatives] **196a**, **b**, 2-(halomethyl)benzoic acid derivatives **197** and 6-methylsalicylic acid **198** and its derivatives were among the most frequently encountered precursors/intermediates described in this review. Schemes 34 and 35, therefore, demonstrates the potential of utilizing CNSL phenolic constituents in the syntheses of 3,4-DHICs since all the above mentioned synthetic precursors can be obtained from anacardic acid (**185**) via isoanacardic acid (**186**) and 6-formyl-2-hydroxybenzoic acid (**187**). Consequently, we have initiated synthetic work utilizing anacardic acid as well cardanol and cardol, the other major components of CNSL, for syntheses of some of the above fine

chemicals and others as well as natural products and results will be reported in due course.

CONCLUSION

This review has brought together some of the earliest (past) and the more recent (present) synthetic methodologies toward the mellein-type and other 3,4-DHICs. Moreover, the review has simultaneously proposed potential (projected) synthetic strategies focusing on the utilization of anacardic acid from Cashew Nut Shell Liquid (CNSL) - a readily available natural resource. The utilization of CNSL extracted from the agro-waste Cashew Nut Shells (CNS) will add value to the cashew crop. Therefore, this paper provides a synopsis of the existing and some potential synthetic routes toward melleins and other 3,4-DHICs and, thus, inspire and give opportunities to researchers to choose and apply one or a combination of these synthetic strategies depending on the research resources and facilities are available to them. Work employing some of the proposed strategies is in progress in our laboratories and results will be reported in the near future.

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