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Review

Stereoselective synthesis of monomeric flavonoids

Jannie P.J. Marais [a,*], Daneel Ferreira [a,b], Desmond Slade [a]

[a] *National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy,*
The University of Mississippi, University, MS 38677, USA
[b] *Department of Pharmacognosy, Research Institute of Pharmaceutical Sciences, School of Pharmacy,*
The University of Mississippi, University, MS 38677, USA

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Abstract

Polyphenolic compounds have recently attracted considerable interest in the field of nutrition, health and medicine. This is the result of the growing body of evidence suggesting that these compounds may act as potent antioxidants and/or modulate key biological pathways in vivo in mammals. Studies aimed at comprehending the intricate principles that govern the chemistry of these important natural products have thus accelerated over the past decade. Prominent amongst these is the ability to synthesize monomeric prototypes with and without ^{13}C- and radio-labeling. Endeavors exploiting the stereoselective syntheses of representative classes of flavonoid monomers are reviewed here.

Keywords: Stereoselective synthesis; Chalcone epoxides; α-Hydroxydihydrochalcones; β-Hydroxydihydrochalcones; Dihydroflavonols; Flavan-3-ols; Flavan-3,4-diols; Isoflavans; Pterocarpans; Epoxidation; Dihydroxylation

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Contents

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[*] Corresponding author. Tel.: +1 662 915 5941; fax: +1 662 915 7062.
E-mail address: jmarais@olemiss.edu (J.P.J. Marais).

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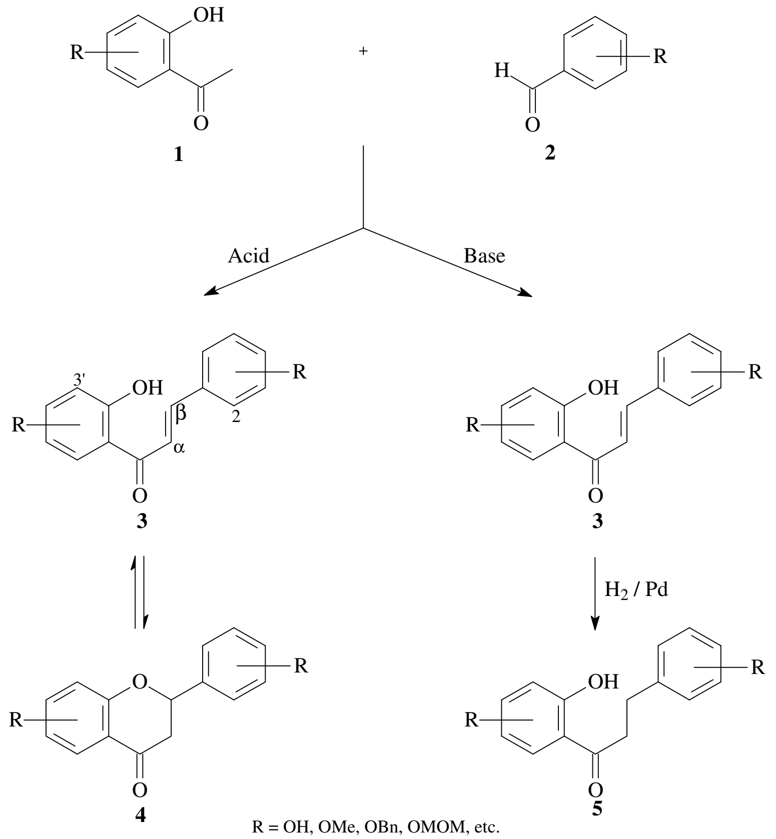
1. Introduction

The study of flavonoid chemistry has emerged, like that of most natural products, from the search for new compounds with useful physiological properties. In addition to the multitude of industrial applications, the oligo- and polymeric proanthocyanidins are now also credited for the profound health-promoting effects of tea, fruit juices and red wine. This is mainly due to their in vitro antioxidant and radical scavenging properties, while the polyflavonoids in red wine have recently been implicated in protection against cardiovascular disorders, e.g., the 'French paradox'. The isolation of the first polymeric proanthocyanidins by Forsyth and Roberts (1960) was followed by the identification of several oligomeric flavonoids in optically active form (Mayer et al., 1966; Drewes et al., 1967; Weinges et al., 1960, 1968; Thompson et al., 1972). Although important progress has been made in the studies of these compounds through acid- (Geissman and Yoshimura, 1966; Haslam, 1974; Fletcher et al., 1977; Botha et al., 1978a, 1981a) or base-catalyzed (Hemingway and Foo, 1983; Foo and Hemingway, 1984) condensation of monomeric units, the systematic study of natural proanthocyanidins is still hampered by the inaccessibility of enantiomeric pure monomeric starting materials. Semisynthetic endeavors of proanthocyanidins are therefore confined to those substitution patterns exhibited by monomeric natural products that are available in quantities sufficient for preparative purposes. Isolation of such compounds often includes tedious processes. In order to alleviate these restrictions, several programs focusing on synthesis of enantiomeric pure flavonoids monomers have been undertaken. However, synthesis of the desired enantiomer in optically pure forms remains a daunting objective and are limited to only a few type of compounds. Chalcone epoxides, α- and β-hydroxydihydrochalcones, dihydroflavonols, flavan-3-ols, flavan-3,4-diols, isoflavans and pterocarpans have thus far been synthesized in reasonable yields and purity.

2. Chalcones, dihydrochalcones and racemic flavanones

Chalcones, and the closely related dihydrochalcones, constitute the most important intermediates in the synthesis of flavonoids and are considered to be the primary C_6–C_3–C_6-precursors to most flavonoids. In general, chalcones are readily accessible via two well established routes which comprise a base-catalyzed aldol condensation or acid mediated aldolization of 2-hydroxyacetophenones **1** and benzaldehydes **2** (Von Konstanecki and Rossbach, 1896; Augustyn et al., 1990a) (Scheme 1). The base-catalyzed aldol condensation represents a



Scheme 1. Acid- and base-catalyzed synthesis of chalcones, racemic flavanones and dihydrochalcones.

more feasible route towards chalcones **3** because the acid protocol is prone to subsequent cyclization to afford the corresponding racemic flavanones **4** (Claisen and Claparéde, 1881). Dihydrochalcones **5** are generally obtained via reduction (H_2/Pd) of the preceding chalcones (Scheme 1).

3. Chalcone epoxides

Owing to the versatile chemistry of epoxides, initial efforts towards synthesis of flavonoids centered on *trans*-chalcone epoxides. Because of the reactivity of 2′-OH chalcone epoxides, most attempts towards their synthesis usually require 2′-OH protection prior to epoxidation (Adams and Main, 1991). Despite the good yields (99–100%) obtained for epoxidation of a few non-natural 2′-OH chalcones utilizing dimethyldioxirane (DMDO), this protocol has not yet been extended to free phenolic chalcones exhibiting natural oxygenation patterns (Adam et al., 1992; Patonay et al., 1993).

In an alternative attempt to obtain the corresponding 2′-OH chalcone epoxides, chalcone epoxide 2′-*O*-tetrahydropyranyl ethers were cleaved in the presence of aq. acidic dioxane (Adams and Main, 1991). Surprisingly, deprotection was established without ring-opening of the highly labile oxirane functionality, an approach found to be unsuccessful when using the methoxymethyl protecting group (Li et al., 1990). In spite of the good yields (88–100%), this protocol was again restricted to a few un-natural analogs. In contrast, the 2′-OH protected chalcone epoxides are readily obtainable in high yields via utilization of H_2O_2/NaOH in methanol (Adams and Main, 1991). The above protocols clearly emphasize the feasibility of chalcone epoxide formation. Thus, the asymmetric synthesis of these precursors had become a prime objective.

3.1. *Asymmetric epoxidation of chalcones*

The asymmetric epoxidation of olefinic bonds plays an important role as initial step in the synthesis of several classes of optically active organic compounds. Sharpless (Katsuki and Sharpless, 1980; Johnson and Sharpless, 1993) and Jacobson (1993) developed viable protocols for the enantioselective epoxidation of allylic alcohols and unfunctionalized olefins. However, attempts regarding the enantioselective epoxidation of α,β-unsaturated ketones, in particular chalcones, has met with limited success.

Since Wynberg and Greijdanus (1978) first reported the utilization of quinine benzylchloride **6** (BQC) and quinidine benzylchloride (BQdC) **7** as chiral phase-transfer catalysts (PTC), the use of PTC has emerged as one of the fundamental techniques for the asymmetric epoxidation of α,β-unsaturated ketones. Utilization of catalysts **6** and **7** in a Weitz–Scheffer reaction (30% aq. H_2O_2/NaOH/toluene) (Weitz and Scheffer, 1921) led to the first preparation of (−)- and (+)-*trans*-chalcone epoxides **14a/b**, **15a/b**, **16a**, **17a**, **18a** and **19a/b** in moderate to high yields (38–92%), but with poor enantiomeric excess (ee, 25–48%) (Helder et al., 1976; Wynberg and Greijdanus, 1978) (Table 1, Scheme 2). In order to assign absolute configuration to the (+)- and (−)-chalcone epoxides, Marsman and Wynberg (1979) compared the configuration of the α-hydroxydihydrochalcone **20a** prepared from (−)-**14a** to that of the similar compound obtained from L-(−)-α-phenyllactic acid with α-(*S*) configuration. Because opposite rotations were found for **20a** and **20b**, *R* and *S* configuration were assigned to the α- and β-carbon, respectively, of the *trans*-epoxyketone (−)-**14a** (Scheme 3).

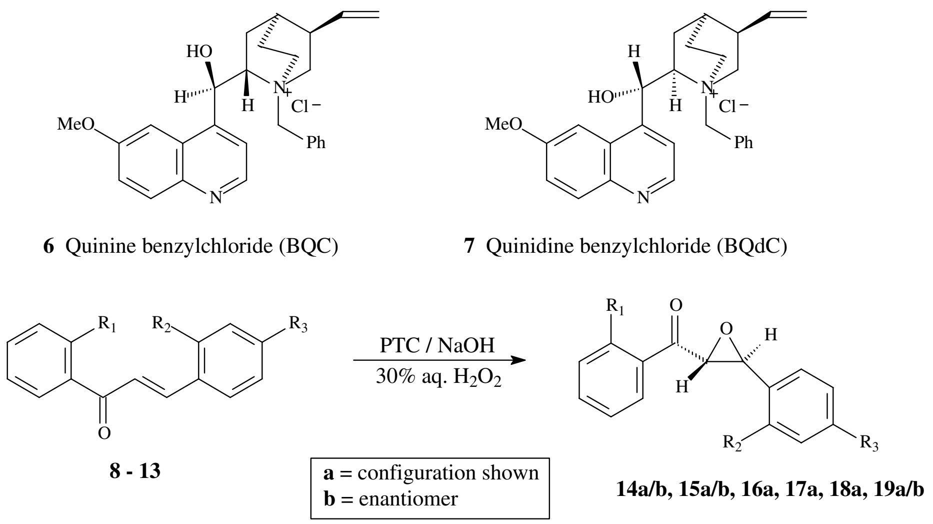
The poor ee obtained in this protocol and several unsuccessful attempts to improve these reactions, resulted in several investigations of alternative catalysts and reaction conditions to enhance the enantioselectivity of the epoxidation of enones (Table 2). However, attempts to synthesize asymmetric epoxides from α,β-unsatured ketones were limited mainly to non-chalcone enones and a few non- and mono-oxygenated chalcone substrates, mostly lacking natural product oxygenation patterns.

As feasible alternative to the utilization of enzymes as catalysts in organic reactions, Julia and Colonna (Julia

Table 1
Epoxidation of chalcones **8**–**13** with BQC **6** and BQdC **7** as PTC

Chalcone	R_1	R_2	R_3	PTC	Epoxide	% Yield	$[\alpha]_{278}$ (°)	% ee
8	H	H	H	**6**	(−)-**14a**	92	−65	31
8	H	H	H	**7**	(+)-**14b**	*	+49	*
9	OMe	H	H	**6**	(−)-**15a**	*	−34	25
9	OMe	H	H	**7**	(+)-**15b**	*	+29	*
10	H	OMe	H	**6**	(−)-**16a**	92	−115	48
11	H	H	Cl	**6**	(−)-**17a**	*	−62	*
12	H	H	NO_2	**6**	(−)-**18a**	*	−33	*
13	OMOM	H	H	**6**	(−)-**19a**	38	−31	26
13	OMOM	H	H	**7**	(+)-**19b**	41	+39	25

* Not reported.



6 Quinine benzylchloride (BQC)

7 Quinidine benzylchloride (BQdC)

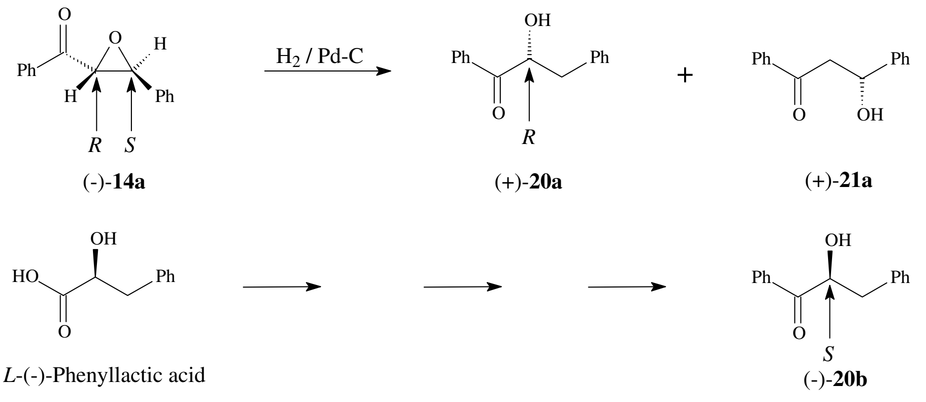
8 - 13

14a/b, 15a/b, 16a, 17a, 18a, 19a/b

Scheme 2. Epoxidation of chalcones **8**–**13** with BQC **6** and BQdC **7** as PTC.

et al., 1980, 1982; Colonna et al., 1983; Banfi et al., 1984) investigated the use of synthetic peptides in the epoxidation of chalcones. These poly-amino acids **23** were prepared via the *N*-carboxy anhydride (NCA) derivatives **22** of the corresponding L- and D-amino acids **21** (Scheme 4). The triphasic system comprising poly-L- or poly-D-alanine, alkaline H_2O_2, and organic solvent (CCl_4 or toluene) was utilized during the enantioselective epoxidation of chalcones **8**–**12** and **24** to afford epoxides **14a/b**, **15a**–**18a** and **25b** in moderate to high yield and ee (Table 3, Scheme 5). The origin of chiral induction in this epoxidation remains unknown, but hydrogen bonding between the carbonyl function of the substrate and the peptide group of the catalyst seems to play the decisive role in superimposing the α-helical structure of the poly-amino acid onto the chalcone. This is substantiated by the fact that maximum ee is reached at maximum α-helical conformation in the catalyst, and poly-L-amino acid lacking amidic hydrogens are ineffective as catalyst from a chemical as well as stereoselective viewpoint.

Because of the potential use of poly-oxygenated chalcone epoxides as chirons in the enantiomeric synthesis of flavonoids and to determine the effect of different levels of oxygenation and substitution patterns on the poly-amino acid catalyzed epoxidation, this protocol was extended to a series of chalcones exhibiting aromatic oxygenation patterns usually encountered in the natural occurring flavonoids (Bezuidenhoudt et al., 1987; Augustyn et al., 1990a). Thus, the triphasic system comprising poly-L- or poly-D-alanine, alkaline H_2O_2 and organic solvent (CCl_4 or toluene) was utilized during the enantioselective epoxidation of chalcones **13** and **26**–**31**, to afford epoxides **19a/b** and **32a/b**–**37a/b** in moderate to high yield and ee (Table 4, Scheme 6). Poly-L-alanine consistently gave higher ee's than poly-D-alanine due to its higher optical purity. Although excellent yields and enantiomeric excess were achieved in the preparation of the (−)-deoxy oxirane **14a** (yield 85%; ee 86%) and the (−)-4,4′-dimethoxy-2′-*O*-methoxymethyl analog **33a**, stereoselectivity was disappointingly low for **19a** and the highly oxygenated compounds **35a** and **36a**.



(-)-**14a**

(+)-**20a**

(+)-**21a**

L-(-)-Phenyllactic acid

(-)-**20b**

Scheme 3. Determination of the absolute configuration of chalcone epoxides.

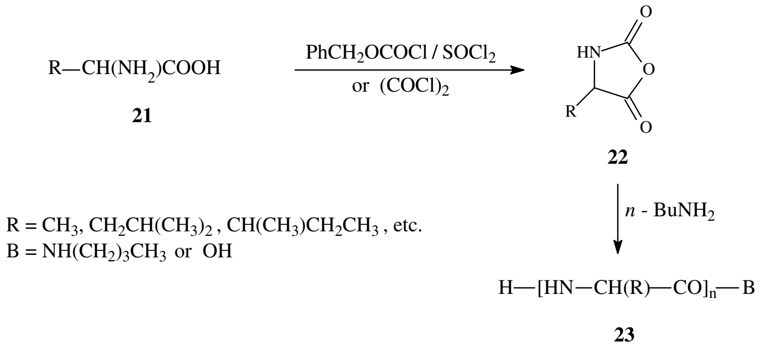
Table 2
Asymmetric epoxidation of electron-deficient olefins

Type of reaction and reaction conditions	Yield and ee	References
1. Bovine serum albumin catalyzed epoxidation		
Bovine serum albumin (BSA) under Weitz–Scheffer conditions and aq. NaOCl with α- and β-cyclodextrins as catalysts	Poor ee	Colonna et al. (1985, 1986)
2. Zinc-mediated asymmetric epoxidation		
Metal-based catalytic systems. Epoxidation of α,β-unsaturated ketones with O_2 in the presence of Et_2Zn and (*R*,*R*)-*N*-methylpseudoephedrine	Good enantioselectivity on various substrates, significant decrease in ee for chalcones	Enders et al. (1996, 1997)
Metal-based polymeric catalytic systems. Polybinaphthyl zinc catalyst for the asymmetric epoxidation of enones in the presence of Bu^tOOH (TBPH)	Good yield (81–95%) and ee (70–74%) on three substrates	Yu et al. (1999)
3. Lanthanide-BINOL systems		
Asymmetric epoxidation of enones using lanthanoid complexes. Several kinds of heterobimetallic chiral catalysts (La- and Yb-BINOL and La- and Yb-3-hydroxymethyl-BINOL complexes) are useful for this procedure, using TBHP and cumene hydroperoxide (CMHP)	Good yields (55–95%) and enantioselectivity (ee: 83–94%) on various chalcone substrates	Bougauchi et al. (1997) and Daikai et al. (1998)
Enantioselective epoxidation of α,β-enones by utilizing chiral La(*O*-*i*-Pr)$_3$-(*S*)-6,6′-dibromo-BINOL and Gd(*O*-*i*-Pr)$_3$-(*S*)-6,6′-diphenyl-BINOL catalysts and CMHP	High yields (81–95%) and enantioselectivity (ee: 73–94%) on various chalcone substrates	Chen et al. (2001)
4. Diethyl tartrate-metal peroxides		
Modified Sharpless protocol, with chiral metal alkyl peroxides as nucleophilic oxidants. Using (+)-diethyl tartrate [(+)-DET] as chiral modifier in the presence of Li-TBHP and *n*-BuLi, yielded the (+)-chalcone epoxide. The (−)-chalcone epoxide was obtained simply via replacing *n*-BuLi with *n*-Bu_2Mg	(+)-Chalcone epoxide: yield, 75%; ee, 62%; (−)-chalcone epoxide: yield, 61%; ee, 94%	Elston et al. (1997)
5. Phase-transfer catalyst		
Enantioselective epoxidation of chalcones utilizing Cinchona alkaloid-derived quaternary ammonium phase-transfer catalysts bearing an *N*-anthracenylmethyl function with sodium hypochlorite as oxidant	Good yields (75–97%) and enantioselectivity (ee: 69–89%) on various chalcone substrates	Lygo and Wainwright (1998, 1999) and Lygo and To (2001)
Use of chiral quaternary cinchonidinium and dihydrocinchonidinium cations for the nucleophilic epoxidation of various α,β-enones, utilizing KOCl in stoichiometric amounts as oxidant, at −40 °C	Excellent yields (70–97%) and ee (91–98.5%) on various substrates	Corey and Zhang (1999)
Catalytic asymmetric epoxidation of enones promoted by aq. H_2O_2 with chiral ammonium salts (cinchonine or quinidine derivatives)	Yields, 88–100% and ee, 65–92% on chalcone substrates	Arai et al. (2002)
Epoxidation of enones under mild reaction conditions, using a new chiral quaternary ammonium bromide with dual functions as phase-transfer catalyst	Good yields (83–99%) and ee (93–97%) on chalcone substrates	Ooi et al. (2004)

(*continued on next page*)

Table 2 (*continued*)

Type of reaction and reaction conditions	Yield and ee	References
Asymmetric epoxidation with optically active hydroperoxides (cumyl hydroperoxide) and mediated by cinchonine- and cinchonidine-derived phase-transfer catalyst	Poor ee on chalcone substrates	Adam et al. (2001)
Epoxidation of chalcones using the phase-transfer catalyst, chiral monoaza-15-crown-5 lariat ethers, synthesized from D-glucose, galactose and mannitol, with TBHP as oxidant	Yields, 28–82% and ee, 3–82% on various chalcone substrates	Bakó et al. (1999, 2004)
Use of optically active solvents [2-(*N*,*N*-diethylamino)-l-butanol or 2-(*N*,*N*-di-*n*-butylamino)-l-butanol], *n*-Bu$_4$NBr as PTC and alkaline H_2O_2	Promising yields (70%), poor ee (8–13%)	Singh and Arora (1987)
6. Epoxidation with chiral dioxiranes		
Involving dimethyldioxirane (DMDO) type of epoxidation utilizing chiral dioxiranes generated in situ from potassium peroxomonosulfate (oxone) and asymmetric ketones	Good yield (80%) and ee (94%) obtained, but only on non-oxygenated chalcones	Wang and Shi (1997a,b, 1999)
2-Substituted-2,4-endo-dimethyl-8-oxabicyclo[3.2.1]octan-3-ones as catalyst for the asymmetric epoxidation of alkenes with oxone	Yield, 24% and ee, 67% of only non-oxygenated chalcones	Klein and Roberts (2002)
7. Poly-amino acid catalyzed epoxidation		
Julia–Colonna asymmetric epoxidation, originally employs a three-phase system, comprising alkaline H_2O_2, an organic solvent (hexane or toluene) and an insoluble polymer (poly-L-/-D-alanine or -leucine)	Good yields and ee, reaction rates slow	Julia et al. (1980), Colonna et al. (1983) and Banfi et al. (1984)
Asymmetric epoxidation using a non-aqueous two-phase system, of urea hydrogen peroxide (UHP) in THF or *tert*-butyl methyl ether, with immobilized poly-L-/-D-leucine	Excellent yields and ee, short reaction times and catalyst recyclable	Adger et al. (1997) and Bentley et al. (1997)
Julia–Colonna stereoselective epoxidation under non-aqueous conditions using poly-amino acid (poly-L-/-D-alanine or-leucine) on silica (PaaSiCat)	Excellent yields and ee, highly active catalyst and recycling of catalyst	Geller and Roberts (1999) and Carde et al. (1999)
β-*Peptides as catalyst*. Poly-β-leucine in Julia–Colonna asymmetric epoxidation	Good yields (70%)	Coffey et al. (2001)
Polyethylene glycol (PEG)-bound poly-L-leucine acts as a THF soluble catalyst for the Julia–Colonna asymmetric epoxidation of enones	Excellent ee even with short chain length polyleucine	Flood et al. (2001)



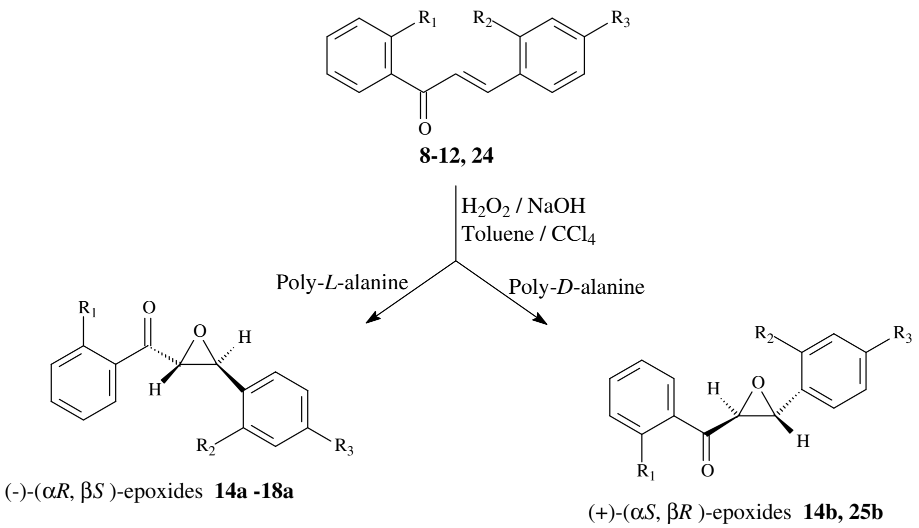
Scheme 4. Preparation of poly-amino acid catalysts.

Table 3
Epoxidation of chalcones **8**–**12** and **24** with poly-L- and poly-D-alanine as PTC

Chalcone	R_1	R_2	R_3	Catalyst	Epoxide	% Yield	$[\alpha]_{278}$ (°)	% ee
8	H	H	H	L	(−)-**14a**	85	−184	86
8	H	H	H	D	(+)-**14b**	53	+194	90
9	OMe	H	H	L	(−)-**15a**	54	−67	50
10	H	OMe	H	L	(−)-**16a**	29	−13	*
11	H	H	Cl	L	(−)-**17a**	47	−148	66
12	H	H	NO_2	L	(−)-**18a**	83	−205	82
24	H	H	OMe	L	(+)-**25b**	53	−230	*

* Not reported.

Although the Julia asymmetric epoxidation has proven to be a reliable reaction and afforded the epoxides of poly-oxygenated chalcone substrates in good yield and moderate to high ee's, this protocol is not without limitations as reaction times are often unacceptably long and requires continuous addition of oxidant and base. Degradation of the poly-amino acid under such reaction conditions also poses difficulties. Bentley and Roberts found satisfactory solutions to many of these problems by conducting the asymmetric epoxidation in a two-phase non-aqueous system consisting of oxidant, a non-nucleophilic base, immobilized poly-amino acid and an organic solvent (Itsuno et al., 1990; Lasterra-Sanchez et al., 1996; Bentley et al., 1997). This procedure afforded chiral epoxides in high yields and optical purity of a series of enones with a substantial reduction in reaction times and was also extended successfully to chalcone substrates (Nel et al., 1998, 1999a, Section 4, and Van Rensburg et al., 1996, 1997a, Section 5).

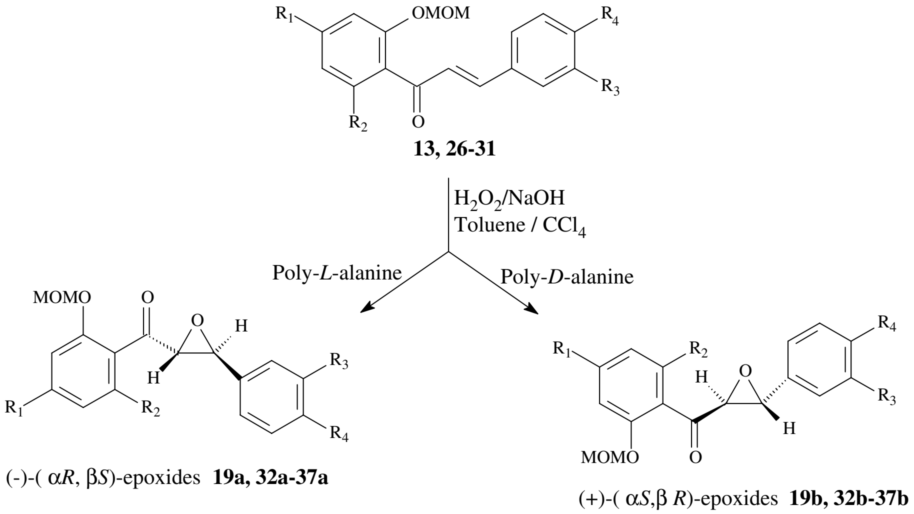


Scheme 5. Epoxidation of chalcones **8**–**12** and **24** with poly-L- and poly-D-alanine as PTC.

Table 4
Asymmetric epoxidation of chalcones **13** and **26**–**31** using poly-L- and poly-D-alanine as catalysts

Epoxides	R_1	R_2	R_3	R_4	Alanine	% Yield	$[\alpha]_{278}$ (°)	% ee
(−)-**19a**	H	H	H	H	L	65	−50	38
(+)-**19b**	H	H	H	H	D	57	+75	53
(−)-**32a**	H	H	H	OMe	L	64	−76	66
(+)-**32b**	H	H	H	OMe	D	38	+52	46
(−)-**33a**	OMe	H	H	OMe	L	74	−122	84
(+)-**33b**	OMe	H	H	OMe	D	26	+77	53
(−)-**34a**	OMe	H	OMe	OMe	L	46	−79	62
(+)-**34b**	OMe	H	OMe	OMe	D	34	+31	25
(−)-**35a**	OMe	OMe	H	OMe	L	*	*	32
(+)-**35b**	OMe	OMe	H	OMe	D	*	*	20
(−)-**36a**	OMe	OMe	OMe	OMe	L	*	*	*
(+)-**36b**	OMe	OMe	OMe	OMe	D	*	*	*
(−)-**37a**	OMOM	H	H	OMe	L	43	*	70
(+)-**37b**	OMOM	H	H	OMe	D	36	*	36

[*] Not reported.

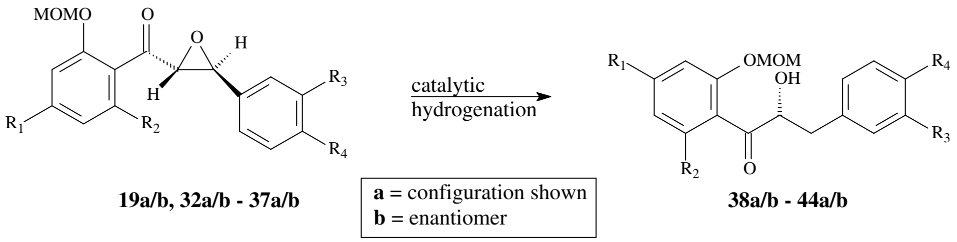


Scheme 6. Asymmetric epoxidation of chalcones **13** and **26**–**31** using poly-L- and poly-D-alanine as catalysts.

Table 5
Synthesis of α-hydroxydihydrochalcones **38a/b**–**44a/b**

Substrate (% ee)	R_1	R_2	R_3	R_4	Catalyst – H_2	Product	% Yield	% ee
(−)-**19a** (38)	H	H	H	H	$Pd/BaSO_4$	(+)-**38a**	92	27
(+)-**19b** (53)	H	H	H	H	$Pd/BaSO_4$	(−)-**38b**	61	54
(−)-**32a**(66)	H	H	H	OMe	$Pd/BaSO_4$	(+)-**39a**	51	61
(+)-**32b** (46)	H	H	H	OMe	$Pd/BaSO_4$	(−)-**39b**	72	48
(−)-**33a** (84)	OMe	H	H	OMe	$Pd/BaSO_4$	(+)-**40a**	88	76
(+)-**33b** (53)	OMe	H	H	OMe	$Pd/BaSO_4$	(−)-**40b**	70	52
(−)-**34a** (62)	OMe	H	OMe	OMe	10% Pd/C	(+)-**41a**	42	61
(+)-**34b** (25)	OMe	H	OMe	OMe	10% Pd/C	(−)-**41b**	40	16
(−)-**35a** (32)	OMe	OMe	H	OMe	5% Pd/C	(+)-**42a**	*	24
(+)-**35b** (20)	OMe	OMe	H	OMe	5% Pd/C	(−)-**42b**	*	19
(−)-**36a** (*)	OMe	OMe	OMe	OMe	10% Pd/C	(+)-**43a**	*	14
(+)-**36b** (*)	OMe	OMe	OMe	OMe	10% Pd/C	(−)-**43b**	*	16
(−)-**37a** (70)	OMOM	H	H	OMe	$Pd/BaSO_4$	(+)-**44a**	50	65
(+)-**37b** (36)	OMOM	H	H	OMe	$Pd/BaSO_4$	(−)-**44b**	46	32

[*] Not reported.



19a/b, 32a/b - 37a/b **38a/b - 44a/b**

Scheme 7. Synthesis of α-hydroxydihydrochalcones **38a/b–44a/b**.

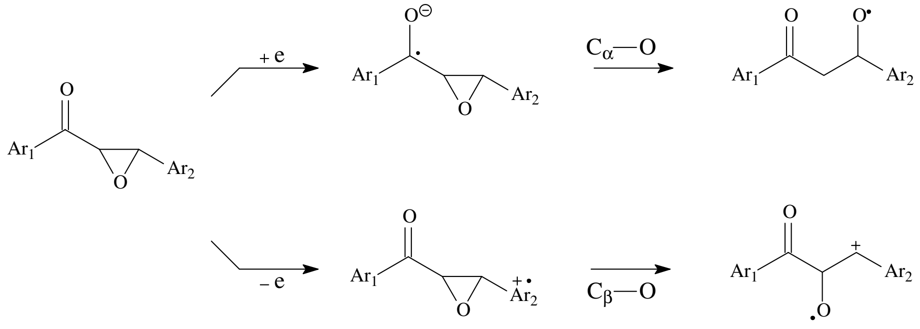
4. α- and β-Hydroxydihydrochalcones

α- and β-Hydroxydihydrochalcones constitute rare groups of C_6–C_3–C_6 metabolites presumably sharing a close biogenetic relationship with the α-methyldeoxybenzions and isoflavonoids (Bhakuni et al., 1973; Shukla et al., 1973; Bezuidenhoudt et al., 1981; Beltrami et al., 1982; Ferrari et al., 1983; Thakkar and Cushman, 1995). Wynberg prepared an aromatic deoxy α-hydroxydihydrochalcone via catalytic hydrogenation of the corresponding chalcone (Marsman and Wynberg, 1979). However, by utilizing the versatile epoxidation methodology, Bezuidenhoudt et al. (1987) and Augustyn et al. (1990a,b) extended this protocol to the enantioselective synthesis of a series of α-hydroxydihydrochalcones. Treatment of (−)-**19a**, **32a**–**37a** and (+)-chalcone epoxides **19b**, **32b**–**37b** with either Pd-$BaSO_4$/H_2 or Pd-C/H_2 afforded (+)-**38a**–**44a** and (−)-α-hydroxydihydrochalcones **38b**–**44b**, respectively, in moderate to high yields (Table 5, Scheme 7).

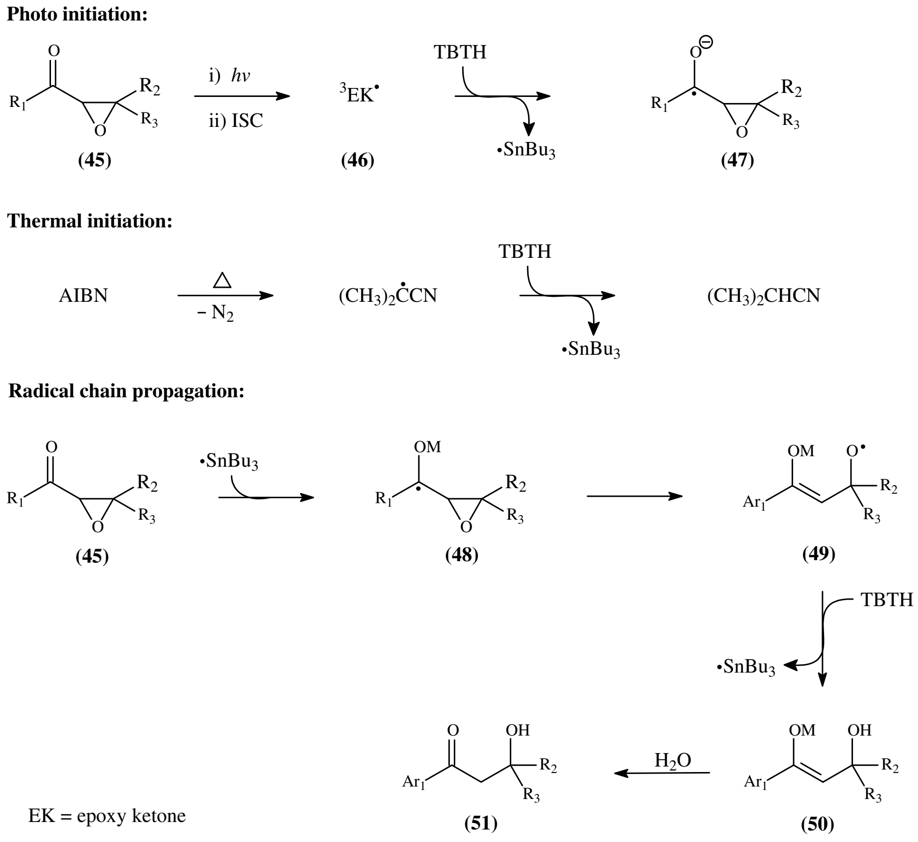
Although several procedures, comprising diverse reagents such as benzeneselenolate ion, samarium diiodide, aluminium amalgam/ultrasound and metallic lithium in liquid ammonia, have been used for the reductive ring-opening of α,β-epoxyketones to form the β-hydroxyketone (Molander and Hahn, 1986; Otsubo et al., 1987; Moreno et al., 1993; Engman and Stern, 1994), the most general reagent for these conversions is tributyltin hydride (TBTH)/azoisobutyronitrile (AIBN). This procedure was first reported by Hasegawa et al. (1992), utilizing TBTH under both photochemical and thermal conditions for the regioselective reductive conversion of α,β-epoxyketones into β-hydroxyketones. The ring-opening under these conditions occurs regioselectively because generation of the radical anion from α,β-epoxy carbonyl compounds causes selective C_α–O bond cleavage to form the β-hydroxyketone. Radical cations from these substrates may also undergo selective C_β–O bond cleavage to form the α-hydroxyketone (Scheme 8).

The photochemical reaction is initiated by excitation of the epoxy ketones to excited triplet states via efficient intersystem crossings (ISC) (Scheme 9) (Kumar et al., 1985). Hydrogen abstraction by the epoxy ketone triplet **46** from TBTH forms the ketyl **47** and tributyltin radicals. In the initiation of the thermal reaction, a catalytic amount of tributyltin radical is generated from the hydrogen abstraction of TBTH by the carbon radical derived from the thermal decomposition of azoisobutyronitrile (AIBN). The tributyltin radical generated in situ, through both initiation processes, adds to the ground state epoxy ketones **45** to form [(tributylstannyl)oxy]methyl radicals **48**, which undergo C_α–O bond cleavage to give the oxy radicals **49**. Subsequent hydrogen abstraction by **49** from TBTH gives β-hydroxytributylstannyl enol ethers **50**, which are hydrolyzed to β-hydroxyketones **51** during workup.

Owing to the excellent results reported by Hasegawa et al. (1992) for the regioselective reductive conversion of α,β-epoxyketones into β-hydroxyketones, Nel et al. (1998, 1999a) applied this method to a series of chalcone epoxides comprising the methyl ethers of substrates with natural hydroxylation patterns. Since the Julia asymmetric epoxidation of chalcones often gives disappointing



Scheme 8. α- and β-Opening of epoxyketones utilizing free radicals.



Scheme 9. β-Opening of the epoxyketone utilizing AIBN and TBTH.

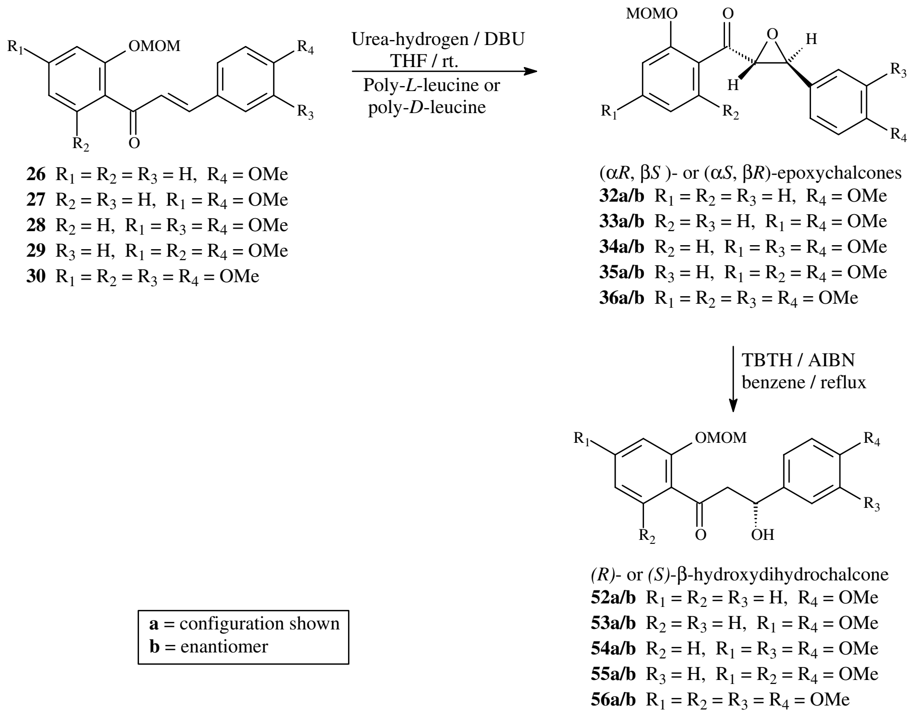
Table 6
β-Hydroxydihydrochalcone formation

Chalcone	Poly-amino acid	Chalcone epoxide	% Yield	% ee	β-Hydroxydihydrochalcone	% Yield	% ee
26	PLL	**32a**	71	85	**52a**	73	85
26	PDL	**32b**	69	81	**52b**	70	80
27	PLL	**33a**	80	95	**53a**	83	91
27	PDL	**33b**	76	90	**53b**	90	88
28	PLL	**34a**	64	88	**54a**	78	84
28	PDL	**34b**	61	87	**54b**	81	85
29	PLL	**35a**	36	60	**55a**	79	55
29	PDL	**35b**	33	61	**55b**	76	61
30	PLL	**36a**	21	53	**56a**	83	48
30	PDL	**36b**	19	50	**56b**	78	47

stereoselectivity, Nel et al. (1998, 1999a) used the improved two-phase non-aqueous system with poly-amino acids as asymmetric catalysts, recently developed by Bentley and Roberts (Lasterra-Sanchez et al., 1996; Bentley et al., 1997). Thus, treatment of enones **26**–**30** with immobilized poly-L-leucine (PLL)/urea–hydrogen peroxide complex (UHP) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in dry THF, afforded the (−)-(α*R*,β*S*)-*trans*-epoxychalcones **32a**–**36a** in moderate to high yields (21–80%) and improved optical purity (53–95% ee). The enantiomeric (+)-(α*R*,β*S*)-*trans*-epoxychalcones **32b**–**36b** were similarly obtained using immobilized poly-D-leucine (PDL) (yield, 19–76%; ee, 50–90%). Chalcone epoxides **32a/b**–**36a/b** were next treated with TBTH/AIBN in refluxing benzene afforded the (*R*)-**52a**–**56a** and (*S*)-2′-*O*-methoxymethyl-β-hydroxydihydrochalcones **52b**–**56b** in excellent yields (70–90%) and without loss of optically purity (Table 6, Scheme 10).

5. Dihydroflavonols

Dihydroquercetin, dihydrokaempferol and dihydromyricetin, the most common members of the dihydrofl-



26 $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
27 $R_2 = R_3 = H$, $R_1 = R_4 = OMe$
28 $R_2 = H$, $R_1 = R_3 = R_4 = OMe$
29 $R_3 = H$, $R_1 = R_2 = R_4 = OMe$
30 $R_1 = R_2 = R_3 = R_4 = OMe$

(αR, βS)- or (αS, βR)-epoxychalcones
32a/b $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
33a/b $R_2 = R_3 = H$, $R_1 = R_4 = OMe$
34a/b $R_2 = H$, $R_1 = R_3 = R_4 = OMe$
35a/b $R_3 = H$, $R_1 = R_2 = R_4 = OMe$
36a/b $R_1 = R_2 = R_3 = R_4 = OMe$

(R)- or *(S)*-β-hydroxydihydrochalcone
52a/b $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
53a/b $R_2 = R_3 = H$, $R_1 = R_4 = OMe$
54a/b $R_2 = H$, $R_1 = R_3 = R_4 = OMe$
55a/b $R_3 = H$, $R_1 = R_2 = R_4 = OMe$
56a/b $R_1 = R_2 = R_3 = R_4 = OMe$

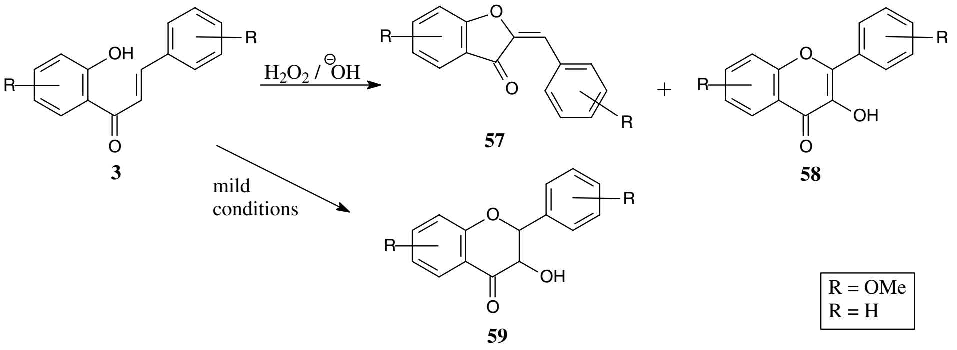
a = configuration shown
b = enantiomer

Scheme 10. β-Hydroxydihydrochalcone formation.

avonols (3-hydroxyflavanones), are widely distributed in the plant kingdom (Bohm, 1994). Apart from exhibiting important biological properties (Bohm, 1975) these compounds may be used in the semi-synthesis of oligomeric proanthocyanidins (Delcour et al., 1983). This semi-synthetic approach is, however hampered by the predominant natural occurrence of dihydroflavonols exhibiting (2*R*,3*R*)-2,3-*trans*-configuration (≅85%), as well as tedious isolation processes. Although the Algar–Flynn–Oyamada (AFO) protocol (Geissman and Fukushima, 1948; Dean and Podimuang, 1965) was mainly used for the oxidation of chalcones **3** to aurones **57** and flavonols **58** via an epoxide intermediate, Saxena et al. (1985) and Patonay et al. (1993) demonstrated that by using somewhat milder reaction conditions, this reaction can also be utilized for the synthesis of racemic dihydroflavonols **59** (yield: 38–73%) (Scheme 11). Despite the amendments, the formation of aurones and flavonols remained predominant and emphasized the need for a more controlled approach.

The Wheeler reaction, generally used for the synthesis of aurones, was adapted to afford the 2,3-*trans*-dihydroflavonol **63a/b** in a good yield (83%), but it became clear that the applicability of this protocol was limited, since 6′-substituted analogs yielded aurones only (Donnelly and Doran, 1975, 1979, 1990a,b) (Scheme 12).

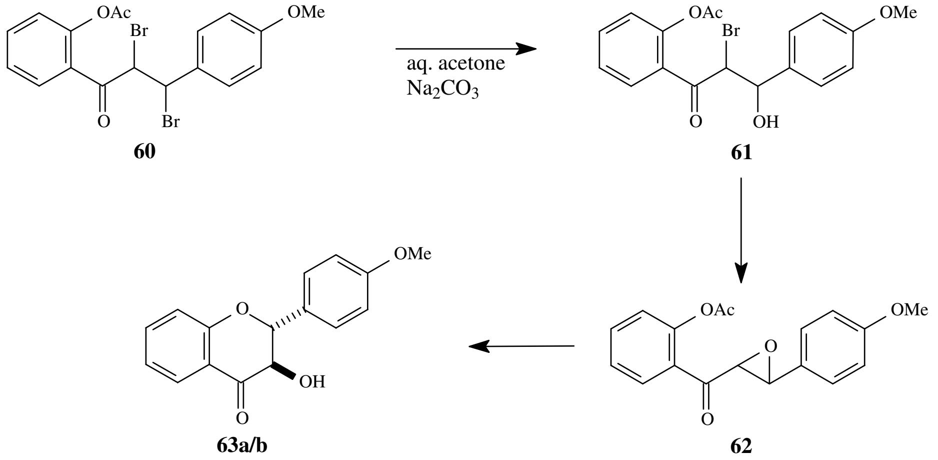
Cyclization of 2′-hydroxy-α,3,4,4′-tetramethoxychalcone **64** with sodium acetate in ethanol furnished both 3,3′,4′,7-*O*-tetramethyl-2,3-*trans*- and 3,3′,4′,7-*O*-tetramethyl-2,3-*cis*-dihydroflavonols **65** and **66** in 22% and 11% yields, respectively (Scheme 13). However this



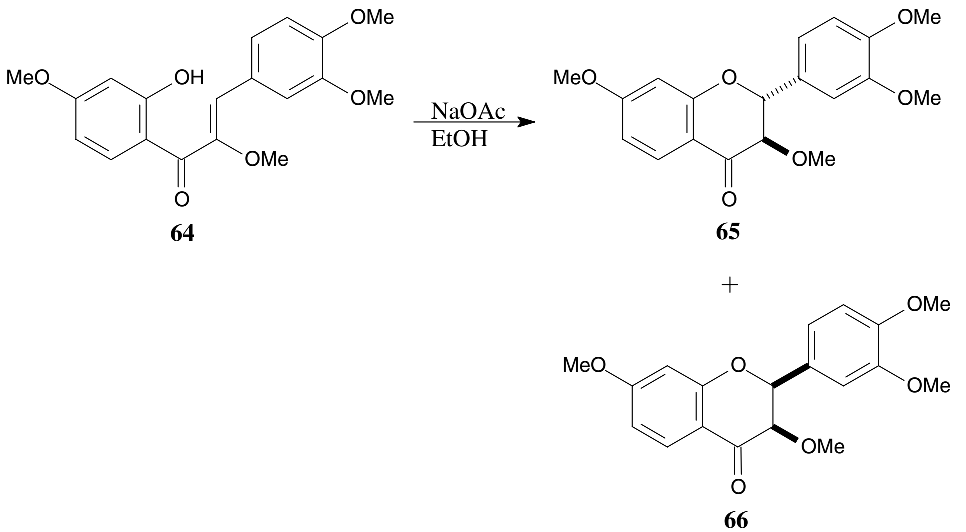
3 **57** **58** **59**

R = OMe
R = H

Scheme 11. Aurone, flavonol and dihydroflavonol formation, utilizing the AFO protocol.



Scheme 12. The Wheeler reaction towards dihydroflavonol synthesis.

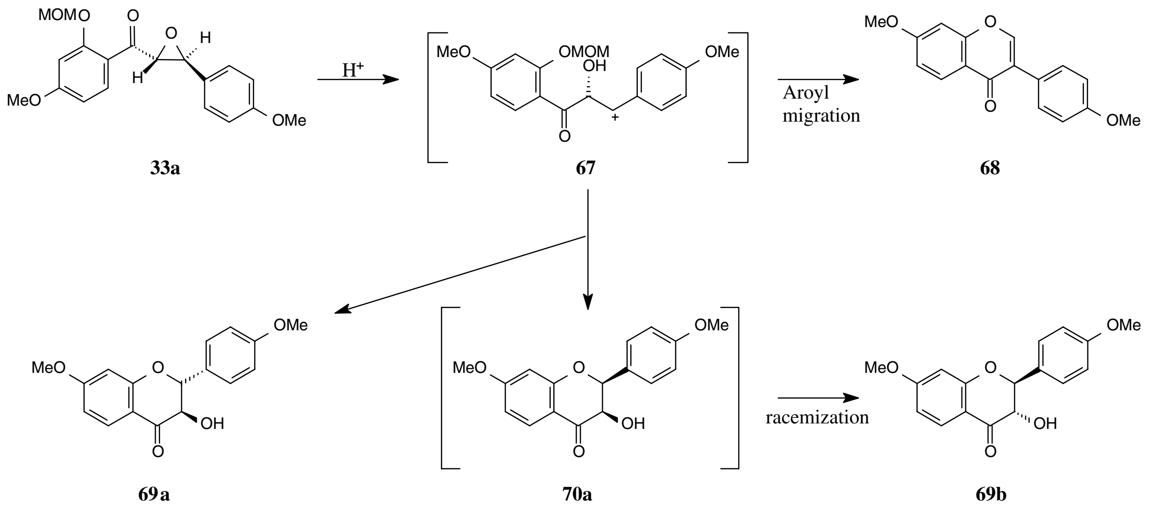


Scheme 13. Chalcone cyclization with NaOAc in EtOH to yield *trans*- and *cis*-dihydroflavonols.

method was not applicable to cyclization of α-OH-chalcones (Van der Merwe et al., 1972; Ferreira et al., 1975).

Initial attempts towards acid-catalyzed cyclization of the chalcone epoxide to the corresponding (2*R*,3*R*)-2,3-*trans*-**69a** and (2*S*,3*R*)-2,3-*cis*-dihydroflavonols **70a** were hampered by two major difficulties, i.e., aryl migration with formation of the artifact, 4′,7-dimethoxyisoflavone **68** and the epimerization/racemization of the thermodynamically less stable (2*S*,3*R*)-2,3-*cis*-4′,7-dimethoxydihydroflavonol **70a** to yield (2*S*,3*S*)-2,3-*trans*-dihydroflavonol **69b** (Augustyn et al., 1990a) (Scheme 14). The "loss" of optical purity in the conversion **33a** → **69a** indicates competition between protonation of the heterocyclic oxygen and hydrolysis of the 2′-*O*-acetal functionality, hence leading to a considerable degree of S_N1 character for the cyclization step with concomitant racemization at C-β of a presumed carbocationic intermediate **67**, yielding dihydroflavonols **69a** and **70a**. The thermodynamically less stable (2*S*,3*R*)-2,3-*cis*-dihydroflavonol **70a** is rapidly racemized at C-3 to give a mixture with **69b** under the prevailing acidic conditions. Formation of the isoflavone **68** is attributed to acid-catalyzed cleavage of the highly reactive oxirane functionality prior to deprotection.

In order to enhance the S_N2 nature of the ring closure step and thus the formation of **69a**, methods aimed at the selective removal of the 2′-*O*-methylmethoxy group under mild conditions were explored. Lewis acids such as $MgBr_2$ and BF_3–OEt_2 smoothly cleave alkoxymethyl ethers and acetals under mild conditions (Kim et al., 1991a,b). It was anticipated that deprotection of the 2′-*O*-methoxymethyl group with concomitant cyclization would enhance the preservation of optical integrity. Treatment of (−)-(α*R*,β*S*)-chalcone epoxide (86% ee) with $MgBr_2$-etherate indeed afforded (2*R*,3*R*)-2,3-*trans*-4′,7-dimethoxydihydroflavonol with virtually no



Scheme 14. Attempts towards synthesis of (2*R*,3*R*)-2,3-*trans*-**69a** and (2*S*,3*R*)-2,3-*cis*-dihydroflavonols **70a** using acid-catalyzed cyclization.

loss of optical purity but in a modest 20% chemical yield, as well as 4′,7-dimethoxyisoflavone (4%). In order to circumvent the problem of isoflavone formation, Van Rensburg et al. (1996, 1997a) investigated methods aimed at the initial nucleophilic opening of the oxirane functionality, followed by deprotection and cyclization. The excellent nucleophilic and nucleofugic properties of mercaptans (Barrett et al., 1989) prompted evaluation of thiols in the presence of Lewis acids and resulted in the selection of the phenylmethanethiol–tin(IV) chloride ($BnSH/SnCl_4$) system as the reagent of choice for the oxirane cleavage (Chini et al., 1992). Treatment of the series of chalcone epoxides **32a/b**–**36a/b** with BnSH/$SnCl_4$, selectively cleaved the C_β–O bond of the oxirane functionality at −20 °C and effectively deprotected the methoxymethyl group at 0 °C to give the corresponding α,2′-dihydroxy-β-benzylsulfanyldihydrochalcones **71a/b**–**75a/b** as diastereomeric mixtures (*syn*:*anti*, ca. 2.3:1) in 86–93% yield. Treatment of these α-hydroxy-β-benzylsulfanyldihydrochalcones **71a/b**–**75a/b** with the thiophilic Lewis acid, silver tetrafluoroborate ($AgBF_4$) in CH_2Cl_2 at 0 °C gave the 2,3-*trans*-dihydroflavonols **63a/b**, **69a/b** and **76a/b**–**78a/b** in good yield and albeit in low proportions, for the first time also the 2,3-*cis* analogs **70a/b** and **79a/b**–**82a/b** (Table 7, Scheme 15).

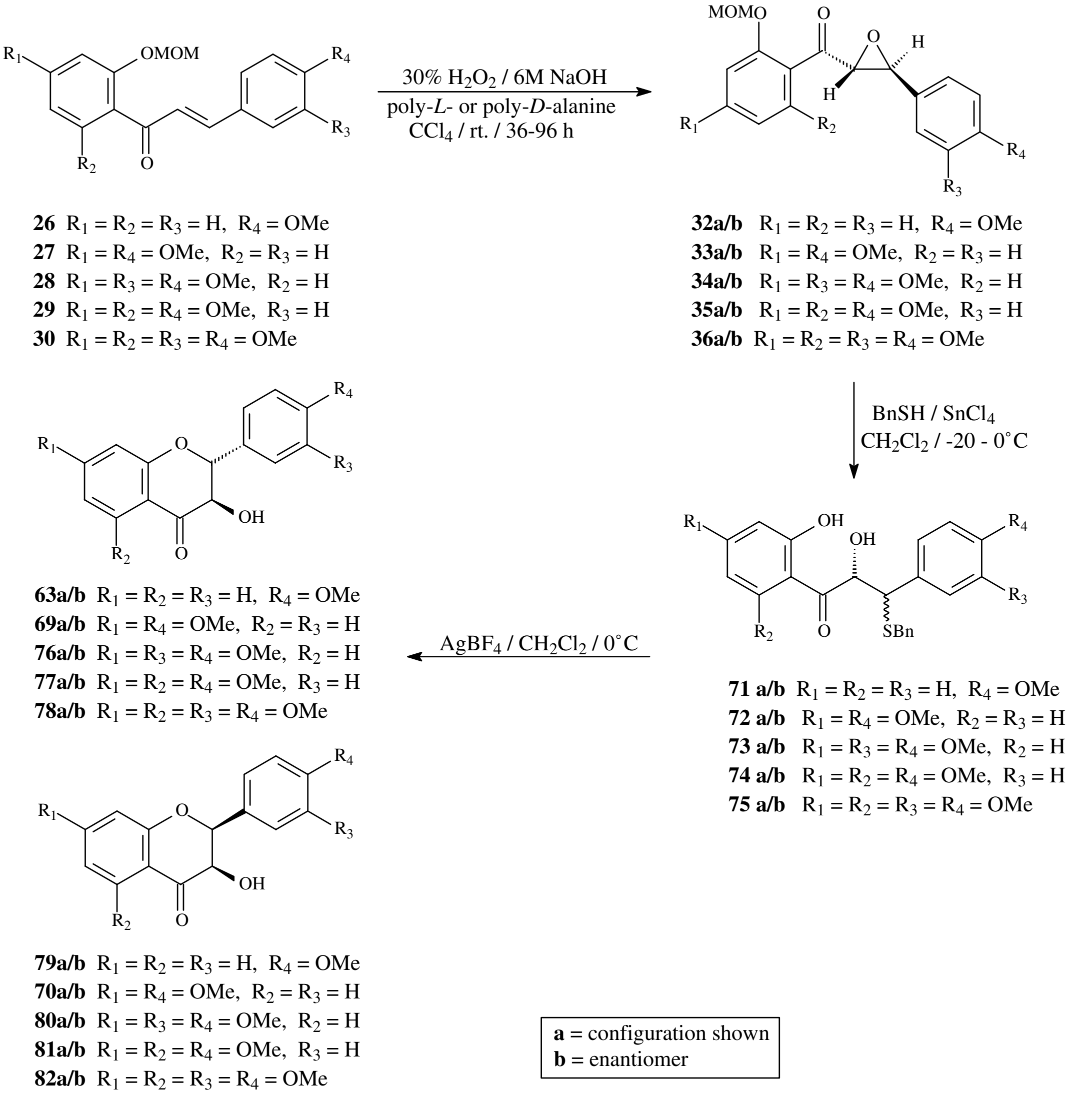
6. Flavan-3-ols and flavan-3,4-diols

Flavan-3-ols represent the largest class of naturally occurring C_6–C_3–C_6 monomeric flavonoids with catechin and epicatechin occurring almost ubiquitously. Flavan-3-ols have also received considerable interest over the last few years on account of their importance as the constituent units of condensed tannins (Porter, 1988 and Porter, 1994). In addition, these compounds serve as the nucleophilic entities in the semisynthesis of oligomeric proanthocyanidins (Botha et al., 1978a,b, 1981b, 1982; Delcour et al., 1983; Van der Westhuizen et al., 1981; Young et al., 1985; Steynberg et al., 1998).

Progress in the study of these complex phenolics is often hampered by the limited availability of naturally occurring flavonoid nucleophiles with 2,3-*trans* and especially 2,3-*cis* configuration. One of the most common ways for the synthesis of flavan-3-ols and the closely related flavan-3,4-diol analogs, involves the

Table 7
Asymmetric synthesis of dihydroflavonols

Chalcone epoxide	% Yield	% ee	Dihydrochalcone	% Yield	Dihydroflavonol	% Yield	% ee	*trans*:*cis*
32a	99	84	**71a**	86	**63a/79a**	86	83	93:7
32b	98	69	**71b**	90	**63b/79b**	83	69	94:6
33a	98	86	**72a**	93	**69a/70a**	71	84	79:21
33b	98	74	**72b**	90	**69b/70b**	72	75	83:17
34a	99	67	**73a**	89	**76a/80a**	81	68	85:15
34b	98	58	**73b**	91	**76b/80b**	79	58	86:14
35a	97	70	**74a**	89	**77a/81a**	65	69	78:22
35b	97	53	**74b**	89	**77b/81b**	64	53	84:16
36a	79	49	**75a**	91	**78a/82a**	61	47	82:18
36b	76	49	**75b**	88	**78b/82b**	63	44	80:20

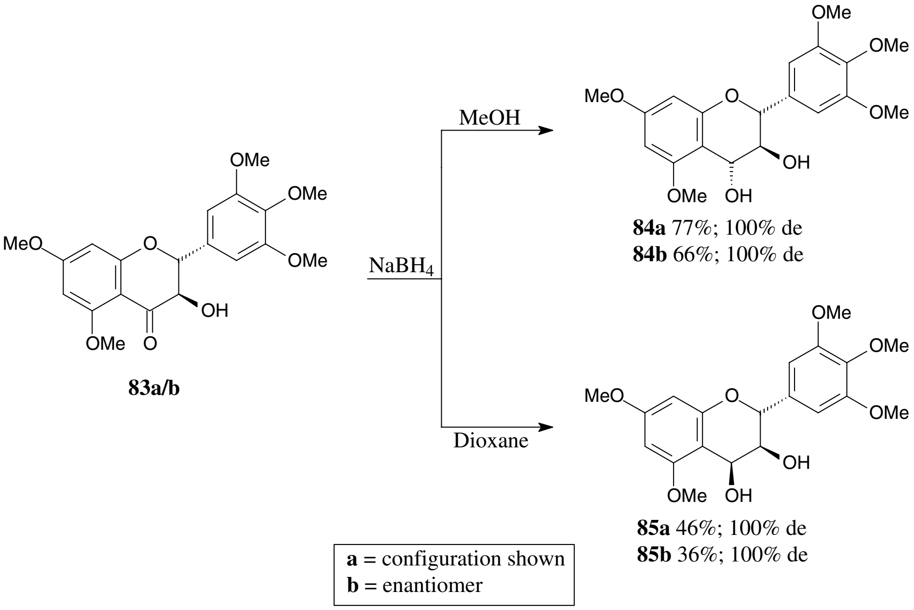


Scheme 15. Asymmetric synthesis of dihydroflavonols.

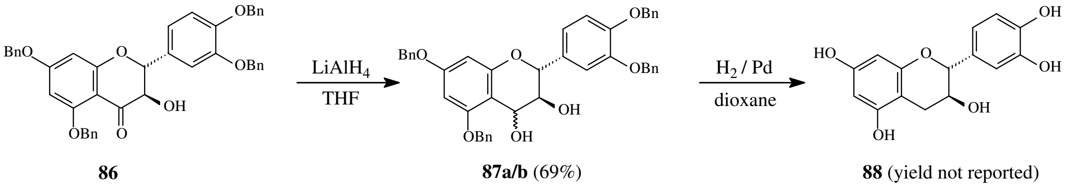
transformation of dihydroflavonols. Reduction of the dihydroflavonols **83a** and **83b** with sodium borohydride in methanol affords the 2,3-*trans*-3,4-*trans*-flavan-3,4-diols **84a/b**, while reduction in an aprotic solvent like dioxane, yielded the C_4-epimers **85a/b** exclusively (Scheme 16) (Takahashi et al., 1984; Onda et al., 1989). Such reversal in the direction of hydride attack could probably be explained in terms of the presence of hydrogen bonding in aprotic solvents.

Catechin **88** represents the only flavan-3-ol synthesized from the corresponding dihydroflavonol (Weinges, 1958; Freudenberg and Weinges, 1958). Consecutive treatment of *trans*-3-*O*-acetyldihydroquercetin tetra-*O*-benzyl ether **86** with $LiAlH_4$ and H_2/Pd gave the free phenolic flavan-3-ol **88** in optically pure form (Scheme 17).

^{13}C-labeled (±)-catechin has recently been synthesized in ten steps starting from $K^{13}CN$ **89** (Nay et al., 2000). The (*E*)-1-[^{13}C]-*O*-di-*O*-benzylcaffeic acid **94** (C_6–C_3-unit) was firstly synthesized starting from the labeled acetonitrile (Scheme 18). 1-[^{13}C]Acetonitrile **90** was obtained from potassium [^{13}C]cyanide **89**. Condensation of **90** and 3,4-dibenzyloxybenzaldehyde yielded **92** which upon dehydration gave a mixture of *Z*- and *E*-cinnamonitrile **93** in a 1:3 ratio. Compound **93** was hydrolyzed to form **94** in 34% overall yield. The *Z*-isomer could not be recovered, most probably due to the complete isomerization to the *E* form during the hydrolysis step. The intermediate chalcone **96** was formed by acylation of the benzylated phloroglucinol with the caffeic acid derivative **94**, using trifluoroacetic anhydride (TFAA). Flavan-3,4-diol **99** was obtained in 58% yield in three steps from **96** by the Clark-Lewis method (Clark-Lewis and Skingle, 1967; Kawamoto et al., 1989) and included a borohydride reduction of **97** and Lewis acid-catalyzed cyclization into racemic flavene



Scheme 16. Reduction of dihydroflavonols with $NaBH_4$ to afford flavan-3,4-diols.



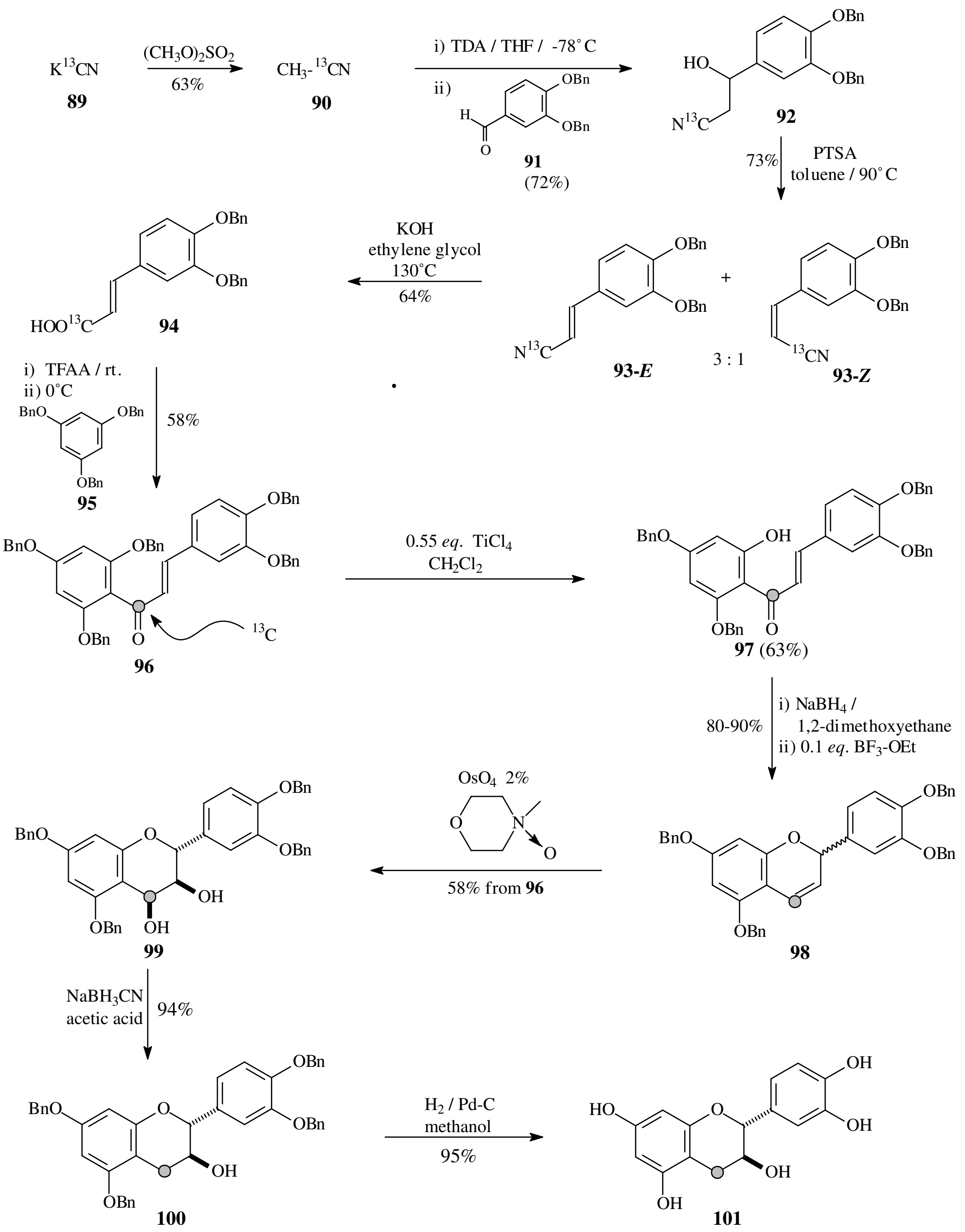
Scheme 17. Reduction of *trans*-3-*O*-acetyldihydroquercetin tetra-*O*-benzylether **86** to yield catechin **88**.

98, which was then directly transformed by an osmium-catalyzed dihydroxylation to the 2,3-*trans*-3,4-*cis*-isomer **99** with high diastereoselectivity. Reduction of the resulted flavan-3,4-diol and deprotection afforded 4-[^{13}C]-(±)-catechin **101**.

A slightly different but improved approach was used by the same group (Arnaudinaud et al., 2001a,b) to synthesize the flavan-3,4-diol unit **99** for the formation of ^{13}C-labelled (−)-procyanidin B-3 (Scheme 19). Improved yields were reported and the number of steps to the pivotal intermediate chalcone **97** was reduced. The benzylated [^{13}C]-phloroacetophenone **102** was synthesized (60% yield) from phloroglucinol tri-*O*-benzyl ether **95** (Kawamoto et al., 1996) and activated 1-[^{13}C]-acetic acid/TFAA. Selective deprotection of **102** by $TiCl_4$ gave phloroacetophenone 2,4-di-*O*-benzylether **103** (80%). Crotonization of **103** with 3,4-dibenzyloxybenzaldehyde in the presence of NaH led to the tetrabenzylated chalcone **97** (89%). The flavan-3,4-diol **99** was obtained from the intermediated chalcone precursor **97** as discussed previously, by reduction, cyclization and osmium-catalyzed dihydroxylation. The $TiCl_4$-catalyzed condensation of **101** with (2*R*,3*S*)-tetrabenzyloxycatechin resulted in the isolation of procyanidin B-3.

(+)-[^{13}C]-Catechin **101a** and (−)-[^{13}C]-epicatechin **107** were isolated in high ee, respectively, by the formation of their tartaric acid derivatives (Nay et al., 2001). The resolution process included the esterification of the 3-OH group of **100a/b** with L-dibenzoyltartaric acid monomethyl ester to give a mixture of diastereomers **104** and **105** (92%) (Scheme 20). The (+)-catechin derivative **104** was crystallized in hexane/dichloromethane (3:1) (de > 99%), while the (−)-*ent*-catechin derivative **105** remained in solution. The diastereomeric pure (de = 99%) (−)-*ent*-catechin derivative **106** was also isolated by crystallization after hydrolysis (MeOH/H_2O/KOH) of **105**, following esterification with the D-tartaric acid derivative. (+)-[^{13}C]-catechin **101a** was isolated in a high yield and ee (99%) after hydrolysis and reduction/deprotection steps. Epimerization at C-2 of (−)-[^{13}C]-*ent*-catechin **101b**, using 1% (w/v) aq. Na_3PO_4, led to an equilibrium mixture of (−)-**101b** and (−)-[^{13}C]-epicatechin **107** in an approximate 3:1 ratio after 20 h at 25 °C (ee > 99%).

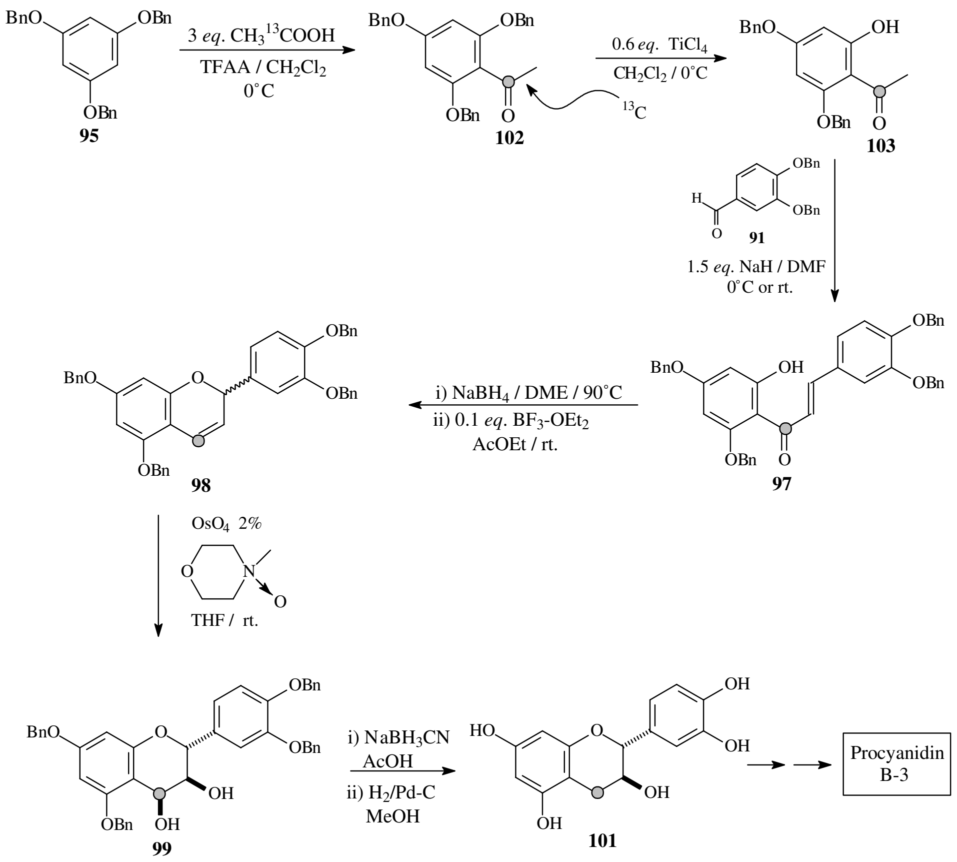
In order to address the issue of stereocontrol at C-2 and C-3 of the flavan-3-ol molecular framework, Van Rensburg et al. (1997b,c) designed a concise protocol based upon the transformation of *retro*-chalcones into



Scheme 18. Synthesis of ^{13}C-labelled (±)-catechin.

1,3-diarylpropenes (Table 8, Scheme 21). These compounds are then subjected to asymmetric dihydroxylation to give poly-oxygenated diarylpropan-1,2-diols, which are used as chirons for essentially enantiopure flavan-3-ols.

The series of derivatized (*E*)-*retro*-chalcones **108–112** ($J_{\alpha,\beta}$ 15.8–16.0 Hz) were prepared by base-catalyzed condensation of the appropriately oxygenated acetophenones and benzaldehydes. Compounds **108–112** were transformed by consecutive reduction (Pd-H_2 and $NaBH_4$) and elimination {$SOCl_2$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (1,8-DBU)} of the ensuing alcohols **113–117** to afford exclusively the (*E*)-1,3-diarylpropenes (deoxodihydrochalcones) **118–122** ($J_{1,2}$ 16 Hz) in good overall yield (65–73%). Owing to the excellent results obtained by Sharpless et al. (Sharpless et al., 1977, 1992; Kwong et al., 1990; Jeong et al., 1992; Amberg et al., 1993; Gobel and Sharpless, 1993; Wang et al., 1993; Kolb et al., 1994a,b; Norrby et al., 1994) during asymmetric dihydroxylation (AD reaction) of olefins with AD-mix-α or AD-mix-β these stereoselec-

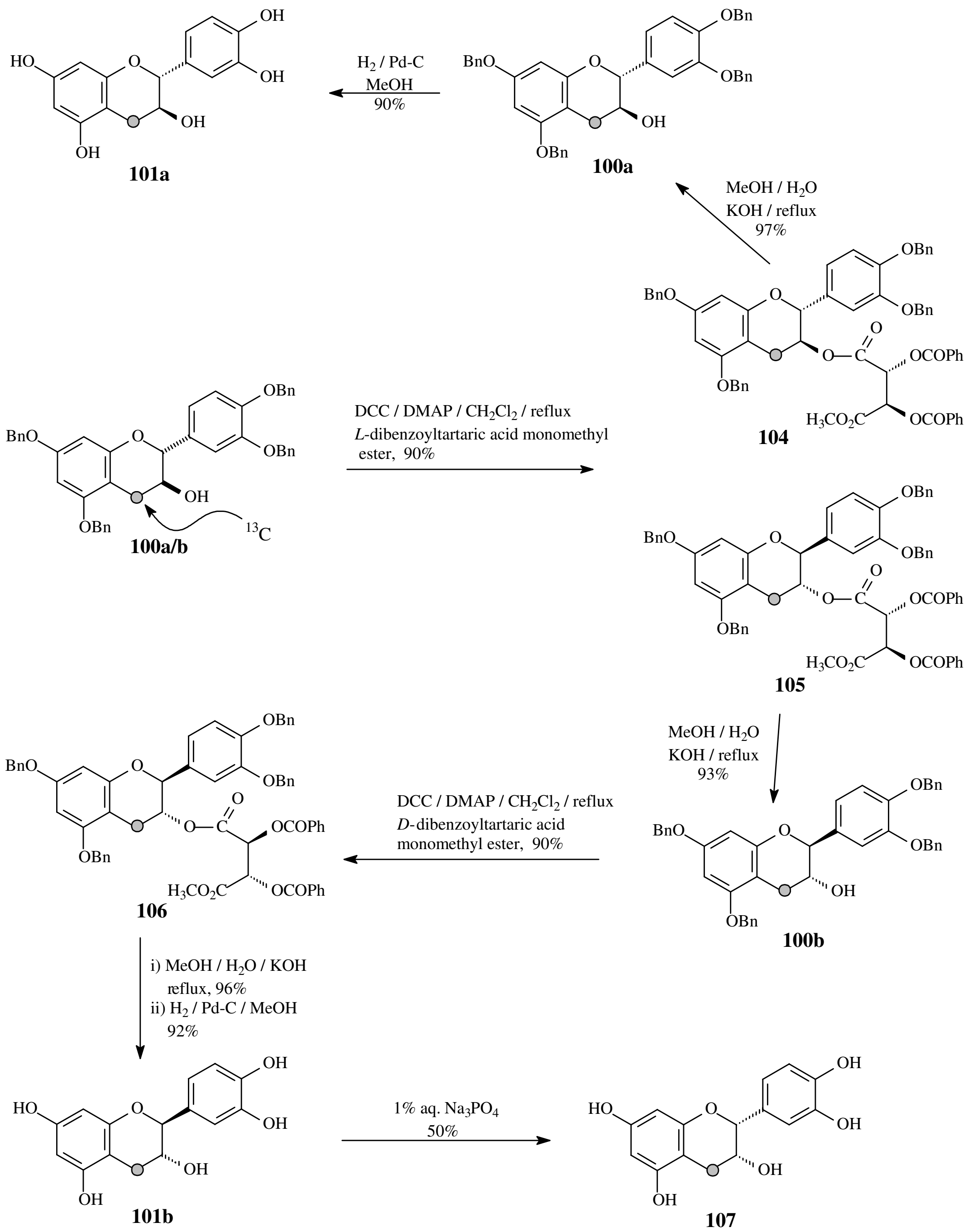


Scheme 19. Synthesis of ^{13}C-labelled procyanidin B-3.

tive catalysts were utilized for the introduction of chirality at C-2 and C-3 in the flavan-3-ol framework.

Thus, treatment of the protected (*E*)-propenes **118**–**122** at 0 °C with AD-mix-α in the two-phase system ^{t}BuOH:H_2O (1:1) afforded the (+)-(1*S*,2*S*)-*syn*-diols **123a**–**127a** ($J_{1,2}$ 5.8–6.5 Hz) in high yields (80–86%) and optical purity (99% ee). The (−)-(1*R*,2*R*)-*syn*-diols **123b**–**127b** were similarly obtained by using AD-mix-β (yield: 82–87%, 99% ee). The absolute configuration was tentatively assigned according to the Sharpless model for AD-mix (Scheme 22). The successful Lewis acid-catalyzed phenylmethanethiol ring-opening and cyclization of chalcones epoxides in the synthesis of dihydroflavonols (Section 5, Van Rensburg et al., 1996, 1997a) prompted evaluation of this protocol in the cyclization of diols **123a/b**–**127a/b**. Thus, the Lewis acid $SnCl_4$ in the presence of BnSH was utilized for selective substitution of the benzylic C(1)–OH (−20 °C) and subsequent removal of the methoxymethyl group (0 °C) in **124a**, to give the benzylthio derivative **138** (70%, mixture of *syn* and *anti*) (Scheme 23). However, treatment of the benzylthio ether **138** with the thiophilic Lewis acid ($AgBF_4$) resulted in slow (24 h) and low percentage conversion (10–20%) into flavan-3-ols **129a**/**134a**. In order to transform the diols more effectively into the corresponding flavan-3-ols, methods aimed at selective removal of the 2′-*O*-methoxymethyl group and subsequent ring closure under mild acidic conditions were explored. Simultaneous deprotection and cyclization of diols **123a/b**–**127a/b** in the presence of 3 M HCl in MeOH, followed by acetylation, yielded the 2,3-*trans*- (yield: 48–68%) **128a/b**–**132a/b** and for the first time 2,3-*cis*-flavan-3-ols (yield: 17–22%) **133a/b**–**137a/b** in excellent enantiomeric excess (> 99%). Assignment of the absolute configuration of the resulting flavan-3-ol derivatives **128a/b**–**137a/b** by ^{1}H NMR and CD data, confirmed the configuration of the diols as derived from the Sharpless model.

The potential of this protocol in the chemistry of the oligomeric proanthocyanidins and condensed tannins in general is evident, especially in view of its aptitude to the synthesis of free phenolic analogs. The latter analogs are as conveniently accessible by simply using more labile protecting groups instead of *O*-methyl ethers. This was illustrated by Nel et al. (1999b) by synthesis of the 4′,7-dihydroxyflavan-3-ol diastereomers to confirm (2*R*,3*S*)-guibourtinidol **160a** as a new natural product (Table 9, Scheme 24). Owing to the acid lability of methoxymethyl derivative, the MOM functionality was used as a protecting group. This method was later extended to the synthesis of the full range of flavan-3-ols, comprising different

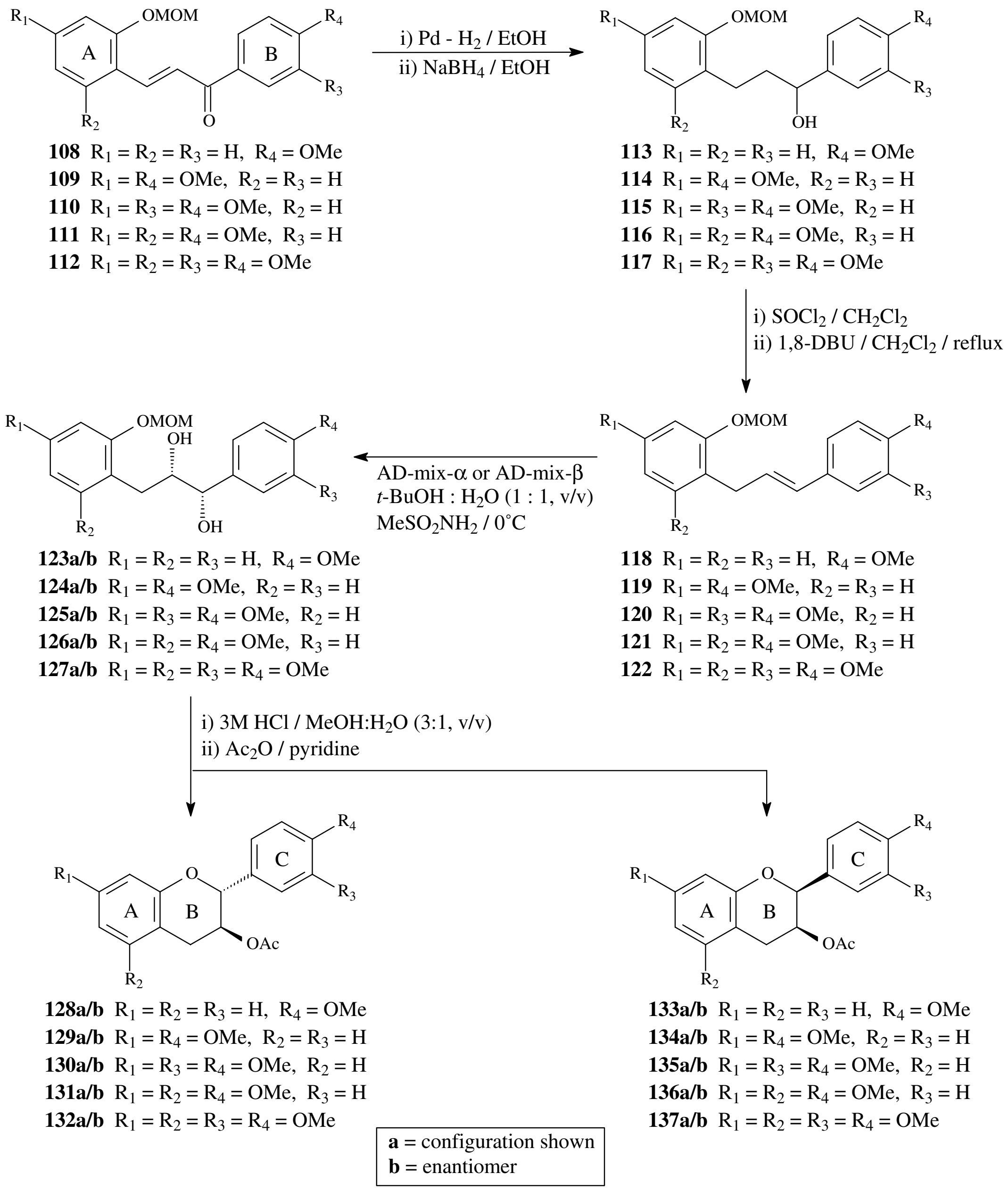


Scheme 20. Resolution process and synthesis of optically pure (+)-[^{13}C]-catechin **101a** and (−)-[^{13}C]-epicatechin **107**.

oxygenated phenolic substitutions as found in nature (Nel et al., 1999c) (Table 9; Scheme 24). The (*E*)-*retro*-*O*-methoxymethylchalcones were prepared by base-catalyzed condensation of the appropriated methoxymethylbenzaldehydes and methoxymethylacetophenones. The reaction conditions and reagents are similar to those described earlier and also included hydrogenation and reduction of chalcones **139**–**143** to afford the 1,3-diarylpropan-1-ols **144**–**148**, which are converted into the (*E*)-1,3-diarylpropenes **149**–**153** using 1,8-DBU. Treatment of **149**–**153** with AD-mix-α and AD-mix-β in the two-phase system (^{t}BuOH/H$_2$O; 1:1) afforded the (1*S*,2*S*)- **154a**–**158a** and the (1*R*,1*R*)-*syn*-diols **154b**–**158b**, respectively. However, the last step involved simultaneous deprotection and cyclization of the (1*S*,2*S*)-*syn*-diols **154a**–**158a** with 3 M HCl in methanol at 60 °C to give respectively the (2*R*,3*S*)-2,3-*trans*-flavan-3-ols **88a** and **159a**–**162a** and (2*S*,3*S*)-2,3-*cis*-flavan-3-ols **163a**–**167a**. The (1*R*,2*R*)-*syn* diols **154b**–**158b** similarly afforded the (2*S*,3*R*)-*trans*- and (2*R*,3*R*)-*cis*-flavan-3-ols **88b** and **159b**–**167b**.

Table 8
Synthesis of flavan-3-ols **128a/b–137a/b**

Propan-1-ols	% Yield	Propenes	% Yield	1,2-Diols	% Yield	% ee	Flavan-3-ols	% Yield	% ee	*trans*:*cis*
113	99	**118**	73	**123a**	82	99	**128a/133a**	87	99	1:0.33
				123b	84	99	**128b/133b**	88	99	1:031
114	98	**119**	74	**124a**	86	99	**129a/134a**	88	99	1:036
				124b	82	99	**129b/134b**	90	99	1:0.33
115	99	**120**	70	**125a**	85	99	**130a/135a**	82	99	1:0.32
				125b	83	99	**130b/135b**	80	99	1:0.30
116	98	**121**	68	**126a**	80	99	**131a/136a**	71	99	1:0.32
				126b	83	99	**131b/136b**	70	99	1:0.33
117	99	**122**	66	**127a**	80	99	**132a/137a**	66	99	1:0.34
				127b	87	99	**132b/137b**	65	99	1:0.35



108 $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
109 $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
110 $R_1 = R_3 = R_4 = OMe$, $R_2 = H$
111 $R_1 = R_2 = R_4 = OMe$, $R_3 = H$
112 $R_1 = R_2 = R_3 = R_4 = OMe$

113 $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
114 $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
115 $R_1 = R_3 = R_4 = OMe$, $R_2 = H$
116 $R_1 = R_2 = R_4 = OMe$, $R_3 = H$
117 $R_1 = R_2 = R_3 = R_4 = OMe$

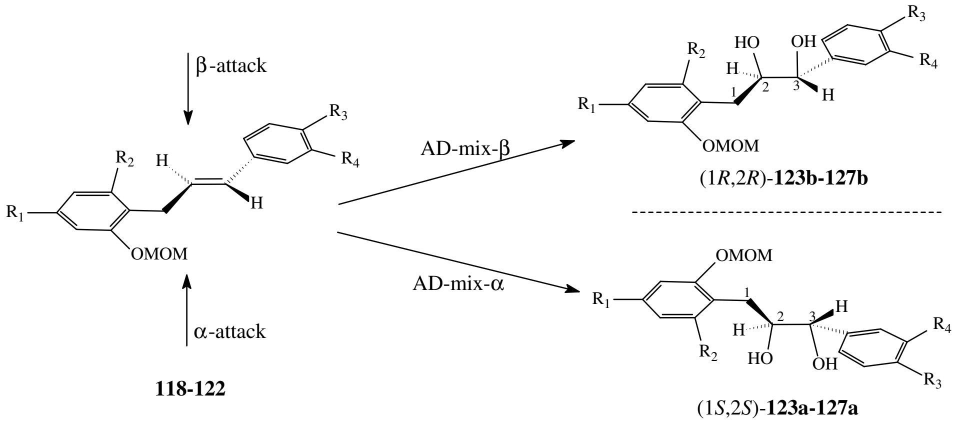
123a/b $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
124a/b $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
125a/b $R_1 = R_3 = R_4 = OMe$, $R_2 = H$
126a/b $R_1 = R_2 = R_4 = OMe$, $R_3 = H$
127a/b $R_1 = R_2 = R_3 = R_4 = OMe$

118 $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
119 $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
120 $R_1 = R_3 = R_4 = OMe$, $R_2 = H$
121 $R_1 = R_2 = R_4 = OMe$, $R_3 = H$
122 $R_1 = R_2 = R_3 = R_4 = OMe$

128a/b $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
129a/b $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
130a/b $R_1 = R_3 = R_4 = OMe$, $R_2 = H$
131a/b $R_1 = R_2 = R_4 = OMe$, $R_3 = H$
132a/b $R_1 = R_2 = R_3 = R_4 = OMe$

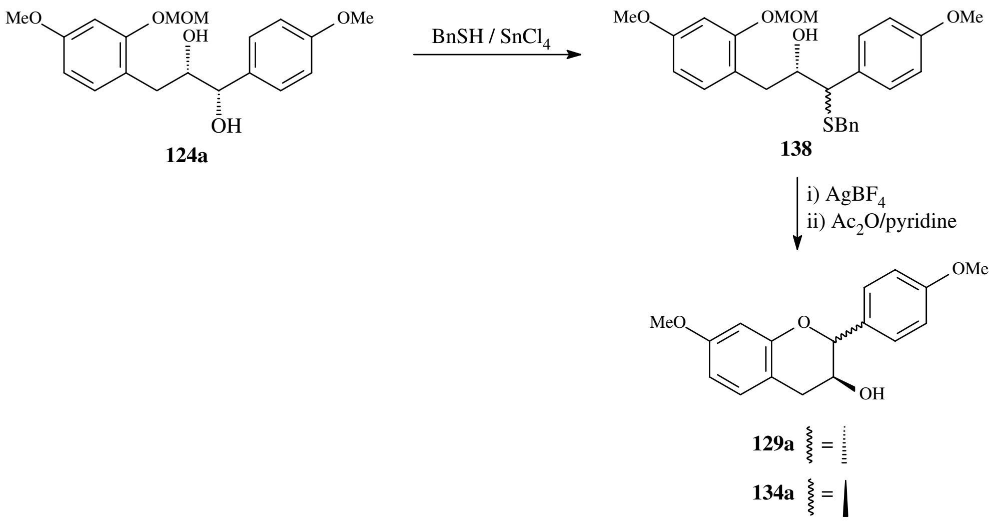
133a/b $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
134a/b $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
135a/b $R_1 = R_3 = R_4 = OMe$, $R_2 = H$
136a/b $R_1 = R_2 = R_4 = OMe$, $R_3 = H$
137a/b $R_1 = R_2 = R_3 = R_4 = OMe$

Scheme 21. Synthesis of flavan-3-ols **128a/b–137a/b**.



R_1, R_2, R_3, R_4 = H, OMe

Scheme 22. Sharpless model for diastereoselectivity in asymmetric dihydroxylation.



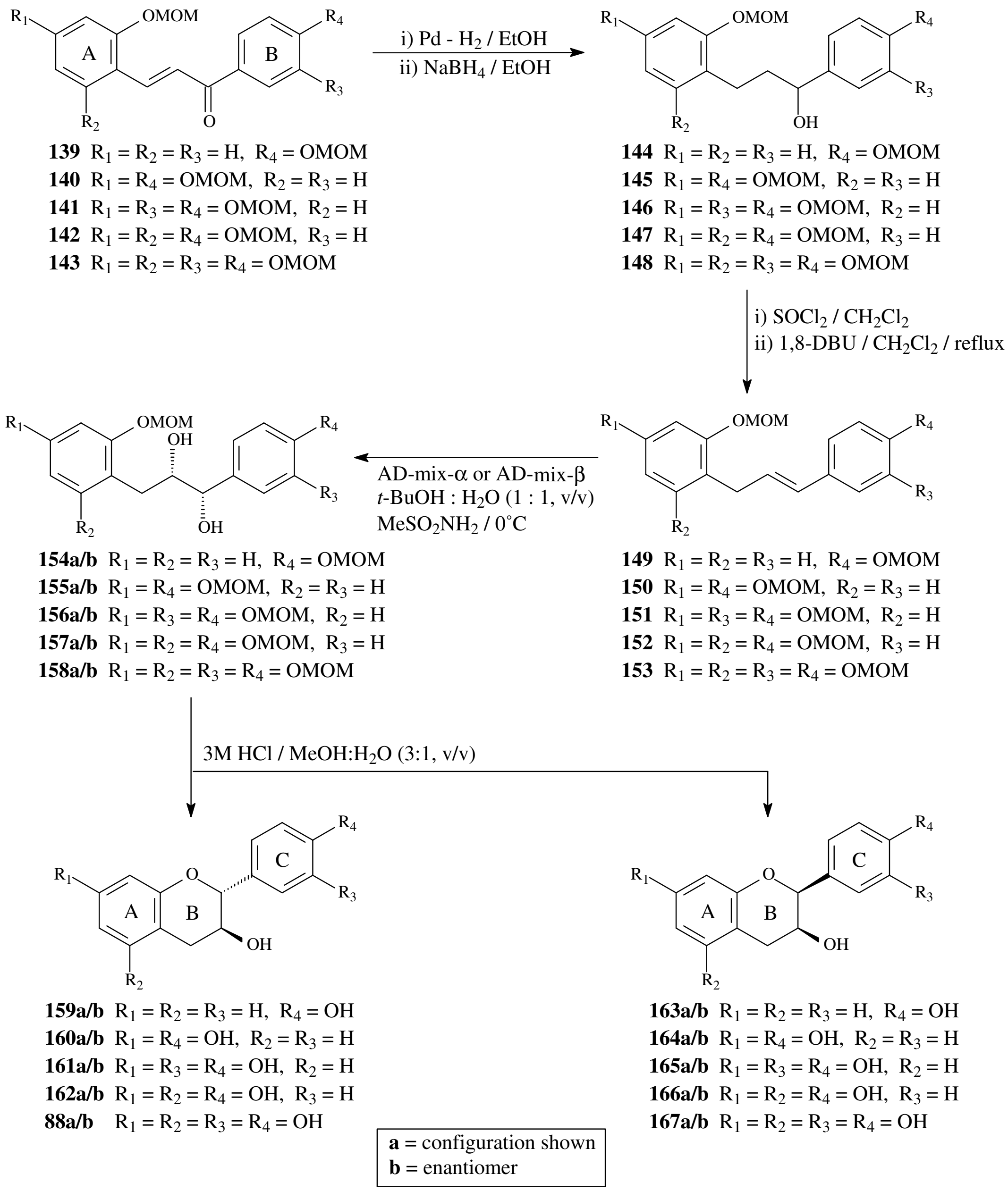
Scheme 23. Formation of flavan-3-ols using BnSH/SnCl$_4$ and thiophilic Lewis-acids.

Table 9
Synthesis of free phenolic flavan-3-ols **88a/b** and **159a/b–167a/b**

Propan-1-ols	% Yield	Propenes	% Yield	1,2-Diols	% Yield	% ee	Flavan-3-ols	% Yield	% ee	*trans*:*cis*
144	99	**149**	67	**154a**	77	99	**159a/163a**	86	99	1:0.32
				154b	76	99	**159b/163b**	83	99	1:030
145	99	**150**	69	**155a**	79	99	**160a/164a**	78	99	1:030
				155b	78	99	**160b/164b**	81	99	1:0.33
146	99	**151**	66	**156a**	77	99	**161a/165a**	75	99	1:0.29
				156b	79	99	**161b/165b**	74	99	1:0.32
147	98	**152**	62	**157a**	77	99	**162a/166a**	64	99	1:0.28
				157b	76	99	**162b/166b**	64	99	1:0.23
148	99	**153**	60	**158a**	75	99	**88a/167a**	66	99	1:0.32
				158b	73	99	**88b/167b**	63	99	1:0.29

7. Isoflavonoids

Apart from the isoflavones, pterocarpans represent the second largest group of natural isoflavonoids and have received considerable interest on account of their medicinal properties (Dewick, 1994). They are potent phytoalexins, act as antitoxins and display antifungal, antiviral and antibacterial properties (Perrin, 1964; Mansfield, 1982; Nakagawa et al., 1982; Ingham, 1983; Máximo and Lourenço, 1998). Almost all pterocarpans



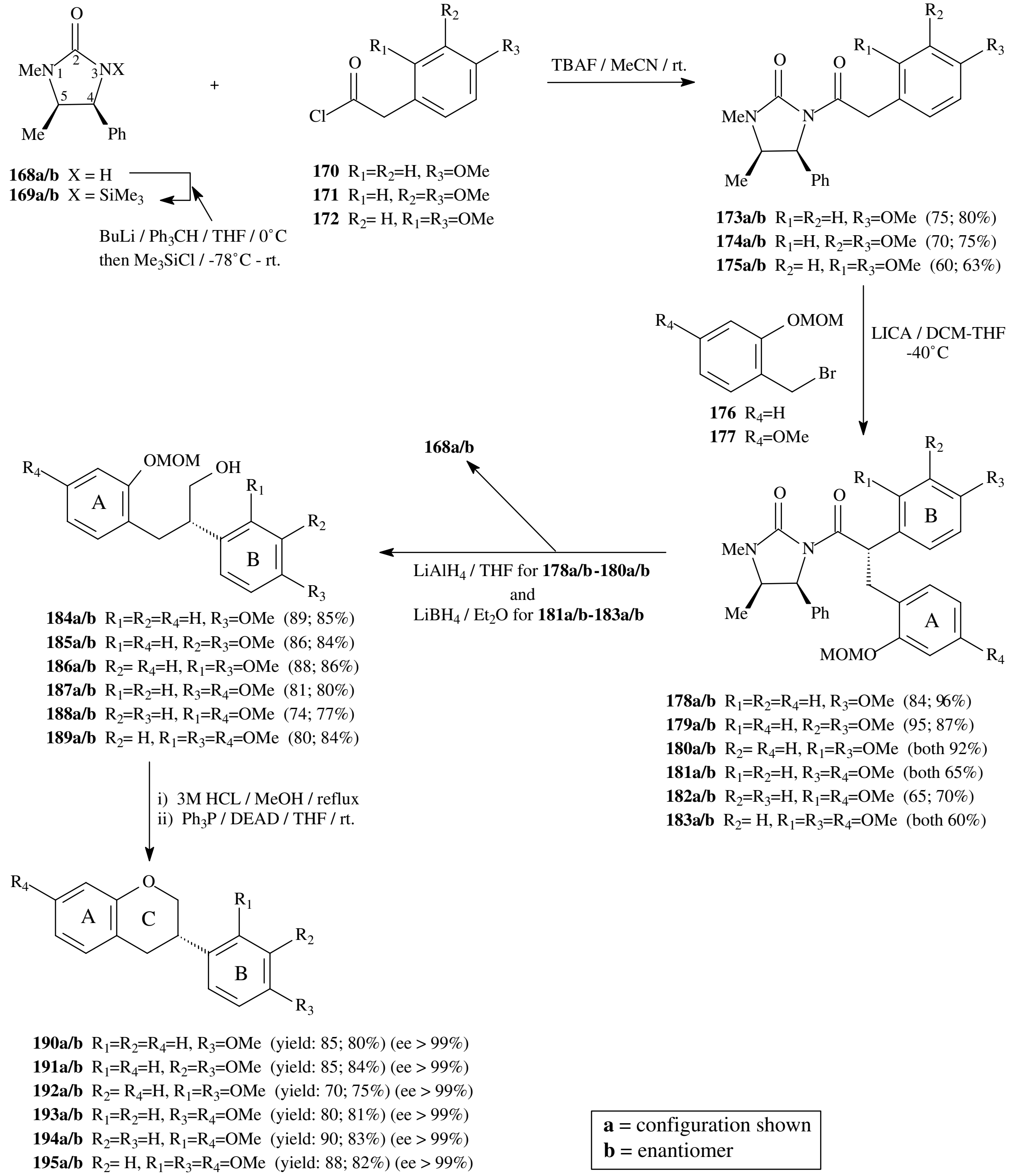
Scheme 24. Synthesis of free phenolic flavan-3-ols **88a/b** and **159a/b**–**167a/b**.

are phytoalexins and therefore biologically active, thus, most are produced by plants, but only when required and are therefore rare and difficult to isolate. Synthetic routes to optically pure pterocarpans, exhibiting the aromatic oxygenation patterns of natural occurring isoflavonoids, are limited by the lack of readily accessible starting materials. These restrictions and the challenge to form the tetracyclic ring system with stereocontrol led to the development of various synthetic approaches.

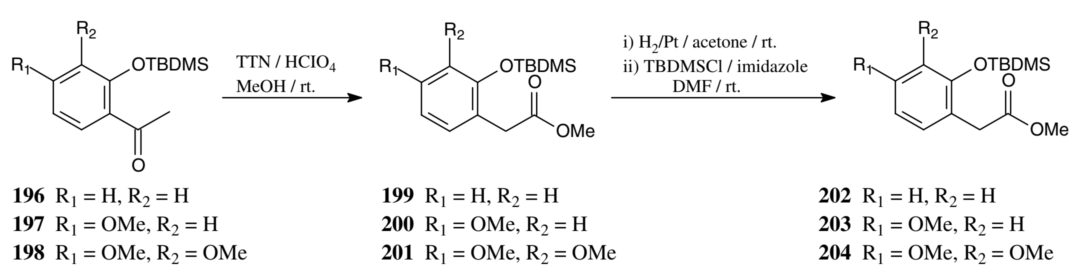
Synthetic endeavors towards pterocarpans comprise Heck arylation (Ishiguro et al., 1982; Narkhede et al., 1990), the reduction and cyclization of the corresponding 2′-hydroxyisoflavanones (Krishna Prasad et al., 1986), cycloaddition reactions of 2*H*-chromenes with 2-alkoxy-1,4-benzoquinones (Engler et al., 1990; Subburaj et al., 1997) and 1,3-Michael-Claisen annulation (Ozaki et al., 1988, 1989). Only two methods, i.e., asymmetric dihydroxylation of an isoflav-3-ene (Pinard et al., 1998) and subsequent "hydrogenative cyclization" or 1,4-benzoquinone cyclo-addition reactions utilizing chiral Ti(IV) complexes (Engler et al., 1991, 1999), permitted enantioselective access to this class of compounds.

7.1. Isoflavans

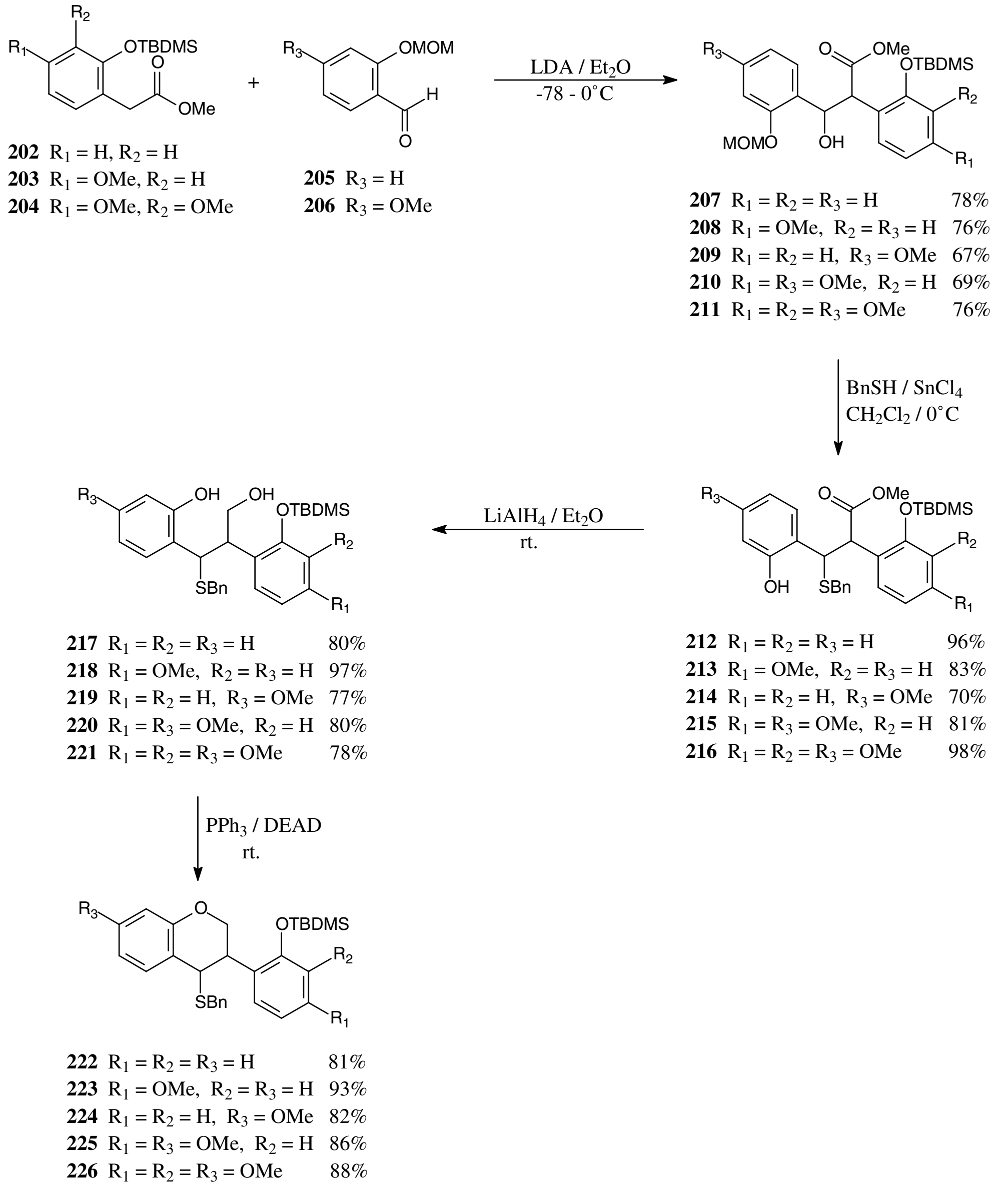
Given the fact that the configuration of the C-3 stereocenter would dictate the configuration at C-2



Scheme 25. Stereoselective synthesis of (*R*)- and (*S*)-isoflavans.



Scheme 26. The synthesis of phenylacetates **202**–**204**.



202 $R_1 = H, R_2 = H$
203 $R_1 = OMe, R_2 = H$
204 $R_1 = OMe, R_2 = OMe$

205 $R_3 = H$
206 $R_3 = OMe$

207 $R_1 = R_2 = R_3 = H$ 78%
208 $R_1 = OMe,\ R_2 = R_3 = H$ 76%
209 $R_1 = R_2 = H,\ R_3 = OMe$ 67%
210 $R_1 = R_3 = OMe,\ R_2 = H$ 69%
211 $R_1 = R_2 = R_3 = OMe$ 76%

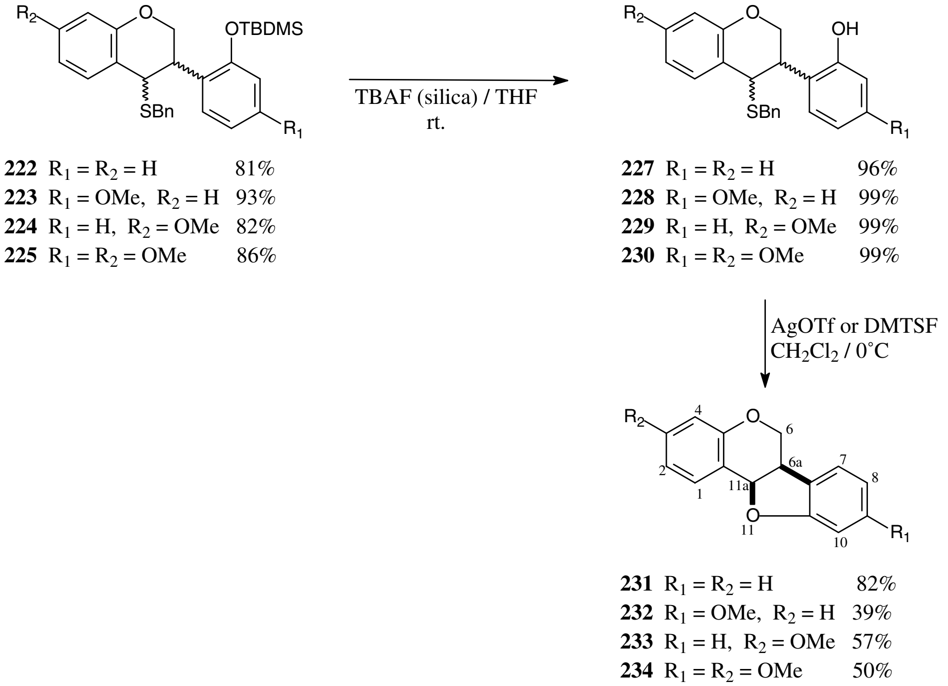
212 $R_1 = R_2 = R_3 = H$ 96%
213 $R_1 = OMe,\ R_2 = R_3 = H$ 83%
214 $R_1 = R_2 = H,\ R_3 = OMe$ 70%
215 $R_1 = R_3 = OMe,\ R_2 = H$ 81%
216 $R_1 = R_2 = R_3 = OMe$ 98%

217 $R_1 = R_2 = R_3 = H$ 80%
218 $R_1 = OMe,\ R_2 = R_3 = H$ 97%
219 $R_1 = R_2 = H,\ R_3 = OMe$ 77%
220 $R_1 = R_3 = OMe,\ R_2 = H$ 80%
221 $R_1 = R_2 = R_3 = OMe$ 78%

222 $R_1 = R_2 = R_3 = H$ 81%
223 $R_1 = OMe,\ R_2 = R_3 = H$ 93%
224 $R_1 = R_2 = H,\ R_3 = OMe$ 82%
225 $R_1 = R_3 = OMe,\ R_2 = H$ 86%
226 $R_1 = R_2 = R_3 = OMe$ 88%

Scheme 27. Direct synthesis of pterocarpans **222**–**226** via condensation of phenylacetates with benzaldehydes.

or C-4 in the 3-phenylchroman framework, Versteeg et al. (1995, 1998, 1999) embarked on the synthesis of a series of isoflavans which would then afford stereoselective access to other classes of chiral isoflavonoids. The protocol included the stereoselective α-benzylation of the phenylacetic acid derivatives and subsequent reductive removal of the chiral auxiliary and cyclization for the construction of the isoflavan backbone (Scheme 25). Owing to the efficiency of the asymmetric alkylation reactions of chiral imide enolates, (4*S*,5*R*)-(+)- and (4*R*,5*S*)-(−)-1,5-dimethyl-4-phenyl-2-imidazolidinones **168a** and **168b** were used as chiral auxiliaries in the benzylation reactions (Close, 1950; Roder et al., 1984; Evans et al., 1987; Cardillo et al., 1988; Drewes et al., 1993). The basicity of the imidazolidinones was decreased by utilizing the trimethylsilyl ethers **169a** and **169b** in the acylation step using the phenylacetyl chlorides **170**, **171** and **172**. The ensuing *N*-acyl imidazolidinones **173a/b**–**175a/b** were then alkylated with the appropriate 2-*O*-methoxymethylbenzyl bromides **176** and **177** in good to excellent yields with only one diastereomer isolated (de, > 99%). Removal of the chiral auxiliary was effected by reductive deamination using $LiAlH_4$ in THF for imides **178a/b**–**180a/b** and a saturated solution of $LiBH_4$ in ether for analogs **181a/b**–**183a/b** to give the 2,3-diarylpropan-1-ols **184a/b**–**189a/b** (Cardillo et al., 1989; Paderes et al., 1991). Acidic deprotection (3 M HCl in MeOH), followed by cyclization under Mitsunobu conditions (Shih et al., 1987) finally afforded the target isoflavans **190a/b**–**195a/b** in excellent yields and in nearly enantiopure form (ee > 96–99%).



222 $R_1 = R_2 = H$ 81%
223 $R_1 = OMe$, $R_2 = H$ 93%
224 $R_1 = H$, $R_2 = OMe$ 82%
225 $R_1 = R_2 = OMe$ 86%

227 $R_1 = R_2 = H$ 96%
228 $R_1 = OMe$, $R_2 = H$ 99%
229 $R_1 = H$, $R_2 = OMe$ 99%
230 $R_1 = R_2 = OMe$ 99%

231 $R_1 = R_2 = H$ 82%
232 $R_1 = OMe$, $R_2 = H$ 39%
233 $R_1 = H$, $R_2 = OMe$ 57%
234 $R_1 = R_2 = OMe$ 50%

Scheme 28. Synthesis of (6a,11a)-*cis*-pterocarpans **231**–**234**.

Table 10
Formation of (6a,11a)-*cis*-**243a/b**, **244a**,**b** and (6a,11a)-*trans*-pterocarpans **245a/b**

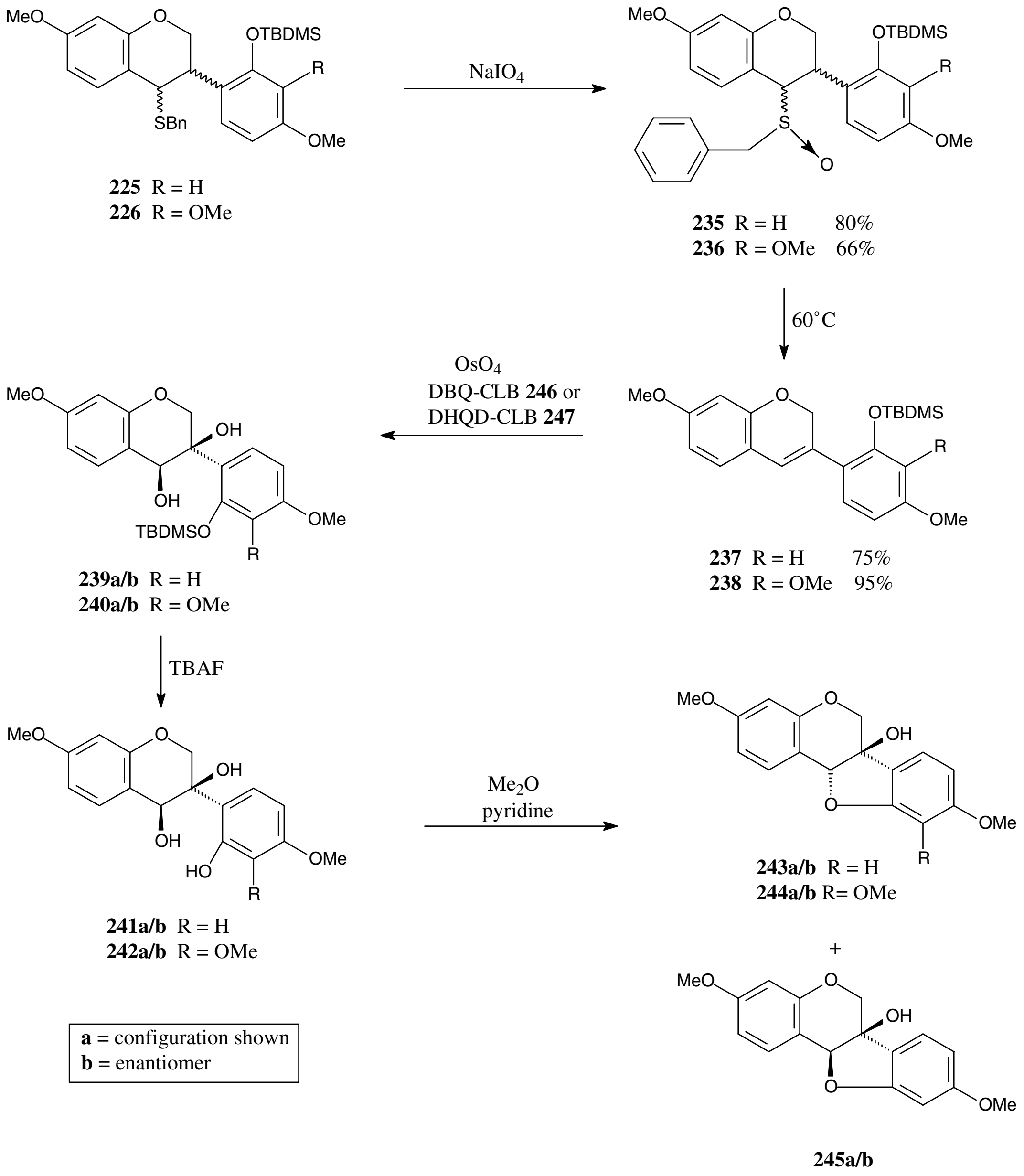
Isoflav-3-ene	Ligand	Diol	Yield (%)	ee (%)	2′-OH	Yield (%)	Pterocarpan	Yield (%)	ee (%)
237	**246**	**239a** (3*R*,4*S*)	65	>99	**241a**	100	**243a** (6a*R*,11a*R*)	70	>99
	247	**239b**(3*R*,4*S*)	68	>99	**241b**	100	**243b** (6a*S*,11a*S*)	75	>99
					241a	100	**245a** (6a*R*,11a*S*)	10	>99
					241b	100	**245b** (6a*S*,11*R*)	9	>99
238	**246**	**240a**(3*R*,4*S*)	66	>99	**242a**	100	**244a** (6a*R*,11a*R*)	75	>99
	247	**240b**(3*R*,4*S*)	63	>99	**242b**	100	**244b** (6a*S*,11a*S*)	73	>99

The stereochemistry of the alkylation step is explicable in terms of the preferential formation of a *Z*-enolate (Evans et al., 1982). Attack of the electrophile is then directed to the face of the enolate opposite the phenyl moiety on the chiral auxiliary. The chiral auxiliary having a 4*S*-configuration led to propanols exhibiting positive optical rotations and those from 4*R*-*N*-acyloxazolidinones showing negative values and are in line with observations by Evans et al. (1982). Alkylation of (4*S*,5*R*)-(+)-*N*-phenylacetylimidazolidinones resulted in (+)-propanols and (3*S*)-isoflavans and (4*R*,5*S*)-(−)-*N*-phenylacetylimidazolidinones in (−)-propanols and (3*R*)-isoflavans.

7.2. Pterocarpans

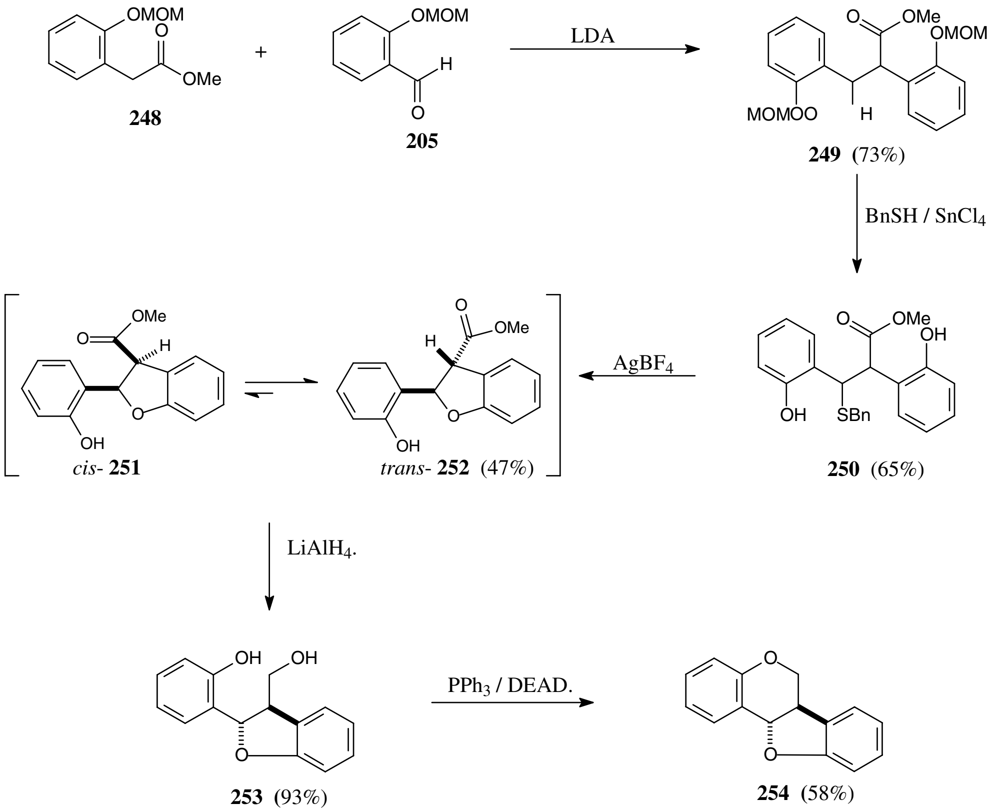
Despite identification of the first 6a-hydroxypterocarpan, (+)-pisatin, by Cruickshank and Perrin (1960), synthetic protocols to these potent phytoalexins are limited by lengthy multi-step routes and a lack of diversity as far as phenolic hydroxylation patterns are concerned. These confinements are so restrictive that only two 6a-hydroxypterocarpans, i.e., pisatin and variabilin, have been synthesized (Bevan et al., 1964; Mansfield, 1982; Pinard et al., 1998).

The results reported for the stereoselective aldol condensation between methyl ketones and aldehydes employing diisopropylethylamine and chiral boron triflates (Paterson and Goodman, 1989) prompted investigation of a more direct synthetic approach to address the issue of stereocontrol at C-6a and C-11a of the pterocarpan framework (Van Aardt et al., 1998, 1999, 2001). Depending on the lability and/or stability of protecting groups under certain reaction conditions, this protocol included methoxymethyl protection of the benzaldehydes **205** and **206** (labile in the presence of Lewis acids such as $SnCl_4$) and phenylacetates **202**–**204** as *t*-butyldimethylsilyl (TBDMS) ethers (stable under acidic



Scheme 29. Synthesis of 6a-hydroxypterocarpans **243a/b**–**245a/b**.

conditions and mild deprotection). Since 2-hydroxy-, 2-hydroxy-4-methoxy- and 2-hydroxy-3,4-dimethoxy-phenylacetic acids are not commercially available, the required phenylacetates **199**–**201** were prepared via a thallium(III)nitrate (TTN) oxidative rearrangement (McKillop et al., 1973) of 2-benzyloxyacetophenones **196**–**198** (Scheme 26). Debenzylation and silylation afforded the requisite acetates **202**–**204** in high yields. Because of the efficiency towards the stereoselective aldol condensation, lithium diisopropylamide (LDA) was selected as the deprotonating agent (Meyers and Reider, 1979; Pirrung and Heathcock, 1980). Subsequent condensation between the ester enolates and the benzaldehydes afforded the 2,3-diaryl-3-hydroxypropanoates **207**–**211** in moderate to good yields (67–78%) (Scheme 27). Since acid deprotection of the MOM-group led to decomposition (Greene and Wuts, 1991), $SnCl_4$ in the presence of $PhCH_2SH$ as nucleophile was utilized as selective deprotecting agent to afford the 2,3-diaryl-3-benzylsulfanylpropanoates **212**–**216** in 70–96% yield. Subsequent reduction of **212**–**216** with $LiAlH_4$ (yield: 77–97%) and ensuing cyclization under Mitsunobu conditions (Mitsunobu, 1981) [PPh_3/DEAD (diethylazodicarboxylate)] afforded the 4-benzylsulfanylisoflavans **222**–**226** in good overall yields. These compounds can now act as important precursors for the carbon-backbone in the synthesis of (6a,11a)-*cis*-pterocarpans, and *cis*- and *trans*-6a-hydroxypterocarpans.



Scheme 30. Synthesis of (6a,11a)-*trans*-pterocarpan **254**.

Thus, cleavage of the silyl ethers using tetrabutylammonium fluoride (TBAF) on silica (Clark, 1978) gave 4-benzylsulfanyl-2′-hydroxyisoflavans **227**–**230** which were converted to the 6a,11a-*cis*-pterocarpans **231**–**234** in yields of 39-82% using the thiophilic Lewis acids, dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) or silver trifluoromethanesulfonate (CF_3SO_3Ag) (Trost and Murayama, 1981; Williams et al., 1984; Trost and Sato, 1985) (Scheme 28).

Isoflav-3-enes **237** and **238** were obtained via periodate oxidation of the *cis*- and *trans*-4-benzyl-sulfanylisoflavans **225** and **226** followed by thermal elimination of the sulfoxides **235** and **236** (Emerson et al., 1967; Kice and Campbell, 1967; Trost et al., 1976) (Table 10, Scheme 29). Owing to the instability of isoflav-3-enes **237** and **238**, swift transformation to the corresponding isoflavan-3,4-diols was essential. The commercially available AD-mix-α or -β was not reactive enough to effect asymmetric dihydroxylation. Therefore, treatment of isoflav-3-enes **237** and **238** in CH_2Cl_2 at −78 °C with stoichiometric amounts of OsO_4 in the presence of the chiral catalyst dihydroquinine *p*-chlorobenzoate (DHQ-CLB) **246**, afforded (−)-(3*R*,4*S*)-*syn*-diols **239a** and **240a** in acceptable yields (63–68%) and excellent enantiomeric excesses (>99%) (Kolb et al., 1994a; Pinard et al., 1998). The (+)-(3*S*,4*R*)-*syn*-diols **239b** and **240b** were similarly obtained by using dihydroquinidine *p*-chlorobenzoate (DHQD-CLB) **247** as chiral ligand. Deprotection (TBAF suspended on silica) of diols **239a/b** and **240a/b** afforded 2′-hydroxyisoflavan-3,4-diols **241a/b** and **242a/b** in quantitative yields which then served as precursors to the respective 6a-hydroxypterocarpans **243a/b** and **244a/b**. Attempted cyclization employing Mitsunobu conditions was unsuccessful. However, selective mesylation (Ms_2O, pyridine) activated the secondary 4-hydroxy sufficiently to afford the requisite (6a,11a)-*cis*-6a-hydroxypterocarpans **243a/b** and **244a/b** in good yields and essentially optically pure form. It is interesting to note that cyclization of diols (3*R*,4*S*)-**241a** and (3*S*,4*R*)-**241b** also afforded the (6a*R*,11a*S*)- and (6a*S*,11a*R*)-*trans*-6a-hydroxyptercarpans **245a** and **245b**, respectively, as minor products (9–10% yield) and was the first report on the formation of the configurationally hindered 6a,11a-*trans*-analogs.

In all reported pterocarpan syntheses, formation of the six membered B-ring invariably preceeds closure of the five membered C-ring. Once the B-ring is formed Dreiding models indicate that it becomes virtually impossible to close the C-ring in a configuration other than the 6a,11a-*cis*-form. It was envisaged that the reversal of the order of cyclization, i.e., initial C-ring formation followed by B-ring closure, may provide synthetic access to the hitherto unknown (6a,11a)-*trans*-pterocarpans.

Thus, aldol condensation between the MOM-protected phenylacetate **248** and benzaldehyde **205**, using LDA for enolate generation, afforded the 2,3-diaryl-3-hydroxy-propanoate **249** in 73% yield (Scheme 30). Deprotection of the acetal functionalities of **249** using $SnCl_4/PhCH_2SH$ as above afforded 2,3-diaryl-3-benzylsulfanylpropanoate **250** in 65% yield. Cyclization ($AgBF_4$) of **250** to first form the pterocarpan C/D-ring system, afforded the thermodynamically more stable *trans*-fused 2,3-disubstituted dihydrobenzofuran **252** (47%; $J_{2,3} = 8.5$ Hz). Subsequent reduction ($LiAlH_4$) gave the primary alcohol **253** (93%), which was converted under Mitsunobu cyclization conditions into the (6a,11a)-*trans*-pterocarpan **254** ($J_{6a,11a} = 13.5$ Hz in 58% yield).

8. Concluding remarks

The methods towards the synthesis, both stereoselective and non-stereoselective, of monomeric flavonoid reviewed here now provide a firm foundation for further developments in this area. This review will hopefully provide an essential background for researchers interested in the synthesis of polyphenolic flavonoid prototypes, and will also stimulate further interest to direct future synthetic efforts. It is also clear that there is still a lot to be done, especially in terms of methods development and also to address the syntheses of analogs that have not been covered in this review.

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Daneel Ferreira Daneel Ferreira graduated from the University of Pretoria, South Africa in 1964. He completed the B.Sc. (Hons.) and M.Sc. programmes of the Chemistry Department, University of the Orange Free State, Bloemfontein, South Africa through part time studies. In 1969 he was appointed as Technical Assistant in the Chemistry Department at UOFS, obtained the D.Sc. degree in Organic Chemistry in 1973 and progressed to the ranks of Professor of Organic Chemistry in 1985. He spent 1977 as a Visiting Lecturer at Imperial College, London where he worked under the supervision of the late Sir Derek Barton. His main area of research is in the study of the chemistry of flavonoids and proanthocyanidins where he focusses on structure elucidation (up to the tetraflavanoid level) via physical methods, especially NMR and CD, semi-synthesis of oligomers, stereoselective syntheses of monomeric precursors, and the development of general methodologies to manipulate the molecular backbone of the C_6–C_3–C_6 unit. He was invited to establish a Research Unit for Polyphenol- and Synthetic Chemistry at UOFS by the Foundation for Research Development, Pretoria and was duly appointed as Director in 1990. He held this position until 1998 before joining the Thad Cochran National Center for Natural Products Research, University of Mississippi in 1999 as Visiting Scholar, and was promoted to Principal Scientist in 2000. He was offered the Chair of the Department of Pharmacognosy, University of Mississippi, in 2004 where he continues with research of the chemistry of Natural Products.

Jannie P.J. Marais Jannie P.J. Marais studied at the University of the Free State, Bloemfontein, South Africa where he obtained his PhD in Organic Chemistry in 2002 under joint supervision of Prof E.V. Brandt, Dr. H. van Rensburg and Dr. D. Ferreira. His research work focused on characterization of the free phenolic profile of South African red wine, and the stereoselective synthesis of constituent flavonoids, e.g., flavan-3,4-diols and flavanones. He joined the National Center for Natural Products Research at the University of Mississippi as a Postdoctoral Associate in July of 2002, where he currently works with Dr. Ferreira on the stereoselective synthesis of flavanoid precursors, the semisynthesis of proanthocyanidin oligomers, and characterization of the proanthocyanidin profiles of selected transgenic plants.

Desmond Slade Desmond Slade graduated from the University of Stellenbosch, South Africa in 2000, where he obtained his PhD (Chemistry) on the chemical characterization of the interdigital secretion of the black wildebeest under the supervision of Professor Ben V. Burger. He started as a Postdoctoral Research Associate at the National Center for Natural Products Research, University of Mississippi, at the end of 2000, working on the synthesis of antimalarial 8-aminoquinolines and the synthesis of buprenorphine-3-β-D-glucuronide and norbuprenorphine-3-β-D-glucuronide and their deuterated analogs under the supervision of Dr. Daneel Ferreira. Since 2003, he is an Associate Research Scientist in the Center where he is also involved in cannabinoid research.