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THE USE OF CYCLOHEXA-3,5-DIENE-1,2-DIOLS IN ENANTIOSPECIFIC SYNTHESIS

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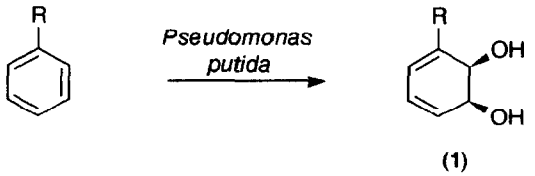
1 Introduction

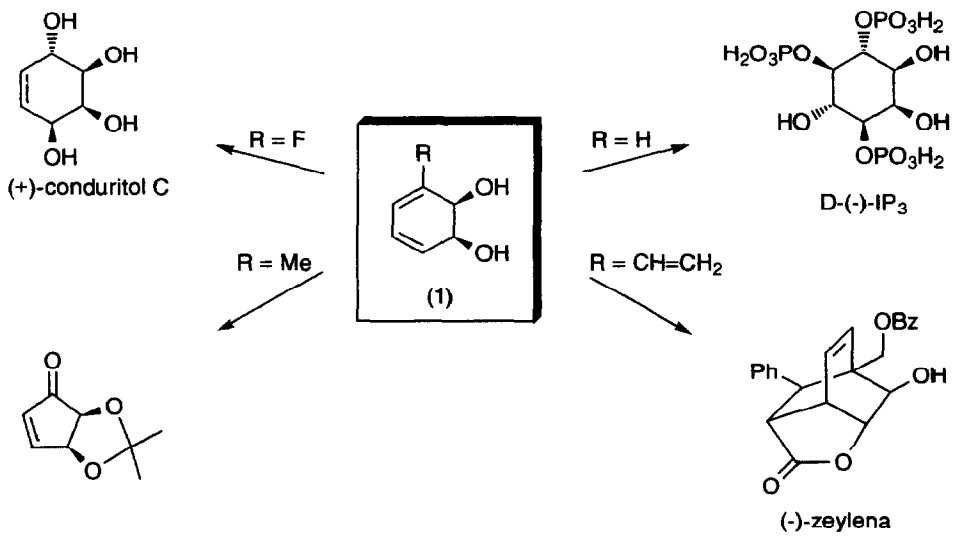
The developing demand for homochiral compounds has led chemists to investigate a variety of approaches to such molecules. One promising method, which has seen rapid growth over the last five years, lies in the use of microbial enzymes to convert achiral aromatic compounds to reactive *cis*-cyclohexa-3,5-diene-1,2-diols (**1**) (Scheme 1), usually with excellent enantiocontrol.[1]



(1)

Scheme 1

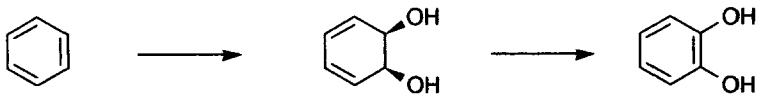
Rapid progress in this area should continue, now that several of these cyclohexadienediols have become commercially available.[2] The formation of the diols (**1**) and their application in organic syntheses is the subject of the present review. Scheme 2 shows examples taken from the recent literature in which the cyclohexadienediols have been used in the synthesis of homochiral compounds as diverse as conduritol enzyme inhibitors, inositol phosphate cell messengers, chiral cyclopentenones for prostaglandin targets and complex natural products arising biosynthetically from arene oxides.



Scheme 2

1.1 Benzenoid *cis*-Dihydrodiols

The fascinating ability of microorganisms to degrade aromatic compounds has been much investigated. In his pioneering work, Gibson[3] established in 1968 that the conversion of benzene to catechol (**3**) (Scheme 3) by the bacteria *Pseudomonas putida* involved a *cis*-dihydrodiol intermediate ("benzene *cis*-glycol") (**2**).

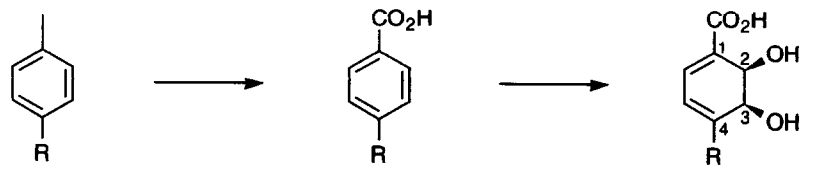


(2) (3)

Scheme 3

Normally, the bacteria also possess dehydrogenase enzymes which catalyse the further oxidation of (**2**) to catechol (**3**), but a mutant strain (39/D) was isolated which lacked this dehydrogenase ability.[4,5] The dienediol intermediate thus accumulated in the solution and could be purified by extraction into ethyl acetate. When the mutant was grown on glucose, in the presence of benzene, oxygen-18 labelling experiments proved that both atoms of oxygen in the diol arose from atmospheric oxygen.[5] Gibson's seminal contribution, made in 1970, was the discovery that toluene was converted under these conditions to chiral *cis*-glycol (**1**, R = Me). Moreover, the enzymic conversion tolerated a wide variety of mono- and *p*-disubstituted aromatics. The positions of oxidation of the aromatic ring were those adjacent to the substituent, as also found for other aromatic compounds such as *p*-chlorotoluene[6] and ethylbenzene.[7] Later results, with Ziffer,[8] proved the absolute stereochemistry of adducts (**1**, R = Me, Et, Cl and Ph) to be as shown in Scheme 1 [*i.e.* 1*S*,2*R* for (**1**, R = Me)].

Other strains of *Pseudomonas putida* can cause initial oxidation of the methyl group in *p*-cymene (**4a**) to give *p*-cumate and thence the diol (**5a**) (Scheme 4).[9] The trifluoromethyl group is well tolerated in these enzymic oxidations, and *p*-trifluoromethylbenzoic acid gave a dihydrodiol (**5b**) similar to (**5a**);[10] a range of chiral carboxy-substituted cyclohexadienediols has thus become accessible.



(4)

(5) **a** R = $CHMe_2$
b R = CF_3
c R = Br

Scheme 4

The crystal structure of the diol formed by the oxidation of *p*-bromobenzoic acid using the mutant strain JT 107 has been shown by X-ray crystallography to be (2*R*,3*R*), as drawn in (**5c**).[11] Hydroxylation may even

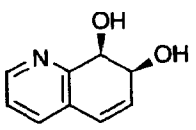
occur at a substituted aromatic position, as in the conversion of 3,5-difluorobenzoic acid by *Pseudomonas putida* (strain JT 103) to the chiral diol (**6**) in Scheme 5.[12]

Scheme 5

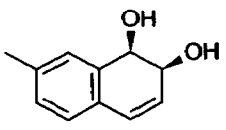
Modern techniques of biotechnology allow quite high yields of these benzenoid *cis*-glycols to accumulate in the reaction growth medium. Yields of up to 30 g/L of broth can be obtained in favourable cases,[1,13,14] although other examples (**1**, R = C≡CH or SMe) have proved more troublesome and indirect methods for their preparation from halogeno-metabolites may be more rewarding (see Section 2.4). The arene *cis*-glycols are usually isolated as reasonably stable, crystalline solids, although they are subject to acid-catalysed elimination in acidic conditions, to yield phenols.

1.2 Bicyclic Arene *cis*-Dihydrodiols

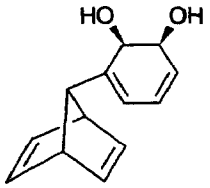
Naphthalene and aza-arenes such as quinoline are converted by *Pseudomonas putida* mutants to dihydroarene diols [*e.g.* quinoline gives (**7**)], with the aza-arene systems in particular yielding dihydrodiols which are relatively stable towards acid-catalysed elimination.[15] It has recently been shown that 2-methylnaphthalene is attacked exclusively at the less substituted aromatic ring by *Pseudomonas putida* (mutant NCIB 9816) to give diol (**8**), a fragment relevant to the synthesis of biologically active compactin and forskolin.[16] Although some *Pseudomonas* species (strain BM 2) will attack the double bond of alkenes (as in norbornadiene), 7-phenylnorbornadiene is preferentially oxidised at the phenyl group to give the chiral diol (**9**) (41%), believed to have the absolute configuration shown.[17]



(**7**)

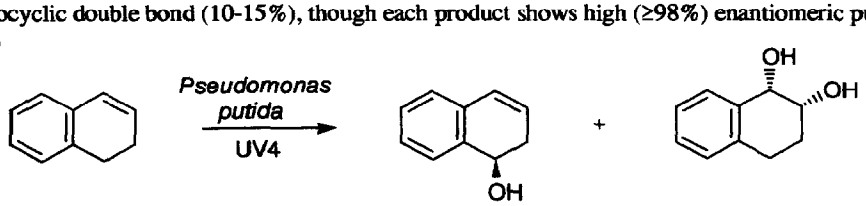


(**8**)



(**9**)

In contrast, the related dihydroaromatics tend to give benzylic hydroxylation (85-90%) and *cis*-diol by attack at the exocyclic double bond (10-15%), though each product shows high (≥98%) enantiomeric purity (Scheme 6).[18,19]



Scheme 6

1.3 Configuration of Arene *cis*-Dihydrodiols

The original determination of absolute stereochemistry of the toluene metabolite, (**1**, R = Me) was made by hydrogenation and conversion to (-)-2*R*-methyladipic acid,[8] and confirmed by X-ray crystallography of a Diels-Alder adduct.[20] The absolute configurations of other metabolites (**1**, R = Et, Cl and Ph) followed from a study of their CD spectra. More recent work has led to a general method for determining the enantiomeric excess (*e.e.*) and absolute configuration of *cis*-dihydrodiol metabolites, using homochiral α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) derivatives.[21] Diels-Alder cycloaddition of the diol to 4-phenyl-1,2,4-triazoline-3,5-dione and conversion to crystalline single di-MTPA diastereoisomers gave compounds whose ^{1}H and ^{19}F NMR spectra showed signals characteristic of the original configuration. All the diols formed in the microbial oxidation have the absolute configuration shown in (**1**). They are generally of >98% *e.e.*, with the exception of the fluorodiol (**1**, R = F) where the *e.e.* is only ≈60%: however, even for this latter diol, simple recrystallisation is capable of providing enantiomerically pure material.[22,23] The determination of *e.e.* by the above method can also be applied to the *cis*-dihydrodiols from bicyclic arenes and aza-arenes, by initial hydrogenation to yield the more stable *cis*-tetrahydrodiols, followed by diesterification using MTPA derivatives.[24]

2 Reactions of Arene *cis*-Dihydrodiols

The arene dihydrodiols show a rich variety of chemical reactions, as might be expected for a cyclohexadiene derivative; in some cases, the two hydroxyl groups are distinguishable in reactivity, leading to further sets of chiral compounds based on chemoselective reactions.

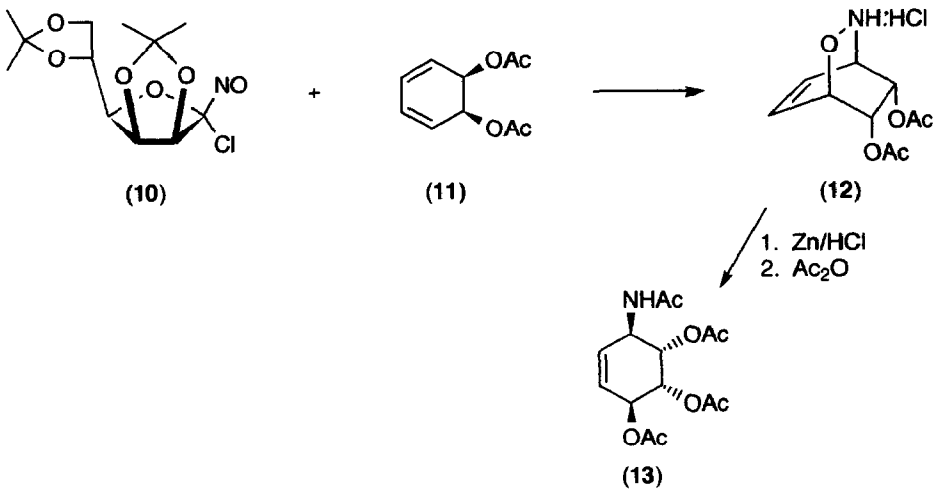
The symmetrical (*meso*) diol (**2**) has been used in several enantiospecific syntheses. Thus, asymmetric Diels-Alder reactions to chiral dienophiles can provide high enantioselectivity. Alternatively, reaction at some stage with a chiral reagent leads to diastereoisomers which may be separated and converted to individual enantiomers of product after removal of the chiral auxiliary. Enzymatic esterase or transferase reactions on symmetrical diacetates or diols provides another means of introducing enantioselectivity.

The other distinct route to chiral products uses the very high (generally >98%) enantioselectivity of the microbial dioxygenase enzyme to provide the diols as the source of chirality which is carried through the synthesis. Typical electrophilic reactivity towards the alkene bonds leads to easy epoxidation, carbene addition, ozonolysis and osmylation reactions. The *cisoid* conjugated diene shows all the possibilities of 1,4-addition: Diels-Alder reactivity, dimerisation and singlet oxygen reactivity. Sections 2.4-2.9 provide examples of these popular approaches.

2.1 Asymmetric Diels-Alder Reactions

Reaction of the diene with an optically-active dienophile in an asymmetric Diels-Alder cycloaddition allows the introduction of chirality to the *meso* series of cyclohexa-3,5-diene-1,2-diols. For example,

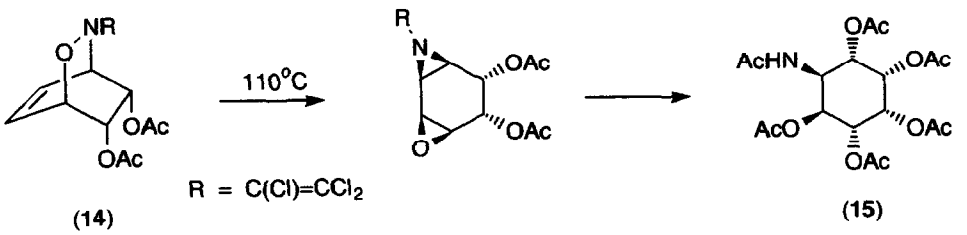
Werbitzky and co-workers[25] have shown a very brief enantioselective route to aminocyclitols, *via* a hetero-Diels-Alder reaction of the activated nitroso-mannose derivative (**10**) with the *cis*-diacetate (**11**). Cycloaddition of the nitroso dienophile occurs *anti* to the acetate groups, and with high optical yield (*e.e.* = 94% at -40°C). The resultant dihydrooxazine (**12**) is then easily reduced with zinc/hydrochloric acid to give conduramine A1 tetraacetate (**13**) (82%, Scheme 7).



(10) (11) (12) (13)

Scheme 7

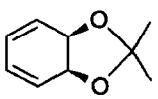
Other researchers[26] have developed routes to chiral aminocyclitols of relevance to the aminoglycoside antibiotics, by thermal rearrangement of the substituted dihydrooxazines (**14**) to epoxyepimines, followed by epoxide and aziridine ring opening in acidic conditions. Scheme 8 shows the synthesis of (-)-*allo*-inosamine hexa-acetate (**15**) by this route.



(14) (15)

Scheme 8

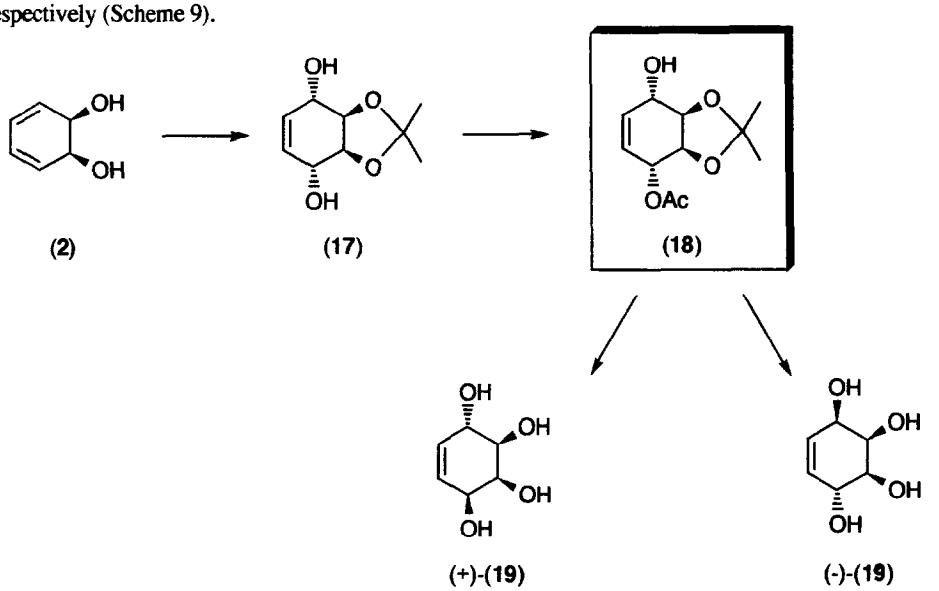
Piepersberg and co-workers[27] have recently claimed an even higher enantiomeric excess (>97%) than for (**12**) by using the 1,2-*O*-isopropylidene derivative (**16**) of the parent dihydrodiol as the diene component, and have converted the intermediate conduramine into *cis*-1,3-diamino-dideoxyinositol isomers of the streptamine type.



(16)

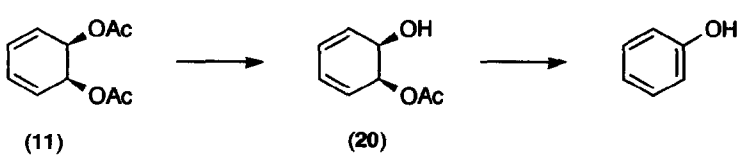
2.2 Chiral Induction

Microbial oxidation of benzene makes the symmetrical dihydrodiol (2) a very easily accessible species, and there have been several recent successes in converting (2) to chiral derivatives by the use of other enzymic processes. Johnson,[28] for example, has described the preparation of (+) and (-)-conduritol C (19), *via* the symmetrical cyclohexenediol (17) and exploiting the lipase from *P. cepacia* (Amano P-30 lipase) for chiral acetylation to yield the mono-acetate (18) (>95% *e.e.*). Subsequent reactions, with or without inversion at the carbon bearing the acetoxy group, led to enantioselective syntheses of conduritols (+)-(19) and (-)-(19), respectively (Scheme 9).



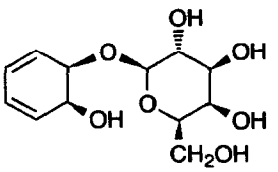
Scheme 9

Crout's group[29] have adopted a different approach to homochiral derivatives in the cyclohexadienediol series. Faced with the limitation that enzymatic hydrolysis of the diacetate (11) could not be used for resolution, because the intermediate mono-acetate (20) rapidly undergoes elimination of acetic acid to yield phenol (Scheme 10), they applied the significant technique of glycosyl transfer.

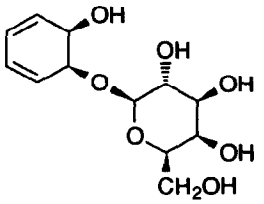


Scheme 10

Resolution was achieved by galactosyl transfer to the diol (2) from lactose as donor, catalysed by the β-galactosidase of *E. coli*, to yield the diastereoisomeric β-galactosides (**21**) and (**22**), initially formed in a 9:1 ratio and separable by HPLC.

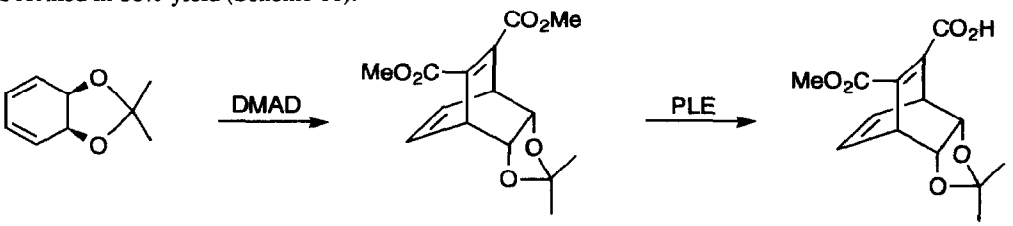


(21)



(22)

A less direct route to chiral derivatives of the cyclohexadienediol has involved Diels-Alder addition of dimethyl acetylenedicarboxylate to the isopropylidenated diene (**16**) (70% yield), followed by stereoselective partial hydrolysis of the prochiral diester (**23**) using pig liver esterase; the optically active mono-ester (**24**) was formed in 88% yield (Scheme 11).[30]



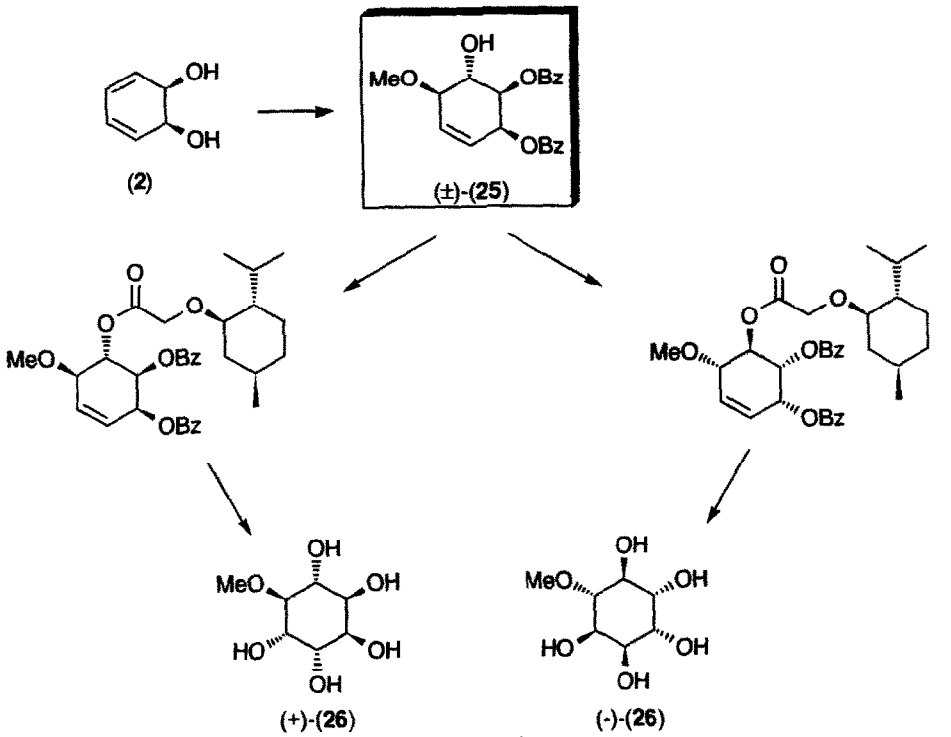
(16) (23) (24)

Scheme 11

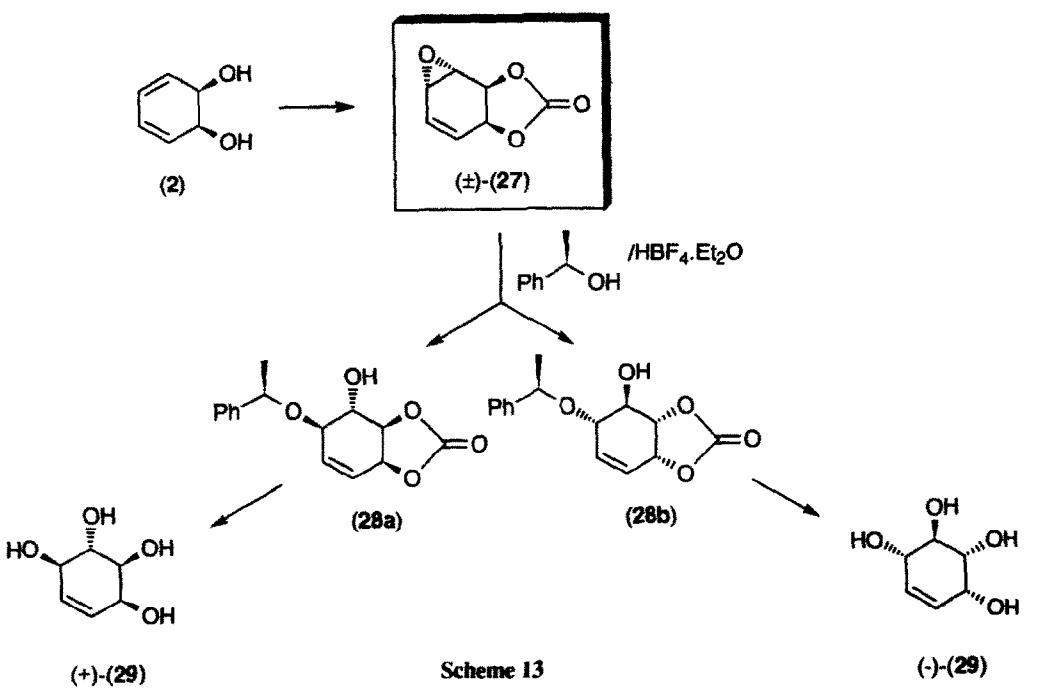
2.3 Use of Chiral Auxiliaries

The use of the commercially available (but symmetrical) benzene *cis*-glycol (**2**) in enantiospecific syntheses is best shown by two examples from the work of Ley and his group.[31,32] In the total synthesis of the naturally-occurring D-(+)-pinitol (**26**) and its unnatural L-(-)-antipode, the key resolution stage involved the preparation of the menthoxyacetic ester diastereoisomers from the racemic alcohol intermediate (**25**) (Scheme 12). The stereoisomers were subsequently separated by HPLC and individually converted to the cyclitols (+)-(**26**) and (-)-(**26**).[31]

An alternative approach was used in the syntheses of the two enantiomers of conduritol F (**29**) from benzene *cis*-glycol (**2**): regiospecific opening of a racemic epoxide intermediate (**27**) by (*R*)-(+)-*sec*-phenethyl alcohol in the presence of tetrafluoroboric acid etherate yielded the diastereoisomeric alcohols (**28a**) and (**28b**) (Scheme 13).[32] Simple deprotection of the individual isomers by sodium/liquid ammonia then gave (+)- and (-)-conduritol F (**29**) in good yield (80-85%).



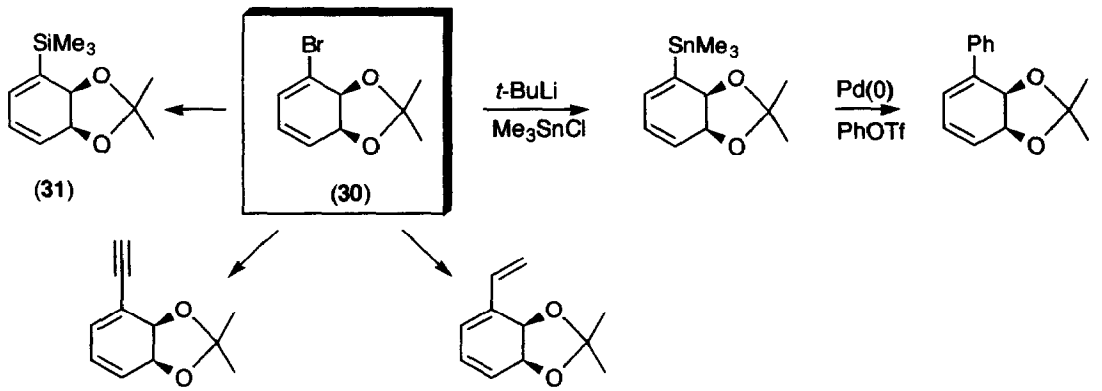
Scheme 12



Scheme 13

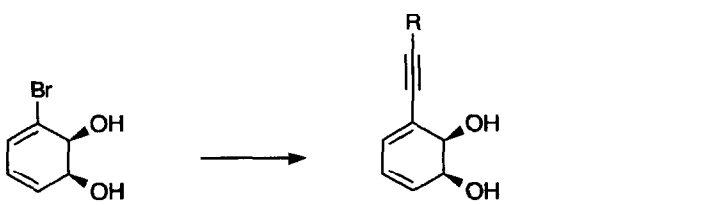
2.4 Metallation

Microbial oxidation of aromatics to dihydrodiols is sometimes low yielding (e.g. phenylacetylene, which gives only 50 mg of product per L of culture) or the diols are not formed from the enzymic process (e.g. trimethylsilylbenzene). However, several recent reports have shown that it possible to prepare a range of 3-substituted arene dihydrodiol derivatives indirectly by metallation of the readily available 3-halo derivatives.[33-35] Thus, reaction of the bromoacetal (**30**) with *t*-butyl lithium at -100°C, followed by trapping with trimethylsilyl chloride gave (**31**) in 41% yield. Other 3-unsaturated derivatives are available from (**30**), as shown in Scheme 14.[33]



Scheme 14

Even the free diol (**32**) can be used in these metallations, as seen by the conversion to various acetylenic diols (**33**) in good yields, using palladium(0)-mediated coupling [$Pd(PPh_3)_4$, CuI and n-$BuNH_2$] with trimethylsilyl acetylene, phenylacetylene or 1-hexyne (Scheme 15).[34]



(**32**)

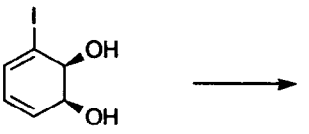
(**33**) a; R = Me_3Si (78%)
b; R = Ph (91%)
c; R = n-Bu (70%)

Scheme 15

The iodo-compound (**34**) has proved to be a versatile intermediate, giving products not available from the bromo-compound. The substitution of these vinylic halides by palladium(0) coupling with organotin compounds provides a mild synthetic route to other novel chiral 3-substituted dihydrodiols: Scheme 16 shows

the formation of the allylbenzene (**35a**) and the benzonitrile (**35b**) derivatives from coupling with allyltributyltin and tributyltin cyanide, respectively.[35]

Metallation reactions of these types are based on the accessibility of halodiols (**32**) and (**34**), and are likely to become of increasing importance in extending considerably the range of dihydrodiols that are available as the starting points in future enantiospecific syntheses.



(**34**) (**35**) a; R = $CH_2CH{=}CH_2$ (31%)
b; R = CN (52%)

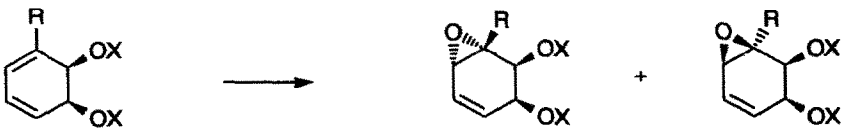
Scheme 16

2.5 Cyclohexadiene Oxidations

Several useful functionalisations of the arene dihydrodiol ring rely upon electrophilic attack at one of the diene double bonds, either *via* epoxidation or *via* osmylation. Carbenoid additions to the double bonds have also been explored, whilst ozonolysis presents a method for selective cleavage of the cyclohexadiene ring. For each reaction, control of the appropriate reagents and conditions can achieve useful stereoselectivity and chemoselectivity, as shown in the following sections.

2.5.1 Epoxidation

Peracid epoxidation of cyclohexadienes is generally more rapid than epoxidation of cyclohexenes, and there has therefore been no difficulty in controlling the extent of reaction with dihydrodiols to give cyclohexene epoxide intermediates in high yield, as shown in Scheme 17. As with many peracid reactions, the stereochemistry of attack on *protected* dihydrodiol derivatives has been from the less hindered direction *anti* to the substituents, with a strong (but not complete preference).[36,37,39] Larger silyl protecting groups (e.g. *t*-$BuPh_2Si$) were more effective in this shielding than acetate or benzoate protection.[31] Bulky cyclic protection of the diol [as in the *O*-isopropylidene derivative (**16**)] has ensured exclusive epoxidation from the opposite side of the cyclohexadiene ring (Scheme 17).[39,40]



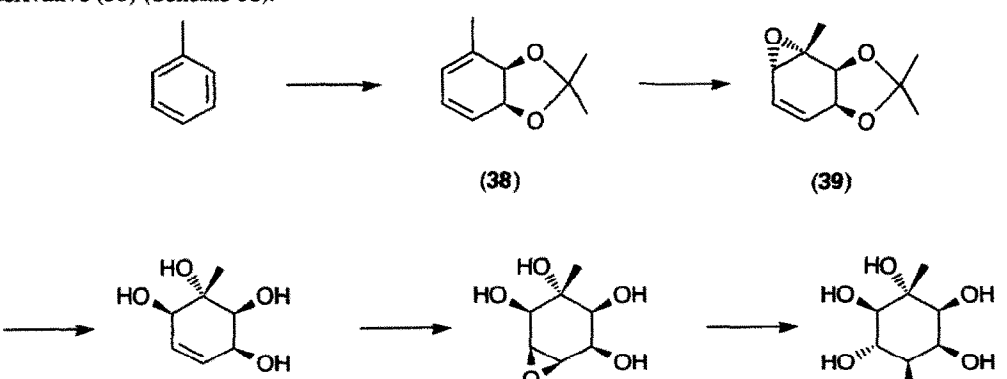
(36) (37)

		Ratio (36) : (37)	Reference
R = H	X = Bz	84 : 16	36
R = H	X = $SiBu^tPh_2$	94 : 6	31
R = H	X,X = >C=O	82 : 18	37
R = H	X = H	15 : 85	38
R = Me	X = Ac	80 : 20	39
R = Me	X,X = $>CMe_2$	exclusive : —	39, 40

Scheme 17

In contrast, the accelerated rate of attack by peracids on the double bond of allylic *alcohols* (in which hydrogen bonding makes attack from the *syn* direction more rapid) causes a marked and useful reversal in stereoselectivity of epoxidation: the parent diol (2) (R = X = H in Scheme 17), for example, gave a 15:85 ratio of epoxides (**36**) and (**37**) resulting from *anti* and *syn* attack, respectively.[38]

In the case of unsymmetrically substituted dihydrodiols, the chemoselectivity of attack is an important feature. For electron-donating substituents on the diene (e.g. R = Me), attack by peracid occurs entirely at the more substituted double bond.[39,40] This reaction has been exploited in the total synthesis of (-)-laminitol (**40**) from toluene, in which isomer (**39**) was the sole isolated product from epoxidation of the protected diol derivative (**38**) (Scheme 18).



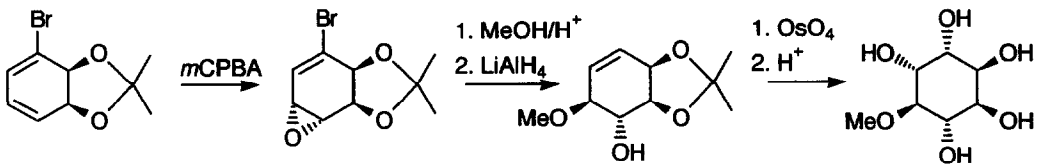
(38) (39)

(-)-(40)

Scheme 18

Acid-catalysed ring opening of the vinylic epoxide occurred easily, and after a preferential *syn* epoxidation of the resulting tetrol, the *C*-methylated cyclitol (-)-laminitol (**40**) was obtained by a final acid-catalysed ring opening.[40]

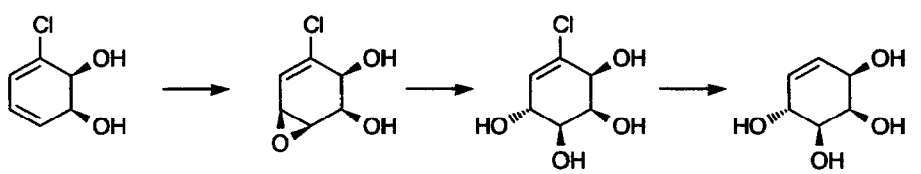
Epoxidation of the chiral diols derived from the halobenzenes presents some worthwhile synthetic possibilities. The bromoacetal (**30**) was attacked by peracid stereoselectively and exclusively at the less substituted double bond to give epoxide (**41**) in 80% yield.[41] Subsequent epoxide ring opening by methanol, reductive dehalogenation ($LiAlH_4$) and osmylation gave a short synthesis from bromobenzene of the unnatural isomer of pinitol, (-)-(**26**) (Scheme 19). Enantiodivergent results were obtained simply by reversing the sequence of the two stages of oxidation of bromoacetal (**30**): thus, osmylation of (**30**) followed by epoxidation gave the complementary isomer of pinitol, (+)-(**26**).[41,42] By this manipulation, both enantiomers of product become available from a single enantiomer of arene dihydrodiol.



(**30**) (**41**) (-)-(**26**)

Scheme 19

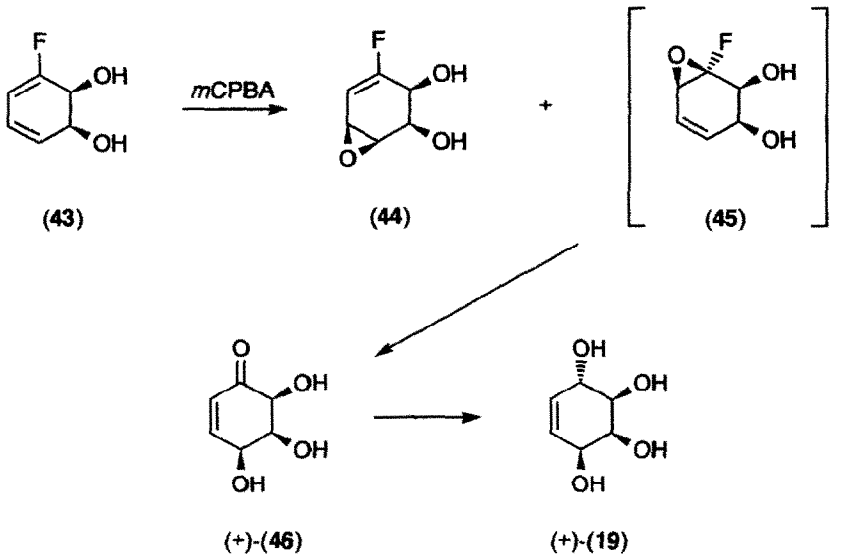
A complementary approach has been used in the conversion of chlorobenzene to (-)-conduritol C.[38] Epoxidation of the unprotected chlorodiol (**42**) gave *syn* stereoselectivity (>95%) and regioselective attack at the unchlorinated double bond (Scheme 20). Acid-catalysed addition of water and reductive dechlorination (sodium/liquid ammonia) led, in a very brief enantiospecific route, to (-)-conduritol C (**19**).



(**42**) (-)-(**19**)

Scheme 20

The homochiral fluorodiol (**43**), derived from fluorobenzene, gave interesting results on peracid epoxidation.[43] Apart from attack at the disubstituted double bond (as seen for the corresponding chloro- and bromodiols), there was evidence for competitive reaction at the fluorinated double bond, to give an unisolated α-fluoroepoxide (**45**) [(**44**) : (**45**) = 2 : 1]. In the presence of water and an acid catalyst, (**45**) was transformed into the stable, crystalline enone (+)-(**46**) in *ca.* 25% overall yield (Scheme 21). This short route from aromatic compound to chiral enone deserves further exploitation; here, enone (**46**) was used in a short synthesis of (+)-conduritol C, (+)-(**19**), by Luche reduction ($CeCl_3/NaBH_4$) of the enone triacetate.[43]



(43) (44) (45)

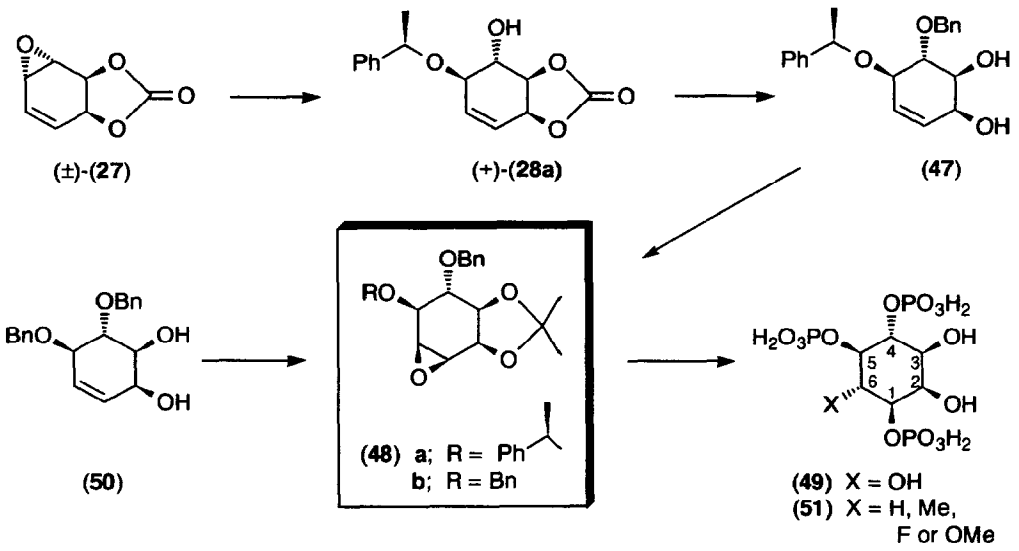
(+)-(46) (+)-(19)

Scheme 21

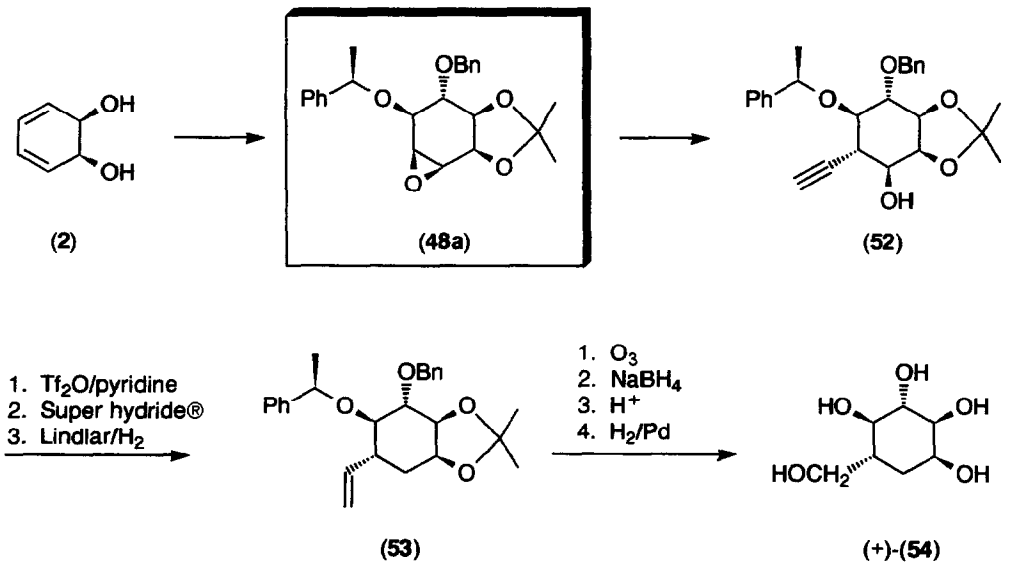
Vinylic epoxides derived from these reactions undergo a facile acid-catalysed ring opening that is both regiospecific (allylic C-O cleavage) and stereospecific (S_N2-like), which has led to several applications in natural product synthesis. Resolution of racemic epoxides *via* diastereoisomer formation can be carried out as a step subsequent to, or as a consequence of, ring opening, as in Schemes 12 and 13 respectively.

Ley's group have used this approach for the total synthesis of the enantiomers of the key compound in the phosphatidylinositol cycle, *myo*-inositol 1,4,5-trisphosphate (**49**).[37] The racemic epoxycarbonate (**27**) was reacted with (*R*)-(+)-*sec*-phenethyl alcohol, the diastereoisomer (**28a**) was separated and converted *via* the conduritol F intermediate (**47**) to the pivotal epoxide (**48a**) (Scheme 22). Regioselective ring opening of (**48a**), followed by deprotection, phosphorylation, hydrogenolysis and final acidification gave the natural isomer, D-(-)-1,4,5-IP_3 (**49**).[44,45] The whole sequence was repeated using the alternative diastereoisomer (**28b**) (Scheme 13) to yield the enantiomer L-(+)-1,4,5-IP_3. In a related investigation, epoxidation of the dibenzylated intermediate (**50**) and subsequent opening of the epoxide group in (**48b**) at C-6 by a variety of nucleophiles gave a range of 6-substituted *myo*-IP_3 analogues (**51**), of potential interest as cellular second messengers.[46]

The resolved epoxide (**48a**) has also been used in the total synthesis of a pseudo-sugar of interest as an enzyme inhibitor (Scheme 23). Opening of the epoxide ring of (**48a**) by lithium acetylide ethylene diamine complex gave the acetylenic alcohol (**52**) which was deoxygenated and the triple bond partially reduced. The final steps in the route involved ozonolysis of the vinyl group in (**53**), reduction to alcohol and deprotection to afford pseudo-α-D-glucopyranose (**54**).[47]



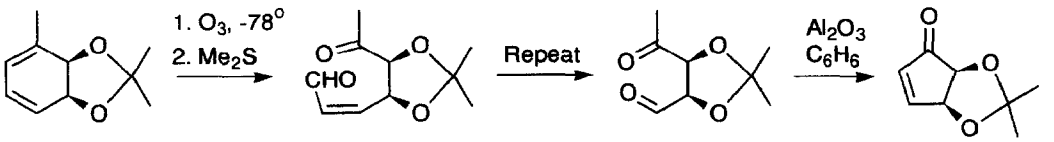
Scheme 22



Scheme 23

2.5.2 Ozonolysis

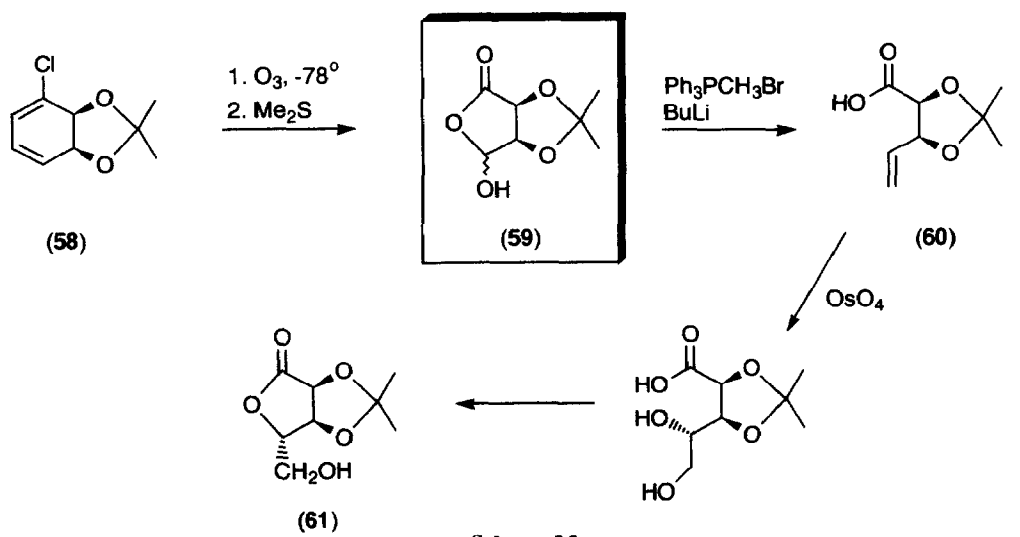
Hudlicky[39] has provided examples in which ozonolysis of conjugated cyclic dienes such as (**38**) (Scheme 24) can be carried out quantitatively in a stepwise manner, with initial attack at the more substituted site. The intermediate unsaturated dicarbonyl compound [e.g. (**55**)] can be treated with ozone again, to give higher yields of the saturated dicarbonyl products than by direct double ozonolysis. Exposure of (**56**) to alumina in benzene at reflux gives an aldol reaction, leading to a brief synthesis of cyclopentenone (+)-(**57**), thus available in three steps and 45% overall yield from toluene, and suitable for conversion to prostaglandins.[48]



(**38**) (**55**) (**56**) (+)-(**57**)

Scheme 24

The significant feature of ozonolysis of the chloroacetal (**58**) is that the chlorine atom is lost, yet chirality is retained in the hydroxylactone product (**59**). Differentiation of the two carbonyl groups in (**59**) has allowed its use as a versatile, protected chiral C_4 synthon. Scheme 25, for example, shows an application to the synthesis of L-ribonolactone (**61**), by Wittig reaction at the masked aldehyde group, osmylation (which occurs *anti* with respect to the isopropylidene group) and spontaneous lactonisation of the hydroxyacid.[49]

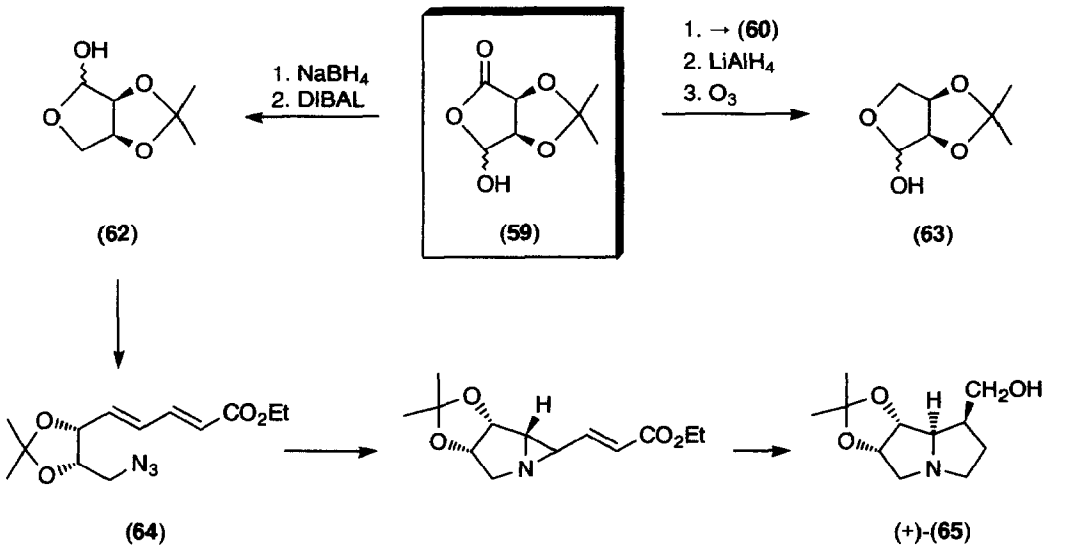


(**58**) (**59**) (**60**) (**61**)

Scheme 25

The key ozonolysis product (**59**) has been used in an enantiodivergent approach to protected L- and D-erythrose, (**62**) and (**63**), respectively.[50] Control of the site of carbonyl reduction in (**59**) was effected by initial reaction at the aldehyde group, followed by DIBAL treatment to give the L-enantiomer (**62**); alternatively, protection of the aldehyde group by Wittig conversion to (**60**), and subsequent reduction ($LiAlH_4$) and ozonolysis gave the D-erythrose isomer (**63**) (Scheme 26).

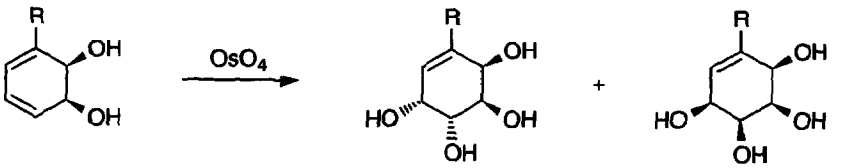
These enantiospecific routes to tetroses (**62**) and (**63**) were later developed into syntheses of the pyrrolizidine alkaloids, the trihydroxyheliotridanes (**65**).[51] The configuration at C-2 and C-3 in L-erythrose derivative (**62**) was transferred to the target molecule by Wittig reaction at the aldehyde group of (**62**), and substitution reactions led to the azide (**64**). Heating the azide gave a vinyl aziridine by intramolecular azide/alkene cycloaddition; flash vacuum pyrolysis and reduction then yielded the (+)-enantiomer of the alkaloid (**65**), in ten steps from chlorobenzene. The optical isomer (-)-(**65**) was likewise produced from D-erythrose (**63**).



Scheme 26

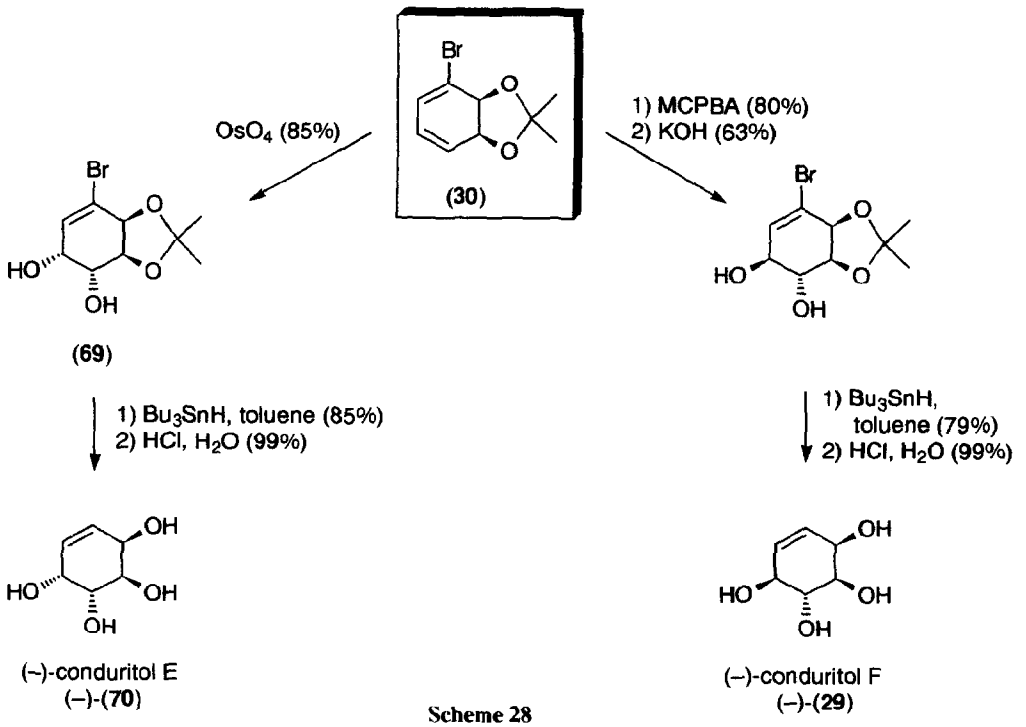
2.5.3 Osmylation

Attack of osmium tetroxide on the double bonds of *cis*-cyclohexadiene-1,2-diols occurs reasonably easily, but not always with the required selectivity either in terms of stereo- or regiochemistry. Thus, the parent diol (**2**) is attacked by OsO_4 to yield the *anti*- and *syn*-tetrols (**67a**) and (**68a**) in a 3:1 ratio,[52] (Scheme 27). The stereoelectronic factors which normally favour addition of OsO_4 *anti* to the allylic C–O bonds of the alkene are not overwhelming for the cyclohexadienediols.



Scheme 27

For the toluene metabolite, (**66**), osmylation gives a mixture of chiral tetrols in which *anti* addition has occurred at the disubstituted double bond [(**67b**):(**68b**) = 2:1], but there is also appreciable competition (*ca.* 25%) from attack at the trisubstituted double bond.[52] In contrast, reaction of the bromoacetal (**30**) with OsO_4 resulted in *anti* addition entirely at the non-brominated double bond to afford diol (**69**) in 85% yield (Scheme 28). Reductive debromination (Bu_3SnH) and hydrolysis gave a synthesis of (-)-conduritol E (**70**).[53] Although the conduritol isomer is repeatedly referred to as (+)-conduritol E in the preliminary communication, it is obvious from the known absolute configuration of (**30**)[35] and from the later full paper[23] that the synthesised isomer is (-)-conduritol E. As shown in Scheme 28, the bromoacetal (**30**) was also capable of providing brief enantiospecific access to (-)-conduritol F, (-)-(**29**), *via* a sequence of epoxidation, nucleophilic ring opening and a similar reductive dehalogenation step.[53]

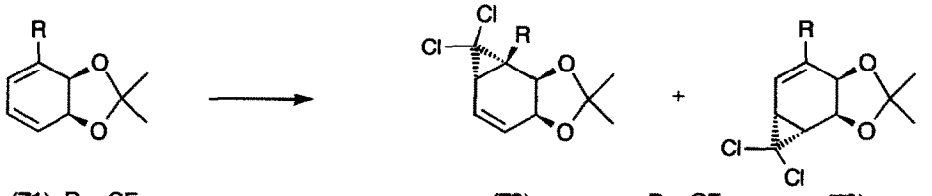


Scheme 28

Stereocontrolled *anti* osmylation of conduritol intermediates derived from the bromoacetal (**30**) has also provided a key step in the enantiospecific syntheses of (+)- and (-)-pinitol (**26**) (Scheme 19).[41]

2.5.4 Cyclopropanation

The reactivity of electrophilic carbenes towards cyclohexadiene-1,2-diol derivatives has been explored. Whilst isopropylidene protection of the diol is sufficient to ensure that attack by carbene on the diene system is from the sterically more accessible *anti* direction, the regioselectivity of cyclopropane formation is determined by the electronic effect of the substituent (R) present on the cyclohexadiene ring (Scheme 29).



(**71**) R = CF_3
(**74**) R = F
(**38**) R = Me

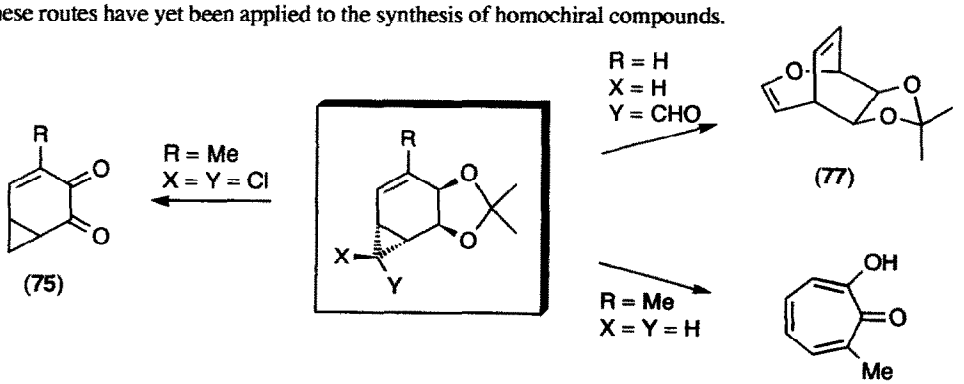
(**72**)

a R = CF_3
b R = F
c R = Me

(**73**)

Scheme 29

Thus, the trifluoromethyl-substituted acetal (**71**) reacted with dichlorocarbene regioselectively at the less substituted double bond to give (**73a**),[54,55] whereas the fluorodiene (**74**) gave the two isomeric dichlorocyclopropanes (**72b**) and (**73b**) in a ratio 1:2,[54] very similar to the selectivity of epoxidation of the fluorodiol (**43**) (Scheme 21).[43] Dichlorocarbene reacted with the toluene-derived acetal (**38**) to afford the cyclopropanes (**72c**) and (**73c**), which were more easily separated after acid hydrolysis, in a ratio 1.2:1.[56] Other carbenes, notably carboethoxycarbene, gave substituted vinylcyclopropanes by this reaction, and Scheme 30 shows how such adducts have potential as the source of a range of structures, such as σ-homo-*o*-benzoquinones (**75**), α-tropolones (**76**)[56] and oxabicyclics (**77**) by oxy-Cope rearrangement,[55] though not all these routes have yet been applied to the synthesis of homochiral compounds.



(**75**)

(**77**)

(**76**)

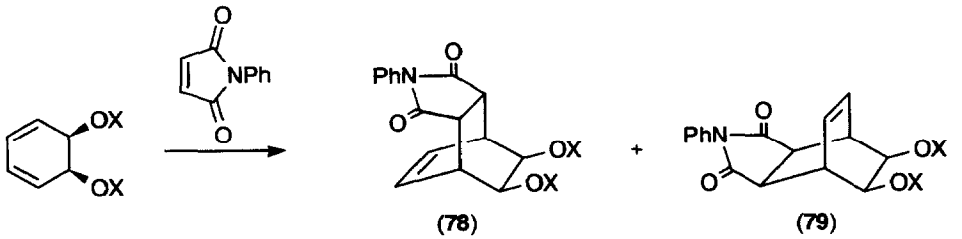
Scheme 30

2.6 1,4-Additions

The ability of *cisoid* conjugated cyclohexadienes to undergo Diels-Alder reaction to asymmetric heterodienophiles has already been discussed in Section 2.1 as a way of providing access to chiral adducts. A range of conventional Diels-Alder reactions has been carried out on chiral cyclohexadiene-1,2-diols, including studies of their dimerisation, by several research groups. Recent developments have begun to provide interesting examples of intramolecular Diels-Alder reactions in these systems. Lastly, the 1,4-cycloaddition of singlet oxygen to the conjugated diene has enabled useful 1,4-stereocontrol in approaches to conduritol and inositol targets.

2.6.1 Diels-Alder Reaction

[2+4] Cycloaddition of *N*-phenylmaleimide as dienophile to *cis*-cyclohexadienediol (2) and its derivatives occurred preferentially at the more sterically hindered *syn* face of the diene, for stereoelectronic reasons (Scheme 31).[57] The trimethylsilylated dienediol, for example, gave exclusively the *syn, endo* adduct (**78**). Cyclic protected diols such as the dimethylsilylene ether and the cyclic acetal (**16**) reacted in competition experiments about 100 times faster, but with much reduced facial stereoselectivity. Not surprisingly, the *syn:anti* ratio has been found to be solvent dependent;[54] the trifluoromethylated acetal (**71**) reacted with *N*-ethylmaleimide to give adducts similar to (**78**) and (**79**) in a 43:57 ratio in benzene.[55,58]

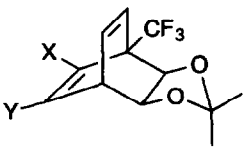


(78) (79)

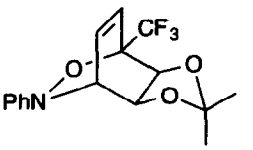
		Ratio (78) : (79)
(2)	X = H	94 : 6
(11)	X = Ac	88 : 12
	X = $SiMe_3$	exclusive : —
	X,X = >$SiMe_2$	65 : 35
(16)	X,X = >CMe_2	60 : 40

Scheme 31

Reaction of a protected dienediol with an acetylenic dienophile has been mentioned (Scheme 11),[30] and such additions in unsymmetrical situations show regioselectivity: methyl propiolate reacted with acetal (**71**) to yield the two *anti* bicyclooctadienes, (**80**) and (**81**) respectively, in a 3:1 ratio.[58] In a related manner, the heterodienophile nitrosobenzene added to the same acetal (**71**) to give the adduct (**82**) in 90% yield.

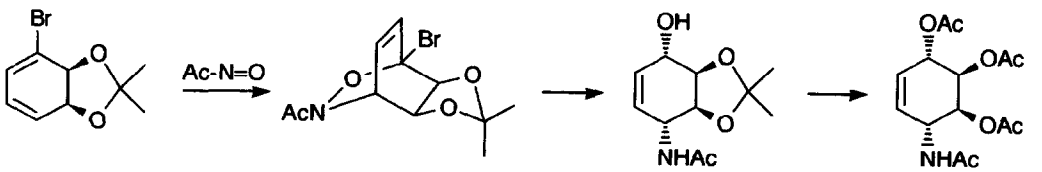


(80) X = H, Y = CO_2Me
(81) X = CO_2Me, Y = H



(82)

Aminocyclitols are significant synthetic targets, with activity as enzyme inhibitors or antibiotics. Hudlicky's group[59] have exploited the Diels-Alder reaction of a nitrosyl dienophile to the key bromoacetal (30) to yield a single enantiomer of the adduct (83) in 51% yield (Scheme 32). By the use of aluminium amalgam as a reducing agent, cleavage of the N-O bond of (83) occurred with debromination, thus preserving the *cis* arrangement of the 1,4-*O*,*N*-groups in the acetal product (84) (77%). Hydrolysis and acetylation finally gave conduramine A1 tetraacetate (13), in a route which deserves contrast with the asymmetric Diels-Alder approach of Werbitzky (Scheme 7).[25]



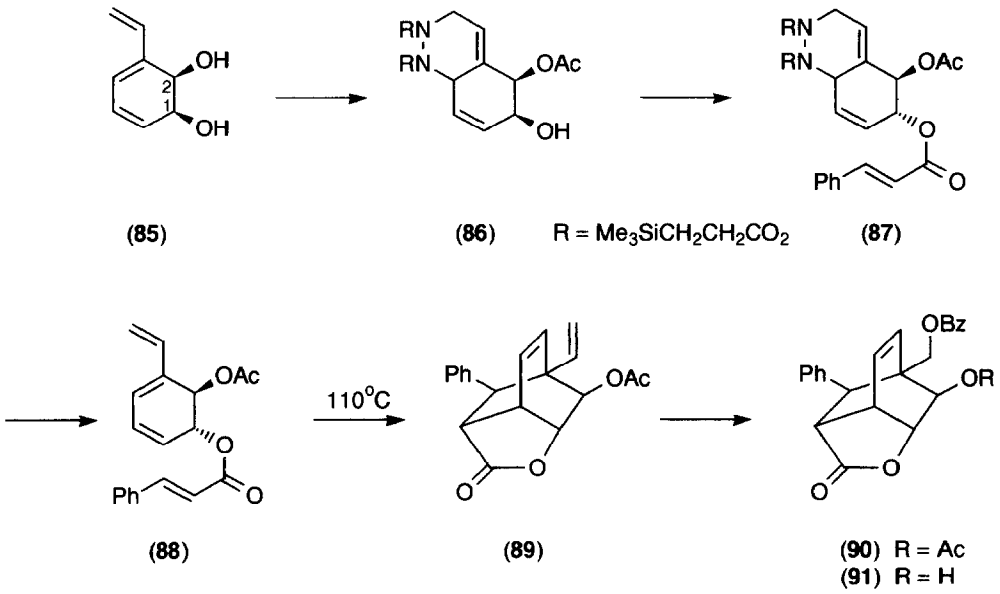
(30) (83) (84) (13)

Scheme 32

2.6.2 Intramolecular Diels-Alder Reaction

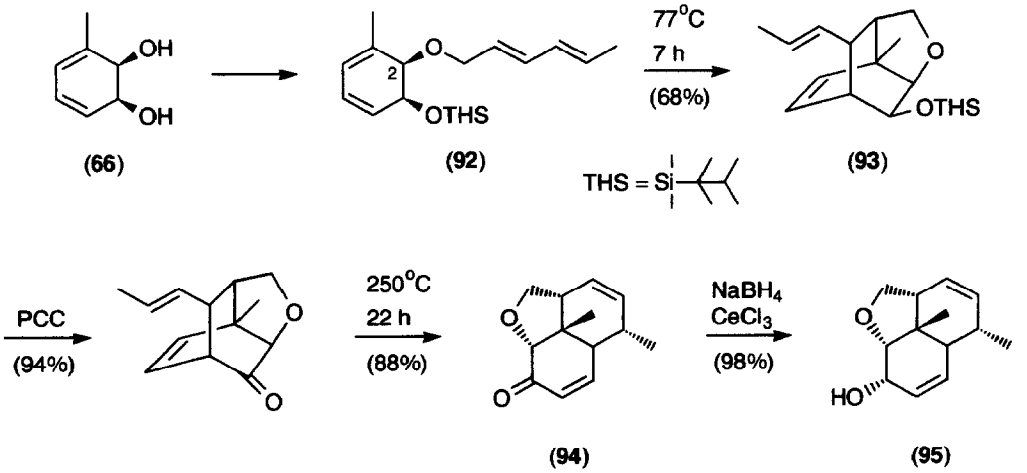
The structure of the plant metabolite (-)-zeylena (91) is believed to be derived biogenetically from the nucleophilic opening of a benzene oxide intermediate by cinnamic acid, followed by intramolecular Diels-Alder reaction. In order to mimic this process in chemical synthesis from a *cis*-cyclohexadienediol precursor, inversion of configuration at C-3 in a suitable intermediate would be required. Scheme 33 shows the successful realisation of this route to (90), starting with the *P. putida* microbial conversion of styrene to the *cis*-diol (85).[60] Protection of the reactive triene system as the azodicarboxylic ester adduct was followed by manipulation to acetylate the C-2 hydroxyl group, as in (86). Mitsunobu inversion (Ph_3P/DEAD) at C-1 of (86) with cinnamic acid successfully gave (87) (55-70%), although it should be noted that attempts to carry out the Mitsunobu reaction on several other unprotected diol derivatives led to their aromatisation (*cf.* Scheme 10). Triene regeneration gave cyclohexadiene (88), which was converted to the intramolecular Diels-Alder adduct (89) in 94% yield by heating in benzene at 110°C. Finally, functionalisation of the exocyclic

vinyl group yielded (-)-zeylena acetate (**90**).



Scheme 33

Intramolecular Diels-Alder reaction has also been used in a chiral approach to the tricyclic system (**95**), which is part of that found in morphine.[61] Toluene *cis*-glycol (**66**) was converted to the 1-silyl protected diol bearing a 2-sorbyl substituent (**92**) (Scheme 34). Heating the latter in CCl_4 gave tricyclic adduct (**93**) by Diels-Alder reaction of the cyclohexadiene system to the proximal double bond of the sorbyl group.

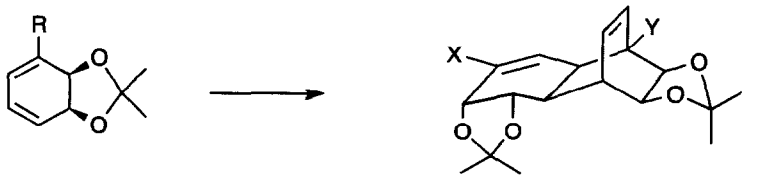


Scheme 34

The target tricyclic system (**95**), which would be the product of Diels-Alder reaction between the sorbyl diene system and one double bond of the cyclohexadiene, was not formed. However, the desired adduct could be reached by oxidation of the Diels-Alder adduct (**93**), followed by Cope rearrangement to enone (**94**) and subsequent reduction. Intramolecular cycloaddition similar to the conversion (**92**)→(**93**) has also been found on heating examples of 2-*O*-allyl substituted cyclohexadienediols derived from styrene and *o*-chlorostyrene.[62]

2.6.3 Dimerisation

Three laboratories have separately reported the facile dimerisation of isopropylidenated derivatives of the cyclohexa-3,5-diene-1,2-diols stored as neat oils, even at 0°C, over a period of days.[33,58,63] Roberts and co-workers[58] noted that the trifluoromethylated acetal (**71**) gave dimer (**96a**), by reaction of the diene system with the remote (disubstituted) double bond of another molecule of (**71**) acting as dienophile (Scheme 35). A similar dimerisation occurred for the halogenated dienediols (**30**) and (**58**).[33,63] The stereochemistry of the dimers has been assigned from NMR methods [for (**96a**)][58] and later by X-ray crystallography.[63] In all cases, the adduct was a single stereoisomer resulting from bond formation at the faces opposite to the isopropylidenedioxy groups. It has proven possible reductively to dehalogenate the dibromo-dimer [(**96b**)→(**96d**)] by treatment with tributyltin hydride, whereas the dichloro-dimer (**96c**) was reduced under these conditions only as far as the vinylic chloride (**97**).[63] Such brief synthetic access (in four steps) from aromatics to single enantiomers of highly functionalised carbotricyclic compounds awaits exploitation.



(**71**) R = CF_3
(**30**) R = Br
(**58**) R = Cl

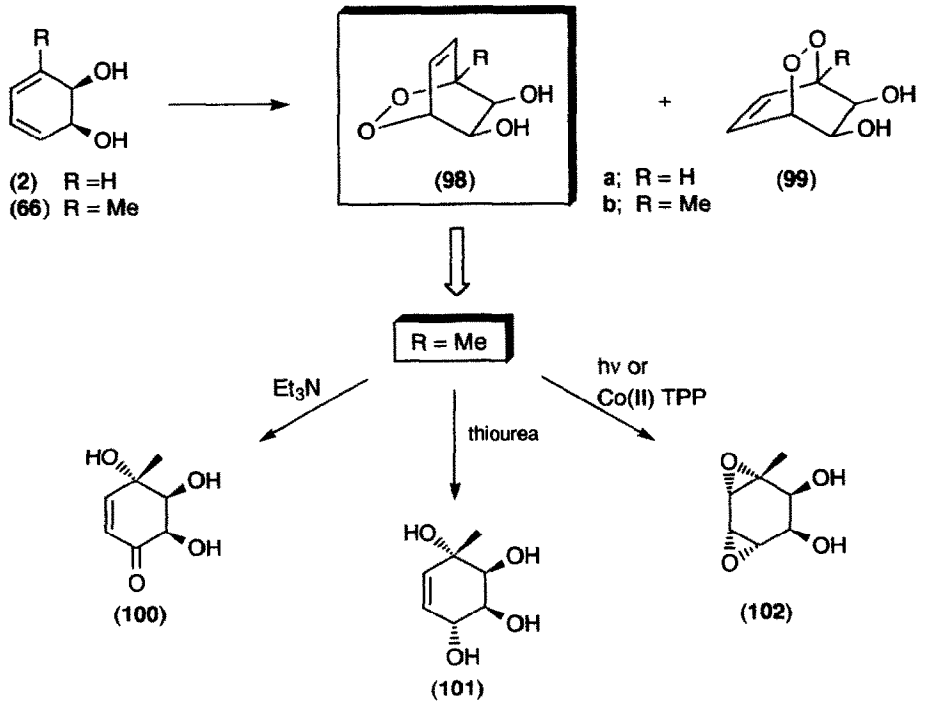
(**96**) **a**; X = Y = CF_3
b; X = Y = Br
c; X = Y = Cl
d; X = Y = H

(**97**) X = Cl, Y = H

Scheme 35

2.6.4 Singlet Oxygen Reaction

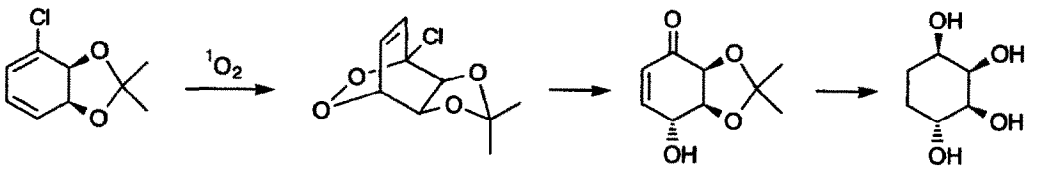
In contrast to Diels-Alder cycloaddition (Section 2.6.1), the attack of photochemically-generated singlet oxygen ($^1O_2$) on the parent *cis*-cyclohexadienediol system (**2**) occurred preferentially from the *anti* face, to give the *anti* (**98a**) and *syn* (**99a**) endoperoxides in the ratio 2.8:1;[64] similarly, the toluene derived diol (**66**) gave the homochiral endoperoxides (**98b**) and (**99b**) in a 1.6:1 ratio.[65] Subsequent reduction of (**98**) and (**99**) by thiourea in methanol led efficiently to cyclohex-5-ene-1,2,3,4-tetrols (having the conduritol A and D stereochemistry, respectively) in extremely brief three-stage routes from arene to tetrol. As indicated in Scheme 36, each endoperoxide is capable of enantiospecific conversion to diverse synthetic intermediates, such as cyclohexenones (**100**), *C*-methyl analogues of conduritols (**101**)[65] and *cis*-diepoxides (**102**)[22] suitable for conversion to inositols and inosamines (*cf.* Scheme 8).[26] In common with the Diels-Alder reaction, the stereochemistry of $^1O_2$ addition to the *cis*-cyclohexadienediols was significantly altered by isopropylidene protection of the diol, and cyclic acetal (**38**) gave entirely *anti* endoperoxide.[39]



Scheme 36

A further application of the chlorobenzene-derived acetal (**58**) has appeared, relying on a stereospecific reaction with $^1O_2$ to give the *anti* isomer of the α-chloroendoperoxide (**103**) (Scheme 37).[66] In this example,

thiourea reduction led to loss of HCl from the resultant chlorohydrin, thereby producing the protected enone (**104**). Subsequent hydrogenation and L-selectride reduction steps gave (-)-dihydroconduritol C (**105**). Alternatively, the double bond of the product could be retained *via* protection of the hydroxyl group of the enone (**104**) as a *t*-butyldimethylsilyl ether, followed by L-selectride reduction and hydrolysis, which gave a further route to (-)-conduritol C, (-)-(**19**).[42] A method of treatment of the endoperoxide (**103**) with aluminium amalgam led to its complete reduction to the 2,3-*O*-isopropylidene conduritol A, although in this example the symmetry of the product implies a loss of chirality.[23]

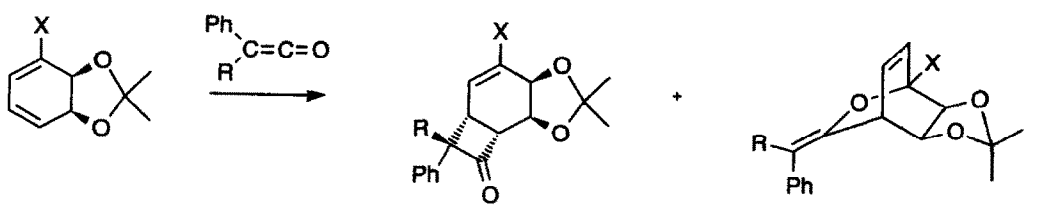


(**58**) (**103**) (**104**) (-)-(**105**)

Scheme 37

2.7 [2+2] Cycloadditions

In comparison with the large number of photochemical and thermal [2+2] cycloadditions known for simple cyclohexadienes, there have been only two reports to date of [2+2] cycloaddition to *cis*-cyclohexadienediols.[54,55] The acetal (**16**) of the parent dienediol, when heated under reflux with diphenylketene, gave a 5:4 mixture of the cyclobutanone (**106a**) and the unexpected enol ether (**107a**), the latter being the product of [4+2] addition of the diene to the ketene carbonyl group (Scheme 38). For both products, the stereochemistry of attack is from the *anti* face of the protected dienediol. In contrast, reaction of (**16**) with methylphenylketene gave the [2+2] cycloaddition product (**106b**) (42%) as the only isolated product.[54] Surprisingly, reaction of the fluorodiene acetal (**74**) with diphenylketene gave the cyclobutanone (**106c**) as only a minor product (9%), with the enol ether (**107c**) (77%) formed as the major adduct.[55]



(**16**) X = H
(**74**) X = F

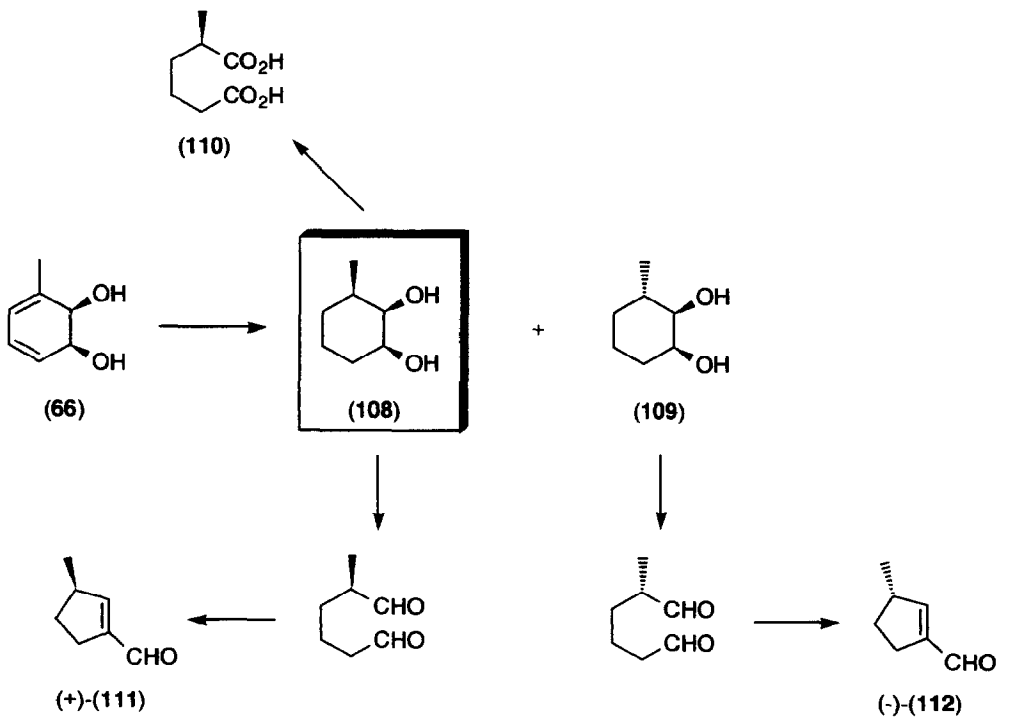
(**106**) **a**; X = H, R = Ph
b; X = H, R = Me
c; X = F, R = Ph

(**107**)

Scheme 38

2.8 Reductions

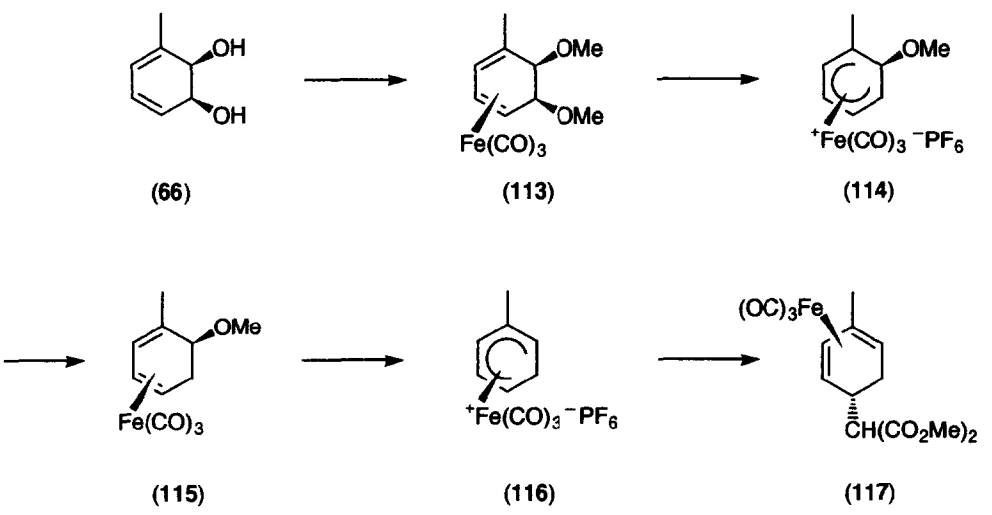
Hydrogenation of the *cis*-dihydrodiol (**66**) derived from toluene was originally used in the proof of its absolute stereochemistry, since the major cyclohexanediol formed was shown by NMR spectroscopy to have the all *cis* configuration (**108**);[8] Jones oxidation led to the known 2*R*-methyladipic acid (**110**) (Scheme 39). The two diols (**108**) and (**109**), which are formed in a 7:3 ratio on hydrogenation, can be separated *via* formation of their monobenzoates, and can act as complementary sources of chirality.[39] Periodate cleavage of each diol leads to 1,6-dialdehydes, suitable for intramolecular aldol reaction. The two cyclopentenyl carboxaldehyde synthons with *R* (**111**) and *S* (**112**) configuration are thus available, and have some relevance to sesquiterpene targets. It is worth noting that periodate cleavage of the original cyclohexadienediols, whilst a useful route to *cis,cis* isomers of muconaldehydes,[67] is of limited application in this area because it destroys the chirality of molecules such as (**66**).



Scheme 39

2.9 Organotransition Metal Derivatives

The ability of cyclohexadienes to form stable η^4-organometallic derivatives has been extensively used in synthesis, often giving rise to excellent regio- and stereocontrol in the subsequent reactions of the complexes. The arene *cis*-dihydrodiols make obvious candidates for such chemistry, because they can lead directly to homochiral organometallic complexes. Thus, reaction of the dimethyl ether of (**66**) with $Fe_2(CO)_9$ gave a single stereoisomer of the tricarbonyliron complex (**113**),[68] with organometallic bonding occurring to the surface of the diene which bears the two alkoxy groups[69] (Scheme 40). It was possible to obtain the cationic η^5-dienyl complex (**114**) chemoselectively by removal of the less hindered methoxy group on treatment with bulky trityl tetrafluoroborate. Reduction by sodium borohydride then led to the neutral diene complex (**115**). Repetition of the cation-forming process, this time using trifluoroacetic acid, yielded the completely demethoxylated (but chiral) complex (**116**). Alkylation of (**116**) could be carried out with complete stereocontrol, exclusively from the direction *anti* to the iron atom, giving homochiral (**117**).



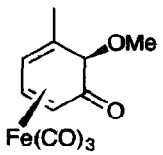
(**66**) (**113**) (**114**)

(**115**) (**116**) (**117**)

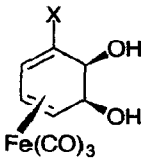
Scheme 40

The overall process of Scheme 40 corresponds to the use of a synthetic equivalent of a chiral cyclohexa-3,5-diene 1,2-dication.[70] In the use of trityl tetrafluoroborate for the conversion (**113**)→(**114**), hydride abstraction from the cyclohexadiene ring was generally a minor reaction, although under different conditions, it proved possible to isolate the iron dienone complex (**118**) in 32% yield after hydrolysis.[71] A range of other tricarbonyliron derivatives (**119**) of *cis*-cyclohexadienediols, together with their acetates and methyl ethers, have been prepared and their chiroptical properties examined.[72] Microbial oxidation of acetophenone by a *Pseudomonas putida* strain (ICI 11767) gives rise to an anomalous and unstable monohydroxylated product, characterised as the η^4-diene complex (**120**) by reaction with $Fe_2(CO)_9$.[73]

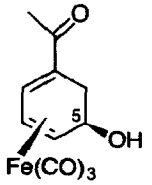
Interestingly, compound (**120**), formed as a single diastereoisomer and enantiomer, is closely related to the η^4-diene complex (**115**), but with hydroxyl substitution at C-5 instead of C-6.



(**118**)



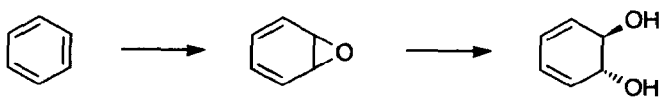
(**119**) X = Me, Cl or OMe



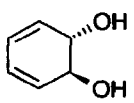
(**120**)

3 Arene *trans*-Dihydrodiols

Mammalian metabolism of benzene proceeds through enzyme-catalysed oxidation to the arene oxide, followed by various steps, one of which is enzyme-catalysed hydration to yield the chiral benzene *trans*-1,2-dihydrodiol (**121**) (Scheme 41).[74] Both *in vivo* metabolism and *in vitro* studies with liver microsomes have shown that the *trans*-cyclohexadienediol (-)-(**121**) can be formed with at least 50% optical purity under these conditions.



(-)-(**121**)



(+)-(**121**)

Scheme 41

3.1 Optical Resolution

The recent publication[75] of an enzymatic method for resolution of the benzene *trans*-dihydrodiol (**121**) has considerably enhanced the opportunities for the preparation of enantiospecific targets in this area. Racemic *trans*-diol diacetate (**122**) is easily available in five steps from cyclohexa-1,4-diene.[76] Its hydrolysis, catalysed by porcine liver esterase (pH 7.8, 0°C) gave the enantiomerically enriched monoacetate (**123**), and after recycling of material, the (*R,R*) diol isomer, (-)-(**121**) (97% *e.e.*). The remaining diacetate, enriched in the (*S,S*) isomer, was eventually hydrolysed by base to give the enantiomer, (+)-(**121**) (96% *e.e.*) (Scheme 42).

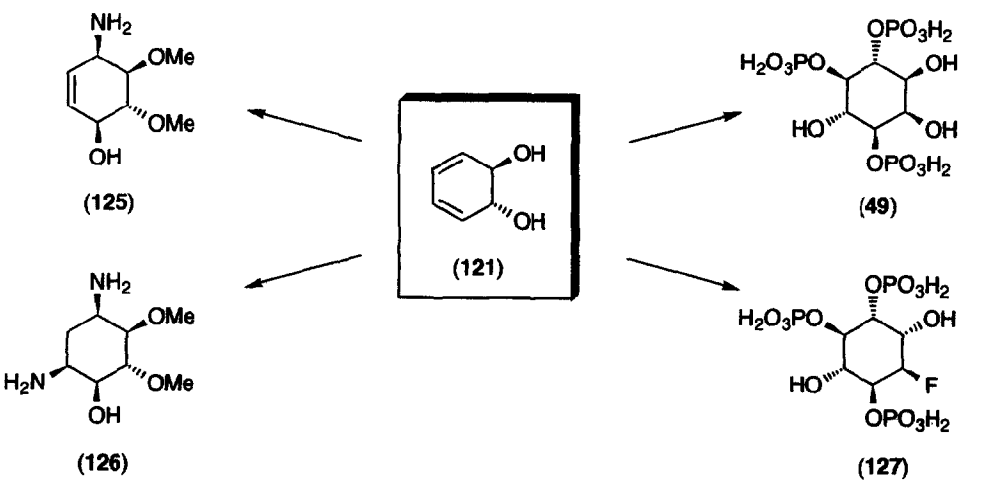
Scheme 42

3.2 Synthetic Targets

m-Chloroperoxybenzoic acid epoxidation of the homochiral *trans*-diols (**121**) occurred *syn* to an adjacent hydroxyl group, yielding the individual enantiomers of the benzene diol epoxide (**124**), which were shown to be equally mutagenic in bacterial testing (Scheme 43).[75]

Scheme 43

The availability of the *trans*-dihydrodiol (**121**) as resolved enantiomers makes accessible a good range of chiral target molecules, using established reactions. Scheme 44 shows the application of the dihydrodiol to the synthesis of conduramines (**125**),[77] aminocyclitol antibiotics of the 2-deoxystreptamine type (**126**),[78] *chiro*-inositol 2,3,5-trisphosphate[79] and *myo*-inositol 1,4,5-trisphosphate (**49**) cell messengers,[80] and a fluorinated inositol phosphate analogue (**127**).[81] All these existing routes can now be exploited to give the desired homochiral isomers of biologically-active molecules.



Scheme 44

4 References

1. Brief review: D. A. Widdowson, D. W. Ribbons and S. D. Thomas, *Janssen Chim. Acta*, 1990, **8**, 3.
2. Available from: ICI Fine Chemicals, Hexagon House, Blackley, Manchester M9 3DA, UK; Genencor International Inc., Rochester, NY, USA; Janssen Chimica, B-2440 Geel, Belgium.
3. D. T. Gibson, J. R. Koch and R. E. Kallio, *Biochemistry*, 1968, **7**, 2653.
4. D. T. Gibson, M. Hensley, H. Yoshioka and T. J. Mabry, *Biochemistry*, 1970, **9**, 1626.
5. D. T. Gibson, G. E. Cardini, F. C. Maseles and R. E. Kallio, *Biochemistry*, 1970, **9**, 1631.
6. D. T. Gibson, J. R. Koch, C. L. Schuld and R. E. Kallio, *Biochemistry*, 1968, **7**, 3795.
7. D. T. Gibson, B. Gschwendt, W. K. Yeh and V. M. Kobal, *Biochemistry*, 1973, **12**, 1520.
8. H. Ziffer, D. M. Jerina, D. T. Gibson and V. M. Kobal, *J. Am. Chem. Soc.*, 1973, **95**, 4048; H. Ziffer, K. Kabuto, D. T. Gibson, V. M. Kobal and D. M. Jerina, *Tetrahedron*, 1977, **33**, 2491.
9. J. J. DeFrank and D. W. Ribbons, *J. Bacteriol.*, 1977, **129**, 1356; G. J. Wigmore and D. W. Ribbons, *J. Bacteriol.*, 1980, **143**, 816.
10. J. J. DeFrank and D. W. Ribbons, *Biochem. Biophys. Res. Commun.*, 1976, **70**, 1129.
11. S. J. C. Taylor, D. W. Ribbons, A. M. Z. Slawin, D. A. Widdowson and D. J. Williams, *Tetrahedron Lett.*, 1987, **28**, 6391.
12. J.T. Rossiter, S. R. Williams, A. E. G. Cass and D. W. Ribbons, *Tetrahedron Lett.*, 1987, **28**, 5173.
13. R. O. Jenkins, G. M. Stephens and H. Dalton, *Biotechnol. Bioeng.*, 1987, **29**, 873.
14. S. C. Taylor, in *"Enzymes in Organic Synthesis"*, Ciba Foundation Symposium lll, Pitman, London, 1985, p. 71.
15. D. R. Boyd, R. A. S. McMordie, H. P. Porter, H. Dalton, R. O. Jenkins and O. W. Howarth, *J. Chem. Soc., Chem. Commun.*, 1987, 1722.
16. M. E. Deluca and T. Hudlicky, *Tetrahedron Lett.*, 1990, **31**, 13.
17. P. J. Geary, R. J. Pryce, S. M. Roberts, G. Ryback and J. A. Winders, *J. Chem. Soc., Chem. Commun.*, 1990, 204.
18. D. R. Boyd, R. A. S. McMordie, N. D. Sharma, H. Dalton, P. Williams and R. O. Jenkins, *J. Chem. Soc., Chem. Commun.*, 1989, 339.
19. D. R. Boyd, M. R. J. Dorrity, J. F. Malone, R. A. S. McMordie, N. D. Sharma, H. Dalton and P. Williams, *J. Chem. Soc., Perkin Trans. I*, 1990, 489.
20. V. M. Kobal, D. T. Gibson, R. E. Davis and A. Garza, *J. Am. Chem. Soc.*, 1973, **95**, 4420.
21. D. R. Boyd, M. R. J. Dorrity, M. V. Hand, J. F. Malone, N. D. Sharma, H. Dalton, D. J. Gray and G. N. Sheldrake, *J. Am. Chem. Soc.*, 1991, **113**, 666.
22. H. A. J. Carless and O. Z. Oak, unpublished results.
23. T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent and J. D. Price, *J. Chem. Soc., Perkin Trans. I*, 1991, 2907.
24. D. R. Boyd, N. D. Sharma, R. Boyle, R. A. S. McMordie, J. Chima and H. Dalton, *Tetrahedron Lett.*, 1992, **33**, 1241.
25. O. Werbitzky, K. Klier and H. Felber, *Liebigs Ann. Chem.*, 1990, 267.
26. H. Braun, W. Burger, G. Kresze, F. P. Schmidtchen, J. L. Vaerman and H. G. Viehe, *Tetrahedron: Asymmetry*, 1990, **1**, 403.
27. K. Schürrle, B. Beier and W. Piepersberg, *J. Chem. Soc., Perkin Trans. I*, 1991, 2407.

28. C. R. Johnson, P. A. Plé and J. P. Adams, *J. Chem. Soc., Chem. Commun.*, 1991, 1006.
29. D. H. G. Crout, D. A. MacManus and P. Critchley, *J. Chem. Soc., Chem. Commun.*, 1991, 376.
30. I. C. Cotterill, S. M. Roberts and J. O. Williams, *J. Chem. Soc., Chem. Commun.*, 1988, 1628.
31. S. V. Ley and F. Sternfeld, *Tetrahedron*, 1989, **45**, 3463.
32. S. V. Ley and A. J. Redgrave, *Synlett*, 1990, 393.
33. S. V. Ley, A. J. Redgrave, S. C. Taylor, S. Ahmed and D. W. Ribbons, *Synlett*, 1991, 741.
34. T. Hudlicky and E. E. Boros, *Tetrahedron: Asymmetry*, 1992, **3**, 217.
35. D. R. Boyd, M. V. Hand, N. D. Sharma, J. Chima, H. Dalton and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1991, 1630.
36. S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron Lett.*, 1987, **28**, 225.
37. S. V. Ley and F. Sternfeld, *Tetrahedron Lett.*, 1988, **29**, 5305.
38. H. A. J. Carless, *J. Chem. Soc., Chem. Commun.*, 1992, 234.
39. T. Hudlicky, H. Luna, G. Barbieri and L. D. Kwart, *J. Am. Chem. Soc.*, 1988, **110**, 4735.
40. H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1991, **32**, 1671.
41. T. Hudlicky, J. D. Price, F. Rulin and T. Tsunoda, *J. Am. Chem. Soc.*, 1990, **112**, 9439.
42. T. Hudlicky, F. Rulin, T. Tsunoda, H. Luna, C. Andersen and J. D. Price, *Isr. J. Chem.*, 1991, **31**, 229.
43. H. A. J. Carless and O. Z. Oak, *J. Chem. Soc., Chem. Commun.*, 1991, 61.
44. S. V. Ley, M. Parra, A. J. Redgrave and F. Sternfeld, *Tetrahedron*, 1990, **46**, 4995.
45. S. V. Ley, *Pure Appl. Chem.*, 1990, **62**, 2031.
46. S. V. Ley, M. Parra, A. J. Redgrave, F. Sternfeld and A. Vidal, *Tetrahedron Lett.*, 1989, **30**, 3557.
47. S. V. Ley and L. L. Yeung, *Synlett*, 1992, 291.
48. C. R. Johnson and T. D. Penning, *J. Am. Chem. Soc.*, 1988, **110**, 4726.
49. T. Hudlicky and J. D. Price, *Synlett*, 1990, 159.
50. T. Hudlicky, H. Luna, J. D. Price and F. Rulin, *Tetrahedron Lett.*, 1989, **30**, 4053.
51. T. Hudlicky, H. Luna, J. D. Price and F. Rulin, *J. Org. Chem.*, 1990, **55**, 4683.
52. H. A. J. Carless, K. Busia and S. S. Malik, unpublished results.
53. T. Hudlicky, J. D. Price and H. F. Olivo, *Synlett*, 1991, 645.
54. W. Downing, R. Latouche, C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback and J. O. Williams, *J. Chem. Soc., Perkin Trans. I*, 1990, 2613.
55. M. F. Mahon, K. Molloy, C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik, J. O. Williams and J. A. Winders, *J. Chem. Soc., Perkin Trans. I*, 1991, 1255.
56. M. G. Banwell and M. P. Collis, *J. Chem. Soc., Chem. Commun.*, 1991, 1343.
57. J. R. Gillard and D. J. Burnell, *J. Chem. Soc., Chem. Commun.*, 1989, 1439.
58. C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik and J. O. Williams, *J. Chem. Soc., Perkin Trans. I*, 1989, 1160.
59. T. Hudlicky and H. F. Olivo, *Tetrahedron Lett.*, 1991, **32**, 6077.
60. T. Hudlicky, G. Seoane and T. Pettus, *J. Org. Chem.*, 1989, **54**, 4239.
61. T. Hudlicky, C. H. Boros and E. E. Boros, *Synthesis*, 1992, 174.
62. T. Hudlicky, E. E. Boros and C. H. Boros, *Synlett*, 1992, 391.
63. T. Hudlicky, E. E. Boros, H. F. Olivo and J. S. Merola, *J. Org. Chem.*, 1992, **57**, 1026.
64. H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 1719.
65. H. A. J. Carless, J. R. Billinge and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 3113.
66. T. Hudlicky, J. D. Price, H. Luna and C. M. Andersen, *Synlett*, 1990, 309.

67. B. T. Golding, G. Kennedy and W. P. Watson, *Tetrahedron Lett.*, 1988, **29**, 5991.
68. P. W. Howard, G. R. Stephenson and S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1988, 1603.
69. P. W. Howard, G. R. Stephenson and S. C. Taylor, *J. Organomet. Chem.*, 1988, **339**, C5.
70 G. R. Stephenson, R. P. Alexander, C. Morley and P. W. Howard, *Phil. Trans. R. Soc. Lond. A*, 1988, **326**, 545.
71. P. W. Howard, G. R. Stephenson and S. C. Taylor, *J. Organomet. Chem.*, 1989, **370**, 97.
72. G. R. Stephenson, P. W. Howard and S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1991, 127.
73. P. W. Howard, G. R. Stephenson and S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1990, 1182.
74. R. A. Aleksejczyk, G. A. Berchtold and A. G. Braun, *J. Am. Chem. Soc.*, 1985, **107**, 2554.
75. M. V. Ganey, R. E. Padykula, G. A. Berchtold and A. G. Braun, *J. Org. Chem.*, 1989, **54**, 2787.
76. K. L. Platt and F. Oesch, *Synthesis*, 1977, 449.
77. B. Beier, K. Schürrle, O. Werbitzky and W. Piepersberg, *J. Chem. Soc., Perkin Trans. I*, 1990, 2255.
78. K. Schürrle, B. Beier, O. Werbitzky and W. Piepersberg, *Carbohydr. Res.*, 1991, **212**, 321.
79. H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, 1990, **31**, 1617.
80. H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, 1990, **31**, 3449.
81. H. A. J. Carless and K. Busia, *Carbohydr. Res.*, 1992, in press.