Chem. Soc. Rev., 1990, **19**, 1–19

Non-Enzymatic Asymmetric Transformations Involving Symmetrical Bifunctional Compounds

By R. S. Ward
CHEMISTRY DEPARTMENT, UNIVERSITY COLLEGE OF SWANSEA, SINGLETON PARK, SWANSEA SA2 8PP

1 Introduction — Dienes and Alkenes

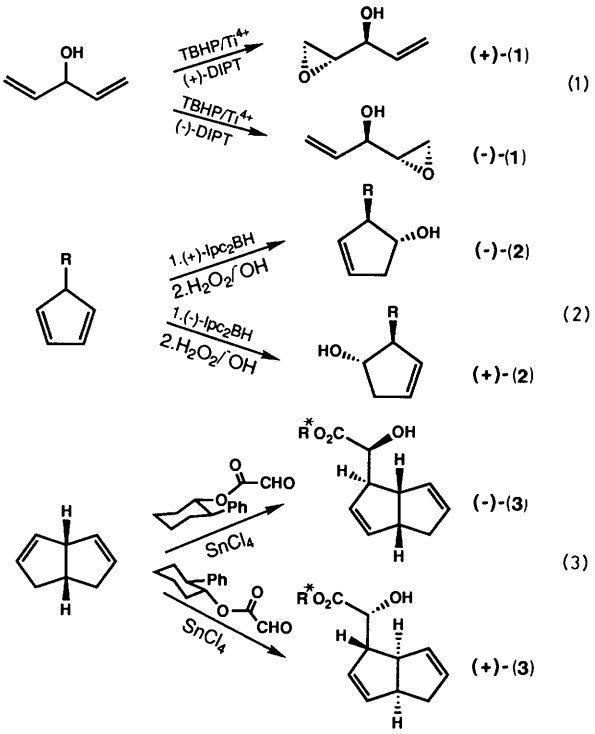
When a plane of symmetry is present in a bifunctional molecule the two halves are in most cases enantiotopic and can therefore be differentiated by reagents capable of chiral recognition.[1] An enantioselective reaction will convert such a molecule into either of two enantiomeric products (*e.g.* equations 1 and 2 — a list of the abbreviations used for reagents is given on page 19).[2–5] Furthermore, it has been shown that the enantiomeric purity of the product of such a reaction increases as the reaction proceeds due to kinetic resolution of the products formed.[6] Similarly, a diastereoselective reaction will convert such a compound into either of two diastereomeric products (*e.g.* equation 3).[1] This reaction is of particular interest since it involves both enantiotopic group selectivity (by the diene) and diastereotopic face selectivity (by both the diene and the aldehyde) leading to one of eight possible stereoisomeric products.

These reactions are examples of a growing number of transformations in which achiral bifunctional compounds having a plane of symmetry (including *meso* compounds) are converted into chiral non-racemic (enantiomerically enriched) products. While the ability of enzymes to differentiate between enantiotopically related functional groups is well known [7] the utility of non-enzymatic methods to achieve the same result is less well recognized. This strategy has, however, been used as a key step in the synthesis of a number of important target molecules (see below).

In all of the above reactions one, or in some cases two, new chiral centres are generated, demonstrating that the enantioselective or diastereoselective differentiation of prochiral functional groups in a symmetrical bifunctional molecule provides an efficient method for creating new chiral centres. Note that in equation 3 no fewer than four new chiral centres are produced.

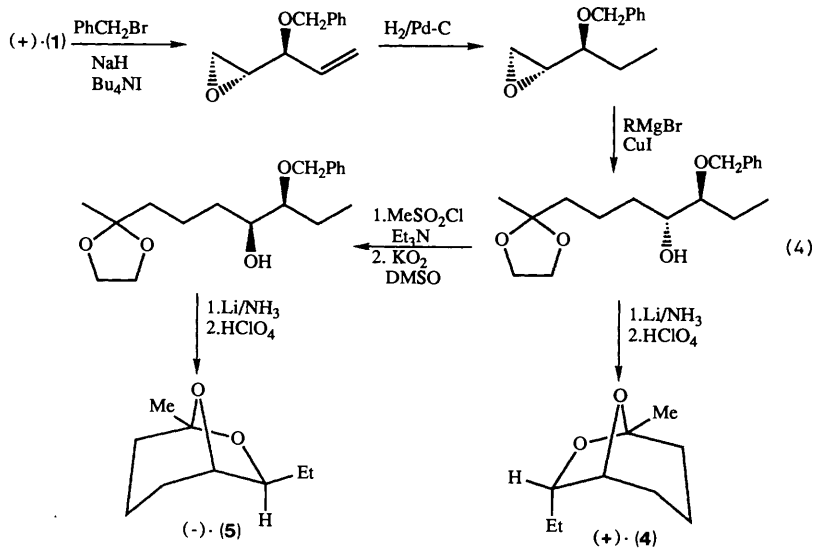
Equations 4–8 illustrate the uses made of compounds (1)—(3) in asymmetric

[1] J. K. Whitesell and D. E. Allen, *J. Org. Chem.*, 1985, **50**, 3025; *J. Am. Chem. Soc.*, 1988, **110**, 3585.
[2] S. Hatakeyama, K. Sakurai, and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1985, 1759.
[3] R. E. Babine, *Tetrahedron Lett.*, 1986, **27**, 5791.
[4] B. Hafele, D. Schroter, and V. Jager, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 87.
[5] J. J. Partridge, N. K. Chadha, and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1973, **95**, 532 and 7171.
[6] S. L. Schreiber, T. S. Schreiber, and D. B. Smith, *J. Am. Chem. Soc.*, 1987, **109**, 1525; S. L. Schreiber and M. T. Goulet, *ibid.*, 1987, **109**, 4718.
[7] For a review see J. B. Jones, in 'Enzymes in Organic Synthesis', CIBA Foundation Symposium, 1985, **111**, pp. 3—21 and M. Ohno, *ibid.*, pp. 171—178; *cf.* H. J. Gais, G. Bulow, A. Zatorski, M. Jentsch, P. Maidonis, and H. Hemmerle, *J. Org. Chem.*, 1989, **54**, 5115.



synthesis. Thus, the epoxy alcohol (+)-(1) has been used to synthesize (+)-*endo*- and (−)-*exo*-brevicomin (equation 4).[2] GLC analysis revealed that (+)-(4) and (−)-(5) were contaminated with only 3% of the corresponding *exo* and *endo* isomers respectively. From these results, and by comparison of the optical rotations with literature values for the pure compounds, it was deduced that the asymmetric epoxidation of the divinyl carbinol to produce (+)-(1) had proceeded with 90:10 enantioselectivity and with 97:3 diastereoselectivity. The epoxy-alcohol (+)-(1) has also been used to synthesize 4-*O*-benzyl-D-digitoxose (6) and 4-*O*-benzyl-D-olivose (7) (equation 5).[3] The unsaturated alcohols (−)-(2) (R = CH_3) and (−)-(2) (R = CH_2CO_2Me) have been used to synthesize loganin (8) and prostaglandin $F_{2\alpha}$(9) respectively (equations 6 and 7),[5] while the hydroxy ester (+)-(3) has been converted into (−)-specionin (−)-(10) (equation 8).[1] Analysis of the ^1H NMR spectra of (−)-(2) (R = CH_3) and of diastereomeric esters prepared from it indicated that the asymmetric hydroboration product had a minimum optical purity of 95% and was uncontaminated by the *cis* alcohol. Furthermore, comparison of the optical rotation of (−)-(2) (R = CH_2CO_2Me) with that of the optically pure hydroxy-ester obtained by resolution indicated that this asymmetric hydroboration product was also at least 96% optically pure.

The following sections describe a number of other reactions in which this same

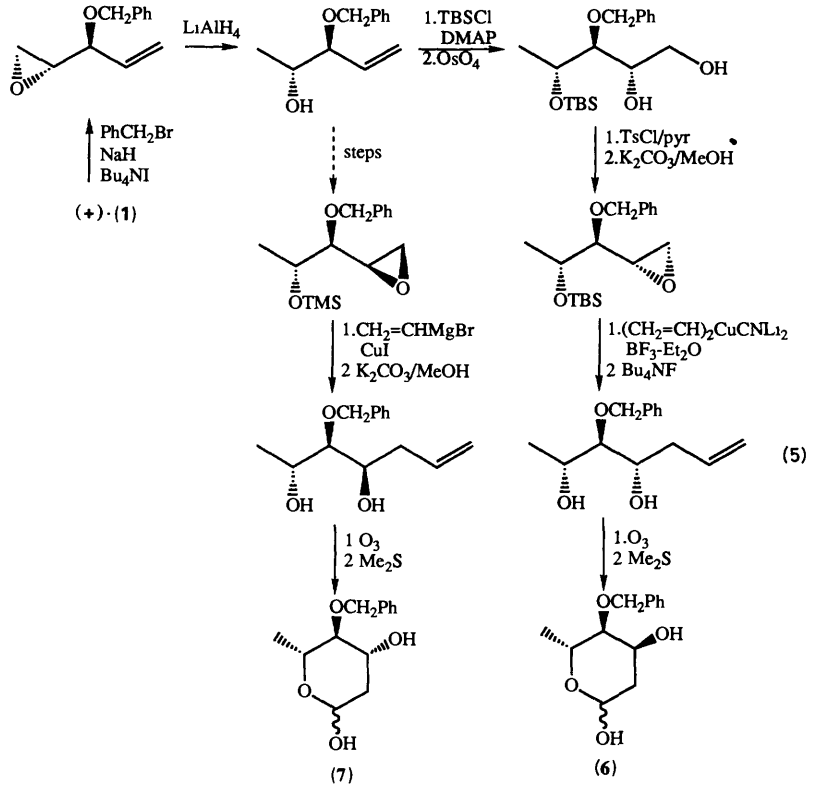


strategy has been employed. Equations 9 and 10 show two further examples of reactions involving alkenes. Equation 9 shows the Sharpless epoxidation of a *meso* compound which involves enantioselective discrimination between the two double bonds,[6] while equation 10 shows an example involving asymmetric hydroboration of a *meso* compound.[8] The former reaction (equation 9) illustrates how this strategy can be used to differentiate between the two ends of a symmetrical molecule in such a way as to allow selective homologation in a two directional chain synthesis. Equation 10 differs from the other examples given thus far in that a second addition reaction cannot occur, so that enhancement of the enantiomeric purity by selective destruction of the minor enantiomer is not possible in this case. The optical purity of the product obtained from the latter reaction was measured by ^{1}H NMR using a homochiral shift reagent and shown to be 92%. The later steps in the synthesis of (+)-hirsutic acid (+)-(11) were identical with those employed in an earlier synthesis of the racemic material.

2 Acids and Anhydrides

The diastereoselective reactions of symmetrically substituted anhydrides with a homochiral alcohol or amine provide a further illustration of the above methodology (see equations 11—13).[9–11] The enantioselective ring opening of an anhydride can also be achieved by reaction with an achiral alcohol in the presence of a catalytic amount of a homochiral amine, although in this case only

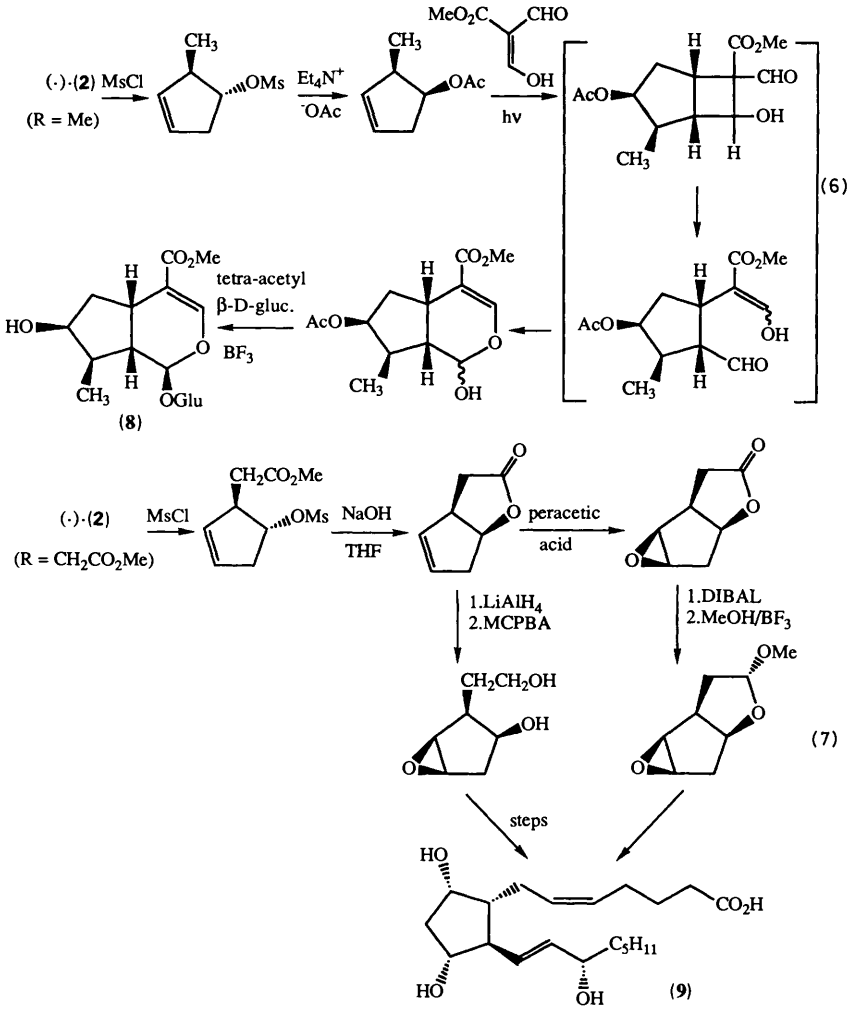
[8] A. E. Greene, M.-J. Luche, and A. A. Serra, *J. Org. Chem.*, 1985, **50**, 3957.
[9] M. Ohshima and T. Mukaiyama, *Chem. Lett.*, 1987, 377.
[10] T. Rosen and C. H. Heathcock, *J. Am. Chem. Soc.*, 1985, **107**, 3731.
[11] Y. Kawakami, J. Hiratake, Y. Yamamoto, and J. Oda, *J. Chem. Soc., Chem. Commun.*, 1984, 779.



a modest enantiomeric excess is obtained (equation 14).[12] The mono-ester or mono-amide produced in these reactions can be converted into either of two enantiomeric lactones by reduction using lithium borohydride or boranedimethyl sulphide (see equations 13 and 14).[11,12] Alternatively, the enantioselective reduction of an anhydride (equation 15),[13] or the diastereoselective reduction of an imide, prepared by reaction of the anhydride with a homochiral amine (equation 16),[14] can be used to generate the required lactone directly, the latter method giving by far the higher enantiomeric excess.

A highly enantioselective method of lactone formation involves the diastereoselective cleavage of the diamide formed by reacting a diacid with (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (equation 17).[15] However, the enantiomeric excess of the

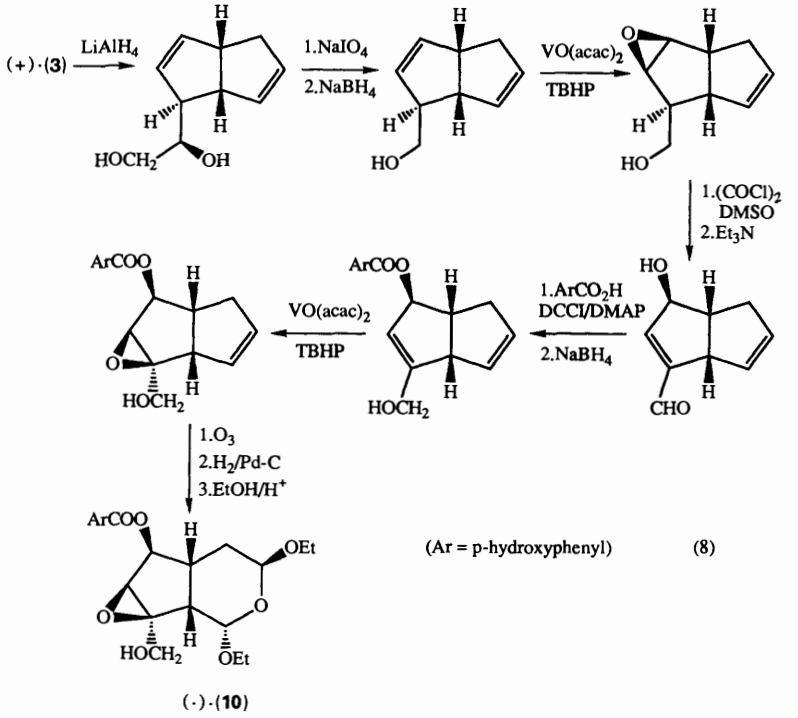
[12] J Hiratake, M Inagaki, Y Yamamoto, and J Oda, *J Chem Soc, Chem Commun*, 1985, 1717, *J Chem Soc, Perkin Trans 1*, 1987, 1053
[13] K Osakada, M Obana, T Ikariya, M Saburi, and S Yoshikawa, *Tetrahedron Lett*, 1981, **22**, 4297
[14] T Mukaiyama, H Yamashita, and M Asami, *Chem Lett*, 1983, 385
[15] A Sakamoto, Y Yamamoto, and J Oda, *J Am Chem Soc*, 1987, **109**, 7188



corresponding five-membered lactone prepared using this method was considerably lower than that in the six-membered series and, furthermore, the lactone obtained had the opposite absolute configuration.

The enantioselective lactonization of the sodium salt of 4-hydroxypimelic acid can be achieved by enantioselective protonation using a homochiral proton source (equation 18).[16] For example, treatment with (1*S*)-(+)-10-camphorsulphonic acid affords the *S*-lactone in quantitative yield and 94% e.e. Further

[16] K. Fuji, M. Node, S. Terada, M. Murata, H. Nagasawa, T. Taga, and K. Machida, *J. Am. Chem. Soc.*, 1985, **107**, 6404.

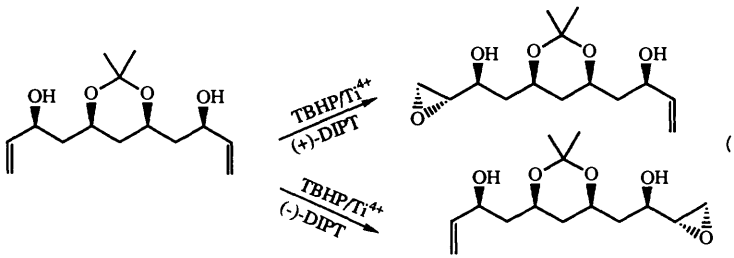


reduction using either lithium aluminium hydride or boranedimethyl sulphide again adds extra versatility to this approach.

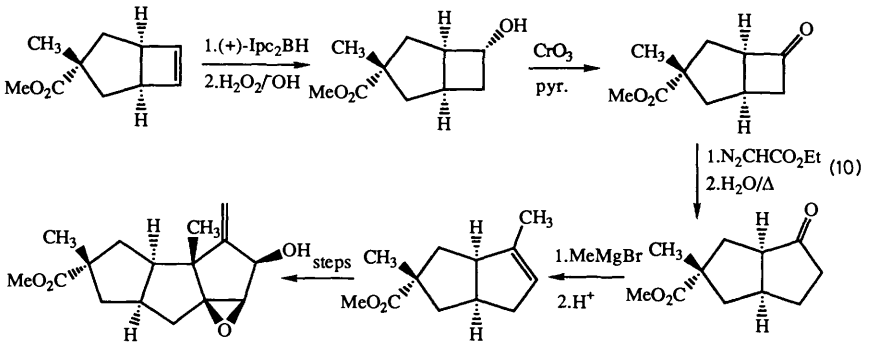
Enantiomerically enriched propane-1,3-diol derivatives can be prepared by reduction of the mono-menthyl esters of monoalkyl malonic acids (equation 19).[17] The method depends largely upon the diastereoselective formation of the mono-menthyl ester and subsequent separation of the diastereomeric alcohols. However, in the case of the menthyl half ester of ethylmalonic acid, crystallization afforded a single diastereoisomer (12; R = Et) in 82% yield through a crystallization-induced second-order asymmetric transformation. The optical purities of the products were determined by analysis of the ^{1}H NMR spectra of their Mosher esters prepared by reaction with (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid.

An alternative method which has been used to introduce asymmetry into an achiral diacid or anhydride is to react the bifunctional starting material with two equivalents of an appropriate homochiral reagent (*e.g.* a thiazoline thione or an alcohol) to give a diamide or diester which will then react diastereoselectively

[17] M. Ihara, M. Takahashi, N. Taniguch, K. Yasui, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1987, 619; *J. Chem. Soc., Perkin Trans. 1*, 1989, 897.

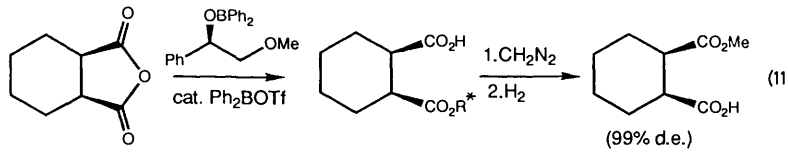


(9)



(10)

(+)-(**11**)



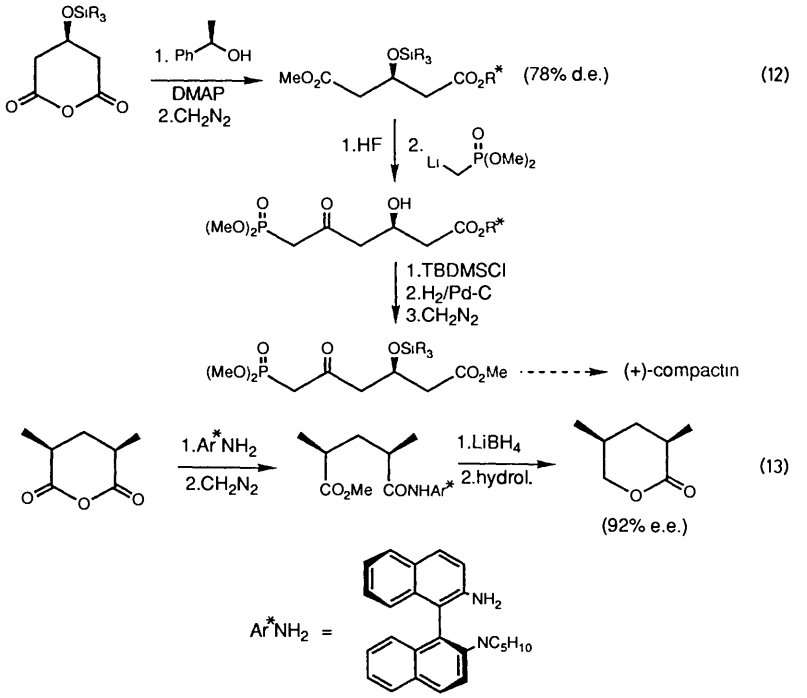
(11)

(99% d.e.)

with an achiral reagent, as shown in equations 20 and 21.[18,19] This strategy depends upon the principle that the introduction of *two* identical chiral groups into a symmetrical molecule having a prochiral centre can change the original symmetrical environment into an unsymmetrical one. Thus, in the second step of equation 20 piperidine attacks selectively only one of the two amide groups. The piperidine derivative produced then reacts with various nucleophiles to give the chiral non-racemic product. Yamamoto *et al.* (equation 21) have used a similar method for the construction of alicyclic compounds, by reacting dimenthyl succinate with a series of α,ω-dihalides. This represents a useful alternative to other methods (*e.g.* the asymmetric Diels–Alder reaction) for the asymmetric

[18] Y. Nagao, T. Inoue, E. Fujita, S. Terada, and M. Shiro, *J. Org. Chem.*, 1983, **48**, 132; *Tetrahedron*, 1984, **40**, 1215; Y. Nagao, T. Ikeda, T. Inoue, M. Yagi, M. Shiro, and E. Fujita, *J. Am. Chem. Soc.*, 1982, **104**, 2079; *J. Org. Chem.*, 1985, **50**, 4072; Y. Nagao, Y. Hagiwara, Y. Hasegawa, M. Ochiai, T. Inoue, M. Shiro, and E. Fujita, *Chem. Lett.*, 1988, 381.

[19] A. Misumi, K. Iwanaga, K. Furuta, and H. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 3343.



synthesis of carbocyclic systems. The observed stereocontrol can be explained in terms of the preferred *S-trans* conformation of the *E,E*-dienolate (13) of the diester.

3 Ketones

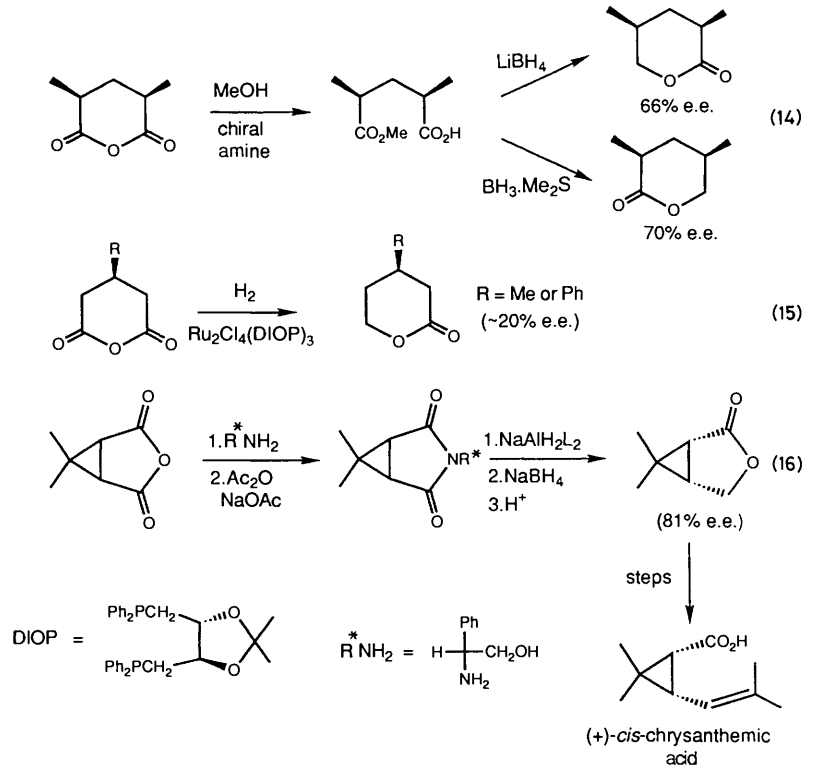
A number of examples of enantioselective deprotonation of prochiral ketones have been reported using homochiral lithium amide bases such as (14) and (15). The degree of asymmetric induction achieved is highly dependent upon the structure of the base used and also upon the substituent groups present in the ketone. The enolates can be trapped as their enol silyl ethers which are valuable precursors for further synthesis (*e.g.* equations 22 and 23).[20,21]

An alternative approach developed by Yamamoto *et al.*[22] involves reacting the ketone with a homochiral diol to give a ketal which undergoes diastereoselective

[20] R. Shirai, M. Tanaka, and K. Koga, *J. Am. Chem. Soc.*, 1986, **108**, 543; H. Izawa, R. Shirai, H. Kawasaki, H. Kim, and K. Koga, *Tetrahedron Lett.*, 1989, **30**, 7221; A. E. Greene, A. A. Serra, E. J. Barreiro, and P. R. R. Costa, *J. Org. Chem.*, 1987, **52**, 1169.

[21] N. S. Simpkins, *J. Chem. Soc., Chem. Commun.*, 1986, 88; C. M. Cain and N. S. Simpkins, *Tetrahedron Lett.*, 1987, **28**, 3723; R. P. C. Cousins and N. S. Simpkins, *Tetrahedron Lett.*, 1989, **30**, 7241.

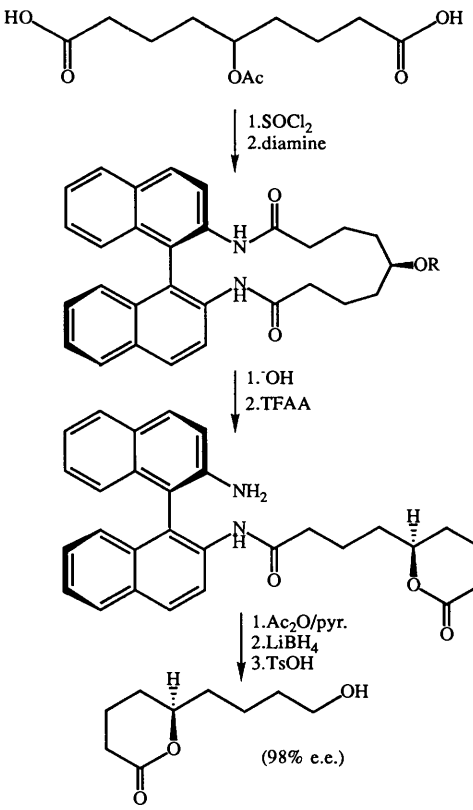
[22] Y. Naruse and H. Yamamoto, *Tetrahedron Lett.*, 1986, **27**, 1363; *Tetrahedron*, 1988, **44**, 6021.



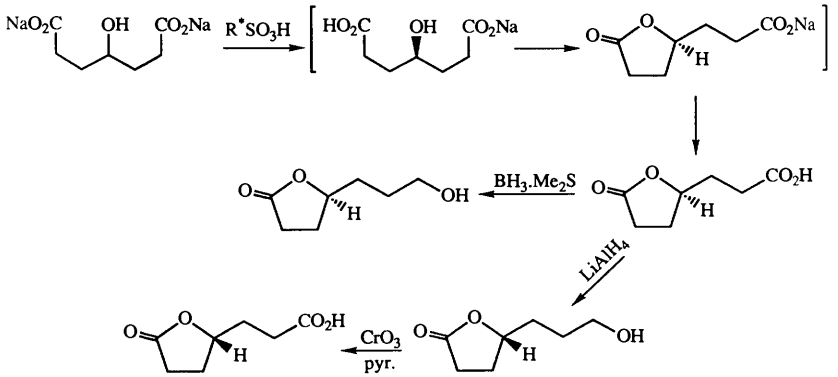
cleavage on treatment with tri-isobutylaluminium to give an enol ether (equation 24). In this case the diastereomeric ratio is little affected by the nature of the alkyl group present in the ketone. The preferred conformer of the aluminium bonded ketal is thought to be (16), which undergoes diastereoselective deprotonation as indicated leading to (17).

A particularly intriguing example is provided by the reaction shown in equation 25 in which a symmetrical achiral ketone reacts with a homochiral phosphonamide.[23] The reaction is enantioselective and the product, which has an axis of chirality, is obtained in high enantiomeric purity. A more recent example of this type of transformation is shown in equation 26,[24] although in this case a two-step procedure is required since the chiral group forms part of the phosphonic acid residue and a second step is therefore required in order to recover the chiral auxiliary.

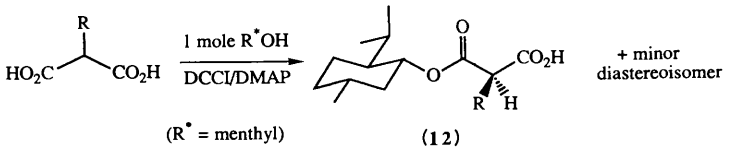
[23] S. Hanessian, D. Delorme, S. Beaudoin, and Y. Leblanc, *J. Am. Chem. Soc.*, 1984, **106**, 5754.
[24] H. J. Gais, G. Schmiedl, W. A. Ball, J. Bund, G. Hellmann, and I. Erdelmeier, *Tetrahedron Lett.*, 1988, **29**, 1773; *cf.* H. Rehwinkel, J. Skupsch, and H. Vorbrüggen, *Tetrahedron Lett.*, 1988, **29**, 1775.

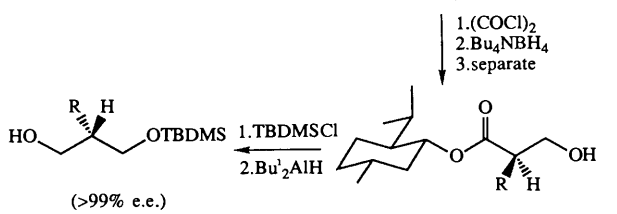

HO
OH
O
OAc
O
1.SOCl2
2.diamine
H
N
O
OR
N
H
O
1.⁻OH
2.TFAA
NH2
N
H
H
O
O
O
1.Ac2O/pyr.
2.LiBH4
3.TsOH
H
OH
O
O
(98% e.c.)

(17)

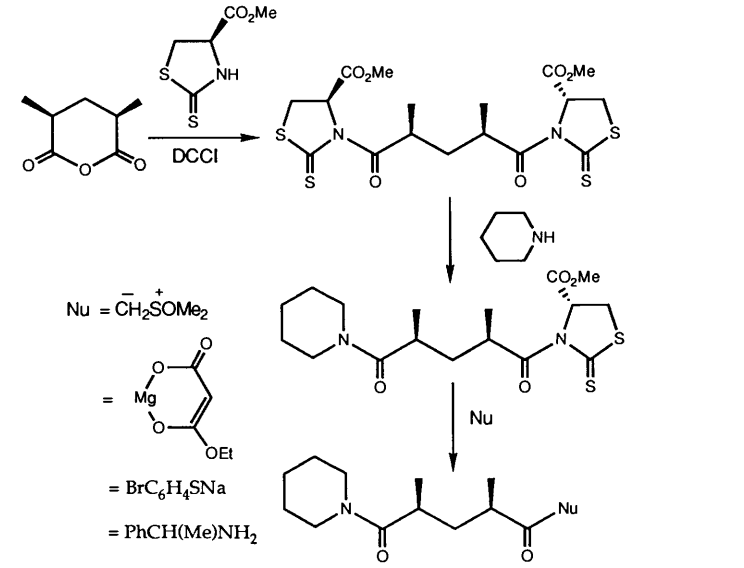

NaO2C
OH
CO2Na
R*SO3H
HO2C
OH
CO2Na
O
O
CO2Na
H
O
O
OH
H
BH3.Me2S
O
O
CO2H
H
LiAlH4
O
O
CO2H
H
CrO3
pyr.
O
O
OH
H

(18)

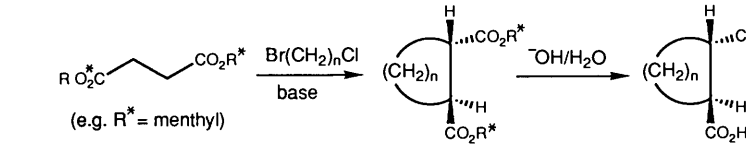

1 mole R*OH
DCCI/DMAP
+ minor diastereoisomer
(R* = menthyl)
(12)


1.(COCl)2
2.Bu4NBH4
3.separate
1.TBDMSCl
2.Bu'2AlH
OTBDMS
OH
(>99% e.e.)

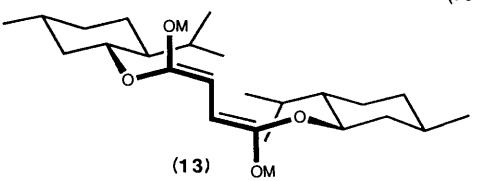
(19)


DCCI
Nu = CH2SOMe2
= BrC6H4SNa
= PhCH(Me)NH2
Nu

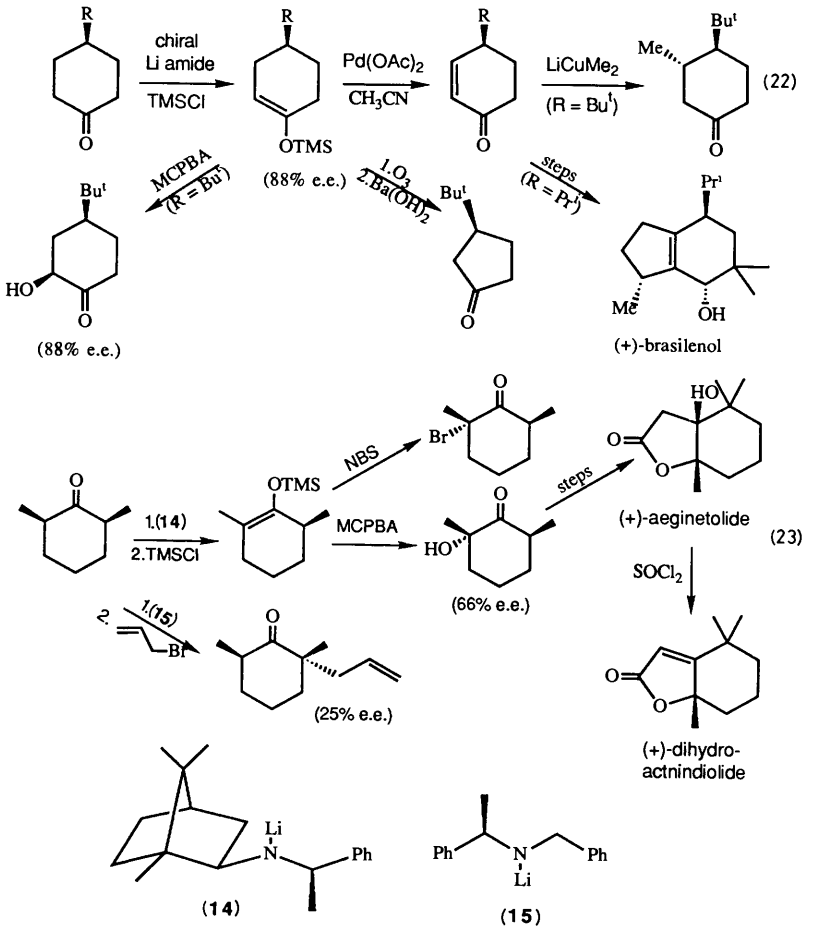
(20)


Br(CH2)nCl
base
-OH/H2O
(e.g. R* = menthyl)
(75-99% e.e.)

(21)


OM
OM

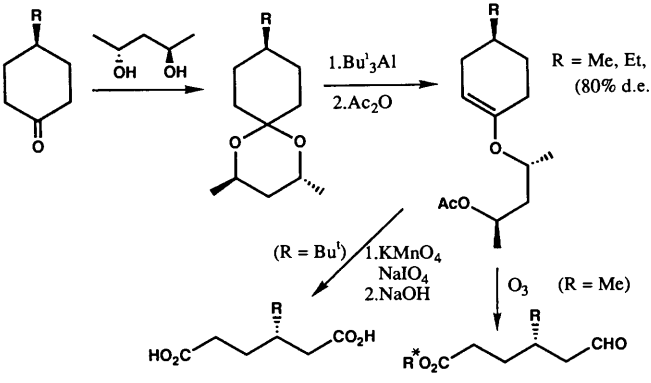
(13)



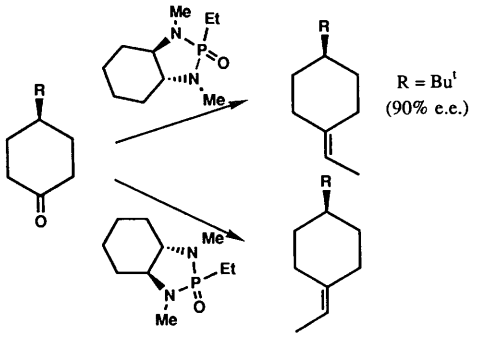
A number of intramolecular reactions of 1,3-diketones involving asymmetric induction have been reported and these have been extensively utilized in steroid synthesis (*e.g.* equation 27).[25,26]

1,2-Diketones can also be persuaded to undergo diastereoselective addition by first converting them into an α-keto-enamine by reaction with a homochiral

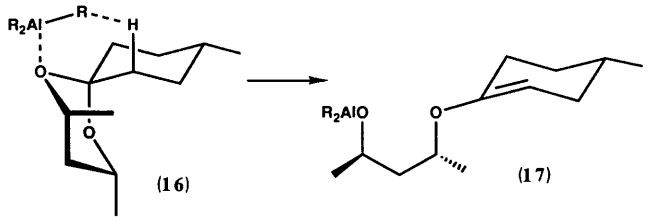
[25] U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 496; D. R. Parrish and Z. G. Hajos, *J. Org. Chem.*, 1974, **39**, 1615.
[26] N. Cohen, *Acc. Chem. Res.*, 1976, **9**, 412.



(24)

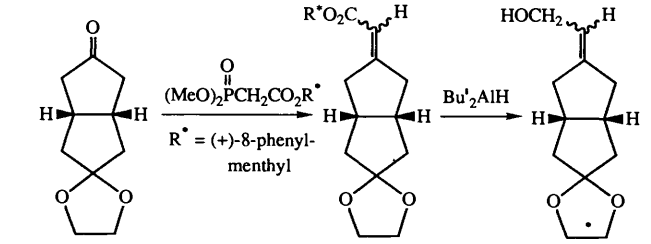


(25)



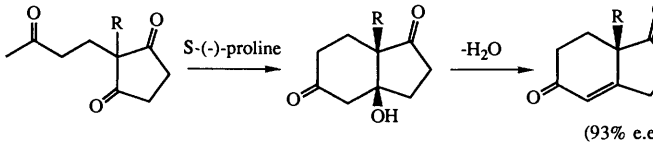
secondary amine (*e.g.* equation 28).[27] The use of proline-derived and other homochiral amines in enamine reactions is of course well known and has seen a number of elegant applications in asymmetric synthesis.[28] Surprisingly, in this

[27] T. Fujisawa, M. Watanabe, and T. Sato, *Chem. Lett.*, 1984, 2055.
[28] J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, 1977, **42**, 378; J. K. Whitesell and S. W. Felman, *ibid.*, 1663.



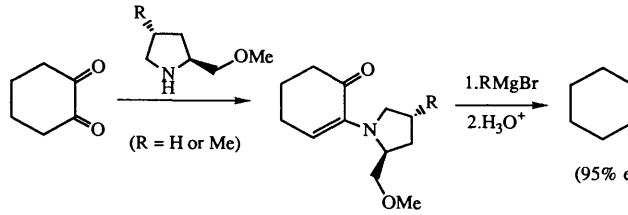
(26)

(90% e.c.)



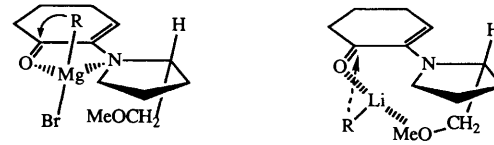
(27)

(93% e.c.)



(28)

(95% e.c.)



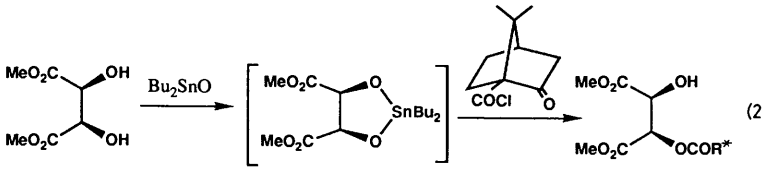
(18) (19)

particular case, organolithium reagents give products having the opposite configuration to those obtained using the Grignard reagents. The explanation proposed to account for this behaviour is shown in structures (18) and (19) in which the methoxymethyl group on the pyrrolidine ring adopts a purely steric role in the Grignard reaction but coordinates with the metal in the organolithium reaction, and thereby controls the preferred direction of addition of the alkyl group.

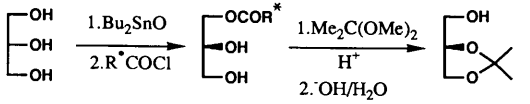
4 Diols

Acylation of a *meso* diol using a homochiral amine as catalyst affords a monoacyl derivative having only a modest enantiomeric excess.[29] The two hydroxyl groups of a *meso* diol can, however, be more effectively differentiated by

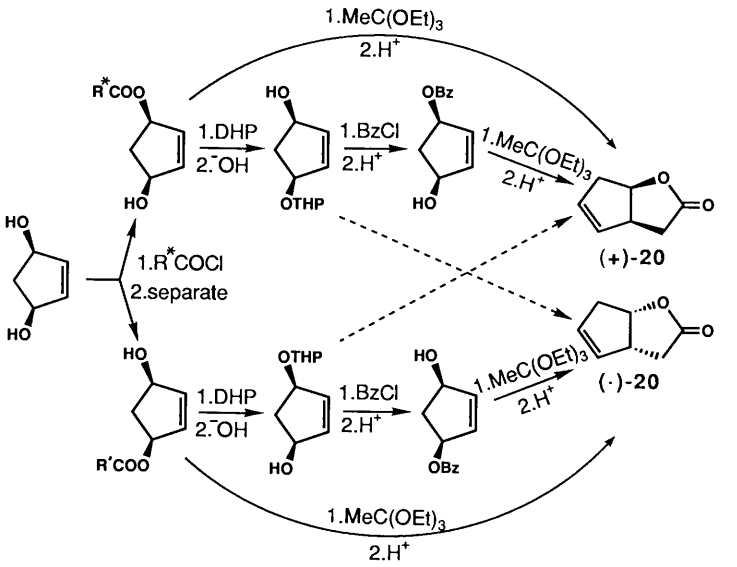
[29] L. Duhamel and T. Herman, *Tetrahedron Lett.*, 1985, **26**, 3099.



(29)



(30)

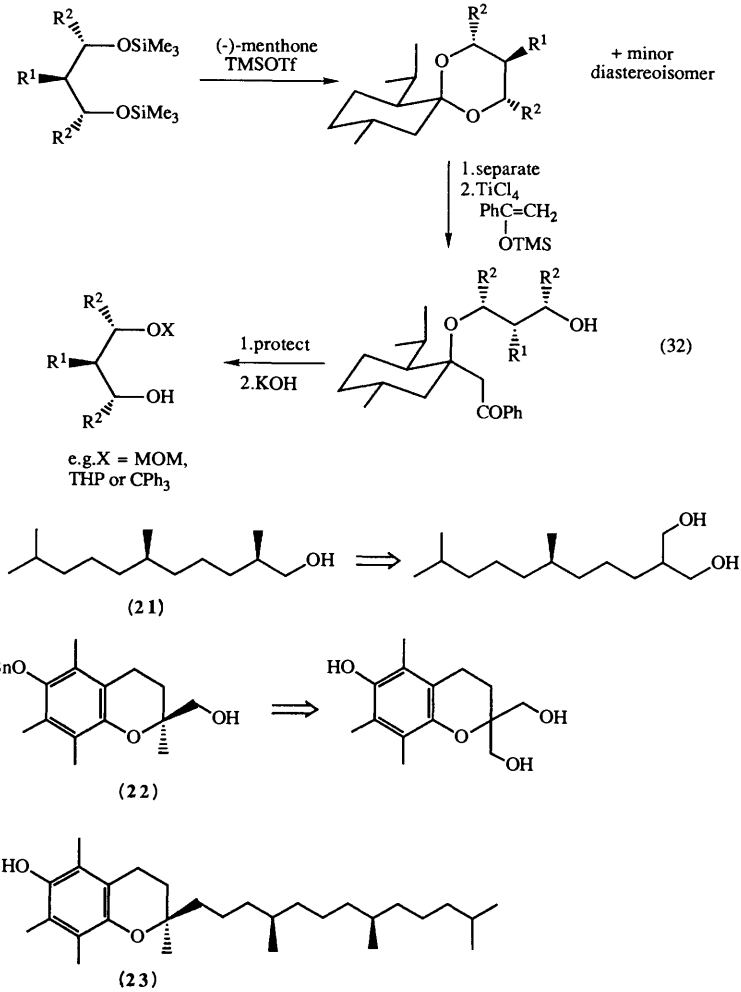


(31)

reaction with *one* equivalent of a homochiral acyl halide after prior treatment with dibutyltin oxide (*e.g.* equation 29).[30] The same procedure can also be used to prepare homochiral derivatives from glycerol by differentiating between the two primary hydroxyl groups (*e.g.* equation 30).[31] Differentiation can also be achieved by reacting a tin(II) derivative of the diol with benzoyl chloride in the presence of a homochiral diamine.[32]

Even under conditions where significant diastereoselectivity is not achieved the separated diastereomers, obtained by reacting the *meso* compound with one

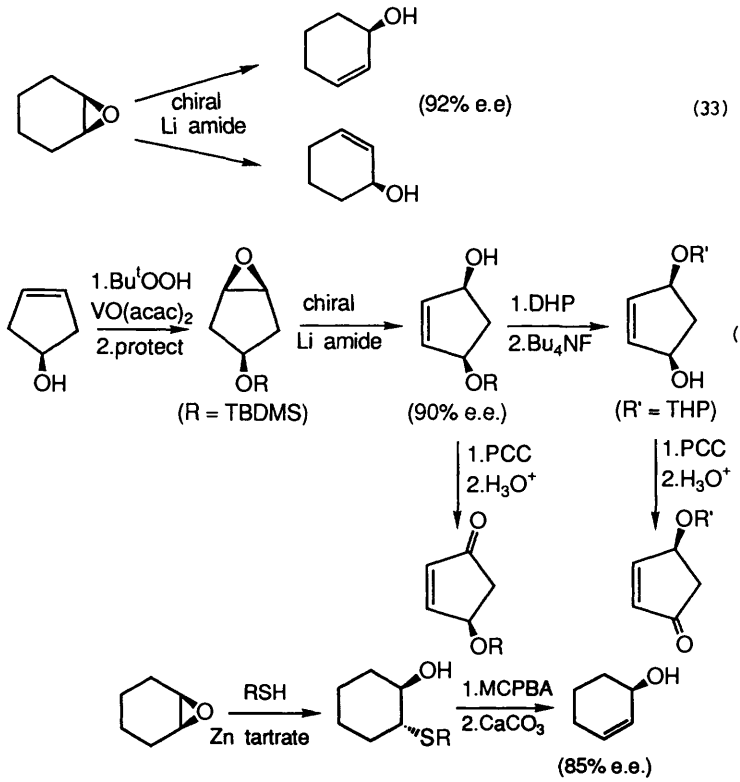
[30] T. Mukaiyama, I. Tomioka, and M. Shimizu, *Chem. Lett.*, 1984, 49.
[31] T. Mukaiyama, Y. Tanabe, and M. Shimizu, *Chem. Lett.*, 1984, 401.
[32] J. Ichikawa, M. Asami, and T. Mukaiyama, *Chem. Lett.*, 1984, 949.



equivalent of a homochiral acyl halide, can be manipulated to provide an enantioconvergent synthesis of a required product. In such a way it is theoretically possible to convert the total amount of the starting material into either enantiomer of the product by an appropriate choice of protection/deprotection steps. For example, the prostaglandin precursors (+)- or (−)-(20) can be prepared from *cis*-cyclopentene-1,4-diol as shown in equation 31.[33]

A general method for differential functionalization of symmetrical 1,2-, 1,3-, and 1,4-diols utilizing a highly selective ring-cleavage reaction of spiroacetals derived

[33] M. Nara, S. Terashima, and S. Yamada, *Tetrahedron*, 1980, **36**, 3161 and 3171.

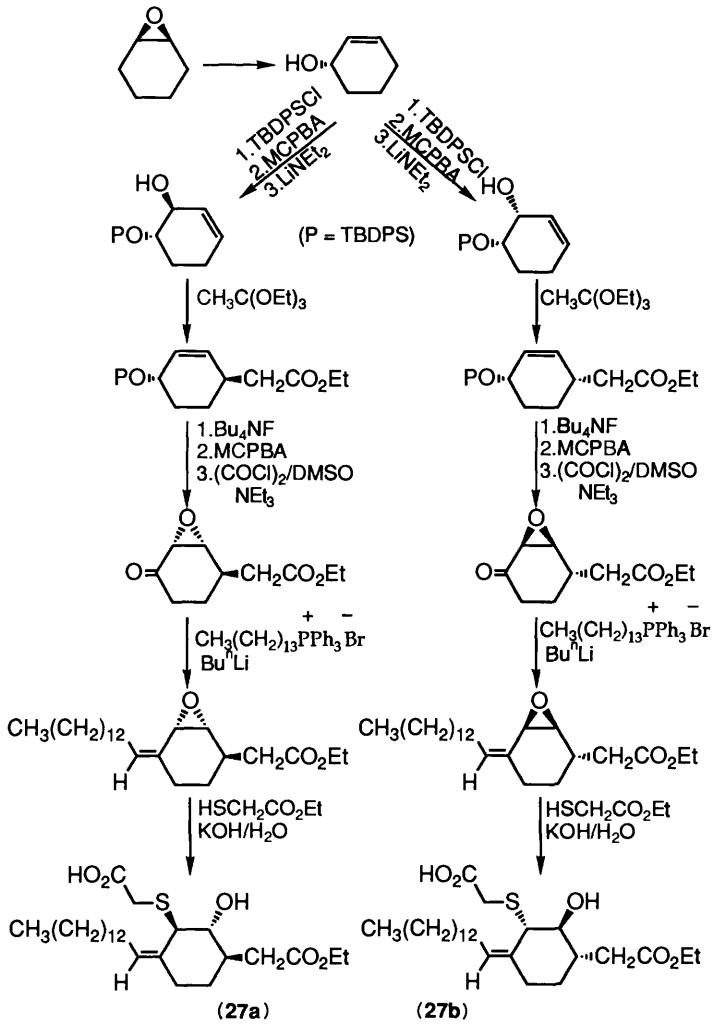


from (−)- or (+)-menthone has also been reported (equation 32).[34] One of two diastereoisomeric spiroacetals is selectively produced, and the less hindered equatorial C–O bond of the major spiroacetal is selectively cleaved on treatment with $TiCl_4$ (*cf.* equation 24). The ring-cleavage reaction proceeds with high stereoselectivity (>95% d.e.) and the resulting ring-cleavage products can be transformed into mono-protected derivatives with high optical purities (>95% e.e.). The strategy has been used to prepare (21) and (22) which are key intermediates in the total synthesis of naturally occurring (2*R*,4′*R*,8′*R*)-α-tocopherol (23).

5 Epoxides

The enantioselective deprotonation of an achiral epoxide using a homochiral base represents a convenient way of generating an optically active allylic alcohol,

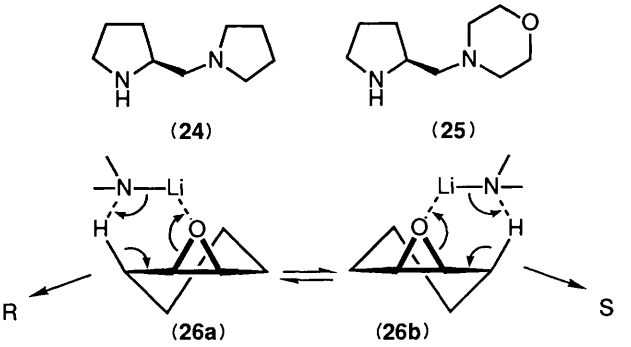
[34] T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake, and A. Oku, *J. Am. Chem. Soc.*, 1987, **109**, 527; T. Harada, I. Wada, and A. Oku, *Tetrahedron Lett.*, 1987, **28**, 4181; T. Harada, K. Sakamoto, Y. Ikemura, and A. Oku, *ibid.*, 1988, **29**, 3097; T. Harada, I. Wada, and A. Oku, *J. Org. Chem.*, 1989, **54**, 2599.



(36)

and has been perfected to allow such compounds to be obtained in high enantiomeric purity (*e.g.* equations 33 and 34).[35–38] It has been shown that optimum results are obtained using lithium amides prepared from 2-substituted aminoethyl pyrrolidines [*e.g.* (24) and (25)]. Since it is known that the deprotonation of cyclohexene oxide is highly selective for the *syn* proton that

[35] J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, 1980, **45**, 755.
[36] M. Asami, *Chem. Lett.*, 1984, 829; *Tetrahedron Lett.*, 1985, **26**, 5803.
[37] M. Asami and H. Kırıhara, *Chem. Lett.*, 1987, 389.
[38] S. K. Hendrie and J Leonard, *Tetrahedron*, 1987, **43**, 3289.



occupies a quasiaxial orientation, any model to account for the observed enantioselectivity needs to be able to distinguish between the two equilibrating enantiomeric conformations (26a) and (26b). An alternative approach is shown in equation 35 in which nucleophilic addition by a thiol in the presence of a homochiral agent is followed by oxidation and elimination of the thioether group to generate the allylic alcohol.[39]

Finally, a recently reported synthesis of two leucotriene analogues (27a) and (27b) illustrates the use of an allylic alcohol produced in this way as a starting point for asymmetric synthesis (equation 36).[40] The later steps involve epoxidation of the allylic alcohol or its t-butyldiphenylsilyl ether to produce two diastereomeric cyclohexenediol derivatives which are subjected to a Claisen ortho-ester rearrangement. Further epoxidation followed by stereospecific opening of the epoxide ring yield the two enantiomeric products (27a) and (27b).

Abbreviations

DIPT	di-isopropyl tartrate
Ipc_2BH	di-isopinocampheylborane
DMAP	4-dimethylaminopyridine
DCCI	dicyclohexylcarbodiimide
TBDMS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
PCC	pyridinium chlorochromate
acac	acetylacetonate
Ts	*para*-toluenesulphonyl
Ms	methanesulphonyl
Tf	trifluoromethanesulphonyl
TMS	trimethylsilyl
TMSOTf	trimethylsilyltrifluoromethanesulphonate
DHP	dihydropyran
THP	tetrahydropyranyl
NBS	*N*-bromosuccinimide
MCPBA	*meta*-chloroperoxybenzoic acid
MOM	methoxymethyl

[39] H. Yamashita and T. Mukaiyama, *Chem. Lett.*, 1985, 1643.
[40] J. S. Sabol and R. J. Clegge, *Tetrahedron Lett.*, 1989, **30**, 3377.