Tetrahedron Vol. 43, No. 14, pp. 3289 to 3294, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

PREPARATION OF PROLINE DERIVED LITHIUM AMIDE BASES AND THEIR USE IN ENANTIOSELECTIVE DEPROTONATION OF MESO EPOXIDES

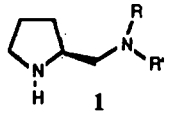
SHIRLEY K. HENDRIE AND JOHN LEONARD *

Department of Chemistry and Applied Chemistry
University of Salford, Salford, M5 4WT, U.K.

(*Received in UK* 15 *April* 1987)

Abstract: An alternative method of preparation for a range of proline derived chiral lithium amide bases is described. (S)-2-(Pyrrolidinomethyl) pyrrolidine, prepared by the new route, has been used to deprotonate *cis* and *trans* ^{t}butyldimethylsiloxy-3,4-epoxycyclopentane enantioselectively, thus generating chiral *cis* and *trans* ^{t}butyldimethylsiloxy-2-cyclopenten-4-ols. The products had higher enantiomeric purity than those produced when the base was prepared by a previously reported method.

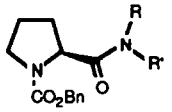
We have been studying a variety of synthetic methods which involve the use of chiral lithium amide bases to induce chirality during the transformation of an achiral molecule into a chiral compound. Among the bases we have been using are a series of compounds with the general structure **1**. These are derived from proline and have been used previously as mediators in a variety of enantioselective reactions.[1-6]



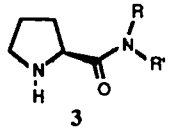
1

A general method for the synthesis of these bases was published some years ago and we originally followed this method to synthesise (S)-2-(pyrrolidinomethyl) pyrrolidine **10**.[7,8] However, the route is expensive to carry out on a large scale and suffers from the added drawback that the chiral centre is located in a potentially racemising environment at several stages in the sequence. Indeed, when we synthesised **10** by the literature route and used it in chiral induction methodology, the products of the reactions were less enantiomerically pure than expected (see later for example).

We therefore decided to develop an alternative, efficient and practically simple route to the base which would avoid intermediates which have possible racemisation problems. Our strategy was to reduce the proline to prolinol, convert the alcohol to a leaving group and displace this by an amine to form the new C-N bond. Thus structures **2** and **3**, in which the chiral centre is in a potentially racemising position adjacent to a carbonyl group, are avoided. We thought that the nucleophilic substitution step might be a problem due to steric interactions, but after some experimentation we found a very simple solution.



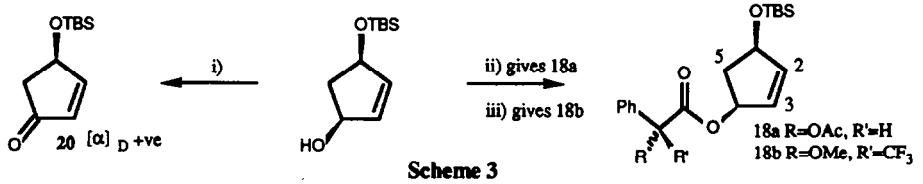
2



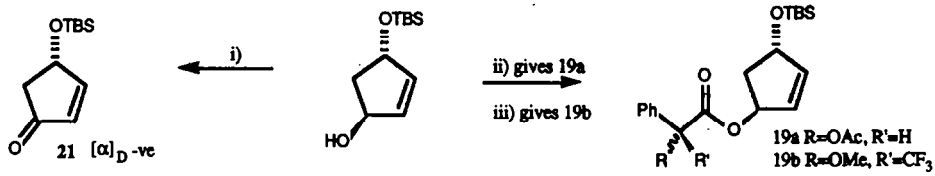
3

Analysis of the Enantiomeric Purity of the Products.

In the previously reported studies of the *cis* epoxide opening reactions optical rotation measurements had been used to determine the ee's of the product. These measurements can be inaccurate, especially on a small scale, with compounds of low rotation and we therefore decided to devise an NMR method for the determination of ee's. We prepared both O-acetyl mandelate esters **18a** and **19a**[16] and Mosher's esters **18b** and **19b**[17] to determine the enantiomeric purities of the reaction products. Tables 1 and 2 give details of the main features of the NMR spectra of the esters. The signals highlighted in bold type were well resolved and the relative intergrals of the diastereomeric protons were used to estimate the relative proportions of the enantiomers present. To provide a reference reactions were also carried out using lithium diisopropylamide, to give racemic products, whose Mosher's ester derivatives were prepared. The sense of the absolute stereochemistry induced in the allylic alcohols was determined by measuring the direction of the optical rotations of the corresponding enones **20** and **21**, which are known compounds[12] (Scheme 3).



Scheme 3



Reagents: i)PCC/CH_2Cl_2 ii)(R)Acetyl mandelic anhydride/DCC/DMAP/CH_2Cl_2 iii)(R)Mosher's acid chloride/Et_3N

TABLE 1†

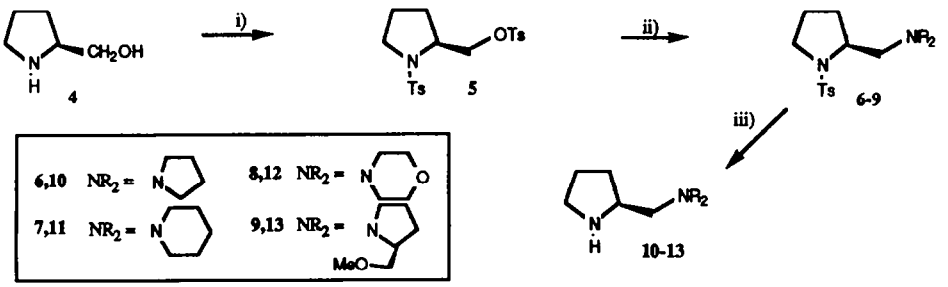
	Mandelate Ester 18a				Mosher's Ester 18b			
H	δ (Maj.)	δ (Min.)	Mult.	J (Coupled Proton)	δ (Maj.)	δ(Min.)	Mult.	J (Coupled Proton)
H-1	4.68	4.68	m	7.3(5a)	5.67	5.67	m	
H-2	**5.71**	**5.88**	td	5.6(3), 1.6(1), 1.6(4)	**6.01**	**6.03**	td	5.6(3), 1.6(1), 1.6(4)
H-3	**5.93**	**5.96**	td	5.6(1), 1.6(1), 1.6(4)	**5.86**	**5.95**	td	5.6(2), 1.6(1), 1.6(4)
H-4	5.49	5.49	m		4.72	4.72	m	
H-5 α	**2.80**	**2.68**	td	13.8(5β), 7.3(1), 7.3(4)	2.86	2.80	td	13.8(5β), 7.9(1), 7.9(4)
H-5 β	**1.65**	**1.40**	td	13.8(5α), 5.2(1), 5.2(4)	**1.72**	**1.64**	td	13.8(5α), 5.0(1), 5.0(4)
H-6	5.88	5.88	s					
OAc	2.18	2.18	s			3.55	m	
OMe	-				3.55			

TABLE2†

	Mandelate Ester 19a				Mosher's Ester 19b			
H	δ (Maj.)	δ (Min.)	Mult.	J (Coupled Proton)	δ (Maj.)	δ(Min.)	Mult.	J (Coupled Proton)
H-1	5.00	4.91	m		5.00	5.00	m	
H-2	**5.78**	**5.95**	ddd	5.6(3), 1.9(1), 0.76(4)			m	
H-3	**5.78**	**6.02**	ddd	5.6(1), 2.3(1), 1.35(4)			m	
H-4	5.98	5.78	~dd				m	
H-5a			m		**2.26**	**2.17**	ddd	14(5b), 6.5(1/4), 2.1(1/4)
H-5b			m		2.11	2.10	ddd	14(5a), 6.8(1/4), 2.9(1/4)
H-6	**5.82**	**5.83**	s					
OAc	2.22	2.22	s					
OMe	-				3.52	3.52	m	

†*NMR spectra run at 400 MHz.*

The initial step was bistosylation of prolinol, which served two purposes. The tosyl group on nitrogen provided a cheap protecting group, while the O-tosyl group acted as a leaving group. Not surprisingly, displacement of the O-tosyl group was quite slow, but it could be substituted by a variety of amines, by simply refluxing in toluene. Finally, the N-tosyl protecting group was removed by treatment with lithium in ammonia. All the steps in this sequence are high yielding and can be performed on a large scale. A range of secondary amines have been used as substituents and this is illustrated in scheme 1.

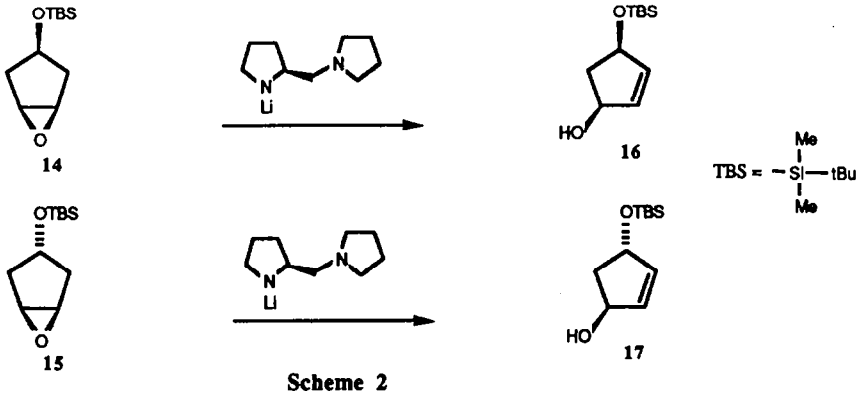


Reagents: i)pTs-Cl/Et_3N/CH_2Cl_2/reflux ii)HNR_2/Toluene/reflux iii)Li/NH_3/THF/EtOH (Ts = p)$MeC_6H_4SO_2$

Scheme 1

Enantioselective Epoxide Opening Reactions

A recent report described the use of chiral lithium amide bases to deprotonate *meso* epoxide **14** with a high degree of enantiotopic selectivity, thus generating the chiral allylic alcohol **16** with a high degree of enantiomeric induction.[9] When this work was published we also were working independently on the same transformation and on the deprotonation of the *trans* epoxide **15**,[10,11] but had not achieved such a high degree of enantiomeric induction as that reported. We therefore decided to investigate the reaction more thoroughly in order to clarify the results.



Scheme 2

The known secondary amine (S)-2-(pyrrolidinomethyl)pyrrolidine **10** had previously been employed to open cyclohexene oxide with a high degree of enantiomeric induction [12,13] and for this reason we chose to start our studies using the same base, which was initially prepared by the literature route (Method A).

The deprotonation/epoxide opening reactions of the *cis* and *trans meso* compounds **14** and **15** were carried out by adding the epoxides to an ice cooled solution of the lithium amide. The reactions of the *cis* epoxide were carried out at ice bath temperature, but under these conditions the *trans* epoxide opened very slowly and its reactions were generally allowed to warm to room temperature.

For our initial studies (S)-2-(pyrrolidinomethyl)pyrrolidine was prepared by the literature method (Method A). The products obtained had modest ee's and there was clearly a major difference between the enantiomeric purity of our *cis* product and that reported by other workers (see Table 3). We thought it unlikely that the difference in methods of analysis could be solely responsible for this and another possibility was that the base we were using was of low enantiomeric purity, due to partial racemisation during preparation. When the epoxide opening reactions were repeated using the base prepared by the new method illustrated in Scheme 1 (Method B), the products had higher ee's. This indicated that the base prepared by this method had higher enantiomeric purity. The enantiomeric purities of our product from opening of the *cis* epoxide are still not as high as those reported by other workers, but we think that this discrepancy may be due to the difference in methods of analysis. The effect of solvent on the reaction was very different between the *cis* and *trans* epoxides. The best solvent for opening the *cis* epoxide was benzene, but when the *trans* epoxide was opened in benzene, the product had very low enantiomeric purity. Opening the *trans* epoxide in THF gave product with the highest enantiomeric purity (78%), but the yield in this solvent was very low. A good yield and reasonable enantiomeric induction was achieved when reaction of the *trans* epoxide was carried out in ether.

TABLE 3

Epoxide	Product	Solvent	Temp°C	Yield %†	ee(A)%	ee(B)%	ee(Lit.)[9]
14	16	THF	0	65	40	50	66
14	16	ETHER	0	58	40	60	70
14	16	BENZENE	0	73	40	76	90
15	17	ETHER	0 to RT	95	32	64	-

†All yields are for pure material isolated by flash chromatography

ee(A) - Base used was prepared by method A

ee(B) - Base used was prepared by method B.

Acknowledgement: We would like to thank the SERC for financial support (S.K.H.) and the SERC NMR services at Sheffield and Warwick Universities for running 400 MHz proton NMR spectra

Experimental

General

Melting points were determined on an electrothermal apparatus and are uncorrected Optical rotations (α_D) were measured on an Optical Activity AA10 automatic polarimeter. Infra red spectra were recorded on a Perkin Elmer 397 spectrometer and NMR spectra were measured at 60 MHz on a Varian EM 360 instrument, at 90 MHz on a Perkin Elmer R32 instrument, at 300 MHz on a Bruker AC 300 instrument or at 400 MHz on a Bruker WH 400 instrument. The NMR line positions or centres of multiplets are given in the δ scale with tetramethyl silane (TMS) as the internal standard, the multiplicities and coupling constants (Hz) are indicated in parenthesis. Mass spectra were run on a Kratos MS 30 instrument. For analytical thin layer chromatography Merck silica (F254) pates were used and for preparative chromatography Merck Kelselgel (40 -63μ) silica was used.

(S)(-)-*N,O Bis*(*p*-Toluenesulphonyl)-2-hydroxymethyl pyrrolidine 5[15]

A solution of (S)-prolinol (10 g, 0.1M), triethylamine (20g, 21.4 ml, 0.2M) and p-toluene sulphonyl chloride (46 g, 0.2M) in dichloromethane (200ml) was refluxed for 24 hrs. After cooling the mixture was washed with water (2 x 25 ml) and the organic layer was dried over magnesium sulphate and evaporated. The crude product was recrystallized from ethanol to provide 26.4 g (65% yield) of the ditosyl compound: m.p. 92-94°, white needles (lit. 93-94)[5]; $[\alpha]_D^{25}$ -123.2° ($CHCl_3$); ^1H NMR 60 MHz) ($CDCl_3$) δ 1.75 (m, 4H,), 2.45 (s, 3H), 2.53 (S, 3H), 2.9-4.4 (m, 5H), 7.21 (~t, 4H), 7.75 (dd, 4H); ν_{max} 1590, 1350, 1160, cm^{-1}; m/e (CH_4, CI) 410(M+1,96%), 411(21.5), 238(100).

General method for displacement of the O-tosyl group from 5 by secondary amines to give compounds 6-9.

A solution of **(S)(-)-*N,O* Bis(*p*-toluenesulphonyl)-2-hydroxymethyl pyrrolidine 5**, (24.54g, 0.06 moles), pyrrolidine (or other secondary amine) (17g, 0.24moles) and DBU (0.91g) in toluene (400mls), was heated at reflux for 24hrs, or until no starting material remained as indicated by TLC. The solvent was then removed on a rotary evaporator and the product was crystallised. If crystallisation proved difficult, the material could be purified by flash chromatography.

(S)-*N*-(*p*-Toluenesulphonyl)-2-(pyrrolidinomethyl) pyrrolidine 6 (yield 70%)

mp. 80-82°, pale yellow crystals; $[\alpha]_D^{25}$ -128.4° ($CHCl_3$); ^1H NMR (60 MHz) δ 1.80 (m, 8H,), 2.45 (s, 3H), 2.70 (s, 3H), 3.0-3.9 (m, 6H), 7.55 (dd, 4H); ν_{max} 1600, 1340, 1160 cm^{-1}; m/e (CH_4, CI) 309 (M+1, 39%), 91 (56), 84 (100), Found M+1 309.1617, calc. for $C_{16}H_{25}N_2O_2S$ = 309.1636

(S)-*N*-(*p*-Toluenesulphonyl)-2-(piperidinomethyl) pyrrolidine 7 (yield 75%)

mp. 80-81°; $[\alpha]_D^{25}$ -126.4° (c=10, $CHCl_3$); ^1H NMR (90 MHz) δ 1.2-2.0 (m, 10H), 2.1-2.8 (m, 8H), 2.8-4.1 (m, 4H), 7.5 (dd, 4H); ν_{max} 1600, 1450, 1340, 1160 cm^{-1}; m/e (CH_4, CI) 323 (M+1, 87%), 322 (6.4), 321 (32), Found 321.1615, calc. for $C_{17}H_{25}N_2O_2S$ = 321.1636.

(S)-*N*-(*p*-Toluenesulphonyl)-2-(morpholinomethyl) pyrrolidine 8 (yield 74%)

mp. 110-112°; $[\alpha]_D^{25}$ -123.6° (c=10, $CHCl_3$); ^1H NMR (90 MHz) δ 1.3 - 2.0 (m, 4H), 2.2 - 2.7 (m, 10H) 3.2 (m, 2H) 3.7 (t, 4H) 7.5 (dd. 4H); ν_{max} 1600, 1340, 1160, 670 cm^{-1}; m/e (CH_4, CI) 325 (100%), 324 (6), 323 (25), 100 (93), Found 224.0752, calc. for $C_{11}H_{10}NO_2S$ = 224.0745, Found 100.0762, calc. for $C_5H_{10}NO$ = 100.0762.

(2S, 2S')-2-Methoxymethyl-1-[N-*p*-toluene sulphonyl pyrrolidin-2-yl) methyl] pyrrolidine 9 (yield 98%)

$[\alpha]_D^{25}$ -133° (c=5, EtOH); ^1H NMR (90 MHz) δ 1.7 (m, 8H), 2.4 (s, 3H Me), 2.4 - 4.0 (m, 10H) 3.3 (s, 3H), 7.5 (dd, 4H); νmax 1600, 1340, 1160 cm^{-1}; m/e (CH_4, CI) 353 (100%), 199 (86), 128 (65) 84 (38), Found M^+ 352.1820, calc. for $C_{18}H_{28}N_2O_3S$ = 352.1821

General method for removal of N-tosyl group from the bases.

To a solution of the N-tosyl base (eg 6 12.40g, 0.04 moles) in THF/EtOH/NH_3(liq.) (200/10/200 ml), under nitrogen at -78°, excess lithium was added and the mixture was then allowed to reflux for 15 mins. The condenser was then removed and after the ammonia had evaporated the mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 x 200 ml). The combined organic layers were dried and concentrated, leaving a brown oil, which was purified by bulb to bulb distillation.

(S)-2-(Pyrrolidinomethyl) pyrrolidine 10 (yield 68%)

$[\alpha]_D^{25}$ +8.3° (c = 2.4, EtOH); ^1H NMR (90MHz) δ 1.70 (m, 8H), 2.50 (m, 7H), 3.0 (m, 3H); ^{13}C NMR (75 MHz, DEPT)[18] δ 23 (2 x CH_2), 24 (CH_2), 30 (CH_2), 45 (CH_2), 54 (2 x CH_2), 57 (CH), 61 (CH_2), (no other peaks were detected); ν_{max} 3300 cm^{-1}; m/e (CH_4, CI) 155 (100%), 154 (76), 153 (66), 84 (90), Found M+1 155.1551, Calc. for $C_9H_{19}N_2$ = 155.1547

(S)-2-(Piperidinomethyl) pyrrolidine 11 (yield 75%)

bp. 100°, (1mm Hg); $[\alpha]_D^{25}$ +1.8 (c = 2.2, benzene), $[\alpha]_D^{25}$ +14 (c = 10, EtOH) ; ^1H NMR (90MHz) δ 1.1 - 2.0 (m, 10H), 2 - 3.5 (m, 9H), 2.5 (s, 1H, NH); ^{13}C NMR (75 MHz, DEPT) δ 23.9 (CH_2), 24.4 (CH_2), 25.4 (2 x CH_2), 29.4 (CH_2), 45.3 (CH_2), 54.5 (2 x CH_2) , 55.0 (CH), 64.15 (CH_2)(no other peaks were detected); ν_{max} 3350, 1450, 1140 cm^{-1}; m/e (CH_4, CI) 168 (M^+, 6%), 167 (15), 98 (100), 84 (43), 70 (34), Found M+1 169.1704, Calc for $C_{10}H_{21}N_2$ = 169.1704

(S)-2-(Morpholinomethyl) pyrrolidine 12 (yield 75%)

$[\alpha]_D^{25}$ +10.4° (c = 10, EtOH); ^1H NMR (MHz) δ 1.1 - 2.1 (m, 4H), 2.2 - 3.4 (m, 10H), 3.7 (t, 4H); ^{13}C NMR (75 MHz, DEPT) δ 24.7 (CH_2), 29.7 (CH_2), 45.8 (CH_2), 53.8 (2 x CH_2), 54.8 (CH), 64.2 (CH_2), 66.7 (2 x CH_2) (no other peaks were detected); ν_{max} 3350, 1395, 1000 cm^{-1}; m/e (NH_3, CI) 173 (17%), 171 (100), Found 171.1496, Calc for $C_9H_{19}N_2O$ = 171.1496

(2S, 2S')-2-Methoxymethyl-1-[pyrrolidin-2-yl) methyl] pyrrolidine 13 (yield 73%)

bp.130° (0.7 mm Hg); $[\alpha]_D^{25}$ -5.6° (c = 10, EtOH); ^1H NMR (MHz) δ 1.7 (m, 8H), 2.0 - 3.5 (m, 10H), 2.8 (s, 1H, NH), 3.3 (s, 3H, OMe); ^{13}C NMR (75 MHz, DEPT) δ 23.2 (CH_2), 24.9 (CH_2), 26.2 (CH_2), 29.9 (CH_2), 46.1 (CH_2), 55.7 (CH_2) 58.1 (CH_3), 58.9 (CH), 61.0 (CH_2), 63.8 (CH), 76.3 CH_2); ν_{max} 3400, 1602, 1115 cm^{-1}; m/e (NH_3, CI) 199 (100%), 85 (27), 70 (40), Found M+1 199.1808, Calc for $C_{11}H_{23}N_2O$ = 199.1809

Opening of *cis*-^{t}butyldimethylsilloxy-3,4-epoxycyclopentane 14 to *cis*-^{t}butyldimethylsilloxy-2-cyclopenten-4-ol 16.

General method exemplified by reaction with (S)-2-(pyrrolidinomethyl) pyrrolidine as the base and benzene as solvent:

^{n}Butyl lithium (0.56ml, 1.5M, 0.84mmol) was added to a solution of (S)-2-(pyrrolidinomethyl) pyrrolidine 10 (148mg, 0.96mmol), in dry benzene (3cm^3) at 0°C, under N_2. After 30 mins. epoxide 14 (100mg, 0.54mmol), in benzene (2cm^3) was added and the mixture was stirred until no epoxide remained, as indicated by TLC. The solution was then diluted with CH_2Cl_2, washed with water, dried, evaporated and the residue purified by flash chromatography. (Yields are provided in the table, in the text)

^1H NMR (60 MHz) δ 0.0 (s, 6H), 0.8 (s, 9H), 1.4 (m, 1H), 1.9 (s, 1H), 2.6 (m, 1H) 4.5 (m, 2H), 5.8 (t, 2H); ν_{max} 3340, 1250, 1070, 900 cm^{-1}; m/e (CH_4 CI) 215 (20%), 214 (6), 197 (15), 115 (61), 83 (91).

Opening of *trans*-^{t}butyldimethylsiloxy-3,4-epoxycyclopentane 15 to *trans*-^{t}butyldimethylsiloxy-2-cyclopenten-4-ol 17.

^{n}Butyl lithium (0.56ml, 1.5M, 0.84mmol) was added to a solution of (S)-2-(pyrrolidinomethyl) pyrrolidine (148mg, 0.96mmol), in dry ether (3cm^3) at 0°C, under N_2. After 30 mins. the *trans* epoxide (100mg, 0.54mmol), in ether (2cm^3) was added and the mixture was allowed to warm to room temperature and stirred until no epoxide remained, as indicated by TLC (about 6hr.). The solution was then diluted with CH_2Cl_2, washed with water, dried, evaporated and the residue purified by flash chromatography.

^{1}H NMR (60 MHz) δ 0.0 (s, 6H), 0.8 (s, 9H), 2.5 (m, 2H), 4.9 (m, 2H), 5.8 (s, 2H); ν_{max} 3350, 1240, 1050, cm^{-1}.

References.

1. *Asymmetric Synthesis, Vol.2, Ch.1,* Ed. J.D. Morrison, **Acad. Press**. (1983)
2. T. Mukaiyama, M. Asami, J. Hanna and S. Kobayashi, *Chem. Lett.*, (1977) 783.
3. T. Mukaiyama, N. Minowa, T. Oriyama and K. Narasaka *Chem. Lett.*, (1986) 97
4. T. Mukaiyama, N. Yamasaki, R.N. Stevens and M. Murakami *Chem. Lett.*, (1986) 213.
5. N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, (1982) 1441
6. M. Asami and T. Mukaiyama, *Heterocycles* (1979) ***12***, 499.
7. M. Asami, H. Ohno, S. Kobayashi and T. Mukaiyama, *Bul. Chem. Soc. Jap.*, (1978) ***51***, 1869.
8. T. Sone, K. Hirol and S. Yamada, *Chem. Pharm. Bull.*, (1973) ***21***, 2331
9. M. Asami, *Tetrahedron Lett.*, (1985) 5803.
10. Epoxides **14** and **15** were prepared from 3-cyclopentenol by one of two routes. Directed mCPBA epoxidation of 3-cyclopentenol[11] provided a cis epoxide, which was converted to ^{t}butyldimethylsilyl ether **14** in quantitative yield over the two steps. Alternatively, the sequence of these two steps could be reversed to provide a 1:1 mixture of epoxides **14** and **15**, which were easily separated by flash chromatography, again in quantitative yield.
11. H.M. Hess and H.C. Brown, *J. Org. Chem.*, (1967) ***32***, 4138
12. J. K. Whitesell and S. Felman, *J. Org. Chem.*, (1980) ***45***, 3548.
13. M. Asami, *Chem. Lett.*, (1984) 829.
14. T. Tanaka, S.Kurozumi, T. Toru, S. Miura, M. Kobayashi and S. Ishimoto, *Tetrahedron*, (1976) ***32***, 1713.
15. Z. Dokuzovic, N.K. Roberts, J.F. Sawyer, J. Whelan and B. Bosnich *J. Am. Chem. Soc.*, (1986) ***108***, 2034
16. J.K. Whitesell and D. Reynolds, *J. Org. Chem.*, (1983) ***48***, 3584
17. J.A. Dale, D.L. Dull and H.S. Mosher, *J. Org. Chem.*, (1969) ***34***, 2543
18. A. Derome, Modern NMR Techniques for Chemistry Research, **Pergamon** (1987)