Asymmetric Synthesis of Mellein Methyl Ether: Use of *ortho*-Toluate Carbanions Generated by Chiral Bases

Andrew C. Regan and James Staunton*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

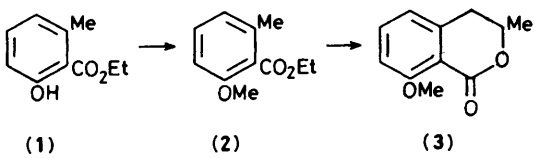
An *ortho*-toluate carbanion generated from (**2**) by the chiral lithium amide base of (**6**), (**7**), or (**11**) undergoes an enantioselective aldol-type reaction with acetaldehyde to give mellein methyl ether (**3**), in up to 53% enantiometric excess.

Addition of organolithium reagents to the carbonyl group is an important carbon–carbon bond forming reaction, and in recent years there has been considerable interest in the use of chiral complexing agents in this reaction to effect asymmetric induction.[1]

An attractive extension to this idea would be the use of a chiral base which could first generate a carbanion, and then serve as a chiral complexing agent, thus leading to the possibility of asymmetric induction in addition reactions.

We have investigated this possibility, making use of our experience in the field of *ortho*-toluate carbanion chemistry,[2–4] and now report our successful preliminary findings.

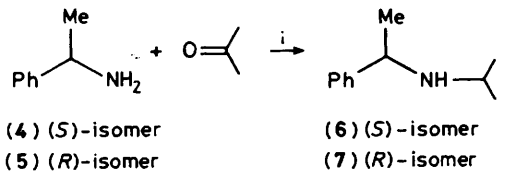
The readily available ethyl ester of 6-methylsalicylic acid[5] (**1**) was methylated (dimethyl sulphate–potassium carbonate–acetone) to give (**2**), which was treated with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C. The resulting bright orange anion was quenched with excess of acetaldehyde after 30 min, giving mellein methyl ether (**3**)† in 52% yield, with identical ^{1}H n.m.r. data to those reported[6] (Scheme 1).



(**1**) (**2**) (**3**)

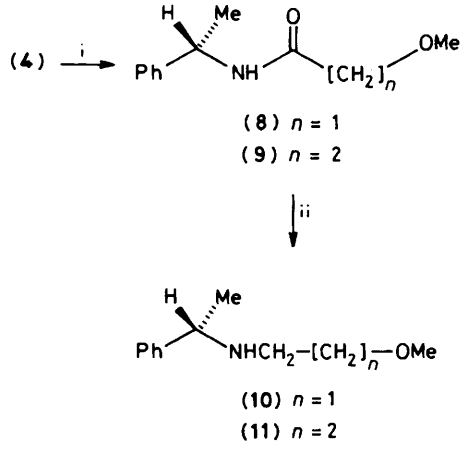
Scheme 1

† For this compound ^{1}H n.m.r., i.r., and mass spectra as well as microanalysis and/or mass measurement were in agreement with the assigned structure.



(4) (*S*)-isomer (6) (*S*)-isomer
(5) (*R*)-isomer (7) (*R*)-isomer

Scheme 2. *Reagents:* i, $NaBH_3CN$, MeOH, HCl.



Scheme 3. *Reagents:* i, $MeO[CH_2]_nCOCl$, pyridine, CH_2Cl_2; ii, $LiAlH_4$ or BH_3, THF.

The chiral amines (**6**)† and (**7**) were prepared by the reaction of (*R*)- or (*S*)-1-phenylethylamine (**4**) or (**5**) with acetone in the presence of sodium cyanoborohydride, following the general procedure of Borch[7] (Scheme 2). The lithium amide of (**6**) was prepared in THF with n-butyl-lithium and used in place of LDA in the above reaction. This resulted in a 78% yield of mellein methyl ether after purification by preparative t.l.c., with an enantiomeric excess of 10%. Enantiomeric excess (e.e.) was determined by the direct method of ^1H n.m.r. in the presence of the chiral shift reagent $Eu(tfc)_3$ [tfc = 3-trifluoromethylhydroxymethylene-(−)-camphorato]. This resulted in a downfield shift of the methoxy singlet of mellein methyl ether into the signal-free region between δ 5 and 6. The signals for the two enantiomers were shifted by different amounts and became well separated. Addition of the methyl ether derived from natural (*R*)-mellein produced by *Aspergillus melleus* increased the intensity of the more downfield signal, and showed that the (*S*)-enantiomer (**6**) gave (*R*)-mellein methyl ether in excess. Complementary results were obtained using the (*R*)-enantiomer (**7**).

This result was encouraging, and we reasoned that greater induction might be obtained with a bidentate base which could have chelating properties towards metal atoms. Accordingly the amines (**10**)† and (**11**)† were prepared from (**4**) as in Scheme 3.

Use of the lithium amide of (**10**) led to isolation of starting material only; this amide appears to be insufficiently basic to deprotonate (**2**). However the lithium amide of (**11**) gave mellein methyl ether in 51% yield and 49% enantiomeric excess. Diluting the reaction 5 times from 0.25 M to 0.05 M gave a 41% yield and a synthetically useful enantiomeric excess of 53% (ratio of enantiomers: 3.3 to 1).

Cooling the reaction from −78 to −120 °C did not improve the induction (46% e.e.) and use of ether as a solvent gave very little reaction.

The product can be enriched in the major enantiomer by recrystallisation. One recrystallisation from ether–hexane recovering 50% of the material increased the enantiomeric excess from 53 to 78%, as judged by n.m.r. (ratio of enantiomers: 8.0 to 1). Measurement of the optical rotation confirmed this result: $[\alpha]_D^{23}$ −192.7° (*c* 0.00546 in $CHCl_3$), *i.e.* optical purity 75%, based on $[\alpha]_D^{22}$ −255° (*c* 0.052 in $CHCl_3$) measured for the methyl ether derived from natural (*R*)-mellein.

Thus we have realised the idea of using a chiral agent both as a base and as a chiral complexing agent. The bases used have the advantage of being readily available in both enantiomeric forms, they can be recovered and re-used, and their use is illustrated by an efficient enantioselective synthesis of mellein methyl ether.

We thank the S.E.R.C. for financial support.

Received, 21st March 1983; Com. 367

References

1 J.-P. Mazaleyrat and D. J. Cram, *J. Am. Chem. Soc.*, 1981, **103**, 4585; T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *ibid.*, 1979, **101**, 1455, and references cited therein.
2 F. J. Leeper and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1978, 406.
3 G. E. Evans, F. J. Leeper, J. A. Murphy, and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1979, 205.
4 F. J. Leeper and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1979, 206.
5 V. B. Piskov, *Zh. Org. Khim.*, 1965, **1**, 1242 (*Chem. Abs.*, 1965, **63**, 13095d); V. B. Piskov and L. K. Osanova, *Sint. Prir. Soed., Anal. Fragm., Akad. Nauk SSSR, Otd. Obshch. Tekh. Khim.*, 1965, 50 (*Chem. Abs.*, 1966, **65**, 3782b); J. A. Murphy, Ph.D. Thesis, University of Cambridge, 1979.
6 M. Guyot and D. Molho, *Tetrahedron Lett.*, 1973, 3433.
7 R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.