Asymmetric Synthesis of Glycidic 2-Oxazolines

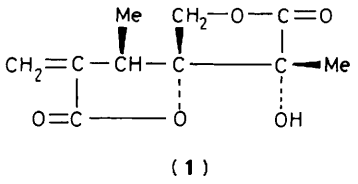
Richard Liddell and Chris Whiteley*

Department of Chemistry and Biochemistry, Rhodes University, Grahamstown, South Africa

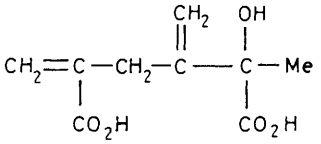
A stereospecific synthesis of 4*S*,5*S*-(−)-2-[(2*R*)-2,3-epoxy-2,3-dimethylbutyl]-4-methoxymethyl-5-phenyl-2-oxazoline *via* a Darzens condensation of 4*S*,5*S*-(−)-2-(1-bromoethyl)-4-methoxymethyl-5-phenyl-2-oxazoline with propan-2-one is reported.

Oxazolines are not only used as carboxy group protecting agents[1] but also as optically active units for the stereospecific synthesis of carboxylic acids and esters.[2,3]

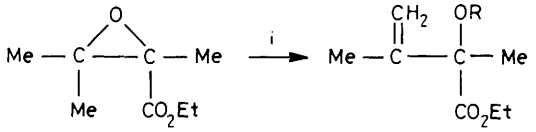
In an investigation into the total synthesis of swazinecic acid dilactone (**1**) the dicarboxylic acid (**2**) was synthesised[4,5] as an important intermediate (Scheme 1). Unfortunately, (**2**)



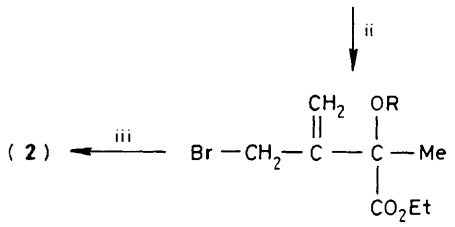
(1)



(2)



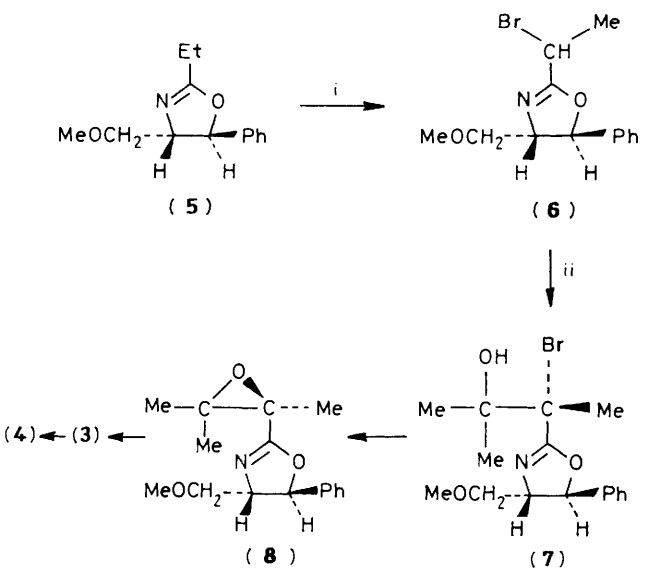
(3) (4)



Scheme 1. i, $LiClO_4$; ii, *N*-bromosuccinimide; iii, (BuC≡C)-[CH_2=C(CO_2Et)]CuLi.

and its precursor (**4**, R = $SiMe_3$) resisted all attempts at resolution with ephedrine or brucine carboxylate salts.[6] Rearrangement to the γ-hydroxy αβ-unsaturated system and lactonisation occurred.

We now report the preparation of the glycidic oxazoline (**8**) (Scheme 2) possessing the *R* configuration at the α-carbon, which readily transformed into (**3**), also with the correct 2*R* configuration. Commercially available† (4*S*,5*S*)-(−)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline was first converted into its methyl ether (**5**) [NaH, MeI, tetrahydrofuran (THF)] then brominated (n-butyl-lithium, Br_2, THF, −80 °C) to afford 4*S*,5*S*-(−)-2-(1-bromoethyl)-4-methoxymethyl-5-phenyl-2-oxazoline (**6**) as a diastereoisomeric mixture in 90% yield.‡ A corresponding α-iodo-oxazoline was also prepared though the yields were somewhat lower (not optimised, the



(5) (6) (7) (8) (4) (3)

Scheme 2. i, Bu^nLi, THF, Br_2; ii, $LiNPr^i_2$, THF, Me_2CO.

product gave satisfactory elemental analysis). To minimise the formation of dimers[7] it was necessary to add the lithio anion to the bromine in THF at −80 °C in the absence of light.[8] The ^{1}H n.m.r. spectrum of (**6**) revealed the presence of a diastereotopic methyl group and a proton attached to the asymmetric centre at C-2. Purification and separation into the corresponding enantiomers was achieved by silica gel chromatography.§

This appears to be the first successful procedure for the direct introduction of a halogen at the α-position of the oxazoline ring. Indirect methods[9] involve cyclisation between ethyl imidate hydrochlorides and substituted aminodiols.

The glycidic oxazoline (**8**) was then prepared (81% yield)¶ using a modified Darzens condensation of (**6**) and propan-2-one with lithium di-isopropylamide in THF at −80 °C. In order to produce the correct 2*R* configuration in (**8**) the immediate precursor (**7**) would have to be *S* (since epoxidation reverses configuration). According to Meyers *et al.*[9b] and the Cahn–Ingold–Prelog ruling this would necessitate the introduction of a 'high-priority' halogen at the α-carbon of (**5**) before proton abstraction and reaction with propan-2-one. The product (**8**) was purified by chromatography (silica gel) and its ^{1}H n.m.r. spectrum** showed no diastereotopic effect suggesting the formation of only one enantiomer {$[\alpha]_D^{24}$ −46.4° (*c* 0.85, $CHCl_3$)}.

This stereospecific synthesis of glycidic oxazolines paves the way to the preparation of the esters (**3**) and the important intermediate dicarboxylic acid (**2**) possessing the correct 2*R* configuration.

† Aldrich Chemical Co., Milwaukee, Wisconsin.

‡ The bromo-oxazoline (**6**) gave satisfactory elemental analysis. ^{1}H n.m.r. ($CDCl_3$, 60 MHz), δ 1.94, 1.96 (3H, dd, *J* 7 Hz, CH_3C·Br); 3.4 (3H, s, OCH_3); 3.6 (2H, m, OCH_2); 4.2 (1H, dq, C=N–CH); 4.7, 4.75 (1H, dq, *J* 7 Hz, CH·Br); 5.46 (1H, d, CH–O); 7.4 (5H, s, aromatic). Mass spectrum: *m/z* 299/297 (21%), 254/252 (66), 218 (73), 154/152 (53), 146 (76), 112 (100). ^{13}C n.m.r. ($CDCl_3$) 22.41, 22.5 (CH_3); 36.3, 36.6 (CH·Br); 59.2 (CH_3O); 73.7 (CH_2O); 74.5 (CH–N); 84.01 (CH–O); 125.3, 128.1, 128.6 (aromatic C); 140.3 (quat. aromatic C); 166.6 p.p.m. (C=N).

§ The *S* enantiomer was separated, $[\alpha]_D^{24}$ −25.85° (*c* 0.53, $CHCl_3$). Optical purity was based upon the highest rotation values obtained.

¶ Based on v.p.c. using 80 × 0.3 cm, 1.5% OV17 on Chromosorb Q. The product gave satisfactory analyses.

** ^{1}H n.m.r. ($CDCl_3$, 60 MHz) δ 1.40 [6H, s, $(CH_3)_2$C]; 1.63 [3H, s, N=C–C(CH_3)O]; 3.4 (3H, s, OCH_3); 3.6 (2H, m, CH_2O); 4.2 (1H, m, C=N–CH); 5.46 (1H, d, CH–O); 7.4 (5H, s, aromatic). Mass spectrum: *m/z* 275 (43%); 229 (48), 201 (25), 171 (55), 159 (77), 149 (100), 131 (70).

Financial support from the Council for Scientific and Industrial Research (South Africa) is gratefully acknowledged.

Received, 19th August 1983; Com. 1135

References

1 J. A. Frump, *Chem. Rev.*, 1971, **71**, 483; A. I. Meyers and E. D. Mickelich, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 270.
2 E. W. Colvin, 'Comprehensive Organic Chemistry,' Pergamon Press, Oxford, 1979, vol. 2, p. 760.
3 A. I. Meyers, *Acc. Chem. Res.*, 1978, **11**, 375; A. I. Meyers and K. A. Lutomski, *J. Am. Chem. Soc.*, 1982, **104**, 879; J. M. Wilson and D. J. Cram, *ibid.*, p. 881.
4 C. G. Gordon-Gray and C. G. Whiteley, *J. Chem. Soc., Perkin Trans.* 1, 1977, 2040.
5 For other synthetic studies see: S. E. Drewes and N. D. Emslie, *J. Chem. Soc., Perkin Trans.* 1, 1981, 2089; S. E. Drewes, N. D. Emslie, A. T. Pitchford, and B. W. Wallace, *S. Afr. J. Chem.*, 1982, **35**, 115.
6 A successful resolution of the acid of (**4**) (R = H) using quinine has recently been reported, F. B. Armstrong, E. L. Lipscomb, D. H. G. Crout, M. B. Mitchell, and S. R. Prakash, *J. Chem. Soc., Perkin Trans.* 1, 1983, 1197.
7 A. I. Meyers, personal communication.
8 R. T. Arnold and S. T. Kulenovic, *J. Org. Chem.*, 1978, **43**, 3687.
9 (a) A. I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc.*, 1974, **96**, 268; (b) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *ibid.*, 1976, **98**, 567; (c) S. Shibata, H. Matshushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, *Heterocycles*, 1981, **16**, 1901.

Printed by Heffers Printers Ltd Cambridge England