Asymmetric Synthesis of Glycidic 2-Oxazolines

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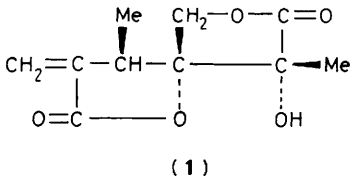
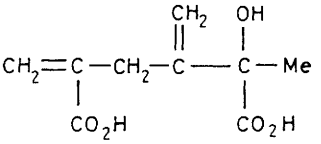
A stereospecific synthesis of 4*S*,5*S*-(−)-2-[(2*R*)-2,3-epoxy-2,3-dimethylbutyl]-4-methoxymethyl-5-phenyl-2-oxazoline *via* a Darzens condensation of 4*S*,5*S*-(−)-2-(1-bromoethyl)-4-methoxymethyl-5-phenyl-2-oxazoline with propan-2-one is reported.

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)



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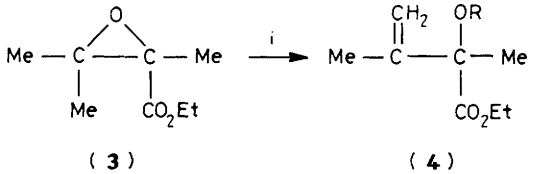

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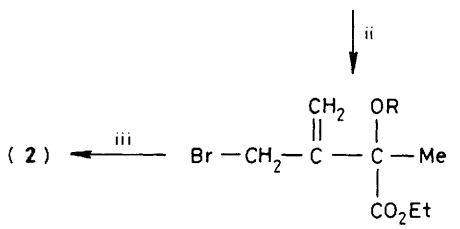
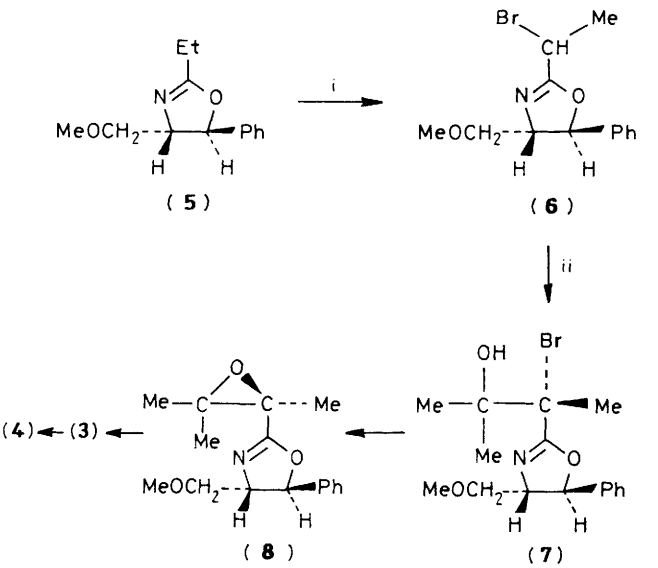


Scheme 1. i, $LiClO_4$; ii, *N*-bromosuccinimide; iii, (BuC≡C)-[CH_2=C(CO_2Et)]CuLi.

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



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.

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‡ 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).

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