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Synthesis and enantiomeric excess determination of (6S)-1-(trimethylsilyloxy)-6-(N-methyl-N-benzyloxycarbonylamino)cyclohexene

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Abstract: The title compound was obtained with high regioisomeric and enantiomeric purity starting from the tartrate salt of (1S,2S)-1-hydroxy-2-methylaminocyclohexane. The determination of the enantiomeric excess both of the title compound and of its precursor (2S)-2-(N-methyl-N-benzyloxycarbonylamino)cyclohexanone was determined by NMR experiments with chiral shift reagents. © 1997 Elsevier Science Ltd. All rights reserved.

In the course of our work on the synthesis of the Trinem antibiotic $GV129606^{1}$ 1 the preparation of a sample of the silyl enol ether (6S)-1-(trimethylsilyloxy)-6-(N-methyl-N-benzyloxycarbonylamino)-cyclohexene 2 (Figure 1) was required.

Samples of racemic 2 were easily prepared through the synthetic route described in Scheme 1 according to the procedure previously described for some analogous substrates.² As the synthesis of the enantiomerically pure N-methylaminocyclohexanol (1S,2S)-3 was reported in the literature,³ the optically active (S)-2 could be obtained via the same synthetic route used to prepare the racemic substrate. However, the configurational stability of the intermediate ketone (S)-5 under the reaction conditions used either in the oxidation step or in the formation of the silyl enol ether (S)-2 could represent an issue and, therefore, suitable analytical methods for the enantiomeric excess determination of (S)-5 and (S)-2 were required.

determination of the enantiomeric purity of (S)-5 and (S)-2 was The approa-MHz ¹H-NMR ched by 400 spectroscopy using chiral lanthanide shift reagents.⁴ A number of shift reagents were investigated on the racemic mixtures of 5 and 2.5 Significant splitting of the signals of the enantiomers ($\Delta\delta$) was obtained with tris(d,d-dicampholylmethanate)Europium(III), tris[3-(heptafluoropropylhydroxymethylene)-dcamphorate]Europium (III), tris(3-trifluoroacetyl-d-camphorate)Europium(III) and tris(1,1,1,2,2,3,3heptafluoro-7,7-dimethyl-4,6-octanedionate)Europium(III). The best results, for both (S)-5 and (S)-2, were obtained in CDCl₃ solution with tris[3-(heptafluoropropylhydroxymethylene)-dcamphorate]Europium(III), Eu(hfc)₃. In the spectra recorded on (S)-5, suitable splittings were



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Figure 1.



iii) Na₂Cr₂O₇/H₂SO₄ or PCC oxidation ; iv) TMSOTf / triethylamine / CH₂Cl₂ / 0°C.

Scheme 1.

detected both in the aromatic region ($\Delta\delta=10$ Hz) and on the N-CH₃ signal ($\Delta\delta=13$ Hz). On the other hand, in the case of the silvl enol ether (S)-2 only a splitting of the signals in the aromatic region ($\Delta\delta=12$ Hz) was visible.

The oxidation of the alcohol (1S,2S)-4, easily obtained from a sample of enantiomerically pure (1S,2S)-N-methyl-aminocyclohexanol tartrate salt, was initially performed with either oxalyl chloride/DMSO (Swern oxidation) or pyridiniumchlorocromate (PCC). The former procedure produced a significant loss of e.e. and the isolated (S)-5 showed only a moderate enantiomeric excess (ca. 70%). The PCC protocol generally gave (S)-5 with a higher e.e. (92-96%) although, in few cases, it was observed that a prolonged contact of the crude product on the silica gel column resulted in some loss of e.e.⁶ Good results were also obtained adopting the reported⁷ Na₂Cr₂O₇/H₂SO₄ oxidation protocol that gave satisfactory pure samples of (S)-5 as a colourless oil. Compared to the PCC procedure the Na₂Cr₂O₇/H₂SO₄ oxidation gave (S)-5 with a slight lower e.e. (88–92%) but allowed a more efficient and easy removal of the chromium salts during the work-up thus avoiding any further purification of the crude (S)-5 on a silica gel column.

The ketone (S)-5 was then converted into the silyl enol ether (S)-2 by means of the previously described protocol.² As expected (S)-2 was obtained with a high regiocontrol; less than 3% of the more substituted regioisomer was in fact detected by NMR in the crude reaction mixture. More interestingly it was observed that the silyl enol ether (S)-2 always showed the same e.e. of the starting ketone (S)-5.

In conclusion, efficient procedures for the preparation and characterisation of both (S)-2 and its precursor (S)-5 have been established and a further interesting feature of the TMSOTf/triethylamine enolising reagent mixture^{2,8} has been disclosed.

Experimental

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping in a phosphomolybdic acid solution

followed by heating. Flash chromatography⁹ was performed on E. Merck silica gel (230–400 mesh). ¹H-NMR spectra were recorded at 400 MHz in CDCl₃: chemical shifts are reported in ppm respect to residual CHCl₃ at 7.26 downfield from the TMS line, as external reference. NMR assignments are assisted by NOE and 2D-techniques.

Mass spectra were recorded in FAB (70 eV) mode using 3-nitrobenzylalcohol as matrix. All optical rotations [α] values were obtained at the sodium D line, at 20°C.

Preparation of (1S,2S)-1-hydroxy-2(N-methyl-N-benzyloxycarbonylamino)cyclohexane 4

To a solution of (1S,2S)-1-hydroxy-2-methylaminocyclohexane tartrate salt (15.0 g, 53.7 mmol, $[\alpha]$ =+45, c=1, in H₂O; m.p.=149°C) and NaHCO₃ (18.0 g, 214.8 mmol) in H₂O (100 mL) was added THF (50 mL). The resulting mixture was cooled at 0°C then benzyloxycarbonylchloride (13.7 g, 80.5 mmol) was added dropwise. After stirring for 30 min at 0°C, diethyl ether (150 mL) was added and the separated organic layer successively extracted with brine (2×50 mL). The organic layer was dried on Na₂SO₄ and concentrated under vacuum. The crude material was purified over a silica gel column yielding 12.0 g (85%) of (S)-4 showing: ¹H-NMR: 7.40–7.28 (m, 5); 5.16 (s, 2); 3.98–3.72 (m, 1); 3.54 (m, 1); 2.87 (s, 3); 2.18–2.06 (m, 1); 1.99 (d, 1); 1.84–1.66 (m, 3); 1.56–1.12 (m, 4); IR: 3416; 1676; HRMS *m*/z calcd for C₁₅H₂₂NO₃ (MH⁺) 264.159969, obsd 264.159510.

Preparation of (2S)-2(N-methyl-N-benzyloxycarbonylamino)cyclohexanone 5

To a suspension of pyridiniumchlorocromate (10.7 g, 49.5 mmol) in dry dichloromethane (200 mL) was slowly added a solution of (1*S*,2*S*)-1-hydroxy-2(*N*-methyl-*N*-benzyloxycarbonylamino)-cyclohexane (8.7 g, 33.0 mmol) in dry dichloromethane (60 mL). The mixture was stirred for 24 h at room temperature then was diluted with diethyl ether (600 mL) and filtered through a pad of silica gel. The organic layer was concentrated under vacuum to give 7.9 g (yield=90%) of ketone (*S*)-5 showing: enantiomeric excess=94% (¹H-NMR with chiral reagent shifts); $[\alpha]$ =+38, c=1, in CHCl₃; ¹H-NMR: 7.38–7.26 (m, 5); 5.15–5.10 (m, 2); 4.48,4.54 (m,m, 1); 2.90,2.87 (s,s, 3); 2.56–2.44 (m, 1); 2.44–2.20 (m, 1); 2.20–1.50 (m, 6); IR: 1720; 1695; HRMS *m*/z calcd for C₁₅H₂₀NO₃ (MH⁺) 262.144319, obsd 262.143890.

Preparation of (6S)-1(trimethylsilyloxy)-6(N-methyl-N-benzyloxycarbonylamino)cyclohexene 2

To a cooled (0°C) solution of the ketone (S)-5 (2.60 g, 10 mmol) in dry dichloromethane (30 mL) was added triethylamine (1.96 mL, 14 mmol) and the trimethylsilyltriflate (2.32 mL, 12 mmol). After 30 min the reaction mixture was poured into a 5% solution of NH₄Cl and extracted (3×50 mL) with diethyl ether. The combined organic layers were dried on Na₂SO₄, concentrated under vacuum and then purified by flash chromatography (ethyl acetate/cyclohexane=30/70) to give 2.7 g (yield=80%) of (S)-2 showing: enantiomeric excess=94% (¹H-NMR with chiral reagent shifts); [α]=-32, c=1, in CHCl₃; ¹H-NMR: 7.40–7.25 (m, 5); 5.16–5.14 (m, 2); 5.05, 5.02 (m, m, 1); 4.73, 4.59 (m, m, 1); 2.78, 2.75 (s, s, 3); 2.14–1.50 (m, 6); 0.14, 0.13 (s, s, 9); HRMS *m*/z calcd for C₁₈H₂₈NO₃ (MH⁺) 334.183847, obsd 334.183100.

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optically active (S)-5 and (S)-2 were observed to be configurationally stable for at least 2 hours after the end of the NMR experiments.

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