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

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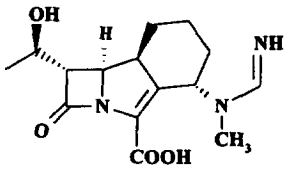
Abstract: The title compound was obtained with high regioisomeric and enantiomeric purity starting from the tartrate salt of (1*S*,2*S*)-1-hydroxy-2-methylaminocyclohexane. The determination of the enantiomeric excess both of the title compound and of its precursor (2*S*)-2-(*N*-methyl-*N*-benzyloxycarbonylamino)cyclohexanone 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 (6*S*)-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 (1*S*,2*S*)-**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.

The determination of the enantiomeric purity of (*S*)-**5** and (*S*)-**2** was approached by 400 MHz ^{1}H-NMR 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)-d-camphorate]Europium (III), tris(3-trifluoroacetyl-d-camphorate)Europium(III) and tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)Europium(III). The best results, for both (*S*)-**5** and (*S*)-**2**, were obtained in $CDCl_3$ solution with tris[3-(heptafluoropropylhydroxymethylene)-d-camphorate]Europium(III), $Eu(hfc)_3$. In the spectra recorded on (*S*)-**5**, suitable splittings were



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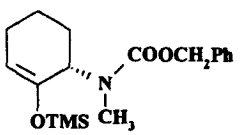

(S)-2

Figure 1.

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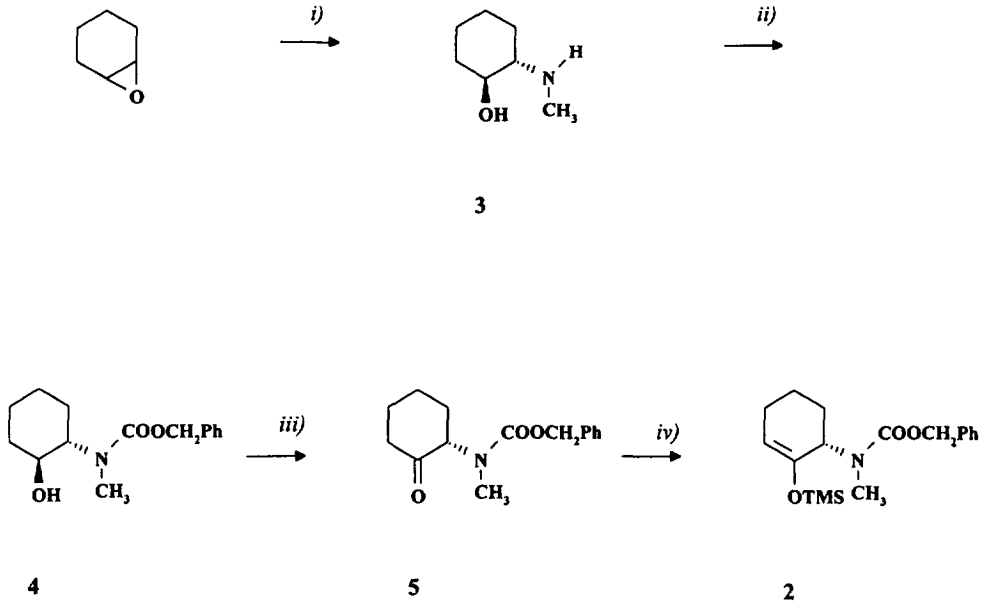

i) H_2NCH_3 (aq.) / EtOH / 80°C ; *ii)* Benzylchloroformate / $NaHCO_3$ / water:THF = 2:1 v/v / 0°C ;
iii) $Na_2Cr_2O_7/H_2SO_4$ or PCC oxidation ; *iv)* TMSOTf / triethylamine / CH_2Cl_2 / 0°C.

Scheme 1.

detected both in the aromatic region ($\Delta\delta$=10 Hz) and on the N–CH_3 signal ($\Delta\delta$=13 Hz). On the other hand, in the case of the silyl 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 (1*S*,2*S*)-**4**, easily obtained from a sample of enantiomerically pure (1*S*,2*S*)-*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 reported[7] $Na_2Cr_2O_7/H_2SO_4$ oxidation protocol that gave satisfactory pure samples of (*S*)-**5** as a colourless oil. Compared to the PCC procedure the $Na_2Cr_2O_7/H_2SO_4$ 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 chromatography[9] was performed on E. Merck silica gel (230–400 mesh). ^{1}H-NMR spectra were recorded at 400 MHz in $CDCl_3$: chemical shifts are reported in ppm respect to residual $CHCl_3$ 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 (1*S*,2*S*)-1-hydroxy-2-methylaminocyclohexane tartrate salt (15.0 g, 53.7 mmol, [α]=+45, c=1, in H_2O; m.p.=149°C) and $NaHCO_3$ (18.0 g, 214.8 mmol) in H_2O (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 Na_2SO_4 and concentrated under vacuum. The crude material was purified over a silica gel column yielding 12.0 g (85%) of (*S*)-**4** showing: ^{1}H-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 $C_{15}H_{22}NO_3$ (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% (^{1}H-NMR with chiral reagent shifts); [α]=+38, c=1, in $CHCl_3$; ^{1}H-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 $C_{15}H_{20}NO_3$ (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 NH_4Cl and extracted (3×50 mL) with diethyl ether. The combined organic layers were dried on Na_2SO_4, 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% (^{1}H-NMR with chiral reagent shifts); [α]=−32, c=1, in $CHCl_3$; ^{1}H-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 $C_{18}H_{28}NO_3$ (MH^+) 334.183847, obsd 334.183100.

References

1. a) Perboni, A.; Donati, D.; Tarzia, G. *Eur. Pat. Appl.* EP0502468 A1, **1992**; C.A. **1993**, *118*, 80719; b) Pecunioso, A. *et al.*, forthcoming paper.
2. Rossi, L.; Pecunioso, A. *Tetrahedron Lett.* **1994**, *35*, 5285.
3. a) Mousseron, M.; Granger, R. *Bull. Soc. Chim. Fr.* **1947**, 850; b) Kay, J. B.; Robinson, J. B. *J. Chem. Soc. (C)*, **1969**, 248; c) Pracejus, H.; Pracejus, G.; Costisella, B. *J. prakt. Chem.* **1987**, 235.
4. Morrill, T. C.; *Lanthanide Shift Reagents in Stereochemical Analysis*, in 'Methods in Stereochemical Analysis' VCH Inc. Press: **1986**.
5. The NMR spectra on **5** and **2** were recorded in $CDCl_3$ at 25°C and 27°C respectively in the presence of ca. 1 molar equivalent of Eu(hfc)$_3$. Under these experimental conditions both the

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.

6. A partial racemisation on a silica gel column was previously reported for a similar substrate. See: Aube', J.; Wolfe, M. S.; Yantiss, R. K.; Cook, S. M.; Takusagawa, F. *Synthetic Commun.* **1992**, *22*, 3003.
7. Brown, H. C.; Garg, C. P.; Liu, K. T. *J. Org. Chem. Soc.* **1971**, *36*, 387.
8. a) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1 and references cited therein; b) Simchen, G.; Kober, W., *Synthesis* **1976**, 259.
9. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, **43**, 2923–2925.

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