Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 13-16, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0957-4166/96 $15.00 + 0.00

0957-4166(95)00409-2

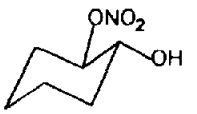
Enantioselective Synthesis of (1R,2R)- and (1S,2S)-2-Nitroxycyclohexan-1-ols

Deevi Basavaiah,* Subramanian Pandiaraju and Kannan Muthukumaran

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India

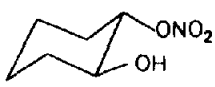
Abstract: A simple and convenient methodology has been developed for the synthesis of (1R,2R)- and (1S,2S)-2-nitroxycyclohexan-1-ols in enantiomerically pure form *via* pig liver acetone powder (PLAP) mediated hydrolysis of racemic *trans*-1-acetoxy-2-nitroxycyclohexane.

Nitrate esters find widespread therapeutical importance as drugs for treatment of heart and vascular diseases.[1,2] *trans*-2-Nitroxycyclohexan-1-ol[1] is one such molecule which has attracted our attention. Despite the importance of this molecule as an useful drug, very few methods were reported in the literature for its synthesis in racemic form.[3-5] And to the best of our knowledge there is no report in the literature for the synthesis of *trans*-2-nitroxycyclohexan-1-ol in enantiomerically enriched form. Owing to the current interest and challenges in synthesizing chiral drugs[6] in enantiomerically pure form, it is highly desirable to obtain both the enantiomers of *trans*-2-nitroxycyclohexan-1-ol in homochiral form. We herein disclose the first enantioselective synthesis of both (1R,2R)-2-nitroxycyclohexan-1-ol **1** and (1S,2S)-2-nitroxycyclohexan-1-ol **2** *via* pig liver acetone powder (PLAP) mediated hydrolysis of racemic *trans*-1-acetoxy-2-nitroxycyclohexane.



(1R,2R)

1



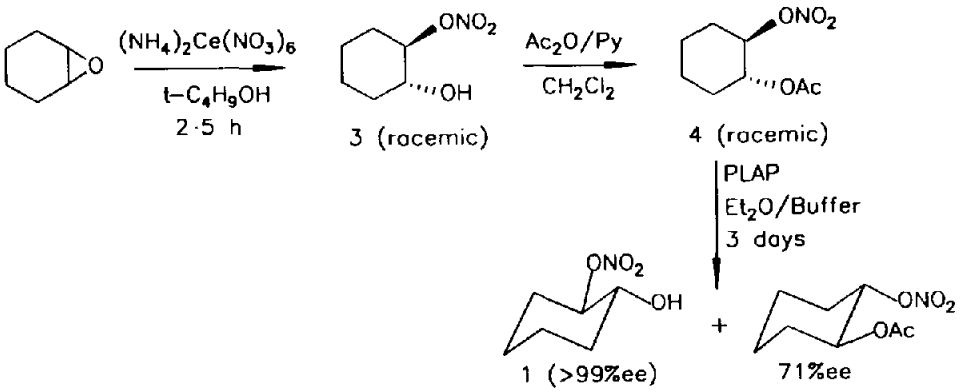
(1S,2S)

2

During our research program on the synthesis and application of various chiral 2-substituted cyclohexan-1-ols[7-9] we required enantiopure *trans*-2-*tert*-butoxycyclohexan-1-ol. In an attempt to obtain racemic *trans*-2-*tert*-butoxycyclohexan-1-ol according to the literature procedure[10] we have treated cyclohexene oxide (100mM) with ammonium cerium (IV) nitrate (CAN) (25 mM) in *tert*-butanol (75 mL) for 2.5 h at room temperature

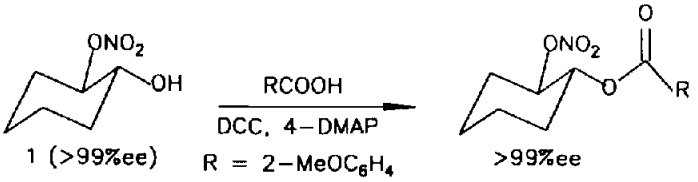
which furnished *trans*-2-nitroxycyclohexan-1-ol[11,12] **3** b.p. 110-111°C\7 mm (lit.[3] b.p. 100°C\3 mm) as colorless liquid in 67% yield (**Scheme 1**). The *trans* stereochemistry of **3** was confirmed by **2D NOESY** experiment.

Scheme 1



The racemic *trans*-2-nitroxycyclohexan-1-ol **3** was converted into the corresponding acetate **4** by treating it with Ac_2O\pyridine. Enantioselective hydrolysis of this acetate **4** (20.3 g, 100 mM) with PLAP (20 g) in biphasic media for 3 days [ether\phosphate buffer (0.5 M, pH = 8.0)] afforded, after column chromatography (2% ethyl acetate in hexane) followed by single crystallization (hexane), 5.6 g (yield 35%) of (-)-*trans*-2-nitroxycyclohexan-1-ol **1** $[\alpha]_D^{22}$-71.5 (c 1.17, CH_2Cl_2) as colorless crystals [m.p 55-56°C] and 10.52 g (yield 52%) of unhydrolyzed (+)-acetate $[\alpha]_D^{22}$ +16.8 (c 1.70, acetone) as colorless liquid.

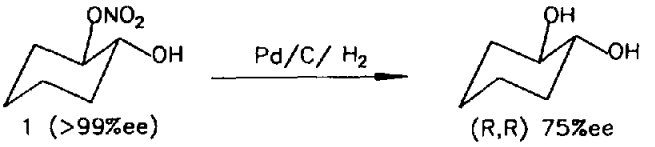
We have successfully determined the enantiomeric purity of **1** to be >99% by the HPLC analysis (CHIRALCEL OD column, 5% i-PrOH in hexane, 0.5 mL\min) of its 2-methoxybenzoate derivative (obtained by treating **1** with o-anisic acid and dicyclohexylcarbodiimide (DCC) in the presence of catalytic amount of 4-dimethylaminopyridine (4-DMAP) (**Eq.1**)] with reference to its racemic analog.



(1)

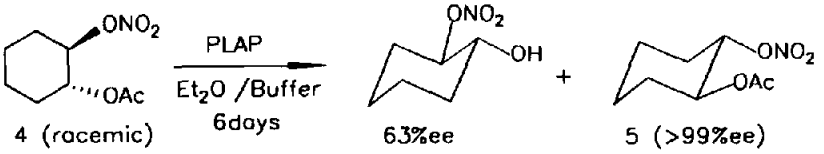
In order to assign the absolute stereochemistry of **1**, we have subjected this molecule to hydrogenolysis (30-35 psi) in ethyl acetate using Pd\C as catalyst which afforded (R,R)-cyclohexan-1,2-diol m.p. 111-112°C, $[\alpha]_D^{22}$-30.1 (c 0.94, $CHCl_3$), [lit[13] m.p. 113-114°C, $[\alpha]_D^{20}$-40 (c 0.32, $CHCl_3$), 100% ee, conf. (R,R)] in 75% ee and in 82% yield (**Eq.2**).

Therefore, we have assigned (R,R)-configuration to the molecule **1**. The fall in the enantiomeric purity of (R,R)-cyclohexane-1,2-diol is attributed to partial racemization during hydrogenolysis.



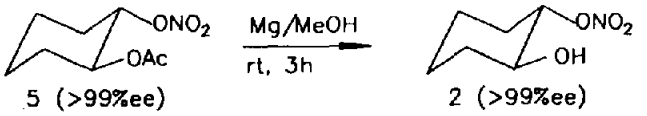
1 (>99%ee) (R,R) 75%ee (2)

With a view to obtain (1S,2S)-2-nitroxycyclohexan-1-ol **2** in enantiomerically pure form, the racemic acetate **4** (20.3 g, 100 mM) was subjected to similar enzymatic hydrolysis with PLAP (20 g) for more time (6 days) which afforded 8.87 g (yield 55%) of (-)-alcohol $[\alpha]_D^{22}$-45.4 (c 1.22 CH_2Cl_2) and 7.41 g (yield 36%) of enantiopure (+)-acetate **5** $[\alpha]_D^{22}$ +23.5 (c 1.22, acetone) (**Eq.3**).



4 (racemic) 63%ee 5 (>99%ee) (3)

The conversion of this (+)-acetate **5** into the corresponding (+)-alcohol **2** demands a chemoselective cleavage of acetoxy function in the presence of nitroxy function. In fact we have achieved this transformation using Mg\MeOH as a chemoselective cleavage reagent[14,15] (**Eq.4**). Thus, the enantiopure (+)-alcohol **2** ($[\alpha]_D^{22}$+71.8 (c 0.43, CH_2Cl_2) was obtained as colorless crystals (m.p. 58-59°C) in >99% ee (determined by HPLC analysis similar to that of **1**)



5 (>99%ee) 2 (>99%ee) (4)

In conclusion we have achieved a simple and convenient synthesis of (1R,2R)- and (1S,2S)-2-nitroxycyclohexan-1-ols in enantiomerically pure form.

Acknowledgements: We thank Rajiv Gandhi foundation (JNCASR, IISc campus, Bangalore, India) for funding this project. We thank the UGC (New Delhi) for the special assistance programme in organic chemistry and COSIST

programme in organic synthesis in the School of Chemistry, University of Hyderabad, Hyderabad. SP and KMK thank UGC (New Delhi) for research fellowship.

References and Notes:

1. Bron, J.; Sterk, G.J.; Vanden Werf, J.F.; Timmerman, H.; *Eur. Pat. Appl. EP.* 359335, **1990**, *Chem. Abst.* **1990**, 113, 184719x.
2. Blum, S.W.; Quinn, J.B.; Howe, B.B.; Hefner, M.A.; Winbury, M.M. *J. Pharmacol. Exp. Ther.*, **1971**, 176, 684-691, *Chem. Abst* **1971**, 74, 97581d.
3. Brook, A.G.; Wright, F.G. *Canad. J. Chem.*, **1951**, 29, 308-319
4. Mincione, E.; Lanciano, F. *Tetrahedron Lett.*, **1980**, 21, 1149-1150.
5. Iranpoor, N.; Salehi, P. *Tetrahedron* **1995**, 51, 909-912.
6. Stinson, S.C. *Chem. & Eng. News (Washington)*, **1992**, Sept.28, 46-79.
7. Basavaiah, D.; Ramakrishna, P.; Bharathi, T.K. *Tetrahedron: Asymm.*, **1995**, 6, 439-454.
8. Basavaiah, D.; Bharathi, T.K. *Tetrahedron Lett.* **1991**, 32, 3417-3420.
9. Basavaiah, D.; Dharma Rao, P. *Tetrahedron: Asymm.*, **1994**, 5, 223-234.
10. Iranpoor, N.; Baltork, I.M. *Synth. Commun.*, **1990**, 20, 2789-2797.
11. **Spectral data for 3:** ^{1}H NMR ($CDCl_3$) (200 MHz): δ 1.18-1.56 (m, 4H), 1.64-1.92 (m, 2H), 2.02-2.32 (m, 2H), 2.51 (br s, 1H, D_2O washable) 3.56-3.78 (m, 1H), 4.72-4.92 (m, 1H); ^{13}C NMR ($CDCl_3$) (50 MHz): δ 23.54, 23.83, 28.81, 33.19, 70.50, 87.33; IR (neat) νmax\cm^{-1}: 1628, 3381. Analysis calcd. for $C_6H_{11}NO_4$: C, 44.71; H 6.88; N, 8.69 found C, 44.68; H, 6.86; N, 8.66.
12. Very recently synthesis of **3** was reported by Iranpoor and Salehi *via* the opening of cyclohexene oxide with CAN in CH_3CN (*see* ref.5).
13. Itano, K.; Yamasaki, K.; Kihara, C.; Tanaka, O. *Carbohyd. Res.*, **1980**, 87, 27-34.
14. Basavaiah, D.; Pandiaraju, S.; Naqui Ali, M.; Muthukumaran, K., *Unpublished results*.
15. For other recent applications of Mg\MeOH see: a). Pak, C.S.; Lee, E.; Lee, G.H. *J. Org. Chem.*, **1993**, 58, 1523-1530. b). Xu, Y.C; Lebeau, E.; Walker, C. *Tetrahedron Lett.* **1994**, 35, 6207-6210. c). Chavan, S.P.; Ethiraj, K.S. *Tetrahedron Lett.* **1995**, 36, 2281-2284.

(*Received in UK* 3 *October* 1995; *accepted* 8 *November* 1995)