Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Novel Chiral Auxiliary for Enantioselective Synthesis of Tertiary Alcohol

Brindaban C. Ranu [a], Rupak Chakraborty [a] & Dipak C. Sarkar [a]

[a] Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta, 700 032, India

Published online: 23 Sep 2006.

To cite this article: Brindaban C. Ranu, Rupak Chakraborty & Dipak C. Sarkar (1991) A Novel Chiral Auxiliary for Enantioselective Synthesis of Tertiary Alcohol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:15-16, 1619-1624, DOI: 10.1080/00397919108021061

To link to this article: http://dx.doi.org/10.1080/00397919108021061

SYNTHETIC COMMUNICATIONS, 21(15&16), 1619-1624 (1991)

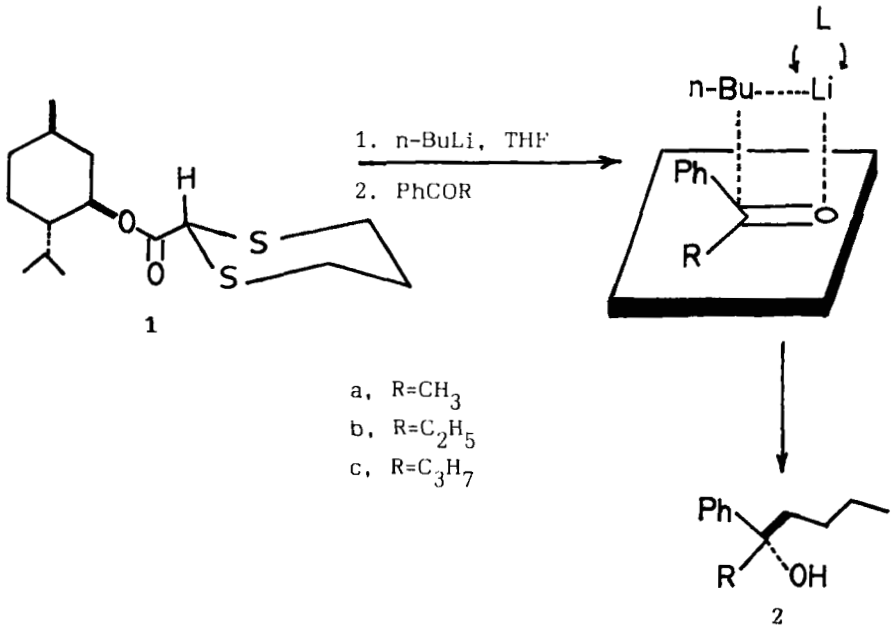
A NOVEL CHIRAL AUXILIARY FOR ENANTIOSELECTIVE SYNTHESIS OF TERTIARY ALCOHOL

Brindaban C. Ranu*, Rupak Chakraborty, and Dipak C. Sarkar

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, India.

ABSTRACT : The use of 1-menthyl ester of 1,3-dithiane-2-carboxylic acid as a chiral auxilary for the conversion of acetophenone, propiophenone and butyrophenone to the corresponding optically active tertiary alcohols 2-phenylhexan-2-ol, 3-phenylheptan-3-ol and 4-phenyloctan-4-ol, has been demonstrated.

Enantioselective synthesis of tertiary hydroxy compound in an acyclic chain is a challenging problem in the field of asymmetric synthesis. Thus, although, quite a number of excellent methods have been developed in the past few years for the synthesis of optically active secondary alcohols,[1,2a] methodologies for chiral tertiary alcohols are very few.[2] One general approach involves the asymmetric addition of organometallic reagent to a prochiral carbonyl compound in presence of a chiral auxiliary. Most commonly used chiral auxiliaries for this purpose are various amino alcohols and diamines; but these are found not to be very efficient.[2,3] Thus, there is a need to develop new auxiliaries. In the course of our some other synthetic investigations, we have discovered that 1-menthyl ester of 1,3-dithiane-2-carboxylic acid **1** induces



Scheme-1

asymmetric addition of n-butyl lithium to a ketone leading to an optically active tertiary alcohol.

In a typical reaction, 1-menthyl ester of 1,3-dithiane-2-carboxylic acid **1** was treated with n-butyl lithium for 1.5 h at -20°C after which acetophenone was added and left in the refrigerator for 18 h. Decomposition with water and extraction with ether furnished a crude material which on purification by distillation produced the chiral alcohol **2a**, $[\alpha]_D^{25}$ -5.63° (c 11.8, EtOH) (ee 55.3%) in 70% yield (Scheme-1). The menthyl ester **1** was recovered unchanged without loss of its optical purity. Presumably, n-butyl lithium forms a complex with

dithiane ester **1** through cordination with oxygen and sulphur and then participates in the addition reaction. Use of thiocompounds as chiral auxiliaries involving oxygen and sulfur for coordination with metal are now being explored and of current interest.[2c,4]

This reaction thus introduces a new type of chiral auxiliary for the creation of asymmetric quaternary carbon centre in acyclic chains. The enantioselectivity observed in case of alcohol **2a** is also much improved compared to those using diamine and amino alcohol as chiral auxiliaries[3] and thus this chiral auxiliary **1** inherits some promise in the field of asymmetric synthesis.

We are now actively engaged in testing the generality of this reaction and found that propiophenone and butyrophenone also furnished the optically active 3-phenylheptan-3-ol **2b**, $[\alpha]_D^{25}$ -5.46° (c 2.14, $CHCl_3$), and 4-phenyloctan-4-ol **2c** $[\alpha]_D^{25}$ -1.52° (c 0.524, $CHCl_3$) under similar treatment with n-butyl lithium in presence of chiral auxilary **1**. Further investigations for improvement of optical yield and its useful application in natural products synthesis, as well as to uncover various aspects of reaction sequence, are being carried out and will be reported in due course.

Experimental

^1H NMR spectra were recorded in 200 MHz and 60 MHz on XL-200 and A-60 spectrometers of Varian Associates in $CDCl_3$ and CCl_4 solutions with Me_4Si as internal standard. IR spectra were

recorded on a Perkin Elmer 298 spectrometer. Optical rotations were measured in a Perkin Elmer 141 polarimeter. Elemental analysis were done in our laboratory and are consistent with calculated values. Tetrahydrofuran (THF) was dried over potassium and benzophenone and distilled just before use.

1-Menthyl ester of 1,3-dithiane-2-carboxylic acid **(1)**. - A solution of 1,3-dithiane-2-carboxylic acid (16 g, 0.097 mol) [prepared by the alkaline hydrolysis of corresponding ethyl ester[5]] in benzene (450 ml) was refluxed with l-menthol (15 g, 0.096 mol) in presence of p-toluenesulfonic acid (1 g) for 16 h under nitrogen using a Dean-Stark water separator. The reaction mixture was then washed successively with water, aqueous sodium bicarbonate solution and water, dried (Na_2SO_4) and evaporated to leave a solid product (25 g, 80%). This was crystallized in methanol three times to furnish an analytically pure sample of **1**, m.p. 92°C, $[\alpha]_D^{25}$ -54.6° (c 1, $CHCl_3$); IR (KBr) : 1715 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 0.7-1.8 (m, 18 H), 1.9-2.2 (m, 2H), 2.56-2.76 (m, 2H), 3.3-3.5 (m, 2H), 4.2 (s, 1H), 4.38 (m, 1H).

(S)-2-phenylhexan-2-ol **(2a)**. - To a stirred solution of l-menthyl ester of 1,3-dithiane-2-carboxylic acid **1** (1 mmol) in dry THF (25 ml) at -20°C was added a solution of n-butyl lithium (2 mmol) in hexane dropwise under nitrogen and stirring was continued at -20°C for 1 h after which acetophenone (1 mmol) in THF (5 ml) was added dropwise. The mixture was

stirred for half an hour and stored at 0°C in the refrigerator overnight (18 h). The reaction mixture was then decomposed with water and extracted with ether (4 x 25 ml). The ether extract was washed with brine, dried (Na_2SO_4) and evaporated to leave a viscous liquid which on fractional distillation (short path) produced a low boiling liquid as the tertiary alcohol **2a**, (70%) $[\alpha]_D^{25}$ -5.63° (c 11.8, EtOH), ee 55.3% (based on the reported[3a] optical rotation), IR (neat) : 3100-3600 cm^{-1}, ^1H NMR ($CDCl_3$) : δ 0.84 (t, 3H, J = 6 Hz), 1.06-1.34 (m, 4H), 1.54 (s, 3H), 1.8 (s, 1H), 1.82 (t, 2H, J = 6 Hz), 7.24-7.5 (m, 5H).

The starting menthyl ester **1** was recorded unchanged from the residue.

Similar procedure was followed for the synthesis of tertiary alcohols **2b** and **2c**.

3-Phenylheptan-3-ol **(2b)** : Yield : 65%, $[\alpha]_D^{25}$ -5.46° (c 2.14, $CHCl_3$); IR (neat) : 3150-3600 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 0.53-0.93 (2t, 6H, J = 8 Hz), 1.0-1.36 (m, 4H), 1.53-2.0 (m, 4H), 7.16 (m, 5H).

4-Phenyloctan-4-ol **(2c)**. Yield : 60%, $[\alpha]_D^{25}$ -1.52° (c 0.524, $CHCl_3$); IR (neat) : 3100-3600 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 0.66-1.49 (m, 13H), 1.49-1.83 (m, 4H), 7.09 (m, 5H).

Acknowledgement : This work has been supported by a grant (No.SP/S1/G-49/88) from DST, New Delhi and R.C. thanks CSIR, for awarding him a Junior Research Fellowship.

References.

1. (a) Corey, E.J.; Yu, C.M.; Lee, D.H. J. Am. Chem. Soc. **1990**, 112, 878. (b) Marchand, A.P.; Reddy, G.M. Tetrahedron Lett. **1990**, 31, 1811 and related references cited therein.

2. (a) Solladie, G. 'Asymmetric Synthesis', Ed. Morrison, J.D. Academic press, Inc. : New York, 1983, Vol.2A, Chapter 6. (b) Fujimura, O.; Takai, K.; Utimoto, K. J. Org. Chem. **1990**, 55, 1705 and references cited therein. (c) Fujisawa, T.; Takemura, I.; Ukaji, Y. Tetrahedron Lett. **1990**, 31, 5479.

3. (a) Boireau, G.; Abenhaim, D.; Bourdais, J.; Basch, E.H. Tetrahedron lett. **1976**, 4781. (b) Zweig, J.S.; Luche, J.L.; Barreiro, E.; Crabbe, P. Tetrahedron lett. **1975**, 2355.

4. Swindell, C.S.; Blase, F.R.; Eggleston, D.S.; Krause, J. Tetrahedron Lett. **1990**, 31, 5409 and references cited therein.

5. Eliel, E.L.; Hartman, A.A. J. Org. Chem. **1972**, 37, 505.

(Received in UK 19 April, 1991)