Tetrahedron: Asymmetry Vol. 4, No. 9, pp. 1973-1976, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

An Improved Synthesis and Resolution of (±)-*cis,cis*-Spiro[4.4]Nonane-1,6-Diol

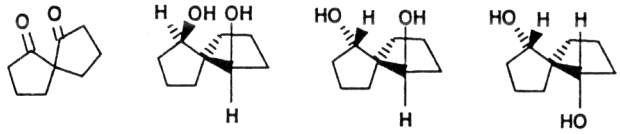
James A. Nieman, Masood Parvez and Brian A. Keay*

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4

(*Received in UK* 23 *June* 1993; *accepted* 28 *July* 1993)

Abstract: (±)-*cis,cis*-Spiro[4.4]nonane-1,6-diol (**2**) is synthesized stereoselectively in four steps (51%) beginning with ethyl 2-oxocyclopentanecarboxylate. An improved resolution of diol **2** is described by preparing diastereomeric ketals of (1R)-(+)-camphor. The relative stereochemistry of *cis,cis*-diol **2** is unambiguously assigned *via* an X-ray crystal structure of the bis-(p-nitrobenzoate) derivative.

The synthesis of chiral auxiliaries for use as ligands in metal catalyzed asymmetric transformations has been the focus of many research groups in the last decade.[1] Of the many successful chiral auxiliaries reported to date, some have had a C_2 axis of symmetry associated with them.[2] Many derivatives of binaphthol[3] and tartaric acid[1b,1f,1i,4] have provided asymmetric transformations with high enantiomeric excesses (e.e.). Until recently, a class of C_2 symmetric compounds had not been employed as chiral auxiliaries in asymmetric transformations; namely C_2 symmetric spiro compounds. In 1992, Kumar *et al* reported[5] that (+)-1R,5R,6R- and (-)-1S,5S,6S-spiro[4.4]nonane-1,6-diol were effective chiral ligands for the asymmetric reduction of aromatic ketones when complexed with aluminum. His successful reduction has prompted us to disclose our recent results in the same area. We herein provide a diastereoselective synthesis and resolution of (±)-*cis,cis*-spiro[4.4]nonane-1,6-diol (**2**). In addition the relative stereochemistry of is confirmed to be *cis,cis* from an x-ray crystal structure of the bis-(p-nitrobenzoate) derivative.

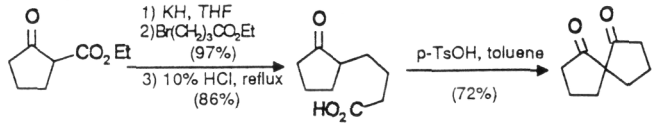


1 **2** (cis,cis) **3** (cis,trans) **4** (trans,trans)

Although previous syntheses of dione **1**[6-8] and diol **2**[7-9] have been reported, they have been low yielding and/or have produced a mixture of diastereomeric diols (**2-4**). In addition, the resolution of dione **1** has been tedious since the chiral diastereomeric oxamohydrazides do not separate on a silica gel column and require two to three careful crystallization's to obtain the oxamohydrazide optically pure.[9] Microbial reduction of optically pure dione **1** provided diastereomeric mixtures of diols **3** and **4**, however, diol **2** was not formed.[10]

Our synthetic route involved the treating the anion of ethyl 2-oxocyclopentanecarboxylate (**5**), formed by the addition of 1.1 equivalents of potassium hydride in THF,[11] with ethyl 4-bromobutyrate provided the expected alkylated product (97%, Scheme 1). This diester was hydrolyzed and decarboxylated by refluxing in 10% HCl for 12 hours to provide acid **6** in 86% yield.[12,13] Gerlach *et al*[8] has reported that dione **1** can be prepared in 81% yield by treating acid **6** with polyphosphoric acid in acetic acid. In our hands dione **1** was

consistently produced in only 52% yield. The cyclization was effected by treating acid **6** with p-toluenesulphonic acid (0.5 equiv.) in refluxing toluene (azeotropic removal of the water) to provide racemic dione **1** (72%).[14]



Scheme 1

Previous reductions of dione **1** with LAH or Red-Al® have provided diastereomeric mixtures of diols **2-4**, which have proven to be difficult to separate.[7,9] Treating dione **1** with 3 equivalents of lithium *tert*-butyldiisobutylaluminium hydride in THF at -78°C , however, provided (±)-*cis,cis*-diol **2** in 85% yield; *cis,trans*-diol (**3**) and *trans,trans*-diol (**4**) were not detected by ^{1}H NMR. An X-ray crystal structure[15] was obtained on the bis-(p-nitrobenzoate) derivative of diol **2** (Figure 1), since previous stereochemical assignments of diols **2-4** were made by chemical and kinetic correlation's only.[7-10] The *cis,cis* relationship of the alcohol's is clearly evident from the X-ray crystal structure. Thus, (±)-*cis,cis*-diol **2** was stereoselectively synthesized in four steps in 51% overall yield from ethyl 2-oxocyclopentanecarboxylate (**5**).

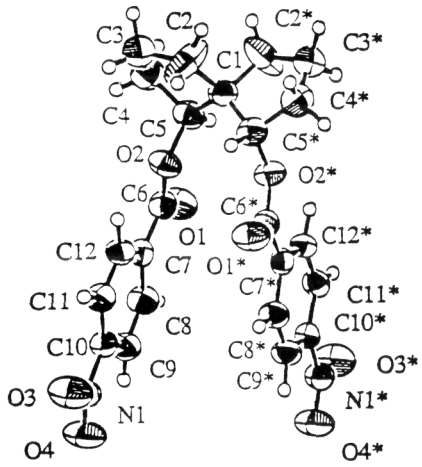
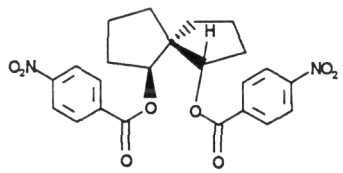
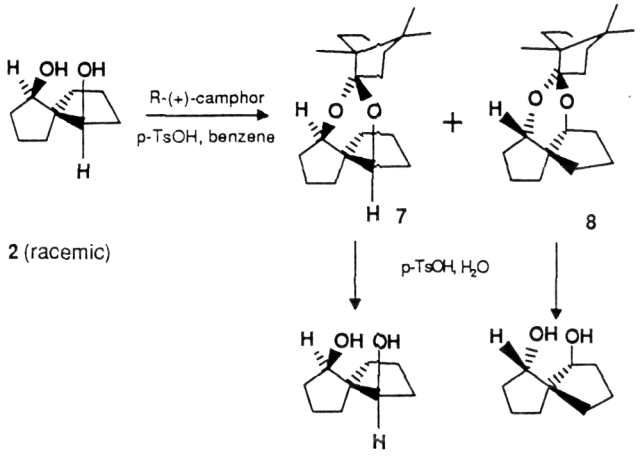


Figure 1



Bis-(p-nitrobenzoate) of Diol 2

Gerlach[8] has reported that the *trans,trans*-diol **4** can be resolved by a) preparing the diastereomeric bisesters of diol **4** from (-)-camphanoic acid, and b) separating the diasteriomers on a column of silica gel. Diol **2** was conveniently resolved by preparing diastereomeric cyclic ketals of (1R)-(+)-camphor. Thus, racemic diol **2**, (1R)-(+)-camphor (3 equiv.), and p-toluenesulphonic acid (0.02 equiv.) were refluxed in benzene (93 mL/g diol **2**) with azeotropic removal of water. Standard workup[16] provided two ketals **7** and **8** (Scheme 2),[17a] which were easily separated on a column of silica gel (neat hexane, R_f 0.36 and 0.19, total yield = 87%). The ketals **7** or **8** were readily hydrolyzed by heating in a mixture of methylene chloride:water (40:1) with p-toluenesulphonic acid (0.3 equiv.) for three hours to produce (-)-1R,5R,6R-diol **9** and (+)-1S,5S,6S-diol **10** respectively (90%, Scheme 2).[17b,18,19]



Scheme 2 **9** (-)-1*R*,5*R*,6*R* **10** (+)-1*S*,5*S*,6*S*

To summarize, we have developed a short, stereoselective synthesis of racemic *cis,cis*-diol **2**, which can be resolved by the preparation of diastereomeric ketals of (1R)-(+)-camphor to produce a 40% yield of resolved *cis,cis*-diols **9** and **10**. In addition, the relative stereochemistry of *cis,cis*-diol **2** was confirmed by an X-ray structure of the bis-(p-nitrobenzoate) derivative. Application of diols **9** and **10** in asymmetric transformations will be the subject of further communications.[22]

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada, The Merck Frosst Centre for Therapeutic Research (Pointe-Claire, Quebec, Canada), and the University of Calgary Research Board for financial support.

References and Notes

(1) For recent reviews, see: a) Rossiter, B.E.; Swingle, N.M. *Chem. Rev.* **1992**, *92*, 771. b) Duthaler, R.O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807. c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. d) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. e) Davis, F.A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. f) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935. g) Chan, T.H.; Wang, D. *Chem. Rev.* **1992**, *92*, 995. h) Kagan, H.B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. i) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(2) Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581.

(3) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis*, **1992**, 503. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(4) Seebach, D.; Plattner, D.A.; Beck, A.K.; Wang, Y.M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta.* **1992**, *75*, 2171. Duthaler, R.O. Hafner, A.; Riediker, M. *Pure Appl. Chem.* **1990**, *62*, 631. Narasaka, K. *Synthesis*, **1991**, 1.

(5) Srivastava, N.; Mital, A.; Kumar, A. *J.C.S., Chem. Commun.* **1992**, 493.

(6) a) Carruthers, W.; Orridge, A. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2411.

(7) a) Cram, D.J.; Steinberg, H. *J. Am. Chem. Soc.* **1954**, *76*, 2753. b) Hardegger, E.; Maeder, E.; Semarne, H.M.; Cram, D.J. *J. Am. Chem. Soc.* **1959**, *81*, 2729.

(8) a) Gerlach, H.; *Helv. Chim. Acta.* **1968**, *51*, 1587. b) Gerlach, H.; Muller, W. *Helv. Chim. Acta.* **1972**, *55*, 2279.

(9) a) Harada, N.; Ochiai, N.; Takada, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1977**, 495. b) Harada, N.; Ai, T.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 232.

(10) a) Nakazaki, M.; Chikamatsu, H.; Asao, M. *J. Org. Chem.* **1981**, *46*, 1147. b) Nakazaki, M.; Chikamatsu, H.; Nishino, M.; Murakami, H. *J. Org. Chem.* **1981**, *46*, 1151.

(11) The use of sodium hydride provided the alkylated product in poor yields ranging from 40-75%. Better yields were obtained with potassium hydride, see: Piers, E.; Friesen, R.W.; Keay, B.A. *Tetrahedron*, **1991**, *47*, 4555.

(12) Bachmann, W.E.; Struve, W.S. *J. Am. Chem. Soc.* **1941**, *63*, 2589.

(13) The synthesis of acid **6** can be performed in one pot in 80% yield without the isolation of the alkylated product.

(14) We have found p-toluenesulphonic acid in toluene more effective than naphthalene-2-sulphonic acid in xylene (reported by Carruthers, ref. 6) for the preparation of dione **1**.

(15) Crystal Data: empirical formula $C_{23}H_{22}N_2O_8$ (454.44), space group Pccn (#56), a = 7.112(2) Å, b = 13.545(2) Å, c = 22.640(2) Å, V = 2181.0(10) Å^3, Z = 4, d = 1.38 g/cm^3; Mo-K_α radiation (23°C); total of 2261 reflections in the range $0 < 2\theta < 50°$, of which 941 were used ($I>3.00\sigma(I)$) in the structure solution; R = 0.042 and Rw = 0.030.

(16) Standard Workup: Cool the mixture to room temperature and add solid anhydrous potassium carbonate. After stirring 5 minutes, the mixture was filtered and the benzene removed to leave an oil.

(17) a) Ketal **7**: mp 34-36°C, bp 84-90°C (0.06 mm Hg), $[\alpha_o]_D^{21}$ = +4.3 (c 0.18, 0.1 dm, CH_2Cl_2). Ketal **8**: bp 81-88°C (0.06 mm Hg), $[\alpha_o]_D^{21}$ = -18.1 (c 0.17, 0.1 dm, CH_2Cl_2). b) Diol **9**: bp 70-78°C (0.06 mm Hg), $[\alpha_o]_D^{23}$ = -101.4 (c 0.11, 0.1 dm, abs. EtOH). Diol **10**: bp 68-76°C (0.05 mm Hg), $[\alpha_o]_D^{23}$ = +97.1 (0.09, 0.1 dm, abs. EtOH). The e.e. of diols **9** and **10** was determined to be 100% by using the chiral shift reagent Pra-OPT® with both the racemic mixture (diol **2**) and resolved diols.

(18) An $[\alpha_o]_D^{20}$ = -99.6 has been calculated from a scalemic mixture containing an e.e. of 26% in favour of diol **9**, see: Kabuto, K.; Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* **1984**, *25*, 5801.

(19) The absolute stereochemistry of dione **1** or diols **2-4** have been empirically determined by Horeau's method,[8] MTPA esters with achiral lanthanide shift reagents,[18] and chemical correlation's.[20] These assignments were later supported by employing the exciton chirality method with theoretical basis.[9,18,21]

(20) a) Falk, H.; Frostle, W.; Hofer, O.; Schlogl, K. *Monatsch. Chem.* **1974**, *105*, 598. b) Falk, H.; Frostle, W.; Schlogl, K. *Monatsch Chem.* **1974**, *105*, 574.

(21) a) Kuritani, H. Iwata, F.; Sumiyoshi, M.; Shingu, K. *J. Chem. Soc., Chem. Commun.* **1977**, 542. b) Lightner, D.A.; Christiansen G.D.; Melquist, J.L. *Tetrahedron Lett.* **1972**, 2045.

(22) All compounds provided analytical and/or spectroscopic data consistent with their structures.