Synthesis of Enantiomerically Pure Diols and Diketones from Norbornadiene

Chong-lin Cai, Chun-Gu Xia*

State Key Laboratory of Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, and Graduate School of the Chinese Academy of Sciences, Lanzhou 730000, P. R. of China
Fax +86(931)8277088; E-mail: cgxia@ns.lzb.ac.cn
Received 9 December 2005; revised 6 February 2006

Abstract: The preparation of (1R,4R)-bicyclo[2.2.1]heptane-2,5-dione from norbornadiene with >99% ee is described. This compound was used to make the synthetically useful (1R,2R,4R,5R)-exo,exo-2,5-diphenylbicyclo[2.2.1]heptane-endo,endo-2,5-diol and (1R,2R,4R,5R)-endo,endo-bicyclo[2.2.1]heptane-2,5-diol, which may prove to be valuable building blocks for novel ligand synthesis.

Key words: norbornadiene, stereoselective reduction, chiral diols

Norbornadiene is inexpensive and possesses some useful stereochemical features, such as C2 symmetry and a rigid hydrocarbon backbone, that can be used in the design of chiral ligands. In 1992, chiral norbornadiol 4 was synthesized1 and, in recent years, a number of novel chiral ligands have been prepared from norbornadiene that have generated excellent results in some asymmetric reactions.2,3 The chiral dione 5, prepared from norbornadiene, has also been used to synthesize some important compounds.4 These encouraging results prompted us to synthesize more derivatives of norbornadiene with the aim of developing novel chiral ligands.

In this article, we describe the preparation of novel chiral diols 8 and 9. As shown in Scheme 1, norbornadiene was hydrosilylated with trichlorosilane in the presence of a palladium catalyst coordinated with MOPS5 ligand,1,2,6 then converted into the methylsilicate 3 by treatment with methanol and triethylamine. In the oxidation step (from 3 to 4), a yield of 57% was achieved through the use of CH3COOOH as oxidant and the diol 4 was obtained with an enantiomeric excess of 99%. Moreover the reaction proceeded smoothly and quickly under these conditions, with the milky polysiloxanes7 initially formed, dissolving within four hours to give a transparent liquid. As shown in Scheme 2, the novel chiral diol 8, with >99% ee, could be prepared from dione 5, which was obtained through the Swern oxidation of 4. Our initial synthetic approach toward diol 9 started from dione 5, which we intend to reduce with NaBH4 in an endo-selective fashion directly. Unfortunately, the reduction product proved to be the mixture of two isomers 9 and 10 with the predominant diol being 9.8,9 The pure ester 11, prepared through acetylation of this mixture, could be isolated, however, a large silica gel column (1 g mixture/600 g silica gel, acetate–petroleum ether, 1:10) was required in order to achieve the necessary purity. Subsequent hydrolysis of 11 gave the diol 9 in low overall yield.

Because of the difficulties associated with isolating the ester 11, we developed an alternative route to the target diol 9. As shown in Scheme 3, through NaBH4 reduction, we were able to prepare compound 13, which GC-MS analyses showed to contain only traces of 14, from the monoprotected diketone 12. Subsequent BH3·THF-mediated reduction10 of 13 at −78 °C gave almost exclusively diol 9, containing only traces of 10. Although this methodology successfully led to the target diol 9, its long synthetic route was still deemed unsatisfactory. We thus tried a variety of reducing agents in order to prepare pure diol 9 directly from dione 5. As shown in Table 1, Li(t-BuO)3AlH (entry 5) could only partially reduce one keto of the dione to produce a mixture of 13 and 14. Using LiAlH4 and LiAl(OCH3)3 (entries 3 and 4), the stereoselectivity of the reduction was lower than that with NaBH4. Gratifyingly, BH3·THF-mediated reduction (entries 6 and 7) resulted in the clean formation of 9, containing less than 7% of diol...
after stirring at –78 °C for five hours. A single recrystallization from diethyl ether gave pure 9 with a yield of 72%.

In summary, we have developed a convenient route to (1R,2S,4R,5S)-exo,exo-bicyclo[2,2,1]heptane-2,5-diol 4 from norbornadiene with enantiomeric excesses exceeding 99%. Starting from the dione 5, we have prepared the novel diols (1R,2R,4R,5R)-exo,exo-2,5-diphenylbicyclo[2,2,1]heptane-endo,endo-2,5-diol 8 and (1R,2R,4R,5R)-endo,endo-bicyclo[2,2,1]heptane-2,5-diol 9. The two chiral diols have $C_2$ symmetry and a rigid hydrocarbon backbone and thus constitute promising building blocks with which to prepare novel chiral ligands.11–15

Unless otherwise noted, all starting materials and solvents were obtained from commercial suppliers and used without purification. THF was distilled over Na and LiAlH$_4$. CH$_2$Cl$_2$ and DMSO were distilled over CaH. Norbornadiene and oxalyl chloride were distilled immediately prior to use. MOPS was prepared according to the reported procedures,5 and LiAl(OME)$_3$H and LiAl(t-BuO)$_3$ were prepared according to reported methods.16,17 Visualization of TLC-spots was effected by exposure to iodine or to 5% sulfuric acid in EtOH. MS spectra was recorded on a HP-5928A MS. 1H NMR and

Table 1 Reducation of Dione 5 with Different Reducing Agents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Agent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Total yield (%)</th>
<th>purity (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH$_4$·NiCl$_2$ b</td>
<td>3</td>
<td>25</td>
<td>91</td>
<td>82.5</td>
</tr>
<tr>
<td>2</td>
<td>NaBH$_4$·CeCl$_3$ b</td>
<td>3</td>
<td>25</td>
<td>89</td>
<td>82.1</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH$_4$ b</td>
<td>3</td>
<td>25</td>
<td>88</td>
<td>61.1</td>
</tr>
<tr>
<td>4</td>
<td>LiAl(OMe)$_3$H$_2$ c</td>
<td>3</td>
<td>25</td>
<td>81</td>
<td>72.6</td>
</tr>
<tr>
<td>5</td>
<td>LiAl(t-BuO)$_3$H b</td>
<td>170</td>
<td>25</td>
<td>47</td>
<td>81.3 d</td>
</tr>
<tr>
<td>6</td>
<td>BH$_3$·THF e</td>
<td>1</td>
<td>0</td>
<td>100</td>
<td>83.4</td>
</tr>
<tr>
<td>7</td>
<td>BH$_3$·THF f</td>
<td>5</td>
<td>–78</td>
<td>100</td>
<td>93.2</td>
</tr>
</tbody>
</table>

a The content of compound 9 in the mixture of 9 and 10, quantified by GC-MS analysis of the acetylated diol mixture (excess acetyl chloride).

b Dione 5 (62 mg, 0.5 mmol) was dissolved in a solution of either NiCl$_2$·6H$_2$O or CeCl$_3$·7H$_2$O (0.4 M in MeOH, 2.5 mL) and NaBH$_4$ (1 mmol) was slowly added with stirring, the mixture was allowed to react for 10 min, then hydrolyzed and extracted with THF.

c Dione 5 (0.25 M) was added to the hydride at 0 °C in THF (ratio H$_2$/dione, 6:1) and the reaction was quenched with H$_2$O after the required time.

d Under these conditions, a mixture of 13 and 14 was obtained. The purity is expressed as the content of compound 13 in the mixture.

e BH$_3$·THF (0.5 M) was added slowly to the dione 5 in THF below the temperature indicated, the reaction was quenched with H$_2$O after the indicated time.
A solution of oxalyl chloride (1.0 mL, 11 mmol) in \( \text{CH}_2\text{Cl}_2 \) (25 mL) was placed in a double-jacketed 100 mL Schlenk flask under \( \text{N}_2 \) gas. Norbornadiene (10 mL, 97.6 mmol) was slowly added at \(-15^\circ\text{C}\) and stirred for 10 min, followed by the slow addition of HSiCl3 (24 mL, 237 mmol). The reaction was stirred at \(-5^\circ\text{C}\) for 3 d then excess silane was removed under reduced pressure at \(40^\circ\text{C}\). The yellowish solid obtained was dissolved in \( \text{THF} \) (30 mL) and added to a solution of \( \text{Et}_2\text{N} \) (167 mL) in \( \text{MeOH} \) (150 mL) held below \(0^\circ\text{C}\) and the reaction was stirred for 30 min. The solvent was then removed under reduced pressure and the residue was poured into \( \text{H}_2\text{O} \) (50 mL) and extracted with \( \text{Et}_2\text{O} \) (4 \( \times \) 20 mL). The organic phase was washed with HCl (2\%, 2 \( \times \) 10 mL) then stirred. \( \text{NaHCO}_3 \) (2 \( \times \) 10 mL) and dried with MgSO4. GC-MS analyses showed that the MW of the predominant product was 336, with only traces of other isomers being detected. Removal of the solvent under reduced pressure gave the crude compound.

The prepared oxidant was added below \(-0^\circ\text{C}\) to a mixture of \( \text{BH}_3\cdot\text{THF} \) (1 M, 4 mL) below \(-78^\circ\text{C}\) and the reaction temperature was allowed to rise to r.t. The mixture was dried with MgSO4 and K2CO3, filtered, and the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography (Et2O–MeOH, 13:1).

Yield: 363.4 mg (57\%); white crystals; mp 138–140 \( ^\circ\text{C} \); \([\alpha]_\text{D}^{20} +4.3 \) (c \(1.00\), CHCl3).

\( ^1\text{H} \) NMR (DMSO): \( \delta = 2.95 \) (m, 2 H, bridgehead), 2.35 (m, 2 H, bridge), 2.14 (t, 2 H, 3 and 6 exo), 2.08 (d, 2 H, 3 and 6 endo).

\( ^13\text{C} \) NMR (DMSO): \( \delta = 121.34 \) (CO), 48.52 (bridgehead), 38.8 (CH3), 36.3 (bridge).

(1R,2R,4S,5S)-exo,exo-Bicyclo[2.2.1]heptane-2,5-diol (4) A 50 mL three-neck round-bottom flask equipped with magnetic stirrer and thermometer was charged with dine 5 (400 mg, 3.2 mmol) in THF (30 mL). To the stirred solution was slowly added BH3·THF (0.5 M, 8 mL, 4 mmol) solution [made by diluting BH3·THF (1 M, 4 mL) with THF (4 mL)] below \(-78^\circ\text{C}\) and the reaction mixture was stirred at \(-78^\circ\text{C}\) for 5 h. The reaction was then quenched through the addition of \( \text{H}_2\text{O} \) (0.7 mL) and stirred for a further 20 min at \(-78^\circ\text{C}\) before allowing the reaction temperature to rise to r.t. The mixture was dried with MgSO4 and K2CO3, filtered, and the crude product was eluted through small quantities of silica gel (2 g, EtO–EtOH, 10:1) to remove traces of inorganic impurities, to give white crystals (413 mg, 100\%) that migrated as one spot by TLC and one peak by GC-MS but did not correspond to the diol 4. The diol product mixture of 9 and 10 was acetylated with excess acetyl chloride and pyridine, and the ester products thus obtained were analyzed by GC-MS. Two peaks were visible, indicating the presence of two esters, of which one occupied 93.2\% of the two-ester mixture. Because of the stereoselectivity in the reaction, we predicted that the predominant diol should be 9 (the work showed in Scheme 3 and the data quoted subsequently confirmed this). The diol product was purified through a single recrystallization from \( \text{Et}_2\text{O} \).

Yield: 288 mg (72\%); mp 129–130 \( ^\circ\text{C} \); \([\alpha]_\text{D}^{20} +7 \) (c \(1.00\), MeOH).

\( ^1\text{H} \) NMR (DMSO): \( \delta = 4.39 \) (s, 2 H, OH), 4.01 (s, 2 H, C2 and C5), 1.93 (s, 2 H, bridgehead), 1.48 (d, 4 H, exo, endo of C3 and C5). 1.25 (s, 2 H, bridge).

HRMS (EI): \( m/z \) [M – H2O]1(calcd for C7H12O2: 110.73; found: 110.73).

(1R,2R,4R,5R)-exo,exo,exo,exo-Diphenylbicyclo[2.2.1]heptane-endo,endo,endo,endo-5-diol (8) A 100 mL, three-neck round-bottom flask equipped with magnetic stirrer and thermometer was charged with dine 5 (100 mg, 0.806 mmol) in THF (40 mL). PhMgBr (2.5 M, 1 mL, 2.42 mmol) added to the stirred solution below \(0^\circ\text{C}\) and the mixture was stirred at r.t. for 3 h before sat. \( \text{NH}_4\text{Cl} \) (40 mL) was added. The mixture was stirred for 30 min, then the aqueous layer was extracted with \( \text{Et}_2\text{O} \) (4 \( \times \) 15 mL). The combined organic layers were dried (MgSO4) and the solvent was removed under reduced pressure to give the crude product that was purified by column chromatography (hexane-EtO, 2:1).

Yield: 124 mg (55\%); white crystals; mp 129–130 \( ^\circ\text{C} \); \([\alpha]_\text{D}^{20} +34 \) (c \(1.00\), MeOH); HPLC analyses indicated 99\% ee (chiralcel OD-H, 0.5 mL/min, hexane–i-PrOH, 60:40).

\( ^1\text{H} \) NMR (DMSO): \( \delta = 7.24–7.57 \) (m, 10 H, Ph-H), 2.71 (m, 4 H, 2 \( \times \) OH and 2 \( \times \) bridgehead), 2.44 (d, 2 H, 3 and 6 endo), 2.20 (d, 2 H, 3 and 6 exo), 1.76 (s, 2 H, bridge).

\( ^13\text{C} \) NMR (DMSO): \( \delta = 128.37 \) (m–Ph), 79.17 (C2 and C4), 48.91 (bridgehead), 41.79 (C3 and C6), 40.14 (bridge).

EIMS: \( m/z \) = 280 \( [M]^+ \).
Acknowledgment

The study was financially supported by the Natural Science Foundation of China (No. 20402017).

References