SHORT COMMUNICATION

Formation and Structural Analysis of Novel Dibornyl Ethers


Department of Chemistry, Rhodes University, Grahamstown, 6140, Republic of South Africa.

* To whom correspondence should be addressed; email: P.Kaye@ru.ac.za

Received 24 January 2002; Revised and Accepted 20 March 2002

Abstract

One- and two-dimensional NMR spectroscopy has been used to establish the regio- and stereochemistry of novel dibornyl ethers, obtained by acid-catalysed condensation of camphor-derived α-hydroxybornanones.

Keywords Dibornyl ethers; structure analysis; camphor derivatives.

The results of some of our previous studies on the use of camphor-derived chiral auxiliaries in asymmetric synthesis\(^1,^2\) indicated the desirability of increasing the steric bulk of the "blocking group" in these systems. To this end, various methods of preparing the chiral auxiliary \(3\) by the monoketalisation of camphorquinone \(1\) (Scheme 1) were explored, but without success since the diketal is formed exclusively.\(^3\) In an attempt to obtain the 3-hydroxy analogue, 3-exo-hydroxycamphor \(7\) (prepared from camphorquinone \(1\) by either of the two pathways shown in Scheme 1) was heated with catechol in the presence of \(p\)-toluenesulfonic acid to afford a crystalline compound ("dimer I"), shown by NMR spectroscopy to contain six methyl groups and twenty different carbon atoms. In another
approach, designed to exploit the greater reactivity of the 3-carbonyl group, 2-exo-hydroxy-3-bornanone 8 was reacted similarly to afford an isomeric product ("dimer II").

![Diagram of chemical reactions]

**Scheme 1** Reagents: i, HOCH₂CH₂OH, TsOH; ii, H₃O⁺; iii, NaBH₄, MeOH; iv, H₂, Raney Ni, EtOH; v, TsOH, C₆H₆.

The ¹H NMR spectrum for each of the dimeric products revealed six well-resolved methyl singlets, the corresponding six methyl carbons being confirmed by the DEPT and ¹³C NMR spectra. The presence of two different carbonyl carbons and the apparent doubling of the typical "camphor" ¹H- and ¹³C NMR signals (see Table 1) clearly suggested formation of dimeric products which lack C₂ symmetry. High-resolution MS analysis indicated a common molecular formula (C₂₀H₃₀O₃) consistent, in each case, with the condensation of two α-hydroxybornanone units to afford dimeric ethers. Banks et al.⁵ have identified the 2-endo-hydroxyepicamphor dimer, first reported by Manasse⁶ in 1902, as a bridged bis(methyl ketal). Rautenstrauch et al.⁷ characterised two pinacols, obtained by alkali metal–ammonia reduction of (+)-[3,3-D₂]camphor, as the endo,exo and exo,exo isomers. However, in a subsequent study, Pradhan et al.⁸ revised one of these assignments, and reported the formation of endo,exo and endo,endo pinacols in which the monoterpenoid units were linked by C(2)–C(2') bonds. Bonnat et al.⁹ have recently reported the synthesis of various C–C-linked bithiocamphor derivatives from thiocamphor, and McNulty et al.¹⁰ have described the stereoselective, oxidative dimerisation of (+)-camphor to the 3-exo,3'-exo C–C-linked bicamphor. To our knowledge, however, the formation of analogous oxygen-linked dimers (ethers) is unprecedented.
Table 1 400 MHz $^1$H and 100 MHz $^{13}$C NMR spectroscopic data$^a$ for the dibornyl ethers 9 and 10 in CDCl$_3$.

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>9 (Dimer I)</th>
<th>10 (Dimer II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-, 8', 9'-, 9'-Me, 10-, 10'-Me</td>
<td>0.86, 0.88, 0.89, 0.91, 0.92, 1.00 (18H, 6 x s)</td>
<td>0.82, 0.82, 0.86, 0.95, 0.96, 0.97 (18H, 6 x s)</td>
</tr>
<tr>
<td>5-, 5', 6-, 6'-CH$_2$</td>
<td>1.30–1.94 (8H, m)$^b$</td>
<td>1.36–1.89 (8H, m)$^b$</td>
</tr>
<tr>
<td>4-H, 4'-H</td>
<td>2.12, 2.15 (2 x d)</td>
<td>2.05 (1H, d), 2.31(1H,t)</td>
</tr>
<tr>
<td>2'-H, 3-H</td>
<td>3.95, 3.99 (2H, 2 x s)</td>
<td>3.81 (1H, s, 2-H), 4.25 (1H, d, 3-H)</td>
</tr>
<tr>
<td>C-10, C-10'</td>
<td>8.9, 13.0</td>
<td>9.3, 10.5</td>
</tr>
<tr>
<td>C-9, C-9'</td>
<td>17.7, 19.4</td>
<td>18.5, 18.7</td>
</tr>
<tr>
<td>C-8, C-8'</td>
<td>19.7, 21.1</td>
<td>18.6, 19.9</td>
</tr>
<tr>
<td>C-7, C-7'</td>
<td>42.7, 46.3</td>
<td>42.6, 46.1</td>
</tr>
<tr>
<td>C-6, C-6'</td>
<td>24.0, 24.8</td>
<td>20.7, 21.3</td>
</tr>
<tr>
<td>C-5, C-5'</td>
<td>25.8, 28.9</td>
<td>31.8, 33.7</td>
</tr>
<tr>
<td>C-4, C-4'</td>
<td>49.2, 60.0</td>
<td>48.3, 59.2</td>
</tr>
<tr>
<td>C-3, C-2'</td>
<td>84.2, 85.4</td>
<td>217.8, 217.9</td>
</tr>
<tr>
<td>C-2, C-3'</td>
<td>217.2, 218.4</td>
<td>85.6, 81.7</td>
</tr>
<tr>
<td>C-1, C-1'</td>
<td>50.2, 57.3</td>
<td>50.0, 58.4</td>
</tr>
</tbody>
</table>

$^a$ In ppm; the order of citation does not imply signal assignment.

$^b$ Complex of multiplets.

Condensation of two molecules of 3-exo-hydroxycamphor 7 might be expected to afford the 3-exo,3'-endo ether, formation of the 3-exo,3'-exo analogue being precluded both mechanistically (since nucleophilic attack should favour the less hindered endo-face of one unit) and spectroscopically (since both exo,exo and endo,endo ethers should exhibit $C_2$ symmetry and thus give rise to only ten signals in their $^{13}$C NMR spectra). However, careful analysis of the 3-H, 4-H and 4'-H signal multiplicities and the C-1, C-1', C-4 and C-4' chemical shifts permitted identification of the isolated product ("dimer I") as the 2'-endo,3-exo ether 9 (Scheme 2).$^{11}$ The significant chemical shift differences (see Table 1) between the C-1 nuclei [57.3 (C-1) and 50.2 ppm (C-1')], on one hand, and between the C-4 nuclei [49.2 (C-4) and 60.0 ppm (C-4')], on the other, locate the deshielded nuclei (C-1 and C-4') adjacent to the magnetically anisotropic carbonyl group in their respective monomeric units,$^{12}$ thus establishing the C(2')–O–C(3) regiochemistry of the ether link in compound 9. The stereochemistry may be deduced from the relevant $^1$H signal multiplicities. The 3-H nucleus resonates as a singlet at 3.99 ppm, the absence of vicinal coupling implying its endo-orientation and, hence, the presence of a 3-exo ether link. The 4-H nucleus resonates...
as a doublet \( (J \approx 5 \text{ Hz}) \) at ca. 2.1 ppm, reflecting coupling to the 5-exo-H nucleus alone. The absence of vicinal coupling between the 4-H and 3-endo-H or 5-endo-H nuclei is typical of the camphor derivatives that we have studied, and is consistent with torsion angles approaching 80°. Furthermore, it seems reasonable to assume that normal, acid-catalysed etherification would involve nucleophilic attack by one monomeric unit at the less hindered endo-face of the second, resulting in a 2'-endo,3-exo ether linkage for "dimer I", as illustrated in structure 9. This conclusion is supported by NOE interactions, evident in the NOESY spectrum, between the 2'-exo-H nucleus and the 8'- and 10'-methyl nuclei, and between the 3-endo-H nucleus and the 4-H and 5-endo-H nuclei (Figure 1a).

Following similar arguments, "dimer II" may be identified as the 2-exo,3'-endo isomer 10, the determining factors being, once again, the significant chemical shift differences [between the C-1 and C-1' and C-4 and C-4' nuclei (see Table 1)] and the signal multiplicities of the vicinal 3'-and 4'-protons. In this case, however, vicinal coupling \( (J = 5 \text{ Hz}) \) between these protons is apparent and is supported by the 2-D (COSY) data; such coupling implies exo-orientation of the 3'-proton and, hence, a 3'-endo ether link. Further
confirmation of the structure of “dimer II” is provided by NOE interactions between the 2-endo-H nucleus and the 10-methyl and 3'-exo-H nuclei, on one hand, and the 3'-exo-H nucleus and the 8'-methyl and 4'-H nuclei, on the other (Figure 1b).

Figure 1  Selected NOE interactions in (a) “dimer I” 9; and (b) “dimer II” 10.

Formation of the 2'-endo,3-exo ether link in compound 9 ("dimer I") suggests isomerisation of some of the 3-exo-hydroxycamphor precursor 7 to the 2-exo-hydroxy analogue 8, which could well occur by the equilibrium shown in Scheme 3. Formation of compound 10 ("dimer II") requires similar isomerisation of the 2-exo-hydroxy precursor 8. The realisation that either precursor (7 or 8) might be expected to yield both "dimer I" and "dimer II" prompted a careful examination of the reaction mixtures. This led to the discovery that 3-exo-hydroxycamphor 7 indeed affords both "dimer I" (9; 47%) and "dimer II" (10; 27%). A third dimer, identified as the 3-exo,3'-endo isomer 11, has also been obtained from the ketol 7 as a minor component, but subsequent attempts to isolate this elusive compound have proved unsuccessful. The 2-exo-hydroxy precursor 8, however, appears to afford "dimer II" (10; 90%) exclusively. In an earlier attempt to prepare an iminolactone derivative, reaction of 3-hydroxycamphor 7 with glycine in the presence of PTSA afforded "dimer I" in 92% yield. The apparent failure of either precursor to produce the 2-exo,2'-endo analogue may be rationalised in terms of steric constraints at C-2 in the bornane systems.

While acid-catalysed etherification could account for the observed dimerisation, an alternative (or parallel) mechanistic pathway for the formation of "dimer I" 9 from ketol 7 could be envisaged, involving the hemiacetal and enol intermediates, 14 and 15 respectively (Scheme 3). A similar sequence could account for the formation of "dimer II"
10 from ketol 8. However, formation of "dimer II" from ketol 7 would still require some isomerisation of the precursor, and firm conclusions about the mechanism must await the results of a detailed kinetic-mechanistic study.

![Scheme 3](image)

**Experimental**

NMR spectra were obtained from CDCl₃ solutions on a Bruker AMX400 NMR spectrometer and are referenced using the solvent signals (δ₋H 7.25 and δ₋C 77.0 ppm). NOE interactions were established from NOESY spectra. High-resolution data were obtained on a Kratos double-focussing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit). The known 3-hydroxycamphor 7 was obtained either by direct, selective Raney nickel reduction of camphorquinone 1, or via the monoacetal 6 as indicated in Scheme 1. The preparation of the isomeric ketol 8 has also been reported previously. Computer modelling was effected using the software package HYPERCHEM.7

**Reaction of 3-hydroxycamphor 7 with p-toluenesulfonic acid**

A mixture of 3-hydroxycamphor 7 (2.00 g, 11.8 mmol) and p-toluenesulfonic acid (0.14 g) in dry benzene (26 ml) was boiled under reflux overnight using a Dean-Stark trap. After cooling, water (20 ml) was added and the resulting mixture was extracted with EtOAc (4 × 20 ml). The combined organic extracts were dried (anhyd.
MgSO₄), and the solvents were evaporated in vacuo. Flash chromatography of the residue [elution with hexane–EtOAc (9:1)] afforded the following products:

(a) the 2'-endo-3-exo-dibornyl ether 9 ("dimer I") (0.88 g, 47%), as colourless crystals, mp 104–109 °C (Found: M⁺, 318.2180. C₂₀H₃₀O₃ requires M, 318.2195);
(b) the 2-exo-3'-endo-dibornyl ether 10 ("dimer II") (0.5 g, 27%),¹⁷ as colourless crystals, mp 98–102 °C (Found: M⁺, 318.2191. C₂₀H₃₀O₃ requires M, 318.2195); and
(c) the 3-exo-3'-endo-dibornyl ether 11 ("dimer III") (0.36g; 19%), as colourless crystals, mp 158–163 °C (Found: M⁺, 318.2181. C₂₀H₃₀O₃ requires M, 318.2195); δH (400 MHz; CDCl₃) 0.85, 0.88, 0.90, 0.91, 0.97 and 1.01 (18H, 6 × s), 1.31 - 1.96 (8H, complex of multiplets), 2.07 (1H, d, 4H), 2.28 (1H, t, 4'-H), 3.51 (1H, s, 3-H) and 4.35 (1H, d, 3'-H); δC (100 MHz; CDCl₃) 9.0, 9.4, 18.7, 19.0, 19.8, 19.9, 21.1, 24.9, 29.1, 31.5, 42.9, 46.6, 47.0, 48.1, 57.4, 58.2, 81.4, 82.1, 215.7 and 217.2.

Acknowledgements
The authors thank the National Research Foundation (NRF) for bursaries (to S.S.R., J.M.M. and W.E.M.) and the Deutscher Akademischer Austauschdienst (DAAD) for a bursary (to J.M.M.), Rhodes University and the NRF for generous financial support and referees for helpful comments.

References and Notes
4 Catechol, although present in the initial reactions, plays no part in the observed transformations and was subsequently excluded.

11 The primed locants designate nuclei of the *endo*-linked moiety.

12 Chemical shifts calculated for comparable nuclei, using the ChemWindow $^{13}$C NMR module, are 58.8 (C-1), 43.5 (C-1'), 38.9 (C-4) and 53.2 ppm (C-4').

13 Torsion angles obtained from an energy minimised computer model of 3-exo-hydroxycamphor 7 were as follows: $\phi$ (4-H, 3-H<sub>endo</sub>) = 81.5°; $\phi$ (4-H, 5-H<sub>endo</sub>) = 75.5°; and $\phi$ (4-H, 5-H<sub>exo</sub>) = 43.4°.


17 The 2-exo,3'-endo-dibornyl ether 10 was also obtained in 90% yield by similar treatment of 2-exo-hydroxy-3-bornanone 8.