P.T. Kaye, A.R. Duggan, J.M. Matjila, W.E. Molema and S.S. Ravindran, *S. Afr. J. Chem*., 2002, **55**, 111-118, <http://journals.sabinet.co.za/sajchem/>, <http://ejour.sabinet.co.za/images/ejour/chem/chem_v55_a10.pdf>.

SHORT COMMUNICATION

Formation and Structural Analysis of Novel Dibornyl Ethers

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Received 24 January 2002; Revised and Accepted 20 March 2002

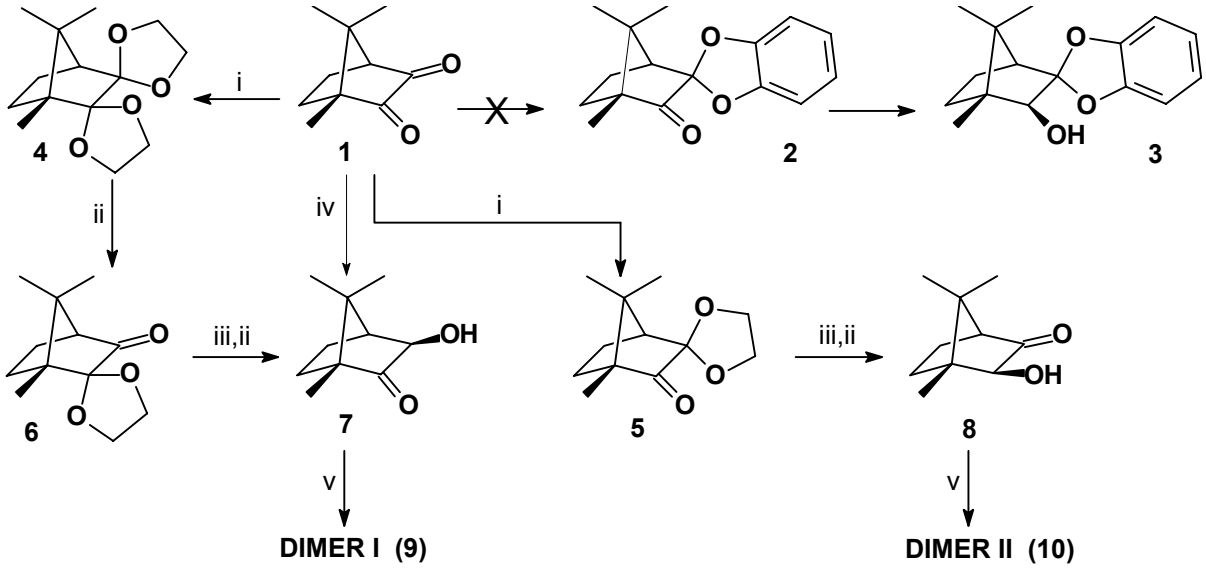
Abstract

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").[4]



Scheme 1 *Reagents:* i, $HOCH_2CH_2OH$, TsOH; ii, H_3O^+; iii, $NaBH_4$, MeOH; iv, H_2, Raney Ni, EtOH; v, TsOH, C_6H_6.

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 ^{13}C NMR spectra. The presence of two different carbonyl carbons and the apparent doubling of the typical "camphor" ^1H- and ^{13}C NMR signals (see Table 1) clearly suggested formation of dimeric products which lack C_2 symmetry. High-resolution MS analysis indicated a common molecular formula ($C_{20}H_{30}O_3$) 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 Manasse[6] in 1902, as a bridged bis(methyl ketal). Rautenstrauch *et al.*[7] characterised two pinacols, obtained by alkali metal–ammonia reduction of (+)-[3,3-D_2]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.

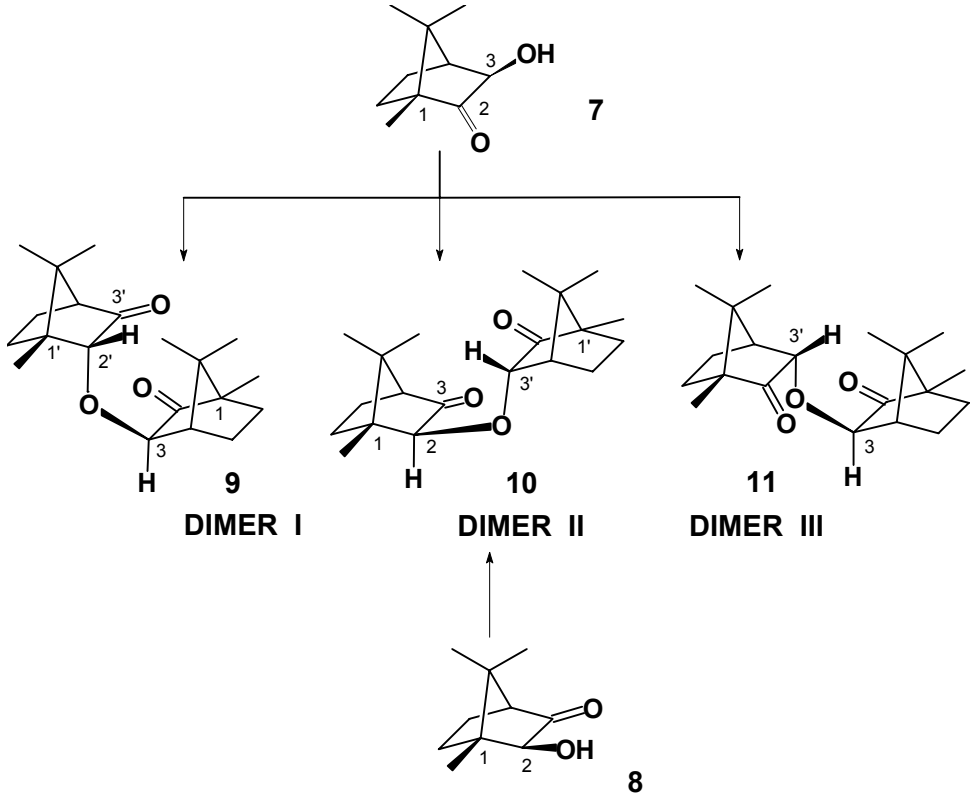
Table 1 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectroscopic data[a] for the dibornyl ethers **9** and **10** in $CDCl_3$.

Nucleus	**9** (Dimer I)	**10** (Dimer II)
8-, 8'-, 9'-, 9'-Me, 10-, 10'-Me	0.86, 0.88, 0.89, 0.91, 0.92, 1.00 (18H, 6 x s)	0.82, 0.82, 0.86, 0.95, 0.96, 0.97 (18H, 6 x s)
5-, 5'-, 6-, 6'-CH_2	1.30–1.94 (8H, m)[b]	1.36–1.89 (8H, m)[b]
4-H, 4'-H	2.12, 2.15 (2 x d)	2.05 (1H, d), 2.31(1H,t)
2'-H, 3-H	3.95, 3.99 (2H, 2 x s)	3.81 (1H, s, 2-H), 4.25 (1H, d, 3-H)
C-10, C-10'	8.9, 13.0	9.3, 10.5
C-9, C-9'	17.7, 19.4	18.5, 18.7
C-8, C-8'	19.7, 21.1	18.6, 19.9
C-7, C-7'	42.7, 46.3	42.6, 46.1
C-6, C-6'	24.0, 24.8	20.7, 21.3
C-5, C-5'	25.8, 28.9	31.8, 33.7
C-4, C-4'	49.2, 60.0	48.3, 59.2
C-3, C-2'	84.2, 85.4	217.8, 217.9
C-2, C-3'	217.2, 218.4	85.6, 81.7
C-1, C-1'	50.2, 57.3	50.0, 58.4

[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* 5 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°.[13] 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).



Scheme 2

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 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).

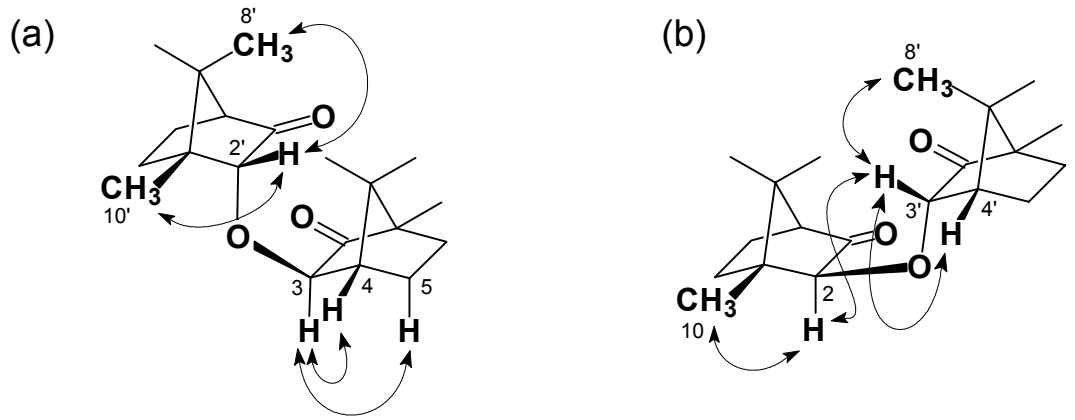
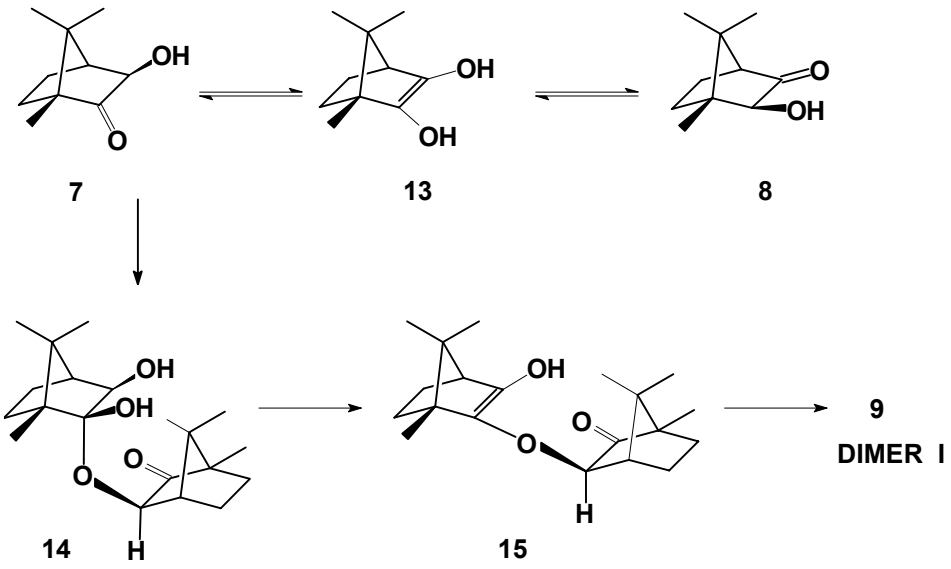


Figure 1 Selected NOE interactions in (a) “dimer I” **9**; and (b) “dimer II” **10**.

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,[14] 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,[3] 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

Experimental

NMR spectra were obtained from $CDCl_3$ 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**[2] was obtained either by direct, selective Raney nickel reduction of camphorquinone **1**,[15] or *via* the monoacetal **6** as indicated in Scheme 1. The preparation of the isomeric ketol **8** has also been reported previously.[16] 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.

$MgSO_4$), 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. $C_{20}H_{30}O_3$ 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. $C_{20}H_{30}O_3$ 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. $C_{20}H_{30}O_3$ requires *M*, 318.2195); δ_H (400 MHz; $CDCl_3$) 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); δ_C (100 MHz; $CDCl_3$) 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.

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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: ϕ (4-H, 3-H_{endo}) = 81.5°; ϕ (4-H, 5-H_{endo}) = 75.5°; and ϕ (4-H, 5-H_{exo}) = 43.4°.

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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**.