Stereoselective Oxidative Dimerization of (1*R*)-Camphor. A Short Synthesis of *exo,exo*′-3,3′-Biisoborneol

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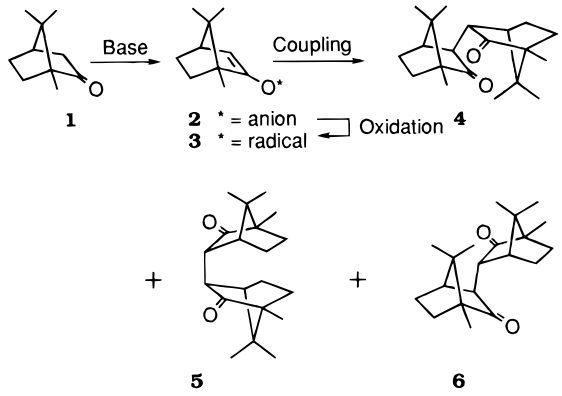
Introduction

The oxidative dimerization of enolates and their derivatives has been exploited for preparing 1,4-diketones and succinic acid derivatives.[1−4] The reaction has aroused considerable mechanistic interest in view of the nature of the electron-transfer effected by different oxidants, such as Cu(II) salts or elemental iodine, and of its application for synthesizing useful intermediates.[5]

Recently, efforts have focused on improving the diastereoselectivity of the carbon−carbon bond forming step.[5,6] Reports[7] that acyclic enolates bearing chiral auxiliaries dimerize with high stereoselectivity imply that chiral cyclic enolates would behave the same way. However, the oxidation of norbornanone and camphor enolates was stated[2] to give the exo,exo′, endo,endo′, and exo,endo′ 3,3′-dimers **4**, **5**, and **6** as a mixture. This last result is surprising since the bornane skeleton normally confers a high degree of asymmetric induction.[8] In the case of (1*R*)-camphor (**1**), the reaction of the enoxy radical **3** arising by oxidation of the enolate anion **2** should be subject to stereoelectronic or steric control. In other words, coupling of **3** with **2** or **3** is expected to give either *exo,exo*′ (**4**) or *endo,endo*′-3,3′-bicamphor (**5**) (Scheme 1). It therefore seems possible that **4**−**6** could have arisen by base-equilibration of the initial kinetic product or by indiscriminate coupling.[9] Consequently, by choosing the appropriate experimental conditions for kinetic control a single dimer should be obtainable.

Scheme 1



Results and Discussion

We now describe how (1*R*)-camphor (**1**) can be oxidatively dimerized to give exclusively the *exo,exo*′-bicamphor **4** and the C_2-symmetric 1,4-diol *exo,exo*′-3,3′-biisoborneol (**9**) by subsequent reduction in situ. In the original procedure,[2] a solution of **2,** prepared from **1** and LDA in THF at 0 °C, was allowed to react for 30 min with a solution of $CuCl_2$ in dimethyl formamide (DMF) at −78 °C. Repetition of this experiment merely confirmed the previous result; all three bicamphors were obtained. We concluded that the lack of selectivity might be due to the overly rapid formation of radical **3** from **2** and that a less polar solvent would retard electron transfer, thereby favoring kinetic control. However, it had already been noticed[2] that coupling was ineffective when THF or toluene was used as cosolvent for $CuCl_2$. Evidently, oxidation had failed owing to the insolubility of $CuCl_2$. Clearly, high solubility of the copper salt in the cosolvent, especially at −78 °C, is essential for success. Accordingly, $Cu(OTf)_2$ was dissolved in toluene at −78 °C together with a little pyridine to ensure solubility. To it was added a solution of the lithium salt of **2**, prepared in toluene at 0 °C. A dramatic change was observed. Coupling was slower, requiring 48 h to consume 60% of the camphor, and more importantly, it was completely stereoselective. A single bicamphor was formed that was subsequently identified as the exo,exo′ 3,3′-isomer **4**.[10] Attempts at isolating **4** revealed a hitherto-unnoticed event. Partial dehydrogenation occurred, presumably by aerial oxidation, giving (*E*)- and (*Z*)-2,2′-dioxo-3,3′-bibornanylidenes (**7** and **8**) as minor products (Scheme 2).[11]

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(9) The photolysis of *exo*- or *endo*-(1*R*)-3-bromocamphor proceeds through the enoxy radical **3** in its singlet excited state to give a mixture of **4**, **5**, and **6** in a ratio of 1:1:2. A solution of KOH in MeOH readily isomerizes **4** to **5** via **6** (Orita, K.; Yorita, K.; Miyazawa, M.; Suginome, H. *Synlett* **1994**, 937−938).

(10) The configuration of **4** follows from its reduction with LAH (see procedure A, Experimental Section).

(11) Bicamphor **4** on treatment with sodium hydride in DMF followed by addition of $K_3[Fe(CN)_6]$ was reported to give only the *E*-isomer **7** (ref 12). For the formation of **7** as a byproduct from bithiocamphor, see ref 13.

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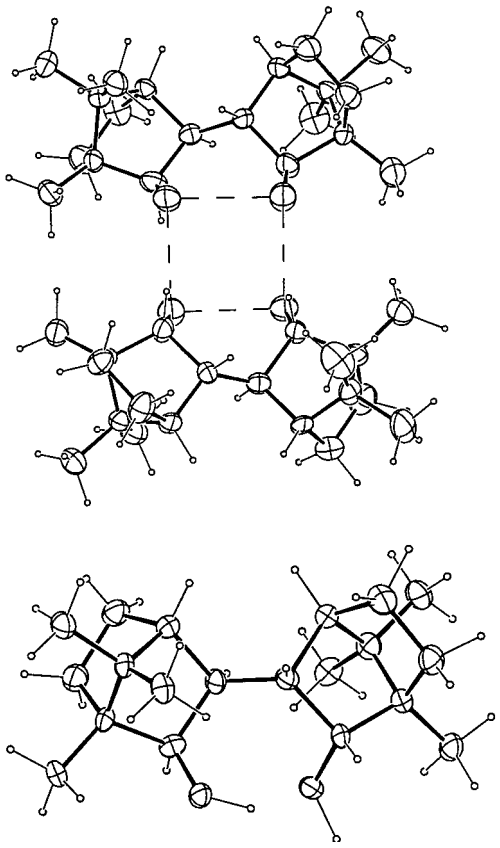
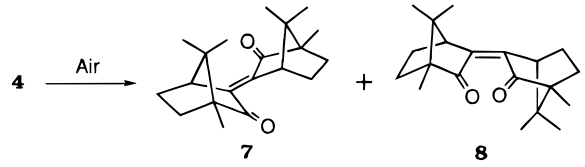
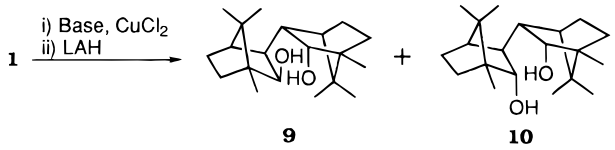


Figure 1. Perspective drawings of the X-ray structures of diols **9** (lower) and **10** (upper).

Scheme 2



Scheme 3



Considering the lability of **4** under the above-described conditions, it was decided to improve the foregoing procedure. The cheaper oxidant, anhydrous $CuCl_2$, was obtained as a homogeneous solution in pyridine by adjunction of tetramethylethylenediamine (TMEDA). Next, the lithium salt of **2** in toluene (Scheme 1) was added at −78 °C. After the coupling stage, the reaction mixture was poured directly into a suspension of lithium aluminum hydride (LAH) in THF. Obviously, **4** was formed as before and subsequently reduced. Instead of a single diol, a second was obtained as well, in yields of 50 and 10%, respectively (Scheme 3). Their structures were determined by X-ray as **9**, the expected *exo,exo*′-2,2′-diol of C_2 symmetry, and **10** the exo,endo′ epimer (Figure 1).

The precise mechanism of coupling remains uncertain. A likely possibility is the combination of enoxy radical **3** either with another molecule of **3** or with camphor enolate **2**. In the latter instance, further oxidation of the resulting radical anion affords **4**.[14] In both cases, bond formation occurs on the exo faces of both molecules in a stereoelectronic fashion. As expected, the reduction of **4** by LAH follows a course similar to that of camphor.[15] Attack by hydride ion occurs mainly on the endo face of the carbonyl group owing to steric hindrance by the 7,7-dimethyl substituents and the exo-3 attachment. The yield of both diols in a pure state (60%) may be regarded as satisfactory since some product sublimes on workup. A little isoborneol is also formed from unreacted camphor but is easily removed on purifying the diols.

Conclusion

In conclusion, we have demonstrated that the kinetically controlled oxidation of camphor enolate is entirely feasible and that dimerization occurs stereoselectively on the exo face to give *exo,exo*-3,3′-bicamphor (**4**). The use of toluene as solvent and $Cu(OTf)_2$ in toluene/pyridine or $CuCl_2$ in pyridine/TMEDA as oxidant is of critical importance in ensuring kinetic control. These results have obvious implications for related intermolecular oxidative enolate dimerizations where stereocontrol has not been achieved so far. We also show that the procedure provides convenient access to the potentially valuable C_2-symmetric 1,4-diol **9** or BIBOL,[16] which has obvious features in common with BINOL[17] and TADDOL.[18] Extensions of the coupling methodology to other chiral ketones of natural origin, such as menthone, and the utilization of BIBOL as a chiral ligand are under investigation.[19]

Experimental Section

General Methods. Melting points are uncorrected. Flash chromatography (FC) was performed with 70−230 mesh silica gel. All solvents were distilled from glass prior to use. Toluene and tetrahydrofuran were distilled from sodium metal/benzophenone, while pyridine was distilled from calcium hydride, all under dry nitrogen. (1*R*)-Camphor was recrystallized from ethanol/water (2:1) and dried over P_2O_5 for not less than 24 h prior to use. Cupric chloride was dried in a oven at 150 °C for 15 min and stored (P_2O_5) until used. All glassware was flame-dried under a stream of Ar before use.

Infrared spectra were recorded as thin films on NaCl. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$, using tetramethylsilane as internal standard. Proton-decoupled ^{13}C spectra were recorded at 75 MHz with $CDCl_3$ (δ 77.7) as internal standard.

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(14) It is possible that dimerization of enoxy radicals **3** is indiscriminate (ref 9). The slow release of **3** may favor its stereoelectronically controlled capture by camphor enolate **2** as the rate-determining step (cf. ref 7a).

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(16) The procedure also provides a one-pot synthesis of **4**, which previously has only been accomplished by a circuitous route from camphor through the intermediacy of (1*R*,1*R*′)-*exo,exo*′-3,3′-bithiocamphor (refs 12 and 13).

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(19) Few methods are presently available for preparing C_2-symmetric 1,4-diols; however, see: P. A. Evans, V. S. Murthy, *J. Org. Chem*. **1998**, *63*, 6768.

(1*R*,1′*R*,2*R*,2′*R*,3*S*,3′*S*,4*R*,4′*R*)-3,3′-Bi(1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol) (BIBOL, 9) and (1*R*,1′*R*,2*R*,2′*S*,3*S*,3′*S*, 4*R*,4′*R*)-3,3′-Bi(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol) (10). Procedure A. Lithium hexamethyldisilazane (1.0 M in THF, 0.68 mL, 0.68 mmol, 1.05 equiv) was added to a solution of (1*R*)-camphor (**1**, 0.1 g, 0.65 mmol) in toluene (2 mL) at 0 °C with stirring for 1.5 h. The resulting enolate solution was cooled to −78 °C and transferred to a solution of $Cu(OTf)_2$ (0.593 g, 1.65 mmol, 2.5 equiv) in toluene (4 mL) containing pyridine (0.64 mL), at −78 °C. After the cooled mixture was stirred for 48 h, lithium aluminum hydride (LAH, 0.50 g, 1.31 mmol, 2.0 equiv) was added with further stirring for 12 h at −78 °C. Excess LAH was quenched by slowly adding concentrated aqueous NH_4Cl at 0 °C. The resulting solution was extracted with Et_2O (4 × 15 mL). The combined organic layers were washed (saturated aqueous NaCl), dried (Na_2SO_4), filtered, and evaporated to give 110 mg of solid. Purification over SiO_2 (hexane−AcOEt 97.5:2.5) afforded **9** (33 mg, 33%), followed by **10** (17 mg, 17%). For spectral and other data, see below.

Procedure B. To a solution of **1** (0.1 g., 0.66 mmol) in dry toluene (1.0 mL) under Ar at 0 °C was added dropwise LDA (0.46 mL of 1.5 M in hexane) with stirring for 1 h. To the resulting solution, cooled to −78 °C, was added a solution of $CuCl_2$ (0.093 g, 0.69 mmol) in dry pyridine (5 mL) and TMEDA (1.0 mL) by cannula under Ar. After the mixture was stirred at −78 °C for 24 h, it was allowed to warm to room temperature. Next, the mixture was transferred by syringe to a previously cooled (−78 °C) suspension of LAH (0.049 g, 1.3 mmol) in dry THF (1.5 mL) and stirred at 0 °C for 24 h. Quenching excess LAH by slowly adding H_2O, dilution with CH_2Cl_2, treatment with aqueous 1 N HCl, drying (Na_2SO_4), filtration, and evaporation in vacuo gave a viscous yellow oil. Chromatographic purification (silica gel, hexane/AcOEt 97.5:2.5) furnished **9** (50.3 mg, 50%) as colorless crystals: mp = 176−178 °C; $[\alpha]^{22}_D$ = +71.1 (*c* = 0.18, MeOH); IR 2883 (m), 2946 (s), 3355 (s,b) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.8 (s, 3H, CH_3), 0.9 (s, 3H, CH_3), 0.95 (m, 2H, CH_2), 1.2 (s, 3H, CH_3), 1.5 (ddd, *J* = 10.4, 10.4, 2.4 Hz, 1H, CH_2), 1.65 (s, 1H, CH), 1.7 (m, 1H, CH_2), 2.1 (dd, *J* = 4.8, 2.2 Hz, 1H, CH), 2.45 (d, *J* = 2.98 Hz, 1H, OH), 3.75 (m, 1H, C*H*OH); ^{13}C NMR δ 83.3, 51.7, 50.1, 49.5, 47.4, 34.3, 30.2, 22.7, 22.2, 12.2; MS *m*/*z* (rel) 306 (1.6), 288 (22.7), 152 (41.9); HREIMS calcd for $C_{20}H_{34}O_2$ 306.2558, found 306.2574. Crystals of **9** suitable for X-ray were obtained by slow recrystallization from AcOEt (see below). Subsequent fractions gave the epimeric alcohol **10** (9.7 mg, 10%) as colorless crystals: mp = 161−163 °C; $[\alpha]^{22}_D$ = +99.2 (*c* = 0.14, $CHCl_3$); IR 2871 (m), 2948 (s), 3336 (s,b); ^1H NMR (300 MHz, $CDCl_3$) δ 0.8 (s, 3H, CH_3,), 0.85 (s, 3H, CH_3,), 0.9 (s, 3H, CH_3), 0.91 (m, 1H, CH), 0.95 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.05 (m, 1H, CH_3), 1.1 (s, 3H, CH_3), 1.2 (m, 2H), 1.5 (m, 2H), 1.6−1.8 (m, 4H), 1.8−2.0 (m, 2H), 3.1 (s, 2H, OH), 3.85 (m, 2H, CHOH); ^{13}C NMR: δ 83.7, 82.3, 55.5, 53.8, 50.0, 49.9, 49.4, 49.3, 47.7, 47.2, 33.7, 31.4, 30.4, 26.5, 22.8, 22.5, 21.9, 20.8, 13.7, 12.2; MS *m*/*z* (rel) 302 (13.4), 288 (22.0), 152 (36.2); HREIMS calcd for $C_{20}H_{34}O_2$ 306.2558, found 306. 2575; HREIMS calcd for $C_{20}H_{32}O$ ($M^+ - H_2O$) = 288.2453, found 288.2451. Crystals of **10** suitable for X-ray were obtained by slow recrystallization from $CHCl_3$ (see below).

Crystal Data for 9: $C_{20}H_{34}O_2$, *M* = 306.5; μ = 0.541 mm^{-1}, *F*(000) = 510, d_x = 1.13 g·cm^{-3}, trigonal, $P3_2$, *Z* = 3, *a* = 11.4149-(3) Å, *c* = 11.9304(5) Å, *V* = 1346.26(8) $Å^3$, crystal from AcOEt solution, colorless prism 0.20 × 0.40 × 0.60 mm. Cell dimensions and intensities measured at 170 K. *R* = 0.049, R_w = 0.048 for 2129 contributing reflections ($|F_o| > 4\sigma(F_o)$). The rotation about the central C(1)−C(1′) bond is precluded by an intramolecular hydrogen bond (O(1)···O(1′) = 2.677(5) Å; O(1)−H(01)···O(1′) = 140(4)°). The molecular packing shows that molecules are associated by hydrogen bonds to form helical chains parallel to the (001) direction (O(1′)···O(1) $1 - y - x$, $1 - x$, $z + 1/3$ = 2.812-(6) Å; O(1′)−H(01′)···(O1) = 152(5)°).

Crystal Data for 10: $C_{20}H_{34}O_2$, *M* = 306.5; μ = 0.50 mm^{-1}, *F*(000) = 680, d_x = 1.12 g·cm^{-3}, monoclinic, $P2_1$, *Z* = 4, *a* = 10.7203(9) Å, *b* = 12.082(1) Å, *c* = 14.304(1) Å, β = 99.900(5)°, *V* = 1825.1(3) $Å^3$, crystal from $CHCl_3$ solution, colorless prism 0.25 × 0.28 × 0.32 mm. Cell dimensions and intensities measured at 200 K. *R* = 0.059, R_w = 0.058 for 3817 contributing reflections ($|F_o| > 4\sigma(F_o)$). Both molecules in the asymmetric unit are similar and are associated in pairs by hydrogen bonds through their hydroxyl groups. Intermolecular hydrogen bonds: O(1a)···O(1b) = 2.779(8) Å, O(2a)···O(2b) = 2.720(7) Å. Intramolecular hydrogen bonds: O(1a)···O(2a) = 2.758(6) Å, O(1b)···O(2b) = 2.739(6) Å.

(*E*)- and (*Z*)-2,2′-Dioxo-3,3′-bibornanylidenes (7 and 8). Diketone **4**, produced by the above-described procedures with omission of the reduction step, was allowed to stand in the air for 24 h. The formation of a 3:1 mixture of **7** and **8** in a 16% yield was spontaneous. Chromatographic purification of the mixture (silica gel, hexane/AcOEt 95:5) afforded first the *E* isomer **7** as a yellow solid: mp = 98−100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (s, 6H), 0.94 (s, 6H), 0.95 (s, 6H), 1.48−1.22 (m, 4H), 1.68 (ddd, *J* = 11.4, 11.4, 3.7 Hz, 2H), 2.15−2.05 (m, 2H), 3.74 (d, *J* = 4.3 Hz, 2H); ^{13}C NMR δ 212.4, 141.2, 58.5, 48.8, 46.5, 30.9, 26.3, 21.2, 18.7, 9.6. Further purification yielded **8** as a yellow solid, which underwent isomerization over several days to an approximately 3:1 mixture of **7** and **8** (as judged by NMR). *Z* Isomer **8**: ^1H NMR δ 0.8 (s, 6H), 0.95 (s, 6H), 0.96 (s, 6H), 1.2−1.5 (m, 4H), 1.6−1.8 (m, 2H), 2.0−2.2 (m, 2H), 2.6 (d, *J* = 4.0 Hz, 2H); ^{13}C NMR δ 203.1, 144.3, 59.1, 51.6, 45.8, 30.2, 26.4, 21.1, 18.8, 9.9.

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Supporting Information Available: Tables of atomic coordinates, displacement parameters, bond lengths, bond angles, dihedral angles, and atomic numbering schemes for **9** and **10**. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, England (Fax: +44-(1223)-336033. E-mail: deposit@ccdc.cam.ac.uk). This material is available free of charge via the Internet at http://pubs.acs.org.

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