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Stereospecific Preparation of Chiral 1,5-Diketone by One-Methylene Incorporated Dimerization Reaction of *d*-Camphor Enolate and Reduction of the 1,5-Diketone

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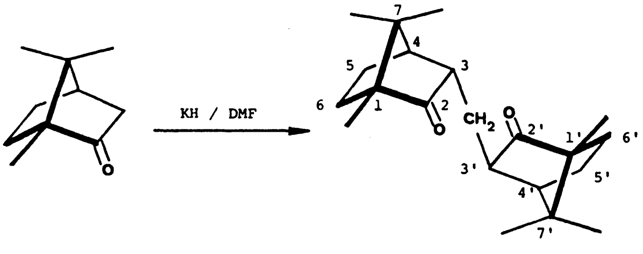
Synopsis. The reaction of *d*-camphor with *N,N*-dimethylformamide (DMF) in the presence of potassium hydride stereoselectively gave bis[(1*R*,3*S*,4*R*)-2-oxo-3-bornyl]methane (**1**). This new condensation reaction is proposed to proceed by an attack of the *d*-camphor enolate to DMF and a subsequent reduction. Three chiral diols were obtained from the reduction of **1**.

New-type chiral auxiliaries can be expected to facilitate new developments and some improvements of asymmetric reactions. Such auxiliaries are worth consideration, provided they can be readily prepared from natural compounds by simple procedures. Since *d*-camphor is a cheap chiral pool, a number of effective chiral auxiliaries has been produced by its structural modification and then used for some potential asymmetric reactions.[1)]

We found a new reaction under way to prepare new chiral auxiliaries from *d*-camphor.[2)] In the reaction of *d*-camphor with equimolar quantities of sodium/benzyl chloride in DMF solvent at ambient temperature, the expected α-benzylated compound was obtained in very low yield. By applying conditions of more elevated temperature (50—80 °C) and/or potassium hydride[3)] in order to increase the yield of the α-alkylated product, an unknown compound (mp 198.5—199.5 °C) (**1**) having a similar IR spectrum to that of starting *d*-camphor was mainly obtained. The reaction without alkyl halide under the same conditions also gave only the compound **1** in high yield.

The structure of **1** was determined to be bis-[(1*R*,3*S*,4*R*)-2-oxo-3-bornyl]methane by analyzing the physical data (as described below). The formura $C_{21}H_{32}O_2$ of **1**, derived from its elemental analysis and MS (M^+ 316), corresponded to that of a compound to be made up of two camphors and one methylene. A characteristic structure suited for **1** could be deduced to have high symmetry from eleven different peaks of carbon resonance, in which each camphor binds with a methylene at the carbonyl α-position (C-3).

The stereochemistry at C-3, while that at C-3′ is treated in the same manner from the symmetry, was ascertained to be endo on the basis of the following NMR studies. a) The observed γ effect on the ^{13}C chemical shift at C-5 suggests that the methylene bridge situates in endo direction; the ^{13}C chemical shift at C-5 of **1** was observed 6.9 ppm upfield than that at C-5 of *d*-camphor, as observed in *endo*-3-methyl-2-norbornanone system.[4)] b) In addition, in the ^{1}H NMR spectra such a rigid camphor system permits the application of the Karplus equation[5)] to compound **1** with confidence. If the methylene bridge of **1** is endo at C-3, the dihedral angle between H-3 and H-4 is close to about 40°. From 2D cosy and 2DJ experiments with the 200 MHz NMR, the coupling constant between H-3 and H-4 was determined to be 5.0 Hz which supports to be the endo configuration. Further, the long-range coupling (1.5 Hz) between H-3 and H-5β was observed in **1** by virtue of the "W" configuration[6)] of these protons.



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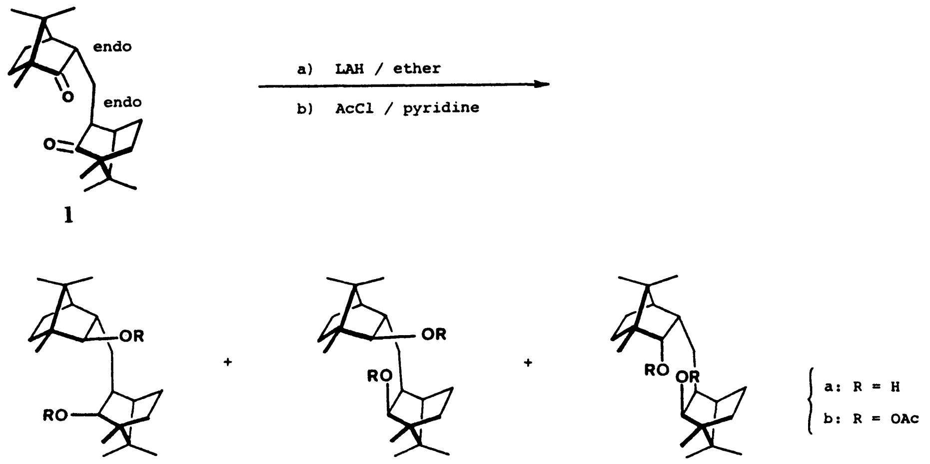

1

2a, b (exo, exo) **3a, b** (exo, endo) **4a, b** (endo, endo)

Consequently, in the one-methylene incorporated dimerization reaction of *d*-camphor enolate, thermodynamically more stable endo, endo-isomer turned out to be predominantly produced under the applied conditions, in which steric repulsions are minimized between the methyl groups at C-7 and C-7′ and the bridged methylene reductively incorporated from the formyl group of DMF used as a solvent.[2] This chiral diketone **1** expected to find utility for various asymmetric reactions.

As several chiral diols have been used as chiral modificators of lithium aluminum hydride (LAH),[7] we also tried the reduction of the chiral 1,5-diketone **1** in order to obtain new chiral diols. The reduction of **1** with LAH in diethyl ether easily gave a mixture of diols **2a**—**4a**.

The stereochemistry of **2a**—**4a** was determined on the basis of the coupling constants between H-2 and H-3 and/or H-2′ and H-3′ in the diols and diacetates. Compound **2a** with a coupling constant of 4.0 Hz is exo,exo-isomer and compound **3a** with two different coupling constants (4.0 and 9.5 Hz) is exo,endo-isomer, while the compound **4a** with J=9.9 Hz corresponds to endo,endo-isomer. Furthermore, the peak numbers in the ^{13}C NMR spectra of **2a** and **4a** suggested that both are symmetrical structures.

Diols, **2a** (47%) and **3a** (40%), are major and diol **4a** (6%) is minor in the reduction of **1** with LAH (ether, room temperature). The selectivity in the reduction of **1** with diisobutylaluminum hydride (THF, −78 °C) is not so different from that with LAH. On the other hand, the reduction of **1** with lithium tri-*s*-butylhydroborate (THF, −78 °C) gave only diol **2a** in a low yield.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, diethyl ether (ether) was distilled from lithium aluinum hydride (LAH), and *N,N*-dimethylformamide (DMF) was distilled from K_2CO_3 immediately prior to use. All the melting points were uncorrected. IR spectra were determined with a JASCO A-302 infrared spectrophotometer. Optical rotations were observed with a Union Giken PM-101 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were determined with Hitachi R-90H and R-250H NMR spectrometers. 2D cosy and 2DJ experiments were performed with a Varian XL-200E NMR spectrometer. Mass spectra were measured on a Hitachi RMU-6L instrument at 70 eV. Merck silica gel 60 (230—400 mesh) was used for flash column chromatography.

Synthesis of Bis[(1*R*,3*S*,4*R*)-2-oxo-3-bornyl]methane (1). Potassium hydride (200 mg, 5 mmol) dispersed in mineral oil (35 wt%) was washed several times with petroleum ether. Onto the hydride was added DMF (10 cm^3) under argon atmospher. The solution was stirred at room temperature until the evolution of gas ceased. To the resulting mixture was added dropwise a solution of (1*R*)-(+)-camphor (609 mg, 4 mmol) in THF (3 cm^3). Then the reaction mixture was stirred at 50 °C for 3 h and quenched with 5% HCl at 0 °C. After extraction with ether, the ethereal solution was washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent gave a residue, which was purified by flash

Table 1. Diols Prepared from **1** and Their Diacetates

Compd	Mp / °C	$[\alpha]_D^{20}$/° (c 1.0, $CHCl_3$)	IR/cm^{-1} (Nujol)	^{1}H NMR δ/ppm (J/Hz) ($CDCl_3$)	^{13}C NMR δ/ppm ($CDCl_3$)	Anal.[a] (C, H)
2a	202—206	−15.4	3320 (OH)	0.85 (s, 6H); 0.87 (s, 6H); 1.09 (s, 6H); 1.30—1.60 (m, 12H); 2.04—2.32 (m, 2H); 2.91 (s, 2H); 3.21 (d, 2H, J=4.0)	11.8; 20.1; 20.8; 21.1; 31.7; 34.9; 47.3; 47.9; 49.7; 50.0; 84.6	$C_{21}H_{36}O_2$
3a	184—186	+31.9	3400 (OH)	0.84 (s, 12H); 0.90 (s, 6H); 1.45 (s, 2H); 1.03—2.25 (m, 14H); 3.08 (d, 1H, J=4.0); 3.91 (d, 1H, J=9.5)	11.8; 14.4; 18.8; 19.9; 20.4; 20.5; 21.2; 26.0; 27.0; 34.8; 37.6; 46.4; 47.0; 47.8; 48.1; 48.5; 49.8; 50.6; 77.1; 87.0	$C_{21}H_{36}O_2$
4a	209—212	+26.1	3350 (OH)	0.83 (s, 6H); 0.89 (s, 12H); 1.26—2.13 (m, 16H); 3.90 (d, 2H, J=9.9)	14.1; 18.0; 20.1; 20.3; 22.0; 25.8; 36.9; 46.1; 47.7; 50.1; 76.9	$C_{21}H_{36}O_2$
2b	128—129	−25.8	1735 (OAc)	0.75 (s, 6H); 0.84 (s, 6H); 0.99 (s, 6H); 1.34—1.58 (m, 14H); 4.32 (d, 2H, J=3.7)	11.5; 19.3; 19.9; 20.4; 21.2; 31.6; 34.0; 44.6; 47.8; 48.1; 49.7; 86.6; 170.2	$C_{25}H_{40}O_4$
3b	Oil	+27.8	1730 (OAc) (Neat)	0.75 (s, 6H); 0.84 (s, 3H); 0.90 (s, 3H); 0.93 (s, 3H); 0.99 (s, 3H); 1.34—1.58 (m, 14H); 2.03 (s, 3H); 2.13 (s, 3H); 4.29 (d, 1H, J=3.7); 4.98 (d, 1H, J=9.9)	11.5; 13.9; 18.5; 19.4; 19.9; 20.5; 21.1; 21.2; 25.8; 26.8; 34.0; 36.1; 44.2; 46.5; 47.6; 47.7; 49.5; 78.8; 86.6; 170.4; 171.2	$C_{25}H_{40}O_4$
4b	109—112	+81.2	1735 (OAc)	0.76 (s, 6H); 0.89 (s, 6H); 0.93 (s, 6H); 1.13—1.55 (m, 14H); 2.06 (s, 6H); 4.97 (d, 2H, J=10.1)	14.0; 18.6; 20.0; 20.6; 21.0; 27.0; 35.8; 46.6; 47.5; 49.5; 79.3; 171.1	$C_{25}H_{40}O_4$

a) Microanalyses for all compounds were satisfactorily done in ±0.3% of calculated values.

column chromatography to give diketone **1** (537 mg) in 85% yield: mp 198.5—199.5 °C; $[\alpha]_D^{18}$+82° (c 1.07, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.88 (s, 3H×2), 0.89 (s, 3H×2), 1.00 (s, 3H×2), 1.25—1.38 (m, 1H×2), 1.52—1.77 (m, 4H×2), 1.69 (t, J=7.0 Hz, 2H), 2.03 (t, J=5.0 Hz, 1H×2), 2.39 (tdd, J=7.0, 5.0, and 1.5 Hz, 1H×2); ^{13}C NMR ($CDCl_3$) δ=9.5 (q), 19.3 (q), 19.5 (q), 20.1 (t), 24.7 (t), 31.1 (t), 45.8 (s), 46.0 (d), 47.5 (s), 58.7 (s), 220.8 (s); MS (70 eV) 316 (M$^+$ 19.4), 301 (2.8), 288 (base), 273 (8.9), 260 (2.7), 255 (2.4), 245 (2.0), 165 (6.2), 152 (43.7), 137 (13.6), 124 (24.5), 109 (20.0); Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%. Found: C, 79.82; H, 10.62%.

Synthesis of Diols (2a, 3a, and 4a) by the Reduction of Diketone 1 with LAH. To a suspension of excess LAH (3.0 g, 79 mmol) in ether (300 cm^3) was added dropwise a solution of **1** (13.6 g, 43 mmol) in ether (50 cm^3) at room temperature under argon atmosphere. The solution was refluxed for 1 h and then quenched with ethyl acetate (10 cm^3) at 0 °C. After the addition of water (80 cm^3), the ethereal layer was separated and washed with 10% HCl (20 cm^3), 10% Na_2CO_3 (10 cm^3), and brine (20 cm^3). The organic layer was dried over $MgSO_4$. Evaporation of the solvent gave a mixture of diols; bis[(1*R*,2*R*,3*S*,4*R*)-2-hydroxy-3-bornyl]methane **2a**, [(1*R*,2*R*,3*S*,4*R*)-2-hydroxy-3-bornyl][(1*R*,2*S*,3*R*,4*R*)-2-hydroxy-3-bornyl]methane **3a**, and bis[(1*R*,2*S*,3*S*,4*R*)-2-hydroxy-3-bornyl]methane **4a**, (12.8 g) in 93% yield. The mixture showed R_f values of 0.5, 0.2, and 0.15, corresponding to **2a**, **3a**, and **4a**, respectively, on its thin-layer chromatography using Merck silica gel 60 on an aluminium sheet with ethyl acetate/hexane (1 : 5). Each diol was isolated by flash column chromatography with ethyl acetate/hexane (1 : 10). Their physical data, along with that of their diacetates, are listed in Table 1.

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