(μmol/mg): Leu, 1.03; Phe, 3.09. Found: Leu, 1.06; Phe, 3.23.

28a$_2$: ^{1}H NMR (Me_2SO-d_6) δ 0.75 (d, J = 6 Hz), 0.82 (d, J = 6 Hz), 1.08 (s), 1.15 (s), 1.25–1.45 (m), 1.27 (s), 1.45–1.58 (m), 1.58–1.70 (m), 2.48–2.90 (m), 2.99 (dd, J_1 = 14 Hz, J_2 = 5 Hz), 3.81 (br), 4.04–4.22 (m), 4.41 (q), 4.45–4.55 (br m), 4.78 (br s), 6.88 (d, J = 9 Hz), 7.05–7.33 (m), 7.35 (s), 7.69 (d, J = 8 Hz), 7.85–8.00 (m); HPLC 85% (contains 11% *N*-de-Boc'd compound); FABMS, m/e 967 (M + 1), 968 (M + 2), 867, 803, 703/4/5, 590. Amino acid analysis: Calcd (μmol/mg): Leu, 1.03; Phe, 3.09. Found: Leu, 1.03; Phe, 2.96.

Acknowledgment. We gratefully acknowledge the efforts of those who have assisted in this work including Dr. David Cochran and Mrs. Joan Murphy (NMR spectra), Dr. Harri Ramjit and Mr. Brian Haggert (EI mass spectra), Mr. Jack Smith (FAB mass spectra), Mr. John Moreau (CHN determinations), Mrs. Susan Fitzpatrick (amino acid analyses), Dr. Dominic Ip (TGA), and Mrs. Mary Banker (manuscript preparation). We are also indebted to Drs. Mark Bock and Roger Freidinger for valuable comments and suggestions and to Dr. Joshua Boger for a gift of BocACHPA.

Supplementary Material Available: Crystallographic data including tables of the atomic positional and thermal parameters, bond distances, and bond angles for **2b** (3 pages). Ordering information is given on any current masthead page.

Notes

Chiral Synthetic Intermediates via Asymmetric Hydrogenation of α-Methyl-α,β-unsaturated Aldehydes by Bakers' Yeast†

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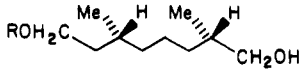
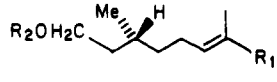
Microbial-mediated reactions are a useful means of preparing chiral intermediates for synthetic studies.[1] The enantioselective microbial hydrogenation of the double bond in α-[2] or β-methyl-α,β-unsaturated aldehydes[3] (or alcohols or acetals) is well documented: Common baker's yeast appears to be particularly versatile and is easy to use for this purpose.

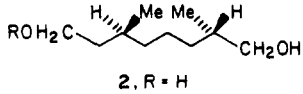
Herein we describe the preparation of (2*S*,6*R*)-2,6-dimethyl-1,8-octanediol (**1**) and of its 6-epimer (**2**) in an enantiomerically pure form by the yeast reduction (*Saccharomyces cerevisiae*) of **3** and **4**, which were prepared in their turn from (*R*)-citronellol (**5**)[4] and from its enantiomer (**6**),[5] respectively. By the same procedure **7** and **8** were obtained starting from the corresponding 8-acetoxy aldehydes **9** and **10** related to citronellyl acetates **11** and **12**.



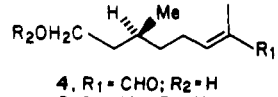
1, R = H
7, R = Ac



3, R_1 = CHO; R_2 = H
5, R_1 = Me; R_2 = H
9, R_1 = CHO; R_2 = Ac
11, R_1 = Me; R_2 = Ac

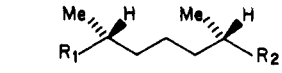


2, R = H
8, R = Ac

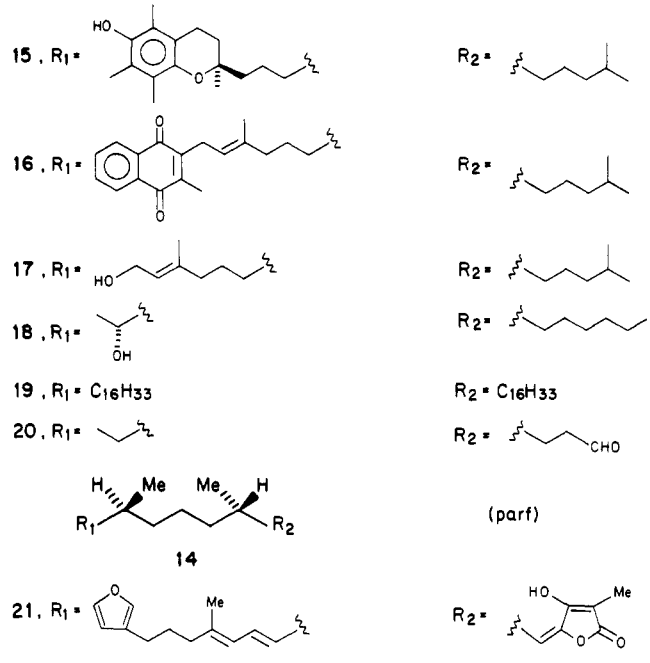


4, R_1 = CHO; R_2 = H
6, R_1 = Me; R_2 = H
10, R_1 = CHO; R_2 = Ac
12, R_1 = Me; R_2 = Ac

A 1,5-dimethylated acyclic unit (**13**, **14**) is present in a number of biologically important natural products: e.g., tocopherols (vitamin E, **15**); phylloquinones (vitamin K_1, **16**); phytol (**17**); insect pheromones of pine sawflies (**18**),[6] of tsetse flies (**19**),[7] and of red flour beetles (**20**);[8] fascicu-



13 (pref)



15, R_1 = ; R_2 =
16, R_1 = ; R_2 =
17, R_1 = ; R_2 =
18, R_1 = ; R_2 =
19, R_1 = $C_{16}H_{33}$; R_2 = $C_{16}H_{33}$
20, R_1 = ; R_2 =

14 (parf)

21, R_1 = ; R_2 =

† This work is dedicated to the memory of Professor Luigi Canonica, deceased unexpectedly (Aug 17 1984).

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(3) Gramatica, P.; Manitto, P.; Ranzi, B. M.; Delbianco, A.; Francavilla, M. *Experientia* **1982**, *38*, 775.

(4) (*R*)-(+)-Citronellol was prepared by *S. cerevisiae* reduction of a readily available achiral compound, geraniol (**28**).[3] "Natural citronellal" from Java citronella oil is only 75–80% optically pure (Morrison, J. D. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, pp 2–3).

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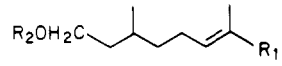
latin (21), a marine sponge sesquiterpenoid.[9] Thus, compounds like 1, 2, and particularly 7 and 8 can be regarded as suitable chirons[10] for the synthesis of the above natural products.

(*R*)-(+)-Citronellol (5) [ee >98% by ^{1}H NMR analysis with Eu(tfc)$_3$][3] was oxidized by selenium dioxide to give the aldehyde 3 having *E* configuration.[11] Reduction of 3 by a suspension of bakers' yeast afforded the diol 1 (in 30% isolated yield),[12] which was shown to be diastereomerically pure (>95%) by high-field ^{13}C NMR analysis. A 1:1 diastereomeric mixture of the diol, prepared by catalytic hydrogenation of 22, was used as reference. Analogously, 2 (>90% diastereomerically pure) was prepared using (*S*)-(−)-citronellol (6)[5] as the starting material for the oxidation to the aldehyde 4. An equimolecular mixture of 1 and 2 was also obtained by baker's yeast reduction of racemic diol 22.

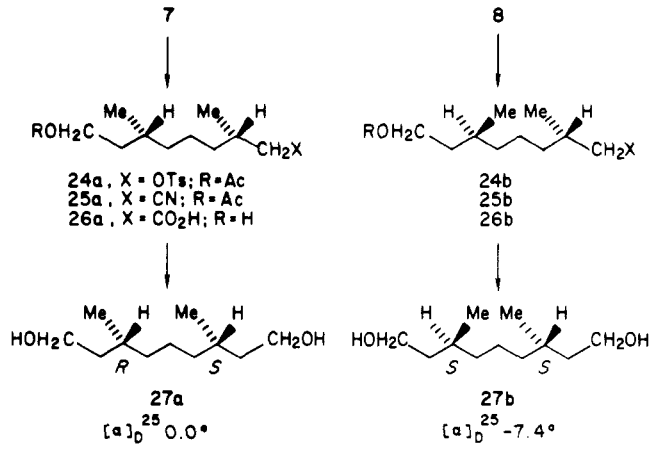


22, R_1 = CH_2OH; R_2 = H
23, R_1 = CH_2OH; R_2 = Ac

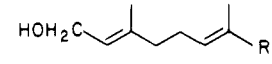
Three conclusions can be drawn from these experiments: (i) no epimerization occurs at C-6 of the α,β-unsaturated aldehydes (or alcohols) during the microbial reduction; (ii) the introduction of the asymmetric center at C-2 is highly stereoselective; (iii) the same absolute configuration of C-2 results starting from both (*R*)- and (*S*)-citronellol.

In order to establish the absolute configuration of the asymmetric carbon arising from microbial reduction, the 8-acetoxy aldehydes 9 and 10 were separately reduced by bakers' yeast to obtain the monoesters 7 and 8 (35% yields after purification from minor amounts (10%) of the corresponding deprotected diols).[13] Each was shown to be diastereomerically pure by ^{13}C NMR comparison with a 1:1 diastereomeric mixture obtained via hydrogenation of 23. 7 and 8 were then constitutionally symmetrized as outlined in Scheme I. The monoprotected alcohols were converted to the tosylates **24a,b**, which were then transformed into the nitriles **25a,b**. Alkaline hydrolysis of these afforded the hydroxy acids **26a,b** which were finally reduced with lithium aluminum hydride to the corresponding consitutionally symmetric diols **27a,b**. It was observed that the diol resulting from the *R* form of citronellyl acetate, namely, **27a** via 7, was optically inactive, whereas that from the *S* form (**27b**) exhibited significant optical rotation. This fact allowed the configuration *S* to be assigned to the C-2 of all the products (1, 2 and 7, 8) isolated after yeast reduction.[14]

Scheme I



Considering that 1 was synthesized via two microbial reductions from geraniol (28),[4] we succeeded in obtaining it (enantiomerically and diastereomerically pure) by one-pot double hydrogenation of 29 (prepared in turn by selenium dioxide oxidation of 28) using baker's yeast as the reducing agent (40% yield based on 28).



28, R = Me
29, R = CHO

It can be pointed out that, in principle, the microbial transformation reported here provides C_{10} synthons for building up molecules containing the 1,5-dimethylated acyclic unit (13, 14) in any one of the possible stereoisomeric forms. In fact, compounds such as 7 and 8 have two chiral centers in "pref" and "parf" relationship,[15] respectively; in addition, their different ending groups may selectively be elaborated to give the building block in the stereoform wanted for synthetic purposes.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker WP80 SY, ^{13}C NMR spectra were recorded either on a Varian XL-100 spectrometer operating at 25.2 MHz or a Bruker CXP300 operating at 75.47 MHz. Chemical shifts are reported in δ from internal Me_4Si. Optical rotations were measured in a 1.0-dm cell on a Perkin-Elmer Model 241 polarimeter. Gas chromatographic analyses were performed on a Carlo Erba Fractovap 2400V gas chromatograph with glass columns (FFAP 10%), using nitrogen (1.6 atm) as carrier gas. GC–MS spectra were recorded on a Varian MAT 112 gas chromatograph–mass spectrometer. TLC was carried out on silica gel Merck 60 F_{254} plates, normally using benzene–ethyl acetate (1.5:1) as eluent. Flash column chromatography was performed on silica gel Merck 60 (230–400 mesh). Bakers' yeast was "Distillerie Italiane" brand from Eridania [S. Quirico-Trecasali (Parma, Italy)]. "Usual workup" means that the organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated under vacuum.

General Procedure for Fermentations. The substrate (10 g) was gradually added to a suspension of bakers' yeast (1.5 kg) in preboiled distilled water (10 L). The mixture was stirred at 25–30 °C for 2–5 days, while other bakers' yeast (1 kg) was added in several portions. Completion of the reduction was monitored by GC and TLC analyses. The workup was selected according to the product to be isolated: After addition of H_2SO_4 (in the case of citronellol) or NaCl (in other instances), the product was

(5) (*S*)-(−)-Citronellol is commercially available (ee >95% by ^{1}H NMR analysis with Eu(tfc)$_3$).

(6) (a) Baker, R.; Winton, P.; Turner, R. W. *Tetrahedron Lett.* **1980**, *21*, 1175. (b) Bystrom, S.; Hogberg, H. B; Norin, T. *Tetrahedron* **1981**, *37*, 2554 and references cited therein.

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(8) Mori, K.; Kuwahara, S.; Ueda, H. *Tetrahedron* **1983**, *39*, 2439.

(9) Cafieri, F.; Fattorusso, E.; Santacroce, C.; Minale, L. *Tetrahedron* **1972**, *28*, 1579.

(10) Hanessian, S. "Total Synthesis of Natural Products: The Chiron Approach"; Pergamon Press: Oxford, 1983; pp 21–26.

(11) (a) Plattner, J. J.; Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 4933. (b) Bhalerao, U. T.; Plattner, J. J.; Rapoport, H. *Ibid.* **1970**, *92*, 3429. (c) Bhalerao, U. T.; Rapoport, H. *Ibid.* **1971**, *93*, 4835.

(12) The fact that no substantial amounts of byproducts were detected in the reaction mixture could be due to a parallel degradation of the starting material by yeast.

(13) In this regard we found that the ratio of monoprotected/unprotected diols, resulting from 8-acyloxy aldehydes, can be increased with the pivaloyl esters as starting materials.

(14) The same configuration has been reported for other 2-methylalkanols prepared by yeast reduction of the corresponding 2-methyl-2-(*E*)-alkenals (or the equivalent alcohols or acetals); see ref 2a,b.

(15) Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.

(16) Iwagawa, T.; Hase, T. *Phytochemistry* **1983**, *22*, 255.

steam-distilled and continuously extracted by ether for 8 h (procedure A); otherwise, the product was extracted by ether in a Soxhlet apparatus for 40 h (procedure B). Drying with anhydrous $MgSO_4$ and evaporation of the solvent gave the desired product, which was then purified by flash chromatography.

(*R*)-(+)-Citronellol (5). Geraniol (10 g, **28**) was reduced by bakers' yeast for 2–3 days. The workup according to the procedure A gave **5**[3] (25% yield): $[\alpha]^{25}_D$ +5.1° (*c* 30, $CHCl_3$); ee >98% by ^1H NMR analysis with $Eu(tfc)_3$.

(*S*)-(−)-Citronellol (6): commercial sample (Fluka); $[\alpha]^{25}_D$ −4.9° (*c* 85, $CHCl_3$); ee >95% by ^1H NMR analysis with $Eu(tfc)_3$.

(6*R*)-(+)-2,6-Dimethyl-8-hydroxy-2-octenal (3). **3** was prepared by selenium dioxide oxidation of **5** as reported in ref 16 (36% yield): $[\alpha]^{25}_D$ +5.45° (*c* 15.9, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 9.05 (2-CH_3), 19.3 (6-CH_3), 26.5 (C-4), 29.3 (C-6), 35.5 (C-5), 39.5 (C-7), 60.4 (C-8), 139.0 (C-2), 154.9 (C-3), 195.05 (C-1); GC–MS (*T* = 195 °C, t_R 9 min), *m/e* (relative intensity) 170 (M^+, 1), 155 (1), 152 (2), 137 (5), 123 (7), 109 (7), 97 (52), 95 (28), 84 (25), 81 (25), 69 (28), 67 (30), 55 (50), 41 (100). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.27; H, 10.62.

(6*S*)-(−)-2,6-Dimethyl-8-hydroxy-2-octenal (4). **4** was prepared in the same way as for **3** starting from commercial **6** (34% yield): $[\alpha]^{25}_D$ −5.3° (*c* 2.9, $CHCl_3$).

2,6-Dimethyl-8-hydroxyocta-2,6-dienal (29). Geraniol (**28**) was oxidized, by the same procedure employed for citronellol, to give **29** (30% yield): IR (liquid film) 3400, 2700, 1675, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (1 H, br s, exchangeable with D_2O, OH), 1.7 (6 H, d, *J* = 1.2 Hz, CH_3C=), 2–2.7 (4 H, m, CH_2), 4.1 (2 H, d, *J* = 6.7 Hz, CH_2OH), 5.4 (1 H, tq, *J* = 6.7, 1.2 Hz, $CHCH_2OH$), 6.4 (1 H, tq, *J* = 7, 1.2 Hz, CH=), 9.35 (1 H, s, (*E*)-CHO); ^{13}C NMR ($CDCl_3$) δ 9.22 (2-CH_3), 16.19 (6-CH_3), 27.18 (C-4), 37.84 (C-5), 59.04 (C-8), 124.94 (C-7), 137.0 (C-6), 139.49 (C-2), 153.56 (C-3), 194.80 (C-1); MS (dis), *m/e* (relative intensity) 168 (M^+, 4), 150 (18), 135 (34), 121 (39), 84 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.24; H, 9.53.

(2*S*,6*R*)-(−)-2,6-Dimethyloctane-1,8-diol (1). **1** was prepared by bakers' yeast reduction of **3** (5 g) for 2–3 days. The workup was according to the procedure B; crude **1** was purified by flash chromatography over silica gel–$AgNO_3$ (10%) with benzene–ethyl acetate (1:1.5) as eluent to give pure **1** (30% yield). **1** was also prepared in 40% yield by one-pot fermentation of **29** for 5–6 days: $[\alpha]^{25}_D$ −6.3° (*c* 9.5, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 16.57 (2-CH_3), 19.66 (6-CH_3), 24.21 (C-4), 29.52 (C-6), 33.41 (C-3), 35.74 (C-2), 37.39 (C-5), 39.90 (C-7), 61.08 (C-8), 68.20 (C-1); diastereomeric purity >95%.

(2*S*,6*S*)-(−)-2,6-Dimethyloctane-1,8-diol (2). **2** was prepared in the same way as for **1** by bakers' yeast reduction of **4** (35% yield): $[\alpha]^{25}_D$ −15.5° (*c* 4.1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 16.52 (2-CH_3), 19.60 (6-CH_3), 24.20 (C-4), 29.40 (C-6), 33.31 (C-3), 35.70 (C-2), 37.25 (C-5), 39.98 (C-7), 61.05 (C-8), 68.25 (C-1); diastereomeric purity >90%.

(*RS*)-2,6-Dimethyloct-2-ene-1,8-diol (22). Racemic 2,6-dimethyl-8-hydroxy-2-octenal (prepared by SeO_2 oxidation of (*RS*)-citronellol) (535 mg, 3.15 mmol) in dry ether (10 mL) was reduced with $LiAlH_4$ (130 mg, 3.42 mmol) for 1.5 h at 0 °C. Dilute H_2SO_4 (10%) was added, and the ether was separated, washed with water, aqueous $NaHCO_3$, and brine, and dried ($MgSO_4$) to give **22** (400 mg, 74% yield). This was directly used for the next step: IR (liquid film) 3350, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, *J* = 6 Hz, CH_3CH), 1–1.6 (7 H, m, CH_2, CH, and OH), 1.7 (3 H, s, CH_3C=), 2.08 (2 H, dt (q-like), *J* = 7 Hz, CH_2C=), 3.7 (2 H, t, *J* = 6.4 Hz, CH_2OH), 4.0 (2 H, br s, =CCH_2OH), 5.4 (1 H, tq, *J* = 7, 1 Hz, CH=C); GC–MS (*T* = 195 °C, t_R 10 min), *m/e* (relative intensity) 154 ($M^+ - H_2O$, 1), 139 (7), 121 (18), 81 (45), 69 (49), 55 (75), 43 (100). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.41; H, 11.48.

(2*RS*,6*RS*)- and (2*RS*,6*SR*)-2,6-Dimethyl-1,8-octanediol. **22** (300 mg, 1.74 mmol) in EtOH (100 mL) was hydrogenated over PtO_2 (50 mg) for 8 h at room temperature. Filtration of the catalyst and evaporation of the solvent gave a crude product, which was flash chromatographed (1.2:1 $CHCl_3$–AcOEt) to isolate pure title product (170 mg, 56% yield): IR (liquid film) 3350, 1050, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (6 H, d, *J* = 6 Hz, 2 CH_3CH), 1.0–1.8 (12 H, m, CH_2, CH and OH), 3.47 (2 H, 2 d, *J* = 6.4 Hz, $CHCH_2OH$), 3.68 (2 H, t, *J* = 6.4 Hz, CH_2CH_2OH); ^{13}C NMR ($CDCl_3$), see spectra of **1** and **2**; GC–MS (*T* = 195 °C, t_R 11 min), *m/e* (relative intensity) 156 ($M^+ - H_2O$, 22), 141 (27), 123 (10), 77 (100). Anal. Calcd for $C_{10}H_{22}O_2$: C, 68.92; H, 12.72. Found: C, 69.10; H, 12.75.

(*R*)-(+)-2,6-Dimethyl-8-acetoxyoct-2-enal (9). A solution of **3** (4 g, 23.5 mmol) in acetic anhydride (10 mL, 105.8 mmol) and dry pyridine (10 mL) was allowed to stand at room temperature overnight. The usual workup gave **9** (4 g, 80% yield): $[\alpha]^{25}_D$ +7.8° (*c* 13.7, $CHCl_3$); IR (liquid film) 2720, 1740, 1685, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, d, *J* = 5.5 Hz, CH_3CH), 1.1–1.7 (5 H, m, CH_2 and CH), 1.74 (3 H, d, *J* = 1.2 Hz, CH_3C=), 2.0 (3 H, s, CH_3CO), 2.37 (2 H, dt (q-like), *J* = 7 Hz, CH_2C=), 4.1 (2 H, t, *J* = 7 Hz, CH_2OAc), 6.45 (1 H, tq, *J* = 7, 1.2 Hz, CH=C), 9.38 (1 H, s, (*E*)-CHO); ^{13}C NMR ($CDCl_3$) δ 9.1 (2-CH_3), 19.2 (6-CH_3), 20.8 (CH_3(Ac)), 26.4 (C-4), 29.7 (C-6), 35.35 (C-5 and C-7), 62.5 (C-8), 139.3 (C-2), 153.9 (C-3), 170.6 (CO(Ac)), 194.4 (C-1); GC–MS (*T* = 195 °C, t_R 7 min) *m/e* (relative intensity) 213 (M^+ + 1, 2), 212 (M^+, 3), 170 (20), 152 (52), 126 (63), 109 (66), 97 (100). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.58; H, 9.32.

9 was also obtained by SeO_2 oxidation of citronellyl acetate (**11**) in 25% overall yield from citronellol (**5**).

(*S*)-(−)-2,6-Dimethyl-8-acetoxyoct-2-enal (10). **10** was prepared by acetylation of **4** in the same way as for **9** (85% yield): $[\alpha]^{25}_D$ −7.3° (*c* 2.4, $CHCl_3$).

(2*S*,6*R*)-(−)-2,6-Dimethyl-8-acetoxyoctan-1-ol (7). **9** was reduced by bakers' yeast for 2–3 days. The workup according to the procedure A gave crude **7**, which was flash chromatographed over silica gel–$AgNO_3$ (10%) (1.5:1 benzene–AcOEt) to obtain pure **7** in 35% yield. The residue of distillation was then worked up according to the procedure B to give the diol **1** in 10% yield after purification by flash chromatography (1:1 benzene–AcOEt): $[\alpha]^{25}_D$ −4.9° (*c* 15, $CHCl_3$); IR (liquid film) 3350, 1740, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (6 H, d, *J* = 6.5 Hz, CH_3CH), 1.0–1.9 (11 H, m, CH_2, CH, and OH), 2.05 (3 H, s, CH_3CO), 3.47 (2 H, 2 d, *J* = 6.5 Hz, CH_2OH), 4.1 (2 H, t, *J* = 6.5 Hz, CH_2OAc); ^{13}C NMR ($CDCl_3$) δ 16.60 (2-CH_3), 19.52 (6-CH_3), 20.95 (CH_3(Ac)), 24.20 (C-4), 29.84 (C-6), 33.35 (C-3), 35.50 (C-2), 35.75 (C-7), 37.12 (C-5), 63.01 (C-8), 68.29 (C-1), 171.3 (CO(Ac)); diastereomeric purity >95%; GC–MS (*T* = 195 °C, t_R 8 min), *m/e* (relative intensity) 174 (1), 126 (21), 110 (15), 96 (32), 81 (75), 69 (100). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.37; H, 10.98.

(2*S*,6*S*)-(−)-2,6-Dimethyl-8-acetoxyoctan-1-ol (8). Prepared in the same way as for **7** by bakers' yeast reduction of **10** (44% yield): $[\alpha]^{25}_D$ −11.6° (*c* 5.9, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 16.54 (2-CH_3), 19.47 (6-CH_3), 20.94 (CH_3(Ac)), 24.21 (C-4), 29.87 (C-6), 33.40 (C-3), 35.59 (C-2), 35.78 (C-7), 37.17 (C-5), 63.02 (C-8), 68.35 (C-1), 171.2 (CO(Ac)); diastereomeric purity >92%.

(2*RS*,6*RS*)- and (2*RS*,6*SR*)-2,6-Dimethyl-8-acetoxyoctan-1-ol. The title compound was prepared in the same way as for (2*RS*,6*RS*)- and (2*RS*,6*SR*)-2,6-dimethyl-1,8-octanediol, starting from racemic **23** (45% overall yield): ^{13}C NMR ($CDCl_3$), see spectra of **7** and **8**.

(3*S*,7*R*)-3,7-Dimethyl-1,9-nonanediol (27a). *p*-TsCl (440 mg, 2.3 mmol) was added to a stirred and ice-cooled solution of **7** (360 mg, 1.66 mmol) in dry pyridine (9 mL). The mixture was stirred overnight at 0–5 °C under argon. Usual workup gave crude **24a** (500 mg, 84%), which was directly used for the next step: IR (liquid film) 1740, 1600, 1460, 1360, 1245, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (6 H, 2 d, *J* = 6.7 Hz, CH_3CH), 1.0–2.0 (10 H, m, CH_2 and CH), 2.03 (3 H, s, CH_3CO), 2.44 (3 H, s, CH_3Ar), 3.83 (2 H, 2 d, *J* = 6.5 Hz, CH_2OTs), 4.06 (2 H, t, *J* = 6.7 Hz, CH_2OAc), 7.32 (2 H, d, *J* = 8 Hz, 2 H ortho to SO_3R), 7.80 (2 H, d, *J* = 8 Hz, 2 H ortho to CH_3).

NaCN (84 mg, 1.7 mmol) was added to a solution of **24a** (480 mg, 1.29 mmol) in Me_2SO (6 mL). The mixture was stirred for 14 h at 65 °C under argon. It was then poured into ice–water and extracted with ether. Usual workup gave **25a**, which was purified by flash chromatography (9:1 benzene–AcOEt) to give pure product (183 mg, 63%): $[\alpha]^{25}_D$ +5.3° (*c* 18.3, $CHCl_3$); IR (liquid film) 2250, 1735 cm^{-1}; ^1H NMR δ 1.01 (6 H, 2 d, *J* = 6.2 Hz, CH_3CH), 1.2–2.0 (10 H, m, CH_2 and CH), 2.06 (3 H, s, CH_3CO), 2.28 (2 H, 2 d, *J* = 6.5 Hz, CH_2CN), 4.1 (2 H, t, *J* = 6.7 Hz, CH_2OAc); MS (dis), *m/e* (relative intensity) 225 (M^+, 2).

Aqueous KOH (0.5 g in 6 mL, 8.92 mmol) was added to a solution of **25a** (112 mg, 0.61 mmol) in 95% EtOH (3 mL). The mixture was heated under reflux for 2 days and then concentrated

under vacuum. The residue was diluted with water, acidified with ice-diluted HCl and extracted with ether. The ethereal solution was washed with aqueous $NaHCO_3$, and the aqueous layer was acidified with dilute HCl and extracted with ether. Usual workup gave pure **26a** in 75% yield: $[\alpha]^{25}_D$ −3.5° (*c* 6.4, CHCl3); IR ($CHCl_3$) 3620, 3000–2500, 1710, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (6 H, 2 d, J = 6 Hz, CH_3CH), 1.0–2.4 (12 H, m, CH_2 and CH), 3.65 (2 H, t, J = 6.4 Hz, CH_2OH), 5.0 (2 H, br s, exchanged with D_2O, COOH and OH). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.60; H, 10.85.

A solution of **26a** (50 mg, 0.25 mmol) in dry ether (12 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (19 mg, 0.5 mmol) in dry ether (6 mL)). The stirring was continued for 3 h at room temperature under argon. Subsequent workup gave the crude product (42 mg), which was flash chromatographed (1:1.5 benzene–AcOEt) to obtain pure **27a** in 78% yield: $[\alpha]^{25}_D$ 0.0° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (6 H, d, J = 6 Hz, CH_3CH), 1.0–1.8 (14 H, m, CH_2, CH, and OH), 3.64 (4 H, t, J = 6.7 Hz, 2 CH_2OH); MS (dis), *m/e* (relative intensity) 189 (M^+ + 1, 1). Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.01; H, 12.76.

(3*S*,7*S*)-(−)-3,7-Dimethyl-1,9-nonanediol (27b). **27b** was prepared through the same pathway reported for **27a**, starting from 8 (37% overall yield). **26b**: $[\alpha]^{25}_D$ −9.3° (*c* 2.7, $CHCl_3$). **27b**: $[\alpha]^{25}_D$ −7.4° (*c* 1.7, $CHCl_3$).

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Registry No. 1, 98105-56-7; **2**, 98105-60-3; **3**, 98168-99-1; **4**, 98169-00-7; **5**, 1117-61-9; **6**, 7540-51-4; **7**, 98105-57-8; **8**, 98105-61-4; **9**, 98168-98-0; **10**, 98169-01-8; **22**, 98168-95-7; **27a**, 98105-59-0; **27b**, 98169-02-9; **29**, 77878-85-4; (±)-2,6-dimethyl-8-hydroxy-2-octenal, 98168-96-8; (2*RS*,6*RS*)-2,6-dimethyl-1,8-octanediol, 98168-97-9; (2*RS*,6*SR*)-2,6-dimethyl-1,8-octanediol, 98169-03-0; (2*RS*,6*RS*)-2,6-dimethyl-8-acetoxyoctan-1-ol, 98105-58-9; (2*RS*,6*SR*)-2,6-dimethyl-8-acetoxyoctan-1-ol, 98105-62-5; geraniol, 106-24-1; **24a**, 98244-62-3; **25a**, 98267-82-4; **26a**, 98244-63-4; **26b**, 98244-64-5.

Precursors in the Alkylation of 2-Naphthol with Benzyl Alcohol in the Presence of a Base

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We previously reported the reaction of potassium 2-naphthyl oxide (2-NK) with a primary alcohol at high temperatures (200 °C) followed by acidification to afford the corresponding 1-alkyl-2-naphthol in good yield.[2] Most characteristic in a series of these reactions are the following: (1) only primary alcohols are capable of performing this alkylation and (2) no isomerization of incoming *n*-alkyl groups takes place, an observation in marked contrast to typical Friedel–Crafts alkylations.

By applying milder reaction conditions for the alkylation, we were able to isolate three precursors and confirmed that the actual reaction involved the benzaldehyde produced from benzyl alcohol. We here report characterization of these precursors, i.e., 1-(α-hydroxybenzyl)-2-naphthol (**1**), benzylidene-1,1′-bis(2-naphthol) (**2**), and 1-[α-(benzyloxy)benzyl]-2-naphthol (**3**), and discuss their transformation to the final product, 1-benzyl-2-naphthol (**4**).

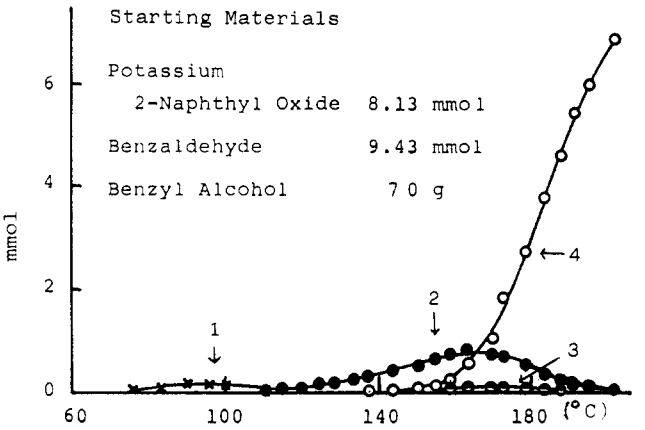

Figure 1. Temperature dependence of formation of 1, 2, 3, and 4. Rate of increasing temperature, 0.5 °C/min. Benzaldehyde was added at 68 °C.

Results and Discussion

As reported previously, 1-alkyl-2-naphthol was obtained in good yield when the mixture of 2-NK and a primary alcohol was heated at temperatures higher than 200 °C in an autoclave.[2] However, the alkylation occurred even at 170 °C under an atmospheric pressure if benzyl alcohol, relatively reactive alcohol, was employed. Therefore, we examined the alkylation pathway by use of this alcohol. Another advantage of using benzyl alcohol is that the Guerbet-type dimerization of the alcohol does not take place. Formation of such dimeric alcohols is inevitable in this series of reactions and makes it difficult to study the reaction pathway.

The final product **4** did not form in an atmosphere of oxygen-free nitrogen. The alkylation, however, did occur when either a small amount of benzaldehyde or air was present in the mixture of 2-NK and benzyl alcohol (see Experimental Section). On the other hand, the formation ratio of the precursors **1**, **2**, and **3** and the final product **4** was varied in a stirred mixture of 2-NK, benzyl alcohol, and benzaldehyde depending on the reaction temperature. Results are shown in Figure 1.

Precursors **1**, **2**, and related compounds have been synthesized by a variety of methods different from ours. An organometallic reagent and an aldehyde are generally employed to synthesize **1** and related compounds. For example, **1** was prepared from 2-hydroxy-1-naphthylaldehyde and phenylmagnesium bromide.[3] Pope and Howard prepared 2,4-dihydroxybenzhydrol from resorcinol and benzaldehyde in an aqueous alkaline solution.[4] Bennett and his co-workers prepared derivatives of **2**, such as *p*-methoxybenzylidene-1,1′-bis(2-naphthol), in the presence of hydrochloric acid.[5] Although Allan and his co-workers investigated the reaction of 2-naphthol with acetaldehyde in the presence of hydrochloric acid, they did not isolate such products as Bennett did.[6]

From Figure 1, the reaction pathway may be outlined as follows:

(a) Precursor **1** firstly forms.

(b) Precursor **1** changes into precursor **2**.

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