solution of 1β (71.1 mg, 0.115 mmol), methanol (6.5 mg, 0.203 mmol), and lithium perchlorate (234.7 mg) in anhydrous acetonitrile (10 mL) was placed in an undivided cell fitted with two Pt foils (1 cm × 2 cm) and an Ag/AgCl reference electrode. Electricity was then passed under a constant voltage, 2.0 V vs. Ag/AgCl, at 30 °C for 4 h. After confirmation of disappearance of 1 (TLC monitoring), the mixture was concentrated under vacuum. The residue was mixed with ether (30 mL) and then with water (20 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Chromatography on a silica gel column (8:1 hexane–ethyl acetate) gave **2** (R = $C_6H_5CH_2$, R′ = CH_3) (51.5 mg, 81% yield), α/β = 37:63.

Registry No. β-1 (R = CH_3CO, Ar = C_6H_5), 4468-72-8; α-1 (R = CH_3, Ar = C_6H_5), 3149-61-9; β-1 (R = $C_6H_5CH_2$, Ar = C_6H_5), 72366-52-0; β-1 (R = $C_6H_5CH_2$, Ar = 2,4,6-$(CH_3)_3C_6H_2$, 104550-44-9; α-1 (R = H, Ar = C_6H_5), 4630-62-0; β-1 (R = H, Ar = C_6H_5), 1464-44-4; β-1 (R = H, Ar = 2,4,6-$(CH_3)_3C_6H_2$, 31617-31-9; α-2 (R = CH_3CO, R′ = CH_3), 604-70-6; β-2 (R = CH_3CO, R′ = CH_3), 4860-85-9; α-2 (R = CH_3, R′ = CH_3), 605-81-2; β-2 (R = CH_3, R′ = CH_3), 3149-65-3; α-2 (R = $C_6H_5CH_2$, R′ = CH_3), 17791-37-6; β-2 (R = $C_6H_5CH_2$, R′ = CH_3), 19488-61-0; α-2 (R = $C_6H_5CH_2$, R′ = methyl 2,3,4-tri-*O*-benzyl-α-D-glucos-6-yl), 55094-26-3; β-2 (R = $C_6H_5CH_2$, R′ = methyl 2,3,4-tri-*O*-benzyl-α-D-glucos-6-yl), 56632-57-6; α-2 (R = $C_6H_5CH_2$, R′ = c-C_6H_{11}), 56632-55-4; β-2 (R = $C_6H_5CH_2$, R′ = c-C_1H_{11}), 56632-56-5; α-2 (R = $C_6H_5CH_2$, R′ = *t*-C_4H_9), 67525-69-3; β-2 (R = $C_6H_5CH_2$, R′ = *t*-C_4H_9), 78153-80-7; α-2 (R = H, R′ = CH_3), 97-30-3; β-2 (R = H, R′ = CH_3), 709-50-2; α-2 (R = H, R′ = methyl 2,3,4-tri-*O*-methyl-α-D-glucos-6-yl), 104550-45-0; β-2 (R = H, R′ = methyl 2,3,4-tri-*O*-methyl-α-D-glucos-6-yl), 104550-46-1; α-2 (R = H, R′ = C_2H_5), 19467-01-7; β-2 (R = H, R′ = C_2H_5), 3198-49-0; α-2 (R = H, R′ = $(CH_3)_3CCH_2$), 25320-97-2; β-2 (R = H, R′ = (CH_3),3CCH_2), 5285-03-0; α-2 (R = H, R′ = $(CH_3)_2CH$), 25320-92-7; β-2 (R = H, R′ = $(CH_3)_2CH$), 5391-17-3; α-2 (R = H, R′ = c-C_6H_{11}), 25320-98-3; β-2 (R = H, R′ = c-C_6H_{11}), 5284-99-1; α-2 (R = H, R′ = *t*-C_4H_9), 33538-53-3; β-2 (R = H, R′ = *t*-C_4H_9), 29074-04-2; **3** (R = $C_6H_5CH_2$), 53008-65-4; **3** (R = CH_3), 4153-24-6; **7**, 18311-26-7; CH_3OH, 67-56-1; c-$C_6H_{11}OH$, 108-93-0; *t*-C_4H_9OH, 75-65-0; C_2H_5OH, 64-17-5; $(CH_3)_3CCH_2OH$, 75-84-3; $(CH_3)_2CHOH$, 67-63-0; 2,4,6-trimethylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside, 104550-47-2; penta-*O*-acetyl-β-D-glucose, 604-69-3; methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucoside, 18685-93-3; methyl 2,3,4-tri-*O*-benzyl-6-*O*-acetyl-α-D-glucoside, 82231-38-7; methyl 2,3,4-tri-*O*-methyl-6-*O*-trityl-α-D-glucoside, 6984-43-6; phenyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucoside, 72366-52-0.

Supplementary Material Available: Experimental details of compounds and methods used in this study (8 pages). Ordering information is given on any current masthead page.

Ryoji Noyori,* Isao Kurimoto
Department of Chemistry
Nagoya University
Chikusa, Nagoya 464, Japan
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Total Synthesis of a Slightly Unnatural Product. Confirmation of the Stereostructure of the Archaebacterial C_{40} Diol by Synthesis of a Stereoisomer[1]

Summary: Diol **2** has been prepared by stereorational total synthesis; comparison of **2** with samples of naturally derived and synthetic diol 1 by 125-MHz ^{13}C NMR spectroscopy demonstrates that such stereoisomers can be distinguished by this technique and adds confirmation to the assigned stereostructure of the archaebacterial lipids derived from 1.

Sir: In a recent publication[2] we reported the stereorational total synthesis of diol 1 and advanced ^{13}C NMR evidence that it is identical with the so-called "archaebacterial C_{40} diol". In order to be fully confident that stereoisomers of the gross structure 1 can be distinguished by the analytical method used, and therefore of the identity of our synthetic material with the naturally derived diol, we thought it worthwhile to synthesize a stereoisomer of 1. Isomer **2** was chosen as the secondary synthetic target for two reasons. First, we reasoned that, of the many stereoisomers of 1, the ^{13}C NMR spectrum of **2** would be most like that of 1. Like 1, diol **2** has C_2 symmetry and can show a maximum of 20 ^{13}C NMR resonances. In addition, the stereochemical differences in these two isomers occur only at C-15 and C-18, far away from the functional ends of the chain. Second, structures 1 and **2** are the most likely stereoisomeric forms of the archaebacterial C_{40} diol on biosynthetic grounds.[2] In this paper, we report the synthesis of **2**, which is different by ^{13}C NMR spectroscopy from the naturally derived diol.

The synthetic strategy employed for the preparation of **2** was similar to that used for our earlier synthesis of 1—sequential aldol addition and Claisen rearrangement.[3] Evans' asymmetric aldol strategy[4] was used to acquire the desired chirality. As shown in Scheme I, the di-*n*-butylboron enolate of *N*-propionyloxazolidone **3** was condensed with acrolein to obtain an aldol, which was converted by four straightforward steps into allylic propionate **4**. This material was converted into unsaturated acids **5** and **6** by Ireland's modification of the Claisen rearrangement.[5] Isomer **5** (88% diastereomeric purity) resulted from rearrangement of the enolate produced from **4** by reaction with lithium diisopropylamide (LDA) in tetrahydrofuran (THF). Isomer **6** (86% diastereomeric purity) was obtained from rearrangement of the enolate produced from **4** by reaction with LDA in a mixture of THF and hexamethylphosphoric triamide (HMPA). Isomers **5** and **6** were converted into the C_{10} synthons **7** and **8**, respectively. Alkylation of the anion of **8** with iodide **7** produced the C_{20} compound **9**, which was converted by a four-step sequence into bromo ether **10**. The Grignard reagent derived from bromide **10** was oxidized with silver nitrate to give a bis(*tert*-butyldiphenylsilyl) ether of **2**. Deprotection of this substance provided **2**, contaminated by minor diastereomers.[6]

Compound **2** was compared by ^{13}C NMR spectroscopy[7] with an authentic sample of the C_{40} diol that was obtained

(1) This is part 37 in a series of publications on acyclic stereoselection; for part 36 see: Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.

(2) Heathcock, C. H.; Finkelstein, B. L.; Aoki, T.; Poulter, C. D. *Science (Washington, DC)* **1985**, 229, 862.

(3) For other applications of the aldol-Claisen strategy for 1,5-stereoselection, see: (a) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825. (b) Heathcock, C. H.; Jarvi, E. T.; Rosen, T. *Tetrahedron Lett.* **1984**, *25*, 243. For an application of the strategy for 1,4-stereoselection, see: (c) Heathcock, C. H.; Finkelstein, B. L. *J. Chem. Soc., Chem. Commun.* **1983**, 919.

(4) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(5) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(6) Compounds **5** and **6** were used as obtained from the Claisen rearrangements (88% and 86% diastereomeric purity, respectively). Assuming no kinetic resolution in the coupling reactions leading to **9** and to the bis(*tert*-butyldiphenylsilyl) ether of **2**, it may be calculated that the final diol contains 57% of diastereomer **2** and smaller amounts of several other diastereomers. Only two of the minor isomers are calculated to be present to the extent of greater than 2%. Neither of these isomers (9.3% and 7.8%) are C_2-symmetric and both will theoretically give rise to 40 signals.

(7) We thank Mr. Eric Lodge, University of California, for assistance in obtaining the ^{13}C NMR spectrum.

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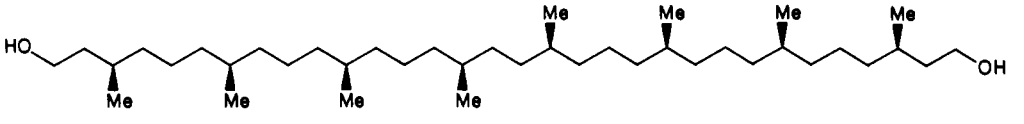
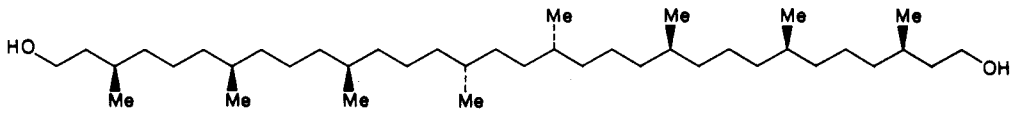
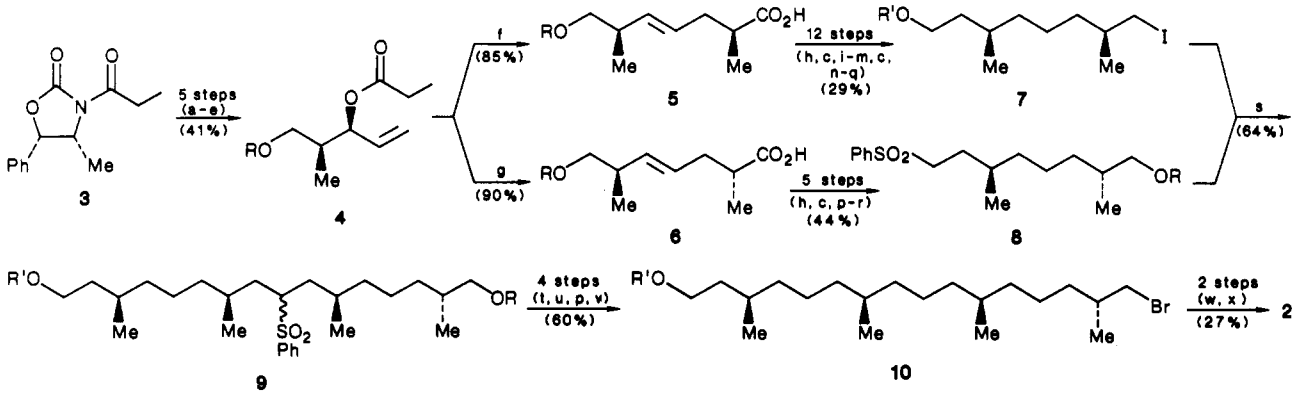


1



2

Scheme I[a]



[a] (a) (1) $(n\text{-Bu})_2$BOTf, Hunig's base, CH_2Cl_2, 0 °C; (2) acrolein, −78 °C; (b) KOH, MeOH, 0 °C; (c) $LiAlH_4$, THF; (d) 1.1 equiv of *t*-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2; (e) propionyl chloride, pyridine, CH_2Cl_2; (f) (1) LDA, THF, −78 °C; (2) *t*-$BuMe_2SiCl$, HMPA, THF, −78 °C to room temperature; (3) reflux, 2 h; (4) K_2CO_3, MeOH, 0 °C; (g) (1) LDA, 23% HMPA in THF, −78 °C; (2) *t*-$BuMe_2SiCl$, THF, −78 °C to room temperature; (3) reflux, 2 h; (4) K_2CO_3, MeOH, 0 °C; (h) 1 atm H_2, PtO_2, EtOH; (i) $MeOCH_2CH_2OCH_2Cl$, Hunig's base, DMAP, CH_2Cl_2, 0 °C to room temperature; (j) HF, CH_3CN, 0 °C; (k) *p*-TsCl, pyridine, DMAP, CH_2Cl_2; (l) KCN, 18-crown-6, CH_3CN, reflux 48 h; (m) 1.2 equiv of diisobutylaluminum hydride, hexane, CH_2Cl_2, −78 °C; (n) *t*-$BuPh_2SiCl$, Et_3N, CH_2Cl_2, 0 °C to room temperature; (o) Me_3SiCl, NaI, CH_3CN, CH_2Cl_2, −40 °C; (p) $MeSO_2Cl$, pyridine, CH_2Cl_2; (q) *n*-$Bu_4N^+I^-$, THF, reflux 5 h; (r) 2 equiv of $LiCH_2SO_2Ph$, 30% HMPA in THF, −30 °C to room temperature; (s) (1) addition of 1.0 equiv of *n*-BuLi to **7**, 40% HMPA in THF, −78 °C to 30 °C; (2) addition of **8** at −25 °C; (3) warm to room temperature; (t) 6% Na(Hg), MeOH; (u) 1% HCl, ether, THF, 0 °C; (v) *n*-$Bu_4N^+Br^-$, THF, reflux; (w) (1) Mg, THF, reflux; (2) $AgNO_3$; (x) HCl, EtOH, THF.

from *Methanobacterium thermoautotrophicum*.[8] At 125.76 MHz, a $CDCl_3$ solution of diol **2** showed 17 resonances,[9] of which 7 differ by at least 0.05 ppm from corresponding resonances in the naturally derived diol. The greatest differences are seen in the resonances from C-2 ($\Delta\delta$ = −0.05), C-8 ($\Delta\delta$ = −0.06), C-12 ($\Delta\delta$ = −0.05), C-16 ($\Delta\delta$ = −0.14), the C-11 methyl group ($\Delta\delta$ = +0.06), and the C-15 methyl group ($\Delta\delta$ = +0.06) ($\Delta\delta = \delta_1 - \delta_2$). The spectrum of a 1:1 mixture of **2** and the naturally derived diol confirmed the conclusion that the two compounds are different.

In addition to providing confirmation for the previously assigned stereochemistry of the archaebacterial C_{40} diol, the present synthesis further demonstrates the versatility of the aldol-Claisen sequence for establishing remote stereochemical relationships. It is worthy of note that only one act of asymmetric synthesis is used in the synthesis of diol **2** (the aldol reaction of imide **3** with acrolein). By controlling the stereochemistry of enolate formation, the relative stereochemistry of **4** is parlayed into the syn and anti relationships of **5** and **6**. These substances are both "pseudosymmetrical", in that the two ends of the seven-carbon chain are differentiated by their oxidation state. Whereas in the present synthesis we convert **5** into **7** and **6** into **8**, we could have used **5** and **6** to prepare the enantiomers of **7** and **8**, simply by rearranging the sequence of transformations so as to homologate the other end of the chain. *In principle, compound 4 (or, for that matter, any of its stereoisomers) can be converted into any of the 132 stereoisomers of diol 1*!

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Registry No. **2**, 104486-21-7; **3**, 77877-20-4; **4**, 104486-22-8; **5**, 104486-23-9; **6**, 104486-24-0; **7**, 104423-51-0; **8**, 104423-52-1; **9**, 104423-53-2; **10**, 104423-50-9.

Clayton H. Heathcock,* Peggy A. Radel
Department of Chemistry
University of California
Berkeley, California 94720
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(8) The authentic sample was kindly supplied by Dr. Tadashi Aoki and Prof. C. Dale Poulter, of the University of Utah.

(9) Diol **2** showed resonances at δ 19.688, 19.737, 19.775, 24.377, 24.486, 29.548, 32.792, 32.813, 33.054, 34.433, 37.325, 37.365, 37.392, 37.459, 37.500, 39.993, and 61.280. Line shape and peak height suggests that the 19.688, 24.486, and 37.500 ppm resonances are each due to two carbons. The ^{13}C NMR spectrum of **1** has been reported elsewhere.[2]

Total Synthesis of (±)-Cortisone. Double Hydroxylation Reaction for the Construction of Corticoid Side Chain

Summary: An 18-step synthesis of (±)-cortisone has been achieved with the aid of silicon-based new synthetic sequences, in particular, homoenolate chemistry.

Sir: Owing to their remarkable physiological properties coupled with the structural complexity,[1] cortisone (1) and

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