Notes

Efficient Preparation of Chiral C_2-Symmetrical 2,6,9-Trioxabicyclo[3.3.1]nonanes from Cholesteryl Benzoate

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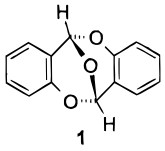
The formation of 2,6,9-trioxabicyclo[3.3.1]nonanes from salicylaldehydes and related compounds has been known for quite some time[1,2] and since the discovery of these compounds isolated examples of other dimerizations involving β-hydroxy aldehydes and ketones have been reported, mainly as unwanted side-reactions.[3,4] In the case of simple anhydro dimers of salicylaldehydes such as **1**, the trioxabicyclononane nucleus places the aryl



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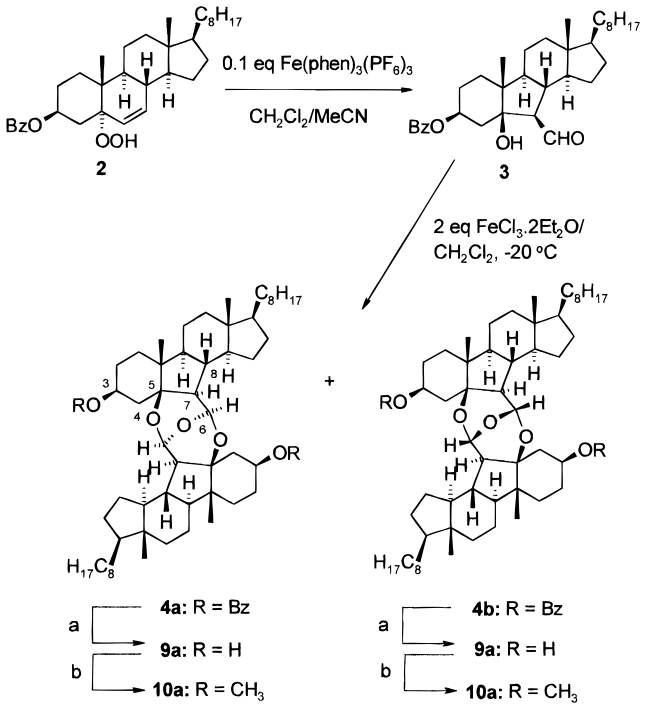
rings at an approximately 93° angle to one another thereby imparting a convex and a concave face to the molecule. As these compounds possess a C_2-axis of symmetry, there is potential for suitably functionalized derivatives of the individual enantiomers to participate in chiral recognition processes or to form inclusion complexes. However, to date no examples of individual resolved enantiomers have been reported. Attempts to confer asymmetry onto these compounds by mono derivatization have been made to enable separation of the resulting diastereomers, but on the whole no high yielding direct methods have been developed.[5] Apart from these reports, exploitation of the trioxabicyclononanes has not been made, presumably due to the limited synthetic methods and range of substrates available for their preparation. Nevertheless, it is also worthy to note that the trioxabicyclononane moiety features in the preussomerins, a class of fungal metabolites in which some of the members possess biological activity.[6]

As part of an ongoing study of the reactions of cyclic allylic hydroperoxides[7] we discovered that the acid-catalyzed Hock cleavage affords aldols as the primary

Scheme 1



Reagents: a. 15% KOH in MeOH/ DME, Δ; b. NaH, MeI/ THF, Δ

products via simple enols.[8] In those cases where the carbonyl group and the hydroxyl group of the aldol are anti, acid-catalyzed retroaldolization readily takes place to give either the expected carbonyl products, or, in the presence of Cu(II) and oxygen, α-hydroperoxy carbonyl compounds.[9] Cis aldols, on the other hand are resistant to acid-catalyzed retroaldolization but susceptible to other transformations. In the case of cis aldol **3** a remarkably facile dimerization takes place to give **4a** and **4b** thereby providing entry to a new class of functionalized trioxabicyclononanes. Details of this reaction are now presented.

Treatment of the hydroperoxide **2**, obtained from cholesteryl benzoate and singlet oxygen, with $FeCl_3 \cdot 2Et_2O$, in CH_2Cl_2 under nitrogen at −25 °C rapidly gave the aldol as predominantly the cis diastereomer **3** (Scheme 1). However, upon exposure to $FeCl_3 \cdot 2Et_2O$ above −10 °C, the hydroperoxide **2** was converted, via **3**, into two diastereomers of the 2,6,9-trioxabicyclo[3.3.1]nonane **4a** and **4b** in a combined yield of 43% and a ratio of 2:1, together with the aldol **3** (21%) and some enal **5**. In contrast, treatment of the hydroperoxide **2** with outer sphere oxidants such as $Fe(phen)_3(PF_6)_3$[10] or $Cu(OSO_2CF_3)_2$[11] in $MeCN/CH_2Cl_2$ under nitrogen at −20 °C led smoothly to the aldol **3**; subsequent warming of the reaction mixture did not provide the dimers. When the isolated aldol was treated with $FeCl_3 \cdot 2Et_2O$ (2 equiv) in CH_2Cl_2 at −20 °C, TLC showed steady formation of **4a**

(1) Jones, P. R.; Gelinas, R. M. *J. Org. Chem.* **1981**, *46*, 194 and cited references. Bachet, P. B.; Brassy, C.; Guidi-Morosini, C. *Acta Crystallogr.* **1986**, *C42*, 1630.
(2) Kulkarni, V. S.; Hosangadi, B. D. *Synth. Commun.* **1986**, *16*, 191.
(3) Lumma, W. C., Jr.; Ma, O. H. *J. Org. Chem.* **1970**, *35*, 2391.
(4) Padmanabhan, S.; Ogawa, T.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2114.
(5) Jones, P. R.; Langan, M. E. *Synth. Commun.* **1988**, *18*, 433.
(6) Weber, H. A.; Baenziger, N. C.; Gloer, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 6718; for compounds possessing Ras farnesyl-protein transferase activity see: Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296.
(7) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 449.
(8) Vonwiller, S. C.; Warner, J. A.; Mann, S. T.; Haynes, R. K. *J. Am. Chem. Soc.* **1995**, *117*, 11098.
(9) Vonwiller, S. C.; Warner, J. A.; Mann, S. T.; Haynes, R. K. *Tetrahedron Lett.*, submitted for publication.
(10) Schlesener, C. J.; Amatore, C.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3567.
(11) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843.

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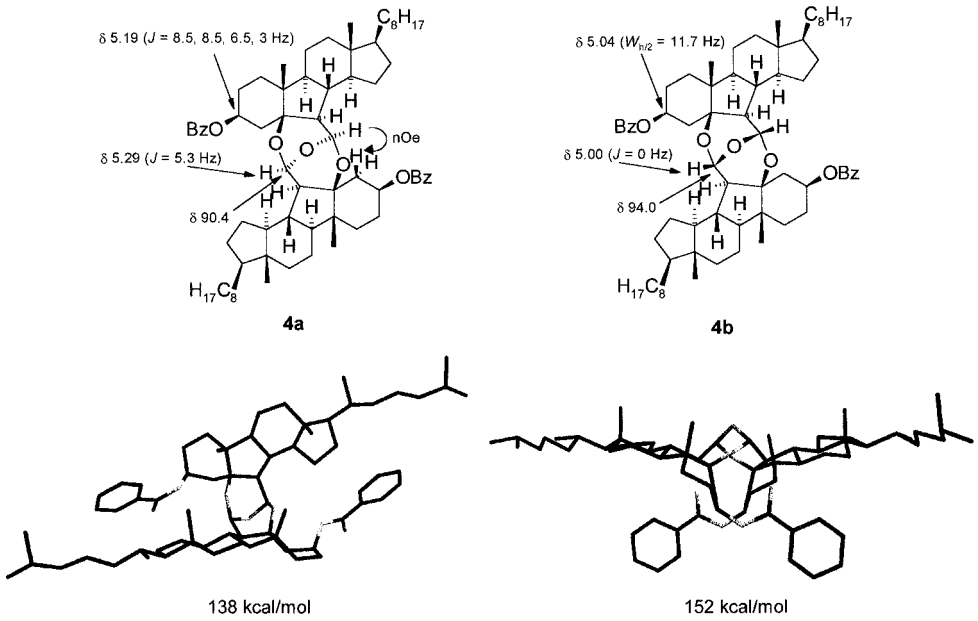
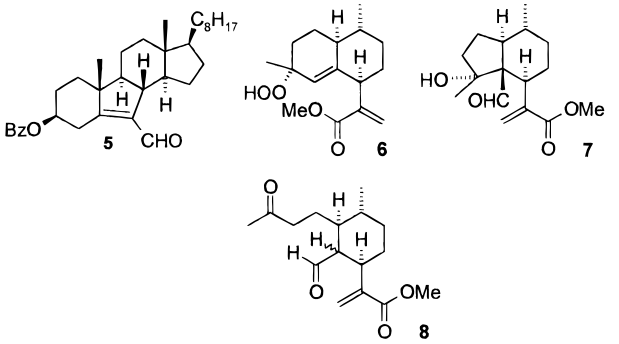


Figure 1. Summary of diagnostic NMR data and stereochemical features of **4a** and **4b** as indicated from energy-minimized structures.[12] Hydrogen atoms have been omitted for clarity.

and **4b** which were isolated in a combined yield of 83% and a ratio of *ca.* 2:1. Treatment of the hydroperoxide **2** with CF_3SO_3H led to the formation of the major dimer **4a** (21%), only negligible amounts of **4b**, and substantial amounts of **5** resulting from competing dehydration. In contrast, CF_3SO_3H catalyzes the smooth conversion of the trans aldol **7** derived from the qinghao acid methyl ester hydroperoxide **6** into the dicarbonyl compound **8** upon warming from −25 °C to 25 °C in CD_2Cl_2, and no dimer is observed.[8]



The structures of the dimers **4a**,**b** are indicated through ^1H and ^{13}C NMR spectra, which reveal the absence of double bonds, the presence of a methine proton adjacent to two oxygen atoms at δ 5.29 (doublet, J = 5.3 Hz) (**4a**) and δ 5.03 (singlet) (**4b**), and an acetal carbon at 90.4 ppm (**4a**) and 94.0 ppm (**4b**). The IR spectra contained no OH absorptions. Both diastereomers displayed distinct $M^+ + 1$ (*m*/*z* 1028) and $M^+ + NH_4$ (*m*/*z* 1045) peaks in their CI(NH_3) mass spectra.

The stereochemical features of each dimer were determined by a combination of 2D COSY and NOESY NMR experiments and molecular modeling.[12] The results are summarized in Figure 1. The major dimer **4a** has the norcholestane ring systems placed at a 65° angle to one another with the methyl groups projecting into the cavity. This is supported by NOE enhancements between H6 and H4′β and the *o*-phenyl protons of the benzoyl group.[13] The coupling between H6 and H7 of 5.3 Hz is consistent with the calculated dihedral angle of 36° produced in an energy-minimized structure with the assigned stereocenters. The conformation of the A-ring tended to minimize as a boat rather than a chair such that the 3-benzoyloxy groups are aligned with the alkyl side chains thereby increasing van der Waals contacts. Couplings of $J_{3\alpha,2\alpha} = 8.9$ Hz, $J_{3\alpha,2\beta} = 8.9$ Hz, $J_{3\alpha,4\alpha} = 6.7$ Hz, and $J_{3\alpha,4\beta} = 3.3$ Hz support a conformation in which H3α is no longer equatorial and H2α has deviated from its axial orientation. This is clearly evident when a comparison is made with the A-ring of the aldol **3** which is in the chair conformation: the couplings for H3α in this case are $J_{3\alpha,2\alpha} = J_{3\alpha,2\beta} = J_{3\alpha,4\alpha} = J_{3\alpha,4\beta} = 3.4$ Hz, indicating an equatorial orientation. The minor dimer **4b** which differed only in the stereochemistry of the acetal carbons displayed no measurable coupling between H6 and H7, consistent with the calculated dihedral angle of 92°. Such a structure has the norcholestane ring systems aligned in one plane with the A-rings projecting below the plane. In both cases the absence of doubling up of signals in the NMR spectra clearly indicates C_2-symmetry.

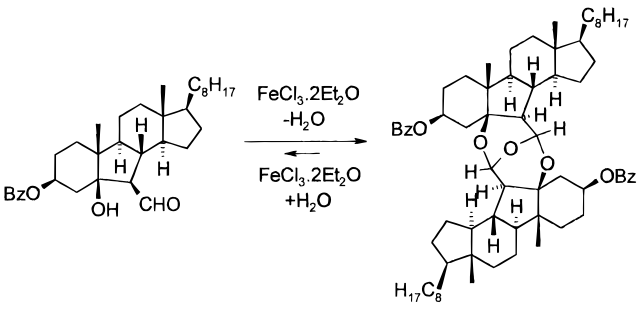
The mixture of benzoate dimers **4a**,**b** was readily hydrolyzed with 15% KOH in methanol/dimethoxyethane under gentle reflux to give the diols **9a** and **9b** in high isolated yields (59% and 26%, respectively, or total of 85%). The diastereomers differed substantially in polarity and were readily separated by chromatography on silica. NMR spectral data indicated that all stereocenters were retained in the operation. Methylation of each of the diols with sodium hydride/methyl iodide in THF was sluggish at room temperature but proceeded at a steady rate under gentle reflux to give the diethers **10a** (92%) and **10b** (84%).

The ease with which the dimerization takes place under the above conditions is noteworthy especially in view of the fact that the usual conditions for preparation of anhydro dimers of salicylaldehydes, such as heating

(12) MM2 in SPARTAN version 4.0; Wavefunction Inc., 18401 Von Karman, Suite 370, Irvine, California 92715.

(13) Atom numbering is based on the parent cholestane skeleton.

Scheme 2



with PPE,[2] cause facile dehydration of **3** to the enal **5**. Another example of dimerization of an aliphatic aldol involves a substrate that by virtue of methyl substitution is unable to undergo competing dehydration.[3] The success of the present example is attributed to a favorable equilibrium induced by the ferric chloride, in which the acid sensitive acetal groups become buried within a hydrophobic shroud and are thereby shielded from competing hydrolysis (Scheme 2). Addition of a water-sequestering agent such as anhydrous Na_2SO_4 or powdered 4 Å molecular sieves as distinct from a dehydrating agent enables the reaction to go to near completion with minimal competing enal formation.

As the starting aldol **3** is chiral and nonracemic the dimers themselves are chiral and nonracemic and represent the first examples of this type. The C_2-symmetry and unusual topography in which these compounds, in particular **4a** and derivatives, are found to possess a hydrophilic core and a hydrophobic outer surface suggest the potential for interesting cation complexation and transport properties. The consequences of this are currently under investigation.

Experimental Section

Materials. Diethyl ether was distilled from 18 M H_2SO_4 and stored over sodium wire. CH_2Cl_2 was dried over P_2O_5 and distilled under nitrogen prior to use. MeCN was dried over P_2O_5, distilled under reduced pressure from P_2O_5, and stored under N_2 over activated 4 Å molecular sieves. $Fe(phen)_3(PF_6)_3$ was prepared according to the method of Kochi.[10] $FeCl_3$ was dried with thionyl chloride. The etherate was prepared by suspending ferric chloride in CH_2Cl_2 and adding 2 equiv of dry ether with stirring to give a clear yellow solution. Other solvents and commercially available reagents were purified in the standard manner.

Preparation of the Aldol 3. Cholesteryl benzoate (1.00 g; 2.04 mmol) in pyridine (45 mL) containing hematoporphyrin sensitizer was irradiated (tungsten lamp, 500 W) for 17 h in a water-cooled Pyrex flask such that the bath temperature did not exceed 20 °C. The reaction proceeded to near completion. The pyridine was removed by distillation at 20 °C under high vacuum, and then the residue was dissolved in ether (50 mL) and stirred with activated charcoal for 30 min. Filtration through Celite followed by evaporation of the solvent gave a viscous oil which was purified by flash chromatography (ether/petroleum ether, 20:80). The hydroperoxide mixture so obtained (0.86 g) was then dissolved in CH_2Cl_2 (45 mL), and the solution was cooled to −15 °C under N_2. A solution of $Fe(phen)_3(PF_6)_3$ (7.5 mL; 0.022 M in MeCN; 0.17 mmol) was added dropwise, and then the reaction mixture was stirred for 1.75 h with slow warming to 10 °C. Ether (150 mL) was added to precipitate the catalyst, the red solid was filtered off with Celite, and the colorless filtrate was evaporated to give a solid residue. The solid was purified by flash chromatography (ether/petroleum ether, 25:75) followed by recrystallization from petroleum ether to give the aldol **3** as fine needles (0.53 g; 50% overall): mp 143−145 °C; IR ($CHCl_3$) 3600 w (OH), 3510 br w (OH), 2954 s, 2936 s, 2869 m, 2725 w, 1714 vs (C=O, ester and aldehyde), 1280 s, 1120 m cm^{-1}; ^1H NMR (400 MHz) δ 0.741 (3H, s), 0.863 (3H, d, J = 6.6 Hz), 0.867 (3H, d, J = 6.6 Hz), 0.925 (3H, d, J = 6.5 Hz), 1.005 (3H, s), 1.07−1.55 (18 H, m), 1.683 (1H, ddd, J = 15.3, 9.0, 6.1 Hz), 1.79−1.89 (3H, m), 2.002 (1H, dd, J = 15.5, 3.9 Hz), 2.086 (1H, ddd, J = 12.9, 3.2, 3.2 Hz), 2.22−2.27 (2H, m), 2.32 (1H, dd, J = 15.5, 3.2 Hz), 2.506 (1H, s, OH), 5.381 (1H, dddd, J = 3.4, 3.4, 3.4, 3.4 Hz), 7.43−7.47 (2H, m), 7.55−7.59 (1H, m), 7.96−7.99 (2H, m), 9.712 (1H, d, J = 2.8 Hz). Preirradiation of the signal at 1.00 ppm (19-CH_3) resulted in enhancements at 2.51 ppm (OH) (1.1%), at 7.96−7.99 ppm (C_6H_5 *ortho*) (1.9%) and at 9.71 ppm (CHO) (1.3%). Preirradiation of the signal at 2.51 ppm (OH) resulted in enhancements at 1.00 ppm (19-CH_3) (3%), 7.96−7.99 (C_6H_5 *ortho*) (8.7%), and 9.71 ppm (CHO) (3.3%). Preirradiation of the signal at 9.71 ppm (CHO) resulted in enhancements at 1.00 ppm (19-CH_3) (1.9%), 2.25 ppm (H7) (6.1%), 2.51 ppm (OH) (1.4%). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.48, 18.31, 18.74, 21.55, 22.52, 22.77, 23.80, 24.49, 24.76, 27.98, 28.17, 28.32, 35.59, 36.17, 39.46, 39.50, 39.64, 42.29, 44.66, 45.62, 51.34, 55.67, 56.04, 70.74, 83.63, 128.56, 129.38, 130.15, 133.16, 165.52, 203.87. MS m/z 505 (M − OH, < 1%), 400 (M − C_6H_5COOH, 5), 383 (15), 3822 (27), 367 (11), 354 (51), 145 (22), 133 (22), 122 (33), 110 (58), 105 (100), 95 (38), 77 (50), 69 (31), 55 (51), 43 (88), 41 (52); Anal. Calcd for $C_{34}H_{50}O_4$: C, 78.12; H, 9.64. Found: C, 77.92; H, 9.41.

Formation of the Dimers 4a,b. The aldol **3** (468.5 mg; 0.90 mmol) was dissolved in dichloromethane (21 mL) and treated with $FeCl_3$ dietherate (0.17 M in dichloromethane; 1.80 mmol; 10.4 mL; 2 equiv) at −20 °C under nitrogen. This imparted a bright yellow coloration to the reaction mixture and resulted in gradual formation of the dimers. Stirring was continued at −20 °C for 18 h during which time the reaction mixture remained a deep orange color. Anhydrous sodium sulfate (1.0 g) was next added as a solid, and stirring was continued for a further 7 h. The reaction was quenched by pouring onto a stirred ice-cold solution of saturated $NaHCO_3$ solution. The iron residues were removed by filtration through Celite, and the resulting mixture was extracted with ether. The ether extracts were washed with brine and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The product mixture was fractionated by flash chromatography (ether/petroleum ether, 25:75) to give the dimers **4a**,**b** in an approximately 2:1 ratio (381 mg; 83%) and recovered aldol **3** (67 mg; 14%) as white solids. Higher reaction temperatures led to substantial dehydration of the aldol and lower yields of the dimers. The individual dimers were separated by flash chromatography on silica (ether/petroleum ether, 2:98 to 7.5:92.5) to give first the major diastereomer **4a** as a white solid. This was recrystallized from acetonitrile/ether as fine needles: mp 189−190.5 °C; IR (CCl_4) 2951 vs, 2870 s, 1717 s (C=O), 1468 m, 1452 m, 1383 m, 1277 s, 1161 m, 1117 s, 1082 m, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.666 (3H, s), 0.878 (3H, d, J = 6.5 Hz), 0.883 (3H, d, J = 6.5 Hz), 0.916 (3H, d, J = 6.5 Hz), 1.063 (3H, s), 1.537 (1H, dd, J = 10.8, 5.1 Hz), 1.63−1.73 (2H, m), 1.796 (1H, dd, J = 15, 6.5 Hz), 1.97−2.05 (2H, m), 2.09−2.18 (1H, m), 2.402 (1H, dd, J = 15, 3.2 Hz), 5.186 (1H, dddd, J = 8.5, 8.5, 6.5, 3 Hz), 5.291 (1H, d, J = 5.3 Hz), 7.39−7.44 (2H, m), 7.52 −7.57 (1H, m), 7.98−8.01 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.15, 17.74, 18.85, 21.16, 22.53, 22.80, 23.99, 24.76, 25.29, 28.02, 28.43, 32.79, 35.64, 36.32, 37.77, 38.70, 39.53, 39.60, 43.98, 46.83, 54.45, 55.92 (2C), 56.77, 71.42, 82.22, 90.44, 128.12, 129.63, 130.88, 132.57, 166.67; MS (CI/NH_3) m/z 1045 (M + NH_4^+, 1%), 1028 (M + 1, <1), 906 (2), 523 (100). Anal. Calcd for $C_{68}H_{98}O_7$: C, 79.49; H, 9.61. Found: C, 79.23; H, 9.45.

The more polar minor diastereomer **4b** was obtained as a fine powder: mp 102−104.5 °C from MeCN; IR (KBr) 2946 vs, 2867 s, 1720 s (C=O), 1467 m, 1451 m, 1383 m, 1277 s, 1188 s, 1117 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.654 (3H, s), 0.879 (3H, d, J = 6.5 Hz), 0.884 (3H, d, J = 6.6 Hz), 0.919 (3H, d, J = 6.4 Hz), 1.009 (3H, s), 2.022 (1H, d, J = 12.5 Hz), 2.383 (1H, d, J = 15.4 Hz), 5.031 (1H, s), 5.04 (1H, br m, $W_{h/2}$ = 11.7 Hz), 7.35−7.39 (2H, m), 7.49−7.53 (1H, m), 8.04−8.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 18.8, 22.5, 22.8, 24.0, 24.5, 24.8, 28.0, 28.6, 30.1, 35.7, 36.3, 39.5, 39.7, 39.8, 43.8, 44.3, 46.8, 51.9, 54.7, 55.5, 56.6, 70.1, 82.7, 94.0, 128.0, 129.6, 131.5, 132.3, 166.1; MS (CI/NH_3) m/z 1045 (M + NH_4^+, 15%), 1028 (M + 1, 6), 906 (2), 523 (100). Anal. Calcd for $C_{68}H_{98}O_7$: C, 79.49; H, 9.61. Found: C, 79.70; H, 9.48.

Hydrolysis to the Diols 9a,b. The dimer mixture from above (381 mg; 0.37 mmol) was dissolved in DME (8 mL) and

then treated with KOH in methanol (7 mL; 15%) for 10 min at room temperature. The mixture was then heated under gentle reflux for 1 h, becoming orange in color, cooled, and then poured onto water. The product was extracted into ether, and the combined extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent left a residue which was fractionated by flash chromatography (ether/petroleum ether; 80:20). The less polar major isomer **9a** was obtained as a pale yellow solid which upon trituration with methanol, filtration, and drying was obtained as a colorless powder (178 mg; 59% or 50% from **3**): mp 186−188 °C; IR (KBr) 2947 vs, 1467 m, 1158 s, 1102 s, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.668 (3H, s), 1.029 (3H, s), 0.742 (1H, ddd, J = 11.8, 11.8, 5.1 Hz), 0.858 (3H, d, J = 6.6 Hz), 0.863 (3H, d, J = 6.6 Hz), 0.914 (3H, d, J = 6.5 Hz), 1.029 (3H, s), 1.451 (1H, dd, J = 15.4, 5.2 Hz), 1.535 (1H, dd, J = 11.0, 5.5 Hz), 1.861 (1H, d, J = 10.4 Hz), 1.960 (1H, ddd, J = 11.7, 11.7, 11.7 Hz), 2.202 (1H, dddd, J = 13.8, 10.2, 3.6, 3.6 Hz), 2.379 (1H, dd, J = 15.1, 2.2 Hz), 3.972 (1H, br m, $W_{h/2}$ = 19.6 Hz), 5.445 (1H, d, J = 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 16.9, 18.9, 21.0, 22.5, 22.8, 23.9, 25.4, 28.0, 29.9, 33.7, 35.6, 36.2, 37.3, 39.4 (2 signals), 39.5, 40.5, 43.9, 46.8, 55.5, 55.59, 55.61, 57.2, 67.4, 83.5, 89.8; MS (CI/NH_3) m/z 820 (M + 1, 100%), 837 (M + NH_4, 3%). Anal. Calcd for $C_{54}H_{90}O_5$: C, 79.16; H, 11.07. Found: C, 78,91; H, 10.86.

The more polar minor isomer **9b** was obtained, after changing the eluting solvent to ether (100%), as a brittle glass (79 mg; 26% or 22% from **3**): mp 95−97 °C; IR (KBr) 2942 vs, 2920 vs, 1468 m, 1181 s, 1100 m, 997 m, 969 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.663 (3H, s), 0.860 (3H, d, J = 6.6 Hz), 0.865 (3H, d, J = 6.6 Hz), 0.908 (3H, d, J = 6.5 Hz), 1.019 (3H, s), 1.473 (1H, d, J =10.0 Hz), 1.602 (1H, dd, J = 14.8, 4.8 Hz), 1.681 (1H, ddd, J = 11.6, 10.2, 10.2 Hz), 1.856 (1H, br m, $W_{h/2}$ = 22 Hz), 2.027 (1H, ddd, J = 12.8, 3.2, 3.2 Hz), 2.251 (1H, dd, J = 14.8, 1.7 Hz), 2.872 (1H, d, J = 10.1 Hz), 3.931 (1H, br m, $W_{h/2}$ = 17.8 Hz), 5.098 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 18.0, 18.8, 21.2, 22.5, 22.8, 23.9, 24.6, 28.0, 28.5, 28.9, 30.7, 35.7, 36.2, 39.5, 39.6, 39.9, 44.4, 46.4, 46.9, 53.0, 54.9, 55.4, 56.1, 67.6, 85.7, 94.3; MS (C. I./NH_3) m/z 820 (M + 1, 100%), 837 (M + NH_4, 5%). Anal. Calcd for $C_{54}H_{90}O_5$: C, 79.16; H, 11.07. Found: C, 79.30; H, 10.98.

Methylation of the Major Diol. Sodium hydride (43.2 mg; 1.08 mmol; 60% dispersion in oil) was washed with dry pentane (2 × 2 mL), dried under a nitrogen stream, and then suspended in dry THF (6 mL). The diol **9a** (122.8 mg; 0.150 mmol) in THF (5 mL) was then added followed by methyl iodide (56 μL; 0.90 mmol). The resulting mixture was heated under gentle reflux for 24 h. After cooling in ice the reaction mixture was treated with water and extracted with ether. The combined extracts were washed with brine and dried (Na_2SO_4). The crude product obtained after evaporation of the solvent was purified by flash chromatography (ether/petroleum ether; 10:90) to give the dimethyl ether **10a** as a white solid (117.8 mg; 92%). Crystallization from methanol afforded small prisms, mp 79−82 °C. IR (KBr) 3469 br m, 2946 vs, 1469 m, 1088 m, 981 m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.652 (3H, s), 0.747 (1H, ddd, J = 11.9, 11.9, 4.4 Hz), 0.861 (3H, d, J = 6.6 Hz), 0.865 (3H, d, J = 6.6 Hz), 0.915 (3H, d, J = 6.5 Hz), 0.980 (3H, s), 1.510 (1H, dd, J = 10.5, 5.0 Hz), 1.642 (1H, dd, J = 14.5, 5.5 Hz), 1.851 (1H, dddd, J = 13.0, J = 9.0, J = 5.3, J = 3.6 Hz), 1.967 (1H, ddd, J = 11.6, 11.6, 11.6 Hz), 2.009 (1H, ddd, J = 12.7, 3.4, 3.4 Hz), 2.150 (1H, dd, J = 14.4, 4.4 Hz), 3.254 (3H, s), 3.474 (1H, m, $W_{h/2}$ = 18 Hz), 5.279 (1H, d, J = 5.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.1, 17.6, 18.9, 21.1, 22.6, 22.8, 23.8, 24.6, 25.3, 28.0, 32.4, 35.6, 36.3, 37.4, 39.5, 39.6, 43.8, 46.6, 53.8, 55.6, 55.7, 56.1, 56.5, 75.7, 82.0, 90.3. MS (CI/NH_3) m/z 847 (M + 1, 3%), 816 [M − (2 × CH_3), 35], 433 (100). Anal. Calcd for $C_{56}H_{94}O_5$: C, 79.38; H, 11.18. Found: C, 79.51; H, 11.71.

Methylation of the Minor Diol. The minor diol **9b** (93.0 mg; 114 μmol) in THF (5 mL) was methylated under the above conditions, and then the crude product obtained after evaporation of the solvent was purified by flash chromatography (ether/petroleum ether; 20:80) to give the dimethyl ether **10b** as a white crystalline solid (81.1mg; 84%). Crystallization from methanol afforded small prisms: mp 227−231 °C; IR (KBr) 3567 w, 3370 br m, 2946 vs, 1468 m, 1181 s, 1079 m, 970 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.663 (3H, s), 0.861 (3H, d, J = 6.6 Hz), 0.867 (3H, d, J = 6.6 Hz), 0.908 (3H, d, J = 6.5 Hz), 0.959 (3H, s), 1.609 (1H, d, J = 10 Hz), 1.723 (1H, dd, J = 14.4, 4.9 Hz), 2.015 (1H, ddd, J = 12.7, 2.9, 2.9 Hz), 2.158 (1H, dd, J = 14.4, 5.2 Hz), 3.331 (3H, s), 3.440 (1H, m, $W_{h/2}$ = 16 Hz), 5.085 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6, 18.5, 18.8, 21.4, 22.5, 22.8, 23.9, 24.7, 25.5, 28.0, 28.6, 30.4, 35.7, 36.3, 39.5, 39.6, 39.8, 43.4, 44.4, 47.3, 52.1, 54.7, 55.4, 56.1, 56.3, 75.5, 84.0, 94.2. MS (CI/NH_3) m/z 847 (M + 1, 14%), 816 [M − (2 × CH_3), 68], 647 (100). Anal. Calcd for $C_{56}H_{94}O_5$: C, 79.38; H, 11.18. Found: C, 79.08; H, 11.55.

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Supporting Information Available: Tabulated NMR data with assignments for compounds **4a**, **4b**, **9a**, **9b**, **10a**, and **10b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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