proposed structures and could not be reconciled with models generated for the rearrangement products.

Conformational Exchange. In the course of examining the 1D spectrum of the diester 4 in DMSO-d_6 at pH 4.0, a number of extraneous peaks were present which we first assumed to originate from minor impurities. However, two subsequent observations indicated that these extra peaks originated not from impurities but were due to a minor conformational isomer that under these conditions was in slow exhange. First, the signals associated with what was assumed to originate from a second component essentially disappeared on addition of D_2O or H_2O to the sample and were not observed when the same sample was run at pH 6.0 in DMSO. Convincing evidence that the additional peaks originated from a second component in equilibrium with the major conformer was obtained from the NOESY spectrum for a DMSO solution at pH 4.0. This NOESY spectrum contained a large number of exchange crosspeaks between signals of the major and minor components, clearly indicating that the two species in solution are in equilibrium. A region of the NOESY spectrum of the diester is shown in Figure 2 and clearly reveals the increased intensity of the exchange crosspeaks, cf. (ANH, aNH), (BNH, bNH), (B1′, b1′), and (FNH, fNH), relative to the crosspeaks observed for dipolar couplings. A comparison of the relative intensities of peaks from the major conformer with those in the minor conformer in the 1D spectrum indicated that the concentration of minor conformer under these conditions (DMSO at pH 4.0) is <10%.

Following the observations of exchange NOEs in the spectrum of the diester, the NOESY spectra of both OA-7653 and the diacid 3 in DMSO solution at pH 4.0 were also observed to show exchange crosspeaks consistent with the existence of two observable conformations, one major and the second occurring at the level of ≃10% of the other. Unfortunately, it was not possible to derive any details of the structure of the minor conformation which could be used to derive information on the structural differences between the major and minor conformations. However, the pattern of chemical shift differences between the major and minor components is the same for all three compounds (see Table II). The rather significant difference in chemical shift of the B1′ resonance in the major and minor conformations throughout the series is noteworthy.

The existence of slow conformational exchange in teicoplanin and in OA-7653 and its derivatives in DMSO solution suggests that the occurrence of this phenomena in this class of antibiotics should be considered along with other reasons such as aggregation as a source of line-broadening in the ^1H spectra of these antibiotics.

Conclusions. The structure of the antibiotic OA-7653 places it with vancomycin and its analogues[21] in a subgroup where the variable G and F residues both originate from aliphatic amino acids. A further similarity with vancomycin is that the F residue in OA-7653 is the amino acid glutamine, whereas this position in vancomycin is occupied by asparagine. The glutamine residue is shown to undergo facile acid hydrolysis without rearrangement in providing the diacid 3. Like teicoplanin, OA-7653, the diacid 3 and its dimethyl ester 4 are each shown to exist in DMSO solutions as a pair of conformers that exchange at a rate comparable to the NMR time scale.

Acknowledgment. We are indebted to C. Pan and J. Dingerdissen for carrying out the fermentations and biological assays and providng assistance with the isolation. The FAB MS and GC-CI-MS data were kindly provided by G. Roberts and L. Killmer.

Supplementary Material Available: Figure showing a comparison of the 500-MHz 1D spectra of compounds 2, 3, and 4, which illustrate the signal profiles of the glutamate side chains in these compounds; table of complete ^1H chemical shift assignments for OA-7653 and its derivatives 3 and 4; table identifying proton pairs involved in through-space connectivities from the NOESY spectra of OA-7653, the diacid 3, and ester 4; and a table showing distance data derived from the computer model of OA-7653 with that obtained from the values calculated from quantitative NOE intensities for OA-7653 and compounds 3 and 4 (10 pages). Ordering information is given on any current masthead page.

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A Formal Total Synthesis of (±)-Laurenene

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The tetracyclic α,β-unsaturated ketone 2, a key intermediate in the Itô and Crimmins syntheses of racemic laurenene, is prepared in nine steps from the known functionalized triquinane 3. Despite the presence of considerable steric congestion, 3 smoothly undergoes conversion to the silylated cyanohydrin and subsequently to nitrile 6. In the key step, the anion of 6 is efficiently alkylated from its β face to give only 7. Following reduction of the nitrile function to an angular methyl group, the keto aldehyde 9 is elaborated and cyclized effectively under acidic conditions. Neither the structurally related methyl ketone 14 nor the intermediates 16 and 17 could be made to undergo analogous ring closure under a variety of reaction conditions.

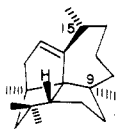
In 1979, Corbett and co-workers reported the isolation of a new diterpene hydrocarbon from the volatile oil of *Dacrydium cupressinum*.[1] This levorotatory substance, for which the name laurenene was proposed, was identified as Nature's only known fenestrane molecule, chiefly on the strength of X-ray crystallographic analysis of a brominated derivative.[2] The Otago, New Zealand group headed by

(1) Corbett, R. E.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1774.

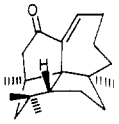
(2) Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1791.

0022-3263/88/1953-0477$01.50/0

Weavers has since elaborated some of the unusual chemical properties intrinsic to 1.[3]



1



2

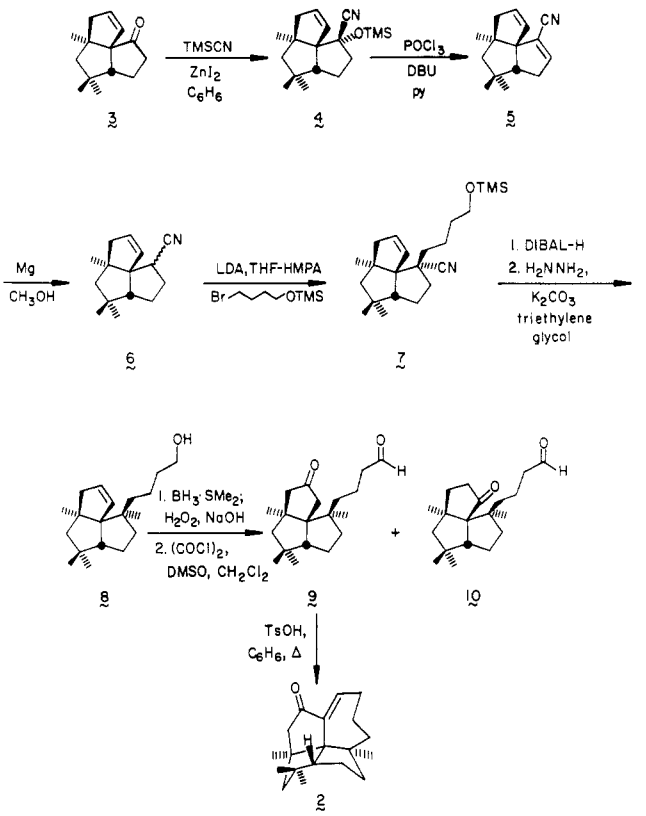
Laurenene is also recognized to be an angular triquinane.[4] Understandably, this molecule has commanded considerable synthetic interest. This activity has recently culminated in the completion of two total syntheses at the hands of Itô[5] and of Crimmins.[6] In the first approach, the third contiguous quaternary carbon of 1 (at C-9) was formed by stereocontrolled Claisen rearrangement. Subsequent elaboration and aldolization of a tricyclic keto aldehyde gave 2, with introduction of the C-15 methyl substituent ultimately being accomplished by a sequence revolving around a cyanation step.[5] The second route involved an elevated temperature intramolecular [2 + 2] photochemical cycloaddition and subsequent reductive cleavage of the cyclobutane ring to set the central quaternary carbon and pendant side chain. Following conversion to 2, stereocontrolled introduction of the last methyl group was achieved by means of the Still rearrangement.[6]

We have also pursued a synthesis of laurenene and have developed an efficient alternative preparation of 2. The present scheme takes advantage of the ready availability of tricyclic ketone 3, a key intermediate in Leone-Bay's route to (±)-silphinene[7] (Scheme I). Despite the sterically hindered nature of the carbonyl group in 3, reaction with trimethylsilyl cyanide and a catalytic amount of zinc iodide[8] in benzene solution at room temperature provided for virtually quantitative acquisition of 4. Although conversion to unsaturated nitrile 5 could be realized by heating with phosphorus oxychloride in pyridine at 150 °C in a sealed tube, the added presence of DBU[9] was found to deliver 5 more efficiently (92%) under less forcing conditions. Chemospecific reduction of the α,β-unsaturated nitrile functionality was achieved by means of magnesium in methanol.[10] Although both epimers of 6 were produced (57% α, 43% β), this issue was of no consequence since generation of the α-cyano carbanion was to ensue.

With 6 in hand, its direct alkylation was next visualized. We were well aware of the vagaries associated with defining a priori the stereochemical course of carbon–carbon bond formation in sterically congested angular triquinane systems.[11,12] In the present circumstances, the projected alkylation would serve to install the last of the three vicinal quaternary centers. Although the region suffers from serious steric crowding, the linear cyano group was anticipated to be a positive feature. Additionally, Dreiding models of this anion lent strong credence to the proposition that entry of the electrophile from the β direction would be kinetically favored.

To assess the actual state of affairs, 6 was deprotonated

Scheme I



3 4 5 6 7 8 9 10 2

with lithium diisopropylamide and treated with 1-bromo-4-[(trimethylsilyl)oxy]butane[13] in a mixed tetrahydrofuran–HMPA solvent system. Workup gave rise to a single alkylation product in 83% yield. Although we were not immediately in a position to define the stereochemistry of 7 unambiguously, the indicated formulation was ultimately established by conversion to 2.

Transposition of the nitrile function into the requisite angular methyl group was accomplished without incident by sequential diisobutylaluminum hydride and Wolff–Kishner[14] reductions. The latter step also effected deblocking of the silyl ether to deliver alcohol 8 directly.

When 8 was hydroborated at 50 °C with the borane–dimethylsulfide complex[15] and the diol mixture was directly oxidized under Swern conditions,[16] the regioisomeric keto aldehydes 9 and 10 were isolated in 72% overall yield. Their separation was readily achieved by short column chromatography,[17] and the desired regioisomer 9 was found to dominate by a factor of 6.2:1. Closure of the seven-membered ring by intramolecular aldolization proceeded

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(4) (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (b) Paquette, L. A. *Ibid.* **1984**, *119*, 1. (c) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry—Syntheses and Reactions*; Verlag Chemie: Heidelberg, 1987.

(5) Tsunoda, T.; Amaike, M.; Tambunan, U. S. F.; Fujise, Y.; Itô, S.; Kodama, M. *Tetrahedron Lett.* **1987**, *28*, 2537.

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(9) Sugihara, Y.; Wakabayashi, S.; Saito, N.; Murata, I. *J. Am. Chem. Soc.* **1986**, *108*, 2773.

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(11) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358.

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(14) Hansen, H.-J.; Sliwka, H.-R.; Hug, W. *Helv. Chim. Acta* **1979**, *62*, 1120.

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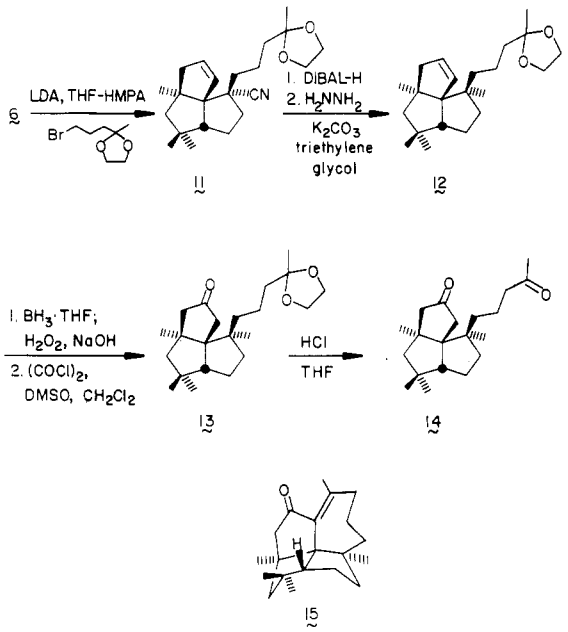
(16) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(17) Hunt, B. J.; Rigby, W. *Chem. Ind. (London)* **1967**, 1868.

Scheme II

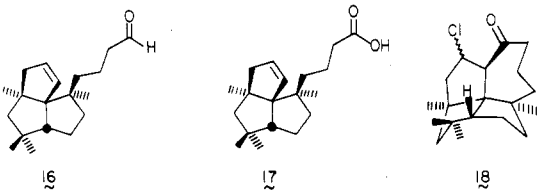


smoothly under acidic conditions to give **2** in 78% yield from **9**.

Although the transformation of **2** into laurenene requires in theory only the stereocontrolled 1,4-addition of a methyl group and conversion of the residual carbonyl functionality into an olefinic center, this specific chemical change has been implemented only with considerable difficulty.[5,6] The problem stems in large part from the topology inherent in **2**, which serves to direct approaching nucleophiles strongly to the β surface of C-15 (as drawn herein). Access from the α direction is presumably impeded by the pair of angular methyl groups present there.

Were the methyl-substituted enone **15** available, proper setting of C-15 stereochemistry would be reduced simply to formal 1,4-delivery of hydrogen from the sterically open face. Consequently, we have given some attention to obtaining **15**. Alkylation of the anion of **6** with 5-bromo-2-pentanone ethylene ketal[18] gave **11** in 62% yield along with 36% of recovered starting material (Scheme II). The nitrile to methyl reduction was achieved uneventfully as before. When recourse was next made to the hydroboration–Swern oxidation sequence, ketone **13** was obtained (54%) together with its regioisomer (24%). Acidic hydrolysis of **13** led cleanly to **14**. However, all attempts to effect the cyclization of **14** went unrewarded. In no instance was evidence uncovered for the formation of **15**. The insight gained from these experiments was that the rate of cyclization in this case is exceedingly slow or that retro-aldol cleavage of the seven-membered ring compound, if formed, occurs more rapidly than the closure step.

Two irreversible methods of ring formation were therefore scrutinized. Following pyridinium chlorochromate oxidation of **8** to give **16**, this aldehyde was exposed to a variety of Lewis acids in an effort to achieve intramolecular Prins reaction.[19] However, no ene reaction was seen. The acid chloride derived from **17** was similarly subjected to Lewis acid promoted Friedel–Crafts cyclization.[20] Only when $AlCl_3$ was utilized was conversion to **18** apparent (mass spectral analysis). However, the yield and purity of this product were so low as to discourage further efforts along these lines.



In summary, the synthetic exercise has been a limited success. Intramolecular aldolization to produce the laurenene framework proceeds efficiently from **9**. However, strong kinetic impedance to closure of the seven-membered ring is seen in **14**, **16**, and **17**. The inoperability of this latter group of reactions may have its origin in the need for the two angular methyl groups to approach each other more closely as bond formation giving rise to the cycloheptane ring commences.

Experimental Section

Trimethylsilyl Cyanohydrin 4. A solution of **3** (331 mg, 1.62 mmol), zinc iodide (4 mg), and trimethylsilyl cyanide (0.32 mL, 2.4 mmol) in dry benzene (4.9 mL) was stirred at room temperature for 18 h and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 3% ethyl acetate in petroleum ether) to give 472 mg (96%) of **4** as a clear colorless oil: IR (neat, cm^{-1}) 3050, 2960, 2220, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (m, 1 H), 5.67 (m, 1 H), 2.42 (td, J = 16.8, 2.0 Hz, 1 H), 2.24 (td, J = 16.8, 2.0 Hz, 1 H), 2.17 (m, 3 H), 1.83 (m, 2 H), 1.75 (d, J = 1 Hz, 13.1 H), 1.69 (d, J = 13.1 Hz, 1 H), 1.32 (s, 3 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.24 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) 137.1, 130.0, 121.6, 79.9, 77.3, 59.3, 52.3, 50.6, 40.8, 39.7, 33.2, 27.4, 25.4, 23.0, 1.2; MS, m/z (M^+) calcd 303.2019, obsd 303.1989.

α,β-Unsaturated Nitrile 5. A solution containing **4** (315 mg, 1.04 mmol), phosphorus oxychloride (0.69 mL, 7.4 mmol), DBU (0.70 mL, 4.7 mmol), and dry pyridine (10 mL) was heated at the reflux temperature for 20 h and allowed to cool. The dark reaction mixture was poured into cold 5% hydrochloric acid (25 mL) and ether (25 mL). The aqueous phase was extracted with ether (3 × 25 mL), and the combined organic layers were dried and concentrated. The residue was purified by column chromatography (silica gel, 4% ethyl acetate in petroleum ether) to give 205 mg (92%) of **5** as a clear colorless liquid: IR (neat, cm^{-1}) 3050, 2960–2820, 2220, 1640, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (t, J = 2.5 Hz, 1 H), 5.77 (m, 1 H), 5.53 (m, 1 H), 2.50–2.36 (series of m, 5 H), 1.72 (d, J = 13.3 Hz, 1 H), 1.65 (d, J = 13.3 Hz, 1 H), 1.17 (s, 3 H), 1.06 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.0, 135.3, 131.3, 119.8, 117.0, 79.2, 60.3, 57.9, 51.2, 51.0, 40.5, 35.1, 29.6, 27.3, 26.8; MS, m/z (M^+) calcd 213.1518, obsd 213.1475. Anal. Calcd for $C_{15}H_{19}N$: C, 84.45; H, 8.98. Found: C, 84.44; H, 9.09.

Chemospecific Reduction of 5. A three-necked 250-mL round-bottomed flask equipped with a condenser, magnetic stirring bar, stopper, and septum was charged with magnesium turnings (2.65 g, 109 mmol). The reaction vessel was dried with a flame and allowed to cool. A solution of **5** (802 mg, 3.76 mmol) in methanol (67 mL) was introduced via cannula, and the mixture was stirred for 11 h. Cold 6 N hydrochloric acid (70 mL) was added in one portion, followed by ether (70 mL). The aqueous phase was extracted with ether (3 × 70 mL), and the combined organic layers were dried and concentrated. The residue was purified by column chromatography (silica gel, 4% ethyl acetate in petroleum ether) to give 767 mg (95%) of **6**, a clear colorless liquid, as a 1.3:1 mixture of epimers (^1H NMR analysis). For the β isomer: IR (neat, cm^{-1}) 2960, 2220, 1455, 1255; ^1H NMR (300 MHz, CCl_3) δ 5.73 (m, 1 H), 5.67 (m, 1 H), 2.90 (dd, J = 10.5, 6.4 Hz, 1 H), 2.55 (d, J = 17.7 Hz, 1 H), 2.35 (d, J = 17.7 Hz, 1 H), 2.17 (m, 1 H), 2.00 (m, 1 H), 1.90–1.60 (series of m, 4 H), 1.33 (m,

(18) Bellas, T. E.; Brownlee, R. G.; Silverstein, R. M. *Tetrahedron*, **1969**, *25*, 5149.

(19) For example: van der Gen, A.; Wiedkaup, K.; Swoboda, J. J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 2656.

(20) See, for example: Nozoe, S.; Furakawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195.

1 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.0, 130.4, 121.3, 72.9, 62.1, 59.8, 50.9, 50.5, 39.5, 37.1, 30.3, 29.8, 28.5, 27.6, 25.0; MS, m/z (M^+) calcd 215.1674, obsd 215.1669.

Alkylation of 6 with 1-Bromo-4-[(trimethylsilyl)oxy]butane. To a solution of lithium diisopropylamide [from diisopropylamine (0.49 mL, 3.5 mmol), *n*-butyllithium (2.2 mL of 1.57 M in hexane, 3.4 mmol), and 20 mL of anhydrous tetrahydrofuran at 0 °C for 30 min] cooled to −78 °C was added dry HMPA (2.8 mL) and a precooled solution of **6** (616 mg, 2.86 mmol) in anhydrous tetrahydrofuran (10 mL). After 1 h of stirring, a solution of 1-bromo-4-(trimethylsiloxy)butane (0.77 g, 3.4 mmol) in the same solvent (10 mL) was introduced, and the reaction mixture was allowed to warm to room temperature during 5 h. Water (40 mL) and ether (40 mL) were added, and the aqueous phase was extracted with ether (3 × 40 mL). The combined organic extracts were dried and concentrated. The residue was purified by short column chromatography (TLC grade silica gel, 4% ethyl acetate in petroleum ether) to give 854 mg (83%) of **7** as a clear colorless oil: IR (neat, cm^{-1}) 2955, 2230, 1465, 1385, 1365, 1255, 1102, 875, 845; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 1 H), 5.56 (m, 1 H), 3.58 (m, 2 H), 2.37 (t, J = 2.0 Hz, 2 H), 2.18 (m, 2 H), 1.95–1.35 (series of m, 13 H), 1.45 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 0.11 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 136.4, 128.8, 124.4, 76.0, 62.2, 61.5, 59.5, 51.8, 49.8, 47.9, 38.6, 37.0, 34.8, 33.3, 32.8, 27.8, 25.1, 24.8, 22.4, -0.5; MS, m/z (M^+) calcd 359.2644, obsd 359.2680.

Reduction of 7 to Tricyclic Alcohol 8. A magnetically stirred solution of **7** (707 mg, 1.97 mmol) in dry benzene (20 mL) was treated with diisobutylaluminum hydride (3.0 mL of 1.0 M in hexane, 3.0 mmol). After 1 h, ethanol (1 mL) and water (20 mL) were introduced, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic phases were dried and concentrated to leave a residue, which was taken up in a triethylene glycol (68 mL). Hydrazine hydrate (3 mL) and potassium carbonate (3.29 g) were added, and the mixture was deoxygenated (N_2) and heated at 260 °C for 19 h. After cooling, water (140 mL) and ether (140 mL) were added, and the aqueous phase was extracted with ether (3 × 140 mL). The combined organic layers were dried and concentrated. The residue was purified chromatographically (silica gel, 15% ethyl acetate in petroleum ether) to give 342 mg (63%) of **8** as a clear, colorless oil: IR (neat, cm^{-1}) 3340, 2940, 1450, 1385, 1375, 725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1 H), 5.58 (m, 1 H), 3.64 (t, J = 6.6 Hz, 2 H), 2.35–1.20 (series of m, 15 H), 1.33 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 140.0, 127.5, 76.7, 63.1, 61.8, 59.5, 53.4, 49.5, 49.3, 38.7, 38.3, 34.8, 34.2, 33.9, 28.6, 26.3, 24.4, 20.5, 19.0; MS, m/z (M^+) calcd 276.2453, obsd 276.2457. Anal. Calcd for $C_{19}H_{32}O$: C, 82.54; H, 11.67. Found: C, 82.43; H, 11.68.

Hydroboration–Oxidation of 8. To a solution of **8** (119 mg, 0.43 mmol) in tetrahydrofuran (4.3 mL) was added the borane–dimethyl sulfide complex (0.52 mL of 2.0 M in tetrahydrofuran, 1.0 mmol). Heating of the mixture at 50 °C was maintained for 19 h. Following cooling to 0 °C, ethanol (1 mL), 6 N sodium hydroxide (1 mL), and 30% hydrogen peroxide (1 mL) were added in turn. This mixture was stirred at room temperature for 24 h, at which point ether (2 mL) was added, and the aqueous phase was extracted with ether (3 × 2 mL). Following drying and concentration of the combined organic layers, there was isolated 127 mg (100% crude yield) of the diol as an oily solid.

To a cold (−78 °C) solution of oxalyl chloride (0.086 mL, 0.99 mmol) in dry dichloromethane (7.2 mL) was added 0.15 mL of dimethyl sulfoxide. After 2 min, the diol mixture (azeotropically dried with anhydrous benzene, 3 × 3 mL; 127 mg, 0.43 mmol) dissolved in dichloromethane (7.2 mL) was introduced. Stirring was maintained for 15 min at −78 °C before triethylamine (0.60 mL, 4.3 mmol) was added in one portion. After 5 min, the cooling bath was removed, and the contents were allowed to warm to room temperature. Water (15 mL) was added, the aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic layers were dried and concentrated. Purification of the residue by short column chromatography (TLC grade silica gel, 15% ethyl acetate in petroleum ether) gave 13 mg (10%) of **10** and subsequently 78 mg (62%) of **9**.

For **9**: clear, colorless oil; IR (neat, cm^{-1}) 2965, 2720, 1742, 1465, 1409, 1387, 1208; ^{1}H NMR (300 MHz, C_6D_6) δ 9.33 (t, J = 1.3 Hz, 1 H), 2.24 (AB q, J = 18.3 Hz, $\Delta\nu_{AB}$ = 90.0 Hz, 2 H), 2.08 (AB q, J = 19.0 Hz, $\Delta\nu_{AB}$ = 21.1 Hz, 2 H), 1.93 (dd, J = 10.0, 7.1 Hz, 1 H), 1.78 (m, 2 H), 1.5–0.8 (series of m, 10 H), 1.00 (s, 3 H), 0.95 (s, 3 H), 0.88 (s, 3 H), 0.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 218.7, 202.2, 68.1, 61.0, 59.5, 54.4, 50.5, 47.8, 47.1, 44.6, 38.6, 38.4, 37.0, 35.3, 29.0, 25.5, 24.0, 19.7, 17.6; MS, m/z (M^+) calcd 290.2246, obsd 290.2256.

For **10**: clear, colorless oil; IR (neat, cm^{-1}) 2950, 2715, 1726, 1466, 1415, 1388, 1130; ^{1}H NMR (300 MHz, C_6D_6) δ 9.29 (J = 1.3 Hz, 1 H), 2.80 (dd, J = 10.9, 6.4 Hz, 1 H) 2.25–1.90 (m, 3 H); 1.8–1.0 (series of m, 13 H), 1.16 (s, 3 H), 0.99 (s, 3 H), 0.94 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 220.2, 200.6, 77.3, 59.4, 58.7, 52.0, 48.3, 44.4, 38.8, 38.0, 37.5, 37.0, 35.3, 32.5, 28.9, 25.1, 24.1, 20.3, 17.3; MS, m/z (M^+) calcd 290.2246, obsd 290.2237.

Cyclization of 9. A solution of **9** (23 mg, 0.079 mmol) and *p*-toluenesulfonic acid (22 mg, 0.12 mmol) in benzene (7.9 mL) was heated at the reflux temperature for 4 h, cooled, and treated with water (10 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic layers were dried and concentrated. Column chromatographic purification (silica gel, 5% ethyl acetate in petroleum ether) of the residue gave 16.7 mg (78%) of **2** as a pale yellow oil that crystallized on standing; IR ($CHCl_3$, cm^{-1}) 2950, 1707, 1633, 1467, 1551, 1240; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (t, J = 6.9 Hz, 1 H), 2.88 (dd, J = 10.9, 7.7 Hz, 1 H), 2.34 (approx q, J = 6 Hz, 2 H), 2.22 (AB q, J = 17.3 Hz, $\Delta\nu_{AB}$ = 29.5 Hz, 2 H), 2.1–1.4 (series of m, 10 H), 1.44 (s, 3 H), 1.05 (s, 3 H), 1.04 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (20 MHz, C_6D_6) ppm 203.5, 145.1, 138.4, 71.2, 60.1, 60.0, 53.8, 50.4, 47.8, 46.6, 40.3, 38.5, 34.1, 28.9, 27.1 (2 C), 25.8, 21.8, 20.6; MS, m/z (M^+) calcd 272.2140, obsd 272.2179.

Alkylation of 6 with 5-Bromo-2-pentanone Ethylene Ketal. To a solution of lithium diisopropylamide [from diisopropylamine (0.47 mL, 3.4 mmol), *n*-butyllithium (2.1 mL of a 1.56 M solution in hexane, 3.3 mmol), and 20 mL of anhydrous tetrahydrofuran at 0 °C for 30 min] cooled to −78 °C was added HMPA (2.6 mL). A precooled solution of the bromo ketal (709 mg, 3.39 mmol) and tetrahydrofuran (10 mL) was next introduced, and the reaction mixture was allowed to warm to room temperature over 3.5 h. Water (45 mL) and ether (45 mL) were added, and the aqueous layer was extracted with ether (3 × 45 mL). The combined organic extracts were dried and concentrated, and the residue was purified by short column chromatography (TLC grade silica gel, 6% ethyl acetate in petroleum ether) to give 214 mg (36%) of unreacted **6** and 598 mg (62%) of **11** as a clear, colorless oil: IR (neat, cm^{-1}) 3050, 2950, 2228, 1465, 1380, 1266, 1223, 1072, 1053, 725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (m, 1 H), 5.56 (m, 1 H), 3.92 (m, 4 H), 2.36 (t, J = 2.0 Hz, 2 H), 2.18 (m, 2 H), 1.9–1.4 (series of m, 11 H), 1.45 (s, CH_3), 1.31 (s, CH_3), 1.08 (s, CH_3), 1.02 (s, CH_3); ^{13}C NMR (20 MHz, C_6D_6) ppm 136.9, 128.7, 124.0, 109.9, 76.3, 64.7 (2 C), 61.9, 59.7, 52.1, 50.2, 48.3, 39.6, 38.7, 37.3, 35.6, 33.4, 27.8, 25.3, 25.0, 24.1, 20.9; MS, m/z (M^+) calcd 343.2511, obsd 343.2496.

Reduction of 11. To a solution of **11** (496 mg, 1.44 mmol) in dry dichloromethane (14 mL) at 0 °C was added DIBAL-H (2.2 mL of a 1.0 M solution in hexane, 2.2 mmol). The reaction mixture was allowed to stir at 0 °C for 45 min prior to quenching with ethanol (1.0 mL) and water (15 mL). The aqueous layer was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were dried and concentrated. The residue was taken up in triethylene glycol (43 mL), hydrazine hydrate (1.9 mL), andd potassium carbonate (2.09 g), degassed, and heated at 250 °C for 18 h. After the mixture was cooled to room temperature, water (80 mL) and ether (80 mL) were added, and the aqueous layer was extracted with ether (5 × 80 mL). The combined organic extracts were dried and concentrated to leave a residue, which was purified by column chromatography (silica gel, 5% ethyl acetate in petroleum ether) to give 224 mg (48%) of **12** as a clear, colorless liquid: IR (neat, cm^{-1}) 3050, 2950, 1470, 1382, 1265, 1225, 1065, 726; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1 H), 5.58 (m, 1 H), 3.93 (m, 4 H), 2.30–2.05 (m, 4 H), 1.76–1.1 (series of m, 11 H), 1.33 (s, CH_3), 1.31 (s, CH_3), 1.02 (s, CH_3), 0.98 (s, CH_3), 0.93 (s, CH_3); ^{13}C NMR (75 MHz, C_6D_6) ppm 139.3, 126.8, 109.2, 76.1, 63.7 (2 C), 61.1, 58.8, 52.6, 48.9, 48.7, 39.9, 38.6, 37.5, 34.2, 33.4, 27.9, 25.5, 23.7, 23.1, 18.3; MS, m/z (M^+) calcd 332.2715, obsd 332.2696. Anal. Calcd for $C_{2H3}6O_2$: C, 79.45; H, 10.95. Found: C, 79.68; H, 10.94.

Hydroboration–Oxidation of 12. To a neat sample of **12** (167 mg, 0.502 mmol) cooled to −10 °C was added to borane–tetra-

hydrofuran complex (0.70 mL of a 1.0 M solution in THF, 0.70 mmol). The reaction mixture was allowed to stand at −10 °C for 44 h, warmed to 0 °C, and quenched with ethanol (1.0 mL), 6 N sodium hydroxide solution (1.0 mL), and hydrogen peroxide (30%, 1.0 mL). Following warming to room temperature and stirring for an additional 17 h, ether (2 mL) was added, and the aqueous layer was extracted with ether (3 × 2 mL). The combined organic extracts were dried and concentrated to give 175 mg (99% crude yield) of the alcohols as a clear, colorless oil.

To a solution of oxalyl chloride (0.052 mL, 0.60 mmol) and dry dichloromethane (5.0 mL) at −78 °C was added dimethyl sulfoxide (0.085 mL, 1.2 mmol). The reaction mixture was allowed to stir at −78 °C for 2 min before a solution of the alcohol [azeotropically dried with benzene (3 × 1 mL); 175 mg, 0.499 mmol] and dichloromethane (2 mL) was introduced. The reaction mixture was allowed to stir at −78 °C for 15 min, triethylamine (0.35 mL, 2.5 mmol) was added in one portion, stirring was continued for 5 min at −78 °C, and the cooling bath was removed. After the reaction mixture reached room temperature, saturated sodium bicarbonate solution (10 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried and concentrated to leave a residue, which was purified by short column chromatography (TLC grade silica gel, 5% ethyl acetate in petroleum ether) to give 42 mg (24%) of the isomeric keto ketal as a clear, colorless oil: IR (neat, cm^{-1}) 2955, 1727, 1477, 1387, 1379, 1220, 1209, 1130, 1067; ^1H NMR (300 MHz, C_6D_6) δ 3.55 (s, 4 H), 2.86 (dd, J = 6.0, 11.1 Hz, 1 H), 2.3–1.9 (series of m, 4 H), 1.8–1.1 (series of m, 12 H), 1.33 (s, CH_3), 1.18 (c, CH_3), 1.01 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 222.7, 110.1, 77.5, 64.6 (2 C), 59.4, 58.6, 52.1, 48.5, 39.8, 38.8, 38.1, 37.2, 35.2, 32.5, 28.7, 25.1, 23.9, 23.8, 20.4, 19.0; MS, m/z (M^+) calcd 348.2664, obsd 348.2701.

Continued elution afforded 94 mg (54%) of **13** as a clear, colorless, and homogeneous oil: IR (neat, cm^{-1}) 2950, 1743, 1468, 1378, 1255, 1220, 1060; ^1H NMR (300 MHz, C_6D_6) δ 3.58 (s, 4 H), 2.32 (AB q, J = 17.6 Hz, $\Delta\nu_{AB}$ = 118 Hz, 2 H), 2.08 (AB q, J = 18.2 Hz, $\Delta\nu_{AB}$ = 35.4 Hz, 2 H), 1.96 (m, 1 H), 1.63 (t, J = 7.9 Hz, 2 H), 1.6–1.0 (series of m, 10 H), 1.32 (s, CH_3), 1.03 (s, CH_3), 0.95 (s, CH_3), 0.88 (s, CH_3), 0.84 (s, CH_3); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.5, 110.1, 68.3, 64.7 (2 C), 61.6, 59.7, 54.6, 50.3, 48.2, 47.4, 40.8, 39.6, 38.3, 37.6, 35.3, 29.0, 25.6, 24.4, 24.1, 20.0, 19.9; MS, m/z (M^+) calcd 348.2664, obsd 348.2691.

Deketalization of 13. To a solution of **13** (150 mg, 0.431 mmol) in tetrahydrofuran (26 mL) at room temperature was added 5% aqueous hydrochloric acid (13 mL). The reaction mixture was allowed to stir for 15 min, concentrated, and extracted with saturated sodium bicarbonate solution (50 mL). Ether (50 mL) was added, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic extracts were dried and concentrated. The residue was purified by column chromatography (silica gel, 20% ethyl acetate in petroleum ether) to give 129 mg (98%) of **14** as a clear, colorless oil: IR (neat, cm^{-1}) 2955, 1740, 1715, 1465, 1410, 1365, 1205; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (AB q, J = 18.0 Hz, $\Delta\nu_{AB}$ = 110 Hz, 2 H), 2.42 (t, J = 7.3 Hz, 2 H), 2.35–2.15 (m, 4 H), 2.14 (s, CH_3), 1.8–1.1 (series of m, 9 H), 1.37 (s, CH_3), 1.10 (s, CH_3), 1.07 (s, CH_3), 1.04 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 218.6, 208.5, 68.1, 61.1, 59.5, 54.4, 50.5, 47.8, 47.2, 44.3, 38.6, 38.4, 37.0, 35.3, 29.9, 28.9, 25.5, 24.0, 19.7, 19.2; MS, m/z (M^+) calcd 304.2403, obsd 304.2418.

Oxidation of 8 to Aldehyde 16. To a well-stirred suspension of pyridinium chlorochromate (500 mg, 2.3 mmol), powdered 3-Å molecular sieves (0.55 g), and sodium acetate (20 mg, 0.24 mmol) in dry dichloromethane (10 mL) was added via cannula a solution of **8** (217 mg, 0.785 mmol) in the same solvent, and stirring was maintained for 1 h. The reaction mixture was diluted with ether (60 mL), filtered through a pad of silica gel, and concentrated. Chromatographic purification of the residue (silica gel, 4% ethyl acetate in petroleum ether) afforded 153 mg (71%) of **16** as a clear, colorless liquid: IR (neat, cm^{-1}) 2955, 2715, 1728, 1470, 1385, 1375, 725; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (m, 1 H), 5.61 (m, 2 H), 2.40–1.10 (series of m, 15 H), 1.33 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.7, 139.6, 127.8, 76.6, 61.8, 59.5, 53.4, 49.5, 49.3, 44.8, 38.5, 38.3, 34.9, 34.2, 28.6, 26.2, 24.3, 18.9, 17.2; MS, m/z (M^+) calcd 274.2296, obsd 274.2289.

Oxidation of 8 to Carboxylic Acid 17. To a cold (0 °C) solution of **8** (142 mg, 0.514 mmol) in acetone (26 mL) was added 14 drops of Jones reagent (2.67 M). The mixture was stirred at 0 °C for 10 min prior to the introduction of water (30 mL) and ether (30 mL). The aqueous phase was extracted with ether (3 × 30 mL), and the combined organic layers were dried and concentrated. Purification of the residue by column chromatography (silica gel, 20% ethyl acetate in petroleum ether) gave **17** (126 mg, 85%) as a clear, colorless oil: IR (neat, cm^{-1}) 3050, 2955, 2680, 1710, 1470, 1450, 1385, 1375, 1280, 915, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1 H), 5.59 (m, 1 H), 2.34–1.15 (series of m, 15 H), 1.33 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.8, 139.6, 127.8 76.6, 61.8, 59.4, 53.4, 49.4, 49.3, 38.4, 38.3, 34.9, 34.8, 34.2, 28.7, 26.2, 24.3, 19.8, 18.9; MS, m/z (M^+) calcd 290.2245, obsd 290.2249.

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