Absolute Stereochemistry of the Squalene Synthase Inhibitor Zaragozic Acid C

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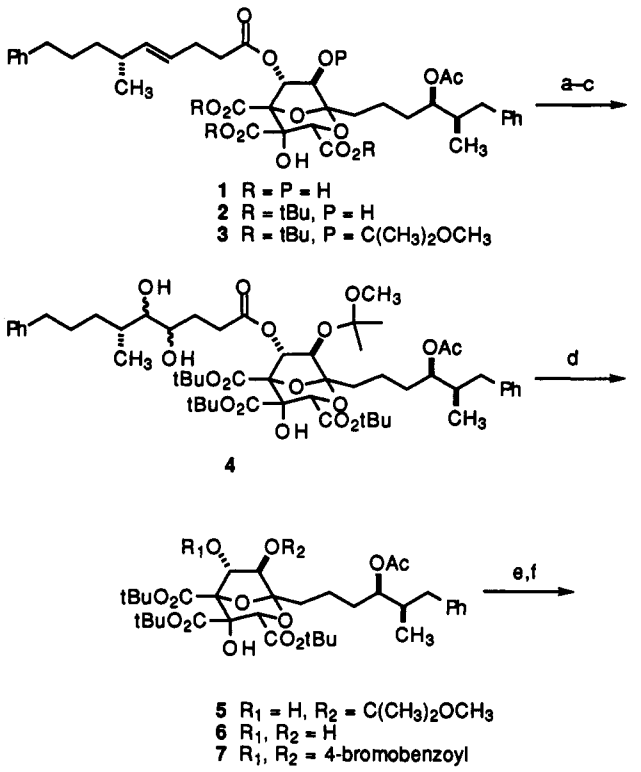
The zaragozic acids are a group of structurally related fungal metabolites which are powerful inhibitors of the enzyme squalene synthase. Squalene synthase catalyses the first biochemical transformation in the metabolic pathway which is committed to the production of cholesterol.[1] The interest in blocking this enzyme as a method of lowering elevated serum cholesterol has led to the independent discovery of these inhibitors by two groups.[2] In previous reports from these laboratories, the chemical connectivities of the zaragozic acids have been elucidated.[3] Zaragozic acid A was more fully characterized in a study by Wilson et al. to include its absolute assignment.[4] Zaragozic acid C represents the simplest member of the class with regard to the C1 chain and provides a desirable challenge for total synthesis. This report describes the relative and absolute stereochemistry of zaragozic acid C.

Zaragozic acid C (1) differs from its closely related congeners zaragozic acids A and B in the lipophilic side chains at C6 and C1. The similarity of the C1 side chain with that of zaragozic acid A suggested that a C6-deacylated-C3,C4,C5 triester would provide a crystallographic solution for the relative stereochemistries of the bicyclic core and C1 chain. Since zaragozic acid C lacked the α,β-unsaturation in the C6 side chain, a new method for selective removal of the C6 ester was required. The presence of a single olefinic bond provided a useful handle for effecting deacylation of the fatty acid residue (Scheme 1).

Zaragozic acid C was subjected to a two-step protecting group protocol. Thus, treatment of 1 with 10 equiv of freshly distilled *N,N'*-diisopropyl-*O*-*tert*-butylisourea[5] in dichloromethane afforded the intermediate 3,4,5-tri-*tert*-butyl ester **2**. When triester **2** was treated with 20 equiv of 2-methoxypropene and 5 mol % of pyridinium *p*-toluenesulfonate in dichloromethane at 0 °C the highly acid-sensitive protected derivative **3** was obtained. Exposure of **3** to 3 mol % OsO_4 in the presence of 1.06 equiv of

Scheme 1[a]



[a] Key: (a) *N,N'*-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, 25 °C, 76%; (b) 2-methoxypropene, PPTS, CH_2Cl_2, 0 °C, 90%; (c) OsO_4, *N*-methylmorpholine *N*-oxide, 4:1 acetone/water, 25 °C, 79%; (d) K *tert*-butoxide, DMF, 25 °C, 67%; (e) $CDCl_3$, air, 25 °C, 100%; (f) 4-bromobenzoic anhydride, DMAP, pyridine, 85 °C, 86%.

N-methylmorpholine *N*-oxide in aqueous acetone provided the diols **4** as a 1:1 diastereomeric mixture. Selective deacylation at C6 was accomplished with 1.0 equiv of potassium *tert*-butoxide in DMF.

Diol **5** could not be crystallized. Previous experience had shown the methylmethoxyethyl (MME) protecting group at C7 to be labile to trace quantities of DCl in $CDCl_3$. Exposure of a stirred $CDCl_3$ solution of **5** to the atmosphere furnished triol **6** with no detectable ester cleavage. Triol **6** provided long rods suitable for X-ray crystallography which were grown by evaporation from 2:1 heptane/ethyl acetate. The crystallographic data demonstrated the relative stereochemistries of the core and C1 side chain of zaragozic acid C were identical to those of zaragozic acid A (Figure 1).[6]

Though the absolute assignment seemed almost certain, this was the second member of the class to have a full

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(2) (a) Bergstrom, J. D.; Kurtz, M. M.; Rew. D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Bansal,V.S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O.D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L.; Nallin Omstead, M.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Palaez, F.; Diez, M.; Alberts, A. W. *Proc. Nat. Acad. Sci. U.S.A.* **1993**, *90*, 80–84. (b) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; and Hayes M. V. *J. Antibiot.* **1992**, *45*, 614–622. Sidebottom, P. J.; Highcock, R. M.; Lane, S. J.; Procopiou, P.; Watson, N. S. *J. Antibiot.* **1992**, *45*, 623–633.

(3) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221–10226.

(4) Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151–7158 and references cited therein.

(5) Prepared by reaction of neat *N,N'*-diisopropylcarbodiimide (1.00 equiv) with 2-methyl-2-propanol (1.15 equiv) in the presence of CuCl (0.01 equiv) at ambient temperature for 24 h.

(6) The crystal data and experimental conditions are as follows: formula = $C_{36}H_{54}O_{13}$, M_r = 694.82, monoclinic, $P2_1$, a = 11.889(3) Å, b = 11.037(1) Å, c = 15.321(2) Å, β = 99.88(2)°, V = 1980 Å^3, Z = 2, D_x = 1.165 g cm^{-3}, monochromatized radiation λ(Cu K$_\alpha$) = 1.541 84 Å, μ = 0.69 mm^{-1}, F(000) = 748, T = 296 K. Data collected on a Rigaku AFC5R diffractometer to a 2θ limit of 140° with 1223 observed, $I \geq 3\sigma(I)$, reflections out of 4022 measured. Structure solved by direct methods and refined using full-matrix least-squares on F using 227 parameters. The nonhydrogen atoms were refined with a mixture of isotropic and anisotropic thermal displacements. Hydrogen atom contributions were included in the calculations. Final agreement statistics are: R = 0.071, wR = 0.060, S = 1.93, $(\Delta/\sigma)_{max}$ = 0.02. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in final difference Fourier map 0.32(6) eÅ^{-3} with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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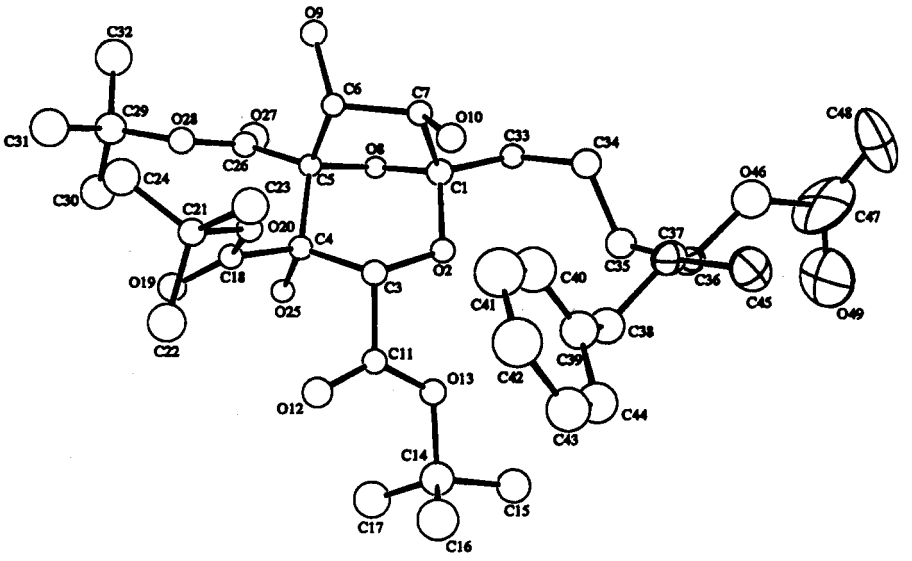


Figure 1. ORTEP drawing of 6.

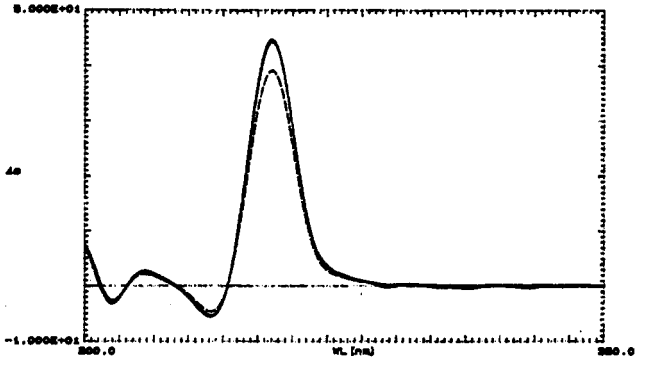
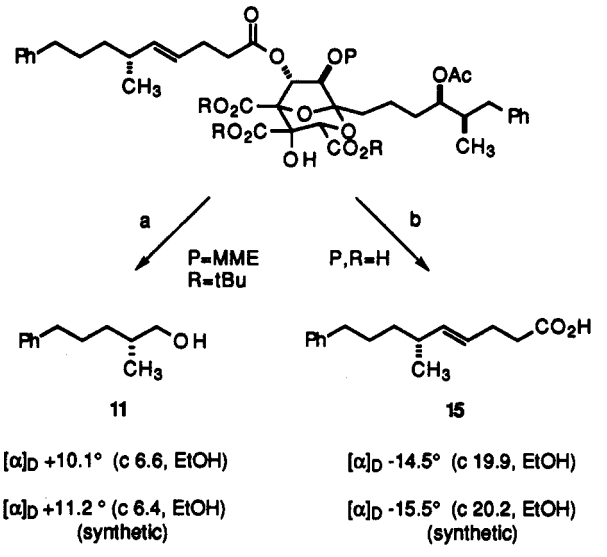


Figure 2. CD spectrum of 7.

structure assignment and an independent determination was performed. By analogy with zaragozic acid A, the absolute stereochemistry of the 6,7-diol moiety was established by conversion of 6 to the bis(4-bromobenzoate) 7 and examination of its CD spectrum at several different concentrations (Figure 2).[7] Consistent with the findings for zaragozic acid A, the CD spectrum of 7 in acetonitrile displayed a strong positive first Cotton effect at 254 nm ($\Delta\epsilon = +43$) and a weaker negative second Cotton effect at 238 nm ($\Delta\epsilon = -12$), establishing the absolute stereochemistry of the 6,7-diol as *R,R*. Though this method for determination of absolute stereochemistry was the same in both cases, the zaragozic acid A assignment contained a secondary confirmation of the absolute configuration at C4′ (C36 in Figure 1) using the *O*-methylmandelate. With the validity of the CD method confirmed for this class, a secondary confirmation was deemed unneccessary for zaragozic acid C. The absolute stereostructure of those two regions can be depicted as in Scheme 1.

The only stereocenter which remained unproven was the C6″ methine on the C6 fatty acid side chain. Samples of alcohol 11 and acid 15 were obtained from 3 and 1, respectively, by ozonolysis/reduction and saponification (Scheme 2).

Scheme 2[a]



11 15

[α]D +10.1° (c 6.6, EtOH) [α]D -14.5° (c 19.9, EtOH)

[α]D +11.2 ° (c 6.4, EtOH) (synthetic) [α]D -15.5° (c 20.2, EtOH) (synthetic)

[a] Key: (a) (i). O_3, CH_2Cl_2/MeOH, -78 °C, (ii) $NaBH_4$, THF, 47%; (b) aqueous NaOH/THF/MeOH, reflux, 89%.

The asymmetric syntheses of 11 and 15 relied on the method of Evans (Scheme 3).[8] The commercially available propionylated oxazolidinone 8 was converted to its sodium enolate and alkylated with cinnamyl bromide to give the adduct 9 as a 97:3 mixture of diastereomers. The desired diastereomer was easily purified by column chromatography. Catalytic hydrogenation was followed by LAH reduction to afford the alcohol 11. A search of the literature revealed only two previous references to 11, both in racemic form.[9] Swern oxidation furnished the air-sensitive aldehyde 12 which was exposed to vinyl magnesium bromide in THF, resulting in the isolation of allylic alcohols 13 as a 60:40 mixture of diastereomers. The mixture was not felt to be of consequence since the subsequent Claisen rearrangement was expected to provide a single compound.

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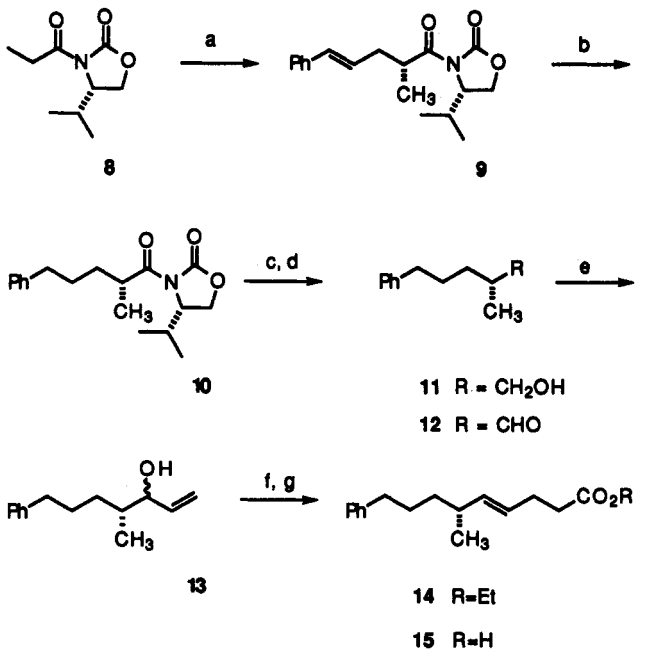
(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

(9) (a) Braun, J. v.; Kirschbaum, G. *Chem. Ber.* **1914**, *47*, 262–269; *Chem. Abstr.* **1914**, *8*; 1125. (b) Julia, M.; Mansuy, D. *C. R. Acad. Sci., Ser. C* **1969**, *269*(24), 1568–1570; *Chem. Abstr.* **1970**, *72*, 78744.

Scheme 3[a]



[a]Key: (a) (i) $NaN(TMS)_2$, THF, −78 °C, (ii) cinnamyl bromide, 87%; (b) H_2, 10% Pd/C, EtOAc, 94%; (c) LAH, THF, 0 °C, 83%; (d) Swern oxidation, 91%; (e) vinylmagnesium bromide, THF, −30 °C, 79%; (f) $CH_3C(OEt)_3$, $EtCO_2H$ (cat.), 138 °C, 2.5 h, 89%; (g) aqueous NaOH, THF, reflux, 99%.

The orthoester method of Johnson[10] yielded a single *trans* ester 14 which was saponified to the acid 15.

Alcohol 11 and acid 15 were fully characterized and found to be indistinguishable from their natural counterparts. The absolute stereochemistry of the C6″ methine was thus assigned as *R*, which is opposite in configuration to the corresponding center in zaragozic acid A. The full stereostucture of zaragozic acid C can now be depicted as 1.

Experimental Section

General Methods. Proton and carbon NMR spectra were recorded at 400 MHz and 100 MHz on a Varian XL400 spectrometer. Chemical shifts are reported in ppm downfield from TMS (at 0.0 ppm) and are referenced with respect to the solvent (δ_H = 7.24 ppm for $CDCl_3$, 5.32 ppm for CD_2Cl_2, and 3.30 ppm for CD_3OD; δ_C = 77.1 ppm for $CDCl_3$, 52.8 ppm for CD_2Cl_2, and 49.0 ppm for CD_3OD). Coupling constants are reported in Hz, and multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, quart = quartet, quint = quintet, hex = hexet, hep = heptet, mult = multiplet, br = broad. Infrared spectra were obtained from samples contained in NaCl solution cells (International Crystal Laboratories; 0.1-mm solution thickness) in dichloromethane using a Perkin-Elmer Model 1600 FTIR spectrometer. Absorbances are reported in cm^{-1} and are characterized as s = strong, m = medium, w = weak, or br = broad. The CD spectrum was obtained on an AVIV Model 62DS CD spectrometer. Optical rotations were determined at 25 °C on a Perkin-Elmer Model 241 polarimeter using the sodium D line (589 nm). Rotations are reported as $[\alpha]_D$ (concentration in g/100 mL, solvent). Mass spectral data were obtained as previously described.[4]

Starting materials and reagents were obtained from Aldrich Chemical Co. and were used without further purification. Solvents were obtained from Fisher Scientific. Solvents and reagents described as dry were stored over activated 4Å molecular sieves and determined to have a water content <100 μg/mL by Karl Fischer titration using a Metrohm Model 684 KF Coulometer. Nonaqueous reactions were conducted under a nitrogen atmosphere. Column chromatography was performed with E. Merck silica gel 60 (43–60 μm). Analytical TLC was carried out with Analtech silica gel GF plates (0.25-mm thickness). HPLC analyses were performed on a Zorbax 5μ ODS analytical column (25 cm × 4.6 mm). An acetonitrile/water (0.1% H_3PO_4) mobile phase gradient was employed in all cases as follows: time (*T*) = 0 min, % CH_3CN = 80, % H_2O = 20; *T* = 10 min, % CH_3CN = 100; *T* = 30 min, % CH_3CN = 100. Flow = 1.50 mL/min. Wavelength = 210 nm.

Zaragozic Acid C 3,4,5-Tris-*tert*-butyl Ester (2). To a solution of zaragozic acid C (1.652 g; 2.273 mmol) in dry CH_2Cl_2 (25 mL) was added freshly distilled *N, N′*-diisopropyl-O-*tert*-butylisourea (4.549 g; 22.73 mmol). After being stirred at ambient temperature for 16 h the heterogenous mixture was poured into hexane (200 mL) and filtered through Celite. Removal of solvents *in vacuo* afforded an oil (2.407 g) which was chromatographed over silica gel with CH_2Cl_2/ethyl acetate (10:1). The fractions were analyzed by HPLC, and those containing the desired (2) were combined and evaporated to give the product as a tan foam (1.546 g; 76%). HPLC: t_R = 12.54 ± 0.2 min. ^1H NMR ($CDCl_3$): δ 7.24 (mult, 5H, Ar-*H*), 7.12 (mult, 5H, Ar-*H*), 5.90 (d, 1H, *J* = 2.2 Hz, C_6-*H*), 5.30 (mult, 2H, C_4-*H*, C_5-*H*), 4.96 (s, 1H, C_2-*H*), 4.85 (br quint, 1H, *J* = 3.8 Hz, C_4-*H*), 4.01 (br s, 1H, C_4 O*H*), 3.93 (t, 1H, *J* = 2.2 Hz, C_7-*H*), 2.81 (d, 1H, *J* = 2.3 Hz, C_7 O*H*), 2.73 (dd, 1H, *J* = 13.5, 5.1 Hz, C_6-*H*), 2.54 (t, 2H, *J* = 7.7 Hz, C_9-H_2), 2.35 (overlapping hepts, 1.4 Hz apart, 2H, *J* = 6.7 Hz, C_5-*H*, C_6-*H*), 2.28 (mult, 3H), 2.07–1.96 (mult, 2H, C_2-H_2), 2.02 (s, 3H, C_4 acetate CH_3), 1.66–1.49 (br mult, 6H, C_2-H_2, C_7-H_2, C_8-H_2), 1.54 (s, 9H), 1.45 (s, 9H), 1.41 (s, 9H), 1.29 (br d, 2H, *J* = 8.1 Hz), 0.91 (d, 3H, *J* = 6.7 Hz, C*H*$_3$), 0.81 (d, 3H, *J* = 6.8 Hz, C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 173 .1, 171.1, 168.6, 165.7, 164.4, 142.6, 140.7, 137.9, 129.1, 128.3, 128.2, 125.8, 125.7, 125.6, 104.8, 89.0, 85.5, 83.7, 83.1, 81.9, 81.0, 76.8, 75.2 (two lines, 4.3 Hz apart), 74.2, 39.4, 38.1, 36.5, 36.0, 35.5, 34.1, 31.0, 30.8, 29.3, 28.1, 28.0 (two lines, 8.2 Hz apart), 27.7, 21.2, 20.7, 19.0, 13.8. MS (POS FAB, LiOAc added): 929, 873, 769, 762 (base peak), 701, 695, 600, 534, 467, 449, 431, 369, 351, 301, 283, 229, 211, 201. HRMS: $C_{52}H_{74}O_{14}$ $(M + Li)^+$ requires *m/z* = 929.5238, found 929.5258.

Zaragozic Acid C 7-(Methylmethoxyethyl) 3,4,5-Tri-*tert*-butyl Ester (3). To a 0 °C solution of 2 (1.546 g; 1.727 mmol) in dry CH_2Cl_2 (25 mL) was added 2-methoxypropene (3.31 mL; 34.54 mmol) followed by 123 μL of CH_2Cl_2 containing PPTS (21.7 mg; 0.086 mmol). After being stirred at 0 °C for 21 h, the cold reaction was poured into excess CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over Na_2SO_4, filtered and evaporated to a foam (1.592 g) which was chromatographed over silica gel with CH_2Cl_2/ethyl acetate/triethylamine (100:10:1). The fractions were analyzed by HPLC, and those containing the desired 3 were combined to give the product as a white foam (1.503 g; 90%). HPLC: t_R = 14.35 ± 0.2 min. ^1H NMR (CD_2Cl_2): 7.25 (mult, 5H, Ar-*H*), 7.16 (mult, 5H, Ar-*H*), 6.32 (br s, 1H, C_6-*H*), 5.31 (mult, 2H, overlapping CD_2Cl_2, C_4-*H*, C_5-*H*), 4.96 (s, 1H, C_3-*H*), 4.85 (br t, 1H, *J* = 5.6 Hz, C_4-*H*), 4.11 (s, 1H, C_7-*H*), 3.97 (br s, 1H, C_4 O*H*), 3.19 (s, 3H, OC*H*$_3$), 2.75 (dd, 1H, *J* = 13.5, 5.1 Hz, C_6-*H*), 2.55 (t, 2H, *J* = 7.8 Hz, C_9-H_2), 2.39–2.22 (mult, 2H, C_2-H_2), 2.10–1.91 (mult, 6H, C_1-H_2, C_3-H_2, C_5-*H*, C_6-*H*), 2.03 (s, 3H, C_4 acetate CH_3), 1.77–1.46 (mult, 8H, C_2-H_2, C_3-H_2, C_7-H_2, C_8-H_2), 1.61 (s, 9H), 1.43 (s, 9H), 1.40 (s, 9H), 1.35 (s, 3H, C_7 MME C*H*$_3$), 1.26 (s, 3H, C_7 MME C*H*$_3$), 0.92 (d, 3H, *J* = 6.8 Hz, C*H*$_3$), 0.85 (d, 3H, *J* = 6.9 Hz, C*H*$_3$). ^{13}C NMR (CD_2Cl_2): δ 170.1, 168.4, 165.4, 142.3, 140.3, 137.0, 128.5, 127.8, 127.6, 125.5, 125.2, 124.9, 104.1, 100.8, 90.0, 85.1, 83.0, 82.9, 82.5, 78.8, 76.9 (two lines, 5.0 Hz apart), 76.1, 75.9, 74.7, 73.4, 49.1, 38.7, 37.6, 36.0, 35.4, 34.8, 33.5, 31.2, 30.5, 28.7, 27.3, 27.1 (two lines, 7.6 Hz apart), 25.2, 23.7, 20.4, 19.8, 18.5, 13.0. MS (POS FAB, LiOAc added): 1002, 1001, 945, 852, 818, 796, 762, 736, 701, 669, 600, 534, 490, 409, 369, 341, 283, 229, 201, 145 (base peak). HRMS: $C_{56}H_{82}O_{15}$ $(M + Li)^+$ requires *m/z* = 1001.5813, found 1001.5801.

4″,5″-Dihydroxyzaragozic Acid C 7-(Methylmethoxyethyl)-3,4,5-tri-*tert*-butyl Ester (4). To a solution of 3 (1.503 g; 1.550 mmol) in acetone (32 mL) was added 8 mL of water dropwise by syringe. After the solution once again become homogeneous,

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N-methylmorpholine *N*-oxide (193 mg; 1.65 mmol) was added followed by 2.5 wt % OsO_4 in 2-methyl-2-propanol (583 μL; 0.046 mmol). After being stirred at ambient temperature for 24 h, the reaction was poured into excess isopropyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over Na_2SO_4, filtered, and concentrated to a foam (1.556 g) which was chromatographed over silica gel with CH_2Cl_2/ethyl acetate/triethylamine (100:2.5:1). The fractions were analyzed by HPLC, and those containing the desired **4** were combined to give the product as a translucent foam (1.226 g; 79%). NMR analysis indicated a 1:1 mixture of diastereomers. HPLC t_R = 10.82 ± 0.2 min. ^{1}H NMR (CD_2Cl_2): δ 7.25 (mult, 5H, Ar-*H*), 7.14 (mult, 5H, Ar-*H*), 6.32 (br s, 1H, C_6-*H*), 4.95 (2 s, 1H total, 1.1 Hz apart, C_3-*H*), 4.86 (br mult, 1H, C_4-*H*), 4.15 (2 d, 1H total, 1.5 Hz apart, J = 4.5 Hz, $C_{4''}$ O*H*, $C_{5''}$ O*H*), 3.97 (d, 1H, J = 2.4 Hz, C_7-*H*), 3.60–3.51 (2 br mult, 0.5H each, $C_{4''}$-*H*, $C_{5''}$-*H*), 3.25–3.19 (mult, 2H), 3.19 (2 s, 1.5H each, 1.6 Hz apart, OC*H*$_3$), 3.09 (br dd, 1H, J = 6.3, 3.4 Hz), 2.75 (dd, 1H, J = 13.3, 4.8 Hz, C_6-*H*), 2.65–2.29 (mult, 9H), 2.10–1.91 (mult, 2H), 2.04 (s, 1.5H, $C_{4'}$ acetate C*H*$_3$), 2.03 (s, 1.5H, $C_{4'}$ acetate C*H*$_3$), 1.75–1.08 (br mult, 8H, C_1-*H*$_2$, C_2-*H*$_2$, $C_{7''}$-*H*$_2$, $C_{8''}$-*H*$_2$), 1.60 (s, 9H), 1.42 (s, 9H), 1.40 (s, 9H), 1.35 (br s, 3H, C_7 MME C*H*$_3$), 1.28 (s, 1.5H, C_7 MME C*H*$_3$), 1.27 (s, 1.5H, C_7 MME C*H*$_3$), 0.90–0.83 (four overlapping d, 6H total, $C_{5'}$ C*H*$_3$, $C_{8''}$ C*H*$_3$). ^{13}C NMR (CD_2Cl_2): 171.1, 171.0, 170.4, 170.3, 168.3, 165.4, 164.1, 164.0, 142.3, 142.2, 140.3, 128.6, 127.6, 125.2, 125.0, 104.1, 100.9, 90.0, 85.1, 83.1, 82.5, 78.6, 77.3, 77.0 (two lines, 4.9 Hz apart), 76.6, 76.3, 76.2, 76.1, 74.7, 73.4, 70.6, 69.7, 53.4, 53.2, 52.9, 52.6, 52.3, 49.1, 38.7, 37.7 (two lines, 7.4 Hz apart), 35.7, 35.5, 34.8, 34.7, 34.6, 34.2, 33.0, 31.2, 30.7, 30.6, 29.9, 29.7, 28.6, 28.5, 27.9, 27.3, 27.2, 25.1, 23.7, 20.4, 18.7, 18.6, 15.4, 13.0, 12.8. MS (POS FAB, LiOAc added): 1036, 979, 802, 796 (base peak), 770, 647, 617, 588, 534, 409, 351, 341, 287, 227, 201. HRMS: $C_{56}H_{84}O_{17}$ (M + Li)$^+$ requires m/z = 1035.5868, found 1035.5905.

6-Desacylzaragozic Acid C-7-(Methylmethoxyethyl) 3,4,5-Tri-*tert*-butyl Ester (5). A solution of **4** (1.195 g; 1.194 mmol) in dry DMF (25 mL) was treated with solid potassium *tert*-butoxide (134 mg; 1.194 mmol). After being stirred at ambient temperature for 16 h the yellow solution was poured into excess isopropyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over Na_2SO_4, filtered, and evaporated to an oil (1.211 g) which was chromatographed over silica gel with CH_2Cl_2/ethyl acetate/triethylamine (100:5:1). The fractions were analyzed by HPLC, and those containing the desired **5** were combined to give the product as an oil (614 mg, 67%). HPLC: t_R = 4.19 ± 0.2 min. ^{1}H NMR (CD_2Cl_2): δ 7.24 (mult, 2H, Ar-*H*), 7.14 (mult, 3H, Ar-*H*), 4.93 (br dd, 1H, J = 5.2, 1.7 Hz, C_6-*H*), 4.84 (br quart, 1H, J = 6.8 Hz, C_4-*H*), 4.81 (s, 1H, C_3-*H*), 4.03 (d, 1H, J = 1.8 Hz, C_7-*H*), 3.83 (s, 1H, C_4 O*H*), 3.25 (s, 3H, OC*H*$_3$), 2.74 (dd, 1H, J = 13.2, 4.9 Hz, C_6-*H*), 2.29 (dd, 1H, J = 13.3, 9.6 Hz, C_6-*H*), 2.03 (s, 3H, $C_{4'}$ acetate C*H*$_3$), 2.02–1.94 (mult, 1H, C_5-*H*), 1.77–1.60 (mult, 4H, C_1-*H*$_2$, C_3-*H*$_2$), 1.56 (s, 9H), 1.52–1.24 (mult, 2H, C_2-*H*$_2$), 1.46 (s, 9H), 1.44 (s, 3H, C_7 MME C*H*$_3$), 1.43 (s, 9H), 1.37 (s, 3H, C_7 MME C*H*$_3$), 0.82 (d, 3H, J = 6.8 Hz, $C_{5'}$ C*H*$_3$). ^{13}C NMR (CD_2Cl_2): δ 170.1, 168.2, 165.6 (two lines overlapping), 140.3, 128.5, 127.6, 125.2, 104.3, 101.0, 90.9, 84.1, 83.1, 82.3, 80.3, 76.8, 76.2, 74.7 (two lines, 2.9 Hz apart), 48.8, 38.7, 37.6, 34.7, 30.6, 27.4, 27.3, 27.2, 25.1, 23.7, 18.5, 12.9. MS (POS FAB; LiOAc added): 774, 718, 623, 574, 568, 534 (base peak), 508, 490, 449, 341, 283, 255, 201, 183, 161. HRMS: $C_{40}H_{62}O_{14}$ (M + Li)$^+$ requires m/z = 773.4299, found 773.4311.

6-Desacylzaragozic Acid C 3,4,5-Tri-*tert*-butyl Ester (6). A solution of **5** (355 mg; 0.460 mmol) in deuteriochloroform (10 mL) was stirred while open to the atmosphere for 72 h with periodic replacement of solvent lost to evaporation. The solvent was removed and the resultant paste layered with hexane. Scratching produced a white solid (321 mg; 100%). To a suspension of this solid (102 mg) in heptane (400 μL) was added ethyl acetate (200 μL). The mixture was warmed to 40 °C, causing complete dissolution. The solution was allowed to stand at ambient temperature for 72 h, causing the formation of long rods suitable for X-ray crystallography. The crystals were rinsed with a small amount of heptane and pumped free of solvent (mp 168–169 °C). ^{1}H NMR (CD_3OD): δ 7.24 (mult, 2H, Ar-*H*), 7.14 (mult, 3H, Ar-*H*), 4.97 (br s, 1H, C_3-*H*), 4.96 (d, 1H, J = 1.8 Hz, C_6-*H*), 4.88 (br quint, 1H, J = 6.0 Hz, C_4-*H*), 4.00 (d, 1H, J = 1.9 Hz, C_7-*H*), 2.74 (dd, 1H, J = 13.3, 7.6 Hz, C_6-*H*), 2.36 (dd, 1H, J = 13.3, 9.1 Hz, C_6-*H*), 2.15 (s, 1H, C_4 O*H*), 2.06 (s, 3H, $C_{4'}$ acetate C*H*$_3$), 2.02 (br mult, 1H, C_5-*H*), 1.91–1.82 (mult, 2H, C_1-*H*$_2$), 1.73–1.66 (mult, 2H, C_3-*H*$_2$), 1.65–1.27 (mult, 2H, C_2-*H*$_2$), 1.60 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H), 0.87 (d, 3H, J = 6.9 Hz, $C_{5'}$ C*H*$_3$). ^{13}C NMR (CD_3OD): δ 172.9, 169.7, 168.2, 167.3, 141.9, 130.2, 129.3, 126.9, 106.3, 93.2, 85.4, 84.2, 84.1, 79.9, 78.2, 76.7, 75.9, 40.6, 39.5, 36.6, 32.7, 32.5, 28.7, 28.4, 28.2, 21.1, 20.1, 14.2. MS (POS FAB, LiOAc added): 701, 645, 590, 550, 534 (base peak), 528, 467, 449, 421, 403, 299, 283, 225, 201, 185, 145. HRMS: $C_{36}H_{54}O_{13}$ (M + Li)$^+$ requires m/z = 701.3724, found 701.3701.

6-Desacylzaragozic Acid C 6,7-Bis-(4-bromobenzoate) 3,4,5-Tri-*tert*-butyl Ester (7). To a solution of **6** (41 mg; 0.059 mmol) in dry pyridine (1 mL) was added 4-bromobenzoic anhydride (78 mg; 0.202 mmol) and DMAP (31 mg; 0.256 mmol). After the solution was stirred at 85 °C for 50 min the solvent was removed *in vacuo* and the residue partitioned between isopropyl acetate and 0.1 N HCl. The organic phase was again washed with 0.1 N HCl and then once with water and once with saturated aqueous sodium bicarbonate. The organic extract was dried over $MgSO_4$, filtered, and concentrated to a residue (61 mg) which was chromatographed over silica gel with hexane/ethyl acetate (1:1) to afford the desired **7** (54 mg; 86%) as a stiff foam. The product was dissolved in a minimum amount of refluxing MeOH and allowed to stand for 48 h, causing the formation of an amorphous white solid (mp 77–79 °C). ^{1}H NMR ($CDCl_3$): δ 7.89 (dd, 2H, J = 8.6, 1.8 Hz, BrAr-*H*), 7.85 (dd, 2H, J = 6.8, 1.8 Hz, BrAr-*H*), 7.60 (dd, 2H, J = 8.6, 1.8 Hz, BrAr-*H*), 7.55 (dd, 2H, J = 7.0, 1.8 Hz, BrAr-*H*), 7.22 (mult, 2H, Ar-*H*), 7.14 (mult, 1H, Ar-*H*), 7.08 (apparent br d, 2H, J = 7.0 Hz, Ar-*H*), 6.74 (d, 1H, J = 1.8 Hz, C_6-*H*), 5.33 (d, 1H, J = 1.8 Hz, C_7-*H*), 5.03 (s, 1H, C_3-*H*), 4.86 (br quint, 1H, J = 3.3 Hz, C_4-*H*), 4.08 (s, 1H, O*H*), 2.72 (dd, 1H, J = 13.3, 4.8 Hz, C_6-*H*), 2.27 (dd, 1H, J = 13.4, 9.8 Hz, C_6-*H*), 2.09–1.96 (mult, 3H, C_3-*H*$_2$, C_5-*H*), 1.97 (s, 3H, $C_{4'}$ acetate C*H*$_3$), 1.73–1.23 (mult, 4H, C_1-*H*$_2$, C_2-*H*$_2$), 1.57 (s, 9H), 1.45 (s, 9H), 1.27 (s, 9H), 0.81 (d, 3H, J = 6.9 Hz, $C_{5'}$ C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 170.8, 168.5, 164.4, 164.5, 163.6, 163.4, 140.7, 132.1, 131.8, 131.5, 131.2, 129.1, 128.9, 128.2, 127.8, 127.7, 125.8, 104.3, 90.0, 86.4, 84.6, 83.8, 81.7, 76.7, 76.5, 75.5, 75.4, 73.9, 39.3, 38.1, 35.9, 30.9. 28.1, 28.0, 27.9, 21.2, 19.1, 13.8. TLC: R_f 0.45 (1:1 hexane/ethyl acetate). MS (POS FAB, LiOAc added): 1069, 1068, 1067, 1011, 900, 899, 898, 834, 833, 832, 755,754, 691, 631, 551, 523, 484, 483, 431, 403, 359, 351, 339, 283, 212, 201. HRMS: $C_{50}H_{60}Br_2O_{15}$ (M + Li)$^+$ requires m/z = 1065.2460 (Br_2 ion, Br = 78.9184), found 1065.2444.

(+)-(*R*)-2-Methyl-5-phenyl-1-pentanol (11) by Ozonolysis of 3. Through a −78 °C solution of **3** (435 mg; 0.44 mmol) in 3:1 CH_2Cl_2/MeOH (16 mL) was bubbled ozone until the purple color of excess ozone appeared. The solution was purged with nitrogen until clear and then treated with a suspension of sodium borohydride (83 mg; 2.19 mmol) in dry THF (5 mL). After being stirred at ambient temperature for 16 h, the reaction was rinsed into excess isopropyl acetate and washed twice with pH 7 phosphate buffer. The organic phase was dried over Na_2SO_4, filtered, and evaporated to a residue (406 mg) which was chromatographed over silica gel with CH_2Cl_2/ethyl acetate/triethylamine (100:10:1) to afford the desired product as an oil (wt = 37 mg; 47%). $[\alpha]_D$: +10.1° (*c* 6.6, EtOH). ^{1}H NMR ($CDCl_3$): δ 7.26 (mult, 2H, Ar-*H*), 7.16 (mult, 3H, Ar-*H*), 3.49 (dd, 1H, J = 10.5, 5.9 Hz, C_1-*H*), 3.41 (dd, 1H, J = 10.4, 6.0 Hz, C_1-*H*), 2.59 (overlapping dt, 2H, J = 11.5, 6.8 Hz, C_5-*H*$_2$), 1.70–1.55 (mult, 3H, C_4-*H*$_2$, C_2-*H*), 1.45 (mult, 1H, C_3-*H*), 1.25 (br s, 1H, O*H*), 1.15 (mult, 1H, C_3-*H*), 0.90 (d, 3H, J = 6.8 Hz, C_2-C*H*$_3$). ^{13}C NMR ($CDCl_3$): 142.6, 128.4, 128.3, 125.7, 68.1, 36.3, 35.7, 32.9, 29.0, 16.6. IR: 3618 s, 3028 w, 2933 m, 2860 m, 1603 w, 1496 w, 1454 w, 1375 w, 1030 m. TLC: R_f 0.30 (10:1 CH_2Cl_2/ethyl acetate). MS: 178, 160, 145, 131, 117, 105, 104, 92, 91 (base peak), 79, 78, 77. HRMS: $C_{12}H_{18}O$ requires m/z = 178.1358, found 178.1357.

(−)-(*R*)-6-Methyl-9-phenyl-(*E*)-4-nonenoic Acid (15) by Hydrolysis of Zaragozic Acid C. To a solution of zaragozic acid C (657 mg; 0.90 mmol) in THF (15 mL) was added 2.5 N NaOH (14.5 mL). MeOH (10 mL) was added and the mixture refluxed for 8 h. After the mixutre was cooled to ambient temperature the THF and MeOH were removed *in vacuo*. The

homogenous aqueous solution was transferred to an Erlenmeyer flask and diluted with water (15 mL). The solution was vigorously stirred with isopropyl acetate (75 mL), and the pH was adjusted to 2.0 with 2 N HCl. The mixture was transferred to a separatory funnel and the aqueous phase discarded. The organic extract was washed once with water, dried over $MgSO_4$, filtered, and concentrated to an oil (wt = 199 mg; 89%). The product was characterized without further purification. $[\alpha]_D$: −14.5° (*c* 19.9, EtOH). ^1H NMR ($CDCl_3$): δ 7.25 (mult, 2H, Ar-*H*), 7.16 (mult, 3H, Ar-*H*), 5.33 (mult, 2H, C_4-*H*, C_5-*H*), 2.55 (t, 2H, *J* = 7.7 Hz, C_5-H_2), 2.39 (dt, 2H, *J* = 1.6, 7.4 Hz, C_2-H_2), 2.28 (mult, 2H, C_3-H_2), 2.06 (hep, 1H, *J* = 6.8 Hz, C_6-*H*), 1.56 (br dquint, 2H, *J* = 2.0, 7.2 Hz, C_8-H_2), 1.26 (d quart, 2H, *J* = 1.9, 7.6 Hz, C_7-H_2), 0.92 (d, 3H, *J* = 6.8 Hz, C_6-CH_3). ^{13}C NMR ($CDCl_3$): δ 180.0, 142.8, 137.9, 128.5, 128.3, 126.1, 125.7, 36.7 (two lines, 4.2 Hz apart), 36.1, 34.4, 29.3, 27.7, 20.9. IR: 3487 br, 3028 m, 2930 s, 2858 s, 1710 s, 1496 w, 1453 m, 1411 w, 1298 w, 1210 w, 1130 w, 972 m. MS: 246, 228, 205, 186, 155, 145, 137, 117, 105, 104, 91 (base peak), 81. HRMS: $C_{16}H_{22}O_2$ requires *m/z* = 246.1620, found 246.1614.

(+)-3-(5-Phenyl-2(*R*)-methyl-1-oxo-4(*E*)-pentenyl)-4(*S*)-isopropyl-1,3-oxazolidin-2-one (9). To a −78 °C solution of **(+)-3-(1-oxopropyl)-4(*S*)-isopropyl-1,3-oxazolidin-2-one (8)** (5.127 g; 27.68 mmol) in dry THF (80 mL) was added $NaN(SiMe_3)_2$ (30.45 mL; 1.0 M in THF) dropwise over 15 min. After the solution was stirred at −78 °C for an additional 30 min, a solution of cinnamyl bromide (10.911 g; 55.36 mmol) in dry THF (30 mL) was added over a 5-min period. The yellow solution was stirred at −78 °C for 1 h and then allowed to warm to −10 °C in an ice/MeOH bath. After being stirred for 15 min, the reaction was quenched with saturated aqueous ammonium chloride (20 mL) and allowed to warm to ambient temperature. The reaction was partitioned between ethyl acetate and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated to an oil (14.97 g). The oil was chromatographed over silica gel with hexane/CH_2Cl_2 (1:1) until the desired product appeared in the eluant. The mobile phase was changed to 100% CH_2Cl_2 and elution continued, affording **9** as a pale yellow oil (7.257 g; 87%) which crystallized on standing (mp 59–61 °C). $[\alpha]_D$: +10.7° (*c* 12.3, EtOH). ^1H NMR ($CDCl_3$): δ 7.28 (mult, 4H, Ar-*H*), 7.17 (mult, 1H, Ar-*H*), 6.40 (d, 1H, *J* = 15.8 Hz, C_5-*H*), 6.18 (dt, 1H, *J* = 15.8, 7.2 Hz, C_4-*H*), 4.44 (dt, 1H, *J* = 8.9, 3.8 Hz, C_4-*H*), 4.24 (t, 1H, *J* = 8.8 Hz, C_5-*H*), 4.16 (dd, 1H, *J* = 9.0, 3.8 Hz, C_5-*H*), 3.95 (hex, 1H, *J* = 6.9 Hz, C_2-*H*), 2.64 (d quint, 1H, *J* = 1.3, 7.0 Hz, C_3-*H*), 2.33 (d quint, 1H, *J* = 1.3, 7.0 Hz, C_3-*H*), 2.26 (d hept, 1H, *J* = 7.0, 3.9 Hz, iPr C*H*), 1.18 (d, 3H, *J* = 6.8 Hz, C_2-CH_3), 0.85 (d, 3H, *J* = 7.0 Hz, iPr C*H*$_3$), 0.73 (d, 3H, *J* = 6.9 Hz, iPr C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 176.4, 153.8, 137.3, 132.4, 128.5, 127.1, 126.9, 126.1, 63.1, 58.5, 37.7, 37.6, 28.4, 17.9, 16.4, 14.5. TLC: R_f 0.50 (CH_2Cl_2). IR: 2967 m, 2937 m, 2876 w, 1777 s, 1699 s, 1603 w, 1487 m, 1463 m, 1386 s, 1364 m, 1301 m, 1207 m, 1058 w, 991 w. MS: 302 (base peak), 301, 300, 286, 207, 185, 173, 172, 171, 157, 145, 130. HRMS: $C_{18}H_{23}NO_3$ $(MH)^+$ requires *m/z* = 302.1756, found 302.1771.

(+)-3-(5-Phenyl-2(*R*)-methyl-1-oxopentyl)-4(*S*)-isopropyl-1,3-oxazolidin-2-one (10). A solution of **9** (4.975 g; 16.51 mmol) in ethyl acetate (55 mL) was hydrogenated in the presence of 10% Pd/C (995 mg) at 40 psi for 4 h. The mixture was filtered through Celite. Removal of volatiles afforded **10** as a pale green oil (4.700 g; 94%). The product was used without further purification. $[\alpha]_D$: +32.4° (*c* 15.0, EtOH). ^1H NMR ($CDCl_3$): δ 7.24 (mult, 2H, Ar-*H*), 7.15 (mult, 3H, Ar-*H*), 4.44 (dt, 1H, *J* = 8.9, 3.5 Hz, C_4-*H*), 4.23 (t, 1H, *J* = 9.0 Hz, C_5-*H*), 4.16 (dd, 1H, *J* = 9.0, 3.6 Hz, C_5-*H*), 3.80 (hex, 1H, *J* = 6.7 Hz, C_2-*H*), 2.60 (d quart, 2H, *J* = 8.0, 6.0 Hz, C_5-H_2), 2.31 (d hep, 1H, *J* = 3.7, 7.0 Hz, iPr C*H*), 1.79 (mult, 1H, C_4-*H*), 1.64 (apparent t, 1H, *J* = 7.6 Hz, C_4-*H*), 1.61 (mult, 1H, C_5-*H*), 1.46 (mult, 1H, C_5-*H*), 1.12 (d, 3H, *J* = 6.7 Hz, C_2-CH_3), 0.88 (d, 3H, *J* = 7.0 Hz, iPr C*H*$_3$), 0.83 (d, 3H, *J* = 6.9 Hz, iPr C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 177.0, 153.7, 142.2, 128.4, 128.3, 63.1, 58.4, 37.3, 35.8, 33.7, 28.8, 28.4, 18.0, 16.5, 14.6. IR: 3028 w, 2968 m, 2935 w, 2876 w, 1777 s, 1700 s, 1596 w, 1487 m, 1462 m, 1386 s, 1301 m, 1237 s, 1207 s, 968 m. MS: 304 (base peak), 302, 288, 185, 175, 173, 152, 147, 130. HRMS: $C_{18}H_{25}NO_3$ $(MH)^+$ requires *m/z* = 304.1913, found 304.1924.

(+)-(*R*)-5-Phenyl-2-methyl-1-pentanol (11). A solution of **10** (4.700 g; 15.49 mmol) in dry THF (30 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1.235 g; 32.53 mmol) in dry THF (30 mL) at −10 °C. After being stirred for 15 min, the mixture was stirred at ambient temperature for 6 h. The reaction was recooled to 0 °C and treated dropwise with MeOH (5 mL) by syringe. After cessation of gas evolution the mixture was allowed to warm to ambient temperature and evaporated to one-fourth its volume. The mixture was partitioned between isopropyl acetate and saturated aqueous Na^+–K^+ tartrate. The organic phase was dried over $MgSO_4$, filtered, and concentrated to a pale yellow residue (4.826 g) which was chromatographed on silica gel with CH_2Cl_2/ethyl acetate (10:1). The desired **11** was recovered as a clear oil (2.277 g; 83%). $[\alpha]_D$: +11.2° (*c* 6.6, EtOH). ^1H NMR ($CDCl_3$): δ 7.26 (mult, 2H, Ar-*H*), 7.16 (mult, 3H, Ar-*H*), 3.49 (apparent dt, 1H, *J* = 10.4, 5.7 Hz, C_1-*H*), 3.40 (apparent dt, 1H, *J* = 10.4, 5.7 Hz, C_1-*H*), 2.60 (overlapping dt, 2H, *J* = 11.6, 7.0, C_5-H_2), 1.71–1.55 (mult, 3H, C_4-H_2, C_2-*H*), 1.45 (mult, 1H, C_3-*H*), 1.25 (br t, 1H, *J* = 5.6 Hz, O*H*), 1.15 (mult, 1H, C_3-*H*), 0.91 (d, 3H, *J* = 6.7 Hz, C_2-CH_3). ^{13}C NMR ($CDCl_3$): δ 142.7, 128.4, 128.3, 125.7, 68.2, 36.3, 35.7, 32.8, 29.0, 16.6. TLC: R_f 0.30 (10:1 CH_2Cl_2/ethyl acetate). IR: 3619 s, 3028 w, 2933 s, 2860 m, 1603 w, 1496 m, 1454 m, 1375 w, 1030 s. MS: 178, 160, 145, 131, 117, 105, 104, 92, 91, 79, 78, 77. HRMS: $C_{12}H_{18}O$ requires *m/z* = 178.1358, found 178.1359.

(−)-(*R*)-5-Phenyl-2-methylpentanal (12). A solution of dry DMSO (2.713 g; 38.00 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a −55 °C solution of oxalyl chloride (1.657 mL; 12.67 mmol) in dry CH_2Cl_2 (12 mL) over a 5-min period. The turbid mixture was stirred for 10 min and then treated dropwise with a solution of **11** (2.245 g; 12.67 mmol) in dry CH_2Cl_2. The reaction was stirred for an additional 15 min and then treated dropwise with triethylamine (10.60 mL; 76.00 mmol) causing a voluminous white precipitate to form. The viscous mixture was stirred for another 15 min and then allowed to warm to ambient temperature and stir an additional hour. The mixture was partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and evaporated to an oil (2.352 g) which was chromatographed over silica gel with CH_2Cl_2 to afford the desired **12** (2.021 g; 91%). $[\alpha]_D$: −14.6° (*c* 23.03, heptane). ^1H NMR ($CDCl_3$): δ 9.58 (d, 1H, *J* = 1.9 Hz, C*H*O), 7.26 (mult, 2H, Ar-*H*), 7.16 (mult, 3H, Ar-*H*), 2.61 (t, 2H, *J* = 7.4 Hz, C_5-H_2), 2.34 (d hex, 1H, *J* = 1.9, 7.0 Hz, C_2-*H*), 1.69 (mult, 3H, C_3-*H*, C_4-H_2), 1.38 (mult, 1H, C_3-*H*), 1.07 (d, 3H, *J* = 7.0 Hz, C_2-CH_3). ^{13}C NMR ($CDCl_3$): δ 183.6, 142.1, 128.4 (two lines, 4.7 Hz apart), 125.8, 39.4, 35.8, 33.1, 29.0, 16.9. TLC: R_f 0.42 (CH_2Cl_2). IR: 3028 w, 2940 m, 2862 m, 1706 s, 1603 w, 1496 w, 1464 m, 1454 m, 1294 w, 1236 m, 994 w. MS: 176, 175, 159 (base peak), 147, 117, 105, 104, 92, 91, 57. HRMS: $C_{12}H_{16}O$ requires *m/z* = 176.1201, found 176.1199.

4(*R*)-Methyl-7-phenyl-1-hepten-3-ol (13). A solution of **12** (1.920 g; 10.96 mmol) in dry THF (15 mL) was added dropwise to a −30 °C solution of vinylmagnesium bromide (32.89 mL; 1 M in THF) over a 15-min period. The reaction mixture was allowed to warm to approximately 0 °C and then quenched with saturated aqueous ammonium chloride (5 mL). Upon reaching ambient temperature the reaction was evaporated to one-fourth its volume and then partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated to a foam (2.211 g) which was chromatographed on silica gel with CH_2Cl_2/ethyl acetate (10:1) to afford the desired **13** as a 60:40 mixture of diastereomers (1.760 g; 79%). ^1H NMR ($CDCl_3$): δ 7.27 (mult, 2H, Ar-*H*), 7.15 (mult, 3H, Ar-*H*), 5.84 (mult, 1H, C_2-*H*), 5.20 (apparent d quart, 1H, *J* = 17.2, 1.5 Hz, C_1-*H*), 5.14 (apparent d quart, 1H, *J* = 10.5, 1.5 Hz, C_1-*H*), 3.98 (br d quart, 0.6H, *J* = 1.4, 6.0 Hz, major C_3-*H*), 3.93 (br d quart, 0.4H, *J* = 1.4, 5.4 Hz, minor C_3-*H*), 2.58 (mult, 2H, C_7-H_2), 1.74–1.47 (mult, 4H), 1.43 (d, 0.4H, *J* = 4.1 Hz, minor O*H*), 1.38 (d, 0.6H, *J* = 4.6 Hz, major O*H*), 1.16 (mult, 1H), 0.89 (apparent t, 3H, *J* = 6.6 Hz, C_4 CH_3). ^{13}C NMR ($CDCl_3$): δ 142.7, 139.8 (two lines, 3.0 Hz apart), 139.2, 128.4, 128.3, 128.1, 125.7, 115.9, 115.8, 115.3 (two lines, 3.7 Hz apart), 76.8, 76.7, 38.5 (two lines, 6.2 Hz apart), 36.3, 32.3, 32.0, 29.4, 29.2, 15.0, 14.4. TLC R_f 0.28 (10:1 CH_2Cl_2/ethyl acetate). IR: 3603 s, 3084 w, 3028 m, 2935 s, 2860 s, 1643 w, 1602 w, 1496 s, 1453 s, 1380 m, 995 s, 929 s. MS: 204, 186, 171, 147, 131, 117, 105, 104, 92, 91 (base peak), 86, 77, 65, 57. HRMS: $C_{14}H_{20}O$ requires *m/z* = 204.1514, found 204.1514.

(−)-(*R*)-6-Methyl-9-phenyl-(E)-4-nonenoic Acid Ethyl Ester (14). To a solution of **13** (430 mg; 2.12 mmol) in triethyl orthoacetate (3.87 mL; 21.16 mmol) was added propionic acid (17 μL; 0.23 mmol). The solution was heated in a 143 °C bath for 2.5 h. The reaction was cooled to ambient temperature, and all volatiles were removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and evaporated to an oil which was chromatographed over silica gel with hexane/CH_2Cl_2 (2:1). The desired **14** was obtained as a colorless oil (516 mg; 89%). $[\alpha]_D$: −13.2° (*c* 27.2, EtOH). ^1H NMR ($CDCl_3$): δ 7.25 (mult, 2H, Ar-*H*), 7.15 (mult, 3H, Ar-*H*), 5.32 (mult, 2H, C_4-*H*, C_5-*H*), 4.08 (quart, 2H, *J* = 7.0 Hz, Et CH_2), 2.55 (br t, 2H, *J* = 7.6 Hz, C_9-H_2), 2.30 (mult, 4H, C_3-H_2, C_2-H_2), 2.06 (hep, 1H, *J* = 6.8 Hz, C_6-*H*), 1.54 (mult, 2H, C_8-H_2), 1.28 (apparent d quart, 2H, *J* = 1.9, 7.0 Hz, C_7-H_2), 1.22 (t, 3H, *J* = 7.1 Hz, Et CH_3), 0.92 (d, 3H, *J* = 6.7 Hz, C_6 CH_3). ^{13}C NMR ($CDCl_3$): δ 173.2, 142.8, 137.5, 128.4, 128.2, 126.4, 125.6, 60.2, 36.7 (two lines overlapping), 36.1, 34.5, 29.3, 28.0, 20.8, 14.3. TLC: R_f 0.25 (2:1 hexane/CH_2Cl_2). IR: 3028 w, 2932 s, 2859 m, 1728 s, 1602 w, 1496 w, 1453 m, 1373 m, 1346 w, 1301 w, 1182 s, 1038 m, 972 m. MS: 274, 229, 228, 211, 183, 171, 155, 145, 137, 117, 109, 105, 104 (base peak), 95, 91, 81, 67. HRMS: $C_{18}H_{26}O_2$ requires *m/z* = 274.1933, found 274.1932.

(−)-(*R*)-6-Methyl-9-phenyl-(*E*)-4-nonenoic Acid (15). A solution of **14** (522 mg; 1.90 mmol) in THF (15 mL) was treated with 2.5 N NaOH (7.60 mL). The two-phase mixture was refluxed for 15 h and then cooled to ambient temperature. The THF was removed *in vacuo* and the homogenous aqueous solution acidified to pH 1.5 with 2 N HCl. The now turbid mixture was extracted with isopropyl acetate (50 mL). The organic extract was washed with water, dried over $MgSO_4$, filtered, and concentrated to a yellow oil (468 mg; 99%). The product was characterized without further purification. $[\alpha]_D$: −15.5° (*c* 20.2, EtOH). ^1H NMR ($CDCl_3$): δ 7.26 (mult, 2H, Ar-*H*), 7.16 (mult, 3H, Ar-*H*), 5.33 (mult, 2H, C_4-*H*, C_5-*H*), 2.55 (t, 2H, *J* = 7.7 Hz, C_9-H_2), 2.39 (dt, 2H, *J* = 1.5, 7.4 Hz, C_2-H_2), 2.28 (mult, 2H, C_3-H_2), 2.07 (hep, 1H, *J* = 6.7 Hz, C_6-*H*), 1.55 (br d quint, 2H, *J* = 2.0, 7.8 Hz, C_8-H_2), 1.26 (apparent d quart, 2H, *J* = 2.0, 7.8 Hz, C_7-H_2), 0.92 (d, 3H, *J* = 6.8 Hz, C_6-CH_3). ^{13}C NMR ($CDCl_3$): δ 180.1, 142.8, 137.9, 128.5, 128.3, 126.0, 125.7, 36.7 (two lines, 4.7 Hz apart), 36.1, 34.4, 29.3, 27.7, 20.9. IR: 3495 br, 3028 m, 2930 s, 2859 m, 1710 s, 1496 w, 1453 m, 1410 w, 1300 w, 1210 w, 1130 w, 972 m. MS: 246, 228, 205, 186, 155, 145, 137, 117, 105, 104 (base peak), 91, 81, 67. HRMS: $C_{16}H_{22}O_2$ requires *m/z* = 246.1620, found 246.1620.

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Supplementary Material Available: ^1H NMR spectra of compounds **2–7** and **9–15** (15 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 page for ordering information.