Efficient Stereoselective Synthesis of the Enantiomers of Highly Substituted Paraconic Acids

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Introduction

The synthesis of butenolides and saturated γ-lactones as optically active fragments is currently receiving considerable attention in light of their utility as synthons for the synthesis of biologically active natural products.[1,2] On the other hand, the γ-butyrolactone unit is one of the most widely present in bioactive natural products.[3] Paraconic acids are a highly substituted kind of bioactive compounds in which the β-position in the lactone ring is occupied by a carboxylic group.[4] Especially important are those highly functionalized γ-lactones in which the α-position is either a methylene (Chart 1), as in the antibiotic antitumorals methylenolactocin (**1**) (R = C_5H_{11})[5] and protolichesterinic acid (**1**) (R = $C_{13}H_{27}$),[6] or a methyl group, as in rocellaric (**2**) (R = $C_{13}H_{27}$)[7] or dihydroprotolichesterinic (**3**) (R = $C_{13}H_{27}$) acids.[7] A few enantioselective approaches to compounds of this class have been reported very recently.[6−8]

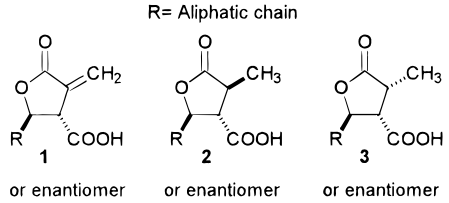
In this paper we report on a short and divergent route to any compound of this class in high enantiomeric purity through a common synthon **4** (Scheme 1), readily available by application of our recently obtained results in the stereoselective synthesis α-(phenylthio) γ-lactones obtained by the base-induced cyclization of enantiomerically enriched γ-(phenylthio)acyl-α,β-unsaturated esters in which the chirality source is an asymmetric epoxidation.[9]

Results and Discussion

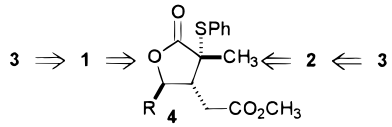
The enolate of the highly substituted γ-butyrolactone **4** was stereoselectively hydroxylated with MoOPH[10] to the α-hydroxy ester **5** (Scheme 2) in 85% yield as the only stereoisomer detected by NMR.[11] Reduction of **5** to the diol **6** was neatly accomplished in 92% yield with a $NaBH_4$ (cat.)−$BH_3{\cdot}S(CH_3)_2$ mixture without affecting the carbonyl lactone.[12]

The key diol **6** was used in a divergent manner. Thus, in order to obtain the γ-substituted α-methyleneparaconic acids, **6** was oxidatively cleaved to **8** using $KMnO_4$−$NaIO_4$, leaving the phenyl sulfide group unaffected.[13] The direct oxidation to the sulfoxide **9** with 1 equiv of *m*-CPBA gave poor yields presumably because of the presence of an acid group in the molecule. Many other methods gave mixtures of sulfone and sulfoxide.[14] We found that the use of $NaIO_4$ in a heterogeneous mixture of solvents (MeOH:benzene:H_2O) cleanly produced the sulfoxide **9** in 55% yield, uncontaminated with sulfone,

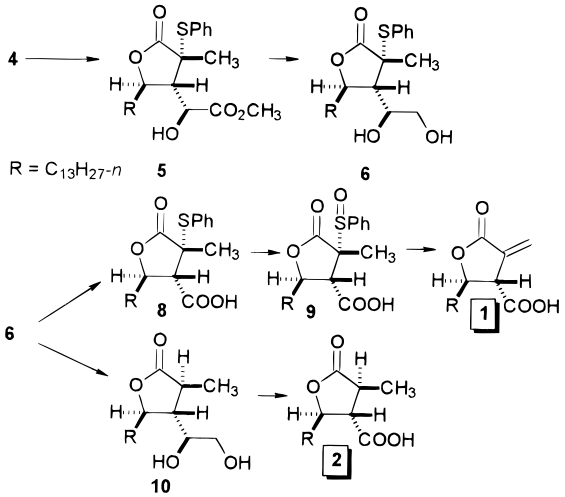
Chart 1



Scheme 1



Scheme 2



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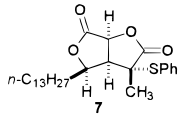
(11) Although the observed stereoselectivity is irrelevant for the present work we have full evidence of the stereochemistry of the created stereocenter by conversion into **7** in which the relative stereochemistry is well determined by NOE studies. For a similar rearrangement, see: (a) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345. (b) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228.



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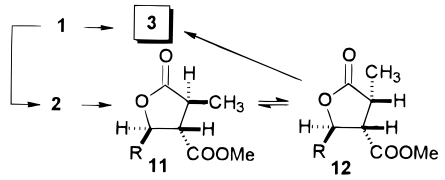
S0022-3263(96)00697-4 CCC: $12.00

Scheme 3



although without complete conversion. Finally, thermal elimination of the sulfoxide group produced (+)-protolichesterinic acid (**1**), mp 103−4 °C, $[\alpha]^{25}_D = +14.2$ (*c* 0.95, $CHCl_3$) [lit.[6] for the enantiomer,[6] mp 103−5 °C, $[\alpha]^{25}_D = -15$ (*c* 1, $CHCl_3$)] in 85% yield.

In order to obtain the saturated products **2** and **3** using the same intermediate **6**, we initially tried the same sequence used to obtain **1**. However, any attempts to remove the phenyl sulfide group or the corresponding sulfone proved fruitless. Thus, we decided to approach the cleavage of the sulfide directly from **6**, which was nicely accomplished using the mixture $NiCl_2-NaBH_4$ under H_2 atmosphere, yielding **10** in 80% yield as the only stereoisomer.[15] At last, the oxidative cleavage of the diol using either RuO_4[16] or $KMnO_4$[13] gave the desired rocellaric acid (**2**), mp 108−9 °C, $[\alpha]^{25}_D = +26.2$ (*c* 1.6, $CHCl_3$) [lit.[7] mp 110−11 °C, $[\alpha]^{25}_D = +24$ (*c* 1.37, $CHCl_3$)] with essentially the same average yield of 90%.

Finally, dihydroprotolichesterinic acid (**3**) was obtained either from **1** or **2** by previously reported procedures. Thus, **1** was hydrogenated using Pd/C as catalyst providing an easily separable mixture of **3** and **2** (6:1).[17] Alternatively, when the methyl ester **11** (Scheme 3) was treated under basic conditions (NaOMe, MeOH) a 1:1 separable mixture of the two epimers **11** and **12** was produced. The saponification of **12** yielded **3**, almost quantitatively mp 101 − 102 °C, $[\alpha]^{25}_D = +41.5$ (*c* 0.55, $CHCl_3$) [lit.[7] mp 106 °C, $[\alpha]^{25}_D = +34.6$ (*c* 2.54, $CHCl_3$)].[17c]

In conclusion, we present a short, general, and efficient approach to the synthesis of any compound of an important class of bioactive compounds in their enantiomeric forms using a divergent strategy in which the kind of compound to be obtained is controlled at the very beginning of the synthesis by the choice of the proper length of the lineal allylic alcohol usable in the asymmetric epoxidation step. Although the presented methodology has been described only for one enantiomeric series, the choice of the suitable enantiomer of the diol **6** permits control of the absolute configuration in the final products.

Experimental Section

Materials and Methods. See ref 2b for details.

Preparation of Methyl (2*R*,3*R*,4*R*)-[4-Methyl-5-oxo-4-(phenylthio)-2-tridecyltetrahydrofuran-3-yl]acetate (4). The γ-butyrolactone **4** was obtained by the general procedure used in ref 2b, with excellent yields, using the (*E*)-hexadec-2-en-1-ol as the starting allylic alcohol (see the supporting information).

Preparation of Methyl (2*S*)-2-Hydroxy-2-[(2*R*,3*R*,4*R*)-4-methyl-5-oxo-4-(phenylthio)-2-tridecyltetrahydrofuran-3-yl]acetate (5). To a solution of hexamethyldisilazane (2 mL, 9.5 mmol) in THF (23.3 mL) was added *n*-butyl lithium (5.4 mL, 1.6 M in *n*-hexane, 8.6 mmol) at 0 °C with stirring. After the mixture was stirred for 15 min, the solution was cooled to −78 °C and the lactone **4** (2 g, 4.3 mmol) was added in THF (20 mL) over a period of 5 min. The mixture was additionally stirred at this temperature for 30 min and then treated with solid oxodiperoxomolybdenum−pyridine−HMPA complex (MoOPH) (3.76 g, 8.6 mmol) in a single portion. The temperature was allowed to warm to −50 °C and stirred for 40 min. The resulting blue-green solution was poured into a mixture of ether (50 mL) and freshly prepared saturated sodium sulfite solution (50 mL). The organic layer was washed with H_2O (2 × 25 mL), dried over $MgSO_4$, and concentrated to provide the crude α-hydroxy ester. Purification by silica gel column chromatography afforded **5** (1.76 g, 85% yield) as a white solid: mp 83−85 °C; $[\alpha]^{25}_D = +59.5$ (*c* 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, $J = 6.3$ Hz, 3 H), 1.20−1.35 (br s, 22 H), 1.43 (s, 3 H), 1.61 (m, 2 H), 2.62 (dd, $J = 10.6$, 2.5 Hz, 1 H), 3.10 (d, $J = 4.1$ Hz, 1 H), 3.89 (s, 3 H), 4.66 (m, 1 H), 4.81 (m, 1 H), 7.39 (m, 3 H), 7.56 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 14.1 (q), 22.2 (q), 22.6 (t), 25.5 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 31.9 (t), 33.8 (t), 53.3 (q), 54.0 (s), 55.7 (d), 67.0 (d), 77.0 (d), 128.2 (s), 128.8 (d), 130.0 (d), 137.6 (d), 173.5 (s), 174.4 (s); IR ($CHCl_3$) (cm^{-1}) 3527, 3021, 2928, 2855, 1762, 1741, 1440, 1221, 1118; MS *m*/*z* (relative intensity) 478 $(M)^+$ (1), 446 (35), 280 (9), 137 (10), 110 (69), 97 (100); HRMS calcd for $C_{26}H_{38}O_4S$ $(M - CH_4O)^+$ 446.2491, found 446.2458. Anal. Calcd. for $C_{27}H_{42}O_5S$: C, 67.75; H, 8.84; S, 6.70. Found: C, 67.91; H, 8.57; S, 6.37.

Preparation of (3*R*,4*S*,5*R*)-4-[(1*S*)-1,2-Dihydroxyethyl]-3-methyl-3-(phenylthio)-5-tridecyldihydrofuran-2-one (6). To a solution of **5** (1.2 g, 2.5 mmol) in dry THF (12.5 mL) was added slowly a 2 M THF solution of borane-methyl sulfide complex (1.5 mL, 3 mmol), and the mixture was stirred at rt for 30 min. Then, $NaBH_4$ (5 mg, 0.13 mmol) was added in one portion to the solution and the resulting mixture was stirred for an additional 1 h, after which time dry methanol (4 mL) was added and stirring continued for 30 min. The solvent was evaporated to give a colorless oil that was purified by silica gel column chromatography, affording the diol **6** (1.04 g, 92% yield) as a white solid: mp 70−72 °C; $[\alpha]^{25}_D = +60.8$ (*c* 1.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3 H), 1.20−1.33 (br s, 20 H), 1.51 (s, 3 H), 1.53 (m, 2 H), 2.07 (m, 2 H), 2.20 (dd, $J = 9.6$, 7.2 Hz, 1 H), 2.61 (d, $J = 4.8$ Hz, 1 H), 3.74 (dd, $J = 10.8$, 7.2 Hz, 1 H), 3.95 (dd, $J = 10.8$, 3.2 Hz, 1 H), 4.27 (m, 1 H), 4.56 (m, 1 H), 7.33 (m, 2 H), 7.41 (m, 1 H), 7.51 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 11.6 (q), 20.1 (t), 20.5 (q), 23.3 (t), 26.8 (t), 27.0 (t), 27.0 (t), 27.0 (t), 27.1 (t), 27.1 (t), 27.1 (t), 29.4 (t), 32.9 (t), 51.4 (s), 51.6 (d), 62.7 (t), 67.8 (d), 78.0 (d), 125.5 (s), 126.4 (d), 127.7 (d), 135.0 (d), 172.3 (s); IR ($CHCl_3$) (cm^{-1}) 3688, 3602, 3429, 3017, 2928, 2855, 1759, 1468, 1379, 1214, 1118, 1026; MS *m*/*z* (relative intensity) 451 $(M + 1)^+$ (8), 450 $(M)^+$ (19), 432 (11), 345 (32), 323 (85), 281 (55), 110 (100), 69 (30). Anal. Calcd. for $C_{26}H_{42}O_4S$: C, 69.29; H, 9.39; S, 7.11. Found: C, 69.34; H, 9.32; S, 6.80.

Preparation of (3*R*,3a*S*,4*R*,6a*S*)-3-Methyl-3-(phenylthio)-4-tridecyldihydrofuro[3,4-*b*]furan-2,6-dione (7). To a solution of lactone **5** (500 mg, 1.05 mmol) in dry toluene (10.5 mL, 0.1 M) was added a catalytic amount of camphorsulfonic acid. The reaction mixture was submitted to reflux for 72 h. Then, the solvent was evaporated and the obtained residue was purified by silica gel column chromatography yielding the bislactone **7** as an oil (355 mg, 76% yield) and remaining starting material **5** (100 mg, 21%). Compound **7**: $[\alpha]^{25}_D = +32.1$ (*c* 1.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3 H), 1.23−1.34 (br s, 20 H), 1.57 (m, 2 H), 1.65 (s, 3 H), 1.91 (m, 2 H), 3.31 (dd, $J = 7.9$, 5.9 Hz, 1 H), 4.61 (ddd, $J = 7.4$, 6.3, 5.9 Hz, 1 H), 4.88 (d, $J = 7.9$ Hz, 1 H), 7.38 (m, 2 H), 7.45 (m, 1 H), 7.55 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 14.1 (q), 20.9 (q), 22.6 (t), 26.7 (t), 29.1 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 29.6 (t), 30.3 (t), 31.9 (t), 47.6 (d), 52.6 (s), 74.0 (d), 80.3 (d), 129.0 (s), 129.5 (d), 130.5 (d), 136.8 (d), 170.2 (s), 175.5 (s); IR ($CHCl_3$) (cm^{-1}) 2928, 2856, 1793, 1467, 1440, 1282, 1171, 1091; MS *m*/*z* (relative intensity) 447 $(M + 1)^+$ (4), 446 $(M)^+$ (14), 161 (10), 109 (49), 97 (100); HRMS calcd for $C_{26}H_{38}O_4S$ $(M)^+$: 446.2491, found 446.2491.

Preparation of (2*R*,3*S*,4*R*)-4-Methyl-5-oxo-4-(phenylthio)-2-tridecyltetrahydrofuran-3-carboxylic Acid (8). To a stirred solution of the diol **6** (500 mg, 1.11 mmol) in a biphasic solvent system (2.3 mL of dioxane−1 mL of H_2O, 0.1 M) were sequen-

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tially added Na_2CO_3 (59 mg, 0.55 mmol), $NaIO_4$ (950 mg, 4.44 mmol) and $KMnO_4$ (35 mg, 0.22 mmol) at rt with stirring. The reaction mixture was stirred for 30 min, after which time TLC showed complete reaction. Then the reaction mixture was diluted with EtOAc (25 mL), treated with HCl (5% v/v) until pH ≃ 1, washed with brine (20 mL), dried over $MgSO_4$, and concentrated and the residue purified by silica gel column chromatography to obtain the carboxylic acid **8** as an oil (400 mg, 83% yield), the sulfoxide **9** (50 mg, 10% yield), and traces of the sulfone (<3% yield). Compound **8**: $[\alpha]^{25}_D = +51.4$ (*c* 1.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3 H), 1.20−1.31 (br s, 20 H), 1.39 (m, 1 H), 1.56 (m, 2 H), 1.62 (s, 3 H), 1.76 (m, 1 H), 3.05 (d, $J = 10.1$ Hz, 1 H), 4.66 (m, 1 H), 5.36 (br s, 1 H), 7.34 (m, 2 H), 7.42 (m, 1 H), 7.56 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 14.1 (q), 22.7 (q), 22.8 (t), 25.5 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.7 (t), 29.7 (t), 29.8 (t), 31.9 (t), 34.3 (t), 53.5 (s), 58.3 (d), 77.7 (d), 128.3 (s), 128.9 (d), 130.3 (d), 137.6 (d), 171.5 (s), 173.9 (s); IR ($CHCl_3$) (cm^{-1}) 3689, 3022, 2928, 2855, 1765, 1731, 1603, 1467, 1377, 1221, 976; MS *m/z* (relative intensity) 435 $(M + 1)^+$ (15), 434 $(M)^+$ (48), 324 (10), 279 (35), 211 (78), 110 (50), 57 (100). Anal. Calcd. for $C_{25}H_{38}O_4S$: C, 69.09; H, 8.81; S, 7.38. Found: C, 68.91; H, 8.62; S, 7.15.

Preparation of (+)-Protolichesterinic Acid (1). To a stirred solution of the lactone **8** (400 mg, 0.92 mmol) in a biphasic solvent system (8 mL of CH_3OH−0.25 mL of C_6H_6−1.9 mL of H_2O, 0.1 M) was added $NaIO_4$ (400 mg, 1.84 mmol) at rt. The reaction mixture was vigorously stirred for 50 h and extracted using CH_2Cl_2 (3 × 15 mL). The resulting organic solution was concentrated, and the crude product was purified by silica gel flash chromatography, to yield **9**, as an isomeric mixture (228 mg, 55% yield) and remaining starting material **8** (160 mg, 40%).

A solution of the mixture of sulfoxides **9** (228 mg, 0.51 mmol) in dry toluene (5 mL, 0.1 M) was submitted to reflux (110 °C) for 1 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography to yield (+)-protolichesterinic acid (**1**) (140 mg, 85% yield), as a solid: mp 103−4 °C; $[\alpha]^{25}_D = +14.2$ (*c* 0.95, $CHCl_3$) [lit.[6] for the enantiomer, mp 103−5 °C, $[\alpha]^{25}_D = -15$ (*c* 1, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.7$ Hz, 3 H), 1.20−1.35 (m, 20 H), 1.36−1.53 (m, 2 H), 1.73 (m, 2 H), 3.62 (m, 1 H), 4.80 (m, 1 H), 6.01 (d, $J = 2.4$ Hz, 1 H), 6.46 (d, $J = 2.9$ Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 14.1 (q), 22.6 (t), 24.7 (t), 29.1 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.5 (t), 29.6 (t), 31.8 (t), 31.9 (t), 35.7 (t), 49.5 (d), 78.9 (d), 125.8 (t), 132.5 (s), 168.2 (s), 173.9 (s); IR ($CHCl_3$) (cm^{-1}) 3020, 2928, 2855, 1761, 1733, 1466, 1398, 1266, 1146, 958; MS *m/z* (relative intensity) 326 $(M + 2)^+$ (3), 325 $(M + 1)^+$ (14), 324 $(M)^+$ (19), 279 (100), 155 (27), 57 (48). Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.32; H, 9.95. Found: C, 69.85; H, 9.86.

Preparation of (3*S*,4*S*,5*R*)-4-[(1*S*)-1,2-Dihydroxyethyl]-3-methyl-5-tridecyldihydrofuran-2-one (10). To a stirred solution of the diol **6** (500 mg, 1.11 mmol) in 95% EtOH (3.7 mL) were added anhydrous $NiCl_2$ (2.88 g, 22.2 mmol) and $NaBH_4$ (420 mg, 11.1 mmol) at 0 °C. The reaction mixture was vigorously stirred under H_2 (1 atm) for 30 min at rt. The reaction mixture was diluted in EtOAc (25 mL) and filtered through a pad of Celite. The combined organic phases were concentrated, and the crude was purified by silica gel chromatography, yielding **10** (311 mg, 82% yield) as a white solid: mp 62−65 °C; $[\alpha]^{25}_D = +17.1$ (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, $J = 6.8$ Hz, 3 H), 1.20−1.35 (br s, 19 H), 1.27 (d, $J = 7.3$ Hz, 3 H), 1.39 (m, 1 H), 1.56 (m, 2 H), 1.78 (m, 1 H), 1.87 (dt, $J = 7.8$, 7.3 Hz, 1 H), 2.57 (dq, $J = 7.3$, 7.3 Hz, 1 H), 2.85 (br s, 2 H), 3.53 (dd, $J = 10.8$, 7.5 Hz, 1 H), 3.70 (dd, $J = 10.8$, 3.0 Hz, 1 H), 3.75 (ddd, $J = 7.5$, 7.3, 3.0 Hz, 1 H), 4.43 (ddd, $J = 8.4$, 7.8, 2.7 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 14.1 (q), 15.7 (q), 22.7 (t), 25.8 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.6 (t), 29.7 (t), 31.9 (t), 36.2 (t), 37.9 (d), 50.8 (d), 65.0 (t), 72.4 (d), 80.8 (d), 179.4 (s); IR ($CHCl_3$) (cm^{-1}) 3444, 2928, 2855, 1760, 1647, 1458, 1276, 1193; MS *m/z* (relative intensity) 343 $(M + 1)^+$ (7), 324 $(M - H_2O)^+$ (9), 311 (15), 281 (44), 141 (90), 71 (100). Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.12; H, 11.19. Found: C, 70.48; H, 10.80.

Preparation of (+)-Rocellaric Acid (2). To a stirred solution of the lactone **10** (275 mg, 0.8 mmol) in a biphasic solvent system (2 mL of CH_3CN−2 mL of CCl_4−3 mL of H_2O) was added $NaIO_4$ (430 mg, 2 mmol) and $RuCl_3 \cdot xH_2O$ (17 mg, 0.08 mmol) at rt. The reaction mixture was vigorously stirred for 2 h. Then, ether (25 mL) was added, and the stirring was continued for 10 min. The mixture was dried with $MgSO_4$ and filtered through a pad of Celite and the residue washed with ether (3 × 10 mL). The combined organic phases were concentrated, and the crude obtained was purified by silica gel flash chromatography, yielding **2** (236 mg, 90% yield), as a white solid: mp 108−9 °C; $[\alpha]^{25}_D = +26.2$ (*c* 1.6, $CHCl_3$) [lit.[7] mp 110−11 °C, $[\alpha]^{25}_D = +24$ (*c* 1.37, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.6$ Hz, 3 H), 1.20−1.32 (br s, 20 H), 1.36 (d, $J = 7.0$ Hz, 3 H), 1.41 (m, 1 H), 1.51 (m, 1 H), 1.70 (m, 1 H), 1.80 (m, 1 H), 2.67 (dd, $J = 11.1$, 9.2 Hz, 1 H), 2.97 (dq, $J = 11.1$, 7.0 Hz, 1 H), 4.47 (dt, $J = 9.2$, 3.9 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 14.1 (q), 14.5 (q), 22.6 (t), 25.3 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.6 (t), 31.9 (t), 34.9 (t), 39.8 (d), 54.0 (d), 79.5 (d), 175.8 (s), 176.7 (s); IR ($CHCl_3$) (cm^{-1}) 3445, 2928, 2855, 1771, 1727, 1647, 1458, 1188, 973; MS *m/z* (relative intensity) 328 $(M + 2)^+$ (3), 327 $(M + 1)^+$ (14), 326 $(M)^+$ (24), 281 (100), 253 (55), 97 (40), 69 (68).

Preparation of Rocellaric Acid Methyl Ester (11). To a solution of rocellaric acid (**2**) (80 mg, 0.24 mmol) in ether (2.5 mL, 0.1 M) was added an ethereal diazomethane solution until a yellow color persisted. Then some drops of acetic acid were added to obtain a colorless solution that was concentrated. The residue was purified by column chromatography, yielding **11** (81 mg, 97% yield) as a white solid: mp 37−38 °C, $[\alpha]^{25}_D = +22.1$ (*c* 0.65, $CHCl_3$) [lit.[7] for the enantiomer, mp 39 °C, $[\alpha]^{25}_D = -22.5$ (*c* 2.18, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3 H), 1.26−1.30 (br s, 20 H), 1.33 (d, $J = 7.1$ Hz, 3 H), 1.49 (m, 2 H), 1.74 (m, 2 H), 2.65 (dd, $J = 11.4$, 9.3 Hz, 1 H), 2.94 (dq, $J = 11.4$, 7.1 Hz, 1 H), 3.77 (s, 3 H), 4.44 (dt, $J = 9.3$, 4.2 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 14.1 (q), 14.4 (q), 22.6 (t), 25.2 (t), 29.2 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.7 (t), 31.8 (t), 34.8 (t), 39.8 (d), 52.5 (q), 54.1 (d), 79.5 (d), 171.1 (s), 176.7 (s); IR ($CHCl_3$) (cm^{-1}) 2928, 2855, 1773, 1736, 1603, 1439, 1261, 1176, 1001; MS *m/z* (relative intensity) 342 $(M + 2)^+$ (6), 341 $(M + 1)^+$ (30), 340 $(M)^+$ (8), 267 (16), 129 (30), 69 (100).

Preparation of Dihydroprotolichesterinic Methyl Ester (12). To a solution of **11** (45 mg, 0.13 mmol) in dry methanol (1.3 mL, 0.1 M) was added sodium hydride (8 mg, 0.26 mmol, 80% in mineral oil). This mixture was heated to 60 °C for 4 h. The mixture was diluted with ethyl ether (10 mL), washed with an aqueous HCl solution (15% w/v, 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated, and the residue was purified by silica gel column chromatography to obtain the methyl esters **11** (20 mg, 44% yield) and **12** (19 mg, 42% yield) as a white solid: mp 49−50 °C; $[\alpha]^{25}_D = +47.2$ (*c* 0.18, $CHCl_3$) [lit.[7] for the enantiomer, mp 58−60 °C, $[\alpha]^{25}_D = -47$ (*c* 0.64, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.7$ Hz, 3 H), 1.20 (d, $J = 7.5$ Hz, 3 H), 1.24−1.34 (br s, 20 H), 1.49 (m, 2 H), 1.66 (m, 2 H), 2.97 (dq, $J = 9.3$, 7.5 Hz, 1 H), 3.10 (dd, $J = 9.3$, 6.5 Hz, 1 H), 3.75 (s, 3 H), 4.70 (dt, $J = 6.5$, 6.5 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 11.8 (q), 14.0 (q), 22.6 (t), 25.3 (t), 29.2 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 31.9 (t), 34.7 (t), 37.1 (d), 50.0 (d), 52.1 (q), 79.4 (d), 170.5 (s), 177.2 (s); IR ($CHCl_3$) (cm^{-1}) 2928, 2855, 1772, 1738, 1461, 1439, 1223, 1216, 1203, 989; MS *m/z* (relative intensity) 342 $(M + 2)^+$ (1), 341 $(M + 1)^+$ (3), 340 $(M)^+$ (7), 281 (100), 157 (34), 129 (59), 101 (62), 69 (89).

Preparation of Dihydroprotolichesterinic Acid (3). Method A. To a stirred solution of lactone **12** (10 mg, 0.029 mmol) in THF:H_2O (5:1, 0.3 mL) was added NaOH (6 mg, 0.15 mmol). The reaction was stirred for 1 h, after which time TLC showed that the starting material had disappeared. Then, concentrated HCl was added at 0 °C until pH ≈ 1 was reached, and the mixture was extracted with AcOEt (4 × 5 mL). The combined organic phases were washed with 10 mL of a saturated solution of brine, dried, and evaporated in vacuo, and the residue was purified by column chromatography to give **3** (9 mg, 95% yield) as a white solid.

Method B. A mixture of (+)-Protolichesterinic acid (**1**) (20 mg, 0.062 mmol) and Pd/C 10% (4 mg, 20% wt) in dry methanol (1 mL) was stirred at rt under atmosphere of H_2 (≈ 1 atm). The reaction was stirred for 6 h, after which time TLC showed the end of the reaction. The solution was filtered, and the filter was washed with ethyl acetate (3 × 5 mL). The combined organic phases were concentrated, and the crude obtained was purified by flash chromatography, yielding **2** (2.6 mg, 13% yield) and **3** (15.4 mg, 76% yield) as a white solid: mp 101−102 °C; $[\alpha]^{25}_D = +41.5$ (*c* 0.55, $CHCl_3$) [lit.[16c] mp 106 °C, $[\alpha]^{25}_D = +34.6$ (*c* 2.54,

$CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3 H), 1.21−1.34 (br s, 20 H), 1.30 (d, J = 7.4 Hz, 3 H), 1.41 (m, 1 H), 1.49 (m, 1 H), 1.68 (m, 2 H), 3.02 (dq, J = 8.5, 7.4 Hz, 1 H), 3.14 (dd, J = 8.5, 6.2 Hz, 1 H), 4.48 (br s, 1 H), 4.67 (ddd, J = 6.3, 6.3, 6.2 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 11.7 (q), 14.1 (q), 22.6 (t), 25.3 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.6 (t), 31.9 (t), 34.6 (t), 36.9 (d), 49.8 (d), 79.4 (d), 177.1 (s), 177.2 (s); IR ($CHCl_3$) (cm^{-1}) 3510, 3029, 2928, 2855, 1770, 1731, 1463, 1262, 1219, 1204, 1094, 1013; MS m/z (relative intensity) 328 $(M + 2)^+$ (1), 327 $(M + 1)^+$ (3), 326 $(M)^+$ (4), 281 (100), 253 (39), 114 (36), 69 (57), 55 (64).

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Supporting Information Available: Copies of ^{13}C-NMR spectra for the new compounds and experimental details for the synthesis of **4** (18 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.

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