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The Synthesis of C3-Methyl, C3-Decarboxy-Zaragozic Acid A -- A Potent Squalene Synthase Inhibitor

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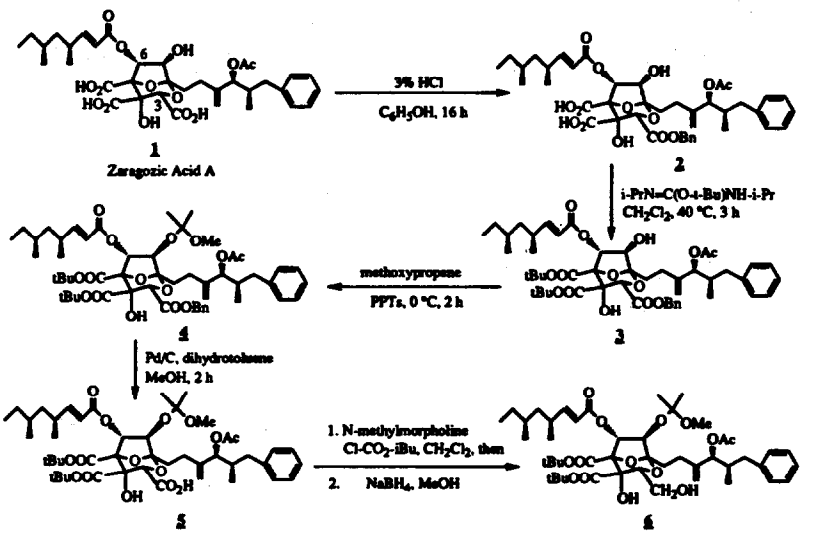
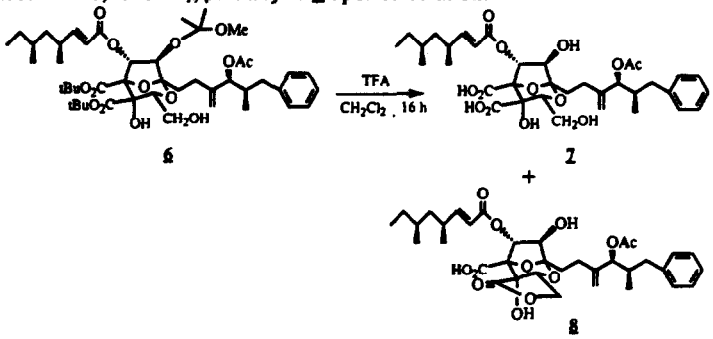
Abstract: The title compound and its C4-pivaloyloxy methyl (POM) ester have been synthesized by converting zaragozic acid A to the key intermediate of the protected C3-hydroxymethyl compound **6**. Subsequent radical deoxygenation *via* the Barton-McCombie procedure, followed by deprotection, afforded the product **11** (L-703,370). This compound possesses squalene biosynthesis inhibitory potency of 22% at 24 mpk and its C4-POM ester, **12** (L-735,142), exhibits an ED_{50} of 1.6 mpk in our oral mouse assay.

Zaragozic acid A, **1**, a potent competitive inhibitor of rat liver squalene synthase with an apparent K_i value of 78 pM, has recently been isolated as one of a family of naturally-occurring fungal metabolites.[1] The structure of **1** has been determined as a 2,8-dioxobicyclo [3.2.1] octane-4,6,7-trihydroxy-3,4,5- tricarboxylic acid.[2] In a broader program directed toward chemical modification of this novel molecule to find analogs with enhanced potency and improved oral absorption, among the many pharmaceutically interesting compounds,[3] the C3-methyl, C3-decarboxy-zaragozic acid A, **11** (L-703,370, 22% inhibition of squalene biosynthesis at 24 mpk in our oral mouse assay),[4] and its pivaloyloxy methyl (POM) ester at C4, **12** (L-735,142, ED_{50}=1.6 mpk oral mouse), have been synthesized[5] as illustrated below.

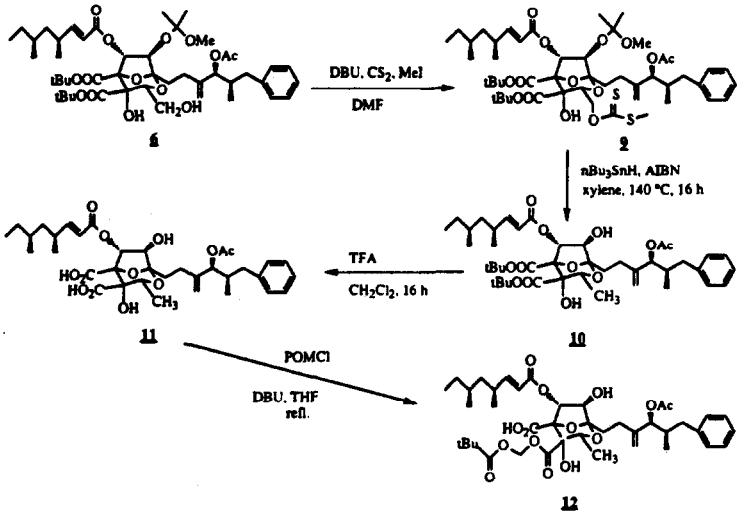


Fischer esterification of zaragozic acid A, **1** (3% HCl, benzyl alcohol),[2a] selectively forms the C3-monobenzyl ester, **2**, in 69% yield after preparative HPLC (Bondapak C8 300Å, 15-20 *um*, CH_3CN : H_2O, 58 : 42). Treatment of **2** with O-*t*-butyl-N,N-diisopropyl isourea in CH_2Cl_2 at 40 °C for 3 h[6] produced the di-*t*-butyl ester, **3**,in 90% yield. Further protection of the C7-hydroxyl group with 2-methoxypropene with pyridinium *p*-toluenesulfonate catalysis in CH_2Cl_2 at 0 °C for 2 h afforded the fully protected compound **4** in 95% yield. Debenzylation by transfer hydrogenation (10% Pd/C, 2,5-dihydrotoluene, CH_2Cl_2, 40 °C, 3 h) gave the C3-carboxylic acid, **5**,[7] in 98% yield. Treatment of the acid **5** with N-methylmorpholine and *i*-butyl chloroformate in CH_2Cl_2 formed the mixed anhydride, and *in situ* reduction with $NaBH_4$ in MeOH[8] produced the hydroxymethyl compound, **6** , in 84% yield after flash chromatography on silica (ethyl acetate : hexane, 3:7). Upon hydrolysis with trifluoroacetic acid (TFA) in CH_2Cl_2, this compound **6** produced a 1:1 mixture of the free C3-hydroxymethyl-zaragozic acid A, **7**, and its corresponding γ-lactone, **8**, in 98% yield. HPLC separation of the two (Dynamax-60A C8 column, 21.4 mm ID x 25 cm L using the following gradient: 50:50:0.005 CH_3CN/H_2O/TFA) provided **7** and **8** in 60 and 30% yield, respectively. The latter was somewhat unstable in aqueous acetonitrile, reverting partially to **7** upon reisolation.



6 **7** **8**

The deoxygenation reaction of **6** was performed according to the procedure of Barton-McCombie by first forming the C3-mono-dithiocarbonate, **9** (DBU, CS_2, MeI), followed by radical-induced deoxygenation of the mono-xanthate with tri-*n*-butyltin hydride in refluxing xylene[9] in 62% yield over the two steps. Deprotection with TFA in CH_2Cl_2 at ambient temperature for 16 h yielded C3-methyl-4,5-dicarboxylic acid, **11**, in 98% yield.



11 **10** **12**

After treating **11** with 1 equiv of DBU, 2 equiv of chloromethyl pivalate in THF and heating the mixture at 60 °C for 48 h, followed by preparative HPLC for removal of the recovered starting material, minor products of C5-POM and C4, C5-diPOM, the C3 methyl, C4-POM ester, **12**, was isolated in 38% yield.

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3. A manuscript on other functional group modifications at C3 is in preparation for submission to *Bioorg. Med. Chem. Lett.* for publication.
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5. Spectral data are recorded: (2) ^{1}H NMR (300 MHz, CD_3OD) δ 7.46-7.12 (m, 10H), 6.88 (dd, J=18, 8.9 Hz, 1H), 6.38 (br s, 1H), 5.48 (d, J=15.2 Hz, 1H), 5.42 (s, 1H), 5.23 (dd, J=14, 5.1 Hz, 2H), 5.14 (s, 1H), 5.04 and 5.00 (2x s, 2x 1H), 4.06 (br s, 1H), 2.71 (m, 1H), 2.54-2.00 (m, 7H), 2.12 (s, 3H), 1.50-1.1 (m, 6H), 1.07 (d, J=6.3 Hz, 3H), 0.90 (m, 9H); MS FAB m/z 793 [M+Li], 799 [M+3Li].; (3) ^{1}H NMR (400 MHz, CD_3OD) δ 7.28-7.14 (m, 5H), 6.88 (dd, J=15.7, 8.5 Hz, 1H), 6.41 (d, J=1.8 Hz, 1H), 5.82 (d, J=15.7 Hz, 1H), 5.18 (s, 1H), 5.08 (d, J=4.6 Hz, 1H), 5.00 and 4.96 (2x br s, 2x 1H), 4.04 (d, J=1.8 Hz, 1H), 2.69 (dd, J=13.3, 6.2 Hz, 1H), 2.10 (s, 3H), 1.63, 1.47 and 1.43 (3x s, 3x 9H), 1.12 (d, J=6.45 Hz, 3H), 0.93-0.84 (m, 9H); (4) ^{1}H NMR (400 MHz, CD_3OD) δ 7.4-7.12 (m, 10H), 6.88 (dd, J=15.6, 8.5 Hz, 1H), 6.48 (d, J=1.85 Hz, 1H), 5.84 (d, J=15.6 Hz, 1H), 5.29 (s, 1H), 5.23 and 5.10 (2x d, J=12 Hz, 2x 1H), 5.07 (d, J=4.8 Hz, 1H), 5.01 and 4.99 (2x s, 2x 1H), 4.23 (d, J=1.85 Hz, 1H), 3.18 (s, 3H), 2.09 (s, 3H), 1.52 and 1.39 (2x s, 2x 9H), 1.34 (s), 1.26 (s), 1.02 (d, J=6.7 Hz, 3H), 0.9-0.8 (m, 9H); (5) ^{1}H NMR (200 MHz, CD_3OD) δ 7.3-7.15 (m, 5H), 6.92 (dd, J=15.6, 8.4 Hz, 1H), 6.50 (d, J=1.7 Hz, 1H), 5.85 (d, J=15.6 Hz, 1H), 5.19 (s, 1H), 5.08 (d, J=4.78 Hz, 1H), 5.02 and 4.97 (2x br s, 2x 1H), 4.25 (d, J=1.7 Hz, 1H), 3.19 (s, 3H), 2.10 (s, 3H), 1.63 and 1.40 (2x s, 2x 9H), 1.35 (s), 1.26 (d, J=5.8 Hz, 3H), 1.02 (d, J=6.73

Hz, 3H), 0.89-0.82 (m, 9H); (6) ^{1}H NMR (400 MHz, CD_3OD) δ 7.29-7.16 (m, 5H), 6.89(dd,J=15.6, 8.53 Hz, 1H), 6.49 (d, J=1.9 Hz, 1H), 5.87 (d, J=15.6 Hz, 1H), 5.06 (d, J=4.56 Hz, 1H), 4.97 and 4.95 (2x s, 2x 1H), 4.64 (t, J=5.99 Hz, 1H), 4.20 (d, J=1.9 Hz, 1H), 3.64-3.52 (m, 2H), 3.19 (s, 3H), 2.67 (dd, J=13.6, 6.3 Hz, 1H), 2.09 (s, 3H), 1.62 (s, 9H), 1.40 (s, 9H), 1.34 (s), 1.27 (s), 1.03 (d, J=6.64 Hz, 3H), 0.88-0.84 (m, 9H); (7) ^{1}H NMR (400 MHz, CD_3OD) δ 7.27-7.14 (m, 5H), 6.84 (dd, J=15.63, 8.5 Hz, 1H), 6.29 (d, J=1.98 Hz, 1H), 5.75 (d, J=15.63, 1H), 5.05 (d, J=4.65 Hz, 1H), 4.98 and 4.94 (2x s, 2x 1H), 4.65 (t , 1H), 4.00 (d, J=1.98 Hz, 1H), 3.63 (m, 2H), 2.66 (dd, J=13.5, 6.3 Hz, 1H), 2.5-2.14 (m), 2.09 (s, 3H), 2.0-1.9 (m), 1.43-1.24 (m), 1.16- 1.11 (m), 1.03 (d, J=6.64 Hz, 3H), 0.88-0.84 (m, 9H); MS FAB m/z 695 [M + 3Li]; (9) ^{1}H NMR (400MHz, CD_3OD) δ 7.28-7.16 (m, 5H), 6.91 (dd, J=15.67, 8.45 Hz, 1H), 6.45 (d, J=1.8 Hz, 1H), 5.85 (d, J=15.67 Hz, 1H), 5.08-5.06 (m, 1H), 5.05 (s, 1H), 5.00 (s, 1H), 4.97 (s, 1H), 4.74 (m, 1H), 4.53 (m, 1H), 4.22 (d, J= 1.8 Hz, 1H), 3.19 (s, 3H), 2.68 (m, 1H), 2.55 (s, 3H), 2.5-2.12 (m), 2.10 (s, 3H), 2.09-1.83 (m), 1.64 (s, 9H), 1.40 (s, 9H), 1.33 (s), 1.27 (s), 1.02 (d, J= 7 Hz, 3H), 0.88 (m, 9H); (10) ^{1}H NMR (300 MHz, CD_3OD) δ 7.34-7.20 (m, 5H), 6.94 (dd, J=15.6, 8.5 Hz, 1H), 6.43 (d, J=1.85 Hz, 1H), 5.86 (d, J= 15.6 Hz, 1H), 5.10 (d, J=4.8 Hz, 1H), 5.03 and 5.00 (2x s, 2x 1H), 4.67 (q, 1H), 4.09 (d, J=1.85 Hz, 1H), 2.78-2.65 (m, 1H), 2.55-2.20 (m), 2.14 (s, 3H), 1.99-1.93 (m, 2H), 1.63 (s, 9H), 1.47 (s, 9H), 1.12 (d, J= 6.24 Hz, 3H), 1.08 (d, J=6.72 Hz, 3H), 0.9 (m, 9H); (11) ^{1}H NMR (300 MHz, CD_3OD) δ 7.33-7.19 (m, 5H), 6.89 (dd, J=15.6, 8.3 Hz, 1H), 6.3 (br s, 1H), 5.85 (d, J=15.6 Hz, 1H), 5.10(d, J=4.8 Hz, 1H), 5.03 and 4.99 (2x s, 2x 1H), 4.67 (m, 1H), 4.03 (br s, 1H), 2.73-2.69 (2x d, J=6.46 Hz, 2x 1H), 2.56-2.18 (m), 2.14 (s, 3H), 1.96 (m, 2H), 1.56-1.22 (m), 1.16 (d, J=5.86 Hz, 3H), 1.08 (d, J=6.4 Hz, 3H), 0.92 (m, 9H); MS FAB m/z 667[M+Li], 673 [M+2Li], 679 [M+3Li]; (12) ^{1}H NMR (400 MHz, CD_3OD) δ 7.27-7.13 (m, 5H), 6.84 (dd, J=15.6, 8.3 Hz, 1H), 6.14 (br s, 1H), 5.87-5.74 (m, 3H), 5.05 (d, J=4.6 Hz, 1H), 4.97 and 4.94(2x s, 2x 1H), 4.58 (m, 1H), 4.0 (br s, 1H), 2.65 (dd, J=13.3, 6.3 Hz, 1H), 2.50-2.13 (m), 2.09 (s, 3H), 1.96 (m, 2H), 1.5-1.2 (m), 1.19 (s, 9H), 1.10 (d, J=6.2 Hz, 3H), 1.03 (d, J=6.6 Hz, 3H), 0.85 (m, 9H), MS FAB m/z 773 [M+Li].

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