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BIOMIMETIC TOTAL SYNTHESIS OF THE ACAT INHIBITOR (+)-PYRIPYROPENE E

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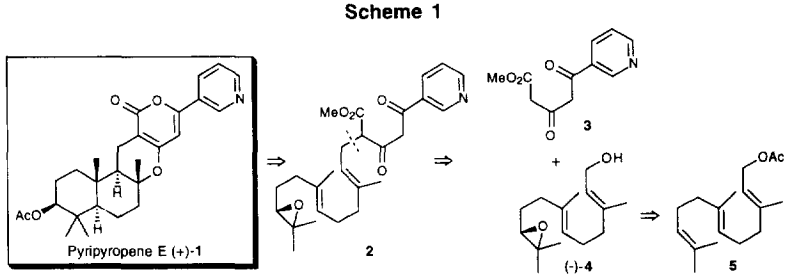
Abstract: The acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor (+)-pyripyropene E (**1**) has been synthesized from farnesyl acetate (9 steps, 9.6% overall yield). The convergent and stereoselective route exploited a biomimetic polyene cyclization as the key transformation. Copyright © 1996 Elsevier Science Ltd

Pyripyropenes A-L, isolated by Ōmura and co-workers[1] from a fermentation broth of *Aspergillus fumigatus*, are potent inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT), the enzyme responsible for intracellular esterification of cholesterol. Recently we disclosed the complete relative and absolute stereochemistry[2a] and first total synthesis of (+)-pyripyropene A, the most active congener.[2b] Pyripyropene E (**1**), the simplest member of the family, proved to be identical to GERI-BP001 M, reported by Bok et al.[3] Parker and Resnick have completed a biomimetic construction of racemic **1**.[4] Herein we describe a similar biomimetic approach to the natural enantiomer of pyripyropene E [(+)-**1**] via a cationic polyene cyclization.[5] This venture comprises one facet of our program aimed at the biomimetic assembly of numerous terpene-based bioactive molecules including the indole diterpenes.[6]

From the retrosynthetic perspective (Scheme 1), we envisioned that cyclization of epoxy diene **2**, initiated by a Lewis acid, would provide the requisite pyripyropene skeleton. Substrate **2** in turn would derive from diketo ester **3** and the known epoxy alcohol (-)-**4**; the latter, incorporating sesquiterpene backbone of **1**, is available from farnesyl acetate (**5**) via Sharpless asymmetric dihydroxylation (AD).[7] The highly regioselective AD protocol recently introduced by Corey made this route particularly attractive.[8]

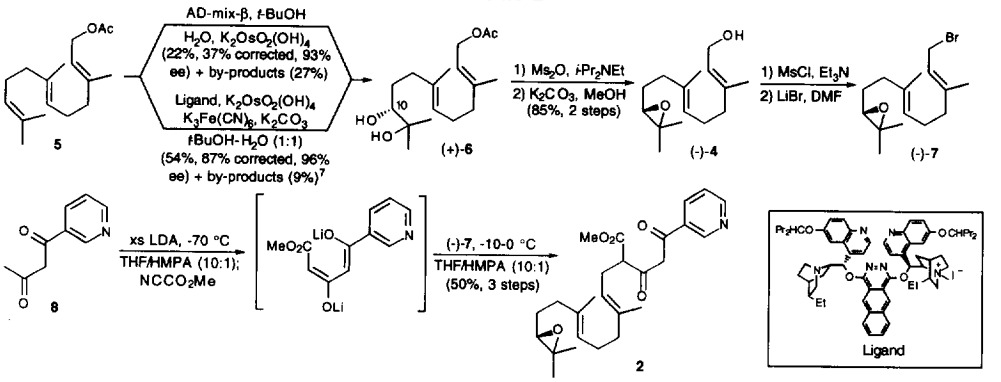
Scheme 1



Dihydroxylation of *E,E*-farnesyl acetate **5** (Scheme 2) with the Sharpless AD-mix-β under standard conditions[7] furnished diol **6**[9] (22% yield, 37% based on consumed **5**) plus the internal diol and tetraol (1:1.5 ratio, 27%). The enantiomeric purity of **6** (ca. 93% ee) was determined by ^{1}H NMR analysis of the C(10) (+)-MTPA esters.[8,10] As anticipated, Corey's cinchona alkaloid ligand gave distinctly superior results [54% yield (87% based on consumed **5**), 96% ee, plus 9% (1:2 mixture) of the internal diol and tetraol].[11] Treatment of diol (+)-**6** with methanesulfonic anhydride (Ms_2O),[12] and then K_2CO_3 in MeOH afforded epoxy alcohol (-)-**4**[7,9] (85% yield), which was converted to bromide (-)-**7** (MsCl, Et_3N, CH_2Cl_2; LiBr, DMF). After aqueous work-up,

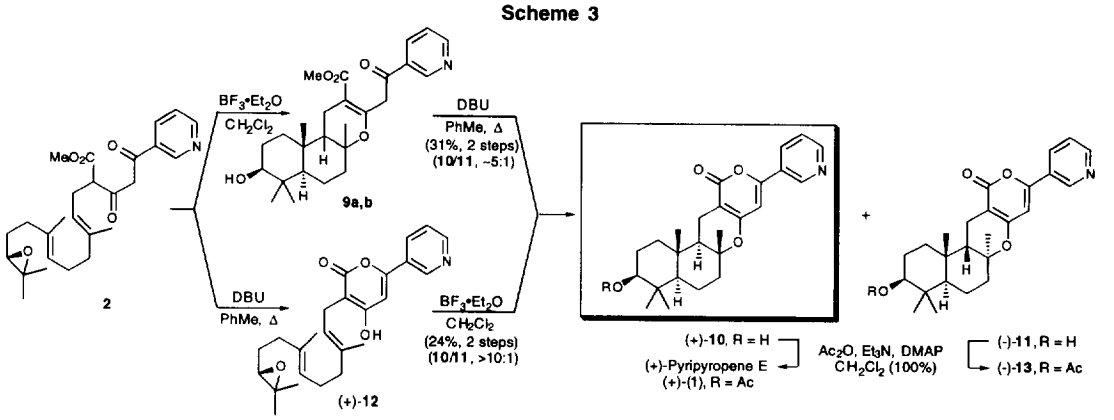
the unstable bromide was immediately employed in the subsequent alkylation step. Generation of the yellow dienolate of nicotinoylacetone (**8**)[13] (3.3 equiv LDA, 10:1, THF/HMPA, -70 °C) followed by acylation with methyl cyanoformate[14] and deprotonation by excess LDA produced the orange dianion of **3**. Addition of this solution to epoxy bromide **7** (10:1 THF/HMPA, -10-0 °C) furnished cyclization substrate (-)-**2**[9] (50% from **4**, 3 steps).

Scheme 2

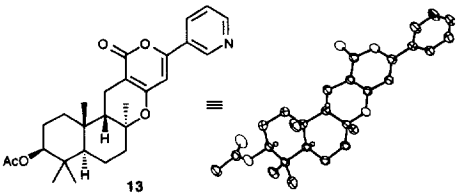


The pyripyropene skeleton could be elaborated from **2** via two different sequences (Scheme 3).[15] Exposure to $BF_3{\bullet}Et_2O$ (CH_2Cl_2, 0 °C, 2 h) effected cationic cyclization to (+)-**9**.[15] Chromatography on silica caused partial decomposition; **9** was therefore carried forward without purification. Closure of the α-pyrone ring (DBU, toluene, reflux, 4 h) provided a mixture of the desired tetracycle (+)-**10**[16] and the trans-syn-trans isomer (-)-**11**[16] (ca. 5:1) in 31% yield overall from **2**. Alternatively, initial formation of the α-pyrone (DBU, toluene) gave (+)-**12**;[15] polyene cyclization induced by

Scheme 3

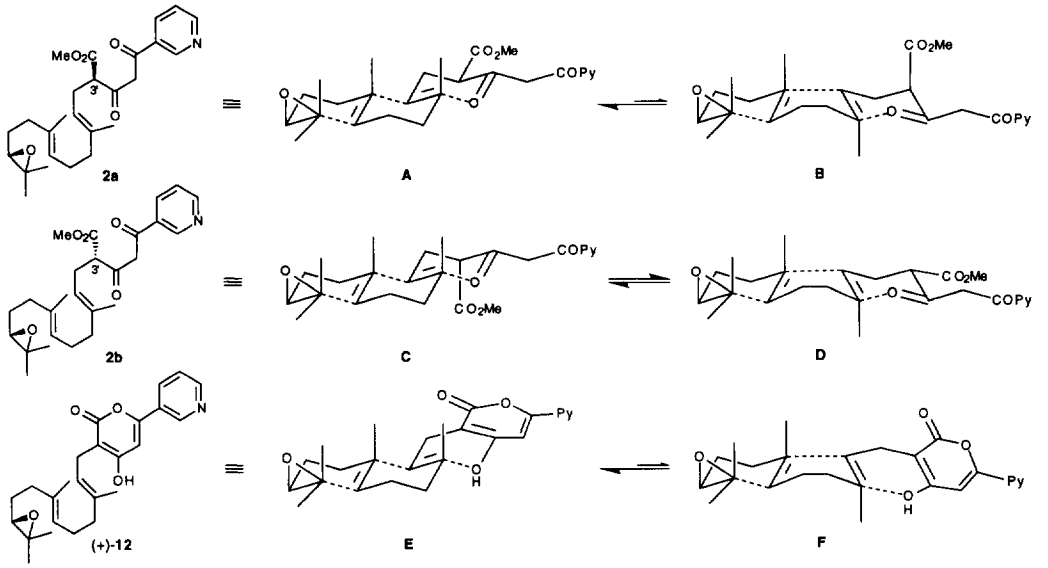


$BF_3{\bullet}Et_2O$ in CH_2Cl_2 then afforded an improved (>10: 1) **10:11** ratio, albeit in lower yield (24% from **2**, 2 steps). Acetylation Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 100%) of the mixture furnished (+)-pyripyropene E (**1**)[17] and (-)-**13**[18] after preparative TLC. Synthetic (+)-**1** was identical in all respects (500-MHz ^1H and 125-MHz ^{13}C NMR, IR, HRMS, sign of optical rotation, melting point and mixed melting point, and TLC in four solvent systems) with a sample of the natural product. The structure of (-)-**13**, initially deduced via extensive NMR studies, was confirmed by single crystal X-ray analysis.[19] In the in vitro ACAT assay, the IC_{50} value of (-)-**13** was >1108 μM [cf., 665 μM for (+)-**1**, 135 nM for pyripyropene A].



Conformational analysis of the cyclization substrates offers a possible rationale for the observed difference in the ratios of **10** to **11** (Figure 1). In the formation of **9** (Scheme 3), the precursor is presumed to be a mixture of C(3') epimers **2a** and **2b**. The former should favor chair-chair-chair conformer **A** in preference to boat **B**, leading to the desired ring-fusion stereochemistry.[20] For **2b**, however, conformers **C** and **D** should be closer in energy, resulting in a mixture of **10** and **11** after α-pyrone ring closure. In the alternative sequence, the stereochemically homogeneous precursor **12** presumably adopts the chair-chair conformation **E**, furnishing the requisite trans-anti-trans isomer **10** exclusively. Parker and Resnick earlier obtained a 7:3 diastereomer mixture (16% yield) in the cationic cyclization of an epoxy diene related to **2**.

Figure 1. Conformers of cyclization substrates: **A**, **C**, **E**, possible precursors of **10**, and **B**, **D**, **F**, possible precursors of **11**.



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9. All analytical samples were purified by flash chromatography or preparative TLC on silca gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry.
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11. Corey reported 64% yield (80% based on recoved starting material) and 96% ee for the same transformation (reference 8). We thank Professor Corey for a preprint of reference 8 and a generous sample of 1,4-bis[*O*-6'-(4-heptyl)hydrocupreidyl] naphthopyridazine monomethiodide.
12. The use of methanesulfonic anhydride rather than methanesulfonyl chloride prevents possible racemization: Mori, K.; Mori, H. *Tetrahedron* **1987**, *43*, 4097.
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15. Cyclization via **9:** At 0 °C to a solution of **2** (50.0 mg, 0.113 mmol) in CH_2Cl_2 (4 mL) was treated with BF_3•Et_2O (30 μL, 0.24 mmol) and stirred for 1.5 h. Et_3N (50 μL) and MeOH (100 μL) were then added and the mixture was allowed to warm to room temperature. After evaporation of most of the solvents in vacuo, the concentrate was diluted with EtOAc (20 mL) and the solution was washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated, affording **9a,b** (5:1, 59.6 mg, 100% yield) as a yellowish solid. The trans-anti-trans isomer (**9a**) was purified by preparative TLC (EtOAc).

    9a: $[\alpha]_D^{25}$ +48° (*c* 0.33, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 159.1, 151.7, 149.1, 147.7, 136.2, 132.5, 127.7, 107.5, 102.7, 79.4, 78.6, 55.0, 51.3, 51.2, 40.4, 38.8, 37.4, 36.6, 28.1, 27.2, 20.5, 19.4, 19.3, 15.5, 15.0; high resolution mass spectrum (CI, methane) *m/z* 442.2590 [(M+H)$^+$; calcd for $C_{26}H_{36}NO_5$: 442.2593].

    A solution of crude **9** (59.6 mg) in toluene (15 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 70 μL, 0.47 mmol), heated at reflux for 4 h, and stirred overnight at room temperature. After concentration the residue was dissolved with EtOAc (20 mL) and the solution was washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered and concentrated. Preparative TLC (EtOAc) gave an ca. 5:1 (^{1}H NMR) mixture of **10**[16] and **11**[16] (14.5 mg, 31% yield).

    Cyclization via **12:** A solution of **2** (210 mg, 0.476 mmol) and DBU (140 μL, 0.936 mmol) in toluene (10 mL) was heated at reflux for 4 h, cooled, and concentrated. The residue was dissolved in EtOAc (20 mL), and the solution was washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered and concentrated, **12** (195 mg, 100% yield).

    12: mp 146-149 °C (dec); $[\alpha]_D^{25}$ +20° (*c* 0.77, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 159.0, 155.4, 150.9, 146.4, 138.7, 134.2, 133.1, 127.1, 124.6, 123.7, 120.8, 104.2, 99.5, 64.8, 59.7, 39.3, 36.3, 27.1, 25.6, 24.9, 22.9, 18.7, 16.1, 16.0; high resolution mass spectrum (CI, methane) *m/z* 410.2350 [(M+H)$^+$; calcd for $C_{25}H_{32}NO_4$: 410.2331].

    At 0 °C a solution of crude **12** (195 mg) in CH_2Cl_2 (15 mL) was treated dropwise with BF_3•Et_2O (138 μL, 1.12 mmol) and stirred for 2 h. The reaction mixture was quenched with Et_3N (0.2 mL) and MeOH (0.6 mL), warmed to room temperature, diluted with EtOAc, and filtered through celite. Concentration and preparative TLC (EtOAc) gave an ca. 10:1 ^{1}H NMR mixture of **10**[16] and **11**[16] (47.5 mg, 24% yield).
16. Analytical samples of **10** and **11** were prepared from **1** and **13**, respectively, by treatment with K_2CO_3 in MeOH. **10**: $[\alpha]_D^{25}$ +73° (*c* 0.24, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 162.8, 155.3, 150.4, 146.1, 133.2, 127.9, 123.8, 100.5, 99.6, 81.1, 78.4, 55.0, 51.5, 40.3, 38.8, 37.5, 36.9, 28.1, 27.2, 20.8, 19.4, 17.3, 15.5, 15.1; high resolution mass spectrum (CI, methane) *m/z* 410.2318 [(M+H)$^+$; calcd for $C_{25}H_{32}NO_4$: 410.2331]. The spectral data are in accord with those reported earlier.[3]

    11: $[\alpha]_D^{25}$ -35° (*c* 0.17, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 162.6, 153.8, 149.6, 147.1, 129.0, 128.2, 125.3, 101.4, 99.9, 81.9, 78.7, 48.1, 46.7, 39.3, 36.8, 36.2, 33.3, 28.8, 28.5, 24.2, 24.0, 18.5, 16.9, 15.8; high resolution mass spectrum (CI, methane) *m/z* 410.2326 [(M+H)$^+$; calcd for $C_{25}H_{32}NO_4$: 410.2331].
17. **1**: $[\alpha]_D^{27}$ +103° (*c* 0.48, MeOH) {lit.[1d] $[\alpha]_D^{28}$ +113° (*c* 1.0, MeOH)}.
18. **13**: mp 272-275 °C (EtOAc); $[\alpha]_D^{25}$ -19° (*c* 0.19, MeOH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 162.9, 162.3, 152.9, 145.8, 142.1, 136.9, 129.8, 125.4, 102.3, 101.1, 82.1, 80.2, 47.9, 46.9, 38.2, 36.8, 36.1, 33.0, 28.8, 24.7, 24.3, 23.9, 21.2, 18.5, 16.9, 16.8; high resolution mass spectrum (CI, methane) *m/z* 452.2445 [(M+H)$^+$; calcd for $C_{27}H_{34}NO_5$: 452.2436].
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