Total Synthesis of (+)-Pyripyropene A. A Potent, Orally Bioavailable Inhibitor of Acyl-CoA:Cholesterol Acyltransferase

Tohru Nagamitsu, Toshiaki Sunazuka, Rika Obata, Hiroshi Tomoda, Haruo Tanaka, Yoshihiro Harigaya, and Satoshi Ōmura*

Research Center for Biological Function, The Kitasato Institute, and School of Pharmaceutical Science, Kitasato University, Minato-ku, Tokyo 108, Japan

Amos B. Smith, III*

Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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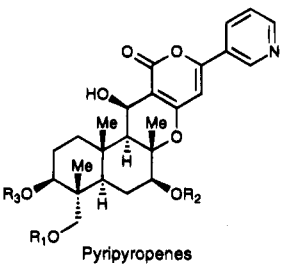
A promising, fundamentally new approach to the prevention and treatment of atherosclerosis is based upon inhibition of acyl-CoA:cholesterol acyltransferase (ACAT), the enzyme that catalyzes intracellular esterification of cholesterol. This strategy may permit suppresion of three distinct, ACAT-dependent steps in the pathology of atherosclerosis: absorption of dietary cholesterol in the gut, hepatic synthesis of lipoproteins, and deposition of oily cholesteryl esters within the developing arterial lesions.[1-3] In 1993, we reported the isolation, planar structures, and initial biological evaluation of the pyripyropenes A–D (**1**–**4**), potent ACAT inhibitors isolated from *Aspergillus fumigatus* FO-1289.[4] These novel, polyoxygenated mixed polyketide–terpenoid (meroterpenoid) metabolites contain a fused pyridyl α-pyrone moiety and eight contiguous stereocenters;[5] subsequently,

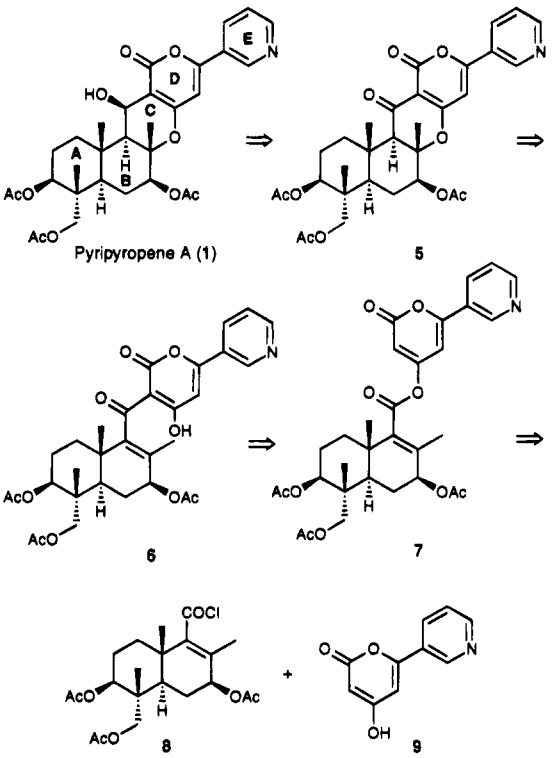


Pyripyropenes
A (1) $R_1 = R_2 = R_3 = Ac$
B (2) $R_2 = R_3 = Ac$, $R_1 =$ COEt
C (3) $R_1 = R_3 = Ac$, $R_2 =$ COEt
D (4) $R_1 = R_2 = Ac$, $R_3 =$ COEt

we determined the relative and absolute stereochemistries of **1** as well, employing NOE-difference and Mosher ester NMR studies in conjunction with X-ray crystallography.[6] The pyripyropenes not only rank as the most effective naturally occurring ACAT inhibitors in vitro, with IC_{50} values of 58, 117, 53, and 268 nM, respectively,[7] but also display oral bioavailability in hamsters.[4a] Herein, we describe the first total synthesis of the most active member of this family, (+)-pyripyropene A (**1**), via a flexible, concise and highly efficient route.[8]

From the retrosynthetic perspective (Scheme 1), we envisioned construction of advanced ketone **5** via acylation of the known hydroxy α-pyrone **9**[9] with acid chloride **8** in the presence of an acid catalyst; isomerization to the C-acyl pyrone **6** and ring closure would then deliver **5** with the requisite anti geometry at the BC ring fusion.

Scheme 1



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(7) Other natural ACAT inhibitors include beauvericin, a cyclodepsipeptide, and AC-183 (IC_{50} 3.0 and 0.94 μM, respectively). The best synthetic inhibitors, with IC_{50} values of 18, 22, 17, and 23 nM, respectively, are DuP-128 [Bilheimer, J. T.; Cromley, D. A.; Higley, C. A.; Wexler, R. R.; Robinson, C. S.; Gillies, P. J. *Abstracts of 9th International Symposium on Atherosclerosis*; Rosemont, IL, 1991; p 94], CP-113,818 [Chang, G.; Hamanaka, E. S.; McCarthy, P. A.; Walker, F. J.; Diaz, T. L.; Johnson, D. A.; Kraus, K. G.; Maloney, M. E.; Martingano, R. J.; Wint, L. T.; Marzetta, C. A.; Goldberg, D. L.; Freeman, A. M.; Long, C. A.; Pettini, J. L.; Savoy, Y. E. *Abstracts of Papers*, 206th National Meeting of the American Chemical Society, Chicago, IL; American Chemical Society: Washington, D.C., 1993; MEDI 46], PD-129,337 [Trivedi, B. K.; Holmes, A.; Scoeber, T. L.; Blankley, C. J.; Roark, W. H.; Picard, J. A.; Shaw, M. K.; Essenburg, A. D.; Stanfield, R. L.; Krause, B. K. *J. Med. Chem.* **1993**, *36*, 3300], and KF-17,828 [Kumazawa, T.; Yanase, M.; Harakawa, H.; Obase, H.; Shirakura, S.; Ohishi, E.; Oda, S.; Kubo, K.; Yamada, K. *J. Med. Chem.* **1994**, *37*, 804].
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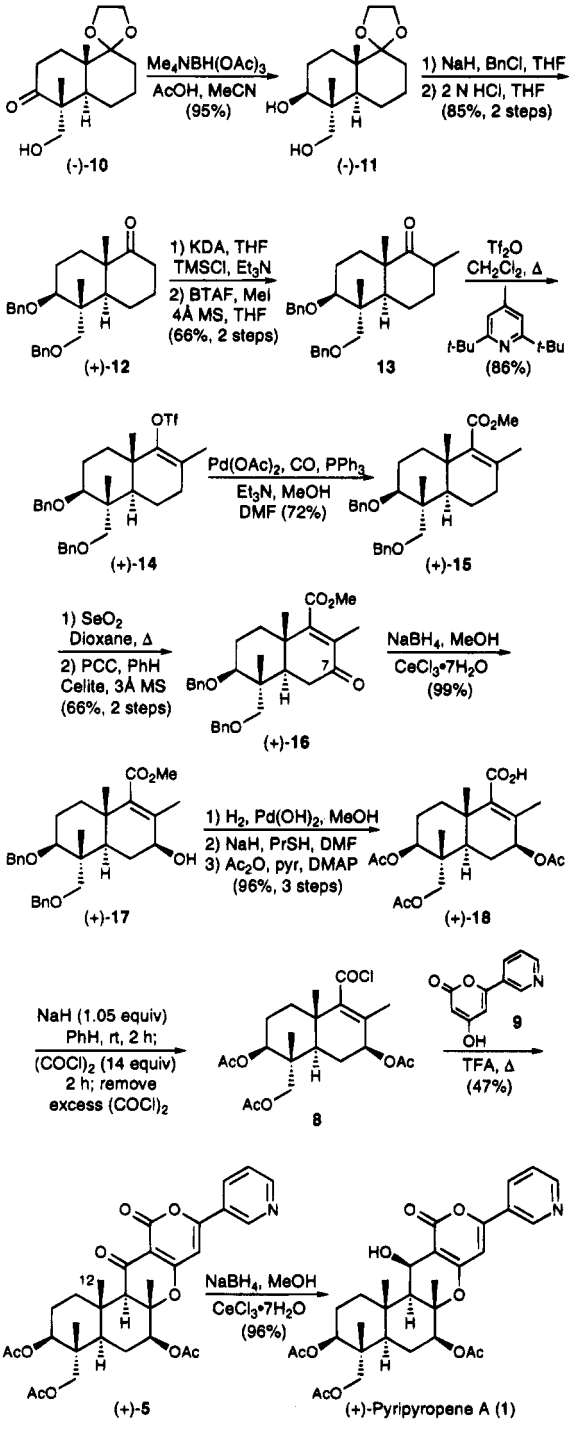
The sesquiterpene subunit **8** was anticipated to derive from alcohol (−)-**10** (Scheme 2), an intermediate in our paspaline total synthesis,[10a] readily available from (+)-Wieland−Miescher ketone in three steps.[10b]

Toward this end, stereoselective reduction of (−)-**10** with tetramethylammonium triacetoxyborohydride[11] (Scheme 2) furnished trans diol (−)-**11**[12] (95% yield, >95% de), which upon dibenzylation and deketalization gave

Scheme 2



(+)-**12**[12] (85%). α-Monomethylation of the B-ring ketone began with the enol silyl ether derivative (KDA, Me_3SiCl); generation of the reactive benzyltrimethylammonium enolate via the Kuwajima protocol [benzyltrimethylammonium fluoride (BTAF), MeI, 4 Å molecular sieves, THF][13] and treatment with methyl iodide then afforded the requisite ketone **13**[12] in 66% yield as a 5:1 mixture of α and β diastereomers.[14] Sulfonylation with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (CH_2Cl_2, reflux)[15] gave enol triflate (+)-**14**,[12] which in turn underwent palladium-catalyzed carbonylation [CO atmosphere, $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF] as described by Stille[16] to produce methyl ester (+)-**15**[12] (72% yield, two steps). Installation of the C(7) β-hydroxyl group first entailed SeO_2 oxygenation (dioxane, reflux)[17] and oxidation of the resultant C(7) α-alcohol to enone (+)-**16**[12] (PCC, Celite, PhH, 3 Å molecular sieves; 66% yield). Stereoselective Luche reduction[18] then provided (+)-**17**[12] quantitatively. Hydrogenolysis of the benzyl ethers, cleavage of the methyl ester,[19] and peracetylation (Ac_2O, DMAP, pyridine) led to carboxylic acid (+)-**18**[12] (96% yield, three steps). The latter was converted to acid chloride **8** [NaH (1.05 equiv), PhH, rt; $(COCl)_2$ (14 equiv); 100%].

The crucial sequence joining hydroxy pyrone **9** with AB subunit **8** proceeded readily in trifluoroacetic acid (80 °C, 4 h); O-acylation followed by in situ 1,3-acyl migration and 1,4-cyclization formed the pentacyclic ketone (+)-**5**[12] in 47% yield for the three steps. An analogous transformation involving achiral coupling partners was described previously by Douglas and Money;[20] the requisite anti BC ring junction in **5** derived from conjugate addition and enolate protonation trans to the C(12) angular methyl group. Stereoselective reduction of **5** ($NaBH_4$, $CeCl_3$, MeOH) then furnished synthetic (+)-pyripyropene A (**1**) (96%) as colorless needles (mp 152−153 °C). The synthetic material was identical in all respects with a sample of the natural product (400-MHz ^1H and 100-MHz ^{13}C NMR, IR, HRMS, optical rotation, melting point and mixed melting point, and TLC in four solvent systems).

The first total synthesis of (+)-pyripyropene A (**1**) has thus been achieved via a convergent and efficient strategy (16 steps, 9.3% overall yield). Importantly, the successful approach is designed to provide flexibility in construction of congeners B−D (**2**−**4**) as well as a range of potentially bioactive analogs.

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Supporting Information Available: Preparative procedures and spectroscopic data for **11**−**18**, **5**, and **1** (7 pages).

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(12) All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 400-MHz ^1H NMR, and 100-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. In addition, compounds **1**, **5**, **11**−**13**, and **15**−**18** gave satisfactory combustion analyses.

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