The First Total Synthesis of a Pyripyropene-Type ACAT Inhibitor, (±)-GERI-BP001†

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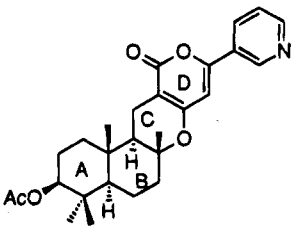
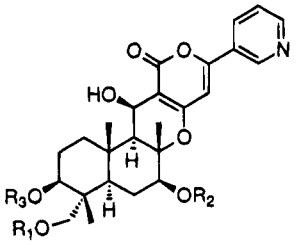
Introduction

GERI-BP001 (**1**) is a natural product which was isolated in 1994 from the culture broth of *Aspergillus fumigatus* F37.[3] Like its structural relatives, the pyripyropenes A–D (**2**),[4] it is an inhibitor of acyl-CoA: cholesterol acyltransferase (ACAT), the enzyme responsible for the intracellular esterification of cholesterol. There is evidence that ACAT inhibitors may lower plasma cholesterol levels and prevent the accumulation of cholesterol esters in arterial lesions. Therefore, members of this class are viewed as being potentially effective for the treatment of atherosclerosis and hypercholesterolemia.[5] Herein we describe an efficient preparation of GERI-BP001 by a scheme which is envisioned as a prototype for the synthesis of the more highly oxygenated and more potent pyripyropenes (**2**).



GERI-BP001 (1)

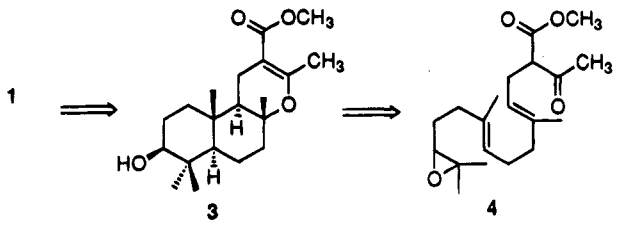


Pyripyropenes (2)

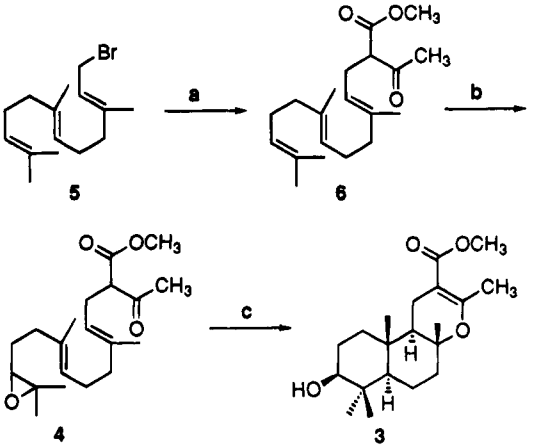
A $R_1 = R_2 = R_3 = Ac$
B $R_2 = R_3 = Ac$, $R_1 = COEt$
C $R_1 = R_3 = Ac$, $R_2 = COEt$
D $R_1 = R_2 = Ac$, $R_3 = COEt$

The ring system of the pyripyropenes suggests a synthetic strategy based on a biomimetic cyclization.[6] In this approach, the A, B, C-ring system of GERI-BP001 (**1**) would be derived from the closure of a modified polyolefin in which the terminating group is the nucleophilic enol of a keto ester (Scheme 1). In particular, the cyclization of epoxy keto ester **4** could afford tricyclic **3**, clearly an appropriate intermediate for elaboration to the target.

Scheme 1



Scheme 2[a]



[a] Key: (a) methyl acetoacetate, NaH, DMF, 4 h, 77%; (b) (1) NBS, THF, H_2O, 12 h; (2) K_2CO_3, CH_3OH, 3 h, 55%; (c) $SnCl_4$, CH_2Cl_2, 0 °C, 2 h, 8%.

The literature describes polyolefin cyclizations in which the terminating nucleophile is a carbonyl oxygen,[7] and these include several cases in which the carbonyl is the ketone of a β-keto ester.[7d,e,f] Nevertheless, the use of a keto ester terminating group with an epoxide initiator is unprecedented. Furthermore, polyolefin cyclizations of epoxides are generally low-yielding procedures.[8] Despite the potential difficulties anticipated in the projected cyclization, the ease of synthesis of substrate **4** and the functional group array in the expected product **3** made this system attractive as a first study.

A Three-Step Synthesis of Alcohol 3

The cyclization substrate **4** was prepared in two steps from *trans,trans*-farnesyl bromide (**5**). Methyl acetoacetate was alkylated under standard conditions (NaH, DMF, Scheme 2) to give keto ester **6**. Then regioselective epoxidation of the terminal double bond (NBS, THF, H_2O[9] followed by treatment with K_2CO_3 in MeOH) afforded the desired intermediate **4**.

Lewis acid-initiated cyclization of substrate **4** ($SnCl_4$, CH_2Cl_2, 0 °C) produced a mixture which contained at least seven components as indicated by TLC. Silica gel chromatography resulted in isolation of a fraction (16% yield)

† This paper is dedicated to our academic father and grandfather, W. S. Johnson.

(1) Recipient of an NSF Career Advancement Award, 1992–93.

(2) Government Assistance in Areas of National Needs Fellow 1992–1993.

(3) Jeong, T.-S.; Kim, S.-U.; Kwon, B.-M.; Son, K.-H.; Kim, Y.-K.; Choi, M.-U.; Bok, S.-H. *Tetrahedron Lett.* **1994,** *35,* 3569.

(4) (a) Tomoda, H.; Nishida, H.; Kim, Y. K.; Obata, R.; Sunazuka, T.; Omura, S.; Bordner, J.; Guadliana, M.; Dormer, P. G.; Smith, A. B., III. *J. Am. Chem. Soc.* **1994,** *116,* 12097. (b) Kim, Y. K.; Tomodo, H.; Nishida, H.; Sunazuka, T.; Obata, R.; Omura, S. *J. Antibiot.* **1994,** *47,* 154. (c) Tomoda, H.; Kim, Y. K.; Nishida, H.; Masuma, R.; Omura, S. *J. Antibiot.* **1994,** *47,* 148. (d) Omura, S.; Tomoda, H.; Kim, Y. K.; Nishida, H. *J. Antibiot.* **1993,** *46,* 1168.

(5) Sliskovic, D. R.; White, A. D. *Trends Pharmacol. Sci.* **1991,** *12,* 194.

(6) For a review on polyolefin cyclizations see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 341. For a review on epoxide cyclizations see: Taylor, S. K. *Org. Prep. Proc. Int.* **1992,** *24,* 247.

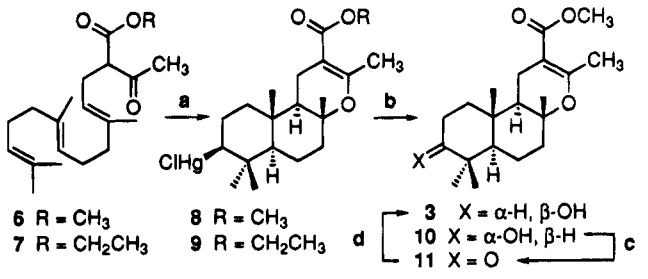
(7) For papers in which a carbonyl oxygen is involved in polyolefin cyclizations see: (a) Mursakulov, J. G.; Semenovsky, A. V.; Smit, W. A.; Kucherov, V. F. *Tetrahedron* **1967,** *23,* 1621. (b) Smit, W. A.; Semeovsky, A. V. *Tetrahedron Lett.* **1965,** *41,* 3651. (c) Kurbanov, M.; Samenovsky, A. V.; Smit, W. A.; Shemlev, L. V.; Kucherov, V. F. *Tetrahedron Lett.* **1972,** *22,* 2175. (d) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978,** *43,* 3693. (e) Gopalan, A. S.; Prieto, R.; Mueller, B.; Peters, D. *Tetrahedron Lett.* **1992,** *33,* 1679. (f) Harring, S. R.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.* **1992,** 503.

(8) For a discussion of the use of the epoxide initiator and the virtues and liabilities of the tetramethylallylic alcohol moiety as its "surrogate" see: Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994,** *59,* 2324.

(9) van Tamelen, E. E.; Curphey, T. J.; *Tetrahedron Lett.,* **1962** (3), 121.

0022-3263/95/1960-5726$09.00/0

Scheme 3[a]



[a] Key: (a) $Hg(OSO_2CF_3)_2{\cdot}C_6H_5N(CH_3)_2$, CH_3NO_2, −20 °C, then NaCl, 45%; (b) O_2, $NaBH_4$, DMF, 71% of a 1:1 mixture of **3** and **10**; (c) Jones reagent, acetone, quantitative; (d) $NaBH_4$, MeOH, 70%.

which consisted of the desired product **3** and one other compound which appeared to be a diastereomer.[10] Recrystallization of this material from hexanes resulted in recovery of tricyclic **3** as a single compound (8% yield from **4**).

Attempts to improve the yield of this key intermediate by varying the Lewis acid [$TiCl_4$ (−78 or 0 °C), $Ti(O^iPr)Cl_3$ (−78 or 0 °C), $BF_3{-}OEt_2$ (−78 or 0 °C), Et_2AlCl (−78 °C), and $MeAlCl_2$ (−78 °C)[11]], afforded mixtures of tricyclic **3** and the previously observed diastereomer in 10−17% yield. Thus, the epoxide, with all catalysts examined, was a sufficient but minimally satisfactory substrate.

A Five-Step, Improved Synthesis of Alcohol 3

Under these circumstances, we speculated that Nishizawa's four-step procedure[12] for the conversion of a polyolefin to a terpenol might improve our ability to access the desired **3**. In this short sequence, a mercuric ion-induced cyclization of a polyolefin substrate is followed by oxidative cleaveage of the cyclized organomercurial. Then an oxidation/reduction procedure is used to epimerize the resulting mixture of alcohols. Indeed, Gopalan *et al.*[7e] had demonstrated the mercuric-initiated cyclization of polyolefin **7** to tricyclic **9** with Nishizawa's reagent, the mercury(II) triflate−*N,N*-dimethylaniline complex.[12]

We therefore subjected our polyolefin intermediate, methyl ester **6**, to these cyclization conditions. The tricyclic organomercurial **8**, uncontaminated by isomers, was easily isolated in 45% yield by silica gel chromatography (Scheme 3). This intermediate was converted to a mixture of the α- and β-hydroxylated stereoisomers **10** and **3** by means of the hydroxylation procedure of Hill and Whitesides ($NaBH_4$, O_2, DMF).[13] Separation by silica gel chromatography provided each alcohol in 35% yield. The undesired α-hydroxylated isomer was oxidized to ketone **11** with Jones reagent and reduced ($NaBH_4$, MeOH) stereoselectively to form the desired β-isomer **3**.

Although the overall yield of tricyclic **3** from cyclization substrate **6** was still low (20% from commercially available farnesyl bromide), its preparation by this latter route was facile and inexpensive in terms of time and reagents. Furthermore, alcohol **3** appeared to be an ideal candidate for elaboration to the target compound.

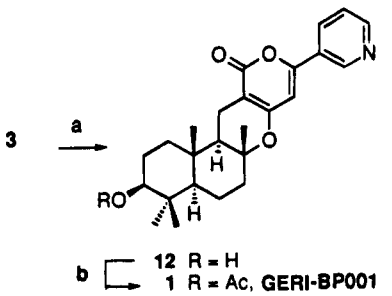
(10) The ratio of **3** and its diastereomer was determined to be 7:3 by integration of the ^{1}H-NMR spectrum.

(11) Corey,E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991,** *32,* 7005.

(12) (a) Nishizawa, M.; Takenaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983,** *24,* 2581. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986,** *51,* 806. (c) Nishizawa, M.; Yamada, H.; Hayashi, Y. *J. Org. Chem.* **1987,** *52,* 4878. (d) Nishizawa, M.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1984,** *25,* 5071. (e) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985,** *103,* 522.

(13) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974,** *96,* 870.

Scheme 4[a]



[a] Key: (a) 3 equiv LDA, ethyl nicotinoate, 2 h, 40%; (b) Ac_2O, Et_3N, CH_2Cl_2, 12 h, quantitative.

Synthesis of (±)-GERI-BP001

Completion of the synthesis requires pyrone annelation and acylation. The remaining two steps were accomplished in acceptable yields.

Previous attempts to effect pyrone annulations similar to the conversion desired here (**3** → **12**) have proven problematic and required strategies with two or more steps.[14] Nevertheless, in our hands, the direct annulation of intermediate **3** was accomplished in 40% yield by a procedure involving 3 equiv of LDA (THF at −78 °C) followed by addition of ethyl nicotinoate (Scheme 4).

Acetylation (Ac_2O, Et_3N, CH_2Cl_2) of intermediate **12** proceeded in quantitative yield. The ^{1}H NMR and ^{13}C NMR spectra of (±)-**1** were identical to those obtained by S.-H. Bok and co-workers for the natural product.[3,15]

Conclusions. The highly convergent, first total synthesis of the ACAT inhibitor GERI-BP001 (**1**) was completed by a very short sequence from the commercially available starting materials, methyl acetoacetate, *trans,trans*-farnesyl bromide, and ethyl nicotinoate. The key transformation, a polyolefin cyclization, provides rapid access to the vinylogous ester **3**, establishing the A,B,C-ring system, which includes all five stereocenters of the target. Annulation of the pyrone ring in one step and then acetylation provided the natural product **1**. The efficiency of this general approach suggests its exploitation in the synthesis of other members of the pyripyropene class.

Experimental Section

General. All reagents were purchased from Aldrich Chemical Co. All reactions were conducted under an argon atmosphere. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. CH_2Cl_2 and MeOH were distilled from CaH_2. IR spectra were taken on a FTIR spectometer. NMR spectra were taken on a 250 or 400 MHz spectrometer. High resolution mass spectra were obtained under EI, CI, or FAB conditions.

Keto Ester 6. A 60% dispersion of NaH in mineral oil (2.10 g, 52.5 mmol) was washed with hexane (3 × 10 mL) and suspended in DMF (50 mL). Methyl acetoacetate (5.8 mL, 54 mmol) was added dropwise. After 30 min, the resulting solution was treated with *trans,trans*-farnesyl bromide (5.00 g, 17.5 mmol) and stirred for 4 h. The reaction mixture was quenched with 50 mL of H_2O, extracted with EtOAc (3 × 100 mL), and washed with H_2O (4 × 50 mL). The organic solution was dried (Na_2SO_4) and concentrated. Column chromatography (ether/hexane, 1:19) afforded 4.35 g (77%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3 H), 1.60 (s, 3 H), 1.63 (s, 3 H), 1.68 (s, 3 H), 1.90−2.15 (m, 8 H), 2.23 (s, 3 H), 2.56 (t, J = 7.3 Hz, 2 H), 3.46 (t, J = 7.5 Hz, 1 H), 3.73 (s, 3 H), 4.97−5.18 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.9, 170.0, 138.6, 135.2, 131.2, 124.3, 123.8, 119.6, 59.6, 52.3, 39.7, 39.6, 29.1, 26.9, 26.7, 26.5, 25.6, 17.6, 16.1, 15.9;

(14) (a) Lewis, C. N.; Spargo, P. L.; Staunton, J. *Synthesis* **1986,** 944. (b) Dhavale, D. D.; Aidhen, I. S.; Shafique, M. *J. Org. Chem.* **1989,** *54,* 3985.

(15) A singlet reported at 0.58 ppm in ref 3 was found to be at 0.85 ppm in the original ^{1}H NMR spectrum.

IR (neat) 2919, 2855, 1747, 1720, 1436, 1150 cm^{-1}; HRMS [M + H]$^+$ calcd 321.2429, found 321.2424.

Epoxide 4. To a solution of keto ester **6** (4.35 g, 13.6 mmol) in 80 mL of H_2O and 30 mL of THF was added NBS (2.66 g, 14.9 mmol). The reaction mixture was stirred for 12 h and then diluted with H_2O (50 mL), extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4), and concentrated. Succinimide was precipitated by the addition of hexane, and the supernatant solution was concentrated to a yellow oil. To this residue (the crude bromohydrin) were added MeOH (50 mL) and K_2CO_3 (5.90 g, 42.4 mmol). The mixture was stirred for 3 h, diluted with H_2O (75 mL), and extracted with EtOAc (3 × 50 mL). The organic solution was dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (EtOAc/hexane, 1:4) afforded 2.66 g (58%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.31 (s, 3 H), 1.62 (s, 3 H), 1.65 (s, 3 H), 1.91–2.19 (m, 8 H), 2.22 (s, 3 H), 2.56 (t, J = 7.3 Hz, 2 H), 2.70 (t, J = 6.3 Hz, 1 H), 3.46 (t, J = 7.5 Hz, 1 H), 3.72 (s, 3 H), 5.03 (t, J = 6.5 Hz, 1 H), 5.12 (t, J = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 202.9, 170.0, 138.4, 134.3, 124.5, 119.7, 64.1, 59.6, 58.2, 52.3, 39.6, 36.3, 29.1, 27.5, 26.9, 26.5, 24.9, 18.7, 16.1, 16.0; IR (neat) 2960, 2926, 1747, 1718, 1436, 1149 cm^{-1}; HRMS [M + H]$^+$ calcd 337.2379, found 337.2382.

Alcohol 3 from Epoxide 4. To a solution of epoxide **4** (2.20 g, 6.50 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added dropwise a solution of $SnCl_4$ in CH_2Cl_2 (13 mL, 1.0 M, 13 mmol). After 2 h the reaction mixture was quenched with Et_3N (5 mL) and MeOH (5mL). Then, after 5 min, it was concentrated until a precipitate appeared. The mixture was then diluted with hexane and filtered. The filtrate was passed through a pad of silica gel and washed through with several aliquots of EtOAc. Concentration followed by column chromatography (EtOAc/hexane, 1:4) furnished 372 mg (17% yield) of a mixture of **3** and an unidentified diastereomer in a 7:3 ratio as determined by ^{1}NMR integration. Recrystallization from hexane afforded 170 mg of pure **3** (8% yield): ^{1}H NMR δ 0.80 (s, 3 H), 0.86 (s, 3 H), 0.96 (dd, J = 1.8, 12.1 Hz, 1 H), 1.01 (s, 3 H), 1.08 (dt, J = 4.5, 12.4 Hz, 1 H), 1.14 (s, 3 H), 1.27–1.34 (m, 2 H), 1.34–1.45 (m, 1 H), 1.50–1.81 (m, 5 H), 1.90–2.03 (m, 2 H), 2.17 (s, 3 H), 2.29 (dd, J = 16.6, 4.3 Hz, 1 H), 3.23 (dd, J = 11.5, 4.8 Hz, 1 H), 3.69 (s, 3 H); ^{13}C NMR δ 169.1, 163.1, 99.8, 78.7, 78.0, 55.1, 51.5, 50.9, 40.5, 38.8, 37.5, 36.5, 28.1, 27.2, 20.5, 20.30, 19.5, 19.3, 15.5, 14.9; IR (CCl_4) 3510, 2948, 2868, 1708, 1619, 1265, 1122 cm^{-1}; HRMS [M + H]$^+$ calcd 337.2379, found 337.2373.

Organomercuric Chloride 8. To mercury(II) oxide red (400 mg, 1.85 mmol) in nitromethane (60 mL) was added trifluoromethanesulfonic anhydride (320 μL, 1.90 mmol) at room temperature, and the mixture was strirred for 2 h until the orange color disappeared. To the resulting solution was added *N,N*-dimethylaniline. The resulting yellow solution was cooled to −20 °C, and keto ester **6** (500 mg, 1.56 mmol) in 10 mL of nitromethane was added dropwise. After the mixture was stirred for 3 h, brine (50 mL) was added, and the resulting heterogeneous solution was warmed to room temperature and stirred for 2 h. The mixture was filtered through a pad of Celite and extracted with EtOAc (3 × 20mL). The combined organic layers were washed with H_2O (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Column chromatography (hexane/EtOAc, 9:1) afforded 380 mg (45%) of a white solid: ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.14 (s, 3 H), 0.96–1.18 (m, 1 H), 1.18–1.25 (m, 1 H), 1.31 (dd, J = 4.8, 12.9 Hz, 1 H), 1.35–1.46 (m, 1 H), 1.48–1.62 (m, 2 H), 1.70–1.86 (m, 2 H), 1.88–2.03 (m, 3 H), 2.18 (s, 3 H), 2.26 (dd, J = 4.2, 16.7 Hz, 1 H), 2.75 (dd, J = 3.6, 13.8 Hz, 1 H), 3.67 (s, 3 H); ^{13}C NMR δ 169.0, 163.0, 99.7, 77.8, 73.1, 58.0, 51.4, 50.9, 41.8, 40.4, 39.0, 36.6, 36.3, 26.3, 25.9, 21.3, 20.5, 20.2, 19.4, 14.8; IR (CCl_4) 2948, 2361, 2342, 1710, 1619, 1435, 1121 cm^{-1}; HRMS [M + H]$^+$ calcd 557.1746, found 557.1751.

Alcohols 3 and 10. Oxygen was bubbled vigorously into a suspension of $NaBH_4$ (270 mg, 0.70 mmol) in DMF (2 mL) for 5 min. Then, while the steady stream of oxygen continued, organomercuric **8** (190 mg, 0.35 mmol) was added dropwise over 30 min using a syringe pump. The mixture was stirred for 5 min after the addition was complete and then quenched with 1 N sulfuric acid (1mL), neutralized with saturated sodium bicarbonate, and extracted with ether (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 15 mL), dried (Na_2SO_4), and concentrated. Preparative plate chromatography afforded **10** (42 mg, 35%) and **3** (41 mg, 35%) as white solids. Data for **10**: ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 0.85 (s, 3 H), 0.96 (s, 3 H), 1.12 (s, 3 H), 1.28–1.50 (m, 6 H), 1.55–1.68 (m, 3 H), 1.85–2.07 (m, 3 H), 2.18 (s, 3 H), 2.30 (dd, J = 4.5, 16.1 Hz, 1 H), 3.42 (bs, 1 H), 3.68 (s, 3 H); ^{13}C NMR δ 169.2, 163.2, 99.8, 78.2, 75.8, 51.2, 50.9, 48.6, 40.5, 37.4, 36.5, 32.1, 28.3, 25.2, 22.0, 20.6, 20.3, 19.4, 19.3, 14.7.

Ketone 11. To a solution of alcohol **10** (20 mg, 0.060 mmol) in acetone (2 mL) was added Jones reagent (40 μL, 1.8 M solution, 0.072 mmol), and the mixture was stirred for 20 min. It was then diluted with H_2O (5 mL), extracted with ether (3 × 6 mL), dried (Na_2SO_4), and concentrated. Preparative plate chromatography afforded 20 mg (100%) of a white solid: ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 3 H), 1.02–1.10 (m, 1 H), 1.04 (s, 3 H), 1.12 (s, 3 H), 1.19 (s, 3 H), 1.39 (dd, J = 4.9, 12.9 Hz, 1 H), 1.42–1.72 (m, 4 H), 1.97–2.09 (m, 3 H), 2.20 (s, 3 H), 2.33 (dd, J = 4.5, 16.3 Hz, 1 H), 2.42 (ddd, J = 3.70, 16.1 Hz, 1 H), 2.58 (ddd, J = 7.4, 16.1 Hz, 1 H), 3.70 (s, 3 H); ^{13}C NMR δ 211.3, 168.9, 163.1, 99.8, 77.7, 54.8, 50.9, 50.8, 47.3, 39.9, 37.9, 36.3, 33.8, 26.6, 21.3, 20.5, 20.48, 20.0, 19.6, 14.5; IR (CCl_4) 2949, 2868, 1709, 1621, 1434, 1122 cm^{-1}; HRMS [M + Na]$^+$ calcd 357.2041, found 357.2050.

Alcohol 3 from Ketone 11. To a suspension of $NaBH_4$ (9 mg, 0.24 mmol) in MeOH (3 mL) at 0 °C was added ketone **11** (40 mg, 0.12 mmol) in MeOH (4 mL). The mixture was warmed to room temperature and after 20 min quenched with 5% aqueous HCl (1 mL). Then it was diluted with H_2O (6 mL) and extracted with EtOAc (3 × 10 mL). The organic solution was dried (Na_2SO_4) and concentrated. The residue was subjected to preparative plate chomatography to afford 28 mg (70%) of alcohol **3**.

Pyripyropene 12. A solution of 0.44 mmol of LDA was prepared by adding *n*-butyllithium (220 μL, 2 M in hexanes, 0.44 mmol) to a solution of diisopropylamine (58 μL, 0.44 mmol) in 3 mL of THF at 0 °C and stirring for 10 min at −78 °C. To this was added a solution of α,β-unsaturated ester **3** (50 mg, 0.149 mmol) in 3 mL of THF. The mixture was stirred for 25 min and then treated with ethyl nicotinoate (30 μL, 0.220 mmol). After 2 h the reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine (10 mL). The organic solution was dried (Na_2SO_4) and concentrated. Preparative plate chromatography (EtOAc) afforded 24 mg (40%) of a white solid: mp 235 °C; ^{1}H NMR δ ($CDCl_3$) 0.82 (s, 3 H), 0.92 (s, 3 H), 1.01 (dd, J = 12.3, 1.9 Hz, 1 H), 1.04 (s, 3 H), 1.11 (dt, J = 4.0, 13.0 Hz, 1 H), 1.27 (s, 3 H), 1.35–1.48 (m, 2 H), 1.51 (dd, J = 12.9, 4.8 Hz, 1 H), 1.57–1.77 (m, 2 H), 1.78–1.89 (m, 2 H), 2.16 (dt, J = 3.1, 12.5 Hz, 1 H), 2.25 (dd, J = 12.9, 17.1 Hz, 1 H), 2.53 (dd, J = 4.7, 17.1 Hz, 1 H), 3.28 (dd, J = 4.4, 11.2 Hz, 1 H), 6.43 (s, 1 H), 7.40 (dt, J = 0.7, 4.8 Hz, 1 H), 8.11 (dd, J = 1.7 Hz, 8.5, 1 H), 8.65 (dd, J = 1.5, 4.8 Hz, 1 H), 9.0 (d, J = 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 164.3, 163.1, 155.9, 151.3, 146.9, 133.0, 127.9, 123.8, 100.6, 99.6, 81.3, 78.7, 55.3, 51.8, 40.6, 39.0, 37.7, 37.1, 28.4, 27.4, 21.0, 19.6, 17.5, 15.7, 15.4; IR (KBr) 3525, 2930, 2863, 1707, 1677, 1639, 1570, 1431, 1125 cm^{-1}; HRMS calcd 409.2253, found 409.2252.

GERI-BP001 (1). Triethylamine (52 μL, 0.371 mmol), DMAP (catalytic), and acetic anhydride (14 μL, 0.148 mmol) were added to a solution of pyripyropene **12** (30 mg, 0.074 mmol) in CH_2Cl_2 (10 mL). After 12 h the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The organic solution was washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by preparative plate chromatography (EtOAc) furnished 34 mg (quantitative yield) of (±)-GERI-BP001, mp 240 °C. For spectroscopic data see refs 3 and 14.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **3**, **4**, **6**, **8**, **10**, **11**, **12**, and (±)-GERI-BP001 (20 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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