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Total synthesis of pyripyropene A

Atsuki Odani, Kaoru Ishihara, Masaki Ohtawa, Hiroshi Tomoda, Satoshi Omura *, Tohru Nagamitsu *

School of Pharmacy, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

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ABSTRACT

The total synthesis of pyripyropene A, a potent ACAT2 inhibitor with high isozyme selectivity, was completed. Key features of the synthetic strategy include Ti(III)-mediated radical cyclization and Peterson olefination for the construction of the AB ring segment and stereoselective dihydro-γ-pyrone formation (C-ring). The total synthesis provided pyripyropene A in 5.3% overall yield over 17 steps.

1. Introduction

Acyl-CoA:cholesterol acyltransferase (ACAT) plays important roles in cholesterol metabolism in mammals. Therefore, a large number of synthetic ACAT inhibitors, such as ureas, imidazoles, and amides have been reported,[1] although to date, no new types of cholesterol-lowering or anti-atherosclerotic agents have come onto the market.[2] Recently, the development of avasimibe[3] and pactimibe[4] has also failed.

During the course of our screening for ACAT inhibitors of natural origin with a chemical structure different from the synthetic ones developed from the 1990s, we discovered a number of new natural products.[5] Among them, the fungal metabolites, pyripyropenes, were one of the most potent ACAT inhibitors in an enzyme assay using rat liver microsomes.[6–8] Accordingly, about 200 derivatives were semisynthetically prepared from pyripyropene A (**1**) for a first structure–activity relationship (SAR) study. Certain derivatives were more potent than PPPA (**1**), and proved to be active in reducing cholesterol absorption in vivo from the intestines of hamsters.[9–14]

Recent molecular biological studies revealed the presence of two isozymes, ACAT1 and ACAT2.[15–18] ACAT1 is ubiquitously expressed, and high-level expression is observed in sebaceous glands, steroidogenic tissues, and macrophages, while ACAT2 is expressed predominantly in the liver and intestine.[19] Therefore, selective inhibitors toward ACAT2 are expected to have the potential to be better drug candidates with fewer side-effects as cholesterol-lowering or anti-atherosclerotic agents. We established a cell-based assay using ACAT1- or ACAT2-expressing CHO cells and studied the selectivity of microbial ACAT inhibitors we had previously discovered.[20] Consequently, we confirmed that PPPA (**1**) is a potent and selective inhibitor toward ACAT2. More recently, the in vivo efficacy of PPPA in atherosclerosis has been also demonstrated.[21] PPPA derivatives synthesized previously were evaluated in this cell-based assay to investigate their selective inhibition toward the ACAT isozymes.[22] Several PPPA derivatives showed more potent ACAT2 inhibitory activity than PPPA (**1**), however, unfortunately, all synthesized PPPA derivatives showed much lower isozyme selectivity than PPPA (**1**). This led us to embark on a second SAR study for the development of new PPPA derivatives with higher isozyme selectivity.[23] Consequently, an efficient synthetic route for PPPA and its derivatives was also necessary. Although the first total synthesis of PPPA (**1**) has previously been reported by our group,[24] it is not suitable for this task because of the presence of several reactions that cannot be scaled up. We report herein another total synthesis of pyripyropene A (**1**), which is a different approach to the first one and a more practical synthesis for the SAR study.

2. Results and discussion

2.1. Retrosynthetic analysis of pyripyropene A

Our retrosynthetic analysis of pyripyropene A (**1**) is shown in Scheme 1. We adopted a reliable procedure reported by our group previously[13] for the conversion of intermediate **2** into **1**. Dihydro-γ-pyrone **2** could be prepared from diketoester **3** by stereoselective intramolecular hetero-Michael addition and protonation, which was expected to be obtained by a coupling between **4** and the

* Corresponding authors. Tel.: +81 3 5791 6101; fax: +81 3 3444 8360 (S.O.); tel.: +81 3 5751 6376; fax: +81 3 3444 6762 (T.N.); e-mail addresses: omura-s@kitasato-u.ac.jp (S. Omura), nagamitsut@pharm.kitasato-u.ac.jp (T. Nagamitsu).

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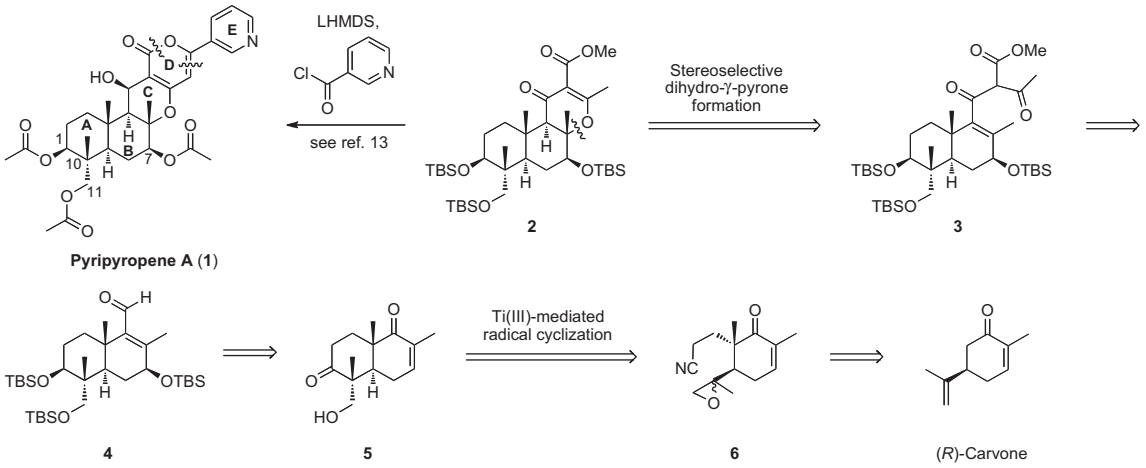
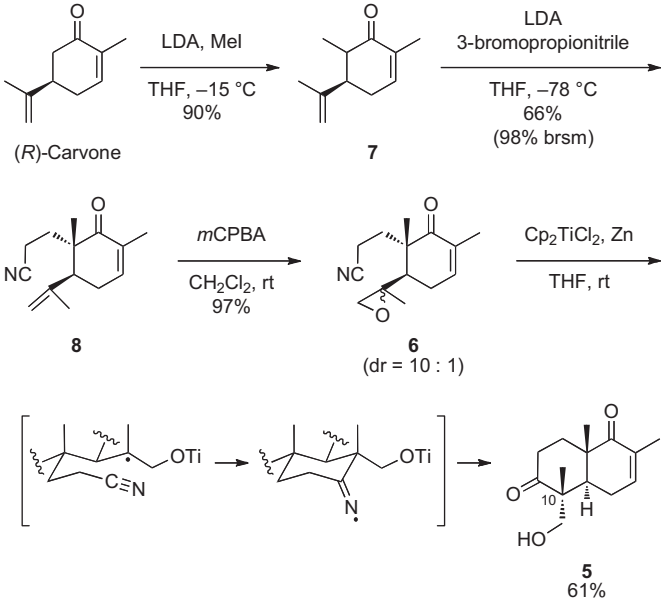


Scheme 1.

methyl acetoacetate unit. The α,β-unsaturated aldehyde **4** was envisaged to be synthesized via functionalization of diketoalcohol **5** as follows: stereoselective reduction of the C1-ketone (pyripyropene A numbering), oxidation of the alkene, and one-carbon elongation of another ketone. The *trans*-fused decaline unit of **5** could be constructed by the Ti(III)-mediated radical cyclization of **6**. The epoxide **6** should be available from a commercially available (*R*)-carvone.

2.2. Synthesis of the key intermediate 5

Synthesis of **5** commenced with methylation of (*R*)-carvone (Scheme 2). Alkylation of the resulting **7**[25] with 3-bromopropionitrile gave **8** in 66% yield (98% brsm) stereoselectively, which was oxidized with *m*CPBA to produce a 10:1 diastereomixture of **6**. Subsequent Ti(III)-mediated radical cyclization[26] of **6** by treatment with Cp_2TiCl_2 and Zn proceeded smoothly to afford the desired diketoalcohol **5** in 61% yield, accompanied by the undesired 10-*epi*-diketoalcohol (20%). After an epoxide



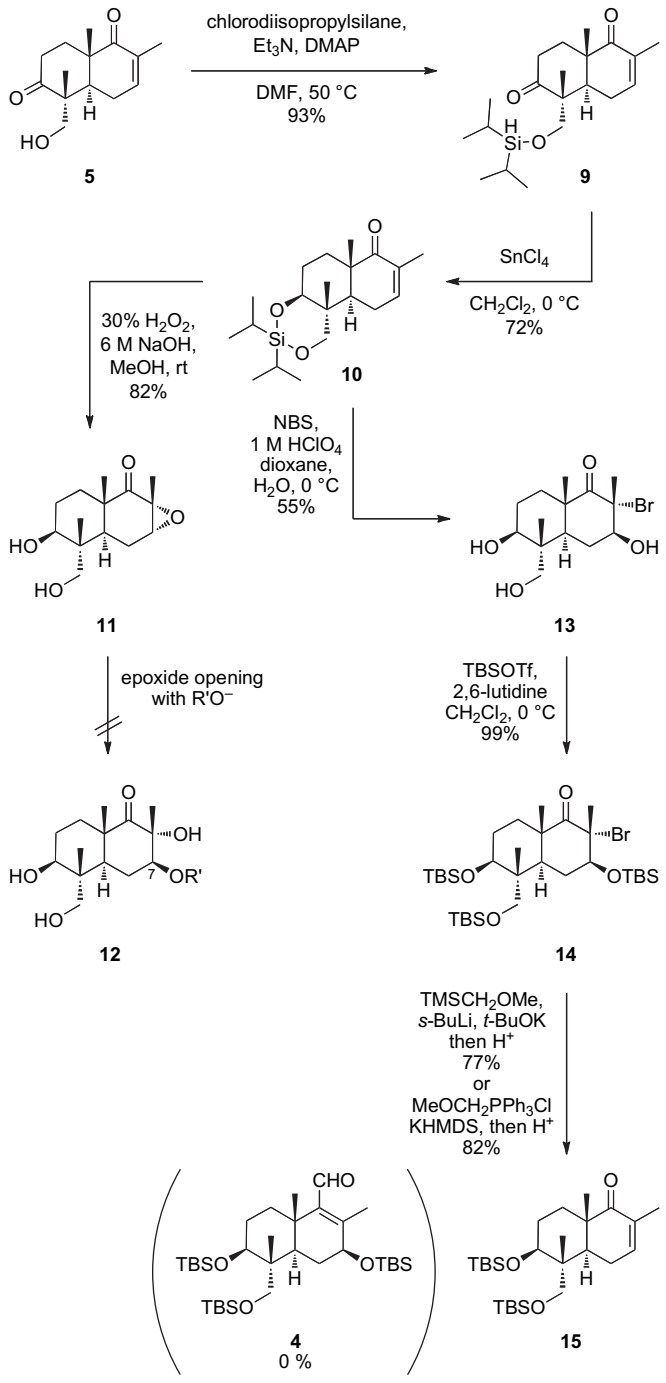
Scheme 2.

reductive opening produced a radical species, the stable chair-like conformation of this intermediate would determine the stereoselectivity of the 6-*exo*-dig cyclization, in which the sterically hindered titanoxy group would be oriented equatorially and might also associate with the nitrile group by chelation.

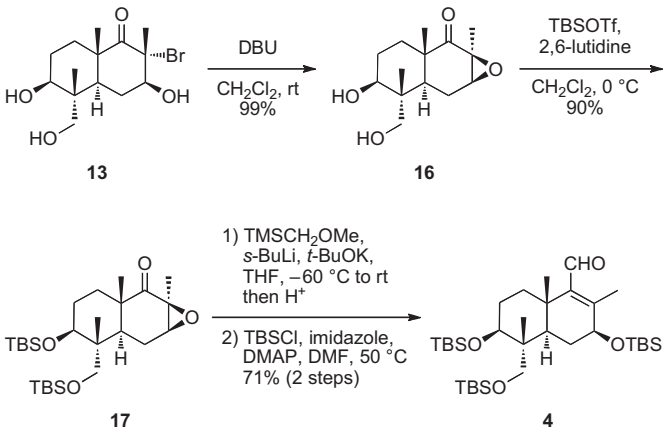
Subsequent stereoselective reduction of C1-ketone in **5** was accomplished by the Davis procedure[27] (Scheme 3). Reaction of **5** with chlorodiisopropylsilane gave silyl ether **9** in 93% yield, which was treated with Tin(IV) chloride to furnish the desired **10** as a single isomer in 72% yield. We next attempted to install the C7-β-hydroxy group by regioselective opening of the α-epoxide. The silylene acetal **10** was oxidized with H_2O_2/6 M NaOH to give α-epoxide **11** in 82% yield. The epoxide opening reactions of **11** under various conditions using carboxylate and alkoxide anions were investigated, but none proceeded. We next examined a bromohydrin reaction proceeding via the more reactive bromonium ion. Consequently, treatment of **10** with NBS and 1 M $HClO_4$[28] provided bromohydrin **13** in 55% yield with hydrolysis of the silylene acetal. The three hydroxy groups of **13** were protected as TBS ethers to furnish **14** in 99% yield. At this stage, the stereochemistries of **14** were confirmed by NOE experiments (see Experimental section). Wittig and Peterson olefinations of **14** were in turn attempted to synthesize the desired key aldehyde **4**, however, the unexpected product **15** was obtained from each reaction in high yield, which could be obtained via E2 elimination instead of the desired olefination reaction due to steric hindrance around the carbonyl group of **14**.

To solve the steric problem, we intended to use β-epoxide **17** as the new substrate for the olefination reactions, instead of **14** (Scheme 4). Treatment of **13** with DBU furnished **16** in quantitative yield, which was protected with TBSOTf to give **17** in 90% yield. The subsequent attempt of the Wittig reaction of **17** with $MeOCH_2PPh_3Cl$/KHMDS was not successful, but the Peterson olefination of **17** employing the Magnus protocol[29] smoothly proceeded to afford the corresponding γ-hydroxy-α,β-unsaturated aldehyde after acidic hydrolysis. The alcohol was protected as a TBS ether to give rise to the key intermediate **4** in 71% yield over two steps. As this aldehyde is susceptible to air oxidation to furnish the corresponding carboxylic acid, which is identical to that derived from **4** by Pinnick oxidation[30] in all respects, the aldehyde **4** was promptly subjected to the next reaction.

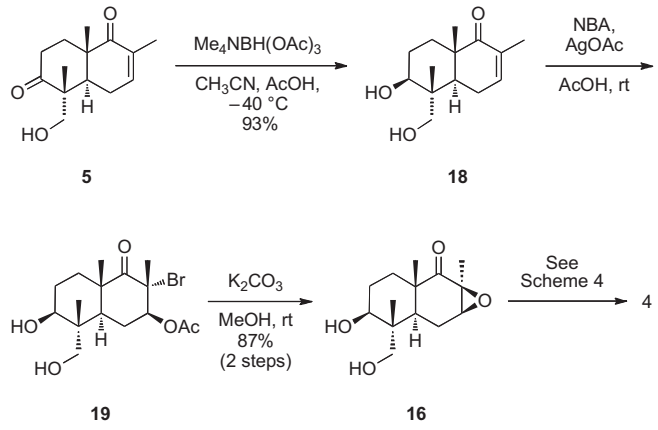
Synthesis of the key aldehyde **4** was accomplished however the conversion of **5** into **16** was not suitable for the scale-up synthesis. Therefore, another route for the synthesis of **16** was developed as shown in Scheme 5. Evans reduction[31] of **5** afforded the desired diol



Scheme 3.



Scheme 4.



Scheme 5.

18 as the sole product in 93% yield. Treatment of **18** with NBA and AgOAc in AcOH[32] afforded **19**, which was subjected to methanolysis to give the β-epoxide **16** in 87% yield over two steps. Then, the β-epoxide **16** was converted to **4** according to Scheme 4. Thus, this route provided the efficient synthesis of the key aldehyde **4**.

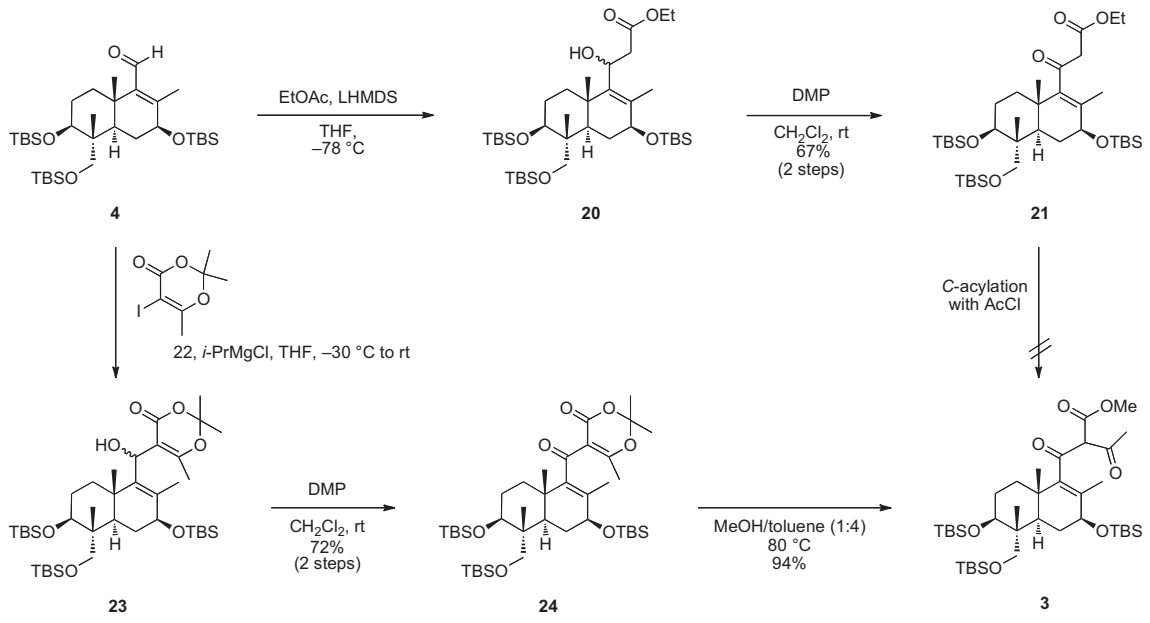
2.3. Synthesis of the diketoester 3

We next investigated an approach to the key synthetic intermediate **3** (Scheme 6). Aldol reaction of **4** with an enolate of ethyl acetate afforded the β-hydroxy ester **20**, which was oxidized to give **21** in 67% yield over two steps. Subsequent C-acylation with acetyl chloride was attempted under various conditions using Lewis acids ($Mg(OEt)_2$,[33] $MgCl_2$,[34] $SmCl_3$[35]), however, the reactions did not proceed. Reaction of lithium and sodium enolates of **21** with acetyl chloride gave *O*-acylated product as a major product.

Next, the coupling reaction of **4** with the 5-iodo-1,3-dioxin-4-one derivative **22** under conditions reported by Knochel et al.[36] was investigated. Treatment of **22** with *i*-PrMgCl gave the corresponding 5-magnesiated-1,3-dioxin-4-one derivative, which was coupled with **4** to furnish **23**. Subsequent Dess–Martin oxidation afforded **24** in 72% yield over two steps. To convert it to **3**, solvolysis was examined. Although methanolysis in the presence of NaH or NaOMe led to decomposition, refluxing in MeOH without base gave the desired **3** in 59% yield, accompanied by 7-hydroxy **3** in 24% yield. Optimization then led to the methanolysis conditions (MeOH/toluene (1:4) at 80 °C) to produce **3** in 94% yield.

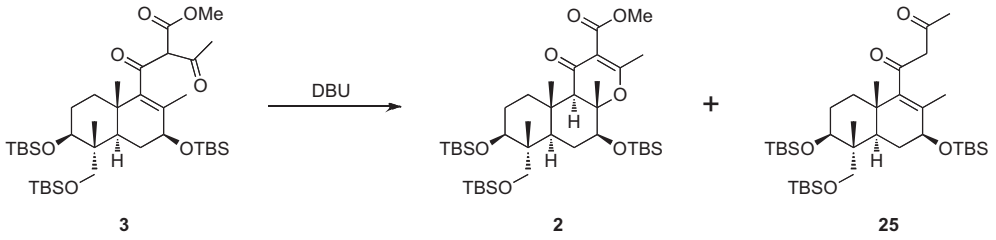
2.4. Synthesis of the dihydro-γ-pyrone 2

With **3** in hand, the stage was set for the stereoselective synthesis of dihydro-γ-pyrone by intramolecular cyclization. First, reactions with some Lewis acids, such as $BF_3 \cdot Et_2O$ and $SnCl_4$ were attempted, but the desired cyclization did not proceed and only TBS-deprotected mixtures were obtained. Therefore, cyclization under basic conditions using DBU was investigated (Table 1). Heating of **3** in the presence of DBU in DMF at reflux gave only undesired product **25** formed by decarboxylation in 70% yield (run 1). The same reaction carried out at 100 °C did not prevent the decarboxylation (run 2). By changing to benzene as a solvent under



Scheme 6.

Table 1
Synthesis of the dihydro-γ-pyrone **2** by intramolecular cyclization



Run	Solvent	Temp	Time (h)	Yield (%)		
				2	**25**	**3**
1	DMF	Reflux	15	—	70	—
2	DMF	100 °C	25	Trace	77	—
3	Benzene	Reflux	13	53	21[a]	16[a]
4	THF	Reflux	8	11	7[a]	46[a]
5	$C_2H_4Cl_2$	Reflux	8	Trace	—	>90
6	Toluene	100 °C	8	68	17[a]	12[a]
7	Toluene	60 °C	156	50	—	20

[a] Estimated by ^{1}H NMR.

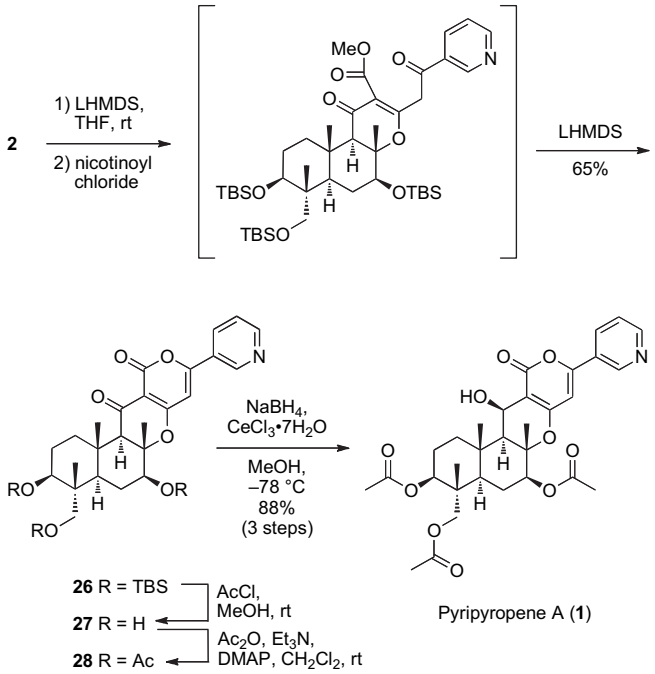
reflux conditions the desired **2** was afforded in 53% yield with an inseparable mixture of unreacted **3** and **25** whose ratio was estimated by ^{1}H NMR (run 3). Use of THF and dichloroethane provided inappropriate conditions (run 4 and 5). Thus, this cyclization proved to be dependent on solvents and prefer aromatic hydrocarbons, such as benzene. When the reaction was attempted at a higher reaction temperature, toluene was selected. Consequently, the reaction in toluene at 100 °C gave the best yield to afford **2** (68%). Although the cyclization in toluene at 60 °C also worked to produce **2** in 50% yield accompanied by unreacted starting material in 20% yield without the undesired decarboxylated product **25**, a longer reaction time was needed.

2.5. Completion of the total synthesis

The conversion of **2** to pyripyropene A (**1**) was obtained by following the procedure reported by our group previously (Scheme 7).[13] Enolization of **2** by LHMDS, γ-acylation with nicotinoyl chloride, and treatment with an additional portion of LHMDS leading to intramolecular cyclization afforded **26** in 65% yield from **2** in one-pot. A two-step sequence of protecting group manipulations provided **28**, which was subjected to Luche reduction to furnish pyripyropene A (**1**) in 88% yield over three steps. Synthetic pyripyropene A (**1**) was completely identical to an authentic sample in all respects (^{1}H and ^{13}C NMR, IR, FABMS, and ACAT2 inhibitory activity and isozyme selectivity).

3. Conclusion

In conclusion, we have achieved a stereocontrolled total synthesis of pyripyropene A (**1**). Key features of the synthetic strategy included the intramolecular Ti(III)-mediated radical cyclization for the construction of the A-ring, stereoselective β-epoxide formation/Peterson olefination for the preparation of the functional groups on



Scheme 7.

the B-ring, and stereoselective intramolecular cyclization for the C-ring formation. Our second total synthesis provided **1** in 5.3% overall yield over 17 steps. Extension of this chemistry to the synthesis of structural analogs of **1** for the structure–activity relationship study is currently under way and will be reported in due course.

4. Experimental section

4.1. General

All reactions were carried out in dried glassware under a nitrogen atmosphere employing standard techniques in handling air-sensitive materials. Commercial reagents were used without further purification unless otherwise indicated. Organic solvents were distilled and dried over molecular sieves of 3 Å or 4 Å. Reactions were performed in flame-dried glassware under positive Ar pressure with stirring by a magnetic stirbar unless otherwise indicated. Cold baths were generated as follows: 0 °C, wet ice/water; −78 °C, dry ice/acetone. Flash chromatography was performed on silica gel 60 N (spherical, neutral, particle size 40–50 μm). TLC was performed on 0.25 mm Merck silica gel 60 F_{254} plates and visualized by UV (254 nm) and phosphomolybdic acid and *p*-anisaldehyde as TLC Stains. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted.

^{1}H- and ^{13}C-NMR spectra were recorded using an internal deuterium lock on Varian Mercury-300, Varian Unity-400, and Varian INOVA-600 spectrometers. All signals are reported in parts per million with the internal reference of 7.26 ppm or 77.0 ppm for chloroform as the standard. Data are presented as follows: multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=mutiplet, br=broad, dd=doublet of doublet), coupling constant (*J*/Hz) and integration. Infrared spectra were recorded on a Horiba FT-710 infrared spectrometer. Absorptions are given in wavenumbers (cm^{-1}). Optical rotations were recorded on a JASCO DIP-1000 polarimeter and reported as follows: $[\alpha]_D^T$, concentration (g/100 mL) and solvent. High resolution mass spectra were obtained on JEOL JMS-700 Mstation and JEOL JMS-T100LP with FAB and ESI high resolution mass spectrometers. The melting points were recorded on a Yanagimoto micro melting apparatus and are uncorrected.

*4.1.1. (5S,6S)-6-(2-Isocyanoethyl)-2,6-dimethyl-5-(prop-1-en-2-yl) cyclohex-2-enone (**8**).* To a solution of diisopropylamine (3.46 mL, 24.7 mmol) in THF (22 mL) was added dropwise *n*-BuLi (1.59 M in THF, 15.7 mL, 24.9 mmol) at −15 °C. After being stirred for 0.5 h, a solution of **7**[24] (2.92 g, 17.8 mmol) in THF (30 mL) was added dropwise. The resulting mixture was stirred for 5 h at −78 °C and treated with 3-bromopropionitrile (4.36 mL, 53.3 mmol). After being stirred for an additional 16 h at −78 °C, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (10:1 hexanes/EtOAc) afforded **8** (2.47 g, 66%) as a colorless oil: $[\alpha]_D^{26}$ −14.3 (*c* 1.0, $CHCl_3$); IR (KBr) 3021, 2927, 2857, 1663, 1443, 1380, 1217, 904, 759, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66–6.63 (m, 1H), 4.90 (dq, *J*=1.6 Hz, 1H), 4.79 (br s, 1H), 2.65 (t, *J*=6.6 Hz, 1H), 2.49–2.45 (m, 2H), 2.41–2.26 (m, 2H), 2.07–1.99 (m, 1H), 1.92–1.84 (m, 1H), 1.77–1.76 (m, 3H), 1.71 (t, *J*=0.6 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 145.1, 143.2, 134.2, 120.3, 115.7, 49.5, 47.4, 32.8, 29.1, 22.6, 18.9, 16.6, 12.8; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{19}NONa$ 240.1364, found 240.1361.

*4.1.2. (5R,6S)-6-(2-Isocyanoethyl)-2,6-dimethyl-5-(2-methyloxiran-2-yl)cyclohex-2-enone (**6**).* To a solution of **8** (7.90 g, 36.4 mmol) in CH_2Cl_2 (182 mL) was added *m*CPBA (10.6 g, 40.0 mmol). After being stirred for 0.5 h at rt, additional *m*CPBA (10.6 g, 40.0 mmol) was added. The resulting mixture was stirred for 0.5 h at rt and then quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) afforded **6** (2.53 g, 97%) (dr=10:1) as a colorless oil: *as a diastereomixture* IR (KBr) 2979, 2928, 2247, 1718, 1665, 1447, 1381, 1200, 1079, 1035, 1011, 866 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68–6.60 (m, 1H), 2.77–2.56 (m, 4H), 2.40–2.29 (m, 1H), 2.17–2.06 (m, 2H), 1.87–1.80 (m, 1H), 1.79–1.77 (m, 3H), 1.59 (dd, *J*=6.1, 3.1 Hz, 1H), 1.16 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 142.1, 134.1, 119.5, 58.0, 57.6, 50.2, 46.6, 33.9, 27.0, 19.3, 18.0, 16.3, 12.4; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{19}NNaO_2$ 256.1314, found 256.1320.

*4.1.3. (4aR,5R,8aS)-5-(Hydroxymethyl)-2,5,8a-trimethyl-4a,5,8,8a-tetrahydronaphthalene-1,6(4H,7H)-dione (**5**).* To a solution of Cp_2TiCl_2 (2.14 g, 8.57 mmol) in THF (23 mL) was added Zn (2.12 g, 12.9 mmol). After being stirred for 1 h at rt, a solution of **6** (1.00 g, 4.29 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 45 min at rt and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was dissolved with EtOAc and washed with 2 N HCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (2:1 to 1:1 hexanes/EtOAc) afforded **5** (613 mg, 61%) and 10-*epi*-**5** (200 mg, 20%) as yellow solids: *data for* **5** $[\alpha]_D^{26}$ −83.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3019, 2970, 1700, 1669, 1459, 1367, 1217, 1054, 1009, 752, 668, 462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73–6.70 (m, 1H), 3.75 (d, *J*=11.7 Hz, 1H), 3.32 (d, *J*=11.7 Hz, 1H), 2.73 (dt, *J*=15.1, 5.7 Hz, 1H), 2.55 (dd, *J*=11.3, 3.9 Hz, 1H), 2.48–2.19 (m, 4H), 2.18 (s, 1H), 1.84–1.76 (m, 1H), 1.78–1.77 (m, 3H), 1.31 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 203.6, 143.1, 133.4, 65.3, 52.6, 43.9, 42.9, 34.9, 32.8, 24.1, 17.6, 17.1, 16.2; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{14}H_{21}O_3$ 237.1491, found 237.1488. *Data for* 10-*epi*-**5** $[\alpha]_D^{27}$ −83.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3475, 2925, 1707, 1668, 1454, 1374, 1045, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73–6.71 (m, 1H), 3.92 (d, *J*=11.2 Hz, 1H), 3.70 (d, *J*=11.2 Hz, 1H), 2.61 (ddd, *J*=16.0, 13.1, 6.5 Hz, 1H), 2.55–2.46 (m,

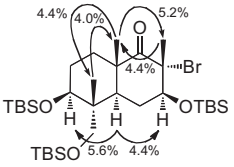
2H), 2.38–2.30 (m, 1H), 2.25 (ddd, *J*=14.3, 6.5, 3.3 Hz, 1H), 2.19 (dd, *J*=11.9, 4.1 Hz, 1H), 2.15 (s, 1H), 1.91 (dt, *J*=14.1, 5.8 Hz, 1H), 1.77–1.76 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2, 203.7, 143.6, 133.4, 65.9, 52.8, 50.1, 44.3, 35.1, 31.6, 24.9, 21.2, 17.4, 16.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{14}H_{21}O_3$ 237.1491, found 237.1490.

*4.1.4. (4aR,5R,8aS)-5-(((Diisopropylsilyl)oxy)methyl)-2,5,8a-trimethyl-4a,5,8,8a-tetrahydronaphthalene-1,6(4H,7H)-dione (**9**).* To a solution of **5** (1.15 g, 4.87 mmol) in DMF (49 mL) were added Et_3N (3.39 g, 24.4 mmol), DMAP (2.97 g, 24.4 mmol), and chlorodiisopropylsilane (1.25 g, 7.31 mmol). The reaction mixture was stirred for 0.5 h at 50 °C, quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (30:1 hexanes/EtOAc) afforded **9** (1.59 g, 93%) as a colorless oil: $[\alpha]_D^{26}$ −17.2 (*c* 1.0, $CHCl_3$); IR (KBr) 2926, 2865, 2095, 1710, 1672, 1464, 1097, 1003, 838, 804 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76–6.73 (m, 1H), 4.08 (s, 1H), 3.97 (d, *J*=9.8 Hz, 1H), 3.34 (d, *J*=9.8 Hz, 1H), 2.80 (dd, *J*=11.4, 4.5 Hz, 1H), 2.55 (ddd, *J*=17.0, 13.3, 6.5 Hz, 1H), 2.46–2.35 (m, 2H), 2.28–2.25 (m, 1H), 2.21 (ddd, *J*=14.1, 6.3, 3.5 Hz, 1H), 1.86 (dt, *J*=13.7, 5.7 Hz, 1H), 1.81–1.79 (m, 3H), 1.21 (s, 3H), 1.01 (s, 3H), 0.97–0.95 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 204.0, 143.6, 133.4, 68.5, 52.4, 43.9, 41.4, 35.2, 30.7, 29.8, 24.4, 18.6, 17.6, 17.5, 17.4, 17.4, 17.0, 16.4, 12.4; HRMS (ESI) $[M+Na]^+$ calcd for $C_{20}H_{34}NaO_3Si$ 373.2175, found 373.2168.

*4.1.5. (4aS,6aS,10aS,10bR)-3,3-Diisopropyl-6a,8,10b-trimethyl-4a,5,6,6a,10,10a-hexahydro-1H-naphtho[2,1-d][1,3,2]dioxasilin-7(10bH)-one (**10**).* To a solution of **9** (386 mg, 1.10 mmol) in CH_2Cl_2 (22 mL) was added $SnCl_4$ (1.0 M in CH_2Cl_2, 22 μL, 22.0 μmol). The reaction was stirred for 1 h at 0 °C, quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (40:1 hexanes/EtOAc) afforded **10** (277 mg, 72%) as a colorless oil: $[\alpha]_D^{27}$ −29.9 (*c* 1.0, $CHCl_3$); IR (KBr) 2945, 2866, 1673, 1465, 1095, 1047, 998, 885, 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61–6.59 (m, 1H), 3.82 (d, *J*=10.4 Hz, 1H), 3.69 (dd, *J*=10.6, 4.7 Hz, 1H), 3.65 (d, *J*=10.6 Hz, 1H), 2.40–2.32 (m, 1H), 2.06–1.99 (m, 1H), 1.96–1.91 (dt, *J*=13.9, 3.1 Hz, 1H), 1.75–1.66 (m, 2H), 1.74–1.71 (m, 3H), 1.58 (dd, *J*=11.5, 4.3 Hz, 1H), 1.51 (dt, *J*=13.7, 5.3 Hz, 1H), 1.20 (s, 3H), 1.07–1.04 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 142.6, 133.4, 79.6, 75.8, 45.5, 44.5, 41.5, 31.7, 26.6, 23.8, 18.1, 17.8, 17.6, 17.1, 17.1, 16.4, 12.7, 12.3, 12.2; HRMS (ESI) $[M+Na]^+$ calcd for $C_{20}H_{34}NaO_3Si$ 373.2175, found 373.2171.

*4.1.6. (1aR,2aS,5S,6R,6aS,7aR)-5-Hydroxy-6-(hydroxymethyl)-1a,2a,6-trimethyloctahydronaphtho[2,3-b]oxiren-2(1aH)-one (**11**).* To a solution of **10** (20.0 mg, 57.1 μmol) in MeOH (1.0 mL) were added an aqueous NaOH solution (6 M in H_2O, 3 μL, 17.2 μmol) and 30% H_2O_2 solution (22 μL, 0.194 mmol). The reaction was stirred for 20 h at rt, quenched with a saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) afforded **11** (11.9 mg, 82%) as a white solid: $[\alpha]_D^{28}$ +45.3 (*c* 1.0, MeOH); IR (KBr) 3021, 2403, 1709, 1520, 1427, 1216, 1039, 929, 762, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (dd, *J*=11.2, 5.1 Hz, 1H), 3.51 (d, *J*=11.2 Hz, 1H), 3.43 (t, *J*=2.0 Hz, 1H), 3.25 (d, *J*=11.2 Hz, 1H), 2.20 (ddd, *J*=14.7, 3.4, 2.7 Hz, 1H), 2.03 (ddd, *J*=14.7, 12.7, 1.4 Hz, 1H), 1.92 (dd, *J*=12.5, 3.7 Hz, 1H), 1.82 (dt, *J*=13.9, 3.4 Hz, 1H), 1.71–1.58 (m, 2H), 1.41 (dt, *J*=13.1, 4.7 Hz, 1H), 1.36 (s, 3H), 1.08 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 72.6, 65.7, 61.2, 57.3, 46.6, 43.6, 33.2, 32.0, 26.9, 22.3, 17.8, 16.7, 13.0; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{22}NaO_4$ 277.1416, found 277.1406.

*4.1.7. (2R,3S,4aS,5R,6S,8aS)-2-Bromo-3,6-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5,8a-trimethyloctahydronaphthalen-1(2H)-one (**14**).* To a solution of **13** (78.0 mg, 0.234 mmol) in CH_2Cl_2 (2.3 mL) at 0 °C were added 2,6-lutidine (271 μL, 2.34 mmol) and TBSOTf (268 μL, 1.17 mmol). The reaction was stirred for 1.5 h at 0 °C, quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (200:1 hexanes/EtOAc) afforded **14** (156 mg, 99%) as a white solid: $[\alpha]_D^{28}$ +13.8 (*c* 1.0, $CHCl_3$); IR (KBr) 2953, 2933, 2889, 2859, 1710, 1468, 1254, 1217, 1100, 899, 841, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, *J*=6.5 Hz, 1H), 3.70 (dd, *J*=10.8, 5.5 Hz, 1H), 3.43 (d, *J*=10.0 Hz, 1H), 3.13 (d, *J*=9.8 Hz, 1H), 2.28 (dd, *J*=12.5, 4.5 Hz, 1H), 2.04–1.94 (m, 2H), 1.79 (s, 3H), 1.72–1.62 (m, 3H), 1.37 (dt, *J*=13.7, 4.7 Hz, 1H), 1.20 (s, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.69 (s, 3H), 0.14 (s, 6H), 0.06–0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 77.6, 71.3, 68.6, 64.2, 46.9, 44.1, 36.1, 33.6, 28.9, 27.2, 26.0, 26.0, 25.9, 25.8, 19.1, 18.1, 18.1, 18.0, 13.0, −3.3, −4.3, −4.7, −4.8, −5.2, −5.3; HRMS (ESI) $[M+Na]^+$ calcd for $C_{32}H_{65}BrNaO_4Si_3$ 699.3271, found 699.3288.



*4.1.8. (4aS,5R,6S,8aS)-6-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5,8a-trimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4H)-one (**15**).* To a solution of $MeOCH_2PPh_3Cl$ (23.0 mg, 66.6 μmol) in THF (100 μL) was added dropwise KHMDS (133 μL, 66.6 μmol) at 0 °C. After being stirred for 0.5 h, a solution of **14** (15.0 mg, 22.2 μmol) in THF (120 μL) was added dropwise. The reaction was stirred for 3 h at rt, quenched with a saturated aqueous NH_4Cl solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (150:1 hexanes/EtOAc) afforded **15** (8.5 mg, 82%) as a white solid: $[\alpha]_D^{28}$ −3.87 (*c* 1.0, $CHCl_3$); IR (KBr) 3020, 2948, 2862, 1664, 1252, 1217, 1099, 843, 761, 672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66–6.64 (m, 1H), 3.67–3.63 (m, 1H), 3.43 (d, *J*=10.0 Hz, 1H), 3.13 (d, *J*=10.0 Hz, 1H), 2.30–2.11 (m, 2H), 2.09 (dd, *J*=11.4, 4.1 Hz, 1H), 1.87 (dt, *J*=14.0, 3.4 Hz, 1H), 1.74–1.73 (m, 3H), 1.69–1.58 (m, 2H), 1.45–1.37 (m, 1H), 1.04 (s, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.76 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 143.6, 133.2, 71.5, 64.1, 44.4, 44.1, 41.0, 31.4, 27.2, 26.1, 26.0, 24.1, 18.3, 18.2, 17.8, 16.5, 13.0, −3.5, −4.8, −5.0, −5.5; HRMS (ESI) $[M+Na]^+$ calcd for $C_{26}H_{50}NaO_3Si_2$ 489.3196, found 489.3205.

*4.1.9. (4aS,5R,6S,8aS)-6-Hydroxy-5-(hydroxymethyl)-2,5,8a-trimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4H)-one (**18**).* To a solution of $Me_4NBH(OAc)_3$ (5.57 g, 21.2 mmol) in CH_3CN (2.1 mL) was added dropwise acetic acid (16.8 mL). A solution of **5** (1.00 g, 4.23 mmol) in CH_3CN (2.1 mL) was added to the mixture at −40 °C. The reaction was stirred for 0.5 h at −40 °C and quenched with 0.5 N potassium sodium tartrate tetrahydrate. The resulting mixture was carefully poured into a saturated aqueous $NaHCO_3$ solution at 0 °C and the neutralized aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and

concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) afforded **18** (935 mg, 93%) as a white solid: $[\alpha]_D^{27}$ −20.3 (*c* 1.0, MeOH); IR (KBr) 3620, 3457, 3020, 2977, 1666, 1217, 1043, 771, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82–6.79 (m, 1H), 3.62–3.58 (m, 1H), 3.53 (d, *J*=11.2 Hz, 1H), 3.27 (d, *J*=11.2 Hz, 1H), 2.43–2.27 (m, 2H), 2.01 (dd, *J*=10.9, 4.8 Hz, 1H), 1.86 (dt, *J*=13.9, 3.4 Hz, 1H), 1.76–1.68 (m, 2H), 1.72–1.70 (m, 3H), 1.47–1.39 (m, 1H), 1.07 (s, 3H), 0.85 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 146.3, 133.7, 72.5, 65.5, 45.5, 44.0, 42.6, 32.7, 27.2, 24.9, 18.2, 16.4, 12.9; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{22}NaO_3$ 261.1467, found 261.1472.

*4.1.10. (1aS,2aS,5S,6R,6aS,7aS)-5-Hydroxy-6-(hydroxymethyl)-1a,2a,6-trimethyloctahydronaphtho[2,3-b]oxiren-2(1aH)-one (**16**).* To a solution of **18** (76.1 mg, 0.210 mmol) in acetic acid (3.2 mL) at rt were added dropwise *N*-bromoacetamide (111 mg, 0.639 mmol) and silver acetate (107 mg, 0.639 mmol). The reaction mixture was stirred for 6.5 h at rt, filtered through a pad of Celite, and concentrated in vacuo. The residue **19** was dissolved with CH_2Cl_2 and washed with an aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. This residue was employed in the next reaction without further purification. To a solution of the crude **19** in MeOH (3.2 mL) at rt was added K_2CO_3 (133 mg, 0.959 mmol). The reaction was stirred for 7 h at rt, quenched with H_2O, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (1:2 hexanes/EtOAc) afforded **16** (70.6 mg, 87%) as a white solid: *data for* **19** (after purification by flash chromatography (1:2 hexanes/EtOAc) of the above crude) $[\alpha]_D^{26}$ +4.12 (*c* 1.0, MeOH): IR (KBr) 3374, 2931, 2077, 1711, 1455, 1381, 1222, 1033, 979, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24 (dd, *J*=8.5, 5.8 Hz, 1H), 3.60 (dd, *J*=9.3, 7.1 Hz, 1H), 3.56 (d, *J*=11.2 Hz, 1H), 3.28 (d, *J*=11.0 Hz, 1H), 2.08–1.98 (m, 2H), 1.93 (dt, *J*=13.9, 3.5 Hz, 1H), 1.83–1.69 (m, 3H), 1.81 (s, 3H), 1.43–1.35 (m, 1H), 1.22 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 78.6, 73.9, 72.2, 65.7, 48.6, 44.1, 38.8, 35.0, 28.6, 27.3, 25.9, 20.4, 12.9; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{23}BrNaO_4$ 357.0677, found 357.0666. *Data for* **16** $[\alpha]_D^{28}$ −12.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3408, 3018, 2978, 2941, 2878, 1701, 1471, 1447, 1383, 1217, 1063, 1043, 999, 761, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (d, *J*=10.6 Hz, 1H), 3.57 (dd, *J*=11.2, 4.5 Hz, 1H), 3.46 (d, *J*=5.5 Hz, 1H), 3.36 (d, *J*=10.6 Hz, 1H), 2.18 (dd, *J*=15.1, 12.9 Hz, 1H), 2.00 (dt, *J*=15.3, 5.7 Hz, 1H), 1.80–1.62 (m, 4H), 1.50 (dt, *J*=13.3, 3.9 Hz, 1H), 1.35 (s, 3H), 1.24 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 73.9, 67.9, 64.2, 57.7, 45.3, 44.0, 43.2, 32.7, 26.2, 21.2, 18.6, 16.3, 11.5; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{22}NaO_4$ 277.1416, found 277.1429.

*4.1.11. (1aS,2aS,5S,6R,6aS,7aS)-5-((tert-Butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)-1a,2a,6-trimethyloctahydronaphtho[2,3-b]oxiren-2(1aH)-one (**17**).* To a solution of **16** (20.0 mg, 78.7 μmol) in CH_2Cl_2 (800 μL) at 0 °C were added 2,6-lutidine (55 μL, 0.474 mmol) and TBSOTf (54 μL, 0.237 mmol). The reaction was stirred for 0.5 h at 0 °C, quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (150:1 hexanes/EtOAc) afforded **17** (34.0 mg, 90%) as a white solid: $[\alpha]_D^{26}$ +11.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3021, 2952, 2884, 2859, 1702, 1467, 1386, 1254, 1217, 1103, 1004, 886, 841, 810, 762, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 (dd, *J*=9.3, 6.9 Hz, 1H), 3.43 (d, *J*=10.0 Hz, 1H), 3.41 (d, *J*=5.1 Hz, 1H), 3.08 (d, *J*=10.0 Hz, 1H), 2.09 (dd, *J*=16.2, 14.3 Hz, 1H), 1.95–1.89 (m, 2H), 1.72 (dt, *J*=10.4, 3.5 Hz, 1H), 1.63–1.57 (m, 2H), 1.44–1.36 (m, 1H), 1.33 (s, 3H), 1.18 (s, 3H), 0.86 (s, 18H), 0.70 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 71.3, 64.3, 64.0, 57.2, 45.2, 44.4, 42.7, 32.5, 26.6, 25.9, 25.7, 21.2, 18.3, 18.1, 18.1, 16.3, 12.2, −2.9, −3.6, −5.0, −5.7; HRMS (ESI) $[M+Na]^+$ calcd for $C_{26}H_{50}NaO_4Si_2$ 505.3145, found 505.3120.

*4.1.12. (3S,4aR,5R,6S,8aS)-3,6-Bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (**4**).* To a solution of $TMSCH_2OMe$ (196 μL, 1.24 mmol) in THF (2.1 mL) was added dropwise *s*-BuLi (1.0 M in THF, 1.24 mL, 1.24 mmol) at −23 °C and the reaction mixture was stirred for 0.5 h at −23 °C. After cooling to −78 °C, the mixture was added dropwise to a solution of **17** (200 mg, 0.415 mmol) in THF (2.0 mL). The reaction mixture was stirred for 0.5 h at −60 °C before *t*-BuOK (184 mg, 1.63 mmol) was added. The resulting mixture was gradually warmed up to rt over 1 h and quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. This residue was employed in the next reaction without further purification. The residue was dissolved in DMF (4.2 mL) and to the solution were added imidazole (113 mg, 1.65 mmol), DMAP (cat.), and TBSCl (187 mg, 1.24 mmol). The resulting solution was stirred for 30 min at 50 °C before additional TBSCl (187 mg, 1.24 mmol) was added. After being stirred for 30 min at 50 °C, the reaction mixture was quenched with H_2O, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (150:1 hexanes/EtOAc) afforded **4** (179 mg, two steps 71%) as a white solid: $[\alpha]_D^{25}$ −22.6 (*c* 1.0, $CHCl_3$); IR (KBr) 2953, 2859, 1681, 1468, 1387, 1254, 1101, 1005, 838, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.1 (s, 1H), 4.16 (dd, *J*=9.2, 7.6 Hz, 1H), 3.71 (dd, *J*=10.7, 6.0 Hz, 1H), 3.42 (d, *J*=9.8 Hz, 1H), 3.17 (d, *J*=9.8 Hz, 1H), 2.44 (dt, *J*=13.3, 3.5 Hz, 1H), 2.01 (s, 3H), 1.85 (dd, *J*=11.6, 7.3 Hz, 1H), 1.68–1.44 (m, 4H), 1.26 (s, 3H), 1.07–0.97 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.64 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 153.6, 144.2, 74.2, 71.4, 64.2, 43.3, 39.8, 37.7, 34.1, 28.7, 27.8, 26.2, 26.1, 26.0, 20.5, 18.3, 18.2, 18.2, 15.2, 13.1, −3.1, −3.5, −4.7, −4.7, −5.0, −5.3; HRMS (ESI) $[M+Na]^+$ calcd for $C_{33}H_{66}NaO_4Si_3$ 633.4167, found 633.4150.

*4.1.13. (3S,4aR,5R,6S,8aS)-3,6-Bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid (Pinnick oxidation of **4**).* To a solution of **4** (27.0 mg, 44.3 μmol) in *t*-BuOH (221 μL) were added H_2O (221 μL) and 2-methyl-2-butene (19 μL, 0.177 mmol) at rt and the reaction mixture was treated with $NaH_2PO_4 \cdot 2H_2O$ (21.0 mg, 0.133 mmol) and $NaClO_2$ (12.0 mg, 0.133 mmol) at 0 °C. After being stirred for 15 h at rt, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (10:1 hexanes/EtOAc) afforded the carboxylic acid (17.0 mg, 61%) as a white solid: $[\alpha]_D^{25}$ +12.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3018, 2949, 2891, 2862, 1696, 1254, 1217, 1097, 1056, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (t, *J*=8.2 Hz, 1H), 3.73 (dd, *J*=9.2, 7.1 Hz, 1H), 3.41 (d, *J*=10.0 Hz, 1H), 3.18 (d, *J*=9.8 Hz, 1H), 1.86 (dd, *J*=11.6, 7.5 Hz, 1H), 1.72 (s, 3H), 1.69–1.49 (m, 5H), 1.38–1.32 (m, 1H), 1.29 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.64 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 139.2, 135.9, 72.3, 71.4, 64.3, 43.3, 40.4, 37.0, 34.7, 29.3, 27.6, 26.1, 26.1, 26.1, 21.0, 18.4, 18.3, 18.3, 17.4, 13.0, −3.2, −3.6, −4.6, −4.7, −5.0, −5.3; HRMS (ESI) $[M+Na]^+$ calcd for $C_{33}H_{66}NaO_5Si_3$ 649.4116, found 649.4099.

4.1.14. (Z)-Ethyl 3-((3S,4aR,5R,6S,8aS)-3,6-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-

*hydroxyacrylate (**21**).* To a solution of LHMDS (1.0 M in THF, 642 μL, 0.642 mmol) in THF (2.0 mL) was added dropwise EtOAc (52 μL, 0.602 mmol) at −78 °C and the reaction mixture was stirred for 0.5 h at −78 °C. To the resulting mixture was added dropwise a solution of **4** (245 mg, 0.401 mmol) in THF (2.0 mL). The reaction mixture was further stirred for 0.5 h at −78 °C. The resulting mixture was then quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. This residue was employed in the next reaction without further purification. The crude **20** was dissolved in CH_2Cl_2 (4.0 mL) and to the solution was added DMP (255 mg, 0.602 mmol). After being stirred for 30 min at rt, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (150:1 hexanes/EtOAc) afforded **21** (186 mg, two steps 67%) as a white solid: $[\alpha]_D^{25}$ +13.1 (*c* 1.0, $CHCl_3$); IR (KBr) 2954, 2932, 2890, 2858, 1612, 1468, 1252, 1218, 1100, 1056, 840, 754 cm^{-1}; *enol form* ^1H NMR (600 MHz, $CDCl_3$) δ 12.2 (s, 1H), 4.91 (s, 1H), 4.21 (q, *J*=7.1 Hz, 2H), 4.09 (br t, *J*=8.0 Hz, 1H), 3.73 (dd, *J*=10.0, 5.0 Hz, 1H), 3.39 (d, *J*=9.7 Hz, 1H), 3.18 (d, *J*=9.7 Hz, 1H), 1.84 (ddd, *J*=13.0, 8.0, 2.0 Hz, 1H), 1.75–1.44 (m, 5H), 1.64 (s, 3H), 1.31 (t, *J*=7.2 Hz, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.63 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.0, 172.6, 140.6, 134.9, 92.9, 72.5, 71.2, 64.1, 60.0, 43.3, 40.5, 37.4, 35.0, 29.2, 27.5, 25.9, 25.9, 25.9, 21.3, 18.1, 18.1, 18.1, 17.1, 14.2, 12.8, −3.4, −3.8, −4.9, −5.2, −5.5; HRMS (ESI) $[M+Na]^+$ calcd for $C_{37}H_{72}NaO_6Si_3$ 719.4534, found 719.4509.

*4.1.15. 5-((3S,4aR,5R,6S,8aS)-3,6-Bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-2,2,6-trimethyl-4H-1,3-dioxin-4-one (**24**).* To a solution of **22** (198 mg, 0.739 mmol) in THF (1.5 mL) at −30 °C was added dropwise *i*-PrMgCl (2.0 M in THF, 369 μL, 0.739 mmol). After being stirred for 0.5 h at −30 °C, to the reaction mixture was added dropwise a solution of **4** (150 mg, 0.246 mmol) in THF (1.0 mL). The resulting mixture was warmed up to rt, stirred for 0.5 h, and quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. This residue was employed in the next reaction without further purification. The crude **23** was dissolved in CH_2Cl_2 (2.5 mL) and DMP (156 mg, 0.369 mmol) was added. The resulting solution was stirred for 15 min at rt and quenched with a saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (150:1 hexanes/EtOAc) afforded **24** (133 mg, two steps 72%) as a white solid: $[\alpha]_D^{27}$ +24.9 (*c* 1.0, $CHCl_3$); IR (KBr) 2948, 2861, 1741, 1653, 1546, 1467, 1383, 1348, 1259, 1208, 1100, 844, 776, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (t, *J*=8.4 Hz, 1H), 3.74 (dd, *J*=10.9, 5.0 Hz, 1H), 3.39 (d, *J*=9.8 Hz, 1H), 3.22 (d, *J*=9.8 Hz, 1H), 2.39 (s, 3H), 2.05 (dd, *J*=13.1, 1.6 Hz, 1H), 1.92–1.86 (m, 1H), 1.70 (s, 6H), 1.68–1.52 (m, 4H), 1.50 (s, 3H), 1.31 (s, 3H), 1.31–1.26 (m, 1H), 0.93 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.65 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 178.0, 157.6, 145.7, 131.4, 110.6, 105.7, 72.5, 71.4, 64.5, 43.3, 39.5, 38.6, 32.6, 29.5, 27.4, 26.0, 25.9, 25.9, 25.5, 25.3, 22.3, 21.4, 18.2, 18.1, 18.1, 16.6, 12.7, −3.4, −3.7, −4.8, −4.8, −5.2, −5.3; HRMS (ESI) $[M+Na]^+$ calcd for $C_{40}H_{74}NaO_7Si_3$ 773.4640, found 773.4630.

*4.1.16. (Z)-Methyl 2-(((3S,4aR,5R,6S,8aS)-3,6-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)(hydroxy)methylene)-3-oxobutanoate (**3**).* β-Ketoester **24** (230 mg, 0.307 mmol) was dissolved in toluene (2.5 mL) and MeOH (614 μL). The reaction mixture was stirred for 5 h at 80 °C, cooled to rt, and concentrated in vacuo. Flash chromatography (150:1 hexanes/EtOAc) afforded **3** (208 mg, 94%) as a white solid: $[\alpha]_D^{25}$ +31.3 (*c* 1.0, $CHCl_3$); IR (KBr) 2954, 2932, 2888, 2858, 1715, 1468, 1441, 1263, 1103, 1056, 841, 774, 708 cm^{-1}; *enol form* ^1H NMR (600 MHz, $CDCl_3$) δ 4.04 (ddd, *J*=9.5, 7.0, 1.0 Hz, 1H), 3.73 (dd, *J*=11.0, 5.0 Hz, 1H), 3.68 (s, 3H), 3.43 (d, *J*=10.0 Hz, 1H), 3.19 (d, *J*=10.0 Hz, 1H), 2.34 (s, 3H), 1.87 (dd, *J*=13.0, 1.5 Hz, 1H), 1.86 (ddd, *J*=13.0, 7.0, 1.5 Hz, 1H), 1.69–1.55 (m, 4H), 1.53 (s, 3H), 1.41 (ddd, *J*=14.0, 5.0, 3.0 Hz, 1H), 1.32 (s, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.65 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.4, 194.1, 167.4, 141.2, 133.7, 111.1, 72.2, 71.4, 64.3, 51.7, 43.3, 39.3, 38.2, 32.8, 29.4, 27.3, 26.0, 25.9, 25.9, 25.9, 22.4, 18.3, 18.1, 18.1, 17.2, 12.8, −3.3, −3.8, −4.8, −4.9, −5.1, −5.6; HRMS (ESI) $[M+Na]^+$ calcd for $C_{38}H_{72}NaO_7Si_3$ 747.4484, found 747.4450.

*4.1.17. (4aS,5S,6aR,7R,8S,10aS,10bR)-Methyl 5,8-bis((tert-butyldimethylsilyl)oxy)-7-(((tert-butyldimethylsilyl)oxy)methyl)-3,4a,7,10a-tetramethyl-1-oxo-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1H-benzo[f]chromene-2-carboxylate (**2**).* To a solution of **3** (25.0 mg, 34.5 μmol) in toluene (345 μL) was added DBU (5 μL, 34.5 μmol). After being stirred for 8 h at 100 °C, the reaction mixture was quenched with H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (100:1 hexanes/EtOAc) afforded **2** (17.0 mg, 68%) as a white solid: $[\alpha]_D^{25}$ +12.1 (*c* 1.0, $CHCl_3$); IR (KBr) 2953, 2932, 2885, 2858, 1685, 1389, 1355, 1254, 1215, 1117, 1060, 839, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, *J*=10.7, 5.0 Hz, 1H), 3.78 (s, 3H), 3.69 (dd, *J*=11.5, 5.2 Hz, 1H), 3.41(d, *J*=9.8 Hz, 1H), 3.12 (d, *J*=9.6 Hz, 1H), 2.60 (dt, *J*=13.5, 3.5 Hz, 1H), 2.28 (s, 1H), 2.16 (s, 3H), 1.72–1.54 (m, 3H), 1.47–1.33 (m, 2H), 1.34 (s, 3H), 1.07 (s, 3H), 0.97–0.93 (m, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.86 (s, 9H), 0.60 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 174.0, 166.6, 111.5, 88.4, 77.8, 71.6, 64.2, 61.2, 52.1, 43.6, 43.4, 37.1, 36.7, 28.9, 27.2, 26.2, 26.1, 26.0, 20.7, 18.4, 18.3, 18.2, 16.0, 14.9, 12.9, −3.0, −4.1, −4.5, −4.7, −5.0, −5.1; HRMS (ESI) $[M+Na]^+$ calcd for $C_{38}H_{72}NaO_7Si_3$ 747.4484, found 747.4458. *Data for* **25** (after careful purification by SGC) $[\alpha]_D^{24}$ +44.3 (*c* 1.0, $CHCl_3$); IR (KBr) 2947, 2862, 1596, 1468, 1383, 1254, 1219, 1093, 844, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (s, 1H), 4.11–4.07 (m, 1H), 3.74–3.70 (m, 1H), 3.40 (d, *J*=9.8 Hz, 1H), 3.18 (d, *J*=9.8 Hz, 1H), 2.10 (s, 3H), 1.84 (ddd, *J*=12.3, 7.0, 1.4 Hz, 1H), 1.71 (dd, *J*=12.9, 1.4 Hz, 1H), 1.62–1.46 (m, 4H), 1.60 (s, 3H), 1.32–1.26 (m, 1H), 1.23 (s, 3H), 0.90 (s, 18H), 0.86 (s, 9H), 0.63 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 189.6, 142.7, 133.3, 103.4, 72.4, 71.3, 64.1, 43.2, 40.5, 37.5, 35.1, 29.3, 27.5, 26.0, 26.0, 25.9, 25.6, 21.2, 18.2, 18.2, 18.1, 17.0, 12.8, −3.4, −3.8, −4.8, −4.9, −5.1, −5.5; HRMS (ESI) $[M+Na]^+$ calcd for $C_{36}H_{70}NaO_5Si_3$ 689.4429, found 689.4395.

*4.1.18. (3S,4R,4aR,6S,6aS,12aR,12bS)-3,6-Bis((tert-butyldimethylsilyl)oxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)-4,6a,12b-trimethyl-9-(pyridin-3-yl)-1,3,4,4a,5,6,6a,12b-octahydrobenzo[f]pyrano[4,3-b]chromene-11,12(2H,12aH)-dione (**26**).* To a solution of LHMDS (1.0 M in THF, 193 μL, 0.193 mmol) in THF (193 μL) at 0 °C was added dropwise a solution of **2** (14.0 mg, 19.3 μmol) in THF (193 μL). The reaction mixture was warmed up to rt and stirred for 4 h. To the mixture was added nicotinoyl chloride hydrochloride (9.0 mg, 57.9 μmol) expeditiously. The resulting mixture was stirred for 2 h at rt, quenched with AcOH, and diluted with H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo.

Flash chromatography (2:1 hexanes/EtOAc) afforded **26** (10.0 mg, 65%) as a white solid: $[\alpha]_D^{27}$ +32.6 (*c* 1.0, $CHCl_3$); IR (KBr) 2939, 2861, 1758, 1541, 1446, 1254, 1217, 1110, 844, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.73 (d, *J*=4.3 Hz, 1H), 8.20 (dd, *J*=8.0, 1.6 Hz, 1H), 7.47 (dd, *J*=8.0, 4.9 Hz, 1H), 6.40 (s, 1H), 3.94 (dd, *J*=10.0, 5.5 Hz, 1H), 3.69 (dd, *J*=11.5, 5.1 Hz, 1H), 3.42 (d, *J*=9.8 Hz, 1H), 3.12 (d, *J*=9.8 Hz, 1H), 2.66 (dt, *J*=10.4, 3.5 Hz, 1H), 2.41 (s, 1H), 1.70–1.41 (m, 5H), 1.44 (s, 3H), 1.13 (s, 3H), 0.97–0.90 (m, 1H), 0.93 (s, 9H), 0.90 (s, 9H), 0.85 (s, 9H), 0.61 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 172.4, 161.9, 157.0, 152.0, 147.0, 134.4, 127.0, 124.1, 100.8, 98.0, 90.9, 71.5, 64.2, 62.7, 43.6, 43.3, 37.0, 37.0, 28.9, 27.2, 26.2, 26.1, 26.0, 18.3, 18.2, 18.2, 15.9, 15.5, 12.9, −3.0, −4.0, −4.3, −4.7, −5.1, −5.1; HRMS (ESI) $[M+Na]^+$ calcd for $C_{43}H_{71}NNaO_7Si_3$ 820.4436, found 820.4454.

*4.1.19. Pyripyropene A (**1**).* Acetyl chloride (18 μL, 0.250 mmol) was added to MeOH (0.1 mL), and the mixture was stirred at rt for 5 min. A solution of **26** (16.8 mg, 0.0250 mmol) in MeOH (0.4 mL) was added to the resulting MeOH solution, and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated in vacuo. A solution of crude triol in CH_2Cl_2 (0.5 mL) was treated with Ac_2O (12 μL, 0.125 mmol), Et_3N (35 μL, 0.250 mmol), and a catalytic amount of DMAP, and the mixture was stirred at rt for 0.5 h. H_2O was added to the mixture and the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. A solution of crude triacetate in MeOH (0.5 mL) was treated with $CeCl_3\cdot 7H_2O$ (65.2 mg, 0.175 mmol) and $NaBH_4$ (6.5 mg, 0.175 mmol), and the mixture was stirred at −78 °C for 0.5 h. Acetone was added to the mixture and the resulting solution was diluted with EtOAc. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (15:1 CH_2Cl_2/MeOH) to afford PPPA (**1**) (12.8 mg, 88% for three steps) as a white solid: mp 153–154 °C; $[\alpha]_D^{24}$ +71.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3424, 2946, 2862, 1738, 1702, 1413, 1272, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (dd, *J*=1.6, 0.4 Hz, 1H), 8.69 (ddd, *J*=4.8, 1.6, 0.8 Hz, 1H), 8.10 (ddd, *J*=8.0, 1.6, 0.4 Hz, 1H), 7.40 (ddd, *J*=8.0, 4.8, 0.8 Hz, 1H), 6.46 (s, 1H), 5.03–5.00 (m, 2H), 4.80 (dd, *J*=11.6, 4.0 Hz, 1H), 3.79 (d, *J*=12.0 Hz, 1H), 3.72 (d, *J*=12.0 Hz, 1H), 2.94 (br s, 1H), 2.19–2.15 (m, 4H), 2.10 (s, 3H), 2.05 (s, 3H), 1.91–1.71 (m, 3H), 1.69 (s, 3H), 1.64–1.54 (m, 3H), 1.45 (s, 3H), 1.45–1.38 (m, 1H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 170.3, 170.0, 164.0, 162.2, 157.2, 151.4, 146.7, 133.2, 127.2, 123.7, 102.9, 99.4, 83.2, 77.6, 73.5, 64.9, 60.1, 54.7, 45.4, 40.3, 37.9, 36.1, 25.2, 22.6, 21.1, 21.1, 20.7, 17.4, 16.2, 13.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{31}H_{38}NO_{10}$ 584.2480, found 584.2496.

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References and notes

1. Roth, B. D. *Drug Discovery Today* **1998**, *3*, 19.
2. Kathawala, F. G.; Heider, J. C. In *Antilipidemic Drugs*; Witiak, D. T., Newman, H. A. I., Feller, D. R., Eds.; Elsevier: New York, NY, 1992; pp 159–195.
3. Tardif, J. C.; Gregoire, J.; L'Allier, P. L.; Anderson, T. J.; Bertrand, O.; Reeves, F.; Title, L. M.; Alfonso, F.; Schampaert, E.; Hassan, A.; McLain, R.; Pressler, M. L.; Ibrahim, R.; Lesperance, J.; Blue, J.; Heinonen, T.; Rodes-Cabau, J. *Circulation* **2004**, *110*, 3372.
4. Nissen, S. E.; Tuzcu, E. M.; Brewer, H. B.; Sipahi, I.; Nicholls, S. J.; Ganz, P.; Schoenhagen, P.; Waters, D. D.; Pepine, C. J.; Crowe, T. D.; Davidson, M. H.; Deanfield, J. E.; Winsniewski, L. M.; Hanyok, J. J.; Kassalow, L. M. *N. Engl. J. Med.* **2006**, *354*, 1253.
5. Tomoda, H.; Ōmura, S. *Pharmacol. Ther.* **2007**, *115*, 375.
6. Ōmura, S.; Tomoda, H.; Kim, Y. K.; Nishida, H. *J. Antibiot.* **1993**, *46*, 1168.
7. Tomoda, H.; Kim, Y. K.; Nishida, H.; Masuma, R.; Ōmura, S. *J. Antibiot.* **1994**, *47*, 148.
8. Kim, Y. K.; Tomoda, H.; Nishida, H.; Sunazuka, T.; Obata, R.; Ōmura, S. *J. Antibiot.* **1994**, *47*, 154.
9. Obata, R.; Sunazuka, T.; Li, Z.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **1995**, *48*, 749.
10. Obata, R.; Sunazuka, T.; Tomoda, H.; Harigaya, Y.; Ōmura, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2683.
11. Obata, R.; Sunazuka, T.; Li, Z.; Tian, Z.; Harigaya, Y.; Tabata, N.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **1996**, *49*, 1133.
12. Obata, R.; Sunazuka, T.; Kato, Y.; Tomoda, H.; Harigaya, Y.; Ōmura, S. *J. Antibiot.* **1996**, *49*, 1149.
13. Obata, R.; Sunazuka, T.; Tian, Z.; Tomoda, H.; Harigaya, Y.; Ōmura, S. *J. Antibiot.* **1997**, *50*, 229.
14. Obata, R.; Sunazuka, T.; Tian, Z.; Tomoda, H.; Harigaya, Y.; Ōmura, S.; Smith, A. B., III. *Chem. Lett.* **1997**, *26*, 935.
15. Chang, C. C.; Huh, H. Y.; Cadigan, K. M.; Chang, T. Y. *J. Biol. Chem.* **1993**, *268*, 20747.
16. Anderson, R. A.; Joyce, C.; Davis, M.; Reagan, J. W.; Clark, M.; Shelness, G. S.; Rudel, L. L. *J. Biol. Chem.* **1998**, *273*, 26747.
17. Cases, S.; Novak, S.; Zheng, Y. W.; Myers, H. M.; Lear, S. R.; Sande, E.; Welch, C. B.; Lusis, A. J.; Spencer, T. A.; Krause, B. R.; Erickson, S. K.; Farese, R. V., Jr. *J. Biol. Chem.* **1998**, *273*, 26755.
18. Oelkers, P.; Behari, A.; Cromley, D.; Billheimer, J. T.; Sturley, S. L. *J. Biol. Chem.* **1998**, *273*, 26765.
19. Parini, P.; Davis, M.; Lada, A. T.; Erickson, S. K.; Wright, T. L.; Gustafsson, U.; Sahlin, S.; Einarsson, C.; Eriksson, M.; Angelin, B.; Tomoda, H.; Ōmura, S.; Willingham, M. C.; Rudel, L. L. *Circulation* **2004**, *110*, 2017.
20. (a) Lada, A. T.; Davis, M.; Kent, C.; Chapman, J.; Tomoda, H.; Ōmura, S.; Rudel, L. L. *J. Lipid Res.* **2004**, *45*, 378; (b) Ohshiro, T.; Rudel, L. L.; Ōmura, S.; Ishibashi, S.; Tomoda, H. *J. Antibiot.* **2007**, *60*, 43.
21. Ohshiro, T.; Matusda, D.; Sakai, K.; Degirolamo, C.; Yagyu, H.; Rudel, L. L.; Ōmura, S.; Tomoda, H. *Arterioscler., Thromb., Vasc. Biol.* **2011**, *31*, 1108.
22. Bligh, E. G.; Dyer, W. *Can. J. Biochem. Physiol.* **1959**, *37*, 911.
23. More recently, new PPPA derivatives with higher ACAT2 inhibitory activity and isozyme selectivity than those of PPPA have been developed in our second SAR study. They will be reported in due course.
24. Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Ōmura, S.; Smith, A. B., III. *J. Org. Chem.* **1995**, *60*, 8126.
25. Srikrishna, A.; Babu, R. R.; Beeraiah, B. *Tetrahedron* **2010**, *66*, 852.
26. (a) Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silvo, A. I.; Rubio González, R. *Synlett* **2004**, 1011; (b) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627.
27. Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761.
28. Fukushima, D. K.; Dobriner, S.; Rosenfeld, R. S. *J. Org. Chem.* **1961**, *26*, 5025.
29. Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553.
30. (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175; (b) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825; (c) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
31. (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939; (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
32. Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269.
33. Deschenaux, P.; Kallimopoulos, T.; Evans, H.; Guillarmod, A. *Helv. Chem. Acta* **1989**, *72*, 731.
34. Calo, F.; Richardson, J.; Barrett, A. B. M. *Org. Lett.* **2009**, *21*, 4910.
35. Shen, Q.; Huang, W.; Wang, J.; Zhou, X. *Org. Lett.* **2007**, *9*, 4491.
36. Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 6847.