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Convergent Synthesis of Pyragonicin

Shunya Takahashi,*,† Yayoi Hongo,† Narihito Ogawa,† Hiroyuki Koshino,† and Tadashi Nakata‡

RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama, 351-0198, Japan, and Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3 Kagurazaka, Shinjuku-Ku, Tokyo 162-8601, Japan

shunyat@riken.go.jp

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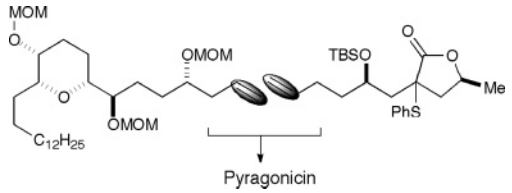

This paper describes a second-generation synthesis of an antitumor tetrahydropyran (THP) acetogenin, pyragonicin. The key step involved an olefin cross-metathesis between the THP segment and the terminal γ-lactone residue. The coupling reaction in the presence of Grubbs' second-generation catalyst resulted in an unseparable mixture of a desired coupling product and its one-carbon eliminated product while the use of Grubbs' first-generation catalyst afforded the former exclusively. A novel MOM-migrating reaction found in a cyclization reaction is also discussed.

The annonaceous acetogenins from the Annonaceae plant are a relatively new class of natural products that have a wide range of biological activities such as antitumor, cytotoxic, antimicrobial, antimalarial, pesticidal, and immunosuppressive effects.[1] They are characterized by the presence of one to three tetrahydrofuran (THF) rings in the center of a long alkyl chain with a butenolide moiety at the end and classified into three types according to the number of THF rings and their connection patterns. Besides such classical types, acetogenins have also been discovered that bear a double bond, a tetrahydropyran (THP) ring, and an oxirane ring (s) in the long chain. Their structural diversity and remarkable biological activities have attracted the attention of synthetic organic chemists, and this has consequently stimulated efforts to synthesize these natural products.[2]

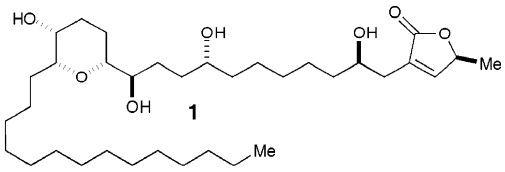

FIGURE 1. Structure of pyragonicin.

Recently, we have been engaged in synthetic studies on acetogenins, resulting in the total synthesis of nonclassical THP acetogenins.[3−7] In the synthetic study of such acetogenins, construction of the cyclic-ether moiety and its coupling with the γ-lactone residue are major problems throughout the synthetic course. In particular, mild reaction conditions are needed for such coupling because the γ-lactone part is unstable under basic conditions.[8] Several methods including Sonogashira coupling,[9] Wittig reaction,[10] and alkylation of γ-lactone[11] have been reported. However, a more efficient method for the coupling is still required for total synthesis of these natural products and detailed examination of their biological activity. In a previous paper, we demonstrated that an intermolecular cross-metathesis is a powerful tool for total syntheses of acetogenins.[12] To extend the methodology, we planned to synthesize acetogenins of greater complexity. Here, we describe the second-generation synthesis of pyragonicin (**1**) based on the method (Figure 1). Pyragonicin (**1**), which was isolated from the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae),[13] is a new member of the family possessing an

* Corresponding author. Phone: +81-48-467-9223. Fax: +81-48-462-4627.
† RIKEN.
‡ Tokyo University of Science.

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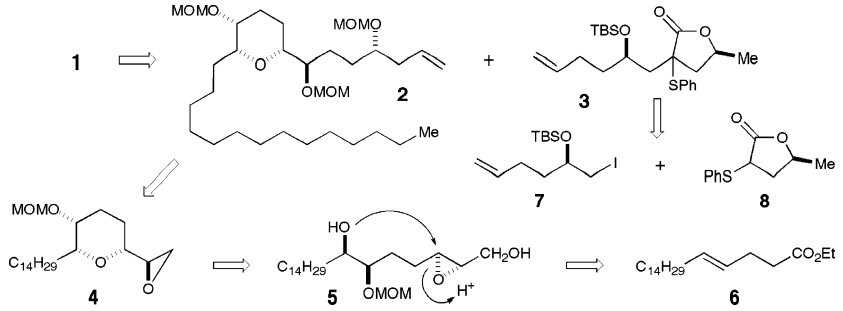
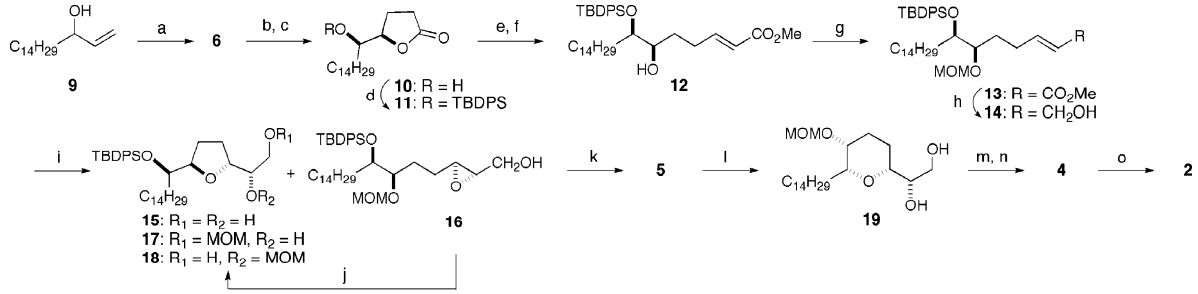
SCHEME 1. Synthetic Plan of Pyragonicin (1)



SCHEME 2. Synthesis of the Segment 2[a]



[a] Reagents and conditions: (a) $CH(OEt)_3$, propionic acid, 135−140 °C, 77%; (b) AD-mix β, $MeSO_2NH_2$, *t*-BuOH−H_2O, 0 °C; (c) 3 N KOH, methanol, 60 °C, and then *p*-TsOH, CH_2Cl_2, rt, 74% (two steps); (d) TBDPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 88%; (e) DIBAL, CH_2Cl_2, −78 °C; (f) $Ph_3P{=}CHCO_2Me$, toluene, 70 °C, 91% (two steps); (g) MOMBr, *i*-Pr_2NEt, CH_2Cl_2, rt, 90%; (h) DIBAL, toluene, −78 °C, 96%; (i) L-DET, Ti(O-*i*-Pr)$_4$, *t*-BuO_2H, MS4A, CH_2Cl_2, −23 °C, 21% for **15**, 64% for **16**; (j) CSA, CH_2Cl_2, rt, 50% for **15**, 26% for **17**, and 16% for **18**; (k) TBAF, THF, rt, 73%; (l) CSA, CH_2Cl_2, rt, 73%; (m) BzCl, pyridine, CH_2Cl_2, −20 °C to rt, and then MsCl, −20 °C to rt; (n) aq NaOH, MeOH−THF, 0 °C; 67% (two steps); (o) ref 7.

axial hydroxyl group on the THP ring.[14] The acetogenin was active in the BST assay and showed a selective inhibitory effect against PACA-2 (pancreatic cancer) cell lines.

In our first-generation synthesis of **1**,[7] the carbon backbone was constructed by Wittig reaction of formyl γ-lactone with phosphonium ylide derived from tetrahydropyran (THP) segment **2** in which the THP ring was synthesized by a SmI_2-induced reductive cyclization of β-alkoxyacrylate derivative. Our new synthetic process directed toward **1** includes an intermolecular cross-metathesis[15] of **2** and lactone **3** as illustrated in Scheme 1. According to the previous results,[7] disconnection of the pentenyl unit in **2** leads to THP derivative **4**. This would be synthesized from epoxy alcohol **5** through a 6-*exo* cyclization. The chiral oxygen functions in **5** will be installed by the Sharpless protocol.[16] Therefore, unsaturated ester **6** with the requisite carbon skeleton was selected as the starting material. On the other hand, the lactone **3** should be prepared by an alkylation of γ-lactone **8**[17] with iodide **7**.

Synthesis of **2** began from asymmetric dihydroxylation (AD-mix β, methanesulfonamide, *t*-BuOH-water) of **6** which was obtained by ortho ester Claisen rearrangement of **9**[18] (Scheme 2). The resulting dihydroxy ester was, upon hydrolysis, subjected to lactonization under acidic conditions to afford hydroxy lactone **10**[19] as a white solid (74% yield after recrystallization). The free hydroxy group was protected as the corresponding *tert*-butyldiphenylsilyl ether to give **11**. The use of other *O*-protecting groups such as tetrahydropyranyl ether and *tert*-butyldimethylsilyl ether was found to be unreliable at a later stage. Compound **11** was treated with diisobutylaluminum hydride (DIBAL) and then methyl triphenylphosphoranylideneacetate to give unsaturated ester **12** in 91% yield from **11**. Methoxymethylation of **12** led to MOM ether **13**, which was reduced with DIBAL to afford allyl alcohol **14** in good yield. The alcohol **14** was epoxidized with Ti(O-*i*-Pr)$_4$ and *t*-BuO_2H in the presence of L-diethyl tartrate to give epoxide **16** along with tetrahydrofuran **15**. The stereochemistry of the latter was confirmed by chemical transformation of **16** (vide infra). The silyl group in **16** was removed with tetrabutylammonium fluoride to provide alcohol **5**. Exposure of this to acidic conditions [D-10-camphorsulfonic acid (CSA), dichloromethane] led to a cyclic-ether formation to give THP ether **19** in 73% yield. In this case, a trace amount of THF derivative was also observed. As anticipated, attempts[20] for direct 6-*exo* cyclization from **16** into **19** gave unsatisfactory results; treatment of **16** with CSA in dichloromethane provided **15** (50%), 1-*O*-MOM derivative **17** (26%), and 2-*O*-MOM ether **18** (16%). A facile rearrangement of the MOM group seems to be due to the neighboring group participation of a 1- or 2-hydroxyl group to the intermediary cation (i) (Figure 2). Although formyl acetals[21] are sometimes

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(20) Cyclization of the corresponding 6-*O*-THP analogue with CSA in 2-methyl-2-propanol−dichloromethane resulted in a complex mixture.

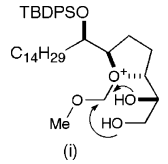
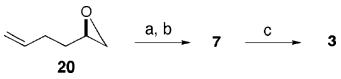


FIGURE 2. Intramolecular MOM migration.

isolated in cleaving MOM derivatives of 1,2- and 1,3-diols, this MOM migration is of interest. The application of this interesting reaction is now underway. Successive treatment of **19** with benzoyl chloride and methanesulfonyl chloride in pyridine provided mesyl benzoate, which, upon treatment with base, furnished epoxide **4** in 67% yield. This new route was quite simple and required only 13 steps for the preparation of **4** from **9** (cf. 18 steps from 2,3-*O*-isopropylidene-D-threitol in the previous route). The epoxide **4** was transformed into the terminal olefin **2** according to the literature.[7]

SCHEME 3. Preparation of γ-Lactone Segment 3[a]



[a] Reagents and conditions: (a) LiI, AcOH, aq THF, 0 °C; (b) TBSCl, imidazole, DMF, rt, 75% (two steps); (c) SHMDS, **8**, THF, −20 °C, then HMPA, −20 to +5 °C, 61%.

Compound **3** was prepared from known compounds (**8** and **20**[22]) in three steps. The epoxide **20** reacted with lithium iodide[23] in the presence of acetic acid to give iodohydrin, which was silylated to provide silyl ether **7** in 75% yield from **20** (Scheme 3). Alkylation of the lactone **8** was achieved by treatment with sodium hexamethyldisilazide in THF at −20 °C followed by addition of **7** in the presence of hexamethylphosphoric triamide (HMPA), giving segment **3** in 61% yield.

Having completed construction of both segments, we next turned to the final C−C bond formation (Scheme 4). Intermolecular cross-metathesis[24] between **2** and **3** was initially tried using Grubbs' second-generation catalyst **24**.[25] Treatment of **2** and 3.0 molar equiv of **3** with the catalyst (30 mol %) in dichloromethane at 40 °C gave coupling products in 51% yield.[26] In the ^{1}H NMR spectrum, olefinic proton signals were severely overlapped and observed at δ 5.29−5.44 (m), except for a couple of minor olefinic signals at δ 5.24 (dd, J = 15.1, 7.5 Hz) and 5.55 (dt, J = 15.1, 6.6 Hz). The major olefinic signals were expected to be due to a desired coupling product **21** while the minor pair was estimated to be derived from olefin signals of a minor component other than **21**. Being an unseparable mixture, these compounds were, without separation, employed for further spectroscopic analyses.[27] By the detailed analyses of 2D-NMR including HSQC-TOCSY, one of the allylic positions of the double bond in the minor product was revealed to be MOMoxy methine (J = 7.5 Hz), and the other was assigned to the β-position of TBDMSoxy methine, suggesting that there is an elimination of one methylene carbon (C-9)[28] and no migration of the double bond in **21**. Furthermore, the coupling products showed an ion peak at *m*/*z* 959.6028 along with the pseudo parent ion peak at *m*/*z* 973.6253 corresponding to $[M + Na]^+$ of **21** in the HRFAB-MS spectra. These results indicate that the minor product was **22** eliminated one-carbon from **21**.[29] The compound **22** seemed to result from the initital isomerization of the double bond in **2** followed by metathesis with **3** via elimination of propene. To suppress the side reaction,[30] addition of 1,4-benzoquinone[31] was attempted. The contamination, however, was not prevented, although the chemical yield was improved (64%). On the other hand, the use of Grubbs' first-generation catalyst **25**[32] gave a promising result. Thus, **2** and **3** (3.0 molar equiv) was treated with the catalyst (30 mol %) in dichloromethane at 40 °C to provide **21**[33] in 43% yield (78% yield based on the starting material **2** consumed).[34] No contamination of **22** was confirmed by the ^{1}H NMR and MS analyses. Recovered olefin **2** was again submitted to the metathesis under the same conditions, and a total 57% yield of **21** was attained. In both cases, the production of homodimers derived from **2** was traced judging by TLC analysis. The olefin **21** underwent hydrogenation[35] with diimide to give γ-lactone **23** in 94% yield. Oxidation of **23** followed by *syn*-elimination provided butenolide, in which all protecting groups were subsequently cleaved by hydrogen chloride in methanol−dichloromethane to give pyragonicin (**1**). The spectroscopic and physical properties of **1** were consistent with those of an authentic sample previously synthesized by us.[7]

In summary, we have succeeded in convergent synthesis of **1** via an olefin cross-metathesis between THP segment **2** and lactone **3**. The strategy described herein should be applicable to the preparation of other types of acetogenins.

Experimental Section

(2′*R*,3*RS*,5*S*,8′*S*,11′*R*,12′*R*,15′*R*,16′*R*)-3-[2′-(*tert*-Butyldimethylsilanyloxy)-8′,11′,15′-(trimethoxymethoxy)-12′,16′-oxidotriacont-5′-enyl]-5-methyl-3-phenylsulfanyldihydrofuran-2-one (21). To a stirred mixture of **2** (14.0 mg, 25.0 μmol) and **3** (31.6 mg, 75.0 μmol) in dichloromethane (0.8 mL) was added Grubbs' first-generation catalyst **25** (3.7 mg, 4.1 μmol), and the mixture was

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(26) The geometrical isomer ratio (E/Z = ca. 4/1) was judged by the intensities of separated signals in the ^{13}C NMR spectrum.
(27) Upon hydrogenation (*p*-$NHNH_2$, NaOAc), the coupling products gave the corresponding saturated compounds, which showed two ion peaks at *m*/*z* 961.6218 and 975.6458 in the HR−FABMS spectra, showing that the minor component was not a positioning isomer of **21** concerning the double bond.
(28) The numbering system in ref 13 was adopted.
(29) A trace amount of another isomers eliminated C-6 of **21** was also detected by 2D-NMR, but the full assignment was impossible because of the complicated signals.
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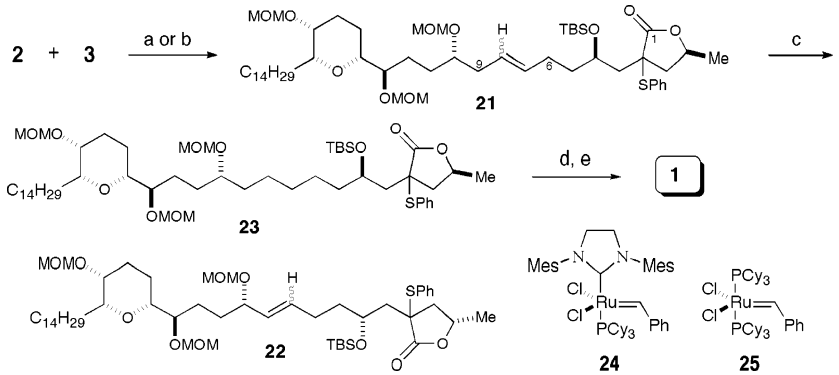
(33) The ratio (E/Z = ca. 1/1) was judged by the intensities of Me-Si signals in the ^{1}H NMR spectra.
(34) The lactone **3** was also recovered easily by silica gel chromatography (∼30% yield).
(35) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996−6000.

SCHEME 4. Olefin Cross-Metathesis and Total Synthesis of 1[a]



[a] Reagents and conditions: (a) **24**, 1,4-benzoquinone, CH_2Cl_2, 40 °C, 64% for **21** + **22**; (b) **25**, CH_2Cl_2, 40 °C, 57% for **21** (after one recycling of recovered **2**); (c) *p*-$TsNHNH_2$, NaOAc, aq DME, 85 °C, 94%; (d) *m*-CPBA, CH_2Cl_2, 0 °C, and then toluene, 105 °C; (e) 10% HCl−MeOH, CH_2Cl_2, rt, 73% (two steps).

stirred at 40 °C for 4 h. More catalyst **25** (3.5 mg, 3.9 μmol) was added, and the mixture was stirred at 40 °C for 3 h and rt for 17 h. Florisil was added with stirring, and the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated to give a syrup, which was purified by preparative TLC (*n*-hexane−ethyl acetate = 4:1, 5 developments) to give **21** (10.2 mg) as a colorless syrup. Recovered starting material **2** (6.3 mg) again reacted with **3** (14.2 mg) in the presence of **25** (3.2 mg) in dichloromethane (0.6 mL) at 40 °C for 10 h and was treated as described above to give **21** (3.4 mg). A total of 13.6 mg (57%) of **21** was obtained.

21 (*E*/*Z* = ca. 1/1): IR (neat) 2924, 2853, 1769, 1471, 1182, 1147, 1097, 1032, 916, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers at C(3)) δ 0.02, 0.03, 0.04 (1.36H, each s), 0.11, 0.12, 0.15, 0.16 (4.64H, each s), 0.86−0.90 (12H, m), 1.21−2.44 (50.23H, m), 3.02 (0.77H, m), 3.29−3.59 (5H, m), 3.36, 3.37, 3.38 (9H, each s), 3.87 (0.23H, m), 4.29 (0.77H, m), 4.52 (0.77H, m), 4.59−4.82 (6.23H, m), 5.37−5.44 (2H, m), 7.29−7.41 (3H, m), 7.54−7.56 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers at C(3)) δ −4.2, −3.9, −3.8, 14.1, 18.0, 20.4, 21.3, 22.0, 22.4, 22.7, 25.7, 25.9, 26.4, 26.6, 27.5, 27.8, 29.3, 26.6, 29.7, 29.8, 30.0, 31.9, 32.3, 37.6, 38.1, 39.5, 41.2, 41.6, 42.5, 54.9, 55.3, 55.5, 55.7, 69.0, 69.1, 69.8, 71.0, 73.3, 73.6, 79.9, 80.0, 80.8, 95.1, 95.3, 97.1, 125.9, 126.3, 126.5, 128.9, 129.0, 129.5, 129.7, 130.0, 130.3, 130.8, 132.1, 132.4, 136.7, 137.0, 175.0, 177.4; HRMS calcd for $C_{53}H_{94}O_{10}SSiNa$ $[M + Na]^+$ 973.6235, found 973.6217.

(2′*R*,3*RS*,5*S*,8′*S*,11′*R*,12′*R*,15′*R*,16′*R*)-3-[2′-(*tert*-Butyldimethylsilanyloxy)-8′,11′,15′-(trimethoxymethoxy)-12′,16′-oxidotriacontanyl]-5-methyl-3-phenylsulfanyldihydrofuran-2-one (23). To a stirred mixture of **21** (18.5 mg, 19.4 μmol) and tosylhydrazine (241 mg, 1.29 mmol) in 1,2-dimethoxyethane (2.9 mL) was added dropwise a solution of sodium acetate (131 mg, 1.59 mmol) in water (2.4 mL) at 85 °C over 2 h. After 1 h, the reaction mixture was cooled to rt and then extracted with ethyl acetate. The extracts were washed with water and brine, dried, and concentrated. Chromatography on silica gel with *n*-hexane−ethyl acetate (1:0 → 10:1 → 4:1) as the eluent gave **23** (17.4 mg, 94%) as a colorless syrup: IR (neat) 2924, 2853, 1768, 1471, 1183, 1147, 1098, 1032, 916, 853 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2, mixture of diastereomers at C(3)) δ 0.03, 0.05 (1.2H, each s), 0.12, 0.16 (4.8 H, each s), 0.87−0.90 (12H, m), 1.21−2.09 (46.8H, m), 2.31−2.42 (0.4H, m), 3.02 (0.8H, dd, *J* = 14.2, 7.8 Hz), 3.26−3.53 (5H, m), 3.34, 3.35, 3.36 (9H, each s), 3.87 (0.2 H, m), 4.26 (0.8H, m), 4.52 (0.8H, m), 4.59−4.73 (6.2H, m), 7.35−7.43 (3H, m), 7.53−7.56 (2H, m); ^{13}C NMR (100 MHz, CD_2Cl_2, mixture of diastereomers at C(3)) δ −4.7, −3.8, −3.7, 14.2, 18.2, 20.5, 21.5, 22.2, 23.1, 24.8, 25.7, 26.1, 26.6, 28.1, 29.7, 30.0, 30.1, 30.3, 30.4, 32.3, 34.6, 38.3, 38.8, 39.9, 41.6, 42.1, 42.7, 55.6, 55.7, 55.8, 69.8, 70.5, 71.6, 73.7, 74.1, 77.8, 80.2, 80.3, 95.6, 95.7, 97.2, 129.3, 129.9, 130.2, 131.0, 137.0, 137.4, 175.1, 177.5; HRMS calcd for $C_{53}H_{96}O_{10}SSiNa$ $[M + Na]^+$ 975.6391, found 975.6403.

(2′*R*,5*S*,8′*S*,11′*R*,12′*R*,15′*R*,16′*R*)-3-(2′,8′,11′,15′-Tetrahydroxy-12′,16′-oxidotriacontanyl)-5-methyl-5*H*-furan-2-one (Pyragonicin, 1). To a stirred solution of **23** (17.4 mg, 18.2 mmol) in dichloromethane (0.5 mL) was added *m*-CPBA (70−75% assay; 4.5 mg) at 0 °C. After 1 h, aqueous saturated $NaHCO_3/Na_2S_2O_3$ (1:1) was added, and the resulting mixture was extracted with ether. The extracts were washed with aqueous saturated $Na_2S_2O_3$, water, and brine, dried, and concentrated. The residue was dissolved in toluene (1.0 mL). The solution was heated at 100−105 °C for 1 h with stirring and concentrated. The residue was passed through a short column of silica gel {*n*-hexane−ethyl acetate (10:1 → 2:1)} to give butenolide (14.1 mg, 90%). To a stirred solution of the butenolide (10.8 mg, 0.01 μmol) in dichloromethane (0.5 mL) was added a 10% HCl solution in methanol (0.3 mL) at 0 °C, and the mixture was stirred at rt for 13 h. After addition of $NaHCO_3$, the resulting mixture was concentrated, diluted with water, and then extracted with ethyl acetate. The extracts were washed with water and brine, dried, and then concentrated. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate = 2:1 → 0:1 → $CHCl_3$/methanol = 10:1) to give a syrup (7.3 mg), which was treated with *n*-hexane−ether to afford **1** (6.2 mg, 81%) as a white powder; $[\alpha]^{21}_D = +12.6$ (*c* 0.11, $CHCl_3$) {lit.[13] $[\alpha]^{23}_D = -25.6$ (*c* 0.008, $CHCl_3$), lit.[7] $[\alpha]^{24}_D = +13.8$ (*c* 0.11, $CHCl_3$), lit.[14] $[\alpha]^{23}_D = +10.3$ (*c* 0.13, $CHCl_3$)}; IR (neat) 3500, 2917, 2851, 1736, 1462, 1082, 1047, 1026, 991 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.8 Hz), 1.21−1.76 (43H, m), 1.43 (3H, d, *J* = 6.8 Hz), 2.00 (1H, brd, *J* = 11 Hz), 2.40 (1H, brdd, *J* = 15.1, 7.3 Hz), 2.52 (1H, brd, *J* = 15.1 Hz), 3.24 (1H, ddd, *J* = 10.2, 7.8, 2.4 Hz), 3.35 (1H, brdd, *J* = 7.8, 6.3 Hz), 3.50 (1H, m), 3.59−3.66 (2H, brs), 3.85 (1H, m), 5.05 (1H, qd, *J* = 6.8, 1.0 Hz), 7.18 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.1, 21.5, 22.7, 25.5, 25.6, 28.4, 29.3, 29.4, 29.6, 29.7, 30.5, 31.6, 31.9, 33.3, 37.2, 66.0, 69.9, 71.5, 74.3, 78.0, 80.1, 81.0, 131.1, 151.9, 174.7; HRMS calcd for $C_{35}H_{65}O_7$ $[M + H]^+$ 597.4730, found 597.4752.

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Supporting Information Available: Experimental procedures and NMR spectra of **1**, **3**, **7**, **11**−**19**, and **21**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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