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Yamaguchi-Type Lactonization as a Key Step in the Synthesis of Marine Metabolites: (+)-Luffalactone

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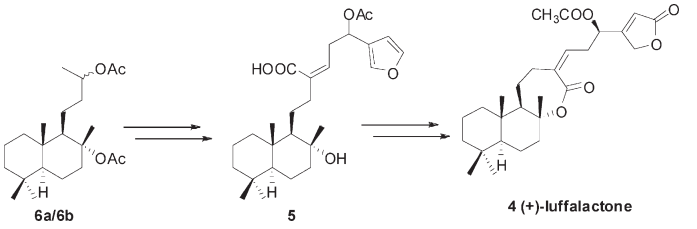

A Yamaguchi-type cyclization of **5** and subsequent photochemical oxidation of the furanic ring are the key steps in the first synthesis of the marine metabolite (+)-luffalactone **4** and its epimer at C-16, 16-*epi*-luffalactone, **27**. With this work, we have successfully established the absolute configuration of the natural product. The key intermediate **5** was obtained from the easily accessible diacetate **6a/6b**.

Introduction

Natural products continue to play a highly significant role in drug discovery, and a great number of marine bioactive metabolites with promising therapeutic properties have been identified.[1] To remain competitive with other drug discovery methods, natural product research needs to constantly improve the speed of screening, isolation, and structure elucidation processes.[2]

Drug discovery from marine natural products has enjoyed a renaissance in the past few years.[3] As selected examples, ziconotide (for the treatment of pain) and yondelis (for the treatment of sarcoma of soft tissue and other different types of sarcomas) can be highlighted.

Among many other structures, marine organisms produce a wide array of terpenoid skeletons, distinguished by characteristic structural features. Especially striking is the frequent occurrence of sesterterpenes in sponges, and one of the prime sources of these is C_{25} terpenoids compounds.[4]

These new metabolites can be classified as anti-inflammatory, antitumor, antibiotic, or antifouling.[5] Among anti-inflammatory compounds three types of sesterterpenes can be highlighted: manoalide **1**, scalaradial **2**, and cacospongionolide **3** type compounds[6] (Figure 1).

The western Pacific sponge *Luffariella variabilis* is the major source of manoalide. Its isolation and structural elucidation was reported by de Silva and Scheuer.[7] Manoalide acts as a potent anti-inflammatory agent as it irreversibly inhibits the enzyme phospholipase A_2.[8]

In order to provide large quantities of manoalide, Faulkner et al. collected over four hundred *L. variabilis* from three different locations in Palau. As a result of this work, they described[9] luffalactone **4** (Figure 1), a new tetracyclic sesterterpene acetate that coexisted with manoalide in some of the specimens. Luffalactone presented a γ-butenolide ring

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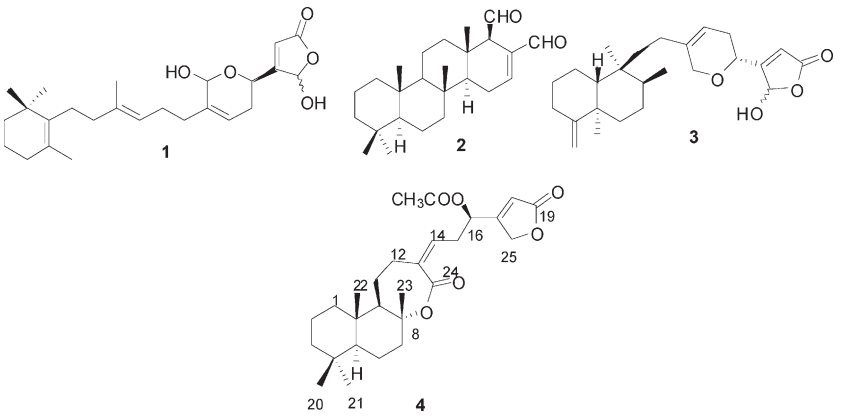


FIGURE 1. Several anti-inflammatory compounds isolated from marine sponges.

instead of the γ-hydroxybutenolide ring, characteristic of *Luffariella* metabolites, and showed anti-inflammatory activity.

The absolute configuration at C-16 was not established for compound **4** at that time.

Considering our experience in the synthesis of a wide variety of enantiopure bioactive terpene butenolides starting from natural building blocks, such as sclareol,[10] *ent*-halimic acid,[11] and zamoranic acid,[12] we decided to attempt the first synthesis of luffalactone, which we present herein.

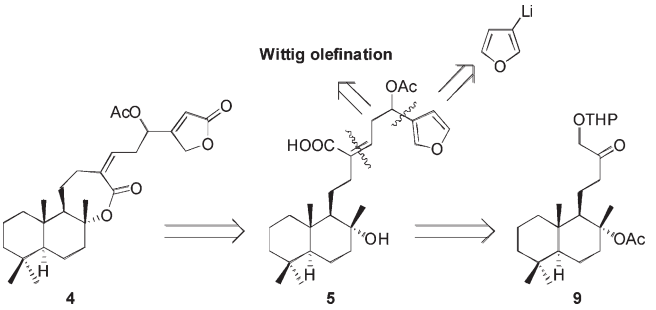
Results and Discussion

In order to obtain luffalactone we designed the following retrosynthetic scheme (Scheme 1), which shows compound **5** as the key intermediate of the synthesis. A Yamaguchi-type lactonization will afford the lactone ring (24−8), and then transformation of the furanic moiety into the required γ-butenolide will lead to the targeted molecule, **4**.

Intermediate **5** can be synthesized from **9** (Scheme 1) by a Wittig-type olefination reaction with an appropriate phosphonium ylide followed by addition of 3-furyllithium to give the desired intermediate **5**.

To synthesize **9**, we used the diacetyl derivate **6a/6b** as starting material, which is easily obtained from sclareol.[13]

SCHEME 1. Retrosynthetic Analysis of Luffalactone 4



Scheme 2 shows the reaction sequence performed to reach intermediate **9**.

Chemoselective hydrolysis of **6a/6b** and further oxidation of the secondary alcohol in C-13 using Ley's reagent[14] gave methyl ketone **7**. Transformation of **7** with LDA in presence of TMSCl[15] and then oxidation of the obtained silyl enol ether with OsO_4[16] gave the α-hydroxy ketone **8** with 95% yield in two steps. Protection of the primary alcohol with dihydropirane yielded **9** quantitatively.

With **9** in our hands, a three-carbon side chain was added through a Wittig reaction[17] with (2-carboxyethyl)triphenylphosphonium bromide. Subsequent esterification of the resulting acid with MeI[18] gave **10**. Several conditions were tested for these reactions, obtaining the best yield of **10** when a mixture of THF/DMSO was used as solvent. Only one stereoisomer of the olefin was observed. We conclude that the double bond had *Z* stereochemistry as obvious coupling between H-15 and H-24 was observed in ROESY NMR.

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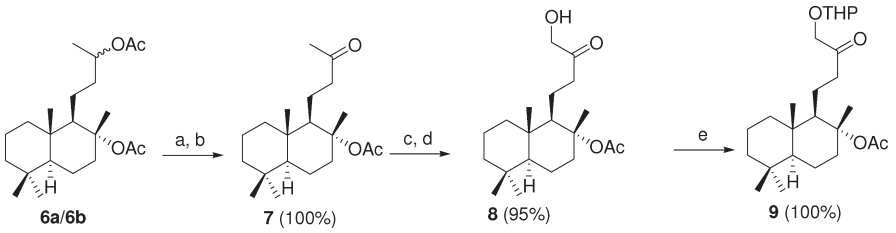
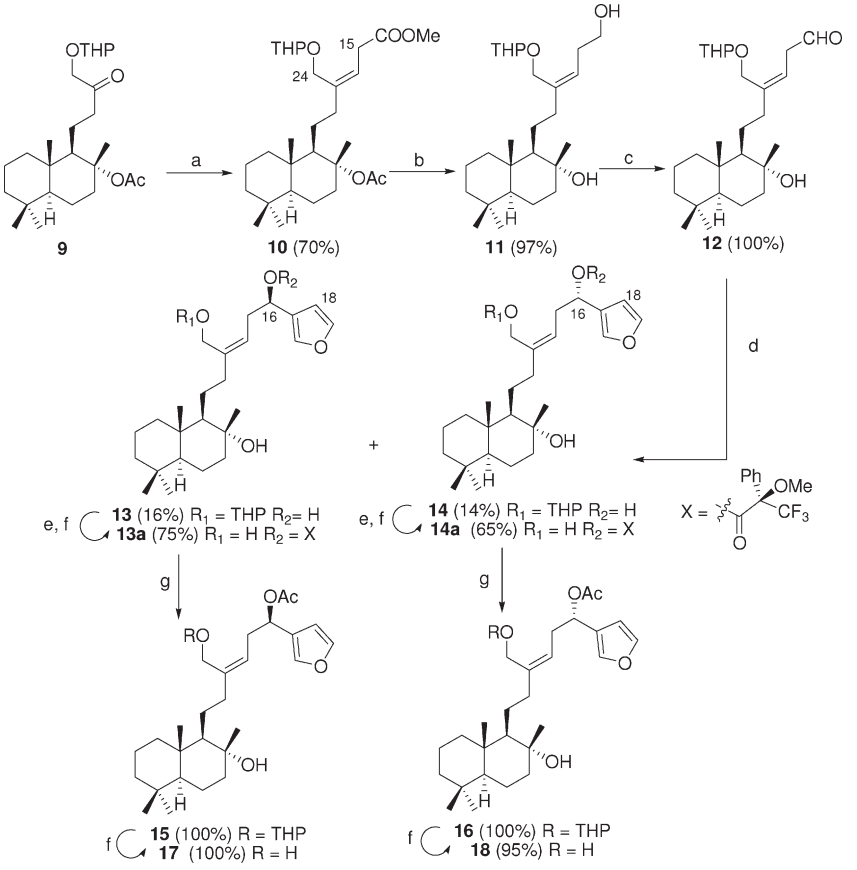
SCHEME 2. Synthesis of Intermediate 9[a]



[a]Reagents and conditions: (a) K_2CO_3/MeOH 3%, 6 h; (b) TPAP, NMO, DCM, 6 h; (c) LDA, TMSCl, THF, −78 °C, 3 h; (d) OsO_4, NMO, *t*BuOH/THF/H_2O, 24 h; (e) DHP, *p*TsOH, benzene, 30 min.

SCHEME 3. Synthesis of 17 and 18[a]



[a]Reagents and conditions: (a) (2-carboxyethyl)triphenylphosphonium bromide, *n*-BuLi, THF/DMSO; −5 °C, then MeI; (b) LAH, Et_2O, 0 °C; (c) Dess−Martin periodinane, DCM; (d) 3-bromofuran, *n*-BuLi, Et_2O, −78 °C; (e) (+)-MTPA, DMAP, DCC, DCM; (f) cat. *p*TsOH/MeOH; (g) Ac_2O, pyr.

Reduction of **10** with LAH and subsequent oxidation of the primary alcohol **11** with Dess−Martin periodinane[19] yielded aldehyde **12**. Addition of 3-furyllithium[20] to **12** gives a mixture 1:1 of diastereoisomers **13** and **14**, which were separated by column chromatography. The low yield of this reaction is due to the instability of the aldehyde, which, in spite of being purely isolated, rapidly decomposes.

To determine the absolute configuration at C-16 of furane derivates **13** and **14**, modified Mosher's method[21] was used. Alcohols **13** and **14** were treated with (+)-MTPA to obtain the corresponding esters. However, due to the presence of the THP group, NMR studies of the esters were too complicated to accurately determine the stereochemistry of C-16. To avoid this problem, we carried out the hydrolysis of the

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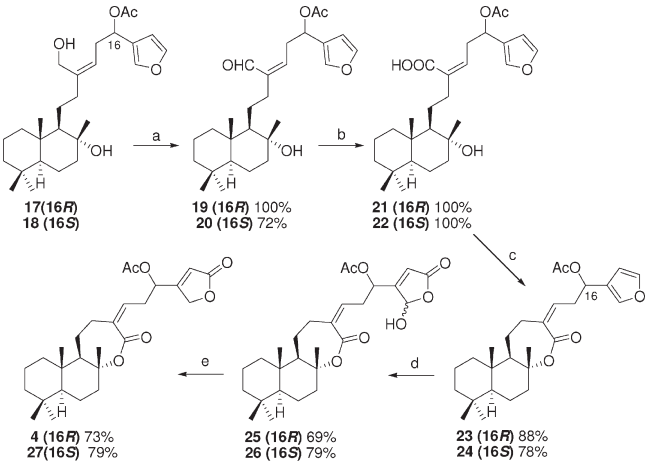
SCHEME 4. Synthesis of Luffalactone and 16-Epiluffalactone[a]



[a]Reagents and conditions: (a) Dess−Martin periodinane, DCM; (b) $NaClO_2$ 5%, *t*BuOH, NaH_2PO_4, 2-methyl-2-butene; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene; then DMAP; (d) O_2, Rose Bengal, *hv*, DCM; (e) $NaBH_4$, EtOH.

THP group under mild acidic conditions (catalytic *p*-TsOH/MeOH). At that point, with compounds **13a** and **14a** in our hands, we were able to perform the required NMR studies. Comparison between NMR spectra of each parent compound and its derivative, especially the δ of H-18 (6.40 and 6.44 ppm for **13** and **13a**, respectively, and 6.40 and 6.30 ppm for **14** and **14a**, respectively) confirmed the (*R*)-configuration for **13** at C-16 and the (*S*)-configuration for **14** at the same position (Scheme 3).

Acetylation of **13** led to **15** and, in the same way, **16** was obtained from **14**. Hydrolysis of **15** and **16** yielded the enantiopure compounds **17** and **18**, respectively. Both **17** and **18** are the key intermediates for the synthesis of luffalactone and its epimeric analogue.

The synthesis of **4** was carried out separately as it is shown in Scheme 4. The key step to reach luffalactone and 16-*epi*-luffalactone from **17** and **18** is a Yamaguchi-type macrolactonization[22] of the acids **21** and **22**.

Oxidation of **17** and **18** to the corresponding acids required two steps (Scheme 4). First, oxidation of the alcohols gave the α,β-unsaturated aldehydes **19** and **20** using Dess−Martin periodinane as oxidant, and second, further oxidation gave the acids with $NaClO_2$.[23] To accomplish the lactonization between the acid group and the tertiary alcohol of **21** and **22**, they were treated first with 2,4,6-trichlorobenzoyl chloride and Et_3N in toluene, and then with DMAP,[24] obtaining the lactones **23** and **24** with 88% and 78% yield, respectively.

Conversion of the furanic ring into the γ-hydroxybutenolide was carried out following Faulkner's methodology.[25] Photochemical oxidation of **23** and **24** with $^1O_2$ in the presence of Rose Bengal irradiating with a 200 W lamp for 5 h gave the hydroxybutenolides **25** (69%) and **26** (79%). Reduction with $NaBH_4$[26] transformed the γ-hydroxybutenolide ring into the required γ-butenolide present in **4** and **27**.

The spectroscopic characteristics of **4**, as well as its optical rotation $[\alpha]_D^{22} = +18.2$ ($c = 0.27$ C_6H_6), are identical to those corresponding to the natural product described by Faulkner as (+)-luffalactone $[\alpha]_D^{22} = +18.8$ ($c = 0.48$ C_6H_6).

It can be concluded that the stereochemistry of (+)-luffalactone at C-16 is *R*. The absolute stereochemistry of this natural product has been established as (5*S*,8*R*,9*R*,10*S*,16*R*).

Conclusions

Enantioselective synthesis of (+)-luffalactone has been accomplished, and its absolute stereochemistry is now established. Since (+)-luffalactone, 16-*epi*-luffalactone, and the γ-hydroxybutenolides **25** and **26** have promising structures to act as inhibitors of phospholipase A_2 they will be subjected to activity tests, which will be published in due course.

Experimental Section

Methyl 8α-Acetoxy-24-(2-tetrahydropiranyloxy)-17,18,19,25-tetranor-8,14-*seco*-luffol-13(*Z*)-en-16-oate (10). To a solution of (2-carboxyethyl)triphenylphosphonium bromide (1.06 g, 2.56 mmol) in 12 mL of a mixture of THF/DMSO 4:1 cooled at −5 °C was added *n*-BuLi dropwise 1.6 M in hexane (3.2 mL, 5.12 mmol). After the mixture was stirred for 10 min, **9** (270 mg, 0.64 mmol) was added as a solution in 12 mL of THF/DMSO 4:1 via cannula. The reaction was vigorously stirred at −5 °C for 2 h, with progress controlled by TLC. Then, 1.0 mL of MeI was added (17 mmol), and the resulting mixture was stirred at rt overnight. After addition of 20 mL of water, the mixture was extracted with EtAcO and the organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The crude obtained after removal of the solvent was purified by column chromatography eluting with hexane/EtAcO 8:2 to yield 216 mg of **10** (0.45 mmol, 70%): $[\alpha]_D^{22} = -8.2$ ($c = 0.56$ $CHCl_3$); IR (film) 2944, 2872, 1728, 1388, 1251 1126, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.56 (1H, t, $J = 7.1$ Hz), 4.57 (1H, t, $J = 3.3$ Hz), 4.18 (1H, dd, $J = 11.9$, 1.8 Hz), 4.03 (1H, dd, $J = 11.9$, 1.8 Hz), 3.88−3.83 (1H, m), 3.68 (3H, s), 3.52−3.49 (1H, m), 3.18 (2H, d, $J = 7.1$ Hz), 2.63 (1H, dd, $J = 1.6$, 12.3 Hz), 2.26−2.12 (1H, m), 1.93 (3H, s), 1.80−1.70 (1H, m), 1.70−1.65 (2H, m), 1.65−1.63 (1H, m), 1.62−1.56 (1H, m), 1.55−1.45 (6H, m), 1.52−1.48 (2H, m), 1.47 (3H, s), 1.45−1.40 (2H, m), 1.42−1.39 (1H, m), 1.25−1.15 (1H, m), 1.15−1.10 (1H, m), 1.05−0.95 (1H, m), 1.00−0.90 (1H, m), 0.86 (3H, s), 0.84 (3H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 172.8, 170.5/170.4, 140.6, 120.3, 97.8, 88.2, 64.5/64.6, 62.3/62.4, 59.0, 55.9, 52.0, 42.1 (×2), 39.7, 39.0, 38.9, 33.6, 33.3 (×2), 30.8, 25.7, 25.2, 23.2, 21.7, 20.7, 20.2, 19.7, 18.5, 15.9; HRMS [M + Na] 515.3323, calcd for $C_{29}H_{48}O_6Na$ 515.3343.

16(*R*)-Acetoxy-19,25-epoxy-8,14-*seco*-luffola-13(*Z*),17(25),18-triene-8α,24-diol (17). To a solution of **15** (18 mg, 0.036 mmol) in 3.5 mL of MeOH was added *p*-TsOH (2 mg, 0.01 mmol). After being stirred at rt for 4 h, the mixture was diluted with water (5 mL) and extracted with EtAcO. The extracts were washed with water and brine and dried over anhydrous Na_2SO_4. After solvent removal, **17** was quantitatively obtained: $[\alpha]_D^{22} = +2.2$ ($c = 0.14$

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$CHCl_3$); IR (film) 3401, 2925, 2853, 1738, 1236, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.44 (1H, s), 7.38 (1H, t, J = 1.9 Hz), 6.41 (1H, d, J = 1.9 Hz), 5.83 (1H, t, J = 6.8 Hz), 5.25 (1H, t, J = 7.5 Hz), 4.20 (1H, d, J = 12.2 Hz), 4.04 (1H, d, J = 12.2 Hz), 2.64 (1H, ddd, J = 6.8, 7.5, 14.2 Hz), 2.23 (1H, ddd, J = 6.8, 7.5, 14.2 Hz), 2.30−2.20 (2H, m), 2.06 (3H, s), 1.90−1.85 (2H, m) 1.80−1.70 (1H, m), 1.70−1.65 (2H, m), 1.65−1.63 (1H, m), 1.52−1.48 (2H, m), 1.45−1.40 (1H, m), 1.42−1.39 (1H, m), 1.22−1.14 (1H, m), 1.13 (3H, s), 1.05−1.00 (1H, m), 1.00−0.90 (1H, m), 0.95−0.90 (1H, m), 0.86 (3H, s), 0.79 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 170.3, 143.2, 142.5, 140.3, 127.5, 123.3, 108.9, 74.5, 68.6, 60.7, 60.0, 56.1, 44.2, 41.9, 39.9, 39.4, 39.0, 33.3, 33.2, 29.6, 24.1, 23.9, 21.5, 21.2, 20.5, 18.4, 15.4; HRMS [M + Na] 469.2929, calcd for $C_{27}H_{42}O_5Na$ 469.2924.

16(*R*)-Acetoxy-19,25-epoxy-8,14-*seco*-luffola-13(*Z*),17(25),18-trien-24,8α-olide (23). Compound **21** (17 mg, 0.036 mmol) was dissolved in 1 mL of dry toluene under Ar and cooled at 0 °C. Then, 0.61 mL of a solution of Et_3N in toluene (100 μL in 10 mL, 0.043 mmol) and 0.62 mL of a solution of 2,4,6-trichlorobenoyl chloride in toluene (100 μL in 10 mL, 0.040 mmol) were added. The reaction was stirred at rt overnight. After that, 0.88 mL of a solution of DMAP in toluene (50 mg in 5 mL, 0.072 mmol) was added, and the whitish mixture was stirred at rt for 2 h more. After evaporation of the solvent, the obtained crude was purified by column chromatography eluting with hexane/EtAcO 8:2 and 7:3 to yield 14 mg of **23** (0.032 mmol, 88%): $[\alpha]_D^{22}$ = +19.1 (c = 0.45 $CHCl_3$; IR (film) 2930, 2867, 1740, 1708, 1237, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.47 (1H, br s), 7.37 (1H, t, J = 1.6 Hz), 6.41 (1H, dd, J = 1.6, 0.7 Hz), 5.87 (1H, dd, J = 6.1, 7.4 Hz), 5.71 (1H, t, J = 6.8 Hz), 2.90−2.82 (1H, m), 2.41 (1H, ddd, J = 2.1, 5.4, 13.7 Hz), 2.06 (3H, s), 2.10−2.05 (1H, m), 2.02−1.98 (1H, m), 1.90−1.85 (2H, m), 1.80−1.70 (1H, m), 1.65−1.60 (1H, m), 1.65−1.63 (1H, m), 1.60−1.50 (2H, m), 1.52−1.48 (2H, m), 1.45−1.40 (1H, m), 1.42−1.39 (1H, m), 1.39 (3H, s), 1.22−1.10 (1H, m), 1.00−0.90 (1H, m), 0.95−0.90 (1H, m), 0.89 (3H, s), 0.80 (3H, s), 0.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 170.3 (×2), 143.3, 140.6, 138.0, 133.2, 124.2, 108.9, 86.9, 67.8, 58.0, 55.4, 43.3, 41.4, 39.9, 38.6, 34.6 (×2), 33.5, 33.3, 25.5, 22.3, 21.7, 21.2, 19.5, 18.7, 15.2; HRMS [M + Na] 465.2597, calcd for $C_{27}H_{38}O_5Na$ 465.2611.

16(*R*)-Acetoxy-8,14-*seco*-luffola-13(*Z*),17-dien-24,8α-19,25-diolide (4, Luffalactone). To a solution of **25** (6.4 mg, 0.015 mmol) in 1 mL of EtOH cooled at 0 °C was added $NaBH_4$ (1.5 mg, 0.04 mmol). The reaction was stirred at this temperature for 5 min and diluted with 2 mL of water and titrated with HCl 2 M. The resulting mixture was extracted with EtAcO, and the combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The obtained crude after removal of the solvent was purified by column chromatography eluting with hexane/EtAcO 7:3 to yield 5 mg of **4** (0.011 mmol, 73%): $[\alpha]_D^{22}$ = +19.2 (c = 0.27 $CHCl_3$); IR (film) 2927, 2852, 1782, 1752, 1703, 1229, 1042 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, δ ppm) 5.64 (1H, dd, J = 2.0, 3.4 Hz), 5.45 (1H, t, J = 5.6 Hz), 5.30 (1H, t, J = 7.1 Hz), 4.15 (1H, ddd, J = 0.9, 2.0, 17.6 Hz), 4.06 (1H, ddd, J = 0.5, 2.0, 17.6 Hz), 2.72−2.65 (1H, m), 2.40−2.30 (1H, m), 1.99 (1H, ddd, J = 3.2, 5.5, 13.1 Hz), 1.86 (1H, dt, J = 3.1, 13.0 Hz), 1.84 (1H, br t, J = 13.1 Hz), 1.76 (1H, dd, J = 4.7, 13.0 Hz), 1.60 (3H, s), 1.55−1.52 (1H, m), 1.40−1.35 (1H, m), 1.34−1.32 (2H, m), 1.32−1.30 (2H, m), 1.22−1.18 (1H, m), 1.20−1.15 (1H, m), 1.13 (3H, s), 1.01 (1H, ddd, J = 3.7, 12.9, 13.2 Hz), 0.80−0.75 (1H, m), 0.78 (3H, s), 0.69 (3H, s), 0.56 (1H, dd, J = 4.4, 13.6 Hz), 0.55−0.50 (1H, m), 0.50 (3H, s); ^{13}C NMR (100 MHz, C_6D_6, δ ppm) 172.1, 168.7, 168.5, 165.9, 139.9, 130.6, 116.5, 85.5, 69.9, 69.0, 57.7, 54.9, 43.3, 41.3, 39.5, 38.2, 34.3, 33.2 (×2), 32.9, 25.3, 22.1, 21.5, 19.9, 19.3, 18.7, 14.9; HRMS [M + Na] 481.2554, calcd for $C_{27}H_{38}O_6Na$ 481.2561.

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Supporting Information Available: Full experimental section and copies of IR, NMR, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.