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Synthesis of the Scalarane Sesterterpenoid 16-deacetoxy-12-*epi*-scalarafuranacetate

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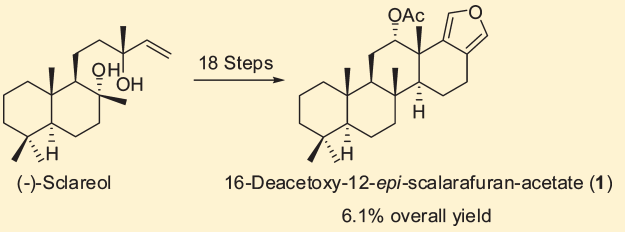
Supporting Information

ABSTRACT: The marine natural product 16-deacetoxy-12-*epi*-scalarafuranacetate, isolated from *Spongua officinalis*, was synthesized in 18 linear steps, starting from (−)-sclareol, with high stereoselectivity and an overall yield of 6.1%. The intermediate 16-deacetoxy-12-*epi*-scalarafuran could be easily transformed into a series of natural scalarane sesterterpenoids in a few steps.

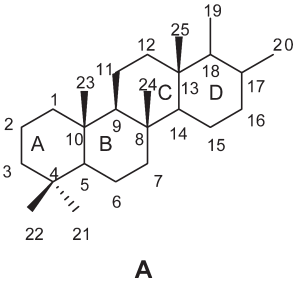


With the development of modern separation and purification techniques, more and more scalarane sesterterpenoids have been isolated from various marine organisms, especially sponges.[1−6] Most of them share the same scalarane skeleton **A** (Figure 1). The main structural variations of these kinds of natural products are the oxygenated functional groups on C-12 and C-16 as well as C-19 and C-20, which are usually functional groups, such as aldehyde, γ-butenolide, lactam, and a furan ring. Nearly all scalarane sesterterpenoids exhibit diverse and promising biological activities, such as antimicrobial,[7] anti-inflammatory,[8] cytotoxic,[9−11] and antifeedant properties.[12]

Despite their potential biological activities, few or only simple scalarane sesterterpenoids have been synthesized. The main synthetic difficulty lies in their challenging structures, especially the oxygenated functional group at the C-12 position that is a prerequisite for the biological activity of the most of investigated scalaranes.[13−18] The natural product that is the focus of this paper, 16-deacetoxy-12-*epi*-scalarafuranacetate (**1**), was first isolated from *Spongua officinalis* in 1989 (Figure 2). A biological activity study showed that it had definite cytotoxicity (LD50 = 180 μg/mL).[19] Up until now, there has been no report on the synthesis of this natural product. In this paper, we propose a strategy for the synthesis of the natural product **1** aiming to solve the difficulties in the construction of the correct chiral center at C-12 and ABCD tetracyclic framework of the C-12 oxygenated scalarane sesterterpenoids.

The synthesis of **1** was performed using (−)-sclareol as an AB-ring synthon, which was incorporated into the tetracyclic framework following an AB → ABC → ABCD ring annulation strategy, with electrophilic cyclization and an intramolecular Diels−Alder reaction as key synthetic steps.

As shown in Scheme 1, following our previously reported synthetic reference, methyl *ent*-isocopalate was obtained in four steps with an overall yield of 61% starting from commercially available (−)-sclareol.[20]



A

Figure 1. Common scalarane skeleton.

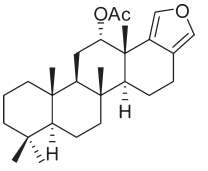


Figure 2. Natural product of 16-deacetoxy-12-*epi*-scalarafuranacetate.

First of all, a chiral hydroxyl group needs to be installed at C-12. This was achieved by *m*-CPBA-promoted stereoselective epoxidation on the double bond followed by ring opening to form compound **4** in 77% yield over two steps (Scheme 2).[21] In the epoxidation, the steric influence of the ester group caused the oxygen to be introduced from the bottom side of the ring. In the presence of sodium methoxide, **4** was obtained with the correct stereochemistry on C-12.

The next reaction sequence was to assemble the D ring by an intramolecular Diels−Alder reaction. Therefore, after the hydroxyl group in compound **4** was protected as the silyl ether, the ester was converted into aldehyde **7** through reduction and activated

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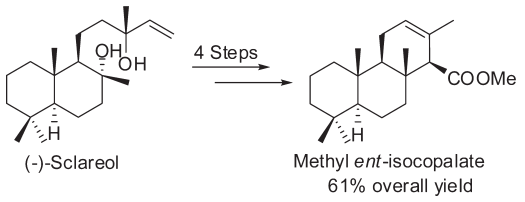
MnO_2 oxidation. By surveying a range of conditions, we found that treatment of compound **7** under Wittig conditions (*n*-BuLi and methyltriphenylphosphonium iodide at 0 °C) led to the formation of conjugated diene **8**.[22] In order to perform the desired intramolecular Diels–Alder reaction, an alkyne was needed. Therefore, the protecting group on compound **8** was removed and the hydroxyl group was alkylated with 3-bromopropyne under the optimized conditions (sodium hydroxide and TBAI) to provide compound **10** in 55% yield.[23,24] An ester group was then introduced at the terminal position of the alkyne using ethyl chloroformate with *n*-BuLi at −78 °C to give compound **11**. The key intramolecular Diels–Alder cyclization successfully constructed the D ring with good stereoselectivity and 96% yield.[25] The identity of compound **12** was confirmed by a single-crystal X-ray diffraction structure analysis (see the Supporting Information).

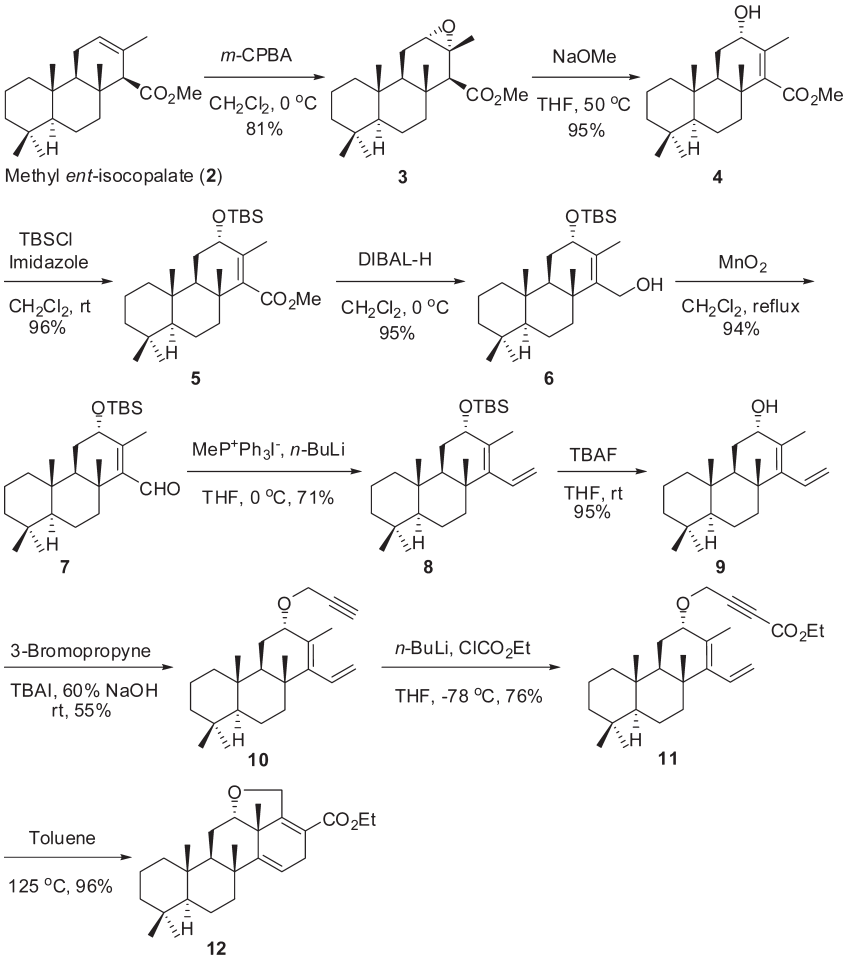
Scheme 1. Synthesis of the Intermediate Methyl *ent*-Isocopalate



As shown in Scheme 3, the tetrahydrofuran ring in compound **12** was opened cleanly by treatment with Ac_2O and zinc iodide, accompanied by spontaneous lactonization to give compound **13**.[15] In the next step, the C-12 ester and the lactone in compound **13** were reduced by DIBAL-H. Upon quenching, different acidic conditions were investigated.[24] It was found that strong acids, such as 5% HCl and TsOH, led to complicated mixtures. In the presence of silica gel as a weak acid, the desired product **14** could be obtained in 70% yield with the endocyclic 14,15-double bond remaining intact. This double bond could not be hydrogenated under the classic Pd/C conditions, which may be due to its steric hindrance. After several trials, we found that *p*-toluenesulfonyl hydrazide and sodium acetate could reduce the double bond to give **15**. The targeted compound, 16-deacetoxy-12-*epi*-scalarafuranacetate **1**, was finally obtained by acetylation of **15**. Comparisons of specific optical rotation ($[\alpha]^{28}_D$ = +65 (*c* 0.5, $CHCl_3$) vs lit.[8] $[\alpha]^{25}_D$ = +68 (*c* 0.5, $CHCl_3$)), ^1H NMR, ^{13}C NMR, and HMRS data of our synthetic **1** established the structural identity with the natural scalarane sesterterpenoid 16-deacetoxy-12-*epi*-scalarafuranacetate.[19]

In summary, we have finished the total synthesis of the scalarane sesterterpenoid marine natural product 16-deacetoxy-12-*epi*-scalarafuranacetate in 18 linear steps with high stereoselectivity and an overall yield of 6.1% starting from (−)-sclareol. This synthetic route has two key features. One is the construction of the requisite chiral center on C-12. The other is the building of

Scheme 2. Building a Chiral Center on C-12 and D Ring



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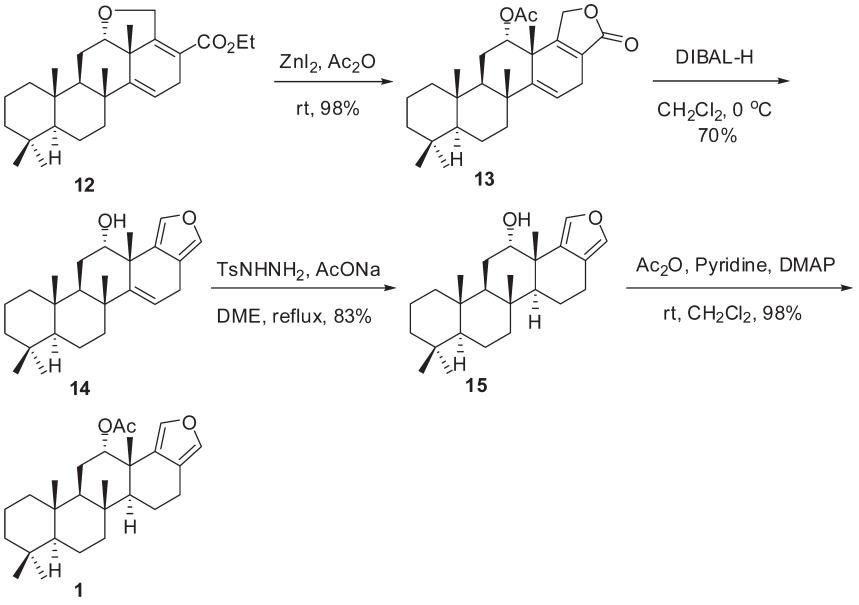
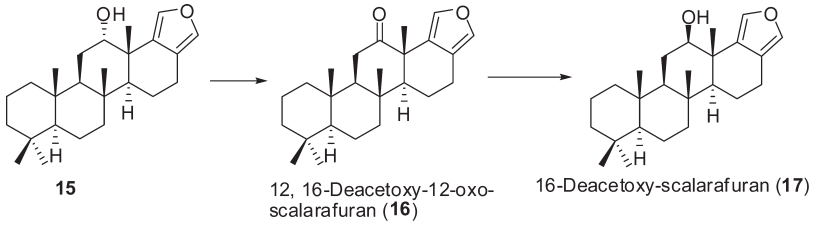
Scheme 3. Furan Ring Construction



Scheme 4. Application of Intermediate 15



the D ring using an intramolecular Diels–Alder reaction with high stereoselectivity and in excellent yield. Furthermore, the key intermediate **15** could be easily transformed to a series of natural scalarane sesterterpenoids in a few steps, as shown in Scheme 4. Therefore, we developed a general and effective synthesis route to C-12 oxygenated scalarane sesterterpenoids. Further investigations are underway to extend our method to the synthesis of scalarane sesterterpenoids **16** and **17**.

EXPERIMENTAL SECTION

General Methods. Commercial reagents and solvents were used without further purification. The purity determination of the compounds and reaction monitoring were accomplished by TLC on silica gel Polygram SILG/UV 254 plates. All yields refer to isolated products. Melting points were determined using a digital melting-point apparatus and are uncorrected. NMR spectra were recorded for ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz using TMS as internal standard on a 400 MHz spectrometer. The following abbreviations are used to describe peak patterns where appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants are reported in hertz (Hz). HRMS were obtained using ESI or EI ionization.

Experimental Procedures and Compound Characterization Data. *Epoxide* ***3***. To a stirred solution of **2** (1.0 g, 3.1 mmol) in anhydrous CH_2Cl_2 (50 mL) was added *m*-CPBA (1.3 g, 6.2 mmol) in several batches at 0 °C (ice–water bath). The resulting solution kept stirring at room temperature for 5 h. It was diluted with CH_2Cl_2 (50 mL) and quenched with saturated aqueous Na_2SO_3 (10 mL). The organic layer was separated and washed with saturated aqueous Na_2SO_3 (50 mL), saturated aqueous $NaHCO_3$ (3 × 30 mL), and brine (3 × 30 mL), respectively. It was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude material by flash column chromatography (EtOAc/petroleum ether 1/80) gave epoxide **3** (0.85 g, 81%) as a white solid.

Mp: 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.05 (s, 1H), 2.48 (s, 1H), 2.04 (dd, J = 4.0, 11.2 Hz, 1H), 1.74 (t, J = 14.0 Hz, 1H), 1.60–1.47 (m, 5H), 1.40–1.32 (m, 2H), 1.29 (s, 3H), 1.24 (m, 1H), 1.19–1.11 (m, 2H), 1.08 (s, 3H), 1.02–0.90 (m, 2H), 0.84 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H).

Alcohol ***4***. To a stirred solution of **3** (1.7 g, 5.0 mmol) in anhydrous THF (50 mL) was added sodium methoxide dropwise (9 mL, 30% in methanol). The resulting solution was heated to 50 °C for 5 h. It was then quenched with water. After methanol was removed under vacuum, the residue was extracted with EtOAc (3 × 30 mL) and the organic phase was dried over anhydrous Na_2SO_4. It was concentrated under vacuum and purified by flash column chromatography (EtOAc/petroleum ether 1/10) to give alcohol **4** (1.6 g, 95%) as a white solid.

Mp: 95–96 °C. $[\alpha]^{29}_D$ = −71.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (d, J = 3.6 Hz, 1H), 3.76 (s, 3H), 1.82–1.78 (m, 2H), 1.75 (s, 3H), 1.69 (m, 1H), 1.64–1.56 (m, 4H), 1.48–1.42 (m, 4H), 1.39–1.29 (m, 2H), 1.19 (s, 3H), 1.14 (m, 1H), 0.94 (m, 1H), 0.89

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(s, 3H), 0.87 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 142.0, 131.3, 69.2, 56.6, 51.2, 49.8, 42.0, 39.5, 38.0, 37.9, 36.9, 33.3, 27.5, 21.3, 19.7, 18.4, 18.3, 16.3.

TBS-Protected Alcohol ***5***. To a stirred solution of **4** (1.8 g, 5.40 mmol) in anhydrous CH_2Cl_2 (50 mL) was added imidazole (1.5 g, 21.6 mmol) and then TBSCl (2.8 g, 18.8 mmol). The resulting solution was stirred overnight at room temperature. It was then quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude material by flash column chromatography (EtOAc/petroleum ether 1/150) gave **5** (2.3 g, 96%) as a yellow oil.

$[\alpha]^{25}_D$ = −46.7 (*c* 1.0, $CHCl_3$). IR (neat): 2929, 2858, 1727, 1464, 1387, 1255, 1226, 1060, 1045, 1026, 1005, 926, 831, 774, 671 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (s, 1H), 3.74 (s, 3H), 1.68 (m, 4H), 1.64 (s, 3H), 1.64−1.52 (m, 3H), 1.52−1.40 (m, 4H), 1.37−1.28 (m, 3H), 1.15 (s, 3H), 0.92 (s, 9H), 0.86 (s, 6H), 0.83 (s, 3H), 0.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 140.9, 131.9, 69.6, 56.3, 51.1, 49.3, 42.1, 39.5, 38.0, 37.8, 37.0, 33.3, 33.2, 28.0, 25.9, 21.4, 19.8, 18.7, 18.5, 18.4, 18.1, 16.3, −4.2, −4.7. MS (ESI): *m*/*z* 317, 285, 218. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{48}NaO_3Si$ 471.3270, found 471.3268.

Allyl Alcohol ***6***. To a stirred solution of **5** (15.0 g, 33.4 mmol) in anhydrous CH_2Cl_2 (250 mL) was added DIBAL-H dropwise (53.5 mL, 1.25 mol/L in toluene) at −78 °C. The resulting solution was stirred at −78 °C for 3 h and slowly warmed to 0 °C. It was then quenched with methanol and filtered, and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated under vacuum and subjected to flash column chromatography (EtOAc/petroleum ether 1/30) to give **6** (14.2 g, 95%) as a white solid.

Mp: 119−121 °C. $[\alpha]^{24}_D$ = −43.0 (*c* 1.0, $CHCl_3$). IR (neat): 3389, 2932, 2857, 1462, 1387, 1254, 1058, 1022, 986, 837, 771 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (d, *J* = 11.6 Hz, 1H), 4.08 (d, *J* = 11.2 Hz, 1H), 3.98 (d, *J* = 2.0 Hz, 1H), 1.97 (d, *J* = 6.0 Hz, 1H), 1.78 (s, 3H), 1.66−1.55 (m, 6H), 1.46−1.40 (m, 6H), 1.27−1.04 (m, 2H), 0.93 (s, 12H), 0.86 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H), 0.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 133.2, 70.8, 58.1, 56.2, 49.8, 42.1, 39.6, 39.0, 37.6, 36.9, 33.3, 33.2, 27.9, 26.0, 25.7, 21.3, 20.0, 18.6, 18.2, 17.1, 16.3, −4.0, −4.6. MS (ESI): *m*/*z* 431, 421, 403, 393. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{48}NaO_2Si$ 443.3321, found 443.3324.

Aldehyde ***7***. To a stirred solution of **6** (2.5 g, 5.9 mmol) in anhydrous CH_2Cl_2 (100 mL) was added activated MnO_2 (4.1 g, 48 mmol). The resulting mixture was refluxed for 12 h. It was then filtered, and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated under vacuum and subjected to flash column chromatography (EtOAc/petroleum ether 1/80) to give aldehyde **7** (2.3 g, 94%) as a white solid.

Mp: 103−104 °C. $[\alpha]^{24}_D$ = −30.5 (*c* 1.1, $CHCl_3$). IR (neat): 2953, 2936, 2861, 1679, 1461, 1368, 1257, 1074, 1046, 1004, 839, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1H), 4.03 (d, *J* = 3.2 Hz, 1H), 2.49 (m, 1H), 2.04 (s, 3H), 1.74−1.61 (m, 6H), 1.44−1.38 (m, 5H), 1.17 (s, 3H), 1.17−1.12 (m, 2H), 0.94 (s, 9H), 0.86 (s, 6H), 0.83 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 149.3, 144.3, 71.2, 56.3, 49.7, 42.1, 39.7, 38.6, 37.5, 37.1, 33.2, 27.4, 25.9, 21.3, 19.8, 18.5, 18.1, 16.8, 16.4, −4.0, −4.7. MS (ESI): *m*/*z* 419, 318, 274, 261. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{47}O_2Si$ 419.3345, found 419.3346.

Diene ***8***. To a stirred solution of methyltriphenylphosphonium iodide (7.8 g, 19 mmol) in anhydrous THF (100 mL) was added *n*-BuLi dropwise (7.8 mL, 2.5 mol/L in hexane) at 0 °C (ice−water bath). After 1 h of stirring at 0 °C, a solution of **7** (1.0 g, 2.4 mmol) in anhydrous THF (10 mL) was added dropwise. The resulting solution was stirred for 2 h before it was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude material by flash column chromatography (100% petroleum ether) gave diene **8** (0.7 g, 71%) as a colorless oil.

$[\alpha]^{24}_D$ = −45.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (dd, *J* = 6.4, 11.2 Hz, 1H), 5.29 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.98 (dd, *J* = 2.4, 15.2 Hz, 1H), 4.01 (m, 1H), 1.91 (dd, *J* = 5.2, 6.8 Hz, 1H), 1.77−1.70 (m, 2H), 1.68 (s, 3H), 1.61−1.56 (m, 3H), 1.52−1.36 (m, 4H), 1.34−1.14 (m, 4H), 1.07 (s, 3H), 0.94 (s, 9H), 0.89 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H), 0.12 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 134.9, 127.9, 118.8, 70.9, 56.2, 49.6, 42.2, 39.6, 39.1, 38.6, 37.1, 33.3, 28.1, 26.0, 21.4, 19.4, 18.9, 18.7, 18.3, 16.4, −4.1, −4.6. MS (ESI): *m*/*z* 419, 318, 274, 261. HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{27}H_{48}KOSi$ 455.3111, found 455.3113.

Deprotected Diene ***9***. To a stirred solution of **8** (240 mg, 0.58 mmol) in anhydrous THF (15 mL) was added TBAF dropwise (1.2 mL, 1.0 mol/L in THF) at 0 °C (ice−water bath). The resulting solution was stirred overnight at room temperature. It was then quenched with water and extracted with EtOAc (3 × 30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the crude material by flash column chromatography (EtOAc/petroleum ether 1/20) gave **9** (165 mg, 95%) as a white solid.

Mp: 95−97 °C. $[\alpha]^{28}_D$ = −64.1 (*c* 1.0, $CHCl_3$). IR (neat): 3296, 2996, 2931, 2868, 1461, 1404, 1388, 1262, 1094, 1012, 998, 916, 804 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (dd, *J* = 6.0, 11.6 Hz, 1H), 5.29 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.96 (dd, *J* = 2.4, 15.2 Hz, 1H), 3.99 (d, *J* = 3.2 Hz, 1H), 1.78 (s, 3H), 1.75−1.69 (m, 5H), 1.64−1.55 (m, 2H), 1.43 (m, 1H), 1.39−1.28 (m, 3H), 1.25−1.13 (m, 2H), 0.96 (s, 3H), 0.91−0.87 (m, 2H), 0.86 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 134.3, 127.1, 119.2, 70.4, 56.4, 50.2, 42.1, 39.6, 39.3, 38.8, 37.0, 33.2, 27.5, 21.3, 19.4, 18.7, 18.6, 18.5, 16.5. HRMS (ESI): *m*/*z* [2 M + Na]$^+$ calcd for $C_{42}H_{68}NaO_2$ 627.5117, found 627.5128.

Diene Alkyne ***10***. TBAI (32 mg, 0.08 mmol) and **9** (260 mg, 0.86 mmol) was dissolved in 3-bromopropyne (1.4 mL, 15 mmol) at 0 °C (ice−water bath). Aqueous NaOH (1.0 mL, 60%) was added dropwise. The resulting solution was stirred for 36 h before it was quenched with water and extracted with EtOAc (3 × 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the crude material by flash column chromatography (EtOAc/petroleum ether 1/250) gave **10** (160 mg, 55%) as a yellow oil.

$[\alpha]^{19}_D$ = −9.4 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (dd, *J* = 6.4, 11.2 Hz, 1H), 5.31 (dd, *J* = 2.8, 8.8 Hz, 1H), 5.00 (dd, *J* = 2.8, 14.8 Hz, 1H), 4.30−4.14 (m, 2H), 3.88 (d, *J* = 4.0 Hz, 1H), 2.42 (t, *J* = 2.4 Hz, 1H), 1.91 (d, *J* = 13.6 Hz, 1H), 1.79 (s, 3H), 1.75−1.67 (m, 3H), 1.64−1.56 (m, 2H), 1.48−1.42 (m, 2H), 1.41−1.36 (m, 3H), 1.33−1.22 (m, 2H), 1.14 (m, 1H), 0.99 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H). MS (ESI): *m*/*z* 339, 265, 250. HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{24}H_{36}KO$ 379.2403, found 379.2404.

Diene Alkyne Derivative ***11***. To a stirred solution of **10** (340 mg, 0.56 mmol) in anhydrous THF (10 mL) at −78 °C was added *n*-BuLi dropwise (1.6 mL, 2.5 mol/L in hexane). The solution was kept at −78 °C for 1 h. To it was then added ethyl chloroformate (0.50 mL, 0.72 mmol), and the stirring was continued for 1 h. The reaction mixture was warmed to 0 °C before it was quenched with water. It was extracted with CH_2Cl_2 (3 × 30 mL) after THF was removed under vacuum. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the crude material by flash column chromatography (EtOAc/petroleum ether 1/200) gave **11** (310 mg, 76%) as a white solid.

Mp: 109−111 °C. $[\alpha]^{20}_D$ = −6.2 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (dd, *J* = 6.4, 11.2 Hz, 1H), 5.32 (dd, *J* = 2.8, 8.8 Hz, 1H), 5.01 (dd, *J* = 2.4, 15.2 Hz, 1H), 4.35 (t, *J* = 16.8 Hz, 1H), 4.26 (t, *J* = 7.2 Hz, 1H), 3.87 (d, *J* = 3.6 Hz, 1H), 1.91 (d, *J* = 14.4 Hz, 1H), 1.79 (s, 3H), 1.75−1.67 (m, 3H), 1.64−1.61 (m, 2H), 1.57−1.47 (m, 2H), 1.44−1.39 (m, 2H), 1.36−1.31 (m, 5H), 1.26 (m, 1H), 1.16 (m, 1H), 0.98 (s, 3H), 0.93−0.89 (m, 2H), 0.88 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 147.5, 134.2, 125.3, 119.4,

84.2, 78.2, 77.2, 62.1, 56.1, 55.9, 50.1, 42.1, 39.4, 39.0, 38.8, 37.0, 33.2, 29.7, 22.1, 21.3, 19.4, 18.7, 18.6, 18.5, 16.5, 14.0. MS (ESI): m/z 435, 285, 217. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{27}H_{40}NaO_3$ 435.2875, found 435.2872.

Tetrahydrofuran ***12***. **11** (290 mg, 0.70 mmol) and anhydrous toluene (15 mL) was stirred in a reaction vial in a preheated oil bath at 125 °C for 36 h. Upon cooling, the solution was concentrated under vacuum and subjected to flash column chromatography (EtOAc/petroleum ether 1/80) to give tetrahydrofuran **12** (250 mg, 96%) as a white solid.

Mp: 151−152 °C. $[\alpha]^{24}_D$ = −92.1 (c 1.3, $CHCl_3$). IR (neat): 3423, 2978, 2959, 2925, 2861, 1705, 1680, 1386, 1259, 1304 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (d, J = 6.4 Hz, 1H), 4.98 (dd, J = 2.8, 12.0 Hz, 1H), 4.34 (dd, J = 3.6, 10.4 Hz, 1H), 4.27−4.14 (m, 2H), 3.92 (t, J = 3.2 Hz, 1H), 3.35 (dd, J = 6.4, 14.0 Hz, 1H), 2.66 (d, J = 20.4 Hz, 1H), 1.97−1.94 (m, 3H), 1.72−1.64 (m, 2H), 1.63−1.45 (m, 4H), 1.42−1.37 (m, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.08−1.04 (m, 2H), 0.89 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 163.8, 155.1, 121.8, 117.8, 83.1, 68.8, 60.4, 56.1, 48.5, 45.5, 41.8, 40.4, 39.7, 38.6, 37.4, 33.4, 33.2, 27.0, 24.3, 23.4, 22.9, 21.6, 18.5, 15.7, 14.4. MS (ESI): m/z 413, 305, 261, 217. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{27}H_{41}O_3$ 413.3056, found 413.3055.

Lactone ***13***. Zinc iodide (60 mg, 0.18 mmol) and **12** (50 mg, 0.12 mmol) in acetic anhydride (2 mL) was stirred for 24 h at room temperature. It was then quenched with water and extracted with EtOAc (3 × 30 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine (2 × 10 mL) before drying over anhydrous Na_2SO_4. It was concentrated under vacuum and purified by flash column chromatography (EtOAc/petroleum ether 1/10) to give lactone **13** (51 mg, 98%) as a white solid.

Mp: 120−121 °C. $[\alpha]^{24}_D$ = +16.9 (c 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (t, J = 4.0 Hz, 1H), 4.98 (s, 1H), 4.84 (dd, J = 1.6, 15.2 Hz, 1H), 4.51 (dd, J = 2.4, 14.4 Hz, 1H), 3.70 (d, J = 2.4 Hz, 1H), 2.99 (d, J = 22.4 Hz, 1H), 2.85 (dd, J = 2.4, 19.6 Hz, 1H), 2.39 (m, 1H), 2.02 (s, 3H), 1.98−1.86 (m, 3H), 1.74−1.69 (m, 2H), 1.63−1.55 (m, 4H), 1.45 (s, 3H), 1.41−1.32 (m, 3H), 1.24 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 170.4, 164.6, 148.1, 123.5, 116.8, 75.7, 68.6, 56.3, 49.9, 41.8, 41.6, 40.9, 40.4, 39.8, 37.4, 33.3, 33.2, 27.6, 25.0, 22.4, 21.8, 21.4, 21.3, 18.7, 18.5, 16.0. MS (ESI) m/z 427. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{27}H_{39}O_4$ 427.2848, found 427.2849.

Furan Alcohol ***14***. To a stirred solution of **13** (150 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C was added DIBAL-H dropwise (1.2 mL, 1.25 mol/L in toluene). The reaction mixture was kept at −78 °C for 3 h before it was slowly warmed to 0 °C. The mixture was quenched with methanol, and silica gel was added (500 mg). The resulting mixture was stirred for another 5 h before filtration, and the filter cake was washed with CH_2Cl_2 (3 × 10 mL). The filtrate was concentrated under vacuum and subjected to flash column chromatography (EtOAc/petroleum ether 1/80) to give furan alcohol **14** (90 mg, 70%) as a white solid.

Mp: 199−200 °C. $[\alpha]^{17}_D$ = +18.2 (c 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 1H), 7.24 (d, J = 1.2 Hz, 1H), 5.81 (dd, J = 2.8, 2.4 Hz, 1H), 4.14 (t, J = 2.8 Hz, 1H), 3.29 (dd, J = 5.6, 15.6 Hz, 1H), 3.13 (m, 1H), 1.95 (d, J = 7.6 Hz, 1H), 1.95 (m, 3H), 1.74−1.68 (m, 2H), 1.67−1.60 (m, 3H), 1.56−1.52 (m, 2H), 1.47 (s, 3H), 1.44−1.28 (m, 3H), 1.24 (s, 3H), 1.14 (m, 1H), 0.93 (s, 3H), 0.91 (m, 1H), 0.88 (s, 2H), 0.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 137.3, 135.3, 130.6, 119.6, 117.5, 74.3, 56.3, 48.5, 42.0, 41.3, 41.0, 40.5, 39.6, 37.5, 33.3, 33.2, 32.1, 25.3, 23.4, 21.4, 20.8, 18.9, 18.6, 16.3. MS (ESI) m/z 369, 349, 342. HRMS (ESI): m/z [M + K]$^+$ calcd for $C_{25}H_{36}KO_2$: 407.2352, found 407.2353.

16-Deacetoxy-12-epi-scalarafuran ***15***. To a stirred solution of **14** (30 mg, 0.08 mmol) in DME (10 mL) was added $TsNHNH_2$ (600 mg, 3.2 mmol). After the solution was refluxed for 1 h, sodium acetate (4.0 mL, 1.0 mol/L) was added in several portions over 3 h. Reflux was continued for 3 h before quenching with water. After the solvent was removed under vacuum, it was extracted with EtOAc (3 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude material by flash column chromatography (EtOAc/petroleum ether 1/100) to give 16-deacetoxy-12-*epi*-scalarafuran **15** (25 mg, 83%) as a white solid.

Mp: 158−159 °C. $[\alpha]^{14}_D$ = +14.2 (c 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 1H), 7.14 (s, 1H), 4.12 (t, J = 2.8 Hz, 1H), 2.76 (dd, J = 5.2, 10.8 Hz, 1H), 2.40 (m, 1H), 1.98 (s, 1H), 1.89−1.77 (m, 4H), 1.74−1.64 (m, 2H), 1.63−1.59 (m, 3H), 1.51−1.28 (m, 4H), 1.26 (s, 3H), 1.20−1.07 (m, 3H), 0.96 (m, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 134.8, 132.5, 121.4, 73.4, 56.5, 51.3, 50.2, 42.1, 41.7, 40.9, 39.6, 38.0, 37.0, 33.3, 33.2, 26.7, 23.0, 21.3, 21.1, 18.6, 18.3, 17.8, 17.5, 16.2. MS (ESI): m/z 371, 305, 261, 217. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{39}O_2$ 371.2950, found 371.2948.

16-Deacetoxy-12-epi-scalarafuranacetate ***1***. To a stirred solution of **15** (20 mg, 0.05 mmol) in anhydrous CH_2Cl_2 (5 mL) was added pyridine (20 μL, 0.15 mmol), DMAP (1 mg, catalytic amount), and Ac_2O (10 μL, 0.10 mmol) sequentially at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 12 h and then concentrated under vacuum. The crude material was directly purified by flash column chromatography (EtOAc/petroleum ether 1/200) to provide **1** (23 mg, 98%) as a white solid.

Mp: 132−134 °C. $[\alpha]^{28}_D$ = +64.9 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 6.98 (d, J = 1.6 Hz, 1H), 5.37 (t, J = 2.8 Hz, 1H), 2.76 (m, 1H), 2.43 (m, 1H), 1.93 (s, 3H), 1.89 (m, 1H), 1.84−1.79 (m, 3H), 1.65−1.62 (m, 3H), 1.59−1.55 (m, 3H), 1.47−1.36 (m, 4H), 1.29 (s, 3H), 1.19−1.04 (m, 2H), 0.94 (s, 3H), 0.90 (d, J = 2.4 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 136.8, 135.1, 132.1, 120.4, 75.3, 56.7, 52.7, 51.4, 42.0, 41.7, 39.7, 38.8, 37.8, 37.0, 33.3, 33.2, 26.7, 22.3, 21.3, 20.9, 18.5, 18.2, 18.0, 17.4, 16.1. HRMS (EI): m/z [M]$^+$ calcd for $C_{27}H_{40}O_3$ 412.2977, found 412.2979.

■ ASSOCIATED CONTENT

Supporting Information. Figures and a CIF file giving ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Lu, Q.; Faulkner, D. J. *J. Nat. Prod.* **1997**, *60*, 195.
(2) Rueda, A.; Zubía, E.; Ortega, M. J.; Carballo, J. L.; Salvá, J. *J. Org. Chem.* **1997**, *62*, 1481.

(3) Pettit, G. R.; Tan, R.; Melody, N.; Cichacz, Z. A.; Herald, D. L.; Hoard, M. S.; Pettit, R. K.; Chapuis, J. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2093.
(4) Hernández-Guerrero, C. J.; Zubiá, E.; Ortega, M. J.; Carballo, J. L. *Tetrahedron* **2006**, *62*, 5392.
(5) Kamel, H. N.; Kim, Y. B.; Rimoldi, J. M.; Fronczek, F. R.; Ferreira, D.; Slattery, M. *J. Nat. Prod.* **2009**, *72*, 1492.
(6) Mahidol, C.; Prawat, H.; Sangpetsiripan, S.; Ruchirawat, S. *J. Nat. Prod.* **2009**, *72*, 1870.
(7) Hochlowski, J. E.; Faulkner, D. J.; Bass, L. S.; Clardy, J. *J. Org. Chem.* **1983**, *48*, 1738.
(8) Crews, P.; Bescansa, P. *J. Nat. Prod.* **1986**, *48*, 1041.
(9) Ryu, G.; Matsunaga, S.; Fusetani, N. *J. Nat. Prod.* **1996**, *59*, 515.
(10) Pettit, G. R.; Cichacz, Z. A.; Tan, R.; Hoard, M. S.; Melody, N.; Pettit, R. K. *J. Nat. Prod.* **1998**, *61*, 13.
(11) Youssef, D. T. A.; Yamaki, R. K.; Kelly, M.; Scheuer, P. J. *J. Nat. Prod.* **2002**, *65*, 2.
(12) Walker, R. P.; Thompson, J. E.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4976.
(13) Mirand, C.; Massiot, G.; Lévy, J. *J. Org. Chem.* **1982**, *47*, 4171.
(14) Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927.
(15) Abad, A.; Agulló, C.; Cuñat, A. C.; Llosá, M. C. *Chem. Commun.* **1999**, *5*, 427.
(16) Meng, X.-J.; Liu, Y.; Fan, W.-Y.; Hu, B.; Du, W.; Deng, W.-P. *Tetrahedron Lett.* **2009**, *50*, 4983.
(17) Fan, W.-Y.; Wang, Z.-L.; Li, H.-C.; Fossey, J. S.; Deng, W.-P. *Chem. Commun.* **2011**, *47*, 2961.
(18) Ungur, N.; Kulcițki, V. *Phytochem. Rev.* **2004**, *3*, 401.
(19) De Giulio, A.; De Rosa, S.; Di Vincenzo, G.; Zavodnik, N. *J. Nat. Prod.* **1989**, *52*, 1258.
(20) Hua, S.-K.; Wang, J.; Chen, X.-B.; Xu, Z.-Y.; Zeng, B.-B. *Tetrahedron* **2011**, *67*, 1142.
(21) Morzycki, J. W.; Gryszkiewicz, A.; Jastrzębska, I. *Tetrahedron* **2001**, *57*, 2185.
(22) Monica, C. D.; Sala, G. D.; D'urso, D.; Izzo, I.; Spinella, A. *Tetrahedron Lett.* **2005**, *46*, 4061.
(23) Abad, A.; Agulló, C.; Cuñat, A. C.; García, A. B.; Giménez-saizb, C. *Tetrahedron* **2003**, *59*, 9523.
(24) Grisé, C. M.; Rodrigue, E. M.; Barriault, L. *Tetrahedron* **2003**, *64*, 797.
(25) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1780.