JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

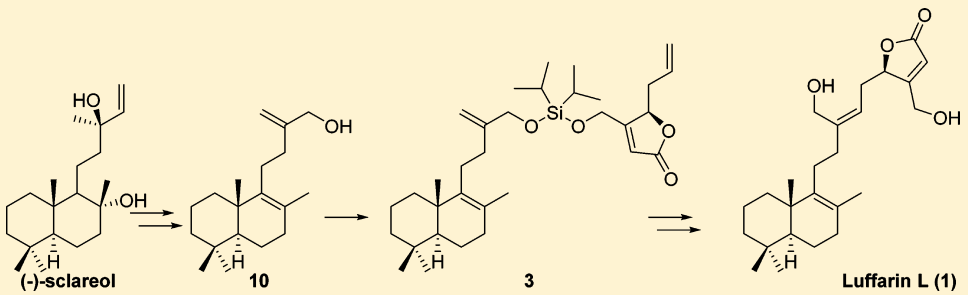
Synthesis of Luffarin L and 16-*epi*-Luffarin L Using a Temporary Silicon-Tethered Ring-Closing Metathesis Reaction

Aitor Urosa,[†] Isidro S. Marcos,[†] David Díez,[†] José M. Padrón,[‡] and Pilar Basabe*[,†]

[†]Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caídos, 1-5, 37008, Salamanca, Spain

[‡]BioLab, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Universidad de La Laguna, C/Astrofísico Francisco Sánchez 2, 38206, La Laguna, Spain

Supporting Information

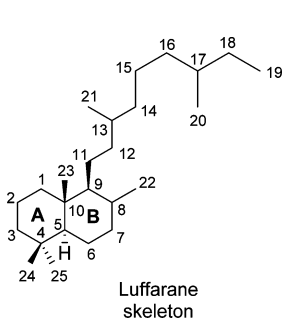


ABSTRACT: The first synthesis of luffarin L (**1**) and 16-*epi*-luffarin L (**2**) by a silicon-tethered ring closing metathesis as a key step has been achieved. The stereochemistry and absolute configuration of the natural sesterterpenolide luffarin L (**1**) and a new route for the stereoselective synthesis of sesterterpenolides with a luffarane skeleton have been established.

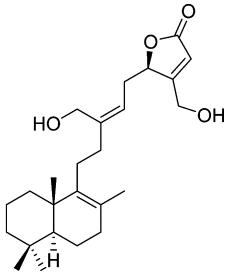
INTRODUCTION

The synthesis of natural products is a fundamental pillar of organic and biological chemistry. During the most recent decades, many contributions related to natural products, especially terpenes, have been reported.[1−3] Among them, the sesterterpenes have been attractive as synthetic objectives due to their structural diversity and biological activities.[4]

Luffarin L (**1**) is a sesterterpenolide with a luffarane skeleton isolated by Butler and Capon[5] from the sponge *Luffariella geometrica*. This sesterterpene can be considered an excellent synthetic objective in order not only to confirm its structure and absolute configuration but to study its biological activity as analogous with the butenolide fragment in the side chain.[6−11] Therefore, SAR studies will be conducted not only with the natural compound but with various synthetic analogues.



Luffarane skeleton



Luffarin L (**1**)

A useful alternative to the total synthesis is to use natural products as starting material, as they possess part of the carbon skeleton and some stereogenic centers present in the molecule objective. Several enantiopure bioactive sesterterpenoid compounds have been synthesized by us starting from natural chiral building blocks such as *ent*-halimic acid, isolated from *Halimium viscosum*,[12] and (−)-sclareol,[13−18] a commercial compound isolated from *Salvia sclarea*. In Figures 1 and 2 are found the structures of sesterterpenes synthesized from (−)-sclareol[13−18] and from *ent*-halimic acid, respectively.[19−21] In previous work, we have carried out the synthesis of the sesterterpenolides with the luffarane skeleton luffalactone[15] and luffarin I.[17]

Herein we report the first enantioselective synthesis of luffarin L (**1**) and 16-*epi*-luffarin L (**2**) involving the combination of temporary silicon-tethering methodology[22,23] with ring-closing metathesis,[24−26] the key step of this synthesis. This methodology has been demonstrated to be a useful method for natural product synthesis.[27−29]

RESULTS AND DISCUSSION

The retrosynthetic route that appears in Scheme 1 was designed for the synthesis of luffarin L (**1**) and its epimer 16-*epi*-luffarin L (**2**). As depicted in Scheme 1, in the retrosynthetic analysis of the synthesis of luffarin L (**1**) and 16-*epi*-luffarin L (**2**) the key step to obtain the luffarane skeleton is a temporary silicon-tethered ring-closing metathesis intramolecular reaction of intermediates **3** and **4**. These compounds can be obtained from the nor-diterpenic fragment **10**, synthesized from commercial (−)-sclareol (Scheme 2),

Received: April 20, 2015
Published: May 15, 2015

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

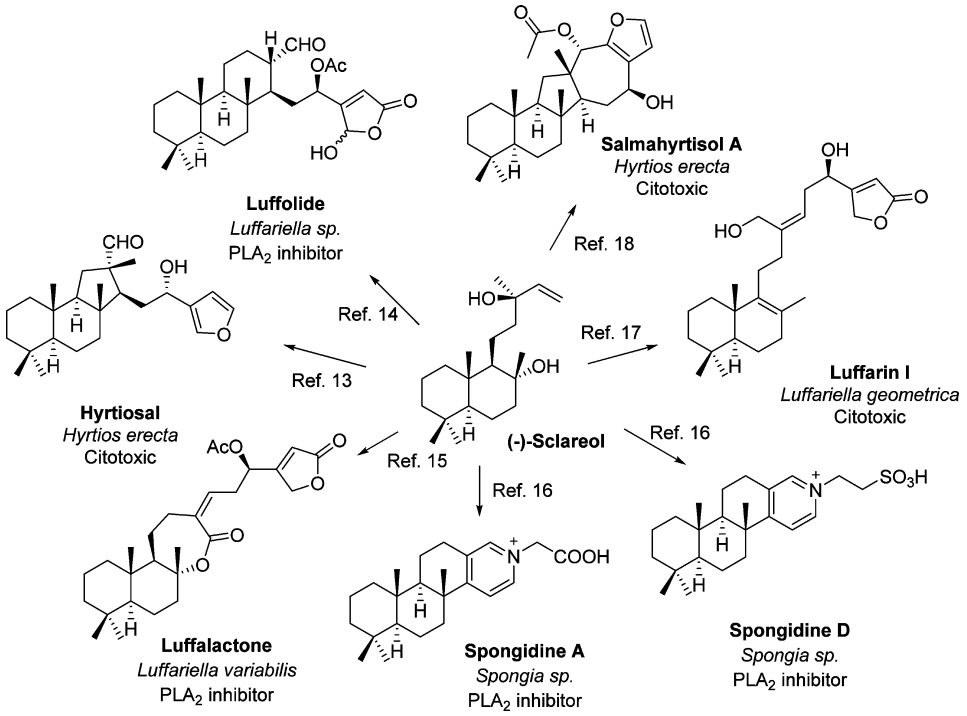


Figure 1. Active sesterterpenoids synthesized from (−)-sclareol.

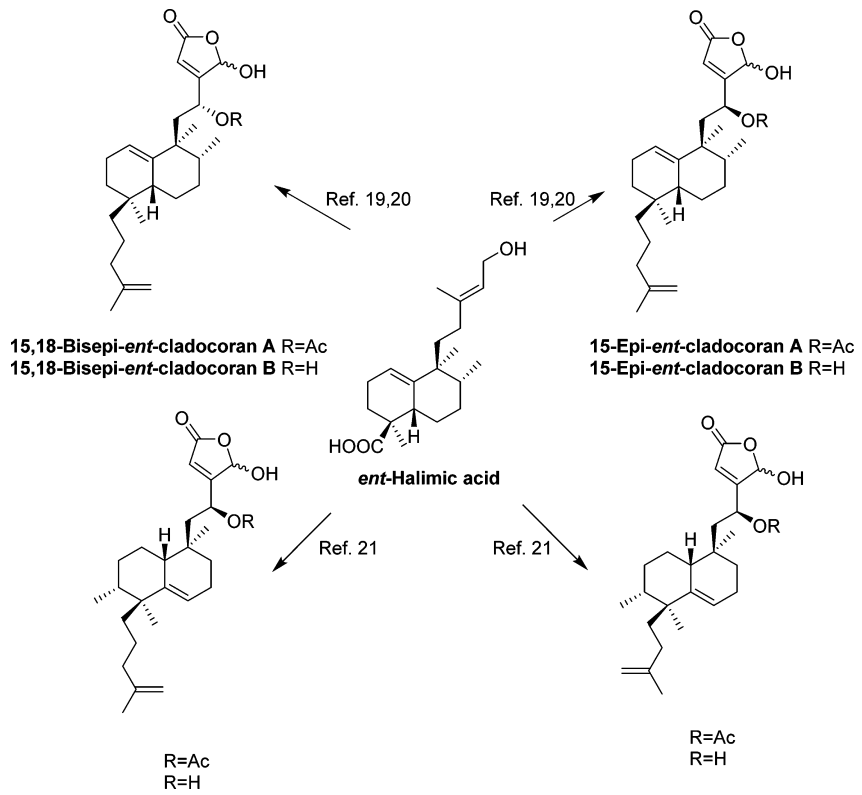


Figure 2. Antitumor sesterterpenolides analogous to dysidiolide synthesized from *ent*-halimic acid.

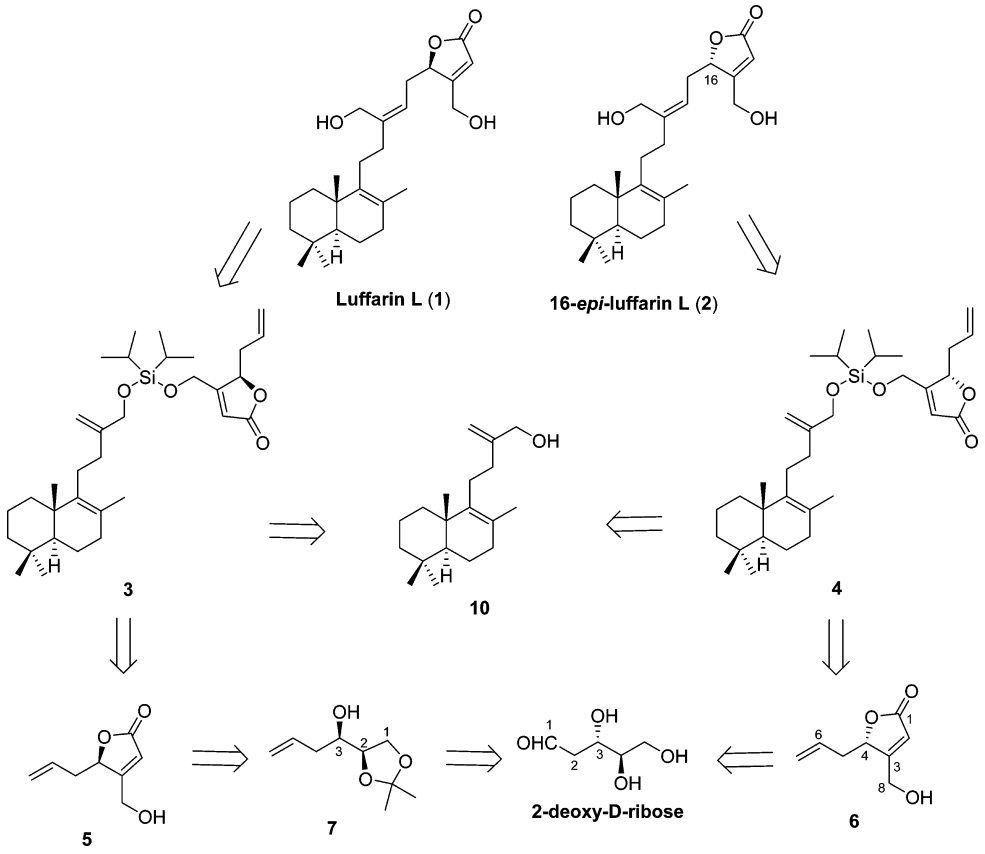
and furanones **5** and **6**, obtained from 2-deoxy-D-ribose (Schemes 3 and 4).

Starting from (−)-sclareol, ketone **8** was obtained as reported previously.[17] This compound was readily transformed into allylic alcohol **10** in two steps by a Wittig reaction of **8** to obtain **9** and the subsequent deprotection of the THP group (Scheme 2).

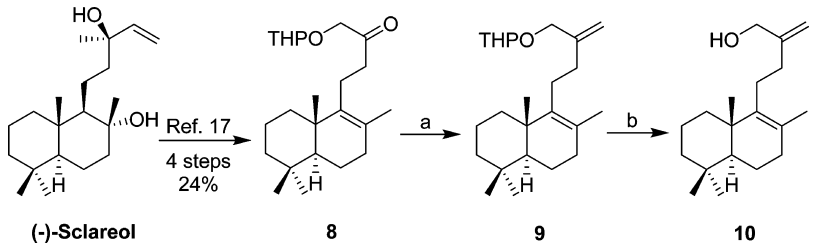
Wittig[30,31] reaction of 2-deoxy-D-ribose (Scheme 3) gave triol **11** in excellent yield, the intermediate for the synthesis of lactones **5** and **6** (Schemes 3 and 4). The 1,2-protection of **11** was carried out with 2,2-dimethoxypropane[32] and *p*-toluenesulfonic acid in order to obtain **12** that by a Mitsunobu-type inversion[33−35] led to intermediate **7**. This compound was deprotected with PPTS to give triol **13** that by treatment with

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

Scheme 1. Retrosynthetic Analysis of Luffarin L (1) and 16-*epi*-Luffarin L (2)



Scheme 2. Synthesis of Nor-diterpenic Intermediate 10[a]



[a]Reagents and conditions: (a) Ph_3PMeBr, NaHMDS, THF,−78 °C to rt (57%); (b) *p*TsOH, MeOH, rt (99%).

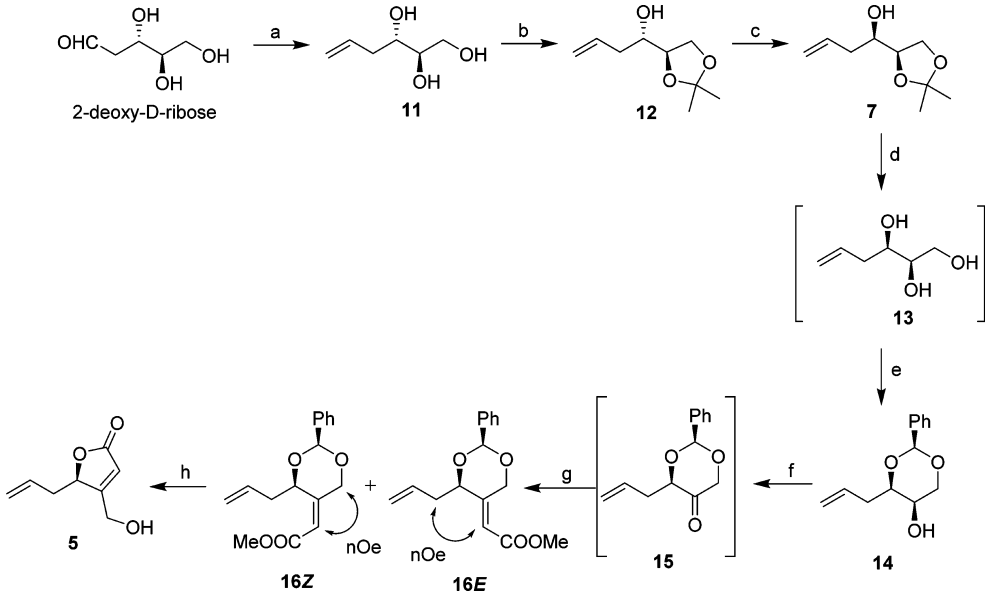
benzaldehyde dimethyl acetal in the presence of camphorsulfonic acid gave **14**. Oxidation of **14** with Dess−Martin periodinane[36−39] led to ketone **15**[40] that without isolation was transformed by Wittig reaction into compound **16*Z***. The olefination reaction was optimized under diverse conditions[41] using several reactants, bases, and temperatures to obtain the desired regioisomer **16*Z***. The best conditions were obtained using methyl *P*,*P*-bis(2,2,2-trifluoroethyl)phosphonoacetate[42] and KHMDS in THF at −78 °C. Thus, **16*Z*** was obtained in 46% yield, while the corresponding *E*-isomer was in 18% yield. Both isomers were separated by column chromatography. The double bond geometry of both esters was determined by ROESY experiments. Reaction of **16*Z*** with camphorsulfonic acid in MeOH (Scheme 3) and in the presence of H_2O not only produced the deprotection but caused the transesterefication reaction in order to give the desired product **5**[43] in 83% yield.

The synthesis of lactone **6** was carried out starting from **11** by an analogous sequence as described above (Scheme 4). The protection of **11** with benzaldehyde dimethylacetal in the presence of CSA gave **17**. This compound was oxidized to ketone **18** and without isolation it was transformed under the same Wittig conditions as before, into a 45:11 mixture of **19*Z*:19*E*** in favor of the required double bond stereochemistry. Final deprotection with CSA in aqueous MeOH led to the desired lactone **6**.

Ring-Closing Metathesis Silicon-Assisted and Synthesis of Luffarin L (1) and 16-*epi*-Luffarin L (2). Once lactones **5** and **6** were obtained, the synthesis of luffarin L and 16-*epi*-luffarin L was continued using the following methodology. In order to carry out the RCM reaction between nor-diterpenic fragment **10** and lactones **5** and **6**, these compounds were linked through the formation of a silicon tether (Scheme 5), a technique widely used with satisfactory results.[44−46] In this manner intermediates **3** and **4** were obtained in satisfactory yield, with lactones **5** and **6** recovered to some extent but not terpene intermediate **10**. With these compounds in hand, it was necessary to establish the appropriate conditions of the ring-closing metathesis (RCM) in order to obtain compounds **20** and **21**. Several conditions were tested, and the best ones are shown in Table 1.

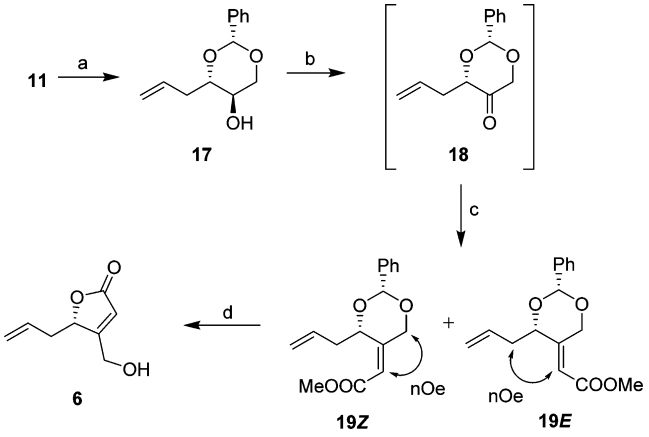
DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

Scheme 3. Synthesis of Lactone 5[a]



[a]Reagents and conditions: (a) Ph_3PMeBr, *t*BuOK, THF, 40 °C (85%); (b) $Me_2C(OMe)_2$, acetone, *p*TsOH (78%); (c) i: PhCOOH, Ph_3P, DIAD, THF, 0 °C to rt. ii: KOH/MeOH 10%, MeOH (42%); (d) PPTS, MeOH, 70 °C; (e) $PhCH(OMe)_2$, DCM, CSA (35% over two reactions); (f) DMP, DCM, rt; (g) $(CF_3CH_2O)_2P(O)CH_2COOMe$, KHMDS, THF. −78 °C to −10 °C (46% for **16*Z*** and 18% for **16*E*** over two steps); (h) CSA, H_2O, MeOH, rt (83%).

Scheme 4. Synthesis of Lactone 6[a]



[a]Reagents and conditions: (a) $PhCH(OMe)_2$, CSA, DCM (81%); (b) DMP, DCM, rt; (c) $(CF_3CH_2O)_2P(O)CH_2COOMe$, KHMDS, THF, −78 °C to −10 °C (45% for **19*Z*** and 11% for **19*E*** in two reactions); (d) CSA, H_2O, MeOH, rt (91%).

Different experiments varying the concentration of diene, the amount of catalyst, the temperature, and the solvent were tested. The best conditions were obtained with the use of 20% of Grubbs second generation catalyst, at 3 mM concentration of diene in toluene, and heating at 80 °C. Under these conditions, **20** and **21** were prepared in good yields and transformations, 63% and 79%, with some quantities of **3** and **4** recovered, respectively. The stereochemistry *Z* for C-13 established for compound **21** shows an NOE between H-12 and H-14; see ROESY in Supporting Information. Furthermore, deprotection of **20** gave luffarin L, as discussed later, having significant differences with the natural product luffarin K with *E* stereochemistry at C-13.[5] Therefore, we were able to obtain the required stereochemistry of olefin Δ^{13} and the unsaturated lactone of the side chain with the correct stereochemistry of C-16 in place.

Deprotection of **20** with HF−pyridine[47] in THF at 0 °C gave compound **1**, that showed ^{1}H NMR and ^{13}C NMR identical to the ones described by Butler and Capon[5] for the natural product luffarin L. The specific optical rotation of **1** ($[\alpha]_D^{20}$ = +22.0; *c* 0.2, $CHCl_3$) was in agreement with that described for luffarin L ($[\alpha]_D^{20}$ = +25.1; *c* 2.1, $CHCl_3$). Similarly, deprotection of **21** led to **2** ($[\alpha]_D^{20}$ = +92.4; *c* 0.2, $CHCl_3$) identified as 16-*epi*-luffarin L.

The antiproliferative activity of compounds **1**/**2** and **20**/**21** was tested against a panel of representative human solid tumor cell lines within our program directed at the discovery of new antitumor agents.[48] The results expressed as GI_{50} are shown in Table 2. Luffarin L (**1**) was slightly more active than its C-16 epimer **2** in terms of GI_{50} against all cell lines (17−31 μM vs 28−51 μM). Notably, the corresponding precursors **20**/**21** displayed an enhanced activity profile with GI_{50} values in the range 12−19 μM. This result is consistent with our previous findings that silyl ethers represent a plausible strategy to enhance the antiproliferative activity of natural products.[49]

CONCLUSIONS

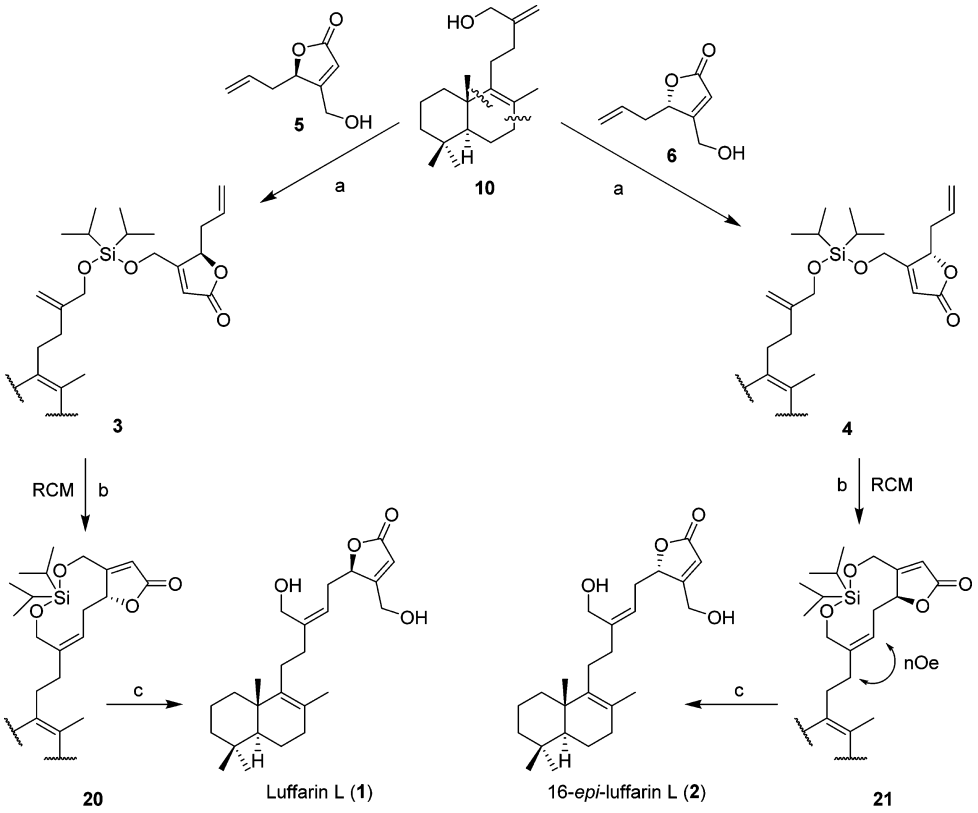
In summary, we have reported for the first time the synthesis of luffarin L, a natural product isolated from *Luffariella geometrica*. The commercially available natural compound (−)-sclareol served as starting material. This synthesis permits confirmation of the structure and absolute stereochemistry of the natural product. The synthetic route involves a silicon-tethered intramolecular ring-closing metathesis that allowed the synthesis of the isomer 16-*epi*-luffarin L. In addition, these compounds show remarkable biological activity toward human cancer cell lines.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on a 200 and 400 MHz (^{1}H) and 50 and 100 MHz (^{13}C) spectrometers. FTIR spectra were recorded as films. HRMS spectra were recorded by using Q-TOF using electrospray ionization.

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

Scheme 5. Synthesis of Luffarin L (1) and 16-*epi*-Luffarin L (2)[a]



[a]Reagents and conditions: (a) iPr$_2$SiCl$_2$, imidazole, DCM, 0 °C, **3** (49%), **4** (60%); (b) Grubbs second generation catalyst, toluene, 80 °C, **20** (63%), **21** (79%); (c) HF−pyridine, THF, 0 °C, **1** (57%), **2** (81%).

Table 1. Experimental Conditions of RCM Reaction

entry	cat. (equiv)[a]	concn (solvent)	T (°C)	3[b]	4[b]	20[c]	21[c]
1	0.10	15 mM (DCM)	40	32	–	–	–
2	0.20[d]	3 mM (DCM)	40	–	–	8	–
3	0.20	3 mM (DCM)	40	38	–	33	–
4	0.20	3 mM (toluene)	80	18	–	63	–
5	0.20	3 mM (toluene)	80	–	24	–	79

[a]Equivalents of second generation Grubbs catalyst. [b]Percentage of recovered starting material. [c]Yield in percentage. [d]Addition of catalyst was done in two portions (0.06 equiv + 0.14 equiv).

15-Nor-16-(2-tetrahydropyranyloxy)labda-8,13-diene: 9. To a suspension of triphenylmethylphosphonium bromide (73 mg, 0.19 mmol) in THF (350 mL) at −20 °C under an argon atmosphere was added slowly 2 M THF solution of NaHMDS (308 mL, 0.19 mmol). The mixture was warmed to room temperature and was stirred for 30 min. Then a solution of **8** (52 mg, 0.14 mmol) in THF (0.1 mL) was added dropwise at −78 °C and stirred for 2.5 h at rt. A saturated aqueous solution of NH_4Cl (1 mL) was added at −78 °C and allowed to warm to room temperature. It was extracted with AcOEt and the combined organic layer washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/AcOEt, 99/1) to obtain 29 mg of **9** as yellow oil (0.08 mmol, 57%). $[\alpha]_D^{20}$ = +89.7 (c 0.5, $CHCl_3$); IR (film) 3075, 2941, 1684, 1647, 1456, 1375, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (1H, s, H_A-14), 4.92 (1H, s, H_B-14), 4.62 (1H, bs, H-2′), 4.21 (1H, d, J = 12.8 Hz, H_A-16), 3.93 (1H, d, J = 12.8 Hz, H_B-16), 3.53−3.50 (2H, m, H-6′), 2.20−1.00 (21H, m), 1.58 (3H, s, Me-17), 0.94 (3H, s, Me-20), 0.88 (3H, s, Me-18), 0.83 (3H, s, Me-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0 (C), 140.2 (C), 126.0 (C), 110.3 (CH_2), 97.8 (CH), 69.7 (CH_2), 62.0 (CH_2), 51.9 (CH), 41.8 (CH_2), 39.0 (C), 36.9 (CH_2), 34.0 (CH_2), 33.6 (CH_2), 33.3 (2, C and CH_3), 30.6/30.4 (CH_2), 26.7 (CH_2), 25.6/25.5 (CH_2), 21.7 (CH_3), 20.0 (CH_3), 19.4 (CH_3), 19.3 (CH_2), 19.0 (2, CH_2); HRMS (EI) calcd for $C_{24}H_{44}NO_2$ requires $(M + NH_4)^+$ 378.3367; found 378.3375.

15-Norlabda-8,13-dien-16-ol: 10. To a solution of **9** (27 mg, 0.08 mmol) in MeOH (7.5 mL) was added p-toluenesulfonic acid (4 mg, 0.023 mmol). The mixture was stirred for 4 h, quenched with water, and extracted with AcOEt. The combined organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain 22 mg of **10** as a yellow oil (0.08 mmol, 99%). $[\alpha]_D^{20}$ = +40.8 (c 0.9, $CHCl_3$); IR (film) 3343, 3075, 2926, 1653, 1458, 1373, 1070,

Table 2. Antiproliferative Activity of Compounds 1/2 and 20/21[a]

	cell line (type)					
compound	A549 (lung)	HBL-100 (breast)	HeLa (cervix)	SW1573 (lung)	T-47D (breast)	WiDr (colon)
1	31 (±6.7)	22 (±6.2)	17 (±1.8)	25 (±1.2)	20 (±4.3)	21 (±2.4)
2	48 (±3.9)	39 (±9.6)	28 (±3.3)	39 (±16)	51 (±3.1)	40 (±13)
20	17 (±2.2)	18 (±4.9)	12 (±1.4)	17 (±3.2)	18 (±1.0)	18 (±0.8)
21	16 (±1.4)	17 (±1.6)	14 (±1.2)	17 (±1.2)	19 (±1.6)	19 (±1.3)

[a]Values are given in μM and are means of two to three experiments; standard deviation is given in parentheses.

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, s, H_A-14), 4.90 (1H, s, H_B-14), 4.10 (2H, s, H-21), 2.20−1.00 (15H, m), 1.57 (3H, s, Me-17), 0.95 (3H, s, Me-20), 0.88 (3H, s, Me-18), 0.83 (3H, s, Me-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9 (C), 140.1 (C), 126.1 (C), 108.4 (CH_2), 65.9 (CH_2), 51.9 (CH), 41.8 (CH_2), 39.0 (C), 36.9 (CH_2), 33.6 (2, CH_2), 33.3 (2, C and CH_3), 26.6 (CH_2), 21.7 (CH_3), 20.1 (CH_3), 19.4 (CH_3), 19.0 (2, CH_2); HRMS (EI) calcd for $C_{19}H_{32}ONa$ requires $(M + Na)^+$ 299.2345; found 299.2342.

2*R*,3*S*-Hex-5-ene-1,2,3-triol: 11. To a suspension of triphenylmethylphosphonium bromide (17 g, 46.8 mmol) in THF (190 mL) at 0 °C was added 20% THF solution of *t*BuOK (26.5 mL, 44.8 mmol). The mixture was stirred for 30 min at 0 °C, and 2-deoxy-D-ribose (2.5 g, 18.7 mmol) was added. It was warmed to 40 °C and stirred for 24 h. Then NH_4Cl (2.5 g) was added at 0 °C, and it was stirred for 12 h. It was filtered and concentrated in vacuo. The resulting crude residue was purified by column chromatography (silica gel, DCM/MeOH, 9/1) to obtain 2.1 g of **11** as a white powder (15.8 mmol, 85%). mp: 54−55 °C; $[\alpha]_D^{20}$ = −9.3 (*c* 1.9, MeOH); IR (film) 3227, 2901, 1464, 1065, 1030, 914, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, tdd, *J* = 17.0, 10.3, and 7.6 Hz, H-5), 5.18 (1H, d, *J* = 17.0 Hz, H_A-6), 5.16 (1H, d, *J* = 10.3 Hz, H_B-6), 3.81−3.76 (3H, m, H-1, H-2), 3.63 (1H, q, *J* = 4.8 Hz, H-3), 2.45−2.25 (2H, m, H-4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.8 (CH), 118.2 (CH_2), 74.1 (CH), 72.5 (CH), 63.3 (CH_2), 37.7 (CH_2); HRMS (EI) calcd for $C_6H_{12}O_3Na$ requires $(M + Na)^+$ 155.0679; found 155.0680.

(2*R*,3*S*)-1,2-Dimethylmethylenedioxyhex-5-en-3-ol: 12. To a solution of **11** (403 mg, 3.04 mmol) in acetone (15 mL) were added 2,2-dimethoxypropane (1.5 mL, 12.2 mmol) and *p*-toluenesulfonic acid (62 mg, 0.32 mmol). The reaction was stirred for 1 h under an anhydrous atmosphere. Then Et_3N (1 mL) was added, and it was concentrated in vacuo. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 9/1) to obtain 453 mg of **12** as a colorless oil (2.38 mmol, 78%). $[\alpha]_D^{20}$ = +16.6 (*c* 1.4, $CHCl_3$); IR (film) 3460, 3076, 2986, 1674, 1456, 1215, 1067, 907 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.89 (1H, tdd, *J* = 17.1, 10.2, and 7.8 Hz, H-5), 5.15 (1H, d, *J* = 17.1 Hz, H_A-6), 5.14 (1H, d, *J* = 10.2 Hz, H_B-6), 4.02−3.96 (2H, m, H_A-1, H-2), 3.94−3.86 (1H, m, H_B-1), 3.77 (1H, dt, *J* = 8.6 and 4.6 Hz, H-3), 2.40−2.10 (2H, m, H-4), 1.42 (3H, s, C-C*H*$_3$), 1.36 (3H, s, C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0 (CH), 118.1 (CH_2), 109.0 (C), 78.1 (CH), 70.4 (CH), 65.2 (CH_2), 37.6 (CH_2), 26.4 (CH_3), 25.2 (CH_3); HRMS (EI) calcd for $C_9H_{16}O_3Na$ requires $(M + Na)^+$ 195.0992; found 195.0988.

(2*R*,3*R*)-1,2-Dimethylmethylenedioxyhex-5-en-3-ol: 7. To a solution of **12** (1.3 g, 7.14 mmol) in THF (20 mL) were added triphenylphosphine (2.8 g, 10.71 mmol) and benzoic acid (1.57 g, 7.85 mmol). Then DIAD (2.15 mL, 10.71 mmol) was added under an argon atmosphere at 0 °C. The reaction was stirred for 1.5 h at rt. It was quenched with water and extracted with AcOEt. The combined organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo.

To a solution of the resulting crude ester in MeOH (142 mL) was added a 10% MeOH solution of KOH (71 mL, 7.1 mmol). The mixture was stirred for 30 min at rt. The solvent was evaporated under pressure, and water was added. It was extracted with AcOEt, and the combined organic layer was washed with water, until neutral pH was reached, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 8/2) to afford 550 mg of **7** as a pale yellow oil (3.02 mmol, 42%). $[\alpha]_D^{20}$ = +8.1 (*c* 0.7, $CHCl_3$); IR (film) 3483, 3078, 2986, 1641, 1381, 1215, 1067, 907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (1H, tdd, *J* = 17.2, 10.2, and 7.1 Hz, H-5), 5.11 (1H, d, *J* = 17.2 Hz, H_A-6), 5.09 (1H, d, *J* = 10.2 Hz, H_B-6), 4.05−3.90 (2H, m, H_A-1, H-2), 3.75−3.70 (1H, m, H_B-1), 3.57 (1H, bs, H-3), 2.19 (2H, t, *J* = 6.6 Hz, H-4), 1.41 (3H, s, C-C*H*$_3$), 1.34 (3H, s, C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0 (CH), 117.8 (CH_2), 109.3 (C), 78.4 (CH), 71.5 (CH), 66.0 (CH_2), 38.2 (CH_2), 26.5 (CH_3), 25.3 (CH_3); HRMS (EI) calcd for $C_9H_{16}O_3Na$ requires $(M + Na)^+$ 195.0992; found 195.0988.

(2*R*,3*R*)-1,3-Benzylidenedioxyhex-5-en-2-ol: 14. To a solution of **7** (550 mg, 3.02 mmol) in MeOH (280 mL) was added pyridinium *p*-toluenesulfonate (830 mg, 3.32 mmol). The solution was warmed to 70 °C and stirred for 14 h. It was allowed to cool to room temperature, Et_3N (2.5 mL) was added, and the solvent was evaporated under pressure.

To a solution of resulting triol in DCM (14 mL) were added benzaldehyde dimethyl acetal (533 μL, 3.93 mmol) and CSA (210 mg, 0.91 mmol). The mixture was stirred for 22 h at rt. Then Et_3N (2.5 mL) was added and concentrated in vacuo. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 9/1 and 85/15) to afford 231 mg of **14** as a colorless oil (1.05 mmol, 35%). $[\alpha]_D^{20}$ = +24.3 (*c* 1.6, $CHCl_3$); IR (film) 3441, 3073, 2978, 2858, 1643, 1454, 1360, 1092, 1028, 918, 750, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55−7.35 (5H, m, Ph), 5.86 (1H, tdd, *J* = 17.2, 10.9, and 7.4 Hz, H-5), 5.56 (1H, s, C*H*-Ph), 5.21 (1H, d, *J* = 17.2 Hz, H_A-6), 5.14 (1H, d, *J* = 10.9 Hz, H_B-6), 4.13 (1H, dd, *J* = 11.8 and 2.0 Hz, H_A-1), 4.02 (1H, d, *J* = 11.8 Hz, H_B-1), 3.93 (1H, t, *J* = 10.8 Hz, H-3), 3.49 (1H, d, *J* = 10.8 Hz, H-2), 2.86 (1H, d, *J* = 10.8 Hz, OH), 2.53−2.45 (2H, m, H-4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2 (C), 133.7 (CH), 129.2/128.5/126.2 (CH), 118.2 (CH_2), 101.6 (CH), 79.9 (CH), 73.0 (CH_2), 65.0 (CH), 35.9 (CH_2); HRMS (EI) calcd for $C_{13}H_{16}O_3Na$ requires $(M + Na)^+$ 243.0992; found 243.0996.

Compounds 16*Z* and 16*E*. To a solution of **14** (430 mg, 1.93 mmol) in DCM (101 mL) was added a 15% DCM solution of DMP (10.7 mL, 3.87 mmol). The reaction was stirred for 1 h under an argon atmosphere at rt. Then it was diluted with AcOEt and washed with a 10% $NaHCO_3$ (aq)/10% $Na_2S_2O_3$ (aq) 1:1 solution. The organic layer was dried (Na_2SO_4) and concentrated in vacuo.

A solution of methyl *P*,*P*-bis(2,2,2-trifluoroethyl)phosphonoacetate (900 μL, 4.26 mmol) in THF (13.3 mL) under an argon atmosphere at −78 °C was added slowly dropwise 0.7 M THF solution of KHMDS (5.7 mL, 3.86 mmol). Then a solution of previous obtained **15** in THF (2.7 mL) was added via cannula. The reaction was stirred for 30 min at −78 °C and 30 min at −10 °C. It was quenched with saturated aqueous solution of NH_4Cl (5 mL) and extracted with Et_2O. The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/AcOEt, 98/2) to obtain 242 mg of **16*Z*** (0.88 mmol, 46%) and 96 mg of **16*E*** (0.35 mmol, 18%), both as a colorless oils.

16*Z*: $[\alpha]_D^{20}$ = +104.4 (*c* 0.8, $CHCl_3$); IR (film) 3075, 2959, 2859, 1721, 1661, 1456, 1381, 1227, 1103, 1028, 918, 746, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.35 (5H, m, Ph), 6.01 (1H, tdd, *J* = 17.2, 10.2, and 7.1 Hz, H-6), 5.88 (1H, bs, H-2), 5.69 (1H, s, C*H*-Ph), 5.59 (1H, t, *J* = 4.8 Hz, H-4), 5.16 (1H, d, *J* = 17.2 Hz, H_A-7), 5.10 (1H, d, *J* = 10.2 Hz, H_B-7), 4.86 (1H, dt, *J* = 12.8 and 1.8 Hz, H_A-8), 4.36 (1H, dt, *J* = 12.8 and 1.1 Hz, H_B-8), 3.74 (3H, s, COO*Me*), 2.67 (2H, t, *J* = 6.0 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C), 157.1 (C), 138.4 (C), 133.7 (CH), 128.9/128.3/126.1 (CH), 117.6 (CH_2), 116.3 (CH), 97.6 (CH), 77.5 (CH), 67.4 (CH_2), 51.5 (CH_3), 38.8 (CH_2); HRMS (EI) calcd for $C_{16}H_{18}O_4Na$ requires $(M + Na)^+$ 297.1097; found 297.1099.

16*E*: $[\alpha]_D^{20}$ = +20.5 (*c* 0.6, $CHCl_3$); IR (film) 3075, 2951, 2841, 1721, 1655, 1435, 1381, 1211, 1026, 918, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.34 (5H, m, Ph), 6.00−5.87 (1H, m, H-6), 5.84 (1H, s, H-2), 5.76 (1H, s, C*H*-Ph) 5.63 (1H, d, *J* = 15.4 Hz, H_A-8), 5.19 (1H, d, *J* = 17.2 Hz, H_A-7), 5.15 (1H, d, *J* = 10.2 Hz, H_B-7), 4.68 (1H, dd, *J* = 15.4 and 1.4 Hz, H_B-8), 4.55 (1H, t, *J* = 6.2 Hz, H-4), 3.73 (3H, s, COO*Me*), 2.64 (2H, q, *J* = 6.2 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C), 152.8 (C), 137.9 (C), 133.5 (CH), 128.9/128.2/126.1 (CH), 117.7 (CH_2), 114.4 (CH), 100.3 (CH), 77.2 (CH), 66.2 (CH_2), 51.5 (CH_3), 36.9 (CH_2); HRMS (EI) calcd for $C_{16}H_{18}O_4Na$ requires $(M + Na)^+$ 297.1097; found 297.1099.

3-Hydroxymethylhepte-2,6-dien-1,4*R*-olide: 5. To a solution of **16*Z*** (109 mg, 0.4 mmol) in MeOH (2.2 mL) were added H_2O (45 μL) and CSA (16 mg, 0.07 mmol). The mixture was stirred for 20 h. It was quenched with $NaHCO_3$ (40 mg) and stirred 15 min. The crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 9/1 and 8/2) to obtain 51 mg of **5** as a pale yellow oil (0.33 mmol, 83%). $[\alpha]_D^{20}$ = −75.8 (*c* 0.3, $CHCl_3$); IR (film) 3418, 3084, 2918, 1748, 1643, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (1H, bs, H-2), 5.72 (1H, tdd, *J* = 17.1, 10.2, and 7.0 Hz, H-6), 5.14 (1H, d, *J* = 17.1 Hz, H_A-7), 5.11 (1H, d, *J* = 10.2 Hz, H_B-7), 5.07 (1H, t, *J* = 4.7 Hz, H-4), 4.56 (1H, d, *J* = 16.8 Hz, H_A-8), 4.46 (1H, d, *J* = 16.8 Hz, H_B-8), 2.73−2.67 (1H, m,

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

H_A-5), 2.46−2.41 (1H, m, H_B-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (C), 170.8 (C), 130.5 (CH), 119.6 (CH_2), 116.1 (CH), 81.2 (CH), 58.8 (CH_2), 36.4 (CH_2); HRMS (EI) calcd for $C_8H_{11}O_3$ requires $(M + H)^+$ 155.0703; found 155.0708.

(2*R*,3*S*)-1,3-Benzylidenedioxyhex-5-en-2-ol: 17. To a solution of **11** (156 mg, 1.18 mmol) in DCM (5 mL), benzaldehyde dimethyl acetal (210 μL, 1.53 mmol) and camphorsulfonic acid (82 mg, 0.35 mmol) were added. The solution was stirred for 22 h at rt. It was quenched with Et_3N (1 mL) and concenterd in vacuo. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 9/1) to obtain 210 mg of **17** as a colorless oil (0.95 mmol, 81%). $[\alpha]_D^{20} = -19.0$ (*c* 1.7, $CHCl_3$); IR (film) 3437, 3073, 2978, 2857, 1641, 1398, 1217, 1074, 1028, 916, 758, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.34 (5H, m, Ph), 6.01 (1H, tdd, *J* = 17.2, 10.2, and 7.1 Hz, H-5), 5.49 (1H, s, C*H*-Ph), 5.21 (1H, d, *J* = 17.2 Hz, H_A-6), 5.14 (1H, d, *J* = 10.2 Hz, H_B-6), 4.26 (1H, dd, *J* = 10.4 and 4.6 Hz, H_A-1), 3.58 (1H, t, *J* = 10.4 Hz, H_B-1), 3.70−3.60 (2H, m, H-2, H-3), 2.66−2.44 (2H, m, H-4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0 (C), 134.0 (CH), 129.2/128.5/126.4 (CH), 117.8 (CH_2), 101.0 (CH), 81.4 (CH), 71.3 (CH_2), 65.8 (CH), 36.8 (CH_2); HRMS (EI) calcd for $C_{13}H_{17}O_3$ requires $(M + H)^+$ 221.1172; found 221.1178.

Compounds 19*Z* and 19*E*. To a solution of **17** (21 mg, 0.095 mmol) in DCM (4.7 mL) was added 15% DCM solution of DMP (395 μL, 0.143 mmol). The mixture was stirred for 1 h under an argon atmosphere. It was diluted with AcOEt, washed with a 10% $NaHCO_3$ (aq)/10% $Na_2S_2O_3$ (aq) 1:1 solution, dried (Na_2SO_4), filtered, and concentrated in vacuo.

To a solution of methyl *P*,*P*-bis(2,2,2-trifluoroethyl)phosphonoacetate (42 μL, 0.19 mmol) in THF (620 μL) under an argon atmosphere at −78 °C were added 0.7 M toluene solution of KHMDS (260 mL, 0.19 mmol) and a solution of previously obtained ketone in THF (130 μL) via cannula. The mixture was stirred for 20 min at −78 °C and 30 min at −10 °C, quenched with a saturated aqueous solution of NH_4Cl (1 mL), and extracted with Et_2O. The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/AcOEt, 98/2) to obtain 12 mg of **19*Z*** (0.044 mmol, 45%) and 3 mg of **19*E*** (0.011 mmol, 11%), both as a colorless oils.

19*Z*: $[\alpha]_D^{20} = -102.3$ (*c* 1.1, $CHCl_3$); IR (film) 3073, 2953, 2859, 1721, 1659, 1437, 1227, 910 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.35 (5H, m, Ph), 6.04−5.96 (1H, m, H-6), 5.88 (1H, bs, H-2), 5.69 (1H, s, C*H*-Ph), 5.59 (1H, bs, H-4), 5.16 (1H, d, *J* = 17.0 Hz, H_A-7), 5.10 (1H, d, *J* = 10.3 Hz, H_B-7), 4.77 (1H, d, *J* = 12.4 Hz, H_A-8), 4.36 (1H, d, *J* = 12.4 Hz, H_B-8), 3.75 (3H, s, COO*Me*), 2.67 (2H, t, *J* = 5.9 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C), 157.1 (C), 138.4 (C), 133.7 (CH), 128.9/128.3/126.1 (CH), 117.6 (CH_2), 116.3 (CH), 97.6 (CH), 77.5 (CH), 67.4 (CH_2), 51.5 (CH_3), 38.8 (CH_2); HRMS (EI) calcd for $C_{16}H_{18}O_4Na$ requires $(M + Na)^+$ 297.1097; found 297.1099.

19*E*: $[\alpha]_D^{20} = -22.3$ (*c* 0.8, $CHCl_3$); IR (film) 3075, 2951, 2841, 1721, 1655, 1435, 1381, 1211, 1026, 918, 750, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.36 (5H, m, Ph), 6.05−5.90 (1H, m, H-6), 5.84 (1H, s, H-2), 5.76 (1H, s, C*H*-Ph), 5.63 (1H, d, *J* = 15.4 Hz, H_A-8), 5.18 (1H, d, *J* = 17.2 Hz, H_A-7), 5.15 (1H, d, *J* = 10.2 Hz, H_B-7), 4.68 (1H, d, *J* = 15.4 Hz, H_B-8), 4.55 (1H, t, *J* = 6.2 Hz, H-4), 3.74 (3H, s, COO*Me*), 2.70−2.60 (2H, m, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C), 152.8 (C), 137.9 (C), 133.5 (CH), 128.9/128.2/126.1 (CH), 117.7 (CH_2), 114.4 (CH), 100.3 (CH), 77.2 (CH), 66.2 (CH_2), 51.5 (CH_3), 36.9 (CH_2); HRMS (EI) calcd for $C_{16}H_{18}O_4Na$ requires $(M + Na)^+$ 297.1097; found 297.1099.

3-Hydroxymethylhepte-2,6-dien-1,4*S*-olide: 6. To a solution of **19*Z*** (360 mg, 1.32 mmol) in MeOH (7.3 mL) were added H_2O (147 μL) and CSA (51 mg, 0.22 mmol). The mixture was stirred for 22 h at rt. It was quenched with $NaHCO_3$ (110 mg) and stirred for 15 min. The reaction was purified by column chromatography (silica gel, hexane/AcOEt, 9/1 and 8/2) to obtain 199 mg of **6** as a pale yellow oil (1.2 mmol, 91%). $[\alpha]_D^{20} = +73.4$ (*c* 1.1, $CHCl_3$); IR (film) 3418, 3084, 2918, 1748, 1643, 908 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (1H, s, H-2), 5.72 (1H, tdd, *J* = 17.1, 10.2, and 7.0 Hz, H-6), 5.20 (1H, d, *J* = 17.1 Hz, H_A-7), 5.17 (1H, d, *J* = 10.2 Hz, H_B-7), 5.07 (1H, t, *J* = 4.7 Hz, H-4), 4.56 (1H, d, *J* = 16.8 Hz, H_A-8), 4.46 (1H, d, *J* = 16.8 Hz, H_B-8), 2.73−2.67 (1H, m, H_A-5), 2.47−2.40 (1H, m, H_B-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C), 170.8 (C), 130.4 (CH), 119.7 (CH_2), 115.5 (CH), 81.7 (CH), 58.5 (CH_2), 36.2 (CH_2); HRMS (EI) calcd for $C_8H_{11}O_3$ requires $(M + H)^+$ 155.0703; found 155.0708.

Compound 3. To a solution of imidazole (78 mg, 1.14 mmol) in DCM (0.49 mL) under an argon atmosphere at 0 °C was added iPr$_2$SiCl$_2$ (76 μL, 0.38 mmol), and the mixture was stirred for 5 min. A solution of **5** (46 mg, 0.3 mmol) in DCM (0.32 mL) was added slowly dropwise for 2 h at 0 °C. The mixture was stirred for 8 h at 0 °C. A solution of **10** (83 mg, 0.3 mmol) in DCM (0.32 mmol) was added, and the reaction was stirred for 14 h at 0 °C. Finally, it was filtered, washing with hexane, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/AcOEt, 98/2 and 97/3) to obtain 53 mg of **3** as a colorless oil (0.098 mmol, 49%) and 15 mg of **5** as a pale yellow oil (0.1 mmol). $[\alpha]_D^{20} = +34.7$ (*c* 1.0, $CHCl_3$); IR (film) 3080, 2943, 2866, 1761, 1647, 1464, 1099, 913 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.02 (1H, s, H-18), 5.71 (1H, tdd, *J* = 17.0, 10.2, and 6.9 Hz, H-15a), 5.17 (1H, d, *J* = 17.0 Hz, H_A-15b), 5.15 (1H, d, *J* = 10.2 Hz, H_B-15b), 5.05−5.00 (1H, m, H-16), 5.02 (1H, s, H_A-14), 4.87 (1H, s, H_B-14), 4.65 (1H, dd, *J* = 16.8 and 1.7 Hz, H_A-20), 4.54 (1H, ddd, *J* = 16.8, 1.7, and 0.6 Hz, H_B-20), 4.19 (2H, s, H-21), 2.80−2.60 (1H, m, H_A-15), 2.45−2.30 (1H, m, H_B-15), 2.10−1.90 (4H, m, H-11, H-12), 1.80−1.00 (13H, m), 1.56 (3H, s, Me-22), 1.07 (12H, s, *Me*-*i*Pr), 0.94 (3H, s, Me-23), 0.88 (3H, s, Me-25), 0.85 (3H, s, Me-24); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6 (C), 171.4 (C), 149.0 (C), 140.3 (C), 130.9 (CH), 126.4 (C), 119.8 (CH_2), 116.0 (CH), 108.4 (CH_2), 81.3 (CH), 65.9 (CH_2), 59.4 (CH_2), 52.1 (CH), 42.0 (CH_2), 39.2 (C), 37.2 (CH_2), 36.8 (2, CH_2), 33.8 (CH_2), 33.6 (2, C and CH_3), 26.8 (CH_2), 21.9 (CH_3), 20.3 (CH_3), 19.7 (CH_3), 19.3 (2, CH_2), 17.5 (4, CH_3), 12.3 (2, CH); HRMS (EI) calcd for $C_{33}H_{54}O_4SiNa$ requires $(M + Na)^+$ 565.3684; found 565.3687.

Compound 4. To a solution of imidazole (68 mg, 0.99 mmol) in DCM (0.43 mL) under an argon atmosphere at 0 °C was added iPr$_2$SiCl$_2$ (66 μL, 0.36 mmol), and the mixture was stirred for 5 min. A solution of **6** (41 mg, 0.27 mmol) in DCM (0.28 mL) was added slowly dropwise for 2 h at 0 °C. The mixture was stirred for 6 h at 0 °C. A solution of **10** (72 mg, 0.27 mmol) in DCM (0.28 mmol) was added, and the reaction was stirred for 18 h at 0 °C. Finally, it was filtered, washing with hexane, and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (silica gel, hexane/AcOEt, 98/2 and 97/3) to obtain 58 mg of **4** as a colorless oil (0.11 mmol, 60%) and recover 13 mg of **6** (0.084 mmol). $[\alpha]_D^{20} = +48.6$ (*c* 0.7, $CHCl_3$); IR (film) 3078, 2943, 2866, 1763, 1649, 1466, 1094, 909 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (1H, s, H-18), 5.71 (1H, tdd, *J* = 17.1, 10.2, and 7.0 Hz, H-15a), 5.19 (1H, d, *J* = 17.1 Hz, H_A-15b), 5.15 (1H, d, *J* = 10.2 Hz, H_B-15b), 5.03−5.01 (1H, m, H-16), 5.02 (1H, s, H_A-14), 4.87 (1H, s, H_B-14), 4.65 (1H, dd, *J* = 16.8 and 1.7 Hz, H_A-20), 4.54 (1H, ddd, J_1 = 16.8, 1.7, and 0.6 Hz, H_B-20), 4.20 (2H, s, H-21), 2.75−2.60 (1H, m, H_A-15), 2.45−2.35 (1H, m, H_B-15), 2.10−1.90 (4H, m, H-11, H-12), 1.80−1.00 (13H, m), 1.56 (3H, s, Me-22), 1.07 (12H, s, *Me*-*i*Pr), 0.94 (3H, s, Me-23), 0.88 (3H, s, Me-25), 0.83 (3H, s, Me-24); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6 (C), 171.5 (C), 149.0 (C), 140.3 (C), 130.9 (CH), 126.5 (C), 119.8 (CH_2), 116.0 (CH), 108.3 (CH_2), 81.3 (CH), 65.9 (CH_2), 59.4 (CH_2), 52.1 (CH), 42.0 (CH_2), 39.2 (C), 37.2 (CH_2), 36.8 (CH_2), 36.5 (CH_2), 33.8 (CH_2), 33.6 (2, C and CH_3), 26.8 (CH_2), 21.9 (CH_3), 20.3 (CH_3), 19.7 (CH_3), 19.3 (2, CH_2), 17.5 (4, CH_3), 12.3 (2, CH); HRMS (EI) calcd for $C_{33}H_{54}O_4SiNa$ requires $(M + Na)^+$ 565.3684; found 565.3687.

Compound 20. To a solution of **3** (53 mg, 0.1 mmol) in toluene (31.4 mL) under an argon atmosphere at 80 °C was added dropwise a solution of Grubbs second generation catalyst (20 mg, 0.02 mmol, 20%) in toluene (1 mL) via cannula. The reaction was stirred for 16 h. Then it was allowed to cool to room temperature and concentrated in vacuo. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 97/3 and 9/1) to afford 25 mg of **20** as a colorless oil (0.052 mmol, 63%) and recover 10 mg of **3** (0.018 mmol). $[\alpha]_D^{20} = -63.0$ (*c* 0.2, $CHCl_3$); IR (film) 2943, 2866, 1757, 1638, 1466, 1086, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, bs, H-18), 5.28−5.23 (1H, m, H-14), 5.22−5.20 (1H, m, H-16), 4.71 (2H, s, H-20), 4.45 (1H, d, *J* = 11.7 Hz, H_A-21), 4.00 (1H, d, *J* = 11.7 Hz,

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

H_B-21), 3.05 (1H, ddd, J = 14.7, 11.2, and 4.0 Hz, H_A-15), 2.65 (1H, dt, J = 14.7, 9.0, and 4.3 Hz, H_B-15), 2.20−1.90 (4H, m, H-11, H-12), 1.80−1.00 (13H, m), 1.55 (3H, s, Me-22), 1.10 (6H, s, *Me*-*i*Pr), 1.04 (6H, s, *Me*-*i*Pr), 0.93 (3H, s, Me-23), 0.88 (3H, s, Me-25), 0.83 (3H, s, Me-24); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C), 171.2 (C), 143.0 (C), 140.1 (C), 126.1 (C), 119.4 (CH), 115.6 (CH), 82.8 (CH), 60.3 (CH_2), 59.2 (CH_2), 51.9 (CH), 41.8 (CH_2), 38.9 (C), 37.0 (CH_2), 36.5 (CH_2), 33.6 (CH_2), 33.3 (2, C and CH_3), 29.8 (CH_2), 26.9 (CH_2), 21.6 (CH_3), 20.1 (CH_3), 19.4 (CH_3), 19.0 (2, CH_2), 17.4/17.3/17.2 (4, CH_3), 12.0/11.8 (CH); HRMS (EI) calcd for $C_{31}H_{54}NO_4Si$ requires $(M + NH_4)^+$ 532.3817; found 532.3802.

Compound 21. To a solution of **4** (15 mg, 0.029 mmol) in toluene (8.4 mL) under an argon atmosphere at 80 °C was added dropwise a solution of Grubbs second generation catalyst (6 mg, 0.006 mmol, 20%) in toluene (1 mL) via cannula. The reaction was stirred for 16 h. Then it was allowed to cool to room temperature and concentrated in vacuo. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 97/3 and 9/1) to afford 9 mg of **21** as a colorless oil (0.017 mmol, 79%) and recover 4 mg of **4** (0.007 mmol). $[\alpha]_D^{20}$ = +113.9 (c 0.6, $CHCl_3$); IR (film) 2941, 2926, 2866, 1757, 1649, 1462, 1055 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.87 (1H, s, H-18), 5.30−5.23 (1H, m, H-14), 5.23−5.15 (1H, m, H-16), 4.71 (2H, s, H-20), 4.46 (1H, d, J = 11.6 Hz, H_A-21), 4.00 (1H, d, J = 11.6 Hz, H_B-21), 3.05 (1H, ddd, J = 14.5, 10.9, and 4.8 Hz, H_A-15), 2.65 (1H, dt, J = 14.5, 9.2, and 4.8 Hz, H_B-15), 2.10−1.90 (4H, m, H-11, H-12), 1.80−1.00 (13H, m), 1.55 (3H, s, Me-22), 1.10 (6H, s, *Me*-*i*Pr), 1.04 (6H, s, *Me*-*i*Pr), 0.92 (3H, s, Me-23), 0.88 (3H, s, Me-25), 0.83 (3H, s, Me-24); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.0 (C), 171.6 (C), 143.2 (C), 140.3 (C), 126.4 (C), 120.0 (CH), 115.8 (CH), 83.1 (CH), 60.5 (CH_2), 59.5 (CH_2), 52.1 (CH), 42.0 (CH_2), 39.2 (C), 37.1 (CH_2), 37.0 (CH_2), 33.8 (CH_2), 33.6 (2, C and CH_3), 30.0 (CH_2), 27.5 (CH_2), 21.9 (CH_3), 20.3 (CH_3), 19.7 (CH_3), 19.3 (2, CH_2), 17.7/17.6/17.5 (4, CH_3), 12.3/12.0 (CH); HRMS (EI) calcd for $C_{31}H_{54}NO_4Si$ requires $(M + NH_4)^+$ 532.3817; found 532.3802.

20,21-Dihydroxyluffara-8,13*Z*,17(18)-trien-19,16*R*-olide: 1 (Luffarin L). To a solution of **20** (9 mg, 0.018 mmol) in THF (940 μL) under an argon atmosphere at 0 °C was added HF−pyridine (5 drops). The reaction was stirred for 40 min at 0 °C. Then $NaHCO_3$ was added slowly at 0 °C until gas liberation stops. It was diluted with Et_2O and filtered through a pad of silica gel eluting with AcOEt. The solvent was evaporated under pressure, and the resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 4/6) to afford 4 mg of **1** as a colorless oil (0.01 mmol, 57%). $[\alpha]_D^{20}$ = +22.0 (c 0.2, $CHCl_3$); IR (film) 3404, 2924, 2853, 1740, 1645, 1462, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (1H, s, H-18), 5.26 (1H, t, J = 7.6 Hz, H-14), 5.10 (1H, t, J = 4.6 Hz, H-16), 4.57 (1H, d, J = 16.2 Hz, H_A-20), 4.50 (1H, d, J = 16.2 Hz, H_B-20), 4.19 (1H, d, J = 12.0 Hz, H_A-21), 4.15 (1H, d, J = 12.0 Hz, H_B-21), 2.85−2.50 (2H, m, H-15), 2.15−1.90 (4H, m, H-11, H-12), 1.80−1.00 (11H, m), 1.56 (3H, s, Me-22), 0.93 (3H, s, Me-23), 0.88 (3H, s, Me-25), 0.83 (3H, s, Me-24); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (C), 170.8 (C), 144.3 (C), 139.9 (C), 126.3 (C), 119.2 (CH), 116.2 (CH), 81.6 (CH), 60.4 (CH_2), 58.7 (CH_2), 51.9 (CH), 41.8 (CH_2), 39.0 (C), 37.0 (CH_2), 36.4 (CH_2), 33.6 (CH_2), 33.3 (2, C and CH_3), 30.3 (CH_2), 27.3 (CH_2), 21.7 (CH_3), 20.1 (CH_3), 19.5 (CH_3), 19.0 (2, CH_2); HRMS (EI) calcd for $C_{25}H_{38}O_4Na$ requires $(M + Na)^+$ 425.2662; found 425.2652.

20,21-Dihydroxyluffara-8,13*Z*,17-trien-19,16*S*-olide: 2 (16-*epi*-Luffarin L). To a solution of **21** (8 mg, 0.016 mmol) in THF (850 μL) under an argon atmosphere at 0 °C was added HF-pyridine (4 drops) slowly. The solution was stirred for 40 min at 0 °C, and $NaHCO_3$ was added slowly at 0 °C until gas liberation stops. It was diluted with Et_2O and filtered through a pad of silica gel eluting with AcOEt. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt, 1/1) to obtain 5 mg of **2** as a colorless oil (0.013 mmol, 81%). $[\alpha]_D^{20}$ = +92.4 (c 0.2, $CHCl_3$); IR (film) 3402, 2936, 1732, 1651, 1454, 1142, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (1H, s, H-18), 5.26 (1H, t, J = 7.7 Hz, H-14), 5.11 (1H, t, J = 4.5 Hz, H-16), 4.57 (1H, dd, J = 16.7 and 1.4 Hz, H_A-20), 4.50 (1H, dd, J = 16.7 and 1.4 Hz, H_B-20), 4.17 (1H, d, J = 12.1 Hz, H_A-21), 4.15 (1H, d, J = 12.1 Hz, H_B-21), 2.85−2.75 (1H, m, H_A-15), 2.60−2.50 (1H, m, H_B-15), 2.20−1.90 (4H, m, H-11, H-12), 1.80−1.00 (11H, m), 1.55 (3H, s, Me-22), 0.93 (3H, s, Me-23), 0.88 (3H, s, Me-25), 0.82 (3H, s, Me-24); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (C), 171.0 (C), 144.3 (C), 139.9 (C), 126.2 (C), 119.2 (CH), 116.1 (CH), 81.6 (CH), 60.4 (CH_2), 58.7 (CH_2), 51.8 (CH), 41.7 (CH_2), 39.0 (C), 36.9 (CH_2), 36.4 (CH_2), 33.6 (CH_2), 33.3 (2, C and CH_3), 30.2 (CH_2), 27.3 (CH_2), 21.7 (CH_3), 20.1 (CH_3), 19.5 (CH_3), 19.0 (2, CH_2); HRMS (EI) calcd for $C_{25}H_{38}O_4Na$ requires $(M + Na)^+$ 425.2662; found 425.2652.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of IR, NMR, and HRMS spectra are included. This material is available free of charge via the Internet at http://pubs.acs.orgThe Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00876.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: 34 923 294574. E-mail: pbb@usal.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank FSE and Junta de Castilla y León (GR178,) for financial support. AUG is grateful to the JCyL-FSE for his fellowship. J.M.P. thanks the EU Research Potential (FP7-REGPOT-2012-CT2012-31637-IMBRAIN), the European Regional Development Fund (FEDER), and the Spanish Instituto de Salud Carlos (III PI11/00840) for financial support.

■ REFERENCES

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley-VCH: Weinheim, Germany, 1989.

(2) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; Wiley-VCH: Weinheim, Germany, 1996.

(3) Nicolaou, K. C.; Sorensen, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, Germany, 2003.

(4) Wang, L.; Yang, B.; Lin, X.-P.; Zhou, X.-F.; Liu, Y. *Nat. Prod. Rep.* **2013**, *30*, 455.

(5) Butler, M. S.; Capon, R. J. *Aust. J. Chem.* **1992**, *45*, 1705.

(6) De Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1981**, *22*, 3147.

(7) De Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611.

(8) Lombardo, D.; Dennis, E. A. *J. Biol. Chem.* **1985**, *260*, 7234.

(9) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759.

(10) Albizati, K. F.; Holman, T.; Faulkner, D. J.; Glaser, K. B.; Jacobs, R. S. *Experientia* **1987**, *43*, 949.

(11) Li, J.; Du, L.; Kelly, M.; Zhou, Y.-D.; Nagle, D. G. *J. Nat. Prod.* **2013**, *76*, 1492.

(12) Urones, J. G.; De Pascual Teresa, J.; Sanchez Marcos, I.; Diez Martin, D.; Martin Garrido, N.; Alfayate Guerra, R. *Phytochemistry* **1987**, *26*, 1077.

(13) Basabe, P.; Diego, A.; Diez, D.; Marcos, I. S.; Urones, J. G. *Synlett* **2000**, 1807.

(14) Basabe, P.; Delgado, S.; Marcos, I. S.; Diez, D.; Diego, A.; De Roman, M.; Urones, J. G. *J. Org. Chem.* **2005**, *70*, 9480.

(15) Basabe, P.; Bodero, O.; Marcos, I. S.; Diez, D.; Blanco, A.; de Roman, M.; Urones, J. G. *J. Org. Chem.* **2009**, *74*, 7750.

(16) Basabe, P.; Blanco, A.; Marcos, I. S.; Diez, D.; Bodero, O.; Martin, M.; Urones, J. G. *Tetrahedron* **2011**, *67*, 3649.

(17) Urosa, A.; Marcos, I. S.; Diez, D.; Basabe, P.; Lithgow, A.; Plata, G. B.; Padron, J. M. *Mar. Drugs* **2015**, *13*, 2407.

(18) Martin, M.; Urosa, A.; Marcos, I. S.; Diez, D.; Padron, J. M.; Basabe, P. *J. Org. Chem.* **2015**, *80*, 4566.

(19) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; Basabe, P.; Hernandez, F. A.; Broughton, H. B.; Urones, J. G. *Synlett* **2002**, 105.

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455

(20) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; Basabe, P.; Garcia, N.; Moro, R. F.; Broughton, H. B.; Mollinedo, F.; Urones, J. G. *J. Org. Chem.* **2003**, *68*, 7496.
(21) Marcos, I. S.; Escola, M. A.; Moro, R. F.; Basabe, P.; Diez, D.; Sanz, F.; Mollinedo, F.; de la Iglesia-Vicente, J.; Sierra, B. G.; Urones, J. G. *Bioorg. Med. Chem.* **2007**, *15*, 5719.
(22) Cusak, A. *Chem.—Eur. J.* **2012**, *18*, 5800.
(23) Evans, P. A. *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*; Wiley-VCH: Weinheim, 2010.
(24) Deiters, A.; Martin, S. F. *Chem. Rev. (Washington, DC, U. S.)* **2004**, *104*, 2199.
(25) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.
(26) Prunet, J. *Eur. J. Org. Chem.* **2011**, *2011*, 3634.
(27) Lee, S.; Paek, S.-M.; Yun, H.; Kim, N.-J.; Suh, Y.-G. *Org. Lett.* **2011**, *13*, 3344.
(28) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702.
(29) Hooper, A. M.; Dufour, S.; Willaert, S.; Pouvreau, S.; Pickett, J. A. *Tetrahedron Lett.* **2007**, *48*, 5991.
(30) Morita, M.; Haketa, T.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1679.
(31) Akoto, C. O.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8055.
(32) Ghosal, P.; Sharma, D.; Kumar, B.; Meena, S.; Sinha, S.; Shaw, A. K. *Org. Biomol. Chem.* **2011**, *9*, 7372.
(33) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
(34) Mitsunobu, O. *Synthesis* **1981**, 1.
(35) Liu, B.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 71.
(36) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X. Y.; Hwang, C. K.; Duggan, M. E.; Yang, Z.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 10239.
(37) Carcano, M.; Vasella, A. *Helv. Chim. Acta* **1998**, *81*, 889.
(38) Odejinmi, S. I.; Rascon, R. G.; Chen, W.; Lai, K. *Tetrahedron* **2012**, *68*, 8937.
(39) Navickas, V.; Maier, M. E. *Tetrahedron* **2010**, *66*, 94.
(40) Ulven, T.; Carlsen, P. H. J. *Eur. J. Org. Chem.* **2001**, 3367.
(41) Valverde, S.; Martin-Lomas, M.; Herradon, B.; Garcia-Ochoa, S. *Tetrahedron* **1987**, *43*, 1895.
(42) Yokokawa, F.; Fujiwara, H.; Shioiri, T. *Tetrahedron* **2000**, *56*, 1759.
(43) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jacquet, C. *J. Org. Chem.* **2003**, *68*, 1821.
(44) Harrison, B. A.; Verdine, G. L. *Org. Lett.* **2001**, *3*, 2157.
(45) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734.
(46) Matsui, R.; Seto, K.; Fujita, K.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 10068.
(47) Dias, L. C.; Polo, E. C.; Ferreira, M. A. B.; Tormena, C. F. *J. Org. Chem.* **2012**, *77*, 3766.
(48) Ríos-Luci, C.; Domínguez-Kelly, R.; León, L. G.; Díaz-Rodríguez, E.; Freire, R.; Pandiella, A.; Cikotiene, I.; Padrón, J. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6641.
(49) Pungitore, C. R.; León, L. G.; García, C.; Martín, V. S.; Tonn, C. E.; Padrón, J. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1332.

DOI: 10.1021/acs.joc.5b00876
J. Org. Chem. 2015, 80, 6447−6455