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Stereoselective Synthesis of (−)-Spicigerolide†

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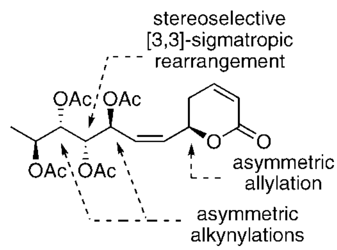

(−)-Spicigerolide was stereoselectively synthesized from a protected (*S*)-lactaldehyde. The synthesis of the polyacetylated framework relied on two Zn-mediated stereoselective additions of alkynes to aldehydes as well as a regiocontrolled [3,3]-sigmatropic rearrangement of an allylic acetate. The pyranone moiety was constructed via ring-closing metathesis.

Introduction

(−)-Spicigerolide (**1**) belongs to a family of polyacetate pyranone-containing natural products that exhibit a broad spectrum of pharmacological properties (Figure 1).[1] These polyoxygenated 6-heptenyl-5,6-dihydro-α-pyrones have been found in several species of the genus *Hyptis* and other related genera.[2,3] In particular, spicigerolide has been isolated from *Hyptis spicigera*, a plant that is used in traditional Mexican medicine to treat gastrointestinal disturbances, skin infections, wounds and insects bites. The Michael acceptor moiety present in all of these molecules potentially endows them with cytotoxic properties. Indeed, spicigerolide and some of its stereoisomers have shown cytotoxic activity in some cell tumoral lines.[1,4] As a result of their biological activity, several stereoselective approaches have already been applied to this group of polyoxygenated compounds. Thus, syntheses of (+)-anamarine (**2**),[5] (−)-anamarine,[6] and spicigerolide (**1**)[1] have been described from carbohydrates. In contrast, the synthesis of (+)-hyptolide (**3**)[7] is based on carbonyl additions, and there are alternate ap-

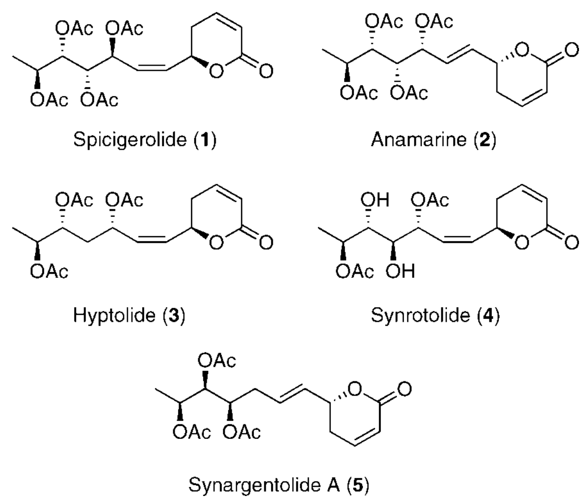

FIGURE 1. Some naturally occurring 5,6-dihydropyran-2-ones.

† Dedicated to Professor Josep Font on the occasion of his 70th birthday.

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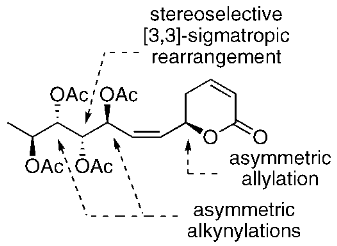
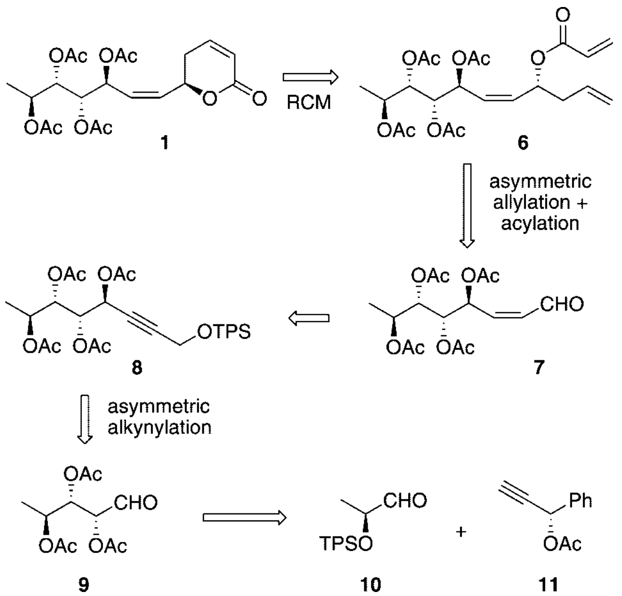
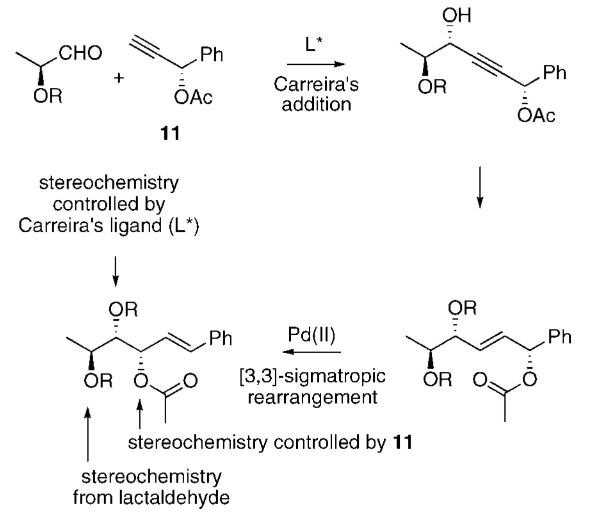
SCHEME 1



SCHEME 2



SCHEME 3



proaches to (+)-anamarine (**2**) that exploit asymmetric dihydroxylation[8] or aldol reactions.[9]

As a part of our work on the stereocontrolled construction of sugar-type polyhydroxylated frameworks,[10] we have explored a novel synthetic approach to these polyacetylated lactones. Specifically, we focused on the synthesis of the (−)-spicigerolide (**1**) as a representative example of this class of compounds. We envisaged that our recently reported methodology[10a] could be applied easily to the synthesis of **1**. In contrast to the previous synthesis,[1b,c] our strategy creates the stereocenters independently rather than relying on carbohydrates as chiral starting materials (Scheme 1).

Analysis of the structure of (−)-spicigerolide prompted us to consider that the pyranone could be obtained by selective olefin ring-closing metathesis (RCM) of the homoallyl acrylate **6**, which in turn could be prepared via asymmetric allylation of aldehyde **7** followed by acylation (Scheme 2).[11] Regarding the remaining polyoxygenated chain, we tried to minimize the use of protecting groups by maintaining the oxygenated functional groups as acetates and using only silicon-derived protecting groups for transient protections. Thus, the α,β-unsaturated aldehyde **7** could arise from the related alkynol **8** obtained by stereoselective alkynylation of aldehyde **9** with a protected 2-propyn-1-ol.

We considered that the key aldehyde **9** could be prepared from the protected (*S*)-lactaldehyde **10** and propargylic acetate **11** via our stereoselective approach to polyhydroxylated arrays.[10a] Therefore, we had to combine two stereoselective reactions: (i) Carreira's asymmetric alkynylation of aldehydes[12] with propargylic esters[13] and (ii) stereoselective [3,3]-sigmatropic rearrangement of an allylic acetate (Scheme 3). Ozonolysis of the olefin moiety would afford aldehyde **9**.

Results and Discussion

As expected, (*R*)-1-phenylprop-2-ynyl acetate (*R*)-**11** reacted with aldehyde **10** under Carreira's conditions[12] mediated by (−)-*N*-methylephedrine ((−)-NME) to afford *anti*,*syn*-**12** in 95% yield as a single stereoisomer. The configuration of the alkyne **11** did not affect the diastereomeric ratio.[14] Analogously, the same Felkin−Anh-type addition was observed when (*S*)-**11** was used, leading to the single stereoisomer *anti*,*anti*-**12** (Scheme 4).[15]

Treatment of *anti*,*syn*-**12** with $LiAlH_4$ reduced the triple bond to an *E*-alkene with concomitant alcohol deprotection leading to a triol (**13**), which was acetylated in situ with acetic anhydride to form the triacetate **14** in 87% yield for the two steps (Scheme 5). Having achieved the right stereochemistry at C-2 and C-3 in **14**, we next attempted to transfer the chirality from C-6 to C-4 by a Pd-catalyzed [3,3]-sigmatropic

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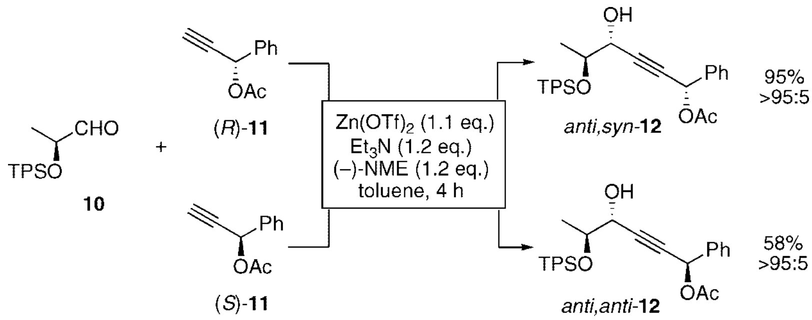
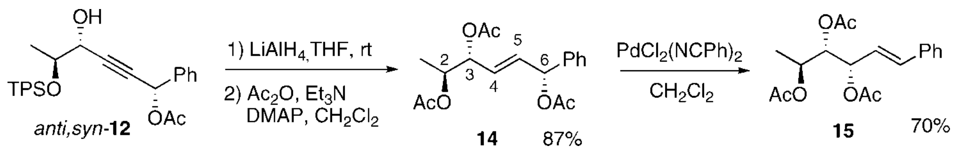
(14) However, addition in the presence of (+)-NME led to the opposite configuration of the new stereocenter (90:10 dr), showing that stereoselectivity is ruled by either the (+) or (−)-NME used. As reported in ref 13a, the influence of the configuration of the silicon-protected lactaldehyde on the stereochemistry of the addition is low when an achiral ligand was used.

(15) The relative stereochemistry of *syn* and *anti* adducts was confirmed by comparison of the spectral data following the analysis in Kojima, N.; Maezaki, N.; Tominaga, H.; Asai, M.; Yanai, M.; Tanaka, T. *Chem. Eur. J.* **2003**, *9*, 4980–4990.

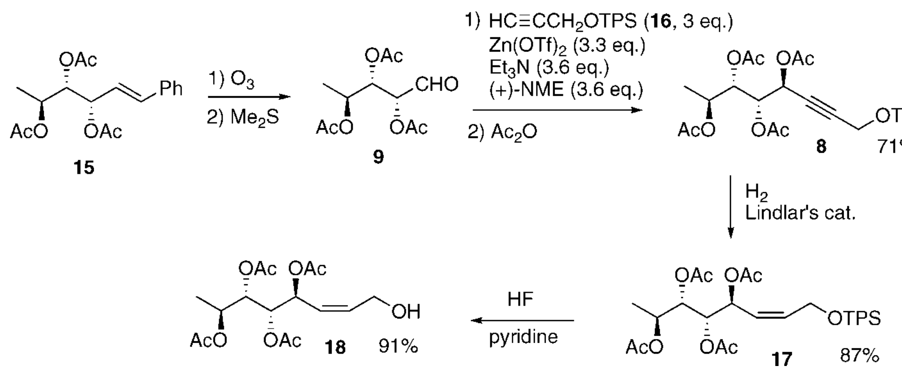
SCHEME 4



SCHEME 5



SCHEME 6



rearrangement.[10a,16] Assuming a six-membered transition state having a chair conformation, we expected this reaction to be stereospecific and, therefore, that the configuration of C-6 in **14** would be conserved at C-4 in **15**. Moreover, this rearrangement is an equilibrium that can be shifted sterically or electronically. In our case, we anticipated that formation of a double bond conjugated with a phenyl group would favor formation of the isomeric allylic triacetate **15**. Indeed, when triacetate **14** was treated with 5% $PdCl_2(NCPh)_2$ in CH_2Cl_2 for 24 h, the rearranged product **15** was obtained as a major product in 70% yield (Scheme 5).

The key aldehyde **9** was obtained by ozonolysis followed by treatment with Me_2S. This unstable aldehyde was immediately submitted to Carreira's asymmetric alkynylation with 2-*tert*-butyldiphenylsilyloxy-1-propyne (**16**) mediated by (+)-*N*-methylephedrine. Unfortunately, aldehyde **9** did not react efficiently under the standard Carreira conditions; instead, 3 equiv of alkyne **16**, zinc triflate, (+)-NME, and triethylamine were required to achieve good yields.[17] Under these conditions, partial acetyl deprotection was observed. Therefore, the crude mixture was acetylated again to afford tetraacetate **8** in 71% yield (for three steps) and as a single diastereoisomer. Partial hydrogenation of the triple bond to the *Z*-olefin with Lindlar's catalyst afforded allylic acetate **17** in 87% yield. Cleavage of the silicon protecting group with TBAF caused the acetyl groups to migrate to the primary alcohol. Fortunately, deprotection with HF/pyridine furnished allylic alcohol **18** in 91% yield without any migration (Scheme 6).

We then focused on assembling the pyranone ring. Swern oxidation of alcohol **18** afforded aldehyde **7** (Scheme 7). Stereoselective allylation of **7** was initially attempted with $(Ipc)_2$B-allyl without success.[18] However, Duthaler's Ti-TADDOL-mediated allylation[19] with **19** provided the expected homoallylic alcohol **20** in good yield (84%) as a separable diastereomeric mixture (87:13). Acylation of alcohol **20** with acryloyl chloride followed by RCM[20] in the presence of the second-generation Grubbs' ruthenium catalyst (**21**, 2% mol) afforded the (−)-spicigerolide (**1**), whose spectroscopic data was identical to that of the natural product.[1]

(16) For recent stereoselective applications, see: (a) Saito, S.; Kuroda, A.; Matsunaga, H.; Ikeda, S. *Tetrahedron* **1996**, *52*, 13919–13932. (b) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687–3696.

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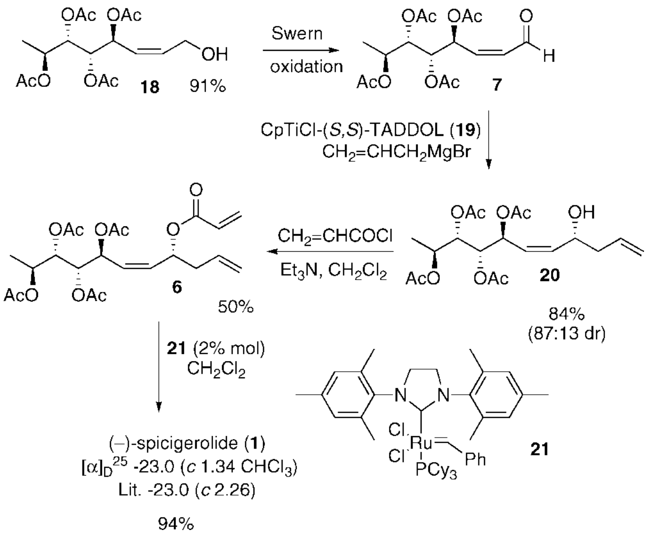
SCHEME 7



Conclusion

We have reported an enantioselective synthesis of (−)-spicigerolide (**1**) that features independent stereocontrolled access to the different chiral centers. It constitutes the first application to natural product synthesis of our recently developed strategy for building polyhydroxylated chains, which is based on Pd(II) [3,3]-sigmatropic rearrangements and Carreira's alkynylations. Furthermore, we were able to shorten the sequence by minimizing the use of protecting groups.

Experimental Section

(1*S*,4*R*,5*S*)-5-*tert*-Butyldiphenylsilyloxy-4-hydroxy-1-phenylhex-2-ynyl Acetate (*anti*,*syn*-12). $Zn(OTf)_2$ (2.4 g, 6.6 mmol) was heated under vacuum in a flask. (−)-NME (1.3 g, 7.2 mmol) was added, and the flask was purged with nitrogen. Anhydrous toluene (10 mL) and Et_3N (1.0 mL, 7.2 mmol) were added, and the mixture was stirred at room temperature for 2 h 30 min. A solution of alkyne (*R*)-**11** (1.04 g, 6.00 mmol) in toluene (5 mL) was added, and the mixture was stirred at room temperature for 30 min. Then, a solution of (*S*)-2-*tert*-butyldiphenylsilyloxypropanal (**10**, 2.25 mg, 7.20 mmol) in toluene (5 mL) was added, and the final mixture was stirred for 4 h (until TLC did not show significant changes). The reaction was quenched with saturated aqueous NH_4Cl and CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude mixture was purified by flash chromatography with silica gel (hexane/AcOEt 70/30) to afford *anti*,*syn*-**12** (2781 mg, 95%, >98% dr) as a colorless oil: R_f 0.30 (hexane/AcOEt 80/20); $[\alpha]^{25}_D$ −5.9 (*c* 0.95, $CHCl_3$); IR (film) 3460, 2932, 1742, 1457, 1369, 1227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.55−7.49 (m, 2H), 7.46−7.41 (m, 2H), 7.40−7.33 (m, 7H), 6.52 (d, J = 1.5 Hz, 1H), 4.32 (ddd, J = 1.6, 3.2, 6.9 Hz, 1H), 4.00 (qd, J = 3.2, 6.3 Hz, 1H), 2.42 (d, J = 6.9 Hz, 1H), 2.08 (s, 3H), 1.12 (d, J = 6.3 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 136.8, 135.9, 135.7, 133.5, 133.4, 129.9, 129.8, 128.9, 128.6, 127.8, 127.7, 127.6, 85.1, 82.6, 72.1, 67.3, 65.5, 26.9, 21.0, 19.3, 18.4; HMRS (ESI+) calcd for $C_{30}H_{34}O_4SiNa$ $(M + Na)^+$ 509.2119, found 509.2120.

(1*R*,4*R*,5*S*,*E*)-1-Phenylhex-2-ene-1,4,5-triol (13). A solution of alkyne *anti*,*syn*-**12** (2.92 g, 6.00 mmol) in anhydrous THF (20 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (1.14 g, 30.0 mmol), in anhydrous THF (50 mL) under N_2. The mixture was stirred at room temperature for 15 h (until TLC did not show significant changes). The reaction was quenched with saturated potassium and sodium tartrate. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Triol **13** was obtained as a colorless oil and used as a crude mixture for the next transformation: R_f 0.31 (AcOEt); $[\alpha]^{25}_D$ +5.9 (*c* 0.58, $CHCl_3$); IR (film) 3347, 2922, 1452, 1366 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.97 (dd, J = 6.0, 15.3 Hz, 1H), 5.86 (dd, J = 6.0, 15.3 Hz, 1H), 5.23 (d, J = 6.0 Hz, 1H), 4.08 (dd, J = 3.3, 6.0 Hz, 1H), 3.87 (qd, J = 3.3, 6.3 Hz, 1H), 2.90−2.40 (bs, 3H), 1.11 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 135.6, 128.8, 128.6, 127.8, 126.2, 75.5, 74.4, 70.2, 17.8; HMRS (ESI+) calcd for $C_{12}H_{16}O_3Na$ $(M + Na)^+$ 231.0992, found 231.0899.

(1*R*,4*R*,5*S*,*E*)-1-Phenylhex-2-ene-1,4,5-triyl Triacetate (14). Anhydrous Et_3N (5.02 mL, 36.0 mmol), Ac_2O (2.84 mL, 30.0 mmol), and DMAP (36 mg, 0.30 mmol) were added to a solution of triol **13** (6 mmol from *anti*,*syn*-**12**) in anhydrous CH_2Cl_2 (100 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature until TLC showed no significant changes. The solvent was removed under reduced pressure, and the mixture was purified by flash chromatography with silica gel (hexane/AcOEt 80/20) to give **14** (1.662 g, 87% from *anti*,*syn*-**12**) as a colorless oil: R_f 0.69 (CH_2Cl_2); $[\alpha]^{25}_D$ −21.8 (*c* 1.05, $CHCl_3$); IR (film) 2924, 1737, 1455, 1369, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 6.28 (d, J = 6.0 Hz, 1H), 5.94 (ddd, J = 1.1, 6.0, 15.6 Hz, 1H), 5.68 (ddd, J = 1.3, 6.7, 15.6 Hz, 1H), 5.38 (ddt, J = 1.0, 3.9, 6.7 Hz, 1H), 5.04 (qd, J = 3.9, 6.6 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 1.97 (s, 3H), 1.17 (d, J = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.9, 169.8, 138.6, 133.1, 128.6, 128.3, 127.1, 126.6, 75.0, 74.4, 70.3, 21.2, 21.0, 21.0, 15.1; HMRS (ESI+) calcd for $C_{18}H_{22}O_6Na$ $(M + Na)^+$ 357.1309, found 357.1299.

(2*S*,3*S*,4*S*,*E*)-6-Phenylhex-5-ene-2,3,4-triyl Triacetate (15). $PdCl_2(NCPh)_2$ (95 mg, 0.25 mmol) was added to a solution of **14** (1.66 g, 4.97 mmol) in CH_2Cl_2 (30 mL) and stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography with silica gel (hexane/Et_2O 70/30) to afford **15** (1.165 mg, 70%) as a colorless solid: R_f 0.41 (hexane/Et_2O 50/50); mp 68−70 °C; $[\alpha]^{25}_D$ +21.2 (*c* 0.40, $CHCl_3$); IR (film) 2925, 1740, 1457, 1370, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 6.69 (d, J = 15.8 Hz, 1H), 6.06 (dd, J = 7.3, 15.9 Hz, 1H), 5.64 (ddd, J = 0.9, 5.7, 7.3 Hz, 1H), 5.30 (t, J = 5.8 Hz, 1H), 5.07 (m, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.1, 169.9, 135.8, 134.9, 128.6, 128.4, 126.7, 122.7, 74.1, 72.2, 67.9, 21.0, 21.0, 20.8, 15.4; HMRS (ESI+) calcd for $C_{18}H_{22}O_6Na$ $(M + Na)^+$ 357.1309, found 357.1301.

(2*S*,3*S*,4*S*,5*S*)-8-(*tert*-Butyldiphenylsilyloxy)oct-6-yne-2,3,4,5-tetrayl Tetraacetate (8). A solution of **15** (167 mg, 0.500 mmol) in a mixture CH_2Cl_2/MeOH (4 mL/1 mL) was treated with O_3 at −78 °C until a blue color appeared. The flask was purged with N_2, and Me_2S (183 μL, 2.50 mmol) was added at −78 °C. The reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was coevaporated with toluene (4 × 30 mL) at 40 °C. The aldehyde **9** was obtained as a colorless oil and used as a crude mixture for the next transformation. $Zn(OTf)_2$ (600 mg, 1.65 mmol) was activated by heating under vacuum. (+)-NME (323 mg, 1.80 mmol) was added, and the flask was purged with N_2. Anhydrous toluene (2 mL) and Et_3N (251 μL, 1.80 mmol) were added, and the mixture was vigorously stirred for 2 h. A solution of alkyne **16** (441 mg, 1.50 mmol) in toluene (0.7 mL) was added and stirred for 30 min, aldehyde **9** (0.5 mmol from **15**) was added in solution in toluene (0.7 mL), and the mixture was stirred for 2 h 30 min. The reaction was quenched with saturated aqueous NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude mixture was treated with 4-DMAP (3.0 mg, 0.025 mmol), anhydrous Et_3N (280 μL, 2.00 mmol), and Ac_2O (142 μL, 1.50 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2. The reaction was stirred until TLC showed no significant change. The solvent was removed under reduced pressure. Purification by flash chromatography with silica gel (hexane/AcOEt 80/20) gave **8** (198 mg, 71% for 3 steps) as a colorless oil: R_f 0.23 (hexane/AcOEt 80/20); $[\alpha]^{25}_D$ +11.2 (*c* 0.80, $CHCl_3$); IR (film) 2933, 1752, 1429, 1371 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.46−7.36 (m, 6H), 5.49 (dt, *J* = 1.6, 7.5 Hz, 1H), 5.45 (dd, *J* = 2.7, 7.5 Hz, 1H), 5.29 (dd, *J* = 2.7, 8.0 Hz, 1H), 4.97 (dq, *J* = 6.4, 8.0 Hz, 1H), 4.30 (d, *J* = 1.6 Hz, 2H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 170.0, 169.6, 169.3, 135.6, 132.8, 129.8, 127.7, 85.2, 78.6, 71.0, 69.6, 67.1, 61.5, 52.5, 26.6, 21.0, 20.7, 20.7, 20.6, 19.1, 16.4; HMRS (ESI+) calcd for $C_{32}H_{40}O_9{}^{28}SiNa$ $(M + Na)^+$ 619.2334, found 619.2308; HMRS (ESI+) calcd for $C_{32}H_{40}O_9{}^{29}SiNa$ $(M + Na)^+$ 620.2329, found 620.2342.

(2*S*,3*S*,4*S*,5*S*,*Z*)-8-(*tert*-Butyldiphenylsilyloxy)oct-6-ene-2,3,4,5-tetrayl Tetraacetate (17). Quinoline (3 μL) and Pd/$CaCO_3$ poisoned with lead (Lindlar's catalyst, 5 wt %, 40 mg) were added to a solution of **8** (147 mg, 0.246 mmol) in AcOEt (8 mL). The mixture was shaken under hydrogen (1−2 atm) until TLC showed complete conversion. The suspension was filtered through a short pad of Celite. The organic layer was washed with 2 N HCl (2 × 1 mL) and brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography with silica gel (hexane/AcOEt 90/10) gave **17** (129 mg, 87%) as a colorless oil: R_f 0.65 (hexane/AcOEt 70/30); $[\alpha]^{25}_D$ −37.8 (*c* 1.19, $CHCl_3$); IR (film) 2935, 1750, 1429, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.66 (m, 4H), 7.45−7.36 (m, 6H), 5.87 (dt, *J* = 6.0, 11.2 Hz, 1H), 5.41−5.28 (m, 3H), 5.23 (dd, *J* = 2.3, 8.4 Hz, 1H), 4.90 (dq, *J* = 6.4, 8.4 Hz, 1H), 4.40 (ddd, *J* = 1.6, 6.0, 13.7 Hz, 1H), 4.33 (ddd, *J* = 1.6, 6.0, 13.7, 1H), 2.00 (s, 3H), 1.98 (s, 3H), 1.98 (s, 3H), 1.91 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 170.0, 169.8, 169.4, 136.6, 135.6, 135.5, 133.5, 133.4, 129.7, 127.7, 124.1, 71.0, 69.7, 67.0, 66.3, 60.2, 26.7, 21.0, 20.9, 20.6, 20.6, 19.1, 16.6; HMRS (ESI+) calcd for $C_{32}H_{42}O_9{}^{28}SiNa$ (M + Na)+ 621.2490, found 621.2485; HMRS (ESI+) calcd for $C_{32}H_{40}O_9{}^{29}SiNa$ $(M + Na)^+$ 622.2486, found 622.2516.

(2*S*,3*S*,4*S*,5*S*,*Z*)-8-Hydroxyoct-6-ene-2,3,4,5-tetrayl Tetraacetate (18). Hydrogen fluoride pyridine (500 μL) was added to a solution of **17** (176 mg, 0.294 mmol) in anhydrous CH_3CN (5 mL) and stirred until TLC showed complete conversion. The mixture was poured onto a solution of KF (10 mL), $NaHCO_3$ (20 mL), and Et_2O (30 mL). The aqueous layer was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography with silica gel (hexane/AcOEt 50/50) gave **18** (96 mg, 91%) as a colorless oil: R_f 0.08 (hexane/AcOEt 70/30); $[\alpha]^{25}_D$ −19.3 (*c* 0.650, $CHCl_3$); IR (film) 3531, 2939, 1746, 1432, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (dt, *J* = 6.8, 11.1 Hz, 1H), 5.60 (dd, *J* = 7.8, 9.9 Hz, 1H), 5.45 (dd, *J* = 9.9, 11.1 Hz, 1H), 5.38 (dd, *J* = 3.1, 7.7 Hz, 1H), 5.28 (dd, *J* = 3.1, 7.9 Hz, 1H), 4.95 (dq, *J* = 6.4, 7.8 Hz, 1H), 4.34 (m, 1H), 4.15 (m, 1H), 2.36 (dd, *J* = 5.8, 6.9 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.1, 170.1, 169.8, 135.8, 125.2, 71.2, 69.7, 67.0, 66.8, 58.5, 21.0, 21.0, 20.7, 20.6, 16.2; HMRS (ESI+) calcd for $C_{16}H_{24}O_9Na$ $(M + Na)^+$ 383.1313, found 383.1305.

(2*S*,3*S*,4*S*,5*S*,8*R*,*Z*)-8-Hydroxyundeca-6,10-diene-2,3,4,5-tetrayl Tetraacetate (20). Oxalyl chloride (21 μL, 0.25 mmol) and DMSO (30 μL, 0.42 mmol) were stirred in anhydrous CH_2Cl_2 (2 mL) for 45 min at −78 °C. A solution of **18** (32.5 mg, 0.090 mmol) in CH_2Cl_2 (1 mL) was added and stirred for 30 min at −78 °C. Et_3N (116 μL, 0.822 mmol) was added and stirred 15 min at −78 °C then 20 min at room temperature. The mixture was poured onto Et_2O (50 mL), and ammonium salts were filtered. The solvent was removed under reduced pressure, and the residue was coevaporated with toluene (4 × 20 mL) at 40 °C. The aldehyde **7** was obtained as a colorless oil and used as a crude mixture for the next transformation. Allylmagnesium bromide (1 M in Et_2O, 117 μL, 0.117 mmol) and CpTiCl-(*S,S*)-TADDOL[19] (**19**, 77 mg, 0.13 mmol) in anhydrous Et_2O (2 mL) were stirred for 1 h 30 at 0 °C. A solution of aldehyde **7** (0.090 mmol from **18**) in Et_2O (1 mL) was added dropwise at −78 °C and stirred for 1 h. The reaction was quenched with pH 7 buffer (1 mL) and stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography with silica gel (hexane/AcOEt 70/30) gave **20** (30.2 mg, 84%) and its minor diastereomer (4.5 mg, 12%) as colorless oils: R_f 0.25 (hexane/AcOEt 70/30); $[\alpha]^{25}_D$ −13.6 (*c* 1.06, $CHCl_3$); IR (film) 3529, 2934, 1748, 1436, 1372 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87−5.66 (m, 3H), 5.48 (m, 1H), 5.37 (dd, *J* = 3.9, 6.4 Hz, 1H), 5.25 (dd, *J* = 3.9, 7.1 Hz, 1H), 5.17−5.07 (m, 2H), 4.96 (dq, *J* = 6.4, 7.0 Hz, 1H), 4.54 (m, 1H), 2.66 (bs, 1H), 2.30 (m, 2H), 2.10 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 169.9, 169.9, 139.1, 133.8, 123.8, 118.1, 71.2, 69.9, 67.3, 67.2, 67.1, 41.4, 21.0, 20.9, 20.8, 20.7, 15.8; HMRS (ESI+) calcd for $C_{19}H_{28}O_9Na$ $(M + Na)^+$ 423.1626, found 423.1623.

(2*S*,3*S*,4*S*,5*S*,8*R*,*Z*)-8-(Acryloyloxy)undeca-6,10-diene-2,3,4,5-tetrayl Tetraacetate (6). Anhydrous Et_3N (30 μL, 0.21 mmol), acryloyl chloride (9 μL, 0.106 mmol), and 4-DMAP (0.3 mg, 0.003 mmol) were added to a solution of **20** (21.3 mg, 0.053 mmol) in anhydrous CH_2Cl_2 (1 mL) under N_2. The reaction was stirred until TLC showed no significant change. The solvent was removed under reduced pressure. Purification by flash chromatography with silica gel (hexane/AcOEt 80/20) gave **6** (11.8 mg, 50%) as a colorless oil: R_f 0.50 (hexane/AcOEt 70/30); $[\alpha]^{25}_D$ −37.0 (*c* 0.84, $CHCl_3$); IR (film) 2925, 1748, 1372 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 6.38 (dd, *J* = 1.6, 17.3 Hz, 1H), 6.09 (dd, *J* = 10.4, 17.3 Hz, 1H), 5.89 (m, 1H), 5.81 (dd, *J* = 1.6, 10.4 Hz, 1H), 5.78−5.58 (m, 3H), 5.45 (m, 1H), 5.36 (dd, *J* = 2.3, 8.7 Hz, 1H), 5.28 (dd, *J* = 2.3, 8.6 Hz, 1H), 5.14−5.04 (m, 2H), 4.95 (dq, *J* = 6.3, 8.6 Hz, 1H), 2.43 (m, 2H), 2.16 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.1, 170.0, 169.5, 164.8, 134.5, 132.8, 130.6, 128.7, 127.4, 118.2, 71.0, 69.6, 69.2, 66.9, 66.6, 39.0, 21.1, 20.9, 20.7, 20.6, 16.6; HMRS (ESI+) calcd for $C_{22}H_{30}O_{10}Na$ $(M + Na)^+$ 477.1731, found 477.1719.

(−)-Spicigerolide (1). A 0.01 M solution of **6** (10.8 mg, 0.025 mmol) in CH_2Cl_2 (2.5 mL) was refluxed in presence of benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidin-ylidene]dichloro(tricyclo-hexylphosphine)ruthenium (**21**, Grubbs' second generation catalyst) (0.4 mg, 0.0005 mmol) for 2 h. The solvent was removed under reduced pressure. Purification by flash chromatography with silica gel (hexane/AcOEt 80/20) gave **1** (9.8 mg, 94%) as a colorless oil: R_f 0.11 (hexane/AcOEt 70/30); $[\alpha]^{25}_D$ −23.0 (*c* 1.34, $CHCl_3$); IR (film) 2925, 1735, 1457, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (ddd, *J* = 2.6, 5.8, 9.8 Hz, 1H), 6.05 (ddd, *J* = 0.9, 2.5, 9.8 Hz, 1H), 5.79 (dd, *J* = 9.3, 10.7 Hz, 1H), 5.51−5.29 (m, 5H), 4.96 (dq, *J* = 6.3, 8.4 Hz, 1H), 2.51 (dddd, *J* = 0.9, 4.3, 5.8, 18.5 Hz, 1H), 2.35 (ddt, *J* = 2.5, 11.1, 18.5 Hz, 1H), 2.12 (s, 3H), 2.12 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.1, 169.9, 169.9, 163.5, 144.8, 132.7, 128.6, 121.4, 73.7, 70.9, 69.2, 66.9, 66.2, 29.2, 21.0, 20.9, 20.8, 20.7, 16.6; HMRS (ESI+) calcd for $C_{20}H_{26}O_{10}Na$ $(M + Na)^+$ 449.1418, found 449.1415.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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