JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

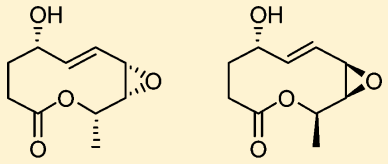
The Total Synthesis and Structural Revision of Stagonolide D

Paresh M. Vadhadiya, Vedavati G. Puranik, and C. V. Ramana*

National Chemical Laboratory (CSIR-NCL), Dr. Homi Bhabha Road, Pune—411 008, India

Supporting Information

ABSTRACT: The total synthesis of the putative structure of stagonolide D has been completed. The relative and absolute configuration of stagonolide D was established by synthesizing its optical antipode. The adopted strategy involves the construction of the central macrolide employing ring-closing metathesis (RCM), followed by selective protecting group manipulations and a final concomitant −OTBS deprotection and displacement of an −OMs placed next to it, resulting in the formation of the epoxide ring.



In 2008, Evidente et al. reported the isolation of five new nonenolides from the solid cultures of *Stagonosporta cirsii*, which have been named as stagonolides B−F (Figure 1, **2**−**6**) considering their origin and structural similarity with that of stagonolide (**1**, Figure 1).[1] The relative stereochemistry and the connectivity of the free hydroxyl groups in stagonolides B−F have been proposed as given in Figure 1 by comparing their spectral data with the herbarumins.[2] In the context of our interest in nonenolide synthesis using ring-closing metathesis (RCM) in general and in understanding how the allylic substituents influence the outcome of the RCM in particular,[3] we have recently documented the total synthesis of stagonolide B and its 4-epimer. The observations we noticed in the total synthesis of multiplolide A and stagonolide B lead to provide some prior approximations on where the RCM could be a difficult proposition in nonenolide ring construction.[3−5] The stagonolide D presents a 2*E*-ene-1,4-*cis*-disubstituted nonenolide, which is a facile system to be constructed by using the RCM reaction.[6,7] Herein, we describe the first total synthesis of the putative structure of stagonolide D and revision of its relative and absolute configurations by synthesizing the optical antipode of stagonolide D. When this paper was in preparation, Nanda and co-workers reported the synthesis of stagonolide D and confirmed its given structure.[8] However, the ^{1}H and ^{13}C NMR spectra of synthetic stagonolide D provided in the Supporting Information corresponds neither with the natural stagonolide D nor with the data of compound **4**.

Figure 1 saliently presents the key retrosynthetic disconnections. The installation of the epoxide unit was identified as the final step in the total synthesis, and a tandem TBS deprotection and concomitant epoxide formation from the mesylate **7** has been planned in this context.[3a] The penultimate intermediate **7** could be realized from the macrolide **8** through selective TBS protection of allylic −OH groups and the subsequent mesylation of the remaining −OH group. The macrolide **8** with a 2*E*-ene-1,4-*cis*-configuration was opted as a key intermediate. The intermediate macrolide **8** could be accessed from the corresponding PMB-protected macrolide **9**, which, in turn, was planned by a RCM of the diene ester **10**. The acid (*S*)-**11** and the alcohol **12** were identified as the key coupling partners for the synthesis of **10**. After a stereochemical comparison, D-xylose has been selected as a starting point for the synthesis of the alcohol fragment **12**. The corresponding retrosynthetic planning in this regard is given in Figure 1.

The synthesis began with the preparation of the alcohol **12** (Scheme 1) from known xylose-1,2-acetonide **15** and by converting it into the 5-deoxy-xylose derivative **16** by selective monotosylation of the C(5)−OH group, followed by deoxygenation with LAH.[9] The hydrolysis of the 1,2-acetonide group of **16** in the presence of allylic alcohol and cat. *p*-TSA gave the anomeric mixture of allyl xylofuranosides **17**. The protection of the free hydroxyl groups in **17** as their PMB ethers resulted in **14**. Subsequently, the compound **14** was subjected to deallylation, followed by one carbon Wittig homologation of the resulting lactols **18**, to afford the alcohol **13**. Alcohol **13**, upon Mitsunobu inversion[10] employing *p*-nitrobenzoic acid as a nucleophile, gave **19**, which, upon base-mediated ester hydrolysis, provided the key alcohol fragment **12**. The acid (*S*)-**11** has been synthesized in our group in the context of the total synthesis of stagonolide B.[3b] The coupling of acid (*S*)-**11** and alcohol **12** was carried out using the Yamaguchi reagent[11] to prepare the key RCM precursor **10**. The RCM of the fully protected diene ester **10** needed substantial optimizations. The optimized conditions involve the use of a second gen. Grubbs' catalyst and prolonged heating (96 h) of the contents in CH_2Cl_2 at 40 °C. The global deprotection of the resulting RCM product **9** by employing TFA gave the macrolide **8** as a white solid. The structure of **8** was confirmed by the spectral analysis, as well as by the single-crystal X-ray diffraction data (Figure 2).

Our next concern was the installation of the oxirane ring. The selective TBS protection of both the allylic −OH groups was carried out by using TBSCl (4 equiv, addition at 0 °C), imidazole in dichloromethane, and DMF at rt for 16 h to procure the di-*O*-TBS derivative **20** in 74% yield.[12] The treatment of **20** with methanesulphonyl chloride in the presence of triethyl amine in DCM gave the penultimate

Received: October 26, 2011
Published: February 6, 2012

ACS Publications © 2012 American Chemical Society

dx.doi.org/10.1021/jo202138g | *J. Org. Chem.* 2012, 77, 2169−2175

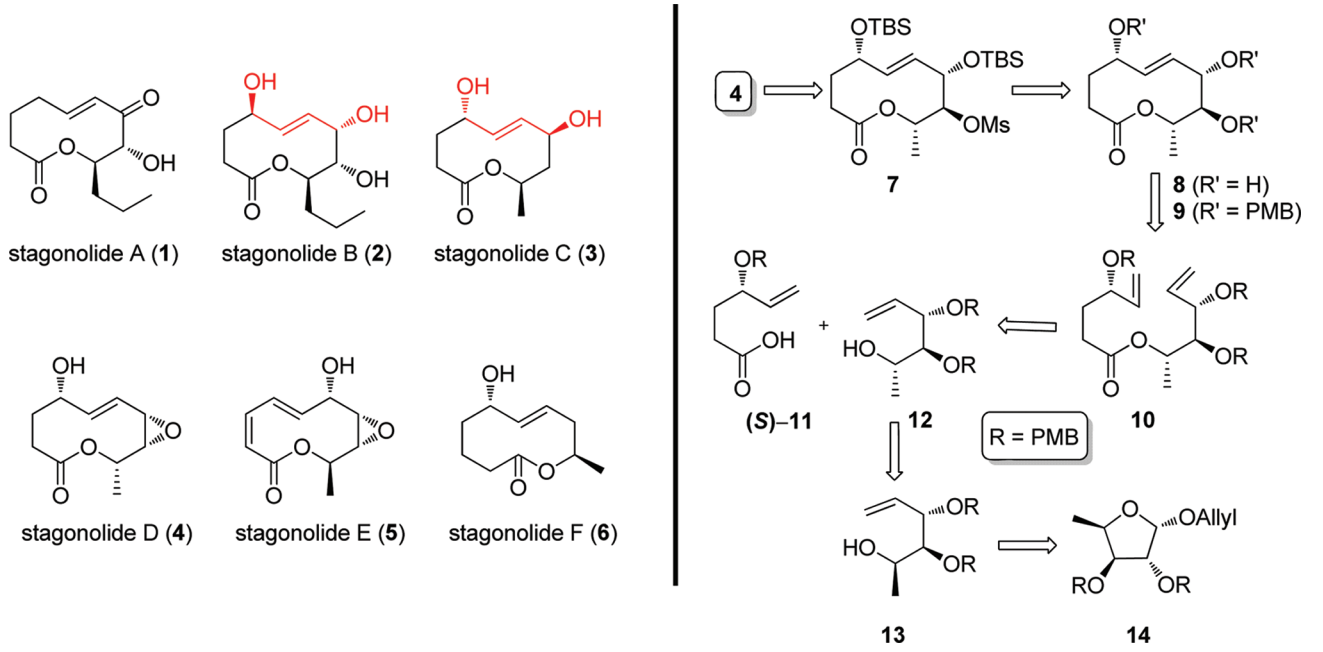
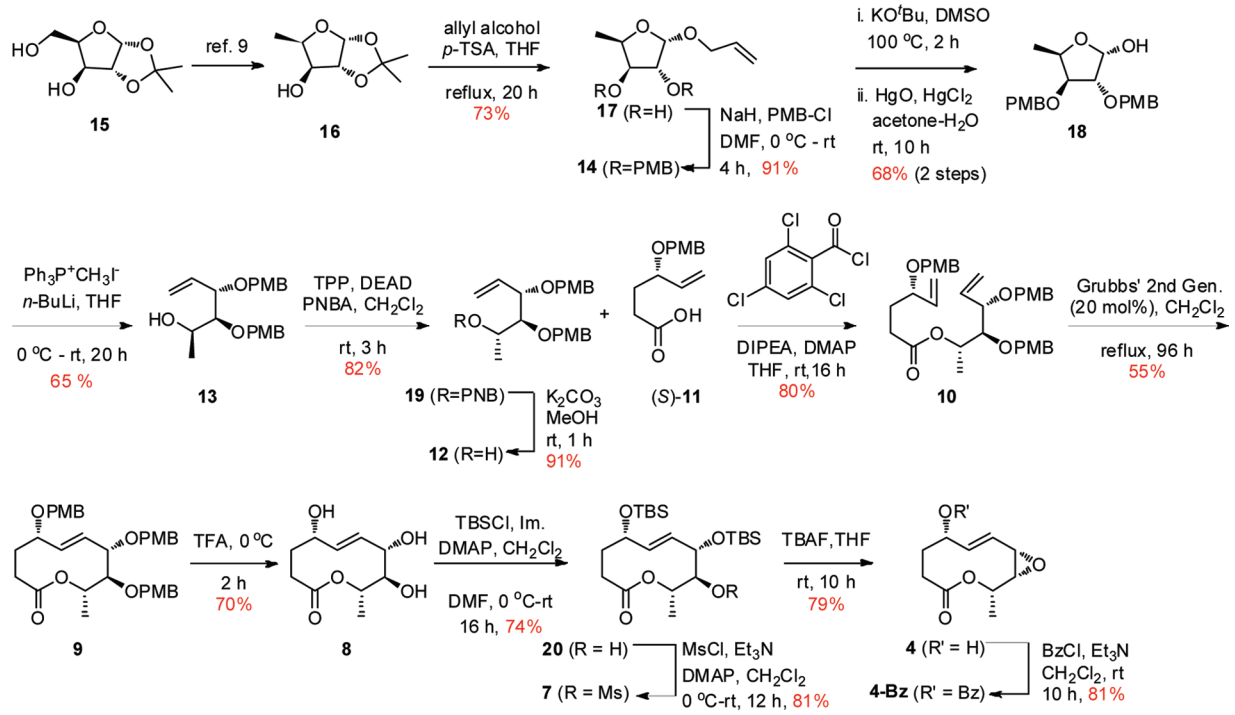


Figure 1. Structures of stagonolides A–F and key retrosynthetic disconnections for stagonolide D.

Scheme 1. Total Synthesis of Putative Structure of Stagonolide D (4)



mesylate **7**. The constitution of the mesylate was established with the help of ^{1}H NMR, COSY, and NOESY data. For example, in the ^{1}H NMR spectrum of **7**, the H–C(8) attached to the mesyloxy group appeared as a br. dd (J = 9.0, 9.6 Hz) at 4.4 ppm, whereas the same H–C(8) in compound **20** was found to resonate at 3.32 (br. dd, J = 8.8, 9.6 Hz), which is indicative of mesylation at C(8)–OH. The observed cross signal between the $H_3C(10)$ and C(8)–H in the NOESY of compound **7** further supports the assigned structure of **7**.

The treatment of compound **7** with TBAF in THF at rt gave a compound whose NMR was characterized by the presence of two sets of signals in a ratio of 2:1, indicating the occurrence of two closely related compounds. However, the data of these two compounds are comparable, but not identical, to that of the data reported for the natural stagonolide D. The major/minor ratio was not substantially temperature-dependent (−50 to +50 °C).[2a] In this regard, to further verify the possibility of two different components instead of equilibrating conformers in synthetic **4**, the corresponding benzoate **4-Bz** was made and subjected to HPLC analysis under different conditions and on different columns (see the Supporting Information for HPLC anlaysis chromatograms). However, on all the occasions, only

dx.doi.org/10.1021/jo202138g | J. Org. Chem. 2012, 77, 2169–2175

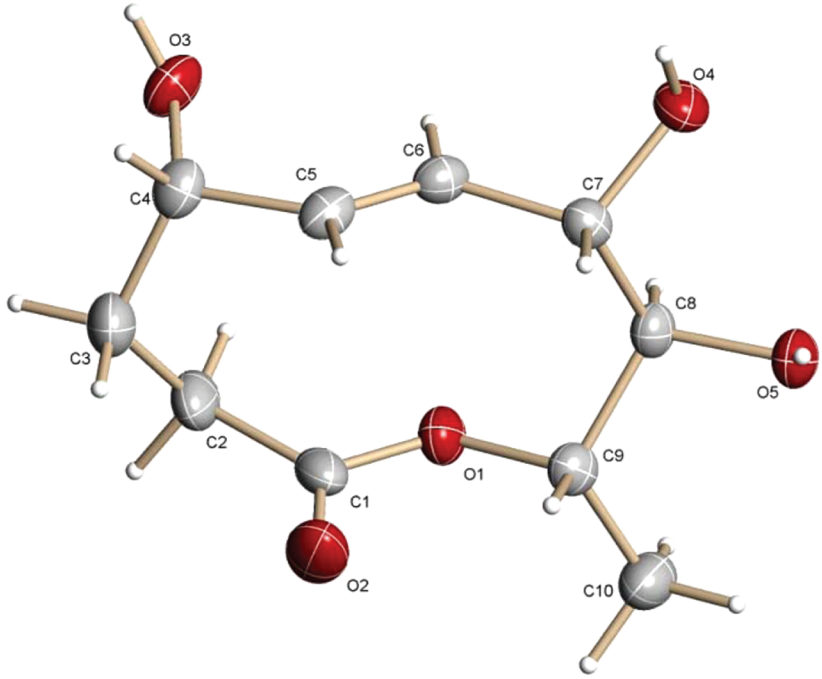
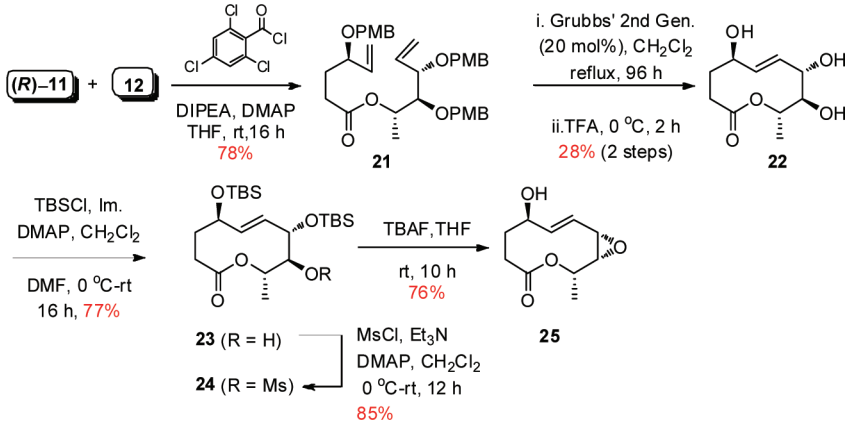


Figure 2. ORTEP diagram of the compound **8** (ellipsoids are drawn at 50% probability).

Scheme 2. Total Synthesis of (+)−Stagonolide D



one compound with >97% purity was detected. This clearly suggests the existence of two different conformers of compound **4** in solution. Furthermore, the structures of the major and the minor conformers of **4** were examined with the help of ^{1}H NMR, COSY, and NOESY data. In the ^{1}H NMR spectrum of **4**, H−C(9) of the major isomer was found to resonate at 5.33 (dq, J = 2.7, 6.8 Hz) and that of the minor isomer at 5.27 (dq, J = 1.6, 6.8 Hz), which clearly indicates that the C(9)−O forms the ester linkage. This is quite important in the context of a recent report by Marco and co-workers, who have revised the nonenolide structure of stagonolide G to a γ-lactone structure.[13] The carbonyl band at 1731 cm^{-1} in the IR spectrum of **4** is also diagnostic of a 10-membered lactone (in stagonolide G, it was 1765 cm^{-1}). The H−C(7) and H−C(8) of the major isomer appear at 3.69 (t, J = 4.2 Hz) and 3.03 (dd, J = 2.7, 4.3 Hz), respectively, whereas the same for the minor isomer appeared at 3.53 (dt, J = 1.4, 4.3 Hz) and 2.90 (dd, J = 1.6, 4.3 Hz), respectively. The observed small $J_{8,9}$ (1.6 and 2.7 Hz) in both of the conformers indicates that these two protons are cis to each other. Furthermore, the cis stereochemistry of the oxirane ring and C(10)−methyl was supported by NOE correlations present between H−C(10) and H−C(8). Thus, this extensive spectral data analysis indicates that these two compounds are equilibrating conformational isomers having the proposed structure of **4**, thus warranting structural revision of stagonolide D

Considering the fact that the spectral data of synthetic **4** and the data reported for the naturally occurring stagonolide D were found to be different mainly in the region of olefin and H−C(4) (Table 2, Supporting Information), compound **25** has been synthesized as an alternative structural possibility. As described in Scheme 2, the synthesis of **25** commenced with the preparation of the RCM precursor diene **21** by the coupling of the acid (*R*)-**11** and the alcohol **12**. As expected, the RCM of diene **21** was sluggish and also the separation of the resulting lactone from the crude reaction mixture was found to be difficult. In this context, the crude RCM reaction mixture was directly subjected to global PMB deprotection by employing TFA to obtain the triol **22** in 28% overall yield over two steps. Selective protection of the allylic hydroxyl groups as their TBS

dx.doi.org/10.1021/jo202138g | *J. Org. Chem.* 2012, 77, 2169−2175

ether gave **23**, followed by mesylation of the remaining −OH group, gave the mesylate **24**. The regioselectivity of mesylation was confirmed with the help of ^{1}H NMR, and the correlation between the methyl group of sulfonate and H−C(7) in the NOESY spectrum of **24**. Similar chemical shifts and coupling constants were noticed for H−C(7) to H−C(10) for mesylates **24** and **7**, thereby providing the assurance that we were on the right track. The mesylate **24** was advanced for the oxirane formation employing TBAF at rt in THF, which gave compound **25**. Compound **25** was also found to be existing as a 10:1 mixture of two equilibrating conformational isomers.[14,15] This was established with the help of ^{1}H NMR, COSY, and NOESY data. The spectral data of the major conformer of compound **25** was in agreement with the data reported for the natural product (Tables 2 and 3, Supporting Information).[1] The opposite sign of the specific rotation of synthetic stagonolide (**25**) [+76.8 (*c* 0.2, $CHCl_3$)] and natural stagonolide [−82.0 (*c* 0.2, $CHCl_3$)][1a] revealed that it was the *anti*-pode of natural stagonolide D.

To conclude, the total synthesis of the putative structure of stagonolide D and of the unnatural enantiomer (+)−stagonolide D has been accomplished, thus revising its proposed relative configuration and also determining its absolute configuration as (4*S*,7*R*,8*R*,9*S*). The key nonenolide unit has been constructed by employing ring-closing metathesis, and the oxirane ring has been formed by a concomitant *O*-TBS deprotection and displacement of an adjacent −OMs group.

EXPERIMENTAL SECTION

General Methods. Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane and DMF from CaH_2, methanol from Mg cake, THF on Na/benzophenone, and triethylamine over KOH. Commercial reagents were used without purification. Column chromatography was carried out by using spectrochem silica gel (60−120, 100−200, 230−400 mesh). ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million relative to chloroform-*d* (δ = 7.25) or TMS and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.

Allyl-5-deoxy-α/β-D-xylofuranosides (17). A solution of **16** (10.0 g, 57.4 mmol), *p*-TSA (2.0 g, 17.2 mmol), and allyl alcohol (25 mL, 344.4 mmol) in anhydrous THF (100 mL) was refluxed for 20 h. After completion, the reaction mixture was neutralized with aq $NaHCO_3$ and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (40 → 50% EtOAc in petroleum ether) to afford **17** (7.3 g, 73%) as a yellow oil. R_f 0.3 (40% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.5 Hz, 3H, minor), 1.30 (d, *J* = 6.6 Hz, 3H, major), 2.68 (br s, 2H), 3.85−4.07 (m, 2H), 4.09−4.27 (m, 2H), 4.31−4.34 (m, 1H, minor), 4.45 (dq, *J* = 4.3, 6.6 Hz, 1H, major), 4.92 (s, 1H, major), 5.10 (d, *J* = 4.1 Hz, 1H, minor), 5.16−5.30 (m, 2H), 5.86 (ddt, *J* = 5.4, 10.6, 17.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2 (minor), 15.3 (major), 68.1 (major), 69.1 (minor), 75.0 (minor), 77.0 (major), 77.7 (minor), 78.8 (minor), 79.1 (major), 80.1 (major), 99.5 (minor), 106.1 (major), 117.7, 133.6 (major), 133.7 (minor) ppm; ESI-MS 197.12 (100%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_8H_{14}O_4Na$, 197.0790; found, 197.0797.

Allyl-2,3-di-*O*-(*p*-methoxybenzyl)-α/β-D-xylofuranosides (14). To a cooled solution of **17** (10.0 g, 57.4 mmol) in anhydrous DMF (80 mL) was added NaH (60% dispersion in mineral oil, 5.3 g, 132.0 mmol), followed by PMB-Cl (16 mL, 121 mmol), and the contents stirred at rt for 4 h. The reaction mixture was quenched with aq Na_2SO_4, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to procure **14** (21.6 g, 91%) as a yellow oil. R_f 0.4 (10% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.4 Hz, 3H, minor), 1.29 (d, *J* = 6.6 Hz, 3H, major), 3.81 (s, 6H), 3.89 (dd, *J* = 3.5, 5.8 Hz, 1H), 3.97−4.16 (m, 2H), 4.20−4.39 (m, 2H), 4.44−4.56 (m, 4H), 4.92 (d, *J* = 4.3 Hz, 1H, minor), 4.97 (d, *J* = 2.0 Hz, 1H, major), 5.18 (ddt, *J* = 1.4, 3.0, 10.5 Hz, 1H), 5.29 (ddt, *J* = 1.6, 3.2, 17.2 Hz, 1H), 5.92 (ddt, *J* = 5.05, 10.6, 17.1 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.5 Hz 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.5 (minor), 16.1 (major), 55.2 (2C), 68.3 (minor), 68.7 (major), 71.5 (major), 71.7 (major), 71.8 (minor), 72.0 (minor), 73.4 (minor), 76.7 (major), 81.9 (minor), 82.3 (major), 83.9 (minor), 87.2 (major), 98.2 (minor), 106.1 (major), 113.7 (2C), 113.8 (2C), 117.0 (major), 117.4 (minor), 129.3 (2C), 129.4 (2C), 129.8, 130.1, 134.4, 159.2, 159.3 ppm; ESI-MS 437.33 (100%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{24}H_{30}O_6Na$, 437.1940; found, 437.1924.

2,3-Di-*O*-(*p*-methoxybenzyl)-α/β-D-xylofuranosides (18). A suspension of **14** (9 g, 21.7 mmol) and KO^{t}Bu (6.1 g, 54.2 mmol) in DMSO (80 mL) was heated at 100 °C for 2 h. The reaction mixture was diluted with brine and extracted with EtOAc. The combined organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. The resulting product (8.8 g, 21.2 mmol) was taken in an acetone/water mixture (9:1, 75 mL), cooled to 0 °C, treated with yellow HgO (5.9 g, 27.6 mmol) and $HgCl_2$ (6.3 g, 23.4 mmol) over a period of 30 min, and stirred for 10 h at rt. The contents were filtered through Celite, and the filtrate was concentrated. The residue was diluted with EtOAc and was washed with sat. KI solution and brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by silica gel column chromatography (20 → 25% EtOAc in petroleum ether) gave **18** (5.6 g, 68%) as a yellow oil. R_f 0.3 (25% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.4 Hz, 1.5H), 1.33 (d, *J* = 6.6 Hz, 1.5H), 3.72−3.77 (m, 1H), 3.81 (br s, 6H), 3.90−3.94 (m, 1H), 4.30 (dq, *J* = 4.3, 6.5 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.49−4.58 (m, 2H), 5.19 (s, 0.5H), 5.41 (br s, 0.5H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 15.3, 55.2 (4C), 71.4, 71.5, 71.8, 72.7, 74.4, 77.7, 80.8, 81.6, 81.8, 84.8, 95.4, 100.9, 113.7 (2C), 113.8 (4C), 113.9 (2C), 128.8, 129.1 (2C), 129.2, 129.2 (2C), 129.4 (2C), 129.4, 129.6 (2C), 129.8, 159.2, 159.3, 159.4, 159.5, ppm; ESI-MS 397.21 (65%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{21}H_{26}O_6Na$, 397.1627; found, 397.1653.

(2*R*,3*S*,4*S*)-3,4-Bis((4-methoxybenzyl)oxy)hex-5-en-2-ol (13). At 0 °C, a solution of methyltriphenylphosphorane ylide [generated by the action of *n*-butyl lithium (12.7 mL, 20.3 mmol) with $Ph_3P^+CH_3Br^-$ (7.63 g, 21.4 mmol) in anhydrous THF (50 mL) at 0 °C] was treated with a solution of **18** (2.0 g, 5.34 mmol) in THF (10 mL) and the contents stirred at rt for 20 h. To this was added sat. NH_4Cl, and it was filtered. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography (12 → 15% EtOAc in petroleum ether) to obtain **13** (1.3 g, 65%) as a yellow oil. R_f 0.5 (25% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +5.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.4 Hz, 3H), 2.30 (d, *J* = 5.3 Hz, 1H), 3.20 (dd, *J* = 4.2, 5.4 Hz, 1H), 3.79 (s, 6H), 3.84−3.93 (m, 1H), 4.01 (dd, *J* = 5.7, 7.6 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 1H), 5.32−5.41 (m, 2H), 5.89 (ddd, *J* = 7.4, 9.9, 17.6, Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 4H), 7.25 (d, *J* = 8.6 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 55.2 (2C), 67.2, 70.2, 74.8, 81.2, 84.8, 113.7 (2C), 113.7 (2C), 118.9, 129.5 (2C), 129.8 (2C), 130.3, 130.4, 135.5, 159.1, 159.3 ppm; ESI-MS 395.22 (100%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{22}H_{28}O_5Na$, 395.1834; found, 395.1831.

(2*S*,3*S*,4*S*)-3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-yl 4-nitrobenzoate (19). To a solution of alcohol **13** (1.5 g, 4.0 mmol), *p*-nitrobenzoic acid (740 mg, 4.43 mmol), and TPP (2.11 g, 8.1

dx.doi.org/10.1021/jo202138g | J. Org. Chem. 2012, 77, 2169−2175

mmol), in THF (10 mL) at 0 °C was added DEAD (1.27 mL, 8.1 mmol), and it was stirred at 0 °C for 1 h and then at rt for 2 h. After completion, THF was removed, and the crude product was dissolved in EtOAc and washed with aq $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. The purification of residue by silica gel column chromatography (8 → 10% EtOAc in petroleum ether) afforded **19** (1.73 g, 82%) as a yellow oil. R_f 0.6 (15% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −3.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.4 Hz, 3H), 3.72 (m, 1H), 3.73 (s, 3H), 3.77 (s, 3H), 3.91 (dd, *J* = 5.7, 8.0 Hz, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 5.22 (dq, *J* = 4.4, 6.4 Hz, 1H), 5.31−5.41 (m, 2H), 5.90 (ddd, *J* = 7.8, 10.7, 16.8 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.1, 55.1, 55.1, 70.1, 72.4, 74.5, 81.0, 82.2, 113.6 (2C), 113.7 (2C), 119.4, 123.3 (2C), 129.6 (2C), 129.7 (2C), 130.1, 130.5, 130.6 (2C), 135.1, 135.8, 150.3, 159.1, 159.2, 163.7 ppm; ESI-MS 544.36 (30%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{29}H_{31}NO_8Na$, 544.1947; found, 544.1903.

(2*S*,3*S*,4*S*)-3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-ol (12). To a solution of **19** (1.7 g, 3.26 mmol) in methanol (15 mL) was added K_2CO_3 (0.9 g, 6.5 mmol), and it was stirred at rt for 1 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (12 → 15% EtOAc in petroleum ether) to afford **12** (1.1 g, 91%) as a yellow oil. R_f 0.3 (15% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +12.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.3 Hz, 3H), 2.81 (d, *J* = 5.7 Hz, 1H), 3.34 (dd, *J* = 5.0, 6.1 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.87 (dd, *J* = 6.2, 12.2 Hz, 1H), 4.01 (dd, *J* = 5.0, 7.3 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 5.29− 5.39 (m, 1H), 5.91 (ddd, *J* = 7.4, 10.9, 18.3 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0, 55.2 (2C), 67.3, 70.2, 73.5, 80.6, 83.1, 113.7 (2C), 113.8 (2C), 119.1, 129.6 (2C), 129.6 (2C), 129.8, 130.4, 134.6, 159.2, 159.3 ppm; ESI-MS 395.22 (100%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{22}H_{28}O_5Na$, 395.1834; found, 395.1873.

(*S*)-((2*S*,3*S*,4*S*)-3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-yl)4-(4-methoxybenzyloxy)hex-5-enoate (10). To a solution of acid (*S*)-**11** (0.8 g, 3.2 mmol) in THF (13 mL) were added 2,4,6-trichlorobenzoyl chloride (0.6 mL, 3.84 mmol) and *N*,*N*-diisopropyl ethyl amine (3.2 mL, 18.4 mmol), and the contents were stirred for 2 h at rt. Subsequently, DMAP (0.78 g, 6.4 mmol) and a solution of **12** (1.19 g, 3.2 mmol) in THF (5 mL) were added, and stirring was continued at rt for 16 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic phase was washed with aq. $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (9 → 10% EtOAc in petroleum ether) to afford **10** (1.55 g, 80%) as a yellow oil. R_f 0.5 (20% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −12.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.5, 3H), 1.75−1.88 (m, 2H), 2.24−2.32 (m, 2H), 3.55 (dd, *J* = 3.8, 6.2 Hz, 1H), 3.68−3.82 (m, 2H), 3.78 (s, 3H), 3.79 (s, 6H), 4.25 (d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.99 (dq, *J* = 3.8, 6.5 Hz, 1H), 5.17−5.34 (m, 4H), 5.62−5.91 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 3H), 6.85 (d, *J* = 8.7 Hz, 3H), 7.23 (d, *J* = 8.7 Hz, 3H), 7.27 (d, *J* = 8.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 30.3, 30.4, 55.2 (3C), 69.8, 70.1, 71.0, 74.5, 78.9, 81.4, 82.6, 113.6 (2C), 113.6 (2C), 113.7 (2C), 117.5, 119.1, 129.3 (2C), 129.4 (2C), 129.6 (2C), 130.3, 130.5, 130.7, 135.2, 138.3, 159.0, 159.0, 159.1, 172.5 ppm; ESI-MS 627.81 (100%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{36}H_{44}O_8Na$, 627.2934; found, 627.2935.

(5*S*,8*S*,9*S*,10*S*,*E*)-5,8,9-Tris(4-methoxybenzyloxy)-10-methyl-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (9). To a solution of **10** (50 mg, 82 μmol) in dry dichloromethane (20 mL) was added the second gen. Grubbs' catalyst (13.5 mg, 13 μmol), and the mixture was degassed under an argon atmosphere thoroughly. The reaction mixture was refluxed for 96 h, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (12 → 15% EtOAc in petroleum ether) to afford **9** (26 mg, 55%) as a white amorphous solid. R_f 0.45 (20% EtOAc in petroleum ether); mp 94−97 °C; $[\alpha]_D^{25}$ +10.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.4 Hz, 3H), 1.99−2.02 (m, 2H), 2.04−2.09 (m, 1H), 2.46 (ddd, *J* = 4.6, 10.1, 14.4 Hz, 1H), 3.41 (t, *J* = 9.2 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.84 (t, *J* = 9.1 Hz, 1H), 4.13 (dd, *J* = 4.3, 6.2 Hz, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.56 (d, *J* = 10.1 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.96 (dq, *J* = 3.6, 6.4 Hz, 1H), 5.39 (dd, *J* = 3.0, 15.9 Hz, 1H), 5.89 (ddd, *J* = 1.2, 10.1, 15.9 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 28.8, 30.4, 55.3, 55.3, 55.3, 69.4, 69.6, 70.4, 74.8, 75.5, 82.5, 84.7, 113.7 (2C), 113.7 (2C), 113.8 (2C), 129.1 (2C), 129.4 (2C), 129.6, 129.8 (2C), 130.4, 130.6, 130.7 (2C), 159.0, 159.2, 159.2, 175.2 ppm; ESI-MS 599.57 (100%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{34}H_{40}O_8Na$, 599.2621; found, 599.2638.

(5*S*,8*S*,9*R*,10*S*,*E*)-5,8,9-Trihydroxy-10-methyl-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (8). A solution of **9** (100 mg, 0.17 mmol) in TFA (2 mL) was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (70 → 100% EtOAc in petroleum ether) to afford **8** (26 mg, 70%) as a white crystalline solid. R_f 0.2 (80% EtOAc in petroleum ether); mp 184−187 °C; $[\alpha]_D^{25}$ −7.6 (*c* 0.3, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.4 Hz, 3H), 1.84−1.89 (m, 1H), 1.98−2.01 (m, 1H), 2.04 (ddd, *J* = 2.4, 5.9, 12.9 Hz, 1H), 2.44 (dt, *J* = 2.1, 13.7 Hz, 1H), 3.22 (t, *J* = 9.2 Hz, 1H), 3.73 (t, *J* = 9.4 Hz, 1H), 4.42 (m, 1H), 4.85 (dq, *J* = 6.4, 9.6 Hz, 1H), 5.50 (dd, *J* = 2.7, 15.7 Hz, 1H), 5.85 (ddd, *J* = 1.6, 9.9, 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 29.0, 33.0, 68.9, 71.4, 77.2, 78.2, 130.7, 133.4, 177.1 ppm; HRMS (*m*/*z*) calcd for $C_{10}H_{17}O_5$, 217.1076; found, 217.1063.

(5*S*,8*S*,9*S*,10*S*,*E*)-5,8-Bis(*tert*-butyldimethylsilyloxy)-9-hydroxy-10-methyl-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (20). At 0 °C, a solution of **8** (30 mg, 0.14 mmol), imidazole (47 mg, 0.69 mmol), and DMAP (4 mg, 0.03 mmol) in DCM−DMF (0.5 mL each) was treated with TBSCl (84 mg, 0.55 mmol), and the contents were stirred at rt for 16 h. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. The residue was purified by column chromatography (4 → 5% EtOAc in petroleum ether) to afford **20** (46 mg, 74%) as a yellow oil. R_f 0.6 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +6.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.71−1.76 (m, 1H), 1.99−2.06 (m, 2H), 2.43 (dt, *J* = 1.5, 13.6 Hz, 1H), 2.91 (s, 1H), 3.32 (dd, *J* = 8.8, 9.5 Hz, 1H), 3.84 (t, *J* = 9.2 Hz, 1H), 4.43 (m, 1H), 4.97 (dq, *J* = 6.4, 9.4 Hz, 1H), 5.47 (dd, *J* = 2.5, 15.4 Hz, 1H), 5.81 (ddd, *J* = 1.6, 9.8, 15.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −5.0, −4.7, −3.6, 18.0, 18.2, 18.2, 25.8 (3C), 25.8 (3C), 28.0, 33.1, 68.8, 69.6, 76.0, 78.6, 130.2, 133.1, 175.4 ppm; ESI-MS 467.35 (33%, $[M + Na]^+$); HRMS (*m*/*z*) calcd for $C_{22}H_{44}O_5Si_2Na$, 467.2625; found, 467.2601.

(2*S*,3*S*,4*S*,7*S*,*E*)-4,7-Bis(*tert*-butyldimethylsilyloxy)-2-methyl-10-oxo-3,4,7,8,9,10-hexahydro-2*H*-oxecin-3-yl Methanesulfonate (7). At 0 °C, a solution of **20** (25 mg, 0.06 mmol), triethylamine (20 μL, 0.14 mmol), and DMAP (cat.) was treated with methanesulphonyl chloride (10 μL, 0.13 mmol) and stirred at rt for 12 h. The reaction was portioned between water and DCM, and the aqueous layer was extracted with DCM. The combined organic layer was dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (7 → 8% EtOAc in petroleum ether) gave **7** (24 mg, 81%) as a yellow oil. R_f 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +18.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 6H), 0.86 (s, 9H), 0.92 (s, 9H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.74−1.76 (m, 1H), 1.95 (tt, *J* = 2.2, 13.2 Hz, 1H), 2.04 (ddd, *J* = 2.1, 6.1, 13.5 Hz, 1H), 2.46 (dt, *J* = 1.5, 13.2 Hz, 1H), 3.08 (s, 3H), 4.12 (t, *J* = 9.2 Hz, 1H), 4.44 (br dd, *J* =

dx.doi.org/10.1021/jo202138g | *J. Org. Chem.* 2012, 77, 2169−2175

9.0, 9.6 Hz, 2H), 5.01 (dq, J = 6.9, 9.6 Hz, 1H), 5.42 (dd, J = 2.3, 15.4 Hz, 1H), 5.82 (ddd, J = 1.5, 9.8, 15.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −5.0, −3.8, −3.3, 18.1, 18.3, 18.5, 25.8 (3C), 26.2 (3C), 27.9, 32.6, 39.3, 68.5, 68.5, 76.1, 84.2, 130.2, 132.4, 175.3 ppm; ESI-MS 545.96 (100%, $[M + Na]^+$); HRMS (m/z) calcd for $C_{23}H_{46}O_7SSi_2Na$, 545.2400; found, 545.2408.

(1*R*,2*S*,7*S*,10*S*,*E*)-7-Hydroxy-2-methyl-3,11-dioxabicyclo-[8.1.0]undec-8-en-4-one (4). To a solution of **7** (30 mg, 0.06 mmol) in dry THF (1 mL), a 1 M solution of TBAF in THF (172 μL, 0.17 mmol) was added at 0 °C, and the contents were stirred at rt for 10 h. To this was added sat. NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified on a silica gel column (40% EtOAc in petroleum ether) to afford **4** (9 mg, 79%) as a yellow oil. R_f 0.4 (60% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +9.1 (c 0.2, $CHCl_3$); IR ($CHCl_3$) ν 3336, 2924, 1733, 1602, 1542, 1456, 1270, 1121 cm^{-1}; HRMS (m/z) calcd for $C_{10}H_{14}O_4Na$, 221.0790; found, 221.0786.

Spectral Data of Major Conformer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, J = 6.8 Hz, 3H), 1.89−2.07 (m, 2H,), 2.14−2.26 (m, 1H,), 2.49 (t, J = 14.0 Hz, 1H,), 3.03 (dd, J = 2.7, 4.1 Hz, 1H), 3.69 (t, J = 4.6 Hz, 1H), 4.54 (br s, 1H), 5.33 (dq, J = 2.7, 6.8 Hz, 1H), 5.68 (ddd, J = 1.1, 3.2, 17.1 Hz, 1H), 5.94 (ddd, J = 1.1, 4.8, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 27.7, 33.4, 55.9, 57.3, 65.1, 68.1, 126.2, 134.0, 174.6 ppm.

Spectral Data of Minor Conformer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, J = 6.8 Hz, 3H), 1.89−2.07 (m, 2H, merged with major conformer signal), 2.14−2.26 (m, 1H, merged with major conformer signal), 2.44−2.53 (m, 1H, merged with major conformer signal), 2.90 (dd, J = 1.6, 4.3 Hz, 1H), 3.53 (dt, J = 1.4, 4.3 Hz, 1H), 4.20 (dt, J = 4.7, 8.3 Hz, 1H), 5.27 (dq, J = 1.5, 6.8 Hz, 1H), 5.53 (dd, J = 1.1, 16.0 Hz, 1H), 5.75 (ddd, J = 1.1, 8.7, 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 31.7, 32.5, 55.8, 57.6, 66.2, 72.7, 120.6, 135.3, 172.1 ppm.

(1*R*,2*S*,7*S*,10*S*,*E*)-2-Methyl-4-oxo-3,11-dioxabicyclo[8.1.0]-undec-8-en-7-yl-4-nitrobenzoate (4-Bz). At 0 °C, to a solution of *p*-nitrobenzoic acid (11 mg, 65 μmol) and DMF (cat.) in DCM (1 mL) was added oxalyl chloride (4 μL, 60 μmol), and the content were stirred at rt for 6 h. The excess of oxalyl chloride was removed under an argon atmosphere. The crude product was dissolved in dry DCM, cooled to 0 °C, and treated with a solution of Et_3N (14 μL, 100 μmol) and alcohol **4** (10 mg, 50 μmol) in DCM (0.5 mL), and the reaction mixture was stirred at rt for 10 h. To this was added water, and the aqueous layer was extracted with DCM. The combined organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified on a silica gel column (20 → 22% EtOAc in petroleum ether) to afford **4-Bz** (14 mg, 81%) as a yellow oil. R_f 0.5 (40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +27.9 (c 0.7, $CHCl_3$); HRMS (m/z) calcd for $C_{17}H_{17}NO_7Na$, 370.0903; found, 370.0931.

Spectral Data of Major Conformer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, J = 6.8 Hz, 3H), 2.21−2.30 (m, 2H), 2.37−2.49 (m, 2H), 3.05 (dd, J = 2.5, 4.1 Hz, 1H), 3.69 (tt, J = 1.3, 4.6 Hz, 1H), 5.42 (dq, J = 2.4, 6.8 Hz, 1H), 5.67 (br s, 1H), 5.74 (dd, J = 1.3, 17.2 Hz, 1H), 5.86 (dd, J = 4.6, 17.1 Hz, 1H), 8.24 (d, J = 8.9 Hz, 2H), 8.30 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 28.9, 31.5, 55.5, 57.5, 65.3, 75.9, 123.0 (2C), 127.5, 128.9, 130.8 (2C), 130.8, 135.3, 163.8, 173.8 ppm.

Spectral Data of Minor Conformer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, J = 6.8 Hz, 3H), 2.11−2.20 (m, 2H), 2.30−2.36 (m, 1H), 2.52−2.58 (m, 1H), 2.94 (dd, J = 1.4, 4.3 Hz, 1H), 3.58 (br d, J = 4.2 Hz, 1H), 5.34 (dq, J = 1.3, 6.8 Hz, 1H), 5.48 (dt, J = 4.2, 8.2 Hz, 1H), 5.74 (dd, J = 1.1, 17.1 Hz, 1H), 5.90 (dd, J = 4.1, 17.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.28 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 30.2, 31.4, 55.7, 57.7, 62.2, 75.7, 122.7, 123.6 (2C), 130.7 (2C), 130.8, 130.8, 135.5, 163.3, 171.9 ppm.

(*R*)-((2*S*,3*S*,4*S*)-3,4-Bis(4-methoxybenzyloxy)hex-5-en-2-yl)-4-(4-methoxybenzyloxy)hex-5-enoate (21). The coupling of acid (*R*)-**11** (1.0 g, 4.0 mmol) and the alcohol **12** (1.5 g, 4.0 mmol) was carried out according to the procedure used for the preparation of **10** to afford **21** (1.89 g, 78%) as a yellow oil. R_f 0.5 (20% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +3.8 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3H), 1.75−1.97 (m, 2H), 2.11−2.43 (m, 2H), 3.56 (dd, J = 3.7, 6.2 Hz, 1H), 3.68−3.75 (m, 1H), 3.78 (s, 3H), 3.79 (s, 6H), 3.82−3.92 (m, 1H), 4.24 (d, J = 11.3 Hz, 1H), 4.28 (d, J = 11.4 Hz, 1H), 4.51 (d, J = 11.4 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.61 (d, J = 11.3 Hz, 1H), 4.67 (d, J = 11.2 Hz, 1H), 4.99 (dq, J = 3.8, 6.4 Hz, 1H), 5.17−5.34 (m, 4H), 5.69 (ddd, J = 7.6, 11.0, 16.4 Hz, 1H), 5.83 (ddd, J = 8.1, 10.6, 16.9 Hz, 1H), 6.82−6.86 (m, 6H), 7.21−7.29 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 30.3, 30.5, 55.2 (3C), 69.8, 70.1, 71.0, 74.6, 79.1, 81.5, 82.6, 113.6 (2C), 113.6 (2C), 113.7 (2C), 117.6, 119.1, 129.3 (2C), 129.4 (2C), 129.6 (2C), 130.3, 130.5, 130.7, 135.2, 138.3, 159.0, 159.0, 159.1, 172.5 ppm; ESI-MS 627.68 (100%, $[M + Na]^+$); HRMS (m/z) calcd for $C_{36}H_{44}O_8Na$, 627.2934; found, 627.2948.

(5*R*,8*S*,9*R*,10*S*,*E*)-5,8,9-Trihydroxy-10-methyl-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (22). The same procedure as in the preparation of **9** was used with the diene **21** (100 mg, 0.16 mmol) to procure the impure macrolide. The above macrolide was suspended at 0 °C in TFA (2 mL) and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (70 → 100% EtOAc in petroleum ether) to obtain **22** (10 mg, 28%) as a yellow viscous liquid. R_f 0.2 (85% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −20.9 (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.4 Hz, 3H), 1.75−1.85 (m, 1H), 1.91−1.98 (m, 1H), 2.05 (dt, J = 1.8, 13.6 Hz, 1H), 2.29 (ddd, J = 2.4, 6.3, 13.8 Hz, 1H), 3.21 (t, J = 9.1 Hz, 1H), 3.67 (t, J = 9.1 Hz, 1H), 4.02 (ddd, J = 4.9, 9.9, 14.2 Hz, 1H), 4.84 (dq, J = 6.4, 9.7 Hz, 1H), 5.33 (dd, J = 9.1, 15.6 Hz, 1H), 5.63 (dd, J = 9.6, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 32.3, 33.8, 71.4, 75.3, 77.5, 77.8, 133.5, 133.9, 176.0 ppm; HRMS (m/z) calcd for $C_{10}H_{16}O_5Na$, 239.0895; found, 239.0871.

(5*R*,8*S*,9*S*,10*S*,*E*)-5,8-Bis(*tert*-butyldimethylsilyloxy)-9-hydroxy-10-methyl-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (23). The same procedure as in the preparation of **20** was used with the triol **22** (25 mg, 0.12 mmol) to procure **23** (40 mg, 77%) as a yellow oil. R_f 0.6 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −12.4 (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.30 (d, J = 6.4 Hz, 3H), 1.81−1.87 (m, 1H), 1.90−2.03 (m, 2H), 2.21−2.32 (m, 1H), 2.82 (s, 1H), 3.28 (dd, J = 8.6, 9.4 Hz, 1H), 3.78 (t, J = 8.6 Hz, 1H), 3.99 (dt, J = 5.4, 9.1 Hz, 1H), 4.95 (dq, J = 6.4, 9.5 Hz, 1H), 5.41 (dd, J = 8.3, 15.7 Hz, 1H), 5.48 (dd, J = 8.6, 15.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.8, −4.6, −3.6, 18.0, 18.1, 18.1, 25.7 (3C), 25.8 (3C), 31.4, 34.00, 69.5, 75.1, 76.4, 78.3, 131.1, 134.8, 173.8 ppm; ESI-MS 467.34 (100%, $[M + Na]^+$); HRMS (m/z) calcd for $C_{22}H_{44}O_5Si_2Na$, 467.2625; found, 467.2603.

(2*S*,3*S*,4*S*,7*R*,*E*)-4,7-Bis(*tert*-butyldimethylsilyloxy)-2-methyl-10-oxo-3,4,7,8,9,10-hexahydro-2*H*-oxecin-3-yl Methanesulfonate (24). The same procedure as in the preparation of **7** was used with the alcohol **23** (20 mg, 0.05 mmol), affording **24** (20 mg, 85%) as a yellow oil. R_f 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −7.6 (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.36 (d, J = 6.6 Hz, 3H), 1.82−1.91 (m, 2H), 1.98 (dt, J = 2.6, 12.7 Hz, 1H), 2.26−2.36 (m, 1H), 3.07 (s, 3H), 4.01 (ddd, J = 5.5, 8.2, 9.5 Hz, 1H), 4.07 (dd, J = 8.1, 8.7 Hz, 1H), 4.39 (dd, J = 8.7, 9.8 Hz, 1H), 4.98 (dq, J = 6.6, 9.8 Hz, 1H), 5.37 (dd, J = 8.1, 15.9 Hz, 1H), 5.45 (dd, J = 8.8, 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.7, −3.9, −3.2, 18.0, 18.2, 18.4, 25.6 (3C), 26.1 (3C), 31.2, 33.5, 39.3, 68.5, 75.1, 75.8, 84.1, 130.6, 134.2, 173.8 ppm; ESI-MS 545.33 (100%, $[M + Na]^+$); HRMS (m/z) calcd for $C_{23}H_{46}O_7SSi_2Na$, 545.2400; found, 545.2408.

(+)-Stagonolide D (25). The same procedure as in the preparation of **4** was used with **24** (20 mg, 0.04 mmol) to procure **25** (6 mg, 76%) as a white crystalline solid. R_f 0.4 (60% EtOAc in petroleum ether); mp 78−81 °C; $[\alpha]_D^{25}$ +76.8 (c 0.2, $CHCl_3$); IR ($CHCl_3$) ν 3435, 2925, 2851, 1731, 1635, 1456, 1384, 1089, 728 cm^{-1}; HRMS (m/z) calcd for $C_{10}H_{15}O_4$, 199.0970; found, 199.0961.

Spectral Data of Major Conformer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, J = 6.8 Hz, 3H), 1.98−2.14 (m, 3H), 2.28 (ddd, J = 1.9, 8.3, 14.2 Hz, 1H), 3.05 (dd, J = 2.6, 4.1 Hz, 1H), 3.65 (br t, J = 4.6 Hz,

1H), 4.13 (ddd, J = 4.4, 8.3, 10.5 Hz, 1H), 5.35 (dq, J = 2.7, 6.8 Hz, 1H), 5.52 (ddd, J = 0.9, 8.3, 17.0 Hz, 1H), 5.65 (dd, J = 4.9, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 31.2, 35.0, 55.4, 58.2, 65.7, 75.1, 128.2, 134.1, 173.5 ppm.

Spectral Data of Minor Conformer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, J = 6.8 Hz, 3H), 1.84−1.90 (m, 1H), 2.16−2.19 (m, 1H), 2.22 (dd, J = 3.9, 5.2 Hz, 1H), 2.54 (ddd, J = 3.8, 12.6, 16.0 Hz, 1H), 2.91 (dd, J = 1.7, 4.3 Hz, 1H), 3.58 (ddd, J = 1.8, 3.2, 4.6 Hz, 1H), 4.58 (br s, 1H), 5.29 (dq, J = 1.5, 6.7 Hz, 1H), 5.72 (td, J = 1.7, 16.0 Hz, 1H), 5.91 (ddd, J = 1.2, 3.2, 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 28.7, 29.7, 56.3, 57.7, 66.1, 68.1, 118.2, 134.7, 172.7 ppm.

■ ASSOCIATED CONTENT

Supporting Information

Comparative ^{1}H and ^{13}C NMR chemical shifts of synthetic **4**, **25**, and natural product; NMR (^{1}H, ^{13}C, and DEPT) and MS spectra of all the new compounds; 2D NMR (COSY and NOESY) spectra of compounds **4**, **7**, **8**, **20**, **22**, **23**, **24**, and **25**; X-ray crystal structure information file of compound **8**; and HPLC chromatograms of compound **4-Bz**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vr.chepuri@ncl.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministry of Science and Technology for funding through the Department of Science and Technology under the Green Chemistry Program (No. SR/S5/GC-20/2007). Financial support from CSIR (New Delhi) in the form of a research fellowship to P.M.V. is gratefully acknowledged. We thank Mr. Ajeet Singh and Dr. Venkat Panchagnula for extending the HRMS facility.

■ REFERENCES

(1) (a) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Mitina, G.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 31−34. (b) Yuzikhin, O.; Mitina, G.; Berestetskiy, A. *J. Agric. Food Chem.* **2007**, *55*, 7707−7711. (c) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 1897−1901.

(2) (a) Rivero-Cruz, J. F.; Garcia-Aguirre, G.; Cerda-Garcia-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337−5344. (b) Rivero-Cruz, J. F.; Macias, M.; Cerda-Garcia-Rojas, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511−514.

(3) (a) Ramana, C. V.; Khaladkar, T. P.; Chatterjee, S.; Gurjar, M. K. *J. Org. Chem.* **2008**, *73*, 3817−3822. (b) Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem.* **2010**, *8*, 398−406.

(4) (a) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Tesler, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913−7919. (b) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem.—Eur. J.* **2006**, *12*, 51−62. (c) Gennari, C.; Castoldi, D.; Sharon, O. *Pure Appl. Chem.* **2007**, *79*, 173−180.

(5) For some recent reviews, see: (a) Riatto, V. B.; Pilli, R. A.; Victor, M. M. *Tetrahedron* **2008**, *64*, 2279−2300. (b) Ferraz, H. M. C.; Bombonato, F. I.; Longo, L. S. Jr. *Synthesis* **2007**, 3261−3285. (c) Gradillas, A.; Paez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(6) For 2*E*-ene-1,4-*cis*-disubstituted nonenolide construction using RCM, see: (a) Ghosh, S.; Rao, R. V. *Tetrahedron Lett.* **2007**, *48*, 6937−6940. (b) Guptali, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195−1202. (c) Liu, J.; Zhang, L.; He, J. M.; He, L.; Ma, B. W.; Pan, X. F.; She, X. G. *Tetrahedron: Asymmetry* **2008**, *19*, 906−911. (d) Krishna, P. R.; Rao, T. J. *Tetrahedron Lett.* **2010**, *51*, 4017−4019.

(7) For 2*E*-ene-1,4-*trans*-disubstituted nonenolide construction using RCM, see: (a) Srihari, P.; Kumaraswamy, B.; Somaiah, R.; Yadav, J. S. *Synthesis* **2009**, 1039−1045. (b) Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622−2628. (c) Mohapatra, D. K.; Dash, U.; Naidu, P. R.; Yadav, J. S. *Synlett* **2009**, 2129−2132. (d) Das, T.; Bhuniya, R.; Nanda, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2206−2211. (e) Chandrasekhar, S.; Balaji, S. V.; Rajesh, G. *Tetrahedron Lett.* **2010**, *51*, 5164−5166. (f) Srihari, P.; Kumaraswamy, B.; Shankar, P.; Ravishashidhar, V.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 6174−6176.

(8) Mahapatra, T.; Das, T.; Nanda, S. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 511−519.

(9) (a) Hildebrandt, B.; Nakamura, Y.; Ogawa, S. *Carbohydr. Res.* **1991**, *214*, 87−93. (b) Rao, A. V. R.; Murthy, V. S.; Sharma, G. V. M. *Tetrahedron Lett.* **1995**, *36*, 139−142.

(10) (a) Mitsunobu., O; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380−2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(11) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(12) (a) Hicks, J. D.; Huh, C. W.; Legg, A. D.; Roush, W. R. *Org. Lett.* **2007**, *9*, 5621−5624. (b) Bose, D.; Fernandez, E.; Pietruszka, J. *J. Org. Chem.* **2011**, *76*, 3463−3469.

(13) (a) Angulo-Pachon, C. A.; Diaz-Oltra, S.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2010**, *12*, 5752−5755.

(14) Some of the signals corresponding to the minor conformer could be seen in the ^{1}H and 2D NMR spectra of the natural product.

(15) In the case of cytospolides, the existence of conformational isomers in solution has been accounted for by high energy barriers required for the flipping of the free allylic-hydroxyl group from the axial to the equatorial position: (a) Lu, S.; Kurtán, T.; Yang, G.; Sun, P.; Mándi, A.; Krohn, K.; Draeger, S.; Schulz, B.; Yi, Y.; Li, L.; Zhang, W. *Eur. J. Org. Chem.* **2011**, 5452−5459. (b) Lu, S.; Sun, P.; Li, T. J.; Kurtan, T.; Mandi, A.; Antus, S.; Krohn, K.; Draeger, S.; Schulz, B.; Yi, Y. H.; Li, L.; Zhang, W. *J. Org. Chem.* **2011**, *76*, 9699−9710.