JOC The Journal of Organic Chemistry

ARTICLE

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Asymmetric Synthesis of the Core Structure of Leucosceptroids A−D

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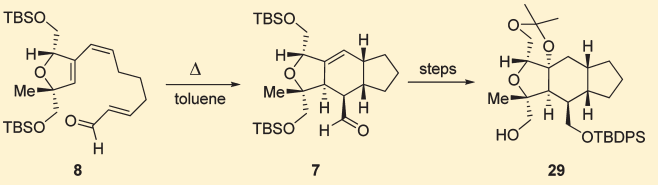
Supporting Information

ABSTRACT: The asymmetric synthesis of the core structure of leucosceptroids A−D has been achieved. The key steps of the synthesis includes the formation of the cis-2,5-disubstituted THF ring by TPAP catalytic oxidative cyclization followed by a highly diastereoselective intramolecular Diels−Alder reaction to fashion the fused tricyclic hydrindane ring system.



INTRODUCTION

Many secondary metabolites including alkaloids, phenolics, and terpenoids, produced from glandular trichomes, possess a wide variety of structures and play an important role in defense against herbivores. Recently, leucosceptroids A (**1**) and B (**2**) were isolated by Li's group from glandular trichomes of *Leucosceptrum canum* and possess antifeedant and antifungal activities. The structures of **1** and **2** were initially elucidated by 2D NMR and MS spectral analysis and subsequently confirmed by X-ray diffraction methods (Figure 1).[1a] The central core of **1** and **2** is structurally unique and embodies a tricyclic ring system in which a highly substituted tetrahydrofuran moiety is fused onto a hydrindane ring system. Surrounding this core, is a highly decorated set of appendages that is diverse in nature and distributed among eight stereogenic centers. Moreover, the additional two sesterterpenoids, leucosceptroids C (**3**) and D (**4**),[1b] were isolated by the same group from the same source. The structure of **3** and **4** share the same tricyclic core with **1** and **2** and uncommon antipodal cyclopentenones. In this regard, leucosceptroids A−D represent challenging synthetic targets for which no synthetic work has been reported. Herein, we describe an efficient approach to the core structure of these secondary metabolites.

The retrosynthetic strategy is depicted in Figure 2 and is based on an intramolecular Diels−Alder approach. The plan is directed at the synthesis of core structure **5** via ring-opening of epoxide **6**. Differentiation of the resulting hydroxyl moieties would occur through selective protection as the acetonide. Diastereoselective introduction of the epoxide ring in **6** was anticipated via hydroxyl-directed epoxidation.[2] Because intramolecular Diels−Alder reactions[3] have proven to be an efficientive method to construct various fused ring systems in natural products, we pursued this approach in fashioning core structure **7** in a stereocontrolled manner. Endo orientation of the approaching dienophile opposite to the larger OTBS group would produce **7** and establish four of the six ring stereocenters in a single step. Key to this approach is the development of an efficient diastereoselective synthesis of the 2,5-disubstituted *cis*-tetrahydrofuran Diels−Alder substrate **8**. This was envisioned from diol **10** using oxidative cyclization[4] and Sonagashira cross-coupling strategies.[5]

RESULTS AND DISCUSSION

Oxidation of 1,2:5,6-diisopropylidene-D-mannitol with $NaIO_4$ followed by nucleophilic addition with 2-methylallylmagnesium chloride afforded secondary alcohol **11**[6] with a 7:4 dr in 68% yield. The stereochemistry at the newly formed center would be eliminated in subsequent steps. After protection with PMB group, acetonide deprotection of **12** produced diol **10** in high yield (Scheme 1). Recently, Stark and co-workers[4a] reported a powerful method to construct enantiopure *cis*-THF-diols with NMO and catalytic TPAP. Inspired by their findings, diol **10** was transformed to desired product **13** in 34% yield (entry 1). The yield of this transformation was further optimized to 55% (entry 3) with NMO in the presence of 8% H_2O. Interestingly, similar yields were obtained without adding water (entries 4). Under all conditions listed, a single diastereomer at C14 was produced (the original dr value of 7:4 relative to C5 remained unchanged). Subsequent protection of diol **13** as its TBS ether provided **14**. The preparation of ketone **9** was achieved in nearly quantitative yield via PMB deprotection and oxidation with Dess−Martin periodinane.[7] The significant NOE correlation between H and Me confirmed the *cis*-THF orientation of these two moieties.

With **9** in hand, the construction of fused tricylic ring system was pursued (Scheme 2). Treatment of **9** with LiHMDS and $PhNTf_2$ afforded enol triflate **15**. Sonagashira cross-coupling reaction between **15** and alkyne **16**[8] proceeded efficiently to afford product **17** in 89% yield for the two steps. Upon careful monitoring, semihydrogenation of the alkyne functionality using Lindlar's catalyst and quinoline afforded *cis*-alkene **18** in 70−80% yield. It is important to stop the reduction just prior to the complete consumption of starting material, otherwise over-reduction begins to predominate.[9] Oxidation of allylic alcohol **18** with MnO_2 yielded IMDA[10] precusor **8**. When **8** was heated with BHT in toluene for 16 h, desired product **7** was isolated in 58% yield as a single diastereomer. This gratifying result can be rationalized by a top-face endo approach of the dienophile that is controlled by nonbonded interactions between substituents on

Received: May 5, 2011
Published: June 06, 2011

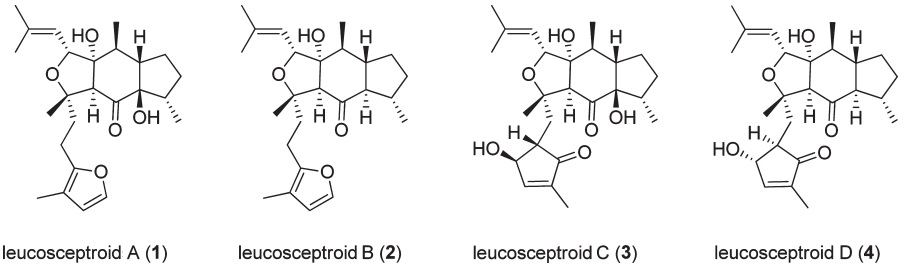


Figure 1. Structures of leucosceptroids A−D.

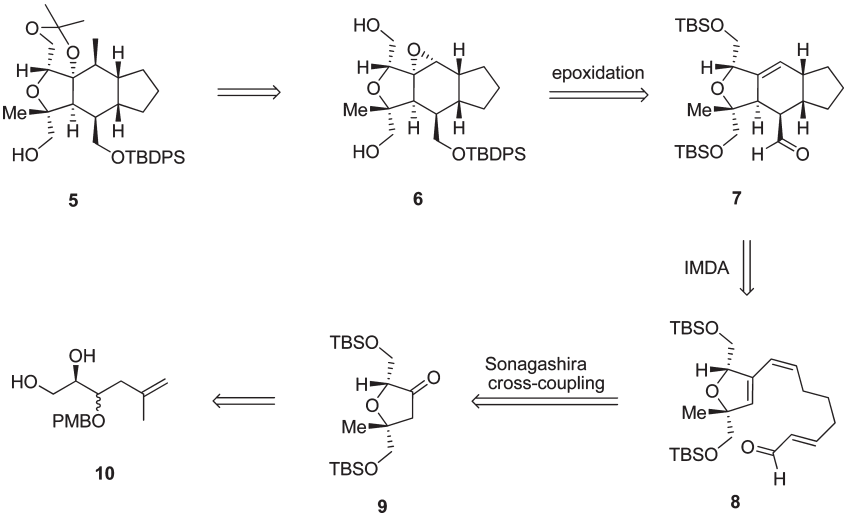
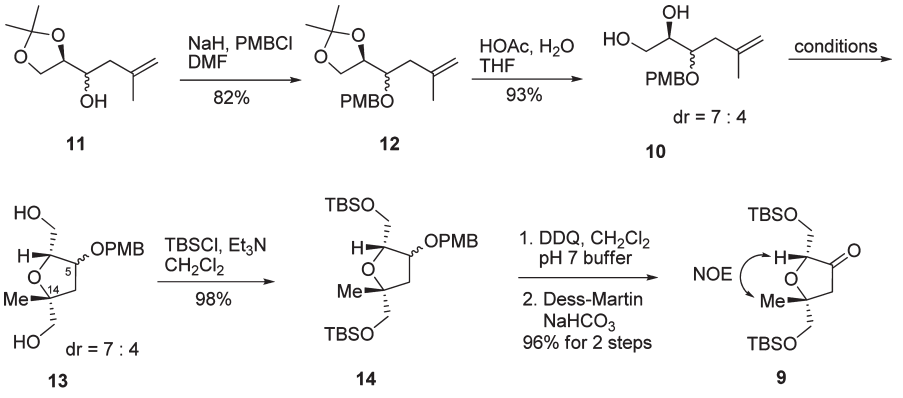


Figure 2. Retrosynthetic analysis.

Scheme 1. Synthesis of Ketone 9



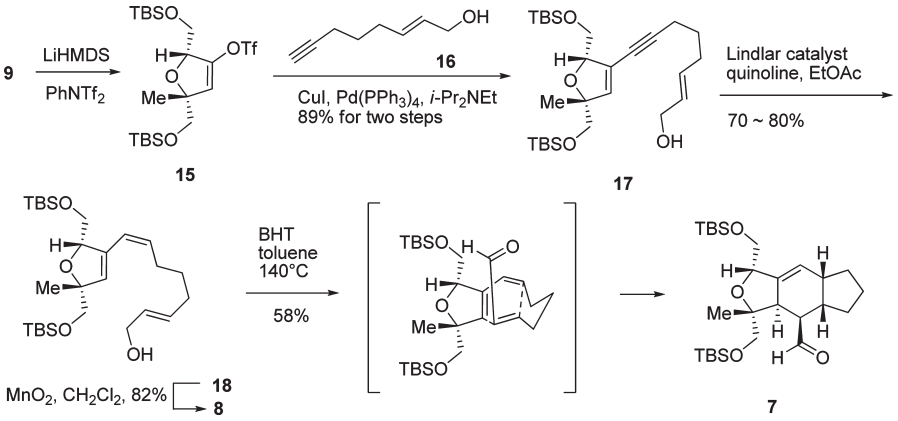
entry	conditions	Yield of **13**
1	5% TPAP, 1.2 equiv NMO•H_2O	34%
2	5% TPAP, 1.2 equiv 50% NMO	20%
3	5% TPAP, 1.3 equiv NMO + 8% H_2O	55%
4	5% TPAP, 1.3 equiv NMO	52%

the chiral THF ring. In this single step, four key stereogenic centers are installed in a highly efficient manner.

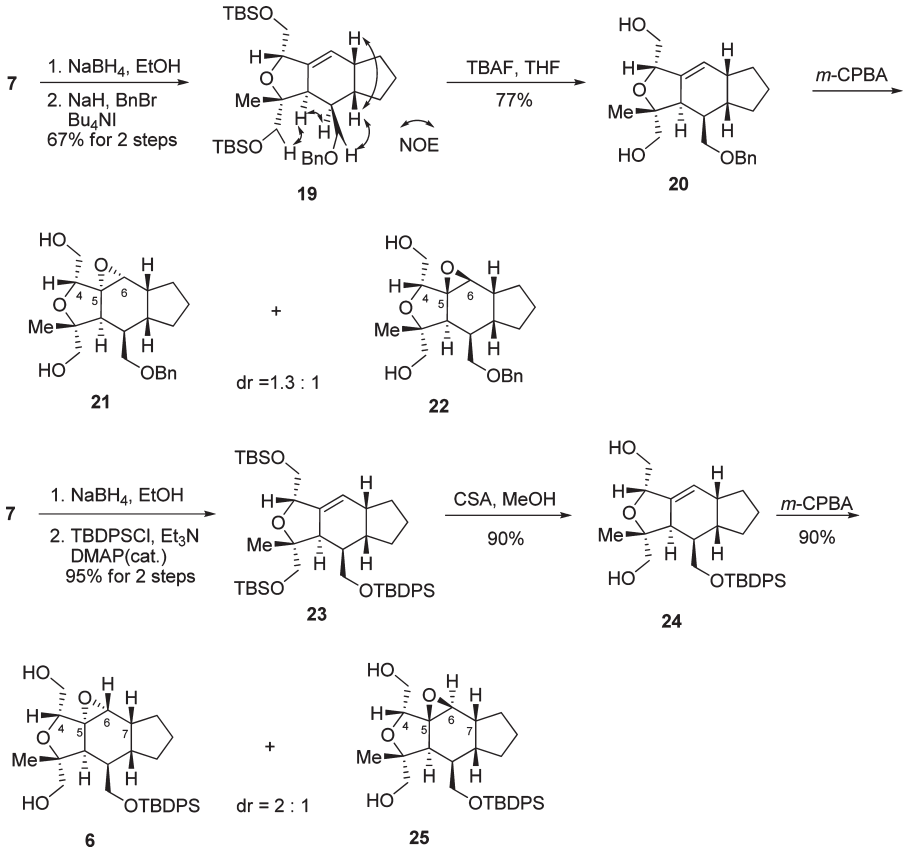
Next, the focus was on the diastereoselective construction of the C5−C6 epoxide ring (Scheme 3). Reduction of **7** followed by protection with benzyl or TBDPS groups provided **19** or **23**, respectively. NOE correlations in **19** further confirmed the stereochemistry of the newly formed four chiral centers that resulted from the IMDA cyclization. Selective deprotection of TBS afforded homoallylic alcohols **20** or **24**. At this point, it was anticipated that hydroxyl-directed epoxidation would take place from the endo face of the *cis*-hydrindane ring and overcome any steric hindrance caused by this ring system. When **20** was treated

dx.doi.org/10.1021/jo200899v |*J. Org. Chem.* 2011, 76, 6169–6176

Scheme 2. Synthesis of 7



Scheme 3. Synthesis of Epoxide 6

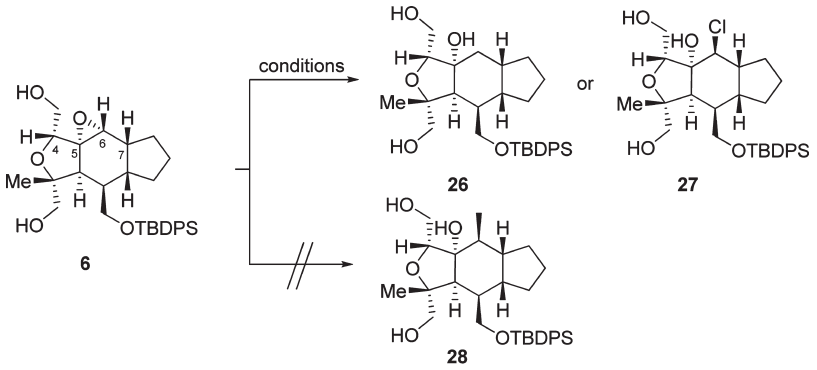


with *m*-CPBA, epoxides **21** and **22** were produced in a 1.3:1 dr, respectively. While the major product is also the desired product, separation of the two diastereomers by column chromatography proved difficult. Similarly, related analogues **6** and **25** can be generated from **24** using *m*-CPBA in 2:1 dr, but unlike **21** and **22**, these diastereomeric epoxides are readily separable by column chromatography in 90% isolated yield. From the ^{1}H NMR spectrum of **6**, the C6 hydrogen is coupled to the C7 hydrogen and appears as a doublet (J = 4.9 Hz) whereas the C6 hydrogen of **25** is a singlet. Based on this coupling information, the stereochemistry was assigned as indicated. As an attempt to improve the diastereoselectivity of the epoxidation, the use of $VO(acac)_2$ and *t*-BuOOH[11] was investigated. Treatment of **24** under these conditions afforded a 9:1 dr of **6** and **25** but in much lower yield (30%). The low yield of this reaction might be attributed to the oxidation of activated hydrogen at C4.

With **6** in hand, an S_N2 epoxide ring-opening at C6 was pursued (Scheme 4). Despite several attempts at nucleophilic ring-opening at C6, we were unable to introduce the requisite methyl substituent. The use of Me_2CuLi resulted in a complex mixture of products, and when MeLi was employed, mostly starting material was recovered

dx.doi.org/10.1021/jo200899v |*J. Org. Chem.* 2011, 76, 6169–6176

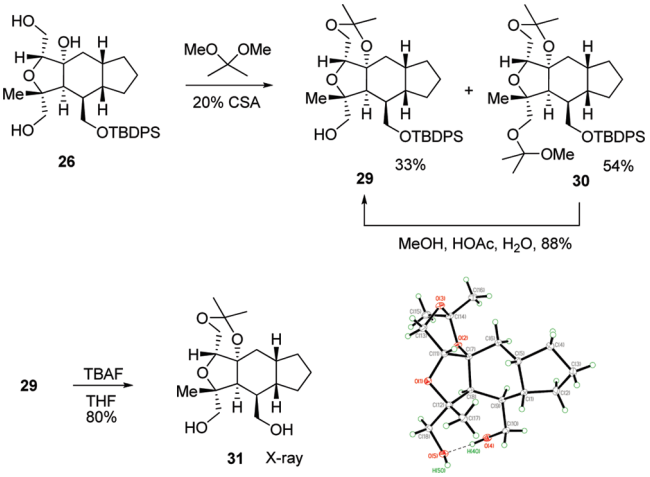
Scheme 4. Epoxide Ring-Opening



entry	conditions[a]	Product (yield)
1	Me_2CuLi, reflux 3 d	Complex product
2	MeLi, reflux 3 d	No reaction
3	MeMgBr (3M in Et_2O), reflux 3 d	**26** (52%)
4	MeMgBr (1M in THF), reflux 3 d	**26** (72%)
5	MeMgCl (3M in THF), reflux 2 d	**27** (40%) + 20% rsm

(a) 40 equiv reagent was added

Scheme 5. Synthesis of 29



from the reaction. Alternatively, Grignard reagents are another choice for this transformation because epoxides are well-known to undergo nucleophilic ring-opening with these reagents. To our surprise, when **6** was treated with MeMgBr (3 M in Et_2O), only reduction product **26** was obtained in 52% yield (entry 3). Using MeMgBr (1 M in THF), the yield of **26** increased to 72% (entry 4). Interestingly, when MeMgCl was tried, **27** was isolated with Cl substituted on C6 in 40% yield (entry 5). One possible reason for failure to introduce the methyl group in **6** is the presence of a dianion that is formed upon addition of excess MeLi. Such a species may prevent attack of a methyl carbanion. We plan to retool the synthesis and pursue the epoxide ring-opening with a fully protected substrate.

Although initial efforts thus far have not succeeded in introducing the C6 methyl substituent, we continued to pursue differentiating the two hydroxyl substituents in **26**. This was accomplished by converting **26** into its acetonide **29** (Scheme 5). When the reaction was carried out with 20% CSA in 2,2-dimethoxypropane, desired product **29** was obtained in 33% yield in addition to ketal **30** in 54% yield.[12] Fortunately, ketal **30** can be converted to **29** in high yield (88%) without loss of the acetonide functionality. An X-ray crystal structure of **31** was obtained after removal of TBDPS group from **29** which unequivocally confirmed the structure and stereochemical assignments previously made.

CONCLUSION

In summary, a concise and efficient synthesis of the core structure of leucosceptroids A−D (**1**−**4**) has been achieved. The construction of the cis-2,5-disubstituted THF ring was accomplished through a TPAP-catalytic cyclization which set the stage for a Sonagashira cross-coupling reaction followed by an IMDA reaction to establish the fused tricyclic core ring system in a highly stereocontrolled manner. Future efforts will focus on introducing the C6 methyl substituent and completion of the total synthesis.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were commercial grade and purified prior to use when necessary. Visualization was performed by ultraviolet light and/or by staining with potassium permanganate. All ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, at room temperature.

Experimental Procedure. *(R)-4-(1-(4-Methoxybenzyloxy)-3-methylbut-3-enyl)-2,2-dimethyl-1,3-dioxolane* ***12***. To a stirred solution of 1,2:5,6-diisopropylidene-D-mannitol (917 mg, 3.5 mmol) in CH_2Cl_2 (8 mL) was added sat. $NaHCO_3$ (0.4 mL) and $NaIO_4$ (1.28 g, 6 mmol) slowly at 0 °C. After 3 h at rt, $MgSO_4$ (0.5 g) was added and the reaction was stirred for 20 min. The solid was filtered, and the solvent was removed under reduced pressure. The resulting residue was used for the next step without purification. To a stirred solution of crude aldehyde in THF (5 mL) was added 2-methylallylmagnesium chloride (0.3 M in THF, 25 mL, 1.1 equiv) at −78 °C over 20 min. After addition, the reaction was warmed to rt and stirred overnight. The reaction was quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10−12.5% EtOAc/hexane) to afford **11** (885 mg, 68% for two steps) as a colorless oil. To a stirred

dx.doi.org/10.1021/jo200899v |J. Org. Chem. 2011, 76, 6169–6176

solution of **11** (885 mg, 4.75 mmol) in DMF (9 mL) was added NaH (380 mg, 9.5 mmol, 2 equiv) at 0 °C. After 30 min at rt, PMBCl (1.15 g, 7.4 mmol, 1.5 equiv) was added at 0 °C. The reaction was stirred for 2 h at rt and quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (4−5% EtOAc/hexane) to afford **12** (1.2 g, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23−7.29 (m, 2H), 6.84−6.89 (m, 2H), 4.79−4.83 (m, 2H), 4.56−4.65 (m, 2H), 3.62−4.20 (m, 7H), 2.18−2.27 (m, 2H), 1.68−1.77 (m, 3H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.4, 142.54, 142.49, 131.0, 130.9, 129.7, 129.6, 114.0, 113.9, 113.5, 113.3, 109.4, 109.2, 78.1, 77.8, 77.4, 72.9, 72.5, 66.1, 66.0, 55.5, 40.5, 39.3, 26.8, 26.7, 25.6, 25.5, 23.2, 23.1; HRMS calcd for $C_{18}H_{26}O_4$ $[M + Na]^+$ 329.1723, found 329.1722; IR ν_{max} (film) 2936, 2856, 1610, 1512, 1245, 1076, 1031 cm^{-1}.

(R)-3-(4-Methoxybenzyloxy)-5-methylhex-5-ene-1,2-diol ***10***. A stirred solution of **12** (1.2 g, 4 mmol) in HOAc (12 mL), H_2O (4 mL), and THF (4 mL) was heated to 40 °C. After 15 h at 40 °C, the reaction was diluted with EtOAc and neutralized with $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 60 mL), and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (35−50% EtOAc/hexane) to afford **10** (965 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23−7.25 (m, 2H), 6.86−6.90 (m, 2H), 4.83−4.86 (m, 2H), 4.60−4.64 (m, 1H), 4.40−4.46 (m, 1H), 3.81 (s, 3H), 3.60−3.79 (m, 4H), 2.10−2.50 (m, 4H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.7, 159.6, 142.4, 142.1, 130.3, 130.1, 129.9, 129.8, 114.20, 114.17, 114.0, 113.8, 79.8, 77.5, 72.7, 72.6, 72.0, 64.5, 63.3, 55.5, 39.7, 38.9, 23.2, 23.0; HRMS calcd for $C_{15}H_{22}O_4$ $[M + Na]^+$ 289.1410, found 289.1409; IR ν_{max} (film) 3403, 2932, 1610, 1512, 1245, 1076, 1031 cm^{-1}.

((2R,5R)-4-(4-Methoxybenzyloxy)-2-methyltetrahydrofuran-2,5-diyl)dimethanol ***13***. To a stirred solution of **10** (622 mg, 2.3 mmol) in CH_2Cl_2 (45 mL) were added NMO (350 mg, 3 mmol, 1.3 equiv) and TPAP (40 mg, 0.12 mmol, 0.05 equiv) at rt. After 16 h, the reaction was quenched with 2-propanol. The solvent was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (40−75% EtOAc/hexane) to afford **13** (360 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.21−7.27 (m, 2H), 6.86−6.90 (m, 2H), 4.43−4.57 (m, 1H), 4.32−4.42 (m, 1H), 4.17−4.30 (m, 1H), 4.05−4.17 (m, 1H), 3.82−3.90 (m, 1H), 3.81 (s, 3H), 3.57−3.64 (m, 2H), 3.39−3.49 (m, 1H), 2.82 (b, 1H), 2.48 (b, 1H), 2.30−2.40 (m, 1H), 1.78−1.92 (m, 1H), 1.20−1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.7, 159.5, 130.4, 129.7, 129.6, 129.5, 114.2, 114.1, 84.5, 84.3, 83.3, 80.72, 80.69, 80.5, 71.7, 71.3, 69.2, 68.7, 63.5, 62.5, 55.5, 39.8, 39.4, 24.5, 24.2; HRMS calcd for $C_{15}H_{22}O_5$ $[M + Na]^+$ 305.1359, found 305.1359; IR ν_{max} (film) 3420, 2932, 1512, 1245, 1076, 1031 cm^{-1}.

Tetrahydrofuran ***14***. To a stirred solution of **13** (159 mg, 0.56 mmol) in CH_2Cl_2 (2 mL) were added cat. DMAP, Et_3N (440 mg, 4.4 mmol, 8 equiv), and TBSCl (405 mg, 2.7 mmol, 4.8 equiv) at 0 °C and stirred overnight at rt. The mixture was quenched with sat. $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.5−1.8% EtOAc/hexane) to afford **14** (282 mg, 98%). One isomer of **14:** $[\alpha]_D^{20}$ = 4.8 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 4.44 (d, 2H, *J* = 5.4 Hz), 4.04−4.09 (m, 2H), 3.80 (s, 3H), 3.63 (dd, 1H, *J* = 4.1, 10.6 Hz), 3.49 (dd, 1H, *J* = 6.2, 10.6 Hz), 3.42 (d, 1H, *J* = 10.0 Hz), 3.36 (d, 1H, *J* = 10.0 Hz), 2.19 (dd, 1H, *J* = 6.4, 13.1 Hz), 1.75 (dd, 1H, *J* = 3.5, 13.1 Hz), 1.29 (s, 3H), 0.885 (s, 9H), 0.884 (s, 9H), 0.042 (s, 3H), 0.040 (s, 3H), 0.032 (s, 3H), 0.030 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.3, 130.9, 129.5, 114.0, 84.5, 84.1, 81.1, 71.2, 69.9, 64.2, 55.5, 39.4, 26.18, 26.16, 24.5, 18.57, 18.54, −5.11, −5.15, −5.16, −5.25; HRMS calcd for $C_{27}H_{50}O_5Si_2$ $[M + Na]^+$ 533.3089, found 533.3088; IR ν_{max} (film) 2932, 2856, 1512, 1249, 1098, 840, 778 cm^{-1}.

Another isomer of **14:** $[\alpha]_D^{20}$ = −19.4 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.24 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 4.50 (d, 1H, *J* = 11.6 Hz), 4.39 (d, 1H, *J* = 11.6 Hz), 4.07−4.09 (m, 1H), 3.98−4.01 (m, 1H), 3.89 (dd, 1H, *J* = 7.4, 9.8 Hz), 3.81 (s, 3H), 3.72 (dd, 1H, *J* = 5.1, 9.8 Hz), 3.58 (d, 1H, *J* = 9.2 Hz), 3.41 (d, 1H, *J* = 9.2 Hz), 2.28 (dd, 1H, *J* = 1.6, 13.8 Hz), 1.66 (dd, 1H, *J* = 5.2, 13.8 Hz), 1.22 (s, 3H), 0.89 (s, 18H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.2, 131.0, 129.2, 113.9, 83.0, 82.5, 79.3, 71.2, 69.8, 61.7, 55.5, 39.9, 26.19, 26.13, 24.9, 18.55, 18.48, −5.06, −5.10, −5.18; HRMS calcd for $C_{27}H_{50}O_5Si_2$ $[M + Na]^+$ 533.3089, found 533.3088; IR ν_{max} (film) 2932, 2856, 1512, 1249, 1098, 840, 778 cm^{-1}.

(2R,5R)-2,5-Bis((tert-butyldimethylsilyloxy)methyl)-5-methyldihydrofuran-3(2H)-one ***9***. To a stirred solution of **14** (282 mg, 0.55 mmol) in CH_2Cl_2 (10 mL) + pH 7 buffer (1 mL) was added DDQ (162 mg, 0.72 mmol, 1.3 equiv) at 0 °C. After 1.5 h at rt, the reaction was quenched with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was used for the next step without purification. To a stirred solution of crude product in CH_2Cl_2 (16 mL) were added $NaHCO_3$ (462 mg, 5.5 mmol, 10 equiv) and Dess−Martin reagent (466 mg, 1.1 mmol, 2 equiv). After 2 h at rt, the reaction was quenched with sat. Na_2SO_3 and sat. $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (3.5−4% EtOAc/hexane) to afford **9** (205 mg, 96%). $[\alpha]_D^{20}$ = 61.7 (*c* = 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.05 (t, 1H, *J* = 3.1 Hz), 3.84 (dd, 1H, *J* = 3.7, 10.9 Hz), 3.79 (dd, 1H, *J* = 2.5, 10.9 Hz), 3.69 (d, 1H, *J* = 9.8 Hz), 3.59 (d, 1H, *J* = 9.8 Hz), 2.49 (d, 1H, *J* = 17.8 Hz), 2.27 (d, 1H, *J* = 17.8 Hz), 1.31 (s, 3H), 0.87−0.89 (m, 18H), 0.03−0.06 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 215.0, 81.8, 81.0, 70.3, 63.7, 46.7, 26.12, 26.08, 23.7, 18.6, 18.5, −5.16, −5.18, −5.24, −5.30; HRMS calcd for $C_{19}H_{40}O_4Si_2$ $[M + Na]^+$ 411.2357, found 411.2355; IR ν_{max} (film) 2927, 2856, 1766, 1472, 1254, 1112, 836, 778 cm^{-1}.

(E)-8-((2S,5R)-2,5-Bis((tert-butyldimethylsilyloxy)methyl)-5-methyl-2,5-dihydrofuran-3-yl)oct-2-en-7-yn-1-ol ***17***. To a stirred solution of **9** (434 mg, 1.1 mmol) in THF (2.2 mL) was added LiHMDS (1 M in THF, 1.7 mmol, 1.5 equiv) at −78 °C. After 30 min, $PhNTf_2$ in THF (2.2 mL) was added, and the reaction was warmed to rt. After 1 h, the reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0.8−1% EtOAc/hexane) to afford **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.84 (s, 1H), 4.79−4.82 (m, 1H), 3.71−3.78 (m, 2H), 3.62 (d, 1H, *J* = 9.6 Hz), 3.52 (d, 1H, *J* = 9.6 Hz), 1.36 (s, 3H), 0.87−0.89 (m, 18H), 0.03−0.06 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.1, 119.0, 88.3, 81.9, 69.9, 63.6, 26.1, 26.0, 23.7, 18.6, 18.4, −5.26, −5.42. A flask was charged with **15** (1.1 mmol), alkyne **16** (154 mg, 1.2 mmol, 1.1 equiv), $Pd(PPh_3)_4$ (127 mg, 0.11 mmol, 0.1 equiv), and CuI (105 mg, 0.55 mmol, 0.5 equiv) purged with N_2. DMF (9 mL) and *i*-Pr_2NEt (709 mg, 5.5 mmol, 5 equiv) were added. After 30 min at rt, the reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (6−9% EtOAc/hexane) to afford **17** (497 mg, 89% for two steps). $[\alpha]_D^{20}$ = 14.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.98 (s, 1H), 5.66−5.69 (m, 2H), 4.75−4.78 (m, 1H), 4.08−4.12 (m, 2H), 3.80 (dd, 1H, *J* = 2.8, 11.0 Hz), 3.69 (dd, 1H, *J* = 4.4, 11.0 Hz), 3.56 (d, 1H, *J* = 9.4 Hz), 3.52 (d, 1H, *J* = 9.4 Hz), 2.33 (t, 2H, *J* = 7.2 Hz), 2.14−2.20 (m, 2H), 1.57−1.63 (m, 2H), 1.29 (s, 3H), 0.88−0.89 (m, 18H), 0.02−0.07 (m, 12H); ^{13}C NMR (100 MHz,

dx.doi.org/10.1021/jo200899v |*J. Org. Chem.* 2011, 76, 6169–6176

$CDCl_3$) δ (ppm): 137.7, 132.1, 130.1, 121.9, 94.2, 90.8, 88.3, 74.2, 70.2, 65.4, 63.9, 31.5, 28.1, 26.2, 26.1, 23.3, 19.1, 18.8, 18.5, −5.0, −5.1, −5.17, −5.20; HRMS calcd for $C_{27}H_{50}O_4Si_2$ $[M + Na]^+$ 517.3140, found 517.3127; IR ν_{max} (film) 3403, 2927, 2856, 1637, 1472, 1249, 1094, 836, 778 cm^{-1}.

(2E,7Z)-8-((2S,5R)-2,5-Bis((tert-butyldimethylsilyloxy)methyl)-5-methyl-2,5-dihydrofuran-3-yl)octa-2,7-dien-1-ol ***18***. To a stirred solution of **17** (620 mg, 1.2 mmol) in EtOAc (60 mL) were added Lindlar catalyst (253 mg) and quinoline (186 μL). The reaction was stirred under hydrogen atmosphere for 4 h, and the solid was filtered. The solvent was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (7−8% EtOAc/hexane) to afford **18** (500 mg, 80%) + recovered starting material (rsm) (30 mg, 5%). $[\alpha]_D^{20}$ = −46.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.55−5.76 (m, 5H), 4.78−4.82 (m, 1H), 4.06−4.10 (m, 2H), 3.67 (dd, 1H, J = 4.1, 10.8 Hz), 3.64 (dd, 1H, J = 4.5, 10.8 Hz), 3.54 (d, 2H, J = 1.7 Hz), 2.19−2.23 (m, 2H), 2.05−2.10 (m, 2H), 1.47−1.55 (m, 2H), 1.40 (b, 1H), 1.29 (s, 3H), 0.88−0.89 (m, 18H), 0.02−0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.1, 135.0, 133.0, 131.0, 129.6, 120.9, 90.4, 88.2, 70.6, 66.3, 63.9, 32.1, 29.3, 29.2, 26.2, 26.1, 23.8, 18.6, 18.5, −5.11, −5.13, −5.15; HRMS calcd for $C_{27}H_{52}O_4Si_2$ $[M + Na]^+$ 519.3296, found 519.3285; IR ν_{max} (film) 3403, 2927, 2856, 1472, 1254, 1094, 836, 778 cm^{-1}.

(2E,7Z)-8-((2S,5R)-2,5-Bis((tert-butyldimethylsilyloxy)methyl)-5-methyl-2,5-dihydrofuran-3-yl)octa-2,7-dienal ***8***. To a stirred solution of **18** (172 mg, 0.34 mmol) in CH_2Cl_2 (3.4 mL) was added MnO_2 (2.4 g, 2.72 mmol, 80 equiv). After 36 h at rt, the solid was filtered. The solvent was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (4−4.5% EtOAc/hexane) to afford **8** (142 mg, 82%). $[\alpha]_D^{20}$ = −51.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.51 (d, 1H, J = 7.8 Hz), 6.84 (dt, 1H, J = 6.6, 15.6 Hz), 6.12 (dd, 1H, J = 7.8, 15.6 Hz), 5.79 (d, 1H, J = 11.6 Hz), 5.66 (s, 1H), 5.58 (dt, 1H, J = 7.0, 11.6 Hz), 4.79−4.82 (m, 1H), 3.62−3.69 (m, 2H), 3.47−3.57 (m, 2H), 2.26−2.39 (m, 4H), 1.60−1.68 (m, 2H), 1.29 (s, 3H), 0.87−0.89 (m, 18H), 0.03−0.06 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.1, 158.2, 136.1, 133.9, 133.4, 131.2, 121.6, 90.5, 88.1, 70.5, 66.2, 32.5, 29.1, 28.0, 26.22, 26.18, 26.16, 26.13, 23.8, 18.6, 18.5, −5.12, −5.14, −5.16; HRMS calcd for $C_{27}H_{50}O_4Si_2$ $[M + Na]^+$ 517.3140, found 517.3138; IR ν_{max} (film) 2927, 2856, 1694, 1637, 1472, 1249, 1089, 836, 778 cm^{-1}.

(1S,3R,3aR,4R,4aS,7aR)-1,3-Bis((tert-butyldimethylsilyloxy)methyl)-3-methyl-3,3a,4,4a,5,6,7,7a-octahydro-1H-indeno[5,6-c]furan-4-carbaldehyde ***7***. To a stirred solution of **8** (142 mg, 0.28 mmol) in toluene (28 mL) was added BHT (62 mg, 0.28 mmol, 1 equiv). The reaction was stirred at 140 °C for 15 h, and the solvent was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.8% to 2.5% EtOAc/hexane) to afford **7** (82 mg, 58%). $[\alpha]_D^{20}$ = 1.7 (c = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.77 (d, 1H, J = 5.6 Hz), 5.58 (d, 1H, J = 1.6 Hz), 4.46−4.49 (m, 1H), 3.66 (dd, 1H, J = 4.4, 10.0 Hz), 3.54−3.60 (m, 3H), 2.86−2.90 (m, 1H), 2.72−2.82 (m, 2H), 2.16−2.22 (m, 1H), 1.76−1.90 (m, 2H), 1.42−1.56 (m, 4H), 1.03 (s, 3H), 0.87−0.89 (m, 18H), 0.04−0.06 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 205.9, 139.7, 123.1, 84.6, 79.4, 71.0, 66.7, 51.7, 43.2, 41.2, 36.3, 32.6, 30.2, 26.2, 26.1, 23.6, 21.8, 18.6, 18.4, −5.15, −5.17, −5.23, −5.3; HRMS calcd for $C_{27}H_{50}O_4Si_2$ $[M + Na]^+$ 517.3140, found 517.3135; IR ν_{max} (film) 2927, 2856, 1721, 1472, 1254, 1107, 836, 778 cm^{-1}.

Benzyl Ether ***19***. To a stirred solution of **7** (117 mg, 0.23 mmol) in EtOH (6 mL) was added $NaBH_4$ (15 mg, 0.46 mmol, 2 equiv) at 0 °C. After 1 h at rt, the reaction was quenched with sat. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by short column (9% EtOAc/hexane) and used for the next step. To a stirred solution of alcohol in DMF (0.9 mL) was added NaH (22 mg, 0.56 mmol, 2.5 equiv) at 0 °C. After 45 min at rt, the reaction was treated with BnBr (75 mg, 0.46 mmol, 2 equiv) and cat. Bu_4NI at 0 °C and stirred for 3 h at rt. The reaction was quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1% EtOAc/hexane) to afford **19** (89 mg, 67% for 2 steps). $[\alpha]_D^{20}$= 30.2 (c = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27−7.37 (m, 5H), 5.36 (d, 1H, J = 1.4 Hz), 4.48 (d, 1H, J = 11.9 Hz), 4.41 (d, 1H, J = 11.9 Hz), 4.28−4.38 (m, 1H), 3.68 (dd, 1H, J = 5.2, 9.0 Hz), 3.58−3.65 (m, 3H), 3.49 (dd, 1H, J = 5.4, 10.0 Hz), 3.30 (t, 1H, J = 9.0 Hz), 2.72−2.78 (m, 1H), 2.54−2.60 (m, 1H), 2.44−2.52 (m, 1H), 2.34−2.40 (m, 1H), 1.74−1.84 (m, 1H), 1.58−1.68 (m, 1H), 1.44−1.56 (m, 2H), 1.34−1.42 (m, 2H), 1.14 (s, 3H), 0.88−0.90 (m, 18H), 0.03−0.05 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5, 138.9, 128.5, 127.8, 127.6, 122.4, 84.9, 78.4, 73.2, 71.2, 70.8, 66.8, 43.9, 40.5, 36.6, 35.8, 32.0, 28.8, 26.2, 26.1, 23.6, 20.5, 18.6, 18.5, −5.12, −5.17, −5.27; HRMS calcd for $C_{34}H_{58}O_4Si_2$ $[M + Na]^+$ 609.3766, found 609.3764; IR ν_{max} (film) 2927, 2856, 1472, 1254, 1107, 836, 778 cm^{-1}.

((1S,3R,3aR,4R,4aS,7aR)-4-(Benzyloxymethyl)-3-methyl-3,3a,4,4a,5,6,7,7a-octahydro-1H-indeno[5,6-c]furan-1,3-diyl)dimethanol ***20***. To a stirred solution of **19** (65 mg, 0.11 mmol) in THF (1.1 mL) was added TBAF (1 M in THF, 0.44 mmol, 4 equiv). After 75 min at rt, the reaction was quenched with sat. NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.5−2% MeOH/CH_2Cl_2) to afford **20** (31 mg, 77%). $[\alpha]_D^{20}$ = 61.0 (c = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27−7.37 (m, 5H), 5.38 (d, 1H, J = 1.6 Hz), 4.48 (d, 1H, J = 11.9 Hz), 4.41 (d, 1H, J = 11.9 Hz), 4.40−4.44 (m, 1H), 3.66−3.71 (m, 2H), 3.50−3.62 (m, 3H), 3.30 (dd, 1H, J = 6.2, 9.2 Hz), 3.00 (b, 1H), 2.90−2.95 (m, 1H), 2.68 (b, 1H), 2.50−2.58 (m, 1H), 2.26−2.36 (m, 2H), 1.74−1.84 (m, 1H), 1.62−1.72 (m, 1H), 1.44−1.58 (m, 2H), 1.34−1.42 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.4, 128.6, 127.9, 127.8, 123.0, 85.9, 78.6, 73.2, 71.5, 67.7, 66.3, 41.2, 41.1, 36.4, 36.2, 31.9, 29.1, 23.5, 19.8; HRMS calcd for $C_{22}H_{30}O_4$ $[M + Na]^+$ 381.2036, found 381.2036; IR ν_{max} (film) 302, 2927, 2856, 1472, 1254, 1107, 836, 778 cm^{-1}.

TBDPS Ether ***23***. To a stirred solution of **7** (110 mg, 0.22 mmol) in EtOH (6 mL) was added $NaBH_4$ (15 mg, 0.46 mmol, 2 equiv) at 0 °C. After 1 h at rt, the reaction was quenched with sat. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by short column (9% EtOAc/hexane) and used for the next step. To a stirred solution of alcohol in CH_2Cl_2 (2 mL) were added cat. DMAP, imidazole (28 mg, 0.44 mmol, 2 equiv), and TBDPSCl (90 mg, 0.33 mmol, 1.5 equiv) and stirred for 2.5 h at rt. The mixture was quenched with sat. $NaHCO_3$ and diluted with Et_2O, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.2−1.5% EtOAc/hexane) to afford **23** (160 mg, 95%). $[\alpha]_D^{20}$ = 25.6 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62−7.65 (m, 4H), 7.36−7.48 (m, 6H), 5.31 (d, 1H, J = 1.6 Hz), 4.22−4.25 (m, 1H), 3.88 (dd, 1H, J = 5.1, 10.0 Hz), 3.57 (dd, 1H, J = 4.9, 10.0 Hz), 3.40−3.56 (m, 4H), 2.70−2.75 (m, 1H), 2.55−2.62 (m, 1H), 2.44−2.52 (m, 1H), 2.22−2.30 (m, 1H), 1.72−1.80 (m, 1H), 1.58−1.64 (m, 1H), 1.44−1.56 (m, 2H), 1.32−1.42 (m, 2H), 1.05 (s, 9H), 0.96 (s, 3H), 0.87−0.90 (m, 18H), 0.02−0.05 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.3, 135.85, 135.83, 134.32, 134.26, 129.7, 127.8, 122.3, 84.9, 78.4, 70.6, 66.8, 64.1, 43.6, 39.6, 39.1, 35.7, 32.0, 28.9, 27.2, 26.19, 26.18, 23.6, 20.6, 19.5, 18.6, 18.5, −5.1, −5.2, −5.3; HRMS calcd for $C_{43}H_{70}O_4Si_3$ $[M + Na]^+$ 757.4474, found 757.4468; IR ν_{max} (film) 2936, 2856, 1472, 1112, 836, 702 cm^{-1}.

((1S,3R,3aR,4R,4aS,7aR)-4-((tert-Butyldiphenylsilyloxy)methyl)-3-methyl-3,3a,4,4a,5,6,7,7a-octahydro-1H-indeno[5,6-c]furan-1,3-diyl)-dimethanol ***24***. To a stirred solution of **23** (36 mg, 0.05 mmol) in MeOH (0.5 mL) was added CSA (2.3 mg, 0.01 mmol, 0.2 equiv). After 2.5 h at rt, the reaction was quenched with Et_3N and MeOH was

concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.2−1.6% MeOH/CH_2Cl_2) to afford **24** (23 mg, 90%). $[\alpha]_D^{20}$ = 51.7 (*c* = 1.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62−7.65 (m, 4H), 7.36−7.50 (m, 6H), 5.31 (d, 1H, *J* = 1.4 Hz), 4.36−4.40 (m, 1H), 3.78 (dd, 1H, *J* = 6.0, 10.4 Hz), 3.57−3.69 (m, 2H), 3.40−3.56 (m, 3H), 2.90−2.95 (m, 1H), 2.44−2.52 (m, 1H), 2.36−2.44 (m, 2H), 2.10−2.18 (m, 1H), 1.82−1.94 (m, 1H), 1.70−1.82 (m, 1H), 1.58−1.65 (m, 1H), 1.44−1.56 (m, 2H), 1.28−1.38 (m, 2H), 1.05 (s, 9H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.1, 135.80, 135.77, 133.9, 129.9, 127.9, 123.1, 85.8, 78.6, 67.5, 66.3, 64.3, 41.0, 40.2, 38.9, 36.0, 32.0, 29.0, 27.1, 23.6, 20.1, 19.4; HRMS calcd for $C_{31}H_{42}O_4Si$ $[M + Na]^+$ 529.2745, found 529.2742; IR ν_{max} (film) 3417, 2936, 2856, 1472, 1112, 822, 702 cm^{-1}.

*Epoxides **6** and **25***. To a stirred solution of **24** (170 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (321 mg, 1.3 mmol, 4 equiv). After 48 h at rt, the reaction was quenched with sat. Na_2SO_3, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1−1.6% MeOH/CH_2Cl_2) to afford **6** (100 mg, 60%) and **25** (52 mg, 30%). **6**: $[\alpha]_D^{20}$ = 30.6 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63−7.67 (m, 4H), 7.36−7.48 (m, 6H), 3.83−3.86 (m, 1H), 3.52−3.80 (m, 6H), 3.35 (b, 1H), 3.29 (d, 1H, *J* = 4.9 Hz), 3.06 (d, 1H, *J* = 4.9 Hz), 2.61 (b, 1H), 2.22−2.30 (m, 1H), 1.77−1.83 (m, 1H), 1.50−1.58 (m, 2H), 1.35−1.47 (m, 3H), 1.16−1.22 (m, 1H), 1.19 (s, 3H), 1.08 (s, 9H), 0.40−0.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.0, 135.7, 133.1, 132.7, 130.3, 130.2, 128.11, 128.06, 84.4, 74.2, 69.3, 68.2, 64.7, 63.4, 60.4, 39.5, 37.9, 37.8, 32.5, 32.4, 28.4, 27.2, 25.3, 21.6, 19.3; HRMS calcd for $C_{31}H_{42}O_5Si$ $[M + Na]^+$ 545.2694, found 545.2689; IR ν_{max} (film) 3363, 2932, 2856, 1472, 1427, 1112, 1067, 702 cm^{-1}.

25: $[\alpha]_D^{20}$ = 10.8 (*c* = 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61−7.65 (m, 4H), 7.35−7.44 (m, 6H), 3.91 (dd, 1H, *J* = 4.4, 9.6 Hz), 3.84 (t, 1H, *J* = 3.3 Hz), 3.71−3.80 (m, 2H), 3.56 (d, 1H, *J* = 11.7 Hz), 3.50 (dd, 1H, *J* = 3.6, 11.8 Hz), 3.37 (d, 1H, *J* = 11.7 Hz), 3.07 (s, 1H), 2.73 (d, 1H, *J* = 5.1 Hz), 2.32−2.40 (m, 2H), 2.24 (b, 2H), 1.76−1.88 (m, 2H), 1.58−1.75 (m, 2H), 1.36−1.46 (m, 2H), 1.25−1.34 (m, 1H), 1.09 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.9, 135.8, 134.29, 134.26, 129.9, 129.8, 127.9, 85.0, 79.0, 67.8, 66.6, 65.4, 63.4, 57.7, 40.4, 39.6, 39.4, 35.2, 33.5, 31.7, 27.2, 26.1, 20.8, 19.4; HRMS calcd for $C_{31}H_{42}O_5Si$ $[M + Na]^+$ 545.2694, found 545.2690; IR ν_{max} (film) 3363, 2932, 2856, 1472, 1427, 1112, 1067, 702 cm^{-1}.

*((1R,3R,3aR,4aS,7aS,8R,8aR)-8-((tert-Butyldiphenylsilyloxy)methyl)-3a-hydroxy-1-methyldecahydro-1H-indeno[5,6-c]furan-1,3-diyl)dimethanol **26***. To a stirred solution of **6** (15.5 mg, 0.03 mmol) in THF (0.6 mL) was added MeMgBr (3 M in Et_2O, 1.2 mmol, 40 equiv). After 72 h at 80 °C, the reaction was quenched with sat. NH_4Cl and extracted with Et_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.2−2.5% MeOH/CH_2Cl_2) to afford **26** (8.3 mg, 52%). Alternative method: To a stirred solution of **6** (30.5 mg, 0.06 mmol) in THF (0.2 mL) was added MeMgBr (1 M in THF, 2.4 mmol, 40 equiv). After 72 h at 80 °C, the reaction was quenched with sat. NH_4Cl, extracted with Et_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.2−2.5% MeOH/CH_2Cl_2) to afford **26** (22 mg, 72%). $[\alpha]_D^{20}$ = 34.6 (*c* = 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64−7.69 (m, 4H), 7.37−7.48 (m, 6H), 3.84−3.96 (m, 2H), 3.62−3.78 (m, 5H), 3.21 (b, 1H), 3.10 (b, 1H), 2.80 (b, 1H), 2.64 (d, 1H, *J* = 5.4 Hz), 1.95−2.05 (m, 1H), 1.78−1.86 (m, 2H), 1.74 (dd, 1H, *J* = 4.8, 14.0 Hz), 1.44−1.60 (m, 3H), 1.36 (dd, 1H, *J* = 11.8, 14.0 Hz), 1.26 (s, 3H), 1.20−1.28 (m, 2H), 1.08 (s, 9H), 0.64−0.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.0, 135.7, 133.3, 133.2, 130.3, 130.1, 128.1, 128.0, 84.7, 83.5, 80.6, 71.7, 65.1, 62.1, 52.7, 41.4, 37.8, 36.5, 35.2, 33.1, 32.9, 27.2, 25.3, 20.8, 19.4; HRMS calcd for $C_{31}H_{44}O_5Si$ $[M + Na]^+$ 547.2850, found 547.2846; IR ν_{max} (film) 3394, 2932, 2856, 1472, 1107, 1071, 702 cm^{-1}.

*((1R,3R,3aR,4S,4aR,7aR,8R,8aR)-8-((tert-Butyldiphenylsilyloxy)methyl)-4-chloro-3a-hydroxy-1-methyldecahydro-1H-indeno[5,6-c]furan-1,3-diyl)dimethanol **27***. To a stirred solution of **6** (14.5 mg, 0.03 mmol) in THF (0.5 mL) was added MeMgCl (3 M in THF, 1.2 mmol, 40 equiv). After 48 h at 80 °C, the reaction was quenched with sat. NH_4Cl, extracted with Et_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1.2% MeOH/CH_2Cl_2) to afford **27** (6.3 mg, 40%) and rsm (2.8 mg, 20%). $[\alpha]_D^{20}$ = 28.1 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64−7.69 (m, 4H), 7.37−7.48 (m, 6H), 4.47 (b, 1H), 4.02−4.22 (m, 3H), 3.79 (d, 1H, *J* = 13.3 Hz), 3.58−3.72 (m, 4H), 3.25 (b, 1H), 2.91 (d, 1H, *J* = 4.9 Hz), 2.86 (b, 1H), 2.20−2.28 (m, 1H), 1.94−2.06 (m, 1H), 1.70−1.84 (m, 2H), 1.54−1.62 (m, 2H), 1.40−1.48 (m, 1H), 1.29 (s, 3H), 1.20−1.28 (m, 1H), 1.08 (s, 9H), 0.60−0.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.0, 135.7, 133.1, 133.0, 130.3, 130.2, 128.08, 128.07, 86.2, 84.2, 78.3, 72.2, 71.4, 64.7, 63.3, 57.0, 42.4, 40.9, 39.8, 34.2, 33.1, 27.1, 25.9, 20.1, 19.4; HRMS calcd for $C_{31}H_{43}ClO_5Si$ $[M + Na]^+$ 581.2460, found 581.2454; IR ν_{max} (film) 3394, 2927, 2860, 1476, 1472, 1111, 1076, 702 cm^{-1}.

*Acetonide **29***. To a stirred solution of **26** (32 mg, 0.06 mmol) in 2, 2-dimethoxypropane (1 mL) was added CSA (4.6 mg, 0.02 mmol, 0.3 equiv). After 4 h at rt, the reaction was quenched with Et_3N, and 2, 2-dimethoxypropane was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (12% to 18% EtOAc/hexane) to afford **30** (22 mg, 54%) and **29** (11.5 mg, 34%). To a stirred solution of **30** (22 mg, 0.035 mmol) in MeOH (1.5 mL) were added HOAc (20 μL) and H_2O (20 μL). After 3.5 h at rt, the reaction was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (18% EtOAc/hexane) to afford **29** (18 mg, 90%). $[\alpha]_D^{20}$ = 24.6 (*c* = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64−7.69 (m, 4H), 7.35−7.46 (m, 6H), 4.08 (dd, 1H, *J* = 4.1, 12.9 Hz), 3.85 (dd, 1H, *J* = 3.1, 12.9 Hz), 3.72−3.78 (m, 1H), 3.60−3.68 (m, 4H), 3.14 (b, 1H), 2.80 (d, 1H, *J* = 5.1 Hz), 1.97−2.05 (m, 1H), 1.92 (dd, 1H, *J* = 4.1, 13.3 Hz), 1.82−1.86 (m, 1H), 1.72−1.80 (m, 1H), 1.44−1.60 (m, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.31 (t, 1H, *J* = 13.5 Hz), 1.26 (s, 3H), 1.22−1.28 (m, 1H), 1.12−1.18 (m, 1H), 1.07 (s, 9H), 0.60−0.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.1, 135.8, 133.5, 133.4, 130.1, 130.0, 128.0, 127.9, 98.5, 85.2, 84.2, 72.9, 71.9, 65.3, 60.3, 53.0, 42.5, 39.1, 37.1, 34.5, 33.8, 33.5, 29.3, 27.1, 26.2, 25.8, 20.2, 19.4; HRMS calcd for $C_{34}H_{48}O_5Si$ $[M + Na]^+$ 587.3163, found 587.3157; IR ν_{max} (film) 3452, 2932, 2856, 1472, 1370, 1107, 1071, 702 cm^{-1}.

*Diol **31***. To a stirred solution of **29** (22 mg, 0.039 mmol) in THF (0.4 mL) was added TBAF (1 M in THF, 0.08 mmol, 2 equiv). After 3 h at rt, the reaction was quenched with NH_4Cl and diluted with Et_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (50% to 60% EtOAc/hexane) to afford **31** (10 mg, 80%). $[\alpha]_D^{20}$ = 12.3 (*c* = 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.10 (dd, 1H, *J* = 4.5, 12.9 Hz), 3.84 (dd, 1H, *J* = 3.4, 12.9 Hz), 3.72−3.80 (m, 2H), 3.50−3.68 (m, 3H), 2.99 (b, 1H), 2.71 (d, 1H, *J* = 5.5 Hz), 2.29 (b, 1H), 1.85−2.10 (m, 5H), 1.68−1.75 (m, 3H), 1.42−1.50 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H), 1.22−1.28 (m, 1H), 1.10−1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 98.5, 85.0, 84.3, 72.5, 71.3, 64.0, 60.2, 52.5, 42.9, 39.0, 37.2, 34.6, 34.0, 33.9, 29.2, 26.1, 20.4; HRMS calcd for $C_{18}H_{30}O_5$ $[M + Na]^+$ 349.1985, found 349.1989; IR ν_{max} (film) 3480, 2932, 2856, 1472, 1370, 1112, 1071 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. Full spectroscopic data for all new compounds and X-ray crystallographic data of **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

The authors thank Dr. Lev Zakharov of the Chemistry Department, University of Oregon, for providing X-ray crystallographic analysis. Support from the Nesvig Foundation, Markel Foundation, and U.S. Army RDECOM Acquisition Center, Natick Contracting Division, Natick, MA, under Contract No. W911QY-10-C-0176 is gratefully acknowledged.

REFERENCES

(1) (a) Luo, S.-H.; Luo, Q.; Niu, X.-M.; Xie, M.-J.; Zhao, X.; Schneider, J. G.; Li, S.-H. *Angew. Chem., Int. Ed.* **2010**, *49*, 4471. (b) Luo, S. H.; Weng, L. H.; Xie, M. J.; Li, X. N.; Hua, J.; Zhao, X.; Li, S. H. *Org. Lett.* **2011**, *13*, 1864.

(2) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(3) Recent reviews on intramolecular Diels−Alder reaction, see:(a) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (b) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983.

(4) (a) Cheng, H.; Stark, C. B.W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1587. (b) Donohoe, T. J.; Winship, P. C. M.; Walter, D. S. *J. Org. Chem.* **2009**, *74*, 6394. (c) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766.

(5) Recent reviews on Sonagashira cross-coupling reaction, see: (a) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834.

(6) Kiren, S.; Williams, L. J. *Org. Lett.* **2005**, *7*, 2905.

(7) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(8) **16** was prepared from 5-hexyn-1-ol, see: Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771.

(9) Once hemihydrogenation is finished, the over-reduced product is generated quickly. In addition, the R_f value of desired product **18** is indistinguishable from the over-reduced product, so this side-product should be avoided. The starting material **17**, however, has an R_f value different from that of **18**, so it can be recovered.

(10) For select examples of intramolecular Diels−Alder (IMDA) reactions of (*E*,*Z*,*E*) trienes, see: (a) Munakata, R.; Ueki, T.; katakai, H.; Takao, K.-I.; Tadano, K.-I. *Org. Lett.* **2001**, *3*, 3029. (b) Chang, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 253. (c) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4725. (d) Paquette, L. A.; Chang, J.; Liu, Z. *J. Org. Chem.* **2004**, *69*, 6441. (e) Munakata, R.; Ueki, T.; katakai, H.; Kurosaka, J.; Takao, K.-I.; Tadano, K.-I. *J. Am. Chem. Soc.* **2004**, *126*, 11254.

(11) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

(12) (a) Meresse, P.; Monneret, C.; Bertounesque., E. *Tetrahedron* **2004**, *60*, 2657. (b) Paterson, I.; Gardner, N. M.; Guzman. E. Wright, A. E. *Bioorg. Med. Chem.* **2009**, *17*, 2282.