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Stereodivergent Route to the Carbocyclic Core of 2′,3′-Olefinic Carbanucleosides: Toward the Synthesis of (L)-(+)- and (D)-(−)-Carbovir

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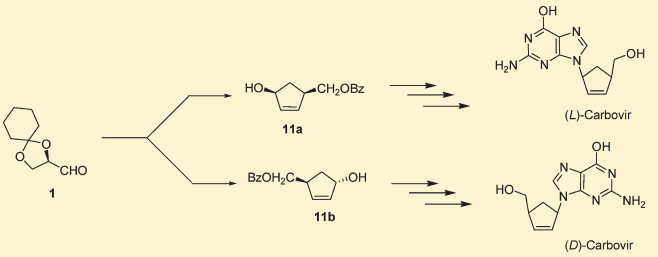
Supporting Information

ABSTRACT: (*R*)-2,3-Cyclohexylideneglyceraldehyde (**1**) has been elegantly exploited for a stereodivergent construction of the potential precursors (**11a** and **11b**) of (L)-(+)- and (D)-(−)-carbovirs, respectively. The key steps in this approach were Luche's allylation of formaldehyde with allylic bromide **4c** to produce **5** and ring-closing metathesis of **10b** using Grubbs' first-generation catalyst to obtain **11**. The moderate stereoselectivity of Luche's allylation reaction resulted in attaining stereodivergence in this approach which could be realized finally through easy chromatographic separation of the two isomers of the metathesis product to obtain homochiral precursors **11a** and **11b** in good amounts.



The emerging drug-resistant viral strains and toxicity are major concerns in antiviral chemotherapy. To overcome such difficulties, there has been a continuing search for new antiviral compounds that led to the synthesis of a variety of sugar-modified nucleosides.[1] Many nucleoside-based drugs are currently in use against viral infections.[2] Carbocyclic nucleosides (alternately called carbanucleosides in short form) are structural analogues of natural and synthetic nucleosides where the ring oxygen is replaced by a methylene unit. They have emerged as the target of intense investigation due to their interesting biological activities and greater metabolic stabilities to nucleoside phosphorylases, which cleave the glycosidic bond of the normal nucleosides.[3] Since the discovery of naturally occurring carbanucleosides aristeromycin **I**[4] and neplanocin A **II**[5] that exhibited good antiviral and antitumor activities, syntheses of their unnatural analogues became a topic of immense attention.[6] Some prominent members among them are (−)-carbovir D-**III**,[7] a potent and selective inhibitor of HIV reverse transcriptase (as its triphosphate), its pro-drug abacavir **IV**,[8] carbocyclic 2′,3′-didehydro-2′,3′-dideoxyadenine **V**,[8,9] entecavir **VI**,[10] etc (Figure 1).

The aforementioned nucleosides (**I**−**VI**) have D-configuration. Among them, compounds **III**, **IV**, and **V** are structurally classified as 2′,3′-olefinic carbanucleosides. Of all, D-carbovir (D-**III**) was the first analogue which exhibits potent anti-HIV activity in vitro. The first preparation of this isomer of carbovir was reported by Vince et al. in 1988.[11a] The preparation of its enantiomer (L-**III**) (Figure 1) was initially attended through approaches like chemoenzymatic[11b,12,13] and [2 + 3] asymmetric cycloaddition.[14] The anti-HIV and anti-HBV activities reside in its β-D enantiomer.[15] However, it is reported that the triphosphates of β-D- and β-L-carbovirs were approximately equipotent as HIV-reverse transcriptase inhibitors, and the β-L-carbovir triphosphate exhibited more potent anti-HBV activity.[15,16] The above-mentioned findings prompted synthetic chemists to develop various methodologies until recently for the synthesis[6,17] of both D- and L-carbovirs (**III**) and their various analogues with a view to combating a wide range of viral diseases. Furthermore, as representative examples of 2′,3′-olefinic carbanucleosides, any synthesis of either D-(**III**) or L-(**III**) assumes considerable significance in view of its application for the preparation of the similar isomers of other members of this class.

Retrosynthetic analysis (Scheme 1) of **III** suggested that for convergent preparation of its (L)-(+)- and (D)-(−)-enantiomers it is desirable to construct the basic carbocyclic core, i.e., 1,4-disubstituted 2,3-cyclopentene precursors ($\mathbf{X_1}$ and $\mathbf{X_2}$) which should be amenable for stereodifferentiating necleobase additions in the desired manner compatible with the enantiomer of **III** to be obtained. In this regard, there is a scope to develop efficient strategies to have access to branched 1,6-dienes $\mathbf{D_1}$ and $\mathbf{D_2}$ that would give rise to $\mathbf{X_1}$ and $\mathbf{X_2}$, respectively, through ring-closing metathesis reaction.[18] In our ongoing program on the synthesis of bioactive compounds, we have been making versatile application of easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde (**1**)[19a] for the synthesis of a number of biomolecules possessing varied structural features.[19] We present here another novel application of **1** to develop a very simple and stereodivergent route (Scheme 2) for simultaneous entry into two intermediates **11a** and **11b**, which due to their structural similarity with $\mathbf{X_2}$ and $\mathbf{X_1}$ are potentially useful precursors for formal synthesis of L-(**III**) and D-(**III**), respectively.

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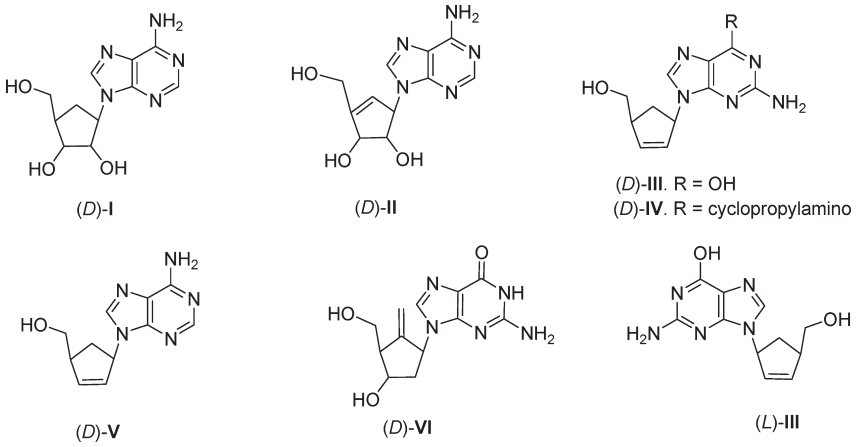
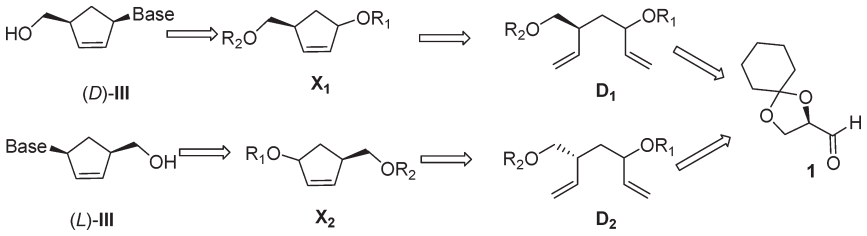


Figure 1. Some well-known carbanucleosides.

Scheme 1



In this mission, we started with silylated homoallylic alcohol (**2a**)[19d] derived from **1**. Ozonolysis of its olefin and reduction of the resulting ozonide in situ with PPh_3 gave relatively unstable aldehyde **2b**. This was quickly subjected to Wittig−Horner olefination to obtain unsaturated ester **3**. Dibal reduction of **3** afforded allylic alcohol **4a** in good yield. This was converted into the allylic bromide **4c** in two steps [mesylation and bromination of the corresponding mesylate (**4b**) with NaBr] in good overall yield. In the next crucial step, formaldehyde (separately produced by heating paraformaldehyde) was subjected to allylation on treatement with compound **4c** following Luche's procedure.[20] The allylation reaction took place efficiently (73.5% yield) to obtain homoallylic alcohol **5** as a mixture of diastereomers **5a** and **5b** which could not be separated from each other by column chromatography. The mixture of **5a** and **5b** was benzoylated to produce **6a**,**b**, also obtained as an inseparable mixture of diastereomers. This was deketalized in the presence of aqueous trifluoroacetic acid to produce diol **7** as a mixture of diastereoisomers **7a**,**b**. Conversion of the 1,2-diol unit of **7** into the bisolefin diastereomeric mixture **9a**,**b** was accomplished in two steps, viz., (a) dimesylation and (b) treatment of the resulting dimesylate **8** with zinc. Desilylation of **9** on treatment with TBAF afforded an inseparable diastereomeric mixture of 1,6-dienes **10a**, **b** which was subjected to ring-closing metathesis reaction using a first-generation Grubbs' catalyst [$Cl_2(PCy_3)_2RuCHPh$].[18c] The metathesis reaction produced 1,4-disubstituted 2-cyclopentene **11** in 90.5% yield, as a mixture of *cis*-**11a** and *trans*-**11b**. To our delight, compounds **11a** and **11b** were found to be easily separable from each other by column chromatography (silica gel, 0−10% EtOAc in hexane) to obtain both of them in homochiral form (*cis*-**11a**:*trans*-**11b** 48.3:51.7). In hindsight, the stereoselectivity in Luche's allylation (step vi, Scheme 2) for the preparation of **5** could be tentatively reflected from the relative ratio of the isolated amounts of **11a** and **11b**, as the subsequent steps did not involve any stereodifferentiating reactions. The relative stereochemistry (*cis*-**11a** and *trans*-**11b**) between the substituents at C-1 and C-4 in the 2,3-cyclopentene **11** could be determined by analyzing the chemical shifts of their CH_2 protons at C-5 in their respective ^1H NMR spectra that were found to be comparable with the reported pattern.[17f,n] The signals due to $H_{5\alpha}$ and $H_{5\beta}$ [$H_{5\alpha}$: 1.52 (d, t, J = 13.8, 4.5 Hz); $H_{5\beta}$: 2.4−2.6 (m, 1H)] in *cis*-**11a** were found to be widely separated from each other, whereas the corresponding signals of *trans*-**11b** were found to be almost overlapping [$H_{5\alpha}$ and $H_{5\beta}$: δ-1.9−2.1, m, 2H].

Both compounds **11a** and **11b**, possessing a free secondary hydroxyl at C-1 and a benzoyloxymethyl at C-4, have good skeletal as well as stereochemical resemblance with the known precursors[17b,c,e] of (L)-(+)- and (D)-(−)-**III**, respectively. For example, the 4-*O*-silyl ether analogue[17c] of *trans*-**11b** has been utilized for the synthesis of D-(−)-**III** through Mitsunobu coupling with 2-amino-6-chloropurine that was associated with inversion at C-1. On the other hand, the corresponding dicarbonate[17e] and 4-*O*-tritylhydroxymethyl-1-acetyl[17b] analogues of *cis*-**11a** have individually been utilized for the synthesis of L-(+)-**III** through tetrakis-Pd-mediated coupling with the same base employing Trost's procedure[6g,17a] that took place along with stereochemical retention at C-1.

Thus, a simple and stereodivergent approach has been developed for the formal synthesis of both enantiomers of carbovir (**III**) through judicious utilization of **1**.[19a] This work also demonstrates another application of Grubb's metathesis[18] for the syntheses of different carbocycles[21] by constructing the

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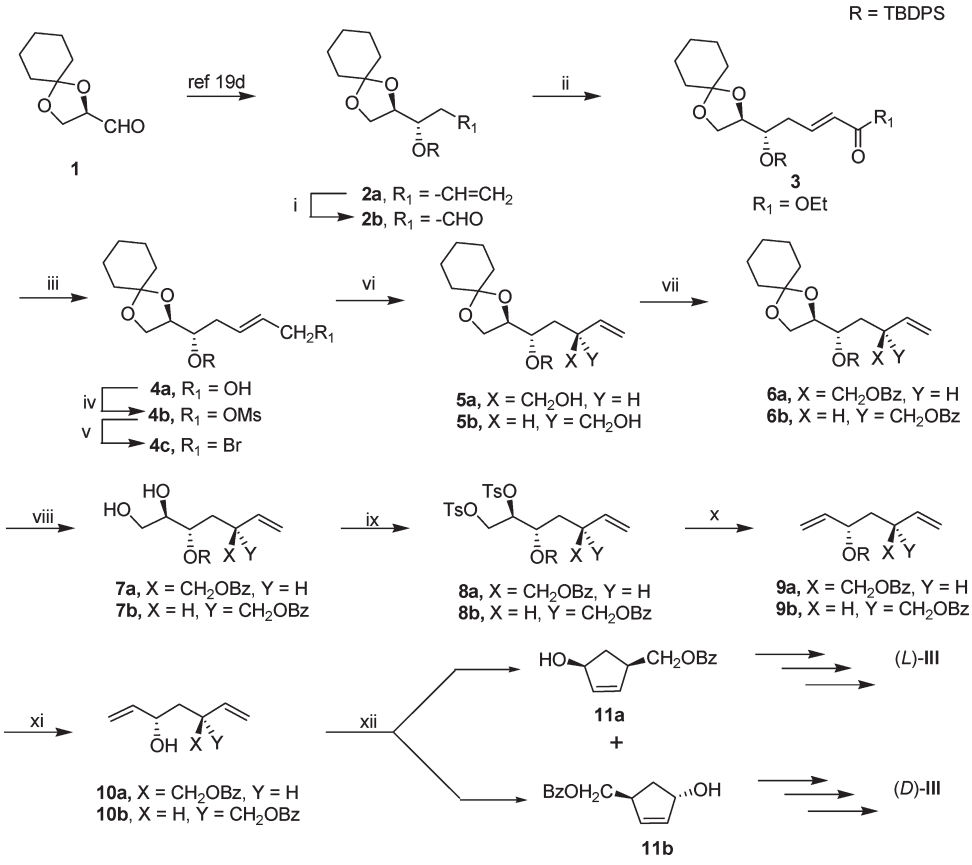
Scheme 2[a]



[a] (i) O_3, PPh_3, Dry CH_2Cl_2, −78 °C; (ii) NaH, $C_2H_5COOCH_2P(O)(OC_2H_5)_2$, Dry THF, 25 °C; (iii) DIBAL-H, Dry THF, −78 °C ; (iv) MsCl, Et_3N, Dry CH_2Cl_2, 0 °C; (v) NaBr, $NaHCO_3$, Dry Acetone, 25 °C; (vi) Zn/NH_4Cl, CH_2O, THF, 25 °C; (vii) BzCN, Et_3N, Dry CH_2Cl_2, 25 °C; (viii) Aq. TFA (80%), CH_2Cl_2, 0 °C; (ix) TsCl, Py, DMAP, 25 °C; (x) Zn, NaI, Dry DMF, 80 °C; (xi) TBAF, Dry THF, 0 °C; (xii) $(PCy_3)_2Cl_2RuCHPh$, Dry Benzene, 60 °C, 24 h.

2′,3′-olefinic carbocycle skeleton of **III**. The efficacy of this approach was due to its use of **1** as the staring material which is available in multigram scale[19a] and its involvement with a series of operationally simple and efficiently scaleable reactions. Among them, Luche's allylation[20] of formaldehyde with **4c** (step vi, Scheme 2) to obtain a C-branched homoallylic alcohol **5** has been judiciously exploited to ultimately have a smooth access to the precursor (**10a,b**) of the methathesis reaction. It is worth noting that the moderate stereoselectivity of this crucial allylation reaction proved highly advantageous to achieve its stereodivergence in this route. This was finally realized by column chromatographic separation of the Grubb's metathesis product **11** to obtain good amount of both diastereomers **11a** and **11b** which eventually could be treated as the potential precursors of both enantiomers of carbovir. It can be presumed that the same intermediates **11a** and **11b**, either themselves or in their other hydroxyl protected forms, could be useful for the syntheses of other 2′,3′-olefinic carbocyclic nucleosides possessing (L)- and (D)- configurations, respectively.

EXPERIMENTAL SECTION

Chemicals used as starting materials are commercially available and were used without further purification. All solvents used for extraction and chromatography were distilled twice at atmospheric pressure prior to use. The organic extracts were desiccated over dry Na_2SO_4.

(3*S*,4*R*)-3-*O*-*tert*-Butyl-diphenylsilyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-pentanal (2b). To a cooled (−78 °C) solution of **2a** (4.8 g, 10.65 mmol) in dichloromethane (40 mL) was bubbled ozone gas for 5 min until the reaction mixture became blue. The bluish solution was stirred for 10 min more and treated with dry triphenylphosphine (4.2 g, 15.97 mmol). The mixture was gradually brought to room temperature and stirred for 3 h more. The reaction mixture was concentrated in vacuo, and the residue was passed through a short silica gel column eluting with 10% EtOAc in hexane to afford **2b** (4.14 g, 86%) as a colorless oil. This was found to be unstable on long-standing and hence was used immediately for the next step without further purification. A small portion of **2b** was used for its spectroscopic characterization. $[\alpha]_D^{25}$ = −13.52 (*c*, 1.12, $CHCl_3$). ^{1}H NMR: δ 1.09 (s, 9H), 1.2−1.5 (m, 10H), 2.56 (m, 2H), 3.55−3.62 (m, 1H), 3.8−3.9 (m, 1H), 4.0−4.1 (m′, 2H), 7.5 (m, 6H), 7.6−7.8 (m, 4H), 9.61 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR: 19.2, 23.6, 23.7, 25.0, 26.8, 34.4, 35.8, 48.1, 66.8, 70.6, 78.2, 110.1, 127.6, 127.7, 129.9, 130.0, 132.9, 135.7, 200.3.

(5*S*,6*R*)-Ethyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-2*E*-enoate 3. To a cooled (0 °C) suspension of sodium hydride (0.47 g, 50% suspension in oil, 9.8 mmol, washed once with dry hexane) in THF (20 mL) was added dropwise triethyl phosphonoacetate (2.21 g, 9.86 mmol) in THF (10 mL) over a period of one hour under argon atmosphere. After the addition was over, the reaction mixture was gradually brought to room temperature and stirred until it became clear. Again the temperature was brought down to 0 °C, and a solution of **2b** (4.06 g, 8.97 mmol) in dry THF (20 mL) was

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added dropwise over a period of 1 h. The mixture was stirred at 0 °C for 1 h and stirred at room temperature overnight (completion of reaction confirmed from TLC). The mixture was cooled to 0 °C, treated with water, neutralized by dropwise addition of dilute HCL (2%), and extracted twice with EtOAc. The combined organic layer was washed successively with water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, hexane:EtOAc 20:1) of the residue afforded pure **3** (3.75 g, 7.175 mmol, 80%) as a colorless oil. $[\alpha]_D^{29} = +19.54$ (*c*, 0.87, $CHCl_3$). ^{1}H NMR: δ 1.04 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.35−1.59 (m, 10H), 2.27−2.37 (m, 2H), 3.6−3.7 (m, 1H), 3.8−4.0 (m, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.66 (d, *J* = 15.6 Hz, 1H), 6.90 (td, *J* = 8, 15.6 Hz, 1H), 7.5 (m, 6H), 7.6−7.8 (m, 4H). ^{13}C NMR: 14.2, 19.3, 23.7, 23.9, 25.1, 26.5, 26.9, 34.7, 36.1, 37.0, 60.0, 66.5, 73.3, 77.5, 109.6, 123.7, 127.60, 127.68, 129.82, 129.89, 133.2, 133.4, 134.8, 135.9, 144.7, 166.2. Anal. Calcd for $C_{31}H_{42}O_5$ Si: C, 71.23; H, 8.10. Found: C, 71.51; H, 8.24.

(5*S*,6*R*)-5-*O*-*tert*-Butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-1,5,6,7-tetrahydroxy-hept-2*E*-ene 4a. To a cooled (−78 °C) solution of **3** (3.7 g, 7.08 mmol) in dry THF (30 mL) was added dropwise DIBALH (14.2 mL, 1.0 M solution in hexane) over a period of one hour. The mixture was stirred for 1 h at the same temperature until the reaction was complete (confirmed by TLC). To the mixture was added methanol (15 mL). The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a celite pad. Concentration of the filtrate under reduced pressure and column chromatography (silica gel, 0−25% EtOAc in hexane) of the residue afforded pure **4a** (3.1 g, 91%) as a colorless oil. $[\alpha]_D^{26} = +18.71$ (*c*, 0.962, $CHCl_3$). ^{1}H NMR: δ 1.04 (s, 9H), 1.35−1.59 (m, 10H, overlapped with brs, 1H), 2.1−2.2 (m, 2H), 3.7−4.1 (m, 6H), 5.4−5.5 (m, 2H), 7.3 −7.4 (m, 6H), 7.6−7.7 (m, 4H). ^{13}C NMR: 19.2, 23.7, 23.8, 25.0, 26.8, 34.6, 36.0, 36.9, 63.2, 65.8, 73.3, 77.3, 109.3, 127.4, 127.6, 129.5, 131.8, 133.3, 133.9, 135.81, 135.86. Anal. Calcd for $C_{29}H_{40}O_4$ Si: C, 72.46; H, 8.39. Found: C, 72.21; H, 8.29.

(5*S*,6*R*)-1-Bromo-5-*O*-tert-butyl-diphenylsilyl--6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-2*E*-ene (4c). To the cooled (0 °C) solution of **4a** (3.0 g, 6.25 mmol) and tryethylamine (1.07 g, 10.60 mmol) in dry DCM (15 mL) was added methanesulfonylchloride (0.93 g, 8.11 mmol) dropwise over a period of 15 min. The mixture was stirred for 3 h at room temperature and treated with water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water and brine and dried over Na_2SO_4, Solvent removal under reduced pressure afforded yellow oily liquid containing the crude mesylated product (**4b**) in almost quantitative yield which was used in the next reaction without further purification.

To a solution of crude mesylate (**4b**) in dry acetone (20 mL) were added dry NaBr (0.78 g, 7.5 mmol) and a catalytic amount of $NaHCO_3$. It was then stirred overnight while **4b** disappeared totally (cf. TLC). The reaction mixture was concentrated under reduced pressure to get rid of the acetone, washed with dilute aqueous HCl (2%) for neutrality, and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford a colorless liquid which was chromatographed on silica gel (EtOAc/hexane 0−2%) to afford pure **4c** (3.06 g, 5.63 mmol, 90%). The compound tended to become colored on long-standing probably due to its being unstable and hence was immediately used for the next step. $[\alpha]_D^{27} = +28.71$ (*c*, 1.01, $CHCl_3$). ^{1}H NMR: δ 1.04 (s, 9H), 1.36−1.59 (m, 10H), 2.1−2.2 (m, 2H), 3.6−3.7 (m, 1H), 3.8−4.0 (m, 5H), 5.4−5.7 (m, 2H), 7.3−7.4 (m, 6H), 7.6−7.7 (m, 4H). ^{13}C NMR: 19.3, 23.8, 23.9, 25.1, 26.9, 34.7, 36.1, 36.8, 45.0, 66.3, 73.4, 77.4, 109.4, 127.53, 127.57, 128.5, 129.7, 131.0, 133.3, 133.8, 135.9.

(5*S*,6*R*)-3-Hydroxymethyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-1-ene (5a,b). To a solution of bromide **4c** (2.0 g, 3.67 mmol) in distilled THF (10 mL) at room temperature was added zinc dust (0.5 g, 7.65 mmol). The mixture was stirred for 10 min. To this stirred mixture, gaseous formaldehyde (formed by heating paraformaldehyde in another container at 180 °C in a heating mantle under the flow of argon) was bubbled through an inlet tube. After stirring this reaction mixture for 30 min, saturated NH_4Cl (2 mL) was added dropwise into it with continued bubbling of formaldehyde gas. After 1 h, heating of paraformaldehyde was stopped, while the reaction mixture was stirred overnight at room temperature. The bromide was found to be consumed totally (TLC). The mixture was filtered, and the filtrate was thoroughly washed with EtOAc. The organic layer was washed with dilute aqueous HCl to dissolve the turbid suspension. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, 0−20% EtOAc in hexane) of the residue afforded pure **5** (1.27 g, 70%) containing a chromatographically inseparable mixture of diastereomers **5a** and **5b** as a colorless oil. ^{1}H NMR: δ 1.04 (s, 9H), 1.3−1.6 (m, 12H, overlapped with a brs, 1H), 2.28 (m, 1H), 3.0−3.3 (m, 2H), 3.6−4.0 (m, 4H), 4.8−5.0 (m, 2H), 5.1−5.2 (m, 1H), 7.2−7.4 (m, 6H), 7.6−7.7 (m, 4H). ^{13}C NMR: 19.2, 19.3, 23.7, 23.8, 25.0, 26.8, 34.5, 34.6, 35.1, 35.9, 36.1, 42.4, 42.6, 65.0, 65.4, 66.3, 66.5, 71.8, 72.3, 78.1, 78.3, 109.6, 116.8, 117.2, 127.4, 129.6, 133.2, 133.5, 133.7, 135.8, 139.3. Anal. Calcd for $C_{30}H_{42}O_4$ Si: C, 72.83; H, 8.56. Found: C, 73.01; H, 8.24.

(5*S*,6*R*)-3-Benzyloxymethyl-5-*O*-*tert*-butyl-diphenylsilyl-6,7-*O*-cyclohexylidene-5,6,7-trihydroxy-hept-1-ene (6a,b). To a cooled (0 °C) solution of the alcohol **5** (1.25 g, 2.52 mmol) and triethylamine (303 mg, 3 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of benzoylcyanide (0.36 g, 2.7 mmol) in CH_2Cl_2 (10 mL) in 5 min. The mixture was stirred at 0 °C for 1 h and then at room temperature for 4 h. The solution was treated with water. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with diluted aqueous HCl until neutral, water, and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, EtOAc/hexane 0−5%) of the residue afforded pure **6** (1.12 g, 92%) as a mixture of diastereomers **6a** and **6b**. ^{1}H NMR: δ 1.04 (s, 9H), 1.35−1.7 (m, 12H), 2.6 (m, 1H), 3.7−4.1 (m, 6H), 4.8−4.9 (m, 2H), 5.1−5.5 (m, 1H), 7.3−7.4 (m, 9H), 7.6−7.7 (m, 4H), 7.8−8.0 (m, 2H). ^{13}C NMR: 19.3, 23.7, 23.8, 25.0, 26.8, 34.6, 34.7, 35.6, 35.9, 36.639.0, 39.2, 66.3, 66.5, 67.3, 67.5, 71.6, 72.1, 78.4, 109.6, 116.5, 116.7, 127.5, 128.1, 129.3, 129.6, 130.1, 130.2, 132.6, 133.2, 133.6, 133.7, 135.8, 138.4, 166.1. Anal. Calcd for $C_{37}H_{46}O_5$ Si: C, 74.21; H, 7.74. Found: C, 74.35; H, 7.46.

(5*S*,6*R*)-3-Benzyloxymethyl-5-*O*-*tert*-butyl-diphenylsilyl-5,6,7-trihydroxy-hept-1-ene (7a,b). To a cooled (0 °C) solution of **6a,b** (2.20 g, 2.12 mmol) in distilled CH_2Cl_2 (30 mL) was added 80% aqueous trifluoroacetic acid (10 mL). The mixture was stirred for three hours at 0 °C. The reaction mixture was diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed successively with 2% $NaHCO_3$ for neutrality, water, and brine and dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography (silica gel, MeOH/$CHCl_3$ 0−5%) of the residue afforded pure **7** (1.32 g, 70%) as a mixture of diastereomers **7a** and **7b**. ^{1}H NMR: δ 1.06 (s, 9H), 1.2−1.6 (m, 2H), 2.02 (bs, 2H), 2.41 (m, 1H), 3.5−4.0 (m, 6H), 4.8−4.9 (m, 2H), 5.0−5.5 (m, 1H), 7.2−7.6 (m, 9H), 7.8−7.96 (m, 4H), 8.08−8.5 (m, 2H). ^{13}C NMR: 19.3, 26.9, 34.5, 34.7, 39.4, 39.5, 62.7, 62.9, 67.0, 67.5, 73.1, 73.4, 77.2, 116.9, 117.1, 127.6, 127.7, 128.2, 129.4, 129.91, 129.96, 130.1, 132.7, 132.84, 132.89, 133.1, 133.2, 135.8, 137.7, 138.0, 166.2. Anal. Calcd for $C_{31}H_{38}O_5$ Si: C, 71.78; H, 7.38. Found: C, 71.61; H, 7.44.

(5*S*)-3-Benzyloxymethyl-5-*O*-*tert*-butyl-diphenylsilyl-1,6-hexadiene (9a,b). To a cooled (0 °C) solution of **7** (1.30 g, 2.5 mmol) in dry pyridine (10 mL) were added *p*-tolunesulfonylchloride (1.2 g, 6.26 mmol) and dimethylaminopyridine (100 mg). The mixture was gradually brought to room temperature over a period of 6 h and then

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stirred overnight. The reaction mixture was treated with 5% aqueous HCl and water for neutrality. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water and brine and dried. It was concentrated under reduced pressure to afford the crude ditosylated product **8** (confirmed by TLC and IR of crude) which was taken in dry DMF (15 mL). To this solution were added Zn dust (0.50 g, 7.52 mmol) and dry NaI (1.12 g, 7.50 mmol). The mixture was stirred overnight at 90 °C. The mixture was filtered, and the residue was thoroughly washed with EtOAc. The combined organic layer was washed with dilute aqueous HCl to dissolve the turbid material. The aqueous layer was separately extracted with EtOAc. The combined organic layer was washed with water and brine and dried. Solvent removal under reduced pressure and column chromatography (silica gel, 0−10% EtOAc in hexane) of the residue afforded pure diene **9** (1.05 g, 86.6%) as a mixture of diastereomers **9a** and **9b**. ^{1}H NMR: δ 1.06 (s, 9H), 1.2−1.8 (m, 2H), 2.3−2.8 (m, 1H), 4.0−4.2 (m, 3H), 4.8−5.0 (m, 4H), 5.1−5.9 (m, 2H), 7.2−7.6 (m, 9H), 7.8−7.96 (m, 4H), 8.08−8.5 (m, 2H). ^{13}C NMR: 19.2, 19.3, 39.0, 39.5, 39.7, 67.5, 67.6, 72.8, 72.9, 115.0, 115.3, 116.3, 116.7, 127.31, 127.36, 127.4, 127.8, 128.2, 129.5, 130.3, 132.8, 133.9, 134.1, 134.2, 135.9, 138.3, 138.7, 140.0, 140.7, 166.3. Anal. Calcd for $C_{31}H_{36}O_3Si$: C, 76.82; H, 7.49. Found: C, 77.04; H, 7.34.

(5*S*)-3-Benzyloxymethyl-5-hydroxy-1,6-heptadiene (10a, b). Tetrabutylammonium fluoride in THF (8 mL, 1 M solution) was added to a cooled (0 °C) solution of **9** (968 mg, 2 mmol) obtained above in THF (30 mL). The resulting solution was stirred overnight at room temperature. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (10 mL). The mixture was diluted with EtOAc while two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed successively with water and brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0−5% MeOH/$CHCl_3$) afforded pure **10** (459 mg, 93.2%) as a mixture of diastereomers **10a** and **10b**. ^{1}H NMR: 1.5−1.7 (m, 2H), 1.9 (bs, 1H), 2.5−2.9 (m, 1H), 4.1−4.3 (m, 3H), 5.0−5.2 (m, 4H), 5.6−5.9 (m, 2H), 7.3−7.5 (m, 3H), 8.02 (d, J = 8.1 Hz, 2H). ^{13}C NMR: 38.1, 38.2, 39.7, 67.1, 67.6, 70.0, 70.8, 114.0, 115.1, 116.4, 117.0, 128.1, 129.3, 130.0, 132.7, 138.2, 138.6, 140.5, 141.2, 166.3. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.44; H, 7.36.

(1*S*,4*S*)-4-(Benzyloxymethyl)-cyclopenten-2-enol (11a) and (1*S*,4*R*)-4-(Benzyloxymethyl)-cyclopenten-2-enol (11b). A solution of diene **10** (150 mg, 0.6097 mmol) in dry benzene (50 mL) was degassed by bubbling argon. To it was added Grubb's first -generation catalyst[18] (30.57 mg, 0.0372 mmol) in one portion. The resulting pink solution was stirred under heating (60 °C) for 24 h. The solvent was removed under reduced pressure, and the dark residue was purified by column chromatography (silica gel, 0−10% hexane in EtOAc) to afford **11a** (57.9 mg) and **11b** (62.0 mg) in homochiral form.

Compound ***11a***. R_f 0.5 (EtOAc:hexane 1:9). $[\alpha]_D^{24}$ = +52.31 (*c*, 1.51, $CHCl_3$). ^{1}H NMR: 1.52 (dt, J = 13.8, 4.5 Hz, 1H), 2.25 (bs, 1H), 2.4−2.6 (m, 1 H), 2.9−3.1 (m, 1H), 4.2−4.4 (m, 2H), 4.81−4.86 (m, 1H), 5.9 (m, 2H), 7.3−7.5 (m, 3H), 7.9−8.0 (m, 2H). ^{13}C NMR: 36.8, 43.7, 67.7, 76.5, 128.2, 129.3, 130.0, 132.7, 134.1, 135.4, 166.3. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.32; H, 6.53.

Compound ***11b***. R_f 0.4 (EtOAc:Hexane 1:9). $[\alpha]_D^{24}$ = −139.55 (*c*, 1.34, $CHCl_3$). ^{1}H NMR: 1.69 (s, 1H), 1.9−2.1 (m, 2H), 3.3−3.4 (m, 1H), 4.1−4.3 (m, 2H), 4.9 (m, 1H), 5.9−6.0 (m, 2H), 7.3−7.6 (m, 3H), 8.0 (m, 2H). ^{13}C NMR: 37.1, 44.0, 67.6, 76.6, 128.2, 129.4, 130.1, 132.8, 135.2, 135.3, 166.4. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.87; H, 6.42.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H and ^{13}C NMR spectra of compounds **2b**, **3**, **4a**, **4c**, **5a,b**, **6a,b**, **7a,b**, **9a,b**, **10a,b**, **11a**, and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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