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One-Pot Stereoselective Double Intramolecular Oxymercuration: Synthesis of Four Isomers of an Unsymmetrical Bis-Tetrahydrofuran Ring System

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Stereoselective one-pot double intramolecular oxymercuration has been demonstrated to be the key reaction in the efficient preparation of the mono-hydroxylated bis-tetrahydrofuran ring system present in asimitrin and salzmanolin, two naturally occurring biologically active nonclassical acetogenins.

Introduction

In recent years, the Annonaceous acetogenins have been the focus of extensive synthetic efforts as a result of their remarkable range of biological activities such as antitumor, antifeedant, immunosuppressive, pesticidal, anthelmintic, and microbial activities. In particular, after the identification of uvaricin[1] as an in vivo active antitumor agent there has been significant interest in the isolation and biological evaluation of acetogenins derived from the Annonaceous family.[2] Annonaceous acetogenins are known to be highly potent and selective antitumor agents. More interestingly, some members of this family have been shown to possess the ability to combat resistance in multi-drug-resistant cancerous cells.[3,4] The origin of the selective cytotoxicity of acetogenins is believed to result from their complexation with ubiquinone-linked NADH oxidase present in the plasma membrane of tumor cells. Acetogenins also bind NADH-ubiquinone oxidoreductase (Complex I), which is a membrane protein present in the mitochondrial electron-transport system.[5–9] Complex I has been implicated in several diseases including idiopathic Parkinson's disease, maturity onset diabetes, stroke-like episodes, and Huntington's disease.[10] However, the precise mode of complexation of acetogenins with target proteins has not been delineated.

Structurally, the Annonaceous acetogenins are a series of C_{35}/C_{37} natural products derived from C_{32}/C_{34} fatty acids that are combined with a 2-propanol unit. They are usually characterized by a long aliphatic chain bearing a terminal methyl-substituted α,β-unsaturated γ-lactone ring (sometimes rearranged to a keto lactone) with one, two, or three tetrahydrofuran (THF) rings located along the hydrocarbon chain and a number of oxygenated moieties (OH, OAc, ketones, epoxides) and/or double bonds being present. To a lesser extent, tetrahydropyran (THP) ring compounds and acyclic compounds are also found.

Asimitrin (**1**), a mono-hydroxylated unsymmetrical bis-tetrahydrofuran acetogenin, was isolated from the seeds of *Asimina triloba* in 2005.[11] Salzmanolin (**2**), another mono-hydroxylated unsymmetrical bis-tetrahydrofuran acetogenin, was isolated by Queiroz et al. in 2003[12] and displayed significant activities towards a cancer cell line when compared with normal cells (Vero, $ED_{50} > 1 \times 10^{-2}\ \mu g\,mL^{-1}$). These novel acetogenins were found to be selectively cytotoxic against prostate (PC-3) and colon adenocarcinoma (HT-29) with about 10000 and 100 times the potency of adriamycin, respectively. Because of their diverse array of biological activities and by virtue of their extremely limited availability in nature, these compounds have attracted the attention of synthetic organic chemists worldwide (Figure 1).

The stereocontrolled construction of the tetrahydrofuran unit plays a pivotal role in the total synthesis of Annonaceous acetogenins. Among the more successful approaches to bis-tetrahydrofuran ring formation are the cyclization of hydroxy epoxides[13] and hydroxyalkenes,[14] and variations of the Williamson ether synthesis.[15] Protocols based on Sharpless epoxidation and dihydroxylation,[16] the addition of chiral allenyltin reagents to aldehydes,[17] and the elaboration of natural enantiopure materials[18] have been employed in the synthesis of the tetrahydrofuran precursors.

We have recently shown that stereoselective intramolecular oxymercuration can be employed effectively with excellent selectivity in the synthesis of the bis-tetrahydrofuran ring system present in nonclassical acetogenins.[19] As a fur-

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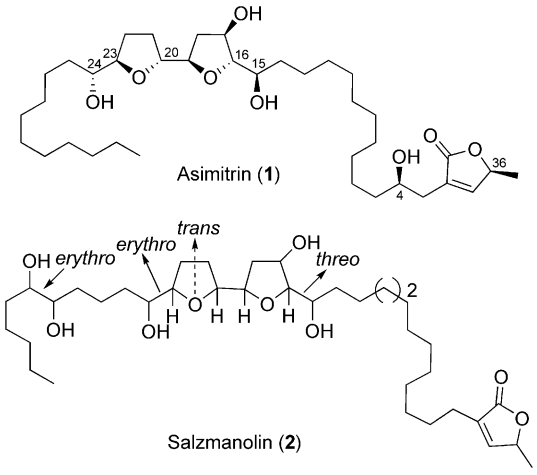
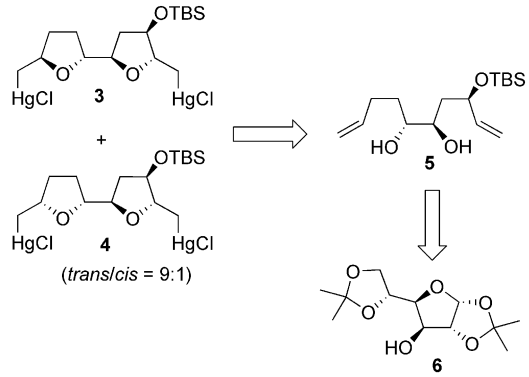


Figure 1. Structures of asimitrin and salzmanolin.

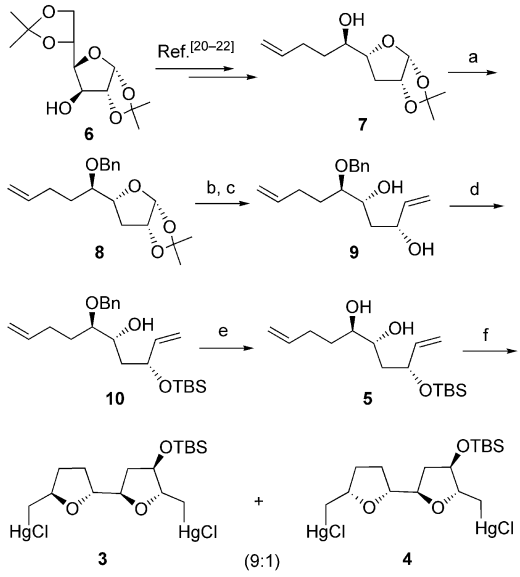
ther test of this protocol for the synthesis of the system present in asimitrin, we reported the first stereoselective synthesis of the C10–C34 fragment of asimitrin.[20] In both these syntheses, the bis-tetrahydrofuran ring system was prepared by stereocontrolled off-template construction of the first tetrahydrofuran ring by utilizing an intramolecular oxymercuration protocol followed by a second one at the end. In this paper we report a one-pot double intramolecular oxymercuration protocol for the synthesis of the mono-hydroxylated bis-tetrahydrofuran ring system present in asimitrin and salzmanolin. Our retrosynthetic strategy is depicted in Scheme 1. The one-pot stereoselective intramolecular oxymercuration of **5** would lead to **3** and **4**. Diol **5** would be furnished from **6** following the selective protection of the allylic hydroxy group, one-carbon homologation, and copper-catalyzed epoxide ring-opening as the key reactions.



Scheme 1. Retrosynthetic analysis for mono-hydroxylated bis-tetrahydrofuran ring system.

Results and Discussion

The synthetic endeavor commenced starting from the commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**): The secondary hydroxy group was converted into its tosylate derivative. Treatment with DBU resulted in the elimination of the tosylate group to afford the olefin. Hydrogenation of the resulting double bond in the presence of Raney Ni in ethanol at 40 psi gave the reduced product, the spectral and analytical data of which were in good agreement with reported values.[21] Selective deprotection of the 5,6-*O*-isopropylidene group and treatment of the resulting diol with NaH and TsCl afforded the epoxide. Copper-catalyzed epoxide ring-opening with allylmagnesium bromide in the presence of CuCN furnished the alcohol **7** in 84% yield (Scheme 2).[22]



Scheme 2. Reagents and conditions: (a) NaH, BnBr, THF, 0 °C to r.t., 12 h, 91%; (b) 60% AcOH, H_2SO_4 (catalytic), 55 °C, 6 h, 90%; (c) PPh_3MeBr, *n*BuLi, THF, –10 °C to r.t., 12 h, 87%; (d) 2,6-lutidine, TBSOTf, CH_2Cl_2, –78 °C, 2 h, 94%; (e) Na, naphthalene, THF, –25 °C, 20 min, 89%; (f) $Hg(OAc)_2$, CH_2Cl_2, room temp., 2 h, 86%.

Treatment of compound **7** with BnBr in the presence of NaH afforded the benzyl ether derivative **8** in 91% yield. Compound **8** was treated with 60% acetic acid in the presence of a catalytic amount of sulfuric acid at 55 °C to afford the hemiacetal, which, after purification by silica gel column chromatography, was subjected to one-carbon homologation[23] with $Ph_3P{=}CH_2$ to produce the olefin **9**. The allylic hydroxy group was selectively protected as its TBS ether **10** in 94% yield. Deprotection of the benzyl group with Na in the presence of naphthalene afforded the crucial intermediate **5**. Now the requisite structural skeleton was set for stereoselective double intramolecular oxymercuration. Diastereoselective intramolecular oxymercuration of diol **5** with mercury(II) acetate in dichloromethane gave a *trans*/*cis* mixture of tetrahydrofuran derivatives with 9:1 selectivity. The stereoisomers **3** and **4** were conveniently separated by flash silica gel column chromatography and their purities and structures confirmed by ^1H and ^{13}C NMR and mass spectral analysis and the relative stereochemistries were ascertained by NOESY experiments. As depicted in Figure 2, there are strong NOE interactions between H15

and H16, and H23 and H24. No NOE interactions were observed, however, between H16 and H17, H16 and H19, and H20 and H23, which confirms the *trans* relationships.

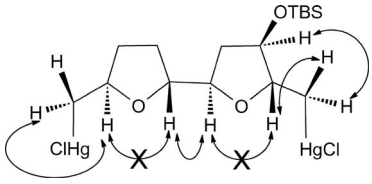
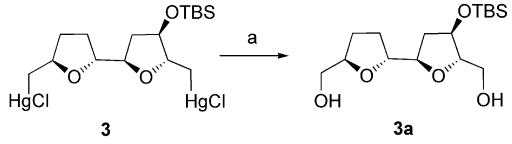


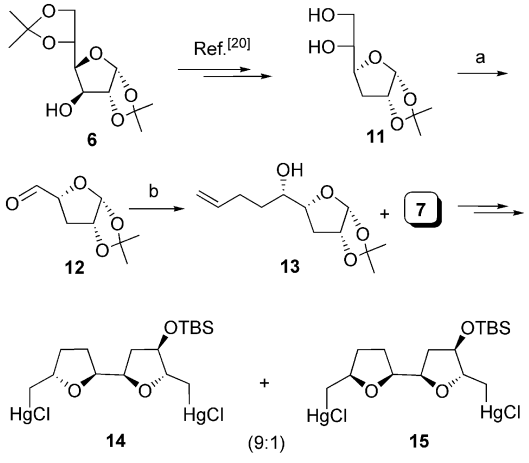
Figure 2. Selected NOE correlations of **3**.

Next our task was to convert the mercury chloride group into a hydroxy functionality. Demercuration of **3** was carried out under a stream of oxygen in the presence of sodium borohydride to afford the diol **3a** in 81% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) O_2, $NaBH_4$, DMF, r.t., 1 h, 81%.

Similarly, compound **13** was prepared from known intermediate **12** by a slight modification of a reported procedure[24] in which the Grignard reaction was carried out in diethyl ether by reverse addition of the Grignard reagent at 0 °C to improve the diastereoselectivity (4:1) in favor of **13**. Compound **13** was separated conveniently by silica gel column chromatography from the crude reaction mixture.[19] Following the same sequence of reactions as described in Scheme 2, compounds **14** and **15** were synthesized in 89% yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) $NaIO_4$, SiO_2, CH_2Cl_2, r.t., 30 min, 97%; (b) homoallylmagnesium bromide, CuCN, 0 °C, 1 h, 95% (**13/7** = 4:1).

Conclusions

Four isomers of the mono-hydroxylated bis-tetrahydrofuran ring system present in asimitrin and salzmanolin, two naturally occurring biologically active nonclassical acetogenins, have been synthesized starting from the commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose by a one-pot stereoselective double intramolecular oxymercuration reaction as the key step. The total synthesis of asimitrin and its isomers is in progress, which will prove the absolute stereochemistry, is underway and will be reported in due course.

Experimental Section

General: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under argon in oven- or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF and diethyl ether from Na and benzophenone, CH_2Cl_2 from CaH_2, MeOH, EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and are reported in cm^{-1}. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) and coupling constants (*J*) are reported in Hz.

(3*R*,5*R*,6*R*)-2,2-Dimethyl-5-[(*R*)-oxiran-2-yl]tetrahydrofuro[2,3-*d*]-[1,3]dioxole: Diol **11** (3.0 g, 14.7 mmol) in THF (20 mL) was added to a slurry of NaH (1.17 g, 29.4 mmol) in THF (30 mL) at 0 °C. After 20 min, *p*-toluenesulfonyl chloride (2.8 g, 14.7 mmol) in THF (20 mL) was added and the mixture was stirred at 0 °C. After completion (monitored by TLC), the reaction was quenched by the slow addition of water. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with Na_2SO_4, concentrated, and purified by silica gel column chromatography using ethyl acetate and hexane (12%) to give epoxide **8** (2.46 g, 90%) as a colorless liquid.

(*R*)-1-[(3*R*,5*R*,6*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*]dioxol-5-yl]-pent-4-en-1-ol (7): A solution of allyl bromide (1.4 mL, 16.12 mmol) was added dropwise to a suspension of magnesium metal pieces (0.52 g, 21.52 mmol) in diethyl ether (15 mL) and the mixture was stirred for 30 min at room temperature. CuCN (47 mg, 0.54 mmol) was added at once, which resulted in a color change to dark brown. After cooling to –10 °C, the epoxide (2.0 g, 10.75 mmol) in diethyl ether (20 mL) was added dropwise. The reaction mixture was stirred for 1 h at –10 °C, quenched by the slow addition of a saturated NH_4Cl solution, and the resulting suspension was stirred for another 30 min at room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried with Na_2SO_4, concentrated, and purified by silica gel column chromatography using ethyl acetate and hexane (8%) to afford compound **7** (2.05 g, 84%) as a colorless liquid. $[\alpha]_D^{26}$ = –2.02 (*c* = 1.3, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3488, 2986, 2940, 1640, 1598 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.91–5.71 (m, 2 H), 5.04–4.87 (m, 2 H), 4.69 (ddd, *J* = 1.3, 4.0, 6.0 Hz, 1 H), 3.89 (dt, *J* = 3.0, 8.2 Hz, 1 H), 3.71 (dt, *J* = 4.0, 8.2 Hz, 1 H), 2.69 (br. s, 1 H), 2.30–1.60 (m, 6 H), 1.47 (s, 3 H), 1.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 138.2, 114.7, 112.3, 106.1, 84.6, 80.7, 71.9, 33.5, 32.4, 29.7, 26.8, 25.9 ppm. MS (ESI): *m*/*z* = 251 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{12}H_{20}O_4Na$ [M + Na]$^+$ 251.1259; found 251.1262.

(3*R*,5*R*,6*R*)-5-[(*R*)-1-(Benzyloxy)pent-4-enyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (8): Compound **7** (1.63 g, 7.188 mmol) in THF (10 mL) was added slowly to a suspension of NaH (0.34 g, 8.62 mmol) in dry THF (15 mL) at 0 °C. After 20 min, benzyl bromide (0.94 mL, 7.9 mmol) was added at 0 °C. The reaction mixture was stirred for 12 h at room temperature. After completion (monitored by TLC), the reaction mixture was quenched with ice-cooled water and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography using ethyl acetate and hexane (4%) to afford compound **8** (2.08 g, 91%) as a colorless liquid. $[\alpha]_D^{26}$ = –5.4 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3031, 2985, 1640, 1377, 1067 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.37–7.16 (m, 5 H, Ph), 5.83–5.62 (m, 2 H, C*H*=CH_2, CHOC*H*OO), 5.01–4.89 (m, 3 H, CH=C*H*$_2$, CH_2C*H*OCHOO), 4.71–4.54 (m, 2 H, OC*H*$_2$Ph), 4.07 (m, 1 H, C*H*OCHOCH$_2$), 3.67–3.57 (dt, *J* = 3.2, 8.7 Hz, 1 H, CH_2C*H*OCHO), 2.30–1.87 (m, 4 H, =CHC*H*$_2$CH$_2$, CHOC*H*$_2$CHO), 1.53 (s, 3 H, CH_3), 1.5–1.36 (m, 2 H, CH_2C*H*$_2$CHO), 1.31 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.1, 138.4, 128.2, 128.0, 127.3, 114.9, 112.4, 106.2, 84.2, 80.5, 80.1, 77.0, 73.6, 34.1, 31.0, 29.5, 27.2, 26.2 ppm. MS (ESI): *m*/*z* = 341 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{19}H_{26}O_4Na$ $[M + Na]^+$ 341.1728; found 341.1727.

(3*R*,5*R*,6*R*)-6-(Benzyloxy)deca-1,9-diene-3,5-diol (9): A 60% acetic acid solution (10 mL) and catalytic conc. H_2SO_4 were added to benzylated compound **8** (1.77 g, 5.56 mmol) and the mixture was stirred at 55 °C. After 6 h, the reaction mixture was diluted with ethyl acetate and neutralized with a saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer washed with ethyl acetate (4 × 30 mL). The combined organic layers were dried with Na_2SO_4, concentrated, and purified by silica gel column chromatography using ethyl acetate and hexane (18%) to afford the lactol (1.3 g, 90%) as a white solid.

*n*BuLi (4.0 mL, 10.0 mmol) was added dropwise to a stirred solution of methyltriphenylphosphonium bromide (5.35 g, 15.0 mmol) in THF (40 mL) at –10 °C. After stirring the reaction for 1 h, the hemiacetal (1.39 g, 5.0 mmol) was added in THF (10 mL) to the reaction mixture –10 °C. Stirring was continued for 12 h at room temperature. The reaction was quenched with a saturated NH_4Cl solution. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried with Na_2SO_4, concentrated, and the crude purified by silica gel column chromatography using ethyl acetate and hexane (10%) to obtain compound **9** (1.2 g, 87%) as a viscous liquid. $[\alpha]_D^{27}$ = –17.2 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3421, 3081, 2936, 1644, 1452, 1078 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.26 (m, 5 H, Ph), 5.93–5.7 (m, 2 H, CHOHC*H*=CH_2, CH_2=C*H*CH_2), 5.31–4.93 (m, 4 H, 2 CH=C*H*$_2$), 4.56 (ABq, *J* = 11.33, 33.9 Hz, 1 H, OC*H*$_2$Ph), 4.40 (m, 1 H, CH_2C*H*OHCH=), 3.88 (m, 1 H, CHOC*H*OHCH$_2$), 3.35–3.39 (q, *J* = 6.04 Hz, 1 H, CH_2C*H*OCHOH), 2.6 (br. s, 1 H, CHO*H*), 2.19–2.10 (m, 2 H, =CHC*H*$_2$CH$_2$), 1.79–1.54 (m, 4 H, CHOHC*H*$_2$CHOH, CH_2C*H*$_2$CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.6, 138.2, 128.4, 127.8, 114.9, 114.2, 81.7, 72.5, 70.0, 69.7, 38.8, 29.3, 29.2 ppm. MS (ESI): *m*/*z* = 299 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623; found 299.1638.

(3*R*,5*R*,6*R*)-6-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)deca-1,9-dien-5-ol (10): 2,6-Lutidine (0.6 mL, 5.21 mmol) and TBDMSOTf (1.0 mL, 4.34 mmol) were added to a solution of compound **9** (1.2 g, 4.34 mmol) in CH_2Cl_2 (25 mL) at –78 °C. The reaction was stirred at 0 °C for 2 h. After completion (monitored by TLC), the reaction was quenched with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried with Na_2SO_4, concentrated, and purification of the crude product by silica gel column chromatography using ethyl acetate and hexane (5%) afforded the TBS ether **10** (1.59 g, 94%) as a colorless liquid. $[\alpha]_D^{28}$ = +5.3 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3483, 3074, 2950, 1641, 1461, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.22 (m, 5 H, Ph), 5.87–5.7 (m, 2 H, 2 CH_2=C*H*), 5.25–4.9 (m,4 H, 2 CH=C*H*$_2$), 4.55 (ABq, *J* = 13.6, 24.9 Hz, 2 H, OC*H*$_2$Ph), 4.45 (m, 1 H, CH_2C*H*OSi), 3.87 (m, 1 H, CHOC*H*OHCH$_2$), 3.30–3.23 (dt, *J* = 4.5, 6.8 Hz, 1 H, CH_2C*H*OCHOH), 2.63 (br. s, 1 H, CHO*H*), 2.19–2.08 (m, 2 H, =CHC*H*$_2$CH$_2$), 1.80–1.50 (m, 4 H, CHOHC*H*$_2$CHOSi, CH_2C*H*$_2$CHO), 0.91 (s, 9 H, 3 CH_3), 0.09 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.9, 138.5, 128.3, 127.9, 127.7, 114.7, 114.1, 81.7, 72.4, 71.5, 68.6, 39.9, 29.7, 28.0, 25.8, 18.1, –4.5, –5.1 ppm. MS (ESI): *m*/*z* = 413 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{23}H_{38}O_3NaSi$ $[M + Na]^+$ 413.2487; found 413.2502.

(3*R*,5*R*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)deca-1,9-diene-5,6-diol (5): Small pieces of sodium metal (0.12 g, 5.34 mmol) were added to a stirred solution of naphthalene (0.91 g, 7.12 mmol) in THF (20 mL) at room temperature and the reaction was stirred until the sodium metal had completely dissolved. The resulting dark green solution of sodium naphthalinide was cooled to –25 °C and TBS ether **10** (1.39 g, 3.56 mmol) was added dropwise in dry THF (10 mL). The resulting reaction mixture was stirred at –25 °C for 20 min. After completion (monitored by TLC), the reaction was quenched with a saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, concentrated, and purification of the crude product by silica gel column chromatography using ethyl acetate and hexane (8%) afforded compound **5** (0.95 g, 89%) as a colorless liquid. $[\alpha]_D^{28}$ = –3.3 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 3079, 2929, 1641, 1064 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.98–5.70 (m, 2 H, 2 CH_2=C*H*), 5.35–4.92 (m, 4 H, 2 CH=C*H*$_2$), 4.61–4.48 (m, 1 H, CH_2C*H*OSi), 3.81–3.70 (m, 1 H, CHOHC*H*OHCH$_2$), 3.68–3.62 (m, 1 H, CH_2C*H*OHCHOH), 3.35 (br. s, 1 H, CHO*H*), 2.43 (br. s, 1 H, CHO*H*), 2.30–2.05 (m, 2 H, =CHC*H*$_2$CH$_2$), 1.97–1.78 (m, 1 H, CHOHC*H*$_2$CHOSi), 1.67–1.48 (m, 3 H, CHOHC*H*$_2$-CHOSi, CH_2C*H*$_2$CHOH), 0.93 (s, 9 H, 3 CH_3), 0.12 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 139.9, 138.4, 114.8, 96.1, 74.0, 72.3, 70.9, 39.7, 32.7, 29.9, 25.8, 18.1, –4.6, –5.2 ppm. MS (ESI): *m*/*z* = 323 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{16}H_{32}O_3Na$ Si $[M + Na]^+$ 323.2018; found 323.2019.

[(2*R*,2′*R*,4*R*,5*R*,5′*R*)-5,5′-Bis(chloromercuriomethyl)octahydro-2,2′-bifuran-4-yloxy](*tert*-butyl)dimethylsilane (3) and [(2*R*,2′*R*,4*R*,5*R*,5′*S*)-5,5′-Bis(chloromercuriomethyl)octahydro-2,2′-bifuran-4-yloxy](*tert*-butyl)dimethylsilane (4): $Hg(OAc)_2$ (1.98 g, 7.2 mmol) was added to a stirred solution of compound **5** (0.9 g, 3.0 mmol) in CH_2Cl_2 (30 mL) at room temperature and the mixture was stirred for 1 h. After completion (monitored by TLC), the reaction was quenched with brine and stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2 (2 × 25 mL), dried with Na_2SO_4, concentrated, and purification of the crude by silica gel column chromatography using ethyl acetate and hexane (15%) furnished second eluted *trans* isomer **3** (1.78 g) and first eluted *cis* isomer **4** (199 mg) as white solids in a 9:1 ratio. Upper spot (*cis*): $[\alpha]_D^{32}$ = –5.6 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 1079 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.43–4.24 (m, 3 H, C*H*OC*H*O, CHOSi), 4.02–3.80 (m, 2 H, HgCH$_2$C*H*O, HgCH$_2$C*H*OSi), 2.49–2.12 (m, 4 H, 2 ClHgCH$_2$), 2.09–1.80 (m, 6 H, 3 CH_2 in THF rings), 0.94 (s,

9 H, 3 CH_3), 0.12 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 96.2, 81.1, 81.0, 80.1, 78.4, 73.5, 39.2, 39.0, 35.3, 30.3, 28.1, 26.3, 18.5, –4.0, –4.4 ppm. MS (ESI): *m*/*z* = 795 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{30}O_3NaSiCl_2Hg_2$ [M + Na]$^+$ 795.0651; found 795.0620. Lower spot (*trans*): $[\alpha]_D^{32}$ = –10.6 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.51–3.94 (m, 5 H, 4 CHO, CHOSi), 2.39–2.15 (m, 6 H, 2 $ClHgCH_2$, 1 CH_2 of THF rings), 1.88–1.72 (m, 2 H, 1 CH_2 of THF rings), 1.70–1.48 (m, 2 H, 1 CH_2 of THF rings), 0.96 (s, 9 H, 3 CH_3), 0.15 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 96.2, 80.7, 80.2, 78.5, 73.7, 38.6, 38.2, 36.5, 30.2, 29.4, 28.4, 26.3, 18.5, –4.3 ppm. MS (ESI): *m*/*z* = 795 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{30}O_3NaSiCl_2Hg_2$ [M + Na]$^+$ 795.0651; found 795.0678.

[(2*R*,2′*R*,4*R*,5*S*,5′*R*)-4-(*tert*-Butyldimethylsilyloxy)octahydro-2,2′-bifuran-5,5′-diyl]dimethanol (3a): O_2 was bubbled through a long syringe needle into a stirred solution bis-mercurated compound **3** (0.2 g, 0.26 mmol) in dry DMF (5 mL) for 10 min. In an another flask, a suspension of $NaBH_4$ (0.03 g, 0.78 mmol) in DMF (2 mL) was prepared and O_2 was passed through it for 20 min. The former reaction mixture was added dropwise to the latter through a cannula over 10 min. The reaction mixture was diluted with ethyl acetate, filtered, and concentrated. DMF was removed under reduced pressure and the resulting crude brown oily material was purified by silica gel column chromatography using ethyl acetate and hexane (85%) to afford diol **3a** (0.069 g, 81%) as a colorless liquid. $[\alpha]_D^{30}$ = –8.5 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3403, 2958, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.60 (br. s, 1 H, CH_2OH), 4.46 (br. s, 1 H,CH_2OH), 4.35–3.99 (m, 5 H, 4 CHO, CHOSi), 3.97–3.81 (m, 2 H, CH_2OH), 3.78–3.68 (dd, *J* = 2.8, 11.7 Hz, 1 H, CH_2OH), 3.56–3.47 (dd, *J* = 5.3, 11.9 Hz, 1 H, CH_2OH), 2.45–2.27 (m, 4 H, 2 CH_2 of THF rings), 2.07–1.97 (m, 2 H, CH_2 of THF rings), 1.25 (s, 9 H, 3 CH_3), 0.07 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 81.5, 81.1, 80.4, 80.0, 79.8, 64.3, 62.6, 38.4, 37.6, 33.8, 24.6, 19.0, –5.1, –5.3 ppm. MS (ESI): *m*/*z* = 355 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{32}O_5Na$ Si [M + Na]$^+$ 355.2354; found 355.2378.

(*S*)-1-[(3*R*,5*R*,6*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*]dioxol-5-yl]-pent-4-en-1-ol (13): Silica-supported $NaIO_4$ (19.6 g) was added to a stirred solution of diol **11** (2.0 g, 9.8 mmol) in CH_2Cl_2 (70 mL) and the mixture was stirred vigorously for 30 min at room temperature. After completion (monitored by TLC), the reaction mixture was filtered off and the solvent was evaporated under reduced pressure. The crude aldehyde (1.64 g, 97%) obtained was used for the Grignard reaction without further purification.

A solution of homoallyl bromide (1.45 mL, 14.25 mmol) was added dropwise to a suspension of Mg metal pieces (0.68 g, 28.5 mmol) in anhydrous diethyl ether (25 mL) and the mixture was stirred for 30 min at room temperature. CuCN (42 mg, 0.475 mmol) was added at once, which resulted in an immediate color change to dark brown. After cooling to –20 °C, the crude aldehyde (1.63 g, 9.5 mmol) in diethyl ether (15 mL) was added dropwise. The reaction mixture was stirred for 30 min at –20 °C and quenched by the slow addition of a saturated NH_4Cl solution. The resulting suspension was stirred for another 30 min. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3× 40 mL). The combined organic layers were dried with Na_2SO_4, concentrated, and purified by silica gel column chromatography using ethyl acetate and hexane (8%) to afford upper isomer **7** (minor) (0.411 g) and further elution afforded lower isomer **13** (major; 1.639 g) as colorless liquids in a 1:4 ratio. Major isomer: $[\alpha]_D^{26}$ = –5.3 (*c* = 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.84 (m, 1 H, $CH{=}CH_2$), 5.76 (d, *J* = 3.8 Hz, 1 H, OCHO), 5.08–4.93 (m, 2 H, $CH{=}CH_2$), 4.69 (m, 1 H, $CH_2CHOCHOO$), 3.95–3.88 (dt, *J* = 3.0, 8.3 Hz, 1 H, $CH_2CHOCHOH$), 3.76–3.68 (dt, *J* = 3.8, 8.3 Hz, 1 H, $CHOCHOHCH_2$), 2.31–1.91 (m, 4 H, $CHCH_2CH_2$, $CHOCH_2CHO$), 1.58–1.38 (m, 8 H, 2 CH_3, CH_2CH_2CHOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 114.9, 112.6, 106.0, 84.0, 80.8, 71.4, 32.4, 31.4, 29.8, 27.3, 26.3 ppm.

(3*R*,5*R*,6*R*)-5-[(*S*)-1-(Benzyloxy)pent-4-enyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole: $[\alpha]_D^{29}$ = +9.3 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.31–7.20 (m, 5 H, Ph), 5.81 (m, 1 H, $CH{=}CH_2$), 5.7 (d, *J* = 3.8 Hz, 1 H, OCHO), 5.04–4.9 (m, 2 H, $CH{=}CH_2$), 4.68 (m, 1 H, $CH_2CHOCHOO$), 4.55 (ABq, *J* = 11.3, 12.8 Hz, 2 H, OCH_2Ph), 4.0–3.93 (dt, *J* = 3.8, 8.3 Hz, 1 H, $CH_2CHOCHO$), 3.70 (m, 1 H, $CHOCHOCH_2$), 2.29–2.03 (m, 4 H, $=CHCH_2CH_2$, $CHOCH_2CHO$), 1.85–1.62 (m, 2 H, CH_2CH_2CHO), 1.46 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.7, 138.4, 128.3, 127.8, 127.5, 114.5, 112.1, 106.3, 81.8, 80.6, 79.1, 72.4, 33.4, 30.4, 28.6, 27.0, 26.0 ppm.

(3*R*,5*R*,6*S*)-6-(Benzyloxy)deca-1,9-diene-3,5-diol: $[\alpha]_D^{30}$ = –9.1 (*c* = 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.33–7.23 (m, 5 H, Ph), 5.89 (m, 1 H, $CHOHCH{=}CH_2$), 5.75 (m, 1 H, $CH_2{=}CHCH_2$), 5.30–4.92 (m, 4 H, 2 $CH{=}CH_2$), 4.57 (ABq, *J* = 11.7, 24.4 Hz, 1 H, OCH_2Ph), 4.42 (m, 1 H, $CH_2CHOHCH{=}$), 4.09–4.05 (dt, *J* = 2.9, 10.7 Hz, 1 H, $CHOCHOHCH_2$), 3.39–3.35 (dt, *J* = 3.9, 8.8 Hz, 1 H, $CH_2CHOCHOH$), 2.31–2.02 (m, 2 H, $=CHCH_2CH_2$), 1.76–1.66 (m, 2 H, $CHOHCH_2CHOH$), 1.56–1.48 (m, 2 H, CH_2CH_2CHO) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.7, 138.2, 128.3, 127.7, 127.6, 114.8, 114.2, 81.4, 71.9, 69.9, 68.8, 37.6, 29.6, 28.0 ppm.

(3*R*,5*R*,6*S*)-6-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)deca-1,9-dien-5-ol: $[\alpha]_D^{28}$ = –7.5 (*c* = 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.34–7.22 (m, 5 H, Ph), 5.89–5.69 (m, 2 H, 2 $CH_2{=}CH$), 5.26–4.89 (m, 4 H, 2 $CH{=}CH_2$), 4.57 (ABq, *J* = 11.3, 20.4 Hz, 2 H, OCH_2Ph), 4.47 (m, 1 H, CH_2CHOSi), 4.01–3.94 (dt, *J* = 2.3, 8.3 Hz, 1 H, $CHOCHOHCH_2$), 3.38–3.31 (dt, *J* = 3.8, 8.3 Hz, 1 H, $CH_2CHOCHOH$), 2.76 (br. s, 1 H, CHO*H*), 2.27–2.01 (m, 2 H, $=CHCH_2CH_2$), 1.75–1.44 (m, 4 H, $CHOHCH_2CHOSi$, CH_2CH_2CHO), 0.92 (s, 9 H, 3 CH_3), 0.09 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.5, 138.6, 138.5, 128.3, 127.8, 127.5, 114.6, 114.2, 81.6, 72.2, 71.8, 69.2, 38.8, 29.6, 28.9, 25.8, 18.1, –4.5, –5.1 ppm.

(3*R*,5*R*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)deca-1,9-dien-5,6-diol: $[\alpha]_D^{26}$ = –3.0 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.92–5.73 (m, 2 H, 2 $CH_2{=}CH$), 5.30–4.92 (m, 4 H, 2 $CH{=}CH_2$), 4.56 (m, 1 H, CH_2CHOSi), 3.83–3.54 (m, 2 H, $CHOHCHOHCH_2$, $CH_2CHOHCHOH$), 2.34–2.03 (m, 2 H, $=CHCH_2CH_2$), 1.86–1.37 (m, 4 H, $CHOHCH_2CHOSi$, CH_2CH_2CHOH), 0.92 (s, 9 H, 3 CH_3), 0.11 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.5, 138.3, 114.8, 114.7, 73.5, 72.4, 71.3, 36.1, 31.0, 30.1, 25.7, 18.0, –4.7, –5.3 ppm.

[(2*R*,2′*S*,4*R*,5*R*,5′*R*)-5,5′-Bis(chloromercuriomethyl)octahydro-2,2′-bifuran-4-yloxy](*tert*-butyl)dimethylsilane (15): Upper spot (*cis*). $[\alpha]_D^{29}$ = –16.3 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.48 (m, 1 H, CHO), 4.33–4.19 (m, 2 H, 2 CHO), 4.09–3.96 (m, 2 H, 2 CHO), 2.53–2.22 (m, 4 H, 2 $ClHgCH_2$), 2.18–2.10 (m, 2 H, CH_2 of THF rings), 1.89–1.78 (m, 2 H, CH_2 of THF rings), 1.68–1.46 (m, 2 H, CH_2 of THF rings), 0.95 (s, 9 H, 3 CH_3), 0.13 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 81.0, 80.9, 80.4, 78.8, 73.8, 39.4, 39.1, 36.6, 30.0, 26.2, 29.7, 18.4, –4.5, –4.5 ppm.

[(2*R*,2′*S*,4*R*,5*R*,5′*S*)-5,5′-Bis(chloromercuriomethyl)octahydro-2,2′-bifuran-4-yloxy](*tert*-butyl)dimethylsilane (14): Lower spot (*trans*).

$[\alpha]_D^{26}$ = +2.6 (c = 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.42 (m, 1 H, CHO), 4.34–4.19 (m, 2 H, 2 CHO), 4.14 (m, 1 H, CHO), 3.94 (m, 1 H, CHO), 2.34–2.08 (m, 6 H, 2 $ClHgCH_2$, 1 CH_2 of THF rings), 1.88–1.75 (m, 2 H, 1 CH_2 of THF rings), 1.60–1.41 (m, 2 H, 1 CH_2 of THF rings), 0.95 (s, 9 H, 3 CH_3), 0.14 (s, 6 H, 2 $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 80.5, 80.2, 80.0, 78.4, 73.6, 38.5, 38.1, 36.4, 29.6, 28.1, 26.1, 18.3, –4.4, –4.5 ppm.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of new compounds.

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