Anionic Cyclization Approach toward Perhydrobenzofuranone: Stereocontrolled Synthesis of the Hexahydrobenzofuran Subunit of Avermectin

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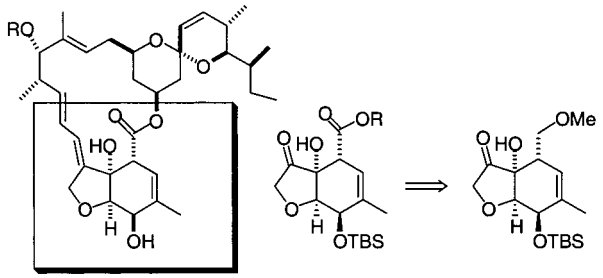
A facile anionic cyclization approach toward stereocontrolled synthesis of the hexahydrobenzofuran subunit **3** of avermectin is described. As a model study, treatment of iodo compound **7** with *n*-BuLi at −100 °C effected metal−halogen exchange and subsequent anionic cyclization to afford perhydrobenzofuranone **8**. For the total synthesis of subunit **3**, compound **9** was dihydroxylated to give diol **10**. Protection of the hydroxyl groups of diol **10** gave compound **11**. Ketone **11** was then converted into the required enone **12** using Saegusa's protocol. On iodination followed by Luche reduction, enone **12** yielded α-iodo allylic alcohol **14**, which on alkylation afforded ether **15**. Conversion of the ester unit of **15** into a Weinreb amide group followed by anionic cyclization gave enone **17**. 1,4-Addition of $(MeOCH_2)_2CuCNLi_2$ to enone **17** followed by cleavage of the acetal unit afforded ketone **19**. Preferential acetylation of the secondary alcoholic function of **19** afforded compound **20**. The stereochemistry of **20** is confirmed by single-crystal X-ray analysis. Elimination of HOAc from **20** gave the crucial olefin **21**. Hydrolysis of the acetate unit of **21** followed by protection of the resulting alcoholic function yielded *tert*-butyldimethylsilyl ether **23**. Introduction of a hydroxyl group at the ring junction of **23**, using Davis's procedure, finally afforded the hexahydrobenzofuran subunit **3**.

Introduction

The isolation of avermectin and milbemycin families of highly functionalized pentacyclic macrolides from *Streptomyces* is a significant development in the treatment of parasitic diseases.[1] In particular, avermectins are effective against parasites in two major classes, nematodes and arthropods. Several synthetic derivatives of avermectins assumed commercial significance as a method to control parasitic infection.[2] These architectually challenging natural products coupled with their potent antiparasitic activity have attracted much attention among synthetic chemists. Many total syntheses of avermectins are reported.[3] In this complex architecture of avermectins **1**, Scheme 1, the hexahydrobenzofuran subunit **2** offers a significant synthetic challenge. In particular, the stability of this component is amazing as it contains two highly labile functional groups that might undergo successive β-elimination to give a benzenoid ring. Furthermore, subsequent enolization of the furanone moiety might yield a benzofuran system. Nevertheless, these aromatizations did not occur at all during isolation of these natural products under highly acidic conditions.

Scheme 1



1 **2** **3**

Fraser-Reid and Prashad reported the first enantioselective synthesis of the hexahydrobenzofuran subunit via an intramolecular nitrile oxide 1,3-dipolar cycloaddition strategy.[4] Hanessian and co-workers subsequently

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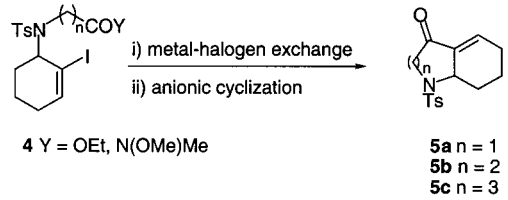
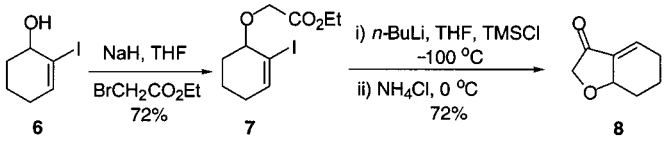
Scheme 2



4 Y = OEt, N(OMe)Me

5a n = 1
5b n = 2
5c n = 3

Scheme 3



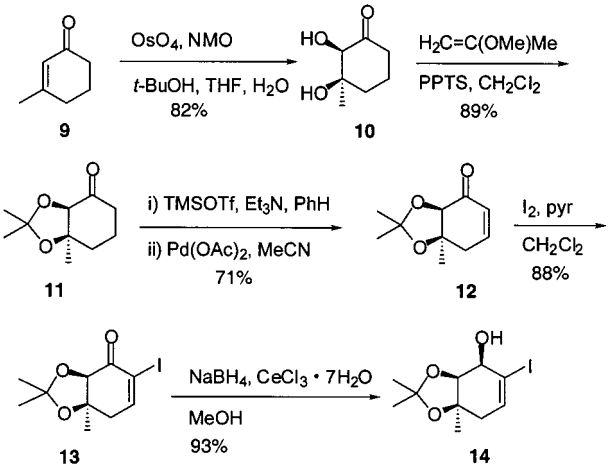
6 **7** **8**

achieved[5] a stereoselective synthesis of the same subunit; they likewise used a chiral starting material toward preparation of an optically active analogue of hexahydrobenzofuran. Hirama and co-workers accomplished a stereoselective synthesis of the hexahydrobenzofuran subunit using an aldol-condensation strategy.[6] About the same time, Williams and Klinger developed[7] a stereoselective approach to the hexahydrobenzofuran subunit via intramolecular Claisen condensation. Uang et al. published[8] an enantioselective approach to the subunit using an asymmetric Diels−Alder reaction. Barrett et al. reported[9] a synthesis of an intermediate closely related to the hexahydrobenzofuran subunit. Ley et al. prepared[10] a hexahydrobenzofuran subunit lacking a crucial double bond and employed that method for a total synthesis[3f] of avermectin B_{1a}. Smith and Fujiwara developed a preparation of highly demanding hexahydrobenzofuran subunit **2** for the total synthesis of avermectins.[11] We recently described an anionic cyclization approach to the synthesis of perhydroindolone **5a**, perhydroquinolone **5b**, and perhydrobenzoazepinone **5c**, Scheme 2, and successfully applied this method to a total synthesis of (−)-brunsvigine.[12] Herein we report our results on a stereocontrolled synthesis of the hexahydrobenzofuran subunit **3** of avermectin using a similar anionic cyclization approach.

Results and Discussion

As a model study, we first applied the anionic cyclization method to the synthesis of perhydrobenzofuranone **8**, Scheme 3. The perhydrobenzofuran skeleton is the core skeleton of many natural products, such as avermectins,[1] milbemycins,[13] phyllanthocin,[14] burchellin,[15] and breynolide.[16] On alkylation with ethyl bromoacetate using NaH as a base, allylic alcohol **6**[17] was converted to ester **7**. Treatment of **7** with *n*-BuLi in the presence of TMSCl effected metal−halogen exchange and anionic cyclization to afford perhydrobenzofuranone **8** in 72% yield.

Scheme 4



9 **10** **11** **12** **13** **14**

Having established the method for preparation of perhydrobenzofuranone, we turned our attention to the application of this method for total synthesis of the hexahydrobenzofuran subunit of avermectins. Our synthetic plan to prepare allyic alcohol **14** containing the necessary substituents of hexahydrobenzofuran subunit **3** is outlined in Scheme 4. Dihydroxylation of commercially available 3-methylcyclohex-2-en-1-one (**9**) with osmium tetroxide and *N*-morpholine *N*-oxide[18] afforded diol **10** in 82% yield. Protection of the diol unit of **10** gave ketone **11**. Ketone **11** was then smoothly converted into the required enone **12** in 71% yield according to Saegusa's protocol.[19] Enone **12** was iodinated at the α-position through Johnson's procedure[20] to give the corresponding iodo enone **13**. Luche reduction[13] of compound **13** gave allylic alcohol **14** as a single diastereomer in 93% yield.

Once the required allylic alcohol **14** was in hand, it was smoothly alkylated with ethyl bromoacetate, using NaH as a base, to give compound **15** in 97% yield. Ester **15** was then transformed into Weinreb amide **16** in 85% yield.[21] Initially we tried anionic cyclization with ester **15**, but the yield of product **17** was low (10−20%). When the same reaction was carried out with Weinreb amide **16**, cyclized product **17** was obtained in excellent yield,[22] Scheme 5.

Enone **17** was then treated with CuCN and (methoxymethyl)lithium in the presence of TMSCl to afford compound **18** in 87% yield, Scheme 6; 1,4-addition occurred stereoselectively at the less hindered α-face.

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(17) Compound **6** was prepared via Luche reduction (Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226) of 2-iodo-2-cyclohexen-1-one, which was obtained from iodination of 2-cyclohexen-1-one according to Johnson's method (ref 20).
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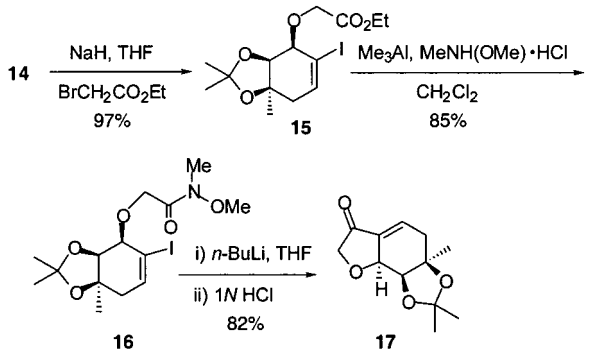
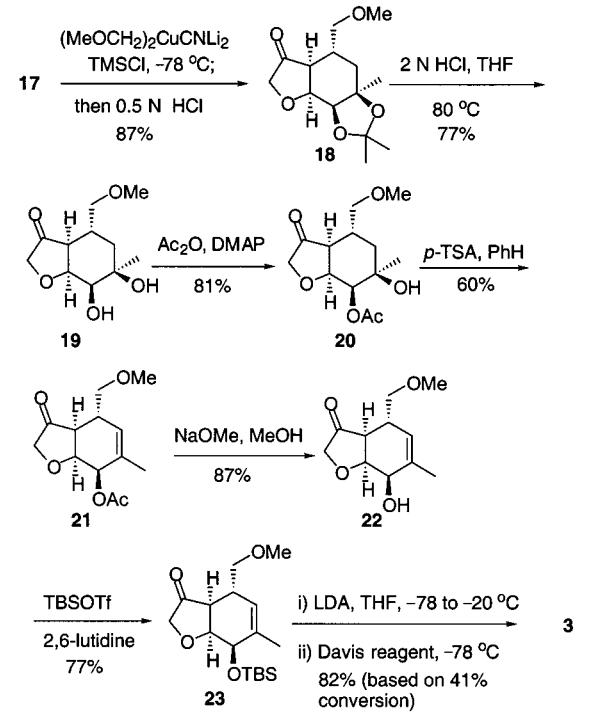
Scheme 5



Scheme 6



Cleavage of the acetal unit with HCl produced diol **19**, which on preferential acetylation of the secondary alcohol unit with acetic anhydride and DMAP at room temperature yielded tertiary alcohol **20**. The stereochemistry of compound **20** was confirmed by a single-crystal X-ray analysis.[23] Heating of **20** with *p*-TSA in refluxing benzene gave the desired product **21** along with two olefin isomers as the minor products. The ratio of the major isomer **21** to the two minor isomers together was 4.5:1. Recrystallization from CH_2Cl_2/*n*-hexane (10:1) afforded the pure major product **21** in 60% yield. The minor products were difficult to separate and were not fully characterized. Compound **21** was then carefully hydrolyzed with NaOMe in methanol at room temperature to give alcohol **22** in 88% yield. Protection of the secondary alcohol of **22** using TBSOTf afforded compound **23** in 77% yield. Introduction of the required hydroxyl group at the ring junction was finally carried out according to Davis's procedure.[24] Treatment of compound **23** with LDA at −78 to −20 °C in THF followed by reaction with Davis's reagent afforded target compound **3** in 82% yield (based on 41% conversion), Scheme 6.

In conclusion, we have developed a general and efficient method to synthesize the perhydrobenzofuranone skeleton using the anionic cyclization as a key step, and successfully applied this method toward total synthesis of the hexahydrobenzofuran subunit of avermectins. This anionic cyclization approach is potentially useful for the synthesis of other natural products containing the perhydobenzofuran skeleton.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded in $CDCl_3$ solution at 400, 500, or 600 MHz. ^{13}C NMR spectra were recorded at 100, 125, or 150 MHz. Mass spectra were recorded by electron impact (70 eV) or FAB ionization. IR spectra were recorded on a spectrometer. Melting points were determined with an open capillary tube and are uncorrected.

2-Iodo-2-cyclohexen-1-ol (6). To a solution of α-iodocyclohexenone (693 mg, 3.12 mmol) in dry methanol (10 mL) at 0 °C was added $CeCl_3$•$7H_2O$ (769 mg, 3.12 mmol); the reaction mixture was stirred for 10 min. $NaBH_4$ (141 mg, 3.74 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 1 h; excess $NaBH_4$ was then quenched with water (10 mL). The resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried ($MgSO_4$). Removal of solvent followed by column chromatography (silica gel, EtOAc/*n*-hexane, 1:3) afforded compound **6** (650 mg, 93%) as a colorless solid: IR (neat) 3370, 3028, 1625, 1426, 1161, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (t, 1 H, J = 4.0 Hz), 4.11 (s, 1 H), 2.65 (s, 1 H), 2.10−1.52 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.42 (CH), 103.20 (C), 71.34 (CH), 31.82 (CH_2), 28.97 (CH_2), 17.24 (CH_2); MS (EI) *m*/*z* 224 (M^+, 3), 97 (100); HRMS (EI) *m*/*z* calcd for C_6H_9IO 223.9698, found 223.9694.

Ethyl 2-[(2-Iodo-2-cyclohexenyl)oxy]acetate (7). To NaH (78 mg, 80% in mineral oil, 2.61 mmol) washed with dry benzene (3 × 1 mL) was added dry DMF (0.5 mL). The mixture was cooled to 0 °C. A solution of alcohol **6** (195 mg, 0.87 mmol) in dry DMF (2 mL) was added. The reaction mixture was stirred at 0 °C for 30 min. Ethyl bromoacetate (436 mg, 2.61 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 6 h. Excess NaH was quenched with H_2O (5 mL). The reaction mixture was extracted with diethyl ether (3 × 10 mL). The organic layer was washed with brine (15 mL) and dried ($MgSO_4$). Removal of solvent followed by column chromatography (silica gel, EtOAc/*n*-hexane, 1:4) afforded compound **7** (195 mg, 72%) as a yellow oil: IR (neat) 2929, 1746, 1627, 1441, 1375, 1280, 1203, 1120, 1030 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.23 (t, 1 H, J = 3.6 Hz), 4.08 and 4.04 (AB q, 2 H, J = 16.0 Hz), 3.91 (q, 2 H, J = 7.1 Hz), 3.72 (dd, 1 H, J = 3.8 and 3.8 Hz), 1.85−1.77 (m, 1 H), 1.65−1.44 (m, 4 H), 1.25−1.16 (m, 1 H), 0.93 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.1 (C), 142.2 (CH), 98.6 (C), 80.5 (CH), 68.0 (CH_2), 60.4 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 17.4 (CH_2), 14.2 (CH_3); MS (EI) *m*/*z* 183 ([M − I]$^+$ 100), 105 (43); HRMS (FAB) *m*/*z* calcd for $C_{10}H_{16}IO_3$ [M + H] 311.0146, found 311.0146.

2,3,5,6,7,7a-Hexahydrobenzo[*b*]furan-3-one (8). To a stirred solution of substrate **7** (100 mg, 0.32 mmol) in dry THF (6.5 mL) at −100 °C was added TMSCl (52 mg, 0.48 mmol). A solution of *n*-BuLi in *n*-hexane (2.0 M, 0.2 mL, 0.39 mmol) was slowly added at −100 °C, and the reaction mixture was maintained at −70 °C for 20 min. The cooling bath was removed; the reaction mixture was stirred for 10 min and quenched at 0 °C with a saturated solution of NH_4Cl (10 mL). The reaction mixture was extracted with diethyl ether (3 × 10 mL). The organic layer was washed with $NaHCO_3$ (15 mL) and brine (15 mL) and dried ($MgSO_4$). Removal of solvent followed by column chromatography (silica gel, EtOAc/*n*-hexane, 1:4) afforded pure compound **8** (32 mg, 72%) as a

(23) The X-ray data and the crystal structure of compound **20** are in the Supporting Information.

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colorless oil: IR (neat) 2918, 1703, 1617, 1436, 1181, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75−6.71 (m, 1 H), 4.52−4.45 (m, 1 H), 4.04 and 3.95 (AB q, 2 H, J = 16.4 Hz), 2.38−2.18 (m, 3 H), 1.96−1.87 (m, 1 H), 1.61−1.48 (m, 1 H), 1.41−1.29 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3 (C), 137.1 (C), 134.1 (CH), 79.7 (CH), 71.8 (CH_2), 28.3 (CH_2), 25.5 (CH_2), 18.8 (CH_2); MS (EI) *m*/*z* 138 (M^+, 11), 110 (37), 108 (29), 80 (40), 79 (100); HRMS (EI) *m*/*z* calcd for $C_8H_{10}O_2$ 138.0681, found 138.0681.

(2*R,3*R**)-2,3-Dihydroxy-3-methylcyclohexan-1-one (10).** To a solution of enone **9** (1.47 g, 13.3 mmol) in THF (25 mL) were added *N*-methylmorpholine *N*-oxide (1.87 g, 16.0 mmol), *tert*-butyl alcohol (12 mL), water (2 mL), and then OsO_4 (13.3 mL, 0.67 mmol, 0.05 M in *tert*-butyl alcohol) at room temperature. The reaction mixture was stirred for 24 h, then quenched with solid Na_2SO_3 (4.00 g, 32 mmol), and stirred at room temperature for 15 min. Florisil (4.00 g) was added. The mixture was stirred for 15 min and then filtered through Celite. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane,1:1) gave diol **10** (1.57 g, 82%) as a colorless oil. Recrystallization from 1:8 diethyl ether/benzene afforded **10** as white crystals: mp 46.5−48.5 °C; IR (neat) 3387, 2933, 1716, 1455, 1375, 1315, 1228, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 1 H), 2.57−2.50 (m, 1 H), 2.39−2.23 (m, 1 H), 2.11−1.95 (m, 2 H), 1.92−1.75 (m, 2 H), 1.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8 (C), 80.2 (CH), 76.5 (C), 38.4 (CH_2), 35.4 (CH_2), 26.8 (CH_3), 21.3 (CH_2); MS (EI) *m*/*z* 144 (M^+, 6), 127 (100); HRMS (EI) *m*/*z* calcd for $C_7H_{12}O_3$ 144.0786, found 144.0786.

(3a*R,7a*R**)-2,2,7a-Trimethylperhydro-1,3-benzodioxol-4-one (11).** To a solution of diol **10** (1.55 g, 10.8 mmol) and pyridinium *p*-toluenesulfonate (136 mg, 0.541 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added 2-methoxypropene (3.89 g, 54.1 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ solution (80 mL) and brine (80 mL). The organic layer was dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:8) gave acetonide **11** (1.77 g, 89%) as a colorless oil: IR (neat) ν 2951, 1725, 1455, 1376, 1217, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 1 H), 2.62−2.54 (m, 1 H), 2.28−2.20 (m, 1 H), 2.05−1.94 (m, 2 H), 1.75−1.55 (m, 2 H), 1.41 (s, 3 H), 1.40 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8 (C), 110.3 (C), 84.3 (CH), 84.0 (C), 38.2 (CH_2), 35.2 (CH_2), 27.7 (CH_3), 27.4 (CH_3), 26.8 (CH_3), 19.2 (CH_2); MS (EI) *m*/*z* 184 (M^+, 0.71), 169 (21), 127 (14); HRMS (EI) *m*/*z* calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1099.

(3a*R,7a*R**)-2,2,7a-Trimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-one (12).** A solution of acetonide **11** (921 mg, 5.00 mmol) and triethylamine (759 mg, 7.50 mmol) in dry benzene (25 mL) was treated with trimethylsilyl trifluoromethanesulfonate (1.22 g, 5.50 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h, quenched with saturated $NaHCO_3$ solution (30 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with brine (40 mL) and dried ($MgSO_4$). Concentration gave a crude oil. The crude oil was dissolved in acetonitrile (50 mL) and treated with palladium acetate (1.46 g, 6.50 mmol). The mixture was stirred at room temperature for 24 h, diluted with diethyl ether (50 mL), filtered through Celite, and concentrated to give a crude oil. Column chromatography (silica gel, EtOAc/*n*-hexane, 1:8 to 1:4) gave recovered ketone **11** (82 mg, 9%) and product **12** (648 mg, 71%) as a colorless oil. Data for **12**: IR (neat) 2988, 2936, 1682, 1453, 1380, 1228, 1094, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, 1 H, J = 10.2, 4.3 Hz), 6.16 (dt, 1 H, J = 10.2, 2.0 Hz), 4.01 (s, 1 H), 2.82 (ddd, 1 H, J = 19.0, 4.3, 2.0 Hz), 2.51 (ddd, 1 H, J = 19.0, 4.3, 2.0 Hz), 1.44 (s, 3 H), 1.43 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6 (C), 148.3 (CH), 128.0 (CH), 109.6 (C), 80.6 (CH), 80.5 (C), 36.1 (CH_2), 28.0 (CH_3), 27.7 (CH_3), 26.3 (CH_3); MS (EI) *m*/*z* 167 ([M − CH_3]$^+$, 34), 125 (42), 114 (82), 99 (64), 97 (46), 96 (67), 95 (72); HRMS (EI) *m*/*z* calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0946.

(3a*R,7a*R**)-5-Iodo-2,2,7a-trimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-one (13).** To a solution of enone **12** (278 mg, 1.53 mmol) in CH_2Cl_2 (8 mL) were added pyridine (3.7 mL) and iodine (1.55 g, 6.12 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and diluted with diethyl ether (80 mL). The reaction mixture was washed with 1 N $Na_2S_2O_3$ solution (50 mL) and brine (40 mL) and dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:4) gave iodo enone **13** (414 mg, 88%) as a yellow solid. The solid was recrystallized from 1:10 CH_2Cl_2/*n*-hexane to afford **13** as yellow crystals: mp 74−75 °C; IR (neat) 2986, 2934, 1688, 1601, 1453, 1377, 1333, 1224, 1093, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, apparent t, 1 H, J = 4.5, 4.5 Hz), 4.15 (s, 1 H), 2.83 (dd, 1 H, J = 19.1, 4.5 Hz), 2.56 (dd, 1 H, J = 19.1, 4.5 Hz), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6 (C), 156.4 (CH), 110.3 (C), 101.2 (C), 80.8 (C), 79.9 (CH), 39.6 (CH_2), 28.1 (CH_3), 27.9 (CH_3), 26.4 (CH_3); MS (EI) *m*/*z* 308 (M^+, 65), 293 ([M − CH_3]$^+$, 33), 265 (54), 181 ([M − I]$^+$, 38); HRMS (EI) *m*/*z* calcd for $C_{10}H_{13}IO_{13}$ 307.9911, found 307.9908.

(3a*S,4*R**,7a*R**)-5-Iodo-2,2,7a-trimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol -4-ol (14).** To a cooled (−78 °C) solution of α-iodo enone **13** (973 mg, 3.16 mmol) was added $CeCl_3 \cdot 7H_2O$ (1.24 g, 3.32 mmol) in methanol (32 mL) and sodium borohydride (126 mg, 3.32 mmol). The reaction mixture was stirred for 40 min and then quenched with water (40 mL). The resulting mixture was extracted with diethyl ether (3 × 40 mL). The combined organic layer was washed with brine (50 mL) and dried $MgSO_4$. Concentration and column chromatography (silica gel, CH_2Cl_2) gave iodo alcohol **14** (914 mg, 93%) as a yellow solid. The solid was recrystallized from 1:10 CH_2Cl_2/*n*-hexane to afford **14** as white crystals: mp 75.5−77.5 °C; IR (neat) 3440, 2984, 2931, 1631, 1376, 1229, 1138, 1079, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.42−6.38 (m, 1 H), 4.24 (d, 1 H, J = 3.6 Hz), 3.93−3.86 (m, 1 H), 2.94 (d, 1 H, J = 8.8 Hz), 2.29 (dd, 1 H, J = 16.2, 6.6 Hz), 1.82 (dm, 1 H, J = 16.2 Hz), 1.33 (s, 3 H), 1.30 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3 (CH), 109.2 (C), 103.8 (C), 83.1 (CH), 80.1 (C), 69.3 (CH), 39.4 (CH_2), 27.3 (CH_3), 27.1 (CH_3), 27.0 (CH_3); MS (EI) *m*/*z* 310 (M^+, 7), 295 (14), 281 (12), 207 (36), 114 (48), 89 (100); HRMS (EI) *m*/*z* calcd for $C_{10}H_{15}IO_3$ 310.0068, found 310.0053.

Ethyl 2-{[(3a*S,4*R**,7a*R**)-5-Iodo-2,2,7a-trimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-yl]oxy}acetate (15).** Sodium hydride (178 mg, 80% in mineral oil, 5.94 mmol) was washed with anhydrous benzene (3 × 1.5 mL). THF (2 mL) was added. The suspension was cooled to 0 °C. A solution of **14** (613 mg, 1.98 mmol) in THF (10 mL) was added to the NaH suspension dropwise. After the resulting mixture was stirred for 30 min, ethyl bromoacetate (992 mg, 5.94 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature, stirred for 3 h, and then quenched with water (15 mL). The mixture was extracted with diethyl ether (3 × 30 mL). The organic layer was washed with brine (40 mL) and dried over $MgSO_4$. Concentration and column chromatography (silica gel, CH_2Cl_2) gave iodo ester **15** (760 mg, 97%) as a yellow oil: IR (neat) 2940, 1744, 1612, 1445, 1377, 1191, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54−6.50 (m, 1 H), 4.55 (d, 1 H, J = 2.8 Hz), 4.44 and 4.29 (AB q, 2 H, J = 16.8 Hz), 4.24−4.15 (m, 2 H), 3.87−3.84 (m, 1 H), 2.35 (dd, 1 H, J = 16.4, 6.8 Hz), 1.81 (dm, 1 H, J = 16.4 Hz), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.27 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C), 136.1 (CH), 109.3 (C), 98.4 (C), 83.3 (CH), 80.3 (C), 77.4 (CH), 67.9 (CH_2), 60.7 (CH_2), 39.9 (CH_2), 27.1 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 14.0 (CH_3); MS (EI) *m*/*z* 381 ([M − CH_3]$^+$, 20), 339 (89), 194 (33), 114 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{21}IO_5$ 396.0435, found 396.0431.

***N*-Methoxy-*N*-methyl-2-{[(3a*S**,4*R**,7a*R**)-5-iodo-2,2,7a-trimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-yl]oxy}acetamide (16).** To a suspension of *N*,*O*-dimethylhydroxylamine in CH_2Cl_2 (6 mL) at 0 °C was added trimethylaluminum (1.91 mL 1.6 M in *n*-hexane, 3.05 mmol) dropwise (*caution: vigorous evolution of gas occurred*). After the addition, the cooling bath was removed. The clear solution was stirred at room temperature for 30 min and then cooled to −10

°C. A solution of **15** (485 mg, 1.22 mmol) in CH_2Cl_2 (4 mL) was added. The reaction mixture was stirred at −10 °C for 2 h and at 0 °C for another 1 h and then quenched with HCl solution (1 N, 10 mL) slowly (*caution: vigorous evolution of gas occurred*) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 × 12 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (25 mL) and dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:1) gave amide **16** (428 mg, 85%) as a yellow solid. The solid was recrystallized from CH_2Cl_2/*n*-hexane (1:10) to afford **16** as white crystals: mp 89−90 °C; IR (neat) 2950, 1673, 1444, 1377, 1255, 1103, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.52−6.48 (m, 1 H), 4.73−4.65 (m, 2 H), 4.47 (d, 1 H, J = 16.8 Hz), 3.91−3.89 (m, 1 H), 3.68 (s, 3 H), 3.17 (s, 3 H), 2.32 (dd, 1 H, J = 16.4, 6.8 Hz), 1.78 (dm, 1 H, J = 16.4 Hz), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 135.7 (CH), 109.1 (C), 99.3 (C), 83.6 (CH), 80.4 (C), 77.2 (CH), 67.9 (CH_2), 61.3 (CH_3), 39.9 (CH_2), 32.0 (CH_3), 27.2 (CH_3), 26.9 (CH_3), 26.8 (CH_3); MS (EI) m/z 411 (M^+, 7), 354 (100); HRMS (EI) m/z calcd for $C_{13}H_{19}INO_5$ (M − CH_3) 396.0310, found 396.0305. Anal. Calcd for $C_{14}H_{22}INO_5$: C, 40.89; H, 5.39; N, 3.41. Found: C, 40.72; H, 5.36; N, 3.42.

(3a*R,8a*S**,8b*S**)-2,2,3a-Trimethyl-3a,4,6,7,8a,8b-hexahydrofuro-[2′,3′:3,4]benzo[*d*][1,3]dioxol-6-one (17).** To a solution of amide **16** (101 mg, 0.246 mmol) in THF (5 mL) at −100 °C was added *n*-BuLi (0.15 mL, 2.0 M in *n*-hexane, 0.30 mmol) over 5 min. The reaction mixture was stirred at −70 °C for 30 min. The solution was quenched by HCl (1.0 N, 5 mL) at 0 °C and stirred for 5 min. The resulting mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with brine (15 mL) and dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:2) gave enone **17** (46 mg, 82%) as a white solid: mp 56−58 °C; IR (neat) 2935, 1725, 1658, 1443, 1376, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95−6.91 (m, 1 H), 4.70−4.66 (m, 1 H), 4.49 (d, 1 H, J = 3.6 Hz), 4.33 and 4.23 (AB q, 2 H, J = 16.8 Hz), 2.73 (dd, 1 H, J = 17.2, 6.8 Hz), 1.91 (dt, 1 H, J = 17.2, 3.0 Hz), 1.49 (s, 3 H), 1.37 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (C), 134.5 (C), 132.8 (CH), 109.4 (C), 82.1 (CH), 81.1 (C), 78.6 (CH), 73.8 (CH_2), 38.6 (CH_2), 27.8 (CH_3), 26.7 (CH_3), 26.4 (CH_3); MS (EI) m/z 224 (M^+, 13), 209 (24), 195 (47), 167 (35); HRMS (EI) m/z calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1043.

(3a*R,5*R**,5a*S**,8a*S**,8b*S**)-5-(Methoxymethyl)-2,2,3a-trimethylperhydrofuro[2′,3′:3,4]benzo[*d*][1,3]dioxol-6-one (18).** To a solution of $MeOCH_2SnBu_3$ (382 mg, 1.14 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (0.57 mL, 2.0 M in *n*-hexane, 1.14 mmol). The reaction mixture was stirred for 15 min. CuCN (55 mg, 0.62 mmol) was added. The mixture was warmed to −60 °C, stirred for 1 h, and then cooled to −78 °C. A solution of enone **17** (99 mg, 0.44 mmol) and chlorotrimethylsilane (143 mg, 1.32 mmol) in THF (3 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature slowly over 5 h, then quenched with HCl (0.5 M, 8 mL), and stirred for 15 min at 0 °C. The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ (15 mL) and brine (15 mL) and dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:2) gave product **18** (104 mg, 87%) as a colorless oil: IR (neat) 2928, 1756, 1640, 1450, 1377, 1120, 1111, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (dd, 1 H, J = 9.3, 2.8 Hz), 4.20 (d, 1 H, J = 2.8 Hz), 4.11 and 3.99 (AB q, 2 H, J = 16.6 Hz), 3.50 (dd, 1 H, J = 9.2, 4.8 Hz), 3.41 (dd, 1 H, J = 9.2, 3.2 Hz), 3.31 (s, 3 H), 2.65 (dd, 1 H, J = 9.3, 9.3 Hz), 2.30−2.20 (m, 1 H), 1.55 (dd, 1 H, J = 14.0, 2.8 Hz), 1.33 (s, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.21 (dd, 1 H, J = 14.0, 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6 (C), 108.3 (C), 81.8 (CH), 80.0 (C), 76.7 (CH), 75.1 (CH_2), 70.6 (CH_2), 58.9 (CH_3), 43.6 (CH), 37.4 (CH_2), 31.2 (CH), 27.4 (CH_3), 26.5 (CH_3), 25.6 (CH_3); MS (EI) m/z 270 (M^+, 56), 255 (61), 213 (100); HRMS (EI) m/z calcd for $C_{14}H_{22}O_5$ 270.1467, found 270.1474.

(3a*S,4*R**,6*R**,7*S**,7a*S**)-6,7-Dihydroxy-4-(methoxymethyl)-6-methylperhydrobenzo[*b*]furan-3-one (19).** To a solution of **18** (104 mg, 0.38 mmol) in THF (2 mL) was added HCl (2 N, 2 mL). The reaction mixture was heated at 80 °C for 8 h, cooled to room temperature, and extracted with CH_2Cl_2 (6 × 8 mL). The combined organic layer was dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc) gave diol **19** (68 mg, 77%) as a colorless oil: IR (neat) 3380, 2903, 1755, 1643, 1386, 1260, 1181, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (t, 1 H, J = 4.0 Hz), 4.23 (d, 1 H, J = 16.8 Hz), 3.80 (d, 1 H, J = 16.8 Hz), 3.50 (dd, 1 H, J = 8.8, 4.0 Hz), 3.39 (dd, 1 H, J = 9.4, 4.8 Hz), 3.35 (dd, 1 H, J = 9.4, 3.2 Hz), 3.29 (s, 3 H), 3.22 (br s, 2 H), 2.42 (dd, 1 H, J = 11.2, 4.0 Hz), 1.99−1.85 (m, 2 H), 1.53 (t, 1 H, J = 13.2 Hz), 1.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1 (C), 80.8 (CH), 72.2 (CH), 72.1 (CH_2), 71.8 (C), 70.8 (CH_2), 58.9 (CH_3), 47.2 (CH), 40.2 (CH_2), 29.2 (CH), 26.0 (CH_3); MS (EI) m/z 230 (M^+, 15), 213 ([M − OH]$^+$, 100); HRMS (EI) m/z calcd for $C_{11}H_{18}O_5$ 230.1154, found 230.1153.

(3a*S,4*R**,6*R**,7*S**,7a*S**)-6-Hydroxy-4-(methoxymethyl)-6-methyl-3-oxoperhydrobenzo[*b*]furan-7-yl Acetate (20).** To a solution of diol **19** (57.0 mg, 0.248 mmol) and 4-(dimethylamino)pyridine (45.0 mg, 0.371 mmol) in CH_2Cl_2 (3 mL) was added acetic anhydride (30.0 mg, 0.296 mmol) at room temperature. The reaction mixture was stirred for 1 h and then quenched with HCl (1 N, 6 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (10 mL) and brine and dried over $MgSO_4$. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:1) gave alcohol **20** (54.7 mg, 81%) as a colorless solid. Recrystallization from CH_2Cl_2/*n*-hexane (1:8) afforded **20** as white crystals: mp 110−111 °C; IR (neat) 3502, 2909, 1743, 1378, 1242, 1103, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (d, 1 H, J = 4.0 Hz), 4.46 (t, 1 H, J = 4.0 Hz), 4.28 (d, 1 H, J = 17.2 Hz), 3.81 (d, 1 H, J = 17.2 Hz), 3.56 (s, 1 H), 3.45 (dd, 1 H, J = 9.3, 5.2 Hz), 3.37 (dd, 1 H, J = 9.3, 3.0 Hz), 3.32 (s, 3 H), 2.53 (dd, 1 H, J = 11.2, 4.0 Hz), 2.19 (s, 3 H), 2.12−2.00 (m, 1 H), 1.93 (dd, 1 H, J = 13.6, 3.6 Hz), 1.66 (t, 1 H, J = 13.6 Hz), 1.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3 (C), 170.5 (C), 78.7 (CH), 73.3 (CH), 71.7 (CH_2), 71.0 (C), 70.9 (CH_2), 58.9 (CH_3), 47.3 (CH), 40.9 (CH_2), 29.4 (CH), 25.9 (CH_3), 20.8 (CH_3); MS (EI) m/z 213 ([M − OAc]$^+$, 100); HRMS (EI) m/z calcd for $C_{13}H_{20}O_6$ 272.1260, found 272.1252. A single-crystal X-ray analysis of **20** was performed.[23]

(3a*S,4*R**,7*R**,7a*S**)-4-(Methoxymethyl)-6-methyl-3-oxo-2,3,3a,4,7,7a,-hexahydrobenzo[*b*]furan-7-yl Acetate (21).** To a solution of alcohol **20** (72.8 mg, 0.267 mmol) was added PTSA·H_2O (5.0 mg, 0.027 mmol) in benzene (8 mL). The mixture was heated at reflux for 9 h and cooled to room temperature. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:1) gave a white solid, consisting of major product **21** and two minor olefin isomers according to ^1H NMR analysis. The ratio of the major isomer **21** to the two minor isomers together was 4.5:1. Recrystallization from CH_2Cl_2/*n*-hexane (1:10) afforded **21** as white crystals (102 mg, 60%): mp 94−95 °C; IR (neat) 2905, 1747, 1442, 1374, 1235, 1120, 1059, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60−5.56 (m, 1 H), 5.39 (d, 1 H, J = 3.6 Hz), 4.65 (dd, 1 H, J = 9.6, 3.6 Hz), 4.10 and 4.05 (AB q, 2 H, J = 16.8 Hz), 3.45 (dd, 1 H, J = 8.8, 5.2 Hz), 3.41 (dd, 1 H, J = 8.8, 5.2 Hz), 3.36 (s, 3 H), 2.99−2.83 (m, 1 H), 2.72 (dd, 1 H, J = 9.6, 4.4 Hz), 2.01 (s, 3 H), 1.81 (br s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4 (C), 170.0 (C), 132.9 (C), 128.1 (CH), 76.7 (CH), 75.1 (CH_2), 72.0 (CH), 70.9 (CH_2), 59.0 (CH_3), 43.7 (CH), 34.9 (CH), 21.2 (CH_3), 20.9 (CH_3); MS (EI) m/z 254 (M^+, 9), 195 (90), 163 (100); HRMS (EI) m/z calcd for $C_{13}H_{18}O_5$ 254.1154, found 254.1149. The minor products were not purified and fully characterized.

(3a*S,4*R**,7*R**,7a*S**)-7-Hydroxy-4-(methoxymethyl)-6-methyl-2,3,3a,4,7,7a-hexahydrobenzo[*b*]furan-3-one (22).** To a solution of **21** (85 mg, 0.335 mmol) in methanol (5 mL) was added $NaOCH_3$ (73 mg, 1.35 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and then quenched with water. The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Concentration and column chromatography (silica gel, EtOAc/

n-hexane, 1:1) gave product **22** (62 mg, 87%) as a white solid. This solid was recrystallized from CH_2Cl_2/*n*-hexane (1:8) to afford **22** as white crystals: mp 79−80 °C; IR (neat) 3432, 2881, 1758, 1448, 1380, 1192, 1117, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45−5.48 (m, 1 H), 4.55 (dd, 1 H, J = 8.6, 4.0 Hz), 4.21 (d, 1 H, J = 3.6 Hz), 4.17, 4.05 (AB q, 2 H, J = 16.4 Hz), 3.37 (d, 2H, J = 5.2 Hz), 3.32 (s, 3 H), 2.85−2.80 (m, 1 H), 2.65(ddd, 1 H, J = 8.7, 3.6, 1.2 Hz), 1.80 (br s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6 (C), 135.6 (C), 125.3 (CH), 78.3 (CH), 75.2 (CH_2), 70.8 (CH_2), 69.9 (CH), 58.9 (CH_3), 43.9 (CH), 34.6 (CH), 21.1 (CH_3); MS (FAB) *m*/*z* 213 ($M + H^+$, 100), 195 (35), 163 (41); HRMS (FAB, $M + H^+$) *m*/*z* calcd for $C_{11}H_{17}O_4$ 213.1127, found 213.1127.

(3a*S,4*R**,7*R**,7a*S**)-7-[(*tert*-Butyldimethylsilyl)oxy]-4-(methoxymethyl)-6-methyl-2,3,3a,4,7,7a-hexahydrobenzo[*b*]furan-3-one (23)**. To a solution of **22** (38 mg, 0.18 mmol) and 2,6-lutidine (44 mg, 0.41 mmol) in dry THF (2 mL) was added TBSOTf (0.061 mL, 0.27 mmol) dropwise at 0 °C. The mixture was stirred for 3 h at 0 °C, then quenched with water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (15 mL) and brine (15 mL) and dried over Na_2SO_4. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:5) gave product **23** (45 mg, 77%) as a colorless oil: IR (neat) 2930, 1760, 1473, 1362, 1253, 1197, 1122, 1075 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.49 (br s, 1 H), 4.38 (dd, 1 H, J = 9.7, 2.9 Hz), 4.20, 4.06 (AB q, 2 H, J = 16.1 Hz), 4.19(d, 1 H, J = 4.5 Hz), 3.51 (dd, 1 H, J = 9.0, 4.6 Hz), 3.42 (dd, 1 H, J = 9.0, 5.5 Hz), 3.35 (s, 3 H), 2.87−2.90 (m, 1 H), 2.55 (ddd, 1H, J = 9.7, 5.4, 1.4 Hz), 1.76 (br s, 3 H), 0.79(s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4 (C), 135.8 (C), 127.6 (CH), 79.9 (CH), 75.4 (CH_2), 73.0 (CH), 71.5 (CH_2), 59.1 (CH_3), 42.6 (CH), 35.2 (CH), 25.6 (CH_3), 21.6 (CH_3), 17.9 (C), −4.5 (CH_3), −4.9 (CH_3); MS (FAB) 327 ($[M + H]^+$, 35), 269(78), 73-(100); HRMS (FAB, $M + H^+$) *m*/*z* calcd for $C_{17}H_{31}O_4Si$ 327.1992, found 327.1997.

(3a*R,4*S**,7*R**,7a*R**)-7-[(*tert*-Butyldimethylsilyl)oxy]-3a-hydroxy-4-(methoxymethyl)-6-methyl-2,3,3a,4,7,7a-hexahydrobenzo[*b*]furan-3-one (3)**. To a solution of *i*-Pr_2-NH (0.025 mL, 0.18 mmol) in THF (2 mL) was added *n*-BuLi (2.3 M in hexane, 0.078 mL, 0.18 mmol) dropwise at 0 °C. After being stirred for 0.5 h at 0 °C, the mixture was cooled to −78 °C; compound **23** (17 mg, 0.052 mmol) in THF (0.5 mL) was added dropwise. The mixture was stirred for 0.5 h at −78 °C and then allowed to warm to −20 °C over 1 h. The mixture was cooled to −78 °C again; 2-sulfonyloxaziridine (23 mg, 0.088 mmol) in THF (0.25 mL) was added dropwise. The mixture was stirred at −78 °C for 1.2 h and quenched at −78 °C with saturated NH_4Cl solution (0.5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Concentration and column chromatography (silica gel, EtOAc/*n*-hexane, 1:3) gave product **3** (6 mg, 34%, 82% yield based on 41% conversion) as a colorless oil and recovered starting material **23** (10 mg, 59%). Data for compound **3**: IR (neat) 3431, 2929, 1770, 1472, 1386, 1253, 1110, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (br s, 1 H), 4.43 (br s, 1 H), 4.33, 4.09 (AB q, 2 H, J = 17.0 Hz), 4.02 (d, 1 H, J = 4.5 Hz), 3.67 (dd, 1 H, J = 10.0, 4.0 Hz), 3.56 (dd, 1 H, J = 10.0, 6.0 Hz), 3.37 (s, 3 H), 2.66−2.69 (m, 1 H), 1.81 (br s, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2 (C), 136.5 (C), 121.5 (CH), 82.3 (CH), 78.1 (C), 72.3 (CH_2), 70.1 (CH_2), 69.2 (CH), 59.2 (CH_3), 35.4 (CH), 25.8 (CH_3), 20.3 (CH_3), 18.3 (C), −4.8 (CH_3), −4.6 (CH_3); MS (FAB) 343 ($M + H^+$, 9), 325 (20), 285 (7), 73(100); HRMS (FAB, $M + H^+$) *m*/*z* calcd for $C_{17}H_{31}O_5Si$ 343.1941, found 343.1949.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of compounds **6**−**8**, **10**−**23**, and **3** and the X-ray crystal structure and data of compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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