Synthesis of the C38−C44 Segment of Altohyrtin A − With an Addendum on the Preparation of 8-Oxabicyclo[3.2.1]oct-6-en-3-one

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The densely funkctionalized C38–C44 segment F of altohyrtin A with its five contiguous stereogenic centers was prepared in 10 steps and in 28 % overall yield (two steps per stereogenic center), from 8-oxabicyclo[3.2.1]oct-6-en-3-one as a template. The preparation of the title compound **1**, m.p. 38 °C, is described on a 0.5-m scale in a three-step-two-stage reaction from acetone and furan. The oxacycle was stored without change at room temperature.

Introduction

The altohyrtins[1] have recently been isolated and shown to be extremely potent cancer growth inhibitors, especially against chemoresistant tumor types.[2] The absolute stereochemistry of altohyrtin A was proposed by Kitagawa et al.[3] and was confirmed by total synthesis.[4] Although several synthetic approaches[5] leading to fragments of altohyrtin A have been published, including that of the C38−C44 segment, so far only Evans et al. and Kishi et al. have achieved a total synthesis of altohyrtin A and C, respectively (Figure 1).[4]

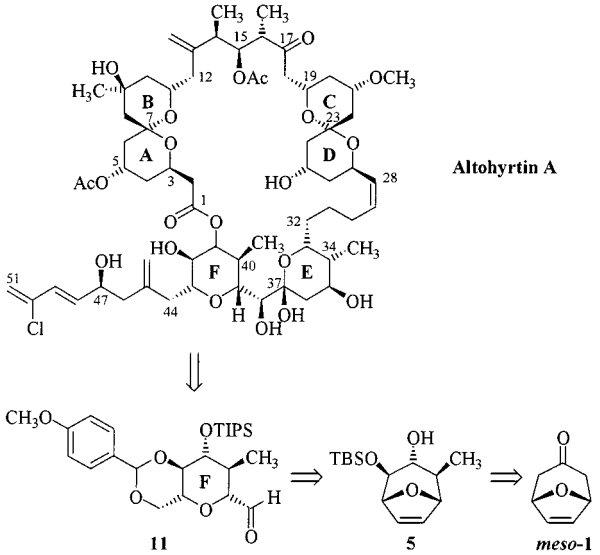
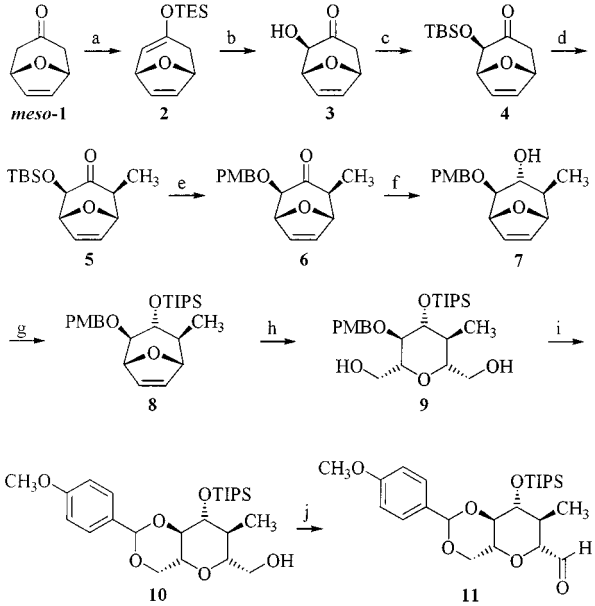


Figure 1. Retrosynthesis of F-segment **11** from **1**

Results and Discussion

We here report a simple and efficient synthesis of the protected C38−C44 F-segment **11** (Scheme 1). We started with the inexpensive and easily accessible *meso*-8-oxabicyclo[3.2.1]oct-6-en-3-one (**1**), deprotonated it with chiral lithium amide base and trapped the resulting enolate with triethylsilyl chloride, to obtain **2**. *m*CPBA oxidation of the silyl enol ether **2** in dichloromethane (DCM) at −35 °C furnished the rearranged Rubottom product, which was desilylated in situ to bicyclic α-hydroxy ketone **3**. The alcohol



Scheme 1. Reagents: (a) (i) LiCl, (+)-bis[(*R*)-1-phenylethyl]amine, THF, −78 °C, (ii) BuLi, ***meso*-1**, THF, −115 °C, (iii) TESCl, NEt_3, −78 °C (95%); (b) (i) *m*-CPBA, DCM, −35 to −25 °C, (ii) TFA, −25 °C (71%, 95% ee); (c) TBSCl, imidazole, DMF (96%); (d) LDA, TMEDA, MeI, THF, −78 °C (91%); (e) (i) 2 N HCl, EtOH, room temp., 5 h, (ii) PMB trichloroacetimidate, (+)-camphorsulfonic acid (CSA), DCM (84%); (f) (i) L-Selectride, THF, −78 °C, (ii) NaOH, H_2O_2, 0 °C (87%); (g) 2,6-lutidine, TIPSOTf, DCM, −40 °C (97%); (h) (i) O_3, DCM/MeOH, −95 °C, (ii) $NaBH_4$ (94%); (i) DDQ, molecular sieves (3 Å), degassed DCM, −60 to 0 °C, 4 h (82%); (j) *N*-methylmorpholine *N*-oxide (NMO), Pr_4NRuO_4, DCM, room temp., 1.5 h (79%)

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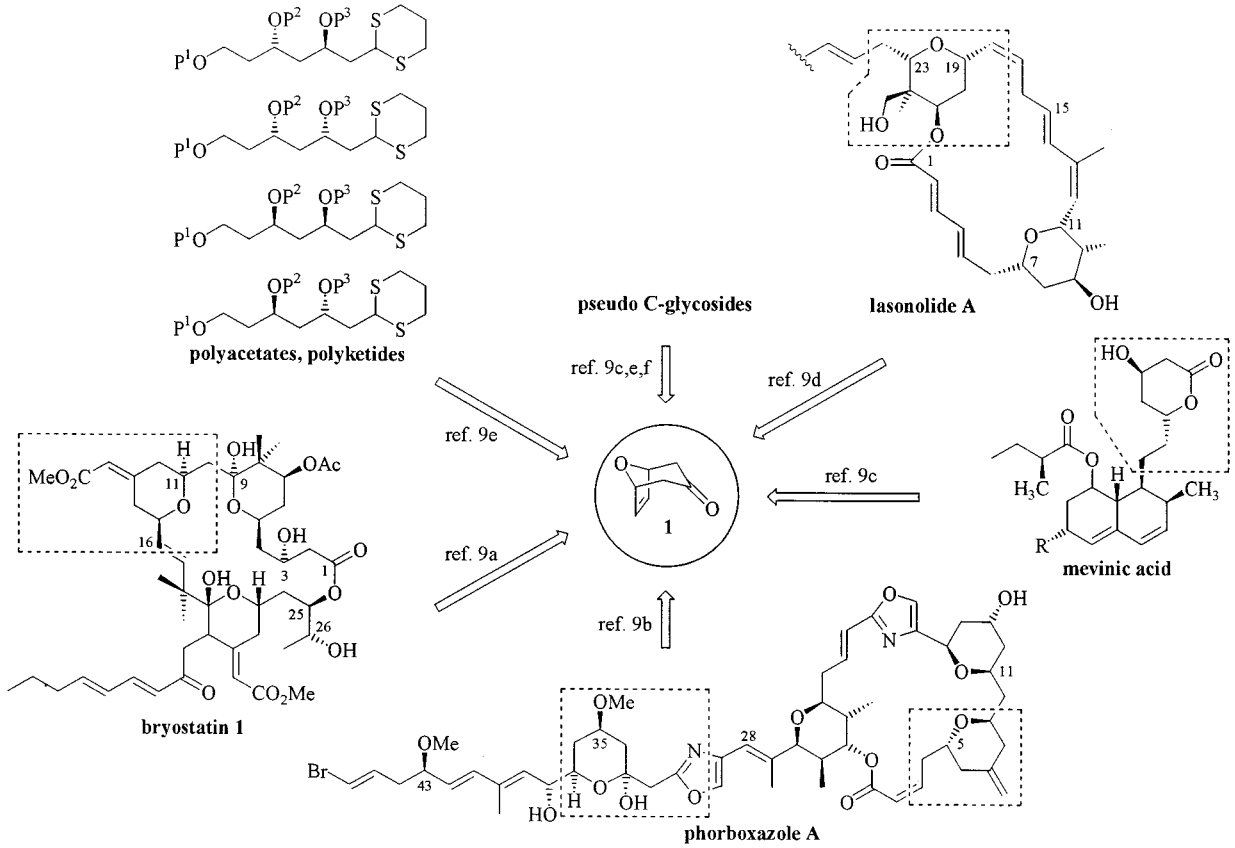


Scheme 2. Oxabicyclic ketone **1**, synthetic equivalent of a polyacetate aldol adduct

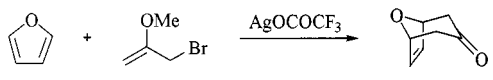
group was protected as TBS ether **4**. After axial methylation at the α′-position to form **5** (91% yield),[6] the TBS ether was reprotected as the *p*-methoxybenzyl (PMB) ether **6**. Treatment of the ketone with L-Selectride yielded the axial alcohol **7** exclusively. All three substituents of the bridged tetrahydropyran **7** are axial. After being protected as the TIPS ether **8**, its olefinic bridge was cleaved by ozonolysis and was reduced in situ with $NaBH_4$. Oxidative ring closure of the resulting (3-hydroxymethylcyclohexyl)methanol **9** with DDQ in degassed DCM[7] led to the formation of the benzylidene acetal **10** in good yield. The hydroxy group at C38 did not interfere with this acetalization. Our sequence was completed by oxidation at C38, giving the desired protected aldehyde **11** of the F-segment. All five substituents of the tetrahydropyran moiety in **9**, **10** and **11** adopted equatorial positions. Aldehyde **11** is ready for coupling with the neighboring E-segment C31−C37.

Conclusion

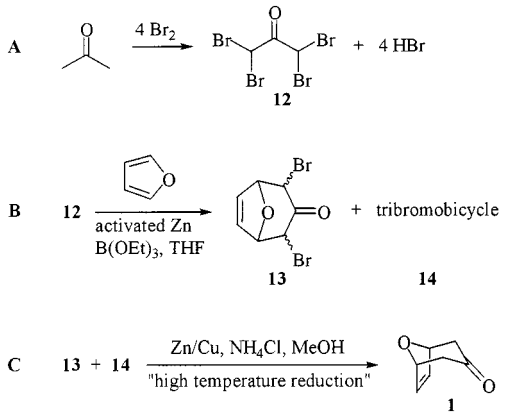
In summary, the densely functionalized C38−C44 F-segment **11** of altohyrtin A with its five contiguous stereogenic centers was prepared from **1** in 10 steps and in 28% overall yield. To our knowledge, this is one of the shortest and most efficient routes to this segment.

Addendum on the Synthesis of 8-Oxabicyclo[3.2.1]oct-6-en-3-one, a Universal Building Block

Title compound **1** has been known for over two decades[8] and continues to be highly useful and versatile in organic synthesis. Recent applications include the synthesis of a variety of tetrahydropyran units that occur in marine natural products, pseudo-C-glycosides and other bioactive substances. Oxabicycle **1** is not only a source of cyclic and acyclic polyketides of the simple polyacetate pattern, it is also possible to "load" stereochemistry on **1** and to introduce further stereogenic centers. Representative examples are outlined in Scheme 2.[9] Originally, **1** was prepared by reaction of 2-methoxyallyl bromide with silver trifluoroacetate in the presence of furan (Scheme 3).[10] Soon afterwards, further routes to **1** began to appear.[11] Our 1,1,3,3-tetrabromopropanone/triethyl borate−Zn/Cu pro-



Scheme 3. Silver salt route to oxabicycle



Scheme 4. Synthesis of **1** from furan and acetone

cedure[12] has been used widely (Scheme 4). However, scale-up has not been straightforward. Unfortunately, a persistent error has also crept into the literature, in that oxabicycle **1** has been described as a sensitive compound which has to be stored under argon at −20 °C in the dark.[13] These comments and general experimental difficulties may have discouraged further extensive applications of **1**.

We show here that **1** is not oily, but is a crystalline colorless solid, m.p. 38 °C, as we reported originally.[8] When **1** is pure, it is indefinitely stable at room temperature. We describe here a verified procedure for the preparation of **1** on a 0.5-M scale in 52−56% yield (31−34.9 g isolated). The following Notes should be borne in mind:

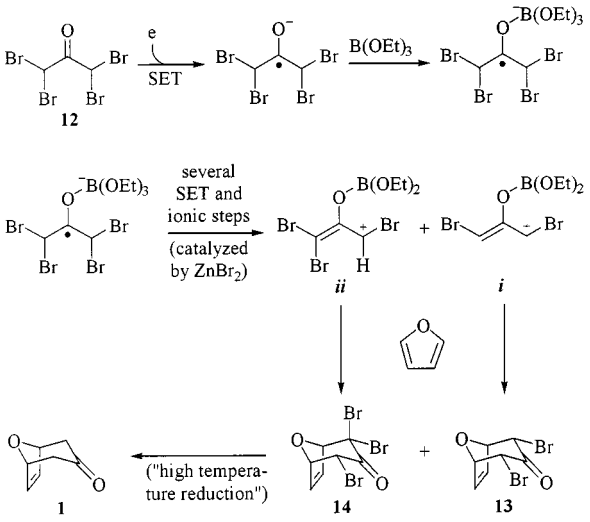
1. 1,1,3,3-Tetrabromopropanone (**12**) was obtained as a crystalline colorless solid after recrystallization from cooled light petroleum ether (step A). Lengthy and tedious workup is circumvented if the crystalline product is directly frozen out from the mother liquor. There is also no need to neutralize large amounts of HBr (Scheme 4, step A). Crystalline **12** facilitates handling and overall control during the following two steps B and C (Scheme 4).

2. Cycloaddition was initiated by the addition of a catalytic amount of bromine. (Note that volatile bromine-containing compounds are lachrymatory.)

3. After the flask had been charged with reagents, the reaction was kept going by temperature control. If the reaction breaks off, it is difficult or impossible to restart it, and the yield drops sharply. The preferred reaction temperature is above that of boiling tetrahydrofuran (b.p. 66 °C, temperature control by ice/water).

4. In step C, a "high-temperature reduction" of the first-formed brominated cycloadducts is feasible. The temperature window for this reduction was widened to 0−10 °C. Under these conditions, reductive removal of bromine proceeds steadily, without an induction period.

5. It is essential to first of all work up the reaction mixture with brine. If water or ice are added first, to quench the reaction mixture, emulsions are formed, and many extractions with $CHCl_3$ are required to isolate **1**. Product is lost, also because **1** is highly soluble in water (ca. 125 g/l) and tends to decompose at room temperature on extended contact with acid.



Scheme 5. Proposed mechanism (see Scheme 4)

6. After removal of $CHCl_3$, the crude cycloadduct was filtered through a short column containing solid K_2CO_3 on filter paper. During this stage, HBr, which adheres persistently to **1**, was removed. If the HBr was not removed at this stage, the cycloadduct decomposed, presumably with formation of 2-acetonylfuran. We also isolated **1** by kugelrohr distillation.[13b] However, scale-up was problematic, and decomposition of the cycloadduct tended to take place, especially if the HBr was not removed beforehand. Purification of **1** by removal of major quantities of HBr by column chromatography (alumina or silica gel) is not feasible.

The cycloaddition may be visualized as single electron transfer (SET), facilitated by triethyl borate, alternating with Lewis acid mediated ionic steps, to generate the crucial boron oxyallyl cation, such as **i**, which is captured by furan to yield the dibromo bicycle **13**. A simplified, abbreviated reaction sequence is outlined in Scheme 5.

In summary, after many iterative experiments, we have optimized our route to oxabicycle **1**.

Experimental Section

General Remarks: IR: Perkin−Elmer 1710 infrared spectrometer. − ^{1}H NMR and ^{13}C NMR: Bruker AM 400 spectrometer; in deuterated chloroform with tetramethylsilane as internal standard. ^{13}C-NMR signal assignments for each signal; DEPT measurements; multiplicities are indicated by 1° (primary), 2° (secondary), 3° (tertiary) and 4° (quaternary). − MS: Finnigan MAT 312 (70 eV) or a VG Autospec spectrometer at room temp. unless otherwise stated. − Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30−60 μm). − Analytical TLC was carried out on aluminum-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). − E (diethyl ether) and THF were distilled from sodium and benzophenone before use. CH_2Cl_2 (DCM) was distilled from CaH_2 before use. DMF was dried with BaO and distilled from CaH_2 before use. *tert*-Butyl methyl ether (MTBE), ethyl acetate (EA) and light petroleum ether (PE, bp 40−60 °C) were distilled before use.

(+)-(1*R*,5*R*)-3-(Triethylsiloxy)-8-oxabicyclo[3.2.1]octa-2,6-diene [(+)-2]: (+)-Bis[(*R*)-1-phenylethyl]amine (18.1 g, 80.5 mmol) in

THF (50 mL) was added under argon to dry LiCl (1.93 g, 45.5 mmol). The mixture was cooled to −78 °C and *n*BuLi (52.5 mL, 84.0 mmol, 1.6 M solution in hexane) was added dropwise over 40 min. The resulting pink solution was stirred for 15 min at −78 °C, for 15 min at room temp., and was then recooled to −115 °C. A solution of **1** (8.7 g, 70 mmol) in THF (250 mL) was added slowly over 130 min. The mixture was stirred for 1 h at −115 °C and was then allowed to reach −78 °C. Triethylsilyl chloride (16.5 mL, 98.0 mmol) was added by syringe, followed by triethylamine (13.7 mL, 98.0 mmol). The mixture was allowed to reach room temp. and was then filtered through Celite. After the solvent was removed, the crude product was purified by column chromatography (E/PE) to afford **(+)-2** (15.9 g, 95%), a yellowish, viscous liquid. The stereoselectivity of the asymmetric deprotonation was conveniently estimated after the last stage, yielding **(+)-11**, 83% *ee*. − IR ($CHCl_3$): $\tilde{\nu}$ = 3001 cm^{-1}, 2960, 2876, 1640, 1456, 1416, 1352, 1312, 1240, 1196, 1016. − ^{1}H NMR: δ = 6.43 (dd, *J* = 2, 6 Hz, 1 H, H7), 5.94 (dd, *J* = 2, 6 Hz, 1 H, H6), 5.15 (d, *J* = 5 Hz, 1 H, H2), 4.88 (dd, *J* = 1, 5 Hz, 1 H, H5), 4.75 (d, *J* = 5 Hz, 1 H, H1), 2.61 (dd, *J* = 8, 16 Hz, 1 H, $H4_{ax}$), 1.69 (d, *J* = 16 Hz, 1 H, $H4_{eq}$), 0.92 [t, *J* = 8 Hz, 9 H, $Si(CH_2CH_3)_3$], 0.06 [q, *J* = 8 Hz, 6 H, $Si(CH_2CH_3)_3$]. − ^{13}C NMR: δ = 147.4 (C3), 128.1 (C7), 126.3 (C6), 106.7 (C2), 77.5 (C1), 75.2 (C5), 32.8 (C4), 6.7 [$Si(CH_2CH_3)_3$], 5.1 [$Si(CH_2CH_3)_3$]. − MS; *m/z*: 238 (3) [M^+], 219 (10), 218 (20), 217 (100), 189 (80), 162 (10), 161 (46), 159 (27), 145 (22), 133 (21), 105 (23), 103 (19), 87 (24), 75 (32). − HRMS: calcd. for $C_{13}H_{22}O_2Si$ [M^+] 238.1389; found 238.1388.

(−)-(1*R*,2*R*,5*R*)-2β-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-one [(−)-3]: *m*CPBA (17.9 g, 72.6 mmol) was added portionwise at −35 °C to a solution of **(+)-2** (15.7 g, 66.0 mmol) in DCM (190 mL). The temperature of the reaction mixture was kept below −25 °C. After 1 h, trifluoroacetic acid (5.1 mL, 66 mmol) was added. The mixture was allowed to reach 0 °C, was then diluted with DCM (100 mL) and quenched with sat. aq. NH_4Cl solution. The organic layer was washed with water (200 mL) and brine (200 mL). The combined aqueous layer was extracted with EA (3 × 300 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was evaporated. The precipitated solid was suction-filtered, washed with PE, and purified by column chromatography (E/PE) to give **(−)-3** (6.57 g, 71%), colorless solid. − IR ($CHCl_3$): $\tilde{\nu}$ = 3432 cm^{-1}, 3084, 2980, 2912, 1824, 1716, 1648, 1404, 1332, 1272, 1176, 1064, 1040, 1008, 948. − ^{1}H NMR: δ = 6.46 (dd, *J* = 2, 6 Hz, 1 H, H7), 6.32 (dd, *J* = 2, 6 Hz, 1 H, H6), 5.31 (m, 1 H, H5), 4.94 (s, 1 H, H1), 3.71 (s, 1 H, H2), 3.62 (s br, 1 H, O-H), 3.06 (dd, *J* = 5, 16 Hz, 1 H, $H4_{ax}$), 2.33 (d, *J* = 16 Hz, 1 H, $H4_{eq}$). − ^{13}C NMR: δ = 205.4 (C3), 136.6 (C6), 129.5 (C7), 82.4 (C2), 77.4 (C5), 75.3 (C1), 44.5 (C4). − MS; *m/z*: 140 (5) [M^+], 111 (1), 97 (5), 94 (3), 81 (14), 72 (2), 70 (5), 69 (100), 65 (3). − HRMS: calcd. for $C_7H_8O_3$ [M^+] 140.0473; found 140.0474.

(−)-(1*R*,2*R*,5*R*)-2β-(*tert*-Butyldimethylsilyloxy)-8-oxabicyclo[3.2.1]-oct6-en-3-one [(−)-4]: NEt_3 (0.6 mL, 4.6 mmol) was added to a solution of **(−)-3** (6.40 g, 46.1 mmol), imidazole (7.80 g, 115 mmol) and TBSCl (8.30 g, 55.3 mmol) in DMF (23 mL); the resulting mixture was stirred at 30 °C for about 12 h. The reaction mixture was purified by column chromatography (E/PE) to afford **(−)-4** (11.2 g, 91%), yellow liquid. − $[\alpha]_D^{20}$ = −29.4 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2959 cm^{-1}, 2932, 1720, 1256, 1104, 1084, 856, 840. − ^{1}H NMR: δ = 6.39 (dd, *J* = 2, 6 Hz, 1 H, H7), 6.13 (dd, *J* = 2, 6 Hz, 1 H, H6), 4.97 (br. d, *J* = 5 Hz, 1 H, H5), 4.77 (br. s, 1 H, H1), 3.63 (s, 1 H, H2), 3.03 (dd, *J* = 5, 16 Hz, 1 H, $H4_{ax}$), 2.25 (br. d, *J* = 16 Hz, 1 H, $H4_{eq}$), 0.88 [t, *J* = 3 Hz, 9 H, $SiC(CH_3)_3$], 0.13/0.07 [s, 6 H, $SiC(CH_3)_2$]. − ^{13}C NMR: δ = 204.1 (C3), 136.9 (C7), 129.4 (C6), 83.1 (C3), 77.5 (C1), 75.5 (C5), 45.0 (C4), 25.6 [$SiC(CH_3)_3$], 18.1 [$SiC(CH_3)_3$], 5.7 [$SiC(CH_3)_2$]. − MS; *m/z*: 254 (23) [M^+], 197 (31), 195 (5), 171 (31), 169 (23), 138 (15), 130 (30), 129 (35), 128 (100), 125 (21), 103 (28), 101 (30), 99 (15), 81 (32), 75 (41). − HRMS: calcd. for $C_{13}H_{22}O_3Si$ [M^+] 254.1338; found 254.1335.

(+)-(1*R*,2*R*,4*S*,5*R*)-2β-(*tert*-Butyldimethylsilyloxy)-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one [(+)-5]: *n*BuLi (37.4 mL, 59.8 mmol, 1.6 M solution in hexane) was added at −78 °C to a solution of diisopropyl amine (7.80 mL, 55.2 mmol) in THF (40 mL). The mixture was stirred for 15 min at −78 °C and 30 min at room temp. Then the LDA solution was recooled to −78 °C and silyl ether **(−)-4** (11.7 g, 46.0 mmol) in THF (40 mL) was added dropwise over 10 min. After being stirred for 1 h at −78 °C and 30 min at room temp., the mixture was cooled again to −78 °C and TMEDA (9.0 mL, 60 mmol) and methyl iodide (14.4 mL, 230 mmol) were added. The mixture was stirred for 30 min, was then allowed to reach room temp., and was diluted with MTBE (100 mL). The organic layer was washed with sat. aq. $NaHCO_3$ solution and brine. The combined aqueous layers were extracted with MTBE (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), concentrated and purified by column chromatography (E/PE) to yield **(+)-5** (11.2 g, 91%), yellow liquid. − $[\alpha]_D^{20}$ = +27.1 (*c* = 1 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3088 cm^{-1}, 3072, 2944, 2880, 2856, 1716, 1684, 1408, 1388, 1264, 1004, 936. − ^{1}H NMR: δ = 6.37 (dd, *J* = 2, 6 Hz, 1 H, H7), 6.12 (dd, *J* = 2, 6 Hz, 1 H, H6), 4.74 (s br, 1 H, H1), 4.63 (s, 1 H, H5), 3.58 (t, *J* = 1 Hz, 1 H, H2), 2.31 (m, 1 H, H4), 1.42 (d, *J* = 7 Hz, 3 H, H9), 0.88 [s, 9 H, $Si(CH_3)_3$], 0.11/0.09 [s, 6 H, $Si(CH_3)_2$]. − ^{13}C NMR: δ = 207.5 (C3), 137.1 (C7), 19.5 (C6), 83.0 (C1), 82.0 (C5), 75.5 (C2), 50.7 (C4), 25.6 [$SiC(CH_3)_3$], 18.0 [$SiC(CH_3)_3$], 17.0 (C9), −5.0/−5.2 [$SiC(CH_3)_2$]. − MS; *m/z*: 269 (2) [M^++1], 268 (4) [M^+], 253 (1), 237 (2), 185 (5), 165 (1), 143 (100), 129 (3), 115 (3), 101 (7), 81 (5), 75 (19), 73 (22). − HRMS: calcd. for $C_{14}H_{24}O_3Si$ [M^+] 268.1493; found 268.1495.

(+)-(1*R*,2*R*,4*S*,5*R*)-2β-(*p*-Methoxybenzyloxy)-4β-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one [(+)-6]: A solution of **(+)-5** (11.0 g, 41.0 mmol) in EtOH (62 mL) and 2 N HCl (90 mL) was stirred for about 12 h at room temp. The reaction mixture was extracted with DCM (4 × 200 mL), the organic layer was dried ($MgSO_4$), and the solvent was removed. The crude product and trichloroacetimidate [preparation: to a solution of *p*-methoxybenzyl alcohol (13.8 g, 100 mmol) in E (300 mL) was added NaH (0.8 g, 20 mmol, 60% suspension in mineral oil) at 0 °C. After 5 min, trichloroacetonitrile (10.0 mL, 100 mmol) was added and the mixture was stirred for 50 min at 0 °C and 2 h at room temp., then the solvent was removed] were dissolved in DCM (200 mL), and CSA (1.9 g, 40 mmol) was added. The mixture was stirred for about 12 h and was then quenched by addition of sat. aq. $NaHCO_3$ solution. The organic layer was washed with 10% NaOH (2 × 100), dried ($MgSO_4$), the solvent was removed, and the crude product was purified by column chromatography (E/PE) to give **(+)-6** (9.2 g, 82%), yellow oil. − $[\alpha]_D^{20}$ = +83.6 (*c* = 1 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3076 cm^{-1}, 3060, 2968, 2908, 2872, 2840, 1712, 1612, 1512, 1248, 1176, 1056. − ^{1}H NMR: δ = 7.30 (m, 2 H, arom. H), 6.89 (m, 2 H, arom. H), 6.39 (dd, *J* = 2, 6 Hz, 1 H, H7), 6.10 (dd, *J* = 2, 6 Hz, 1 H, H6), 4.90 (s br, 1 H, H1), 4.67 (s br, 1 H, H5), 4.39/4.65 (d, *J* = 12 Hz, 2 H, H10), 3.80 (s, 3 H, H17), 3.34 (t, *J* = 1 Hz, 1 H, H2), 2.39 (m, 1 H, H4), 1.48 (d, *J* = 7 Hz, 3 H, H9). − ^{13}C NMR: δ = 207.3 (C3), 159.6 (C14), 137.4 (C11), 130.6 (C7), 129.6 (C6), 114.0 (C12, C13, C15, C16), 82.4 (C1), 81.4 (C5), 80.0 (C2), 71.7 (C10), 55.5 (C17), 50.8 (C4), 16.9 (C9). − MS (80 °C); *m/z*: 274 (1) [M^+], 245 (1), 153 (1), 137 (5), 121 (100), 109 (3), 95 (3), 77 (6).

(1*R*,2*R*,3*S*,4*S*,5*R*)-3α-Hydroxy-2β-(*p*-methoxybenzyloxy)-4β-methyl-8-oxabicyclo[3.2.1]oct-6-ene (7): L-Selectride (46.0 mL, 46.0 mmol, 1 M solution in THF) was added over 100 min (perfusor) at −78 °C to a solution of **(+)-6** (8.90 g, 32.5 mmol) in THF (135 mL). After complete addition, the mixture was stirred for 30 min at −78 °C and then allowed to reach 0 °C. Water (2 mL) was added, followed by NaOH (10.9 g, 273 mmol) in water (25 mL). H_2O_2 (27.8 mL, 273 mmol, 30% solution in water) was added slowly, the mixture was stirred for 1 h and was then neutralized with half-conc. HCl. The aqueous layer was saturated with NaCl and was extracted with DCM (4 × 200 mL). The organic layer was dried ($MgSO_4$), the solvent was removed and the crude product was purified by column chromatography (E/PE) to afford **7** (7.8 g, 87%), yellow liquid. − IR ($CHCl_3$): $\tilde{\nu}$ = 3548 cm^{-1}, 3000, 2952, 2880, 1612, 1584, 1464, 1408, 1300, 1248, 1112, 1036. − ^1H NMR: δ = 7.30 (m, 2 H, arom. H), 6.89 (m, 2 H, arom. H), 6.21 (dd, *J* = 2, 6 Hz, 1 H, H7), 6.14 (dd, *J* = 2, 6 Hz, 1 H, H6), 4.83 (s br, 1 H, H1), 4.74 (d, *J* = 12 Hz, 1 H, H10), 4.59 (s br, 1 H, H5), 4.43 (d, *J*12 Hz, 1 H, H10), 4.00 (m, 1 H, H3), 3.80 (s, 3 H, H17), 3.46 (m, 1 H, H2), 2.66 (d, *J* = 11 Hz, 1 H, OH), 1.85 (m, 1 H, H4), 1.19 (d, *J* = 7 Hz, 3 H, H9). − ^{13}C NMR: δ = 159.5 (C14), 133.8 (C7), 130.2 (C11), 129.4 (C6), 114.1 (C12, C13, C15, C16), 83.5 (C1), 78.6 (C5), 75.2 (C2), 71.6 (C10), 55.4 (C15), 34.5 (C4), 13.9 (C9). − MS (80 °C); *m*/*z*: 276 (1) [M^+], 155 (3), 137 (2), 122 (27), 121 (100), 110 (2), 95 (50), 91 (12). − HRMS: calcd. for $C_{16}H_{20}O_4$ [M^+] 276.1360; found 276.1362.

(+)-(1*R*,2*R*,3*S*,4*S*,5*R*)-2β-(*p*-Methoxybenzyloxy)-4β-methyl-3α-(triisopropylsilyloxy)-8-oxabicyclo[3.2.1]oct-6-ene [(+)-8]: 2,6-Lutidine (6.90 mL, 31.2 mmol) was added at −40 °C to a solution of alcohol **7** (7.30 g, 26.0 mmol) in DCM (100 mL); this was followed by the addition of TIPS triflate (6.8 mL) in DCM (27.2 mL). The mixture was allowed to reach 0 °C and the reaction was monitored by TLC. To complete the reaction, the mixture was cooled again and a further portion of TIPS triflate (113 μL) in DCM (450 μL) was added. After complete reaction, cyclohexane (110 mL) and $NaHCO_3$ solution (0.15 N) were added. The organic phase was washed with brine and the combined aqueous layers were extracted with DCM (3 × 200 mL). The combined organic phases were dried ($MgSO_4$), the solvent was removed and the crude product was purified by column chromatography (E/PE) to yield **(+)-8** (11.2 g, 97%), colourless solid. − $[\alpha]_D^{20}$ = +18.6 (*c* = 1 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3056 cm^{-1}, 2940, 2864, 1612, 1512, 1464, 1248, 1144, 1104, 1064, 1012. − ^1H NMR: δ = 7.34 (m, 2 H, arom. H), 6.86 (m, 2 H, arom. H), 6.16 (s, 2 H, H7, H6), 4.80 (d, *J* = 12 Hz, 1 H, H10), 4.69 (s br, 1 H, H1), 4.61 (d, *J* = 12 Hz, 1 H, H10), 4.58 (s br, 1 H, H5), 4.25 (dd, *J* = 1, 5 Hz, 1 H, H3), 3.78 (s, 3 H, H17), 3.46 (dd, *J* = 2, 5 Hz, 1 H, H2), 1.79 (m, 1 H, H4), 1.05 {s, 21 H, H9, Si[CH(CH_3)$_2$]$_3$}, 1.03 {s, 3 H, Si[CH(CH_3)$_2$]$_3$}. − ^{13}C NMR: δ = 158.8 (C14), 133.4 (C7), 131.5 (C11), 130.5 (C6), 128.8 (C13, C15), 113.5 (C12, C16), 83.2 (C1), 80.8 (C5), 75.7 (C2), 72.4 (C10), 68.0 (C3), 55.1 (C15), 35.4 (C4), 17.6 {Si[CH(CH_3)$_2$]$_3$}, 13.8 (C9), 12.2 {Si[CH(CH_3)$_2$]$_3$}. − MS (100 °C); *m*/*z*: 432 (0) [M^+], 389 (6) [$M^+ - C_3H_7$), 311 (2), 269 (2), 201 (5), 122 (13), 121 (100), 115 (3), 95 (53), 84 (28), 77 (3), 69 (3). − FAB-MS; *m*/*z*: 455 (100) [M^++Na], 431 (87) [$M^+ - 1$], 389 (17), 325 (45), 295 (27), 157 (35).

(+)-(2*R*,3*S*,4*S*,5*R*,6*S*)-[2-(Hydroxymethyl)-3-*p*-(methoxybenzyloxy)-5-methyl-4-(triisopropylsilyloxy)tetrahydropyran-6-yl]methanol [(+)-9]: A solution of **(+)-8** (1.99 g, 4.6 mmol) in DCM/methanol (1:4, 40 mL) was ozonolyzed at −95 °C. The reaction was monitored by TLC. After complete reaction, N_2 was bubbled through the solution to destroy excess ozone. The ozonide was reduced with $NaBH_4$ (382 mg, 10.1 mmol) and the mixture was allowed to reach 0 °C within ca. 3 h. MTBE (50 mL) and sat. aq. NH_4Cl solution (50 mL) were added. The aqueous layer was saturated with NaCl and extracted with EA. The combined organic layers were dried ($MgSO_4$). After the solvent was removed, the crude product was purified by column chromatography (EE/PE) to give **(+)-9** (2.02, 94%), colorless foam. − $[\alpha]_D^{20}$ = +22.8 (*c* = 1 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3404 cm^{-1}, 2940, 2864, 1612, 1512, 1464, 1248, 1132, 1116, 1088, 1056. − ^1H NMR: δ = 7.19−6.82 (m, 4 H, arom. H), 4.52/4.41 (d, *J* = 11 Hz, 2 H, H10), 4.20 (m, 1 H, HOCH_2CH), 3.92−3.88 (m, 1 H, HOCH_2CH), 3.81 (dd, *J* = = 2, 12 Hz, 1 H, H8), 3.77 (s, 3 H, OCH_3), 3.71 (dd, *J* = = 2, 12 Hz, 1 H, H7), 3.65 (m, 1 H, H8), 3.63−3.59 (m, 1 H, H4), 3.50 (dd, *J* = 5, 12 Hz, 1 H, H7), 3.27 (m, 1 H, H3), 1.67 (m, 1 H, H5), 1.09−0.98 {m, 21 H, Si[CH(CH_3)$_2$]$_3$, H9}, 0.92 {d, *J* = 7 Hz, 3 H, Si[CH(CH_3)$_2$]$_3$}. − ^{13}C NMR: δ = 159.2 (C14), 130.2 (C11), 129.5 (C15, C13), 113.6 (C16, C12), 77.3 (C6), 76.2 (C2), 74.0 (C3), 72.9 (C4), 72.1 (C10), 63.2 (C8), 62.4 (C7), 55.2 (C17), 37.4 (C5), 18.5 {Si[CH(CH_3)$_2$]$_3$}, 13.9 (C9), 13.2 {Si[CH(CH_3)$_2$]$_3$}. − MS (50 °C); *m*/*z*: 468 (0) [M^+], 265 (4), 254 (5), 195 (3), 179 (2), 155 (2), 131 (3), 121 (100), 105 (45), 87 (10), 73 (9). − FAB-MS; *m*/*z*: 491 (27) [M^+ + Na], 221 (6), 147 (12), 133 (6), 121 (100).

(+)-(2*R*,3*S*,4*S*,5*R*,6*S*)-[10-*p*-(Methoxyphenyl)-5-methyl-4-(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3]dioxin-6-yl]methanol [(+)-10]: A reaction flask was dried (heat gun) and charged with activated molecular sieves (3 Å, approx. 2 g) and DDQ (909 mg, 4.00 mmol) under a stream of argon. DCM (40 mL, degassed) was added. Diol **(+)-9** (937 mg, 2 mmol) in DCM (20 mL, degassed) was added dropwise at −60 °C. The reaction mixture turned dark-green immediately. The mixture was allowed to reach 0 °C within 4 h, then MTBE (50 mL) and sat. aq. $NaHCO_3$ solution (25 mL) were added. After filtration, the organic layer was washed with water and brine. The aqueous phase was extracted with MTBE and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography (MTBE/PE) to afford **(+)-10** (762 mg, 82%), colorless, viscous oil. − ^1H NMR: δ = 7.40 (m, 2 H, arom. H), 6.87 (m, 2 H, arom. H), 5.48 (s, 1 H, H10), 4.36 (dd, *J* = = 5, 10 Hz, 1 H, H8), 4.03 (dd, *J* = = 5, 10 Hz, 1 H, H8), 3.99 (t, *J* = = 5 Hz, 1 H, H3), 3.80 (s, 3 H, H17), 3.76 (dd, *J* = = 2, 12 Hz, 1 H, H7), 3.69 (dd, *J* = = 4, 12 Hz, 1 H, H7), 3.63 (t, *J* = = 10 Hz, 1 H, H4), 3.54 (m, 1 H, H2), 3.50 (m, 1 H, H6), 2.10 (br. s, 1 H, OH), 1.84 (m, 1 H, H5), 1.09−0.98 [m, 21 H, Si(CH_3)$_2$]$_3$, H9), 0.92 {d, *J* = 7 Hz, 3 H, Si[CH(CH_3)$_2$]$_3$}. − ^{13}C NMR: δ = 159.9 (C14), 130.2 (C11), 127.5 (C15, C13), 113.4 (C16, C12), 102.1 (C10), 81.7 (C3), 77.4 (C2), 71.1 (C6), 69.5 (C8), 65.5 (C4), 63.4 (C7), 55.2 (C17), 37.3 (C5), 18.6 {Si[CH(CH_3)$_2$]$_3$}, 14.0 (C9), 13.3 Si{CH[CH$_3$)$_2$]$_3$}.

(+)-(2*R*,3*S*,4*S*,5*R*,6*S*)-[10-(*p*-Methoxyphenyl)-5-methyl-4-(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3]dioxin-6-yl]carbaldehyde [(+)-11]: A mixture of **(+)-10** (760 mg, 1.60 mmol), NMO (281 mg, 2.40 mmol) and activated molecular sieves (3 Å) in DCM (16 mL) was stirred for 10 min under N_2. Then Pr_4NRuO_4 (TPAP) (34 mg, 0.096 mmol) was added and stirring was continued for 1 h. The reaction mixture was filtered through a short column (silica gel, MTBE/PE) to give **(+)-11** (590 mg, 79%), colorless, viscous oil. − $[\alpha]_D^{20}$ = +19.6 (*c* = 1 in $CHCl_3$), 83% *ee* by NMR shift measurements. − IR (KBr): $\tilde{\nu}$ = 2940 cm^{-1}, 2864, 2740, 2036, 1740, 1616, 1516, 1464, 1384, 1216, 1148, 1080. − ^1H NMR: δ = 9.58 (m, 1 H, H7), 7.36 (m, 2 H, arom. H), 6.84 (m, 2 H, arom. H), 5.50 (s, 1 H, H10), 4.35 (dd, *J* = 5, 10 Hz, 1 H, H8), 4.27 (m, 1 H, H6), 4.09 (dd, *J* = 5, 10 Hz, 1 H, H8), 4.01 (dd, *J* = 2, 10 Hz, 1 H, H2), 3.79 (s, 3 H, H17), 3.71 (t, *J* = 10 Hz, 1 H, H3), 3.56 (dd, *J* = 2,

10 Hz, 1 H, H4), 1.94 (m, 1 H, H5), 1.12−0.98 {m, 24 H, H9, Si[C*H*(CH_3)$_2$]$_3$}. − ^{13}C NMR: δ = 200.3 (C7), 159.9 (C14), 130.2 (C11), 127.3 (C15, C13), 113.1 (C16, C12), 101.8 (C10), 81.0 (C3), 80.8 (C2), 71.2 (C6), 69.2 (C8), 64.6 (C4), 55.2 (C7), 37.7 (C5), 18.3 {Si[CH(*C*H_3)$_2$]$_3$}, 13.1 {Si[*C*H(CH$_3$)$_2$]$_3$}, 12.7 (C9). − MS (120 °C); *m/z*: 464 (0) [M$^+$], 421 (100) [M$^+$-C_3H_7], 286 (15), 267 (3), 242 (4), 241 (23), 199 (33), 187 (9), 159 (9), 135 (11), 121 (46), 103 (12), 75 (15). − HRMS: calcd. for $C_{25}H_{40}O_6Si$ [M$^+$] 421.2048; found 421.2046.

1,1,3,3-Tetrabromopropanone (12). − Step A: HBr (51 mL, 0.45 mol, 48% aqueous solution) was added at 0 °C to acetone (110 mL, 1.5 mol). Bromine (310 mL, 5.9 mol) was added dropwise over ca. 3 h to the well-stirred solution. The mixture was cooled until the evolution of HBr ceased (ca. 2 h) and was then stirred for 10 d at room temperature with exclusion of light. Usually the product precipitates as an orange solid. The reaction mixture was shock-frozen with liquid N_2. After 3−4 h at room temperature, the supernatant aqueous layer was decanted and the waxy residue was suction-filtered (exposure to metallic surfaces and apparatus should be avoided during workup). The filter cake was washed several times with ice-cold PE until the filtrate became colorless. The resulting white solid was dried (oil pump) to afford **12**, 499 g (89%); m.p. 38 °C (see Note 1). − IR (KBr): $\tilde{\nu}$ = 3009 cm^{-1}, 1734, 1270, 1219, 1140, 1089, 1027. − ^{1}H NMR: δ = 6.35 (s, 2 H). − ^{13}C NMR: δ = 183.3 (C=O), 34.0 (CH). − MS; *m/z*: 378 (1), 377 (2), 376 (6), 374(8) [M$^+$], 215 (7), 203 (48), 210 (90), 199 (50), 175 (40), 173 (77), 133 (13), 123 (63), 122 (100), 121 (63), 120 (98).

8-Oxabicyclo[3.2.1]oct-6-en-3-one (1). − Step B: A 1-L flask was charged with activated zinc dust (35.9 g, 550 mmol) (obtained by brief treatment with dil. HCl, washing with water, acetone, E and drying), heated, and flushed with N_2. Furan (43.7 mL, 600 mmol) in THF (100 mL) was added. A solution of **12** (187 g, 500 mol) and triethyl borate (110 mL, 650 mmol) in THF (100 mL) was added dropwise over 30 min to this suspension. The progress of the reaction was maintained by temperature control. After addition of 80% of the tetrabromopropanone/triethyl borate solution, bromine (250 μL) was added (see Note 2). After complete addition, the temperature of the mixture reached 32 °C. The mixture was stirred for 30 min and was heated slightly. After 5 min, the exothermic reaction started. If necessary, the dark-brown to black reaction mixture was cooled with an ice-bath to avoid the reaction getting out of control. The preferred reaction temperature is above that of boiling tetrahydrofuran (see Note 3). The mixture was stirred for 1 h at room temp. and was then cooled to −15 °C. Ice-cold water (300 mL) was added, and the mixture was stirred for 20 min at room temp. The mixture was filtered, the residue was washed several times with E (altogether 1200 mL), and the combined organic phases were washed with water (2 × 200 mL) and brine (400 mL). The aqueous layer was re-extracted with E (3 × 200 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated (max. 30 °C). The residue (209 g) was dissolved in MeOH (125 mL). − **Step C:** Zinc dust (114 g, 1.74 mol) was added under vigorous stirring (KPG stirrer) to a refluxing solution of copper acetate (6.5 g, 325 mmol) in glacial acetic acid (166 mL). After 5 min, the mixture was cooled to room temperature and the supernatant liquid was decanted. The Zn/Cu couple was washed with glacial acetic acid (200 mL), water (200 mL), acetone (200 mL), and E (3 × 200 mL) and was then dried (oil pump). To a suspension of the resulting Zn/Cu couple and NH_4Cl (125.7 g, 2.35 mol) in MeOH (500 mL) was added a small portion of cycloaddition product in MeOH (ca. 10%) at −78 °C. After 15 min at −78 °C, the mixture was placed into an ice bath and addition of brominated cycloadduct was continued (temperature of the reaction mixture: 0−10 °C, see Note 4). After complete addition, the mixture was stirred for 1 h at room temperature; it was then cooled to 0 °C and suction-filtered. The residue was washed with several portions of E. The combined organic phases were washed once with brine (500 mL) (see Note 5) and the aqueous layer was re-extracted with $CHCl_3$ (5 × 300 mL). The combined organic phases were dried ($MgSO_4$), concentrated and then filtered through solid K_2CO_3 (see Note 6). The residue was washed with $CHCl_3$, the solvent was removed and the crude product was purified by column chromatography (silica gel, solvent E/PE, 1:10) to afford **1** (31−34.9 g, 52−56%), m.p. 38 °C, the aqueous solution of which was neutral to pH indicator paper. − IR (KBr): $\tilde{\nu}$ = 2969 cm^{-1}, 2909, 1713, 1246, 1039. − ^{1}H NMR: δ = 6.27 (s, 2 H, H6, H7), 5.04 (d, *J* = 5, 2 H, H1, H5), 2.76 (dd, *J* = 5, 16.6, 2 H, $H2_{ax}$, $H4_{ax}$), 2.34 (dd, *J* = 0.6, 16.6, 2 H, $H2_{eq}$, $H4_{eq}$). − ^{13}C NMR: δ = 205.3 (C3), 133.3 (C6, C7), 77.1 (C1, C5), 46.5 (C2, C4).

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