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Chemoenzymatic Taxanes Approach Using Both Enantiomers of the Same Building Block. 2. Taxol CD Ring Unit

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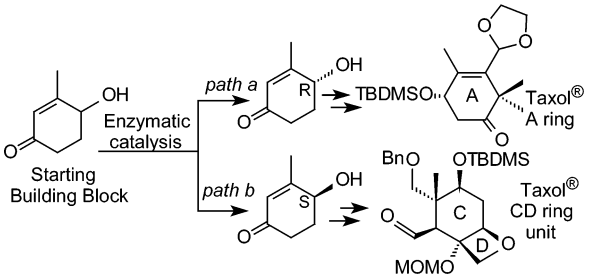

The enantioselective synthesis of the Taxol CD ring unit has been achieved starting from an enantiopure building block, the enantiomer of those previously utilized in the synthesis of the A ring unit. The key features of the present synthesis are astute use of both enantiomers of the same building block and complete control in the construction of five consecutive chiral centers.

Paclitaxel (Taxol, Figure 1),[1] a tetracyclic diterpenoid originally isolated[2] from the bark of the Pacific yew tree *Taxus brevifolia*, and its synthetic analogue docetaxel (Taxotere, Figure 1),[3] have attracted considerable interest owing to their remarkable chemotherapeutic activities. The low natural availability of Taxol has stimulated intense attention from synthetic chemists, and to date, six total syntheses have been accomplished.[4] Works focused on the structure−activity relationships (SAR)[1,5] have revealed that the C-4 acetoxy group with the oxetane,[6] the C-2 benzoyloxy group,[7] and the C-2′, C-3′ substituents at the C-13 side chain[8] are essential for the antitumor activity. In this context, convenient access to the fully functionalized A ring and CD ring unit for the construction of the sterically congested eight-membered B ring of Taxol, or analogues with a comparable biological profile, remain necessary.

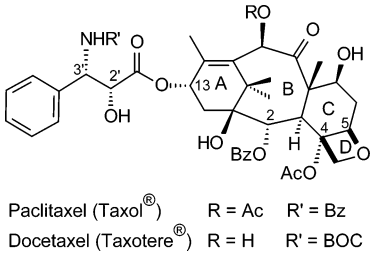

FIGURE 1. Structures of paclitaxel (Taxol) and docetaxel (Taxotere).

Driven by the increased demand of chiral drugs in enantiomerically pure form, the synthesis of enantiopure compounds has emerged into one of the most important fields of organic synthesis. In this context, catalytic asymmetric synthesis, including both metal- or enzyme-catalyzed reactions, has been a highly active area of research. Today, kinetic resolution of racemates mediated by enzymes has become an efficient process and is a

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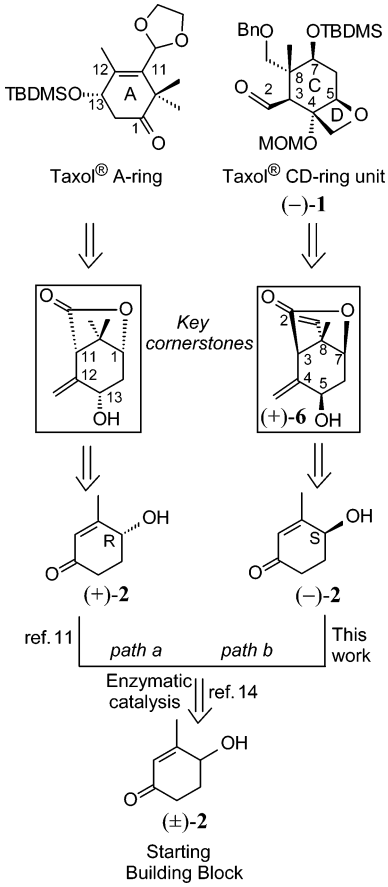
valuable tool.[9] Despite its widespread use, one obvious limitation with this type of enzymatic resolution is that the maximum theorical yield of each enantiomer is limited to 50%, and in the majority of processes, only one stereomer is desired and there is little or no use for the other.[10]

Examining the absolute configuration of Taxol, and as part of an A + C connection to form the central B ring[4a,b] (Figure 1), we observed that we could turn into an advantage this limitation using both enantiomers of the same building block to develop concise and efficient routes to enantiomerically pure targets (Scheme 1, taxoid numbering). Following this methodology, we previously

SCHEME 1. Retrosynthetic Analysis of Taxol A Ring and CD Ring Unit



reported an entry to the fully functionalized A ring unit[11] (Scheme 1, path a). We present herein a synthesis of the Taxol CD ring unit[12] that demonstrates the validity of our thinking (Scheme 1, path b).

Recently, we developed a stereocontrolled approach toward highly oxygenated taxane C and CD ring unit precursors.[13] Following the published achiral five-step procedure, the enantioselective synthesis of (+)-**6** is described in Scheme 2. Our starting material was (*S*)-(−)-**2** whose absolute stereochemistry[14] correlates correctly with the C-7-hydroxylated center of taxoids. This

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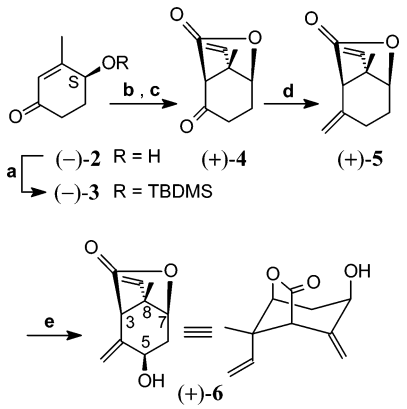
SCHEME 2[a]



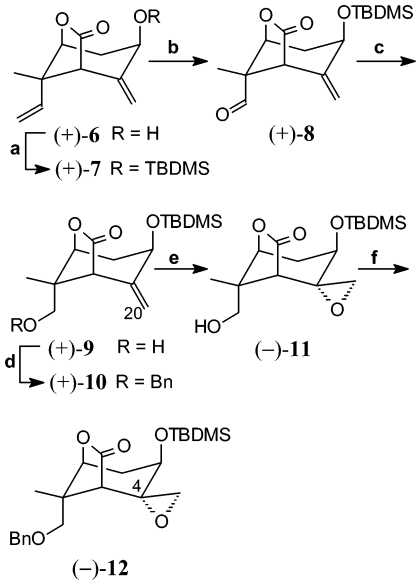
[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt, (96%); (b) CH_2=CHMgBr, CuBr.SMe_2, THF, −78 °C then HMPA and $NCCO_2Me$, −78 °C to rt (81%); (c) 1.2 equiv. *p*-TsOH·H_2O, toluene, reflux (92%); (d) 2.5 equiv of $Ph_3P^+MeI^-$, *t*-BuOK, toluene, reflux (83%); (e) cat. SeO_2, cat. salicylic acid, *t*-BuOOH 70% in water, CH_2Cl_2, reflux (85%).

stereocenter will control the relative (and consequently the absolute) configuration of the remaining centers. The TBDMS (*tert*-butyldimethylsilane)[15]-protected ketol (−)-**3** was converted to (+)-**4** by the copper catalyzed 1,4-addition of vinylmagnesium bromide followed by quenching with methylcyanoformate[16] and treatment of the crude product by *p*-TsOH·H_2O. Wittig olefination of (+)-**4** and stereoselective hydroxylation of (+)-**5** using catalytic selenium dioxide and *t*-BuOOH afforded (+)-**6** as a single stereomer. The target cornerstone (+)-**6** presents the correct C-3, C-5, C-7, and C-8 absolute configurations of taxoids.

With (+)-**6** in hand, Schemes 3 and 4 outline the methodology developed within our group to construct the CD ring unit in a stereocontrolled manner and with the functionalities suitable for elaboration into the Taxol framework. Protection of the secondary alcohol as a TBDS ether gave (+)-**7**. Chemoselective oxidative cleavage of the vinyl double bond using cat. OsO_4 and $NaIO_4$ in THF/water formed aldehyde (+)-**8** and reduction with $NaBH_4$ in methanol furnished alcohol (+)-**9**. At this stage, our attention was directed toward the direct bromohydration of the exocyclic double bond using NBS and water. Our motive for forming the bromohydrin was to introduce directly the requisite leaving group on C-20. For this purpose, (+)-**9** was protected as the benzyl ether (+)-**10**, and the bromohydrin formation protocols[17] currently used were tried in different aqueous organic solvents (acetone, THF, toluene, dichloromethane). Unfortunately, they led to the formation of complex mixtures and the outcome of the reaction could not be clearly established. To solve this problem, we then turned our attention toward the possibility of forming the epoxide of (+)-**9** and to regioselectively cleave it to halohydrin.

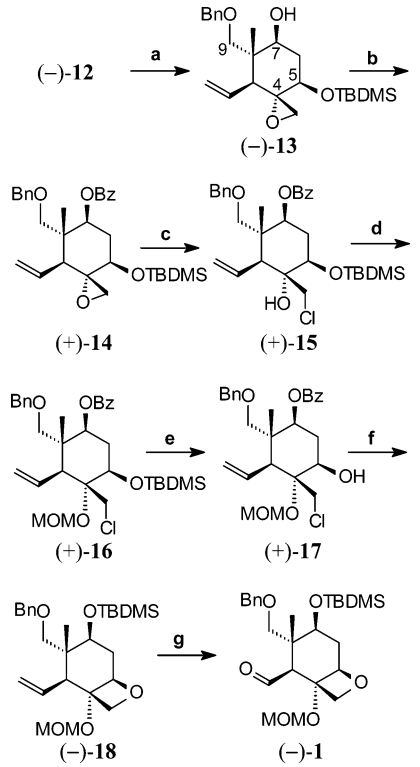
With a hydroxyl group present, the metal-catalyzed epoxidation of a remote double bond can occur if the intermediate, in which the hydroxyl group is coordinated

SCHEME 3[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt (80%); (b) cat. OsO_4, $NaIO_4$, THF/H_2O (3/1), rt (80%); (c) $NaBH_4$, MeOH, −78 °C (90%); (d) BnBr, NaH, NBu_4I, THF, rt (89%); (e) *m*-CPBA, CH_2Cl_2, 37 °C, 5 days (75%); (f) BnBr, NaH, NBu_4I, THF, rt (88%).

SCHEME 4[a]



[a] Reagents and conditions: (a) (i) DIBAL, toluene, −78 °C, (ii) Tebbe reagent, toluene/THF/Pyr, −78 °C to rt (76%); (b) BzCl, DMAP, Pyr, rt (86%); (c) Et_2AlCl, CH_2Cl_2, −78 °C (78%); (d) MOMCl, $(^iPr)_2NEt$, CH_2Cl_2, rt (91%); (e) TBAF, THF, rt (98%), (f) NaH, THF, 40 °C, then TBDMSCl, imidazole, 40 °C (71%); (g) cat. OsO_4, $NaIO_4$, THF/H_2O, rt (82%).

to the metal, can adopt a conformation which minimizes steric interactions when it delivers an oxygen atom to

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the double bond.[18] In this respect, a path using vanadium-catalyzed epoxidation of alcohol (+)-**9** according to the Sharpless procedure[19] was pursued but neither experiment proved fruitful, probably as a direct consequence of the size of the oxidant and the steric hindrance in the vicinity of the exocyclic double bond. So, with some reluctance due to the expected steric hindrance, we focused our attention on *m*-CPBA epoxidation. To our surprise and delight, α-epoxidation to give (−)-**11** could be accomplished efficiently and with perfect stereochemical control. The stereochemistry of (−)-**11** was not proven at this stage but unequivocally established through X-ray crystallography analysis carried out on the crystaline benzyl ether (−)-**12**. Under no conditions was any sign of the *β*-epoxide found. Concurrent studies of the *m*-CPBA epoxidation of (+)-**10** having the primary alcohol function protected as the benzyl ether showed a complete lack of reactivity and simple intermolecular epoxidation does not proceed. It was made clear that precoordination of the peracid to the remote trishomoallylic hydroxyl in (+)-**9**, which is a likely prerequisite to oxirane formation, is allowed in this case.

At this junction, we were mindful that the congested environment in the vicinity of the oxirane ring might again restrict the scope of feasible operations. So, the stereochemistry at C-4 being secured, it was decided that the lactone moiety would be opened at this stage. This was accomplished by a two-step procedure as follows (Scheme 4). Lactone (−)-**12** was reduced with DIBAL in toluene, and the resultant crude mixture of lactols (15% ratio of the opened aldehyde form, based on ^{1}H NMR analysis) underwent Tebbe olefination[20] to produce univocally (−)-**13** in 76% yield for two steps. In the target molecule, we needed to have the C-7 remaining hydroxyl group of (−)-**13** protected as a TBDMS blocking group in order to differentiate this site from the other two alcohol centers at C-4 and C-9. However, the presence of the C-5 TBDMS blocking group, susceptible to removal at a late stage, rendered this path incompatible at the present time. On the basis of these considerations, we decided to install a benzoate protecting group on the secondary alcohol because we were full of hope that this functionality could be removed and replaced during the oxetane ring formation conditions (NaH, THF) like precedence.[21] Fortunately, this will be so (vide infra). This transformation was accomplished in high yield on derivative (−)-**13** giving rise to benzoate ester (+)-**14**. The regioselective ring-opening of epoxides to vicinal halohydrins is a reaction of continued interest and a large variety of reagents are known.[22] Among them, diethylaluminum chloride is extremely useful for the ease of the procedure and the regio- and chemoselectivity observed.[23] The submission of (+)-**14** to this reagent afforded the desired chlorohydrin (+)-**15** in 78% yield. Next, protection of the tertiary alcohol as a methoxymethyl(MOM) ether[24] led to (+)-**16** (91% yield) and subsequent removal of the silyl group from compound (+)-**16** by exposure to TBAF[15] produced derivative (+)-**17** in 98% yield. Compound (+)-**17** was treated with NaH in DMF at 40 °C and the reaction was monitored by TLC. ^{1}H NMR analysis of aliquots showed that the fastest reaction was the removal of the benzoate ester.[21] After complete cyclization, excess TBDMSCl/imidazole were added to give (−)-**18** in 71% overall yield. The structural and stereochemical assignment of (−)-**18** were achieved through the unambiguous rationalization of ^{1}H- and ^{13}C NMR resonances using a combinaison of HMBC, HMQC, DEPT, and NOESY techniques. In particular, a NOESY correlation between the 8*β*-Me (δ_H = 1.02 ppm) and the 6*β*-H (δ_H = 1.93 ppm) and one proton 20-H of the oxetane cycle (δ_H = 4.66 ppm) established the cis spatial orientation of these two protons and the methyl group (Figure 2). Furthermore, strong NOESY correlations between 3α-H (δ_H = 2.85 ppm) and 7α-H (δ_H = 3.94 ppm), 7α-H and 6α-H (δ_H = 2.29 ppm), and in addition, 6α-H and 5α-H (δ_H = 4.91 ppm) established the cis spatial orientation of these protons on the opposite side. Finally, oxidative cleavage of (−)-**18** using cat. OsO_4 and $NaIO_4$ gave the target molecule (−)-**1** in 82% yield.

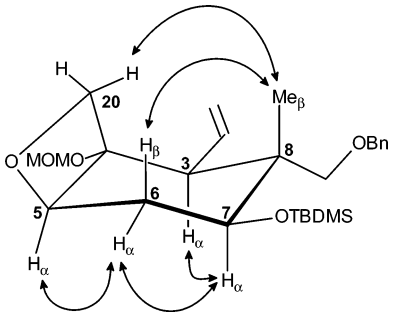

FIGURE 2. Selected NOESY interactions for (−)-**18**.

In summary, five consecutive chiral centers on the fully functionalized Taxol CD ring unit have been successfully generated from only the one chiral center of the keto alcohol (−)-**2** obtained by enzymatic resolution and which correlates correctly with the C-7 hydroxylated center of taxoids. This approach is complementary with our early synthesis of Taxol A ring unit starting from (+)-**2** and discloses the possibility to access to these two substructures using both enantiomers of the same building block.

Experimental Section

(1*R*,3*R*,5*S*,8*S*)-3-(*tert*-Butyldimethylsilyloxy)-8-methyl-2-methylene-7-oxo-6-oxabicyclo[3.2.1]octane-8-carbaldehyde (+)-8. To a stirred solution of (+)-**7** (1.55 g, 5.02 mmol) in 60 mL of a THF/water (3/1) mixture was added a catalytic amount of OsO_4 (4.0 wt. % in water). The solution turned black, sodium metaperiodate (3.20 g, 15.0 mmol) was added, and the

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reaction mixture was stirred for 6 h at rt under an argon atmosphere. After dilution with water and extraction with CH_2Cl_2, the combined extracts were dried with $MgSO_4$ and concentrated in vacuo to afford crude aldehyde. After purification by column chromatography and crystallization from Et_2O−hexane, 1.25 g (80%) of pure aldehyde (+)-**8** was obtained as white crystals. Mp = 75 °C. $[\alpha]^{25}_D = +80.2$ (*c* 1.0, $CHCl_3$). IR (KBr): ν 3078, 2723, 1773, 1649, 891 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.50 (s, 1H), 5.10 (s, 1H), 5.07 (s, 1H), 4.63 (br-d, J = 3.5 Hz, 1H), 4.31 (d, J = 5.2 Hz, 1H), 3.20 (s, 1H), 2.32 (ddd, J = 15.4, 5.2, 1.5 Hz, 1H), 2.16 (dd, J = 15.4, 3.5 Hz, 1H), 1.32 (s, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3 (CH), 173.2 (C), 142.6 (C), 116.1 (CH_2), 81.2 (CH), 69.0 (CH), 57.1 (C), 53.2 (CH), 34.3 (CH_2), 25.4 (CH_3), 18.6 (CH_3), 17.8 (C), −4.8 (CH_3), −5.1 (CH_3). Anal. Calcd for $C_{16}H_{26}O_4Si$: C, 61.90; H, 8.44. Found: C, 62.19; H 8.39.

(3*S*,4*S*,5*R*,6*S*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-5-hydroxymethyl-5-methyl-1-oxaspiro[2.5]octane-4,6-carbolactone (−)-11. To a stirred solution of (+)-**9** (1.00 g, 3.20 mmol) in CH_2Cl_2 (60 mL) was added *m*-CPBA (1.58 g, 6.40 mmol, 70 wt % in water) at rt. The solution was stirred at 37 °C for 5 days. The mixture was poured into a solution of Na_2SO_3 (3.23 g, 25.6 mmol) and extracted with CH_2Cl_2. The organic layer were combined, washed with a saturated solution of $NaHCO_3$, dried, filtered, and concentrated to afford after purification by column chromatography 788 mg (75%) of (−)-**11**. Mp = 110 °C. $[\alpha]^{25}_D = -8.0$ (*c* 1.0, $CHCl_3$). IR (KBr): ν 3431, 1763, 1259, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.48 (br-d, J = 4.0 Hz, 1H), 3.90 and 3.63 (ABX, J = 11.6, 7.9, 4.1 Hz, 2H), 3.55 (d, J = 5.5 Hz, 1H), 2.90 and 2.73 (AB, J = 4.2 Hz, 2H), 2.24 (ddd, J = 15.6, 5.5, 1.5 Hz, 1H), 2.09 (dd, J = 15.6, 4.0 Hz, 1H), 1.92 (br-s, 1H), 1.29 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), −0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (C), 82.2 (CH), 70.6 (CH), 64.6 (CH_2), 60.0 (C), 51.9 (CH), 51.6 (CH_2), 48.0 (C), 32.9 (CH_2), 25.3 (3 CH_3), 21.0 (CH_3), 17.6 (C), −4.7 (CH_3), −4.9 (CH_3). Anal. Calcd for $C_{16}H_{28}O_5Si$: C, 58.50; H, 8.59. Found: C, 58.89; H 8.64.

(3*S*,4*S*,5*R*,6*S*,8*R*)-5-Benzyloxymethyl-8-(*tert*-butyldimethylsilyloxy)-5-methyl-4-vinyl-1-oxaspiro[2.5]octan-6-ol (−)-13. A 780 mg portion (1.86 mmol) of (−)-**12** was dissolved in 30 mL of anhydrous toluene, and a 1 M toluene solution of diisobutylaluminum hydride (4.60 mL, 4.60 mmol) was added dropwise at −80 °C under an argon atmosphere. The reaction mixture was stirred for 20 min at this temperature, quenched with $Na_2SO_4 \cdot 10H_2O$ (4.7 g) and Celite (4.7 g), and allowed to rise to rt. Filtration through a pad of $MgSO_4$ and concentration gave 767 mg of a mixture of lactols and aldehyde as a clear oil. This mixture was used for the next reaction without further purification. To a stirred solution of above mixture of lactols and aldehyde (767 mg) in benzene (10 mL) were added tetrahydrofuran (2.5 mL) and pyridine (100 μL). The resulting mixture was cooled to −78 °C, Tebbe reagent (4.46 mL of 0.5 M in benzene, 2.23 mmol) was added, and the solution was allowed to rise to rt overnight. The reaction mixture was quenched with 15% sodium hydroxide solution (2.5 mL) and diluted with ether. The organic phase was dried, filtered through a Celite pad, and evaporated. Purification by column chromatography gave 592 mg of alcohol (−)-**13** (76% yield from compound (−)-**12**). $[\alpha]^{25}_D = -17.7$ (*c* 1.0, $CHCl_3$). IR (film): ν 3429, 3061, 1258, 1053 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34−7.27 (m, 5H), 5.44 (ddd, J = 16.6, 10.1, 10.1 Hz, 1H), 5.15 (dd, J = 10.1, 2.0 Hz, 1H), 5.08 (dd, J = 16.6, 2.0 Hz, 1H), 4.47 (s, 2H), 3.89 (dd, J = 12.1, 4.8 Hz, 1H), 3.78 (dd, J = 12.1, 4.8 Hz, 1H), 3.39 and 3.27 (AB, J = 9.1 Hz, 2H), 2.97 and 2.56 (AB, J = 5.3 Hz, 2H), 2.33 (d, J = 10.1 Hz, 1H), 2.11 (ddd, J = 12.1, 4.8, 4.8 Hz, 1H), 1.70 (ddd, J = 12.1, 12.1, 12.1 Hz, 1H), 0.97 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7 (C), 130.1 (CH), 128.5 (2 CH), 127.8 (CH), 127.5 (2 CH), 121.2 (CH_2), 78.2 (CH), 73.6 (CH_2), 72.2 (CH_2), 67.8 (CH), 59.9 (C), 47.3 (CH), 44.2 (CH_2), 43.0 (C), 38.6 (CH_2), 25.7 (3 CH_3), 18.1 (C), 10.8 (CH_3), −5.0 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{24}H_{38}O_4Si$: C, 68.86; H, 9.15. Found: C, 68.49; H 9.12.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-4-chloromethyl-4-hydroxy-2-methyl-3-vinylcyclohexyl benzoate (+)-15. Et_2AlCl (5.50 mL of 1 M in hexane, 5.50 mmol) was added dropwise to a solution of (+)-**14** (520 mg, 0.99 mmol) in CH_2Cl_2 (50 mL) at −78 °C, and the reaction mixture was allowed reach rt overnight. The mixture was quenched with 5% HCl, and the organic layer was washed with 10% Na_2CO_3 and brine and dried. Solvent evaporation afforded a residue which was purified by column chromatography to afford 432 mg (78%) of chlorohydrin (+)-**15**. $[\alpha]^{25}_D = +32.6$ (*c* 1.0, $CHCl_3$). IR (film): ν 3409, 3098, 1251, 1053, 721 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 7.3 Hz, 2H), 7.56 (br-t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 7.26−7.18 (m, 5H), 6.23 (ddd, J = 16.5, 10.7, 10.7 Hz, 1H), 5.35 (dd, J = 8.8, 4.4 Hz, 1H), 5.21 (dd, J = 10.7, 2.1 Hz, 1H), 5.19 (dd, J = 16.5, 2.1 Hz, 1H), 4.45 and 4.39 (AB, J = 12.1 Hz, 2H), 3.97 and 3.84 (AB, J = 11.5 Hz, 2H), 3.83 (dd, J = 8.8, 4.4 Hz, 1H), 3.27 and 3.21 (AB, J = 9.0 Hz, 2H), 2.96 (s, OH), 2.60 (d, J = 10.7 Hz, 1H), 2.27 (ddd, J = 14.2, 4.4, 4.4 Hz, 1H), 1.87 (ddd, J = 14.2, 8.8, 8.8 Hz, 1H), 1.05 (s, 3H), 0.80 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7 (C), 138.1 (C), 134.3 (CH), 132.9 (CH), 130.5 (C), 129.6 (2 CH), 128.3 (2 CH), 128.2 (2 CH), 127.6 (2 CH), 127.5 (CH), 119.4 (CH_2), 74.0 (CH_2), 73.8 (C), 73.6 (CH), 73.1 (CH_2), 71.6 (CH), 52.8 (CH), 50.3 (CH_2), 41.4 (C), 32.5 (CH_2), 25.7 (3 CH_3), 17.9 (C), 16.4 (CH_3), −4.4 (CH_3), −5.1 (CH_3). Anal. Calcd for $C_{31}H_{43}ClO_5Si$: C, 66.58; H, 7.75. Found: C, 66.81; H 7.79.

(1*S*,2*S*,3*R*,4*S*,6*R*)-3-Benzyloxymethyl-1-methoxymethoxy-3-methyl-2-vinyl-7-oxabicyclo[4.2.0]oct-4-yloxy-*tert*-butyldimethylsilane (−)-18. To a suspension of NaH (50% dispersion, 46 mg, 0.94 mmol) in DMF (4 mL) was added dropwise at rt a DMF solution (3 mL) of alcohol (+)-**17** (230 mg, 0.47 mmol), and the mixture was stirred at 40 °C. After 2 h, the reaction was complete (aliquots). Imidazole (800 mg, 11.8 mmol) and TBDMSCl (1.42 g, 9.42 mmol) were then added, and the solution was stirred again at 40 °C for 12 h. The reaction mixture was poured into water, and the resulting aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with H_2O and brine, dried ($MgSO_4$), concentrated, and purified by column chromatography to afford 155 mg of oxetane (−)-**18** (71%). $[\alpha]^{25}_D = -6.1$ (*c* 1.0, $CHCl_3$). IR (film): ν 3049, 3053, 1252, 1078 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40−7.24 (m, 5H), 5.69 (ddd, J = 16.9, 10.2, 9.3 Hz, 1H), 5.14 (dd, J = 10.2, 2.1 Hz, 1H), 5.06 (dd, J = 16.9, 2.1 Hz, 1H), 4.91 (br-dd, J = 9.2, 3.8 Hz, 1H), 4.90 and 4.76 (AB, J = 7.3 Hz, 2H), 4.66 and 4.55 (ABX, J = 7.7, 1.2, 0.8 Hz, 2H), 4.46 and 4.28 (AB, J = 11.6 Hz, 2H), 3.94 (dd, J = 11.2, 6.4 Hz, 1H), 3.39 and 3.05 (AB, J = 8.6 Hz, 2H), 3.39 (s, 3H), 2.85 (d, J = 9.3 Hz, 1H), 2.29 (ddd, J = 15.0, 9.2, 6.4 Hz, 1H), 1.93 (ddd, J = 15.0, 11.2, 3.8 Hz, 1H), 1.02 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6 (C), 132.7 (CH), 128.1 (2 CH), 127.5 (2 CH), 127.3 (CH), 120.1 (CH_2), 91.9 (CH_2), 84.3, (CH), 80.0 (C), 75.9 (CH_2), 72.7 (CH_2), 72.3 (CH_2), 68.1 (CH), 55.6 (CH_3), 47.4 (CH), 42.1 (C), 37.0 (CH_2), 25.8 (3 CH_3), 18.0 (C), 10.8 (CH_3), −4.1 (CH_3), −5.1 (CH_3). Anal. Calcd for $C_{26}H_{42}O_5Si$: C, 67.49; H, 9.15. Found: C, 67.87; H 9.12.

(1*S*,2*S*,3*R*,4*S*,6*R*)-3-Benzyloxymethyl-4-(*tert*-butyldimethylsilyloxy)-1-methoxymethoxy-3-methyl-7-oxabicyclo[4.2.0]octane-2-carbaldehyde (−)-1. To a stirred solution of (−)-**18** (100 mg, 0.22 mmol) in 8.0 mL of a THF/water (3/1) mixture was added OsO_4 (0.11 mmol, 4 wt % in water). The solution turned black, sodium metaperiodate (140 mg, 0.66 mmol) was added, and the reaction mixture was stirred for 4 days at rt under an argon atmosphere. After dilution with water and extraction with CH_2Cl_2, the combined extracts were dried with $MgSO_4$ and concentrated in vacuo to afford crude aldehyde. After purification by column chromatography and crystallization from Et_2O−hexane, 82 mg (82%) of pure alde-

hyde (−)-**1** was obtained as a clear oil. $[\alpha]^{25}_{D} = -24.7$ (*c* 1.0, $CHCl_3$). IR (film): ν 2847, 1704, 1391, 1257, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.68 (d, J = 1.1 Hz, 1H), 7.35−7.28 (m, 5H), 4.86 and 4.75 (AB, J = 7.4 Hz, 2H), 4.83 and 4.73 (br-AB, J = 8.7 Hz, 2H), 4.82 (partially overlaped br-dd, J = 9.0, 4.4 Hz, 1H), 4.60 and 4.39 (AB, J = 11.8 Hz, 2H), 3.89 (dd, J = 10.7, 5.6 Hz, 1H), 3.52 and 3.35 (AB, J = 9.3 Hz, 2H), 3.35 (s, 3H), 3.22 (br-s, 1H), 2.25 (ddd, J = 14.8, 9.0, 5.6 Hz, 1H), 1.97 (ddd, J = 14.8, 10.7, 4.4 Hz, 1H), 1.11 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0 (C), 138.0 (C), 128.4 (2 CH), 127.8 (CH), 127.7 (2 CH), 92.1 (CH_2), 84.4 (CH), 78.0 (C), 77.2 (CH_2), 73.1 (CH_2), 72.7 (CH_2), 68.4 (CH), 55.6 and 55.5 (CH_3/CH), 42.7 (C), 36.2 (CH_2), 25.8 (3 CH_3), 18.0 (C), 12.9 (CH_3), −4.1 (CH_3), −5.1 (CH_3). Anal. Calcd for $C_{25}H_{40}O_6Si$: C, 64.62; H, 8.68. Found: C, 64.94; H 8.64.

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Supporting Information Available: Experimental procedures as well as complete ^1H and ^{13}C NMR spectral data of compounds (−)-**3**, (+)-**4**, (+)-**5**, (+)-**6**, (+)-**7**, (+)-**9**, (−)-**12**, (+)-**14**, (+)-**16**, and (+)-**17**. Copies of the high-field ^1H NMR and ^{13}C NMR spectra of all compounds reported herein. NOESY experiments for compound (−)-**18**. X-ray crystal structure of (−)-**12** in CIF format and ORTEP view. This material is available free of charge via the Internet at http://pubs.acs.org.

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