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gem-Dihalocyclopropanes as Building Blocks in Natural-Product Synthesis: Enantioselective Total Syntheses of *ent*-Erythramine and 3-*epi*-Erythramine

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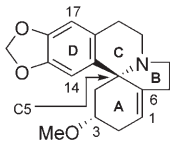
Abstract: *ent*-Erythramine ((−)-**1**), the enantiomer of the alkaloid erythramine, was prepared in 15 steps from known compounds. The first of three pivotal bond-forming steps in the synthesis was a Suzuki–Miyaura cross-coupling reaction of the starting materials to give a bis-silyl ether. The second involved silver(I)-induced electrocyclic ring opening of the *gem*-dichlorocyclopropane formed in the next step and trapping of the ensuing π-allyl cation by the tethered nitrogen atom to give, following cleavage of the allyloxycarbonyl protecting group, an approximately 5:6 mixture of the chromatographically separable diastereoisomeric spirocyclic products. In the third critical bond-forming reaction, the iodide formed from one of the diastereoisomers underwent a radical-addition/elimination reaction sequence that led to (−)-**1** in 89% yield. The application of the same sequence of transformations to the other diastereoisomer afforded 3-*epi*-(+)-erythramine (3-*epi*-(+)-**1**).

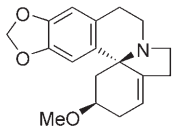
Keywords: alkaloids · cyclopropanes · radical reactions · spirocyclization · total synthesis

Introduction

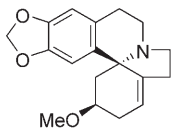
The crystalline compound (+)-erythramine ((+)-**1**) is a representative member of the subset of erythrina alkaloids that



(+)-**1**



(−)-**1**



3-*epi*-(+)-**1**

contain an aromatic D ring. Its structure was established by using a combination of NMR spectroscopy, mass spectrometry, chemical correlation, and biogenetic studies.[1] (+)-Erythramine has been isolated from a variety of plant sources, including the seeds of *Erythrina sandwicensis*, *E. subumbrans*, *E. cristagalli*, and *E. glauca*, as well as the pods and trunk bark of *E. lithiosperma* (Leguminosae).[1,2] Extracts of these and other plants that contain erythrina alkaloids have been used in indigenous medicine, and the alkaloids themselves have been shown to display a range of intriguing biological activities, including curare-like action (attributed to antagonistic effects exerted at neural acetylcholine receptors), hypnotic effects, cardiovascular activity, and molluscicidal properties.[1] Accordingly, a significant amount of effort has been directed towards the development of total syntheses of these natural products and various analogues.[3] Some impressive results have emerged, including those disclosed in very recent publications,[3c,d] which detail further elegant approaches to the ABCD ring system of these natural products. Despite such activity, a total synthesis of erythramine has yet to be reported. Herein, we describe a synthesis of its nonnatural enantiomer, (−)-**1**, by a protocol that will allow ready access to a range of alkaloids in the class and in either antipodal form. This study forms part of an ongoing program of our research group to exploit readily available but underutilized *gem*-dihalocyclopropanes as building blocks for the synthesis of biologically active natural products and their analogues.[4]

Our previously reported strategy[3b] for the construction of the ABCD ring system of the title alkaloids had not been employed hitherto in total synthesis. The pivotal steps associated with our approach to (−)-**1** are shown in Scheme 1. In the final stage of the D→ACD→ABCD ring-forming se-

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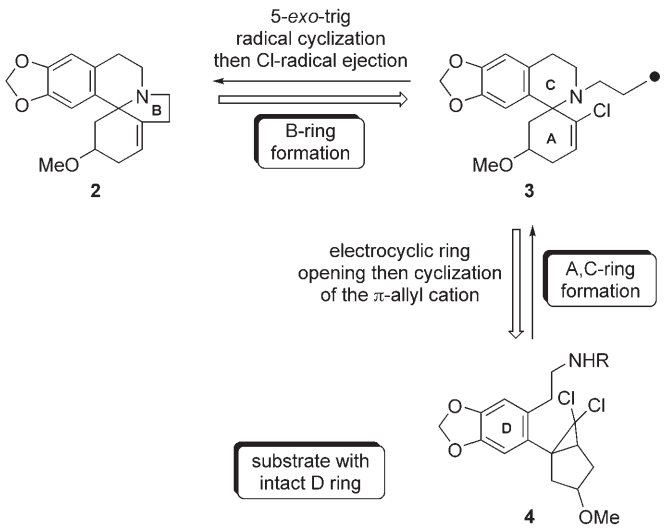


Scheme 1. Retrosynthetic analysis of the erythramine framework **2**.

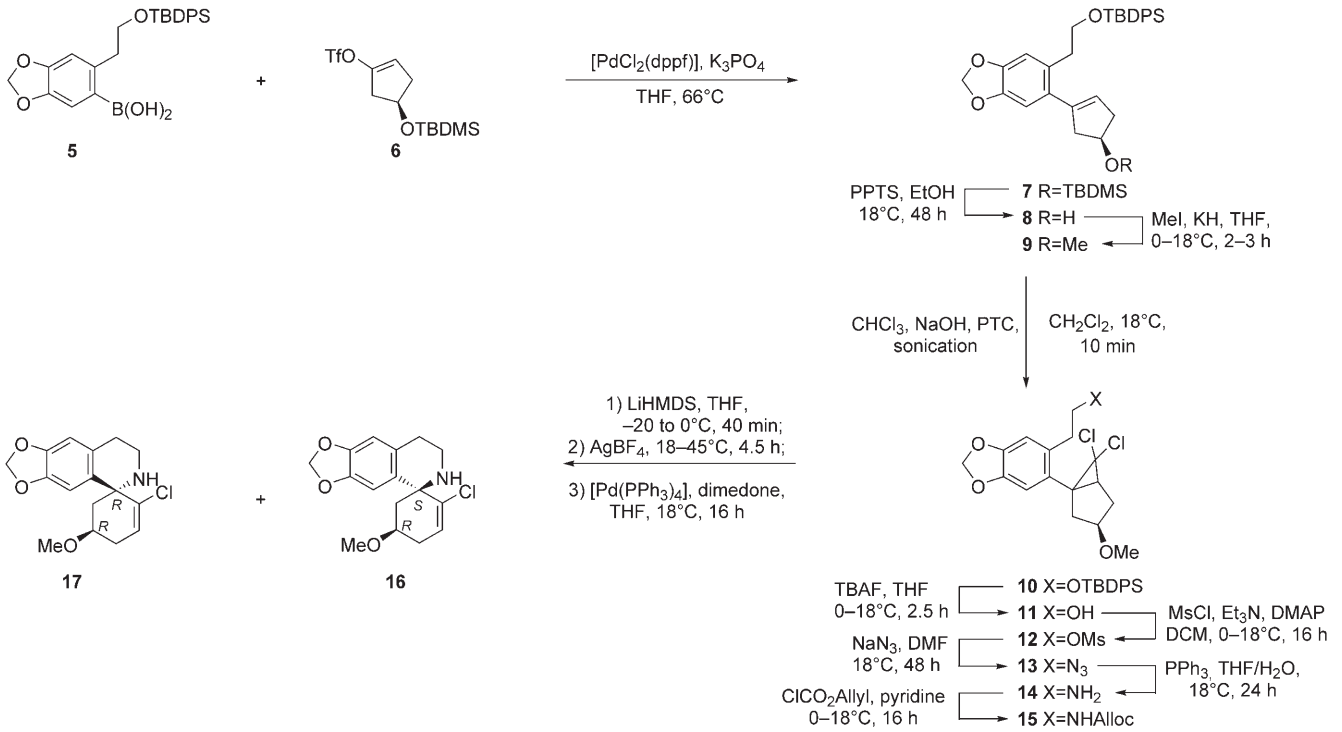
quence, a novel radical-addition/elimination process was expected to install the B ring with the formation of compound **2** from precursor **3**. The $\Delta^{1(6)}$ alkene required in the target compound (−)-**1** would also be incorporated in a regiospecific manner in this radical process. We planned to synthesize the precursor to radical **3** by treating the *gem*-dichlorocyclopropane **4** with a silver(I) salt. Thus, a π-allyl cation would be produced through electrocyclic ring opening of the strained three-membered ring and trapped by the pendant nitrogen atom. Such a sequence of events would deliver a spirocyclic product that incorporated the A and C rings of the erythrina alkaloids. Of course, a pivotal issue associated with the spirocyclization process is the potential capacity of the methoxy group in substrate **4** to exert some level of diastereoselectivity on the reaction and thus establish the required *cis* relationship between the amine and methoxy groups attached to the A ring.

Results and Discussion

A fundamental consideration in the initial phases of our research was the control of absolute configuration, and in particular whether or not the natural or nonnatural enantiomer of erythramine should be targeted. In the end we chose to prepare the latter compound because the biological properties of (+)-erythramine have been evaluated, whereas those of its enantiomer remain unexplored. Furthermore, if the chiral starting material is available in either enantiomeric form, then any synthesis of (−)-erythramine would also represent a route to the natural product, as proved to be the case.

Suzuki–Miyaura cross-coupling[5] of the reaction partners **5** and **6** under standard conditions gave the anticipated product **7** in 92% yield (Scheme 2). A route to substrate **5** had been developed during the course of our earlier model studies in this area,[3b] and compound **6** was accessible through chemoenzymatic techniques from cyclopentadiene.[6] The enantiomer of **6** can be prepared through modification of a procedure described by Paquette and co-workers.[7] The TBDMS group of the bis(silyl ether) **7** was removed selectively by using PPTS in ethanol, and the resulting alcohol **8** (71%) was subjected to O-methylation with methyl iodide in the presence of potassium hydride. The required methoxy-substituted cyclopentene **9** was thus obtained in quantitative yield. The treatment of alkene **9** with dichlorocarbene generated from chloroform under the phase-transfer conditions described by Makosza and Wawrzyniewicz,[8] with accompanying ultrasonication as recommended by Xu and Brinker,[9] afforded the anticipated *gem*-dichlorocyclopropane **10** (91%) as an approximately 2:1 mixture of diastereoisomers. As such carbene addition reactions are strongly influenced by steric effects, the isomer with an *anti* relationship between the methoxy and cyclopropyl groups was presumed to be the major. No effort was made to separate these compounds or their derivatives, because at the relevant point in the synthesis each diastereoisomer was expected to undergo electrocyclic ring opening to give the same π-allyl cation.

Following the assembly of the requisite carbon framework of the spirocyclization precursor **4** (Scheme 1), it was time to introduce the nitrogen-based functionality required as the nucleophile for trapping the cation generated by ring cleavage of the cyclopropyl residue. Our earlier model studies had established that an Alloc-protected primary amine was the most suitable group for this purpose. Accordingly, compound **10** was treated with tetra-*n*-butylammonium fluoride (TBAF) to provide the corresponding alcohol **11** (97%) as an approximately 2:1 mixture of diastereoisomers. This mixture was subjected to mesylation under the conditions defined by Crossland and Servis,[10] but with the additional use of DMAP as a catalyst. The resulting esters **12** (100%) were treated immediately with sodium azide in DMF at 18°C, and the corresponding mixture of azides **13** was obtained in 94% yield. A Staudinger reaction of **13** with triphenylphosphine in aqueous THF then provided the primary amine **14**,

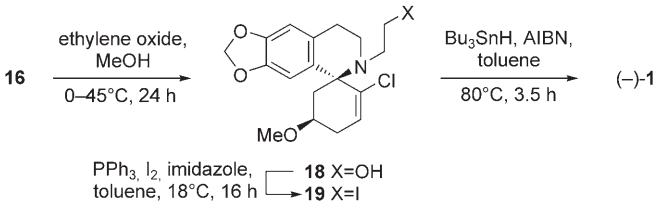


Scheme 2. Synthesis of the spirocyclization substrate **15** and its conversion into the spirocycles **16** and **17**. Alloc = allyloxycarbonyl, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, LiHMDS = lithium hexamethyldisilazide, Ms = methanesulfonyl, PTC = phase-transfer catalyst, PPTS = pyridinium *p*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, TBDMS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

which was not purified but, instead, treated immediately with allyl chloroformate in the presence of pyridine to afford the Alloc carbamate **15** (≡**4** in which R = Alloc) in 95% yield from **13** and as an approximately 2:1 mixture of diastereoisomers. The ^{13}C NMR (75 MHz) spectrum of compound **15** revealed twenty signals corresponding to the major diastereoisomer and a series of related resonances attributable to the minor isomer. The most conspicuous feature of the ^{1}H NMR (300 MHz) spectrum was the appearance of two singlets, at $\delta = 3.26$ and 3.19 ppm, which could be assigned to the hydrogen atoms of the methoxy group. The integration of these two signals indicated a 1:2 ratio of diastereoisomers.

We next investigated the ability of the *gem*-dichlorocyclopropane **15** to engage in the foreshadowed electrocyclic-ring-opening/nucleophilic-trapping sequence. On the basis of our earlier model study,[3b] compound **15** was first converted into its conjugate base (with LiHMDS), and this latter species was then treated with silver tetrafluoroborate to induce cleavage of the cyclopropane ring. The crude mixture thus obtained was treated with a source of Pd^0 and dimedone (conditions defined by Kunz and Unverzagt[11] for the removal of Alloc protecting groups from amines) to give the chromatographically separable diastereoisomeric spirocyclic products **16** and **17** in 26 and 30% yield, respectively. Although the spectroscopic data acquired for these compounds were fully consistent with the assigned structures, they did not enable the unequivocal assignment of configuration. Indeed, the configurations of these two compounds were eventually assigned by single-crystal X-ray analysis of a derivative of compound **16** (see below). The lack of selectivity associated with the transformation of substrate **15** into amines **16** and **17** is disappointing but perhaps unsurprising given the limited steric bulk of the methoxy group and its relative remoteness from the spirocenter that is being assembled.

The reaction sequence used for the elaboration of amine **16**, which incorporates the ACD ring system of the erythrina alkaloids, into the target compound (−)-**1** is shown in Scheme 3. Once again, the approach used was established in our earlier model studies.[3b] Thus, amine **16** was treated with ethylene oxide in methanol to produce the aminoalcohol **18** in 58% yield as a crystalline compound suitable for single-crystal X-ray analysis. The ORTEP representation of the crystal structure clearly reveals a *cis* relationship be-



Scheme 3. Completion of the synthesis of *ent*-erythramine ((−)-**1**). AIBN = azobisisobutyronitrile.

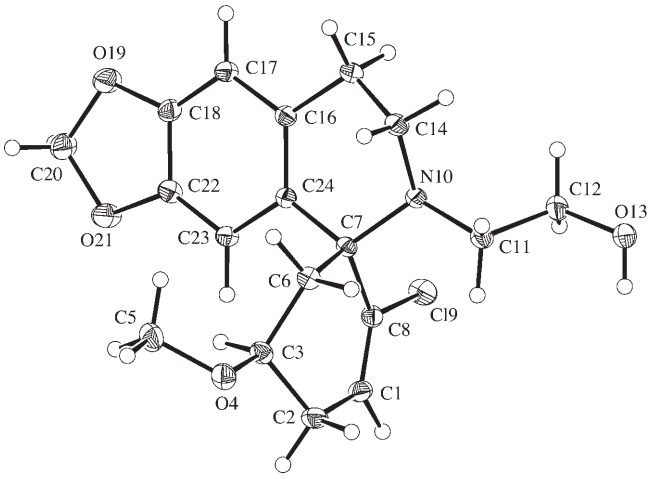
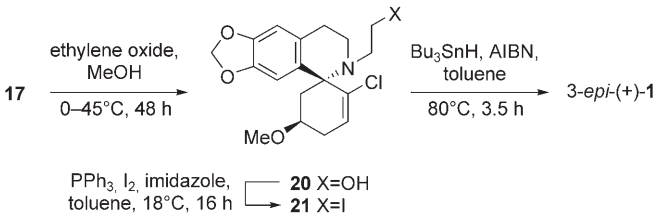


Figure 1. Molecular structure of compound **18** with selected atoms labeled. Anisotropic displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are drawn as circles with small radii.

tween the methoxy and amine residues on the cyclohexenyl A ring (Figure 1). The alcohol **18** was converted readily into the corresponding iodide **19** in 75% yield by using molecular iodine in the presence of imidazole and triphenylphosphine. Compound **19** was then treated with tri-*n*-butyltin hydride and AIBN in toluene. This final step resulted in the efficient formation of the target compound (−)-**1** (89%) by 5-*exo*-trig radical cyclization/chlorine-radical elimination to ensure the establishment of the associated double bond with complete positional fidelity. The ^{1}H and ^{13}C NMR spectral data obtained for *ent*-erythramine ((−)-**1**) were in complete accord with the assigned structure and in agreement with the limited amount of analogous data reported for the natural product. The specific rotation of the synthetic material ($[\alpha]_D^{20} = -187$ ($c = 1.2$ g (100 mL)$^{-1}$, EtOH or $CHCl_3$)) is comparable in magnitude to that recorded for the natural product ($[\alpha]_D^{29.5} = +228$ ($c = 0.19$ g (100 mL)$^{-1}$, EtOH)).[12] The variation between these two values may be attributed, in part, to the difference in the temperature at which the optical rotations were measured. The electron-impact (70 eV) mass spectrum of *ent*-erythramine ((−)-**1**) showed a molecular ion at *m/z* 299. The base peak appeared at *m/z* 240 and almost certainly arises from the successive loss of methyl vinyl ether (MW = 58) and a hydrogen atom. The initial fragmentation most likely involves a retro-Diels–Alder or related process.[13]

An identical reaction sequence was used to convert the spirocyclic amine **17** into 3-*epi*-erythramine (3-*epi*-(+)-**1**; Scheme 4). Thus, compound **17** was treated with ethylene oxide, and the resulting aminoalcohol **20** (79%) was transformed into the corresponding iodide **21** (79%) under the same conditions employed for the conversion of **18** into **19**. Finally, the treatment of compound **21** with tri-*n*-butyltin hydride in the presence of AIBN afforded 3-*epi*-erythramine in quantitative yield. The ^{1}H and ^{13}C NMR spectral data obtained for this previously unreported compound were completely consistent with the assigned structure. The ^{13}C NMR



Scheme 4. Completion of the synthesis of 3-*epi*-erythramine (3-*epi*-(+)-**1**).

spectrum showed the expected eighteen signals. The key features of the ^{1}H NMR (800 MHz) spectrum are two one-proton singlets at $\delta = 6.66$ and 6.48 ppm, a one-proton multiplet at $\delta = 5.69$ ppm, and a three-proton singlet at $\delta = 3.20$ ppm. These signals arise from the aromatic hydrogen atoms 14-H and 17-H, the olefinic hydrogen atom 1-H, and the methoxy group, respectively. As in the case of congener (−)-**1**, the electron-impact (70 eV) mass spectrum of 3-*epi*-erythramine (3-*epi*-(+)-**1**) showed a molecular ion at *m/z* 299, whereas the base peak appeared at *m/z* 240. Significantly, the specific rotation of 3-*epi*-(+)-**1** was of large magnitude and positive in sign ($[\alpha]_D^{20} = +204$ ($c = 1.0$ g (100 mL)$^{-1}$, $CHCl_3$)), as might be expected for a compound that differs from natural erythramine only with respect to the configuration at C3.

Conclusions

The silver(I)-induced electrocyclic ring opening of the conjugate base of compound **15**, which incorporates a tethered nitrogen nucleophile, leads to a π-allyl cation that can be trapped, albeit with little diastereoselectivity, in a spirocyclization process to give a mixture of the Alloc-protected precursors to the amines **16** and **17**. Although the lack of diastereoselectivity detracts from the synthetic approach described herein, the elaboration of these amines to the erythramine analogues (−)-**1** and 3-*epi*-(+)-**1** is an attractive means of generating configurationally varied derivatives of the alkaloid that could be used to establish a quantitative-structure–activity-relationship (QSAR) profile for this and related biologically active natural products. Research directed towards this goal is under way in these laboratories.

Experimental Section

General

Melting points were measured on a Stanford Research Systems Optimelt automated melting-point system and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker 800 or a Varian Gemini 300 NMR spectrometer. Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been filtered through basic alumina immediately prior to use. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra were recorded on a Perkin–Elmer 1800 Series FTIR spectrometer, and samples were analyzed as KBr disks (for solids) or as thin films on KBr plates (for oils).

Low-resolution mass spectra were recorded on a Micromass-Waters LC-ZMD single-quadrupole liquid chromatograph–mass spectrometer or a VG Quattro II triple-quadrupole mass spectrometer by using electron-impact techniques. High-resolution mass spectra were recorded on an Autospec spectrometer. Optical rotations were measured at 20 °C with a Perkin–Elmer 241 polarimeter at the sodium D line (589 nm) with the spectroscopic-grade solvents indicated and at the specified concentration (c) defined in g(100 mL)$^{-1}$. The measurements were carried out in a cell with a path length of 1 dm. Dichloromethane was distilled from calcium hydride, and THF was distilled under nitrogen from sodium benzophenone ketyl. When necessary, reactions were performed under a nitrogen atmosphere.

Syntheses

6: A magnetically stirred solution of thiourea (4.03 g, 53.0 mmol) and rose bengal (≈200 mg) in MeOH (120 mL) was cooled to −40 °C and flushed continuously with oxygen. After 15 min, freshly cracked cyclopentadiene (5.00 g, 75.6 mmol) was added, and the resulting mixture was irradiated at −32 °C with an IXL 375-W heat lamp for 8 h. Oxygenation was then discontinued, and the reaction mixture was shielded from light and stirred at 18 °C for 14 h. The solvent was then removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (70 mL). Et_3N (42.1 mL, 302 mmol), DMAP (924 mg, 7.56 mmol), and Ac_2O (28.5 mL, 302 mmol) were added sequentially to the resulting solution at 0 °C under a nitrogen atmosphere with stirring. The reaction mixture was warmed to 18 °C and stirred for 16 h. NH_4Cl (60 mL of a saturated aqueous solution) was then added, and the mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with brine (1×50 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 15:85→1:1) gave (1*R**,3*S**)-4-cyclopentene-1,3-diol diacetate[14] (7.34 g, 53 % from cyclopentadiene) as a pale-yellow oil. IR (film): $\tilde{\nu}$ = 2950, 1737, 1366, 1232, 1076, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (s, 2H), 5.54 (m, 2H), 2.87 (dt, J = 15.0, 7.6 Hz, 1H), 2.06 (s, 6H), 1.73 ppm (dt, J = 15.0, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8 (CO), 134.7 (CH), 76.7 (CH), 37.2 (CH_2), 21.2 ppm (CH_3); MS (EI, 70 eV): *m/z* (%): 185 (<1) $[M+H]^+$, 184 (<1) $[M]^{+\cdot}$, 169 (3) $[M-CH_3^{\cdot}]^+$, 168 (20), 153 (13), 125 (25), 124 (11), 85 (11), 83 (30), 82 (88), 81 (15), 54 (20), 43 (100); HRMS: *m/z* calcd for $C_9H_{12}O_4$: 184.0736 $[M]^{+\cdot}$; found: 184.0734.

Sodium azide (18 mg, 277 μmol) and lyophilized electric-eel acetyl cholinesterase (EEAC; 2.5 mg, 349 units mg^{-1}) were added sequentially to magnetically stirred sodium dihydrogen phosphate buffer (187 mL of a 1.45 M solution) maintained at 18 °C. When the enzyme had dissolved (≈5 min), (1*R**,3*S**)-4-cyclopentene-1,3-diol diacetate (3.74 g, 20.3 mmol) was added, the reaction flask was sealed, and the mixture was stirred at 18 °C for 23 h. $Na_2S_2O_3$ (15 mL of a 10 % aqueous solution) was then added, and the resulting mixture was stirred at 18 °C for 0.5 h, then extracted with ethyl acetate/diethyl ether (1:1, 9×100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 15:85→7:3) gave (1*R*,3*S*)-(+)-4-hydroxycyclopent-2-enyl acetate[14] (2.41 g, 84 %) as a white crystalline solid. R_f = 0.3 (CH_2Cl_2/hexane/ethyl acetate = 2.5:5.5:8); m.p.: 45–49 °C (lit.:[14b] m.p.: 45–50 °C); $[\alpha]_D^{20}$ = +62.8 (c = 1.0 g(100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3418 (br), 2943, 1735, 1363, 1245, 1091, 1060, 1019, 981 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.07 (m, 1H), 5.94 (m, 1H), 5.46 (m 1H), 4.68 (m, 1H), 2.77 (dt, J = 14.4, 7.3 Hz, 1H), 2.42 (br s, 1H), 2.02 (s, 3H), 1.61 ppm (dt, J = 14.4, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9 (CO), 138.6 (CH), 132.4 (CH), 77.2 (CH), 74.7 (CH), 40.5 (CH_2), 21.2 (CH_3); MS (EI, 70 eV): *m/z* (%): 125 (6) $[M-HO^{\cdot}]^+$, 99 (10), 83 (30), 82 (100), 81 (22), 55 (20), 54 (17), 53 (21), 43 (57), 39 (10); HRMS: *m/z* calcd for $C_7H_{10}O_3$: 125.0603 $[M-HO^{\cdot}]^+$; found: 125.0604.

Anhydrous TBDPSCl (4.52 mL, 17.4 mmol) was added dropwise to an ice-cooled and magnetically stirred solution of (1*R*,3*S*)-(+)-4-hydroxycyclopent-2-enyl acetate (2.24 g, 15.8 mmol) and imidazole (4.30 g, 63.2 mmol) in CH_2Cl_2 (80 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for approximately 5 min, then warmed to 18 °C and stirred at this temperature for 1 h. NH_4Cl (100 mL of a saturated aqueous solution) was then added, and the reaction mixture was extracted with CH_2Cl_2 (2×80 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil, which was purified by flash chromatography (silica, ethyl acetate/hexane = 0.5:99.5→2:3) to give (1*R*,4*S*)-(+)-4-(((1,1-dimethylethyl)diphenylsilyl)oxy)-2-cyclopenten-1-ol acetate (5.88 g, 98 %) as a clear, colorless oil. R_f = 0.8 (ethyl acetate/hexane = 2:3); $[\alpha]_D^{20}$ = +22.0 (c = 1.0 g(100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3071, 2932, 2892, 2858, 1737, 1428, 1368, 1240, 1110, 1064, 1047, 1021, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 4H), 7.45–7.37 (m, 6H), 5.92 (m, 1H), 5.85 (m, 1H), 5.41–5.38 (complex m, 1H), 4.71–4.67 (complex m, 1H), 2.66 (dt, J = 13.7, 7.3 Hz, 1H), 2.07 (s, 3H), 1.75 (dt, J = 13.7, 4.5 Hz, 1H), 1.08 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0 (CO), 138.9 (CH), 135.8 (CH), 134.0 (C_{quat}), 131.4 (CH), 129.9 (CH), 127.8 (CH), 76.9 (CH), 75.8 (CH), 41.1 (CH_2), 27.0 (CH_3), 21.3 (CH_3), 19.2 ppm (C_{quat}); MS (EI, 70 eV): *m/z* (%): 323 (<1) $[M-C_4H_9^{\cdot}]^+$, 263 (18), 246 (18), 245 (56), 242 (76), 241 (100), 201 (14), 200 (47), 199 (96), 197 (30), 181 (51), 139 (24), 135 (29), 105 (15), 77 (23), 66 (14), 57 (15), 43 (34); HRMS: *m/z* calcd for $C_{23}H_{28}O_3Si$: 323.1103 $[M-C_4H_9^{\cdot}]^+$; found: 323.1097.

Anhydrous K_2CO_3 (3.21 g, 23.2 mmol) was added to a magnetically stirred solution of (1*R*,4*S*)-(+)-4-(((1,1-dimethylethyl)diphenylsilyl)oxy)-2-cyclopenten-1-ol acetate (5.88 g, 15.5 mmol) in MeOH (50 mL) at 18 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h, then concentrated under reduced pressure, and the residue was partitioned between diethyl ether (100 mL) and water (100 mL). The aqueous phase was extracted with diethyl ether (3×100 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, ethyl acetate/hexane = 7:93→3:7) to afford (1*R*,4*S*)-(−)-4-(((1,1-dimethylethyl)diphenylsilyl)oxy)-2-cyclopenten-1-ol (5.22 g, 100 %) as a white crystalline solid. R_f = 0.4 (ethyl acetate/CH_2Cl_2/hexane = 2:2.5:5.5); $[\alpha]_D^{20}$ = −2.0 (c = 1.0 g(100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3313 (br), 3070, 2932, 2858, 1427, 1365, 1111, 1069, 1019, 902, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.69 (m, 4H), 7.46–7.37 (m, 6H), 5.91 (m, 1H), 5.86 (m, 1H), 4.67 (m, 1H), 4.52 (m, 1H), 2.57 (dt, J = 13.7, 7.1 Hz, 1H), 1.90 (m, 1H), 1.66 (dt, J = 13.7, 4.6 Hz, 1H), 1.09 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.9 (CH), 135.9 (CH), 135.7 (CH), 134.0 (C_{quat}), 129.8 (CH), 127.8 (CH), 76.1 (CH), 75.1 (CH), 44.6 (CH_2), 27.0 (CH_3), 19.2 ppm (C_{quat}); MS (EI, 70 eV): *m/z* (%): 338 (<1) $[M]^{+\cdot}$, 281 (87) $[M-C_4H_9^{\cdot}]^+$, 204 (19), 203 (74), 201 (44), 200 (94), 199 (100), 197 (39), 183 (11), 181 (41), 143 (14), 141 (19), 139 (84), 135 (26), 121 (20), 105 (20), 78 (14), 77 (50), 66 (33), 57 (31), 45 (19), 41 (11); HRMS: *m/z* calcd for $C_{21}H_{26}O_2Si$: 338.1702 $[M]^{+\cdot}$; found: 338.1709.

Dess–Martin periodinane (216 mg, 514 μmol) was added to a magnetically stirred solution of (1*R*,4*S*)-(−)-4-(((1,1-dimethylethyl)diphenylsilyl)-oxy)-2-cyclopenten-1-ol (145 mg, 428 μmol) in CH_2Cl_2 (8 mL) at 18 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h, then filtered through a pad of celite. The filtrate was concentrated under reduced pressure, and the resulting light-yellow oil was purified by flash chromatography (silica, ethyl acetate/hexane = 1:99→2:23) to give (4*S*)-(+)-4-(((1,1-dimethylethyl)diphenylsilyl)oxy)-2-cyclopenten-1-one[14] (144 mg, 96 %) as a clear, colorless oil. R_f = 0.5 (ethyl acetate/CH_2Cl_2/hexane = 1:2.5:5.5); $[\alpha]_D^{20}$ = +5.2 (c = 1.0 g(100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3071, 2932, 2858, 1723, 1472, 1428, 1355, 1182, 1108, 1070, 898, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.66 (complex m, 4H), 7.45–7.41 (complex m, 6H), 6.12 (m, 1H), 4.95 (m, 1H), 2.56–2.48 (complex m, 2H), 2.38–2.31 (complex m, 1H), 1.08 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.5 (CO), 163.7 (CH), 135.8 (CH), 134.6 (CH), 133.5 (C_{quat}), 130.2 (CH), 128.0 (CH), 71.8 (CH), 44.9 (CH_2), 26.9 (CH_3), 19.2 ppm (C_{quat}); MS (EI, 70 eV): *m/z* (%): 336 (4) $[M]^{+\cdot}$, 281 (38), 280 (73), 279 (100), 261 (30), 249 (31), 223 (45), 201 (58), 199 (74), 197 (41), 183 (26), 174 (52), 173 (84), 167 (58), 157 (27), 141 (55), 135 (20), 105 (30), 81 (40), 77 (49), 53 (50), 45 (24); HRMS: *m/z* calcd for $C_{21}H_{24}O_2Si$: 336.1546 $[M]^{+\cdot}$; found: 336.1542.

A solution of (4*S*)-(+)-4-(((1,1-dimethylethyl)diphenylsilyl)oxy)-2-cyclopenten-1-one (3.00 g, 8.91 mmol) and triethylamine (3.70 mL, 26.5 mmol)

in THF (25 mL) was added dropwise to a stirred solution of L-selectride (10.7 mL of a 1.0 M solution in THF, 10.7 mmol) in THF (75 mL) at −78 °C under nitrogen, and the resulting solution was stirred at −78 °C for 0.5 h. *N*-phenyltrifluoromethanesulfonamide (3.80 g, 10.6 mmol) was then added in one portion to the reaction mixture, which was stirred for a further 5 min at −78 °C then allowed warmed to 18 °C and stirred at 18 °C for 5 h. $NaHCO_3$ (100 mL of a saturated aqueous solution) was added, the phases were separated, and the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica, hexane/ethyl acetate/triethylamine = 96:3:1) to give (4*R*)-4-(((1,1-dimethylethyl)-diphenylsilyl)oxy)-1-cyclopenten-1-yl trifluoromethanesulfonate (3.77 g, 90%) as a clear, colorless oil. R_f = 0.6 (ethyl acetate/hexane = 1:9); $[\alpha]_D^{20}$ = +13.2 (c = 2.0 g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3073, 2933, 2859, 1660, 1426, 1213, 1142, 1112, 1074, 992, 911, 822, 741, 702, 611, 507 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (m, 4H), 7.45–7.41 (complex m, 6H), 5.52 (br t, J = 2.1 Hz, 1H), 4.57 (m, 1H), 2.65 (m, 2H), 2.59–2.40 (complex m, 2H), 1.09 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.5 (C_{quat}), 135.8 (CH), 133.8 (C_{quat}), 130.0 (CH), 127.9 (CH), 118.7 (q, $J_{C,F}$ = 319 Hz, C_{quat}), 115.4 (CH), 70.6 (CH), 41.1 (CH_2), 38.9 (CH_2), 26.9 (CH_3), 19.2 ppm (C_{quat}); MS (ESI+): *m/z* (%): 493 (19) $[M+Na]^+$, 471 (14) $[M+H]^+$, 215 (29), 97 (20), 60 (100); elemental analysis: calcd (%) for $C_{22}H_{25}F_3O_4SSi$: C 56.15, H 5.35, F 12.11, S 6.81; found: C 56.18, H 5.40, F 12.02, S 6.62.

TBAF (2.12 mL of a 1.0 M solution in THF, 2.12 mmol) was added dropwise to a stirred solution of (4*R*)-4-(((1,1-dimethylethyl)diphenylsilyl)-oxy)-1-cyclopenten-1-yl trifluoromethanesulfonate (831 mg, 1.77 mmol) in THF (10 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 5 min, then warmed to 18 °C and stirred at this temperature for 3 h. NH_4Cl (4 mL of a saturated aqueous solution) was then added, and the resulting mixture was extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (1×20 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a dark-orange oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 3:7) gave (*R*)-4-hydroxycyclopenten-1-yl trifluoromethanesulfonate (326 mg, 79%) as a pale-yellow liquid. R_f = 0.2 (ethyl acetate/hexane = 3:7); $[\alpha]_D^{20}$ = +1.8 (c = 1.0 g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3352, 2938, 1662, 1423, 1213, 1140, 1118, 1052, 902, 838, 610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.61 (s, 1H), 4.60 (br s, 1H), 2.98 (m, 1H), 2.90 (m, 1H), 2.54 (d, J = 16.9 Hz, 1H), 2.38 (d, J = 17.2 Hz, 1H), 1.80 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.7 (C_{quat}), 118.7 (q, $J_{C,F}$ = 319 Hz, C_{quat}), 115.5 (CH), 69.1 (CH), 41.4 (CH_2), 38.9 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 232 (5) $[M]^{+\bullet}$, 215 (19), 99 (21), 81 (36), 69 (56), 55 (100), 43 (43); HRMS: *m/z* calcd for $C_6H_7F_3O_4S$: 232.0017 $[M]^{+\bullet}$; found: 232.0021.

Anhydrous TBDMSCl (382 mg, 2.53 mmol) was added dropwise to an ice-cooled and magnetically stirred solution of (*R*)-4-hydroxycyclopenten-1-yl trifluoromethanesulfonate (489 mg, 2.11 mmol) and imidazole (316 mg, 4.64 mmol) in CH_2Cl_2 (20 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for approximately 5 min, then warmed to 18 °C and stirred at this temperature for 1 h. NH_4Cl (20 mL of a saturated aqueous solution) was then added, and the resulting mixture was extracted with CH_2Cl_2 (2×80 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil, which was purified by flash chromatography (silica, hexane/ethyl acetate/triethylamine = 98:1:1) to give (*R*)-4-(((1,1-dimethylethyl)dimethylsilyl)oxy)-1-cyclopenten-1-yl trifluoromethanesulfonate (**6**)[14] (652 mg, 89%) as a clear, colorless liquid. R_f = 0.3 (hexane/ethyl acetate/triethylamine = 98:1:1); $[\alpha]_D^{20}$ = +2.8 (c = 1.05 g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 2956, 2932, 2859, 1661, 1426, 1254, 1213, 1143, 1092, 994, 912, 837, 778, 610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.55 (quint, J = 2.1 Hz, 1H), 4.56 (hept, J = 3.6 Hz, 1H), 2.90 (m, 1H), 2.69 (m, 1H), 2.52 (dm, J = 16.4 Hz, 1H), 2.34 (dm, J = 16.5 Hz, 1H), 0.88 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.6 (C_{quat}), 118.7 (q, $J_{C,F}$ = 345 Hz, C_{quat}), 115.5 (CH), 69.7 (CH), 41.4 (CH_2), 39.2 (CH_2), 25.9 (CH_3), 18.2 (C_{quat}), −4.8 ppm (CH_3); MS (EI, 70 eV): *m/z* (%): 346 (36) $[M]^{+\bullet}$, 345 (83) $[M-H^{\bullet}]^+$, 309 (43), 283 (58), 201 (50), 197 (72), 135 (100), 75 (51), 73 (68), 67 (71), 57 (58); HRMS: *m/z* calcd for $C_{12}H_{21}F_3O_4SSi$: 345.0804 $[M-H^{\bullet}]^+$; found: 345.0803.

7: $[PdCl_2(dppf)]$ (377 mg, 462 μmol), K_3PO_4 (980 mg, 4.62 mmol), and **6** (800 mg, 2.31 mmol) were added sequentially to a magnetically stirred solution of **5**[3b] (2.07 g, 4.62 mmol) in THF (22 mL) at room temperature. The resulting mixture was deoxygenated (by using argon in a freeze–thaw process), heated at reflux under an argon atmosphere for 6 h, then cooled to 18 °C and partitioned between diethyl ether (70 mL) and water (50 mL). The aqueous phase was extracted with diethyl ether (3× 100 mL), and the combined organic phases were washed with brine (1× 80 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 1:99→3:97) gave **7**[1] (1.27 g, 92%) as a pale-yellow oil. R_f = 0.4 (ethyl acetate/hexane = 5:95); $[\alpha]_D^{20}$ = −11.5 (c = 1.0 g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 2930, 2857, 1503, 1483, 1428, 1362, 1251, 1210, 1110, 1044, 938, 835, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (m, 4H), 7.41–7.33 (complex m, 6H), 6.63 (s, 1H), 6.60 (s, 1H), 5.89 (s, 2H), 5.40 (m, 1H), 4.54 (m, 1H), 3.74 (t, J = 7.1 Hz, 2H), 2.87–2.60 (complex m, 4H), 2.53–2.34 (complex m, 2H), 1.03 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4 (C_{quat}), 145.8 (C_{quat}), 140.6 (C_{quat}), 135.7 (CH), 133.9 (C_{quat}), 132.0 (C_{quat}), 130.0 (C_{quat}), 129.7 (CH), 127.7 (CH), 126.3 (CH), 110.6 (CH), 108.6 (CH), 100.9 (CH_2), 72.9 (CH), 65.3 (CH_2), 47.6 (CH_2), 43.3 (CH_2), 36.4 (CH_2), 27.0 (CH_3), 26.1 (CH_3), 19.3 (C_{quat}), 18.3 (C_{quat}), −4.5 (CH_3), −4.6 ppm (CH_3); MS (EI, 70 eV): *m/z* (%): 600 (13) $[M]^{+\bullet}$, 599 (3), 544 (15), 543 (30), 423 (25), 411 (19), 343 (16), 292 (25), 291 (70), 271 (26), 214 (59), 213 (100), 197 (69), 183 (50), 181 (26), 155 (41), 135 (60), 117 (23), 105 (27); HRMS: *m/z* calcd for $C_{36}H_{48}O_4Si_2$: 600.3091 $[M]^{+\bullet}$; found: 600.3090.

8: PPTS (337 mg, 1.34 mmol) was added to a magnetically stirred solution of **7** (807 mg, 1.34 mmol) in EtOH (9 mL) at 18 °C, and the resulting mixture was stirred at this temperature for 48 h. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate (1×50 mL). The resulting solution was washed with brine (1× 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica, ethyl acetate/hexane = 1:4) to give **8** (463 mg, 71%) as a pale-yellow oil. R_f = 0.2 (ethyl acetate/hexane = 1:4); $[\alpha]_D^{20}$ = −6.9 (c = 1.0 g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3339, 3070, 3048, 2930, 2858, 1502, 1484, 1427, 1213, 1111, 1086, 1043, 937, 823, 739, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.59 (m, 4H), 7.42–7.33 (m, 6H), 6.65 (s, 1H), 6.62 (s, 1H), 5.90 (s, 2H), 5.46 (m, 1H), 4.51 (m, 1H), 3.75 (t, J = 7.2 Hz, 2H), 2.87–2.71 (m, 4H), 2.47–2.36 (m, 2H), 1.03 ppm (s, 9H); no signal was observed for the hydrogen atom of the hydroxy group; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4 (C_{quat}), 145.8 (C_{quat}), 140.5 (C_{quat}), 135.7 (CH), 133.8 (C_{quat}), 131.5 (C_{quat}), 130.0 (C_{quat}), 129.7 (CH), 127.7 (CH), 126.1 (CH), 110.6 (CH), 108.5 (CH), 100.9 (CH_2), 72.0 (CH), 65.2 (CH_2), 47.6 (CH_2), 43.3 (CH_2), 36.5 (CH_2), 27.0 (CH_3), 19.2 ppm (C_{quat}); MS (EI, 70 eV): *m/z* (%): 486 (10) $[M]^{+\bullet}$, 429 (25), 411 (29), 333 (23), 214 (71), 213 (100), 199 (87), 183 (70), 181 (40), 155 (72), 135 (56), 115 (30), 105 (24), 91 (53), 77 (27), 57 (19); HRMS: *m/z* calcd for $C_{30}H_{34}O_4Si$: 486.2226 $[M]^{+\bullet}$; found: 486.2223.

9: A solution of the alcohol **8** (1.20 g, 2.47 mmol) and MeI (770 μL, 12.4 mmol) in THF (15 mL) was added dropwise to an ice-cooled and magnetically stirred suspension of KH (≈2 g, 49.9 mmol) in THF (32 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 0 °C for approximately 10 min, then warmed to 18 °C and stirred at this temperature for 3 h. The reaction mixture was then cooled to 0 °C, and NH_4Cl (50 mL of a saturated aqueous solution) was added dropwise. The resulting mixture was extracted with diethyl ether (3×60 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow-orange oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 5:95) gave **9** (1.24 g, 100%) as a clear, colorless oil. R_f = 0.1 (ethyl acetate/hexane = 5:95); $[\alpha]_D^{20}$ = −5.5 (c = 1.0 g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3070, 3048, 2930, 2894, 2858, 1502, 1484, 1427, 1360, 1211, 1111, 1043, 936, 703 cm^{-1};

[1] This material was contaminated with a small amount (≤5%) of the compound derived from protiodeborylation of the boronic acid **5**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (m, 4H), 7.44–7.33 (m, 6H), 6.64 (s, 1H), 6.62 (s, 1H), 5.89 (s, 2H), 5.43 (m, 1H), 4.11 (hept, J = 3.6 Hz, 1H), 3.75 (t, J = 7.3 Hz, 2H), 3.31 (s, 3H), 2.89–2.78 (complex m, 2H), 2.76–2.40 (complex m, 4H), 1.03 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4 (C_{quat}), 145.8 (C_{quat}), 140.5 (C_{quat}), 135.7 (CH), 133.9 (C_{quat}), 131.6 (C_{quat}), 130.0 (C_{quat}), 129.7 (CH), 127.7 (CH), 126.3 (CH), 110.5 (CH), 108.5 (CH), 100.9 (CH_2), 80.9 (CH), 65.3 (CH_2), 56.4 (CH_3), 43.8 (CH_2), 39.7 (CH_2), 36.5 (CH_2), 27.0 (CH_3), 19.3 ppm (C_{quat}); MS (EI, 70 eV): *m/z* (%): 500 (46) $[M]^{+\bullet}$, 444 (23), 443 (54), 215 (32), 214 (92), 213 (100), 199 (82), 183 (95), 181 (50), 155 (85), 135 (66), 115 (40), 91 (52), 77 (27), 57 (30), 41 (26); HRMS: *m/z* calcd for $C_{31}H_{36}O_4Si$: 500.2383 $[M]^{+\bullet}$; found: 500.2380; elemental analysis: calcd (%) for $C_{31}H_{36}O_4Si$: C 74.36, H 7.25; found: C 74.56, H 7.53.

10a and **10b**: Powdered NaOH (593 mg, 14.8 mmol), benzyltriethylammonium chloride (TEBAC; 11 mg, 49 μmol), and $CHCl_3$ (791 μL, 9.88 mmol) were added sequentially to a solution of the alkene **9** (1.24 g, 2.47 mmol) in CH_2Cl_2 (1.80 mL) at 18 °C under a nitrogen atmosphere. The resulting mixture was cooled in an ice bath (to control the ensuing exothermic reaction) and sonicated for 10 min. The resulting mixture was filtered through a pad of celite, which was then washed with copious quantities of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to give a dark-brown oil, which was purified by flash chromatography (silica, ethyl acetate/hexane = 5:95) to give an approximately 2:1 mixture of **10a** and **10b** (1.31 g, 91%) as a viscous, amber-colored oil. R_f = 0.1 (ethyl acetate/hexane = 5:95); IR (film): $\tilde{\nu}$ = 3071, 2931, 2892, 2858, 1503, 1486, 1428, 1382, 1239, 1110, 1043, 938, 824, 737, 703, 614, 505 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$; major diastereoisomer): δ = 7.69–7.63 (complex m, 4H), 7.42–7.34 (complex m, 6H), 6.74 (s, 1H), 6.62 (s, 1H), 5.90 (m, 2H), 3.89 (m, 2H), 3.80 (m, 1H), 3.12 (s, 3H), 2.90 (m, 2H), 2.46 (dd, J = 14.7, 6.2 Hz, 1H), 2.35–1.95 (complex m, 4H), 1.06 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$; major diastereoisomer): δ = 146.9 (C_{quat}), 146.0 (C_{quat}), 135.7 (CH), 133.8 (C_{quat}), 132.7 (C_{quat}), 131.6 (C_{quat}), 129.7 (CH), 127.8 (CH), 109.8 (CH), 108.6 (CH), 101.1 (CH_2), 85.2 (CH), 73.2 (C_{quat}), 64.8 (CH_2), 56.6 (CH_3), 47.8 (C_{quat}), 43.2 (CH_2), 40.7 (CH), 35.8 (CH_2), 35.7 (CH_2), 27.0 (CH_3), 19.3 ppm (C_{quat}); MS (EI, 70 eV): *m/z* (%): 586, 584, and 582 (3, 12, and 16) $[M]^{+\bullet}$, 460 and 458 (23 and 60), 459 and 457 (69 and 100), 259 (13), 229 (23), 224 (28), 199 (18), 183 (11), 135 (13), 91 (10); HRMS: *m/z* calcd for $C_{32}H_{36}{}^{35}Cl_2O_4Si$: 582.1760 $[M]^{+\bullet}$; found: 582.1772.

11a and **11b**: TBAF (1.10 mL of a 1.0 M solution in THF, 1.10 mmol) was added dropwise to a magnetically stirred solution of a mixture of **10a** and **10b** (ca. 2:1; 496 mg, 850 μmol) in THF (10 mL) at approximately 0 °C. The resulting mixture was warmed to 18 °C and stirred at this temperature for 2.5 h. NH_4Cl (10 mL of a saturated aqueous solution) was then added, and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange-brown oil, which was purified by flash chromatography (silica, ethyl acetate/hexane = 3:7) to give an approximately 2:1 mixture of **11a** and **11b** (284 mg, 97%) as a pale-amber oil. R_f = 0.2 (ethyl acetate/hexane = 3:7); IR (film): $\tilde{\nu}$ = 3401, 2931, 2894, 1503, 1486, 1383, 1238, 1097, 1041, 935, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$; major diastereoisomer): δ = 6.84 (s, 1H), 6.54 (s, 1H), 5.94 (m, 2H), 3.95 (m, 2H), 3.27 (s, 3H), 2.88 (m, 2H), 2.71–2.63 (complex m, 1H), 2.48–2.24 (complex m, 3H), 2.17 (m, 1H), 1.85 ppm (m, 1H); no signal was observed for the hydrogen atom of the hydroxy group; ^{13}C NMR (75 MHz, $CDCl_3$; major diastereoisomer): δ = 147.1 (C_{quat}), 146.1 (C_{quat}), 132.1 (C_{quat}), 131.8 (C_{quat}), 109.0 (CH), 108.8 (CH), 101.2 (CH_2), 85.2 (CH), 73.2 (C_{quat}), 63.1 (CH_2), 56.6 (CH_3), 47.8 (C_{quat}), 43.3 (CH_2), 40.7 (CH), 35.7 (CH_2), 35.5 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 348, 346, and 344 (16, 90, and 100) $[M]^{+\bullet}$, 279 and 277 (21 and 46), 265 and 263 (30 and 75), 243 and 241 (24 and 61), 233 (72), 226 and 224 (27 and 65), 213 and 211 (41 and 80), 212 and 210 (30 and 58), 190 (56), 177 (61), 115 (59); HRMS: *m/z* calcd for $C_{16}H_{18}{}^{35}Cl_2O_4$: 344.0582 $[M]^{+\bullet}$; found: 344.0584; elemental analysis: calcd (%) for $C_{16}H_{18}Cl_2O_4$: C 55.67, H 5.26, Cl 20.54; found: C 55.41, H 5.05, Cl 20.71.

12a and **12b**: Et_3N (280 μL, 2.00 mmol), DMAP (10 mg, 80 μmol), and MsCl (155 μL, 2.00 mmol) were added sequentially to a magnetically stirred solution of the alcohols **11a** and **11b** (≈2:1; 276 mg, 799 μmol) in CH_2Cl_2 (8 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was warmed to 18 °C and stirred at this temperature for 16 h. $NaHCO_3$ (8 mL of a saturated aqueous solution) was then added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange oil, which was purified by flash chromatography (silica, ethyl acetate/hexane = 1:3→1:2) to give an approximately 2:1 mixture of **12a** and **12b** (338 mg, 100%) as a pale-yellow oil. R_f = 0.1 (ethyl acetate/hexane = 1:3); IR (film): $\tilde{\nu}$ = 2934, 1504, 1488, 1355, 1238, 1174, 1105, 1041, 955 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$; major diastereoisomer): δ = 6.76 (s, 1H), 6.67 (s, 1H), 5.94 (m, 2H), 4.47 (m, 2H), 3.88 (m, 1H), 3.19 (s, 3H), 3.06 (m, 2H), 3.00 (s, 3H), 2.63 (dd, J = 14.7, 6.2 Hz, 1H), 2.33 ppm (m, 2H); the signals due to two hydrogen atoms were obscured; ^{13}C NMR (75 MHz, $CDCl_3$; major diastereoisomer): δ = 147.3 (C_{quat}), 146.7 (C_{quat}), 132.0 (C_{quat}), 129.5 (C_{quat}), 109.0 (CH), 108.9 (CH), 101.3 (CH_2), 85.3 (CH), 73.1 (C_{quat}), 69.8 (CH_2), 56.5 (CH_3), 47.6 (C_{quat}), 43.1 (CH_2), 40.8 (CH), 37.5 (CH_3), 35.3 (CH_2), 32.2 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 426, 424, and 422 (6, 31, and 44) $[M]^{+\bullet}$, 389 and 387 (7 and 17), 388 and 386 (13 and 11), 293 and 291 (26 and 70), 267, 265, and 263 (10, 18, and 52), 261 and 259 (39 and 95), 255 (69), 235 and 233 (18 and 54), 225 (64), 224 (92), 223 (100), 211 (60), 210 (51), 152 (52), 115 (50), 57 (57), 43 (69); HRMS: *m/z* calcd for $C_{17}H_{20}{}^{35}Cl_2O_6S$: 422.0358 $[M]^{+\bullet}$; found: 422.0360.

13a and **13b**: LiN_3 (320 mg, 6.53 mmol) was added to a magnetically stirred solution of the mesylates **12a** and **12b** (≈2:1; 922 mg, 2.18 mmol) in anhydrous DMF (8 mL), and the resulting mixture was stirred at 18 °C under a nitrogen atmosphere for 48 h. The reaction mixture was then diluted with diethyl ether (30 mL), and the organic phase was washed with water (3 × 10 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 1:9) gave an approximately 2:1 mixture of **13a** and **13b** (757 mg, 94%) as a pale-yellow oil. R_f = 0.3 (major diastereoisomer) and 0.2 (minor diastereoisomer; ethyl acetate/hexane = 1:9); IR (film): $\tilde{\nu}$ = 2932, 2897, 2099, 1504, 1487, 1382, 1240, 1108, 1042, 935, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$; major diastereoisomer): δ = 6.74 (s, 1H), 6.67 (s, 1H), 5.94 (m, 2H), 3.89 (m, 1H), 3.56 (m, 2H), 3.20 (s, 3H), 2.91 (t, J = 7.6 Hz, 2H), 2.64 (dd, J = 14.7, 6.2 Hz, 1H), 2.36–2.10 ppm (complex m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): major diastereoisomer: δ = 147.3 (C_{quat}), 146.5 (C_{quat}), 131.7 (C_{quat}), 131.4 (C_{quat}), 109.0 (CH), 108.8 (CH), 101.3 (CH_2), 85.3 (CH), 73.1 (C_{quat}), 56.6 (CH_3), 51.9 (CH_2), 47.7 (C_{quat}), 43.1 (CH_2), 40.9 (CH), 35.5 (CH_2), 32.0 ppm (CH_2); minor diastereoisomer: δ = 147.3 (C_{quat}), 146.3 (C_{quat}), 132.2 (C_{quat}), 131.6 (C_{quat}), 109.2 (CH), 108.7 (CH), 101.4 (CH_2), 85.9 (CH), 74.5 (C_{quat}), 57.7 (CH_3), 51.6 (CH_2), 45.8 (C_{quat}), 41.7 (CH_2), 38.1 (CH), 33.5 (CH_2), 32.0 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 373, 371, and 369 (10, 45, and 62) $[M]^{+\bullet}$, 344, 342, and 340 (2, 10, and 15), 330, 328, and 326 (5, 24, and 35), 314, 312, and 310 (8, 30, and 46), 212 and 210 (25 and 51), 189 (100); HRMS: *m/z* calcd for $C_{16}H_{17}{}^{35}Cl_2N_3O_3$: 369.0647 $[M]^{+\bullet}$; found: 369.0629; elemental analysis: calcd (%) for $C_{16}H_{17}Cl_2N_3O_3$: C 51.91, H 4.63, Cl 19.15, N 11.35; found: C 51.94, H 4.72, Cl 19.20, N 11.37.

15a and **15b**: PPh_3 (796 mg, 3.03 mmol) was added to a magnetically stirred solution of the azides **13a** and **13b** (≈2:1; 749 mg, 2.02 mmol) in THF/water (10:3, 13 mL), and the resulting mixture was stirred at 18 °C for 16 h. The solvent was then removed under reduced pressure, and the residue, which contained a mixture of the amines **14a** and **14b**, was taken up in ethyl acetate (15 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a pale-yellow, oily solid. A magnetically stirred solution of this material in THF (20 mL) under a nitrogen atmosphere was cooled to 0 °C then treated with pyridine (327 μL, 4.04 mmol) and allyl chloroformate (429 μL, 4.04 mmol). The reaction mixture was stirred at 0 °C for approximately 10 min, then warmed to 18 °C and stirred at this temperature for 16 h. The solvent was then removed under reduced pressure, and the residue taken up in diethyl ether (80 mL). The resulting solution was washed with water (1 × 20 mL) and then brine (1 × 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 1:4) afforded an approximately 2:1 mixture of **15a** and **15b** (824 mg, 95% from **13**) as a pale-yellow, viscous oil. R_f = 0.2 (ethyl acetate/hexane = 1:4); IR (film): $\tilde{\nu}$ = 3337, 2933, 1717,

1504, 1487, 1383, 1240, 1107, 1040, 992, 934, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$; major diastereoisomer): $\delta = 6.66$ (s, 1H), 6.53 (s, 1H), 5.94 (m, 2H), 5.89 (partially obscured m, 1H), 5.25 (m, 2H), 4.84 (br s, 1H, NH), 4.57 (d, $J = 5.5$ Hz, 2H), 3.88 (m, 1H), 3.52–3.48 (complex m, 2H), 3.19 (s, 3H), 2.87–2.70 (complex m, 2H), 2.68–2.61 (complex m, 2H), 2.35–2.05 ppm (complex m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; major diastereoisomer): $\delta = 156.2$ (CO), 147.3 (C_{quat}), 146.2 (C_{quat}), 133.0 (CH), 132.1 (C_{quat}), 131.7 (C_{quat}), 117.7 (CH_2), 108.7 (CH), 108.6 (CH), 101.2 (CH_2), 85.3 (CH), 73.2 (C_{quat}), 65.5 (CH_2), 56.5 (CH_3), 47.8 (C_{quat}), 43.1 (CH_2), 41.6 (CH_2), 40.7 (CH), 35.5 (CH_2), 32.8 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 431, 429, and 427 (2, 10, and 15) $[M]^{+\bullet}$, 393 and 391 (4 and 6), 344 and 342 (13 and 19), 328 and 326 (16 and 25), 320 and 318 (33 and 76), 41 (100); HRMS: *m/z* calcd for $C_{20}H_{23}{}^{35}Cl_2NO_5$: 427.0953 $[M]^{+\bullet}$; found: 427.0953; elemental analysis: calcd (%) for $C_{20}H_{23}Cl_2NO_5$: C 56.08, H 5.41, Cl 16.55, N 3.27; found: C 56.33, H 5.58, Cl 16.19, N 3.23.

16 and **17**: LiHMDS (900 μL of a 1.0 M solution in THF, 900 μmol) was added to a magnetically stirred solution of the *gem*-dichlorocyclopropanes **15a** and **15b** (ca. 2:1; 350 mg, 817 μmol) in anhydrous THF (12 mL) at −20 °C under an argon atmosphere. The reaction mixture was stirred at −20 °C for 10 min, then warmed to 0 °C and stirred at this temperature for a further 0.5 h. $AgBF_4$ (636 mg, 3.27 μmol) was added in one portion, and the reaction mixture was stirred at 0 °C for a further 10 min, then warmed to 18 °C and stirred at this temperature for 0.5 h. The reaction mixture was then heated at 45 °C for 4 h, cooled, and filtered through a pad of celite. The filtrate was concentrated under reduced pressure to give a yellow solid. A magnetically stirred solution of this material in anhydrous THF (10 mL) was treated with dimedone (573 mg, 4.09 mmol) and $[Pd(PPh_3)_4]$ (172 mg, 149 μmol), and the resulting mixture was stirred at 18 °C under an argon atmosphere for 16 h. The reaction mixture was then concentrated under reduced pressure to give a brown semisolid, which was subjected to flash chromatography (silica, $CHCl_3$/MeOH = 9:1 with 5% *v/v* 880 ammonia). The relevant fractions ($R_f = 0.7$ ($CHCl_3$/MeOH = 9:1 with 5% *v/v* 880 ammonia)) were concentrated to give a mixture of the target amines and $Ph_3P(O)$. This mixture was purified further by flash chromatography (silica, methanol/CH_2Cl_2 = 1:99→2.5:97.5) to give **16**[2] (65 mg, 26%) as an orange oil and **17** (76 mg, 30%) as an orange foam. **16**: $R_f = 0.1(1)$ (ethyl acetate/hexane = 2:3); IR (film): $\tilde{\nu} = 2924$, 1502, 1484, 1384, 1234, 1089, 1039, 933 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.54$ (s, 1H), 6.53 (s, 1H), 5.98 (t, $J = 4.1$ Hz, 1H), 5.90 (s, 2H), 3.72 (m, 1H), 3.32 (s, 3H), 3.18 (dd, $J = 8.5$, 3.1 Hz, 2H), 2.94 (m, 2H), 2.62–2.54 (complex m, 3H), 2.46 (m, 1H), 2.01 (dd, $J =$ 14.2, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.4$ (C_{quat}), 146.1 (C_{quat}), 138.1 (C_{quat}), 132.8 (C_{quat}), 129.4 (C_{quat}), 124.5 (CH), 108.8 (CH), 106.7 (CH), 100.9 (CH_2), 73.7 (CH), 60.5 (C_{quat}), 56.6 (CH_3), 40.9 (CH_2), 38.6 (CH_2), 30.9 (CH_2), 29.5 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 309 and 307 (4 and 11) $[M]^{+\bullet}$, 294 and 292 (2 and 5), 278 and 276 (13 and 30), 272 (6), 251 and 249 (31 and 75), 250 and 248 (55 and 100), 232 (58); HRMS: *m/z* calcd for $C_{16}H_{18}{}^{35}ClNO_3$: 307.0975 $[M]^{+\bullet}$; found: 307.0976. **17**: $R_f = 0.0(9)$ (ethyl acetate/hexane = 2:3); IR (film): $\tilde{\nu} = 2930$, 1502, 1483, 1382, 1233, 1095, 1038, 991 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.55 (s, 1H), 6.51 (s, 1H), 5.97 (dd, $J = 6.3$, 2.2 Hz, 1H), 5.90 (br s, 2H), 3.72 (m, 1H), 3.37 (s, 3H), 3.13 (m, 2H), 2.80–2.50 (complex m, 4H), 2.16 (m, 2H), 1.70 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.3$ (C_{quat}), 137.7 (C_{quat}), 132.7 (C_{quat}), 129.2 (C_{quat}), 126.1 (CH), 108.4 (CH), 106.8 (CH), 100.8 (CH_2), 72.6 (CH), 62.6 (C_{quat}), 56.0 (CH_3), 43.4 (CH_2), 39.2 (CH_2), 32.8 (CH_2), 30.0 ppm (CH_2); one signal due to a quaternary carbon atom was obscured and may overlap with another signal; MS (EI, 70 eV): *m/z* (%): 309 and 307 (16 and 39) $[M]^{+\bullet}$, 294 and 292 (4 and 10), 278 and 276 (24 and 50), 272 (11), 251 and 249 (57 and 85), 250 and 248 (77 and 100), 232 (54); HRMS: *m/z* calcd for $C_{16}H_{18}{}^{35}ClNO_3$: 307.0975 $[M]^{+\bullet}$; found: 307.0973.

18: Ethylene oxide (≈2 mL, ≈40 mmol) was added to a solution of the amine **16** (63 mg, 205 μmol) in anhydrous MeOH (1.0 mL) at 0 °C under a nitrogen atmosphere. The reaction vessel was sealed, and the mixture was stirred magnetically at 45 °C for 24 h. The reaction mixture was then cooled to 18 °C, the vessel was opened, and the solvent was removed under reduced pressure to give a yellow oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 2:3) afforded **18** (41 mg, 58%), which crystallized as pale-pink crystals from CH_2Cl_2/hexane. $R_f = 0.2$ (ethyl acetate/hexane = 2:3); decomp. from 109 °C; $[\alpha]_D^{20} = -91.3$ ($c = 1.0$ g $(100\ mL)^{-1}$, $CHCl_3$); IR (disk): $\tilde{\nu} = 3450$ (br), 2924, 1503, 1486, 1384, 1234, 1102, 1037, 932 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.66$ (s, 1H), 6.59 (s, 1H), 6.22 (dd, $J = 7.1$, 2.2, 1H), 5.93 (d, $J = 1.5$ Hz, 1H), 5.92 (d, $J = 1.5$ Hz, 1H), 3.81–3.65 (complex m, 2H), 3.58 (m, 1H), 3.29 (s, 3H), 3.08–2.80 (complex m, 5H), 2.79–2.64 (complex m, 2H), 2.44 (dt, $J = 12.7$, 2.7 Hz, 1H), 2.33 (m, 1H), 2.09 (m, 1H), 1.75 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.6$ (C_{quat}), 145.8 (C_{quat}), 136.2 (C_{quat}), 132.9 (C_{quat}), 128.9 (CH), 127.6 (C_{quat}), 109.0 (CH), 106.8 (CH), 101.1 (CH_2), 72.9 (CH), 67.2 (C_{quat}), 58.4 (CH_2), 56.3 (CH_3), 51.6 (CH_2), 41.8 (CH_2), 37.1 (CH_2), 32.1 (CH_2), 29.6 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 353 and 351 (1 and 4) $[M]^{+\bullet}$, 338 and 336 (<1 and 3), 323 and 321 (10 and 30), 322 and 320 (47 and 100), 316 (5), 295 and 293 (10 and 30); HRMS: *m/z* calcd for $C_{18}H_{22}{}^{35}ClNO_4$: 351.1237 $[M]^{+\bullet}$; found: 351.1240.

19: PPh_3 (155 mg, 591 μmol), imidazole (40 mg, 591 μmol), and iodine (113 mg, 443 μmol) were added to a magnetically stirred solution of the alcohol **18** (52 mg, 148 μmol) in anhydrous toluene (3 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 18 °C for 16 h, then $Na_2S_2O_3$ (2 mL of a saturated aqueous solution) was added, and stirring was continued for 5 min. The mixture was extracted with ethyl acetate (3×20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 4:96) gave **19** (51 mg, 75%) as a white powder. $R_f = 0.1$ (ethyl acetate/hexane = 4:96); decomp. from 121 °C; $[\alpha]_D^{20} = -60.1$ ($c = 1.0$ g $(100\ mL)^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu} = 2922$, 2837, 1502, 1484, 1384, 1234, 1130, 1095, 1039, 931, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.62$ (s, 1H), 6.58 (s, 1H), 6.19 (dd, $J = 6.6$, 2.2 Hz, 1H), 5.92 (d, $J = 1.4$ Hz, 1H), 5.91 (d, $J = 1.4$ Hz, 1H), 3.65 (m, 1H), 3.27 (s, 3H), 3.34–3.16 (partially obscured m, 2H), 3.08–2.97 (complex m, 4H), 2.76–2.61 (complex m, 3H), 2.32–2.26 (complex m, 1H), 2.12 (dd, $J = 9.8$, 2.2 Hz, 1H), 1.75 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.6$ (C_{quat}), 145.7 (C_{quat}), 136.4 (C_{quat}), 132.5 (C_{quat}), 128.4 (CH), 127.7 (C_{quat}), 109.1 (CH), 106.7 (CH), 101.0 (CH_2), 72.7 (CH), 67.2 (C_{quat}), 56.2 (CH_3), 54.6 (CH_2), 43.7 (CH_2), 38.2 (CH_2), 32.2 (CH_2), 29.7 (CH_2), 4.4 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 463 and 461 (15 and 37) $[M]^{+\bullet}$, 433 and 431 (8 and 22), 432 and 430 (35 and 72), 426 (66), 405 and 403 (45 and 84), 336 and 334 (46 and 84), 278 and 276 (75 and 100), 240 (90); HRMS: *m/z* calcd for $C_{18}H_{21}{}^{35}ClINO_3$: 461.0255 $[M]^{+\bullet}$; found: 461.0254.

(−)-**1**: Bu_3SnH (56 μL, 210 μmol) was added over a period of 3.5 h to a magnetically stirred solution of AIBN (5 mg, 33 μmol; added in three equal aliquots over 2 h) and the iodide **19** (44 mg, 95 μmol) in anhydrous toluene (10 mL) at 80 °C under an argon atmosphere. Once the addition of Bu_3SnH was complete, the reaction mixture was cooled to 18 °C and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexane→CH_2Cl_2/hexane = 1:4→CH_2Cl_2/hexane = 1:1→CH_2Cl_2→methanol/CH_2Cl_2 = 2.5:97.5→methanol/CH_2Cl_2 = 5:95→methanol/CH_2Cl_2 = 1:9→methanol/CH_2Cl_2 = 1:4) to give (−)-**1** (25 mg, 89%) as a colorless oil. $R_f = 0.4$ (methanol/CH_2Cl_2 = 1:9); $[\alpha]_D^{20} = -187$ ($c = 1.2$ g $(100\ mL)^{-1}$, ethanol or $CHCl_3$); IR (film): $\tilde{\nu} = 2924$, 1502, 1481, 1371, 1231, 1101, 1080, 1036, 934, 875 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.58$ (s, 1H), 6.57 (s, 1H), 5.90 (d, $J = 1.6$ Hz, 1H), 5.89 (d, $J = 1.6$ Hz, 1H), 5.61 (m, 1H), 3.73 (m, 1H), 3.52 (m, 1H), 3.28 (s, 3H), 3.13 (ddd, $J = 14.4$, 8.0, 2.4 Hz, 1H), 3.00 (m, 1H), 2.97 (m, 1H), 2.73–2.67 (complex m, 2H), 2.60 (dd, $J = 16.8$, 5.6 Hz, 1H), 2.43 (m, 1H), 2.29 (dd, $J =$ 11.2, 4.0 Hz, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.63 ppm (br t, $J = 11.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.5$ (C_{quat}), 145.4 (C_{quat}), 140.6 (C_{quat}), 130.9 (C_{quat}), 126.6 (C_{quat}), 118.5 (CH), 109.2 (CH), 107.9 (CH), 100.8 (CH_2), 73.7 (CH), 64.7 (C_{quat}), 56.2 (CH_3), 47.1 (CH_2), 41.7 (CH_2), 40.8 (CH_2), 31.9 (CH_2), 27.1 (CH_2), 22.5 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 299 (35) $[M]^{+\bullet}$, 298 (10), 284 (6), 269 (20), 268 (54), 242 (80), 241 (95), 240 (100); HRMS: *m/z* calcd for $C_{18}H_{21}NO_3$: 299.1521 $[M]^{+\bullet}$; found: 299.1527.

[2] This material was contaminated with a small amount (≤5%) of triphenylphosphine oxide.

20: Ethylene oxide (≈2 mL, ≈40 mmol) was added to a solution of the amine **17** (114 mg, 370 μmol) in anhydrous MeOH (1.0 mL) at 0 °C under a nitrogen atmosphere. The reaction vessel was sealed, and the mixture was stirred magnetically at 45 °C for 48 h. The reaction mixture was then cooled to 18 °C, the vessel was opened, and the solvent was removed under reduced pressure to give an orange oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 2:3) afforded **20** (103 mg, 79 %) as a white foam. $R_f = 0.1$ (ethyl acetate/hexane = 2:3); $[\alpha]_D^{20} = +124.9$ ($c = 2.0$ g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu} = 3466$ (br), 2928, 2824, 1503, 1485, 1388, 1233, 1130, 1100, 1039, 985, 932, 847, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.59$ (s, 1H), 6.49 (s, 1H), 6.20 (dd, $J =$ 6.5, 2.5 Hz, 1H), 5.90 (br s, 2H), 3.76–3.67 (complex m, 2H), 3.56 (m, 1H), 3.33 (s, 3H), 3.11–2.67 (complex m, 7H), 2.59–2.47 (complex m, 2H), 2.19 (m, 1H), 1.78 ppm (dd, $J = 14.5$, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.5$ (C_{quat}), 146.4 (C_{quat}), 137.1 (C_{quat}), 133.8 (C_{quat}), 128.6 (C_{quat}), 128.2 (CH), 107.7 (CH), 106.9 (CH), 101.0 (CH_2), 73.0 (CH), 67.3 (C_{quat}), 58.0 (CH_2), 56.2 (CH_3), 52.2 (CH_2), 40.6 (CH_2), 39.5 (CH_2), 32.2 (CH_2), 29.9 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 353 and 351 (20 and 45) $[M]^{+\bullet}$, 338 and 336 (5 and 25), 323 and 321 (28 and 62), 322 and 320 (80 and 100), 295 and 293 (50 and 84), 258 (86), 224 (70), 214 (86); HRMS: *m/z* calcd for $C_{18}H_{22}{}^{35}ClNO_4$: 351.1237 $[M]^{+\bullet}$; found: 351.1228.

21: PPh_3 (149 mg, 568 μmol), imidazole (39 mg, 568 μmol), and iodine (108 mg, 426 μmol) were added to a magnetically stirred solution of the alcohol **20** (50 mg, 142 μmol) in anhydrous toluene (3 mL). The resulting mixture was stirred at 18 °C under a nitrogen atmosphere for 16 h, then $Na_2S_2O_3$ (2 mL of a saturated aqueous solution) was added, and stirring was continued for 5 min. The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography (silica, ethyl acetate/hexane = 5:95) gave **21** (52 mg, 79 %) as an off-white foam. $R_f = 0.1$ (ethyl acetate/hexane = 5:95); $[\alpha]_D^{20} = +63.2$ ($c = 1.0$ g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu} =$ 2927, 2823, 1502, 1484, 1387, 1234, 1134, 1107, 1092, 1039, 986, 931, 852 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.58$ (s, 1H), 6.48 (s, 1H), 6.19 (dd, $J = 6.3$, 2.6 Hz, 1H), 5.89 (s, 2H), 3.68 (m, 1H), 3.34 (s, 3H), 3.23–3.15 (complex m, 3H), 2.99–2.55 (complex m, 7H), 2.18 (m, 1H), 1.77 ppm (dd, $J = 14.3$, 11.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 146.4 (C_{quat}), 146.3 (C_{quat}), 137.2 (C_{quat}), 133.8 (C_{quat}), 128.5 (C_{quat}), 128.0 (CH), 107.8 (CH), 106.9 (CH), 100.9 (CH_2), 73.0 (CH), 67.1 (C_{quat}), 56.2 (CH_3), 54.3 (CH_2), 42.6 (CH_2), 40.9 (CH_2), 32.4 (CH_2), 29.8 (CH_2), 4.9 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 463 and 461 (6 and 16) $[M]^{+\bullet}$, 432 and 430 (14 and 37), 426 (29), 405 and 403 (18 and 50), 336 and 334 (20 and 53), 278 and 276 (41 and 100), 240 (56), 73 (52), 69 (70), 43 (75); HRMS: *m/z* calcd for $C_{18}H_{21}{}^{35}ClINO_3$: 461.0255 $[M]^{+\bullet}$; found: 461.0253.

3-*epi*-(+)-**1**: Bu_3SnH (67 μL, 248 μmol) was added over a period of 3.5 h to a magnetically stirred solution of AIBN (5 mg, 33 μmol; added in three equal aliquots over 2 h) and the iodide **21** (52 mg, 113 μmol) in anhydrous toluene (11 mL) at 80 °C under an argon atmosphere. Once the addition of Bu_3SnH was complete, the reaction mixture was cooled to 18 °C and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexane → CH_2Cl_2/hexane = 1:4 → CH_2Cl_2/hexane = 1:1 → CH_2Cl_2 → methanol/CH_2Cl_2 = 2.5:97.5 → methanol/CH_2Cl_2 = 5:95 → methanol/CH_2Cl_2 = 1:9 → methanol/CH_2Cl_2 = 1:4) to give 3-*epi*-(+)-**1** (34 mg, 100 %) as a pale-yellow semisolid. $R_f = 0.4$ (methanol/CH_2Cl_2 = 1:9); $[\alpha]_D^{20} = +204$ ($c = 1.0$ g (100 mL)$^{-1}$, $CHCl_3$); IR (film): $\tilde{\nu} = 2927$, 1502, 1481, 1376, 1230, 1099, 1039, 933, 864 cm^{-1}; ^{1}H NMR (800 MHz, $CDCl_3$): $\delta = 6.66$ (s, 1H), 6.48 (s, 1H), 5.86 (d, $J = 1.6$ Hz, 1H), 5.86 (d, $J = 1.6$ Hz, 1H), 5.69 (m, 1H), 3.57 (m, 1H), 3.50 (m, 1H), 3.20 (s, 3H), 3.14 (m, 1H), 3.10 (m, 1H), 3.03–2.98 (complex m, 1H), 2.79 (m, 1H), 2.55–2.52 (complex m, 2H), 2.41 (m, 1H), 2.34 (m 1H), 2.22–2.18 (complex m, 2H), 1.86 ppm (dd, $J = 14.4$, 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.5$ (C_{quat}), 146.3 (C_{quat}), 141.4 (C_{quat}), 132.3 (C_{quat}), 125.7 (C_{quat}), 119.0 (CH), 108.1 (CH), 107.3 (CH), 100.8 (CH_2), 74.8 (CH), 64.7 (C), 55.9 (CH_3), 46.4 (CH_2), 40.9 (CH_2), 40.0 (CH_2), 30.7 (CH_2), 27.5 (CH_2), 21.7 ppm (CH_2); MS (EI, 70 eV): *m/z* (%): 299 (26) $[M]^{+\bullet}$, 298 (6), 284 (5), 269 (18), 268 (44), 242 (54), 241 (83), 240 (100); HRMS: *m/z* calcd for $C_{18}H_{21}NO_3$: 299.1521 $[M]^{+\bullet}$; found: 299.1519.

Crystallography

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, $\lambda = 0.71073$ Å), and data were extracted by using the DENZO package.[15] The structure was solved by direct methods (SIR92).[16] The structure of compound **18** was refined by using the CRYSTALS program package.[17] CCDC-640224 contains the supplementary crystallographic data for this paper. These data can be obtained free-of-charge from The Cambridge Crystallographic Data Centre at http://www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for **18**: $C_{18}H_{22}ClNO_4$, $M_r = 351.82$, $T = 200(1)$ K, monoclinic, space group $P2_1$, $Z = 2$, $a = 8.9545(2)$, $b = 7.4385(2)$, $c = 12.6365(3)$ Å, $\beta =$ 93.1564(13)°, $V = 840.42(4)$ Å^3, $D_x = 1.390$ g cm^{-3}, 3809 unique data ($2\theta_{max} = 55°$), 3556 with $I > 3.0\sigma(I)$, $R = 0.0269$, $Rw = 0.0316$, $S = 1.0524$, Flack parameter = 0.01(4).

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