Highly Efficient and Enantioselective Synthesis of Carbocyclic Nucleoside Analogs Using Selective Early Transition Metal Catalysis

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The development of synthetic routes to carbocyclic nucleoside analogs has attracted considerable attention, due partly to the interesting biological activity of these compounds and also to the persistent challenges associated with constructing substituted 5-membered carbocycles with defined relative and absolute stereochemistry.[3] Particularly noteworthy members of this class of compounds include the naturally-occurring carbocyclic adenosine analog (−)-aristeromycin (**1**), the biosynthesis[4] and biological activity[5] of which have been subject to recent intensive scrutiny; the related natural product (−)-3′-deoxyaristeromycin (**2**);[6] (−)-carbovir (**3**), a selective inhibitor of HIV reverse transcriptase *in vitro*;[7] and the structurally related (−)-1592U89 succinate (**4**), which has been reported to have a higher oral bioavailability than carbovir and is currently in clinical trials for the treatment of HIV infection (Figure 1).[8]

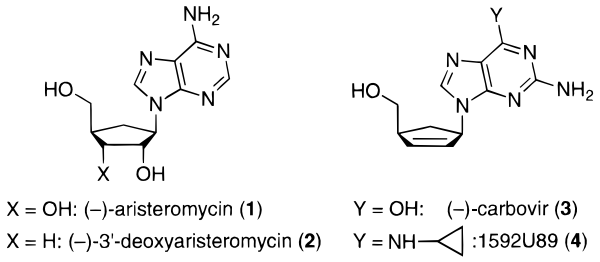

Figure 1.

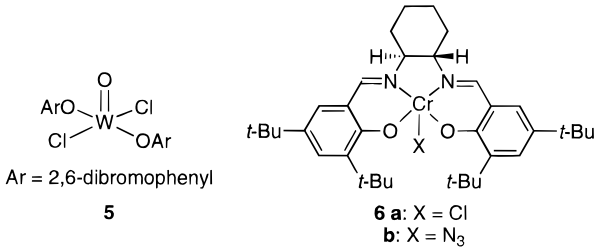

Figure 2.

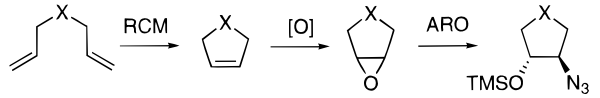

Figure 3.

Our two groups recently uncovered effective catalysts for the highly selective synthesis and manipulation of 5-membered cyclic structures (Figure 2). Complex **5**, generated in situ by the combination of $WOCl_4$ and 2,6-dibromophenol, is a useful and inexpensive catalyst for the ring-closing metathesis (RCM) of acyclic dienes to afford 5- and 6-membered cyclic compounds.[9] The (salen)Cr complex **6** has been identified as a catalyst for the asymmetric ring-opening (ARO) of meso and racemic epoxides by $TMSN_3$,[10] with particularly high enantioselectivity displayed for the opening of epoxides fused to 5-membered rings. The sequential application of these two catalytic transformations, along with an intermediary epoxidation reaction, could constitute an efficient method for the conversion of simple dienes to cyclic 1,2-amino alcohols wherein a new C−C bond has been constructed and two contiguous stereogenic centers have been established with high relative and absolute control (Figure 3). In this paper, the power of this strategy is illustrated in the efficient synthesis of key intermediates leading to the carbocyclic nucleoside analog structures outlined in Figure 1.

The key intermediate epoxide **10** needed for this synthetic approach was obtained in four steps from commercially available diethyl diallylmalonate (Scheme 1). Decarboxylation followed by RCM with catalyst **5** under previously reported conditions[9] produced the 3-cyclopentenecarboxylic ester **8** in 61% overall yield after distillation. Epoxidation of **8** was effected with *m*-chloroperoxybenzoic acid (*m*-CPBA), providing a 3:1 mixture of anti- and syn-isomers.[11] The pure *anti*-epoxide **9** was isolated in 70% yield after chromatogra-

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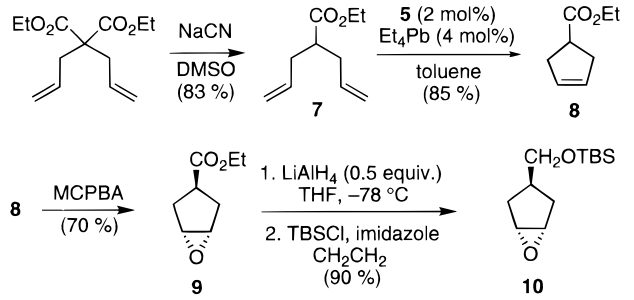
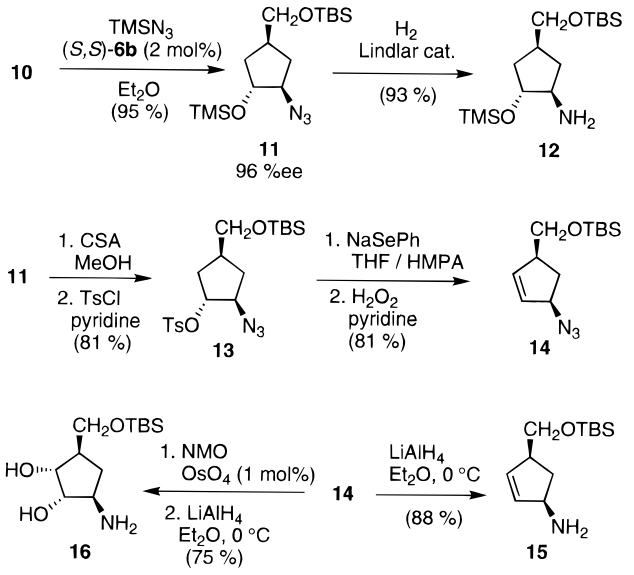
Scheme 1



Scheme 2



phy. Although molybdenum-catalyzed epoxidation of **8** with alkyl hydroperoxides provided superior diastereoselectivity (up to 12:1 anti/syn), competing decomposition of the products resulted in diminished isolated yields of the desired epoxide. Reduction of ester **9** with $LiAlH_4$ and conversion to the *tert*-butyldimethylsilyl (TBS) ether afforded **10** in high yield with no detectable epoxide-opening.

Enantioselective ring opening of epoxide **10** with $TMSN_3$ catalyzed by (*S*,*S*)-**6b** proceeded quantitatively to a single product, providing azido silyl ether **11** in 95% yield and in 96% ee after purification by distillation (Scheme 2).[12] Hydrogenation of azido silyl ether **11** over Lindlar's catalyst provided the enantiomerically enriched 3′-deoxyaristeromycin precursor **12** in 93% yield.[6c]

Synthesis of the carbocyclic cores of compounds **1**, **3**, and **4** required elimination of the TMS ether from **11**. Camphorsulfonic acid (CSA)-catalyzed selective removal of the trimethylsilyl group was followed by tosylation of the resultant secondary alcohol to produce activated intermediate **13**. Attempts to effect elimination directly from **13** using a variety of Brønsted bases either failed altogether or provided very poor yields of the desired alkene **14**. In contrast, nucleophilic tosylate displacement by sodium phenyl selenide[13] and subsequent oxidative elimination of the resulting selenide proved effective and afforded azido cyclopentene **14** in 81% yield. Synthesis of the carbocyclic cores of (−)-carbovir (**3**) and (−)-1592U89 (**4**) was provided by reduction of **14** to amine **15**.[14] Synthesis of the core structure of (−)-aristeromycin (**1**) was achieved by a highly diastereoselective OsO_4-catalyzed dihydroxylation[15] of **14** followed by azide reduction to provide amino diol **16** in 75% yield over two steps.[16]

The approach to carbocyclic nucleoside analogs outlined herein is rendered efficient by virtue of the successive use of catalytic reactions that are not only highly-selective and clean but also afford product with minimal generation of waste byproducts. Application of these early-transition metal-catalyzed reactions to a range of other targets of synthetic and biological interest is under active investigation in our laboratories.

Experimental Section

3-Cyclopentenecarboxylic Acid, Ethyl Ester (8). The reported procedure for the decarboxylation of diethyl diallylmalonate followed by ring-closing metathesis of the resulting diene (**7**)[9] was followed with minor modifications: A 500 mL flask was charged with tungsten oxychloride (0.813 g, 2.38 mmol), 2,6-dibromophenol (1.20 g, 4.76 mmol), and toluene (25 mL), and the resulting mixture was heated to reflux for 1 h under N_2. Volatile materials were removed under reduced pressure, and the solid residue was kept under vacuum for 30 min. The flask was then charged with dry toluene (160 mL), tetraethyllead (1.54 g, 4.76 mmol), and **7** (22.0 g, 131.0 mmol), and the mixture was heated at 90 °C for 1.5 h under N_2. After being cooled to room temperature, the mixture was filtered through a 1 cm pad of silica and the silica pad was rinsed with *tert*-butyl methyl ether (TBME) (300 mL). The organic layers were combined and washed with 1% NaOH (2 × 300 mL), water (2 × 200 mL), and saturated NH_4Cl (200 mL). After drying ($MgSO_4$) and removal of the solvent under reduced pressure, distillation (60−64 °C, 15 Torr) provided **8** (15.60 g, 85%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.10 (quin, J = 8.3 Hz, 1H), 2.65 (d, J = 7.8 Hz, 4H) 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1, 128.9, 60.4, 41.5, 36.3, 14.2.

***trans*-3,4-Epoxycyclopentenecarboxylic Acid, Ethyl Ester (9).** To a cooled (0 °C) solution of cyclopentene ester **8** (17.10 g, 122.00 mmmol) in CH_2Cl_2 (260 mL), *m*-chloroperbenzoic acid (27.54 g, 159.60 mmol) was added in three portions. The reaction was allowed to warm to room teperature and after 4 h filtered to remove the precipitated *m*-chlorobenzoic acid. The solids were rinsed with CH_2Cl_2 (150 mL), and the combined organic layers were then washed with saturated $NaHCO_3$ (200 mL), 10% Na_2SO_3 (200 mL), and saturated $NaHCO_3$ (200 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to give 20.5 g of a clear liquid identified by ^{1}H NMR to be a 3:1 mixture of **9** and its cis diastereomer; purification by flash chromatography provided **9** in pure form (13.43 g, 70.5%): TLC R_f = 0.27−0.28 (1:4 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (q, J = 7.1 Hz, 2H), 3.50 (s, 2H),2.62 (m, 1H), 2.32 (dd, J = 14.1, 8.0 Hz, 2H), 1.86 (dd, J = 14.0, 9.8 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.6, 60.3, 55.9, 37.2, 30.9, 13.9; exact mass (EI) calcd for $(C_8H_{12}O_3)^+$ 156.0786, found 156.0791.

***trans*-4-[(*tert*-Butyldimethylsiloxy)methyl]-1,2-epoxycyclopentane (10).** Under N_2, $LiAlH_4$ (36.2 mL, 36.2 mmol, 1 M in THF) was added in two portions to a cooled (−78 °C) solution of **9** (11.04 g, 70.70 mmol) in dry THF (500 mL). After 4.5 h, the solution was warmed to 0 °C and quenched by the method

(12) Complex **2b** catalyzes the ring opening of epoxides by $TMSN_3$ with the same enantioselectivity as chloride complex **2a**; however, the use of azide complex **2b** avoids the production of minor amounts of a chloride addition side product observed when catalyst **2a** is used: Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389.

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of Fieser[17] (1.4 mL of H_2O, 1.4 mL of 15% NaOH, and 4.1 mL of H_2O). The solution was allowed to warm to room temperature and filtered through a 1 cm pad of Celite. The Celite pad was washed with hot EtOAc (300 mL), and the combined filtrates were concentrated to give a clear oil (7.82 g, 97%).

Imidazole (10.26 g, 150 mmol) and *tert*-butyldimethylsilyl chloride (11.47 g, 76.1 mmol) were added to a solution of the oil (7.82 g) in CH_2Cl_2 (120 mL). When TLC analysis indicated complete consumption of the starting material, the reaction was diluted with CH_2Cl_2 (150 mL) and the solution was washed with saturated $NaHCO_3$ (3 × 200 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (3 × 150 mL); the organic layers were combined, washed with saturated NH_4Cl (3 × 200 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography provided **12** (14.28 g, 91%) as a clear liquid: TLC R_f = 0.43 (1:9 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.52 (d, J = 5.2 Hz, 2H), 3.44 (s, 2H), 2.04 (dd, J = 13.5, 7.6 Hz, 2H), 1.94 (m, 1H), 1.46 (dd, J = 13.6, 9.1 Hz, 2H), 0.86 (s, 9H), 0.004 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.7, 57.2, 35.4, 30.6, 25.9, 18.3, −5.4; exact mass (EI) calcd for $(C_{12}H_{24}O_2Si)^+$ 228.1546, found 228.1552.

(1*R*,2*R*,4*S*)-4-[(*tert*-Butyldimethylsiloxy)methyl]-2-azido-1-(trimethylsiloxy)cyclopentane (11). To a solution of (*S*,*S*)-**6b** (0.94 g, 1.32 mmol) in 20 mL of dry Et_2O was added epoxide **10** (12.1 g, 53.0 mmol) under N_2. After 15 min, $TMSN_3$ (9.14 g, 79.3 mmol) was added, and the resulting brown solution was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was filtered through a 3 cm pad of silica gel with 1:4 EtOAc/hexane (150 mL). The filtrate was concentrated and purified by distillation (115-117 °C, 2 Torr) to provide **11** (17.1 g, 94%, 96% ee). Use of the above procedure with catalyst **6a** provided **11** in 91% yield and 96% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (ddd, J = 6.8, 6.8, and 6.8 Hz, 1H), 3.61 (ddd, J = 9.0, 7.2 and 6.6 Hz, 1H), 3.46 (d, J = 5.5 Hz, 2H), 2.28 (m, 1H), 2.07 (ddd, J = 13.2, 8.0, 7.7 Hz, 1H), 1.75−1.60 (m, 2H), 1.33 (ddd, J = 13.2, 8.7, 8.9 Hz, 1H), 0.89 (s, 9H), 0.13 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 77.3, 68.5, 66.5, 36.2, 35.3, 31.1, 26.0, 18.3, 0.03, −5.4; exact mass (CI, NH_3) calcd for ($C_{15}H_{33}N_3O_2Si_2$ + H) 344.2190, found 344.2191.

(1*R*,2*R*,4*S*)-4-[(*tert*-Butyldimethylsiloxy)methyl]-2-amino-1-(trimethylsiloxy)cyclopentane (12). A 10 mL flask containing 0.0053 g of palladium on calcium carbonate (Lindlar catalyst, 6.3%) and a solution of **11** (0.08 g, 0.232 mmol) in EtOH (4 mL) was stirred at room temperature under a H_2 atmosphere (1 atm). When TLC analysis indicated complete consumption of the starting azide, the hydrogen atmosphere was displaced by N_2, the reaction was filtered through a 1 cm pad of Celite, and the filtrate was concentrated, providing **12** (0.70 g, 95%) as a clear yellow liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.62 (ddd, J = 7.0, 7.0, and 7.0 Hz, 1H), 3.46 (d, J = 5.4 Hz, 2H), 3.00 (ddd, J = 9.4, 6.9, 6.0 Hz, 1H), 2.23 (m, 1H), 2.02 (ddd, J = 12.8, 8.4, and 7.2 Hz, 1H), 1.74 (ddd, J = 12.9, 7.2, and 5.5 Hz, 1H), 1.58 (ddd, J = 13.2, 9.9, 7.2 Hz, 1H), 1.08 (ddd, J = 12.7, 9.3, 8.5 Hz, 1H), 0.89 (s, 9H), 0.11 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 80.7, 67.0, 60.0, 36.1, 35.3, 34.5, 26.0, 18.4, 0.3, −5.3; exact mass (EI) calcd for $C_{19}H_{18}N_4O_3Na$ 373.1277; found 373.1276.

(1*R*,2*R*,4*S*)-4-[(*tert*-Butyldimethylsiloxy)methyl]-2-azido-1-[(*p*-toluenesulfonyl)oxy]cyclopentane (13). (1*S*)-(+)-10-camphorsulfonic acid (0.264 g, 1.14 mmol) was added to a cooled (0 °C) solution of **11** (19.56 g, 56.92 mmol) in MeOH (190 mL). When TLC analysis indicated complete consumption of the starting material (∼10 min), the reaction was quenched by the addition of Et_3N (1 mL), diluted with EtOAc (200 mL), and washed with saturated $NaHCO_3$ (200 mL) and H_2O (2 × 200 mL). The aqueous layers were combined and extracted with EtOAc (2 × 200 mL). All the organic layers were combined, washed with saturated NH_4Cl (200 mL), dried ($MgSO_4$), and concentrated *in vacuo*.

To a cooled (0 °C) solution of the residue in CH_2Cl_2 (75 mL) and pyridine (15 mL) was added *p*-toluenesulfonyl chloride (17.2 g, 90.2 mmol), and the mixture was allowed to warm to room temperature. When TLC analysis indicated complete consumption of the starting alcohol, the reaction was diluted with CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (2 × 100 mL) and saturated NH_4Cl (2 × 100 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (2 × 100 mL). The organic extracts were combined and washed with saturated NH_4Cl (2 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure, and flash chromatography of the residue provided **15** (19.62 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 4.59 (ddd, J = 5.0, 5.0, and 5.0 Hz, 1H), 3.88 (ddd, J = 7.6, 7.6, 4.9 Hz, 1H), 3.46 (dd, J = 5.2, 2.0 Hz, 2H), 2.46 (s, 3H), 2.33 (m, 1H), 2.13 (ddd, J = 13.6, 8.1, 7.9 Hz, 1H), 1.83 (m, 2H), 1.42 (ddd, J = 13.6, 8.0, 7.8 Hz, 1H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 130.0, 129.9, 127.9, 85.7, 66.0, 65.5, 37.2, 33.2, 31.3, 25.9, 21.7, 18.2, −5.5; exact mass (FAB, *m*-nitrobenzylalcohol + NaI) calcd for $(C_{19}H_{31}O_4N_3SiS + Na)^+$ 448.1704, found 448.1702.

(1*R*,4*S*)-1-Azido-4-[(*tert*-butyldimethylsiloxy)methyl]-2-cyclopentene (14). A solution of sodium hydride (0.0056 g, 0.23 mmol) and diphenyl diselenide (0.037 g, 0.12 mmol) in dry THF (3 mL) was allowed to reflux under N_2. After 3 h, HMPA (0.52 g, 0.30 mmol) and **13** (0.067 g, 0.16 mmol) were added, and reflux was resumed under N_2. When TLC analysis indicated complete consumption of the starting material (4.5 h), the reaction was cooled to room temperature, and pyridine (55 μL, 0.68 mmol) and 30% H_2O_2 (0.13 mL) were added to the solution. After 10 h, the reaction was diluted with TBME (15 mL) and washed with H_2O (15 mL) and saturated $NaHCO_3$ (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated, and flash chromatography of the oil provided **14** (0.032 g, 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.03 (ddd, J = 5.6, 3.7, 1.9 Hz, 1H), 5.78 (ddd J = 5.6, 4.2, 2.1 Hz, 1H), 4.36 (m, 1H), 3.54 (dd, J = 2.0, 6.9 Hz, 2H), 2.86 (m, 1H), 2.39 (ddd J = 14.1, 8.3, 5.9 Hz, 1H), 1.53 (ddd, J = 14.1, 9.9, 4.9 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 129.7, 66.8, 66.7, 47.8, 32.8, 25.9, 18.4, −5.3; exact mass (CI) calcd for $(C_{12}H_{23}N_3OSi + NH_4)^+$ 271.1956, found 271.1959.

(1*R*,4*S*)-1-Amino-4-[(*tert*-butyldimethylsiloxy)methyl]-2-cyclopentene (15). Under N_2, $LiAlH_4$ (0.88 mL, 0.88 mmol, 1 M in THF) was added to a cooled (0 °C) solution of **14** (0.20 g, 0.79 mmol) in dry Et_2O (5 mL). When TLC analysis indicated complete consumption of the starting material (1 h), the solution was quenched by the method of Fieser[17] (0.4 mL of H_2O, 0.4 mL of 15% NaOH, and 1 mL of H_2O). The solution was allowed to warm to room temperature and filtered through a 1 cm pad of silica, and the silica pad was washed with hot EtOAc (100 mL). The combined filtrates were concentrated to give **15** (0.70 g, 88%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.72 (dddd, J = 1.7, 5.6, 4.4, 8.2 Hz, 2H), 3.91 (ddd, J = 1.5, 5.4, 7.9 Hz, 1H), 3.54 (ddd, J = 5.8, 9.8, 19.1 Hz, 2H), 2.76 (m, 1H), 2.40 (ddd, J = 5.2, 8.2, 13.4 Hz, 1H), 1.12 (ddd, J = 5.6, 5.6, 13.3 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.0, 133.2, 66.9, 57.8, 47.9, 37.8, 26.0, 18.5, −5.2; exact mass (CI, cool probe) calcd for $(C_6H_{11}N_3O + NH_4)^+$ 159.1246, found 159.1242.

(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-[(*tert*-butyldimethylsiloxy)methyl]-1-cyclopentanamine (16). A solution of *N*-methylmorpholine *N*-oxide (89 μL, 0.51 mmol, 60% in H_2O) and osmium tetraoxide (16 μL, 0.0024 mmol, 0.15 M in H_2O) was added to a cooled (0 °C) solution of **14** (0.062 g, 0.245 mmol) in 1:1 THF/acetone (2.2 mL). When TLC analysis indicated complete consumption of the starting olefin (22 h), the reaction was diluted with CH_2Cl_2 (20 mL) and washed with 10% Na_2SO_3 (20 mL) and NH_4Cl (20 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated, and purification by flash chromatography (1:1 EtOAc:hexanes) provided a yellow oil (0.061 g, 86%).

Under N_2, $LiAlH_4$ (232 μL, 0.232 mmol, 1 M in THF) was added to a cooled (0 °C) solution of the oil (0.061 g, 0.211 mmol) in dry Et_2O (1.3 mL). When TLC analysis indicated complete consumption of the starting material (1 h), the solution was quenched by the method of Fieser[17] (9 μL of H_2O, 9 μL of 15% NaOH, and 27 μL of H_2O). The solution was allowed to warm to room temperature and filtered through a 1 cm pad of Celite. The Celite pad was washed with hot EtOAc (50 mL), and the combined filtrates were concentrated to give **16** (0.048 g, 87%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.97 (dd, J = 5.0, 10.0 Hz, 1H), 3.75 (dd, J = 4.0, 9.9 Hz, 1H), 3.68 (dd, J = 5.8, 11.5 Hz, 1H), 3.61 (dd, J = 5.6, 11.1 Hz, 1H), 3.55 (ddd, J = 6.1,

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6.1, 3.6 Hz, 1H), 2.08−2.14 (m, 2H), 1.02 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 77.1, 74.9, 65.4, 65.0, 44.7, 28.9, 25.9, 18.3, −5.5; exact mass (FAB, *m*-nitrobenzyl alcohol + NaI) calcd for $(C_{12}H_{27}O_3NSi + H)^+$ 262.1838, found 262.1839.

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