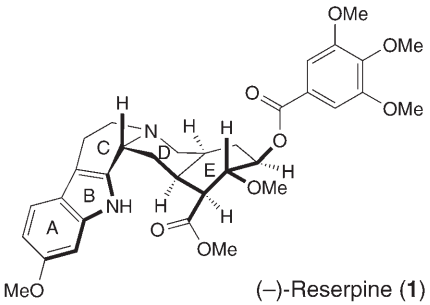
An Efficient Synthesis of a Potential (−)-Reserpine Intermediate from (−)-Shikimic Acid of the Chiral Pool

by **Jian Huang** and **Fen-Er Chen***

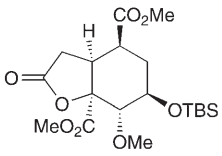
Department of Chemistry, Fudan University, Shanghai, 200433, P. R. China
(fax: +86-21-65643811; e-mail: rfchen@fudan.edu.cn)

A highly stereoselective route to the polysubstituted chiral octahydrobenzofuran **12**, a potential synthon for the *E*-ring core in the (−)-reserpine synthesis, is described. The α-bromo acetal **11** was obtained from inexpensive (−)-shikimic acid (**3**) through a series of highly stereoselective chemical reactions (*Scheme*). Et_3B/Bu_3SnH-Mediated intramolecular radical cyclization of **11** led to compound **12** with the required configuration.

Introduction. – (−)-Reserpine (**1**), a lipid-soluble pentacyclic indole alkaloid, has attracted wide interest of synthetic organic chemists for almost half a century due to both its remarkable bioactivity and structural complexity [1][1]). Eleven elegant strategies have provided successful access to this complex pentacyclic alkaloid since its total synthesis was first accomplished by *Woodward* and co-workers in 1958 [2]. The crucial issue in the reserpine synthesis is the construction of the configurationally complex *E*-ring core with five contiguous stereogenic centers. In the reported syntheses, the most attractive strategy lies in *Hanessian*'s approach [3] in which the easily available (−)-quinic acid (=1α,3*R*,4α,5*R*)-1,3,4,5-tetrahydroxycyclohexanecarboxylic acid) was used as a template from the chiral pool to construct the key *E*-ring core, the chiral hexahydrobenzofuran **2**.



(−)-Reserpine (**1**)



2

TBS = ^{t}BuMe$_2$Si

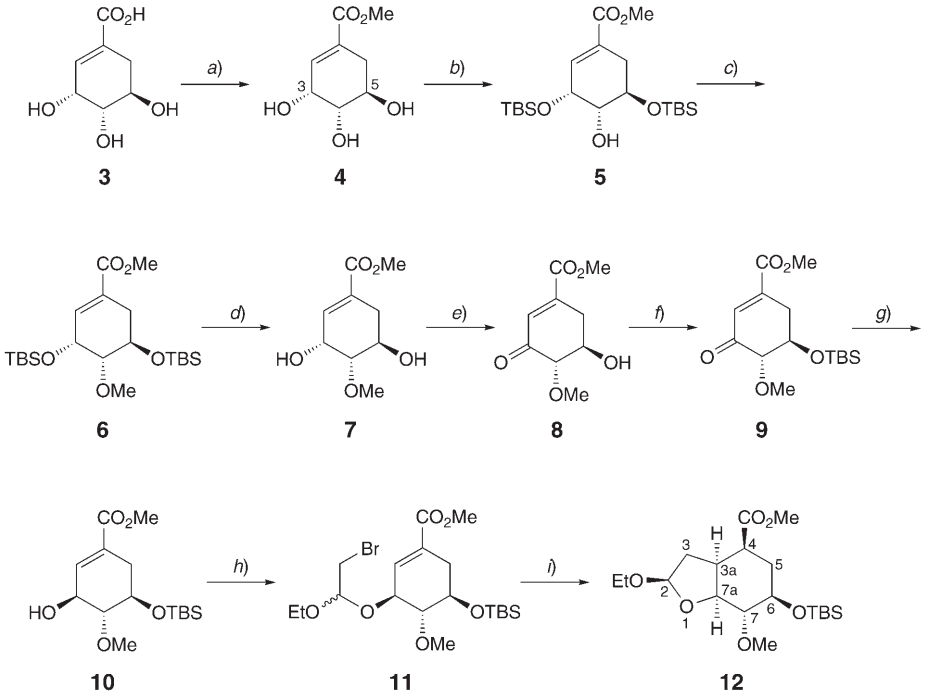
We envisioned that the (2*R*,3a*S*,4*S*,6*R*,7*R*,7a*S*)-octahydrobenzofuran **12**, an analogue of *Hanessian*'s *E*-ring core **2**, is a potential precursor for the *E*-ring segment in the

[1]) For a review on total syntheses of reserpine, see [1b].

(−)-reserpine synthesis. Herein we report an efficient synthesis of **12** by employing inexpensive (−)-shikimic acid (**3**) as starting material.

Results and Discussion. – For the synthesis of **12**, the commercially available (−)-shikimic acid (**3**) was esterificated in MeOH in the presence of acidic cation resin to give the corresponding ester **4**, whose OH groups at C(3) and C(5) were selectively protected as ^{t}BuMe$_2$Si ether to provide compound **5** [4] (*Scheme*). Under usual reaction conditions (MeI/KH or MeI/Ag$_2$O), the methylation of the OH group at C(4) of **5** led to the formation of a mixture of compounds which could not be separated by column chromatography (silica gel). Interestingly, on BaO/Ba(OH)$_2$-mediated methylation with Me$_2$SO$_4$ in DMSO/DMF 1:1, compound **5** furnished methyl ether **6** in 82% yield [5]. Desilylation of **6** with dilute AcOH in THF at 40° for 36 h generated diol **7**, which was subjected to pyridinium dichromate (PDC) oxidation [6] to yield the α,β-unsaturated ester **8** in 85% yield. A ^{t}BuMe$_2$Si group at OH−C(5) of **8** was smoothly

Scheme



TBS = ^{t}BuMe$_2$Si

a) MeOH, acidic cation resin, reflux, 15 h; 96%. *b*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, *N*,*N*-dimethylpyridin-4-amine (DMAP), DMF, 0–25°, 12 h; 95%. *c*) Me$_2$SO$_4$, BaO, Ba(OH)$_2$, DMSO, DMF, 0–25°, 18 h; 82%. *d*) AcOH/H$_2$O/THF 3:1:1, 40°, 36 h; 90%. *e*) PDC, DMF, 15°, 2 h, 85%. *f*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, DMAP, DMF, 0°, 12 h; 90%. *g*) NaBH$_4$, CeCl$_3$ · 7 H$_2$O, MeOH, −20°, 0.5 h; 85%. *h*) BrCH$_2$BrCHOEt, PhNMe$_2$, CH$_2$Cl$_2$, −78 to 25°, 24 h; 83%. *i*) Bu$_3$SnH, Et$_3$B/O$_2$, toluene, 0°, 5 h; 52%.

introduced by reaction of **8** with ^{t}BuMe$_2$SiCl and 1*H*-imidazole in DMF at room temperature (90% yield). Subsequent reduction of **9** under *Luche*'s conditions ($NaBH_4/CeCl_3 \cdot 7\,H_2O$) [7] afforded the allylic alcohol **10** as a single product with the required (3*S*) configuration.

With compound **10** in hand, our next concern was to introduce the α-bromoethyl ether side chain at OH–C(3). Initially, when allylic alcohol **10** was treated with *N*-bromosuccinimide and ethyl vinyl ether [8], no desirable α-bromo acetal **11** was obtained. Later on, treatment of **10** with 1,2-dibromoethyl ethyl ether (generated *in situ* from Br_2 and ethyl vinyl ether) in the presence of *N*,*N*-dimethylaniline led to α-bromo acetal **11** as an inseparable mixture of diastereoisomers (ratio 1.5 : 1, as determined by ^{1}H-NMR). In the final step, the remaining two stereogenic centers of the *E*-ring core of reserpine had to be introduced. Gratifyingly, treatment of **11** with Et_3B/Bu_3SnH [9][2]) induced an intramolecular radical cyclization, delivering the 3a,7a-'*exo*' cyclized product **12** with the required (3a*S*,4*S*) configuration.

The configuration of **12** was unambiguously ascertained by a sequence of 1D selective NOESY experiments as shown in *Fig. 1*. Irradiation of the H–C(7a) resonance at δ 3.99 resulted in NOE enhancements for protons H–C(4) at δ 2.73, H–C(3a) at δ 2.93 and H–C(6) at δ 3.36 (*Fig. 1*,*b*), while irradiation of the H–C(3a) resonance at δ 2.93 resulted in NOE enhancements for H–C(2) at δ 5.11 and H–C(7a) at δ 3.99 (*Fig. 1*,*c*). Key NOE correlations of **12** are presented in *Fig. 2*. The NOE signals between H–C(2), H–C(3a), H–C(4), H–C(6), and H–C(7a) indicated that they had the same relative orientation (α).

Conclusions. – In conclusion, starting from the commercially available (–)-shikimic acid (**3**), we succeeded in establishing an efficient synthetic method for the construction of the (2*R*,3a*S*,4*S*,6*R*,7*R*,7a*S*)-octahydrobenzofuran framework, which is a potential synthon for the *E*-ring segment of (–)-reserpine. Further efforts toward the asymmetric total synthesis of (–)-reserpine are currently underway.

Experimental Part

General. THF was distilled from Na/benzophenone, CH_2Cl_2, toluene from calcium hydride, and DMF and DMSO from calcium hydride under reduced pressure. BaO was ground to a fine powder in a mortar. Other reagents were obtained from commercial sources and used as received. Flash column chromatography (FC): silica gel. M.p.: uncorrected; *WRS-1B* digital melting-point apparatus. Optical rotations: *Jasco P1020* digital polarimeter. IR Spectra: *Jasco FT/IR-4200* spectrometer; $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker Avance-400* spectrometer; at 400 (^{1}H) and 100 (^{13}C) MHz; in $CDCl_3$ or (D_6)DMSO with $CHCl_3$ (δ(H) 7.24) or DMSO (δ(H) 2.49) and $CDCl_3$ (δ(C) 77.0) or (D_6)DMSO (δ(C) 39.5) as internal standards; δ in ppm, *J* in Hz. Mass spectra: *Waters Quattro-Micromass* instrument; electrospray ionization (ESI) techniques; in *m*/*z*.

*(3*R,*4*S,*5*R*)-3,4,5-Trihydroxycyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**4**). A mixture of (–)-shikimic acid (**3**; 20 g, 0.11 mol), acidic cation resin (32 g), and MeOH (600 ml) was heated under reflux for 15 h. After being cooled to r.t., the mixture was filtrated. The filtrate was concentrated and the residue recrystallized from AcOEt: **4** (20.7 g , 96%). White solid. M.p. 112–113°. $[\alpha]_D^{25} = -139$ ($c = 0.7$, MeOH). IR (KBr): 3321, 2901, 1718, 1656, 1433, 1242, 1094, 1069, 747, 609. ^{1}H-NMR ((D_6)DMSO): 6.61 (*m*, =CH); 4.78 (br. *s*, OH); 4.58 (br. *s*, OH); 4.22 (*s*, CH); 3.85 (*dd*, *J* = 10.0, 4.4, CH); 3.66 (*s*, Me); 3.57 (*dd*, *J* = 4.8, 4.8, CH); 3.28 (br. *s*, OH); 2.43 (*dddd*, *J* = 18, 4.8, 2.4, 2.4, 1 H); 2.05 (*ddd*, *J* = 18, 3.6, 1.6,

[2]) For a review on organoboranes as a source of radicals, see [9c].

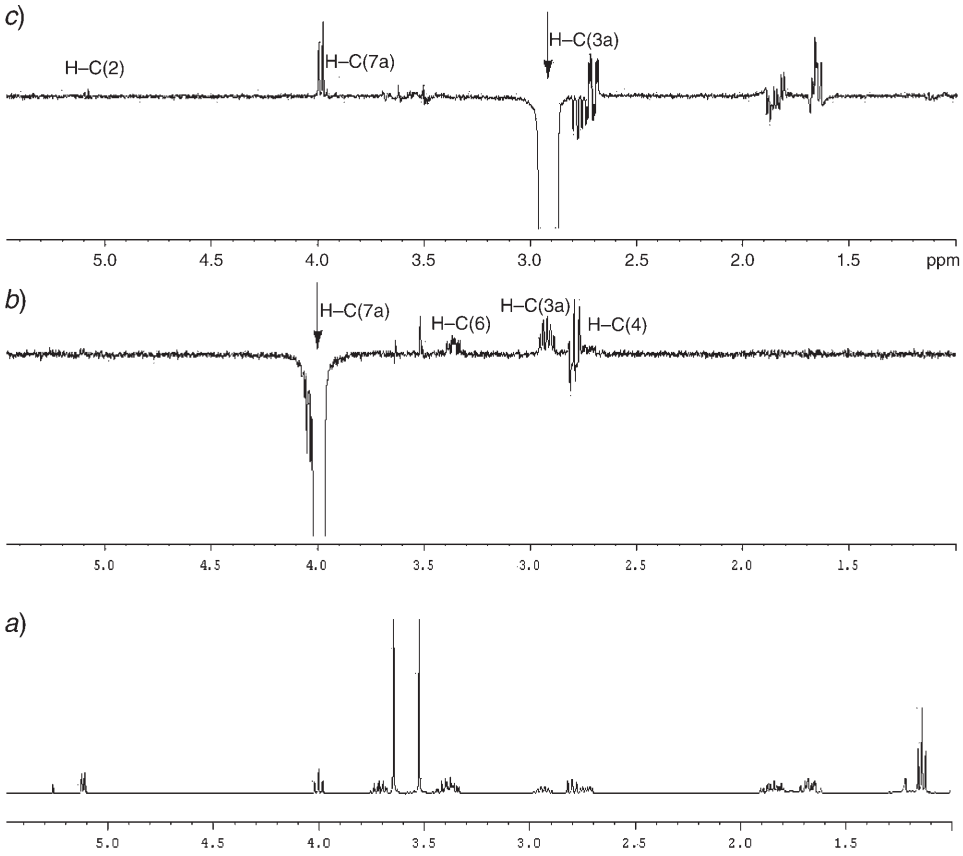


Fig. 1. *a*) *^{1}H-NMR Spectrum of* **12** *in $CDCl_3$.* b*) and* c*) 1D Selective NOESY plots.* Arrows indicate irradiated peaks.

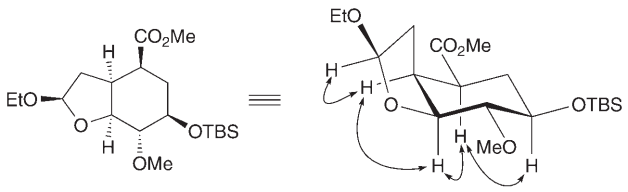


Fig. 2. *Observed NOE correlations of* **12**. TBS = ^{t}BuMe$_2$Si.

1 H). ^{13}C-NMR ((D$_6$)DMSO): 166.7; 139.7; 127.3; 70.0; 66.7; 65.3; 51.5; 29.6. ESI-MS: 211.2 ([*M* + Na]$^+$).

*(3*R*,4*S*,5*R*)-3,5-Bis[[(*tert*-butyl)dimethylsilyl]oxy}-4-hydroxycyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**5**). To a soln. of **4** (15 g, 80 mmol) in DMF (150 ml) at 0° were added sequentially 1*H*-imidazole (14.3 g, 210 mmol) and DMAP (4.8 g, 39.2 mmol). After the soln. turned clear, ^{t}BuMe$_2$SiCl (26.4 g, 175 mmol) was added in three parts at 0°. The resultant soln. was stirred at 0° for 2 h and at 25°

for 10 h. Then the soln. was diluted with AcOEt (400 ml) and washed with sat. aq. NH_4Cl soln. and brine, dried ($MgSO_4$), and concentrated. The residue was purified by FC (AcOEt/hexane 1:9): **5** (31.6 g, 95%) as a viscous oil, which slowly crystallized upon standing. M.p. 40–43° ([4]: M.p. 39–43.5°). $[\alpha]_D^{25} = -65.5$ ($c = 0.81$, MeOH) ([4]: $[\alpha]_D^{21} = -68.7$ ($c = 0.53$, MeOH)). IR (film): 3541, 2952, 2929, 2856, 1704, 1625, 1437, 1248, 1103, 1076, 893, 835, 777. ^{1}H-NMR ($CDCl_3$): 6.57 (*m*, =CH); 4.48 (*s*, CH); 4.13 (*dd*, *J* = 9.2, 3.6, CH); 3.68 (*s*, Me); 3.64 (*dd*, *J* = 4.4, 4.4, CH); 2.56 (*dddd*, *J* = 18.4, 4.4, 2.4, 2.4, 1 H); 2.51 (*s*, OH); 2.17 (*ddd*, *J* = 18.0, 1.2, 1.2, 1 H); 0.87 (*s*, 1 Me_3CSi); 0.80 (*s*, 1 Me_3CSi); 0.09 (*s*, 1 MeSi); 0.08 (*s*, 1 MeSi); 0.02 (*s*, 1 MeSi); 0.01 (*s*, 1 MeSi). ^{13}C-NMR ($CDCl_3$): 167.1; 137.3; 128.5; 70.7; 68.3; 67.6; 51.6; 29.6; 25.74; 25.63; 17.96; −4.7; −4.86; −4.96; −5.03. ESI-MS: 439.3 ($[M + Na]^+$).

*(3*R*,4*S*,5*R*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-4-methoxycyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**6**). To a soln. of **5** (30 g, 72 mmol) in DMF/DMSO 1:1 (484 ml), barium oxide (96 g, 625 mmol) and barium hydroxide octahydrate (54 g, 170 mmol) were added at 0°. Dimethyl sulfate (143 ml, 1.51 mol) was then added dropwise at 0° under N_2. After stirring for 18 h at 0°, the mixture was treated with conc. aq. ammonia soln. (60 ml), and subsequently neutralized (pH 7) at 0° with 4M HCl. The resultant soln. was extracted twice with AcOEt, the org. layer washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by FC (AcOEt/hexane 1:10): **6** (25.4 g, 82%). Viscous oil which slowly crystallized upon standing. M.p. 59–60°. $[\alpha]_D^{25} = -32.3$ ($c = 0.89$, MeOH). IR (film): 2942, 2736, 2708, 1719, 1650, 1434, 1363, 1338, 1258, 1190, 1110, 952, 845, 780. ^{1}H-NMR ($CDCl_3$): 6.70 (*m*, =CH); 4.63 (*s*, CH); 4.15 (*dd*, *J* = 8.8, 4.0, CH); 3.70 (*s*, 1 MeO); 3.47 (*s*, 1 MeO); 3.26 (*dd*, *J* = 4.4, 4.0, CH); 2.56 (*dddd*, *J* = 18.4, 4.4, 2.4, 2.4, 1 H); 2.17 (*ddd*, *J* = 18.4, 1.2, 1.2, 1 H); 0.91 (*s*, 1 Me_3CSi); 0.84 (*s*, 1 Me_3CSi); 0.10 (*s*, 1 MeSi); 0.09 (*s*, 1 MeSi); 0.06 (*s*, 1 MeSi); 0.04 (*s*, 1 MeSi). ^{13}C-NMR ($CDCl_3$): 167.1; 139.2; 127.9; 81.2; 67.8; 67.2; 59.7; 51.6; 30.3; 25.9; 25.7; 18.2; 17.9; −4.4; −4.73; −4.75; −4.85. ESI-HR-MS: 453.7315 ($C_{21}H_{42}NaO_5Si_2^+$; calc. 453.7223).

*(3*R*,4*S*,5*R*)-3,5-Dihydroxy-4-methoxycyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**7**). A mixture of **6** (20 g, 46.4 mmol), AcOH (120 ml, 2.08 mol), tetrahydrofuran (40 ml, 0.488 mol), and H_2O (40 ml, 2.22 mol) was stirred at 40° for 36 h. Then the mixture was concentrated and the residue purified by FC (AcOEt): **7** (8.4 g, 90%). Viscous oil. $[\alpha]_D^{25} = -104$ ($c = 0.96$, MeOH). IR (neat): 3420, 2952, 1707, 1653, 1439, 1263, 1100, 1042, 750, 666. ^{1}H-NMR ($CDCl_3$): 6.84 (*ddd*, *J* = 4.0, 2.0, 2.0, =CH); 4.50 (*dd*, *J* = 4.4, 4.4, CH); 4.09 (*ddd*, *J* = 8.0, 8.0, 5.6, CH); 3.72 (*s*, 1 MeO); 3.49 (*s*, 1 MeO); 3.26 (*dd*, *J* = 8.4, 4.4, CH); 2.82 (*dd*, *J* = 18.0, 5.2, 1 H); 2.48 (br. *s*, 2 OH); 2.21 (*dddd*, *J* = 18.4, 8.4, 2.0, 1.2, 1 H). ^{13}C-NMR ($CDCl_3$): 166.7; 136.1; 130.3; 82.0; 65.2; 63.5; 58.1; 52.0; 31.3. ESI-HR-MS: 225.1967 ($C_9H_{14}NaO_5^+$; calc. 225.1961).

*(4*S*,5*R*)-5-Hydroxy-4-methoxy-3-oxocyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**8**). To a soln. of **7** (8 g, 39.6 mmol) in DMF (133 ml), PDC (17.9 g, 47.7 mmol) was added slowly at 10°. After being stirred at 15° for 2 h, the soln. was diluted with AcOEt (250 ml). The resultant mixture was washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and concentrated. The residue was purified by FC (AcOEt/hexane 1:1): **8** (6.73 g, 85%). Light yellow oil. $[\alpha]_D^{25} = -101.7$ ($c = 0.55$, MeOH) ([3]: $[\alpha]_D = -142.0$ ($c = 1.12$, $CHCl_3$)). IR (neat): 3438, 2955, 2838, 1724, 1694, 1438, 1258, 1195, 1130, 738, 665. ^{1}H-NMR ($CDCl_3$): 6.73 (*d*, *J* = 2.8, =CH); 4.02 (*ddd*, *J* = 20.0, 10.0, 5.2, CH); 3.82 (*s*, 1 MeO); 3.66 (*d*, *J* = 10.4, CH); 3.65 (*s*, 1 MeO); 3.16 (*dd*, *J* = 18.8, 5.2, 1 H); 2.82 (br. *s*, OH); 2.57 (*ddd*, *J* = 18.8, 9.6, 3.2, 1 H). ^{13}C-NMR ($CDCl_3$): 198.0; 165.9; 144.8; 132.3; 87.3; 69.7; 60.3; 52.9; 32.4. ESI-MS: 223.1 ($[M + Na]^+$).

*(4*S*,5*R*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-methoxy-3-oxocyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**9**). To a soln. of **8** (6.5 g, 32.5 mmol) in DMF (100 ml) at 0°, 1*H*-imidazole (3.5 g, 51.4 mmol), DMAP (1.1 g, 9 mmol), and ^{t}BuMe$_2$SiCl (5.9 g, 39.4 mmol) were added sequentially. After being stirred for 12 h at 0°, the soln. was diluted with AcOEt (200 ml) and washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and concentrated. The residue was purified by FC (AcOEt/hexane 1:10): **9** (9.19 g, 90%). Light yellow oil. $[\alpha]_D^{25} = -77.4$ ($c = 0.80$, MeOH) ([3]: $[\alpha]_D = -78.7$ ($c = 1.21$, $CHCl_3$)). IR (neat): 2954, 2930, 2857, 1727, 1697, 1250, 1135, 1117, 836, 779, 666. ^{1}H-NMR ($CDCl_3$): 6.72 (*m*, =CH); 4.12 (*ddd*, *J* = 8.4, 7.2, 4.8, CH); 3.82 (*s*, 1 MeO); 3.54 (*s*, CH); 3.51 (*s*, 1 MeO); 2.93 (*ddd*, *J* = 18.4, 4.8, 0.8, 1 H); 2.58 (*ddd*, *J* = 18.8, 7.2, 2.4, 1 H); 0.86 (*s*, Me_3CSi); 0.07 (*s*, 1 MeSi); 0.06 (*s*, 1 MeSi). ^{13}C-NMR ($CDCl_3$): 198.1; 166.4; 144.5; 131.7; 86.0; 70.6; 59.8; 52.7; 33.2; 25.7; 18.0; −4.7; −5.0. ESI-MS: 337.2 ($[M + Na]^+$).

*(3*S*,4*R*,5*R*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-3-hydroxy-4-methoxycyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**10**). A soln. of **9** (9.0 g, 28.6 mmol) and $CeCl_3 \cdot 7\ H_2O$ (10.6 g, 28.6 mmol) in MeOH (220 ml) was stirred for 0.5 h at 25° and then cooled to −20°. $NaBH_4$ (1.1 g, 28.6 mmol) was added. After

being stirred at $-20°$ for 0.5 h, the mixture was concentrated, and H_2O (40 ml) was added to the residue. The resultant mixture was extracted with Et_2O, the org. layer washed with brine, dried (Na_2SO_4) and concentrated, and the residue purified by FC (AcOEt/hexane 1:4): **10** (7.62 g, 85%). Colorless oil. $[\alpha]_D^{25} = -20.5$ ($c = 1.3$, MeOH). IR (neat): 3429, 2953, 2930, 2857, 1721, 1655, 1437, 1252, 1110, 997, 837, 778, 666. ^{1}H-NMR ($CDCl_3$): 6.84 (*dd*, $J = 2.0, 2.0$, =CH); 4.12 (*s*, CH); 4.10 (*dd*, $J = 6.4, 5.2$, CH); 3.71 (*s*, 1 MeO); 3.48 (*s*, 1 MeO); 3.34 (*dd*, $J = 6.4, 4.4$, CH); 2.84 (br. *s*, OH); 2.54 (*ddd*, $J = 18.0, 2.4, 2.4$, 1 H); 2.37 (*dddd*, $J = 20.0, 3.2, 3.2, 1.6$, 1 H); 0.86 (*s*, Me_3CSi); 0.10 (*s*, 1 MeSi); 0.07 (*s*, 1 MeSi). ^{13}C-NMR ($CDCl_3$): 167.1; 136.9; 127.6; 82.3; 68.6; 67.9; 59.3; 51.8; 30.9; 25.7; 17.9; −4.9; −5.0. ESI-HR-MS: 339.4578 ($C_{15}H_{28}NaO_5Si^+$; calc. 339.4596).

*(3*S*,4*R*,5*R*)-3-[(1*RS*)-2-bromo-1-ethoxyethoxy]-5-{[(*tert*-butyl)dimethylsilyl]oxy}-4-methoxycyclohex-1-ene-1-carboxylic Acid Methyl Ester* (**11**). To a soln. of ethyl vinyl ether (=ethoxyethene; 3.4 ml, 35 mmol) in CH_2Cl_2 (30 ml) at $-78°$ was added dropwise a soln. of Br_2 (1.7 ml, 33.2 mmol) in CH_2Cl_2 (30 ml). After the addition, the mixture was allowed to warm to 25° and stirred for 10 min, then recooled to $-78°$. A soln. of *N*,*N*-dimethylaniline (=*N*,*N*-dimethylbenzenamine; 5.6 ml, 43.8 mmol) and **10** (7 g, 22.1 mmol) in CH_2Cl_2 (30 ml) was added dropwise while the temp. was kept at $-78°$. The mixture was stirred at $-78°$ for 30 min, then allowed to warm to 25°, and stirred for 24 h. The resultant mixture was diluted with CH_2Cl_2 (200 ml), the soln. washed with 1M HCl, sat. aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and concentrated, and the residue purified by FC (AcOEt/hexane 1:10): inseparable diastereoisomer mixture **11** (8.57 g, 83%; 1.5:1 by ^{1}H-NMR). Pale yellow oil. IR (neat): 2976, 1718, 1652, 1255, 1107, 1054, 1011, 836, 666. ^{1}H-NMR ($CDCl_3$): 6.67 (*dd*, $J = 5.6, 2.8$, =CH); 4.92 (*t*, $J = 5.2$, 0.6 H); 4.87 (*t*, $J = 5.2$, 0.4 H); 4.22 (*ddd*, $J = 4.0, 2.0, 2.0$, 0.4 H); 4.16 (*ddd*, $J = 4.0, 2.0, 2.0$, 0.6 H); 3.77–3.59 (*m*, overlapped, 3 H); 3.73 (*s*, 1.2 H); 3.72 (*s*, 1.8 H); 3.58 (*s*, 1.8 H); 3.56 (*s*, 1.2 H); 3.38 (*ddd*, $J = 14.8, 10.4, 4.8$, CH_2Br); 3.18 (*dd*, $J = 17.2, 9.6$, CH); 2.66 (*dd*, $J = 17.6, 5.6$, 1 H); 2.23 (*dddd*, $J = 17.6, 9.6, 3.2, 3.2$, 1 H); 1.24 (*t*, $J = 7.2$, Me); 0.89 (*s*, Me_3CSi); 0.09 (*s*, 1 MeSi); 0.07 (*s*, 1 MeSi). ^{13}C-NMR ($CDCl_3$; diastereoisomer mixture): 166.51; 166.47; 137.4; 136.4; 128.9; 103.3; 101.2; 86.1; 85.3; 78.0; 76.0; 71.11; 70.98; 62.4; 62.3; 61.3; 61.2; 51.99; 51.96; 33.99; 33.86; 32.14; 31.76; 25.81; 18.0; 15.19; 15.04; −4.66; −4.77. ESI-HR-MS: 490.4638 ($C_{19}H_{35}BrNaO_6Si^+$; calc. 490.4626).

*(2*R*,3a*S*,4*S*,6*R*,7*R*,7a*S*)-6-{[(*tert*-Butyl)dimethylsilyl]oxy}-2-ethoxy-7-methoxyoctahydrobenzofuran-4-carboxylic Acid Methyl Ester* (**12**). To a soln. of **11** (2 g, 4.27 mmol) and Bu_3SnH (3.46 ml, 12.8 mmol) in toluene (400 ml) under N_2 at 0°, 1M Et_3B in hexane (21.3 ml, 21.3 mmol) and air (20 ml) were added simultaneously *via* syringe within 3 h. After the addition, the mixture was stirred at 0° for another 2 h and then concentrated. The residue was purified by FC (AcOEt/hexane 1:10): **12** (0.86 g, 52%). Colorless oil. IR (neat): 2954, 2929, 2856, 1737, 1461, 1255, 1108, 1019, 837, 778, 666. ^{1}H-NMR ($CDCl_3$): 5.11 (*d*, $J = 5.2$, CH); 3.99 (*dd*, $J = 7.6, 7.6$, CH); 3.71 (*q*, $J = 7.2$, 1 H); 3.64 (*s*, 1 MeO); 3.52 (*s*, 1 MeO); 3.44–3.33 (*m*, 2 H); 2.93 (*ddd*, $J = 6.4, 12.8, 12.8$, CH); 2.79 (*dd*, $J = 9.2, 7.6$, CH); 2.73 (*ddd*, $J = 13.6, 5.2, 4.4$, CH); 1.86–1.78 (*m*, 2 H); 1.71–1.67 (*m*, 2 H); 1.14 (*t*, $J = 7.2$, Me); 0.846 (*s*, Me_3CSi); 0.04 (*s*, 1 MeSi); 0.02 (*s*, 1 MeSi). ^{13}C-NMR ($CDCl_3$): 173.4; 102.9; 87.4; 83.3; 72.1; 62.7; 60.7; 53.3; 51.8; 38.4; 37.7; 33.3; 30.7; 29.6; 25.8; 18.0; 15.1; −4.59; −4.65. ESI-HR-MS: 411.5675 ($C_{19}H_{36}NaO_6Si^+$; calc. 411.5665).

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Received March 19, 2007