Development of New Chiral Building Blocks for Synthesis of Bicyclo[3.3.0]octane Compounds

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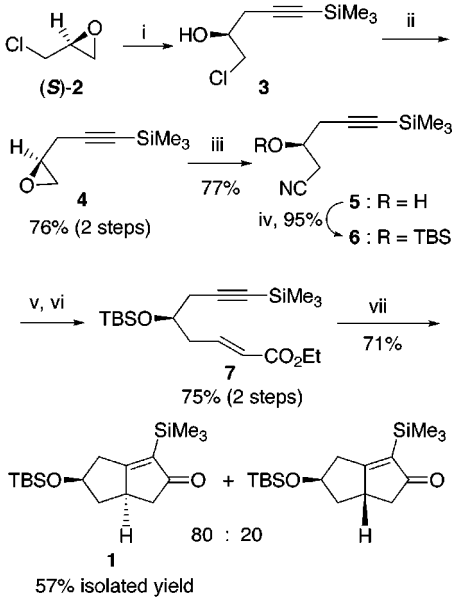
Abstract: Ti(II)-mediated tandem cyclization of (*E*)-5-(*tert*-butyldimethylsilyloxy)-8-trimethylsilyl-2-octen-7-ynoate (**7**) prepared from commercially available optically active epichlorohydrin (**2**) proceeded diastereoselectively to provide 7-(*tert*-butyldimethylsilyloxy)-2-trimethylsilylbicyclo[3.3.0]-oct-1-en-3-one (**1**), which serves as a useful chiral building block or intermediate to prepare a variety of compounds having a bicyclo[3.3.0]octane framework.

Optically active bicyclo[3.3.0]octane compounds containing a functional group(s) at a suitable position(s) have been widely accepted as an efficient chiral building block or intermediate for preparing both natural and nonnatural biologically active compounds such as carbacyclin,[1] alkaloids,[2] and cyclopentanoid and polyquinane natural products.[3] For the asymmetric synthesis of bicyclo[3.3.0]-octanes, increasing attention has been paid to the bicyclization reaction of acyclic 1,6-enyne compounds.[4] Herein, we report an efficient asymmetric synthesis of a new compound, 7-(*tert*-butyldimethylsilyloxy)-2-trimethylsilylbicyclo[3.3.0]oct-1-en-3-one (**1**), starting from commercially available optically active epichlorohydrin (**2**), in which a diastereoselective Ti(II)-mediated bicyclization of 5-siloxy-2-en-7-ynoate is a key step. We also show that **1** serves as a useful starting compound to prepare a variety of compounds having a bicyclo[3.3.0]octane framework, several of which also serve as versatile chiral building blocks.

Scheme 1. Synthesis of 1 Starting from Epichlorohydrin (2)[a]



[a] Key: (i) $Me_3SiC{\equiv}CAlEt_2$, hexanes, 0 °C; (ii) NaOH, CH_2Cl_2, rt; (iii) Et_2AlCN, THF−toluene, −30 °C; (iv) TBSCl, imidazole, CH_2Cl_2, rt; (v) *i*-Bu_2AlH, ether, −20 °C to rt; (vi) $(EtO)_2(O)PCH_2CO_2Et$, NaH, THF; (vii) Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl, −78 to −40 °C then *s*-BuOH.

Preparation of **1** from **2** was carried out according to the reaction sequence shown in Scheme 1. Thus, acetylene epoxide **4** was prepared from (*S*)-**2** (>98% ee, ee = enantiomeric excess) in 75% yield according to the reported procedure with minor modification.[5] Epoxide ring opening of **4** with cyano anion using Et_2AlCN provided **5** in 77% yield, the hydroxy group of which was silylated by treatment with *t*-$BuMe_2SiCl$/imidazole in 95% yield. From the resulting **6**, enyne **7** was prepared in 75% overall yield by reduction of the cyano group to aldehyde using *i*-Bu_2AlH and the following Horner−Wadsworth−Emmons olefination with $(EtO)_2(O)PCH_2CO_2Et$. The reaction of **7** with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl[6,7] afforded a mixture of bicyclic ketone **1**[8] and its C-5 epimer in a ratio of 80:20, and from which **1** was easily isolated in 57% yield by column chromatography.[9] Thus, **1** was prepared from **2** by a seven-step sequence in 23% overall yield. Although we used **2** with an (*S*)-configuration in this synthesis, because both enantiomers of **2** are commercially avail-

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(8) $[\alpha]^{30}_D$ +134.2 (*c* 0.298, $CHCl_3$). The stereochemistry was assigned by the NOE experiments and by derivatization to **13** (see Scheme 2).

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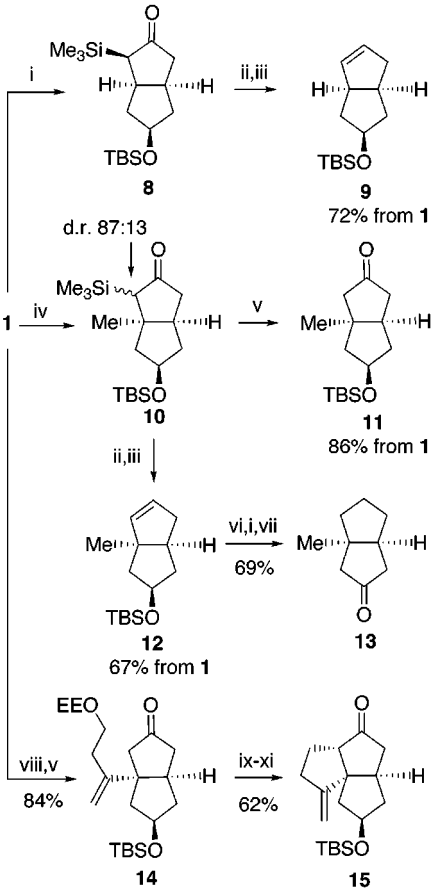
able, the present method allows access to both enantiomers of **1**. We also prepared several enynes of the type **7** having other ether groups besides the *tert*-butyldimethylsilyl (TBS) ether group and carried out their reaction with Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl. We found, however, that reaction of **7** with the TBS group afforded the highest selectivity and yield. Thus, the reaction of methoxymethyl and triphenylsilyl ether derivatives afforded the cyclized product of the type **1** in 55% yield with 69% ds and in 63% yield with 78% ds, respectively. Triisopropylsilyl and (triphenyl)methyl ethers afforded the product of the type **1** and its epimer in a similar ratio of 81:19 and 80:20, respectively, to that of the reaction with **7**; however, in these cases the two diastereomers were inseparable each other by column chromatography.

We have found that compound **1** can serve as a versatile starting substrate to prepare a variety of compounds having a bicyclo[3.3.0]octane structure by taking advantage of its multifunctional character. Several representative transformations are summarized in Scheme 2.

Hydrogenation of the double bond of **1** in the presence of a Pd/C catalyst proceeded quantitatively at room temperature to afford **8**[10,11] as a single product. After reduction of **8** with *i*-Bu$_2$AlH, treatment of the resulting alcohol with KH in THF underwent the Peterson olefination reaction[12] smoothly to afford bicyclo[3.3.0]oct-2-ene compound **9** in 72% overall yield, which might be useful as a new chiral building block by taking advantage of the reactivity of the olefin moiety.[13] The ease of base-promoted Peterson elimination suggests 1,2-cis stereochemistry for the 2-trimethylsilyl-1-cyclopentanol derived from **8**.

Conjugate addition of Me$_2$CuLi to **1** proceeded from the convex face exclusively to afford **10**[10,11] as a mixture of β- and α-trimethylsilyl isomers in a ratio of 87:13, from which desilylated compound **11**[11] was obtained by treatment with K_2CO_3 in MeOH in 86% overall yield from **1**. Reduction of the diastereomeric mixture of **10** with *i*-Bu$_2$AlH and the following Peterson olefination reaction using KH in THF provided **12** in 67% overall yield from **1**. The enantiomeric excess of **12** was confirmed by ^{1}H NMR analyses of the corresponding MTPA esters, after desilylation, to be more than 98%. The result that the compound **12** could be converted to known compound **13**[14] [[α]$^{25}_D$ −37.4 (*c* 0.615, $CHCl_3$) (lit.[14c] [α]$_D$ −22.4 (*c* 0.6, $CHCl_3$))] according to the procedure shown in Scheme 2 confirmed the stereochemistry of **1** shown in Scheme 1. The new compounds **10**−**12** obtained here might find utility respectively as a chiral building block or intermediate for synthesizing compounds having an angularly methylated bicyclo[3.3.0]octane structure,[15] which has been widely found as the main unit or a subunit in biologically important compounds.[3]

Scheme 2. Synthetic Transformation of 1[a]



[a] Key: (i) H_2, Pd/C, MeOH; (ii) *i*-Bu$_2$AlH, ether; (iii) KH, THF; (iv) Me$_2$CuLi, ether; (v) K_2CO_3, MeOH; (vi) TBAF, THF; (vii) PCC, CH_2Cl_2; (viii) H_2C=C(Br)CH_2CH_2OEE, *t*-BuLi, ether then (2-thienyl)Cu(CN)Li, THF; (ix) *p*-PTS, *i*-PrOH−ether; (x) MsCl, Et_3N, THF; (xi) KH, THF.

The synthetic utility of **1** can also be seen in its conversion to decahydrocyclopenta[*c*]pentalene **15**, which has an angular triquinane framework.[3] Thus, **1** reacted with the alkenylcuprate derived from H_2C=C(Li)CH_2CH_2-OEE (EE = 1-ethoxyethyl) and (2-thieny)Cu(CN)Li[16] to afford, after desilylation (K_2CO_3/MeOH), the corresponding conjugate addition product **14** in 84% yield. Then compound **14** was converted to **15**[11] in 62% overall yield by a conventional reaction sequence which involves deprotection of the primary hydroxy group (pyridium *p*-toluenesulfonate/*i*-PrOH−ether) and the following mesylation (methanesufonic acid chloride/Et_3N) and in-

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(10) The product was easily desilylated during column chromatography on silica gel and, therefore, was used for the next reaction without purification. Yields determined by ^{1}H NMR analysis using an internal standard were ~100% and 96% for **8** and **10**, respectively.

(11) The relative stereochemistry was confirmed by NOE experiments.

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(15) See ref 6c and references therein.

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tramolecular cyclization under basic condition (KH/THF). Compound **15** might serve as an intermediate for the synthesis of angular triquinane sesquiterpenes such as pentanelene and isocomane by taking advantage of versatile reactivity of the functionalities present.[17]

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Gemini-2000 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00). IR spectra were recorded on an FT-IR spectrometer (JASCO FT/IR-230) and are reported in wavenumbers (cm^{-1}). Elemental analyses were performed on an Elemental automatic CHN-analyzer. GC−MS (low-resolution mass spectrum, EI) analyses were performed on a Shimadzu QP-5000 GC−mass spectrometer. All reactions sensitive to oxygen and/or moisture were performed under an argon atmosphere. Dry solvents (THF, ethyl ether, and CH_2Cl_2) were purchased from Kanto Chemicals. Ti(O-*i*-Pr)$_4$ was distilled under reduced pressure and was stored under argon. *i*-PrMgCl was prepared from magnesium turnings and *i*-PrCl in ether, titrated, and stored under argon. Other chemicals are commercially available, unless otherwise indicated, and were used as received. The (*S*)-epoxide **4** [[α]$^{25}_D$ +30.0 (*c* 0.39, $CHCl_3$) (lit.[5] (*R*)-isomer: [α]$^{25}_D$ −30.0 (c 1.0, $CHCl_3$))] was prepared according to the reported procedure.[5]

Preparation of Ethyl (5*R*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-8-trimethylsilyl-2-octen-7-ynoate (7). To a solution of epoxide **4** (2.21 g, 14.4 mmol) in 75 mL of THF was added diethylaluminum cyanide (15.8 mL, 1.0 M in toluene, 15.8 mmol) at −30 °C, and the mixture was warmed to rt. After the mixture was stirred at rt for 3 h, saturated aqueous NH_4Cl was added and the white precipitate was filtered off through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and passed through a short silica gel column to afford a crude mixture of (*S*)-6-trimethylsilyl-3-hydroxyhex-5-ynenitrile (**5**) (2.014 g, 77%) as an oil, which was subjected to the next reaction without further purification. A small amount of the residue was chromatographed and analyzed: ^{1}H NMR δ 4.05−4.15 (m, 1H), 2.69 (dd, J = 5.4, 16.8 Hz, 1H), 2.61 (dd, J = 6.6, 16.8, 6.6 Hz, 1H). 2.57 (d, J = 6.0 Hz, 2H), 2.50 (s, 1H), 0.16 (s, 9H); ^{13}C NMR δ 117.2, 100.2, 89.5, 66.1, 27.9, 24.6, −0.26; IR (neat) 3446, 2960, 2900, 2255, 2177, 1415, 1249; [α]$^{33}_D$ +10.0 (*c* 0.648, $CHCl_3$).

To a solution of **5** (2.135 g, 11.8 mmol) and imidazole (1.20 g, 17.7 mmol) in 50 mL of CH_2Cl_2 was added TBDMSCl (2.17 g, 14.1 mmol). After the mixture was stirred for 48 h at rt, saturated aqueous NH_4Cl (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and passed through a short silica gel column to afford (*S*)-3-(*tert*-butyldimethylsilyloxy)-6-trimethylsilylhex-5-ynenitrile (**6**) (3.29 g, 95%) as an oil, which was subjected to the next reaction without further purification. A small amount of the residue was chromatographed and analyzed: ^{1}H NMR δ 4.03−4.10 (m, 1H), 2.68 (dd, J = 4.5, 16.5 Hz, 1H), 2.57 (dd, J = 6.3, 16.5 Hz, 1H), 2.51 (dd, J = 5.4, 16.5 Hz, 1H), 2.44 (dd, J = 6.9, 16.5 Hz, 1H), 0.90 (s, 9H), 0.15 (s, 9H), 0.14 (s, 6H); ^{13}C NMR δ 117.6, 101.5, 88.3, 67.5, 28.6 (two carbons), 25.5, 17.8, −0.23, −4.8, −5.0; IR (neat) 2958, 2931, 2857, 2253, 2180, 1472, 1416, 1364; [α]$^{32}_D$ +14.3 (*c* 0.47, $CHCl_3$).

To a solution of **6** (2.7 g, 9.15 mmol) in 50 mL of ether was added Dibal-H (0.93 M in hexane, 11.8 mL, 10.9 mmol) at −20 °C, and the resulting mixture was stirred at this temperature for 2 h. After being warmed to rt over 0.5 h, the mixture was slowly added to a mixture of aqueous 1 N HCl (50 mL) and hexanes (50 mL). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the corresponding aldehyde, which was directly used in the successive Horner−Wadsworth−Emmons olefination reaction. To a suspension of NaH (589 mg, 55% in oil, 13.5 mmol, the oil was washed off with dry hexanes under nitrogen prior to use) in 50 mL of THF was added triethyl phosphonoacetate (2.7 mL, 13.5 mmol) at 0 °C, and the mixture was stirred at rt for 10 min. After the mixture was cooled to −60 °C, a solution of the crude aldehyde obtained above in THF (10 mL) was added dropwise and the resulting mixture was allowed to warm to rt over 30 min. After the mixture was stirred at rt for 3 h, to it was added saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were concentrated and chromatographed to afford **7** (2.51 g, 75%) as an oil: ^{1}H NMR δ 6.95 (dt, J = 15.6, 7.8 Hz, 1H), 5.86 (dt, J = 15.6, 1.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.96−3.88 (m, 1H), 2.38−2.56 (m, 2H), 2.39 (dd, J = 6.0, 16.8 Hz, 1H), 2.33 (dd, J = 6.6, 16.8 Hz, 1H), 1.28 (t, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.14 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 166.4, 145.2, 124.0, 103.7, 86.9, 70.2, 60.1, 39.5, 28.7, 25.7, 17.9, 14.1, −0.13, −4.7, −4.8; IR (neat) 2957, 2930, 2178, 1724, 1656, 1472, 1367; [α]$^{29}_D$ +18.2 (*c* 0.39, $CHCl_3$). Anal. Calcd for $C_{19}H_{36}Si_2O_3$: C, 61.90; H, 9.84. Found: C, 61.81; H, 9.92.

Ti(II)-Mediated Tandem Cyclization of 1. Synthesis of (5*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-2-trimethylsilylbicyclo[3.3.0]oct-1-en-3-one (1) and Its C-5 Epimer. To a solution of **7** (0.125 g, 0.34 mmol) and Ti(O-*i*-Pr)$_4$ (0.20 mL, 0.68 mmol) in 4 mL of ether was added *i*-PrMgCl (1.1 M solution in ether, 1.23 mL, 1.36 mmol) dropwise at −78 °C. The solution was warmed to −60 to −40 °C over 30 min and stirred at this temperature for 3 h. *s*-BuOH (0.34 mL, 1.0 M solution in ether, 0.34 mmol) was slowly added at −60 °C, and the resulting mixture was stirred at this temperature for 30 min. After addition of saturated aqueous $NaHCO_3$, Celite (0.5 g), and NaF (0.5 g), the mixture was filtered through a pad of Celite. The filtrate was concentrated to give a residue which was chromatographed on silica gel (Wako C100−200, hexanes and ether) to afford a polar compound (63 mg, 57%) and a less polar compound (16 mg, 14%). Peaks on their ^{1}H NMR spectra were assigned by COSY experiments. In NOE difference experiments of these compounds, 4.8% of NOE was observed between protons at C-5 and C-7 on irradiating a proton at C-5 of the former (polar compound) and it was found that the polar one is **1**. **1**: ^{1}H NMR δ 4.51−4.61 (m, 1H), 3.00 (dd, J = 9.0, 19.2 Hz, 1H), 2.75−2.85 (m, 1H), 2.51 (dd, J = 6.6, 17.4 Hz, 1H), 2.33−2.46 (m, 2H), 2.07 (dd, J = 4.2, 17.4 Hz, 1H), 1.15−1.25 (m, 1H), 0.88 (s, 9H), 0.18 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 213.9, 195.0, 135.9, 73.8, 46.0, 42.8, 41.1, 38.6, 25.7, 18.0, −1.4, −4.9, −5.0; IR (neat) 2957, 2857, 1684, 1608, 1472, 1411; [α]$^{30}_D$ +134.2 (*c* 0.298, $CHCl_3$). Anal. Calcd. for $C_{17}H_{32}Si_2O_2$: C, 62.90; H: 9.94. Found: C, 62.97; H, 9.91. **C$_5$-Epimer**: ^{1}H NMR δ 4.57 (t, J = 5.1 Hz, 1H), 3.23−3.32 (m, 1H), 2.89 (dd, J = 5.4, 18.9 Hz, 1H), 2.60 (dd, J = 6.6, 18.0 Hz, 1H), 2.54 (d, J = 18.9 Hz, 1H), 2.09 (dd, J = 7.2, 15.6 Hz, 1H), 1.99 (dd, J = 3.6, 18.0 Hz, 1H), 1.23 (dt, J = 4.8, 12.9 Hz, 1H), 0.89 (s, 9H), 0.18 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 214.5, 197.0, 135.9, 73.9, 45.0, 42.9, 41.1, 39.7, 25.7, 17.9, −1.4, −4.8, −4.9; IR (neat) 2955, 2928, 2856, 1698, 1610, 1471, 1406, 1361; [α]$^{29}_D$ −109.6 (c 0.384, $CHCl_3$). Anal. Calcd for $C_{17}H_{32}Si_2O_2$: C, 62.90; H, 9.94. Found: C, 62.93; H, 9.64.

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Supporting Information Available: Synthesis and characterization of compounds **8**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For synthesis of these terpenes via the intermediates having a similar structure to **15**, see: Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* **1984**, 959. Mehta, G.; Subrahmanyam, D. *J. Chem. Soc., Chem. Commun.* **1985**, 1464. Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835. Imanishi, T.; Ninbari, F.; Yamashita, M.; Iwata, C. *Chem. Pharm. Bull.* **1986**, *34*, 2268. Imanishi, T.; Yamashita, M.; Ninbari, F.; Tanaka, T.; Iwata, C. *Chem. Pharm. Bull.* **1988**, *36*, 1371. Imanishi, T.; Yamashita, M.; Hirokawa, Y.; Tanaka, T. Iwata, C. *Chem. Pharm. Bull.* **1990**, *38*, 1124. Hudlicky, T.; Natchus, M. G.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 4641. Hudlicky, T.; Sinai-Zingde, G. Natchus, M. G.; Ranu, B. C.; Papadopolous, P. *Tetrahedron* **1987**, *43*, 5685. Shizuri, Y.; Maki, S.; Ohkubo, M.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 7167. Hatanaka, M.; Ueno, F.; Ueda, I. *Tetrahedron Lett.* **1996**, *37*, 89.