A New Method for the Introduction of Carbon–Carbon Triple Bond at C-13 in PG Synthesis. A Stereocontrolled Synthesis of ZK 96 480

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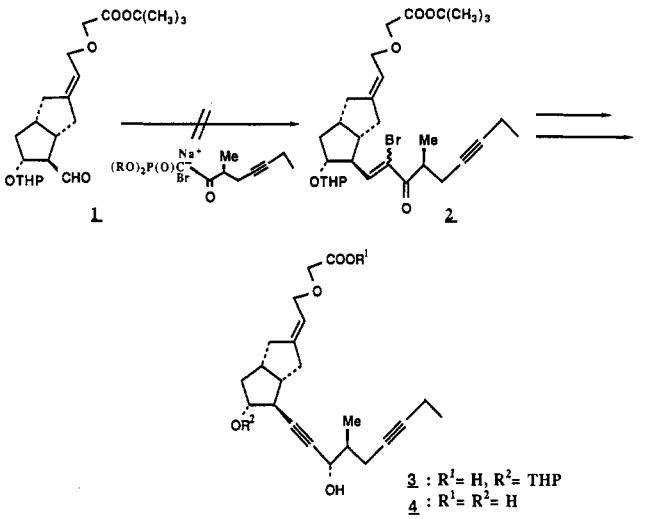
ZK 96 480, a chemically and metabolically stable prostacyclin analogue, has been synthesized from the Corey lactone in a stereocontrolled manner by a route utilizing a newly developed method for introduction of the carbon–carbon triple bond at C-13 (PG numbering) and $Ar{\cdot}Cr(CO)_3$-catalyzed hydrogenation technique. The introduction of the carbon–carbon triple bond has been achieved by the use of α-bromo enolate anions derived from 1,1-dibromo ketones.

In the course of synthetic studies on ZK 96 480 (**4**),[1] a chemically and metabolically stable prostacyclin analogue developed by Schering chemists, we were confronted with the synthetic problem that the aldehyde **1** could not be converted to the α-bromo enone **2**, the precursor of the acetylenic alcohol **3**, by the use of usual α-bromo β-keto phosphonate technique (Scheme I).[1,2] In this paper we wish to report a solution to this synthetic problem, which made it possible to achieve a stereocontrolled synthesis of ZK 96 480 (**4**) starting with Corey lactone.

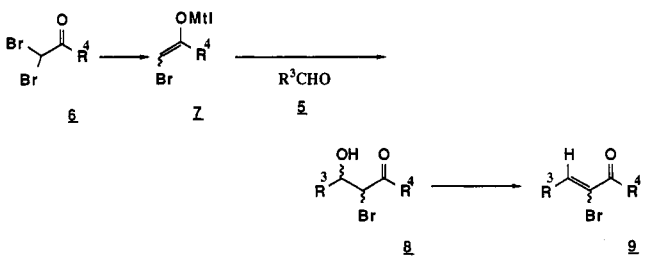
In order to develop the general method for the conversion of aldehydes to α-bromo enones, instead of the usual α-bromo β-keto phosphonate carbanions, we designed α-bromo enolate anions **7**, which were expected to condense with aldehydes **5** more easily to produce β-hydroxy α-bromo ketones **8** convertible to α-bromo enones **9**. Furthermore, it appeared that α-bromo enolate anions would be readily generated from corresponding 1,1-dibromo ketones **6** (Scheme II).[3] At the outset, various 1,1-dibromo ketones **6** were efficiently synthesized from either esters or aldehydes by utilizing (dibromomethyl)lithium.[4,5] It is worthy of note that the 1,1-dibromo ketones with the asymmetric α-methyl substituent could be synthesized without racemization. The results are summarized in Table I.

As a model study for the coupling reaction, the rather simple aldehyde **10**,[7] which also could not be transformed into α-bromo enones **12** by usual α-bromo β-keto phosphonate technique, was utilized. First of all, the zinc enolate derived from **6** ($R^4 = C_5H_{11}$) was allowed to react with the aldehyde **10**, however, giving none of the coupling product. Next we examined the reactivity of the aluminum enolate **7** (Mtl = $AlEt_2$) with **10**. Namely, a THF solution of the 1,1-dibromo ketone **6** ($R^4 = C_5H_{11}$) and the aldehyde **10** was treated with zinc powder and diethylaluminum chloride containing a catalytic amount of copper(I) bromide at −5 °C for ca. 1 h[8] to provide the desired α-bromo β-hydroxy ketone **11** ($R^4 = C_5H_{11}$), which was directly converted to the α-bromo enone **12** ($R^4 = C_5H_{11}$) as a stereoisomeric mixture via the mesylate (CH_3SO_2Cl–Et_3N in CH_2Cl_2) in 65% overall yield together with a small amount of the enone (9%) derived from the β-hydroxy ketone. Similarly, various 1,1-dibromo ketones **6** were reacted with the aldehyde **10** and subsequent dehydration of **11** afforded various α-bromo enones **12**, the precursor of acetylenic alcohols, in good yields. In every case attempted a small amount of the undesired enones, probably formed through the debromination of α-bromo β-hydroxy ketones with zinc, was also produced (6–8%). The results are summarized in Table II.

Scheme I



Scheme II



Utilizing this versatile new technique, we finally attempted to synthesize ZK 96 480 (**4**) in a stereocontrolled

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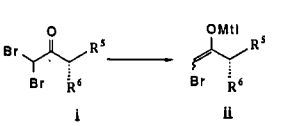
(1) Skuballa, W.; Schillinger, E.; Stürzebecher, C.-St.; Vorbrüggen, H. *J. Med. Chem.* **1986**, *29*, 313.

(2) The use of the α-chloro β-keto phosphonate carbanion produced the α-chloro enone in modest yield. However, epimerization of the methyl group at C-16 (PG numbering) was detected at the α-chloro enone forming step. See: (a) Iseki, K.; Shinoda, M.; Ishiyama, C.; Hayashi, Y.; Yamada, S.; Shibasaki, M. *Chem. Lett.* **1986**, 559. (b) Private communication from Dr. Katsuhiko Iseki.

(3) It was also expected that ii would be generated from i without racemization.



(4) (a) Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010. (b) Villieras, J.; Bacquet, C.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1975**, 1797.

(5) We can select method A or method B depending on the availability of carbonyl compounds.

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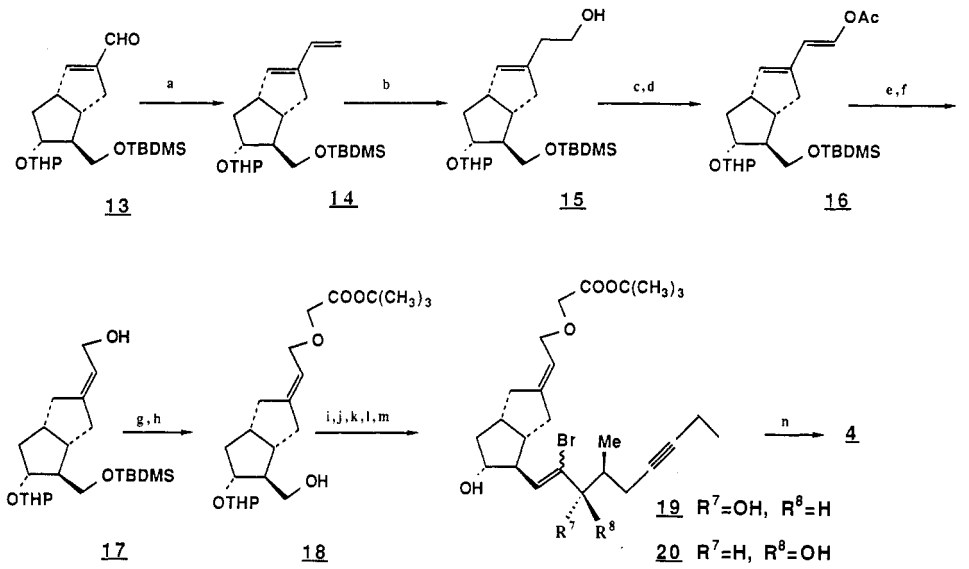
Scheme III[a]



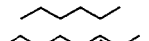
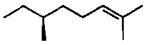
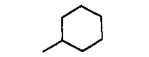
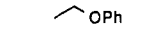
[a] (a) $MePPh_3Br$, *t*-BuOK, THF, room temperature; (b) disiamylborane, THF, 0 °C, then 6 N NaOH, 30% H_2O_2, THF, 0 °C; (c) CrO_3·Py CH_2Cl_2, room temperature; (d) Ac_2O, Et_3N, cat. DMAP, toluene; (e) H_2, Np·$Cr(CO)_3$, THF, 45 °C; (f) K_2CO_3, MeOH, room temperature; (g) $BrCH_2COOC(CH_3)_3$, *n*-Bu_4N·HSO_4, 50% NaOH, CH_2Cl_2, room temperature; (h) TBAF, THF, room temperature; (i) SO_3·Py, Et_3N, DMSO, room temperature; (j) **6** (R^4 = 1(*S*)-methyl-3-hexynyl), Zn, Et_2AlCl, cat. CuBr, THF, −5 °C; (k) MsCl, Et_3N, CH_2Cl_2, −40–0 °C; (l) BINAL-(H), THF, −100 °C; (m) AcOH–THF–H_2O (3:1:1), 60 °C; (n) *n*-Bu_4N·HSO_4 50% NaOH, Et_2O–toluene (2:1), 50 °C.

manner. The enal **13**,[9] now obtainable from Corey lactone in ca. 70% overall yield, underwent Wittig reaction by treatment with the reagent derived from methyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF, giving the diene **14** (96%). The diene **14** was then subjected to hydroboration using disiamylborane followed by oxidative workup to give the alcohol **15** (90%). Oxidation of **15** with Collins' reagent followed by treatment with acetic anhydride in triethylamine provided the dienol acetate **16** (71% from **15**). Naphthalene–$Cr(CO)_3$-catalyzed 1,4-hydrogenation[10] of **16** in degassed THF (100 atm of H_2 pressure, 45 °C, 18 h) provided the allylic acetate in a fully stereocontrolled manner (90%),[11] which was subsequently treated with potassium carbonate in methanol to give **17** (100%). Reaction of **17** with *tert*-butyl bromoacetate (50% aqueous NaOH, CH_2Cl_2, Bu_4N·HSO_4) followed by exposure to tetrabutylammonium fluoride in THF gave the alcohol **18** in 87% overall yield. Oxidation of **18** with SO_3·Py complex (triethylamine and DMSO) afforded the aldehyde **1** (95%), which was treated with the optically pure 1,1-dibromo ketone **6** (R^4 = 1(*S*)-methyl-3-hexynyl) under the same conditions as described above to

Table I

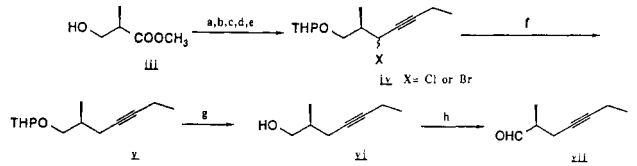
$OHCR^4 \xrightarrow{a} Br_2CHCH(OH)R^4 \xrightarrow{b} Br_2CHCOR^4$ (method A)

$MeOOCR^4 \xrightarrow{c} Br_2CHCOR^4$ (method B)

R^4	yield, % method A	yield, % method B
	50	70
	56[d]	*e*
	50	73
	48[f]	*e*
	57[g]	78[h]
	55	*e*
	44	68

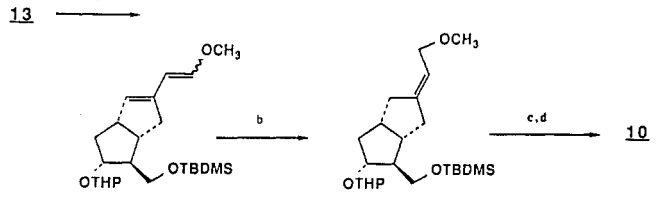
[a] Br_2CHLi (2.5 equiv), THF, −78 °C. [b] Swern oxidation or PCC, CH_2Cl_2, room temperature, or PDC, CH_2Cl_2, room temperature. [c] Br_2CHLi (2.0 equiv), THF–Et_2O (2:3), −100 to −65 °C. [d] $[\alpha]^{26}_D$ −8.1° (*c* 2.296, $CHCl_3$). [e] The preparation using method B was not carried out. [f] $[\alpha]^{22}_D$ +106.1° (*c* 1.50, $CHCl_3$). [g] $[\alpha]^{23}_D$ −106.2° (*c* 1.53, $CHCl_3$). [h] $[\alpha]^{20}_D$ −105.8° (*c* 1.204, $CHCl_3$).

(6) The corresponding aldehyde and the ester were synthesized by the literature method[1] or by the route shown below.



(a) DHP, PPTS, CH_2Cl_2, room temperature; (b) $LiAlH_4$, THF, −20 °C; (c) $(COCl_2)$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (d) EtC≡CH, BuLi, CeCl·$7H_2O$, THF, −78 °C; (e) PPh_3, CBr_4, CH_2Cl_2, 0 °C, or HMPT, CCl_4, Et_2O, 0 °C; (f) Bu_3SnH, AIBN, toluene, 110 °C; (g) PPTS, EtOH, room temperature; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C.

(7) The aldehyde **10** was prepared by the route shown below.

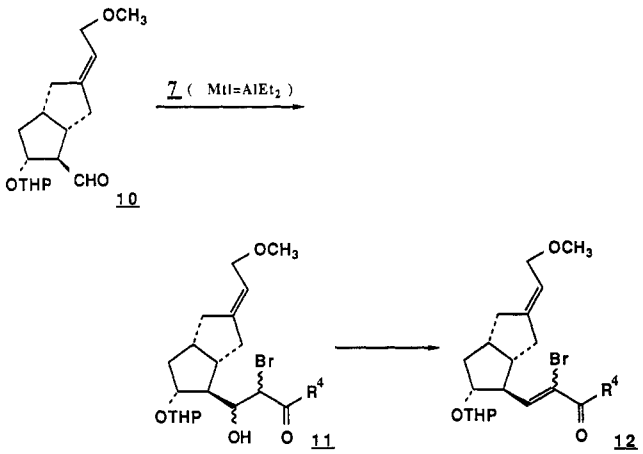


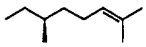
(a) $MeOCH_2P^+Ph_3Cl^-$, LDA, toluene–THF, 0 °C; (b) H_2, MBZ·$Cr(CO)_3$, acetone, 120 °C; (c) TBAF, THF, room temperature; (d) SO_3·Py, Et_3N, DMSO, room temperature.

(8) Maruoka, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1978**, *99*, 7705.
(9) Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1984**, 579.
(10) (a) Shibasaki, M.; Sodeoka, M.; Ogawa, Y. *J. Org. Chem.* **1984**, *49*, 4096. (b) Sodeoka, M.; Shibasaki, M. *Ibid.* **1985**, *50*, 1147. (c) Shibasaki, M.; Sodeoka, M. *Tetrahedron Lett.* **1985**, *26*, 3491. (d) Sodeoka, M.; Shibasaki, M. *Ibid.* **1985**, *26*, 6497. (e) Takahashi, A.; Shibasaki, M. *Ibid.* **1987**, *28*, 1893. (f) Frankel, E. N.; Selke, E.; Grass, C. A. *J. Am. Chem. Soc.* **1968**, *90*, 2446.

(11) None of the stereoisomer (*Z*), which had been actually synthesized by usual Wittig reaction (see ref 1), was detected.

Table II



R^4	yield of 12, %
	65
	59
	55
	63
	48

produce the α-bromo enone **2** in 71% yield without epimerization of the methyl group at C-16 (PG numbering) together with the enone (7%). The α-bromo enone **2** was then reduced with Noyori reagent[12] followed by cleavage of THP group (CH_3COOH–H_2O–THF, 3:1:1), giving the 15α-isomer **19** (69%) together with the undesired 15β-isomer **20** (11%).[13] The diol **19** was finally transformed into ZK 96 480 (**4**) in one step (86%) on exposure to 50% aqueous NaOH (ether–toluene (2:1), $Bu_4N{\cdot}HSO_4$, 55 °C, 48 h), whose spectral data were identical with those of an authentic material.[1] It is worthy of note that no epimerization of the methyl group at C-16 occurred during the synthetic operations described above (Scheme III).

In conclusion, we have developed a general method for the conversion of aldehydes to α-bromo enones, the precursors of acetylenic alcohols. This method combined with Ar·Cr(CO_3)-catalyzed hydrogenation technique[10] has made it possible to achieve a stereocontrolled synthesis of ZK 96 480 (**4**) starting with the Corey lactone.[14]

Experimental Section

General Methods. IR spectra were measured on a JASCO A-202 diffraction grating infrared spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM 390 NMR spectrometer or a Hitachi R-90H Fourier transform NMR spectrometer or a Bruker AN-400 spectrometer with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained from a Hitachi RMU-6MG mass spectrometer and high-resolution mass spectra from a Hitachi M-80A mass spectrometer. Optical rotation was measured on a Horiba SEPA-200 high-sensitive polarimeter.

In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

General Procedure I for Preparation of 1,1-Dibromo Ketones 6. To a stirred solution of 2-methyl-4-heptynal (3.30 g, 25.8 mmol) and dibromomethane (3.60 mL, 51.6 mmol) in THF (50 mL) was added THF solution of lithium dicyclohexylamide (20 mL, 51.6 mmol) at −78 °C over 0.5 h. After being stirred for 1 h at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl at the same temperature and diluted with ether. The resulting ethereal suspension was filtered through a pad of Celite, and the filtrate was extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude 1,1-dibromo-3-methyl-5-octyn-2-ol (5.49 g). To a stirred solution of crude 1,1-dibromo-3-methyl-5-octyn-2-ol (5.49 g, 18.4 mmol) in CH_2Cl_2 (60 mL) were added powdered molecular sieves, 4A (5.49 g), and PCC (7.90 g, 36.8 mmol) at room temperature, and the whole reaction mixture was stirred under the same conditions for 48 h. The reaction mixture was diluted with ether and filtered through a pad of Florisil. The filtrate was concentrated, and the residual oil was purified by silica gel column chromatography (ether–hexane, 1:40) to give 1,1-dibromo-3-methyl-5-octyn-2-one (3.81 g, 50%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.05 (s, 1 H), 3.33 (m, 1 H), 2.31–2.50 (m, 2 H), 2.12–2.20 (m, 2 H), 1.33 (d, J = 6.82 Hz, 3 H), 1.12 (t, J = 7.5 Hz, 3 H); IR (neat) ν_{max} 1740, 1450, 1380, 1320, 1000, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 215 (7), 136 (26), 124 (75), 123 (base peak).

General Procedure II for Preparation of 1,1-Dibromo Ketones 6. To a stirred solution of LDA (20 mmol) in THF–ether (40 mL; ether–THF, 3:1) was added a solution of dibromomethane (3.80 g, 22 mmol) in THF (20 mL) at −100 °C, and the whole reaction mixture was stirred for 15 min (−100 °C). At the same temperature, methyl-2-methyl-4-heptynoate (1.54 g, 10 mmol) in THF (10 mL) was then added to the solution of dibromomethyllithium, and the resulting mixture was stirred for 2.5 h at −100 to −60 °C. The reaction was quenched with 10% aqueous HCl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was purified by silica gel column chromatography (ether–hexane, 1:40) to give 1,1-dibromo-3-methyl-5-octyn-2-one (2.16 g, 73%) as a colorless oil. The spectral data of 1,1-dibromo-3-methyl-5-octyn-2-one thus prepared were identical with those of 1,1-dibromo-3-methyl-5-octyn-2-one synthesized by general procedure I.

General Procedure of Aldol Reaction and Dehydration. A solution of diethylaluminum chloride (0.97 mmol) in hexane was added to a slurry of zinc dust (63 mg, 0.97 mmol) and a catalytic amount of copper(I) bromide (0.09 mmol) in THF (5 mL) with stirring at 20 °C over 0.5 h. The resulting mixture was cooled to −5 °C, and a solution of the 1,1-dibromo ketone **6** (R^4 = 1(*S*)-methyl-3-hexynyl) (345 mg, 1.16 mmol) and the aldehyde **1** (153 mg, 0.39 mmol) in THF (4 mL) was added slowly over 20 min at −5 °C. After 1 h at the same temperature, the reaction was quenched with saturated aqueous $KHCO_3$, and the product was extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford the β-hydroxy-α-bromo ketone. A solution of the crude β-hydroxy-α-bromo ketone in CH_2Cl_2 (3 mL) was treated with methanesulfonyl chloride (0.32 mL, 2.1 mmol) in the presence of triethylamine (1.74 mL, 12.4 mmol) at −40 °C. The resulting suspension was allowed to warm to 0 °C, and further stirring was continued for 10 h at 0 °C. The reaction mixture was poured onto ice–water and extracted with ether. Purification by silica gel column chromatography (ether–hexane, 1:4) gave the α-bromo enone **2** (164 mg, 71%, E:Z = 2:1) as a colorless oil together with the enone (14 mg, 7%). The spectral data of the α-bromo enone thus obtained were as follows: ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 1 H), 5.53 (br t, J = 6.8 Hz, 1 H), 4.60 (m, 1 H), 4.10 (d, J = 6.5 Hz, 2 H), 3.96 (s, 2 H), 3.00 (m, 1 H), 1.50 (s, 9 H), 1.14 (d, J = 6.5 Hz, 3 H), 1.12 (t, J = 7.5 Hz, 3 H); IR (neat) ν_{max} 2950, 1750, 1690, 1620, 1450, 1370, 1230, 1200 cm^{-1}; mass spectrum, m/e (relative intensity) 453 ($M^+ - C_4H_9 - C_5H_8O$), 451 ($M^+ - C_4H_9 - C_5H_8O$), 378 (11), 376 (11), 297 (22), 105 (16), 85 (86), 84 (57), 79 (12), 67 (42), 57 (base peak), 55 (89), 43 (37), 41 (67), 29; HR-MS ($M^+ - C_4H_9 - C_5H_8O$) calcd for $C_{22}H_{28}O_5Br$ 453,11019, found 453.11020, ($M^+ - C_4H_9 - C_5H_8O$) calcd for $C_{22}H_{28}O_5Br$ 451.11244, found 451.11248.

(1*R*,5*S*,6*S*,7*R*)-6-[((*tert*-Butyldimethylsilyl)oxy)methyl]-7-[(tetrahydropyranyl)oxy]-3-vinylbicyclo[3.3.0]oct-2-ene (14). To a stirred suspension of methyltriphenylphosphonium bromide (2.94 g, 8.25 mmol) in THF (10 mL) was added a solution of potassium *tert*-butoxide (0.92 g, 8.25 mmol)

(12) (a) Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843. (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

(13) The 15β-isomer was oxidized (MnO_2, 86%) and protected as a THP ether for recycling.

(14) In the Schering synthesis there is tedious separation of the stereoisomers at C-5 (PG numbering).

in THF (10 mL) at room temperature. After the mixture was stirred for 10 min a THF solution of **13** (1.00 g, 2.75 mmol, 7 mL of THF) was injected via syringe at room temperature and the whole reaction mixture was stirred for 30 min at the same temperature and quenched with saturated aqueous NH_4Cl. After evaporation of THF, the aqueous layer was extracted with ether, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:15) to give **14** as a colorless oil (1.00 g 96%): ^1H NMR ($CDCl_3$) δ 6.52 (dd, J = 10.5, 18 Hz, 1 H), 5.66 (br s, 1 H), 5.01 (d, J = 18 Hz, 1 H), 5.00 (d, J = 10.5 Hz, 1 H), 4.62 (m, 1 H), 3.30–4.16 (m, 5 H), 3.06 (m, 1 H), 0.93 (s, 9 H), 0.06 (s, 6 H); IR (neat) ν_{max} 2950, 1640, 1590, 1470, 1350, 1200 cm^{-1}; mass spectrum, m/e (relative intensity) 378 (M^+), 294 (7), 293 (2), 159 (61), 145 (86), 85 (base peak), 75 (50), 73 (39); HR-MS (M^+) calcd for $C_{22}H_{38}O_3Si$ 378.2587, found 378.2572.

(1*R*,5*S*,6*S*,7*R*)-6-[((*tert*-Butyldimethylsilyl)oxy)methyl]-3-(2-hydroxyethyl)-7-[(tetrahydropyranyl)oxy]bicyclo[3.3.0]oct-2-ene (15). To a stirred solution of **14** (600 mg, 1.58 mmol) in THF (5 mL) was added disiamylborane (1.02 M THF solution, 4.65 mL, 4.74 mmol) at 0 °C, and the stirring was continued at the same temperature for 1.5 h. The reaction was quenched with 6 M aqueous NaOH (3.2 mL) and 30% aqueous H_2O_2 (2.8 mL) at 0 °C, and then the whole reaction mixture was stirred for an additional 1 h at room temperature. After dilution with H_2O, the solution was extracted with AcOEt, washed with saturated aqueous sodium thiosulfate and brine, dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:5) to give **15** as a colorless oil (565 mg, 90%): ^1H NMR ($CDCl_3$) δ 5.40 (br s, 1 H), 4.62 (m, 1 H), 3.26–4.23 (m, 9 H), 3.03 (m, 1 H), 0.90 (s, 9 H), 0.04 (s, 6 H); IR (neat) ν_{max} 3400, 2950, 2880, 1470, 1440, 1380, 1250, 1200 cm^{-1}; mass spectrum, m/e (relative intensity) 255 (6), 237 (6), 159 (23), 145 (12), 85 (base peak), 75 (18), 57 (11); HR-MS ($M^+ - C_4H_9$) calcd for $C_{18}H_{31}O_4Si$ 339.1990, found 339.1999.

(1*R*,5*S*,6*S*,7*S*)-2-(2-Acetoxyvinyl)-6-[((*tert*-butyldimethylsilyl)oxy)methyl]-7-[(tetrahydropyranyl)oxy]bicyclo[3.3.0]oct-2-ene (16). To a stirred solution of **15** (310 mg, 0.78 mmol) in CH_2Cl_2 (30 mL) was added Collins reagent (2.01 g, 7.8 mmol) at room temperature, and the resulting suspension was stirred for 10 min at the same temperature. After dilution with ether, the suspension was filtered through a pad of Florisil, and the filtrate was concentrated thoroughly (to remove pyridine) in vacuo. The product was then purified by silica gel column chromatography (ether–hexane, 1:3) to give the aldehyde (229 mg, 75%) as a colorless oil. To a stirred solution of the aldehyde (348 mg, 0.88 mmol) in toluene (2 mL) were added Ac_2O (0.25 mL, 2.65 mmol), Et_3N (0.49 mL, 3.52 mmol), and a catalytic amount of 4-(dimetylamino)pyridine, and the resulting solution was heated at 65 °C for 3 h. The reaction was quenched with brine, extracted with ether, dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:8) to give **16** (365 mg, 95%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.20 (d, J = 13.5 Hz, 1 H), 6.20 (d, J = 13.5 Hz, 1 H), 5.66 (br s, 1 H), 4.64 (m, 1 H), 3.26–4.30 (m, 6 H), 3.00 (m, 1 H), 2.16 (s, 3 H), 0.90 (s, 9 H), 0.04 (s, 6 H); IR (neat) ν_{max} 2950, 2870, 1760, 1660, 1610, 1460, 1370 cm^{-1}; mass spectrum, m/e (relative intensity) 436 (M^+), 352 (4), 351 (3), 159 (26), 85 (base peak), 75 (16), 73 (16), 57 (13); HR-MS ($M^+ - C_5H_9O$) calcd for $C_{19}H_{31}O_4Si$ 351.1628, found 351.1625.

(1*S*,5*S*,6*S*,7*R*)-6-[((*tert*-Butyldimethylsilyl)oxy)methyl]-(*E*)-3-(2-hydroxyethylidene)-7-[(tetrahydropyranyl)oxy]bicyclo[3.3.0]octane (17). The dienol acetate **16** (123 mg, 0.28 mmol) and naphthalene–$Cr(CO)_3$ (22 mg, 0.08 mmol) were dissolved in THF (10 mL). After strict deoxygenation by three freeze–pump–thaw cycles, the solution was heated at 45 °C with stirring under an atmosphere of hydrogen (100 atm of H_2 pressure) for 18 h and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:5) to give the allylic acetate (110 mg, 89%) as a colorless oil. To a stirred solution of the allylic acetate (110 mg, 0.25 mmol) in CH_3OH (3 mL) was added anhydrous K_2CO_3 (69 mg, 0.5 mmol) at room temperature, and the resulting suspension was stirred at room temperature for 40 min and concentrated. The residue was purified by silica gel column chromatography (ether) to afford **17** (99 mg, 100%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.46 (br t, J = 6.8 Hz, 1 H), 4.55 (m, 1 H), 4.05 (d, J = 6 Hz, 2 H), 0.90 (s, 9 H), 0.04 (s, 6 H); IR (neat) ν_{max} 3440, 2950, 2850, 1470, 1435, 1380, 1360, 1250, 1200 cm^{-1}; mass spectrum, m/e (relative intensity) 237 (8), 159 (15), 145 (12), 85 (58), 75 (13), 73 (17), 61 (base peak), 45 (61); HR-MS (M^+) calcd for $C_{22}H_{40}O_4Si$ 396.2693, found 396.2674.

(1*S*,5*S*,6*S*,7*R*)-6-(Hydroxymethyl)-(*E*)-3-[4-(*tert*-butoxycarbonyl)-3-oxabutylidene]-7-[(tetrahydropyranyl)oxy]bicyclo[3.3.0]octane (18). To a stirred solution of **17** (73 mg, 0.18 mmol) and *tert*-butyl bromoacetate (702 mg, 3.6 mmol) in CH_2Cl_2 (0.2 mL) were added 50% aqueous NaOH (0.8 mL) and tetrabutylammonium hydrogen sulfate (61 mg, 0.18 mmol) at room temperature, and the whole reaction mixture was stirred at the same temperature for 48 h. After dilution with water, the aqueous layer was extracted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:5) to give the *tert*-butyl ester (85 mg, 94%) as a colorless oil. To a stirred solution of the *tert*-butyl ester (85 mg, 0.17 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (1 M THF solution, 0.36 mL, 0.36 mmol) at room temperature, and the whole reaction mixture was stirred for 2.5 h (room temperature). The reaction was quenched with brine, extracted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether:hexane, 2:1) to give **18** (59 mg, 93%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.45 (br, t, J = 7.6 Hz, 1 H), 4.63 (m, 1 H), 4.05 (d, J = 6.5 Hz, 2 H), 3.90 (s, 2 H), 1.50 (s, 9 H); IR (neat) ν_{max} 3450, 2950, 1745, 1460, 1370, 1230, 1200 cm^{-1}; mass spectrum, m/e (relative intensity) 311 ($M^+ - C_5H_9O$), 180 (20), 85 (base peak), 73 (20), 67 (12), 61 (88), 57 (33), 45 (91), 18 (9); HR-MS (M^+) calcd for $C_{17}H_{27}O_5$ 311.18608, found 311.18610.

(1*S*,5*S*,6*S*,7*R*)-6-(2-Bromo-3(*S*)-hydroxy-4(*S*)-methyl-1-nonen-6-ynyl)-7-hydroxy-(*E*)-3-[(4-(*tert*-butoxycarbonyl)-3-oxabutylidene]bicyclo[3.3.0]octane (19). To a stirred solution of **18** (250 mg, 0.63 mmol) in DMSO (3 mL) were added triethylamine (0.52 mL, 3.78 mmol) and a solution of sulfur trioxide–pyridine complex (601 mg, 3.78 mmol) in DMSO (3 mL) at room temperature, and the whole reaction mixture was stirred for 40 min (room temperature). The reaction was quenched with ice–water, extracted with ethyl acetate, washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give the aldehyde **1** (235 mg, 95%) as a pale yellow oil. This aldehyde **1** was then converted to the α-bromo enone **2** by the procedure described above in detail (71%). To a stirred solution of $LiAlH_4$ in THF (1 M THF solution, 1.94 mL, 1.94 mmol) was added EtOH (1 M THF solution, 1.94 mL, 1.94 mmol) at room temperature over 15 min. To this solution was then added (*S*)-(−)-2,2′-dihydroxy-1,1′-binaphthyl (572 mg, 2.0 mmol) in THF (4 mL) at the same temperature, and the whole reaction mixture was stirred for 0.5 h at room temperature. To this BINAL-H THF solution was next injected via syringe the α-bromo enone **2** (115 mg, 0.2 mmol) in THF (3 mL) at −100 °C. After being stirred at the same temperature for 1.5 h, the reaction mixture was warmed to −78 °C and stirred for 2 h. The reaction was quenched with MeOH, extracted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was dissolved in AcOH–THF–H_2O (2 mL, 3:1:1), and the resulting solution was stirred at 65 °C for 6.5 h. The reaction was quenched by dilution with ethyl acetate, and the resulting solution was neutralized with saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 5:1) to give **19** (68 mg, 69%) as a colorless oil and **20** (11 mg, 11%) as a colorless oil. The spectral data of **19** were as follows: ^1H NMR ($CDCl_3$) δ 5.90 (d, J = 10.5 Hz, 2/3 H), 5.68 (d, J = 9.0 Hz, 1/3 H), 5.55 (br t, J = 6.8 Hz, 1 H), 4.10 (d, J = 6.0 Hz, 2 H), 1.12 (t, J = 7.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H); IR (neat) ν_{max} 3450, 2950, 1750, 1460, 1430, 1370, 1230 cm^{-1}; mass spectrum, m/e (relative intenstiy) 494 ($M^+ - H_2O$), 492 ($M^+ - H_2O$), 437 ($M^+ - H_2O - C_4H_9$), ($M^+ - H_2O - C_4H_9$), 357 (3), 281 (19), 145 (12), 105 (40), 79 (19), 57 (base peak), 41 (76), HR-MS ($M^+ - H_2O - C_4H_9$) calcd for $C_{22}H_{28}O_4Br$ 437.11493, found 437.11491; ($M^+ - H_2O - C_4H_9$) calcd for $C_{22}H_{28}O_4Br$ 435.11771, found 435.11777.

ZK 96 480 (4). A solution of **19** (68 mg, 0.13 mmol) in ether–toluene (3 mL, 2:1) was added to tetrabutylammonium hy-

drogen sulfate containing H_2O (2 drops). After adding 50% aqueous NaOH (0.8 mL), the whole reaction mixture was stirred at 55 °C for 48 h. The reaction was quenched with H_2O, acidified with 5% aqueous HCl, extracted with ethyl acetate, washed with H_2O and brine, and concentrated to give ZK 96 480 (**4**) (42 mg, 86%) as a colorless viscous oil: $[\alpha]^{22}_D$ +138.25° (*c* 1.025, $CHCl_3$). Other spectral data were identical with those of an authentic sample.[1]

Registry No. **1**, 112741-41-0; **2**, 106937-28-4; **4**, 94079-80-8; **10**, 112741-21-6; **11** (R^4 = C_5H_{11}), 112741-22-7; **11** (R^4 = $CH_2CHMeCH_2CH_2CH{=}CMe_2$), 112741-23-8; **11** ($R^4$ = $CHMeCH_2C{\equiv}CEt$), 112741-24-9; **11** (R^4 = cyclohexyl), 112741-25-0; **11** (R^4 = CH_2OPh), 112741-26-1; (*E*)-**12** (R^4 = C_5H_{11}), 112741-27-2; (*Z*)-**12** (R^4 = C_5H_{11}), 112741-32-9; (*E*)-**12** (R^4 = (*R*)-$CH_2CHMeCH_2CH_2CH{=}CMe_2$), 112741-28-3; (*Z*)-**12** (R^4 = (*R*)-$CH_2CHMeCH_2CH_2CH{=}CMe_2$), 112835-57-1; **12** ($R^4$ = $CHMeCH_2C{\equiv}CEt$), 112741-29-4; (*E*)-**12** (R^4 = cyclohexyl), 112741-30-7; (*Z*)-**12** (R^4 = cyclohexyl), 112741-33-0; (*E*)-**12** (R^4 = CH_2OPh), 112741-31-8; (*Z*)-**12** (R^4 = CH_2OPh), 112741-34-1; **12** (R^4 = C_5H_{11}) (enone), 112741-35-2; **12** (R^4 = $CH_2CHMeCH_2CH_2CH{=}CMe_2$) (enone), 112741-36-3; **12** (R^4 = $CHMeCH_2C{\equiv}CEt$) (enone), 112741-37-4; **12** (R^4 = cyclohexyl) (enone), 112741-38-5; **12** (R^4 = CH_2OPh) (enone), 112741-39-6; **13**, 92134-25-3; **14**, 112495-28-0; **14** (methoxy deriv), 112763-20-9; **15**, 112636-34-7; **15** (aldehyde deriv), 112741-40-9; **16**, 112835-58-2; **17**, 106937-25-1; **17** (acetate), 106937-24-0; **17** (methyl ether), 112741-47-6; **17** (*tert*-butyloxycarbonylmethyl ether), 106937-26-2; **18**, 106937-27-3; **19**, 112741-42-1; **19** (THP ether), 106937-29-5; **20**, 112835-59-3; **20** (THP ether), 106975-02-4; **20** (oxidized), 112741-48-7; iii, 72657-23-9; iv (X = Cl), 112741-43-2; iv (X = Br), 112741-44-3; v, 112741-45-4; vi, 112741-46-5; vii, 112741-13-6; $MeOCH_2P^+Ph_3Cl^-$, 4009-98-7; $OHCC_5H_{11}$, 66-25-1; (*R*)-$OHCCH_2CHMeCH_2CH_2CH{=}CMe_2$, 2385-77-5; (*R*)-$OHCCHMeCH_2C{\equiv}CEt$, 112741-14-7; $PhOCH_2CHO$, 2120-70-9; $Br_2CHCOC_5H_{11}$, 14799-24-7; (*R*)-$Br_2CHCOCH_2CHMeCH_2CH_2CH{=}CMe_2$, 112741-15-8; (*S*)-$Br_2CHCOCHMeCH_2C{\equiv}CEt$, 112741-16-9; (*R*)-$Br_2CHCOCHMeCH_2C{\equiv}CEt$, 112741-17-0; $Br_2CHCOCH_2OPh$, 112763-19-6; $MeOCOC_5H_{11}$, 106-70-7; (*R*)-$MeOCOCHMeCH_2C{\equiv}CEt$, 112741-20-5; $PhOCH_2CO_2Me$, 2065-23-8; 2-methyl-4-heptynal, 112741-10-3; 1,1-dibromo-3-methyl-5-octyn-2-ol, 112741-11-4; 1,1-dibromo-3-methyl-5-octyn-2-one, 112741-12-5; cyclohexanecarboxaldehyde, 2043-61-0; (cyclohexylcarbonyl)dibromomethane, 112741-18-1; methyl 2-methyl-4-heptynoate, 112741-19-2; methyltriphenylphosphonium bromide, 1779-49-3; *tert*-butyl bromoacetate, 5292-43-3.

Chiral Synthesis via Organoboranes. 15. Selective Reductions. 42. Asymmetric Reduction of Representative Prochiral Ketones with Potassium 9-*O*-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]-nonane

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Potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (9-*O*-DIPGF-9-BBNH, K-glucoride), a new stable chiral borohydride reducing agent, was prepared by reaction of the corresponding borinic ester, 9-*O*-DIPGF-9-BBN, with potassium hydride in THF. The reagent provides high optical induction for asymmetric reduction of prochiral ketones, such as relatively hindered aliphatic ketones, alkyl aromatic ketones, and α-keto esters. In particular, the reduction of hindered α-keto esters provides the corresponding α-hydroxy esters with optical purities approaching 100% ee. Moreover, the reduction of relatively hindered aliphatic ketones such as 3,3-dimethyl-2-butanone, 2,2-dimethylcyclopentanone, spiro[4.4]nonan-1-one, and 2,2-dimethylcyclohexanone yields the corresponding alcohols in 70% ee, 84% ee, 82% ee, and 64% ee, respectively. The reduction of unhindered aliphatic ketones such as 2-butanone, 3-methyl-2-butanone, 2-octanone, and cyclohexyl methyl ketone provides the corresponding alcohols in relatively low optical purities, 3% ee, 39% ee, 27% ee, and 23% ee, respectively. Alkyl aromatic ketones are reduced to the corresponding alcohols, providing products in 78% ee for acetophenone, 92% ee for propiophenone, 87% ee for butyrophenone, 87% ee for isobutyrophenone, 85.4% ee for valerophenone, 97–100% ee for pivalophenone, and 91% ee for 2′-methylacetophenone. The reduction of α-keto esters provides the corresponding α-hydroxy esters in exceptionally high ee, such as 86% ee for methyl pyruvate, 86% ee for ethyl pyruvate, 87% ee for isopropyl pyruvate, 81% ee for *tert*-butyl pyruvate, 92% ee for ethyl 2-oxobutanoate, 94% ee for ethyl 2-oxopentanoate, 98% ee for methyl 3-methyl-2-oxobutanoate, 97% ee for ethyl 3-methyl-2-oxobutanoate, 97% ee for methyl 3,3-dimethyl-2-oxobutanoate, 98% ee for ethyl 3,3-dimethyl-2-oxobutanoate, 93% ee for ethyl 4-methyl-2-oxopentanoate, 92% ee for methyl benzoylformate, 94% ee for ethyl benzoylformate, 93% ee for isopropyl benzoylformate, and 96% ee for ethyl α-oxo-1-naphthaleneacetate. The reduction of relatively more hindered ketones such as 3,3-diethyl-2-pentanone, 2,2,2-triphenylacetone, 2,2,2-triethylacetophenone, 2,2,2-triphenylacetophenone, and 2′,4′,6′-trimethylacetophenone results in a serious decrease in optical purity, 25% ee, 7% ee, 34% ee, 4% ee, and 35% ee, respectively. 4-Chlorobenzophenone is reduced to 4-chlorobenzhydrol in only 11.5% ee. Ethyl 2,2-dimethylacetoacetate is reduced to ethyl 2,2-dimethyl-3-hydroxybutanoate in 43% ee. The reductions of alkyl heterocyclic ketones such as 2-acetylfuran, 2-acetylthiophene, and 3-acetylpyridine afford the corresponding alcohols with 42% ee, 42% ee, and 70% ee, respectively. The reductions of α-halo ketones, 2-chloroacetophenone and 2,2,2-trifluoroacetophenone, yield the corresponding halohydrins in 77% ee and 48% ee, respectively. *trans*-4-Phenyl-3-buten-2-one is reduced to the corresponding allylic alcohol in 60% ee. The reduction of 4-phenyl-3-butyn-2-one provides the corresponding acetylenic alcohol in 61% ee. The reagent also reduces representative cyclic and bicyclic ketones with high stereoselectivities to give the corresponding thermodynamically less stable alcohols, such as 98% for 2-methylcyclohexanone, 96% for 2-phenylcyclohexanone, 99.7% for 2-*tert*-butylcyclohexanone, 94% for 4-*tert*-butylcyclohexanone, 96% for norcamphor, and 96% for camphor.

Over the past decades, the asymmetric reduction of carbonyl compounds has been actively investigated by organic chemists.[2] Most of the early experiments in this area, however, gave disappointingly low optical yields.[3]

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