Lipase-Mediated Preparation of Sugar Building Blocks

Takahiko Taniguchi, Miwako Takeuchi, Kohei Kadota, Adel S. ElAzab, Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Fax +81(22)2176845; E-mail: konol@mail.cc.tohoku.ac.jp

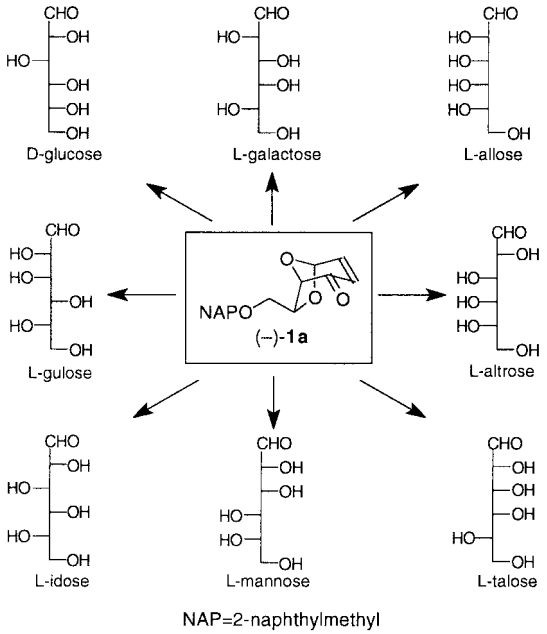
Received 23 March 1999

Abstract: A chiral sugar building block having a dioxabicyclooctane framework has been prepared in enantiomerically pure form, along with two analogs carrying a different protecting group, in an enantiocomplementary way by employing lipase-mediated kinetic resolution as the key step.

Key words: lipase-mediated transesterification, lipase-mediated ester-hydrolysis, chiral building block, oxidative ring-expansion, sugar building block

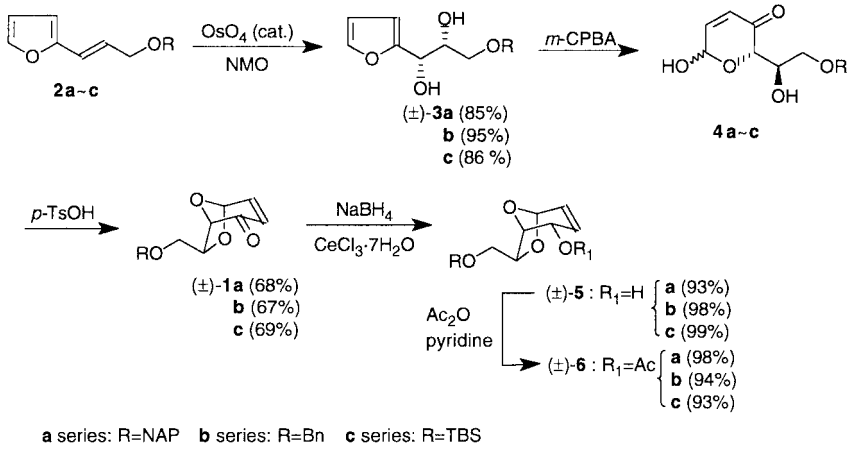
We have recently developed an integrated enantio- and diastereo-controlled route to the eight possible hexoses starting from the chiral enone **1a** having a dioxabicyclooctane framework[1,2] (Scheme 1). The starting chiral enone[1] **1a** as well as its analogues **1b**[3] and **1c**[1] carrying a different protecting group have been prepared in both enantiomerically pure forms from the *E*-2-furfurydenethyl ethers **2a–c** in three steps involving the Sharpless asymmetric dihydroxylation[4] and the Achmatowicz rearrangement.[5] Although the synthesis allowed the generation of the enantiomerically pure enones **1a–c** in satisfactory overall yields, we sought an alternative synthetic procedure which may be carried out in a large scale without using the rather expensive AD-mix reagents used in the Sharpless asymmetric dihydroxylation. We report here a highly efficient synthesis of the chiral enone **1a** and its two analogs **1b** and **1c** carrying a different protecting group by employing either lipase-mediated kinetic transesterification or hydrolysis reaction as the key step.

We first prepared the racemic dioxabicyclooctenone (±)-**1a** in 58% overall yield from 2-(2-furfurydene)ethyl 2-naphthylmethyl ether **2a** via a sequential osmate glycolysis, the peracid-mediated Achmatowicz rearrangement and acidic cyclization[1] via the glycol (±)-**3a** and the 3-pyrone **4a**, quite similar to the chiral counterpart except for the asymmetric dihydroxylation step. Employing the same procedure, *O*-benzyl enone (±)-**1b** and *O*-TBS enone (±)-**1c** were prepared in comparable overall yields from the corresponding furfurydenethyl ether **2b** and **2c**, respectively. The enone (±)-**1a** was then reduced with sodium borohydride/cerium (III) chloride[6] to give diastereoselectively the *endo*-alcohol (±)-**5a** in 93% yield, serving as the substrate for the lipase-mediated kinetic transesterification. The alcohol (±)-**5a** thus obtained was further transformed into the acetate (±)-**6a**, for subsequent lipase-mediated kinetic hydrolysis, in 98% yield under standard conditions. Employing the same procedure, both the *O*-benzyl enone (±)-**1b** and the *O*-TBS enone (±)-**1c** were transformed into the corresponding enols, (±)-**5b** and (±)-**5c**, and the acetates, (±)-**6b** and (±)-**6c**, in comparable yields, respectively (Scheme 2).



Scheme 1

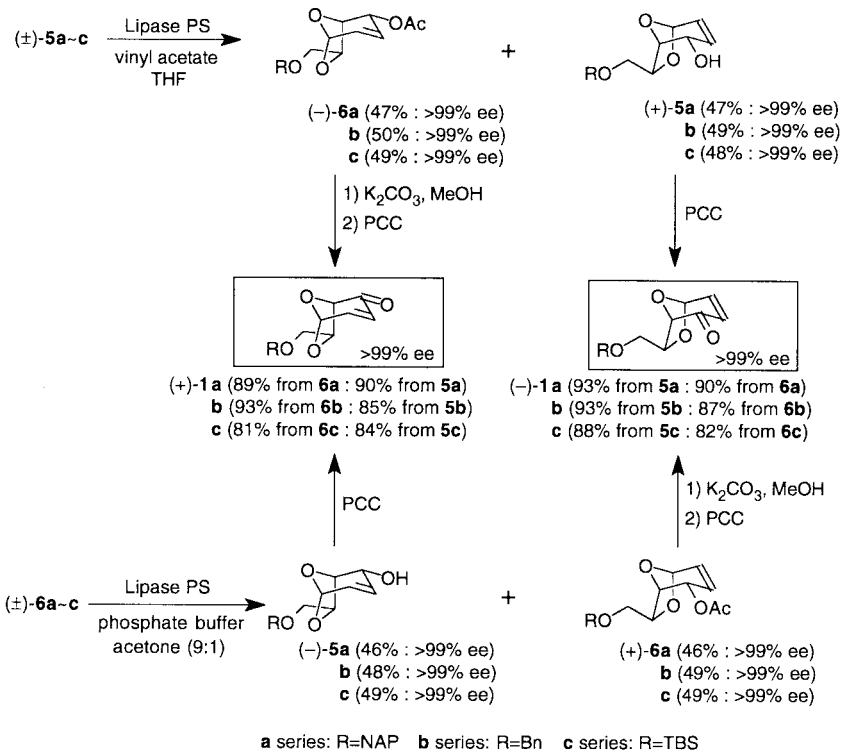
Among the lipases examined, lipase PS (*Pseudomonos* sp., Amano) brought about the best results under both transesterification and hydrolysis conditions.[7–9] Thus, when the alcohol (±)-**5a** was stirred with vinyl acetate in tetrahydrofuran for 24 hours at room temperature in the presence of lipase PS, a clear-cut enantiomeric discrimination occurred to afford the enantiomerically pure acetate (–)-**6a** and the enantiomerically pure alcohol (+)-**5a** in yields of 47 and 47% with E value of >1057.[10,11] Absolute configurations of the products were determined after their transformation into the enone **1a**. The acetate (–)-**6a**, on alkaline methanolysis, gave quantitatively the alcohol (–)-**5a** which, on oxidation with pyridinium chlorochromate (PCC) in dichloromethane, gave the enone (+)-**1a**, identical with the material obtained via the AD-mix-α dihydroxylation in 89% overall yield, while the alcohol (+)-**5a** afforded the enantiomeric enone (–)-**1a**, identical with the material obtained via the AD-mix-β dihydroxylation in 93% yield on PCC oxidation (Scheme 3). Enantiomeric purities of the resolution products were determined as the acetates, (–)-**6a** from (–)-**5a** and (+)-**6a** from (+)-**5a**, to be



Scheme 2

>99% ee, respectively, by HPLC using a column with a chiral stationary phase.

On the other hand, when the racemic acetate (±)-**6a** was stirred in a mixture of a phosphate buffer and acetone (9:1 v/v) in the presence of lipase PS, a clear-cut enantiomeric discrimination also occurred to give the enantiomerically pure alcohol (–)-**5a** and the acetate (+)-**6a** in yields of 46 and 46% with E value of >1057.[10,11] Enantiomeric purities were determined by HPLC using a column with a chiral stationary phase as above which were shown to be >99% ee. As was observed, the enzymatic reactions occurred in an enantiocomplementary way under the transesterification conditions and the hydrolysis conditions as expected.[7,8] Quite similarly, both the enones **1b** and **1c** having a different protecting group were obtained both in >99% ee with E values of >1057[10,11] from the racemic alcohols **5b** and **5c** and the racemic acetates **6b** and **6c** in an enantiocomplementary way via the same lipase-mediated transesterification and hydrolysis conditions, respectively (Scheme 3).



Scheme 3

In summary, we have developed an alternative procedure for the preparation of the sugar building block **1a** along with its two analogs **1b** and **1c** employing a lipase-mediated enantiocomplementary kinetic resolution procedure which exhibited comparable synthetic efficiency to the previously established procedure employing the Sharpless asymmetric hydroxylation. Since the present lipase-mediated procedure allowed facile preparation of highly functionalized bicyclic enones in both enantiomeric forms in enantiomerically pure states without using expensive AD-mix reagents, the enones thus obtained may be more widely used as versatile chiral building blocks not only for the enantiocontrolled construction of sugar derivatives but also for a variety of chiral materials.

Melting points are uncorrected. IR spectra were recorded on a Jasco-IR-700 spectrometer. ^{1}H NMR spectra were recorded on a Gemini 2000 (300 MHz) or Jeol JMX-GX500 (500 MHz) spectrometers. Mass spectra were recorded on a Jeol JM*S*-DX303 instrument. Enantiomeric purities were determined on a Gilson Model-307 instrument equipped with a chiral column. Optical rotations were measured with a Jasco-DIP-370 digital polarimeter.

Benzyl *(E)*-3-(2-Furyl)prop-2-enyl Ether (2b)

To a stirred solution of *(E)*-3-(2-furyl)prop-2-enol (3.70 g, 30 mmol) in THF (70 mL) was added NaH (60% in oil, 1.5 g, 36 mmol) at 0°C. After the H_2 gas evolution had ceased, benzyl bromide (4.7 mL, 39 mmol) and Bu_4NI (1.3 g, 35.2 mmol) were added to the mixture at the same temperature and stirred for 8 h at r.t. The mixture was then treated with MeOH (1 mL, 25 mmol) and NaH (60% in oil, 1.0 g, 24.5 mmol) and diluted with EtOAc (100 mL). The organic layer was washed with H_2O (20 mL) and brine (10 mL), dried ($MgSO_4$), evaporated under reduced pressure and chromatographed on a silica gel column (100 g, elution with EtOAc/hexane, 1:200 then 1:30) to give **2b** (6.1 g, 95%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37–7.28 (m, 6 H), 6.46 (br d, 1 H, *J* = 15.8 Hz), 6.36 (dd, 1 H, *J* = 3.3, 1.8 Hz), 6.25 (dt, 1 H, *J* = 15.8, 5.9 Hz), 6.24 (d, 1 H, *J* = 3.3 Hz), 4.57 (s, 2 H), 4.17 (dd, 2 H, *J* = 5.9, 1.1 Hz).

HRMS: *m/z* calcd for $C_{14}H_{14}O_2$ (M^+) 214.0993. Found 214.0992.

Anal. calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.39; H, 6.63.

(±)-(1*RS*,2*SR*)-1-(2-Furyl)-3-(2-naphthylmethyloxy)propane-1,2-diol [(±)-3a]; Typical Procedure

To a stirred solution of **2a**[1] (1.8 g, 6.8 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (985 mg, 8.2 mmol) in a mixture of THF/H_2O (1:1 v/v, 30 mL) was added OsO_4 (0.2 M in THF, 350 μL, 70 μmol) at 0°C and the mixture was stirred at r.t. for 10 h. To the mixture was then added satd aq Na_2SO_3 solution (10 mL) and, after 10 min, the mixture was extracted with EtOAc (100 mL). The extract was washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (100 g, elution with hexane/EtOAc, 2:1 v/v) to give the diol (±)-**3a** (1.73 g, 85%) as colorless needles; mp 83–85°C (EtOAc).

IR (nujol): ν = 3379 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.85–7.81 (m, 3 H), 7.75 (s, 1 H), 7.52–7.43 (m, 3 H), 7.36 (t, 1 H, *J* = 1.1 Hz), 6.34–6.31 (m, 2 H), 4.78 (d, 1 H, *J* = 4.7 Hz), 4.74 (d, 1 H, *J* = 11.7 Hz), 4.67 (d, 1 H, *J* = 11.7 Hz), 4.16–4.09 (m, 1 H), 3.62 (dd, 1 H, *J* = 9.8, 3.8 Hz), 3.53 (dd, 1 H, *J* = 9.8, 5.5 Hz), 2.95 (d, 1 H, *J* = 4.7 Hz), 2.76 (d, 1 H, *J* = 5.2 Hz).

HRMS: *m/z* calcd for $C_{18}H_{18}O_4$ (M^+) 298.1205. Found 298.1206.

Anal. calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found C, 72.57; H, 6.36.

(±)-(1*RS*,2*SR*)-3-Benzyloxy-1-(2-furyl)propane-1,2-diol [(±)-3b]

The ether **2b** (40 g, 187 mmol) was treated with OsO_4 (0.2 M in THF, 9.5 mL, 1.87 mmol) and NMO (26.2 g) in THF/H_2O (1:1 v/v, 600 mL) under the same conditions described for (±)-**3a** to give (±)-**3b** (43.9 g, 95%); mp 37.0–38.0°C (EtOAc).

IR (nujol): ν = 3406 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38–7.27 (m, 6 H), 6.35–6.32 (m, 2 H), 4.75 (dd, 1 H, *J* = 5.5, 4.8 Hz), 4.57 (d, 1 H, *J* = 11.7 Hz), 4.51 (d, 1 H, *J* = 11.7 Hz), 4.13–4.06 (m, 1 H), 3.58 (dd, 1 H, *J* = 9.9, 3.7 Hz), 3.49 (dd, 1 H, *J* = 9.9, 5.5 Hz), 2.97 (d, 1 H, *J* = 4.4 Hz), 2.75 (d, 1 H, *J* = 5.5 Hz).

HRMS: *m/z* calcd for $C_{14}H_{16}O_4$ (M^+) 248.1048. Found 248.1033.

Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found C, 67.54; H, 6.65.

(±)-(1*RS*,2*SR*)-3-*tert*-Butyldimethylsilyloxy-1-(2-furyl)-propane-1,2-diol [(±)-3c]

The ether **2c** (18 g, 75.6 mmol) was treated with OsO_4 (0.2 M in THF, 3.8 mL, 756 mmol) and NMO (10.6 g, 90.7 mmol) in THF/H_2O (1:1 v/v, 360 mL) under the same conditions described for (±)-**3a** to give (±)-**3c** (17.8 g, 86%) as a colorless oil.

IR (film): ν = 3404 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40 (t, 1 H, *J* = 1.4 Hz), 6.36 (d, 2 H, *J* = 1.4 Hz), 4.74 (dd, 1 H, *J* = 5.5, 4.1 Hz), 3.98–3.92 (m, 1 H), 3.72 (dd, 1 H, *J* = 10.4, 4.0 Hz), 3.61 (dd, 1 H, *J* = 10.4, 4.9 Hz), 3.61 (d, 1 H, *J* = 4.1 Hz), 2.72 (d, 1 H, *J* = 6.3 Hz), 0.91 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.9, 142.3, 128.1, 110.3, 107.6, 73.1, 68.2, 63.9, 25.7, 18.1, –5.7.

HRMS: *m/z* calcd for $C_{13}H_{23}O_3Si$ (M^+–OH) 255.1417. Found 255.1418.

Anal. calcd for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.89. Found C, 57.34; H, 8.88.

(±)-7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one [(±)-1a]; Typical Procedure

To a stirred solution of (±)-**3a** (4.61 g, 15.47 mmol) in CH_2Cl_2 (100 mL) was added *m*CPBA (70%, 4.19 g, 17.01 mmol) at 0°C and the mixture was stirred at r.t. for 3 h. The mixture was filtered through a Celite pad and evaporated under reduced pressure to give the crude pyranone **4a**. Without purification, the crude **4a** was then refluxed in benzene (100 mL) in the presence of *p*-TsOH (29 mg, 0.15 mmol) for 10 h. After cooling, the mixture was diluted with EtOAc (100 mL) and the organic phase was washed with satd aq $NaHCO_3$ solution (3 × 10 mL) and brine (10 mL), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column (100 g, elution with hexane/EtOAc, 8:1 v/v) to give the bicyclic enone diol (±)-**1a** (3.11 g, 68%) as colorless prisms; mp 80–83°C (hexane/EtOAc). Spectroscopic data were identical with those of (+)-**1a**.[1]

(±)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one [(±)-1b]

The diol (±)-**3b** (20 g, 80.6 mmol) was treated with *m*CPBA (70%, 30 g, 120.9 mmol) in CH_2Cl_2 (400 mL) under the same conditions described for (±)-**1a** to give the crude pyranone **4b**. The pyranone **4b** was then refluxed in benzene (400 mL) in the presence of *p*-TsOH (200 mg, 1.05 mmol) to give the enone (±)-**1b** (13.3 g, 67%) as colorless prisms; mp 56.0–57.0°C (hexane/EtOAc).

IR (film): ν = 1721, 1690 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.30–7.19 (m, 5 H), 7.05 (dd, 1 H, *J* = 9.8, 3.1 Hz), 6.01 (d, 1 H, *J* = 9.8 Hz), 5.75 (d, 1 H, *J* = 3.1 Hz), 4.52 (s, 2 H), 3.96–3.93 (m, 1 H), 3.56 (dd, 1 H, *J* = 9.8, 6.1 Hz), 3.46 (dd, 1 H, *J* = 9.8, 6.8 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.0, 147.3, 137.6, 128.5, 127.9, 127.8, 126.9, 96.6, 81.8, 73.5, 73.0, 69.8.

FABMS: *m*/*z* = 245 (M^+ – 1).

Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found C, 67.96; H, 5.93.

(±)-7-*tert*-Butyldimethylsiloxy-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one [(±)-1c]

The diol (±)-**3c** (3.61 g, 13.2 mmol) was treated with *m*CPBA (70%, 3.59 g, 14.6 mmol) in CH_2Cl_2 (80 mL) under the same conditions described for (±)-**1a** to give the crude pyranone **4c**. The pyranone **4c** was then refluxed in benzene (80 mL) in the presence of *p*-TsOH (25 mg, 0.13 mmol) to give the enone (±)-**1c** (2.47 g, 69%). Spectroscopic data were identical with those of (+)-**1c**.[1]

(±)-(1*RS*,2*SR*,5*SR*,7*RS*)-7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(±)-5a]; Typical Procedure

To a stirred solution of (±)-**1a** (595 mg, 2 mmol) and $CeCl_3 \cdot 7H_2O$ (899 mg, 2.4 mmol) in MeOH (12 mL) was added $NaBH_4$ (91 mg, 2.4 mmol) at 0°C and the stirring was continued for 15 min at the same temperature. After evaporation of the solvent under reduced pressure, the residue was dissolved in EtOAc (60 mL) and the organic layer was washed with H_2O (5 mL) and brine (5 mL), and dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (60 g, elution with hexane/EtOAc, 4:1 v/v) to give the alcohol (±)-**5a** (555 mg, 93%) as colorless needles; mp 80–81°C (hexane/EtOAc).

IR (nujol): ν = 3274 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.85–7.82 (m, 3 H), 7.78 (s, 1 H), 7.51–7.44 (m, 3 H), 5.90 (ddd, 1 H, *J* = 9.9, 3.0, 1.9 Hz), 5.70 (dt, 1 H, *J* = 9.9, 1.9 Hz), 5.54 (d, 1 H, *J* = 3.0 Hz), 4.80–4.72 (m, 3 H), 4.54 (ddd, 1 H, *J* = 6.0, 5.8, 1.6 Hz), 4.28 (dt, 1 H, *J* = 4.7, 1.6 Hz), 3.63 (dd, 1 H, *J* = 9.9, 5.8 Hz), 3.55 (dd, 1 H, *J* = 9.9, 6.0 Hz), 1.91 (d, 1 H, *J* = 5.5 Hz).

HRMS: *m*/*z* calcd for $C_{18}H_{18}O_5$ (M^+) 298.1205. Found 298.1208.

Anal. calcd for $C_{18}H_{18}O_5$: C, 72.47; H, 6.08. Found C, 72.53; H, 6.19.

(±)-(1*RS*,2*SR*,5*SR*,7*RS*)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(±)-5b]

The enone (±)-**1b** (1.0 g, 4.1 mmol) was reduced with $NaBH_4$ (184 mg, 4.9 mmol) and $CeCl_3 \cdot 7H_2O$ (1.8 g, 4.9 mmol) in MeOH (20 mL) under the same conditions described for (±)-**1a** to give the alcohol (±)-**5b** (984 mg, 98%).

IR (film): ν = 3420 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.38–7.26 (m, 5 H), 5.91 (ddd, 1 H, *J* = 9.6, 3.0, 1.6 Hz), 5.71 (m, 1 H), 5.53 (d, 1 H, *J* = 3.0 Hz), 4.77 (m, 1 H), 4.60 (s, 2 H), 4.60–4.46 (m, 2 H), 4.28 (dt, 1 H, *J* = 4.7, 1.9 Hz), 3.59 (dd, 1 H, *J* = 9.9, 5.5 Hz), 3.52 (dd, 1 H, *J* = 9.9, 6.3 Hz).

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_4$ (M^+) 248.1049. Found 248.1024.

Anal. calcd for $C_{14}H_{16}O_4$: C, 67.71; H, 6.49. Found C, 67.43; H, 6.38.

(±)-(1*RS*,2*SR*,5*SR*,7*RS*)-7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(±)-5c]

The enone (±)-**1c** (658 mg, 2.44 mmol) was reduced with $NaBH_4$ (411 mg, 2.92 mmol) and $CeCl_3 \cdot 7H_2O$ (1.09 g, 2.92 mmol) in MeOH (25 mL) under the same conditions described for (±)-**1a** to give the alcohol (±)-**5c** (654 mg, 99%). Spectroscopic data were identical with those of (+)-**5c**.[1]

(±)-(1*RS*,2*SR*,5*SR*,7*RS*)-2-Acetoxy-7-(2-naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-ene [(±)-6a]; Typical Procedure

To a mixture of **5a** (1.55 g, 5.2 mmol) and pyridine (630 μL, 7.8 mmol) in CH_2Cl_2 (20 mL) was added Ac_2O (590 μL, 6.2 mmol) at r.t. and the stirring was continued for 12 h at the same temperature. The mixture was diluted with EtOAc (120 mL) and the solution was washed with 10% HCl (2 × 5 mL), H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (130 g, elution with hexane/EtOAc, 6:1 v/v) to give the acetate (±)-**6a** (1.73 g, 98%) as a pale yellow oil.

IR (film): ν = 1741 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.85–7.82 (m, 3 H), 7.77 (s, 1 H), 7.49–7.44 (m, 3 H), 6.01 (ddd, 1 H, *J* = 9.6, 3.0, 1.6 Hz), 5.75–5.68 (m, 2 H), 5.57 (d, 1 H, *J* = 3.0 Hz), 4.76 (d, 1 H, *J* = 13.7 Hz), 4.71 (d, 1 H, *J* = 13.7 Hz), 4.53–4.48 (m, 2 H), 3.65 (dd, 1 H, *J* = 9.6, 5.4 Hz), 3.51 (dd, 1 H, *J* = 9.6, 6.9 Hz), 2.00 (s, 3 H).

HRMS: *m*/*z* calcd for $C_{20}H_{20}O_6$ (M^+) 356.1259. Found 340.1302.

Anal. calcd for $C_{20}H_{20}O_6$: C, 70.57; H, 5.92. Found C, 70.60; H, 5.92.

(±)-(1*RS*,2*SR*,5*SR*,7*RS*)-2-Acetoxy-7-benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene [(±)-6b]

The alcohol (±)-**5b** (1.0 g, 4.0 mmol) was treated with Ac_2O (431 μL, 4.8 mmol) and pyridine (485 μL, 6.0 mmol) in CH_2Cl_2 (10 mL) under the same conditions described for (±)-**6a** to give the acetate (±)-**6b** (1.1 g, 94%) as a colorless oil.

IR (film): ν = 1743 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.38–7.20 (m, 5 H), 6.00 (ddd, 1 H, *J* = 9.3, 3.3, 1.4 Hz), 5.73 (m, 1 H), 5.73 (d, 1 H, *J* = 2.2 Hz), 5.56 (d, 1 H, *J* = 3.3 Hz), 4.59 (d, 1 H, *J* = 12.1 Hz), 4.55 (d, 1 H, *J* = 12.1 Hz), 4.50–4.44 (m, 2H), 3.61 (dd, 1 H, *J* = 9.6, 5.5 Hz), 3.45 (dd, 1 H, *J* = 9.6, 6.9 Hz), 2.01 (s, 3 H).

HRMS: *m*/*z* calcd for $C_{16}H_{18}O_5$ (M^+) 290.1153. Found 290.1177.

Anal. calcd for $C_{16}H_{18}O_5$: C, 66.18; H, 6.35. Found C, 66.38; H, 6.55.

(±)-(1*RS*,2*SR*,5*SR*,7*RS*)-2-Acetoxy-7-*tert*-butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene [(±)-6c]

The alcohol (±)-**5c** (700 mg, 2.57 mmol) was treated with Ac_2O (323 μL, 3.10 mmol) and pyridine (312 μL, 3.86 mmol) in CH_2Cl_2 (10 mL) under the same conditions described for (±)-**6a** to give the acetate (±)-**6c** (750 mg, 93%) as a colorless oil.

IR (film): ν = 1749 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.02 (ddd, 1 H, *J* = 9.6, 3.0, 1.6 Hz), 5.73 (m, 1 H), 5.68 (m, 1 H), 5.52 (d, 1 H, *J* = 3.0 Hz), 4.46 (dt, 1 H, *J* = 4.7, 1.6 Hz), 4.31 (m, 1 H), 3.72 (dd, 1 H, *J* = 9.9, 4.9 Hz), 3.48 (dd, 1 H, *J* = 9.9, 8.5 Hz), 2.08 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

HRMS: *m*/*z* calcd for $C_{11}H_{17}O_5Si$ ($M^+ - C_4H_{10}$) 257.0844. Found 257.0847.

Anal. calcd $C_{15}H_{28}O_5Si$: C, 57.11; H, 8.63. Found C, 57.38; H, 8.55.

(–)-(1*S*,2*R*,5*R*,7*S*)-2-Acetoxy-7-(2-naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-ene [(–)-6a] and (+)-(1*R*,2*S*,5*S*,7*R*)-7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(+)-5a] from the Racemic Alcohol (±)-5a; Typical Procedure

To a stirred solution of the racemic alcohol (±)-**5a** (370 mg, 1.24 mmol) in THF (9 mL) and vinyl acetate (1.1 mL, 12.4 mmol) was

added lipase PS (370 mg) at r.t. and the suspension was stirred at the same temperature for 24 h. After filtration through a Celite pad, the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (40 g, elution with hexane/EtOAc, 5:1 v/v) to give the acetate (–)-**6a** as an oil (175 mg, 47%); $[\alpha]_D^{29}$ –24.9 (*c* = 1.0, $CHCl_3$); the alcohol (+)-**5a** as colorless needles (153 mg, 47%); $[\alpha]_D^{29}$+6.76 (*c* = 1.0, $CHCl_3$); mp 80–81°C (hexane/EtOAc). Enantiomeric purities of the products were determined as >99% ee as the acetate **6a** by HPLC using a column with a chiral stationary phase [CHIRALCEL OD, elution with 3% *i*-PrOH/hexane, retention time:32.1 min for (–)-**6a** and 36.4 min for (+)-**6a** at 0.5 mL/min]. Spectral data were identical with those of (±)-**5a** and (±)-**6a**.

(–)-(1*S*,2*R*,5*R*,7*S*)-2-Acetoxy-7-benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene [(–)-6b] and (+)-(1*R*,2*S*,5*S*,7*R*)-7-benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(+)-5b] from the Racemic Alcohol (±)-5b

The racemic alcohol (±)-**5b** (1.0 g, 4.0 mmol) was treated with vinyl acetate (3.7 mL, 40 mmol) in THF (20 mL) in the presence of lipase PS (1.0 g) under the same conditions described for (±)-**5a** to give the acetate (–)-**6b** (590 mg, 50%) and the alcohol (+)-**5b** (450 mg, 49%) after 24 h. Spectral data of the products were identical with those of the racemates.

(–)-**6b**

$[\alpha]_D^{27}$ –24.8 (*c* = 1.1, $CHCl_3$). Enantiomeric purity was determined as >99% ee by HPLC using a column with a chiral stationary phase [CHIRALCEL OD, elution with 3% *i*-PrOH-hexane, retention time:24.7 min for (–)-**6b** and 42.4 min for (+)-**6b**].

(+)-**5b**

$[\alpha]_D^{27}$+5.4 (*c* = 1.1, $CHCl_3$). Enantiomeric purity was determined as >99% ee after transformation into the acetate (+)-**6b** by HPLC using a column with a chiral stationary phase.

(–)-(1*S*,2*R*,5*R*,7*S*)-2-Acetoxy-7-*tert*-butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene [(–)-6c] and (+)-(1*R*,2*S*,5*S*,7*R*)-7-*tert*-butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(+)-5c]

The racemic alcohol (±)-**5c** (200 mg, 0.73 mmol) in THF (4 mL) was treated with vinyl acetate (677 μL, 7.3 mmol) in the presence of lipase PS (200 mg) under the same conditions described for (±)-**5a** to give the acetate (–)-**6c** (114 mg, 49%) and the alcohol (+)-**5c** (96 mg, 48%). Spectral data of the products were identical with those of the racemates.

(–)-**6c**

mp 44–46°C (hexane/EtOAc); $[\alpha]_D^{27}$ –16.5 (*c* = 1.0, $CHCl_3$).

(+)-**5c**

mp 48–50°C (hexane/EtOAc); $[\alpha]_D^{26}$ +2.9 (*c* = 1.0, $CHCl_3$).

Enantiomeric purity of both products was determined as >99% ee by HPLC using a column with a chiral stationary phase after transformation into the benzoate [CHIRALCEL OD, elution with 1% *i*-PrOH/hexane, retention time:11.5 min for (–)-**6c** and 22.7 min for (+)-**6c** at 0.5 mL/min].

(–)-(1*S*,2*R*,5*R*,7*S*)-7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(–)-5a] and (+)-(1*R*,2*S*,5*S*,7*R*)-2-Acetoxy-7-(2-naphthylmethyloxymethyl)-6,8-dioxabicyclo-[3.2.1]-oct-3-ene [(+)-6a] from the Racemic Acetate (±)-6a; Typical Procedure:

To a stirred solution of the racemic alcohol (±)-**6a** (360 mg, 1.18 mmol) in 0.1 M phosphate buffer (pH 7.0, 8.1 mL) and acetone (0.9 mL) was suspended lipase PS (360 mg) at r.t. and the suspension was stirred at the same temperature for 24 h. After filtration though a Celite pad, the filtrate was extracted with EtOAc (50 mL). The extract was washed with H_2O and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (40 g, elution with hexane/EtOAc, 5:1 v/v) to give the acetate (+)-**6a** as an oil (166 mg, 46%); $[\alpha]_D^{30}$+23.9 (*c* = 1.0, $CHCl_3$); and the alcohol (–)-**5a** as colorless needles (145 mg, 46%); $[\alpha]_D^{28}$ –6.15 (*c* 0.8, $CHCl_3$); mp 79–81°C (hexane/EtOAc). Enantiomeric purities of the products were determined as >99% ee as the acetate **6a** by HPLC using a column with a stationary phase (CHIRALCEL OD, elution with 3% *i*-PrOH/hexane). Spectral data of both products were identical with those of (±)-**5a** and (±)-**6a**.

(–)-(1*S*,2*R*,5*R*,7*S*)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]-oct-3-en-2-ol [(–)-5b] and (+)-(1*R*,2*S*,5*S*,7*R*)-2-Acetoxy-2-benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene [(+)-6b] from the Racemic Acetate (±)-6b

The racemic acetate (±)-**6b** (500 mg, 1.7 mmol) in a mixture of 0.1 M phosphate buffer (pH 7.0, 9 mL) and acetone (1 mL) was treated with lipase PS (500 mg) under the same conditions described for (±)-**6a** to give the alcohol (–)-**5b** (205 mg, 48%) and the acetate (+)-**6b** (245 mg, 49%) after 24 h. Spectral data of the products were identical with those of the racemates.

(–)-**5b**

$[\alpha]_D^{24}$ –5.6 (*c* = 1.0, $CHCl_3$). Enantiomeric purity was determined as >99% ee after transformation into the acetate (+)-**6b**.

(+)-**6b**

$[a]_D^{26}$+25.1 (*c* = 1.0, $CHCl_3$). >99% ee by HPLC (CHIRALCEL OD, elution with 3% *i*-PrOH/hexane).

(–)-(1*S*,2*R*,5*R*,7*S*)-7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(–)-5c] and (+)-(1*R*,2*S*,5*S*,7*R*)-2-Acetoxy-7-*tert*-butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]-oct-3-ene [(+)-6c] from the Racemic Acetate (±)-6c

A mixture of the racemic acetate (±)-**6c** (150 mg, 0.48 mmol), 0.1 M phosphate buffer (pH 7.0, 2.7 mL) and acetone (3 mL) was treated with lipase PS (150 mg) under the same conditions described for (±)-**6a** to give the alcohol (–)-**5c** (63 mg, 49%) and the acetate (+)-**6c** (73 mg, 49%) after 24 h. Spectral data of the products were identical with those of the racemates.

(–)-**5c**

mp 46–48°C (hexane/EtOAc); $[\alpha]_D^{30}$ –2.8 (*c* = 1.1, $CHCl_3$).

(+)-**6c**

mp 36–38°C (hexane/EtOAc); $[\alpha]_D^{28}$ +15.5 (*c* = 1.0, $CHCl_3$).

Enantiomeric purity of both products was determined as >99% ee after transformation into benzoate by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with 1% *i*-PrOH/hexane).

(–)-(1*S*,2*R*,5*R*,7*S*)-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(–)-5a] from (–)-(1*S*,2*R*,5*R*,7*S*)-2-Acetoxy-7-(2-naphthylmethyloxymethyl)-6,8-dioxabicyclo-[3.2.1]oct-3-ene [(–)-6a]; Typical Procedure

To a stirred solution of the acetate (–)-**6a** (150 mg, 0.44 mmol) in MeOH (2 mL) was added solid K_2CO_3 (61 mg, 0.44 mmol) at r.t. and the stirring was continued at the same temperature for 0.5 h. The mixture was diluted with H_2O (3 ml) and extracted with AcOEt (10 ml). The extract was washed with H_2O (3 ml) and brine (3 mL), dried ($MgSO_4$), evaporated under reduced pressure to give the alcohol (–)-**5a** (130 mg, 99%); mp 83–85°C (EtOAc); $[\alpha]_D^{28}$ –6.68 (*c* = 0.7, $CHCl_3$). Spectral data were identical with those of (+)-**5a**.

In a similar manner, the enantiomeric (+)-**6a** was converted to the (+)-alcohol (+)-**5a**;, mp 83–85°C (EtOAc); $[\alpha]_D^{26}$ +6.31 (*c* = 1.0, $CHCl_3$) in 99% yield.

Similarly, (–)-**5b** from (–)-**6b** and (–)-**5c** from (–)-**6c** were obtained in excellent yields, respectively.

(–)-(1*S*,5*S*,7*R*)-7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one [(–)-1a] from (+)-(1*R*,2*S*,5*S*,7*R*)-7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(+)-5a]; Typical Procedure

To a stirred suspension of (+)-**5a** (100 mg, 0.34 mmol), NaOAc (55 mg, 0.67 mmol) and molecular sieves (4Å, 165 mg) in CH_2Cl_2 (2 mL) was added pyridinium chlorochromate (110 mg, 0.51 mmol) at r.t. and the mixture was stirred at the same temperature for 3 h. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure and chromatographed on a silica gel column (10 g, elution with hexane/EtOAc, 10:1 v/v) to give the enone (–)-**1a** (92 mg, 93%) as colorless prisms; mp 80–83°C (hexane/EtOAc); $[\alpha]_D^{29}$ –156.5 (*c* = 0.6, $CHCl_3$). Spectral data were identical with those of (±)-**1a**.

In a similar way, the enantiomeric (–)-**5a** gave the enone (+)-**1a**, mp 80–83°C (hexane/EtOAc); $[\alpha]_D^{29}$ +148.3 (*c* = 0.6, $CHCl_3$), in 90% yield.

(–)-(1*S*,5*S*,7*R*)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one [(–)-1b] from (+)-(1*R*,2*S*,5*S*,7*R*)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol [(+)-5b]

The alcohol (+)-**5b** (200 mg, 0.81 mmol) was oxidized with PCC (259 mg, 1.22 mmol) in CH_2Cl_2 (5 mL) in the presence of NaOAc (131 mg, 1.62 mmol) and molecular sieves (4Å) (390 mg) under the same conditions described for (–)-**1a** to give the enone (–)-**5b** (185 mg, 93%) as colorless prisms, mp 66–68 °C (hexane/EtOAc); $[\alpha]_D^{27}$ –187.7 (*c* = 1.1, $CHCl_3$). Spectral data were identical with those of (±)-**5b**.

On similar treatment, the (–)-alcohol (–)-**5b** afforded the enantiomeric enone (+)-**1b;** mp 64–66°C (hexane/EtOAc); $[\alpha]_D^{25}$ +191.8 (*c* = 1.4, $CHCl_3$), in 96% yield.

(–)-(1*S*,5*S*,7*R*)-7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one [(–)-1c] from (+)-(1*R*,2*S*,5*S*,7*R*)-7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-ol (+)-5c

The alcohol (+)-**5c** (180 mg, 0.66 mmol) was oxidized with PCC (213 mg, 0.99 mmol) in CH_2Cl_2 (4 ml) in the presence of NaOAc (108 mg, 1.32 mmol) and molecular sieves (4Å) (320 mg) under the same conditions described for (–)-**1a** to give the enone (–)-**1c** (145 mg, 81%) as a colorless oil; $[\alpha]_D^{27}$ –187.7 (*c* 1.1, $CHCl_3$). Spectral data were identical with those of (±)-**1c**.

In a similar way, the alcohol (–)-**5c** afforded the enantiomeric enone (+)-**1c** in 88% yield; $[\alpha]_D^{25}$ +191.8 (*c* = 1.4, $CHCl_3$)

Acknowledgement

We are grateful for the Egyptian Associate Channel System Program Scholarship (to A. S. ElAzab).

References

(1) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **1999**, 341.
(2) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. in preparation.
(3) Taniguchi, T.; Ohnishi, H.; Ogasawara, K. *J. Chem. Soc*., *Chem*. *Commun*. **1996**, 1477.
(4) Johnson, R. A.; Sharpless, K. B. *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I.; Eds.; Pergamon Press: New York 1991, Vol. 7, p. 389.
(5) Achmatowicz, O. *Organic Synthesis Today and Tomorrow*, Trost, B. M.; Hutchinson, C. R.; Eds.; Pergamon Press: Oxford, 1980, pp. 307-325.
(6) Luche, J. -L. *J. Am. Chem. Soc*. **1977**, *100*, 2226.
Gemal, A. L.; Luche, J. -L. *J. Am. Chem. Soc*. **1981**, *103*, 5454.
(7) Takano, S.; Yamane, T.; Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 873.
Takano, S.; Setoh, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 157.
Takano, S.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1043.
Takano, S.; Yamada, O.; Iida, H; Ogasawara, K. *Synthesis* **1994**, 592.
(8) A pertinent monograph, see: Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, 1994.
(9) Pertinent reviews, see: Roberts, S. M.; *J. Chem. Soc., Perkin Trans. 1* **1998**, 157 and **1999**, 1.
(10) Chen, C. -S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem*. *Soc*. **1982**, *104*, 7294.
(11) E value was calculated by estimating enantiomeric purities of the products as 99% ee.

Article Identifier:
1437-210X,E;1999,0,08,1325,1330,ftx,en;F12099SS.pdf