Lipase-Mediated Preparation of Enantiopure Isolevoglucosenone

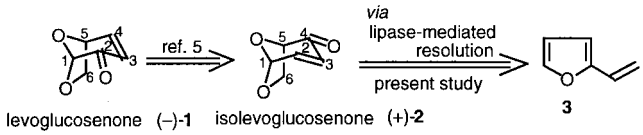
Kohei Kadota, Adel S. ElAzab, Takahiko Taniguchi, Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan
Fax +81(22)2176845; E-mail: konol@mail.cc.tohoku.ac.jp
Received 11 April 2000; revised 12 May 2000

Abstract: A route to enantiopure isolevoglucosenone, a regioisomer of levoglucosenone and a potential chiral building block, has been developed by employing lipase-mediated kinetic resolution as the key step.

Key words: isolevoglucosenone, lipase-mediated kinetic resolution, enantioselective kinetic resolution, enantioselective hydrolysis, chiral building block

Levoglucosenone [(−)-**1**][1] is an acid-catalyzed pyrolysis product of cellulose and is used as a versatile chiral building block[2] owing to its high functionality confined within a biased 6,8-dioxabicyclo[3.2.1]octane framework. However, its acquisition was not efficient and limited to the (−)-enantiomer.[3,4] Recently, we developed the first enantiocontrolled synthesis of both enantiomers of levoglucosenone (**1**) from 2-vinylfuran (**3**) via isolevoglucosenone[5,6] (**2**) by employing the Sharpless asymmetric dihydroxylation (AD) reaction as the key step.[7] During the synthesis we encountered two difficulties: incomplete enantioselectivity in the AD reaction[7] and lower efficiency in the conversion of isolevoglucosenone (**2**) into levoglucosenone (**1**) involving the Wharton rearrangement[8] (Scheme 1).

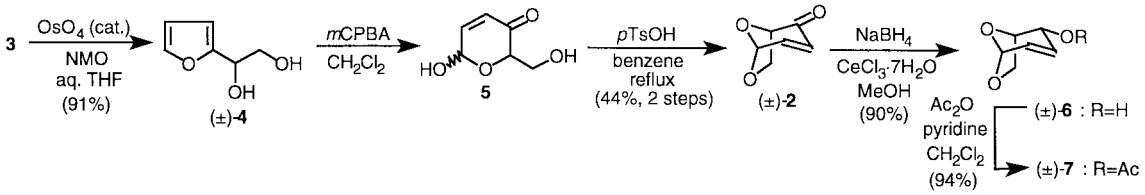


Scheme 1

Levoglucosenone (**1**) owes its stereocontrollability and its versatility to the enone functionality on the biased framework. Since isolevoglucosenone (**2**) possesses the same biased structure, except its isomeric enone disposition, it would be taken as a synthetic equivalent in many respects. We, therefore, explored a new procedure capable of producing enantiopure isolevoglucosenone (**2**), in both enantiomeric forms,[9] so as to utilize it as a versatile chiral building block similarly to levoglucosenone (**1**). We employed lipase-mediated kinetic resolution[10] under both ester-exchange conditions in an organic solvent and ester-hydrolysis conditions in a buffer solution, as the key reaction.[11] We now report the successful use of the lipase-mediated reaction in obtaining enantiopure isolevoglucosenone (**2**) in both enantiomeric forms by the exchange conditions and highly enantioenriched forms (97% and 98% ee) by the hydrolysis conditions.

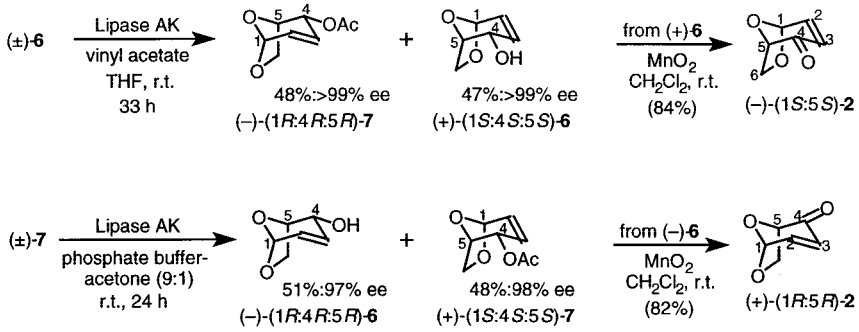
2-Vinylfuran (**3**)[12] was first treated under catalytic dihydroxylation conditions using osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) to give the racemic 1,2-diol (±)-**4**. According to the established method for the asymmetric synthesis,[5] the racemate (±)-**4** was treated with *m*-chloroperbenzoic acid (*m*CPBA) to give the 3-pyranone mixture **5** which was immediately refluxed in benzene with removal of water in the presence of *p*-toluenesulfonic acid to give racemic isolevoglucosenone [(±)-**2**] in 44% yield. In order to carry out enzymatic transesterification and hydrolysis, (±)-**2** obtained was reduced diastereoselectively from the convex face under Luche conditions[13] to give the *endo*-alcohol[6a,b] (±)-**6** which was used as the substrate for the lipase-mediated transesterification. Moreover, the racemic alcohol (±)-**6** was acetylated to give the *endo*-acetate (±)-**7** which was used as the substrate for the lipase-mediated hydrolysis (Scheme 2).

We first examined the lipase-mediated kinetic transesterification with vinyl acetate in an organic solvent using an immobilized lipase. Among the tested lipases, Lipase AK (*Pseudomonas* sp., Amano) exhibited the best result which afforded the enantiopure acetate (−)-(1*R*,4*R*,5*R*)-**7** in 48% yield, with the enantiopure alcohol (+)-(1*S*,4*S*,5*S*)-**6** in 47% recovery yield. Optical purity of the products was determined by HPLC equipped with a column with a chiral stationary phase (CHIRALCEL OD) after transformation into the benzoate having the corresponding chirality. The absolute configuration of the products was determined by the respective transformation into isolevoglucosenone[5] (**2**) each having the corresponding chirality. Thus, the acetate (−)-(1*R*,4*R*,5*R*)-**7** furnished isolevoglucosenone [(+)-(1*R*,5*R*)-**2**] by sequential methanolysis and oxidation via the alcohol[6a,b] (−)-(1*R*,4*R*,5*R*)-**6**,



Scheme 2

Downloaded by: Queen's University. Copyrighted material.



Scheme 3

while the alcohol (+)-(1*S*,4*S*,5*S*)-**6** yielded the enantiomeric non-racemic isolevoglucosenone [(−)-(1*S*,5*S*)-**2**] on oxidation.

Kinetic hydrolysis of the racemic acetate (±)-**7**, on the other hand, also proceeded well in the presence of Lipase AK. Thus, stirring (±)-**7** with Lipase AK in a 9:1 mixture of 0.1 M phosphate buffer and acetone at room temperature afforded enantiocomplementarily the alcohol (−)-(1*R*,4*R*,5*R*)-**6** in 51% yield having 97% ee, with the acetate (+)-(1*S*,4*S*,5*S*)-**7** having 98% ee in 48% recovery yield. Both of the products were transformed into isolevoglucosenone (**2**) having the corresponding chirality (Scheme 3).

In summary, we have established a new procedure producing isolevoglucosenone (**2**) in both enantiomeric forms by employing lipase-mediated kinetic resolution as the key step. The present investigation revealed that the hydrolysis method is a little less satisfactory than the transesterification method in obtaining enantiopure products, but, the present lipase-mediated method is much superior to the asymmetric procedure we have previously established.[5]

IR spectra were recorded on a JASCO-IR-700 spectrometer. ^{1}H NMR spectra were recorded on a Gemini 2000 (300 MHz) spectrometer. Mass spectra were recorded on a Jeol JMS-DX 303 instrument. Optical rotations were measured with a Jasco-DIP-370 digital polarimeter. Optical purity was determined by HPLC on a Gilson Model-307 instrument equipped with a column with a chiral stationary phase.

1-(2-Furyl)ethane-1,2-diol [(±)-4]

To a stirred solution of 2-vinylfuran (**3**; 13.4 g, 142 mmol) and *N*-methylmorphorine-*N*-oxide (20 g, 171 mmol) in aq THF (15:1, v/v 284 mL) was added OsO_4 in THF (0.198 M, 0.8 mL, 0.158 mmol) at 0 °C and the mixture was stirred at r.t. for 48 h. After evaporation of most of the THF under reduced pressure, the residue was extracted with EtOAc (3 × 300 mL) and the extract was washed with brine (2 × 100 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 100 g, elution with EtOAc/hexane, 3:2 v/v) to give the diol (±)-**4** (16.5 g, 91%) as a pale yellow oil. Spectral data were identical with those of the optically active material.[5]

IR (film): ν = 3359 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (1 H, dd, *J* = 1.9, 0.8 Hz), 6.37 (1 H, dd, *J* = 3.3, 1.9 Hz), 6.33 (1 H, br d, *J* = 3.3 Hz), 4.82 (1 H, dd, *J* = 10.4, 4.9 Hz), 3.89 (2 H, t, *J* = 4.9 Hz), 2.59 (1 H, br d, *J* = 4.9 Hz), 2.13 (1 H, m).

HRMS: *m*/*z* calcd for $C_6H_8O_3$: 128.0473, found: 128.0472.

(±)-Isolevoglucosenone [(±)-2]

To a stirred solution of (±)-**4** (3.06 g, 28.1 mmol) in CH_2Cl_2 (70 mL) was added *m*-chloroperbenzoic acid (70%, 7.62 g, 30.9 mmol) at 0 °C and the mixture was stirred at r.t. for 3 h. After filtration through a Celite-pad, the filtrate was evaporated under reduced pressure to give a residue containing the crude pyrone **5**. The residue without separation was dissolved in benzene (94 mL) and refluxed with *p*-TsOH•H_2O (53 mg, 0.28 mmol) for 3 h with removal of water using a Dean−Stark apparatus. After cooling, the mixture was washed with 5% aq $NaHCO_3$ solution (20 mL), brine (20 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 80 g, elution with Et_2O/pentane, 1:5 v/v) to give (±)-**2** (1.56 g, 44%) as a colorless oil. Spectral data were identical with those of the optically active material.[5]

IR (film): ν = 1714 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (1 H, dd, *J* = 9.9, 3.3 Hz), 6.11 (1 H, dt, *J* = 9.9, 1.1 Hz), 5.82 (1 H, dd, *J* = 3.3, 0.5 Hz), 4.79 (1 H, dt, *J* = 6.3, 1.4 Hz), 4.12 (1 H, dd, *J* = 8.2, 6.3 Hz), 3.66 (1 H, dd, *J* = 8.2, 1.4 Hz).

HRMS: *m*/*z* calcd for $C_6H_6O_3$: 126.0316, found: 126.0309.

(±)-7,8-Dioxabicyclo[3.2.1]oct-3-en-2-ol [(±)-6]

To a stirred solution of (±)-**2** (1.1 g, 8.73 mmol) and $CeCl_3$•$7H_2O$ (3.90 g, 10.5 mmol) in MeOH (30 mL) was added $NaBH_4$ (395 mg, 10.5 mmol) at 0 °C. After 10 min at the same temperature, the mixture was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL). The solution was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 30 g, elution with Et_2O/hexane, 1:2 v/v) to give (±)-**6** (1.01 g, 90%) as a colorless oil.

IR (film): ν = 3433 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (1 H, ddd, *J* = 9.9, 3.0, 1.6 Hz), 5.72 (1 H, dt, *J* = 9.6, 1.4 Hz), 5.52 (1 H, d, *J* = 3.0 Hz), 4.85−4.80 (1 H, m), 4.56−5.51 (1 H, m), 4.20 (1 H, dd, *J* = 8.2, 1.9 Hz), 3.95−3.90 (1 H, m), 1.77 (1 H, br d, *J* = 5.8 Hz).

HRMS: *m*/*z* calcd for $C_6H_8O_3$: 128.0473, found: 128.0490.

Anal. calcd for $C_6H_8O_3$: C 56.24 H 6.29, found: C 55.97 H 6.36.

^{1}H NMR spectrum of **6** was identical with that reported.[6a]

(±)-7,8-Dioxabicyclo[3.2.1]oct-3-en-2-yl Acetate [(±)-7]

To a stirred solution of (±)-**6** (400 mg, 3.12 mmol) and pyridine (758 μL, 9.36 mmol) in CH_2Cl_2 (20 mL) was added Ac_2O (885 μL, 9.36 mmol) at r.t. and the mixture was stirred at the same temperature for 12 h. After dilution with Et_2O (15 mL), the mixture was washed successively with 10% HCl (2 × 1 mL), water (2 mL) and brine (2 mL), and dried ($MgSO_4$). After evaporation of the solvent

Downloaded by: Queen's University. Copyrighted material.

under reduced pressure, the residue was chromatographed (SiO_2, 15 g, elution with Et_2O/hexane, 1:3 v/v) to give the acetate (±)-**7** (500 mg, 94%) as a pale yellow oil.

IR (film): ν = 1738 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.98 (1 H, ddd, *J* = 9.6, 3.0, 1.6 Hz), 5.77−5.75 (1 H, m), 5.69 (1 H, dt, *J* = 9.6, 1.9 Hz), 5.55 (1 H, d, *J* = 3.0 Hz), 4.69−4.65 (1 H, m), 4.16 (1 H, dd, *J* = 8.0, 1.9 Hz), 3.96−3.91 (1 H, m), 2.10 (3 H, s).

HRMS: *m*/*z* calcd for $C_8H_{10}O_4$: 170.0578, found: 170.0571.

Anal. calcd for $C_8H_{10}O_4$: C 56.47 H 5.92, found: C 56.51 H 5.86.

Kinetic Transesterification of the Racemic Alcohol (±)-6

A solution of (±)-**6** (700 mg, 5.46 mmol) and vinyl acetate (5.03 mL, 54.6 mmol) in THF (11 mL) was stirred with Lipase AK (immobilized on Celite, *Pseudomonas* sp., Amano) (350 mg) at r.t. for 33 h. After filtration through a Celite-pad, the filtrate was evaporated under reduced pressure and chromatographed (SiO_2, 30 g, elution with Et_2O/hexane, 1:3−1:1 v/v) to give the acetate (−)-(1*R*,4*R*,5*R*)-**7** (445 mg, 48%), $[\alpha]_D^{30}$ −49.0 (*c* = 1.12, $CHCl_3$), as a pale yellow oil and the alcohol (+)-(1*S*,4*S*,5*S*)-**6** (328 mg, 47%), $[\alpha]_D^{32}$ +18.1 (*c* = 1.08, $CHCl_3$), as a colorless solid. Optical purity of the products was determined by HPLC using a column with chiral stationary phase [CHIRALCEL OD, elution with *i*-PrOH/hexane (3:97, v/v) (0.5 mL/min), retention time 18.8 min for (+)-**6** and 22.8 min for (–)-**6**)] both having >99% ee after transformation into the benzoate.

Kinetic Hydrolysis of the Racemic Acetate (±)-7

A mixture of (±)-**7** (880 mg, 5.17 mmol) and Lipase AK (immobilized on Celite, *Pseudomonas* sp., Amano) (880 mg) in 0.1 M phosphate buffer solution (pH 7.2, 18 mL) and acetone (2 mL) was stirred at r.t. for 24 h. After filtration though a Celite-pad, the filtrate was evaporated and chromatographed (SiO_2, 40 g, elution with Et_2O/hexane, 1:3−1:1 v/v) to give the alcohol (−)-(1*R*,4*R*,5*R*)-**6** (339 mg, 51%), $[\alpha]_D^{31}$ −18.4 (*c* = 1.00, $CHCl_3$), as a colorless solid and the acetate (+)-(1*S*,4*S*,5*S*)-**7** (425 mg, 48%), $[\alpha]_D^{29}$ +50.0 (*c* = 1.20, $CHCl_3$), as a pale yellow oil. Optical purity of the products was determined by HPLC using a column with chiral stationary phase (CHIRALCEL OD, elution with *i*-PrOH/hexane (3:97, v/v) (−)-(1*R*,4*R*,5*R*)-**6** as 97% ee and (+)-(1*S*,4*S*,5*S*)-**7** as 98% ee, respectively.

Conversion of (−)-(1*R*,4*R*,5*R*)-7 into (−)-(1*R*,4*R*,5*R*)-6

A solution of (−)-(1*R*,4*R*,5*R*)-**7** (360 mg, 2.12 mmol) in MeOH (12 mL) was stirred with K_2CO_3 (1.47 g, 10.6 mmol) at r.t. for 10 min. The mixture was diluted with H_2O (2 mL) and extracted with Et_2O (2 × 30 mL). The extract was washed with brine (2 × 10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with Et_2O/hexane, 1:2 v/v) to give (−)-(1*R*,4*R*,5*R*)-**6** (250 mg, 92%) as a colorless solid.

Conversion of (+)-(1*S*,4*S*,5*S*)-7 into (+)-(1*S*,4*S*,5*S*)-6

A solution of (+)-(1*S*,4*S*,5*S*)-**7** (420 mg, 2.47 mmol) in MeOH (15 mL) was stirred with K_2CO_3 (1.71 g, 12.4 mmol) at r.t. for 10 min. On treatment as above for (−)-(1*R*,4*R*,5*R*)-**6**, (+)-(1*S*,4*S*,5*S*)-**6** (291 mg, 92%) was obtained as a colorless solid.

(−)-(1*S*,5*S*)-Isolevoglucosenone from (+)-(1*S*,4*S*,5*S*)-6

To a stirred solution of (+)-(1*S*,4*S*,5*S*)-**6** (250 mg, 1.95 mmol) in CH_2Cl_2 (15 mL) was added MnO_2 (3.39 g, 39.0 mmol) at r.t. and the mixture was stirred at the same temperature for 2 h. After filtration through a Celite-pad, the filtrate was evaporated under reduced pressure and chromatographed (SiO_2, 10 g, elution with Et_2O/pentane, 1:5 v/v) to give (−)-(1*S*,5*S*)-**2** (206 mg, 84%), $[\alpha]_D^{30}$ −428.0 (*c* = 1.10, $CHCl_3$) [Lit.[5] $[\alpha]_D^{28}$ −312.0 (*c* = 1.0, $CHCl_3$), 93% ee], as a colorless oil.

(+)-(1*R*,5*R*)-Isolevoglucosenone from (−)-(1*R*,4*R*,5*R*)-6

To a stirred solution of (−)-(1*R*,4*R*,5*R*)-**6** (330 mg, 2.58 mmol) in CH_2Cl_2 (15 mL) was added MnO_2 (4.48 g, 51.6 mmol) at r.t. and the mixture was stirred at the same temperature. On treatment as above for (−)-(1*S*,5*S*)-**2**, (+)-(1*R*,5*R*)-**2** (266 mg, 82%), $[\alpha]_D^{31}$ +425.0 (*c* = 1.10, $CHCl_3$) [Lit.[5] $[\alpha]_D^{31}$ +321.0 (*c* = 1.1, $CHCl_3$), 90% ee], was obtained as a colorless oil.

Acknowledgement

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

References

(1) Shafizadeh, F.; Chin, P. P. P. *Carbohydr. Res.* **1977**, 58, 79.
(2) Pertinent reviews, see:
(a) Witczak, Z. J. In *Studies in Natural Products Chemistry;* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994, Vol. 14, pp 268−282.
(b) Witczak, Z. J. *Pure & Appl. Chem.* **1994**, *66*, 2189.
(c) Ebata, T.; Matsushita, H. *J. Syn. Org. Chem. Jpn.* **1994**, *52*, 1074.
(3) Shibagaki, M.; Takahashi, K.; Kuno, H.; Honda, I.; Matsushita, H. *Chem. Lett.* **1990**, 307.
(4) A route to (+)-enantiomer, see: Witczak, Z. J. *Synlett* **1996**, 108.
(5) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synlett* **1996**, 971.
(6) (a) Ranganayokulu, K.; Singh, U. P.; Murray, T. P.; Brown, R. K. *Can. J. Chem.* **1974**, *52*, 988.
(b) Köll, P.; Schultek, T.; Rennecke, R. -W. *Chem. Ber.* **1976**, 337.
(c) Horton, D.; Roski, J. P.; Norris, P. *J. Org. Chem.* **1996**, *61*, 3783.
(7) For a pertinent review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(8) Ohloff, G.; Uhde, G. *Helv. Chim. Acta* **1970**, *53*, 531. Kawamura, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2403.
(9) Practically, only (+)-isolevoglucosenone is obtained from D-glucose. See Ref. 6.
(10) For pertinent monographs, see: Wong, C. H.; Whitesides, G. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
Patel, R. N. *Stereoselective Biocalaysis*; Marcel Dekker: New York, 1999.
(11) Taniguchi, T.; Takeuchi, M.; Kadota, K.; ElAzab, A. S.; Ogasawara, K. *Synthesis* **1999**, 1325.
(12) Schmidt, U.; Werner, J. *Synthesis* **1986**, 986.
See also: Harris, S. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982.
(13) Luche, J. -L. *J. Am. Chem. Soc.* **1977**, *100*, 2226.
Gemal, A. L.; Luche, J. -L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

Article Identifier:
1437-210X,E;2000,0,10,1372,1374,ftx,en;F01800SS.pdf

Downloaded by: Queen's University. Copyrighted material.