A Practical Preparation of Optically Active *endo*-Bicyclo[3.3.0]octen-2-ols

Takamasa IIMORI, Isao AZUMAYA, Yasuo HAYASHI, and Shiro IKEGAMI*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199–01, Japan.
Received August 13, 1996; accepted September 20, 1996

A practical and economical resolution of *endo*-bicyclo[3.3.0]oct-7-en-2-ol and *endo*-bicyclo[3.3.0]oct-6-en-2-ol was accomplished *via* lipase-catalyzed enantioselective irreversible transesterification with vinyl acetate.

Key words bicyclo[3.3.0]oct-6-en-2-ol; bicyclo[3.3.0]oct-7-en-2-ol; optical resolution; transesterification; lipase

endo-Bicyclo[3.3.0]oct-7-en-2-ol (**1**)[1] is an extremely useful compound, which is suitably functionalized for synthesis of a number of cyclopentanoid natural products.[2] We have also employed it as a synthetic intermediate in our studies on prostacyclin analogues.[3] However, although several attempts to produce the optically active alcohol (−)-**1** have been reported,[4] it is not available in a sufficient quantity to permit its use as a starting material for synthesis. During our studies on the structure–activity relationship of prostacyclin analogues, we required (−)-**1** on a large scale for the synthesis of an enantiomerically pure carbacyclin analogue. We have previously reported the production of (−)-*endo*-bicyclo[3.3.0]oct-6-en-2-ol ((−)-**4**) by using sulfonamides of phenylalanyl chloride as resolving agents.[5] By applying this method to the resolution of (±)-**1**, optically pure alcohol (−)-**1** was obtained in moderate overall yield (25% of theory) *via* *N*-tosyl-(*R*)-phenylalaninate. The requirement of the resolving agent derived from an expensive D-amino acid, however, was an unavoidable disadvantage, and prompted us to seek a more efficient method. In this paper, we wish to report an economical and operationally simple method for preparing multi-gram quantity of optically pure *endo*-bicyclo-[3.3.0]oct-6- and -7-en-2-ols.

Enzyme-catalyzed acyl transfer reactions have recently been used widely to attain high enantio- and regioselectivity with a variety of substrates,[6] and we also reported the application of lipase-catalyzed esterification to the resolution of cyclopentanol derivatives.[7] In this context, we examined the enzymatic resolution of *endo*-bicyclo-[3.3.0]oct-7-en-2-ol (**1**).

Kinetic resolution of (±)-**1** was carried out with 0.05 mass equiv. of lipase (Amano AK or PS) as the catalyst and vinyl acetate (2.0 eq) as the transesterification reagent. The optical yields (ee's) of the unreacted alcohol **1** were calculated based on the optical rotation of the enantiomerically pure alcohol (−)-**1**, $[\alpha]_D^{22}$ −149 (c=1.10, $CHCl_3$), which was obtained *via* recrystallization of the crystalline dinitrobenzoyl derivative **3** (Chart 1). High calculated optical yield obtained by this method ((−)-**1** of run 2 in Table 1) was confirmed by derivatization to the dinitrobenzoate **3** and HPLC analysis using Chiralcell OD. The optical yields of the acetate **2** were calculated based on the acetate (+)-**2** obtained in run 1, $[\alpha]_D^{25}$ +239 (c=1.03, $CHCl_3$), the purity of which was determined by HPLC analysis of its dinitrobenzoate derivative **3**. As shown in Table 1, (−)-*endo*-bicyclo[3.3.0]oct-7-en-2-ol ((−)-**1**), a desired isomer for our synthesis of carbacyclin analogue,[3] was recovered with high optical purity after 12 h incubation with Amano AK (run 2). Amano PS was found to be less effective for this substrate (runs 4 and 5). Since the acetate (+)-**2** was easily converted into (+)-**1** by simple hydrolysis, we were also able to access the optically pure alcohol (+)-**1** in a large quantity.

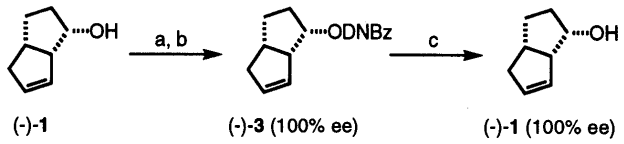
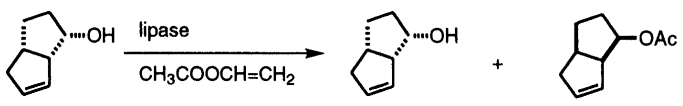


Chart 1. DNBz=3,5-dinitrobenzoyl. (a) DNBzCl, pyridine. (b) recrystallization from ether–hexane. (c) KOH, aq. MeOH

Table 1. Lipase-Catalyzed Enantioselective Transesterification



Run	Lipase	Time (h)	(−)-**1**		(+)-**2**	
			Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	AK	4	52	65	34	100 (>99)
2	AK	12	38	98 (>99)	44	99
3	AK	48	36	96	49	72
4	PS	8	66	32	21	100
5	PS	24	32	92	41	99

a) Isolated yield. *b*) Determined by optical rotation measurement. Values in parenthesis were determined by HPLC analysis of 3,5-dinitrobenzoate derivatives using Chiralcell OD (isopropanol : hexane = 3 : 7).

* To whom correspondence should be addressed.

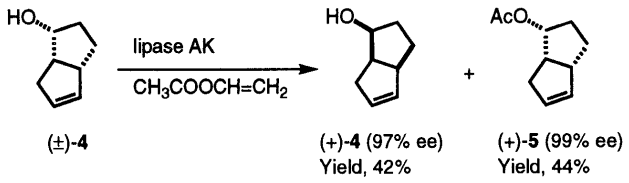


Chart 2

The kinetic resolution method mentioned above was also successfully applied to a double bond regioisomer of (±)-**1** ((±)-**4**). Incubation of (±)-**4** with Amano AK for 12 h afforded the alcohol (+)-**4**, $[\alpha]_D^{27}$ +68.8 (c=0.970, $CHCl_3$), and the acetate (+)-**5**, $[\alpha]_D^{27}$ +11.7 (c=0.900, $CHCl_3$), in 42% and 44% yields, respectively (Chart 2). The enantiomeric purity of (+)-**4** thus obtained was determined to be 97% ee based on the optically pure (−)-alcohol, $[\alpha]_D^{23}$ −71.2 (c=1.12, $CHCl_3$).[5] The optical rotation of the alcohol (−)-**4**, $[\alpha]_D^{27}$ −70.9 (c=0.580, $CHCl_3$), which was derived from the acetate (+)-**5**, indicated the optical yield of (+)-**5** obtained in this kinetic resolution reaction to be 99%. An attempt at HPLC analysis of the benzoate derivatives by using a chiral column (Chiralcell OD or Chiralpack AS) was not successful in this case (*e.g.*, retention times of 47.2 and 48.6 min for the 3,5-dinitrobenzoate of **4** on Chiralcell OD with isopropanol–hexane (1 : 9)). Thus, the alcohol (−)-**4**, the starting material for our synthesis of (+)-isocarbacyclin, was more economically produced by this method than by that of our previous report, in which *N*-(2-naphthalenesulfonyl)-(*R*)-phenylalanyl chloride was employed as a resolving agent.[5]

In conclusion, the lipase-catalyzed transesterification described here affords a facile access to enantiomers of bicyclo[3.3.0]oct-6- and -7-en-2-ols ((+)-**1**, (−)-**1** and (+)-**4**, (−)-**4**), being economical and operationally simple.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-8000 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL GSX-400 spectrometer (400 MHz). High- and low-resolution mass spectra were obtained on a JEOL SX-102A spectrometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Column chromatography was performed by using BW-820 (Fuji Silysia) or Silicagel 60 (Merck), and thin-layer chromatography was carried out on 0.25-mm E. Merck precoated silica-gel glass plates (Art. 5715). Amano AK and PS were supplied by Amano Pharmaceutical Co., Ltd. (Japan).

Lipase-Catalyzed Resolution of (±)-*endo*-Bicyclo[3.3.0]oct-7-en-2-ol ((±)-1) A solution of (±)-**1**[1] (5.0 g, 40 mmol) in vinyl acetate (6.9 g, 80 mmol) was incubated with lipase AK (250 mg) at 23 °C with stirring. After 12 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give an oily residue, which was separated by column chromatography on silica gel with hexane–ether (4 : 1) to afford the alcohol (−)-**1** (1.9 g, 38%) and the acetate (+)-**2** (2.9 g, 44%) as colorless oils. (−)-**1**: $[\alpha]_D^{25}$ −146 (c=1.15, $CHCl_3$, ee >99% by HPLC analysis); lit.[4a] $[\alpha]_D^{25}$ −124 (c=6, $CHCl_3$); lit.[4e] $[\alpha]_D$ −139.14 (c=1.15, $CHCl_3$); lit.[4d] $[\alpha]_D^{20}$ +149 (c=4.81, $CHCl_3$) for the enantiomer. (+)-**2**: $[\alpha]_D^{25}$ +236 (c=1.03, $CHCl_3$); lit.[4d] $[\alpha]_D^{20}$ −232 (c=2.30, $CHCl_3$) for the enantiomer.

A similar reaction, in which the reaction time was shortened (4 h; run 1 of Table 1), afforded the acetate (+)-**2**, $[\alpha]_D^{25}$ +239 (c=1.03, $CHCl_3$) in 34% yield. No enantiomer was detected by HPLC analysis of its dinitrobenzoate derivative (Chiralcell OD, isopropanol–hexane (3 : 7)).

Optically Pure (−)-*endo*-Bicyclo[3.3.0]oct-7-en-2-ol ((−)-1) *via* Crystalline 3,5-Dinitrobenzoate ((−)-3) 3,5-Dinitrobenzoyl chloride (15.5 g, 66.7 mmol) was added to a solution of the alcohol (−)-**1** (6.4 g, 51.6 mmol) in pyridine (50 ml), and the mixture was stirred for 3 h at room temperature. Water was added to this mixture, and the whole was extracted with ether. The organic layer was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After evaporation of the solvent, recrystallization from hexane–ether (2 : 1) afforded the dinitrobenzoate (−)-**3** (10.7 g, 65%) as pale yellow needles, mp 92—93 °C. IR (neat): 1717 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.57 (1H, m), 1.85—2.05 (3H, m), 2.19 (1H, m, 5-H), 2.7—2.9 (2H, m, 6-H), 3.55 (1H, m, 1-H), 5.45—5.5 (2H, m, 2-H, 7-H), 5.81 (1H, m, 8-H), 9.11 (2H, d, J=2 Hz, Ar), 9.22 (1H, t, J=2 Hz, Ar). MS (EI) m/z: 318 (M^+). $[\alpha]_D^{22}$ −151 (c=1.10, $CHCl_3$).

A mixture of the ester (−)-**3** (10.7 g, 33.6 mmol) and 40% aqueous KOH (80 ml) in 200 ml of methanol was stirred for 1 h at room temperature, and extracted with ether. The organic layer was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After evaporation of the solvent, distillation (90 °C at 15 mmHg) afforded optically pure (−)-**1** (3.2 g, 77%). $[\alpha]_D^{22}$ −149 (c=1.10, $CHCl_3$).

(±)-*endo*-Bicyclo[3.3.0]oct-6-en-2-ol ((±)-4) A mixture of (±)-*endo*-bicyclo[3.3.0]oct-6-en-2-one and (±)-*endo*-bicyclo[3.3.0]oct-6-en-3-one prepared by the method of Nee and Roberts[8] was separated by column chromatography on Silicagel 60 (Merck) with pentane–ether (19 : 1). The ketone thus obtained was reduced with $LiAlH_4$ to afford (±)-**4**.

Lipase-Catalyzed Resolution of (±)-4 A solution of (±)-**4** (0.24 g, 2.0 mmol) in vinyl acetate (0.36 g, 4.2 mmol) was incubated with lipase AK (12 mg) at room temperature with stirring. After 12 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give an oily residue, which was separated by column chromatography on silica gel with pentane–ether (4 : 1) to afford the alcohol (+)-**4** (0.10 g, 42%) and the acetate (+)-**5** (0.14 g, 44%) as colorless oils. (+)-**4**: $[\alpha]_D^{27}$ +68.8 (c=0.970, $CHCl_3$); lit.[5] ($[\alpha]_D^{23}$ −71.2 (c=1.12, $CHCl_3$) for the enantiomer. (+)-**5**: $[\alpha]_D^{27}$ +11.7 (c=0.900, $CHCl_3$).

Acknowledgment We are grateful to Misses K. Ichikawa, J. Shimode and J. Nonobe for spectroscopic measurements. This study was performed through Special Coordination Funds of the Science and Technology Agency of the Japanese Government. Partial financial support from the Ministry of Education, Science and Culture of Japan is also gratefully acknowledged.

References and Notes

1) (±)-*endo*-Bicyclo[3.3.0]oct-7-en-2-ol is readily available from 1,3-cyclooctadiene in two steps: Crandall J. K., Chang L.-H., *J. Org. Chem.*, **32**, 532—536 (1967).
2) For example, coriolin: Iseki K., Yamazaki M., Shibasaki M., Ikegami S., *Tetrahedron*, **37**, 4411—4418 (1981). Allamandin, plumericin and allamcin: *a*) Parkes K. E. B., Pattenden G., *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1119—1134; *b*) Trost B. M., Balkovec J. M., Mao M. K.-T., *J. Am. Chem. Soc.*, **108**, 4974—4983 (1986).
3) Iseki K., Mase T., Okazaki T., Shibasaki M., Ikegami S., *Chem. Pharm. Bull.*, **31**, 4448—4455 (1983) and references cited therein.
4) *a*) Kuritani H., Takaoka Y., Shingu K., *J. Org. Chem.*, **44**, 452—454 (1979); *b*) Whitesell J. K., Minton M. A., Felman S. W., *J. Org. Chem.*, **48**, 2193—2195 (1983); *c*) Trost B. M., Belletire J. L., Godleski S., McDougal P. G., Balkovec J. M., Baldwin J. J., Christy M. E., Ponticello G. S., Varga S. L., Springer J. P., *J. Org. Chem.*, **51**, 2370—2374 (1986); *d*) Klempier N., Faber K., Griengl H., *Synthesis*, **1989**, 933—934; *e*) Marotta E., Rastelli E., Righi E., Rosini G., *Tetrahedron: Asymmetry*, **4**, 735—742 (1993).
5) Hashimoto S., Kase S., Shinoda T., Ikegami S., *Chem. Lett.*, **1989**, 1063—1066.
6) Recent reviews: *a*) Faber K., Riva S., *Synthesis*, **1992**, 895—910; *b*) Naemura K., *Yuki Gosei Kagaku Kyokai Shi*, **52**, 49—58 (1994).
7) Hashimoto S., Miyazaki Y., Ikegami S., *Synth. Commun.*, **21**, 833—839 (1991).
8) Nee M., Roberts J. D., *J. Org. Chem.*, **46**, 67—70 (1981).