Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3325–3329

TETRAHEDRON: *ASYMMETRY*

Lipase-mediated kinetic resolution of a synthetic equivalent of 2-hydroxymethylcyclopentadien-5-ol

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Received 19 August 1998; accepted 31 August 1998

Abstract

Racemic 3-hydroxy-2-hydroxymethyl-*endo*-tricyclo[5.2.1.$0^{2,6}$]-dec-4,8-diene serving as a synthetic equivalent of 2-hydroxymethylcyclopentadien-5-ol has been resolved by employing lipase-mediated kinetic transesterification with vinyl acetate in an organic solvent.

1. Introduction

Quite recently, we reported[1] a concise, enantiocontrolled route to naturally occurring antiviral carbocyclic nucleoside (−)-neplanocin A, starting from the enantiomerically pure tricyclic diol **1**. This serves as a synthetic equivalent of chiral 2-hydroxymethylcyclopentadien-5-ol, as its molecular bias allows convex-face selective functionalization and its thermal susceptibility allows generation of cyclopentene functionality. The enantiopure tricyclic diol **1** may be taken as a synthetic equivalent of 2-hydroxymethylcyclopentadien-5-ol **2** which is not accessible in a stable form owing to its mobile cyclopentadienyl system. In this paper, we wish to report a preparation of enantiopure **1** from the Diels–Alder adduct of benzoquinone and cyclopentadiene employing lipase-mediated kinetic transesterification[2] (Fig. 1).

2. Results and discussion

According to the literature procedure,[3] the Diels–Alder adduct[4] **3** between benzoquinone and cyclopentadiene was transformed into the cyclopentenone ester **5** via the epoxide **4** on treatment with ethanolic sodium hydroxide. Although the compound **5** has been reported to be unstable toward a Lewis acidic

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0957-4166/98/$ - see front matter
PII: S0957-4166(98)00353-X

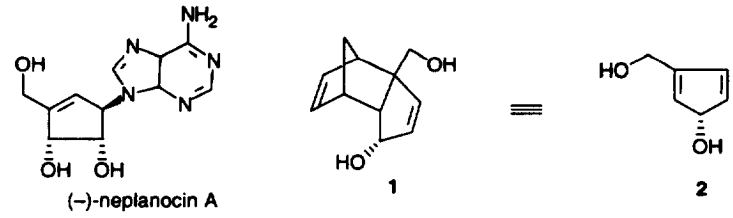
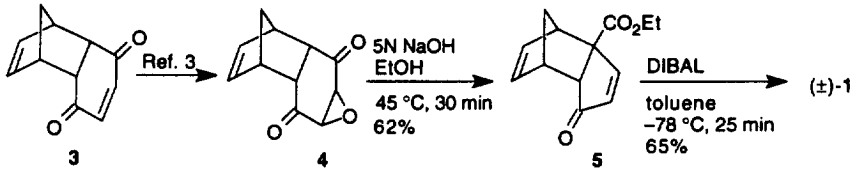


Fig. 1.

borohydride reagent[5a] and other acidic conditions[5b] owing to the fact that it induces concurrent [3.3]-sigmatropic rearrangement, we found that it afforded the diol (±)-**1** in 65% yield without initiation of significant rearrangement on reduction with diisobutylaluminum hydride in toluene at −78°C[6] (Scheme 1).



Scheme 1.

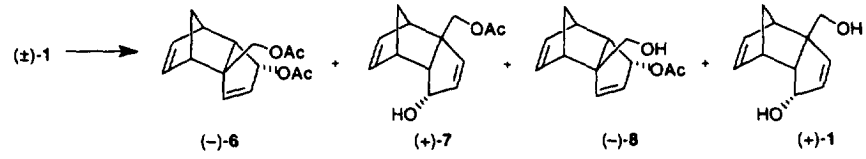
Lipase-mediated transesterification between the racemic diol (±) and 1.6 equivalents of vinyl acetate was next carried out in ether in 0.1M concentration of the substrate at room temperature (Table 1). Among the six lipases tested, only Toyobo LIP was found to be practically useful. The reaction virtually did not take place either with *Rhizopus javanicus* or porcine pancreas, while the three lipases, Lipase MY, Lipase PS and *Candida antarctica*, gave a mixture of enantioenriched products with an impractical level of resolution. Thus, Toyobo LIP furnished the diacetate (−)-**6** in 46% yield with 95% ee and the enantiomerically pure primary monoacetate (+)-**7** in 44% yield when a mixture of racemic diol (±)-**1** was treated with 1.6 equivalents of vinyl acetate in ether at room temperature. The amount of vinyl acetate was deemed to be the most critical to achieve good resolution, since a mixture of four products consisting of the diacetate (−)-**6** (11%, 97% ee), the primary monoacetate (+)-**7** (19%, 65% ee), the secondary monoacetate (−)-**8** (21%, 89% ee), and the unchanged diol (+)-**1** (29%, 71% ee), was produced when the reaction was carried out in the presence of 1.0 equivalent of vinyl acetate under the same conditions. Practically, the reaction may be carried out in *tert*-butyl methyl ether in place of ether which gave

Table 1
Lipase-mediated kinetic transesterification of the racemic diol (±)-**1**

Entry	Lipase	Solvent	Time	Product (Yield[a] %: Enantiomeric Exess[b] % ee)			
				(−)-**6**	(+)-**7**	(−)-**8**	(+)-**1**
1	*Rhizopus javanicus*	Et_2O	8.0	0	0	0	–
2	*Porcine pancreas*	Et_2O	8.0	0	0	trace	–
3	Lipase MY[c]	Et_2O	8.0	1 : 54	7 : 52	22 : 82	62 : 37
4	Lipase PS[d]	Et_2O	8.0	0	0	16 : 77	65 : 38
5	*Candida antarctica*	Et_2O	8.0	15 : 84	33 : 35	0	27 : 84
6	Toyobo LIP[e]	Et_2O	3.5	46 : 95	44 : >99	0	0
7	Toyobo LIP	Et_2O	8.0	11 : 97	19 : 65	21 : 89	29 : 71
8	Toyobo LIP	tBuOM e	5.3	43 : 95	44 : >99	0	0

a. Isolated yield after column chromatography. b. Determined by hplc using a chiral column after convertion into the dibenzoate of **1**. c. *Candida cylindracea* (Meito). d. *Pseudomonas* sp. (Amano). e. *Pseudomonas* sp. (Toyobo).

the diacetate (−)-**6** in 43% yield with 95% ee and the enantiopure primary monoacetate (+)-**7** in 44% yield. Although they did not exhibit high enantioselectivity, it was interesting to observe that Lipase PS (*Pseudomonas* sp., Amano) afforded only the secondary acetate[7] (−)-**8** besides the unchanged starting material (+)-**1**, while *Candida antarctica* afforded the two acetates, the diacetate (−)-**6** and the primary acetate (+)-**7**, without generation of the secondary acetate (−)-**8** besides the unchanged (+)-**1** (Table 1, entries 4 and 5) (Scheme 2).



Scheme 2.

In summary, the racemic ester **5**, obtained from the *meso*-epoxide **4**, was successfully reduced to the racemic diol (±)-**1** without rearrangement which was resolved using lipase LIP to give both enantiomeric diols **1** which serve as a synthetic equivalent of chiral 2-hydroxymethylcyclopentadien-5-ol **2**.

3. Experimental

Melting points were determined on a Yanagimoto hot stage apparatus and are uncorrected. IR spectra were recorded on a JASCO-IR 700 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-2000 (300 MHz) spectrometer. Enantiomeric excesses were measured with a JASCO-DIP-370 digital polarimeter. Enantiomeric excesses were determined on a Gilson Model-307 instrument equipped with a chiral column.

3.1. Ethyl 5-oxo-tricyclo[5.2.1.0]deca-3,8-diene-2-carboxylate[3] **5**

To a stirred solution of **4** (9.28 g, 48.8 mmol) in EtOH (50 ml) was added dropwise 5M NaOH in EtOH (18 ml) at 45°C during 30 min. After evaporation of most of the solvent under reduced pressure, the residue was dissolved in Et_2O (300 ml). The ethereal layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give **5** (6.58 g, 61.8%) as a brown oil. IR (neat): ν=2983, 1741, 1691 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.30 (3H, t, *J*=7.1 Hz), 1.74 (1H, d, *J*=8.8 Hz), 1.95 (1H, d, *J*=8.8 Hz), 3.23 (1H, br s), 3.32 (2H, m), 4.23 (2H, q, *J*=7.1 Hz), 5.95 (1H, d, *J*=5.5 Hz), 6.00 (2H, ddd, *J*=25.8, 5.5, 2.5 Hz), 7.40 (1H, *J*=5.5 Hz). MS: m/z=218 (M^+), 66 (100%). Anal. calcd for $C_{13}H_{14}O_3$ (M^+): m/z=218.0943. Found: m/z=218.0940.

3.2. (±)-2-Hydroxymethyl-5-hydroxytricyclo[5.2.1.0]deca-3,8-diene (±)-1

To a stirred solution of **5** (1.84 g, 8.4 mmol) in toluene (30 ml) was added a 1.5M toluene solution of Bu^i_2AlH (1.97 mg, 29.5 mmol) dropwise at −78°C during 25 min. After 3 h at the same temperature, 28% NH_4OH was added to decompose the excess hydride. After separation of the precipitate by filtration through a Celite pad, the filtrate was evaporated and the residue was chromatographed on an SiO_2 column (elution: hexane:AcOEt=3:1) to give (±)-**1** (0.98g, 65%) as colorless crystals, mp 122–124°C. IR (neat): ν=3270 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.60 (1H, d, *J*=8.8 Hz), 1.68 (1H, d, *J*=8.8 Hz), 2.70 (2H, m), 2.96 (1H, s), 3.67 (1H, d, *J*=10.6 Hz), 3.84 (1H, d, *J*=10.6 Hz), 4.76 (1H, s), 5.53 (1H, dd, *J*=5.5, 1.8 Hz),

5.68 (1H, dd, J=5.5, 1.8 Hz), 5.95 (1H, dd, J=5.8, 3.3 Hz), 6.16 (1H, dd, J=5.8, 2.8 Hz). MS: m/z=178 (M^+), 66 (100%). Anal. calcd for $C_{11}H_{14}O_2$ (M^+): m/z=178.0994. Found: m/z=178.0987.

3.3. Resolution of (±)-1: preparation of (−)- and (+)-2-hydroxymethyl-5-hydroxytricyclo[5.2.1.0]deca-3,8-diene 1

A solution of (±)-**1** (4.1 g, 23.0 mmol) and vinyl acetate (3.2 g, 36.8 mmol) in Et_2O (200 ml) was stirred at room temperature for 3.5 h in the presence of lipase LIP (Toyobo) (1 g). After filtration through a Celite pad, the filtrate was evaporated under reduced pressure and the residue was chromatographed on a silica column (elution: hexane:AcOEt=1:1) to give the diacetate (−)-**6** (2.8 g, 46%), $[\alpha]_D^{26}$ −81.0 (c 1.2, $CHCl_3$), and the monoacetate (+)-**7** (2.2 g, 44%), $[\alpha]_D^{26}$ +133.9 (c 1.0, $CHCl_3$).

The diacetate (−)-**6**: IR (neat): ν=2967, 1734 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.52 (1H, d, J=8.8 Hz), 1.60 (1H, d, J=8.8 Hz), 1.99 (3H, s), 2.01 (3H, s), 2.69 (1H, br s), 2.74 (1H, br s), 4.07 (1H, d, J=10.7 Hz), 4.34 (1H, d, J=10.7 Hz), 5.50 (2H, m), 5.95 (2H, m). MS: m/z=262 (M^+), 94 (100%), 66. Anal. calcd for $C_{15}H_{18}O_4$ (M^+): m/z=262.1205. Found: m/z=262.1203.

The monoacetate (+)-**7**: IR (neat): ν=3440, 2962, 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.60 (1H, d, J=8.8 Hz), 1.68 (1H, d, J=8.8 Hz), 2.05 (3H, s), 2.64 (1H, m), 2.78 (1H, br s), 2.94 (1H, br s), 4.12 (1H, d, J=10.7 Hz), 4.36 (1H, d, J=10.7 Hz), 4.76 (1H, d, J=10.2 Hz), 5.54 (1H, d, J=1.4 Hz), 5.59 (1H, d, J=1.4 Hz), 5.92 (1H, m), 6.16 (1H, m). MS: m/z=220 (M^+), 94 (100%), 66. Anal. calcd for $C_{13}H_{16}O_3$ (M^+): m/z=220.1099. Found: m/z=220.1104.

A solution of (−)-**6** (590 mg, 2.3 mmol) in MeOH (20 ml) was stirred with K_2CO_3 (691 mg, 5.0 mmol) at room temperature overnight. The mixture was diluted with AcOEt (40 ml) and washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give (−)-**1** (330 mg, 83%), mp 136–138°C, $[\alpha]_D^{31}$ −159.7 (c 0.3, EtOH), whose enantiomeric purity was determined to be 95% ee by HPLC using a chiral column (Chiralcel OD: elution with 5% Pr^iOH:hexane) after conversion into the dibenzoate.

Similarly, (+)-**7** (495 mg, 2.3 mmol) was treated with K_2CO_3 (373 mg, 2.7 mmol) in MeOH (20 ml) overnight as above to give (+)-**1** (367 mg, 92%), mp 134–136°C, $[\alpha]_D^{30}$ +154.9 (c 1.0, EtOH), which was determined as >99 ee by HPLC (Chiralcel OD: elution with 5% Pr^iOH:hexane) after conversion into the dibenzoate.

3.4. Resolution of (±)-1 in tert-butyl methyl ether

A solution of (±)-**1** (89 mg, 0.5 mmol) and vinyl acetate (65 mg, 0.75 mmol) in *tert*-BuOMe (3 ml) was stirred at room temperature for 5.3 h in the presence of lipase LIP (90 mg). After filtration through a Celite pad, the filtrate was evaporated under reduced pressure and the residue was chromatographed on a silica column (elution: hexane:AcOEt=3:1) to give the diacetate (−)-**6** (55 mg, 42%:95% ee) and the monoacetate (+)-**7** (48 mg, 44%:>99% ee). The enantiomeric purity was determined as above by HPLC using a chiral column after conversion into the dibenzoate.

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7. Spectral data of **8**: IR (neat): ν=3407, 2963, 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.56 (1H, d, *J*=8.8 Hz), 1.65 (1H, d, *J*=8.8 Hz), 2.08 (3H, s), 2.64 (1H, m), 2.70 (1H, br s), 2.79 (2H, m), 3.70 (1H, d, *J*=10.7 Hz), 3.85 (1H, d, *J*=10.7 Hz), 5.52 (1H, d, *J*=10.2 Hz), 5.65 (1H, m), 5.92 (1H, m), 6.06 (1H, m). MS: m/z=220 (M^+), 94 (100%), 66. Anal. calcd for $C_{13}H_{16}O_3$ (M^+): m/z=220.1099. Found: m/z=220.1089.