Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 365–368

TETRAHEDRON: *ASYMMETRY*

A convenient route to both enantiomers of *endo*-2-benzonorbornenol via lipase catalysed resolution of the racemic mixture

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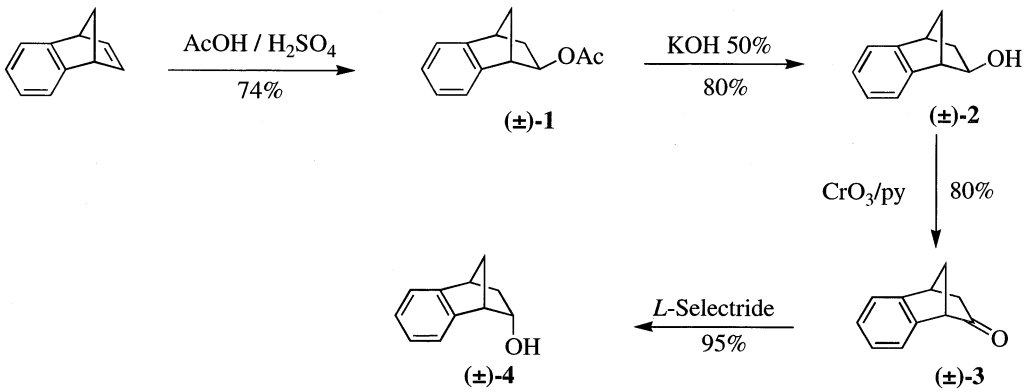
Received 16 January 2001; accepted 15 February 2001

Abstract—Resolution of racemic *endo*-benzonorbornenol (±)-**4** was performed using *Candida antarctica* lipase (Novozym® 435) in benzene (50°C/50 hours) with vinyl acetate as the acyl donor to afford (−)-*endo*-2-benzonorbornenol (−)-**6** and their corresponding (+)-*endo*-2-benzonorbornenyl acetate (+)-**5** in high e.e.s of up to 99% and workable yields of up to 45–46%. © 2001 Elsevier Science Ltd. All rights reserved.

In the course of our research on the preparation of various diastereomers of 8-phenylmenthol[1] and their use as chiral auxiliaries in aza-Diels–Alder reactions[2] we felt it desirable, with a view to enhancing chiral induction, to investigate other alcohols that might also act as π-stacking chiral auxiliaries in these reactions. We describe here a method for preparing (±)-*endo*-2-benzonorbornenol and the subsequent enzymatic resolution of the racemic product into its two enantiomers.

In the only previous synthesis of an enantiomer of *endo*-2-benzonorbornenol, optically active (+)-*endo*- and (+)-*exo*-2-benzonorbornenol were prepared by asymmetric hydroboration of benzonorbornadiene with tetraisopinocampheyldiborane.[3] However, spectroscopic analysis of the (*S*)-mandelate derivative of the (+)-*endo*-product showed an e.e. of only 46%. Since this is clearly insufficient for use as a chiral auxiliary, we decided to use the biocatalytic resolution of racemic *endo*-2-benzonorbornenol (±)-**4**. Benzonorbornadiene was used as the starting material for the synthesis of (±)-**4**, as detailed in Scheme 1.

Treatment of benzonorbornadiene with $AcOH/H_2SO_4$ generated (±)-*exo*-2-benzonorbornenyl acetate, (±)-**1**,[4] saponification of which afforded (±)-*exo*-2-benzonor-



Scheme 1.

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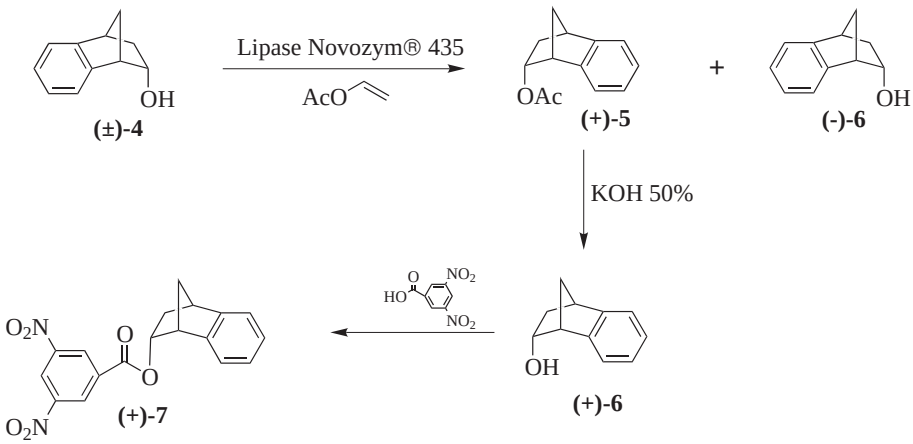
PII: S0957-4166(01)00079-9



Scheme 2.

bornenol (±)-**2**[5] which was then converted into (±)-*endo*-2-benzonorbornenol (±)-**4** by the Sarett oxidation, a procedure we previously used to convert 8-phenylmenthol into 8-phenylneomenthol.[1b] In this case the oxidation afforded (±)-2-benzonorbornenone (±)-**3**, followed by reduction with L-Selectride.

We first tried, unsuccessfully, to resolve racemic (±)-**4** by chemical methods involving the formation of derivatives such as the (*S*)-mandelate[6] or (*S*)-*O*-methylmandelate.[7] An attempt to resolve (±)-**3** by formation of the hydrazone with SAMP[8] was also unsuccessful. We then studied the possibility of using enzymatic transesterification, which has been successfully used to resolve compounds such as α-hydroxy ketones[9] and aryl homoallyl alcohols.[10] The following lipases were investigated in this reaction: *Pseudomonas fluorescens* lipase (Lipase AK), *Candida rugosa* lipase (Lipase AYS), *Aspergillus niger* lipase (Lipase AS), *Pseudomonas cepacia* lipase (Lipase PS), *P. cepacia* lipase immobilised on ceramic particles (Lipase PS-C), *P. cepacia* lipase immobilised on diatomaceous earth (Lipase PS-D) and *Aspergillus* sp. acylase (Acylase Amano), all from Amano Pharmaceutical Co. Ltd.; and *Thermomyces lanugenouus* lipase (Lipozyme® TI 100L), *Rhizomucor miehei* lipase (Lipozyme® RM IM) and *C. antarctica* lipase (Novozym® 435), all from Novo Nordisk.

Using vinyl acetate as an acyl donor, the *C. antarctica* lipase (Novozym® 435), was found to selectively acylate the (+)-*endo*-enantiomer of **4** with high efficiency, allowing subsequent chromatographic separation of the (−)-*endo* enantiomer (−)-**6** from (+)-*endo*-2-benzonorbornenyl acetate (+)-**5**, which was then saponified to (+)-*endo*-2-benzonorbornenol (+)-**6** (Scheme 2).

The typical procedure used for this enzymatic transesterification was as follows: Novozym® 435 (300 mg) was added to a solution of **4** (500 mg; 3.1 mmol) and

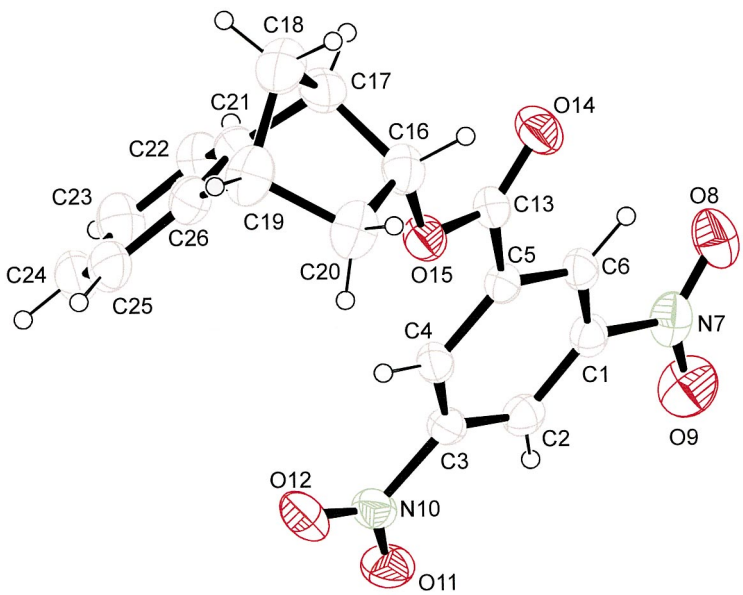


Figure 1. Molecular structure of (+)-**7**.

Table 1.

Entry	Vinyl acetate (equiv.)	Time (h)	T (°C)	Conversion c (%)[a]	Acetate (+)-**5**			Alcohol (−)-**6**			E[b]
					e.e. (%)	Yield (%)	$[\alpha]_D$	e.e. (%)	Yield (%)	$[\alpha]_D$	
1	0.6	21	35	40	>99	49	+110.05	66	44	−53.53	397
2	0.6	24	50	43	>99	40	+110.58	76	28	−62.68	483
3	0.55	50	T.a.	44	>99	36	+110.33	78	44	−65.25	521
4	0.7	50	T.a.	46	>99	47	+110.16	84	42	−68.91	617
5	0.6	50	50	50	>99	45	+109.96	>99	46	−82.80	1059

[a] Conversion of the substrate, $c = e.e._s/(e.e._s+e.e._p)$ (%).
[b] Enantioselectivities of the reactions (E) were determined from the equation $E = \ln[1-c(1+e.e._p)]/\ln[1-c(1-e.e._p)]$, where $e.e._p$ = product enantiomeric excess.

vinyl acetate (0.55–0.70 equiv.) in benzene (35 mL), and the mixture was stirred for 20–50 hours (optimisation of time and temperature is discussed below). The lipase was then removed by filtration, the solvent was removed in a rotary evaporator, and the resulting residue was purified by chromatography on silica gel with 3:1 (v/v) hexane:AcOEt as eluent. The early fractions afforded (+)-*endo*-2-benzonorbornenyl acetate (+)-**5**[11] as an orange oil, and the later fractions (−)-*endo*-2-benzonorbornenol (−)-**6**[12] as a yellowish liquid that crystallised to a white solid. Treatment of the acetate (+)-**5** with KOH/EtOH 50% over 50 hours at room temperature afforded (+)-*endo*-2-benzonorbornenol (+)-**6**,[13] the absolute configuration of which was confirmed as (1*R*) by X-ray diffractometry of its 3,5-dinitrobenzoate (+)-**7**[14] (see Fig. 1).

A series of experiments was completed with reaction times of between 21 and 50 hours and temperatures ranging from room temperature to 50°C, acetate **5** was produced in yields of 36–49% with an e.e. that was always greater than 99%, while the yield of alcohol (−)-**6** ranged from 28 to 46% and its e.e. varied from 66 to >99% (see Table 1, which also lists $[\alpha]_D$ values, substrate conversion rates and enantioselectivities).

The best results were achieved with 0.6 equiv. of vinyl acetate, a reaction time of 50 hours and a temperature of 50°C: under these conditions (+)-**5** and (−)-**6** were obtained in yields of 45–46% and with e.e. of >99%, giving an enantiomer ratio (E) of greater than 1000.

In summary, we have developed a simple, efficient method for the resolution of (±)-*endo*-2-benzonorbornenol by transesterification with *C. antarctica* lipase. The transesterification proceeded with very high E values and workable yields.

Acknowledgements

We thank Amano Pharmaceutical Co. Ltd., Japan, and Novo Nordisk, Denmark, for the generous gifts of lipases and Christian F. Massaguer for helpful conversations. This work was supported by the Xunta de Galicia (Spain) under project XUGA 203079B978.

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11. (+)-(1*R*)-*endo*-2-Benzonorbornenyl acetate (+)-**5**
$[\alpha]_D$ +110.0 (*c* 1, $CHCl_3$). IR (NaCl): 2972, 2870, 1738, 1469, 1441, 1374, 1243, 1191, 1038, 755 cm^{-1}. ^1H NMR ($CDCl_3$): 1.04–1.10 (d×t, 1H, $J_{3endo-3exo}$ = 12.81 Hz, $J_{3endo-2exo}$ = 3.30 Hz, 3_{endo}-H), 1.70–1.73 (d×t, 1H, J_d = 9.50 Hz, J_t = 1.23 Hz, 9-H), 1.83 (s, 3H, C$\underline{H}_3$CO), 1.83–1.89 (m, 1H, 9-H), 2.34–2.43 (d×d×d, 1H, $J_{3exo-3endo}$ = 12.81 Hz, $J_{3exo-2exo}$ = 9.06 Hz, J_{3exo-4} = 4.10 Hz, 3_{exo}-H), 3.32–3.33 (d, 1H, J = 3.34 Hz, 1-H), 3.63–3.66 (d×d, 1H, J_{4-3exo} = 3.66 Hz, J = 0.81 Hz, 4-H), 5.34–5.40 (d×d×d, 1H, $J_{2exo-3exo}$ = 9.06 Hz, J = 4.01 Hz, J = 3.16 Hz, 2_{exo}-H), 7.10–7.23 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): 21.41 (C$\underline{H}_3$C(O)), 36.02 (C-3), 43.78 (C-4), 48.17 (C-1), 48.62 (C-9), 74.73 (C-2), 120.79 (C-5), 123.81 (C-8), 126.06 (C-7), 126.67 (C-6), 142.99 (C-8a), 148.65 (C-4a), 171.64 (C(O)). Anal. calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.47; H, 6.69%.
12. (−)-(1*S*)-*endo*-2-Benzonorbornenol (−)-**6**
$[\alpha]_D$ −82.80 (*c* 1, $CHCl_3$). Mp 92–94°C (hex.). IR (NaCl): 3260, 3015, 2952, 1458, 1293, 1117, 1048, 952, 754 cm^{-1}.

^{1}H NMR ($CDCl_3$): 0.71–0.79 (d×t, 1H, $J_{3endo-3exo}=12.75$ Hz, $J_{3endo-2exo}=3.28$ Hz, 3_{endo}-H), 1.57–1.62 (d×t, 1H, $J_d=9.30$ Hz, $J_t=1.34$ Hz, 9-H), 1.76–1.83 (d×quint, 1H, $J=9.30$, 1.85 Hz, 9-H), 2.23–2.34 (d×d×d, 1H, $J_{3exo-3endo}=12.75$ Hz, $J_{3exo-2exo}=8.87$ Hz, $J_{3exo-4}=4.19$ Hz, 3_{exo}-H), 3.21–3.22 (d, 1H, $J=2.37$ Hz, 1-H), 3.32–3.34 (d×d, 1H, $J_{4-3exo}=4.19$ Hz, $J=1.10$ Hz, 4-H), 4.49–4.55 (d×d×d, 1H, $J_{2exo-3exo}=8.87$ Hz, $J=4.05$ Hz, $J=2.95$ Hz, 2_{exo}-H), 7.03–7.24 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): 39.70 (C-3), 44.26 (C-4), 48.74 (C-9), 50.76 (C-1), 71.98 (C-2), 121.15 (C-5), 124.62 (C-8), 126.20 (C-7), 127.20 (C-6), 141.82 (C-8a), 149.76 (C-4a). Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.61; H, 7.77%.

13. (+)-(1*R*)-*endo*-2-Benzonorbornenol (+)-**6**
    $[\alpha]_D$ +82.80 (*c* 1, $CHCl_3$). Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.35; H, 7.82%.
14. (+)-(1*R*)-*endo*-2-Benzonorbornenyl 3,5-dinitrobenzoate (+)-**7**
    A mixture of (+)-**6** (50 mg; 0.31 mmol), 3,5-dinitrobenzoyl chloride (144 mg; 0.62 mmol, freshly recrystallised from CCl_4), DMAP (76.3 mg; 0.62 mmol) and CH_2Cl_2 (10 mL) was stirred for 48 hours under argon, left to cool and washed with a 0.5 M NaOH solution (3×60 mL), an aqueous HCl solution (0.5 M, 3×80 mL) and a saturated NaCl solution (80 mL). The organic layer was dried (Na_2SO_4), and removal of the solvent then left an oily residue that upon flash chromatography (SiO_2; hexane:EtOAc, 9:1) afforded (+)-**7** as a white solid (101 mg; 91%). Mp 148–150°C (hexane–Et_2O). $[\alpha]_D$ +113.0 (*c* 1, $CHCl_3$). IR (NaCl): 3416, 3115, 2957, 1716, 1632, 1599, 1540, 1461, 1346, 1299, 1177, 1072, 913, 731, 718, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.10–1.18 (d×t, 1H, $J_{3'endo-3'exo}=12.91$ Hz, $J_{3'endo-2'exo}=3.07$ Hz, $3'_{endo}$-H), 1.73–1.77 (d, 1H, $J_d=9.64$ Hz, 9′-H), 1.90–1.95 (d×d×d, 1H, $J=9.64$ Hz, $J=1.78$ Hz, 9′-H), 2.44–2.55 (d×d×d, 1H, $J_{3'exo-3'endo}=12.91$ Hz, $J_{3'exo-2'exo}=8.75$ Hz, $J_{3'exo-4}=3.95$ Hz, $3'_{exo}$-H), 3.39 (s, 1H, 1′-H), 3.70–3.71 (d, 1H, $J_{4'-3'exo}=3.95$ Hz, 4′-H), 5.62–5.69 (d×d×d, 1H, $J_{2'exo-3'exo}=8.75$ Hz, $J=4.15$ Hz, $J=2.65$ Hz, $2'_{exo}$-H), 7.10–7.23 (m, 4H, ArH), 8.70–8.71 (d, 2H, $J=2.15$ Hz, 2-H+6-H), 9.05–9.07 (t, 1H, $J=2.15$ Hz, 4-H). ^{13}C NMR ($CDCl_3$): 36.99 (C-3′), 43.89 (C-4′), 48.35 (C-1′), 48.37 (C-9′), 77.05 (C-2′), 121.40 (C-5), 122.55 (C-8), 123.71 (C-7), 126.53 (C-6), 127.35 (C-4), 129.64 (C-2), 129.87 (C-6), 134.46 (C-3+C-5), 142.51 (C-8a), 148.13 (C-4a), 148.90 (C-1), 162.58 (C(O)). Anal. calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.87; H, 3.91; N, 8.10%.