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Chemoenzymatic Access to Enantiomeric Bicyclo[2.2.1]Heptan-2,5-Diones

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Abstract—A practical integrated process, combining an enzymatic resolution step with a few chemical transformations, is described for the synthesis of (1*R*,4*R*)- and (1*S*,4*S*)-bicyclo[2.2.1]heptan-2,5-diones **1** of high enantiomeric purity, starting from a standard mixture of (±)-*endo*- and *exo*-2-acetoxy-5-norbornene.

Introduction

(±)-Bicyclo[2.2.1]heptan-2,5-dione **1**, which is readily obtained by the addition of formic acid to norbornadiene, followed by Jones oxidation of the resulting diformate esters,[1] has been used as a rigid template for the elaboration of a diphosphine ligand **2**.[2] Dione **1** is also the starting material for the preparation of *anti*-3,5-dihydroxy-heptan-1,7-dicarboxylic acid **3**,[3] a C_2-symmetric synthon possessing two chiral centers, which has been used in the preparation of the lactone rings of avermectins or milbemycins (Scheme I). In view of this, it would be of great use to have a simple preparative access to the pure dione enantiomers which, to our present knowledge, does not yet exist. A recent paper[4] does, however, describe an asymmetric bis-hydrosilylation of norbornadiene which leads to one of the corresponding *exo,exo*-diol diacetate enantiomers with high optical purity.

We herein report the synthesis of diones of high enantiomeric purity, starting from a commercial mixture of norbornenol acetates, which involves very few steps, the key one being an enzymatic resolution method.

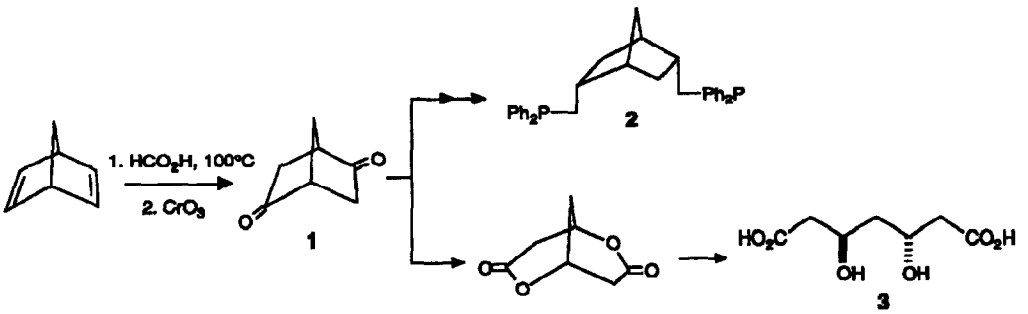
Results and Discussion

Our first attempts, which involved the direct enzymatic resolution of mono- and diesters derived from the racemic diol mixture obtained by the formylation of norbornadiene,[1] were unsuccessful, in agreement with known structural models elaborated for the hydrolysis of such bicyclic esters catalyzed by lipase from *Candida rugosa* (= *Candida cylindracea*)[5] and recent results obtained with other enzymes.[6–8] An enzymatic hydrolysis of *endo*-2-norbornenyl esters,[9,10] having an enantioselectivity coefficient (*E*)[11] of about 15, was not enantioselective enough to be of preparative use. Moreover, the recovery of the exceedingly volatile products[10] was difficult and the subsequent formylation of the norbornenyl ester was, to our surprise, unsuccessful.

For these reasons, we turned to another strategy for the introduction of the second oxygen atom using previously described reactions, the *exo*-epoxidation of an *endo*-2-hydroxy-5-norbornene derivative followed by a regioselective reductive opening of the epoxide ring to give an *endo,exo*-2,5-norbornanediol.[12] We were also aware that the enzymatic resolution of a 5,6-epoxy-*endo*-norbornan-2-yl ester,[10] carried out on an analytical scale, was highly effective (*E* ~ 100) and thus appeared particularly adapted to our purpose.

Analytical enzymatic hydrolyses and transesterifications

Epoxidation of the commercial 2-acetoxy-5-norbornene (a mixture of racemic *endo*- and *exo*-isomers, approximately 8:2) employing magnesium monoperoxyphthalate hexa-

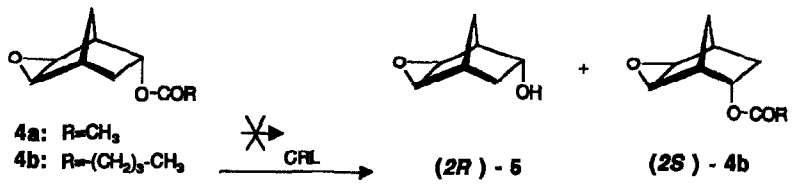


Scheme I.

Keywords: Enzymatic hydrolysis; transesterification; *Candida rugosa* lipase; asymmetric synthon.

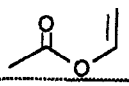
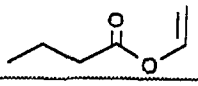
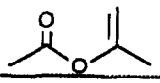
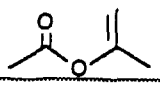
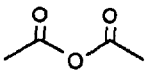
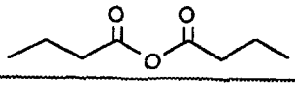
hydrate[13] in ethanol–water afforded, in high yield, the crude epoxide which, upon crystallization, yielded the pure *endo*-epoxyacetate isomer **4a** (about 50 % minimal yield). As previously described,[10] this ester was recovered unchanged, when submitted to hydrolysis with lipase from *C. rugosa*, even for prolonged incubation times. Conversely, the corresponding butyric ester **4b**, prepared by mild alkaline hydrolysis of **4a** followed by esterification with butyric anhydride, was a good substrate for the same enzyme and was easily resolved ($E \sim 92$) on a 400 mg-scale, affording (2*R*)-epoxyalcohol **5** and (2*S*)-epoxyester **4b** of high optical purity (Scheme II). Absolute configurations were attributed from the known stereoselectivity of lipase from *C. rugosa* in this series[5] and confirmed by comparison of the optical rotation of the resulting epoxyalcohol with the epoxidation product of the previously described, corresponding (1*R*,2*R*,4*R*)-*endo*-norbornenol.[9,10]

However, the need for a preliminary exchange of the ester group could be eliminated by working with the same lipase in a transesterification reaction, using the racemic alcohol **5** as a substrate in an anhydrous organic solvent.[14] A preliminary screening for a convenient acyl group donor in various organic solvents was effected, the principal results of which are given in Table 1. The most striking outcome is that, unexpectedly, acetyl donors (entries 1, 3, 4 and 5) are effective donating reagents, although they are systematically less effective than butyryl donors. Moreover, the enantioselectivities measured using vinyl or isopropenyl acetate were higher or comparable to those measured using vinyl butyrate (entry 2). In contrast, other donors such as anhydrides (entries 5 and 6) or esters (entry 7), result in lower enantioselectivities. In the case of isopropenyl acetate, the replacement of toluene by chloroform (entry 4) produced a dramatic effect on the rate and enantioselectivity of the esterification reaction.



Scheme II.

Table 1. Enantioselective esterification[a] of (±)-2-*endo*-hydroxy-5,6-epoxynorbornane by lipase from *C. rugosa* in the presence of various acyl donors and solvents.

	Acylating agent (mol/ mol of substrate)		Solvent	Time (hours)	% conversion	E values[b]
1		(2)	Toluene	66	30	50-90
2		(3)	Toluene	3	46	75
3		(4)	Toluene	66	47	200-500
4		(4)	$CHCl_3$	216	14	12
5		(1)	Toluene	120	15	1.3
6		(1)	Toluene	1.5	40	3.6
7	Tributyrin	(used as solvent)		66	37	12

[a]To the substrate (50 mg) in anhydrous solvent (5 mL) were added 4 Å molecular sieves (50 mg), acyl donor, and lipase from *C. rugosa* (10–20 mg). The suspensions were incubated with shaking at 30 °C.

[b]calculated from % conversion, determined by GC of the reaction mixture (DBwax column, 160 °C) or from enantiomeric excesses of substrate and product.[11] *e.e.s* were determined either by GC of acetate or trifluoroacetate esters on a Chiraldex G-TA 30 capillary column (110 °C) or by HPLC of benzoate esters on a Chiralpack AD column (see Experimental Section).

Preparative aspects

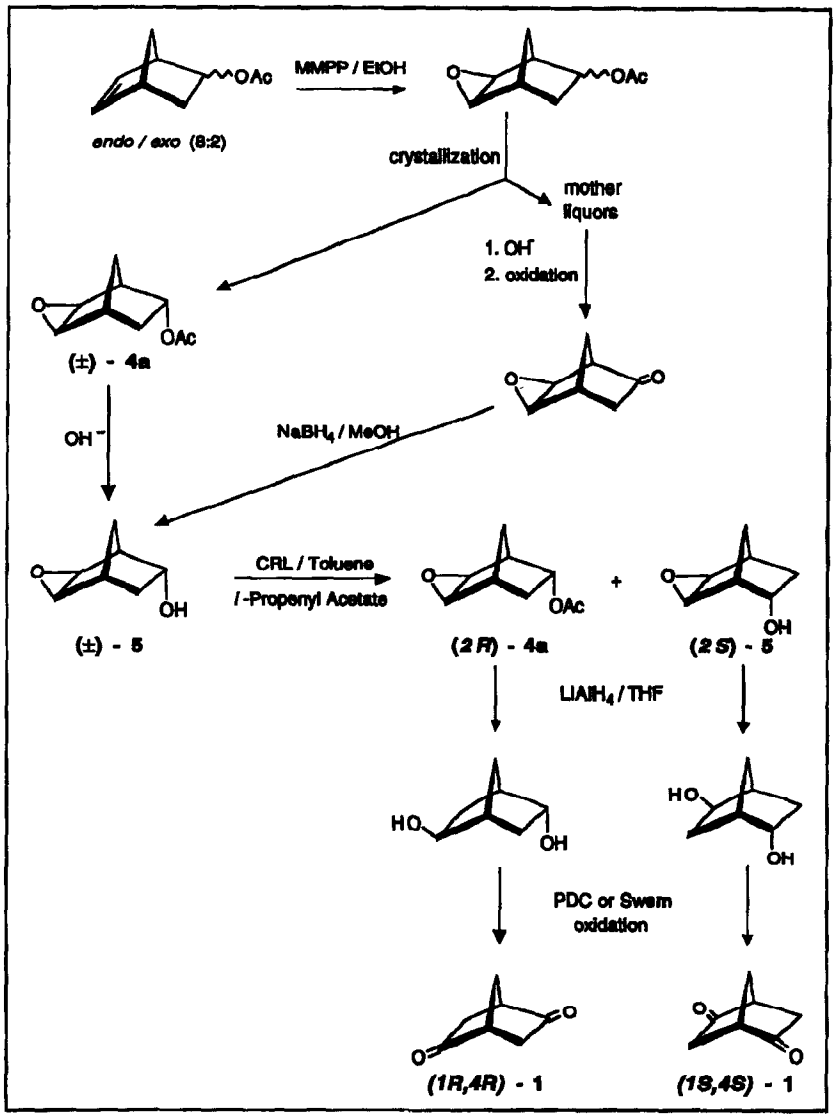
Under the best conditions (entry 3), starting from 3 g of (±)-epoxy alcohol **5**, it was possible to obtain, in a two-stage operation,[9] 1.6 g (40 %) of (2*R*)-epoxyacetate **4b** (96 % *e.e.*) and 1.2 g (40 %) of (2*S*)-epoxyalcohol **5** (> 98 % *e.e.*). Each product was then reduced with lithium aluminum hydride in tetrahydrofuran[12] (65–75 % yield) and the crystallized[15] *endo,exo*-2,5-norbornanediols were submitted to pyridinium dichromate or Swern oxidation,[16] affording the enantiomeric (1*S*,4*S*)- and (1*R*,4*R*)-bicyclo[2.2.1]heptan-2,5-diones (about 70 % yield) in high optical purity (≥ 96 % *e.e.*).

An integrated process, which includes the recycling of unused (±)-*exo*- and *endo*-2-acetoxy-5,6-epoxynorbornanes present in the mother liquors of the epoxyacetate recrystallization, has been designed: mild alkaline hydrolysis, followed by oxidation to epoxynorbornanone and reduction with sodium borohydride in methanol[10] will afford exclusively (≥ 95 %) the *endo*-epoxynorbornanol **5**, which could again be used in the enzymatic transesterification procedure. The entire synthetic process, described in Scheme III, is currently being conducted on a multigram scale in our laboratory, and will be reported in due course.

Experimental Section

General

Melting points are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded on a WM250 Bruker spectrometer at 250 and 62.9 MHz respectively. The residual protons in $CDCl_3$ or pyridine-d_5 were used as reference peaks, with assigned 7.25 and 8.71 ppm chemical shifts, respectively. Signal assignment was aided by 2D ^{1}H homonuclear shift correlated (COSY 45) spectra and ^{13}C distortionless enhanced polarization (DEPT 135) experiments. Optical



Scheme III.

rotations were measured in 1 dm or 0.1 dm cells using a Perkin Elmer 241 spectropolarimeter. Gas chromatography was performed on Varian 3700 or Shimadzu G-8A instruments equipped with flame ionization detectors and Shimadzu C-R3A or C-R6A integrating recorders. OV-1701 (Flexibond™, 0.20 mm x 15 m, Pierce Chem. Co) or Durabondwax (0.32 mm x 30 m, J&W Scientific, Inc.) capillary columns were routinely employed to monitor enzyme reactions, whereas a Chiraldex G-TA capillary column (0.25 mm x 30 m, Astec) was used to determine optical purities. Mass spectrometric analyses (MS) were carried out by electronic impact (EI) on a Hewlett Packard 5972 GC–MS instrument. High resolution mass spectra (HRMS) were supplied by Université P. et M. Curie (Paris). Flash column chromatography was carried out using Merck 60 silica gel (230–400 mesh). Merck $60F_{254}$ precoated glass plates were used for thin layer chromatography. High pressure liquid chromatography was performed using a Chromatem 380 pump, equipped with a Pye–Unicam LC-UV detector, a Shimadzu C-R3A integrating recorder, and a Chiralpack AD column (0.46 x 25 cm, Daicel Chem. Ind.). Lipase from *Candida cylindracea* (*C. rugosa*, E.C.3.1.1.3) was purchased from Sigma Chemical Co. (St Louis, USA).

Determination of enantiomeric excess

Enantiomeric excesses of 2-*endo*-acetoxy-5,6-epoxynorbornanes (Figure 1) and bicyclo[2.2.1]heptan-2,5-diones (Figure 2) were determined directly by GC on a Chiraldex G-TA30 capillary column at 110 °C. Enantiomeric excesses of 2-*endo*-hydroxy-5,6-epoxynorbornanes were determined by GC of their acetate or trifluoroacetate esters on the same column at 110 or 90 °C, respectively. In some cases, enantiomeric excesses of 2-*endo*-hydroxy-5,6-epoxynorbornanes were determined by HPLC of their benzoyl esters on a Chiralpak AD column with hexane–isopropanol (95:5) as solvent (flow rate: 0.5 mL/min, detection at 250 nm).

Preparation of acetyl esters for GC analysis: to the alcohol (~ 10 mg) dissolved in ethyl acetate was added 4-dimethylaminopyridine (0.05 eq.), sodium carbonate (1.5 eq.), and acetic anhydride (1.5 eq.). The mixture was stirred for 18 h, then washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated *in vacuo*, and analyzed without further purification.

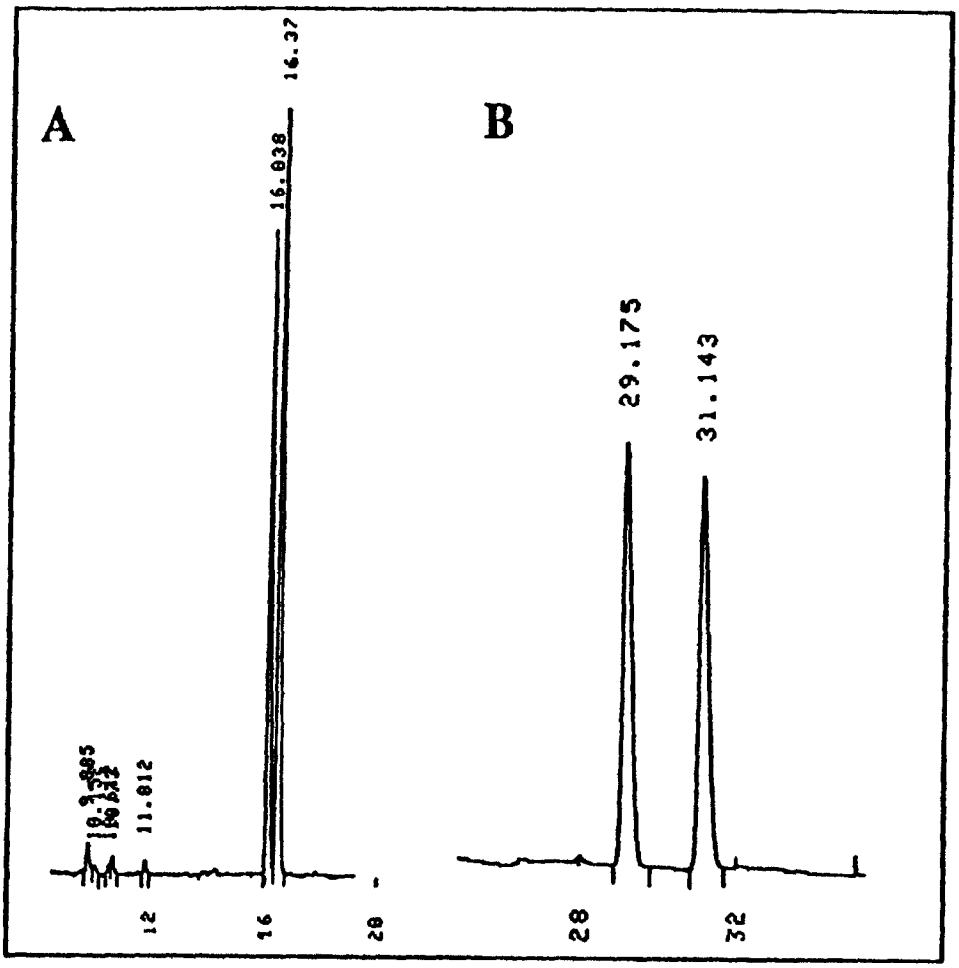


Figure 1. GC analytical separation of enantiomeric *endo*-2-hydroxy-5,6-epoxynorbornane esters on Chiraldex G-TA (see Experimental Section): **A**, trifluoroacetyl esters; **B**, acetyl esters.

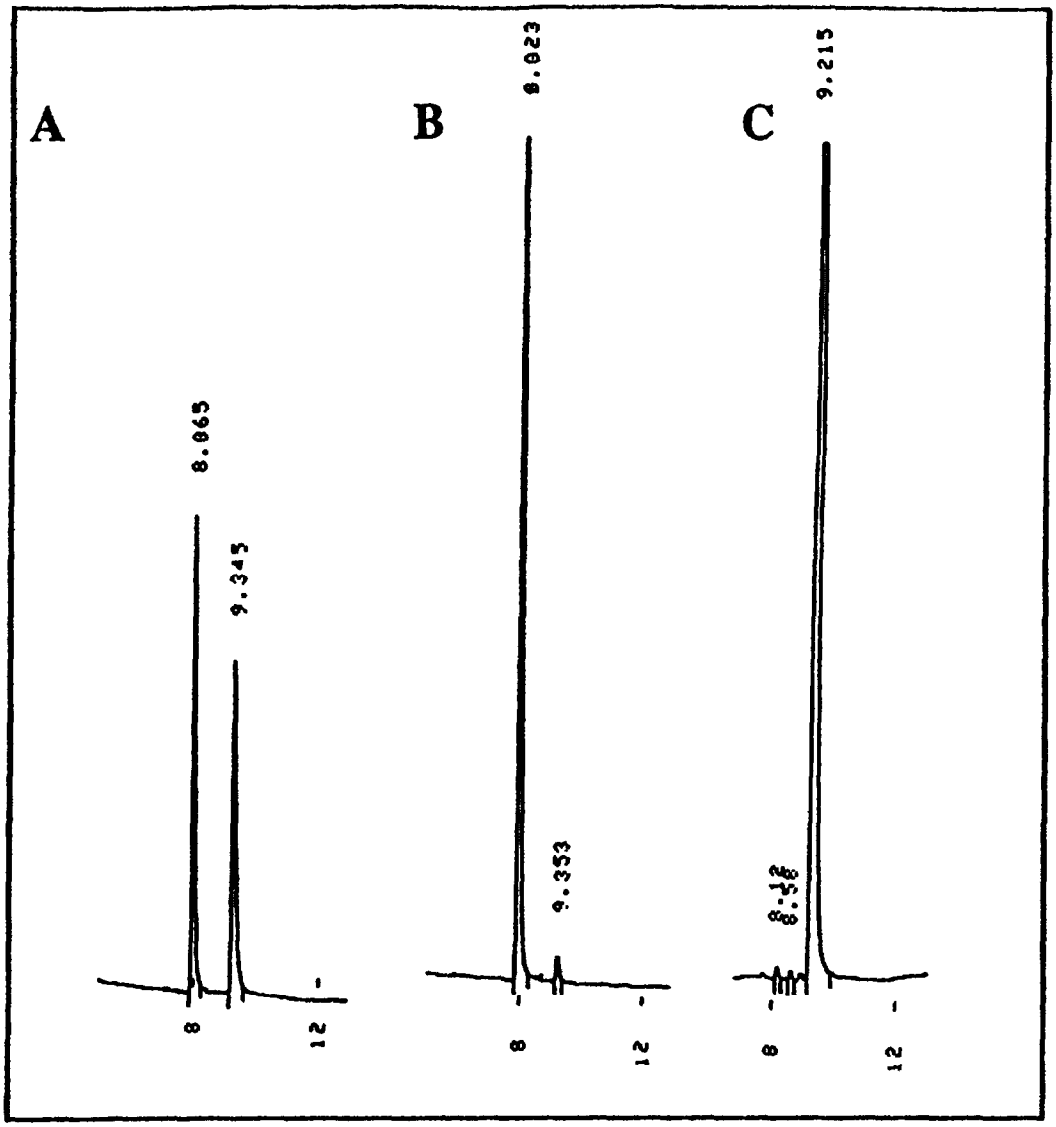


Figure 2. GC analytical separation of enantiomeric bicyclo[2.2.1]heptan-2,5-diones on Chiraldex G-TA (see Experimental Section): **A**, racemic mixture; **B**, 1*S*,4*S*; **C**, 1*R*,4*R*.

Preparation of trifluoroacetyl esters for GC analysis: to the alcohol (1–5 mg) in dichloromethane (0.5 mL) was added trifluoroacetic anhydride (0.2 mL). After stirring for 30 min, the solvent and excess anhydride were evaporated under a stream of nitrogen and the residue was analyzed without further purification.

Preparation of benzoyl esters for HPLC analysis: Dicyclohexylcarbodiimide (1.1 eq.) was added to a mixture of 4-dimethylaminopyridine (0.1 eq.), benzoic acid (2 eq.) and alcohol in dichloromethane, cooled in an ice-water bath. After stirring for 30 min, the reaction mixture was warmed to room temperature and stirred for 30 h. Dicyclohexylurea was removed by filtration and the filtrate was washed twice with 1 N HCl, saturated sodium bicarbonate, water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was analyzed without further purification.

(±)-2-endo-acetoxy-5,6-epoxynorbornane (4a)

A solution of magnesium monoperoxyphthalate hexahydrate (375 g, 0.76 mol) in water (2.6 L) was added to (±)-2-*endo/exo*-acetoxy-5-norbornene (99 g, 0.650 mol) in absolute ethanol (2 L). The mixture was stirred at room temperature for 3 days. Ethanol, along with a portion of water, was evaporated *in vacuo* and the residue (1.2 L) was divided into two parts. Each portion was extracted with ether (1 L), washed with aqueous saturated sodium bicarbonate (3 x 300 mL), 20 % aqueous sodium bisulfite (2 x 300 mL), water (300 mL), and brine (500 mL), and dried over sodium sulfate. The two aqueous phases obtained after the first ether extraction were combined, extracted again with ether (1 L), and washed as above. Evaporation of the solvent from the combined ethereal phases yielded a mixture of the *exo* and *endo* isomers as a slightly yellow oil (80.9 g, 70 %). Three crystallizations from ether–hexane yielded the *endo* isomer (54.3 g, 50 %, > 99 %

endo-isomer by GC). R_f 0.25 (cyclohexane–ethyl acetate, 8:2). Mp 53.5–54 °C (lit.[12]: 53–54 °C). HRMS for $C_9H_{12}O_3$, calc. 168.078642, found 168.078657. MS (EI): 168(1), 150(1) $[M-H_2O]^+$, 140(3), 138(3), 126(9) $[M-CH_2CO]^+$, 108(10), 97(11), 82(81), 43(100).

^{1}H NMR ($CDCl_3$, 250 MHz), δ ppm, *J* Hz: 5.04 (1H, ddd, J_{2-3exo} = 8.8, J_{1-2} = 4.4, $J_{2-3endo}$ = 3, H-2), 3.33 (1H, br.d, J_{5-6} = 3.6, H-6), 3.23 (1H, br.d, J_{5-6} = 3.6, H-5), 2.75 (1H, dm, J_{1-2} = 4.4, H-1), 2.49 (1H, dm, J_{4-3exo} = 4.4, H-4), 2.07 (1H, ddd, $J_{3exo-3endo}$ = 13.5, J_{2-3exo} = 8.8, J_{3exo-4} = 4.4, H-3 *exo*), 2.02 (3H, s, CH_3CO), 1.34 (1H, dm, $J_{7-7'}$ = 10.2, H-7), 1.07 (1H, dm, $J_{3exo-3endo}$ = 13.5, $J_{2-3endo}$ = 3, H-3 *endo*), 0.78 (1H, dm, $J_{7-7'}$ = 10.2, H-7').

^{13}C NMR ($CDCl_3$, 62.9 MHz), δ ppm: 170.28 (CO), 75.97 (CH, C-2), 50.36, 47.66 (CH, C-5 and C-6), 39.99, 36.44 (CH, C-1 and C-4), 32.56, 24.26 (CH_2, C-3 and C-7), 20.45 (CH_3).

The mother liquors were concentrated *in vacuo*, yielding a yellow oil (25.7 g) containing 35 % *endo*-isomer.

*(±)-2-*endo*-butyroxy-5,6-epoxynorbornane (4b)*

To a solution of (±)-2-*endo*-butyroxy-5-norbornene (900 mg, 5 mmol) in ethanol (15 mL) was added magnesium monoperoxyphthalate hexahydrate (3 g, 6.06 mmol) dissolved in water (20 mL). The mixture was stirred at room temperature for 48 h. The solvents were evaporated *in vacuo* and the residue dissolved in ether (100 mL). The ethereal solution was washed with aqueous saturated sodium bicarbonate (2 x 50 mL), 20 % aqueous sodium bisulfite (6 x 50 mL), saturated sodium bicarbonate (2 x 50 mL), water, and brine, dried over sodium sulfate, and evaporated. The crude product was purified by flash chromatography (hexane–ethyl acetate, 95:5 to 9:1), yielding the epoxyester as a colorless oil (819 mg, 83 %). R_f 0.38 (cyclohexane–ethyl acetate, 8:2). MS (EI): 168(2) $[M-CO]^+$, 140(5) $[M-CH_2CH_2CO]^+$, 125(4) $[M-CH_3CH_2CH_2CO]^+$, 107(5), 97(8), 81(81), 71(100).

^{1}H NMR ($CDCl_3$, 250 MHz), δ ppm, *J* Hz: 5.01 (1H, ddd, J_{2-3exo} = 9, J_{1-2} = 4, $J_{2-3endo}$ = 3, H-2), 3.32 (1H, br.d, J_{5-6} = 3.6, H-6), 3.23 (1H, br.d, J_{5-6} = 3.6, H-5), 2.75 (1H, dm, J_{1-2} = 4, H-1), 2.49 (1H, dm, J_{4-3exo} = 4, H-4), 2.25 (2H, t, *J* = 7.3, CH_2CO), 2.07 (1H, ddd, $J_{3exo-3endo}$ = 13.2, J_{2-3exo} = 9, J_{3exo-4} = 4, H-3 *exo*), 1.62 (2H, sextet, *J* = 7.3, CH_2CH_3), 1.33 (1H, dm, $J_{7-7'}$ = 10.2, H-7), 1.06 (1H, dm, $J_{3exo-3endo}$ = 13.2, $J_{2-3endo}$ = 3, H-3 *endo*), 0.93 (3H, t, *J* = 7.3, CH_3CH_2), 0.79 (1H, br.d, $J_{7-7'}$ = 10.2, H-7').

*Enzymatic hydrolysis and resolution of (±)-2-*endo*-butyroxy-5,6-epoxynorbornane (4b)*

To (±)-2-*endo*-butyroxy-5,6-epoxynorbornane **4b** (388 mg, 1.98 mmol) dissolved in 0.1 M, pH 7 sodium phosphate buffer–acetone (9:1, 150 mL), was added lipase from *C. rugosa* (39 mg). The mixture was orbitally shaken at 27 °C for 3 h (39 % conversion). The reaction mixture was saturated with sodium chloride and ethyl acetate (100 mL) was added. After stirring vigorously for 5 min, the phases were separated and the aqueous layer was extracted again with ethyl acetate (6 x 100 mL). The combined organic extracts were washed with aqueous saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. Purification of the crude product by flash chromatography (hexane–ethyl acetate, 6:4 to 1:1) yielded pure alcohol (2*R*)-**5** (83 mg, 33 %), $[\alpha]_D^{21}$ + 42.4 ° (c 1.2, $CHCl_3$) (lit.[10]: + 46.5 °), 96 % *e.e.*, and ester (2*S*)-**4b** (232 mg, 60 %). The isolated butyrate was resubmitted to hydrolysis under the same conditions. After 6 h (57 % total conversion), the reaction mixture was worked up as before. Purification of the crude product yielded alcohol (2*R*)-**5** (16.2 mg, 6 %), and butyrate (2*S*)-**4b** (179 mg, 46 %), $[\alpha]_D^{21}$ – 13.8 ° (c 3.9, $CHCl_3$) (lit [10]: – 13.4 °), > 99 % *e.e.*

*(±)-2-*endo*-hydroxy-5,6-epoxynorbornane (5)*

To a solution of (±)-*endo*-2-acetoxy-5,6-epoxynorbornane (48.7 g, 0.29 mol) in ethanol (400 mL), cooled in a cold water bath, was slowly added 2 N sodium hydroxide (175 mL, 0.348 mol). The mixture was stirred for 85 min, after which time the reaction was quenched with glacial acetic acid (3.3 mL, 0.06 mol). Ethanol and water were removed by rotatory evaporation and the residue was extracted with ethyl acetate (1.4 L). The organic phase was washed with 0.5 N HCl (100 mL), saturated aqueous sodium bicarbonate (200 mL), and brine (2 x 200 mL), dried over anhydrous sodium sulfate, and evaporated *in vacuo* to yield a pale yellow solid (35.1 g, 96 %). The crude product was crystallized from ethyl acetate–hexane to give the pure epoxy alcohol as white crystals (25.3 g, 70 %). The remaining product was purified by flash chromatography (pentane–ethyl acetate, 5:5 to 3:7) yielding additional pure epoxy alcohol (4.4 g, 11 %). R_f 0.23 (pentane–ethyl acetate, 5:5). Mp 190–192 °C, sealed tube (lit.: 160–162 °C,[12] 170–172 °C[10]). HRMS for $C_7H_{10}O_2$, calc. 126.068078, found 126.068107. MS (EI): 126(1), 125(1.5), 107(2.5), 95(4), 81(100).

^{1}H NMR ($CDCl_3$, 250 MHz), δ ppm, *J* Hz: 4.38 (1H, m, H-2), 3.44 (1H, br.d, J_{5-6} = 3.7, H-6), 3.27 (1H, br.d, J_{5-6} = 3.7, H-5), 2.60 (1H, m, H-1), 2.45 (1H, m, H-4), 1.99 (1H, ddd, $J_{3exo-3endo}$ = 13.2, J_{2-3exo} = 9, J_{3exo-4} = 4, H-3 *exo*), 1.55 (1H, br.s, OH), 1.27 (1H, dm, $J_{7-7'}$ = 10.2, H-7), 1.00 (1H, dt, $J_{3exo-3endo}$ = 13.2, $J_{2-3endo}$ = 3, H-3 *endo*), 0.74 (1H, br.d, $J_{7-7'}$ = 10.2, H-7').

^{13}C NMR ($CDCl_3$, 62.9 MHz), δ ppm: 74.13 (CH, C-2), 51.47, 48.98 (CH, C-5 and C-6), 42.36, 37.33 (CH, C-1 and C-4), 35.08, 25.15 (CH_2, C-3 and C-7).

*Preparative enzymatic resolution of (±)-2-*endo*-hydroxy-5,6-epoxynorbornane (5)*

Isopropenyl acetate (10.3 mL, 93.5 mmol) was added to (±) 2-*endo*-5,6-epoxynorbornane (3 g, 23.8 mmol) dissolved in toluene (340 mL). Lipase from *C. rugosa* (1

g) was added and the flask was orbitally shaken at 30 °C. After 14 h an additional 700 mg of lipase was added and after another 8 h, 550 mg of lipase was added. After a total of 25 h, the reaction was stopped by filtration of the mixture through glass fiber paper. The product and remaining substrate were separated by medium pressure liquid chromatography (200 g silica gel, Merck 60H, cyclohexane–ethyl acetate 1:1, followed by cyclohexane–ethyl acetate 2:8 once the first alcohol fraction was detected). The solvent was evaporated to yield the alcohol (1.84 g, 77 % *e.e.*) and the acetate (1.59 g, 40 %, 95.5 % *e.e.*), $[\alpha]_D^{21}$ + 7.4 ° (c 1, $CHCl_3$). The alcohol was resubmitted to esterification under the same conditions using 4 g lipase. The reaction was stopped as before after a total of 20 h (corresponding to a 58 % total conversion). Purification by flash column chromatography (cyclohexane–ethyl acetate, 1:1) yielded the remaining alcohol substrate (1.2 g, 40 %, > 98 % *e.e.*), $[\alpha]_D^{21}$ – 46.7 ° (c 0.85, $CHCl_3$), and the acetate product (0.44 g, 60 % *e.e.*).

Reduction of 2-endo-*acetoxy-5,6-epoxynorbornane (**4a**) to 2,5-dihydroxynorbornane*

Dry tetrahydrofuran (80 mL) was added dropwise to lithium aluminum hydride (2.4 g, 56.7 mmol) under nitrogen. After complete addition, the suspension was refluxed for 1.25 h. After cooling the mixture to room temperature, the flask was placed in a cold water bath and 2-*endo*-acetoxy-5,6-epoxynorbornanol (1.52 g, 9.04 mmol) in tetrahydrofuran (6 mL) was added dropwise. The dropping funnel was rinsed with tetrahydrofuran (5 mL) and the mixture was heated to a reflux for 3.75 h. The flask was cooled in an ice-water bath and water was carefully added dropwise (2.4 mL), followed by aqueous 15 % w/w sodium hydroxide (2.4 mL) and finally water (7.2 mL). The mixture was stirred for 20 min and then filtered, rinsing with tetrahydrofuran and ethyl acetate. The filtrate was dried over anhydrous sodium sulfate and evaporation of the solvent yielded a white solid. Recrystallization from ether–dichloromethane yielded the pure diol as white crystals (614 mg, 53 %). Medium pressure liquid chromatography (200 g silica, dichloromethane–isopropanol, 9:1) of the residue obtained from evaporation of the mother liquor yielded additional pure diol (272 mg, 23 %). R_f 0.16 (dichloromethane–methanol, 9:1). Mp 180–182 °C (sealed tube). $[\alpha]_D^{21}$ + 2.8 ° (c 2.34, MeOH), $[\alpha]_{578}$ + 2.9 °, $[\alpha]_{546}$ + 3.2 °, $[\alpha]_{436}$ + 4.2 °. HRMS for $C_7H_{12}O_2$, calc.128.083728, found 128.083713. MS (EI): 128(2) $[M]^+$, 110(19) $[M-H_2O]^+$, 95(33), 81(24), 66(100).

^{1}H NMR (pyridine-d_5, 250 MHz), δ ppm, *J* Hz: 6.04 (1H, d, J = 3.3, *endo*-OH on C-2), 5.99 (1H, d, J = 3.3, *exo*-OH on C-5), 4.38 (1H, m, J_{2-3exo} = 10, J_{2-3} = $J_{2\text{-}OH}$ = 3.3, J_{2-1} = 1.3, H-2), 4.22 (1H, m, H-5), 2.92 (1H, ddd, $J_{6endo-6exo}$ = 13, $J_{6endo-5}$ = 7, J = 2, H-6 *endo*), 2.40 (1H, br.t, $w_{1/2}$ = 10, H-1), 2.33 (1H, br.d, J = 5, H-4), 2.06–1.93 (2H, m, J = 5, H-3$_{exo}$ and H-7), 1.63 (1H, dm, $J_{6exo-6endo}$ = 13, H-6 *exo*), 1.31 (1H, br.d, $J_{7-7'}$ = 10, H-7'), 1.01 (1H, dt, $J_{3exo-3endo}$ = 13, $J_{2-3endo}$ = 3.3, H-3 *endo*).

^{13}C NMR ($CDCl_3$, 62.9 MHz), δ ppm: 73.70, 70.62 (CH, C-2 and C-5), 44.40, 41.21 (CH, C-1 and C-4), 34.31, 33.03, 32.26 (CH_2, C-3, C-6, and C-7).

Reduction of 2-endo-*hydroxy-5,6-epoxynorbornane (5) to 2,5-dihydroxynorbornane*

The above procedure was used for the reduction of the epoxy alcohol (1.17g, 9.27 mmol) with the exception that only 4 eq. of lithium aluminum hydride were used. Recrystallization yielded the diol as white crystals (355 mg, 30 %) and chromatography of the mother liquor yielded additional pure diol (411 mg, 34 %). $[\alpha]_D^{21}$ – 4.1 ° (c 2.25, MeOH), $[\alpha]_{578}$ – 4.2 °, $[\alpha]_{546}$ – 4.5 °, $[\alpha]_{436}$ – 5.6 °.

Oxidation of 2,5-dihydroxynorbornane to enantiomeric bicyclo[2.2.1]heptan-2,5-diones (1)

(i) *Pyridinium dichromate oxidation.* Diol (706 mg, 5.51 mmol) was dissolved in *N,N*-dimethylformamide (100 mL), pyridinium dichromate (7.05 g, 18.7 mmol) was added and the mixture was stirred under nitrogen for 3 h. Aqueous saturated sodium bicarbonate (100 mL) was added to the reaction mixture and it was shaken vigorously. Dichloromethane (300 mL) was added and the organic phase was washed with aqueous saturated sodium bicarbonate (4 x 100 mL), 0.5 N HCl (100 mL), saturated sodium bicarbonate (100 mL), water (2 x 200 mL), and brine (200 mL), and dried over sodium sulfate. The solvent was evaporated *in vacuo* yielding 501 mg of dione (73 %, 95 % pure by GC).

(ii) *Swern oxidation.* Freshly distilled oxalyl chloride (0.45 mL, 4.8 mmol) in dry dichloromethane (8 mL) was added dropwise to a solution of dry dimethylsulfoxide (0.83 mL, 10.9 mmol) in dry dichloromethane (5 mL), under nitrogen at –78 °C. After stirring for 30 min, 2,5-dihydroxynorbornane (300 mg, 2.34 mmol) in dichloromethane (4 mL) and dimethylsulfoxide (0.6 mL) was added dropwise. After stirring for 3 h, triethylamine (3 mL, 21.8 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature, then stirred for an additional hour. Water (10 mL) was added dropwise, the reaction mixture was diluted with dichloromethane and the organic phase was washed with 0.5 N HCl, aqueous saturated sodium bicarbonate, and brine. The solvent was evaporated *in vacuo* yielding 200 mg of pure dione (70 %). MS (EI): 124(100) $[M]^+$, 95(21), 82(23), 67(87).

^{1}H NMR ($CDCl_3$, 250 MHz), δ ppm, *J* Hz: 2.97 (2H, m, X signal of an ABX system, H-1 and H-4), 2.36 (2H, dm, A signal of an ABX system, J_{AB} = 19, H-3 *exo* and H-6 *exo*), 2.13 (2H, dm, B signal of an ABX system, J_{AB} = 19, H-3 *endo* and H-6 *endo*), 2.08 (2H, m, H-7 and H-7').

^{13}C NMR ($CDCl_3$, 62.9 MHz), δ ppm: 212.04 (CO, C-2 and C-5), 48.48 (CH, C-1 and C-4), 38.80 (CH_2, C-6 and C-3), 36.27 (CH_2, C-7).

(1*S*,4*S*)-**1**: mp 140–141 °C. $[\alpha]_D^{21}$ – 4.5 ° (c 2.44, EtOH), $[\alpha]_{578}$ – 4.5 °, $[\alpha]_{546}$ – 2.9 °, $[\alpha]_{436}$ + 26.6 °, $[\alpha]_{363}$ + 187 °; *e.e.* = 99 %. HRMS for $C_7H_8O_2$, calc. 124.052408, found 124.052383.

(1*R*,4*R*)-**1**: mp 139–140 °C. $[\alpha]_D^{21}$ + 5.0 ° (c 2.0, EtOH), $[\alpha]_{578}$ + 5.0 °, $[\alpha]_{546}$ + 4.0 °, $[\alpha]_{436}$ – 25.5 °, $[\alpha]_{363}$ – 179.5 °; *e.e.* = 96 %. HRMS for $C_7H_8O_2$, calc.124.052408, found 124.052383.

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