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ENZYMATIC RESOLUTION OF NORBORNANE-TYPE ESTERS

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Abstract - Chiral norbornane-type alcohols of high optical purity were prepared via enzymatic resolution of their racemic esters using lipases from *Candida cylindracea* and *Pseudomonas sp.* This method presents a short and efficient access to a number of chiral building blocks on a molar scale for the synthesis of optically active cyclopentane systems.

INTRODUCTION

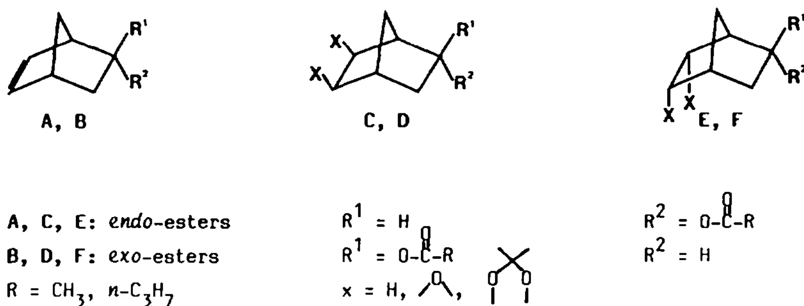
Compounds possessing the norbornane-type framework have gained increasing interest due to their occurrence as natural substances and as starting material for the synthesis of numerous compounds. During the past decade they were employed in the synthesis of prostaglandins[1a], terpenes[1b], steroids[1c], alkaloids[1d], insect deterrents[1e], and carbocyclic nucleoside analogues[1f-1l]. Whereas the majority of bicyclo[2.2.1]heptane derivatives was used as racemates, only recently methods for the preparation of enantiomerically pure material were developed[2a-d]. Among them, the particularly attractive bicyclo[2.2.1]hept-5-en-2-one (1) so far has been prepared in an optically pure form only on a small scale[2a-c]. Using enzymatic methods[3] which permit an easy scaleup of preparative procedures we present now a novel access to a number of enantiomerically pure building blocks possessing the norbornane-skeleton.

RESULTS AND DISCUSSION

In our ongoing study on the use of enzymes and microorganisms in organic syntheses[4a-d] we recently developed a short and efficient access to (+)- and (-)-*endo*-norborn-5-en-2-ol (**2a***, *ent*-**2a***)[4b,5a]. Here we present a more detailed investigation in scope and limitations of this method.

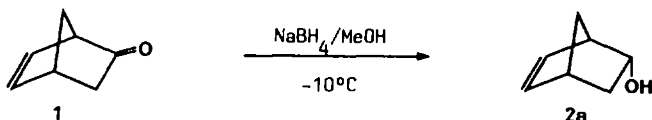
In order to obtain norbornane-type compounds of selected substitutional pattern it was necessary to investigate the steric influence of substrates in the course of the enzymatic hydrolysis. By modification of the double bond in compounds of type **A** and **B** we synthesized a number of substrates showing two types of structure (**C**+**D** and **E**+**F**,resp., see scheme I) which were subjected to enzymatic resolution.

SCHEME I: Types of compounds hydrolysed enzymatically.



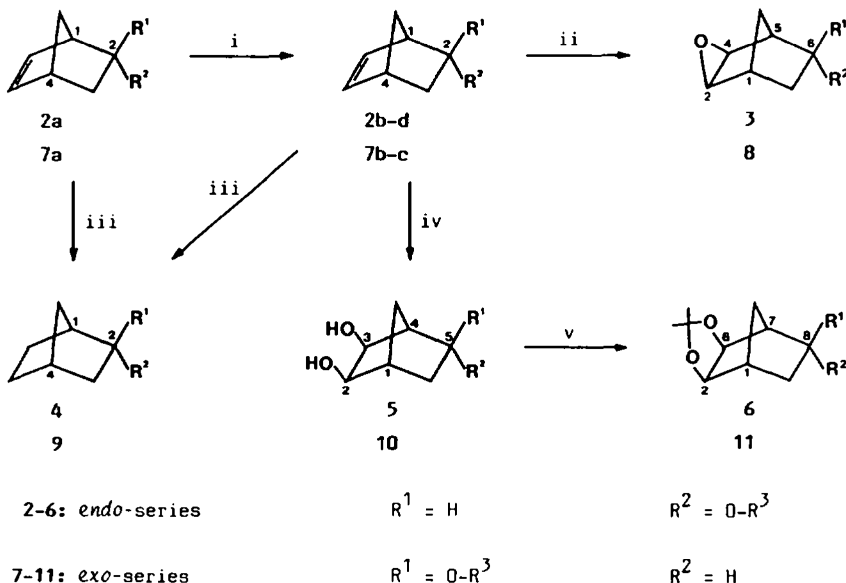
1) Synthesis of Racemic Substrates[5a]

For the synthesis of compounds of type **A** and **C** *endo*-norborn-5-en-2-ol (**2a**) was best suited as starting material.



By modifying methods hitherto employed[6a,b] it was shown that the reduction of norborn-5-en-2-one (**1**) using sodium borohydride in methanol[2a] proceeds highly stereoselective providing a cheap and efficient access to molar amounts of *endo*-norborn-5-en-2-ol (**2a**).

SCHEME II: Synthesis of compounds of type A-D[5a].



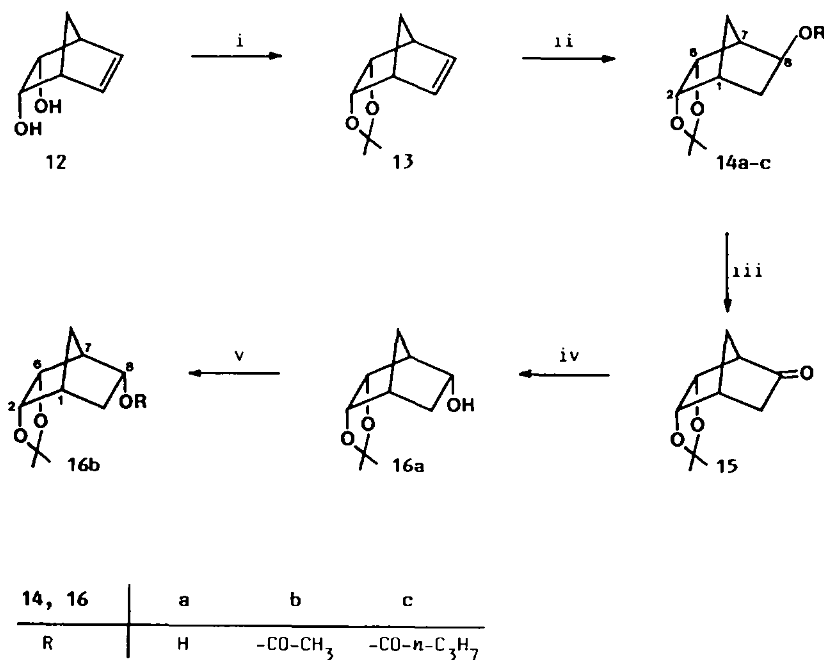
2-11	a	b	c	d
R^3	H	$-CO-CH_3$	$-CO-n-C_3H_7$	$-CO-n-C_7H_{15}$

i) for **2b,c** and **7b,c**: acid anhydride/Py/DMAP, CH_2Cl_2; for **2d**: octanoic acid/ DCC/Py/DMAP, CH_2Cl_2. ii) MCPBA, CH_2Cl_2. iii) H_2/Pd-C, EtOH. iv) OsO_4/N-methylmorpholine-N-oxide·H_2O, acetone. v) for **6b,c** and **11c**: 2,2-dimethoxypropane/H^+.

Esters of *endo*-norborn-5-en-2-ol **2b,c** were prepared according to standard procedures[7]. In case of **2d** we used the DCC method[8]. Catalytic hydrogenation[9] furnished norbornanes **4a-c**. Electrophilic attack of the double bond of **2a-c** either by m-chloroperbenzoic acid[10] or osmium tetroxide[11] gave exclusively the corresponding *exo*-derivatives[1g,12] **3a-c** and **5b,c** (homogeneous by GLC-analysis), the *exo*-configuration of which was confirmed by ^{1}H-NMR spectroscopy[13]. Protection of the vicinal diol of **5b** by transacetalisation using 2,2-dimethoxypropane led to dioxolanes **6b,c**. Transesterification of the latter gave the alcohol **6a**.

Substrates of type B and D (see scheme I) were synthesized by the following sequence: *exo*-norbornenol (**7a**), free of its *endo*-isomer **2a**, was obtained by hydroboration of norbornadiene according to *Brown et al.*[14] and subsequent careful medium pressure liquid chromatography. Catalytic hydrogenation of the unsaturated derivatives[9] **7a-c** gave rise to norbornanes **9a-c**. Epoxidation[10] and dihydroxylation[11] of **7a-c**, as expected, exclusively led to the formation of *exo*-functionalised norbornane systems **8a,c** and **10c**, respectively. Transacetalisation, as mentioned above, gave access to the dioxolane derivative **11c**. Alcohol **11a** and acetate **11b** were obtained by the sequence **11c** → **11a** → **11b** using standard procedures.

SCHEME III: Synthesis of compounds of type E and F.



14, 16	a	b	c
R	H	$-CO-CH_3$	$-CO-n-C_3H_7$

i) 2,2-Dimethoxypropane/H^+. ii) a: B_2H_6, THF; b: H_2O_2/NaOH. iii) PDC, CH_2Cl_2. iv) $NaBH_4$, MeOH. v) Ac_2O/DMAP/Py.

For the synthesis of substrates possessing the *endo*-dioxolane moiety (type E and F, see scheme I) diol 12 seemed to be suited best as starting material. Diels-Alder reaction of cyclopentadiene and vinylene carbonate followed by alkaline hydrolysis[15] led to a 93:7 mixture of 12 and its *exo*-isomer. Purification of the former was accomplished by conventional chromatography furnishing 12 as the more polar fraction. Protection of the vicinal diol gave dioxolane 13. As expected the bulkiness of the dioxolane moiety led to an exclusive formation of the *exo*-alcohol **14a** upon hydroboration[26] of 13. Inversion of the alcoholic center to yield the corresponding *endo-endo*-derivative 16a was performed by two successive steps: Oxidation[16] of 14a led to ketone 15 which in turn was stereoselectively reduced by sodium borohydride to give alcohol 16a. In contrast to the esterification procedure mentioned above, more drastic reaction conditions were necessary (60°C with pyridine as solvent) to obtain substrate 16b.

2) ENZYMATIC HDROLYSES

As published in a preliminary communication[4b], among the group of hydrolytic enzymes, particularly lipases as compared to esterases and proteases have shown to be suited best for our purposes. In an initial screening the following commercially available lipases were tested for their hydrolytic ability on our substrates (all enzymes were obtained in a crude form and were used without purification):

Lipase from *Candida cylindracea*[17,18], from *Pseudomonas sp.*[19], from *Aspergillus sp.*[19], and lipase from porcine pancreas[20]. Whereas both of the former enzymes exhibited good to excellent activity, both of the latter were not able to hydrolyse esters of our type.

The results of a more detailed screening on a milligram scale using both of the more active lipases are depicted in table I.

TABLE I: Screening of enzymes.

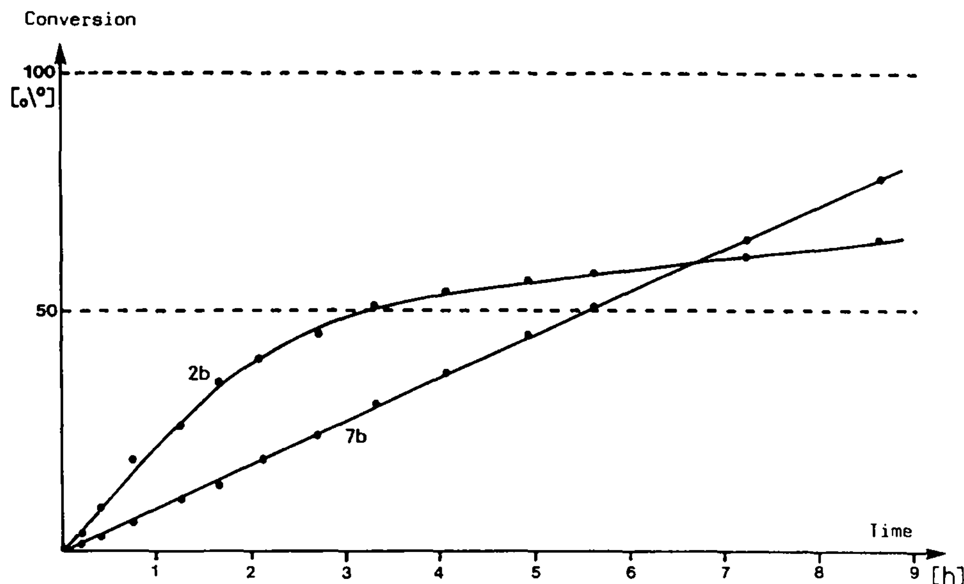
Substrate	Lipase from *Candida cylindracea*	Lipase from *Pseudomonas sp.*	Substrate	Lipase from *Candida cylindracea*	Lipase from *Pseudomonas sp.*
2b	++	++	7b	-	-
2c	++	+	7c	++	-
2d	++	+	8b	-	-
3b	-	-	8c	++	-
3c	++	-	9b	++	-
4b	++	-	9c	++	-
4c	++	-	11b	+	-
6b	-	-	11c	++	-
6c	++	-	14b	-	-
			14c	++	-
			16b	-	-

key: ++ fast conversion, + conversion, - marginal or no conversion.

All substrate-enzyme combinations showing *fast conversion* or *conversion* required a detailed investigation on a preparative scale regarding the optical purity of the products.

At first the course of conversion versus time was examined for the enzymatic hydrolysis of substrates 2b and 7b, showing a characteristic behaviour:

FIGURE I: Enzymatic hydrolysis of 2b and 7b using *Candida cylindracea* lipase.



The reaction rate of substrate 2b slowed down significantly when a conversion of about 50% was reached, indicating an enantioselection of the enzyme. On the other hand no noticeable change was observed with substrate 7b. Hence no substantial optical purity of products was expected in this case.

According to a theoretical study of *Sih et al.*[21] on the relation between the enantiomeric excess of products and the conversion of an enzymatic resolution the optimum in both *chemical and optical* yield for the faster hydrolysed enantiomer is to be expected near 40% conversion, and for the remaining slower hydrolysed enantiomer around 60% conversion.

Therefore, the following strategy was applied: The racemic ester was subjected to enzymatic hydrolysis until 40% conversion was accomplished (determined by the consumption of sodium hydroxide solution from an autoburette[22]). Then the alcohol formed and the remaining ester were extracted from the aqueous phase and were separated by chromatography. This remaining ester was further hydrolysed until an additional 20%conversion (i.e. 60% in total from start) was obtained. Again, by chromatography, the yet unhydrolysed ester was isolated and the alcohol was recycled, since it pro ved to be almost racemic. The alcohol from the first hydrolytic step and the ester from the second step were investigated on their optical purities.

TABLE II: Enzymatic hydrolyses of substrates of type A and C (see scheme II).

Substrate[a]	Conversion 40%				Conversion 60%			
	Product[a]	Absolute Configuration[b]	e.e. using Lipase from *Candida*	e.e. using Lipase from *Pseudomonas*	Product[a]	Absolute Configuration[b]	e.e. using Lipase from *Candida*	e.e. using Lipase from *Pseudomonas*
2b	2a*	1R, 2R, 4R	90[c,d,e]	92[f]	*ent*-2b*	1S, 2S, 4S	>97[f,g]	62[f]
2c	2a*	1R, 2R, 4R	85[d,f]	>97[f]	*ent*-2c*	1S, 2S, 4S	89[f]	87[f]
2d	2a*	1R, 2R, 4R	85[f]	>97[f]	*ent*-2d*	1S, 2S, 4S	78[f]	87[f]
3c	3a*	1R, 2R, 4S, 5S, 6R	94[c,f]	—	*ent*-3c*	1S, 2S, 4R, 5S, 6S	>97[g]	—
4b	4a*	1S, 2R, 4R	75[d,f]	—	*ent*-4b*	1R, 2S, 4S	52[h]	—
4c	4a*	1S, 2R, 4R	59[d]	—	*ent*-4c*	1R, 2S, 4S	72[h]	—
6c	6a*	1R, 2R, 6S, 7S, 8R	85[c,f]	—	*ent*-6c*	1S, 2S, 6R, 7S, 8S	83[g]	—
2c[i]	2a*	1R, 2R, 4R	—	>97[f]	*ent*-2c*	1S, 2S, 4S	>97[f,g]	—

[a] See note 5a. [b] Numbering see scheme II. [c] Determined by ^{1}H-NMR spectroscopy using $Eu(hfc)_3$. [d] Determined by ^{19}F-NMR spectroscopy of the MTPA-ester[28]. [e] Determined by GLC-analysis of camphanic acid esters[2a]. [f] Determined by comparison of optical rotation with enantiomerically pure material. [g] Determined by ^{1}H-NMR spectroscopy using $Eu(hfc)_3$ after hydrolysis to its corresponding alcohol. [h] Determined by ^{19}F-NMR spectroscopy of the MTPA-ester after hydrolysis to its corresponding alcohol. [i] Alteration of enzyme (*Tandem*-experiment), see: 3) Preparative Aspects.

The absolute configuration of products was determined as follows:

2a* was correlated with (+)-(1*R*,4*R*)-norborn-5-en-2-one (**1***), the absolute configuration of which is well established[2a-c,4b,24b]. **3a*** and **6a*** were both correlated by comparison of their behaviour in ^{1}H-NMR spectroscopy using $Eu(hfc)_3$ and the optical rotation value with authentical material synthesized independently from **2a***. The configuration of **4a*** was determined by comparison of the sense of optical rotation with material obtained by hydrogenation of **2a***. All esters from table II were hydrolysed to their corresponding alcohols for determination of absolute configuration.

While lipase from *Candida cylindracea* showed sufficient activity on all substrates listed in table II, *Pseudomonas sp.* lipase exhibited a satisfying speed of conversion only on substrates **2b-d**. By variation of the acyl chain length of the esters of alcohol **2a** both lipases showed an increase of the hydrolytic rate from acetate **2b** slower than butanoate **2c** being equal to octanoate **2d**. To accomplish the desired degree of conversion within a few hours it was found that hydrolyses using *Pseudomonas sp.* lipase required an equal weight amount of enzyme versus substrate, whereas lipase from *Candida cylindracea* could be employed in quantities of 5-10% of substrate weight. Regarding the enantiomeric excess of products an interesting pattern was observed: Upon hydrolyses with substrates **2b-d** up to 40% conversion *Pseudomonas sp.* lipase showed a better enantioselectivity than lipase from *Candida cylindracea*. This behaviour was reversed if the recovered ester was further hydrolysed until 60% conversion (in total) was accomplished. Epoxide **3c** and dioxolane **6c** as well were both enzymatically resolved with good to excellent enantiomeric excess. A lower enantioselection was observed, however, with norbornane systems **4b,c**. It is interesting to note that on substrates of type A and C invariably esters possessing an *R*-configurated alcoholic center were preferably cleaved by both of the lipases.

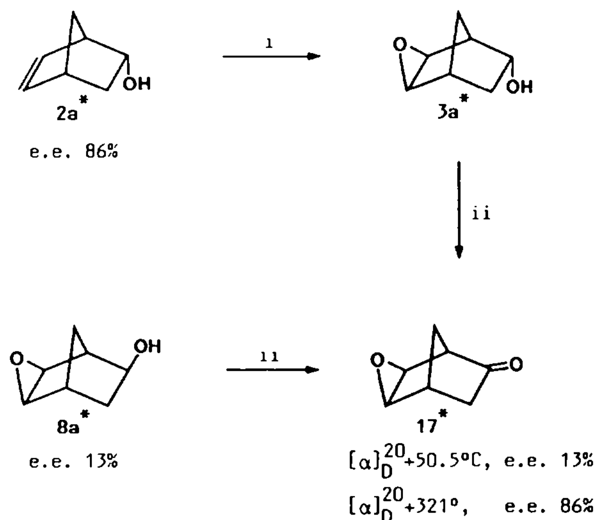
TABLE III: Enzymatic hydrolyses of substrates of type B,D, and F (see schemes II and III) by *Candida cylindracea* lipase.

Substrate[a]	Conversion 40%			Conversion 60%		
	Product[a]	Absolute Configuration[b]	e.e.[c]	Product[a]	Absolute Configuration[b]	e.e.[d]
7c	7a	—	0	7c	—	0
8c	8a*	1R, 2R, 4S, 5S, 6S	13	*ent*-8c*	1S, 2S, 4R, 5S, 6R	14
9b	9a*	1S, 2S, 4R	17	*ent*-9b*	1R, 2R, 4S	10
9c	9a*	1S, 2S, 4R	16	*ent*-9c*	1R, 2R, 4S	22
11b	11a*	1S, 2S, 6R, 7R, 8R	51	*ent*-11b*	1R, 2R, 6S, 7R, 8S	22
11c	11a*	1S, 2S, 6R, 7R, 8R	39	*ent*-11c*	1R, 2R, 6S, 7R, 8S	64
14c	14a*	1S, 2R, 6S, 7R, 8R	22	*ent*-14c*	1R, 2S, 6R, 7R, 8S	14

[a] See table II, footnote a. [b] Numbering see schemes III and IV. [c] Determined by ^{19}F-NMR spectroscopy of the MTPA-esters[2a]. [d] Determined by ^{19}F-NMR spectroscopy of the MTPA-esters after hydrolysis to its corresponding alcohol.

The absolute configuration of products listed in table III was determined as follows:

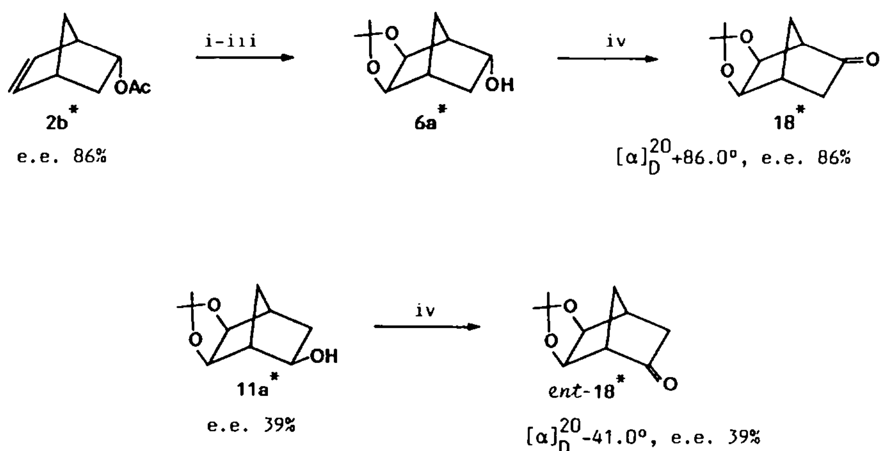
SCHEME IV



i) MCPBA, CH_2Cl_2. ii) PDC, CH_2Cl_2.

8a* (e.e.13%) was oxidized to give ketone 17* which in turn was independently synthesized from 2a* (e.e.86%) in two steps. Sense and value of optical rotation of both samples of 17* were in excellent agreement. 9a* was correlated with literature data[24a-c].

SCHEME V



i) OsO_4/N-methylmorpholine-N-oxide·H_2O, acetone. ii) 2,2-Dimethoxypropane/H^+. iii) NaOMe/MeOH. iv) PDC, CH_2Cl_2.

The absolute configuration of 11a* was determined by chemical synthesis of ketone 18* and *ent*-18* either starting from 2b* or 11a* as depicted in scheme V. Evaluation of the configuration of 14a* was accomplished by ^{19}F-NMR spectroscopy of the MTPA-ester with addition of Eu(fod)$_3$[25]. Esters listed in table III were hydrolysed to their corresponding alcohols for determination of absolute configuration.

As shown in table I, only *Candida cylindracea* lipase was able to hydrolyse esters possessing *exo*-configurated alcoholic centers and, in general, only low to moderate enantiomeric excess was found in the enzymatic resolution of substrates of type B, D and F. While the enantioselection was lost completely for substrate 7c, the only enantiomeric excess greater than 50% was observed for dioxolanes 11b and 11c.

It is interesting to note that *Candida cylindracea* lipase looses its clear preference for the cleavage of *R*-configurated ester groups (observed in substrates possessing *endo*-configuration, substrates of type A and C) if *exo*-esters (type B, D and F) are hydrolysed:

Depending on the steric properties of additional substituents present in substrates of type B, D and F both *R*- and *S*-esters may be cleaved preferentially coming along with a general decline in enantioselection. Obviously an *endo* configuration at the alcoholic center is required for a high enantioselection as may be deduced from tables II and III.

3) PREPARATIVE ASPECTS

Upon examination of the enzymatic resolution of substrate 2c (see table II) it was found that best results in conversions up to 40% were obtained with lipase from *Pseudomonas sp.* (2a* from 2c or 2d, e.e.>97%) whereas *Candida cylindracea* lipase exhibited a better enantioselection during the second

hydrolytic step (*ent*-2b* from 2b, e.e.>97%). From these observations we concluded that changing the enzyme between the hydrolytic steps should lead to the highest optical purities of *alcohol and ent-ester* in a single trial.

This *Tandem*-enzyme experiment (last entry of table II) was performed as follows: Hydrolysis of 2c using *Pseudomonas sp.* lipase (40% conversion) gave alcohol 2a* in >97% optical purity. Further conversion of the remaining ester up to 60% by lipase from *Candida cylindracea* led to *ent*-2c* in >97% enantiomeric excess as well. By means of this alteration of enzymes *both* of the enantiomers were obtained in a *single* run in excellent optical purity.

Upon upscaling the enzymatic resolution of *endo*-norborn-5-en-2-ol (2a) to batches of one mole two problems had to be solved:

a) In contrast to its esters 2b-d, *endo*-norborn-5-en-2-ol (2a) exhibited a remarkable volatility.

b) Large runs requiring equal amounts of enzyme versus substrate weight (particularly with *Pseudomonas sp.* lipase) tended to form emulsions during extractive workup.

Hence upscaling only was performed with lipase from *Candida cylindracea* where 5% of enzyme versus substrate weight were sufficient for a reasonable rate of conversion. Taking into account the high volatility of 2a the following procedure was elaborated:

One mole of *endo*-norborn-5-en-2-yl butyrate (2c) was hydrolysed using *Candida cylindracea* lipase (5% of weight). At a conversion of 40% the mixture of 2a* and *ent*-2a* was extracted with methylene chloride. The alcohol 2a* was directly acetylated with acetic anhydride . The mixture of acetate 2b* and butyrate *ent*-2c* thus obtained was separated by distillation using a split-tube column avoiding the loss-causing chromatographic separation. By means of this procedure even larger batches may be handled in practice.

While our method of preparing chiral bicyclic alcohols and esters has been already employed in the synthesis of enantiomerically pure carbocyclic nucleoside analogues[1i], the likewise obtained ketones 1*, 17* and 18* are of considerable importance for preparative purposes:

Brefeldin A may be synthesized from norbornenone 1*[2d].Since racemic ketone 18 only recently has been used as starting material for the synthesis of carbocyclic nucleoside analogues[1g], the access to enantiomerically pure derivatives is now opened with 18*.

CONCLUSIONS

We have shown that both enantiomers of a number of bicyclic chiral alcohols, esters and ketones of considerable synthetic importance may be obtained in amounts sufficient for multistep syntheses of enantiomerically pure compounds by enzymatic resolution of racemic esters.

ACKNOWLEDGEMENT

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EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter in $CHCl_3$ solution. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker WH 90 or a Varian XL 200 spectrometer. Chemical shifts are reported in δ from TMS as internal standard. s=singlet, d=dublet, t=triplet, m=multiplet and br=broad signal. ^{19}F-NMR measurements were performed on a Bruker WH 90 spectrometer in $CDCl_3$ using CCl_3F as internal standard. Reactions were monitored by TLC using silica gel Merck 60 F_{254} plates, compounds were visualized by spraying with vanilline/sulfuric acid. For column chromatography silica gel Merck 60 was used. *Extractive workup* denotes washing with *N* HCl, sat. $NaHCO_3$ and brine unless otherwise stated. Elemental analyses (C, H, N) for all novel compounds were within 0.4% of calculated values. GLC analyses were performed on a Hewlett Packard 7620 A (2.2m packed column, 3% OV 225 on Supelcoport 100/120) or a Dani 8500 chromatograph (25m capillary column, CP-wax-52 CB), both equipped with FID.

General preparation[7] of esters 2b, 2c, 7b, 7c, 11b, 14b and 14c

A solution of the corresponding alcohol (20mmol) in CH_2Cl_2 (50ml), acid anhydride (26mmol), pyridine (5ml) and DMAP (0.05g) was stirred at room temperature until conversion was complete (TLC, 2-16 hours).Excess anhydride was quenched by addition of MeOH (5ml) and the mixture was subjected to extractive workup. After removal of the solvent, the esters were distilled in vacuo.

(1*RS*,2*RS*,4*RS*)-Bicyclo[2.2.1]hept-5-en-2-yl acetate (2b): yield 90%, bp 72°C/14mm. ^{1}H-NMR: 0.87 (dt, J=12 and 4Hz, 1H), 1.25-1.40 (m, 3H), 1.93 (s, 3H), 2.0-2.3 (m, 1H), 2.8 (br s, 1H), 3.15 (br s, 1H), 5.02 (m, 1H), 5.9 (m, 1H), 6.3 (m, 1H).

(1*RS*,2*RS*,4*RS*)-Bicyclo[2.2.1]hept-5-en-2-yl butyrate (2c): yield 91%, bp 112-3°C/23mm. ^{1}H-NMR: 0.75-1.05 (m, 4H), 1.25-1.85 (m, 4H), 2.00-2.25 (m, 3H), 2.85 (br s, 1H), 3.15 (br s, 1H), 5.32 (dt, J=8 and 3Hz, 1H), 5.97 (m, 1H), 6.36 (m, 1H).

(1*RS*,2*SR*,4*RS*)-Bicyclo[2.2.1]hept-5-en-2-yl acetate (7b): yield 89%, bp 85-7°C/23mm. ^{1}H-NMR: 1.2-1.8 (m, 4H), 2.03 (s, 3H), 2.84 (m, 2H), 4.62 (m, 1H), 5.92 (m, 1H), 6.18 (m, 1H).

(1*RS*,2*SR*,4*RS*)-Bicyclo[2.2.1]hept-5-en-2-yl butyrate (7c): yield 87%, bp 115°C/25mm. ^{1}H-NMR: 0.95 (t, J=7Hz, 3H), 1.31 (m, 1H), 1.37-1.88 (m, 5H), 2.27 (t, J=7Hz, 2H), 2.86 (m, 2H), 4.68 (m, 1H), 5.98 (m, 1H), 6.25 (m, 1H).

(1*RS*,2*RS*,6*SR*,7*RS*,8*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.$0^{2,6}$]dec-8-yl acetate (11b): yield 80%, bp 120-30°C/12mm. ^{1}H-NMR: 1.28 (s, 3H), 1.44 (s, 3H), 1.35-1.95 (m, 4H), 2.04(s, 3H), 2.18-2.44 (br s, 2H), 4.02 (br s, 2H), 4.53 (m, 1H).

(1*RS*,2*SR*,6*RS*,7*SR*,8*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.$0^{2,6}$]dec-8-yl acetate (14b): yield 87%, bp 82-5°C/0.015mm. ^{1}H-NMR: 1.33 (s, 3H), 1.52 (s, 3H), 1.54-1.77 (m, 2H), 1.87-1.97 (m, 1H), 2.05 (s, 3H), 2.25-2.67 (m, 3H), 4.33-4.50 (m, 2H), 5.11 (m, 1H).

(1*RS*,2*SR*,6*RS*,7*RS*,8*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.$0^{2,6}$]dec-8-yl butyrate (14c): The esterification mixture was refluxed for 24h. Yield 90%, bp 102-4°C/0.04mm. ^{1}H-NMR: 0.95 (t, J=7Hz, 3H), 1.1-1.9 (m, 6H), 1.32 (s, 3H), 1.52 (s, 3H), 2.25 (t, J=7 Hz, 2H), 2.25-2.6 (m, 2H), 4.42-4.55 (m, 2H), 5.14 (m, 1H).

Preparation of esters 6b and 11c

The corresponding ester (20mmol) in MeOH (20ml) was added to a solution of sodium (0.23g, 0.01mol) in MeOH (80ml). After stirring overnight at room temperature the solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2. Extractive workup, drying and evaporation gave the alcohols 6a and 11a, respectively, as crystalline solids. Analytical samples were purified by sublimation.

(1*RS*,2*RS*,6*SR*,7*SR*,8*RS*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.$0^{2,6}$]decan-8-ol (6a): 93% yield, mp 58-9°C. ^{1}H-NMR: 0.8 (dt, J=12 and 4 Hz, 1H), 1.05-2.05 (m, 5H), 1.30 (s, 3H), 1.47 (s, 3H), 1.60 (s, 1H, D_2O-exchangeable), 4.14 (d, J=7 Hz, 1H), 4.30 (m, 1H), 4.69 (d, J=7 Hz, 1H).

(1*RS*,2*RS*,6*SR*,7*SR*,8*RS*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.$0^{2,6}$]decan-8-ol (11a): 91% yield, mp 52-4°C. ^{1}H-NMR: 1.0-1.8 (m, 4H), 1.27 (s, 3H), 1.44 (s, 3H), 1.76 (s, 1H, D_2O-exchangeable), 2.27 (br s, 2H), 3.72 (m, 1H), 3.94 (br s, 2H).

General procedure for the preparation of epoxides 3a-c and 8a-c

To a cooled (4°C) solution of the corresponding alcohol or ester (20 mmol) in CH_2Cl_2 (5ml) m-chloroperbenzoic acid (4.2g, 85%, 21mmol) dissolved in CH_2Cl_2 (60ml) was added. When the starting material was consumed (TLC) the solids were filtered off and the solution was subjected to extractive workup. Purification by chromatography and subsequent distillation or sublimation gave the oxiranes.

(1*RS*,2*RS*,4*SR*,5*SR*,6*RS*)-3-Oxatricyclo[3.2.1.0^{2,4}]octan-6-ol (3a): yield 40%, mp 170-2°C (lit.160-2°C[4]), homogeneous by GLC analysis and ^{1}H-NMR. ^{1}H-NMR: 0.87 (d, J=10 Hz, 1H), 1.05 (dt, J=12 and 3Hz, 1H), 1.26 (d, J=10 Hz, 1H), 1.66 (br s, 1H, D_2O-exchangeable), 2.03, (m, 1H), 2.45 (br s, 1H), 2.61 (br s, 1H), 3.30 (d, J=4 Hz, 1H), 3.45 (d, J=4 Hz, 1H), 4.40 (m, 1H).

(1*RS*,2*RS*,4*SR*,5*RS*,6*RS*)-3-Oxatricyclo[3.2.1.0^{2,4}]oct-6-yl acetate (3b): yield 76%, mp 53-4°C, bp 121°C/16mm. ^{1}H-NMR: 0.7-1.5 (m, 3H), 1.9-2.8 (m, 3H), 2.20 (d, J=4Hz, 1H), 2.34 (d, J=4 Hz, 1H), 2.70 (s, 3H), 5.04 (m, 1H).

(1*RS*,2*RS*,4*SR*,5*RS*,6*RS*)-3-Oxatricyclo[3.2.1.0^{2,4}]oct-6-yl butyrate (3c): yield 87%, bp 80°C/0.1mm. ^{1}H-NMR: 0.7-1.85 (m, 8H), 1.95-2.4 (m, 3H), 2.44 (br s, 1H), 2.78 (br s, 1H), 3.23 (d, J=4 Hz, 1H), 3.32 (d, J=4 Hz, 1H), 5.05 (m, 1H).

(1*RS*,2*RS*,4*SR*,5*SR*,6*SR*)-3-Oxatricyclo[3.2.1.0^{2,4}]octan-6-ol (8a): yield 50%, mp 157-9°C. ^{1}H-NMR: 1.05-2.0 (m, 4H), 2.1 (br s, 1H, D_2O-exchangeable), 2.5 (br s, 2H), 3.01 (d, J=4 Hz, 1H), 3.1 (d, J=4 Hz, 1H), 4.0 (m, 1H).

(1*RS*,2*RS*,4*SR*,5*SR*,6*SR*)-3-Oxatricyclo[3.2.1.0^{2,4}]oct-6-yl acetate (8b): yield 88%, bp 105-15°C/14mm[2a]. ^{1}H-NMR: 1.0-2.0 (m, 4H), 2.02 (s, 3H), 2.45-2.65 (m, 2H) 3.08 (br s, 2H), 4.66 (m, 1H).

(1*RS*,2*RS*,4*SR*,5*SR*,6*SR*)-3-Oxatricyclo[3.2.1.0^{2,4}]oct-6-yl butyrate (8c): yield 89%, bp 115-25°C/1.5mm[2a]. ^{1}H-NMR: 0.94 (t, J=7 Hz, 3H), 1.08-2.25 (m, 8H), 2.4-2.65 (m, 2H), 3.08 (br s, 2H), 4.68 (m, 1H).

General procedure for the *cis*-dihydroxylation and transacetalisation

To a solution of the corresponding alkene (50mmol) in acetone (50ml) were added N-methylmorpholine-N-oxide·H_2O (14.8g, 110mmol) and OsO_4 (25mg). After stirring at room temperature for 24 h $NaHSO_3$ (1g) was added and the mixture was filtered trough Celite. The solvent was evaporated, the residue taken up in CH_2Cl_2 and extracted with *N* HCl. The aqueous layer was saturated with NaCl and extracted again. After drying of the combined organic layers (Na_2SO_4) the volatiles were removed *in vacuo* to give the crude diols as oils. Analytical samples were obtained by chromatography. The crude material was taken up in 2,2-dimethoxypropane (50ml) and p-toluenesulfonic acid·H_2O (0.1g) was added. When conversion was complete (TLC) the solution was evaporated, the residue taken up in CH_2Cl_2 and subjected to extractive workup. The organic layer was taken to dryness and the remaining products were purified by distillation.

(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-2,3-Dihydroxybicyclo[2.2.1]hept-5-yl acetate (5b): yield 80%[2a]. ^{1}H-NMR: 0.8 (dt, J=12 and 4 Hz, 1H), 1.1-1.25 (m, 5H), 3.15 (m, 2H, D_2O-exchangeable), 3.80 (d, J=7 Hz, 1H), 4.23 (d, J=7 Hz, 1H), 4.90 (m, 1H).

(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-2,3-Dihydroxybicyclo[2.2.1]hept-5-yl butyrate (5c): yield 95%[2a]. ^{1}H-NMR: 0.73-1.05 (m, 4H), 1.1-2.1 (m, 4H), 2.15-2.55 (m, 5H), 3.44 (br d, 1H, D_2O-exchangeable), 3.61 (br d, 1H, D_2O-exchangeable), 3.80 (t, J=7 Hz, 1H), 4.22 (t, J=7 Hz, 1H), 4.95 (m, 1H).

(1*RS*,2*RS*,6*SR*,7*SR*,8*RS*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-yl acetate (6b): yield 70%[2b], bp 84°C/0.04mm. ^{1}H-NMR: 0.83 (dt, J=12 and 4 Hz, 1H), 1.1-2.5 (m, 5H), 1.40 (s, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 4.14 (d, J=7 Hz, 1H), 4.50 (d, J=7 Hz, 1H), 5.0 (m, 1H).

(1*RS*,2*RS*,6*SR*,7*RS*,8*RS*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-yl butyrate (6c): yield 79%[2b], bp 94°C/0.04mm. ^{1}H-NMR: 0.8-0.95 (m, 4H), 1.5-1.85 (m, 3H), 1.45 (s, 3H), 1.9-2.40 (m, 4H), 2.55 (br d, J=6 Hz, 1H), 4.14 (d, J=6 Hz, 1H), 4.48 (d, J=6 Hz, 1H), 4.98 (m, 1H).

(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-2,3-Dihydroxybicyclo[2.2.1]hept-5-yl butyrate (10c): yield 87%[2a]. ^{1}H-NMR: 0.92 (t, J=7 Hz, 1H), 1.2-2.0 (m, 6H), 2.2-2.95 (m, 4H) 3.4-3.6 (m, 2H, D_2O-exchangeable), 3.68 (s, 2H), 4.57 (m, 1H).

(1*RS*,2*RS*,6*SR*,7*RS*,8*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-yl butyrate (11c): yield 75%[2b], bp 99-101°C/25mm. ^{1}H-NMR: 0.92 (t, J=7 Hz, 3H), 1.25 (s, 3H), 1.45 (s, 3H), 1.35-2.0 (m, 6H), 2.20-2.35 (m, 4H), 4.0 (br s, 2H), 4.53 (m, 1H).

Catalytic hydrogenation of butyrates 4c and 9c

Hydrogenation of 4b and 9c was accomplished with H_2/Pd-C (5%) in MeOH.

(1*RS*,2*RS*,4*RS*)-Bicyclo[2.2.1]hept-2-yl butyrate (4c): 90% yield, bp 108-10°C /16mm. ^{1}H-NMR: 0.95 (m, 4H), 1.13-2.56 (m, 14H), 4.95 (m, 1H).

(1*RS*,2*SR*,4*RS*)-Bicyclo[2.2.1]hept-2-yl butyrate (9c): 83% yield, bp 110-12°C/

17mm. ^{1}H-NMR: 0.75 (t, J=7 Hz, 3H), 1.05-1.9 (m, 10H), 2.1-2.4 (m, 4H), 4.60 (m, 1H).

endo-Bicyclo[2.2.1]hept-5-en-2-ol (2a)

To a cooled solution (-10°C) of norborn-5-en-2-one[2d] (1) (108g, 1.0mol) in MeOH (1l) was added $NaBH_4$ (13.3g, 0.35mol) in small portions at -10 to -7°C internal temperature. After addition was complete, the mixture was quenched with *N* HCl (800ml), saturated with NaCl and extracted with CH_2Cl_2 (3x400ml). The organic layer was separated and washed with saturated $NaHCO_3$ solution (300 ml), dried over Na_2SO_4 and evaporated (60°C, 12mm) to give 92.5-97.0g (84-88%) of 2a. No *exo*-alcohol could be detected by GLC-analysis.

(1*RS*,2*RS*,4*RS*)-Bicyclo[2.2.1]hept-5-en-2-yl octanoate (2d)

A mixture of 2a (4.19g, 38mmol) in CH_2Cl_2 (100ml), octanoic acid (12.1g, 84mmol), pyridine (6ml), DCC (15.7g, 76mmol) and DMAP (0.05g) was stirred at room temperature for 2 h. *N* HCl (50ml) was added and stirring was continued for 30 min. The precipitate was filtered, the organic layer was subjected to extractive workup and dried (Na_2SO_4). Evaporation of the solution gave an oil which was purified by column chromatography (n-hexane/ethyl acetate 19:1). Distillation gave 8.1g (90%) of 2d (bp 106-8°C/0.5mm). ^{1}H-NMR: 0.73-1.06 (m, 4H), 1.15-1.80 (m, 12H), 2.0-2.6 (m, 3H), 2.83 (br s, 1H), 3.15 (br s, 1H). 5.29 (dt, J=8 and 3Hz, 1H), 5.97 (m, 1H), 6.32 (m, 1H).

(1*RS*,2*RS*,6*SR*,7*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-ene (13)

To a stirred solution of diol 12[28] (15g, 0.12mmol) in 2,2-dimethoxypropane (75ml), HBF_4 (1.75ml, 54% in ether) was added. After stirring for 30 min at room temperature the reaction was quenched by addition of excess Na_2CO_3. Then the solids were removed by filtration and washed once with ether. The combined organic solvents were evaporated and the crude product was distilled to yield 17.7g (90%) of 13, bp 64-8°C/11mm. ^{1}H-NMR: 1.27 (s, 3H), 1.33 (s, 3H), 1.54 (dd, J=18 and 8 Hz, 2H), 2.98 (br s, 2H), 4.73 (br s, 2H), 6.13 (br s, 2H).

(1*RS*,2*SR*,6*RS*,7*SR*,8*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decan-8-ol (14a)

Dioxolane 13 (16.6g, 0.1mol) was hydroborated in THF (100ml) following the standard procedure[26] which includes *in situ* generation of B_2H_6 from dimethyl sulfate (7.6g, 60mmol) and sodium borohydride (2.3g, 60mmol). Oxidative workup (H_2O_2, NaOH) afforded the crystalline alcohol 14a (17.5g, 95%). An analytical sample was prepared by sublimation, mp 76°C. ^{1}H-NMR: 1.30 (s, 3H), 1.46 (s, 3H), 1.54-1.96 (m, 4H), 2.23-2.50 (m, 3H), 4.18-4.50 (m, 3H).

(1*RS*,2*SR*,6*RS*,7*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decan-8-one (15)

As described for ketone 18 alcohol 14a (7.20g, 39mmol) was oxidized with PDC (25g, 66mmol) to give ketone 15 (5.0g, 70%), mp 59°C. ^{1}H-NMR: 1.30 (s, 3H), 1.40 (s, 3H), 1.8-2.9 (m, 6H), 4.70 (m, 2H).

(1*RS*,2*SR*,6*RS*,7*SR*,8*RS*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decan-8-ol (16a)

Ketone 15 (3.81g, 21mmol) was reduced in MeOH (40ml) with $NaBH_4$ (0.53g, 15 mmol) as described for 2a to furnish 16a (3.57g, 93%), mp 41-42°C. ^{1}H-NMR: 1.35 (s, 3H), 1.5-2.0 (m, 4H), 1.65 (s, 3H), 2.25-2.4 (m, 2H), 4.2-4.8 (m, 3H), 4.35 (s, 1H, D_2O-exchangeable).

(1*RS*,2*SR*,6*RS*,7*SR*,8*RS*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-yl acetate (16b)

To a solution of alcohol 16a (2.50g, 13.6mmol) in pyridine (15ml) were added acetic anhydride (2.65g, 29mmol) and DMAP (1g). After keeping the mixture for 48h at 60°C, the solvent was removed *in vacuo* and the residue was subjected to extractive workup. The organic phase was evaporated and the remaining oil was filtered through silica gel (n-hexane/ethyl acetate 2:1) and distilled. Yield 2.60g (85%), bp 80°C/0.1mm. ^{1}H-NMR: 1.33 (s, 3H), 1.54 (s, 3H), 1.5-2.1 (m, 5H), 2.04 (s, 3H), 2.4 (br m, 1H), 2.8 (br m, 1H), 3.5 (m, 2H), 5.0 (m, 1H).

(1*RS*,2*RS*,4*SR*,5*SR*)-3-Oxatricyclo[3.2.1.0^{2,4}]octan-6-one (17)

A mixture of alcohol 3a (0.40g, 3.2mmol) and finely powdered PDC (2.4g, 6.4mmol) in CH_2Cl_2 (20ml) was stirred at room temperature for 18 h. The solution was filtered through silica gel, subjected to extractive workup and dried (Na_2SO_4). Evaporation gave a solid which was purified by sublimation (0.15mm/60°C). Yield 0.33g (84%), mp 138-40°C. (lit. 139-40°C[27]). ^{1}H-NMR: 1.1-1.37 (m, 1H), 1.6-2.1 (m, 3H), 2.8-2.9 (br m, 2H), 3.27 (d, J=5 Hz, 1H), 3.46 (d, J=5 Hz, 1H).

(1*RS*,2*RS*,6*SR*,7*SR*)-4,4-Dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decan-8-one (18).
As described above ketone 18 was prepared from alcohol 6a (4.23g, 23mmol) and PDC (15.05g, 40mmol) in CH_2Cl_2 (100ml). Sublimation (0.10mm/50°C) gave 4.0g (96%) of ketone 18, mp 74-6°C (lit. 74-5°C[19]). ^{1}H-NMR: 1.32 (s, 3H), 1.50 (s, 3H), 1.6-2.3 (m, 4H), 2.7 (br s, 2H), 4.3 (m, 2H).

General procedure for the screening of enzymes

To a solution of lipase (10mg) in phosphate buffer (0.1*M*, 2ml, pH 7.5) the ester (10mg) was added. The mixture was then agitated on a rotary shaker at about 200 rpm. Analytical samples were periodically withdrawn and directly applied on TLC plates for analysis.

For a general procedure of enzymatic resolutions for batches of 1-10g of substrate see reference 4b.

Preparation of (+) and (-)-*endo*-norborn-5-en-2-ol on a molar scale
In a 10l Quickfit vessel equipped with an efficient mechanical stirrer $NaH_2PO_4 \cdot H_2O$ (11.6g) was dissolved in 4l of distilled water. The pH was then adjusted to 7.2 by addition of *N* sodium hydroxide solution from a burette. Lipase from *Candida cylindracea*[11] (9.0g, 5% of substrate weight) was added with stirring and the mixture was allowed to equilibrate for about 15 min while the pH was maintained at 7.2. Then *endo*-norborn-5-en-2-yl butyrate (2c, 1.0mol) was added in one portion. By means of *N* sodium hydroxide solution from the burette[22] the pH was kept at 7.2 with vigorous stirring. When a conversion of 40% was accomplished (400ml of *N* NaOH consumed) the reaction was stopped by addition of CH_2Cl_2 (2l). Stirring was discontinued and the phases were separated (occasionally appearing emulsions were broken by centrifugation at 1000-3000g). After repeated extraction of the aqueous phase with CH_2Cl_2 (3x1l) the combined organic phase was dried (Na_2SO_4, then mol sieve 4A for 18 h). To this solution were added Ac_2O (76ml, 0.78mol), pyridine (100ml) and DMAP (2g). After stirring for 24 h at room temperature excess acid anhydride was destroyed by addition of MeOH (100ml) and stirring was continued for 1 h. The mixture was then subjected to extractive workup, dried (Na_2SO_4) and the volatiles were evaporated. By distillation using a split tube column (70 theoretical plates) there was obtained:
(1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl acetate (2b*): bp 72-5°C/13mm, 47g, 77%, $[\alpha]_D^{20}$ +108.8° (c 1.69, $CHCl_3$), e.e. 85%.
(1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl butyrate (*ent*-2c*): bp 96-8°C/13mm, 92g, 85%.
The latter material was subjected to repeated hydrolysis as described above until an additional 20% conversion was accomplished. Esterification and distillation gave:
Acetate 2b: 12.6g, 81%, e.e. very low.
Butyrate *ent*-2c: 76g, 83%, $[\alpha]_D^{20}$ -109.5° (c 2.11, $CHCl_3$), e.e. 89%.

TABLE IV: Optical rotation values in $CHCl_3$ solution.

Compound	$[\alpha]_D^{20}$ [°]	c[g/100ml]	e.e. [%]	notes
2a*	+162	19	>97	a,b
ent-2b*	-129	4.6	>97	a,b
ent-2c*	-120	3.2	>97	a
ent-2d*	-86.5	3.6	87	a
3a*	+46.5	1.9	94	a
ent-3c*	-13.4	4.2	>97	a
4a*	+1.7	2.8	75	a
ent-4b*	-<1	3.1	52	a
ent-4c*	-<1	3.0	72	a
6a*	+5.4	6.4	85	a
ent-6c*	+6.6	3.6	83	a
8a*	+3.2	6.1	13	c
9a*	-<1	5.7	17	c,d
11a*	+3.1	3.9	51	c
ent-11b*	+1.2	2.1	22	c
ent-11c*	+6.1	3.6	64	c
14a*	+1.8	6.3	22	e
17*	+321	2.1	86	f
18*	+86.0	3.4	86	g

a) See scheme II and table II. b) See ref. 4b. c) See scheme II and table III. d) See ref. 24c. e) See scheme III and table III. f) See scheme IV. g) Scheme V. *ent*-8c*, *ent*-9b*, *ent*-9c* and *ent*-14c* had very low values.

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5a Throughout this paper all enantiomerically enriched compounds are designated with an asterisk (*), the other enantiomer is indicated by the prefix *ent*. Compounds without are racemic. The absolute configuration of the enantiomer drawn in schemes I-III corresponds to the starred series, except for 11* and 14*, where *ent*-11* and *ent*-14* are shown.
 b The following abbreviations are used throughout this paper: Py=pyridine, DMAP=4-dimethylaminopyridine, DCC=N,N'-dicyclohexylcarbodiimide, MCPBA=3-chloroperbenzoic acid, MTPA=2-methoxy-2-trifluoromethylphenyl acetic acid, PDC=pyridinium dichromate, Eu(hfc)$_3$=Tris[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato]-europium(III).
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