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# BIOCATALYTIC PREPARATION OF BICYCLO[3.2.0]HEPTANE DERIVATIVES+

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**Abstract:** Bicyclo[3.2.0]hept-2-en-6-ols, central building blocks for the synthesis of chiral cyclobutane and -pentane systems, were prepared with up to >99% e.e. by lipase catalysed resolution of their acetates, butyrates, or isobutyrates. Substituents at C-7 vicinal to the reaction site reduced both enantioselectivity and reaction rate, whereas variation of the acid moiety showed a smaller influence. Among the lipases tested, those from *Pseudomonas sp.* were shown to be superior to those from *Candida cylindracea*, *Mucor sp.* and porcine pancreas.

+*Dedicated to Prof. J. Schurz (University of Graz) on the occasion of his 65th birthday.*

## INTRODUCTION

Bicyclo[3.2.0]hept-2-en-6-ol and derivatives, which are easily accessible in large quantities *via* [2+2] cycloaddition of *in situ* formed ketenes to cyclopentadiene[1], have been shown to be central building units for the synthesis of cyclobutanoid and -pentanoid target molecules[2-4]. Therefore, a number of efforts have been undertaken during the past few years towards the preparation of enantiomerically pure material. The most important methods used are listed below:

1) *Enantioselective reduction* of bicyclo[3.2.0]hept-2-en-6-one derivatives using microorganisms, such as bakers' yeast or the fungus *Mortierella ramanniana*, led to product mixtures (either ketone/alcohol or *endo/exo* alcohols) which are difficult to separate on a large scale. Furthermore, the majority of these procedures are impeded by incomplete conversion and an unsufficient recovery rate due to the large amount of biomass used[5].

2) The use of *isolated dehydrogenases* brought some improvement for above mentioned reactions but the still limited coenzyme recycling represents a remarkable cost factor for large scale preparations[6,7].

3) Thus, *classical resolution techniques via* repeated crystallisation of diastereomeric derivatives is still the process preferred to above mentioned procedures[8,9]. (For a collection of these methods see reference 10).

4) A recent report on the *enzymatic resolution* of bicyclo[3.2.0]hept-2-en-6-yl acetate (**6a**) comes to the conclusion that the latter process is unlikely to compete with methods 1-3 due to a limited enantioselectivity (enantiomeric ratio $E \leq 50$) and reaction times longer than 15 hours[11].

Since it was recently shown that substrates possessing a rigid framework are well suited to study the influence of substrate structure on the enantioselection of enzymes[12], an investigation on the enzymatic resolution of bicyclo[3.2.0]hept-2-en-6-yl esters with respect to the

influence of substituents at C-7 vicinal to the alcoholic center was undertaken.

## RESULTS AND DISCUSSION

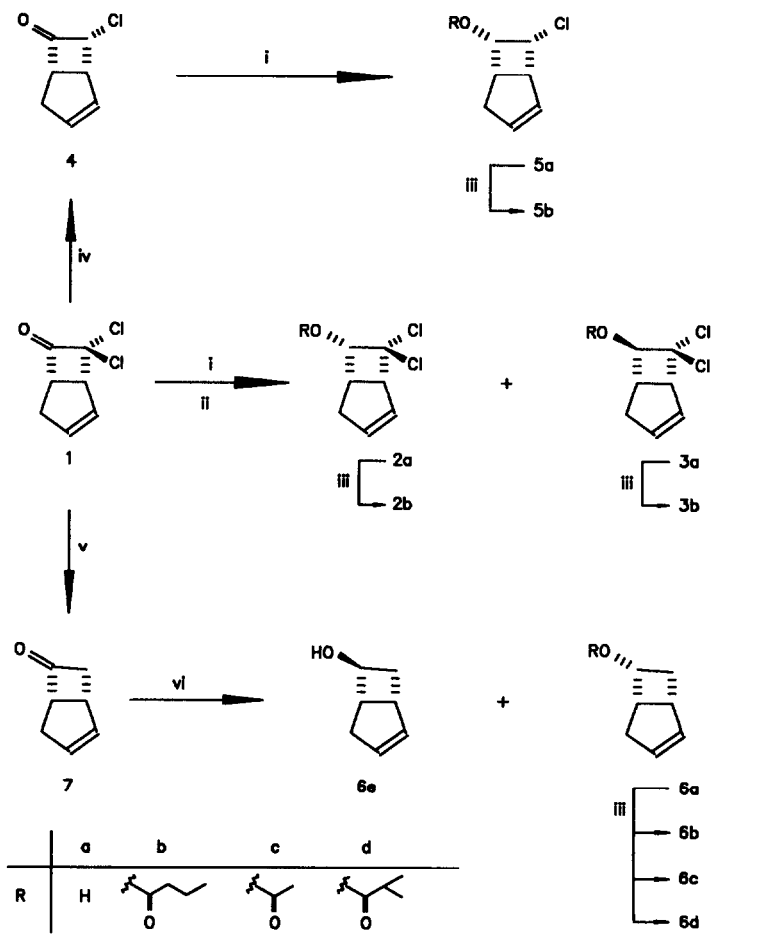
*Synthesis of Substrates*

To study the influence of substrate structure on the course of enzymatic hydrolysis, two groups of substrates were synthesized:

1) Butyrates **2b**, **3b** and **5b** bearing substituents vicinal to the alcoholic center and

2) esters **6b-6d** possessing various acyl moieties.

**Scheme 1**: Synthesis of substrates (all compounds are racemic, only one enantiomer is shown).



As depicted in scheme 1, all substrate esters were synthesized from the easily available dichloroketone 1 following literature procedures. Since it is known that esters possessing an *endo*-configurated alcoholic center are generally resolved with a better enantioselectivity than their corresponding *exo*-isomers[11,13], it was highly desirable to obtain pure *endo*-alcohols **2a**, **5a** and **6a**. Lithium aluminium hydride reduction proved to be highly selective in case of chloroketone **4**, giving **5a** as the sole product[14]. On the other hand, a low stereoselectivity was observed on the reduction of dichloroketone **1** and bicyclo[3.2.0]hept-2-en-6-one (**7**) which led to *endo/exo* mixtures of **2a/3a** and **6a/6e** (~3:1, ~9:1, resp.). Although in both cases *endo/exo* alcohols could be separated on a small scale by conventional column chromatography, this method proved to be extremely laborious upon scaleup. Therefore the *endo*-selectivity of the reduction of ketone **7** was optimized.

Table 1: *Endo/exo*-selectivity of reagents

| *Reagent* | *Solvent* | *Temperature [°C]* | *Ratio of* **6a/6e**[a] |
|---|---|---|---|
| $NaBH_4$ | MeOH | -40 | 86:14 |
| $NaBH_4/CeCl_3$ | MeOH | -40 | 80:20 |
| DIBAH | $PhCH_3$ | -60 | 82:18 |
| $LiAlH_4$ | THF | -80 | 93:7 |
| $LiAl(O\text{-}t\text{-}Bu)_3H$ | THF | 0 | 83:17 |
| $LiAl(O\text{-}t\text{-}Bu)_3H$ | THF | -30 | 89:11 |
| $LiAl(OCH_3)_3H$ | THF | 0 | >96:4 |
| L-Selectride® | THF | -80 | >99:1 |

[a] Determined by GLC analysis.

As shown in table 1, lithium trimethoxy aluminium hydride and L-Selectride® showed good selectivity, thus providing an easy access to pure *endo* alcohol **6a**. For large scale preparations the former reagent was used for economical reasons.

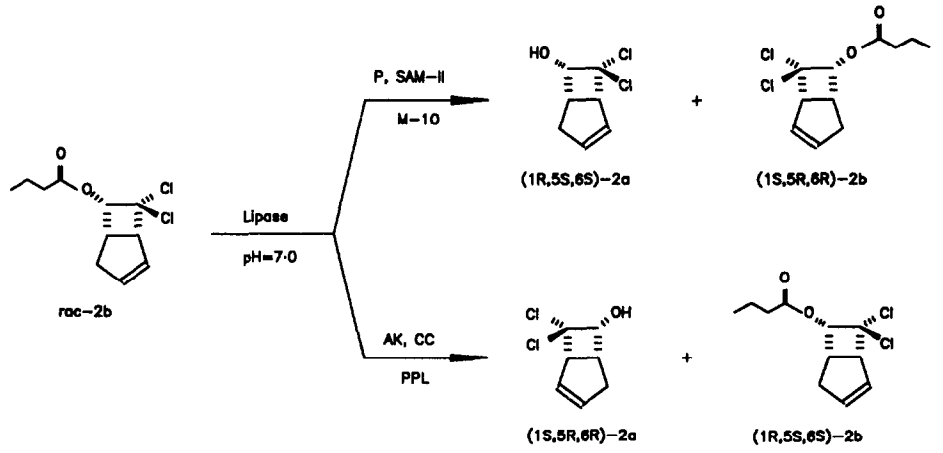
*Enzymatic Hydrolyses*

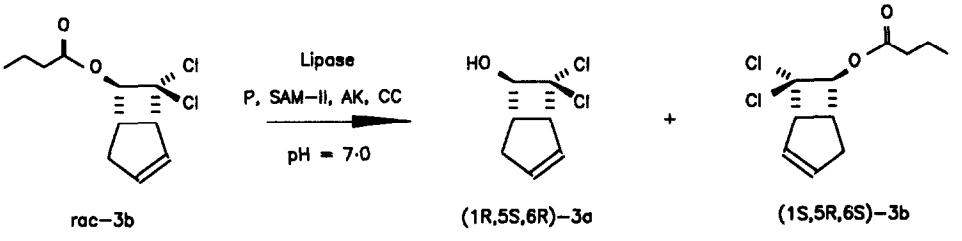
As shown in scheme 2 substrates **2b**, **3b**, **5b** and **6b-6d** were enzymatically hydrolysed using several lipases. Upon examination of the results listed in table 2, the following characteristic points of lipase catalysed hydrolysis of bicyclo[3.2.0]hept-2-en-6-yl esters were found:

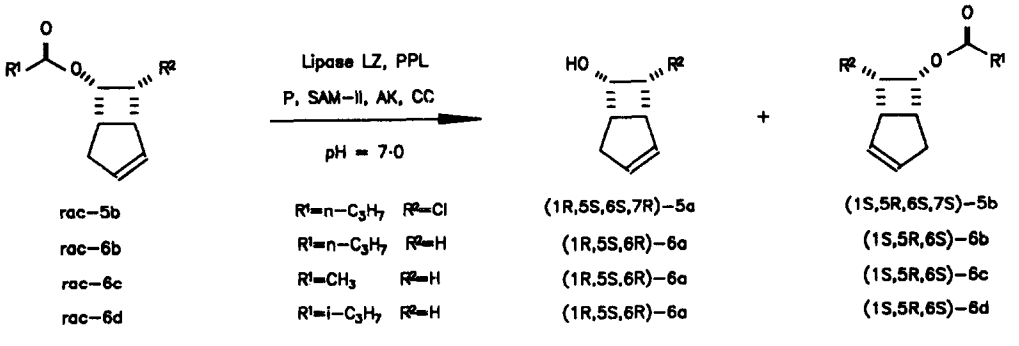
Except for *rac*-**2b** with lipases AK, CC and PPL, where the 1*S*-enantiomer was hydrolysed, in general the 1*R*-alcohol was preferentially formed. Therefore, with respect to selectivity, all lipases showed a clear preference for the same enantiomer of all substrates except **2b**, if the main skeleton is regarded as a whole, even despite an *endo/exo*-change of the alcoholic center at **3b**. Obviously, the enzyme still can "recognize" the chirality of the main basic framework and is able to "neglect" even modifications close to the ester moiety. With substrate **2b**, however, a clear tendency towards one enantiomer is lost even among different

enzymes from the same source and the enantioselectivity remains low.

**Scheme 2** Enzymatic resolution (for racemic starting material only one enantiomer is shown).




| | | | |
|---|---|---|---|
| rac-5b | $R^1$=n-$C_3H_7$ | $R^2$=Cl | (1R,5S,6S,7R)-5a |
| rac-6b | $R^1$=n-$C_3H_7$ | $R^2$=H | (1R,5S,6R)-6a |
| rac-6c | $R^1$=$CH_3$ | $R^2$=H | (1R,5S,6R)-6a |
| rac-6d | $R^1$=i-$C_3H_7$ | $R^2$=H | (1R,5S,6R)-6a |

| |
|---|
| (1S,5R,6S,7S)-5b |
| (1S,5R,6S)-6b |
| (1S,5R,6S)-6c |
| (1S,5R,6S)-6d |

Table 2: Optical purity of products

| *Substrate* | *Lipase*[a] | *Relative Rate [%]*[b] | *Conversion [%]* | *[%] e.e.*[c] *of* *Alcohol* | *Ester* | *E*[d] |
|---|---|---|---|---|---|---|
| | AK | <1 | 50 | 80.8 | 82.0 | 25 |
| | SAM-II | <1 | 20 | 56.2 | n.d. | 4 |
| *rac*-**2b** | P | <1 | 40 | 23.0 | n.d. | 2 |
| | CC | 5 | 50 | 36.1 | n.d. | 3 |
| | PPL | ~1 | 25 | 32.1 | n.d. | 2 |
| | M-10 | <1 | 30 | 17.2 | n.d. | 2 |
| | AK | 4 | 48 | 94.2 | n.d. | 95 |
| *rac*-**3b** | SAM-II | 2 | 60 | 52.2 | n.d. | 7 |
| | P | 3 | 80 | 18.0 | n.d. | 3 |
| | CC | 13 | 51 | 92.0 | 93.7 | 80 |
| *rac*-**5b** | P | ~1 | 45 | 28.0 | n.d. | 2 |
| | AK | 11 | 50 | 98.4 | 98.6 | 620 |
| | SAM-II | 8 | 43 | 98.8 | 74.0 | 370 |
| *rac*-**6b** | P | 14 | 38 | 98.0 | 59.7 | 180 |
| | CC | 7 | 47 | 90.5 | 79.6 | 50 |
| | PPL | ~1 | 52 | 89.0 | 96.2 | 70 |
| | LZ | <1 | 51 | 76.5 | 80.4 | 20 |
| | AK | 59 | 49 | 98.8 | 95.6 | 640 |
| *rac*-**6c** | SAM-II | 37 | 45 | 98.2 | 81.8 | 280 |
| | P | 100 | 50 | 98.4 | 99.3 | 700 |
| | AK | 5 | 47 | 91.0 | 82.0 | 50 |
| *rac*-**6d** | SAM-II | 4 | 43 | 96.2 | 73.1 | 110 |
| | P | 4 | 52 | 91.7 | 98.3 | 110 |

[a] A 100% amount of lipase (w/w) *vs.* substrate was used for **2b**, **3b** and **5b**; for **6b-6d** 20% were sufficient. For a key to abbreviations see experimental part. [b] Calculated from the steady slope of a NaOH consumption *vs.* time plot during 0-20% conversion. [c] For absolute configuration and formulae see Scheme 2. [d] For determination of the enantiomeric ratio (E) see ref. 15.

Substitution of hydrogens vicinal to the alcoholic moiety at C-7 strongly inhibits the speed of conversion: Substrates **2b**, **3b** and **5b** were generally converted with a rate of one or two orders of magnitude lower than unsubstituted derivatives **6b-6d**. From the comparable rates of reaction obtained with the *endo*-monochloro compound **5b** and the dichloro derivative **2b** it seems to be obvious that this effect is caused by the steric hindrance of the *endo*-chloro atom. Dichloro ester **3b**, possessing an *exo*-acyloxy moiety which is less shielded by the main bicyclic framework, was converted at a reasonable rate as were the 7-unsubstituted *endo*-esters **6b-6d**.

A similar negative effect of 7-halogen substitution was observed on the enantioselectivity of all of the enzymes: Whereas **6b-6d** were resolved with good to excellent enantiomeric ratios ranging from 20 to about 700, the values obtained with **2b**, **3b** and **5b** remained below 10 in most cases. Lipases from *Pseudomonas sp.* (AK, SAM-II and P) clearly showed their superiority over *Candida cylindracea* (CC), *Mucor sp.* (M-10, LZ) and porcine pancreatic lipases (PPL). Since the 7-unsubstituted butyrate **6b** was clearly superior to substrates **2b**, **3b** and **5b**, the acid moiety of **6b** was varied to give acetate **6c** and isobutyrate **6d** in order to optimize this procedure for a preparative purpose. Whereas isobutyrate **6d** gave worse results, acetate **6c** was best suited to be resolved with lipase P: The reaction ceased completely at 50% conversion leading to (1*R*,5*S*,6*R*)-**6a** and (1*S*,5*R*,6*S*)-**6b** with greater than 98% e.e.

## CONCLUSIONS

By optimization of substrate structure and appropriate choice of enzyme a convenient method for the enzymatic resolution of bicyclo[3.2.0]hept-2-en-6-yl esters was found. Due to the simplicity of this procedure the method presented here can be a valuable alternative to classical resolution techniques.

## EXPERIMENTAL PART

*General*
Preparative column chromatography was performed on silica gel 60 (230-400 mesh, Merck) and for TLC Merck silica gel 60 $F_{254}$ plates were used. Compounds were visualized by spraying with vanilline/conc. $H_2SO_4$ and heat treatment. GLC analyses were performed on a Hewlett-Packard 7620A (2.2m x 1/8" glass column, 10% SP2100 on Supelcoport 100/120) or on a Dani 8500 chromatograph (J&W capillary column DB 1701, 30m x 0.25mm, 0.25µ film, $N_2$) both equipped with FID. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker MSL 300 (300 and 75.5MHz, resp.) in $CDCl_3$. Chemical shifts are reported from TMS as internal standard in ppm (δ-scale) and coupling constants (*J*) in Hz. s=Singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Elemental analyses (C, H, Cl) of all novel compounds were within 0.5% of calculated values. Optical rotations $[\alpha]_D^{20}$ were measured on a Jasco DIP 370 polarimeter. All commercially obtained compounds were used as received and crude enzyme preparations were employed without further purification. The following abbreviations [] for enzymes were used: *Pseudomonas sp.* lipases (Amano P [P], Amano AK [AK] and Amano SAM-II [SAM-II]), *Mucor sp.* lipases (Amano M-10 [M-10] and Novo Lipozyme-10.000L [LZ]), *Candida cylindracea* lipase (Sigma type VII [CC]) and porcine pancreatic lipase (Sigma type II [PPL]).

*Synthesis of Substrates*
*Preparation of alcohols* **2a**, **3a**, **5a** *and* **6a**
Dichloroketone **1** was obtained by [2+2] cycloaddition of dichloroketene to cyclopentadiene[16,17] which upon $LiAlH_4$ reduction gave both *endo* and *exo* alcohols **2a** and **3a**[18]. These were separated by column chromatography using petroleum ether/ethyl acetate 6:1 as eluent. Selective mono-dechlorination of **1** at room temperature led to *endo*-chloroketone **4**, which upon $LiAlH_4$ reduction furnished *endo*-chloro-*endo*-alcohol **5a** selectively[14]. Complete dehalogenation of **1** at 80°C[19] and subsequent Selectride reduction gave pure *endo*-bicyclo[3.2.0]hept-2-en-6-ol **6a**[20].

*$LiAl(OCH_3)_3H$ reduction of bicyclo[3.2.0]hept-2-en-6-one* (**7**)
To a stirred mixture of $LiAlH_4$ (11.4g, 0.3 mol) in anhydrous THF (500ml), methanol (30.5g, 0.93mol) was added dropwise at 0°C under $N_2$ atmosphere. After stirring was continued for about 20 min, the suspension of $LiAl(OCH_3)_2H$ was slowly added to a solution of **7** (8.6g, 80mmol) in THF (100ml) while the temperature was maintained between -5 and 0°C until TLC indicated complete conversion. Then the reaction was quenched by addition

of sat. $MgSO_4$ solution (25ml) and stirring was continued overnight. After filtration of the solids over a pad of celite 577 the filter cake was refluxed with THF (100ml) for 0.5 h and the combined organic phases were dried ($Na_2SO_4$) and evaporated. Distillation gave 7.54g (86%) of **6a** containing ~3.5% of the corresponding *exo*-isomer **6e**, as shown by GLC analysis, bp 73-75°C/12mm. Spectroscopic data were in agreement with the literature[20].

*Preparation of esters* **2b**, **3b**, **5b** and **6b-d**
Alcohols **2a**, **3a**, **5a** and **6a** were esterified following a standard procedure[21] to give the following substrate esters:
*(1RS,5SR,6SR)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-yl butyrate* (**2b**)
Yield 87%, bp 137-140°C/11mm. $^1$H NMR: 0.98 (t, *J*=7, 3H, γ-$CH_3$), 1.69 (app. sextet, *J*=7, 2H, β-$CH_2$), 2.38 (t, *J*=7, 2H, α-$CH_2$), 2.43-2.52 (m, 2H, H on C-4), 3.45 (dxq, *J*=2 and 6, 1H, H on C-5), 3.92-3.99 (m, 1H, H on C-1), 5.47 (dxd, *J*=6 and 2, 1H, H on C-6), 5.19-5.24 (m, 1H, C=CH), 6.02-6.09 (m, 1H, C=CH). $^{13}$C NMR (DEPT): 13.79 (γ-C), 18.44 (β-C), 32.39 (C-4), 36.03 and 36.25 (C-5, α-C), 65.20 (C-1), 79.23 (C-6), 88.11 (C-7), 128.7 and 138.7 (C-2, C-3), 172.0 (C=O).
*(1RS,5SR,6RS)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-yl butyrate* (**3b**)
Yield 72%, bp 110-120°C/11mm (Kugelrohr distillation). $^1$H NMR: 0.99 (t, *J*=7, 3H, γ-$CH_3$), 1.72 (app. sextet, *J*=7, 2H, β-$CH_2$), 2.42 (dxt, *J*=7 and 2, 2H, α-$CH_2$), 2.56-2.64 (m, 2H, H on C-4), 2.93-3.04 (m, 1H, H on C-5), 3.82-3.91 (m, 1H, H on C-1), 4.97 (dxd, *J*=6 and 2, 1H, H on C-6), 5.87-5.92 (m, 1H, C=CH), 5.97-6.04 (m, 1H, C=CH). $^{13}$C NMR (DEPT): 13.84 (γ-C), 18.52 (β-C), 35.99 (C-4), 37.49 (α-C), 41.02 (C-5), 61.70 (C-1), 83.14 (C-6), 87.35 (C-7), 130.2 and 135.8 (C-2, C-3), 172.5 (C=O).
*(1RS,5SR,6SR,7RS)-7-chlorobicyclo[3.2.0]hept-2-en-6-yl butyrate* (**5b**)
Yield 79%, bp 100-101°C/11mm. $^1$H NMR: 0.98 (t, *J*=7, 3H, γ-$CH_3$), 1.69 (app. sextet, *J*=7, 2H, β-$CH_2$), 2.38 (t, *J*=7, 2H, α-$CH_2$), 2.42-2.62 (m, 2H, H on C-4), 3.20 (q, *J*=6, 1H, H on C-5), 3.64-3.76 (m, 1H, H on C-1), 4.81 (t, *J*=6, 1H, H on C-7), 5.42 (dxt, *J*=3 and 7, 1H, H on C-6), 5.66-5.72 (m, 1H, C=CH), 5.98-6.04 (m, 1H, C=CH). $^{13}$C NMR (DEPT): 13.34 (γ-C), 18.55 (β-C), 33.51 (C-4), 36.19 (α-C), 38.55 (C-5), 52.40 (C-1), 57.54 (C-6), 70.95 (C-7), 129.0 and 135.5 (C-2, C-3), 172.7 (C=O).
*(1RS,5SR,6RS)-bicyclo[3.2.0]hept-2-en-6-yl butyrate* (**6b**)
Yield 86%, bp 90°C/11mm (Kugelrohr distillation). $^1$H NMR: 0.96 (t, *J*=7, 3H, γ-$CH_3$), 1.64 (app. sextet, *J*=7, 2H, β-$CH_2$), 1.70-1.82 (m, 1H, H on C-7), 2.29 (t, *J*=7, 2H, α-$CH_2$), 2.35-2.56 (m, 2H, H on C-4), 2.67-2.79 (m, 1H, H on C-7), 3.01-3.10 (m, 1H, H on C-5), 3.23-3.36 (m, 1H, H on C-1), 5.20 (dxq, *J*=7 and 0.5, 1H, H on C-6), 5.25-5.33 (m, 2H, HC=CH). $^{13}$C NMR (DEPT): 13.33 (γ-C), 18.68 (β-C), 32.70 (C-7), 36.40 and 36.83 (C-4, α-C), 40.80 and 41.40 (C-1, C-5), 68.66 (C-6), 132.3 and 134.3 (C-2, C-3), 173.3 (C=O).
*(1RS,5SR,6RS)-bicyclo[3.2.0]hept-2-en-6-yl acetate* (**6c**)
Yield 87%, bp 70-80°C/11mm (Kugelrohr distillation). $^1$H NMR: 1.72-1.83 (m, 1H, H on C-7), 2.06 (s, 3H, α-$CH_3$), 2.37-2.56 (m, 2H, H on C-4), 2.68-2.79 (m, 1H, H on C-7), 3.01-3.10 (m, 1H, H on C-5), 3.23-3.34 (m, 1H, H on C-1), 5.19 (dxq, *J*=6 and 0.5, 1H, H on C-6), 5.78-5.84 (m, 2H, HC=CH) $^{13}$C NMR (DEPT): 21.04 (α-C), 32.73 (C-4), 36.83 (C-7), 40.76 (C-5), 41.43 (C-1), 68.90 (C-6), 132.4 and 134.3 (C-2, C-3), 170.7 (C=O).
*(1RS,5SR,6RS)-bicyclo[3.2.0]hept-2-en-6-yl isobutyrate* (**6d**)
Yield 90%, bp 80-85°C/11mm (Kugelrohr distillation). $^1$H NMR: 1.15 (d, *J*=7, 3H, β-$CH_2$), 1.18 (d, *J*=7, 3H, β-$CH_3$), 1.71-1.82 (m, 1H, H on C-7), 2.35-2.63 (m, 3H, H on C-4, α-CH), 2.68-2.79 (m, 1H, H on C-7), 3.01-3.10 (m, 1H, H on C-5), 3.23-3.34 (m, 1H, H on C-1), 5.18 (dxq, *J*=6 and 0.5, 1H, H on C-6), 5.78-5.84 (m, 2H, HC=CH).

Table 3: Optical rotation values in $CHCl_3$ solution

| *Compound* | $[\alpha]_D^{20}$ | *c [g/100ml]* | *e.e. [%]* |
|---|---|---|---|
| (1*S*,5*R*,6*R*)-**2a** | +130.3 | 3.08 | 80.8 |
| (1*R*,5*S*,6*S*)-**2b** | -60.4 | 3.57 | 82.0 |
| (1*R*,5*S*,6*R*)-**3a** | -132.0 | 2.24 | 92.0 |
| (1*R*,5*S*,6*S*,7*R*)-**5a** | -56.7 | 4.51 | 28.0 |
| (1*R*,5*S*,6*R*)-**6a** | -75.8 | 2.46 | 98.4 |
| (1*S*,5*R*,6*S*)-**6b** | -26.5 | 2.50 | 59.7 |
| (1*S*,5*R*,6*S*)-**6c** | -36.3 | 2.27 | 99.3 |
| (1*S*,5*R*,6*S*)-**6d** | -10.8 | 2.03 | 98.3 |

*Biocatalytic Procedures*
Preparative enzymatic resolutions were performed with 0.2-2.0g of

substrate as described[22] with the simplification that only one step of the procedure was used.

*Determination of Absolute Configuration and Optical Purity*
Alcohols **2a**, **3a**, **5a** and **6a** were transformed into diastereomeric carbonates using (-)-menthyl chloroformate according to Westley and Halpern[23]. For complete derivatisation of halogenated alcohols **2a**, **3a** and **5a** heating for 3 h at 60°C was necessary. The derivatives could conveniently be separated on a capillary column as specified in the general part. Esters **6b-6d** were chemically hydrolysed into their corresponding alcohols (NaOMe cat./MeOH, r.t.) prior to derivatisation. All halogen containing esters (**2b**, **3b** and **5b**) were hydrolysed enzymatically by prolonged exposure to lipase P for up to 4 days since they underwent decomposition under basic conditions mentioned above. Comparison of optical rotation values with literature data revealed the absolute configuration of **2a**, **5a**[24] and **6a**[10]. **3a** was dechlorinated by tributyl tin hydride following the procedure of Ghosez *et al.*[26] to give *exo*-bicyclo[3,2.0]hept-2-en-6-ol (**6e**) with known absolute configuration[16].

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