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ENZYMATIC RESOLUTION OF NORBOR(NE)NYLMETHANOLS IN ORGANIC MEDIA AND AN APPLICATION TO THE SYNTHESIS OF (+)- AND (−)-*endo*-NORBORNENE LACTONE.

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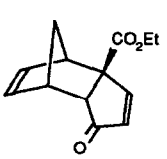
Abstract: The enzymatic resolution of some norbornene carboxylic acids, norbornenylmethanols and -methylamines was evaluated. The kinetic resolution of norbornyl- and norbornenylmethanols by Porcine Pancreatic Lipase (PPL)-catalyzed transesterification in methyl acetate as the solvent leads to corresponding acetates and remaining methanols both of high enantiomeric purity. A useful application is the synthesis of both enantiomers of endo*-norbornene lactone* **8n** *via transesterification of iodolactone* **18**. *The influence of structural variations on the efficiency of the PPL-catalyzed resolution of lactone methanols* **21**, **23**, **25** *and* **28**, *at the optimal reaction conditions established for iodolactone* **18**, *was investigated.*

Introduction

The application of enzymes as chiral catalysts for the synthesis of optically active compounds, starting from either chiral or prochiral substrates, has received widespread interest[1] in synthetic organic chemistry during the last few years. Numerous examples are now known in which readily available and cheap hydrolases, such as Pig Liver Esterase (PLE) and lipases, *e.g.* Porcine Pancreatic Lipase (PPL) and Candida Cylindracea Yeast Lipase (CCL), were shown to be extremely useful and versatile synthetic tools for the preparation of valuable chirons[1].

In relation to our studies aimed at modifying polycyclic structures into chirons for natural product synthesis, we recently reported the efficient PLE-catalyzed resolution of tricyclodecadienone carboxylic ester[2] **1** and *trans*-norbornene diester[3] **2a**. As shown by Bloch *et al.*[4] also the oxygen bridged *exo*-diester **3a** is accep-



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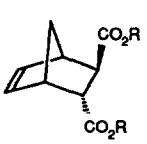

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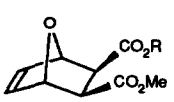
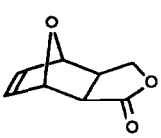
b R = H



3a R = Me
b R = H



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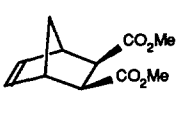
ted as a substrate by PLE. The monoester **3b**, which was obtained with good enantiomeric purity, could readily be converted into either enantiomer of tricyclic lactone **4**. In sharp contrast to these results, the methylene bridged *exo*-diester **5** is hydrolyzed virtually non-stereoselectively by PLE, while the corresponding *endo*-diester **6a** is not hydrolyzed at all[3,4]. Remarkably, Metz[5] showed that the structurally related diester **7a** is readily accepted by PLE furnishing the corresponding halfester **7b** in moderate enantiomeric purity.

However, none of the PLE-catalyzed hydrolyses of substrates **5**, **6a** or **7a** gives access to enantiopure methylene bridged *endo*- or *exo*-tricyclic lactones **8n** and **8x**, which are valuable chirons for the synthesis of natural and pharmaceutical products[6]. The lipases PPL and CCL, in contrast to PLE, do not show any hydrolytic activity toward either tricyclic ester **1** or *trans*-diester **2a** under standard conditions (pH 7.8, 0.1 M phosphate buffer, room temperature). Only for the monoesters **9n** and **9x** some hydrolysis is observed albeit at a very low rate and with hardly any enantioselectivity[7]. These unsatisfactory results were reason to turn our attention to the reverse reaction, *i.e.* the lipase-catalyzed esterification of norborn-5-ene 2-carboxylic acids and norborn-5-en-2-ylmethanols in organic solvents[1d,8].



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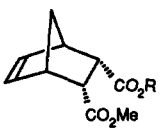
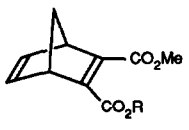
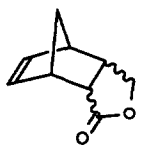


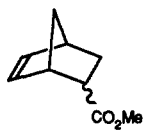
6a R = Me
b R = H



7a R = Me
b R = H



endo: **8n**
exo: **8x**

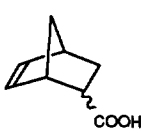


endo: **9n**
exo: **9x**

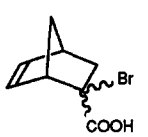
In this paper a successful application of PPL in organic solvents for the resolution of a variety of norbor(ne)nylmethanols, ultimately leading to a formal resolution of *endo*-norbornene lactone **8n**, will be described in detail. Furthermore, the influence of structural variations on the efficiency of these resolutions will be reported.

Norborn-5-ene 2-carboxylic acids and norborn-5-en-2-ylmethanols.

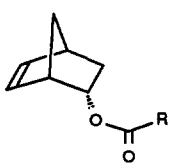
The first attempts were directed toward the CCL-catalyzed esterification of readily available *endo*- and *exo*-carboxylic acids[9] **10n** and **10x**. However, stirring a solution of these acids in hexane containing an excess of either methanol or n-butanol in the presence of the enzyme, did not lead to any ester formation. The addition of small amounts of water and prolonged reaction times did not alter this result. The reason for this failure may be that the substrate is lacking an electron withdrawing group, such as a halogen or a halophenoxy group, at the α-position of the carboxylic acid which, according to the literature[8], is required for an efficient yeast lipase-catalyzed esterification. Therefore, *endo*- and *exo*-α-bromo acids **11n** and **11x**, obtained



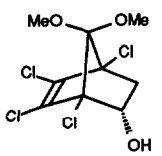
endo: **10n**
exo: **10x**



endo acid: **11n**
exo acid: **11x**



12a R = Me
12b R = n-Pr



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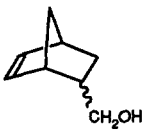
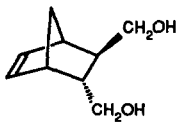
by Diels-Alder addition of α-bromoacrylic acid and cyclopentadiene[10], were treated with yeast lipase in hexane, using either methanol or n-butanol as the nucleophile. Again no ester formation was observed. These results indicate that norbornenes with a carboxylic acid moiety directly connected to the bicyclic skeleton are not accepted as substrate by lipases[11].

Griengl *et al.*[12a] demonstrated that structures in which the norbornene skeleton constitutes the alkyl

moiety of an ester, *e.g.* compounds **12a** and **12b**, are readily accepted by lipases. It has also been shown[12b] that highly substituted norbornene alcohols, such as **13**, are very good substrates for a lipase-catalyzed transesterification in organic solvents. This information was a stimulus to investigate the enzymatic transesterification of norbornenylmethanols **14n**, **14x** and **15**, using PPL, which is known to be a very efficient enzyme for the esterification of alcohols[8], as the catalyst. The enzyme CCL, which has a known lower affinity for alcohols[8], was not included in this study.



endo: **14n**
exo· **14x**



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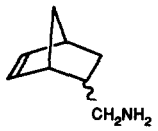


endo: **16n**
exo **16x**

Endo-norbornenylmethanol **14n**, which was prepared by reduction[13] of *endo*-carboxylic acid **10n** using $LiAlH_4$, afforded upon PPL-catalyzed transesterification in methyl acetate as the reaction medium, the acetate of (−)-**14n** in 56% yield with an enantiomeric excess (ee) of 49% and the recovered alcohol (+)-**14n** in 43% yield with an ee of 68%. This alcohol (+)-**14n** has the (2*R*)-configuration, as was deduced by comparison of its optical rotation with that reported in the literature[14]. This result implies that the (2*S*)-hydroxymethyl enantiomer has been esterified preferentially.

Table 1: PPL catalyzed transesterification of norborn-5-en-2-ylmethanols **14n** and **14x** [a].

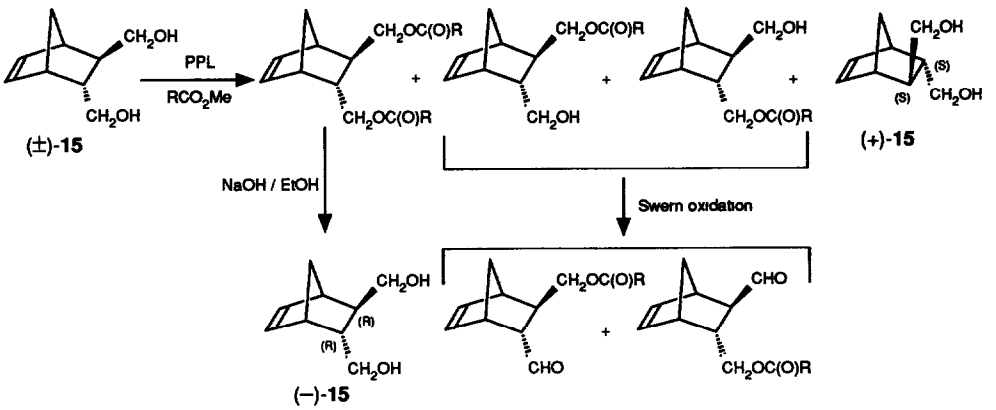
		ester			recovered alcohol		
substr.	time,h	yield[b]	ee[c,d]	config.[e]	yield[b]	ee[c]	config.[e]
14n	44	56	49	2*S*	43	68	2*R*
14x	44	66	25	2*S*	34	61	2*R*

a. reaction conditions: 3.0 mmol of **14n** and 3.2 mmol of **14x**, 15 ml methyl acetate, 600 mg PPL, ambient temperature. For details: see experimental section.
b. yields of isolated materials are given in percentages.
c. given in percentages and determined by comparison of optical rotations with literature data (see experimental section).
d. determined for the alcohols (-)-**14n** and (+)-**14x** obtained by alkaline hydrolysis of the respective acetates.
e determined by comparison of optical rotations with literature data.

Transesterification of *exo*-norbornenylmethanol **14x**, prepared from *exo*-carboxylic acid **10x** by $LiAlH_4$ reduction, proceeded more rapidly under the same conditions. After 44 h, 66% of the acetate of (+)-**14x** with an ee of 25% was obtained, while the remaining alcohol (−)-**14x** was isolated in 34% yield with an ee of 61%. Comparison of optical rotations with literature data[14] revealed that also in this case the (2*S*)-

hydroxymethyl enantiomer has been esterified preferentially. The results obtained with both alcohols **14n** and **14x**, which are collected in Table 1, allow the conclusion that the *exo*-methanol group in **14x** is more accessible to PPL than the *endo*-methanol group in **14n**. The enantioselectivity however, is lower for **14x**, because at a higher conversion the remaining alcohol (−)-**14x** is obtained with a lower enantiomeric purity than in the case of alcohol (+)-**14n** (ee of 61% *vs.*68%).

Scheme 1



Treatment of *trans*-2,3-bis(hydroxymethyl)-norborn-5-ene **15**, obtained by $LiAlH_4$ reduction[13] of the Diels-Alder adduct[9b] **2b** of fumaric acid and cyclopentadiene, with PPL in methyl acetate afforded a mixture of diester, monoesters and remaining diol (Scheme 1). Column chromatography provided the diacetate of (−)-**15**, pure diol (+)-**15** and a mixture of the monoesters (Table 2). Swern oxidation[15] of the alcohol function of these monoesters yielded a 1:3 mixture of ester-aldehydes (according to capillary GLC). A ^{1}H-NMR-analysis revealed that the minor peak should be assigned to the *exo*-aldehyde-*endo*-ester (the signal for the aldehyde proton appears at δ 9.77 ppm) and the major peak to the *endo*-aldehyde-*exo*-ester (aldehyde proton at δ 9.38 ppm, a shielding effect of the olefinic moiety). This result clearly shows the strong preference of PPL for the *exo*-methanol group. The absolute configurations of the respective products were deduced by comparison of their optical rotations with literature data[16]. It is concluded that the (2*R*,3*R*)-diol has been transesterified preferentially.

The PPL-catalyzed transesterification of diol **15** has also been carried out using methyl propionate and methyl butyrate as the solvent (Table 2). In these less polar esters the reaction rate is considerably enhanced, whereas the enantioselectivity is decreased. Furthermore, the preference of PPL for the *exo*-methanol compared to the *endo*-methanol group is less pronounced than in methyl acetate.

Norborn-5-en-2-ylmethylamines

The *endo*- and *exo*-norbornenylmethylamines **16n** and **16x**, which were prepared[17] from *endo*- and *exo*-carboxylic acids **10n** and **10x**, respectively, were also subjected to a PPL-catalyzed N-acylation. For this conversion, methyl propionate appeared to be the medium of choice.

Stirring a solution of *endo*-amine **16n** in methyl propionate for 19 h at 40°C in the presence of the enzyme, afforded 47% of the propionamide of (−)-**16n** and 31% of remaining amine (+)-**16n** both with low

Table 2: PPL catalyzed transesterification of *trans*-2,3-bis(hydroxymethyl)-norborn-5-ene (**15**).[a]

		recovered diol			monoester		diester		
solvent	time,h	yield[b]	ee[c]	config[d]	yield[b]	ratio *endo/exo*[e]	yield[b]	ee[c,f]	config[d,f]
MeCOOMe	44	39	91	2*S*,3*S*	49	1 : 3	10	73	2*R*,3*R*
Et COOMe	44	30	92	2*S*,3*S*	45	1 : 2.5	18	66	2*R*,3*R*
n-PrCOOMe	44	24	88	2*S*,3*S*	44	1 : 2.2	23	58	2*R*,3*R*

a. reaction conditions: 3.2 mmol of diol **15**, 15 ml solvent, 600 mg PPL, ambient temperature. For further details: see experimental section.
b. yields of isolated material are given in percentages
c. given in percentages and determined by comparison of optical rotations with literature data (see experimental section).
d. determined by comparison of optical rotations with literature data.
e. determined by capillary GLC and ^{1}H-NMR, after oxidation of the diol-monoester to the corresponding ester aldehyde (see experimental section).
f. determined for the diol (-)-**15** obtained by alkaline hydrolysis of the diester.

enantiomeric purity (<5%). This result was hardly improved by performing the reaction at ambient temperature. By comparison of the optical rotation with literature data[14] the (2*R*)-configuration was assigned to this amine (+)-**16n**. Amidase Papaine was also applied as a catalyst in the acylation of amine **16n**. However, it has a much lower catalytic activity (after 68 h at 40°C a conversion of only 30% was attained) and virtually no stereoselectivity was observed. These disappointing results can in part be explained by the fact that the amine also reacts spontaneously with the solvent methyl propionate. This was proven by blank experiments in which the amine was stirred in methyl propionate at 40°C in the absence of the enzyme. By GLC-analysis it was shown that after 68 h about 16% of the amine was converted to the corresponding propionamide.

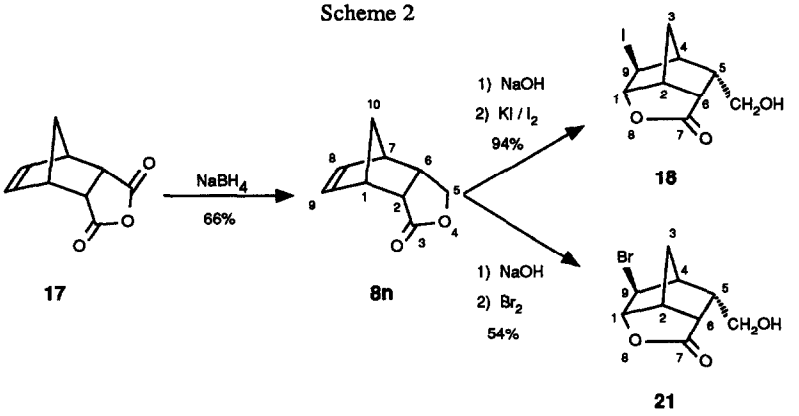
As expected (*cf.* reactions with the corresponding norbornenylmethanols), PPL displayed a higher catalytic activity towards the *exo*-amine **16x**. After 19 h at 40°C, 65% of the amide of (+)-**16x** was isolated along with 35% of remaining amine (–)-**16x**. Again the enantioselectivity was poor: amine (+)-**16x**, which has the (2*S*)-configuration, had an optical purity of no more than 6%. Blank experiments showed that the spontaneous reaction of amine **16x** with the solvent proceeds even faster than in the case of the *endo*-amine **16n**, because after 68 h at 40°C 22% of the amine had reacted to the corresponding amide.

From these results it may be concluded that the amines **16n** and **16x** are very poor substrates for PPL under these conditions.

Enzyme mediated optical resolution of *endo*-norbornene lactone 8n

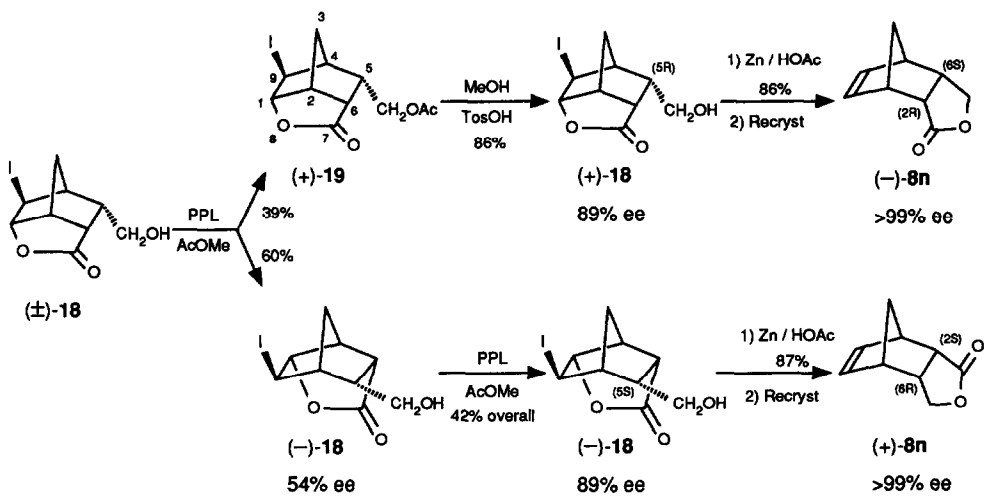
An interesting application of the optical resolution of a norbornenylmethanol derivative, *viz.* iodolactone **18**, is depicted in Scheme 3. Iodolactone **18** can be prepared in good yields by $NaBH_4$ reduction[18] of the readily available anhydride **17** followed by iodolactonization (Scheme 2). The enzymatic resolution of this lactone **18**, using PPL in methyl acetate, constitutes the key-step in the formal resolution of *endo*-norbornene lactone **8n** and proceeds with excellent enantioselectivity. Stirring a mixture of lactone **18** and PPL in methyl

Scheme 2



acetate for 8 days at 40°C afforded, after separation of the products by column chromatography, acetate (+)-**19** in high enantiomeric purity. Acid hydrolysis of this acetate (+)-**19** gave the corresponding alcohol (+)-**18** and subsequent reduction[19] with zinc in acetic acid afforded tricyclic lactone (−)-**8n** in an overall yield of 74%. The enantiomeric purity of the latter could be enhanced by recrystallization leading to enantiopure (−)-**8n**. By comparison of the optical rotation with literature data[20], the absolute configuration of lactone (−)-**8n** was deduced to be (2*R*,6*S*), implying that the (5*R*)-enantiomer of iodolactone **18** has been esterified preferentially.

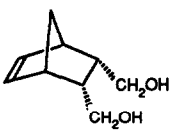
Scheme 3



The enantiomeric purity of 54% of the remaining alcohol (−)-**18**, which has the (5*S*)-configuration, was improved to 89% by a second treatment with PPL (it should be noted that PPL recovered from the first treatment was used here). Zinc - acetic acid reduction and recrystallization finally afforded the enantiopure (2*S*,6*R*)-tricyclic lactone (+)-**8n**.

The ee's of the alcohols (+)- and (−)-**18** were determined by HPLC-analysis of the corresponding (+)-*R*-α-methoxy-α-trifluoromethyl-α-phenyl acetate esters which were prepared according to the procedure of Mosher *et al.*[21].

The simplicity of the procedure outlined in Schemes 2 and 3 clearly demonstrates the high utility of lipases, such as PPL, in synthetic organic chemistry. Other syntheses of optically active lactones (+)- and (−)-**8n**, reported in literature, either involve long multistep sequences starting from homochiral natural products (such as D-mannitol)[20] or from optically active compounds, *e.g.* carboxylic acid **6b**, obtained by classical resolution of suitable precursors[5,22]. The only two enzymatic processes known, involve the oxidation of



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meso-diol **20** using Horse Liver Alcohol Dehydrogenase[23] affording only lactone (+)-**8n** in high enantiomeric purity and the PLE-catalyzed hydrolysis of diester[5] **7a** which proceeds with low enantioselectivity and which again only gives one enantiomer of the lactone, *viz.* (+)-**8n**.

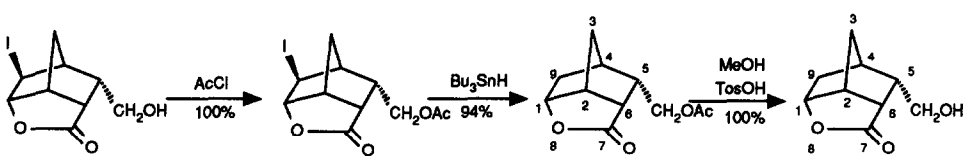
The influence of structural variations on the efficiency of the PPL-catalyzed resolution of norbornylmethanols

The excellent results obtained for the resolution of iodolactone **18** inspired us to investigate the influence of structural variations of the substrate on the efficiency of the PPL-catalyzed transesterification. Four structural variants were selected; their synthesis is depicted in the Schemes 2, 4, 5 and 6.

Bromolactone **21** was obtained from tricyclic lactone **8n** by an alkaline ring-opening followed by reaction with bromine (Scheme 2). The yield of this reaction was strongly dependent on its scale and ranged from ca. 20% for a scale less than 1 mmol to 54% for a 20 mmol scale.

A direct synthesis of the dehalogenated lactone **23** by tributyltin hydride reduction[24] of iodolactone **18** was met with difficulties during the work-up. Preparation through the corresponding acetate **19** appeared to be much easier, because purification of the dehalogenated acetate **22** could be accomplished without difficulties. In this manner alcohol **23** was prepared in three steps from iodolactone **18** in 94% overall yield (Scheme 4).

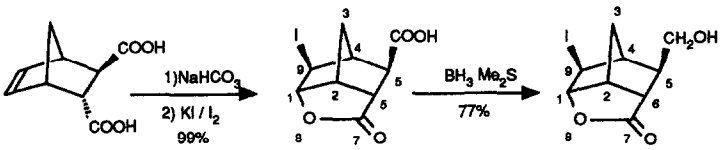
Scheme 4



18 **19** **22** **23**

Iodolactonization of the readily available *trans*-dicarboxylic acid[9b] **2b** led to lactone **24** in high yield. Reduction[25] of carboxylic acid **24** to the corresponding alcohol **25** was achieved by borane - dimethyl sulfide in THF (Scheme 5).

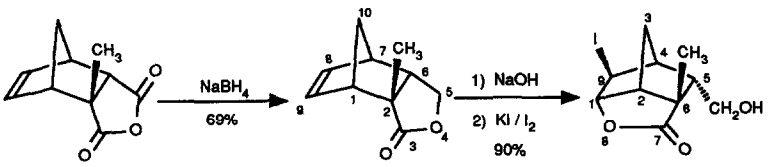
Scheme 5



2b **24** **25**

The 6-methyl iodolactone **28** was synthesized in the same manner as iodolactone **18** (Scheme 6). Reduction[18,26] of the anhydride **26**, obtained by Diels-Alder addition of citraconic anhydride to cyclopentadiene[9a], afforded lactone **27** in a good yield. Alkaline opening of the lactone ring, which for lactone **8n** took place rather smoothly, now required more drastic conditions, *i.e.* heating in a 0.2 M sodium hydroxide solution at reflux. Iodolactonization finally gave the alcohol **28** in high yield.

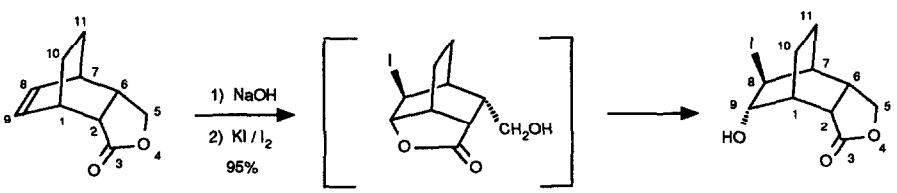
Scheme 6



26 **27** **28**

The synthesis of the structural analog of lactone **18** with a two-carbon bridge, *viz.* lactone **30**, was attempted from lactone **29**. Alkaline ring-opening followed by iodolactonization, however, did not lead to the desired product **30**, but instead to tricyclic lactone **31**, by an intramolecular addition - elimination of the initially formed lactone **30** (Scheme 7). The first indication of a structure completely different from **30** was the relatively high chemical shift of H_9 (δ in the range 4.27 - 4.63 ppm, *cf.* δ for H_1 5.15 ppm for iodolactone **18**) and a downfield shift for the C_5 protons (δ 4.27 - 4.63 ppm, *cf.* δ (-C<u>H</u>$_2$OH) 3.58 for iodolactone **18**). The structure of compound **31** was unambiguously established by an X-ray diffraction analysis[27]. MM-2 calcula-

Scheme 7



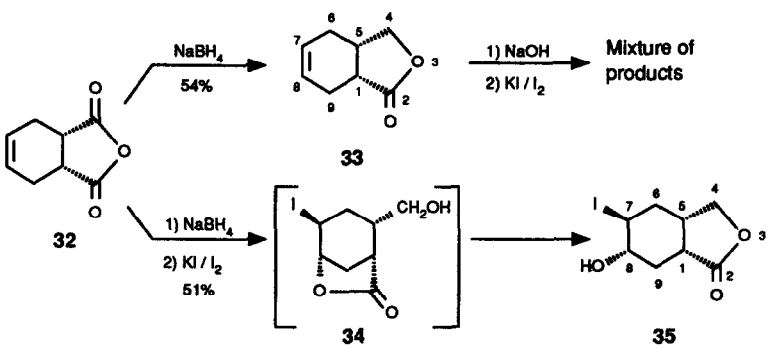
29 **30** **31**

tions clearly showed the lower energy content of **31** (26.5 kcal / mol) compared with **30** (28.8 kcal / mol), in agreement with the observed rearrangement. Similar calculations were carried out for iodolactone **18** (29.4

kcal / mol) and the methylene bridged analog of lactone **31** (31.8 kcal / mol) indicating that for these lactones such a rearrangement is unlikely.

For the sake of comparison, lactone **34** was also considered to be of interest. Its attempted preparation from bicyclic lactone **33**, obtained by $NaBH_4$ reduction[18] of commercially available anhydride **32** (Scheme 8), by an alkaline ring-opening and subsequent iodolactonization, however, led to an unattractive mixture of products. Probably, a partial epimerization of lactone **33** at C_1, leading to the corresponding less strained *trans*-lactone, took place. This epimerization was avoided by immediate iodolactonization of the *cis*-hydroxymethyl carboxylic acid, formed by $NaBH_4$ reduction of **32**. Again, as in the case of the ethylene bridged iodolactone **31**, a rearranged product, *viz.* lactone **35**, was obtained. MM-2 calculations showed lactone **34** to have an energy of 21.2 kcal / mol compared with 17.2 kcal / mol for lactone **35**, indicating that the latter is energetically more favored. It is of interest to note that the melting point of lactone **35** is the same as that reported for **34** in the literature[28], implying that the claimed synthesis of lactone **34** is not correct. The ^{1}H-NMR spectrum of product **35** clearly showed the relatively high chemical shift of H_8 (δ in the range 4.24 - 4.40 ppm, *cf.* δ for H_1 5.15 ppm for iodolactone **18**) and a downfield shift for the C_4 protons (δ 4.29 ppm, *cf.* δ (-$\underline{CH_2}$OH) 3.58 ppm for iodolactone **18**), as also observed for lactone **31**. Furthermore, after conversion of **35** to the corresponding acetate ester (chemically) or propionate ester (enzymatically) a strong downfield shift for H_8 (to δ 5.06 and 4.84 ppm, respectively) and a smaller one for H_7 (to 4.39 and 4.48 - 4.59 ppm, respectively) was observed in the ^{1}H-NMR spectrum. Moreover, the characteristic doublet - doublet pattern for each of the H_4 protons (*cf.* lactone **33**), was not affected in the change from the alcohol **35** to these esters.

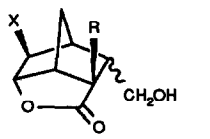
Scheme 8



Before subjecting the lactone alcohols **21**, **23**, **25** and **28** to a PPL-catalyzed transesterification, the optimal reaction conditions for this type of enzymatic resolution were established for substrate **18**. Special attention was given to the solvent which also serves as the acylating agent. The PPL-catalyzed resolution of iodolactone **18** was studied in ten different solvents, *viz.* methyl and ethyl acetate; methyl, ethyl and n-propyl propionate; the methyl esters of butyric, valeric and caproic acid as well as the enol esters vinyl and isopropenyl acetate.

The enzymatic resolution of iodolactone **18** using methyl propionate as the solvent at 40°C appeared to be most efficient. After 91 h, at 40% conversion, the propionate ester of (+)-**18**, which has the (5*R*)-configuration, was obtained with an ee of 95% (*cf.* an ee of 89% at 39% conversion for the acetate of (+)-**18** described above (Scheme 3)). Prolonged reaction times (164 h) only gave a small increase in the conversion

Table 3: PPL-catalyzed resolution of lactone alcohols **18**, **21**, **23**, **25** and **28** in methyl propionate[a].



					propionate		alcohol		
substr.	X	R	-CH_2OH	time,h	ee_p[b,c]	config.[c]	ee_s[c,d]	conv.[e]	E[f]
18	I	H	*endo*	91	95	5*R*	64	40	75
				115	94	5*R*	71	43	70
				164	93	5*R*	78	46	65
21	Br	H	*endo*	43	>98	5*R*	63	39	>>100
				91	97	5*R*	70	42	>>100
				163	96	5*R*	84	47	>>100
23	H	H	*endo*	19	88	5*S*	43	33	25
				67	84	5*S*	72	46	25
				163	76	5*S*	88	54	20
25	I	H	*exo*	19	74	5*S*	78	51	15
28	I	CH_3	*endo*	164	93	5*S*	65	41	55

a. reaction conditions: 2.5 mmol of alcohol, 19 ml methyl propionate, 500 mg PPL, 40°C. For details: see experimental section.

b enantiomeric excess (in %) of the alcohol obtained by alkaline hydrolysis of the propionate.

c. determined by comparison of optical rotations with those of the enantiomerically pure alcohols (see experimental section).

d. enantiomeric excess (in %) of the recovered alcohol.

e. conversion calculated according to the formula conv = ee_s / (ee_s + ee_p) (ref. 29).

f enantiomeric ratio calculated according to the formula E = ln (1 - conv (1 + ee_p)) / ln (1 - conv (1 - ee_p)) (ref. 29).

(from 40 to 46%) and a slightly lower enantiomeric excess for the ester (Table 3)*. Although transesterification using either vinyl or isopropenyl acetate as the solvent proceeded very rapidly (for example, in

* In a later stage of our studies, we found that an acceleration of the reaction in methyl propionate was accomplished by addition of molecular sieves 4Å which trap the liberated methanol. However, the enantioselectivity of the process decreased in the presence of molecular sieves. Attempts to enhance the enantioselectivity by lowering the reaction temperature were now successful, although at the expense of the reaction rate, *e.g.* the propionate of (+)-**18** was isolated with an ee of 95% after 164 h of reaction at ambient temperature (conversion 43%). Despite this small drawback, the addition of molecular sieves represents an improvement of the "key-step" resolution in the synthesis of both (+)- and (-)-*endo*-norbornene lactones **8n** (Scheme 3). The enzymatic resolutions described in this paper were carried out in the *absence* of molecular sieves.

vinyl acetate after 163 h at 40°C a conversion of 65% was achieved), the enantioselectivity was poor. However, these solvents provide a good means of obtaining the remaining alcohol (–)-**18** rapidly and in high enantiomeric purity, *e.g.* in vinyl acetate at 65% conversion alcohol (–)-**18** was isolated with an ee of 97%.

Lactone alcohols **21**, **23**, **25** and **28** were subjected to the optimal conditions established for lactone alcohol **18**, *i.e.* applying methyl propionate at 40°C.

Bromolactone **21** displayed a higher degree of enantioselectivity (E>>100) as well as a higher rate of transesterification when compared to iodolactone **18** (Table 3). Due to this high degree of enantioselectivity the rate of esterification decreased considerably at higher conversion (*cf.* Table 3; conversions after 43, 91 and 163 h). For bromolactone **21** the esterification of the (5*R*)-enantiomer by PPL is favored, similar to the situation with iodolactone **18**.

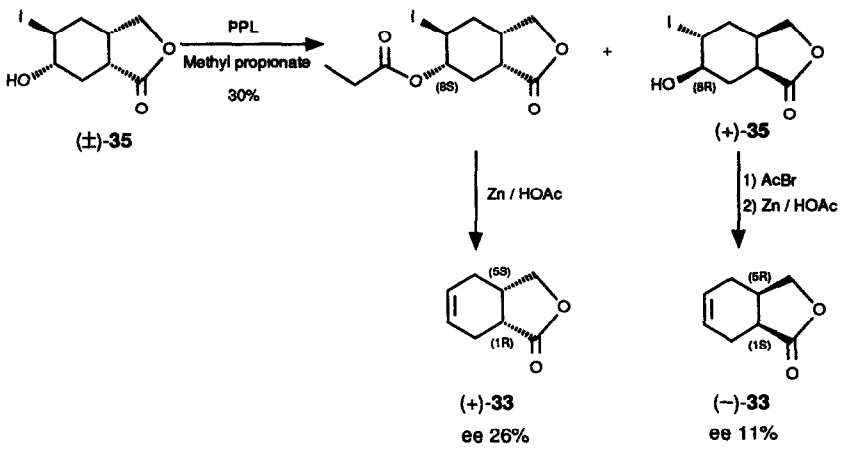
The presence of a halogen atom at C_9 is responsible for good enantioselectivity, as was concluded from the enzymatic esterification of the dehalogenated lactone **23**. Although a conversion of 33% was reached in 19 h, the propionate of lactone (–)-**23** was isolated with a relatively low ee of 88% (Table 3). This moderate selectivity is clearly expressed by the low enantiomeric ratio (E 20 - 25) and by the fact that at prolonged reaction times the conversion easily proceeds past 50% (Table 3). Now the (5*S*)-enantiomer of lactone alcohol **23** has been esterified preferentially. It should be noted however, that the spatial orientation of the CH_2OH-group in this lactone alcohol is the same as in the (5*R*)-halolactone alcohols **18** and **21**. Only due to the priority rules for the assignment of absolute configurations, is the letter symbol different. The *endo*-position of the methanol group is apparently required for a successful resolution, as was concluded from experiments with alcohol **25** possessing this substituent in the *exo*-position. In spite of the good acceptance of **25** by the enzyme, the enantiomeric ratio was low (Table 3) and consequently, the resolution was not satisfactory.

The introduction of a methyl group in α-position to the lactone carbonyl, as in substrate **28**, caused a small decrease in reaction rate of the enzymatic transesterification, in comparison with iodolactone **18**. The propionate of lactone (+)-**28**, having the (5*S*)-configuration, was obtained in the excellent enantiomeric purity of 93% (Table 3).

The results presented above show that the enantiomers of the lactone alcohols studied here, which are esterified preferentially, all have the lactone ring at the front side of the molecule and the CH_2OH-group and the halogen (if present) at the rear. The data in Table 3 clearly indicate a considerable influence of small structural variations on the catalytic activity of PPL as is apparent from the reaction rate as well as from the observed enantioselectivity.

Attempts to esterify lactone alcohol **31** failed completely. Apparently, this substrate cannot be accepted by the enzyme, which may be attributable to the presence of the bicyclo[2.2.2]octane skeleton and/or the secondary alcohol. Interestingly, alcohol **35** was accepted as a substrate by PPL (Scheme 9). After 68 h, 30% of the (8*S*)-alcohol (–)-**35** was converted into the corresponding propionate. The ee was determined after eliminative reduction[19] of this ester using zinc in acetic acid, which afforded bicyclic lactone (+)-**33**. Comparison of the optical rotation of the latter with that reported in the literature[30] gave both the absolute configuration (1*R*,5*S*) and the ee (26%) of lactone (+)-**33**. The remaining alcohol (+)-**35** was first acetylated and then converted into lactone (–)-**33** by means of zinc in acetic acid. The enantiomeric purity of (–)-**33** was again low, *viz.* 11%.

Scheme 9



Mucor Esterase catalyzed resolution.

Another enzyme, *viz.* Mucor Esterase, has also been studied in the resolution of halolactone alcohols **18, 21** and **28**. This esterase was efficient in its catalytical action, although, it displayed a very poor enantioselectivity (Table 4). For all three alcohols enantiomeric ratios (E) between 10 and 20 were found, implying that this enzyme is much less appropriate for the resolution of this type of alcohols than PPL.

Table 4: Mucor Esterase catalyzed resolution of lactone alcohols **18, 21,** and **28** in methyl propionate[a].

		propionate		alcohol		
substr.	time,h	ee_p[b,c]	config.[c]	ee_s[c,d]	conv.[e]	E[f]
18	68	72	5*R*	70	49	13
21	68	67	5*R*	73	52	11
28	68	83	5*R*	49	37	17

a. reaction conditions: 2 5 mmol of alcohol, 19 ml methyl propionate, 500 mg Mucor Esterase, 40°C. For details: see experimental section.
b enantiomeric excess (in %) of the alcohol obtained by alkaline hydrolysis of the propionate
c determined by comparison of optical rotations with those of the enantiomerically pure alcohols (see experimental section).
d. enantiomeric excess (in %) of the recovered alcohol
e. conversion calculated according to the formula conv = ee_s / (ee_s + ee_p) (ref. 29).
f. enantiomeric ratio calculated according to the formula E = ln (1 - conv (1 + ee_p)) / ln (1 - conv (1 - ee_p)) (ref 29)

Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer with TMS as the internal standard. For mass spectra a double focussing VG 7070E mass spectrometer was used. Capillary GLC analyses were performed using a HP 5790A or a HP 5890, containing a cross-linked methyl silicone column (25m). For analytical HPLC (silicagel Si 100, 25 cm) a Spectra Physics 8700 solvent delivery system with a Spectra Physics 8400 variable wavelength UV/Vis detector and a Spectra Physics 4100 computing integrator were used. Column chromatography was performed using Merck Kieselgel 60-F254. For the determination of optical rotations a Perkin Elmer 241 Polarimeter was used. Porcine Pancreatic Lipase (PPL) and Candida Cylindracea Yeast Lipase (CCL) were purchased from Sigma. Mucor Esterase and Papaine were obtained as a gift from Gist-brocades, Delft, The Netherlands. PPL and Mucor Esterase were dried at reduced pressure (~0.02 mbar) during 4h prior to use. The solvents used for the enzymatic resolutions were stored on molecular sieves 4Å (10% w/v). All glassware was oven dried before use.

Endo- and exo-*bicyclo[2.2.1]hept-5-ene 2-carboxylic acid,* **10n** *and* **10x**.

This acid was prepared, as an *endo/exo* mixture (9:1), in 85% yield by Diels-Alder addition of acrylic acid and cyclopentadiene[9]. Pure *exo*-isomer, mp 40-42°C (lit[17a]. 45-46°C) was obtained by acid-base extraction, after conversion of the *endo*-carboxylic acid into the corresponding iodolactone[31]. IR (neat) ν: 3600 - 2500 (s,br), 3000 - 2860 (s,br), 1700 (s), 1420 (m), 1335 (m), 1275 (m), 1250 - 1150 (m,br), 715 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 - 1.49 (3H, m; 2xH_7 and H_3(*endo*)), 1.97 (1H, ddd, J = 4.0, 4.0 and 12.0 Hz; H_3(*exo*)), 2.28 (1H, dd, J = 4.0 and 10.0 Hz; H_2(*endo*)), 2.93 (1H, s(br); H_1 or H_4), 3.11 (1H, s(br); H_4 or H_1), 6.07 - 6.21 (2H, m; H_5 and H_6). Pure *endo*-isomer, mp 41-43°C (lit[17a]. 44-45°C) was obtained by zinc - acetic acid reduction[19] of the iodolactone. IR (neat) ν: 3600 - 2500 (s,br), 3000 - 2860 (s,br), 1700 (s), 1420 (m), 1335 (m), 1275 (m), 1250 - 1150 (m,br), 715 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 - 1.52 (3H, m; 2xH_7 and H_3(*endo*)), 1.73 - 2.07 (1H, m; H_3(*exo*)), 2.85 - 3.05 (2H, m; H_4 and H_2(*exo*)), 3.17 - 3.23 (1H, m; H_1), 5.98 (1H, dd, J = 3.0 and 5.5 Hz; H_6), 6.20 (1H, dd, J = 3.0 and 5.5 Hz; H_5).

Attempted enzymatic esterification of **10n** *and* **10x**.

To a solution of **10n** and **10x** (0.56 g; 4.1 mmol) in dry hexane (20 ml) Yeast Lipase from Candida Cylindracea (400 mg) and n-butanol (0.9 g; 12.2 mmol) were added. The suspension was stirred at room temperature and the reaction was monitored by capillary GLC. After 2 days no product ester was formed. Neither the addition of methanol (0.4 g; 12.2 mmol) nor small amounts of water (up to 0.1%) resulted in any product formation.

Endo- *and* exo-*2-bromo-bicyclo[2.2.1]hept-5-ene* 2-*carboxylic acid,* **11n** *and* **11x**.

11n and **11x** were prepared, as a mixture of *endo/exo* acids (4:6), by Diels-Alder addition of α-bromo acrylic acid and cyclopentadiene[10]. IR ($CHCl_3$) ν: 3600 - 2800 (s,br), 3060 (m), 2960 (s), 2870 (m), 1700 (s), 1430 (s), 1330 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 - 2.11 (3H, m; 2xH_7 and H_3(*endo*)), 2.62 - 2.95 (2H, m;

H_3(*exo*) and H_4), 3.40 (0.4 H, d, J = 3.0 Hz; H_1(*endo*-acid)), 3.57 (0.6 H, d, J = 3.0 Hz; H_1(*exo*- acid)), 5.93 - 6.43 (2H, m; H_5 and H_6), 10.22 (1H, s(br); -COOH). The *exo*-carboxylic acid was separated from the *endo*-acid by PLE-catalyzed hydrolysis of the Diels-Alder adduct of methyl α-bromo-acrylate and cyclopentadiene (40% *endo*-ester, 60% *exo*-ester) at pH 8.0 in water[32]. Pure *exo*-acid was obtained, mp 79-83°C (lit[10]. 93°C (after crystallization)). ^{1}H-NMR ($CDCl_3$) δ: 1.35 -1.68 (3H, m; 2xH_7 and H_3(*endo*)), 2.72 (1H, dd, J = 3.0 and 14 Hz; H_3(*exo*)), 2.92 (1H, s(br); H_4), 3.52 (1H, d, J = 3.0 Hz; H_1), 6.15 (1H, dd, J = 3.0 and 6.0 Hz; H_6), 6.35 (1H, dd, J = 3.0 and 6.0 Hz; H_5), 10.15 (1H, s(br); COOH).

Attempted enzymatic esterification of **11n** *and* **11x**.

To a solution of **11n** and **11x** (0.2 g; 0.9 mmol) in dry hexane (5 ml) Yeast Lipase from Candida Cylindracea (400 mg) and either n-butanol (0.2 g; 2.7 mmol) or methanol (0.1 g; 3.1 mmol) were added. The suspension was stirred at 30°C and the reaction was monitored by capillary GLC. After 18 h no product ester was detected. The addition of small amounts of water (up to 0.1%) did not alter this result.

Racemic endo-*bicyclo[2.2.1]hept-5-en-2-ylmethanol,* (±)-**14n**.

Endo-methanol (±)-**14n** (oil) was prepared in a yield of 96% by $LiAlH_4$ reduction[13] of *endo*-carboxylic acid **10n**. IR (CCl_4) ν: 3600 - 3200 (s,br), 3060 (m), 2980 - 2880 (s), 2860 (s), 1445 (m), 1030 (s), 720 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$)[13] δ: 0.33 - 0.57 (1H, m; H_3(*endo*)), 1.13 - 1.45 (3H, m; 2xH_7 and OH), 1.73 (1H, ddd, J = 2.0, 5.0 and 12 Hz; H_3(*exo*)), 1.97 - 2.37 (1H, m; H_2(*exo*)), 2.70 (1H, s(br); H_1 or H_4), 2.87 (1H, s(br); H_4 or H_1), 3.03 (1H, dd, J = 9.5 and 10 Hz; -CH_2OH), 3.27 (1H, dd, J = 7.0 and 9.5 Hz; -CH_2OH), 5.87 (1H, dd, J = 3.0 and 5.0 Hz; H_6), 6.03 (1H, dd, J = 3.0 and 5.0 Hz; H_5).

Racemic exo-*bicyclo[2.2.1]hept-5-en-2-ylmethanol,* (±)-**14x**.

Exo-methanol (±)-**14x** (oil) was obtained in a yield of 97% by $LiAlH_4$ reduction[13] of *exo*-carboxylic acid **10x**. IR (CCl_4)[33] ν: 3630 (m), 3600 - 3100 (s,br), 3060 (s), 3000 - 2900 / 2860 (s), 1445 (m), 1375 (m), 1335 (s), 1080 (s), 1050 - 1000 (s,br), 975 (m), 905 (s), 860 (s), 705 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$)[33] δ: 1.00 - 1.38 (4H, m; 2xH_7, H_3(*endo*) and H_3(*exo*)), 1.53 - 1.80 (1H, m; H_2(*endo*)), 1.78 (1H, s; OH), 2.76 - 2.83 (2H, m; H_1 and H_4), 3.53 (1H, dd, J = 8.0 and 11 Hz; -CH_2OH), 3.74 (1H, dd, J = 7.0 and 11 Hz; -CH_2OH), 6.02 - 6.17 (2H, m; H_5 and H_6).

Enzymatic resolution of (±)-**14n**.

To a solution of (±)-**14n** (0.37 g; 3 mmol) in methyl acetate (15 ml), PPL (600 mg) was added. The suspension was stirred at room temperature for 44 h, after which the enzyme was filtered off and washed with ether (3x10 ml). After evaporation of the solvents, the product ester and remaining alcohol were separated by column chromatography (silicagel / hexane - ethyl acetate (3:1)). This gave (+)-**14n** (0.16 g; 43%), $[\alpha]^{25}_D$ +61.9° (c 0.6, 95% ethanol) (lit[14]. for (*S*): $[\alpha]_D$ –95° (95% ethanol)), 68% ee, (*R*)-configuration . The product ester (0.28 g; 56%) was converted into the corresponding alcohol by alkaline hydrolysis following the procedure described by Cesti *et al.*[34]. Thus, the acetate (0.28 g; 1.7 mmol) was stirred over night at room temperature in a 1M solution of sodium hydroxide in ethanol (5 ml). After evaporation of the solvent the residue was taken up in water (5 ml) and extracted with ether (4x5 ml). The combined organic layers were dried on $MgSO_4$ and concentrated. The residual oil was purified by column chromatography (silicagel / hexane - ethyl

acetate (3:1)) to give alcohol (–)-**14n**, $[\alpha]^{25}_D$ –46.8° (c 0.63, 95% ethanol), ee 49%, (*S*)-configuration.

Enzymatic resolution of (±)-**14x**.

Methanol (±)-**14x** (0.39 g; 3.2 mmol) was treated according to the procedure described for (±)-**14n**, to give alcohol (–)-**14x** (0.13 g; 34%), $[\alpha]^{25}_D$ –14.6° (c 1.1, 95% ethanol) (lit[14]. for (*R*): $[\alpha]_D$ –23.9° (95% ethanol)), ee 61%, (*R*)-configuration and the acetate of alcohol (+)-**14x** (0.35 g; 66%). Alkaline hydrolysis of the latter afforded (+)-**14x**, $[\alpha]^{25}_D$ +6.0° (c 1.3, 95% ethanol), ee 25%, (*S*)-configuration.

*Racemic 2-*endo*-3-*exo*-bis(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene,* (±)-**15**.

Diol (±)-**15** was obtained by $LiAlH_4$ reduction[13] of the Diels-Alder adduct[9b] **2b** of fumaric acid and cyclopentadiene (generous gift from Dr. F.J.C. van Gastel). IR ($CHCl_3$)[35] ν: 3600 (m), 3600 - 3100 (s), 3050 (m), 3000 - 2800 (s), 1415 (m), 1330 (m), 1090 (m), 1010 (s), 980 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$)[35] δ: 1.08 -1.57 (3H, m; H_3 and 2xH_7), 1.70 - 2.07 (1H, m; H_2), 2.55 (1H, s(br); H_4), 2.78 (1H, s(br); H_1), 2.83 - 3.83 (6H, m; -CH_2OH (*endo*), -CH_2OH (*exo*) and 2x -OH), 5.88 (1H, dd, J = 5.0 and 8.5 Hz; H_6), 6.15 (1H, dd, J = 5.0 and 8.5 Hz; H_5).

Enzymatic resolution of (±)-**15***: general procedure.*

To a solution of diol (±)-**15** (0.50 g; 3.2 mmol) in methyl acetate (15 ml), PPL (600 mg) was added. The suspension was stirred at room temperature for 44 h, then the enzyme was filtered off and washed with ether (3x10 ml). After evaporation of the solvents the remaining diol, both monoesters produced and the diester were separated by column chromatography (silicagel / hexane - ethyl acetate (1:1) → (1:3) → pure ethyl acetate). This gave 0.19 g (39%) of diol (+)-**15**, $[\alpha]^{25}_D$ +52.3° (c 1.3, ethanol) (lit[16]. for (2*S*,3*S*): $[\alpha]_D$ +57.3° (ethanol)), ee 91%, (2*S*,3*S*)-configuration, as well as 0.31 g (49%) of monoacetate and 0.08 g (10%) of diacetate. The diester was converted to the corresponding diol by alkaline hydrolysis according to the procedure described by Cesti *et al.*[34] (see *enzymatic resolution of* (±)-**14n**) furnishing (–)-**15**, $[\alpha]^{25}_D$ –41.9° (c 0.74, ethanol) (lit[16]. for (2*R*,3*R*): $[\alpha]_D$ –56.8° (ethanol)), ee 73%, (2*R*,3*R*)-configuration. The ratio of *endo*- and *exo*-monoacetate was determined after Swern oxidation[15] of the hydroxymethyl group to the corresponding formyl group. Capillary GLC showed a mixture of both aldehydes in a ratio of approx. 1:3. ^{1}H-NMR minor signal (*endo*-aldehyde - *exo*-ester), δ 9.38 (d, J = 2.0 Hz) ppm, major peak (*exo*-aldehyde - *endo*-ester), δ 9.77 (d, J = 2.0 Hz) ppm.

Enzymatic resolution of (±)-**15** using either methyl propionate or methyl butyrate as the solvent was carried out following the procedure described above. The results (yields, ee's, absolute configurations, *endo* / *exo* ratios) are collected in Table 2.

Racemic endo*-2-(aminomethyl)-bicyclo[2.2.1]hept-5-ene,* (±)-**16n**.

Amine (±)-**16n** was prepared in a yield of 60% from *endo*-carboxylic acid **10n** by conversion into the corresponding carboxamide[17a] followed by reduction[17b] with $LiAlH_4$, bp 73-75°C (21 torr) (lit[36]. 61-62°C (12 torr)). IR (CCl_4) ν: 3500 - 3200 (m,br), 3380 (m), 3060 (s), 3000 - 2800 (s,br), 1630 - 1500 (s), 1460 (s), 1380 (s), 1340 (s), 1250 (w), 1150 (w), 1070 (m), 930 (m), 905 (s), 900 - 700 (s,br) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.53 (1H, ddd, J = 3.0, 3.0 and 12 Hz; H_3(*endo*)), 1.19 - 1.50 (3H, m; 2xH_7 and H_3(*exo*)), 1.87 (1H, ddd, J = 4.0, 7.0 and 12 Hz; H_2), 2.36 - 2.52 (2H, m; -C$H_2$$NH_2$), 2.63 - 2.87 (2H, m; H_1 and H_4), 5.90 (1H, dd, J = 3.0 and

6.0 Hz; H_6), 6.13 (1H, dd, J = 3.0 and 6.0 Hz; H_5).

Racemic exo-2-*(aminomethyl)-bicyclo[2.2.1]hept-5-ene,* (±)-**16x**.

Amine **16x** was prepared in a yield of 54% from *exo*-acid **10x** according to the same procedure as used for the synthesis of *endo*-amine **16n**, bp 67-68°C (13 torr) (lit[37]. 54°C (4.5 torr)). IR (CCl_4) ν: 3500 - 3200 (m,br), 3380 (m), 3060 (s), 3000 - 2800 (s,br), 1650 - 1500 (s), 1460 (s), 1455 (s), 1380 (s), 1330 (s), 1070 (s), 905 (s), 900 - 700 (s,br) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 - 1.67 (5H, m; 2xH_7, 2xH_3 and H_2), 2.58 - 2.91 (4H, m; -CH_2NH_2, H_1 and H_4), 5.98 - 6.13 (2H, m; H_5 and H_6).

Enzymatic resolution of (±)-**16n***: general procedure.*

To a solution of *endo*-amine (±)-**16n** (0.25 g; 2.0 mmol) in methyl propionate (15 ml), PPL (200 mg) was added and the suspension was stirred for 19 h at 40°C. The enzyme was filtered off and washed with dichloromethane (3x10 ml). The filtrate was analyzed by capillary GLC showing, besides some small impurities from the enzyme, a mixture of the amide of (−)-**16n** (56%) and of the amine (+)-**16n** (42%). After evaporation of the solvents, the residue was dissolved in dichloromethane (10 ml) and extracted with a 1 M HCl solution (3x4 ml). The combined water layers were washed with dichloromethane (5 ml). The combined organic layers were dried on $MgSO_4$ and evaporated to give 0.17 g (47%) of the propionamide of (−)-**16n**, $[\alpha]^{25}_D$ −2.8° (c 1.0, chloroform). Its ee was not determined. 1 M solution of NaOH was added to the water layers till pH 12 -13. Extraction with dichloromethane (6x10 ml), drying of the combined organic layers on $MgSO_4$ and evaporation of the solvents yielded 0.08 g (31%) of amine (+)-**16n**, $[\alpha]^{25}_D$ +2.0° (c 1.5, chloroform). Its ee was determined after catalytic hydrogenation (Pd/C - H_2) of the olefinic bond and subsequent precipitation of *endo*-2-(aminomethyl)-bicyclo[2.2.1]heptane hydrochloride from chloroform, $[\alpha]^{25}_D$ −0.56° (c 1.0, 95% ethanol) (lit[14]. for (*S*): $[\alpha]_{D,max}$ +11.9° (95% ethanol)), ee ~5%, (*R*)-configuration.

This procedure was repeated with PPL at room temperature for 68 h affording 0.15 g (42%) of the propionamide of (−)-**16n**, $[\alpha]^{25}_D$ −4.8° (c 1.0, chloroform) and 0.14 g (58%) of amine (+)-**16n**, $[\alpha]^{25}_D$ +2.6° (c 1.1, chloroform). The corresponding *endo*-2-(aminomethyl)-bicyclo[2.2.1]heptane hydrochloride had an $[\alpha]^{25}_D$ −0.74° (c 1.0, 95% ethanol), ee ~6%, (*R*)-configuration.

Using Papaine (200 mg / mmol; either straight from the bottle or predried at ~0.04 mbar during 4 h) instead of PPL, the procedure described above (40°C, 68 h) afforded 0.11 g (30%) of the amide, $[\alpha]^{25}_D$ 0° (c 1.0, chloroform) and 0.15 g (63%) of amine, $[\alpha]^{25}_D$ 0° (c 1.0, chloroform).

Enzymatic resolution of (±)-**16x**.

Exo-amine (±)-**16x** (0.25 g; 2.0 mmol) was treated with PPL (200 mg) in methyl propionate (15 ml) as described for the PPL-catalyzed resolution of *endo*-amine (±)-**16n** (40°C, 19 h). Yield: 0.22 g (65%) of the propionamide of (+)-**16x**, $[\alpha]^{25}_D$ +3.1° (c 1.1, chloroform) and 0.09 g (35%) of amine (−)-**16x**, $[\alpha]^{25}_D$ −5.3° (c 1.1, chloroform) (GLC analysis of the crude mixture: 67% of amide and 32% of amine). The amine obtained was converted (*cf.* resolution of (±)-**16n**) into the corresponding *exo*-2-(aminomethyl)-bicyclo[2.2.1]heptane hydrochloride, $[\alpha]^{25}_D$ −1.66° (c 1.0, 95% ethanol) (lit[14]. for (*R*): $[\alpha]_{D,max}$ −26.1° (95% ethanol)), ee ~6%, (*R*)-configuration.

Blank experiments.

A solution of either *endo*-amine (±)-**16n** (0.12 g; 1.0 mmol) or *exo*-amine (±)-**16x** (0.1 g; 0.8 mmol) in methyl propionate (7.5 ml and 6.0 ml respectively) was stirred for 68 h at 40°C, then the reaction mixture was analyzed by capillary GLC. For the *endo*-amine GLC showed a mixture of 16% of amide and 84% of amine, for the *exo*-amine a mixture of 22% of amide and 78% of amine.

(1S,2R*,6S*,7R*)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one,* (±)-**8n**.

$NaBH_4$ reduction[18] of the Diels-Alder adduct[38] **17** of maleic anhydride and cyclopentadiene gave (±)-**8n** in 66% yield, mp 125-127°C (lit[23]. 120-122°C). IR ($CHCl_3$) ν: 3040 (w), 2950 / 2910 / 2870 (s), 1755(s), 1380 (m), 1345 (m), 1170 (m), 1000 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (1H, d, J = 8.0 Hz; H_{10}), 1.64 (1H, d, J = 8.0 Hz; H_{10}), 3.06 - 3.31 (4H, m; H_1, H_2, H_6 and H_7), 3.78 (1H, dd, J = 3.0 and 9.0 Hz; H_5(*endo*)), 4,28 (1H, dd, J = 8.0 and 9.0 Hz; H_5(*exo*)), 6.26 (2H, s(br); H_8 and H_9).

(1S,2R*,4S*,5R*,6S*,9S*)-5-(hydroxymethyl)-9-iodo-8-oxatricyclo[4.2.1.0^{2,6}]nonan-7-one,* (±)-**18**.

A suspension of (±)-**8n** (7.5 g; 50 mmol) in a 0.25 M solution of NaOH in water (250 ml) was stirred at room temperature for ½ h, which resulted in a clear solution. After addition of $NaHCO_3$ (5.3 g; 62.5 mmol), a solution of KI (1.5 M) and I_2 (0.5 M) in water was added until no further decolorization occurred. Stirring was continued for another 15 min., then the aqueous suspension was extracted with dichloromethane (4x100 ml). The combined extracts were washed with a 15% $Na_2S_2O_5$ solution (100 ml) and water (50 ml), dried on $MgSO_4$ and evaporated to give 13.8 g (94%) of slightly yellow (±)-**18**, mp 125-127°C. A sample was re-crystallized from hexane - ethyl acetate (1:1), mp 126.5-128°C. IR ($CHCl_3$) ν: 3600 - 3300 (m), 2980 - 2900 / 2880 (m), 1775 (s), 1345 (m), 1165 (m), 1150 (m), 1005 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (1H, d(br), J = 12.0 Hz; H_3), 2.05 (1H, s; OH), 2.29 - 2.81 (4H, m; H_3, H_4, H_5 and H_6), 3.27 (1H, td, J = 1.0 and 5.0 Hz; H_2), 3.58 - 3.94 (2H, m; -CH_2OH; after addition of CD_3OD: 3.58 (1H, dd, J = 7.5 and 11 Hz) and 3.79 (1H, dd, J = 7.0 and 11 Hz)), 4.14 (1H, d, J = 2.5 Hz; H_9), 5.15 (1H, d, J = 5.0 Hz; H_1). MS (EI) m/e (%): 294 (16; m^+), 276 (18; -H_2O), 262 (8; -CH_2OH), 192 (25), 167 (92; -I), 149 (10; -I, -H_2O), 123 (22; -I,-CO_2), 121 (22), 105 (56; -I, -H_2O, -CO_2), 93 (75), 91 (81), 79 (100), 67 (57), 39 (75). (Found: C 36.74, H 3.79. Calc. for $C_9H_{11}IO_3$: C 36.76, H 3.77%).

Enzymatic resolution of (±)-**18**.

To a solution of (±)-**18** (11.8 g; 40 mmol) in methyl acetate (120 ml), PPL (16 g) was added. The suspension was stirred for 8 days in the dark at 40°C, then the enzyme was filtered off, washed thoroughly with acetone (3x50 ml) and stored for further use (*vide infra*). The filtrates were concentrated and the residue was chromatographed (silicagel / dichloromethane - acetone (9:1)) to give 5.2 g (39%) of acetate (+)-**19**, $[\alpha]^{25}_D$ +53.1° (c 1.0, $CHCl_3$), $[\alpha]^{25}_D$ +53.3° (c 0.42, $CHCl_3$), ee 89% (*vide infra*), and 7.1 g (60%) of alcohol (−)-**18**, $[\alpha]^{25}_D$ −35.1° (c 1.0, $CHCl_3$). A sample of the acetate, mp 103-106°C was recrystallized from hexane - ethyl acetate (1:1), mp 117.5-119°C, $[\alpha]^{25}_D$ +58,9° (c 0.5, $CHCl_3$), ee 98%. IR ($CHCl_3$) ν: 2980 - 2880 (w), 1780 (s), 1740 (s), 1370 (s), 1345 (m), 1165 (m), 1150 (m), 1000(s). ^{1}H-NMR ($CDCl_3$) δ: 1.88 (1H, d(br), J = 11 Hz; H_3), 2.09 (3H, s; -CH_3), 2.30 - 2.79 (4H, m; H_3, H_4, H_5 and H_6), 3.27 (1H, td, J = 1.0 and 5.0 Hz; H_2), 4.00 - 4.40 (3H, m; H_9 and -CH_2OAc), 5.17 (1H, d, J = 5.0 Hz; H_1). MS (EI) m/e (%): 336 (8.5; M^+), 276

(8.1; -CH_3COOH), 209 (15; -I), 192 (18), 167 (29), 149 (60; -I, -CH_3COOH), 121 (16), 105 (100; -I, -CH_3COOH, -CO_2), 93 (44), 79 (29), 43 (100). (Found: C 39.11, H 3.85. Calc. for $C_{11}H_{13}IO_4$: C 39.31, H 3.90%).

Recovered (–)-**18** was subjected to a second PPL treatment as follows: To a solution of this (–)-**18**, $[\alpha]^{25}_D$ –35.1° (c 1.0, $CHCl_3$), (6.7 g; 23 mmol) in methyl acetate (70 ml), PPL (15.6 g; recovered from the first resolution and predried at ~0.2 mbar during 4 h) was added. The suspension was stirred for 8 days in the dark at 40°C, then the enzyme was filtered off and washed with acetone (3x50 ml). After concentration of the filtrates and subsequent chromatography (silicagel / dichloromethane - acetone (9:1)) 4.7 g (70%; 42% on overall basis) of (–)-**18**, mp 102-106°C, $[\alpha]^{25}_D$ –63.8° (c 1.0, $CHCl_3$), ee 89% (*vide infra*), was isolated. Spectral data (IR, ^{1}H-NMR) were in agreement with those for (±)-**18**.

The acetate of (+)-**19** obtained above was converted into (+)-**18** as follows: A solution of (+)-**19** (3.9 g; 12 mmol) in methanol (25 ml) containing a catalytic amount of *p*-toluenesulfonic acid was heated at reflux for 5 h. After evaporation of the solvent the residue was chromatographed (silicagel / dichloromethane - acetone (9:1)) to give 3.0 g (86%) of alcohol (+)-**18**, mp 103-105°C, $[\alpha]^{25}_D$ +62.7° (c 1.0, $CHCl_3$). Spectral data (IR, ^{1}H-NMR) were in agreement with those for (±)-**18**.

The ee's of both (+)- and (–)-**18** were determined by HPLC after conversion of the alcohols into the corresponding Mosher esters[21]. To a solution of the alcohol (60.1 mg; 0.20 mmol) in CH_2Cl_2 (15 drops), (+)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride (51.0 mg; 0.20 mmol) in CH_2Cl_2 (10 drops) was added, followed by dry pyridine (5 drops). The mixture was stirred at room temperature for 1 h, then water (5 ml) was added. Extraction with CH_2Cl_2 (3x5 ml), washing of the combined extracts with 2 N HCl solution (5 ml), saturated $NaHCO_3$ (5 ml) and water (5 ml), drying on $MgSO_4$ and removal of solvents afforded a colorless oil, which, according to capillary GLC, contained no starting material anymore. HPLC analysis (silicagel Si 100, hexane - ethyl acetate (3:1)) of the esters revealed that both alcohols (+)-**18**, $[\alpha]^{25}_D$ +62.7° (c 1.0, $CHCl_3$), and (–)-**18**, $[\alpha]^{25}_D$ –63.8° (c 1.0, $CHCl_3$), were obtained with an ee of 89%.

(1S,2R,6S,7R)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one, (–)-**8n**.

To a solution of (+)-**18**, $[\alpha]^{25}_D$ +62.7° (c 1.0, $CHCl_3$), (2.9 g; 9.9 mmol) in acetic acid (12 ml) zinc powder (2.9 g) was added at 10-15°C, then some more acetic acid (6 ml) was added[19]. The suspension was stirred at 10-15°C for 1 h and subsequently at room temperature for 3 h. The solids were filtered off and successively washed with acetic acid (3x12 ml), water (3x20 ml) and ether (3x20 ml). The aqueous layer was acidified with concentrated HCl to pH 1-2, the layers were separated (if no separation occurred some more water and ether were added) and the water layer was washed with ether (3x75 ml). The combined organic layers were concentrated to give a yellow oil which was redissolved in ether (150 ml) and washed with saturated $NaHCO_3$ (2x20 ml). The combined aqueous layers were reextracted with ether (3x40 ml). The combined organic layers were dried on $MgSO_4$ and concentrated to give a slightly yellow solid (1.3 g; 86%). Recrystallization from hexane gave white (–)-**8n** (1.0g; 65%), mp 125-127°C (lit[20]. 65-67°C); $[\alpha]^{25}_D$ –140.3° (c 0.99, $CHCl_3$) (lit[20]. $[\alpha]^{26}_D$ –148.20° (c 0.52, $CHCl_3$)), ee 95% . A second recrystallization provided enantiopure (–)-**8n**, mp 129-130°C, $[\alpha]^{25}_D$ –147.9° (c 1.0, $CHCl_3$). Spectral data (IR, ^{1}H-NMR) were identical with those for (±)-**8n** (Found: C 71.76, H 6.63. Calc. for $C_9H_{10}O_2$: C 71.98, H 6.71%).

*(1R,2S,6R,7S)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one, (+)-**8n**.*

Zinc - acetic acid reduction of alcohol (−)-**18**, $[\alpha]^{25}_D$ −63.8° (c 1.0, $CHCl_3$), (3.9 g; 13.2 mmol) following the procedure described above for lactone (−)-**8n**, afforded white (+)-**8n** (1.7 g; 87%) which was recrystallized from hexane (1.3 g; 65%), mp 127-129°C (lit[20]. 65-67°C, lit[5,23]. 120-122°C); $[\alpha]^{25}_D$ +145° (c 1.0, $CHCl_3$) (lit[20]. $[\alpha]^{26}_D$ +147.52° (c 0.52, $CHCl_3$); lit[23]. $[\alpha]^{25}_D$ +143.2° (c 5.2, $CHCl_3$); lit[5]. $[\alpha]^{20}_D$ +145° (c 5.2, $CHCl_3$)), ee 97%. A second recrystallization from hexane gave enantiopure (+)-**8n**, mp 128-129°C, $[\alpha]^{25}_D$ +148.3° (c 1.0, $CHCl_3$). Spectral data (IR, ^{1}H-NMR) were identical with those of (±)-**8n**. (Found: C 72.06, H 6.67. Calc. for $C_9H_{10}O_2$: C 71.98, H 6.71%).

(1S,2R*,4S*,5R*,6S*,9S*)-9-bromo-5-(hydroxymethyl)-8-oxatricyclo[4.2.1.0^{2,6}]nonan-7-one, (±)-**21**.*

A suspension of lactone (±)-**8n** (3.0 g; 20 mmol) in 0.25 M solution of aqueous sodium hydroxide (100 ml) was stirred at room temperature for ½ h which resulted in a clear solution. After addition of $NaHCO_3$ (2.5 g; 30 mmol) bromine was slowly added until no further decolorization occurred. Stirring was continued for another 15 min., then the aqueous suspension was extracted with dichloromethane (4x50 ml). The combined extracts were washed with 15% aqueous $Na_2S_2O_5$ (25 ml), water (25 ml), dried on $MgSO_4$ and concentrated to give a slightly orange oil. Chromatography (silicagel / dichloromethane - acetone (9:1)) afforded 2.7 g (54%) of white (±)-**21**, mp 82-86°C. A sample was recrystallized from hexane - ethyl acetate (1:1), mp 85.5-87.5°C. IR ($CHCl_3$) ν: 3650 - 3150 (s), 2960 / 2920 / 2890 (m), 1760 (s), 1340 (m), 1155 (s), 1000 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.71 (1H, dd, J = 1.0 and 11 Hz; H_3), 2.24 - 2.73 (5H, m; -OH, H_3, H_4, H_5 and H_6), 3.22 (1H, td, J = 1.0 and 4.0 Hz; H_2), 3.60 (1H, dd, J = 7.0 and 11 Hz; -CH_2OH), 3.77 (1H, dd, J = 7.0 and 11 Hz; -CH_2OH), 4.07 (1H, d, J = 2.0 Hz; H_9), 4.90 (1H, d, J = 5.0 Hz; H_1). MS (EI) m/e (%): 248/246 (8.9; M^+), 230/228 (1.7/1.8; -H_2O), 167 (50; -Br), 137 (53), 109 (54), 91 (63), 85 (52), 79 (100), 77 (60), 39 (67). (Found: C 43.09, H 4.41. Calc. for $C_9H_{11}BrO_3$: C 43.75, H 4.49 %).

(1S,2R*,4S*,5R*,6S*,9S*)-5-(acetoxymethyl)-9-iodo-8-oxatricyclo[4.2.1.0^{2,6}]nonan-7-one, (±)-**19**.*

To a solution of (±)-**18** (1.5 g; 5.1 mmol) in chloroform (25 ml) acetyl chloride (1.2 g; 15.3 mmol) was added. The mixture was stirred at room temperature under argon, allowing the HCl-gas to escape. After 5 h the mixture was washed with saturated $NaHCO_3$ (3x5 ml), water (10 ml), dried on $MgSO_4$ and concentrated to give 1.7 g (100%) of (±)-**19**, mp 92-96°C. A sample was recrystallized from hexane - ethyl acetate (3:1), mp 95-97°C. Spectral data (IR, ^{1}H-NMR, MS) were identical with those of (+)-**19** described above. (Found: C 39.27, H 3.68. Calc. for $C_{11}H_{13}IO_4$: C 39.31, H 3.90%).

(1R,2R*,4R*,5S*,6S*)-5-(acetoxymethyl)-8-oxatricyclo[4.2.1.0^{2,6}]nonan-7-one, (±)-**22**.*

To a suspension of (±)-**19** (2.9 g; 8.7 mmol) in ethanol (30 ml) a solution of Bu_3SnH (10.4 mmol) in ethanol (25 ml) was added in 10 min. at 15°C under argon[24]. The mixture was stirred at room temperature for 3 h, then a small amount of oxalic acid was added. Stirring was continued for another 15 min., then ethanol was removed. The solution of the residue in chloroform (150 ml) was washed with saturated $NaHCO_3$ (50 ml), water (50 ml), dried on $MgSO_4$ and concentrated. The residual oil was chromatographed (silicagel / dichloromethane - acetone (9:1)) to give 1.7 g (94%) of white (±)-**22**, mp 79-81°C. A sample was recrystallized from hexane - ethyl acetate (3:1), mp 80-82°C. IR ($CHCl_3$) ν: 3000 - 2860 (s), 1770 (s), 1730 (s), 1365 - 1350 (m), 1245 - 1220 (m), 1165 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67 - 1.77 (4H, m; 2xH_3, H_4 and H_9), 2.07 (3H, s;

-CH_3), 2.27 - 2.76 (3H, m; H_5, H_6 and H_9), 3.27 (1H, t, J = 4.5 Hz; H_2), 4.11 (1H, dd, J = 7.0 and 12 Hz; -CH_2OAc), 4.33 (1H, dd, J = 6.0 and 12 Hz; -CH_2OAc), 4.80 (1H, t, J = 5.5 Hz; H_1). MS (EI) m/e (%): 211 (20; $M+1^+$), 168 (51; -$COCH_3$), 150 (20; -CH_3COOH), 139 (19) 122 (22), 106 (91; -CH_3COOH, -CO_2), 93 (30), 91 (61), 80 (42), 78 (79), 43 (100). (Found: C 62.89, H 6.69. Calc. for $C_{11}H_{14}O_4$: C 62.85, H 6.71%).

(1R,2R*,4R*,5S*,6S*)-5-(hydroxymethyl)-8-oxatricyclo[4.2.1.0^{2,6}]nonan-7-one*, (±)-**23**.

A solution of (±)-**22** (1.5 g; 7.0 mmol) in methanol (21 ml), containing a catalytic amount of *p*-toluenesulfonic acid, was heated at reflux over night. Methanol was evaporated and the residue was chromatographed (silicagel / dichloromethane - acetone (9:1)) to give 1.2 g (100%) of (±)-**23** (foam). IR ($CHCl_3$) ν: 3650 - 3250 (m), 2980 / 2960 / 2880 (s), 1760 (s), 1355 (s), 1160 (s), 1100 (m), 1010 (s), 990 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.52 - 1.84 (4H, m; 2xH_3, H_4 and H_9), 2.23 - 2.78 (4H, m; -OH, H_5, H_6 and H_9), 3.24 (1H, t, J = 5.0 Hz; H_2), 3.53 - 3.93 (2H, m; -CH_2OH; after addition of CD_3OD: 3.63 (1H, dd, J = 6.0 and 12 Hz) and 3.82 (1H, dd, J = 9.0 and 12 Hz)), 4.79 (1H, dd, J = 5.0 and 6.0 Hz; H_1). MS (EI) m/e (%): 168 (46; M^+), 150 (1.9; -H_2O), 138 (24), 122 (7), 106 (10; -H_2O, -CO_2), 93 (31), 91 (25), 86 (38), 84 (62), 79 (46), 66 (33), 49 (100). HRMS (EI) m/e: 168.0788 (calc. for $C_9H_{12}O_3$ (M^+): 168.0787).

(1S,2R*,4S*,5S*,6R*,9S*)-9-iodo-7-oxo-8-oxatricyclo[4.2.1.0^{2,6}]nonane5-carboxylic acid*, (±)-**24**.

The adduct **2b** (2.9 g; 16 mmol), prepared from fumaric acid and cyclopentadiene[9b,39], was dissolved in water (50 ml) by adding $NaHCO_3$ (6.8 g; 81 mmol). Then a solution of 0.2 M I_2 / 0.6 M KI was gradually added until no further decolorization occurred. Solid $Na_2S_2O_5$ was added until the color had completely disappeared, then the solution was acidified with 6 M H_2SO_4 to pH 2 and extracted with dichloromethane (5x50 ml). The combined extracts were dried on $MgSO_4$ and concentrated to give 4.9 g (99%) of white (±)-**24**, mp 125-127°C. IR (CH_2Cl_2) ν: 3200 - 2800 (w,br), 1790 / 1775 (s), 1750 (m), 1710 (m), 1345(w), 1170 (m), 1155 (m), 1110 (m), 1005 (s) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 1.80 (1H, dt, J = 1.0 and 11 Hz; H_3), 2.19 (1H, dt, J = 1.0 and 11 Hz; H_3), 2.88 - 2.91 (3H, m; H_4, H_5 and H_6), 3.22 (1H, m; H_2), 4.06 (1H, d, J = 2.5 Hz; H_9), 5.04 (1H, d, J = 5.0 Hz; H_1), 10.10 (1H, s(br); -COOH). MS (EI) m/e (%): 308 (3.3; M^+), 307 (15; -H), 181 (100; -I), 135 (31; -I, -HCOOH), 123 (25), 107 (24), 91 (48; -I, -HCOOH, -CO_2), 79 (97), 77 (26). (Found: C 35.00, H 2.97. Calc. for $C_9H_9IO_4$: C 35.09, H 2.94%).

(1S,2R*,4S*,5S*,6S*,9S*)-5-(hydroxymethyl)-9-iodo-8-oxatricyclo[4.2.1.0^{2,6}]nonan-7-one*, (±)-**25**.

To a solution of acid (±)-**24** (3.1 g; 10 mmol) in dry THF (40 ml) a 2 M solution of BH_3.Me_2S in THF (15 ml) was slowly added at -78°C under argon[25]. After allowing the reaction mixture to reach ambient temperature, stirring was continued for 3 h. Methanol (6 ml) was carefully added and the volatiles were then evaporated to give a white foam. Chromatography (silicagel / dichloromethane - acetone (9:1)) provided 2.3 g (77%) of (±)-**25** (oil). IR ($CHCl_3$) ν: 3600 (w), 3650 - 3200 (m), 2960 / 2930 / 2880 (m), 1780 (s), 1345 (m), 1310 (m), 1170 (m), 1150 (s), 1000 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.91 - 2.38 (5H, m; 2xH_3, H_5, H_6 and -OH). 2.73 (1H, s(br); H_4), 3.16 (1H, dt, J = 1.0 and 5.0 Hz; H_2), 3.57 (2H, d, J = 7.0 Hz; -CH_2OH), 3.88 (1H, d, J = 2.5 Hz; H_9), 5.11 (1H, d, J = 5.0 Hz; H_1). MS (EI) m/e (%): 294 (0.4; M^+), 167 (100; -I), 149 (12; -I, -H_2O), 121 (17), 93 (30), 91 (25), 86 (35), 84 (54), 79 (24), 67 (24), 49 (74). HRMS (EI) m/e: 167.0700 (calc. for $C_9H_{11}O_3$ (M^+-I): 167.0708).

(1S,2R*,6S*,7R*)-2-methyl-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one, (±)-27* .

This lactone was prepared in a yield of 69% by $NaBH_4$ reduction[18,26] of the Diels-Alder adduct[9a] **26** of citraconic anhydride and cyclopentadiene, mp 140.5-142.5°C (lit[26]. 137-139°C). IR (CCl_4) ν: 3070 (w), 2980 / 2910 / 2880 (s), 1770 (s), 1480 (m), 1460 / 1450 (m), 1385 (s), 1370 (m), 1230 / 1215 (s), 1195 (s), 1110 (s), 1095 (s), 1080 / 1070 (s), 995 (m), 710 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (3H, s; -CH_3), 1.69 (1H,d, J = 1.0 Hz; H_{10}), 1.71 (1H, d, J = 1.0 Hz; H_{10}), 2.66 (1H, ddd, J = 3.0, 3.5 and 9.0 Hz; H_6), 2.80 - 2.89 (1H, m; H_1), 2.98 - 3.10 (1H, m; H_7), 3.73 (1H, dd, J = 3.5 and 9.5 Hz; H_5), 4.27 (1H, dd, J = 9.0 and 9.5 Hz; H_5), 6.20 - 6.38 (2H, m; H_5 and H_6).

(1S,2R*,4S*,5S*,6S*,9S*)-5-(hydroxymethyl)-9-iodo-6-methyl-8-oxatricyclo[4.2.1.0^{2,6}]nonan-7-one, (±)-28*.

A suspension of (±)-**27** (0.33 g; 2.0 mmol) in 0.2 M sodium hydroxide (12.5 ml) was heated at reflux over night. After cooling down to room temperature $NaHCO_3$ (0.25 g; 2.5 mmol) was added, followed by slow addition of a solution of 0.2 M I_2 / 0.6 M KI until no further decolorization occurred. The emulsion was then extracted with dichloromethane (4x15 ml) and the combined extracts were washed with 5% $Na_2S_2O_5$ (10 ml), water (10 ml), dried over $MgSO_4$ and concentrated. Chromatography (silicagel / dichloromethane - acetone (9:1)) of the residue afforded, 20 mg (5%) of starting lactone (±)-**27** and 0.55 g (90%) of white (±)-**28**, mp 107-109°C. Recrystallization from hexane - ethyl acetate (2:1) gave analytically pure iodolactone, mp 109-110°C. IR ($CHCl_3$) ν: 3600 - 3300 (m,br), 2960 - 2880 (m,br), 1760 (s), 1350 (m), 1155 (m), 1140 (m), 1100 (m), 1000 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s; -CH_3), 1.84 - 2.13 (3H, m; 2xH_3 and -OH), 2.44 (1H, dt, J = 1.0 and 11 Hz; H_5), 2.74 (1H, m; H_4), 2,84 (1H, dt, J = 1.0 and 5.0 Hz; H_2), 3.53 - 3.91 (2H, m; -CH_2OH; after addition of CD_3OD: 3.60 (1H, dd, J = 8.0 and 11 Hz) and 3.78 (1H, dd, J = 8.0 and 11 Hz)), 4.18 (1H, d, J = 3.0 Hz; H_9), 5.13 (1H, d, J = 5.0 Hz; H_1). MS (EI) m/e (%): 308 (7.9; M^+), 290 (0.5; -H_2O), 192 (57), 181 (100; -I), 163 (4.4; -I, -H_2O), 153 (14), 137 (59; -I, -CO_2), 119 (53; -I, -H_2O, -CO_2), 107 (61), 93 (74), 91 (73), 81 (47), 79 (55). (Found: C 38.81, H 4.21. Calc. for $C_{10}H_{13}IO_3$: C 38.98, H 4.21%).

(1S,2R*,6S*,7R*)-4-oxatricyclo[5.2.2.0^{2,6}]undec-8-en-2-one, (±)-29*.

This lactone was prepared in a yield of 84% by $NaBH_4$ reduction[18] of the Diels-Alder adduct of maleic anhydride and 1,3-cyclohexadiene[9], mp 92-93°C (lit[23]. 86-88°C; lit[40]. 91-92.5°C). IR ($CHCl_3$) ν: 3050 (m), 2970 - 2930 / 2905 / 2870 (s), 1770 (s), 1380 / 1375 (m), 1175 (s), 1150 (m), 1050 (m), 1025, 1010 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 - 1.76 (4H, m; 2xH_{10} and H_{11}), 2.68 - 2.78 (3H, m; H_2, H_6 and H_7), 3.09 (1H, m; H_1), 3.84 (1H, dd, J = 4.0 and 9.0 Hz; H_5), 4.34 (1H, dd, J = 7.0 and 9.0 Hz; H_5), 6.20 - 6.43 (2H, m; H_8 and H_9).

(1R,2S*,6R*,7S*,8R*,9S*)-9-hydroxy-8-iodo-4-oxatricyclo[5.2.2.0^{2,6}]undecan-3-one, (±)-31*.

A suspension of lactone (±)-**29** (0.33 g; 2.0 mmol) in 0.2 M sodium hydroxide (12.5 ml) was stirred at room temperature for 1½ h which resulted in a clear solution. After addition of $NaHCO_3$ (0.25 g; 3.0 mmol), a solution of 0.2 M I_2 / 0.6 M KI was added until no further decolorization occurred. The aqueous emulsion was extracted with dichloromethane (4x10 ml), the combined extracts were washed with a 5% $Na_2S_2O_5$ solution (10 ml), water (10 ml), dried on $MgSO_4$ and concentrated to give 0.59 g (95%) of white (±)-**31**, mp 181-183°C (dec.). Recrystallization from ethyl acetate gave analytically pure (±)-**31**, mp 182.5-183.5°C (dec.). IR ($CHCl_3$) ν: 3580 (m), 3600 - 3200 (m,br), 2980 / 2930 / 2880 (m), 1760 (s), 1160 (m), 1065 (w),

1010 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 - 1.77 (4H, m; 2xH_{10} and H_{11}), 1.98 - 3.00 (5H, H_1, H_2, H_6, H_7 and -OH), 4.27 - 4.63 (4H, m; 2xH_5, H_8 and H_9). MS (EI) m/e (%): 308 (4.0; M^+), 290 (2.2; -H_2O), 181 (100; -I), 163 (7.0; -I, -H_2O), 135 (13; -I, -H_2O, -CO), 119 (22; -I, -H_2O, -CO_2), 107 (15), 93 (22), 91 (19), 79 (31). (Found: C 39.09, H 4.25. Calc. for $C_{10}H_{13}IO_3$: C 38.98, H 4.25%).

(1R,5S*)-3-oxabicyclo[4.3.0]non-7-en-2-one,* (±)-**33**.

This lactone was prepared in a yield of 54% by $NaBH_4$ reduction[18] of anhydride **32** (from Aldrich), bp 91-95°C (0.3 torr) (lit[41]. 85°C (0.1 torr); lit[30]. 80°C (0.05 torr)). IR ($CHCl_3$) ν: 3020 (w), 2980 (w), 2880 / 2840 (m), 1750 (s), 1370 (w), 1125 (s), 1010 / 995 / 980 (m), 945 / 930 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.73 - 1.89 (6H, m; H_1, H_5, 2xH_6 and H_9), 4.00 (1H, dd, J = 2.0 and 9.0 Hz; H_4), 4.31 (1H, dd, J = 4.5 and 9.0 Hz; H_4), 5.70 (1H, s; H_7 or H_8), 5.72 (1H, s; H_8 or H_7).

(1R,5S*,7S*,8S*)-8-hydroxy-7-iodo-3-oxabicyclo[4.3.0]nonan-2-one,* (±)-**35**.

To a suspension of $NaBH_4$ (0.38 g; 10 mmol) in dry THF (5 ml) a solution of anhydride **32** (1.5 g; 10 mmol) in dry THF (10 ml) was slowly added at 0°C. Stirring was continued at 0°C for ½ h and at room temperature for 1½ h. Then, at 0°C 2 M HCl (15 ml) was carefully added, immediately followed by $NaHCO_3$ (2.5 g; 30 mmol). THF was evaporated, then, a solution of 0.5 M I_2 / 1.5 M KI was added until no further decolorization occurred. The aqueous emulsion was extracted with dichloromethane (4x10 ml) and the combined extracts were washed with a 5% $Na_2S_2O_5$ solution (10 ml), water (10 ml), dried on $MgSO_4$ and concentrated. The residual gray solid was chromatographed (silicagel / dichloromethane - acetone (9:1)) to afford 1.4 g (51%) of (±)-**35**, mp 100-104°C (lit[27]. 124-126°C). A sample was recrystallized from hexane - ethyl acetate (2:1), mp 123-124°C (dec.). IR ($CHCl_3$) ν: 3580 (m), 3600 - 3200 (m,br), 3000 - 2900 (m,br), 1765 (s), 1375 (m), 1150 (s), 1120 (m), 1040 (m), 1005 (s), 950 (m), 930 (m), 895 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 - 2.97 (7H, m; H_1, H_5, 2xH_6, 2xH_9 and -OH), 4.00 (1H, dd, J = 2.0 and 9.0 Hz; H_4), 4.11 (1H, t, J = 3.0 Hz; H_7), 4.29 (1H, dd, J = 4.5 and 9.0 Hz; H_4), 4.24 - 4.40 (1H, m; H_8). MS (EI) m/e (%): 282 (6.0; M^+), 265 (11; M+1-H_2O), 155 (100; -I), 137 (12; -I, -H_2O), 125 (12), 109 (34), 93 (33), 81 (84), 79 (58), 67 (35), 55 (46), 41 (55). (Found: C 34.19, H 3.97. Calc. for $C_8H_{11}IO_3$: C 34.06, H 3.93%).

Enzymatic resolution of (±)-**18**: *general procedure*.

To a solution of iodolactone (±)-**18** (0.74 g; 2.5 mmol) in methyl propionate (19 ml), PPL (500 mg) was added and the suspension obtained was stirred in the dark for 91 h at 40°C. The enzyme was filtered off, washed with acetone (3x8 ml) and the filtrates were concentrated. Chromatography (silicagel / dichloromethane - acetone (9:1)) gave 0.42 g (60%) of alcohol (−)-**18** and 0.36 g (42%, containing impurities from the enzyme) of the propionate of (+)-**18**. The propionate was converted into the corresponding alcohol (+)-**18** by acid hydrolysis as described under the synthesis of tricyclic lactones (+)- and (−)-**8n**.

PPL (91 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +67.8° (c 1.0, chloroform), ee 95%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −46.3° (c 1.0, chloroform), ee 64%, (5*S*)-configuration.

PPL (115 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +66.9° (c 1.0, chloroform), ee 94%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −51.2° (c 1.0, chloroform), ee 71%, (5*S*)-configuration.

PPL (164 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +66.0° (c 1.0, chloroform), ee 93%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −56.1° (c 1.0, chloroform), ee 78%, (5*S*)-configuration.

Mucor (68 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +51.2° (c 1.0, chloroform), ee 72%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −49.9° (c 1.0, chloroform), ee 70%, (5*S*)-configuration.

The optical purities of (+)- and (−)-**18** and their absolute configurations were established by comparison of the optical rotations with those for enantiopure (+)-(5*R*)-**18**, $[\alpha]^{25}_D$ +71.0° (c 1.0, chloroform) and (−)-(5*S*)-**18**, $[\alpha]^{25}_D$ −71.8° (c 1.0, chloroform) obtained from enantiopure lactones (−)-(2*R*,6*S*)-**8n**, $[\alpha]^{25}_D$ −147.9° (c 1.0, chloroform) and (+)-(2*S*,6*R*)-**8n**, $[\alpha]^{25}_D$ +148.3° (c 1.0, chloroform), respectively, as described for (±)-**18**.

Enzymatic resolution of (±)-**21**.

The reaction was performed using the general procedure described for (±)-**18**.

PPL (43 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +48.9° (c 0.22, chloroform), ee >98%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −31.2° (c 0.24, chloroform), ee 63%, (5*S*)-configuration.

PPL (91 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +47.7° (c 0.20, chloroform), ee 97%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −35.0° (c 0.21, chloroform), ee 70%, (5*S*)-configuration.

PPL (163 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +47.2° (c 0.22, chloroform), ee 96%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −41.8° (c 0.19, chloroform), ee 84%, (5*S*)-configuration.

Mucor (68 h): alcohol obtained from propionate, $[\alpha]^{25}_D$ +32.9° (c 0.24, chloroform), ee 67%, (5*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −36.0° (c 0.23, chloroform), ee 73%, (5*S*)-configuration.

The optical purities of (+)- and (−)-**21** and their absolute configurations were established by comparison of their optical rotations with those of enantiopure (+)-(5*R*)-**21**, $[\alpha]^{25}_D$ +49.2° (c 0.22, chloroform) and (−)-(5*S*)-**21** ,$[\alpha]^{25}_D$ −49.8° (c 0.23, chloroform) obtained from enantiopure (−)-(2*R*,6*S*)-**8n**, $[\alpha]^{25}_D$ −147.9° (c 1.0, chloroform) and (+)-(2*S*,6*R*)-**8n**, $[\alpha]^{25}_D$ +148.3° (c 1.0, chloroform), respectively, as described for (±)-**21**.

Enzymatic resolution of (±)-**23**.

According to the general procedure described for (±)-**18** the following results were obtained:

PPL (19 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ −37.6° (c 0.47, chloroform), ee 88%, (5*S*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ +18.2° (c 0.46, chloroform), ee 43%, (5*R*)-configuration.

PPL (67 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ −35.7° (c 0.50, chloroform), ee 84%, (5*S*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ +30.7° (c 0.51, chloroform), ee 72%, (5*R*)-configuration.

PPL (163 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ −32.2° (c 0.46, chloroform), ee 76%, (5*S*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ +37.6° (c 0.46, chloroform), ee 88%, (5*R*)-configuration.

The optical purities of (+)- and (−)-**23** and their absolute configurations were established by comparison of the optical data with those of enantiopure (+)-(5*R*)-**23**, $[\alpha]^{25}_D$ +42.8° (c 0.45, chloroform) and (−)-(5*S*)-**23**, $[\alpha]^{25}_D$ −42.5° (c 0.47, chloroform) obtained from enantiopure (+)-(2*S*,6*R*)-**8n**, $[\alpha]^{25}_D$ +148.3° (c 1.0, chloroform) and (−)-(2*R*,6*S*)-**8n**, $[\alpha]^{25}_D$ −147.9° (c 1.0, chloroform), respectively, as described for (±)-**23**.

Enzymatic resolution of (±)-**25**.

Using the general procedure described for (±)-**18** the following results were obtained:

PPL (19 h): alcohol (+)-**25** obtained from the propionate, $[\alpha]^{25}_D$ +33.5° (c 1.1, chloroform), ee 74%, (5*S*)-configuration; recovered alcohol (−)-**25**, $[\alpha]^{25}_D$ −35.0° (c 1.0, chloroform), ee 78%, (5*R*)-configuration.

The optical purities of (+)- and (−)-**25** and their absolute configurations were established by conver-

sion into diols (–)- and (+)-**15**, respectively, as follows: zinc / acetic acid reduction[19] of (+)-(5*S*)-**25** and subsequent $LiAlH_4$ reduction[13] gave pure *trans*-diol (–)-**15**, $[\alpha]^{25}_D$ –41.5° (c 1.0, ethanol) (lit[16]. for (–)-(2*R*,3*R*)-**15**, $[\alpha]_D$ –56.8° (ethanol)). Analogously, (–)-**25** gave diol (+)-**15**, $[\alpha]^{25}_D$ +45.1° (c 1.2, ethanol) (lit[16]. for (+)-(2*S*,3*S*)-**15**, $[\alpha]_D$ +57.3° (ethanol)).

Enzymatic resolution of (±)-**28**.

The reactions were performed using the general procedure described for (±)-**18**.

PPL (164 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +85.2° (c 1.0, chloroform), ee 93%, (5*S*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ –59.5° (c 1.1, chloroform), ee 65%, (5*R*)-configuration.

Mucor (68 h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +74.4° (c 1.0, chloroform), ee 83%, (5*S*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ –44.4° (c 1.1, chloroform), ee 49%, (5*R*)-configuration.

The optical purities of the alcohols (+)- and (–)-**28** were determined by means of GLC analysis of the corresponding (+)-*R*-α-methoxy-α-trifluoromethyl-α-phenyl acetate derivatives prepared by the procedure of Mosher *et al.*[21] (see, preparation of Mosher esters of (+)- and (–)-**18**). The absolute configuration was established as follows: enantiopure lactone (+)-(2*S*,6*R*)-**8n**, $[\alpha]^{25}_D$ +148.3° (c 1.0, chloroform), was converted into enantiopure (–)-(5*R*)-**28**, $[\alpha]^{25}_D$ –92.3° (c 1.0, chloroform), by α-alkylation[42] with LDA / MeI and subsequent ring opening and iodolactonization as described for the synthesis of (±)-**28**.

Enzymatic resolution of (±)-**35**.

This resolution was carried out according to the general procedure described for (±)-**18** (reaction time 68 h). The propionate of (–)-**35** was converted into bicyclic lactone (+)-**33**, $[\alpha]^{25}_D$ +17.3° (c 1.5, chloroform), ee 26%, (1*R*,5*S*)-configuration, by zinc - acetic acid reduction[19] as described for the synthesis of tricyclic lactone (–)-**8n** from iodolactone (+)-**18**. The remaining alcohol (+)-**35**, $[\alpha]^{25}_D$ +10.3° (c 1.0, chloroform), ee 11%, (8*R*)-configuration, first was acetylated as described for the synthesis of acetate (+)-**19** (acetyl bromide was used in stead of acetyl chloride) and then converted into bicyclic lactone (–)-**33**, $[\alpha]^{25}_D$ –7.1° (c 1.3, chloroform), ee 11%, (1*S*,5*R*)-configuration, by a zinc - acetic acid reduction. The optical purities of both lactones (+)- and (–)-**33** and their absolute configurations were established by comparison of the optical rotation with that of enantiopure (–)-(1*S*,5*R*)-**33**, $[\alpha]^{25}_D$ –67.1° (c 1, chloroform), reported in the literature[30].

Propionate of (–)-**35**: IR ($CHCl_3$) ν: 3000 - 2850 (m), 1775 (s), 1730 (s), 1445 (m), 1350 (s), 1325 (s), 1155 (s), 1130 (s), 1075 (s), 1010 (s), 965 (s), 925 (m), 905 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J = 7.5 Hz; $-CH_3$), 2.06 - 2.87 (6H, m; H_1, H_5, 2xH_6 and H_9), 2.38 (2H, q, J = 7.5 Hz; $-CH_2CH_3$), 3.94 (1H, dd, J = 7.0 and 11 Hz; H_4), 4.12 (1H, dd, J = 5.5 and 11 Hz; H_4), 4.48 - 4.59 (1H, m; H_7), 4.84 (1H, t, J = 4.5 Hz; H_8). MS (EI) m/e (%): 339 (2.4; M^++1), 265 (3.2; M^++1 - C_2H_5COOH), 264 (4.2; M^+ -C_2H_5COOH), 211 (13; -I), 155 (63), 137 (26; -I, -C_2H_5COOH), 109 (76), 93 (69; -I, -C_2H_5COOH, -CO_2), 79 (20), 57 (100).

Acetate of (+)-**35**: IR ($CHCl_3$) ν: 3050 - 2920 (m), 2900 (m), 1775 (s), 1730 (s), 1420 (m), 1370 (s), 1315 (m), 1240 - 1180 (s), 1145 (s), 1120 (s), 1040 (s), 1015 (s), 990 (s), 945 (s), 925 (m), 875 (m), 850 (m), 800 - 660 (s(br)) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s; $-CH_3$), 2.07 - 2.16 (1H, m; H_1 or H_5), 2.47 - 3.03 (5H, m; H_5 or H_1, 2xH_6 and H_9), 4.00 (1H, d, J = 9.0 Hz; H_4), 4.29 (1H, dd, J = 4.0 and 9.0 Hz; H_4), 4.39 (1H, dd, J = 3.5 and 7.0 Hz; H_7), 5.06 (1H, dd, J = 3.0 and 6.5 Hz; H_8). MS (EI) m/e (%): 324 (0.3; M^+), 264 (58; -CH_3COOH), 197 (12; -I), 155 (60), 137 (12; -I, -CH_3COOH), 109 (73), 93 (23; -I, -CH_3COOH, -CO_2), 79 (17), 43 (100).

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