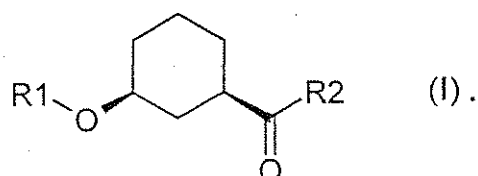


Description

Method for producing the enantiomer forms of cis-configured 3-hydroxycyclohexane
5 carboxylic acid derivatives using hydrolases

The invention relates to a process for preparing chiral nonracemic cis-configured
cyclohexanols or cyclohexanol derivatives of the formula (I)



cis-configured hydroxycyclohexanecarboxylic acid derivatives of the formula (I) are
central building blocks or immediate precursors for the medicinally active
15 compounds described in the DE application No. 103 08 355.3 or WO2004/076426
which allow a therapeutic modulation of the lipid and/or carbohydrate metabolism
and are thus suitable for preventing and/or treating type II diabetes and
atherosclerosis.

20 The syntheses, described in the patent applications mentioned above, of the
nonracemic cis-configured cyclohexanol building blocks or derivatives are unsuitable
for use as industrial processes: the separation of the isomers, for example the
separation of the enantiomers (racemate resolution) by chromatography on a chiral
phase is too complex and too expensive. Moreover, for chromatographic separations
25 of enantiomers, the racemic compound has to be present in good chemical purity,
which in many cases can only be achieved by an additional upstream
chromatography.

In addition, numerous reactions cannot be carried out on an industrial scale. These

include in particular alkylations with NaH in DMF, which, as is known, are a high safety risk (C&EN, September 13, 1982, 5).

5 The methods for synthesizing optically pure cis-configured 3-hydroxycyclohexanecarboxylic acid derivatives also known from the literature are unsuitable for producing relatively large amounts of the central building blocks of the medicinally active compounds mentioned above or unsuitable for developing an industrial process, since the number of steps and/or the yield, the expenditure for purifications, in particular for cis/trans separations, and in many cases also the optical purity are
10 unacceptable.

For example: some of the synthetic methods described in the literature for preparing optically pure cis-configured 3-hydroxycyclohexanecarboxylic acid derivatives are based on the hydrogenation or dearomatization of m-hydroxybenzoic acid or its derivatives and subsequent classical racemate resolution by formation of salts. In
15 the case of the hydrogenation of m-hydroxybenzoic acid in the presence of PtO₂ in ethanol (D. S. Noyce, D. B. Denney, *J. Am. Chem. Soc.* **1952**, 74, 5912; cf. J. A. Hirsch, V. C. Truc, *J. Org. Chem.* **1986**, 51, 2218) it has been described that six crystallizations are required to obtain racemic cis-3-hydroxycyclohexanecarboxylic acid chemically pure in a yield of 13.8%. Noyce and Denney also describe the
20 racemate resolution of cis-3-hydroxycyclohexanecarboxylic acid with the aid of quinine trihydrate. Starting with 500 g of quinine trihydrate and 188.3 g of (R,S)-cis-3-hydroxycyclohexanecarboxylic acid, after several crystallization steps, 162 g of the (+)-cis-3-hydroxycyclohexanecarboxylic acid quinine salt are obtained. Details concerning the optical purity (ee) are not given, optical rotations are stated.
25 In a further method for preparing optically active cis-3-hydroxycyclohexanecarboxylic acid, the precipitation of the racemic cis-configured carboxylic acid with cinchonidine [a) D. S. Noyce, D. B. Denney, *J. Am. Chem. Soc.* **1952**, 74, 5912; b) M. Nakazaki, K. Naemura, S. Nakahara, *J. Org. Chem.* **1979**, 44, 2438] and the subsequent recrystallization of the resulting salt from methanol or ethanol are utilized.

30 The methods described are unsuitable for preparing relatively large amounts of optically active cis-3-hydroxycyclohexanecarboxylic acid derivatives, since the large number of chemical steps and/or purification steps, the use of large amounts of

optically pure chiral auxiliaries for racemate resolution, the unavoidable liberation of the desired stereoisomer from the salt and not least the poor total yields are unpractical and uneconomical.

- 5 The preparation of methyl cis-3-acetoxycyclohexanecarboxylate, albeit in racemic form, has been described in D. S. Noyce, H. I. Weingarten, *J. Am. Chem. Soc.* **1957**, *70*, 3098.

A more recent publication (C. Exl, E. Ferstl, H. Hönig, R. Rogi-Kohlenprath, *Chirality*
10 **1995**, *7*, 211) describes the Rh-catalyzed hydrogenations of (-)-menthyl 3-acetoxybenzoate and (-)-menthyl 4-hydroxybenzoate in methanol/acetic acid at 100 bar and 40°C and 35°C, respectively. In both reactions, at least four products are formed, inter alia the desired product. The substantial disadvantages of the reactions are: a) a large number of steps owing to the preparation of the optically
15 active benzoic esters and the subsequent removal of the chiral auxiliary; b) technically demanding reaction conditions (100 bar); c) unsatisfactory yields and complicated purifications owing to the large number of byproducts and d) low optical purities. In the end, the authors themselves draw the conclusion that their process is of only little practical value.

20 D. A. Evans, G. C. Fu and A. H. Hoveyda (*J. Am. Chem. Soc.* **1992**, *114*, 6671) describe the Ir(I)-catalyzed hydroboration of secondary or tertiary amides of 3-cyclohexenecarboxylic acid. Although yields and diastereoselection are good, there is the problem of removing the trans-isomer. In addition, the conversion of the
25 amides mentioned into the desired compounds of the formula (I) requires either cleavage of the amide bond under relatively drastic conditions with concomitant partial epimerization and lactonization, or else direct rearrangement of the amides into the desired compounds of the formula (I) which means, for example, the stereoselective synthesis of amino acid radicals and entails a large number of steps
30 and is therefore uneconomical. This process is unsuitable for use as an industrial process.

The synthesis of methyl (1R,3R)-3-hydroxy-4-cyclohexenecarboxylate, which is a

direct precursor of methyl (1R,3S)-3-hydroxycyclohexanecarboxylate, in a 500 mg scale has been described (J. A. Marshall, S. Xie, *J. Org. Chem.* **1995**, *60*, 7230 and literature cited). Key step of the synthesis is an asymmetric [4+2]-cycloaddition between an optically active bisacrylate and butadiene in the presence of TiCl₄.

- 5 Removal of the chiral auxiliary gives (R)-3-cyclohexenecarboxylic acid with 95% ee which, via iodolactonization and subsequent elimination of HI, is converted into (1R,5R)-7-oxabicyclo[3.2.1]oct-2-en-6-one. Opening of the unsaturated lactone using NaHCO₃/MeOH yields methyl (1R,3R)-3-hydroxy-4-cyclohexenecarboxylate. There have been several descriptions of the synthesis of (R)- or (S)-3-cyclohexenecarboxylic acid via such cycloadditions. Essentially, the numerous examples differ in
- 10 the chiral auxiliary used. A few publications may be mentioned by way of example: a) W. Oppolzer, C. Chapuis, D. Dupuis, M. Guo, *Helv. Chim. Acta* **1985**, *68*, 2100; b) C. Thom, P. Kocienski, K. Jarowicki, *Synthesis* **1993**, 475; c) B. M. Trost, Y. Kondo, *Tetrahedron Lett.* **1991**, *32*, 1613. On an industrial scale, these reactions
- 15 require particular measures to ensure safe handling of the acrylates and the butadiene.

- A great disadvantage of these syntheses are the large amounts of iodine and potassium iodide used for lactonizing the cyclohexenecarboxylic acid: in the publication of J. A. Marshall and S. Xie, 1.61 g of iodine (about 1 eq.) and 6.0 g
- 20 (about 6 eq.) of potassium iodide are required for preparing 460 mg of methyl (1R,3R)-3-hydroxy-4-cyclohexenecarboxylate by intramolecular cyclization of 760 mg of cyclohexenecarboxylic acid. In the publication of A. S. Raw and E. B. Jang, (*Tetrahedron* **2000**, *56*, 3285), the iodolactonizations are carried out using as much as three times the amount of iodine. Owing to safety considerations
- 25 and from an ecological point of view, it is not feasible to carry out such a reaction on a multi-kg scale. In addition, the preparation of the lactones mentioned requires chromatographic purifications.

- Phenylseleno- and phenylsulfenollactonizations [a) K. C. Nicolaou, S. P. Seitz, W. J. Sipio, J. F. Blount, *J. Am. Chem. Soc.* **1979**, *101*, 3884; b) K. C. Nicolaou, *Tetrahedron* **1981**, *37*, 4097] are not a suitable alternative. Not only are the reagents
- 30 used and/or the products and byproducts formed highly malodorous, in many cases, they are also toxic and cause ecological damage. In most cases, chromatographic purifications are required to remove unwanted subsequent Se or S byproducts. It is

therefore not feasible to carry out such a reaction on a multi-kg scale.

The bromolactonization (C. Iwata, A. Tanaka, H. Mizuno, K. Miyashita, *Heterocycles* **1990**, 31, 987 and literature cited therein), too, does not provide an alternative for the industrial scale, since bromides or bromine sources are to be avoided for ecological reasons and/or require particular precautions.

(R)-Cyclohexenecarboxylic acid can furthermore be obtained by enzymatic desymmetrization of 1,2-cyclohex-4-enedicarboxylic esters (P. Kocienski, M. Stocks, D. Donald, M. Perry, *Synlett* **1990**, 38); however, here, too, the abovementioned disadvantages of the iodolactonization apply.

A further alternative is the reduction of 2-iodo-7-oxabicyclo[3.2.1]octan-6-one (also referred to as 4-iodo-6-oxabicyclo[3.2.1]octan-7-one), the immediate product of the iodolactonization of cyclohexenecarboxylic acid, using Bu_3SnH to give the saturated lactone which can then be converted using, for example, NaOEt in ethanol into ethyl 3-hydroxycyclohexanecarboxylate. The removal of the iodine has been described in numerous examples, inter alia in A. S. Raw, E. B. Jang, *Tetrahedron* **2000**, 56, 3285. Frequently, work-up of the Bu_3SnH reaction and complete removal of the resulting Sn and iodine compounds is difficult and, in many cases, requires additional chromatographic purifications, which is also not desirable for an industrial process. The same applies to the removal of the Se, S and Br compounds in the case of the phenylseleno-, the phenylsulpheno- and the bromolactonization.

The enzymatic racemate resolution of methyl cis-3-hydroxycyclohexanecarboxylate or the tetrahydropyranyl derivative by α -chymotrypsin-catalyzed ester hydrolysis (J. B. Jones, P. W. Marr, *Tetrahedron Lett.* **1973**, 3165) is likewise not a suitable process, since the optical purities of the products are unsatisfactory: the experiments that were carried out gave 42% and 50% ee, respectively. Using an optimized control of the conversion, it is possible to achieve enantiomeric excesses of 85%. On the one hand, this is unsatisfactory, and on the other hand, this is only possible by accepting considerably reduced yields.

The preparation of methyl 3-oxocyclohexene-1-carboxylate and methyl

3-oxocyclohexanecarboxylate by reduction of m-methoxybenzoic acid using sodium in liquid ammonia has been described in M. E. C. Biffin, A. G. Moritz, D. B. Paul, *Aust. J. Chem.* **1972**, 25, 1320.

- 5 The stereoselective microbial reduction of racemic 3-oxocyclohexanecarboxylic esters using *Rhizopus arrhizus* and subsequent separation of the diastereomers also leads to optically active cis-3-hydroxycyclohexanecarboxylic esters (F. Trigalo, D. Buisson, R. Azerad, *Tetrahedron Lett.*, **1988**, 29, 6109 and the literature cited). The complicated separation of the diastereomers makes a scale-up to the industrial
10 scale unattractive.

- The reduction of methyl (R)-3-oxocyclohexanecarboxylate with HLAD (horse liver alcohol dehydrogenase) in the presence of NADH yields the cis/trans mixture of methyl 3-hydroxycyclohexanecarboxylate (J. J. Willaert, G. L. Lemiere, L. A. Joris,
15 J. A. Lepoivre, F. C. Alderweireldt, *Bioorganic Chemistry* **1988**, 16, 223). Accordingly, this method is likewise unsuitable for preparing optically pure cis-3-hydroxycyclohexanecarboxylic acid building blocks.

- The asymmetric reduction of isopropyl 3-oxocyclohexene-1-carboxylate with
20 *Geotrichum candidum* (L. Fonteneau, S. Rosa, D. Buisson, *Tetrahedron: Asymmetry* **2002**, 13, 579), too, is not of any interest, since only the trans-isomer of isopropyl 3-hydroxycyclohexanecarboxylate is formed.

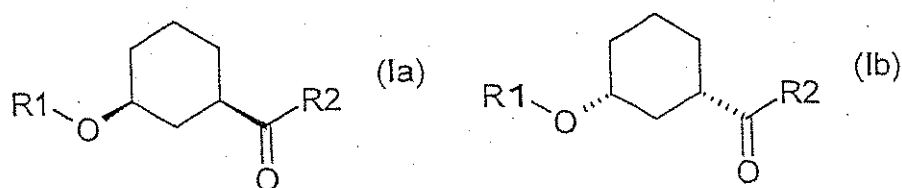
- Examination of the reaction of shikimate dehydrogenase with 3-oxocyclohexane-
25 carboxylic acid in the presence of NADPH shows that this enzyme converts the (S)-enantiomer in a yield of 90% into the corresponding trans-3-hydroxycyclohexanecarboxylic acid (T. D. H. Bugg, C. Abell, J. R. Coggins, *Tetrahedron Lett.* **1988**, 29, 6779). Accordingly, this reaction is also unsuitable.

- 30 Industrial application of the biosynthesis of cyclohexanecarboxylic acid in *Alicyclobacillus acidocaldarius* (formerly *Bacillus acidocaldarius*) and *Streptomyces collinus*, which starts with shikimic acid and proceeds via 3-hydroxycyclohexanecarboxylic acid, is not possible, since 3-hydroxycyclohexanecarboxylic acid is the

trans-configured (1S,3S)-isomer (B. S. Moore, K. Poralla, H. G. Floss, *J. Am. Chem. Soc.* **1993**, *115*, 5267).

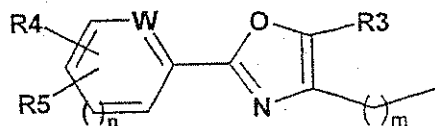
Accordingly, it was an aim of the embodiments disclosed herein to develop a process which does not have the disadvantages mentioned.

In one aspect, there is provided a process for preparing chiral nonracemic compounds of the formulae (Ia) and (Ib)



where:

R¹ is



in which:

R³ is H, (C1-C6)-alkyl, (C3-C8)-cycloalkyl, (C1-C3)-alkyl-(C3-C8)-cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl, (C5-C6)-heteroaryl, (C1-C3)-alkyl-(C5-C6)-heteroaryl or (C1-C3)-alkyl which is fully or partially substituted by F;

R⁴, R⁵ independently of one another are H, F, Cl, Br, CF₃, OCF₃, (C1-C6)-alkyl, O-(C1-C6)-alkyl, SCF₃, SF₅, OCF₂-CHF₂, (C6-C10)-aryl, (C6-C10)-aryloxy, OH, NO₂; or

R⁴ and R⁵ together with the carbon atoms that carry them form a fused partially saturated or unsaturated bicyclic (C6-C10)-aryl or (C5-C11)-heteroaryl ring;

W is CH, N, if $n = 1$;

W is O, S, NR^6 , if $n = 0$;

m is 1-6;

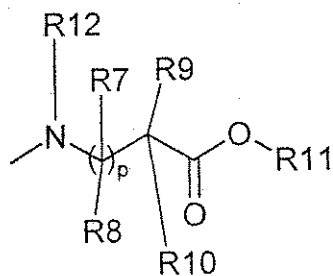
R^6 is H, (C1-C6)-alkyl-phenyl, (C1-C6)-alkyl;

10 or

R^1 is an OH protective group (PG), such as, for example, benzyloxymethyl, benzyl, para-methoxybenzyl, tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), tetrahydropyranyl (THP), 1-ethoxyethyl (EE), 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl;

and

R^2 is



20

in which:

p is 0 – 2;

25 R^7 is H, (C1-C6)-alkyl;

R^8 is H, (C1-C6)-alkyl;

R^9 is H, F, (C1-C6)-alkyl;

R^{10} is H, F, (C1-C6)-alkyl, O-(C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, phenyl, where alkyl, alkenyl, alkynyl and cycloalkyl may optionally be substituted by one or more radicals from the group consisting of hydroxyl, phenyl, (C5-C11)-heteroaryl, O-(C1-C6)-alkyl and $NR^{13}R^{14}$, and phenyl may optionally be substituted by one or more radicals from the group consisting of hydroxyl, O-(C1-C6)-alkyl, F and CF_3 , with the proviso that R^{10} is not $NR^{13}R^{14}$ or O-(C1-C6)-alkyl, if $R^9 = F$;

R^9 and R^{10} together with the carbon atom that carries them are (C3-C8)-cycloalkyl;

R^{10} and R^{12} together are pyrrolidine and piperidine, if $n = 0$;

R^{11} is H, (C1-C8)-alkyl, benzyl, (C1-C4)-alkyl-(C6-C10)-aryl, (C1-C4)-alkyl-O-(C1-C4)-alkyl, phenyl-(C1-C4)-alkyl, where alkyl, benzyl, phenyl, aryl may optionally be mono- or polysubstituted by O-(C1-C6)-alkyl, OCH_2CH_2-OMe , F, Cl, Br, I, $Si(CH_3)_3$, $OSi(CH_3)_3$, $Si(iPr)_3$, $OSi(iPr)_3$, $OCH_2CH_2-SiMe_3$, $OCH_2-Si(iPr)_3$, $O-CH_2-C_6H_5$, $SO_2C_6H_4-p-Me$, SMe , CN , NO_2 , $CH_2COC_6H_5$;

R^{12} is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, benzyl, $CO-(C1-C6)-alkyl$, $CO-phenyl$, $C(O)-O-(C1-C6)-alkyl$, allyloxycarbonyl (ALOC), benzyloxycarbonyl (Cbz, Z), 9-fluorenylmethyloxycarbonyl (Fmoc), (C1-C4)-alkyl-(C6-C10)-aryl, (C1-C4)-alkyl-(C5-C11)-heteroaryl, (C1-C4)-alkyl-O-(C1-C4)-alkyl, phenyl-(C1-C4)-alkyl, (C5-C6)-heteroaryl-(C1-C4)-alkyl; $SO_2-(C1-C6)-alkyl$, $SO_2-(C1-C6)-alkyl-SO_2-(C1-C6)-alkyl$, $SO_2-phenyl$, where phenyl may optionally be substituted by (C1-C6)-alkyl, O-(C1-C6)-alkyl, F, Cl;

R^{13} is (C1-C6)-alkyl;

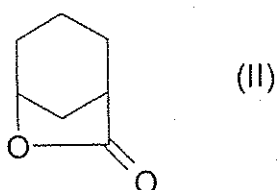
10
R¹⁴ is (C1-C6)-alkyl-phenyl, (C1-C6)-alkyl;

wherein

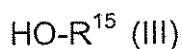
5 A)

a) Lactone opening (LO)

racemic 6-oxabicyclo[3.2.1]octan-7-one of the formula (II)



10 is reacted with a compound of the formula (III)



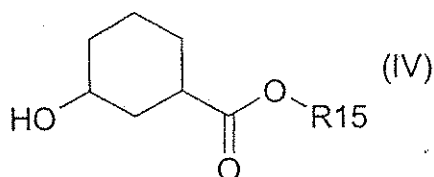
15 where

R¹⁵ is H, (C1-C8)-alkyl, (C3-C8)-cycloalkyl, (C2-C8)-alkenyl, (C2-C8)-alkynyl, benzyl, (C1-C4)-alkyl-(C6-C10)-aryl, (C1-C4)-alkyl-(C5-C11)-heteroaryl, (C1-C4)-alkyl-O-(C1-C4)-alkyl, phenyl-(C1-C4)-alkyl, (C5-C6)-heteroaryl-(C1-C4)-alkyl, where alkyl, benzyl, phenyl, aryl, heteroaryl may optionally be mono- or polysubstituted by phenyl, O-(C1-C6)-alkyl, OCH₂CH₂-OMe, OTs, F, Cl, Br, I, Si(CH₃)₃, OSi(CH₃)₃, Si(iPr)₃, OSi(iPr)₃, OCH₂CH₂-SiMe₃, OCH₂-Si(iPr)₃, OTHP, O-CH₂-C₆H₅, SO₂C₆H₄-p-Me, SMe, CN, NO₂, COOH, CONH₂, CH₂COC₆H₅, CO-benzyloxy, CO-O(C1-C6)-alkyl, NHTs, NHAc, NHBoc, NHAloc, NHbenzyl;

25 in the presence of suitable bases or acids in a suitable solvent (for example with hydroxides such as NaOH or CsOH in water or, for example, with carbonates such as K₂CO₃ in alcohols or, for example, with acids such as HCl in water) or with acid
30 halides such as acetyl chloride in alcohols, preferably acetyl chloride in isopropanol,

where in the case of aqueous reactions the work-up conditions determine whether, for example, the Cs (for example if CsOH is used) or the Na (for example if NaOH is used) or the ammonium salt (for example if NH_3 is used) or else the free acid is obtained,

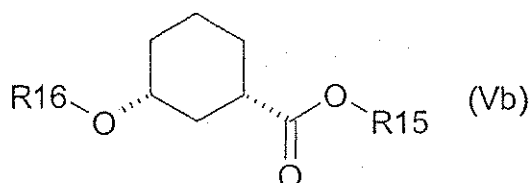
- 5 to give, for example, a racemic cis-configured compound of the formula (IV),



- 10 in which R^{15} is as defined above, or to give a compound of the formula (IV) which, depending on the work-up, may be present in ionic form, for example as Cs^+ , Li^+ , K^+ , NH_4^+ , Ca^{2+} , Ba^{2+} , Mg^{2+} salt and in which R^{15} is also Cs, Li, K, NH_4 , Ca, Ba, Mg, and, if appropriate, the resulting product, for example a compound of the formula (IV) where $\text{R}^{15} = \text{Cs}$, is further converted with an alkylating agent such as benzyl bromide into a compound of the formula (IV) where $\text{R}^{15} = \text{CH}_2\text{C}_6\text{H}_5$, i.e. another product in
- 15 which R^{15} is as defined above;

b) Enzymatic ester formation (EF) + separation (s)

- 20 the resulting compounds of the formula (IV) are subjected to a stereoselective enzymatic ester formation (EF), where an acyl donor (such as, for example, a vinyl ester $\text{R}^{16}\text{-O-CH=CH}_2$, preferably vinyl acetate, or an acid anhydride $\text{R}^{16}\text{-O-R}^{16}$, preferably succinic anhydride and glutaric anhydride) and the enzyme are added to the hydroxyl compounds in an organic solvent (such as, for example, dichloromethane) and the resulting mixture is stirred at from -20 to 80°C and, after
- 25 the reaction has ended, one stereoisomer is present as ester of the formula (Vb)

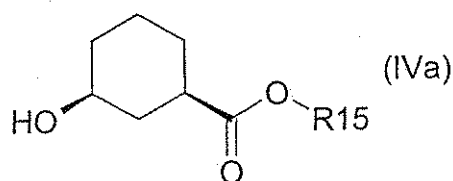


in which

R^{16} C(=O)-(C₁-C₁₆)-alkyl, C(=O)-(C₂-C₁₆)-alkenyl, C(=O)-(C₃-C₁₆)-alkynyl, C(=O)-(C₃-C₁₆)-cycloalkyl, where one or more carbon atoms may be replaced by oxygen atoms and may be substituted by 1-3 substituents from the group consisting of F, Cl, Br, CF₃, CN, NO₂, hydroxyl, methoxy, ethoxy, phenyl, CO-O(C₁-C₄)-alkyl and CO-O(C₂-C₄)-alkenyl, where phenyl, CO-O(C₁-C₄)-alkyl and CO-O(C₂-C₄)-alkenyl for their part may be substituted by 1-3 substituents from the group consisting of F, Cl, Br, CF₃, and

R^{15} is as defined above,

and the other stereoisomer is present unchanged as the alcohol of the formula (IVa)



which compounds can therefore, utilizing their different chemical or physicochemical properties (for example R_f values or different solubilities in water or other solvents), be separated from one another (separation S), for example by simple chromatography on silica gel, by extraction (for example heptane/methanol or org. solvent/water) or else be processed further by a subsequent chemical follow-up reaction of, for example, the hydroxyl compound, in which the ester does not participate, where

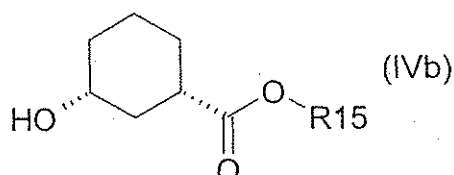
the enantiomers of the formula (IVa) obtained as alcohol are processed further as described under d), or

c) Ester cleavage (EC)

the enantiomers of the formula (Vb) obtained as acylated compounds are

hydrolyzed by known processes to give chemically enantiomeric alcohols (IVb) or, for example by reaction with K_2CO_3 in methanol, transesterified intramolecularly to give the optically active (1S,5R)-6-oxabicyclo[3.2.1]octan-7-one which can be converted into an isomeric form of the product (see schemes below)

5



or the compound of the formula (Vb) is converted, for example, by lipase-catalyzed cleavage of both ester functions into the optically active compound of the formula (IVb, where $R^{15} = H$) which can be converted into an isomeric form of the product (see schemes below);

10

d) Alkylation (Alk- R^1 /Alk-PG)

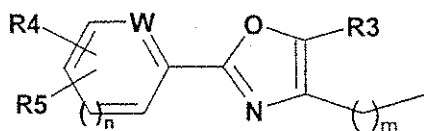
15 further conversion with compounds of the formula (VI)



in which

20

R^1 is



25 and R^3 , R^4 , R^5 , W, n and m are as defined above, or

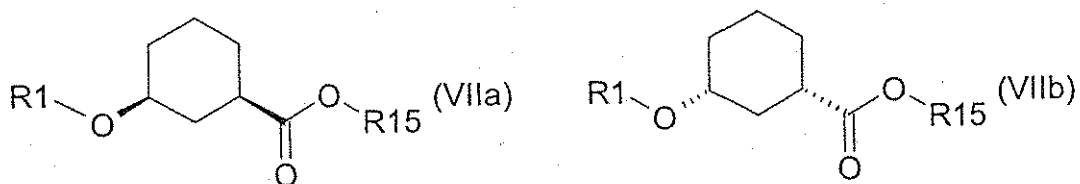
R^1 is an OH protective group (PG) as defined above, except for THP, EE, 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl;

and

X is Cl, Br, I, OTs, OMs, OTf;

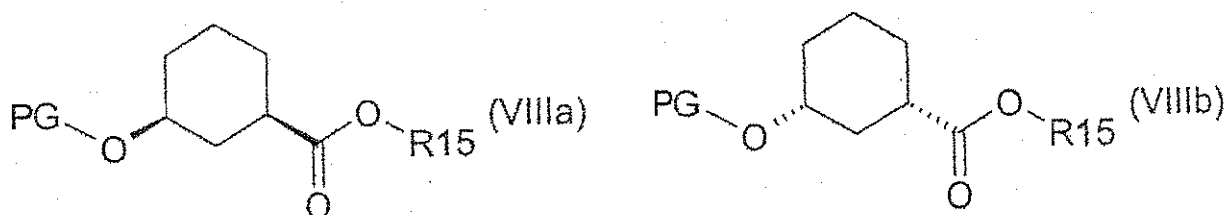
5

in the presence of bases in a suitable solvent to give compounds of the formula (VIIa) or (VIIb);



10

or, in the case of $R^1 = \text{PG}$, to give compounds of the formula (VIIIa) or (VIIIb)



15 or

R^1 is an OH protective group (PG) such as tetrahydropyranyl (THP), 1-ethoxyethyl, 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl;

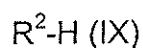
20 and

to introduce the OH protective groups, the compounds of the formula (IVa) or (IVb) are reacted under acid catalysis with the appropriate known enol ethers, also to give
25 compounds of the formula (VIIIa) or (VIIIb);

and

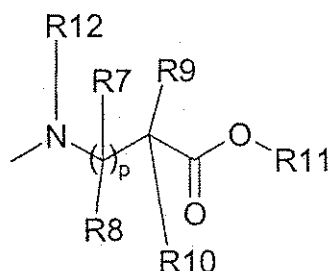
e) Direct reaction or ester cleavage & coupling (DR or EC + C)

- 5 e1) the resulting compounds of the formula (VIIa) or (VIIb) or compounds of the formula (VIIIa) or (VIIIb) are converted in a direct reaction (DR), for example by reacting an amine of the formula (IX)



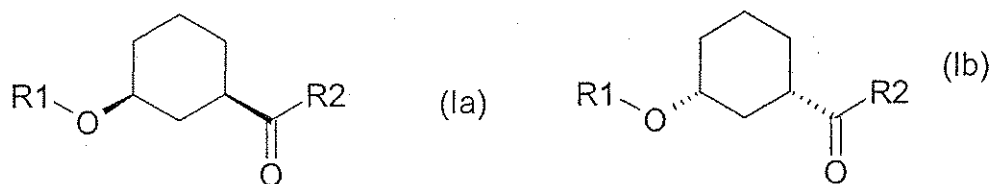
10 in which

R^2 is

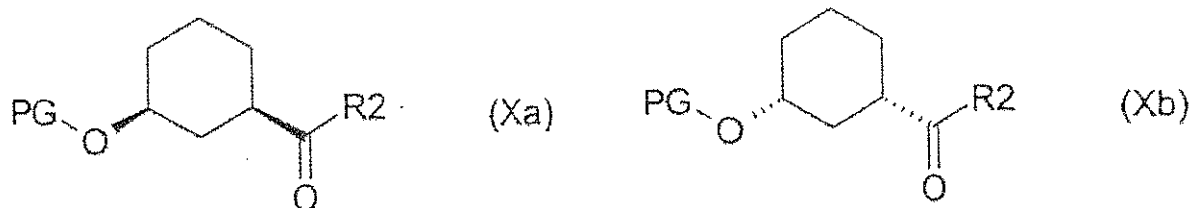


15 where R7, R8, R9, R10, R11, R12 and p are as defined above,

or the corresponding lithium or dimethylaluminum derivative, or by reacting the compounds of the formula (VIIa) or (VIIb) or the compounds of the formula (VIIIa) or (VIIIb) and the amine or amino acid derivative R^2-H of the formula (IX) in the presence of activating reagents or catalysts, such as, for example, the cyanide ion, to give compounds of the formula (Ia) or (Ib) or isomeric forms thereof,



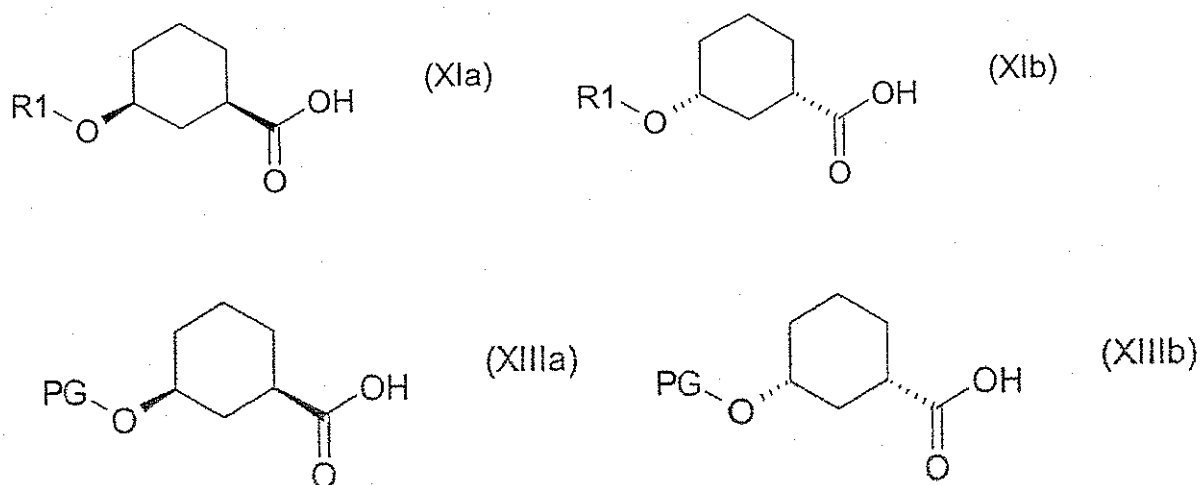
25 or, in the case of $R^1 = PG$, to give compounds of the formula (Xa) or (Xb),



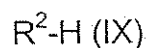
or

- 5 e2) the resulting compounds of the formula (VIIa) or (VIIb) or (VIIIa) or (VIIIb) are subjected to an ester cleavage, for example a basic hydrolysis using aqueous NaOH, an acidic hydrolysis using aqueous HCl or an enzymatic hydrolysis using a lipase, or a hydrogenolysis using H_2 in the presence of Pd/C, and the resulting compounds of the formula (XIa) or (XIb) or (XIIIa) or (XIIIb)

10

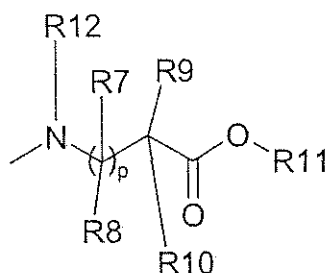


- 15 or the corresponding salts, for example the Li, Na, K, C_5 or NH_4 salt of these compounds, to a subsequent coupling with a compound of the formula (IX)



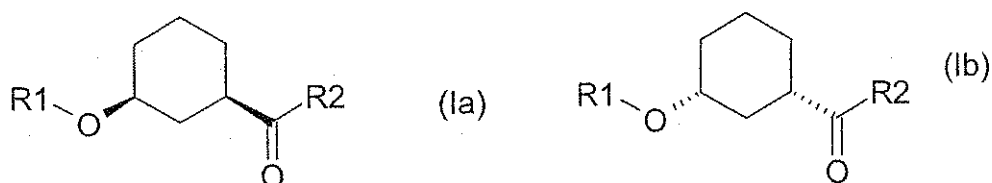
20 in which

R^2 is

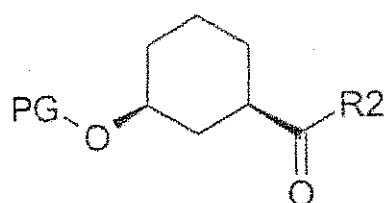


where R7, R8, R9, R10, R11, R12 and p are as defined above,

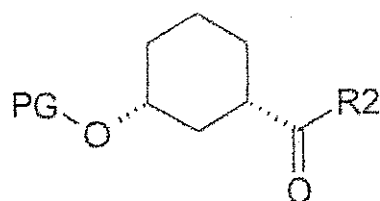
- 5 in the presence of dehydrating or activating reagents, such as, for example, PPA (propanephosphonic anhydride), TOTU ([cyano(ethoxycarbonyl)methyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate), EDC (1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride), HOBt (1-hydroxybenzotriazole), DMAP
- 10 (4-dimethylaminopyridine), DCC (dicyclohexylcarbodiimide), CDI (N,N'-carbonyldiimidazole), to give a compound of the formula (Ia) or (Ib) or an isomeric form thereof;



- 15 and, if appropriate,
- f) Removal of the protective group PG (RPG)
- 20 if R¹ is an OH protective group (PG) as defined above under R¹, the compounds of the formula (Xa) or (Xb)



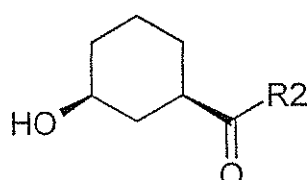
(Xa)



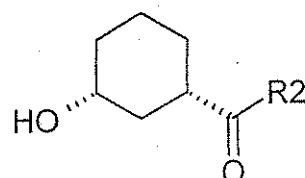
(Xb)

in which R^2 and PG are as defined above

- 5 are converted by removal of the protective group by known processes, such as, for example, removal of PG = benzyloxymethyl or PG = benzyl by hydrogenation over Pd/C, or removal of PG = para-methoxybenzyl using, for example, DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), removal of PG = tert-butyldimethylsilyl, for example, using Bu_4NF , or removal of PG = tetrahydropyranyl (THP), PG =
- 10 1-ethoxyethyl, PG = 1-methyl-1-methoxyethyl or PG = 1-methyl-1-benzyloxyethyl, for example, under acid catalysis using p-toluenesulfonic acid or HCl; into compounds of the formula (XIIa) or (XIIb)



(XIIa)



(XIIb)

- 15 in which R^2 is as defined above, followed by conversion according to the stated process variants into the compounds of the formula (Ia) or (Ib) or isomeric forms thereof;

- 20 it also being possible to change the sequence of the individual reaction steps as described above under A):

A) $LO \rightarrow EF+S [\rightarrow EC] \rightarrow Alk-R^1 \rightarrow DR \text{ or } EC + C \rightarrow \text{product/isomeric form}$

- 25 to:

B) $LO \rightarrow EF+S \xrightarrow{[EC]} DR \text{ or } EC + C \rightarrow Alk-R^1 \rightarrow \text{product/isomeric form}$

or

C) $LO \rightarrow DR \text{ or } EC + C \rightarrow EF + S \xrightarrow{[EC]} Alk-R^1 \rightarrow \text{product/isomeric form}$

5

or

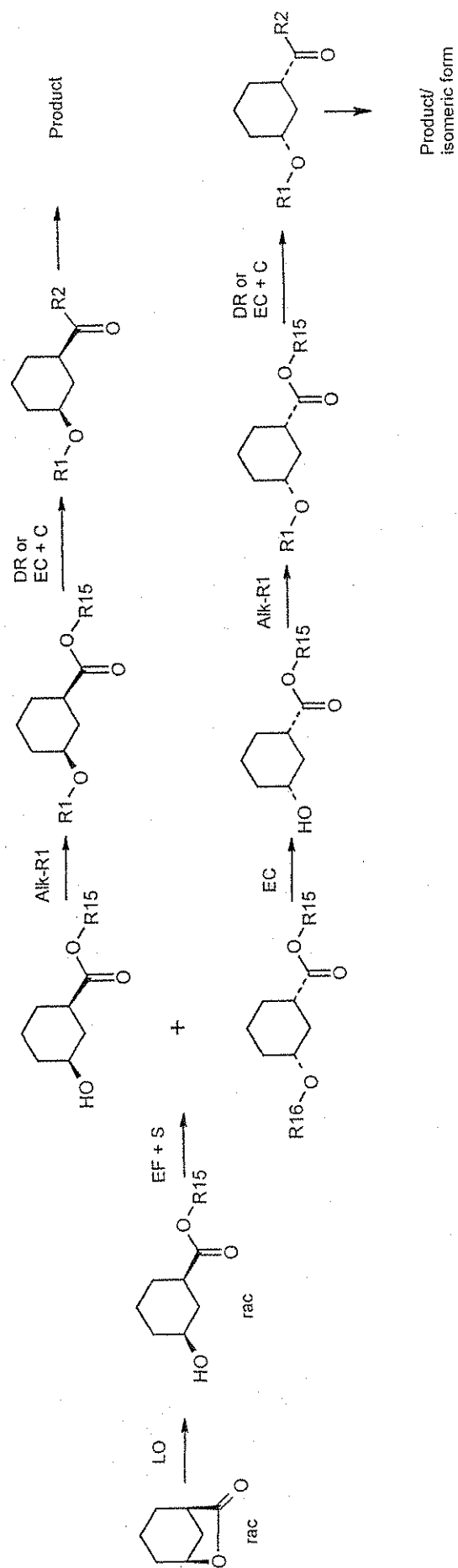
D) $LO \rightarrow EF+S \xrightarrow{[EC]} Alk-PG \rightarrow DR \text{ or } EC + C \rightarrow RPG \rightarrow Alk-R^1 \rightarrow \text{product/isomeric form,}$

or

10 E) $LO \rightarrow Alk-PG \rightarrow DR \text{ or } EC + C \rightarrow RPG \rightarrow EF + S \xrightarrow{[EC]} Alk-R^1 \rightarrow \text{product/isomeric form.}$

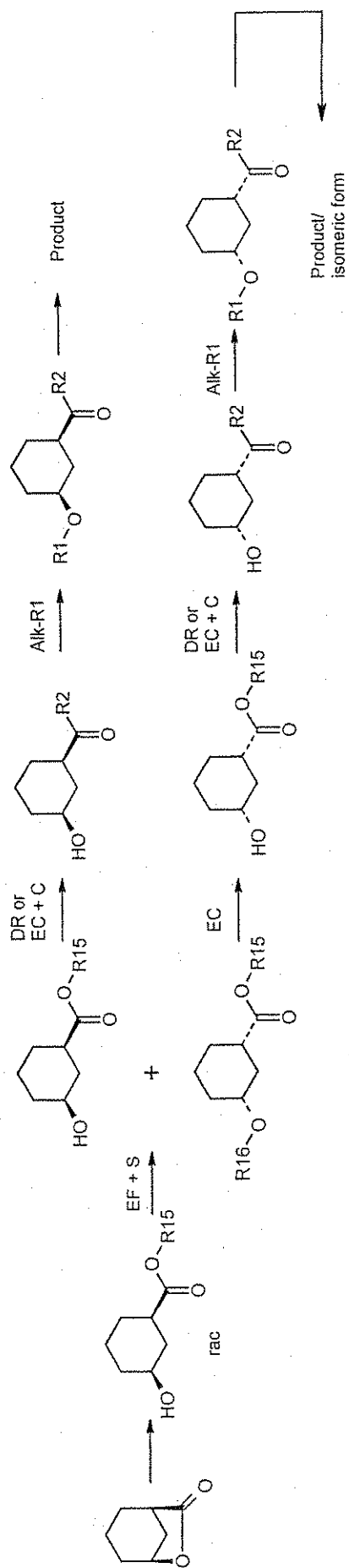
Possible process variants are shown in schemes I to V below:

Scheme A:

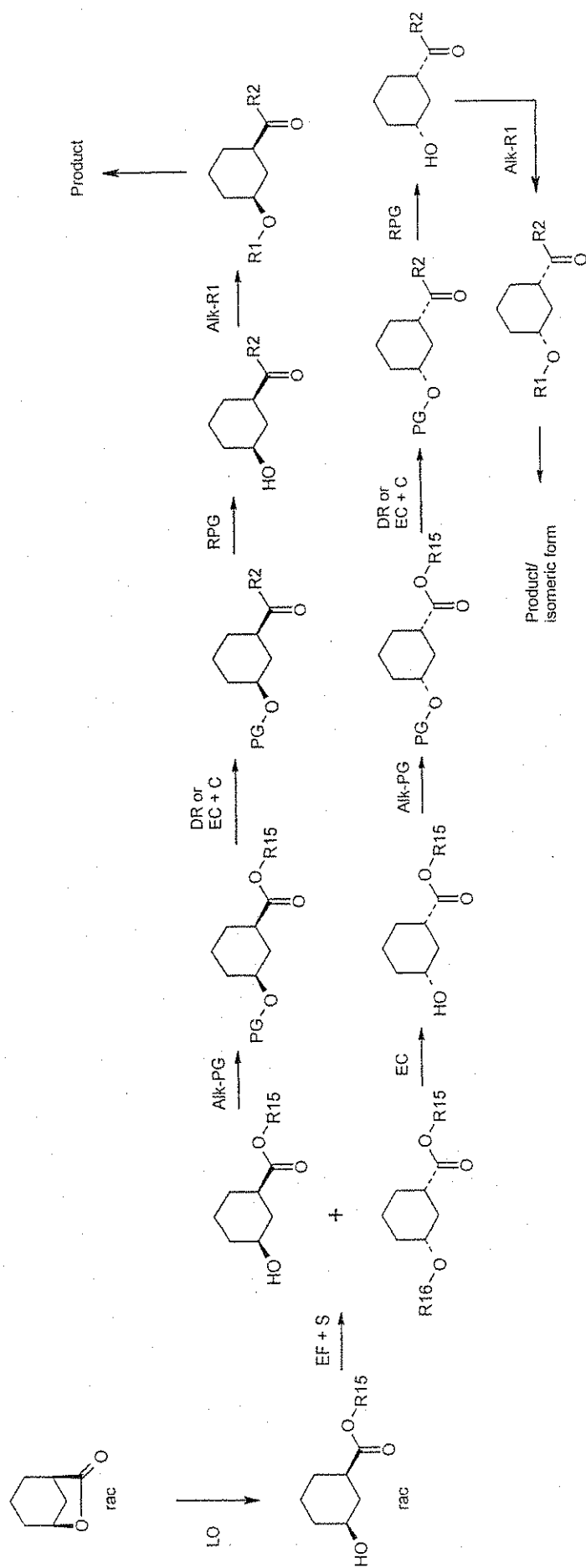


Scheme B:

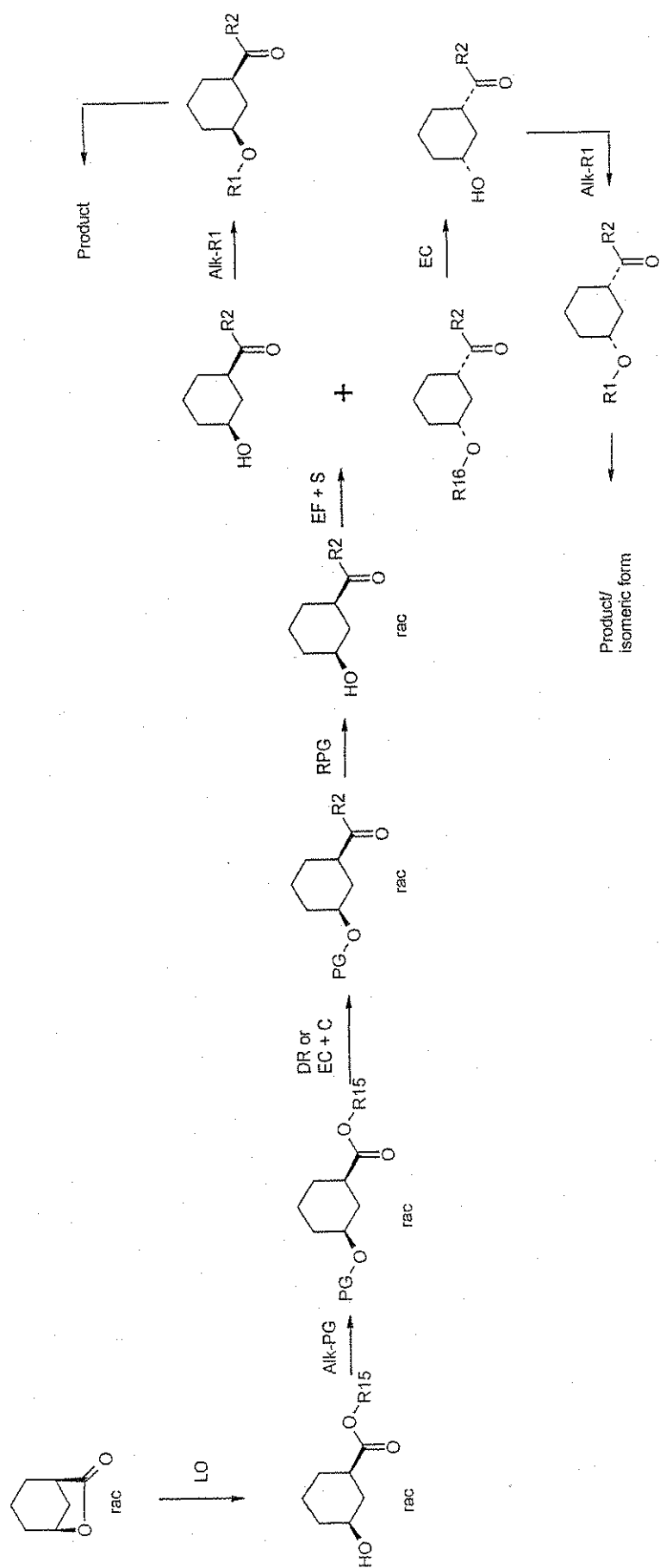
21



Scheme D:



Scheme E:



The compounds of the formulae (Ia) and (Ib) have two centers of asymmetry on the cyclohexane ring. Here, the cis attachment is essential. However, it is also possible for further centers of asymmetry to be present, for example in the radical R². The compounds of the formulae (Ia) and (Ib) can therefore be present in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and diastereomer mixtures. The present invention embraces all these isomeric forms of the compounds of the formulae (Ia) and (Ib). Even if in some cases this has not been described expressis verbis, these isomeric forms can be obtained by known methods.

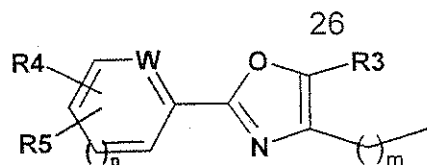
A heteroaromatic ring is to be understood as meaning both monocyclic and bicyclic rings having a maximum of 4 heteroatoms, in particular those having up to 4 nitrogen atoms and/or 1 oxygen or 1 sulfur atom, such as, for example: furan, thiophene, thiazole, oxazole, thiadiazole, triazole, pyridine, triazine, quinoline, isoquinoline, indole, benzothiophene, benzofuran, benzotriazole. Aromatic rings may be mono- or bicyclic and also fused, such as, for example, naphthyl, benzo[1,3]dioxole, dihydrobenzo[1,4]dioxin.

The process according to the invention is economical, simple and quick. It does not require equimolar amounts of optically pure starting materials or auxiliaries, nor expensive reagents, nor reagents etc. posing a particular risk, nor racemate resolution by chromatography on chiral phases, nor unreasonably large amounts of solvents or costly operations.

Preference is given to the abovementioned processes A), B) and D); process A) is particularly preferred.

Preferred is a process for preparing the compounds of the formulae (Ia) and (Ib) in which one or more radicals are as defined below:

R¹ is



or

R¹ is an OH protective group (PG), such as, for example, benzyloxymethyl, benzyl, para-methoxybenzyl, tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), tetrahydropyranyl (THP), 1-ethoxyethyl (EE), 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl;

where

R⁴ is F, Br, CF₃, OCF₃, (C1-C6)-alkyl, O-(C1-C6)-alkyl, phenyl; or

those in which the substituent

R⁴ is located in the meta or para position; or

R⁵ is hydrogen; or

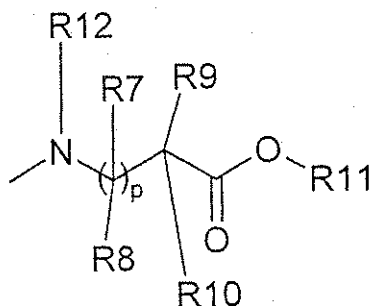
R⁴ and R⁵ together with the phenyl ring = naphthyl; or

R³ is H, (C1-C6)-alkyl, (C3-C8)-cycloalkyl, (C1-C3)-alkyl-(C5-C6)-cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl; or

W is CH, if n = 1; or

m is 1; or

R² is



where

5 p is 0; or

R9 is H, (C1-C6)-alkyl; or

10 R9 and R10 together with the carbon atom that carries them are (C3-C6)-cycloalkyl,
in particular cyclopentyl;

R10 is (C1-C6)-alkyl, where alkyl may optionally be substituted by one or
more radicals from the group consisting of hydroxyl, phenyl, (C5-C11)-
heteroaryl, (C1-C6)-alkoxy and NR13R14, where

15

R13 and R14 are H, (C1-C6)-alkyl;

20 R11 is H, (C1-C8)-alkyl, benzyl, (C1-C4)-alkyl-(C6-C10)-aryl, where alkyl,
benzyl, aryl may optionally be mono- or polysubstituted by OMe,
OCH₂CH₂-OMe, F, Cl, Br, Si(CH₃)₃, OSi(CH₃)₃, OCH₂CH₂-SiMe₃,
O-CH₂-C₆H₅, SMe, CN, NO₂, CH₂COC₆H₅.

Particular preference is furthermore given to a process for preparing the compounds
of the formulae (Ia) and (Ib) in which

25

R10 is (C1-C4)-alkyl, (C1-C4)-alkyl-O-(C1-C4)-alkyl or benzyl;

R11 is H, (C1-C8)-alkyl, benzyl;

very particularly preferably

R10 is (C1-C4)-alkyl or benzyl,

R11 is H, (C1-C8)-alkyl.

Very particular preference is also given to a process for preparing the compounds of the formulae (Ia) and (Ib)

in which

R4 is Br, CF₃, OCF₃, (C1-C6)-alkyl, O-(C1-C6)-alkyl;

R5 is H, (C1-C6)-alkyl, O-(C1-C6)-alkyl or

R4 and R5 together with the phenyl ring = naphthyl;

R3 is CF₃, (C1-C6)-alkyl, (C3-C6)-cycloalkyl, phenyl;

W is CH, if n = 1;

m is 1;

p is 0;

R9 is H, (C1-C6)-alkyl;

R10 is (C1-C6)-alkyl, where alkyl may optionally be substituted by phenyl;

R10 and R12 together with the atoms that carry them are pyrrolidine, if p = 0;

R9 and R10 together with the carbon atom that carries them are (C3-C6)-cycloalkyl;

R11 is H;

5 R12 is H, (C1-C6)-alkyl, benzyl.

The racemic compounds of the formula (IV) are prepared by opening 6-oxabicyclo[3.2.1]octan-7-one with alcohols or in the presence of water.

10 Racemic 6-oxabicyclo[3.2.1]octan-7-one (II) is commercially available and can be synthesized, for example, by dearomatization, for example by hydrogenating m-hydroxybenzoic acid or m-hydroxybenzoic acid derivatives and cyclizing the cis-3-hydroxycyclohexanecarboxylic acid.

The opening of the lactone can, as described in the literature for a large number of lactones (for example in M. Carballido, L. Castedo, C. Gonzalez, *Tetrahedron Lett.* 15 **2001**, 42, 3973), be carried out either under acidic or under basic conditions, for example using water in the presence of hydroxides such as LiOH, for example using water in the presence of acids such as acetic acid, for example using alcohols in the presence of bases such as K₂CO₃ and, for example, using alcohols in the presence 20 of acids such as HCl.

For opening the lactone, it is preferred to use acetyl chloride in alcohols.

To resolve the racemate of the hydroxyl compounds, these are taken up in organic solvents such as, for example, dimethoxyethane (DME), methyl tert-butyl ether 25 (MTBE), diisopropyl ether (DIPE), THF, n-hexane, cyclohexane, toluene, chlorobenzene, acetone, dimethylformamide (DMF), dichloromethane, 1,2-dichloroethane and tert-butanol, acyl donors such as vinyl acetate, vinyl propionate, vinyl butyrate, 2,2,2-trifluoroethyl 2*H*,2*H*-perfluorodecanoate, ethoxyvinyl acetate, p-nitro- or p-chlorophenyl acetate, oxime esters, acetic anhydride, propionic 30 anhydride, succinic anhydride, glutaric anhydride, isovaleric anhydride 2,2,2-trichloroethyl butyrate are added and a suitable enzyme is then added to the reaction mixture, which is stirred at from -20 to 80°C. The proportion of cosolvent in the solution is preferably 10-90%; however, if appropriate, it is also advantageous to

carry out the enzymatic reaction in a pure acyl donor, for example vinyl acetate, without cosolvent.

After the reaction has ended, the products or the enantiomers can be separated in a simple manner, for example by extraction according to methods known from the literature [a). T. Yamano, F. Kikumoto, S. Yamamoto, K. Miwa, M. Kawada, T. Ito, T. Ikemoto, K. Tomimatsu, Y. Mizuno, *Chem. Lett.* **2000**, 448; b). B. Hungerhoff, H. Sonnenschein, F. Theil, *J. Org. Chem.* **2002**, 67, 1781] or by using chromatographic methods.

In a further method, after completion of the enzymatic reaction, the solubility in water of the remaining hydroxyl compound is increased considerably by derivatization, for example by acylation using cyclic anhydrides, such as, for example, glutaric anhydride, or by conversion into a choline ester [a). H. Kunz, M. Buchholz, *Chem. Ber.* **1979**, 112, 2145; b.) M. Schelhaas, S. Glomsda, M. Hänsler, H.-D. Jakubke, H. Waldmann, *Angew. Chem.* **1996**, 108, 82] to achieve separation from the water-insoluble esters or the esters with poor solubility in water by extraction. After the separation, the derivatization of the alcohols can be revised by chemical or enzymatic hydrolysis.

In a particularly interesting option of separating the enantiomers, in the case of the enzymatic acylation the acyl donor is chosen such that the acylated enantiomer is considerably more water-soluble than the unreacted hydroxyl compound. Suitable acyl donors are, for example, cyclic anhydrides, such as succinic anhydride. After the enzymatic acylation has ended, the acylation product carries a free carboxyl group which allows rapid removal of the product by aqueous extraction in basic media using, for example, saturated aqueous NaHCO_3 solution.

The enzymes used are preferably hydrolases from mammalian livers, such as, for example, lipase from porcine pancreas (Fluka) or from microorganisms, such as, for example, lipase B from *Candida antarctica* (Roche Diagnostics), lipase A from *Candida antarctica* (Roche Diagnostics), lipase OF from *Candida rugosa* (Meito Sangyo), lipase SL from *Pseudomonas cepacia* (Meito Sangyo), lipase L-10 from *Alcaligenes spec.* (Roche Diagnostics), lipase QL from *Alcaligenes spec.* (Meito

Sangyo) and glutaryl-7-ACA-acylase (Roche Diagnostics).

Particular preference is given to lipase B from *Candida antarctica* (Roche Diagnostics), and it may be advantageous to use the free enzyme or an immobilized form of the enzyme, for example one of the three products which are currently commercially available.

Each of the enzymes mentioned can be employed in free or in immobilized form (Immobilized Biocatalysts, W. Hartmeier, Springer Verlag Berlin, 1988). The amount of enzyme is chosen freely depending on the reaction rate or the intended reaction time and on the type of enzyme (for example free or immobilized) and can be determined easily by simple preliminary experiments. The enzyme can be recovered by freeze-drying. Separation (and, if appropriate, later re-use) of the enzyme can be facilitated by immobilization.

By carrying out the reaction in a suitable manner, it is always possible to obtain at least one enantiomer in optically pure form. If the desired product is an optically pure ester, the conversion in the case of the enzymatic ester formation should be below (or equal to) 50%. If the desired product is an optically pure alcohol, in the case of an enzyme-catalyzed ester formation the conversion should be above (or equal to) 50%. The conversion of the enzymatic reaction was determined either by GC or HPLC directly from the reaction mixture or by calculation from the optical purities of the reaction products (ester and acid) which were likewise determined directly from the reaction mixture using GC or HPLC on a chiral phase.

The compounds R^1-X of the formula (VI) and the corresponding alcohols R^1-OH , which may serve as precursors, are commercially available or can be prepared by methods known from the literature [a) *The Chemistry of Heterocyclic Compounds* (Ed.: A. Weissberger, E. C. Taylor); Oxazoles (Ed.: I. J. Turchi); b). *Methoden der Organischen Chemie* [Methods of organic chemistry], Houben-Weyl 4th edition, Hetarene III, subvolume 1; c) O. Diels, D. Riley, *Ber. Dtsch. Chem. Ges.* **1915**, 48, 897; d) W. Dilthey, J. Friedrichsen, *J. Prakt. Chem.* **1930**, 127, 292; e) A. W. Allan, B. H. Walter, *J. Chem. Soc. (C)* **1986**, 1397; f) P. M. Weintraub, *J. Med. Chem.*

1972, 15, 419; g) I. Simit, E. Chindris, *Arch. Pharm.* **1971**, 304, 425; h) Y. Goto, M. Yamazaki, M. Hamana, *Chem. Pharm. Bull.* **1971**, 19 (10), 2050-2057].

The compounds R^1-X of the formula (VI) are reacted in the presence of bases with the optically pure cis-configured 3-hydroxycyclohexanecarboxylic acid derivatives. Suitable bases are, for example, hydroxides such as KOH, carbonates such as Cs_2CO_3 , alkoxides such as KOtBu, and also compounds such as LDA, BuLi, LiHMDS, KHMDS, NaH and NaHMDS. Suitable solvents are, for example, THF, MTBE, DME, NMP, DMF, toluene and chlorobenzene.

Introduction of the OH protective groups (PG) by reacting the compounds of the formulae (IVa) and (IVb) with a compound of the formula (VI) is carried out by methods known from the literature (T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc., 1999).

In addition, to introduce OH protective groups such as tetrahydropyranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl into the compounds of the formulae (IVa) and (IVb), it is possible to use the corresponding known enol ethers (for example, dihydropyran and ethyl vinyl ether) using methods known from the literature (T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc., 1999).

R^1 as PG is chosen such that the removal of the PG during the course of the later synthesis can again be facile and selective; PG is thus, for example, benzyloxymethyl, benzyl, para-methoxybenzyl, tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), 1-ethoxyethyl (EE), or tetrahydropyranyl (THP).

The later removal of the protective group is likewise carried out according to known processes, such as, for example, removal of PG = benzyloxymethyl or PG = benzyl by hydrogenation over Pd/C, or removal of PG = para-methoxybenzyl using, for example, DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), or removal of PG = tert-butyldimethylsilyl or PG = tert-butyldiphenylsilyl using, for example, Bu_4NF , or removal of PG = tetrahydropyranyl (THP), PG = 1-ethoxyethyl, PG = 1-methyl-1-methoxyethyl or PG = 1-methyl-1-benzyloxyethyl, for example under acid catalysis using p-toluenesulfonic acid or HCl.

The amines or amino acid derivatives of the formula (IX) are easily accessible. Both the derivatives of the proteinogenic and the nonproteinogenic amino acids are mainly building blocks known from peptide chemistry, the different isomers of which are commercially available as isomerically pure compounds. In addition, the amino acid derivatives of the formula (IX) used can be prepared with the aid of methods known from the literature [a) Houben-Weyl, Methoden der Organischen Chemie, 4th edition, volume E16d, subvolumes I and II; b) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, 9, 3517; c) M. Beller, M. Eckert, *Angew. Chem.* **2000**, 112, 1026].

10

The direct reaction of an ester of the formula (IVa) or (IVb), (VIIa) or (VIIb) or of the formula (VIIIa) or (VIIIb) with an amine or an amino acid derivative of the formula (IX) can be carried out using methods known from the literature [a) M. B. Smith, J. March, March's Advanced Organic Chemistry, 5th edition, John Wiley & Sons, Inc., 2001, p. 510 and literature cited therein; b) literature review R. C. Larock, Comprehensive Organic Transformations, p. 987, VCH Publishers, Inc., 1989], for example via the corresponding lithium or dimethylaluminum derivatives, or in the presence of suitable catalysts, such as, for example, the cyanide ion.

15

20 The ester hydrolyses can be carried out according to methods known from the literature (M. B. Smith, J. March, March's Advanced Organic Chemistry, 5th edition, John Wiley & Sons, Inc., 2001, p. 469 and literature cited therein), for example by basic hydrolysis using aqueous NaOH, an acidic hydrolysis using aqueous HCl, or an enzymatic hydrolysis using a lipase or, for example, in the case of a benzyl ester by hydrogenolysis using H₂ in the presence of Pd/C.

25

The conversion of the cyclohexanecarboxylic acids formed by ester hydrolysis into the compounds of the formula (XIa) or (XIb) is carried out by methods of amide or peptide coupling known from the literature. An abundance of methods for forming amide bonds is available [a) Houben-Weyl, Methoden der Organischen Chemie, 4th edition, volume XV, subvolumes 1 and 2; b) G. Benz in Comprehensive Organic Synthesis (ed.: B. M. Trost), 1991, p. 381; c) Miklos Bodansky, Peptide Chemistry, 2nd edition, Springer Verlag, p. 55].

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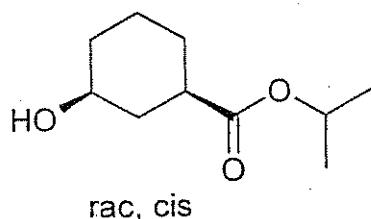
The examples below serve to illustrate the present invention in more detail.

5 Examples:

For scheme A:

Example 1:

10 Preparation of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate



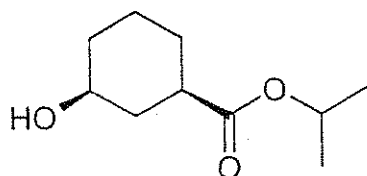
With stirring, 245 ml of acetyl chloride were added slowly to 2.1 l of isopropanol.

15 During the addition, the temperature increased to 45°C but rapidly fell to 35°C afterwards. A solution of 350 g (2.72 mol) of racemic 6-oxabicyclo[3.2.1]octan-7-one and 1.4 l of isopropanol was then slowly added dropwise, and the mixture was stirred at 20-25°C. After 3 h and standing overnight, the reaction had ended. The reaction mixture was concentrated under reduced pressure, taken up in about 1.3 l

20 of methylene chloride and washed with 1 l of semisaturated sodium bicarbonate solution. The organic phase was then dried with MgSO₄ and concentrated under reduced pressure; yield: 501 g (98.9%); ¹H-NMR (CDCl₃): δ = 1.23 (d, 6 H), 1.20-1.45 (m, 4 H), 1.68 (d, 1 H), 1.86 (m, 2 H), 1.95 (m, 1 H), 2.18 (m, 1 H), 2.34 (m, 1 H), 3.63 (m, 1 H), 5.00 (sept, 1 H).

Example 2:

Enzymatic racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate



5

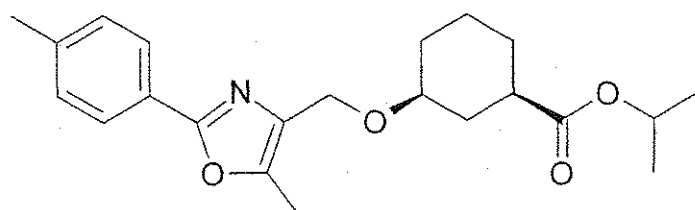
800 g of racemic isopropyl 3-hydroxycyclohexane-1-carboxylate were slowly stirred with 1.5 l of vinyl acetate, 5 l of methylene chloride and 137 g of Novozym 435 at 20-23°C. After about 4 h, the mixture was filtered off and concentrated under reduced pressure. This gave 940 g which were chromatographed on 6 kg of silica gel (n-heptane/EA 2:1 – EA/n-heptane 3:1): 1. Fraction, 484 g, isopropyl (1S,3R)-3-acetoxycyclohexane-1-carboxylate; ¹H-NMR (CDCl₃): δ = 1.22 (d, 6 H), 1.2-1.6 (m, 4 H), 1.8-2.0 (m, 3 H), 2.03 (s, 3 H), 2.20 (m, 1 H), 2.36 (m, 1 H), 4.70 (m, 1 H), 5.00 (sept, 1 H); 80% ee (HPLC on Chiralpak ADH 32 250 × 4.6; 1 ml/min, heptane/EtOH 3:1). 2. Mixed fraction. 3. Fraction, 324 g of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate; ¹H-NMR (CDCl₃): δ = 1.23 (d, 6 H), 1.20-1.45 (m, 4 H), 1.68 (d, 1 H), 1.86 (m, 2 H), 1.95 (m, 1 H), 2.18 (m, 1 H), 2.34 (m, 1 H), 3.63 (m, 1 H), 5.00 (sept, 1 H); > 99% ee (HPLC on Chiralpak ADH 32 250 × 4.6; 1 ml/min, heptane/EtOH 3:1).

20

Example 3:

Preparation of isopropyl (1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)-cyclohexanecarboxylate by alkylation of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate using 4-iodomethyl-5-methyl-2-p-tolyloxazole

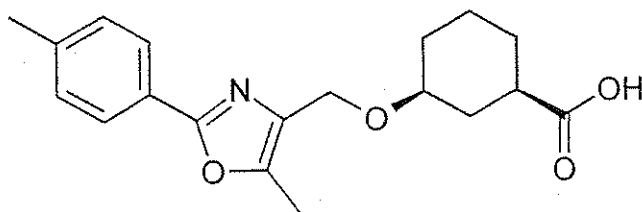
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Under N₂, 100 g (0.54 mol) of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate and 151 g (0.48 mol) of 4-iodomethyl-5-methyl-2-p-tolyloxazole were initially charged in 1 l of NMP and cooled to -20°C. Over a period of about 1 h, 20.4 g of NaH were added a little at a time. During the addition, the temperature was kept below -15°C. The mixture was then stirred at -15°C. After 7 h, the reaction had ended. The reaction mixture was poured into a mixture of 3 l of water and 40 ml of glacial acetic acid. The product was extracted with MTB ether (2 × 700 ml). The organic phase was concentrated under reduced pressure. This gave 180 g of crude product which were directly reacted further.

Example 4:

Preparation of (1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexane-carboxylic acid by hydrolysis of the isopropyl ester

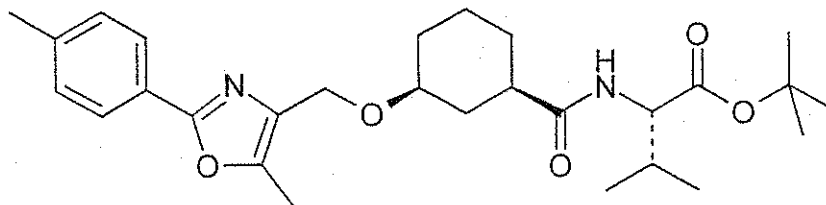


About 360 g from two runs of example 3 were dissolved in 1.6 l of NMP, 400 ml of NaOH were added and the mixture was stirred at RT. After about 1.5 h, the reaction had ended. The reaction solution was poured into 6 l of water and washed three times with in each case 2 l of MTB ether, and using about 450 ml of conc. HCl, the aqueous phase was adjusted to pH 1. The product, which precipitated during this operation, was filtered off, washed with water and dried at 50°C; yield: 85 g; m.p. 144-146°C; ¹H-NMR (CDCl₃): δ = 1.23 – 1.53 (m, 4 H), 1.85 – 2.1 (m, 3 H), 2.36 – 2.45 (m, 8 H), 3.45 (m, 1 H), 4.49 (dd, 2 H), 7.23 (d, 2 H), 7.88 (d, 2 H).

Example 5:

Preparation of tert-butyl 3-methyl-2(S)-{[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino}butyrate by coupling of (1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarboxylic acid with t-butyl

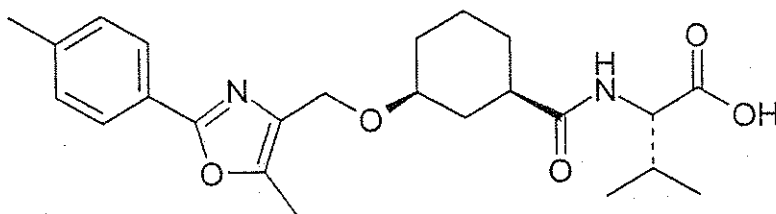
5 (S)-valinate hydrochloride



10 With stirring, 85 g of (1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexane-
carboxylic acid, 70.4 g of t-butyl (S)-valinate hydrochloride and 128 ml of
triethylamine were initially charged in 1.39 l of DMF. The mixture was stirred for
about 10 min and then cooled to 0°C (ice/methanol), and 101 g of TOTU were
added slowly, a little at a time. The mixture was stirred at 0°C for 15 min and then at
15 about 20°C. After 2 h, the reaction had ended. The entire reaction mixture was
poured into 4.5 l of water and extracted 3× with in each case 700 ml of MTB ether,
and the combined organic phases were washed with about 1 l of water to remove
residual DMF, dried with MgSO₄ and concentrated under reduced pressure. The
residue was triturated with DIPE and filtered off with suction; yield: 82 g. The mother
liquor was concentrated and the residue was once more triturated with DIPE; total
20 yield: 90 g; ¹H-NMR (CDCl₃): δ = 0.87 - 0.92 (2 d, 6 H), 1.25 - 1.55 (m, 4 H), 1.46 (s,
9 H), 1.88 (m, 2 H), 2.10 - 2.35 (m, 4 H), 2.38 (s, 3 H), 2.40 (s, 3 H), 3.47 (m, 1 H),
4.46 (dd, 1 H), 4.49 (s, 2 H), 5.97 (d, 1 H), 7.22 (d, 2 H), 7.88 (d, 2 H).

Example 6:

Preparation of 3-methyl-2(S)-{[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)-cyclohexanecarbonyl]amino}butyric acid



5

141.0 g of tert-butyl 3-methyl-2(S)-{[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino}butyrate were dissolved in 700 ml of methylene chloride, and 252 ml of trifluoroacetic acid were added. The reaction mixture was heated at reflux. After a reaction time of about 10 hours, the reaction solution was concentrated under reduced pressure and, twice, about 100 ml of toluene were added and the mixture was concentrated under reduced pressure. The resulting residue was taken up in 1 l of water, and about 150 ml of 33% strength aq. NaOH were added. The Na salt of the carboxylic acid was dissolved, and the solution was washed twice with in each case 70 ml of MTB ether. Using conc. HCl, the aqueous phase was then adjusted to pH 1. The desired product precipitated and was filtered off with suction, washed with water, dried at 50°C under reduced pressure and digested with about 1 l of ethyl acetate; yield: 118.8 g; m.p. 195-196°C; ¹H-NMR (DMSO): δ = 0.86 (d, 6 H), 1.05 -1.3 (m, 4 H), 1.64 (m, 1 H), 1.76 (m, 1 H), 2.04 (m, 4 H), 2.36 (s, 3 H), 2.38 (s, 3 H), ~ 3.35 (m, 1 H), 4.13 (dd, 1 H), 4.40 (s, 2 H), 7.31 (d, 2 H), 7.81 (d, 2 H), 7.84 (d, 1 H), 12.5 (s, br., 1 H).

20

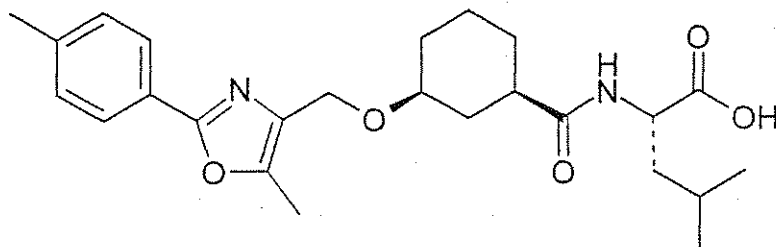
Example 7:

25 3-Methyl-2(S)-{[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino}pentanoic acid

Analogously to the reaction sequence examples 2 - 6, isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate, 4-iodomethyl-5-methyl-2-p-tolyloxazole and tert-butyl (S)-leucinate hydrochloride gave the product 3-methyl-2(S)-{[(1R,3S)-3-(5-methyl-

30

2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino}pentanoic acid;
 $C_{25}H_{34}N_2O_5$ (442.56), MS (ESI): 443 ($M+H^+$).



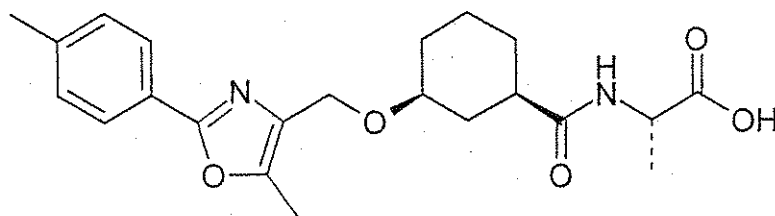
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Example 8:

3-Methyl-2(S)-{[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino}propionic acid

- 10 Analogously to example 7, isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate, 4-iodomethyl-5-methyl-2-p-tolyloxazole and tert-butyl (S)-alaninate hydrochloride gave the product 3-methyl-2(S)-{[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)-cyclohexanecarbonyl]amino}propionic acid; $C_{22}H_{28}N_2O_5$ (400.48), MS (ESI): 401 ($M+H^+$).

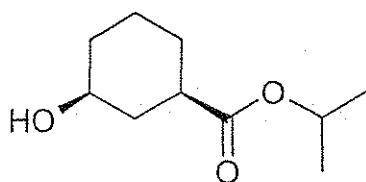
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For scheme B:

- 20 Example 9:

Preparation of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate by enzymatic racemate resolution



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At room temperature, 100 g of racemic isopropyl 3-hydroxycyclohexane-1-carboxylate were stirred slowly with 200 ml of vinyl acetate, 800 ml of methylene chloride and 20 g of Novozym 435. After about 60% conversion (GC), the mixture was filtered off and concentrated under reduced pressure. This gave 110 g of

5 product which were chromatographed on 1 kg of silica gel (n-heptane/EA 2:1):

1. Fraction, 70.9 g, isopropyl (1S,3R)-3-acetoxycyclohexane-1-carboxylate; $^1\text{H-NMR}$ (CDCl_3): $\delta = 1.22$ (d, 6 H), 1.2-1.6 (m, 4 H), 1.8-2.0 (m, 3 H), 2.03 (s, 3 H), 2.20 (m, 1 H), 2.36 (m, 1 H), 4.70 (m, 1 H), 4.99 (sept, 1 H); 62% ee (HPLC on Chiralpak

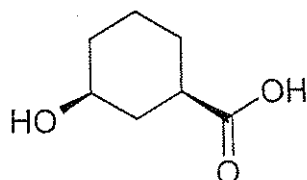
10 ADH 32 250 $\times$ 4.6; 1 ml/min, heptane/EtOH 3:1). 2. Fraction, 35.9 g, isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate; $^1\text{H-NMR}$ (CDCl_3): $\delta = 1.23$ (d, 6 H), 1.20-1.45 (m, 4 H), 1.68 (d, 1 H), 1.86 (m, 2 H), 1.95 (m, 1 H), 2.18 (m, 1 H), 2.34 (m, 1 H), 3.63 (m, 1 H), 5.00 (sept, 1 H); $> 99\%$ ee (HPLC on Chiralpak ADH 32 250 $\times$ 4.6; 1 ml/min, heptane/EtOH 3:1).

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Example 10:

Preparation of (1R,3S)-3-hydroxycyclohexane-1-carboxylic acid by basic hydrolysis of optically pure isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate

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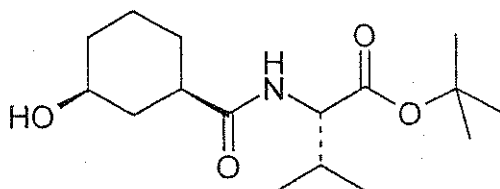


25 1 g (5.4 mmol) of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was stirred at RT in 6 ml of 2N NaOH overnight. A few drops of 11N NaOH were added, and the mixture was again stirred overnight. No more ester could be detected. The mixture was acidified with HCl and concentrated under reduced pressure, the residue was digested with isopropanol and filtered and the resulting solution was concentrated under reduced pressure; yield: 0.6 g; $^1\text{H-NMR}$ (D_2O) agrees with the NMR data of

30 the racemic acid.

Example 11:

Preparation of tert-butyl 2(S)-[[(1R,3S)-3-hydroxycyclohexanecarbonyl]amino]-3-methylbutyrate by coupling (1R,3S)-3-hydroxycyclohexane-1-carboxylic acid with tert-butyl (S)-valinate hydrochloride

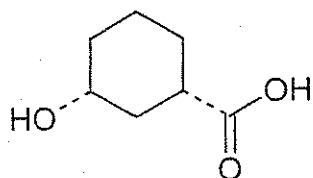


8.15 g (56.5 mmol) of (1R,3S)-3-hydroxycyclohexane-1-carboxylic acid, 19.6 ml of triethylamine and 11.86 g (56.5 mmol) of tert-butyl (S)-valinate hydrochloride were initially charged in 100 ml of DMF and cooled to 0°C, and 22.2 g (67.8 mmol) of TOTU ([cyano(ethoxycarbonyl)methyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate) were added a little at a time. The reaction solution was stirred at 18-22°C overnight. According to LC-MS, the starting material had been converted completely. The DMF was evaporated under reduced pressure and the residue was taken up in ethyl acetate and washed with aqueous NaHCO₃. The organic phase was dried (MgSO₄) and concentrated under reduced pressure: this gave 29.4 g of a red-brown oil. For purification, the product was chromatographed on silica gel (n-heptane/EA 2/1 - 1/1): this gave 11.8 g of a yellow solid which was directly reacted further; ¹H-NMR (CDCl₃): δ = 0.9 (m, 6 H), 1.25 - 1.57 (m, 4 H), 1.47 (s, 9 H), 1.78 - 1.95 (m, 3 H), 2.07 - 2.35 (m, 3 H), 3.67 (m, 1 H), 4.45 (m, 1 H), 6.0 (d, br., 1 H).

By alkylation with 4-iodomethyl-5-methyl-2-p-tolyloxazole, tert-butyl 2(S)-[[(1R,3S)-3-hydroxycyclohexanecarbonyl]amino]-3-methylbutyrate can be converted into tert-butyl 3-methyl-2(S)-[[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino]butyrate.

Example 12:

Preparation of (1S,3R)-3-hydroxycyclohexane-1-carboxylic acid from isopropyl (1S,3R)-3-acetoxycyclohexane-1-carboxylate by enzymatic ester hydrolysis

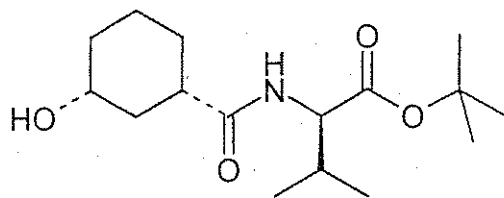


At RT, 10 g of isopropyl (1S,3R)-3-acetoxycyclohexane-1-carboxylate were stirred in 100 ml of phosphate buffer, pH = 7, with 5 g of Novozym 435 for 20 h. No more ester could be detected (TLC or GC). The immobilized enzyme was filtered off and the filtrate was acidified with HCl and concentrated under reduced pressure. The residue was digested with isopropanol. After filtration, the resulting clear solution was concentrated under reduced pressure; yield:

7.2 g; $^1\text{H-NMR}$ (D_2O) agrees with the NMR data of the racemic acid.

Example 13:

Preparation of tert-butyl 2(R)-[[(1S,3R)-3-hydroxycyclohexanecarbonyl]amino]-3-methylbutyrate by coupling (1S,3R)-3-hydroxycyclohexane-1-carboxylic acid with tert-butyl (R)-valinate hydrochloride



2.78 g (19.3 mmol) of (1S,3R)-3-hydroxycyclohexane-1-carboxylic acid, 6.7 ml of triethylamine and 4.04 g (19.3 mmol) of tert-butyl (R)-valinate hydrochloride were initially charged in 60 ml of DMF and cooled to 0°C , and 7.57 g (23.1 mmol) of TOTU ([cyano(ethoxycarbonyl)methyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate) were added a little at a time. The reaction solution was stirred at

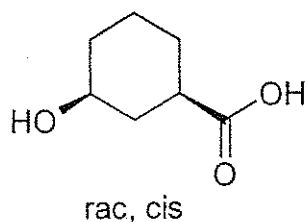
18-22°C overnight. The DMF was evaporated under reduced pressure and the residue was taken up in ethyl acetate and washed with aqueous NaHCO₃. The organic phase was dried (MgSO₄), concentrated under reduced pressure and, for purification, chromatographed on silica gel (n-heptane/EA 2/1 - 1/1): this gave 4.96 g of a yellow solid; ¹H-NMR (CDCl₃): δ = 0.9 (m, 6 H), 1.25 - 1.57 (m, 4 H), 1.47 (s, 9 H), 1.78 - 1.95 (m, 3 H), 2.07 - 2.35 (m, 3 H), 3.67 (m, 1 H), 4.45 (m, 1 H), 6.0 (d, br., 1 H).

By alkylation with 4-iodomethyl-5-methyl-2-p-tolyloxazole, tert-butyl 2(R)-[[(1S,3R)-3-hydroxycyclohexanecarbonyl]amino]-3-methylbutyrate can be converted into tert-butyl 3-methyl-2(R)-[[(1S,3R)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino]butyrate.

For scheme C:

Example 14:

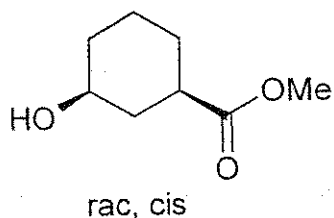
Preparation of racemic cis-3-hydroxycyclohexane-1-carboxylic acid by basic hydrolysis of rac-6-oxabicyclo[3.2.1]octan-7-one



1 g (7.9 mmol) of rac-6-oxabicyclo[3.2.1]octan-7-one and 0.64 g (2 eq.) of NaOH in 20 ml of water were stirred at RT overnight. The mixture was acidified with HCl or acetic acid and concentrated under reduced pressure, the residue was digested with ethyl acetate or isopropanol and the resulting organic solution was concentrated under reduced pressure; yield: 0.6-0.7 g; ¹H-NMR (D₂O): δ = 0.9-1.2 (m, 4 H), 1.6-1.77 (m, 3 H), 1.95 (m, 1 H), 2.17 (m, 1 H), 3.45 (m, 1 H).

Example 15:

Preparation of racemic methyl cis-3-hydroxycyclohexane-1-carboxylate



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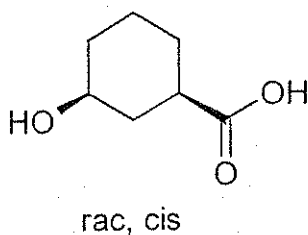
7 ml of acetyl chloride were added slowly, with stirring and gentle cooling with ice, to 10 g (79.3 mmol) of rac-6-oxabicyclo[3.2.1]octan-7-one and 100 ml of methanol.

During the addition, the temperature increased to 45°C but, within 10 min fell to 30°C. After 1 h, the reaction had ended and the reaction mixture was concentrated under reduced pressure; yield: 12.1 g; ¹H-NMR (CDCl₃): δ = 1.15-1.50 (m, 5 H), 1.8-2.0 (m, 3 H), 2.2 (m, 1 H), 2.37 (m, 1 H), 3.65 (m, 1 H), 3.7 (s, 3 H).

10

15 Example 16:

Preparation of racemic cis-3-hydroxycyclohexane-1-carboxylic acid by basic hydrolysis of the racemic methyl ester



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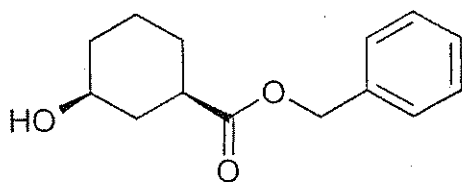
1 g (6.3 mmol) of methyl cis-3-hydroxycyclohexane-1-carboxylate was stirred at RT in 5 ml of THF, 1 ml of water and 1 ml of 11N NaOH overnight. No more ester could be detected. The mixture was acidified with HCl and concentrated under reduced pressure, the residue was digested with ethyl acetate and filtered and the solution was concentrated under reduced pressure; yield:

25

0.7g; $^1\text{H-NMR}$ (D_2O) agrees with the NMR data of the previous example.

Example 17:

5 Preparation of racemic benzyl cis-3-hydroxycyclohexane-1-carboxylate



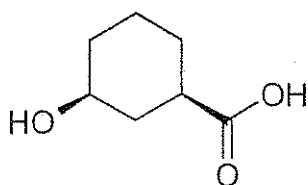
rac, cis

10 0.99 g (7.9 mmol) of rac-6-oxabicyclo[3.2.1]octan-7-one in 4 ml of DMF was stirred at 20-23°C with 0.97 ml (1.2 eq.) of benzyl alcohol and 1.3 g (2.2 eq.) of potassium carbonate. After the reaction had ended, water was added and the mixture was extracted with MTBE. The combined organic phases were washed with saturated NaCl solution, dried with MgSO_4 and concentrated under reduced pressure.

15 Chromatography on silica gel (CH_2Cl_2 - $\text{CH}_2\text{Cl}_2/\text{acetone}$ 19:1 - $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 18:1) gave 0.55 g of the desired product; $^1\text{H-NMR}$ (CDCl_3) agrees with the $^1\text{H-NMR}$ from the reaction of racemic cis-3-hydroxycyclohexane-1-carboxylic acid cesium salt with benzyl bromide.

20 Example 18:

Preparation of cis-3-hydroxycyclohexane-1-carboxylic acid by hydrogenolysis of benzyl cis-3-hydroxycyclohexane-1-carboxylate

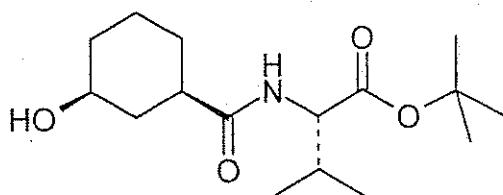


rac, cis

4 g (17.1 mmol) of benzyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved at RT in 100 ml of MeOH, a catalytic amount of Pd (10% on carbon) was added and the mixture was hydrogenated at 5 bar. After the reaction had ended (TLC, LCMS), the catalyst was filtered off through Celite and the solvent was evaporated under reduced pressure. The turbid residue was digested with ethyl acetate and filtered, and the resulting solution was concentrated under reduced pressure; yield: 2.0 g; $^1\text{H-NMR}$ (D_2O) agrees with the NMR data mentioned above.

10 Example 19:

Preparation of tert-butyl 2(S)-[(((1R,3S)-3-hydroxycyclohexanecarbonyl)amino)-3-methylbutyrate by coupling racemic cis-3-hydroxycyclohexane-1-carboxylic acid with tert-butyl (S)-valinate hydrochloride and subsequent stereoselective enzymatic acylation



20 Racemic cis-3-hydroxycyclohexane-1-carboxylic acid and optically pure tert-butyl (S)-valinate hydrochloride were coupled in the presence of triethylamine in DMF using TOTU ([cyano(ethoxycarbonyl)methyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate) (for the reaction conditions, see example 11), and the reaction solution was worked up.

25 10 g of the diastereomer mixture obtained in this manner in 300 ml of vinyl acetate were stirred at 20-23°C with 1 g of lipase B from *Candida Antarctica*. After about 53% conversion, the stereoselective acylation of the hydroxyl group was terminated by filtering off the enzyme. Chromatography gave 4 g of tert-butyl 2(S)-[(((1R,3S)-3-hydroxycyclohexanecarbonyl)amino)-3-methylbutyrate with 96.4% de (HPLC on Chiralpak AD 250 × 4.6; 1 ml/min, heptane/EtOH/MeOH 20:1:1 + 0.1% TFA) and

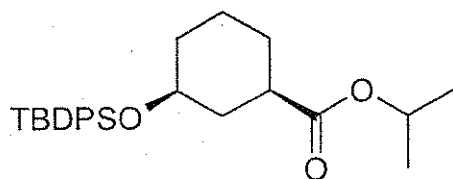
6 g of the (S)-2-(1S,3R)-acetate with > 80% de.

By alkylation with 4-iodomethyl-5-methyl-2-p-tolyloxazole, the substance was converted into tert-butyl 3-methyl-2(S)-{[(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbonyl]amino}butyrate.

For scheme D:

10 Example 20:

Synthesis of isopropyl (1R,3S)-3-(tert-butyldiphenylsilyloxy)cyclohexanecarboxylate



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5.8 g of optically pure isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate were dissolved in 20 ml of DMF, and 9.74 ml of TBDPSCI (tert-butyldiphenylsilyl chloride), 3.2 g of imidazole and 100 mg of DMAP (dimethylaminopyridine) were added and the mixture was stirred at 18-23°C for 4 h. Most of the solvent was distilled off under reduced pressure and the oily residue was partitioned between MTBE and water. The organic phase was dried (MgSO₄) and the solvent was then distilled off under reduced pressure; yield: 14 g of crude product. Chromatography on silica gel (EA/n-heptane 1:6) gave

20

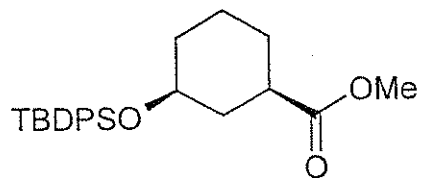
7.0 g of isopropyl (1R,3S)-3-(tert-butyldiphenylsilyloxy)cyclohexanecarboxylate;

25

¹H-NMR (CDCl₃): δ = 1.04 (s, 9 H), 1.19 (d, 6 H), 1.0 – 1.35 (m, 3 H), 1.48 (m, 1 H), 1.65 – 1.82 (m, 3 H), 2.06 (m, 2 H), 3.57 (m, 1 H), 4.95 (m, 1 H), 7.34 – 7.43 (m, 6 H), 7.66 – 7.68 (m, 4 H).

Example 21:

Synthesis of methyl (1R,3S)-3-(tert-butyldiphenylsilyloxy)cyclohexanecarboxylate

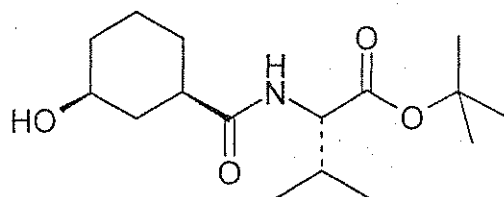


5 11.5 g of methyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate with > 99% ee were dissolved in 100 ml of DMF, 21.5 g of TBDPSCI (tert-butyldiphenylsilyl chloride), 6.5 g of imidazole and 500 mg of DMAP (dimethylaminopyridine) were added and the mixture was stirred at 18-23°C overnight. Most of the solvent was distilled off
10 under reduced pressure and the oily residue was taken up in MTBE and washed with water. The organic phase was dried (MgSO₄) and the solvent was then distilled off under reduced pressure. This gave 28 g of methyl (1R,3S)-3-(tert-butyldiphenylsilyloxy)cyclohexanecarboxylate as a yellowish oil; C₂₄H₃₂O₃Si (396.61), MS (ESI): 397 (M+H⁺).

15 The substance can be used directly for the basic ester hydrolysis and the subsequent coupling with amino acid derivatives such as, for example, tert-butyl alaninate, leucinate and valinate, or the corresponding hydrochloride.

20 Example 22:
Two-step synthesis of tert-butyl 2(S)--[[[(1R,3S)-3-hydroxycyclohexanecarbonyl]-amino]-(3S)-methylbutyrate from (1R,3S)-3-(tert-butyldiphenylsilyloxy)-cyclohexane-1-carboxylic acid

25



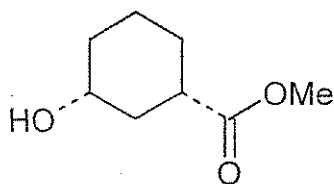
With stirring, 0.35 g of optically pure (1R,3S)-3-(tert-butyldiphenylsilyloxy)-cyclohexanecarboxylic acid (prepared by hydrolysis of, for example, the corresponding isopropyl ester with NaOH in water/isopropanol), 0.38 g of t-butyl (S)-valinate hydrochloride and 0.45 ml of triethylamine were initially charged in 4 ml of DMF. At 0-5°C, 0.36 g of TOTU ([cyano(ethoxycarbonyl)methyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate) was added in small portions, and, with cooling, the mixture was stirred for about 5 minutes. Stirring was then continued at RT. After 16 h, the reaction had ended. The entire reaction mixture was poured into about 60 ml of water and extracted twice with in each case 50 ml of ethyl acetate, and the organic phase was dried with MgSO₄ and concentrated under reduced pressure. The residue (1.4 g) was purified on silica gel (n-heptane/EA 1:1); yield: 394 mg of a white solid.

To remove the TBDPS protective group, tert-butyl 2(S)-{[(1R,3S)-3-(tert-butyldiphenylsilyloxy)cyclohexanecarbonyl]amino}-3-methylbutyrate was reacted in THF with tetrabutylammonium fluoride. Concentration of the reaction mixture and purification on silica gel (n-heptane/EA 3:1) gave 197 mg of the desired compound; C₁₆H₂₉NO₄ (299.41), MS (ESI): 300 (M+H⁺); HPLC (Chiralpak AD 250 × 4.6; 1 ml/min, heptane/EtOH/MeOH 20:1:1 + 0.1% TFA): Rt = 4.9 min.

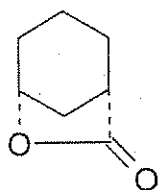
For schemes A, B and D

Example 23:

Preparation of methyl (1S,3R)-3-hydroxycyclohexane-1-carboxylate from isopropyl (1S,3R)-3-acetoxycyclohexane-1-carboxylate - via (1S,5R)-6-oxabicyclo[3.2.1]octan-7-one



2.74 g of isopropyl (1S,3R)-3-acetoxycyclohexane-1-carboxylate from the stereoselective enzymatic ester formation of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate in vinyl acetate/methylene chloride using Novozym 435 were, at 20-23°C, converted in virtually quantitative yield into (1S,5R)-6-oxabicyclo[3.2.1]octan-7-one by stirring with 0.3 g of K_2CO_3 in 30 ml of methanol. After filtration and concentration of the solvent under reduced pressure, (1R,5S)-6-oxabicyclo[3.2.1]octan-7-one



10

was taken up in about 30 ml of methanol and, with stirring and gentle cooling with ice, 1-2 ml of acetyl chloride were added. After the reaction had ended, the reaction mixture was concentrated under reduced pressure; yield: 1.5 g; 1H -NMR ($CDCl_3$): δ = 1.15-1.50 (m, 5 H), 1.8-2.0 (m, 3 H), 2.2 (m, 1 H), 2.37 (m, 1 H), 3.65 (m, 1 H), 3.7 (s, 3 H).

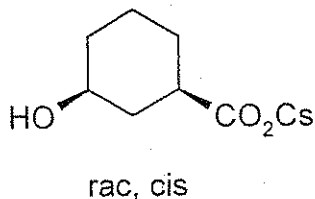
15

Methyl (1S,3R)-3-hydroxycyclohexane-1-carboxylate was directly reacted further.

20 For schemes A, B, C, D, E - two-step conversion of the compound of the formula (II) into a racemic compound of the formula (IV)

Example 24:

Preparation of the racemic cis-3-hydroxycyclohexane-1-carboxylic acid cesium salt

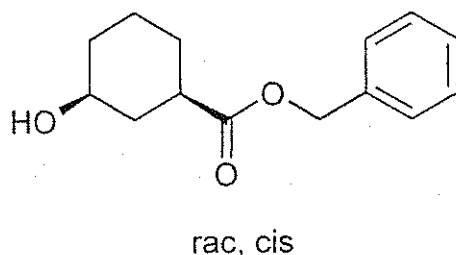


5

10 g (79.3 mmol) of rac-6-oxabicyclo[3.2.1]octan-7-one and 13.5 g (80.3 mmol) of cesium hydroxide monohydrate were stirred in 50 ml of water at RT. After 2 h, the reaction had ended. The mixture was concentrated under reduced pressure, and twice, in each case 50 ml of DMF were added and the mixture was concentrated under reduced pressure; yield: 19.6 g (89.5%); $^1\text{H-NMR}$ (D_2O): $\delta = 1.1\text{-}1.37$ (m, 4 H), 1.75-2.25 (m, 5 H), 3.63 (m, 1 H).

Example 25:

15 Preparation of racemic benzyl cis-3-hydroxycyclohexane-1-carboxylate



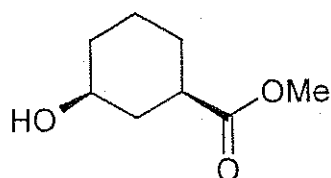
2 g (7.24 mmol) of racemic cis-3-hydroxycyclohexane-1-carboxylic acid cesium salt and 1.1 g (0.81 ml, 6.82 mmol) of benzyl bromide were stirred in 10 ml of DMF at RT. After 4 hours of stirring and standing overnight, the benzylation was complete. The reaction mixture was put into about 100 ml of water and extracted twice with in each case about 50 ml of MTBE. The combined organic phases were washed once with water and then dried using MgSO_4 and concentrated under reduced pressure; crude yield: 1.3 g (76.6%). The crude product was either directly reacted further or chromatographed; $^1\text{H-NMR}$ (CDCl_3): $\delta = 1.17\text{-}1.50$ (m, 4 H), 1.62 (d, 1 H), 1.80-2.0

(m, 3 H), 2.22 (m, 1 H), 2.43 (m, 1 H), 3.62 (m, 1 H), 5.12 (s, 2 H), 7.28-7.40 (m, 5 H).

- 5 Further examples of the enzymatic racemate resolution by stereoselective ester formation

Example 26:

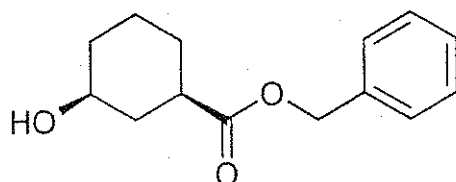
Stereoselective acylation of methyl cis-3-hydroxycyclohexane-1-carboxylate



- 10 500 mg of racemic methyl 3-hydroxycyclohexane-1-carboxylate, 1 ml of vinyl acetate, 4 ml of methylene chloride and 25 mg of Novozym 435 were stirred slowly at room temperature. After about 54% conversion (GC), the reaction was terminated by filtering off the enzyme. The optical purity of methyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was determined as being > 99% ee.

20 Example 27:

Synthesis of benzyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate by stereoselective acylation of racemic benzyl cis-3-hydroxycyclohexane-1-carboxylate

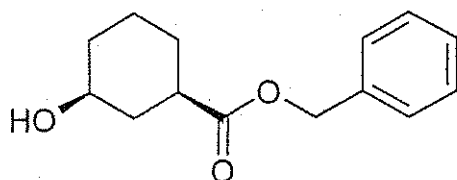


- 25 For 2 h, 108 mg (0.5 mmol) of racemic benzyl 3-hydroxycyclohexane-1-carboxylate were slowly stirred at room temperature in 5 ml of vinyl acetate and 4 ml of methylene chloride with 54 mg of Novozym 435. After filtration and concentration under reduced pressure, the product was chromatographed on silica gel

(n-heptane/EA 2:1); yield: 56 mg of benzyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate; $^1\text{H-NMR}$ (CDCl_3): δ = 1.15-1.5 (m, 4 H), 1.63 (d, 1 H), 1.85 (m, 1 H), 1.95 (m, 2 H), 2.23 (m, 1 H), 2.41 (m, 1 H), 3.62 (m, 1 H), 5.11 (s, 2 H), 7.35 (m, 5 H); ee > 99% (HPLC on Chiracel OJ 250 $\times$ 4.6; 1 ml/min, heptane/EtOH/MeOH 70:1:1).

Example 28:

Synthesis of benzyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate by racemate resolution of racemic benzyl cis-3-hydroxycyclohexane-1-carboxylate

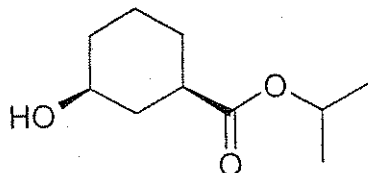


29.5 g of benzyl cis-(1RS,3SR)-3-hydroxycyclohexanecarboxylate were dissolved in about 200 ml of vinyl acetate, 15 g of Novozym 435 were added and the mixture was stirred at 20-23°C. After 75 minutes, the enzyme was filtered off and the solution was concentrated under reduced pressure. Chromatography on silica gel (n-heptane/ethyl acetate 2:1) gave 12 g of benzyl (1R,3S)-3-hydroxycyclohexane-carboxylate; > 99% ee (HPLC on Chiracel OJ 250 $\times$ 4.6; 1 ml/min, heptane/EtOH/CH₃OH 70:1:1); $^1\text{H-NMR}$ (DMSO), δ = 0.98-1.30 (m, 4 H), 1.66-1.82 (m, 4 H), 2.04 (m, 1 H), 2.39 (m, 1 H), 3.39 (m, 1 H), , 4.63 (dd, 2 H), 5.08 (m, 1 H), 7.30-7.40 (m, 5 H).

The reaction also yielded 17 g of the (1S,3R)-acetyl compound; 94% ee (HPLC on Chiracel OJ 250 $\times$ 4.6; 1 ml/min, heptane/EtOH/CH₃OH 70:1:1, after removal of the acetyl group).

Example 29

Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate

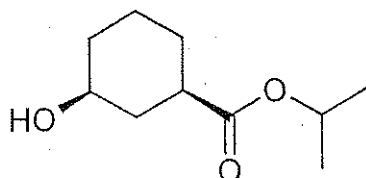


5

200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of acetone, 584 mg (5.78 mmol) of succinic anhydride and 40 mg of Novozym 435 were added and the mixture was stirred at 5°C. After 40-45% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was 72% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was > 97% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

Example 30

20 Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate

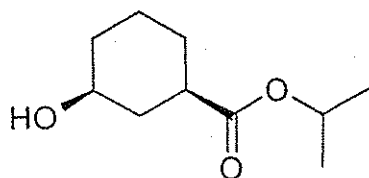


200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of DIPE, 584 mg (5.78 mmol) of succinic anhydride and 40 mg of Novozym 435 were added and the mixture was stirred at 35°C. After about

40% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was 61% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was 94% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

10 Example 31

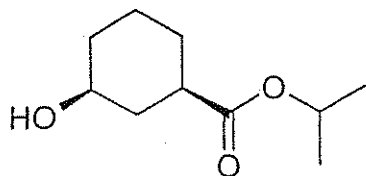
Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate



200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of acetone, 584 mg (5.78 mmol) of succinic anhydride and 160 mg of Novozym 435 were added and the mixture was stirred at 35°C. After 45-49% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was 84% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was 96% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

Example 32

Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate



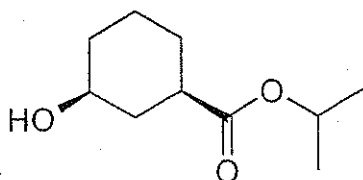
5

200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of MTB ether, 119 mg (1.18 mmol) of succinic anhydride and 160 mg of Novozym 435 were added and the mixture was stirred at 35°C. After 33-37% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was 46% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was 93% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

15

Example 33

20 Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate



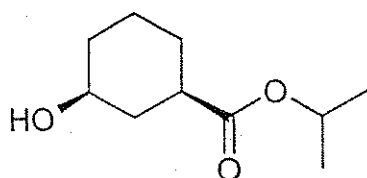
25

200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of THF, Novozym 435 L-2 was added and the mixture was stirred at 35°C. After about 40% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the

unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was 64% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was 97% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

Example 34

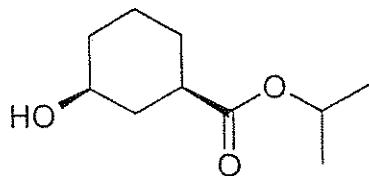
Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate



200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of DIPE, 584 mg (5.78 mmol) of succinic anhydride and 40 mg of Novozym 435 were added and the mixture was stirred at 35°C. After 40-45% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was 70% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was 92% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

Example 35

Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate

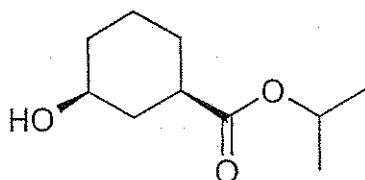


5

200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of n-heptane, 119 mg (1.18 mmol) of succinic anhydride and 160 mg of Novozym 435 were added and the mixture was stirred at 5°C. At about 30% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was 43% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was 96% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

Example 36

Racemate resolution of isopropyl cis-3-hydroxycyclohexane-1-carboxylate

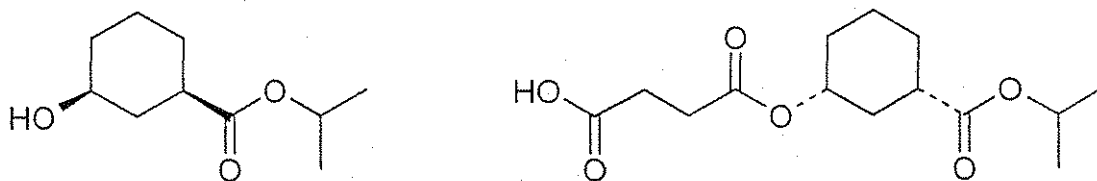


200 mg (1.07 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 10 ml of toluene, 584 mg (5.78 mmol) of succinic anhydride and 160 mg of Novozym 435 were added and the mixture was stirred at 5°C. At about

46-49% conversion, the reaction was terminated by filtering off the enzyme. Using a concentrated sample, the optical purities both of the unreacted substrate and of the acylation product formed were determined. The optical purity of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate was > 76% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7), the optical purity of mono(cis-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate was 91% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

10 Example 37

Preparation of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate and mono(-3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate by stereoselective enzymatic acylation of isopropyl cis-3-hydroxycyclohexane-1-carboxylate with succinic anhydride



2.0 mg (10.7 mmol) of racemic isopropyl cis-3-hydroxycyclohexane-1-carboxylate were dissolved in 100 ml of MTB ether, 5.84 g (57.8 mmol) of succinic anhydride and 1.6 g of Novozym 435 were added and the mixture was stirred at 35°C. At about 50% conversion, the reaction was terminated by filtering off the enzyme. The reaction mixture was dissolved in acetone, concentrated under reduced pressure and then partitioned between diisopropyl ether/n-heptane 4:1 and 1M Na₂CO₃ (aq.). Concentration of the organic phase gave 890 mg of isopropyl (1R,3S)-3-hydroxycyclohexane-1-carboxylate; ¹H-NMR (CDCl₃): δ = 1.23 (d, 6 H), 1.20-1.45 (m, 4 H), 1.68 (d, 1 H), 1.86 (m, 2 H), 1.95 (m, 1 H), 2.18 (m, 1 H), 2.34 (m, 1 H), 3.63 (m, 1 H), 5.00 (sept, 1 H); optical purity: 90% ee (HPLC on Chiralpak AD-H 250 × 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

Using 2N HCl, the aqueous phase was adjusted to pH 6-7 and extracted twice with ethyl acetate. Concentration after drying (Na_2SO_4) gave 1.39 g of mono(3-isopropoxycarbonylcyclohexyl) (1R,3S)-succinate;

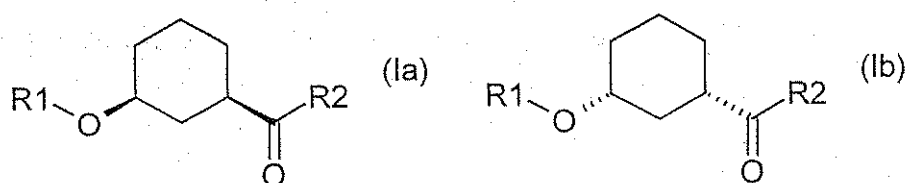
5 $^1\text{H-NMR}$ (CDCl_3): δ = 1.22 (d, 6 H), 1.24-1.41 (m, 3H), 1.47 (q, 1 H), 1.83-2.01 (m, 3 H), 2.17-2.24 (m, 1H), 2.35 (tt, 1 H), 2.58-2.64 (m, 2 H), 2.64-2.71 (m, 2 H), 4.69-4.79 (m, 1 H), 4.99 (sept, 1 H); optical purity: 88% ee (HPLC on Chiralpak AD-H 250 $\times$ 4.6; 1 ml/min, heptane/MeOH/EtOH/TFA 500:100:100:0.7).

10 Isolated products or crude product mixtures were identified by $^1\text{H-NMR}$ and/or mass spectra and/or by GC or HPLC.

The optical purity of the esters and alcohols was determined by HPLC, for example on Chiralpak AD 250 X 4.6 (Daicel) or Chiracel OD 250 x 4.6.

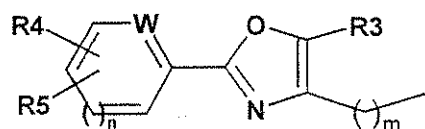
Claims

1. A process for preparing chiral nonracemic compounds of the formulae (Ia)
 5 and (Ib)



where:

10 R^1 is



in which:

15 R^3 is H, (C1-C6)-alkyl, (C3-C8)-cycloalkyl, (C1-C3)-alkyl-(C3-C8)-cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl, (C5-C6)-heteroaryl, (C1-C3)-alkyl-(C5-C6)-heteroaryl or (C1-C3)-alkyl which is fully or partially substituted by F;

20 R^4, R^5 independently of one another are H, F, Cl, Br, CF_3 , OCF_3 , (C1-C6)-alkyl, O-(C1-C6)-alkyl, SCF_3 , SF_5 , OCF_2-CHF_2 , (C6-C10)-aryl, (C6-C10)-aryloxy, OH, NO_2 ; or

25 R^4 and R^5 together with the carbon atoms that carry them form a fused partially saturated or unsaturated bicyclic (C6-C10)-aryl or (C5-C11)-heteroaryl ring;

W is CH, N, if $n = 1$;

W is O, S, NR^6 , if $n = 0$;

m is 1-6;

5

R^6 is H, (C1-C6)-alkyl-phenyl, (C1-C6)-alkyl;

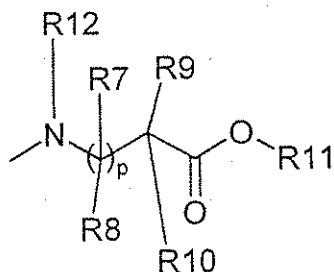
or

10 R^1 is an OH protective group (PG), such as, for example, benzyloxymethyl, benzyl, para-methoxybenzyl, tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), tetrahydropyranyl (THP), 1-ethoxyethyl (EE), 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl;

and

15

R^2 is



in which:

20

p is 0 – 2;

R^7 is H, (C1-C6)-alkyl;

25 R^8 is H, (C1-C6)-alkyl;

R^9 is H, F, (C1-C6)-alkyl;

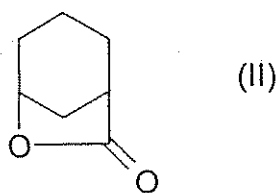
- R^{10} is H, F, (C1-C6)-alkyl, O-(C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, phenyl, where alkyl, alkenyl, alkynyl and cycloalkyl may optionally be substituted by one or more radicals from the group consisting of hydroxyl, phenyl, (C5-C11)-heteroaryl, O-(C1-C6)-alkyl and $NR^{13}R^{14}$, and phenyl may optionally be substituted by one or more radicals from the group consisting of hydroxyl, O-(C1-C6)-alkyl, F and CF_3 , with the proviso that R^{10} is not $NR^{13}R^{14}$ or O-(C1-C6)-alkyl, if $R^9 = F$;
- R^9 and R^{10} together with the carbon atom that carries them are (C3-C8)-cycloalkyl;
- R^{10} and R^{12} together are pyrrolidine and piperidine, if $n = 0$;
- R^{11} is H, (C1-C8)-alkyl, benzyl, (C1-C4)-alkyl-(C6-C10)-aryl, (C1-C4)-alkyl-O-(C1-C4)-alkyl, phenyl-(C1-C4)-alkyl, where alkyl, benzyl, phenyl, aryl may optionally be mono- or polysubstituted by O-(C1-C6)-alkyl, OCH_2CH_2-OMe , F, Cl, Br, I, $Si(CH_3)_3$, $OSi(CH_3)_3$, $Si(iPr)_3$, $OSi(iPr)_3$, $OCH_2CH_2-SiMe_3$, $OCH_2-Si(iPr)_3$, $O-CH_2-C_6H_5$, $SO_2C_6H_4-p-Me$, SMe, CN, NO_2 , $CH_2COC_6H_5$;
- R^{12} is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, benzyl, CO-(C1-C6)-alkyl, CO-phenyl, C(O)-O-(C1-C6)-alkyl, allyloxycarbonyl (ALOC), benzyloxycarbonyl (Cbz, Z), 9-fluorenylmethyloxycarbonyl (Fmoc), (C1-C4)-alkyl-(C6-C10)-aryl, (C1-C4)-alkyl-(C5-C11)-heteroaryl, (C1-C4)-alkyl-O-(C1-C4)-alkyl, phenyl-(C1-C4)-alkyl, (C5-C6)-heteroaryl-(C1-C4)-alkyl; SO_2 -(C1-C6)-alkyl, SO_2 -(C1-C6)-alkyl- SO_2 -(C1-C6)-alkyl, SO_2 -phenyl, where phenyl may optionally be substituted by (C1-C6)-alkyl, O-(C1-C6)-alkyl, F, Cl;
- R^{13} is (C1-C6)-alkyl;
- R^{14} is (C1-C6)-alkyl-phenyl, (C1-C6)-alkyl;

wherein

A)

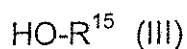
5 a) Lactone opening (LO)

racemic 6-oxabicyclo[3.2.1]octan-7-one of the formula (II)



10

is reacted with a compound of the formula (III)

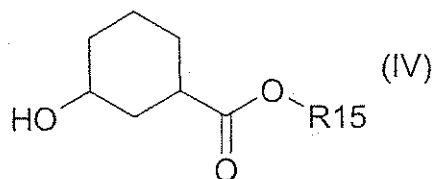


15 where

R^{15} is H, (C1-C8)-alkyl, (C3-C8)-cycloalkyl, (C2-C8)-alkenyl, (C2-C8)-alkynyl, benzyl, (C1-C4)-alkyl-(C6-C10)-aryl, (C1-C4)-alkyl-(C5-C11)-heteroaryl, (C1-C4)-alkyl-O-(C1-C4)-alkyl, phenyl-(C1-C4)-alkyl, (C5-C6)-heteroaryl-(C1-C4)-alkyl, where alkyl, benzyl, phenyl, aryl, heteroaryl may optionally
 20 be mono- or polysubstituted by phenyl, O-(C1-C6)-alkyl, $\text{OCH}_2\text{CH}_2\text{-OMe}$, OTs, F, Cl, Br, I, $\text{Si}(\text{CH}_3)_3$, $\text{OSi}(\text{CH}_3)_3$, $\text{Si}(\text{iPr})_3$, $\text{OSi}(\text{iPr})_3$, $\text{OCH}_2\text{CH}_2\text{-SiMe}_3$, $\text{OCH}_2\text{-Si}(\text{iPr})_3$, OTHP, O- $\text{CH}_2\text{-C}_6\text{H}_5$, $\text{SO}_2\text{C}_6\text{H}_4\text{-p-Me}$, SMe, CN, NO_2 , COOH, CONH_2 , $\text{CH}_2\text{COC}_6\text{H}_5$, CO-benzyloxy, CO-O(C1-C6)-alkyl, NHTs, NHAc, NHBoc, NHALoc, NHbenzyl;

25

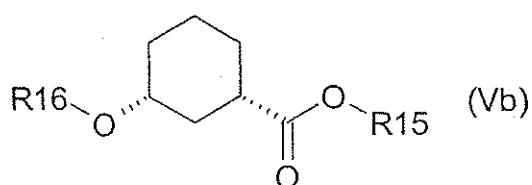
in the presence of suitable bases or acids in a suitable solvent or with acid halides in alcohols, where in the case of aqueous reactions the work-up conditions determine whether the salt or else the free acid is obtained, to give, for example, a racemic cis-configured compound of the formula (IV),



in which R^{15} is as defined above, or to give a compound of the formula (IV) which, depending on the work-up, may be present in ionic form, for example as Cs^+ , Li^+ , K^+ , NH_4^+ , Ca^{2+} , Ba^{2+} , Mg^{2+} salt and in which R^{15} is also Cs, Li, K, NH_4 , Ca, Ba, Mg, and, if appropriate, the resulting product is further converted into another product of the formula (IV);

b) Enzymatic ester formation (EF) + separation (S)

the resulting compounds of the formula (IV) are subjected to a stereoselective enzymatic ester formation (EF), where an acyl donor and the enzyme are added to the hydroxyl compounds in an organic solvent and the resulting mixture is stirred at from -20 to $80^\circ C$ and, after the reaction has ended, one stereoisomer is present as ester of the formula (Vb)



in which

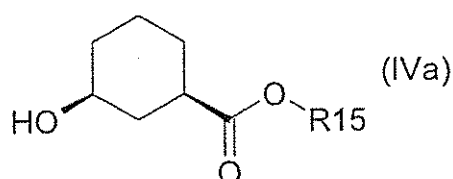
R^{16} is $C(=O)-(C_1-C_{16})$ -alkyl, $C(=O)-(C_2-C_{16})$ -alkenyl, $C(=O)-(C_3-C_{16})$ -alkynyl, $C(=O)-(C_3-C_{16})$ -cycloalkyl, where one or more carbon atoms may be replaced by oxygen atoms and may be substituted by 1-3 substituents from the group consisting of F, Cl, Br, CF_3 , CN, NO_2 , hydroxyl, methoxy, ethoxy, phenyl, $CO-O(C_1-C_4)$ -alkyl and $CO-O(C_2-C_4)$ -alkenyl, where phenyl, $CO-O(C_1-C_4)$ -alkyl and $CO-O(C_2-C_4)$ -alkenyl for their part may be substituted by 1-3

substituents from the group consisting of F, Cl, Br, CF₃, and

R¹⁵ is as defined above,

5

and the other stereoisomer is present unchanged as the alcohol of the formula (IVa)



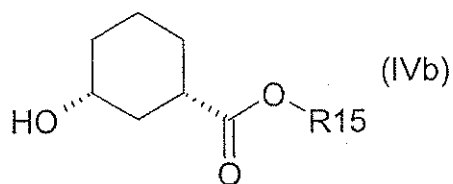
10 which compounds can therefore, utilizing their different chemical or physicochemical properties, be separated from one another or else be processed further by a subsequent chemical follow-up reaction in which the ester does not participate, where

15 the enantiomers of the formula (IVa) obtained as alcohol are processed further as described under d), or

c) Ester cleavage

20 the enantiomers of the formula (Vb) obtained as acylated compounds are hydrolyzed by known processes to give chemically enantiomeric alcohols (IVb) or, for example by reaction with K₂CO₃ in methanol, transesterified intramolecularly to give the optically active (1S,5R)-6-oxabicyclo[3.2.1]octan-7-one which can be converted into an isomeric form of the product

25



or the compound of the formula (Vb) is converted, for example, by lipase-catalyzed cleavage of both ester functions into the optically active compound of the formula (IVb, where $R^{15} = H$) which can be converted into an isomeric form of the product;

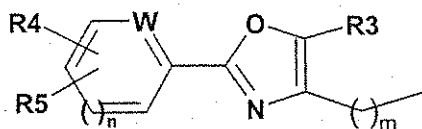
d) Alkylation (Alk- R^1 /Alk-PG)

further conversion with compounds of the formula (VI)



in which

R^1 is



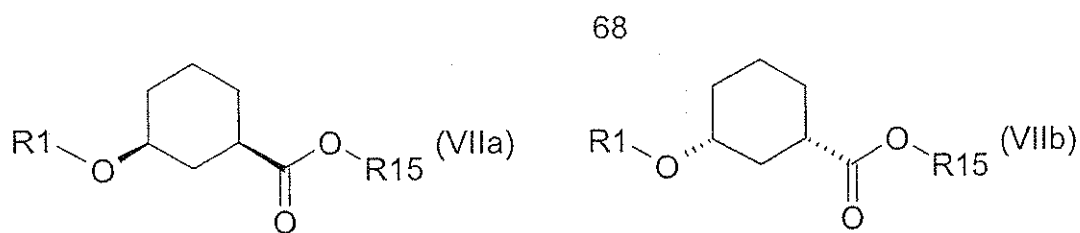
and R^3 , R^4 , R^5 , W, n and m are as defined above, or

R^1 is an OH protective group (PG) as defined above, except for THP, EE, 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl;

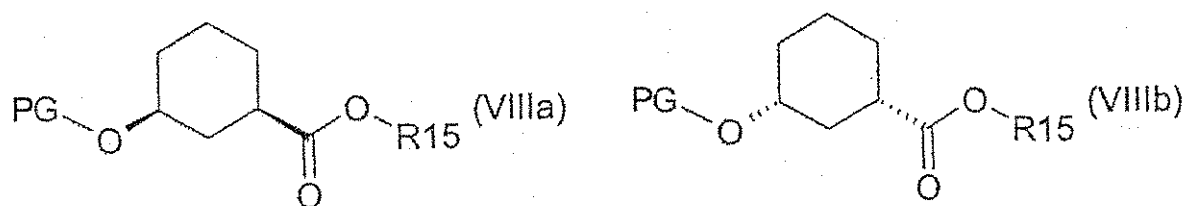
and

X is Cl, Br, I, OTs, OMs, OTf;

in the presence of bases in a suitable solvent to give compounds of the formula (VIIa) or (VIIb);



or, in the case of $R^1 = \text{PG}$, to give compounds of the formula (VIIIa) or (VIIIb)



or

R^1 is an OH protective group (PG) such as tetrahydropyranyl (THP),
 1-ethoxyethyl, 1-methyl-1-methoxyethyl or 1-methyl-1-benzyloxyethyl;

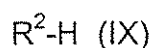
and

to introduce the OH protective groups, the compounds of the formula (IVa) or (IVb)
 are reacted under acid catalysis with the appropriate known enol ethers, also to give
 compounds of the formula (VIIIa) or (VIIIb);

and

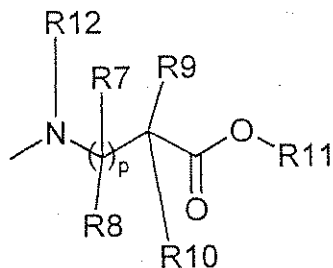
e) Direct reaction or ester cleavage & coupling (DR or EC+C)

e1) the resulting compounds of the formula (VIIa) or (VIIb) or compounds of the
 formula (VIIIa) or (VIIIb) are converted in a direct reaction (DR), for example by
 reacting an amine of the formula (IX)



in which

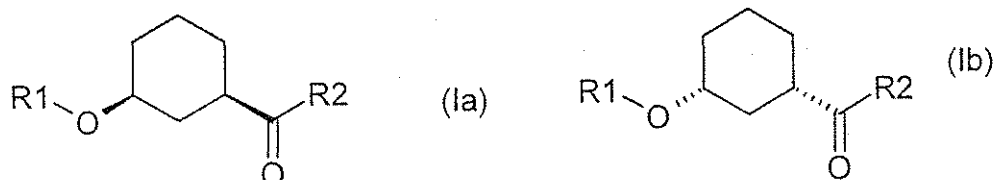
R^2 is



5

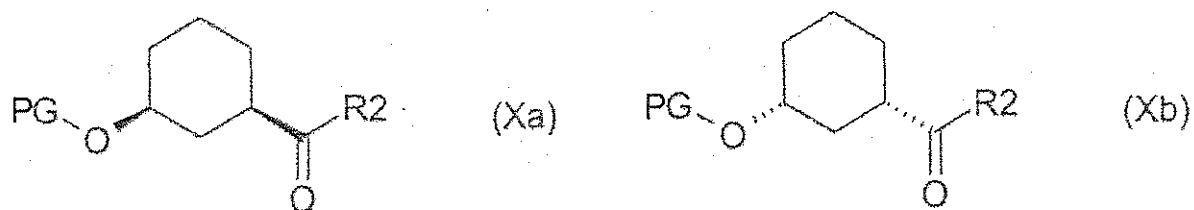
where R7, R8, R9, R10, R11, R12 and p are as defined above,

or the corresponding lithium or dimethylaluminum derivative, or by reacting the compounds of the formula (VIIa) or (VIIb) or the compounds of the formula (VIIIa) or (VIIIb) and the amine or amino acid derivative R^2-H of the formula (IX) in the presence of activating reagents or catalysts, to give compounds of the formula (Ia) or (Ib) or isomeric forms thereof,



15

or, in the case of $R^1 = PG$, to give compounds of the formula (Xa) or (Xb),

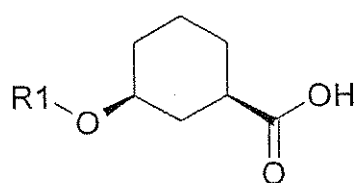


or

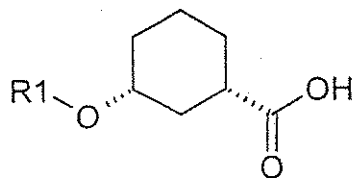
20

e2) the resulting compounds of the formula (VIIa) or (VIIb) or (VIIIa) or (VIIIb) are

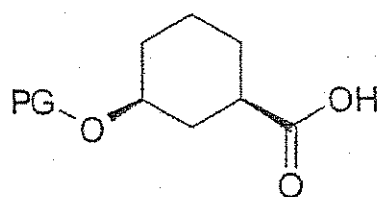
subjected to an ester cleavage, and the resulting compounds of the formula (XIa) or (XIb) or (XIIIa) or (XIIIb)



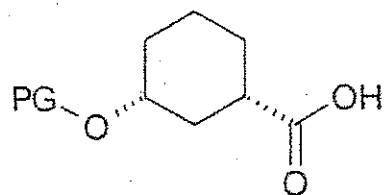
(XIa)



(XIb)

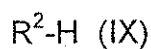


(XIIIa)



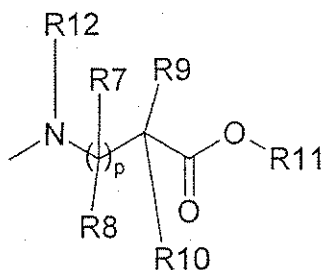
(XIIIb)

or the corresponding salts to a subsequent coupling with a compound of the formula (IX)



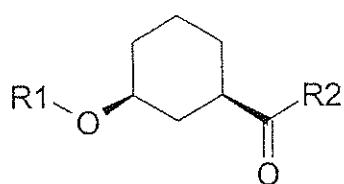
in which

R^2 is

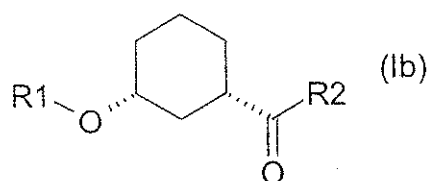


where R7, R8, R9, R10, R11, R12 and p are as defined above,

20 in the presence of dehydrating or activating reagents, to give a compound of the formula (Ia) or (Ib) or an isomeric form thereof;



(Ia)

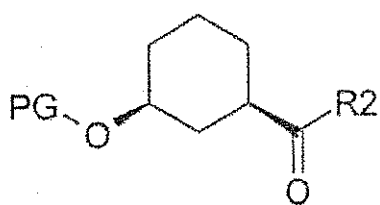


(Ib)

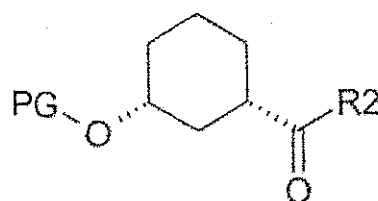
and, if appropriate,

- 5 f) Removal of the protective group PG (RPG)

if R^1 is an OH protective group (PG) as defined above under R^1 , the compounds of the formula (Xa) or (Xb)



(Xa)



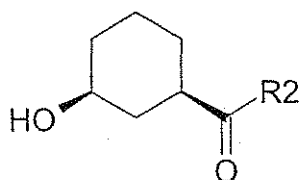
(Xb)

10

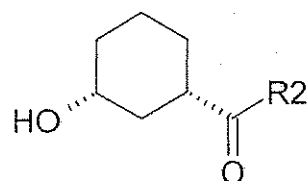
in which R^2 and PG are as defined above

are converted by removal of the protective group by known processes into

- 15 compounds of the formula (XIIa) or (XIIb)



(XIIa)



(XIIb)

- 20 in which R^2 is as defined above, followed by conversion according to the stated process variants into the compounds of the formula (Ia) or (Ib) or isomeric forms thereof;

it also being possible to change the sequence of the individual reaction steps as

described above under A):

A) $LO \rightarrow EF+S \rightarrow [EC] \rightarrow Alk-R^1 \rightarrow DR \text{ or } EC + C \rightarrow \text{product/isomeric form}$

5 to:

B) $LO \rightarrow EF+S \rightarrow [EC] \rightarrow DR \text{ or } EC + C \rightarrow Alk-R^1 \rightarrow \text{product/isomeric form}$

or

10 C) $LO \rightarrow DR \text{ or } EC + C \rightarrow EF + S \rightarrow [EC] \rightarrow Alk-R^1 \rightarrow \text{product/isomeric form}$

or

D) $LO \rightarrow EF+S \rightarrow [EC] \rightarrow Alk-PG \rightarrow DR \text{ or } EC + C \rightarrow RPG \rightarrow Alk-R^1 \rightarrow \text{product/isomeric form,}$

or

15 E) $LO \rightarrow Alk-PG \rightarrow DR \text{ or } EC + C \rightarrow RPG \rightarrow EF + S \rightarrow [EC] \rightarrow Alk-R^1 \rightarrow \text{product/isomeric form.}$

2. The process as claimed in claim 1, wherein the processes A), B) and D) are employed.

20

3. The process as claimed in claim 1 or 2, wherein process A) is employed.

4. The process for preparing the compounds of the formulae (Ia) and (Ib) as claimed in any of claims 1 to 3, wherein

25

R₄ is Br, CF₃, OCF₃, (C1-C6)-alkyl, O-(C1-C6)-alkyl;

R5 is H, (C1-C6)-alkyl, O-(C1-C6)-alkyl or

R4 and R5 together with the phenyl ring = naphthyl;

5 R3 is CF₃, (C1-C6)-alkyl, (C3-C6)-cycloalkyl, phenyl;

W is CH, if n = 1;

m is 1;

10

p is 0;

R9 is H, (C1-C6)-alkyl;

15 R10 is (C1-C6)-alkyl, where alkyl may optionally be substituted by phenyl;

R10 and R12 together with the atoms that carry them are pyrrolidine, if p = 0;

R9 and R10 together with the carbon atom that carries them are (C3-C6)-cycloalkyl;

20

R11 is H,

R12 is H, (C1-C6)-alkyl, benzyl.

Abstract

(EN) The invention relates to a method for producing chiral, non-racemic, cis-configured cyclohexanols or cyclohexanol derivatives of formulae (Ia) and (Ib) wherein the radicals have the designations cited in the description, by means of enzymatic racemic splitting.