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Chemo-enzymatic preparation of optically active *endo*-bicyclo[4.1.0]heptan-2-ols

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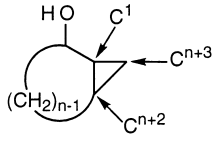
Abstract

Resolutions of *endo*-bicyclo[4.1.0]heptan-2-ols were achieved by acylation in the presence of lipase from *Candida antarctica* (Novozym®). The (1*S*,2*R*,6*R*) enantiomers reacted faster and the enantiomeric ratios were between 60 and 800 for the 6-substituted bicycloalkanols.

1. Introduction

The synthesis of optically active bicyclo[*n*.1.0]alkan-2-ols should be interesting in order to prepare natural compounds with such a feature[1] or analogs, but these compounds are also interesting intermediates for the synthesis of various types of compounds with one or several stereogenic carbon centers. For example, oxymercuration of bicycloalkan-2-ols results in the diastereoselective formation of cycloalkan-1,3-diols derivatives with three stereogenic centers by cleavage of the $C^{(n+2)}$–$C^{(n+3)}$ cyclopropane bond.[2] Substitution of the hydroxyl group by a homolytically cleavable substituent allows the synthesis of cycloalkenes with at least one stereogenic carbon atom by cleavage of the C^1–$C^{(n+3)}$ cyclopropane bond.[3–5]



This cyclopropylcarbinyl-homoallyl rearrangement also allows the preparation of various fused or spiro unsaturated compounds by cascade reactions including radical intramolecular cyclizations when the starting bicycloalkanol bears an unsaturated alkyl chain.[4] Moreover, oxidation of these bicycloalkanols

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into bicyclo[*n*.1.0]alkan-2-ones enables the synthesis of various cycloalkanone derivatives by cleavage of the C^1–$C^{(n+3)}$ cyclopropane bond [6–14] and tandem cyclopropane bond cleavage intramolecular cyclizations have also been reported when an unsaturated alkyl chain is present on the starting material.[11b,12b,14]

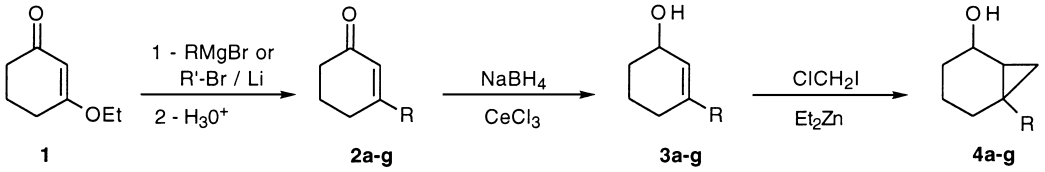
It was shown that cyclopropane bond cleavage occurred in various cases without an absolute configurational change[3,8a,11c,12] of carbon $C^{(n+2)}$ or with inversion of its configuration.[2] The preparation of enantiomerically enriched bicyclo[*n*.1.0]alkan-2-ol derivatives should give access to various types of optically active compounds.

Optically active bicyclo[*n*.1.0]alkan-2-ols are generally prepared by hydroxyl directed cyclopropanation[15,16] of optically active cycloalk-2-en-1-ols[9,17] or by diastereoselective addition of nucleophiles to enantiomerically enriched bicyclo[*n*.1.0]alkan-2-ones.[3,18] Recently we have reported the lipase-catalyzed kinetic resolution of racemic *endo*-bicyclo[4.1.0]heptan-2-ol and that of the corresponding 6-methyl and 1-methyl substituted compounds.[19,20]

In this paper we have focussed on the preparation of optically active 6-substituted *endo*-bicyclo[4.1.0]heptan-2-ols by enzymatic resolution in order to show up the influence of the substituent on the enantioselectivity.

2. Results and discussion

The *endo*-bicycloheptan-2-ols **4a**–**4g** were prepared by reaction under air[21] of cyclohex-2-en-1-ols **3a**–**3g** with the reagent obtained by the addition of $ClCH_2I$ to Et_2Zn.[22] The required cyclohexenols **3a**–**3g** were obtained by reduction of the corresponding cyclohex-2-en-1-ones **2a**–**2g** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$.[23] Reaction of 3-ethoxycyclohex-2-en-1-one **1**[24] with a Grignard reagent[25] (R=C_2H_5, C_8H_{17}, $C_{11}H_{23}$) or with a halogenated compound in the presence of lithium (R=C_4H_9)[26] followed by an aqueous treatment gave the 3-substituted cyclohexenones **2c**–**2f**. It is noteworthy that the 3-benzylcyclohexenone **2g** was obtained by addition of the 4-benzyloxy-1-bromobutane to a mixture of lithium and the 3-ethoxycyclohexenone **1**.[27]

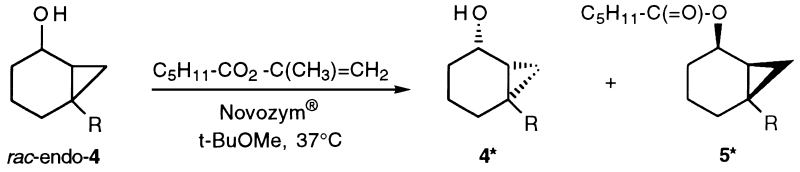


2 - 4	a	b	c	d	e	f	g
R	H	CH_3	C_2H_5	C_4H_9	C_8H_{17}	$C_{11}H_{23}$	CH_2Ph

Transesterifications of isopropenyl hexanoate with these bicycloheptan-2-ols **4a**–**4g** were run in *tert*-butyl methyl ether at 37°C in the presence of Novozym® (an immobilized form of lipase B from *Candida antarctica*) which was found to give higher reaction rates and higher enantioselectivities in the transesterification of isopropenylacetate with **4a** or **4b**.[19] Isopropenyl hexanoate was prepared by heating at reflux a mixture of hexanoic acid and isopropenylacetate in the presence of *para*-toluenesulfonic acid.[28]

Generally, enzyme-catalyzed transesterifications were stopped at about 50% conversion by removing the enzyme by filtration, then bicycloheptyl hexanoates **5*** and unreacted bicycloheptanols **4*** were separated by silica gel column chromatography. Enantiomeric excesses (ees) of bicycloheptanols **4b***–**4g*** were determined by gas chromatography on a chiral capillary column (Cydex B) and those of **4a***

Table 1
Novozym®-catalyzed transesterification of isopropenyl hexanoate with bicyclo[4.1.0]heptan-2-ols **4a–4g**



Entry	Substrate R		Time (h)	Recovered alcohol **4*** Yield(%)	$[\alpha]_D^{20}$ [b]	ee_s(%)	Ester **5*** Yield(%)	$[\alpha]_D^{20}$ [b,c]	ee_p(%) [c]	c	E
1	H	**4a**	1.45	41	-76 (1.8)	99.3	51	+62 (1.6)	87	0.53	80
2 [a]	H	**4a**	0.50	53	-57 (2.0)	75	42	+75 (1.3)	95	0.44	88
3	CH_3	**4b**	2	48	-71 (0.9)	96	44	+65 (0.8)	88	0.52	61
4	CH_2-CH_3	**4c**	1.30	42	-63 (1.3)	99	47.5	+57 (0.7)	92	0.52	126
5	$(CH_2)_3$-CH_3	**4d**	1.15	41	-54 (1.3)	99.7	43	+50 (0.9)	96	0.51	317
6	$(CH_2)_7$-CH_3	**4e**	1.30	48	-42 (1.6)	95	46	+42 (1.0)	90	0.51	119
7	$(CH_2)_{10}$-CH_3	**4f**	1.20	50	-27 (2.7)	88	45	+28 (2.3)	99.6	0.47	>800
8	CH_2-Ph	**4g**	1.15	47	-43 (1.5)	99	44	+41 (2.0)	98	0.50	525

[a] In this experiment one third part of the relative amount of Novozym® was used (see experimental part).
[b] In parenthesis is indicated the concentration in THF.
[c] Measured on the corresponding bicycloheptanol.

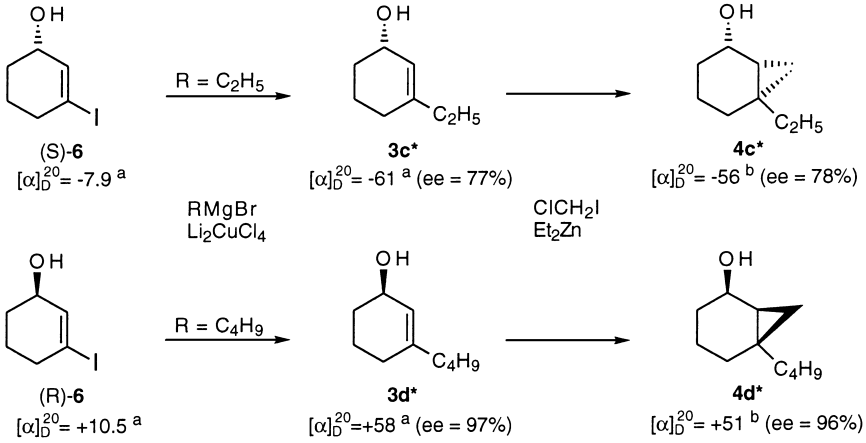
samples were determined by HPLC of the corresponding phenylcarbamate on a chiral OD-H column. Enantiomeric excesses of bicycloheptyl hexanoates **5a***–**5g*** were measured as described above from the corresponding bicycloheptan-2-ols isolated after treatment of these esters with $LiAlH_4$. For each reaction the conversion ratio c and the enantiomeric ratio E were calculated from the enantiomeric excess of the product (ee_p) and the enantiomeric excess of the unreacted substrate (ee_s) using the usual formulas: $(E=Ln[(1-ee_s)(ee_p/(ee_s+ee_p))]/Ln[(1+ee_s)(ee_p/(ee_s+ee_p))]$; $c=ee_s/(ee_s+ee_p)$).[29] Our results are reported in Table 1.

With the parent bicycloheptanol **4a** it was shown that it is possible to isolate, as expected, the unreacted substrate or the ester product with a good ee by running the reaction to more or less than 50% conversion (see entries 1 and 2). The enantioselectivity of the Novozym®-catalyzed transesterification of isopropenyl hexanoate with the bicycloheptanol **4a** (E=80–88)[30] appears to be slightly higher than that observed using isopropenyl acetate (E=51).[19] It should be noticed that the R_f value of a bicycloheptyl hexanoate is higher than that of the corresponding acetate and the separation of reaction products after transesterification was easier when the reaction was performed with isopropenyl hexanoate.

With the 6-substituted bicycloheptanols **4b–4j** the enantiomeric ratio was generally higher than 100 and it seems that the general trend was an increase in selectivity on going from the methyl substituted compound to the one bearing the undecyl substituent. With the more crowded benzylated compound **4g**

the enantioselectivity was sufficient to isolate in one experiment the ester and the unreacted alcohol with very high enantiomeric excess (ee=98%).

Samples of ethylbicycloheptanol **4c** and of butylbicycloheptanol **4d** enriched in the (1*R*,2*S*,6*S*)-[31,38] and (1*S*,2*R*,6*R*)-enantiomers, respectively, were synthesized by cyclopropanation of (*S*)-3-ethylcyclohex-2-enol **3c*** and (*R*)-3-butylcyclohex-2-enol **3d*** prepared by reaction, in the presence of Li_2CuCl_4, of EtMgBr and BuMgBr[32] with the known optically active (*S*)- and (*R*)-3-iodocyclohex-2-enols **6** which were available by the method described by Mori et al.[33]



[a] In $CHCl_3$. [b] In THF.

Comparison of the specific rotation sign and of the retention time in gas chromatography on a Cydex B column of the (1*R*,2*S*,6*S*)-ethylbicycloheptanol and the (1*S*,2*R*,6*R*)-butylbicycloheptanol with those of the optically active bicycloheptanols isolated after the Novozym®-catalyzed transesterification with **4c** and **4d** shows that this enzyme reacts faster with the (1*S*,2*R*,6*R*)-enantiomers. Comparison of the chiroptical properties of optically active bicycloheptanols **4a*** and **4b*** with those reported in the literature[19] also show a fast reaction of this lipase with (1*S*,2*R*,6*R*)-alcohols and the same enantioselectivity of the Novozym®-catalyzed reaction was postulated for all the other cases. The homogeneousness of the specific rotation signs of bicycloheptanols (levorotatory for the unreacted alcohols **4a***–**4g*** and dextrorotatory for those isolated after reduction of bicycloheptyl hexanoates **5a***–**5g***) was in agreement with such an assumption.

3. Conclusion

In summary, this work shows that Novozym®-catalyzed transesterifications allow the preparation of optically active 6-substituted *endo*-bicyclo[4.1.0]heptan-2-ols with a wide range of substituents. The usual enantioselectivity for the '*R*'-isomer generally reported for *Candida antarctica* lipase[34,35] and various lipases[36,37] was also noticed.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 and 50.3 MHz, respectively), or on a AC-250 (250 and 62.9 MHz, respectively), instrument. Chemical shifts are expressed in parts

per million (δ) relative to tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; tt, triplet of triplet; q, quartet; m, multiplet and b for a broadened signal. Infrared spectra were recorded on a Perkin–Elmer 682 spectrometer. Mass spectra were determined on a GC–MS Nermag R10-10 (capillary column: CPSIL5, 25 m) at an ionizing voltage of 70 eV. Column chromatography was carried out with 70–230 mesh silica gel. TLC was performed on 0.25 mm silica gel (Merk $60F_{254}$). Dry solvents were obtained as follows: diethyl ether was distilled over $LiAlH_4$, THF was distilled over sodium–benzophenone radical anions, 1,2-dichloroethane and *tert*-BuOMe were filtered through a short column of basic alumina (activity I). A 25 m×0.25 mm ID Cydex B column was used for the ee measurements (flow carrier: helium). Cyclohexane-1,3-dione, cyclohex-2-en-1-one and 3-methylcyclohex-2-en-1-one were purchased from Acros Organics.

*4.1.1. 3-Ethoxycyclohex-2-en-1-one **1***

This compound was prepared as described in the literature[24] by treatment of cyclohexane-1,3-dione with ethanol in the presence of *p*-toluenesulfonic acid in a distillation apparatus, but the usual solvent (benzene) was replaced by cyclohexane. With these solvents the boiling point of a ternary azeotrope (cyclohexane–ethanol–water: 62.1°C or benzene–ethanol–water: 64.6°C) and that of a binary azeotrope (cyclohexane–ethanol: 64.9°C or benzene–ethanol: 67.8°C) allow removal of first the water formed in the reaction then the excess ethanol.

The 3-substituted cyclohex-2-enones **2c**–**g** were prepared from the ethoxycyclohexenone **1** according to literature procedures.[25,26]

*4.1.2. 3-Ethylcyclohex-2-en-1-one **2c***

The title compound was obtained from ethoxycyclohexenone **1** and ethylmagnesium bromide, 1.4 g, 56%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.88 (t, J=1.6 Hz, 1H), 2.36 (t, J=6.9 Hz, 2H), 2.30 (bt, J=6.4 Hz) and 2.25 (q, J=7.2 Hz) (4H), 2.00 (tt, J=6.9, 6.4 Hz, 2H), 1.12 (t, J=7.2 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 199.4, 167.7, 123.9, 36.8, 30.3, 29.2, 22.2, 10.7.[39]

*4.1.3. 3-Butylcyclohex-2-en-1-one **2d***

The title compound was obtained from ethoxycyclohexenone **1**, 1-bromobutane and lithium, 1.21 g, 56%.[40]

*4.1.4. 3-Octylcyclohex-2-en-1-one **2e***

The title compound was obtained from ethoxycyclohexenone **1** and octylmagnesium bromide, 3 g, 72%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.88 (t, J=1.6 Hz, 1H), 2.38 (t, J=6.8 Hz) and 2.29 (bt, J=6.4 Hz) and 2.22 (bt, J=7.6 Hz) (6H), 1.99 (tt, J=6.8, 6.4 Hz, 2H), 1.60–1.42 (m, 2H), 1.42–1.12 (m, 10H), 0.99 (bt, J=6.8 Hz, 3H); ^{13}C NMR (59.3 MHz, $CDCl_3$) δ 195.6, 163.5, 126.2, 38.0, 37.3, 31.5, 30.8, 29.1, 29.0, 26.5, 23.6, 22.5, 22.4, 12.2; IR (neat) 2940, 2860, 1680, 1630, 1460 cm^{-1}; EI-MS (m/z) 208 (M^+, 13), 137 (3.3), 123 (41), 109 (11), 95 (20), 82 (100).

*4.1.5. 3-Undecylcyclohex-2-en-1-one **2f***

The title compound was obtained from ethoxycyclohexenone **1** and undecylmagnesium bromide, 1.5 g, 43%.[40]

4.1.6. 3-Benzylcyclohex-2-en-1-one ***2g***

The title compound was obtained from ethoxycyclohexenone **1**, 4-benzyloxy-1-bromobutane and lithium, 1.3 g, 50%.[41]

Cyclohex-2-en-1-ols **3a**–**g** were prepared by treatment in methanol of the cyclohex-2-enones **2a**–**g** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$.[23]

4.1.7. Cyclohex-2-en-1-ol ***3a***

882 mg, 90%.

4.1.8. 3-Methylcyclohex-2-en-1-ol ***3b***

1 g, 90%.

4.1.9. 3-Ethylcyclohex-2-en-1-ol ***3c***

1.07 g, 85%.[38b]

4.1.10. 3-Butylcyclohex-2-en-1-ol ***3d***

1.32 g, 86%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.57–5.44 (m, 1H), 4.30–4.11 (m, 1H), 2.09–1.84 (m, 4H), 1.84–1.51 (m, 4H), 1.51–1.12 (m, 5H), 0.87 (bt, J=6.7 Hz, 3H); ^{13}C NMR (59.3 MHz, $CDCl_3$) δ 141.1, 124.7, 66.2, 31.5, 30.0, 28.1, 18.9, 18.7, 13.4, 12.3; IR (neat) 3360, 2940, 2860, 1670, 1450 cm^{-1}; EI-MS (m/z) 154 (M^+, 18), 137 (35), 136 (12), 111 (41), 97 (60), 80 (100).[42]

4.1.11. 3-Octylcyclohex-2-en-1-ol ***3e***

1.34 g, 64%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.56–5.44 (m, 1H), 4.27–4.11 (m, 1H), 2.06–1.87 (m, 4H), 1.87–1.51 (m, 4H), 1.51–1.13 (m, 13H), 0.88 (bt, J=6.8 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 137.9, 126.3, 67.5, 32.9, 31.8, 28.8, 28.5, 28.3, 27.8, 27.5, 25.3, 23.2, 22.6, 13.6; IR (neat) 3330, 2920, 2860, 1660, 1450 cm^{-1}; EI-MS (m/z) 210 (M^+, 12), 193 (4), 192 (10), 97 (100), 79 (10).

4.1.12. 3-Undecylcyclohex-2-en-1-ol ***3f***

1.85 g, 74%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.56–5.42 (m, 1H), 4.27–4.10 (m, 1H), 2.06–1.85 (m, 2H), 1.85–1.51 (m, 4H), 1.51–1.12 (m, 19H), 0.89 (bt, J=6.7 Hz, 3H); ^{13}C NMR (59.3 MHz, $CDCl_3$) δ 136.8, 127.3, 66.9, 33.4, 31.8, 29.8, 29.6, 27.9, 26.6, 25.4, 23.4, 22.4, 20.3, 15.3, 14.2, 13.2, 12.1; IR (neat) 3380, 2940, 2860, 1670, 1450 cm^{-1}.

4.1.13. 3-Benzylcyclohex-2-en-1-ol ***3g***

1.32 g, 70%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46–7.09 (m, 5H), 5.56–5.44 (m, 1H), 4.30–4.15 (m, 1H), 3.29 (s, 2H), 2.12–1.25 (m, 7H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 139.6, 134.9, 128.8, 127.8, 125.9, 124.7, 66.5, 46.4, 29.6, 27.3, 23.4, 19.6, 12.9; IR (neat) 3360, 3100, 3080, 3060, 2940, 2860, 1670, 1450 cm^{-1}; EI-MS (m/z) 188 (M^+, 2), 171 (6), 170 (36), 97 (100), 79 (23), 77 (13).

4.2. Preparation of bicyclo[4.1.0]heptan-2-ol ***4a****. Representative procedure*

To a solution of 196 mg of cyclohex-2-en-1-ol **3a** (2 mmol) in 6 mL of 1,2-dichloroethane cooled at 0°C was added under argon 4 mL of a 1 M solution of Et_2Zn (4 mmol, 2 equiv.) in hexane. The reaction mixture was stirred for 15 min at 0°C and 600 μL of $ClCH_2I$ (8 mmol, 4 equiv.) was added dropwise. The reaction mixture was allowed to return to room temperature, after 15 min the argon flow

was stopped, the flask was equipped with a calcium chloride guard and stirring continued for one hour. Then the reaction mixture was poured into a saturated ammonium chloride solution and extracted with diethyl ether. The organic phases were washed with water and brine, and dried over sodium sulfate. The solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel (pentane:diethyl ether: 80:20) to give 150 mg (67%) of bicyclo[4.1.0]heptan-2-ol **4a**.[22]

Bicyclo[4.1.0]heptan-2-ols **4b**–**g** were prepared following the same procedure.

4.2.1. 6-Methylbicyclo[4.1.0]heptan-2-ol **4b**

151 mg, 60%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.22 (dd, J=6.3, 12.3 Hz, 1H), 1.51–1.12 (m, 8H), 1.09 (s, 3H), 0.51 (dd, J=4.9, 4.9 Hz, 1H), 0.31 (dd, J=4.9, 8.9 Hz, 1H); ^{13}C NMR (59.3 MHz, $CDCl_3$) δ 67.7, 31.8, 29.6, 29.1, 28.3, 25.4, 22.2, 14.0.[15]

4.2.2. 6-Ethylbicyclo[4.1.0]heptan-2-ol ***4c***

274 mg, 98%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.19 (dd, J=6.2, 11.8 Hz, 1H), 1.71–1.29 (m, 6H), 1.29–0.94 (m, 4H), 0.90 (bt, J=7.8 Hz, 3H), 0.49 (dd, J=4.8, 4.8 Hz, 1H), 0.35 (dd, J=4.8, 8.7 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 66.8, 33.7, 29.6, 27.2, 25.1, 24.2, 20.3, 13.4, 10.4; IR (neat) 3380, 3080, 3010, 2960, 2840, 1460 cm^{-1}; EI-MS (m/z) 140 (M^+, 1.3), 125 (2.6), 123 (5.5), 122 (22), 111 (39), 107 (29), 94 (26), 93 (100). Anal. calcd for $C_9H_{16}O$: C, 77.09; H, 11.50; O, 11.41, found: C, 76.82; H, 11.60; O, 11.62.

4.2.3. 6-Butylbicyclo[4.1.0]heptan-2-ol ***4d***

296 mg, 88%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.20 (dd, J=6.2, 12.0 Hz, 1H), 1.73–0.96 (m, 14H), 0.89 (bt, J=7.6 Hz, 3H), 0.48 (dd, J=4.7, 4.7 Hz, 1H), 0.34 (dd, J=4.7, 8.7 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 66.8, 40.9, 29.6, 28.7, 27.6, 25.3, 23.1, 22.7, 20.2, 14.0, 13.7; IR (neat) 3400, 3060, 3000, 2960, 2840, 1460 cm^{-1}; EI-MS (m/z) 168 (M^+, 0.9), 151 (3.3), 150 (13), 125 (9.1), 111 (46), 94 (23), 93 (99), 82 (58), 79 (100). Anal. calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98; O, 9.51, found: C, 78.35; H, 12.13; O, 9.66.

4.2.4. 6-Octylbicyclo[4.1.0]heptan-2-ol ***4e***

269 mg, 60%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.20 (dd, J=6.3, 11.8 Hz, 1H), 1.73–0.96 (m, 22H), 0.8 (bt, J=7.5 Hz, 3H), 0.49 (dd, J=4.6, 4.6 Hz, 1H), 0.35 (dd, J=4.6, 8.5 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 66.8, 41.3, 31.8, 29.8, 29.7, 29.6, 29.3, 27.7, 26.5, 25.5, 23.3, 22.6, 20.3, 14.0, 13.7; IR (neat) 3360, 3060, 3000, 2960, 2840, 1460 cm^{-1}; EI-MS (m/z) 224 (M^+, 15), 207 (9.3), 206 (21), 111 (25), 97 (19), 94 (21), 93 (64), 82 (36). Anal. calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58; O, 7.13, found: C, 79.92; H, 12.62; O, 7.32.

4.2.5. 6-Undecylbicyclo[4.1.0]heptan-2-ol ***4f***

317 mg, 60%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.18 (dd, J=6.2, 12.0 Hz, 1H), 1.71–0.95 (m, 26H), 0.89 (bt, J=7.5 Hz, 3H), 0.45 (dd, J=4.7, 4.7 Hz, 1H), 0.34 (dd, J=4.7, 8.6 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 67.1, 41.3, 31.9, 29.9, 29.8, 29.7, 29.65, 29.6, 29.5, 29.3, 27.8, 26.6, 25.6, 23.4, 22.7, 20.3, 14.0, 13.6; IR (neat) 3370, 3070, 3005, 2960, 2840, 1460 cm^{-1}; EI-MS (m/z) 247 (4.2), 92 (26), 91 (41), 82 (7.9), 79 (100). Anal. calcd for $C_{18}H_{34}O$: C, 81.13; H, 12.86; O, 6.00, found: C, 80.63; H, 12.98; O, 6.25.

*4.2.6. 6-Benzylbicyclo[4.1.0]heptan-2-ol **4g***

267 mg, 66%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43–7.16 (m, 5H), 4.27 (dd, J=4.8, 8.5 Hz, 1H), 2.63 (s, 2H), 1.72–0.96 (m, 8H), 0.60 (d, J=6.3 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 139.8, 129.0, 128.0, 125.9, 66.4, 46.1, 29.7, 27.5, 25.1, 23.4, 19.7, 12.8; IR (neat) 3360, 3080, 3060, 3020, 3000, 2960, 2840, 1450 cm^{-1}; EI-MS (m/z) 202 (M^+, 0.3), 185 (2.7), 184 (16), 111 (11), 94 (5), 93 (59), 91 (100), 77 (39). Anal. calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97; O, 7.91, found: C, 83.37; H, 9.20; O, 7.82.

Table 2
Chromatographic conditions for the determination of the enantiomeric excesses of bicycloheptanols **4c**–**4g** on a Cydex B column (P=0.8 bar)

Compound	Temperature conditions	Retention time (min.)	
		(*1S, 2R, 6R*)	(*1R, 2S, 6S*)
4c	70°C	16	19
4d	90°C	44	54
4e	120°C	88	95
4f	140°C	227	233
4g	95°C (60 min.) then 1°C/min. to 118°C	163	169

4.3. Enzymatic resolution of endo*-bicyclo[4.1.0]heptan-2-ols **4a**. Representative procedure*

Bicyclo[4.1.0]heptan-2-ol **4a** (112 mg, 1 mmol) was dissolved in 4 mL of *tert*-BuOMe in a flask equipped with a magnetic stirrer. To this solution 162 mg of Novozym® and 167 mg of isopropenyl hexanoate (1.07 mmol, 1.07 equiv.) was added and the reaction mixture was stirred at 37°C. The reaction was monitored by TLC; at around 50% conversion, the reaction was stopped by removing the enzyme by filtration, and the solid was washed several times with *tert*-BuOMe. After concentration under reduced pressure the reaction products were separated by silica gel column chromatography (pentane:diethyl ether: 70:30) to give 107 mg of bicyclo[4.1.0]heptan-2-yl hexanoate **5a*** (51%) and 46 mg of recovered alcohol **4a*** (41%).

The bicycloheptyl hexanoate **5a*** was then treated at 0°C in diethyl ether with lithium aluminum hydride. After stirring for one hour at room temperature, wet sodium sulfate was added in order to obtain a clear supernatant solution. After filtration, the solution was concentated under reduced pressure and the optically active bicyclo[4.1.0]heptan-2-ol (yield ~90%) was separated from the hexan-1-ol by silica gel column chromatography (pentane:diethyl ether: from 80:20 to 50:50).

Transesterifications with the bicycloheptanols **4b**–**4g** were made following the same procedure.

For the experiment reported in entry 2 of Table 1, except for the amount of Novozym® (54 mg), the above conditions were used.

Specific rotations of these optically active alcohols **4*** and of those isolated after reduction of esters **5*** are reported in Table 1.

4.4. Determination of enantiomeric excesses

The enantiomeric excesses of bicycloheptanol **4a** samples were determined by HPLC on a Chiracel OD-H column of the corresponding carbamate which was prepared by reaction, over 14 hours, of **4a** with phenylisocyanate in Et_2O.[19]

The enantiomeric excesses of compounds **4b**–**4g** were determined by GLC on a Cydex B column. The chromatographic conditions used for the separation of compounds **4c**–**4g** and the retention times of the enantiomers are shown in Table 2, those of **4b** were reported in the literature.[19]

4.5. Chemical correlation

4.5.1. Preparation of optically active 3-ethylcyclohex-2-en-1-ol *3c**

To a solution of 84 mg of Li_2CuCl_4 (0.38 mmol, 0.15 equiv.) in 4 mL of THF maintained at −20°C under argon, 10.5 mL of a 1 M solution of EtMgBr in THF (10.5 mmol, 4 equiv.) and 586 mg of (−)-3-iodocyclohex-2-en-1-ol **6**[33] in 4 mL of THF were added. After stirring for 14 hours at −20°C and 4 hours at 20°C, the reaction mixture was poured into a saturated ammonium chloride solution and extracted with diethyl ether. The organic phases were washed with water and dried over sodium sulfate. The solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel (pentane:diethyl ether: 90:10) to give 219 mg (66%) of (−)-3-ethylcyclohex-2-en-1-ol **3c**; ee=77%, determined by GLC on a Cydex B column (P=0.8 bar, 70°C), retention time (*S*)-**3c**: 27 min, (*R*)-**3c**: 30 min.

4.5.2. Preparation of optically active 3-butylcyclohex-2-en-1-ol *3d**

The title compound was obtained from 467 mg of (+)-3-iodocyclohex-2-en-1-ol **6**[33] and BuMgBr, following the same procedure as above, 199 mg (72%) of (+)-3-butylcyclohex-2-en-1-ol **3d**; ee=97%, determined by GLC on a Cydex B column (P=0.8 bar, 85°C), retention time (*S*)-**3d**: 39 min, (*R*)-**3d**: 40 min.

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