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Convenient Diastereospecific Synthesis of a Rociverine Precursor and its Resolution by Lipase-Catalyzed Transesterification

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Dedicated to the memory of Professor Giuseppe Bellucci

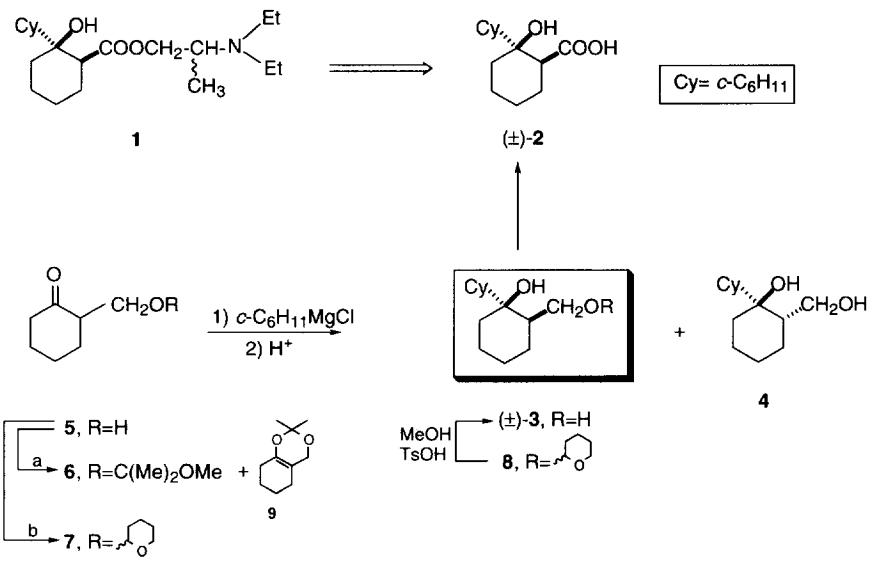
Abstract: (±)-1-Cyclohexyl-*c*-2-hydroxymethyl-*r*-1-cyclohexanol **3**, a precursor of the antimuscarinic drug Rociverine **1**, was obtained diastereospecifically in very high yield, from the Grignard reaction between $C_6H_{11}MgCl$ and an appropriately protected 2-(hydroxymethyl)cyclohexanone. The preparation of enantiomerically enriched *cis* diol (+)-*(1R, 2S)*-**3** and the corresponding 2-acetoxymethyl derivative (+)-*(1S,2R)*-**12** was achieved by lipase PPL-catalyzed transesterification of racemic diol (±)-**3**. Copyright © 1996 Elsevier Science Ltd

The (±)-2-cyclohexyl-*c*-2-hydroxy-*r*-1-cyclohexanecarboxylic acid **2**[1] is the compound of choice for the synthesis of Rociverine **1** a pharmaceutically interesting compound used in common therapy as a spasmolitic agent.[2] Commercial Rociverine **1** is an unresolved mixture of the four possible stereoisomers having a *cis* configuration between the hydroxy and the carboxy substituents of the cyclohexane ring. The four steroisomers of **1** were separately tested for affinity to the five cloned (m_1-m_5) muscarinic receptor subtypes and showed different potency and selectivity levels. These properties are affected only by the two stereogenic centres present on the cyclohexane ring, the third stereogenic carbon being much less influential.[3] The *(1S,2S)* stereoisomers showed a very high m_1 binding selectivity, while the *(1R,2R)* ones were the most potent for all receptor subtypes.[3]

In the search for an enantioselective synthesis of acid **2** it was thought to be fundamental to obtain both the enantiomeric forms *(1R,2S)*-**3** and *(1S,2R)*-**3** of 1-cyclohexyl-*c*-2-hydroxymethyl-*r*-1-cyclohexanol **3**,[4] the ultimate precursor of **2**, in high enantiomeric excess. We describe here the completely diastereoselective synthesis of racemic *cis* diol (±)-**3** and its subsequent kinetic resolution by means of lipase-catalyzed transesterification with vinyl acetate in an organic solvent.

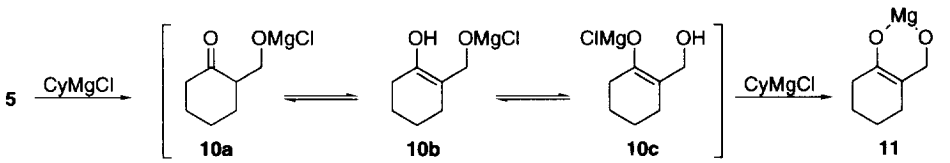
The Grignard reaction between cyclohexyl magnesium chloride (6 eq) with 2-(hydroxymethyl)-cyclohexanone **5** affords a 55:45 mixture of diasteroisomeric diols (±)-*cis* -**3** and (±)-*trans* -**4** (yield 58%). Recrystallization of the crude reaction mixture afforded practically pure (±)-*cis*-**3** (**3**:**4** = 96:4), but in very low yield (12%) (Scheme 1). The essentially complete absence of selectivity in the addition of $C_6H_{11}MgCl$ to 2-(hydroxymethyl)cyclohexanone **5** is somewhat surprising considering that a completely different behaviour was found when an arylmagnesium bromide was used as the nucleophile (cis/trans-diol = 94:6).[5]

Scheme 1



a, 2-Methoxypropene, PyH^+TsO^-, 0°C, 5 min.
b, 3,4-Dihydro-4H-pyrane, PyH^+TsO^-, -10°C, 15 min.

Even when the addition reaction was conducted in the presence of $LiClO_4$ or Bu_4NBr, no appreciable improvement was observed, either in the diastereoselectivity or in the overall yield, although it could have been expected on the basis of previous results reported for enolizable carbonylic compounds.[6] Only when the hydroxyl functionality of **5** was protected with the methoxyisopropylic (MIP) acetal function to give the product **6**, a much more satisfactory yield (96%) and complete diastereoselectivity was achieved in the addition of $C_6H_{11}MgCl$ to **6**, the *cis* isomer (±)-**3** being the only reaction product. In this reaction, the workup of the Grignard reaction (hydrolysis with aqueous dilute HCl) is sufficient to remove the very acid-labile MIP protecting group.[7] Less satisfactory results were obtained when the tetrahydropyranyl group was used as the protecting group (compound **7**). Moreover, in this case the reaction product, the monoprotected diol **8,** required more drastic conditions (MeOH, TsOH) in order to obtain the free diol **3** with a 69% yield based on **5** (Scheme 1). The low yield in the Grignard reaction of **5** may be explained by a partial primary conversion of this easily enolizable ketone into an unreactive and insoluble species, such as the neutral cyclic salt **11**, originating from the monosalified intermediates **10a-c**, by further reaction with the Grignard reagent.



As a matter of fact, large amounts of unreacted **5** (35-40%) were always recovered from its Grignard reaction, even when high excesses of the organometallic reagent and long reaction times were used. The ease of enolization of ketone **5** was confirmed by the fact that the cyclic acetal **9** always was a by-product (8%

after 5 minutes at 0 °C) of the synthesis of acetal **6** by the reaction of **5** with 2-methoxypropene, and become the only product after 5h at r.t. Protection of **5** as in the case of acetal **6** prevents formation of **11** and allows much better yields in the Grignard reaction.

The complete *cis* diastereospecificity observed in this reaction can possibly be rationalized through the intervention of a chelate structure in which the metal of the reagent is coordinated between the oxygens of the carbonyl and of the MIP groups of ketone **6**. The fact that the structurally related 2-methylcyclohexanone gives with PhLi and PhMgBr products of lower diastereomeric purity (88-91% equatorial attack)[8] is consistent with an involvement of oxygen on the vicinal substituent in determining the steric course of the reaction through chelation of the reagent.

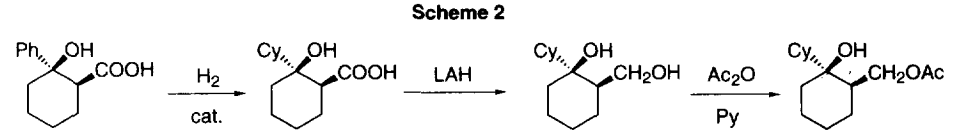
As a next step towards an enantioselective synthesis of **3** we investigated an enzymatic approach involving acetylation of (±)-*cis* **3** with vinyl acetate. Several lipases and different operating conditions (solvents, dilution, temperature) were tested and the most representative examples are shown in the Table.

The use of lipase PS supported onto Hyflo Super Cell,[9] afforded consistent enantioselectivity (53% ee, entry 4, Table) which turned out not to be influenced by the chemical and physical properties (hydrophobicity and dielectric constant) of the solvent used (entries 1, 2, 3 e 5). Better results (63% ee, entry 7, Table) were obtained with lipase PPL using *t*-butyl methyl ether as the solvent. It is worth noting that, differently from PS lipase, PPL lipase allows an effective modulation of the enzymatic reaction, making it synthetically useful. In fact, when the reaction is stopped after 28% conversion, acetate (+)-*(1S,2R)*-**12** is obtained in 78% ee (entry 9, Table), while after 72% conversion, unreacted alcohol (+)-*(1R,2S)*-**3** can be recovered with 85% enantiomeric excess (entry 8, Table). Both with lipase PS and PPL the major enantiomer is the acetate (+)-*(1S,2R)*-**12**, while with lipase CCL (entry 10, Table) the transesterification proceeds with opposite enantioselectivity, the acetate (-)-*(1R,2S)* -**12** being the exceeding enantiomer but, unfortunately, in low yield and unsatisfactory ee (11%).

LAH reduction of (+)-*(1S,2R)*-**12** (78% ee) afforded the corresponding alcohol (-)-*(1S,2R)*-**3** (78% ee) (determined on the corresponding acetate, see Experimental Section) without racemization.

Following the protocol used in every case, the crude product, obtained by stopping the reaction at the time shown in the Table, was subjected to flash chromatography, and the acetate **12** and the unreacted diol **3** fractions were separated. The enantiomeric excess as obtained were measured by chiral GC both for the acetate fraction (directly) and for the diol fraction (after transformation into the corresponding acetate). With a Megadex 1 column the enantiomers of the acetate **12** were base line separated. The relative *cis* configuration of hydroxy and hydroxymethyl groups in (±)-**3**, has been previously firmly established on the basis of IR, ^{1}H NMR spectra and by chemical correlations.[4]

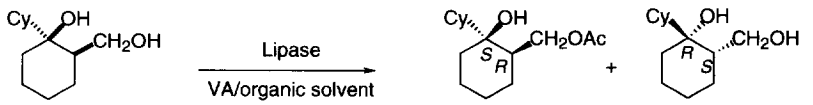
Scheme 2



(-)-*(1S,2R)* -**13** (+)-*(1S,2S)* -**2** (-)-*(1S, 2R)*-**3** (+)-*(1S, 2R)*-**12**

The absolute configuration of the prevailing acetate (+)-*(1S, 2R)*-**12** in the non-racemic mixture of acetates (+)-*(1S, 2R)*-**12** and (-)-*(1R, 2S)*-**12** (obtained in the enzymatic resolution of diol (±)-**3** with PS lipase and PPL), was unambiguously determined by the chemical correlation shown in Scheme 2.

Table. Lipase-Catalyzed Transesterification of (±)-1-Cyclohexyl-*c*-2-hydroxymethyl-*r*-1-cyclohexanol **3**.



(±)-**3** (+)-*(1S, 2R)*-**12** (+)-*(1R, 2S)*-**3**

Entry	Lipase (mg/mmol)	Solvent[a] (ml/mmol)	VA (eq/mmol)	Temp (°C)	Time (h)	Conv.[b]	(+)-*(1S,2R)*-**12**[d] Isolated Yield (%)[c]	ee (%)[e]	(+)-*(1R,2S)*-**3**[d] Isolated Yield (%)[c]	ee (%)[e]	E[f]
1	PS supp. 1500	VA 30	-	45	5	55	91	55	82	52	6.7
2	PS supp. 450	TBME 20	3	27	6	53	77	56	73	50	6.6
3	PS supp. 450	*t*-AmOH 25	10	37	96	47	88	54	85	51	5.3
4	PS supp. 450	CH_2Cl_2 25	3	40	26	56	92	58	83	53	8.1
5	PS supp. 1000	VA/THF 7:3 25	-	37	4.5	52	85	56	76	47	6.4
6	PS supp. 1000	TBME 25	3	27	2.5	17	70	57	89	15	4.1
7	PPL 1000	TBME 25	3	27	11	54	93	65	87	63	10.6
8	PPL 1000	TBME 25	3	27	16	72	91	51	89	85	-
9	PPL 1000	TBME 25	3	27	7	28	85	78	93	45	10.8
10	CCL[g]	TBME	3	40	96	16	-	-	-	-	-

[a] VA = vinyl acetate; TBME = *t*-butyl methyl ether; *t*-AmOH= *t*-amyl alcohol. [b] Conversion (determined by GC and ^{1}H NMR analysis) is referred to the amount of initial hydroxy groups which have been acetylated. [c] Yields are corrected for the extent of substrate conversion. [d] The absolute configuration was determined by chemical correlation with a enantiopure sample of (+)-*(1S, 2R)*-**12** (see text and Experimental Section). [e] ee Values were determined by chiral GC directly for **12** and after acetylation for **3** (see text and Experimental Section). [f] E (enantiomeric ratio) values were calculated from the degree of conversion and the ee of the product according to Chen, C. H.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.*, **1982**, *104*, 7294. [g] In this case there is inversion of enantioselectivity (see text); the ee values were 11% for (-)-*(1R,2S)*-**12** and 8% for (-)-*(1S, 2R)*-**3**.

LAH reduction of the known acid (+)-*(1S, 2S)*-**2**[10] (obtained by catalytic reduction of the already known *cycloxylic acid* (-)-*(1S, 2R)*-**13** [11]) afforded the diol (-)-*(1S, 2R)*-**3**, which after acetylation with Ac_2O, gave the pure acetate (+)-*(1S, 2R)*-**12**. This acetate shows the same retention time, by chiral phase GC, as the predominant enantiomer in the acetate fraction isolated from the lipase-catalyzed reaction mixture on diol (±)-**3**. As for the diol fraction, the results obtained correctly demonstrated that the excess enantiomer is the diol (+)-*(1R, 2S)*-**3**.

In conclusion lipase PPL turned out to be a promising catalyst for the resolution of *cis* diol (±)-**3** by transesterification with vinyl acetate. This synthesis of enantioenriched *cis* diol **3**, which is suitable also for scaling-up application, represents, at the moment, a valid alternative to the classical resolution protocol of acid **13** or **2** by means of diastereoisomeric salts.[10,11] This method may represent a contribution to a highly competitive enantioselective synthesis of Rociverine, particulary if a further screening of lipases and incubation conditions will improve chemical yields and enantiomeric excess.

Experimental Section

Melting points were determined with a Kofler hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker AC 200 instrument at 200 MHz on $CDCl_3$ solution (internal Me_4Si), unless otherwise stated. Chemical shift and *J* coupling values were confirmed, when necessary, with COSY or *J*-RES experiments.[13] C NMR spectra were recorded with the same spectrometer at 50 MHz. Optical rotations were measured with a Perkin-Elmer 241 digital polarimeter with a 1 dm cell. The enzymatic transesterification of (±)-**3** was followed by GC (FI detector) on a OV 225 glass column: column temperature from 170°C to 210°C, ramp rate 4°C/min, injector and detector 250°C; nitrogen flow 30 ml/min. Ee values of (+)-*(1S, 2R)*-**12** and (+)-*(1R, 2S)*-**3** (after its transformation into the corresponding acetate) were determined by GC (FI detector) on a Megadex 1 chiral capillary column [25 m x 0.32 mm (i.d.), 0.25 μm (film thickness)]: column temperature from 150°C to 190°C, ramp rate 1.5°C/min, injector 250°C, detector 300°C; nitrogen flow 0.8 ml/min. The order of increasing retention times was: (-)-*(1R, 2S)*-**12** < (+)-*(1S, 2R)*-**12.** All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV or with ethanolic 10% phosphomolybdic acid and heating. Kieselgel 60 (Merk 230-400 mesh) was used for flash chromatography. All air sensitive reactions were conduced in flame dried glass ware under an Ar atmosphere. Ether and THF were distilled from sodium/benzophenone ketyl under nitrogen atmosphere immediately prior to use; $CHCl_3$ was dried over CaH_2. Vinyl acetate (VA) and 2-methoxypropene were freshly distilled before the use. *t*-Butyl methyl ether (TBME) was distilled from CaH_2 and stored over 4Å molecular sieves activated by heating for at least 24 h at 400°C. *t*-Butanol (*t*-BuOH) was dried over activated 4Å molecular sieves .

Materials

Lipase PS (from *Pseudomonas sp.*) was kindly provided by Amano Pharmaceutical Co. LTD, lipase CCL type VII (from *Candida Cylindracea*) was purchased from Aldrich, lipase PPL type II crude (from porcine pancreas) was puchased from Sigma.

Lipase PS was immobilized onto Hyflo Super Cell following the procedure reported by Bovara.[9]

(+)-*(1S, 2S)*- 2- Cyclohexyl-*c*-hydroxy-*r*-1-cyclohexancarboxylic acid **2** ($[\alpha]_D^{20}$=+7.00 (*c* 1.15, EtOH), {lit.[10] $[\alpha]_D^{20}$=-10.50 (*c* 1.00, NaOH 0.5 N)} obtained from catalytic reduction of (-)-*(1S, 2R)*-**13** {lit.[11] $[\alpha]_D^{20}$= -12.70 (*c* 1.00, NaOH 0.5 N)} and (±)-2-(hydroxymethyl)cyclohexanone **5** were available from previous work.

(±)-1-Cyclohexyl-*c*-2-hydroxymethyl-*r*-1-cyclohexanol, 3 and (±)-1-cyclohexyl-*t*-2-hydroxymethyl-*r*-1-cyclohexanol, 4.

A solution of 2-(hydroxymethyl)cyclohexanone **5** (4.05 g, 31.6 mmol) in anhydrous ether (30 ml) was added dropwise to 2.0 M cyclohexylmagnesium chloride in Et_2O (50 ml) at -15°C. When the addition was complete, the resulting mixture was allowed to warm slowly to r.t. and stirred for additional 4 h. After cooling

the mixture was quenched with saturated aqueous NH_4Cl (40 ml) and 5% aqueous HCl (6 ml), and extracted with Et_2O (5 x 50 ml). Evaporation of the washed (saturated aqueous $NaHCO_3$ and brine) ether extracts afforded a crude solid reaction product consisting of a 55:45 mixture of (±)-*cis* **3** and (±)-*trans* **4** diols which was subjected to flash chromatography. Elution with a 1:1 mixture of hexane and AcOEt afforded pure (±)-*cis* diol **3** (2.3 g, 34% yield) as a solid, m.p. 145-146°C {lit.[4] m.p. 143-144°C} and (±)-*trans* **4** diol (1.6 g, 24% yield) as a solid, m.p. 100°C {lit.[4] 99-100°C}. Moreover, 1.5 g of starting material (37%) were recovered.

(±)-**3** : ^{1}H NMR δ 4.09 (dd, 1 H, *J*=10.9 and 3.02 Hz), 3.54 (dd, 1 H, *J*=10.9 and 2.4 Hz), 1.42-1.99 (m, 15 H), 0.96-1.38 (m, 7 H); ^{13}C NMR δ 76.72, 64.61, 45.51, 41.21, 31.14, 27.87, 26.87, 26.91, 26.70, 26.10, 25.72, 25.66, 21.47.

(±)-**4** : ^{1}H NMR δ. 3.64 (dd, 1 H, *J*=10.8 and 5.9 Hz), 3.50 (dd, 1 H, *J*=10.8 and 9.13 Hz), 1.30-2.59 (m, 22 H);^{13}C NMR δ 74.13, 61.50, 44.55, 43.39, 32.70, 26.82, 26.64, 26.46, 26.10, 25.83, 22.86, 21.78, 21.01.

Alternatively the crude reaction product was recrystallized from petroleum ether (b.p. 80-100°C) yielding practically pure (±)-**3** (0.805 g, 12% yield).

(±)-2-(1-Methoxy-1-methylethoxymethyl)-cyclohexanone, 6 and 1-hydroxy-2-hydroxymethyl cyclohexene isopropylidene acetal, 9.

A solution of **5** (0.780 g, 6.09 mmol) in anhydrous THF (14 ml), containing pyridinium *p*-toluenesulfonate (0.040 g), was treated under stirring at -10°C with 2-methoxypropene (0.87 ml, 9.1 mmol), added over 10 min. The reaction mixture was stirred for 5 min. at 0°C, then quenched with solid Na_2CO_3. Evaporation of the filtered suspension afforded a crude liquid (1.20 g) which was subjected to flash chromatography (9:1 mixture of hexane/AcOEt, containing 0.1% Et_3N) to give first **9** (0.082 g, 8% yield) then (±)-**6** (1.05 g, 86% yield).

9, a liquid: ^{1}H NMR (CD_3CN) δ 3.93 (tt, 2 H, *J*=2.5, and 1.2 Hz), 1.78-1.94 (m, 4 H), 1.56-1.68 (m, 4 H), 1.36 (s, 6 H); ^{13}C NMR (CD_3CN) δ 144.33 103.88, 98.90, 62.53, 27.51, 24.68, 24.61, 24.28, 23.47, 23.22. Anal.Calcd for $C_{10}H_6O_2$: C, 71.39; H, 9.59. Found: C, 71.15 ; H, 9.31.

(±)-**6**, a liquid: ^{1}H NMR (CD_3CN) δ 3.66 (dd, 1 H, *J*=9.5 and 5.2 Hz), 3.25 (dd, 1 H, *J*=9.5 and 7.3 Hz), 3.12 (s, 3 H), 2.43-2.59 (m, 1 H), 2.17-2.47 (m, 3 H), 1.38-2.03 (m, 5 H); ^{13}C (CD_3CN) δ 211.85, 100.3, 60.65, 51.39, 48.67, 42.58, 32.31, 28.51, 25.27, 24.76, 24.68. Anal.Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.25 ; H, 10.39.

When the reaction was protracted for 5 h compound **9** was the sole reaction product (92% yield).

Grignard Reaction between 6 and Cyclohexylmagnesium Chloride.

A 2.0 M cyclohexylmagnesium chloride solution in Et_2O (60 ml) was added dropwise to a solution of acetal **6** (0.750 g, 3.74 mmol) in anhydrous Et_2O (13 ml) at -10°C. When the addition was complete, the resulting mixture was allowed to warm slowly to r.t., and stirred for additional 4 h. Usual work-up afforded pure (±)-**3** (0.760 g, 96% yield).

2-(2-Tetrahydropyranyloxymethyl)cyclohexanone, 7.

A solution of **5** (4.12 g, 32.1 mmol) in anhydrous $CHCl_3$ (50 ml) containing *p*-toluensulfonic acid (0.1 g), was treated dropwise, at -10°C with 3,4-dihydro-2H-pyran (3.68 g, 43.7 mmol). After 15 min. at the same temperature, the mixture was quenched with NEt_3 (0.5 ml), diluted with $CHCl_3$ (20 ml), and washed wit h saturated aqueous $NaHCO_3$ (20 ml). Evaporation of the organic solution afforded a crude liquid (5.6 g) wich was subjected to flash chromatography. Elution with an 8:2 mixture of hexane and AcOEt afforded pure **7**, a

liquid, consisting of an about 1:1 mixture of the corresponding diastereoisomers (4.2 g, 61% yield): ^{1}H NMR δ 4.56-4.64 (m, 2 H), 4.06 (dd, 1 H, *J*=10.1 and 5.0 Hz), 3.77 - 3.95 (m, 2 H), 3.64-3.73 (m, 2 H), 3.43-3.55 (m, 2 H), 3.37 (dd, 1 H, *J*=10.1 and 6.9 Hz), 2.53-2.72 (m, 2 H), 2.22-2.41 (m, 6 H), 1.42-1.96 (m, 22 H); ^{13}C NMR δ 210.72 and 210.72, 98.84 and 98.36, 66.28 and 66.02, 61.67 and 61.58, 50.26 and 50.26, 41.69 and 41.58, 31.07 and 30.85, 30.14 and 30.14, 27.36 and 27.24, 25.01 and 24.86, 24.22 and 24.22, 19.07 and 19.07. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.62 ; H, 9.34.

1-Cyclohexyl-*c*-2-(2-tetrahydropyranyloxymethyl)-*r*-1-cyclohexanol, 8.

Following the same procedure as described above for the preparation of (±)-**3** , treatment of a solution of (±)-**7** (3.8g, 30.0 mmol) in anhydrous Et_2O (50 ml) with 2.0 M cyclohexylmagnesium chloride solution in Et_2O (25 ml) afforded pure **8** as an about 1:1 mixture of the corresponding tetrahydropyranyl diastereoisomers (6.5 g, 73% yield): ^{1}H NMR δ 4.47-4.58 (m, 2 H), 4.06 (dd, 1 H, *J*=9.9 and 3.7 Hz), 3.68-3.87 (m, 2 H), 3.62 (dd, 1 H, *J*=8.4 and 3.2 Hz), 3.39-3.59 (m, 3 H), 3.21 (dd, 1 H, *J*=9.9 and 2.7 Hz), 1.34-1.85 (m, 14 H), 0.95-1.28 (m, 8 H); ^{13}C NMR δ 99.12 and 98.18, 69.65 and 69.27, 61.76 and 61.39, 46.46 and 46.09, 40.55 and 40.48, 35.34 and 35.34, 30.58 and 30.48, 30.38 and 30.14, 27.95 and 27.95, 27.07 and 27.07, 26.93 and 26.70, 26.44 and 26.21, 26.13 and 26.04, 25.91 and 25.91, 25.34 and 25.22, 24.05 and 24.05, 21.35 and 21.28, 18.96 and 18.78.Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.69 ; H, 10.49

A solution of **8** (6.5 g, 21.93 mmol) in MeOH (180 ml) containing *p*-toluensulfonic acid (0.3 g) was stirred at r.t. for 24 h. The reaction mixture was treated with basic resin (Amberlite IRA-400, exchanged with 10% aqueous NaOH) to neutrality. Evaporation of the filtered organic solvent afforded pure (±)-**3** (3.4 g, 73% yield).

Lipase-Catalyzed Transesterification of (±)-3.

The following procedure is typical. Lipase PPL (2.40 g) was added to a solution of the racemic (±)-**3** (0.50 g, 2.4 mmol) in TBME (60 ml) containing VA (7.2 mmol) (entry 7, Table) and the suspension was stirred at 250 rpm at 27°C for 11 h. Dilution with AcOEt, and evaporation of the filtered organic solution afforded a crude reaction product (0.49 g) which was analyzed by ^{1}H NMR and GC to give the conversion ratio shown in the Table. The residue was purified by flash chromatography (8:2 mixture of hexane/AcOEt was used as the eluant): the faster moving fraction afforded purified enantioenriched mixtures of the acetate (+)-*(1S, 2R)* and (-)-*(1R, 2S)*-**12**, while the slower moving fraction afforded an enantioenriched mixture of the (+)-*(1R, 2S)* and (-)-*(1S, 2R)*-**3**. The two chromatographic fractions were analyzed by chiral G.C. as described in the introduction of this section to obtain the ee values shown in the Table.

Reduction of the Enriched Acetate (+)-*(1S, 2R)*-12 with LAH.

A suspension of LAH (0.040 g, 1.0 mmol) in anhydrous Et_2O (5.0 ml) was treated dropwise with a solution of (+)-*(1S, 2R)*-**12** (78% ee) (0.050 g, 0.20 mmol) in anhydrous Et_2O (5.0 ml) at 0°C. The reaction mixture was gently refluxed for 3 h; after cooling water and aqueous NaOH[12] were carefully added. Evaporation of the filtered organic solvent afforded (-)-*(1S, 2R)*-**3** (78% ee determined on the corresponding acetate).

(-)-*(1S, 2R)*-1-Cyclohexyl-*c*-2-hydroxymethyl-*r*-1-cyclohexanol, 3.

Following the same procedure as described above for the preparation of the enriched (-)-*(1S, 2R)*-**3** , treatment of a suspension of LAH (0.40 g, 10.54 mmol) in anhydrous Et_2O (20 ml) with a solution of (+)-*(1S, 2S)*-**2**[10] (0.50 g, 2.21 mmol) in anhydrous Et_2O (20 ml) afforded a crude reaction product which was purified

by flash cromathography. (a 1:1 mixture of hexane and AcOEt was used as the eluant) to yield pure (-)-*(1S, 2S)*-**3** (0.38 g, 80% yield): $[\alpha]_D^{20}$ = -10.66 (*c* 1.22, EtOH).

(+)-*(1S, 2R)*-1-Cyclohexyl-*c*-2-acetoxymethyl-*r*-1-cyclohexanol, 12.

A solution of (-)-*(1S, 2R)*-**3** (0.138 g, 0.65 mmol) in anhydrous pyridine (6.0 ml) was treated at 0°C with Ac_2O (3.0 ml) and the reaction mixture was left at r.t. overnight. Dilution with water, extraction with ether and evaporation of the washed (5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine) organic solution afforded pure (+)-*(1S, 2R)*-**12** (0.135 g, 81% yield), as a solid, m.p. 38-40°C, $[\alpha]_D^{20}$=+5.04 (*c* 1.23, EtOH) (ee >99%): ^{1}H NMR δ 4.28 (dd, 1 H, *J*=11.2 and 4.6 Hz), 3.97(dd, 1 H, *J*=11.2 and 6.7 Hz), 2.06 (s, 3 H), 1.44-1.88 (m, 12 H), 0.92-1.31 (m, 9 H); ^{13}C NMR δ 171.09, 74.59, 65.51, 45.62, 40.30, 31.06, 27.75, 26.85 26.72, 26.66, 26.16, 25.33, 25.12, 21.18, 21.03. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.65 ; H, 10.12.

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