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A general approach towards 2-substituted 3-hydroxy propanoates; application to the synthesis of methyl tropinate

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Abstract: Enantiomerically pure *R* or *S* 2-substituted 3-hydroxy propanoates may be prepared by regioselective BF_3 promoted opening of homochiral styrene oxide by lithium cyanocuprates followed by oxidative cleavage of the aromatic moiety with catalytic ruthenium trichloride. © 1997 Elsevier Science Ltd. All rights reserved.

Derivatives of 2-alkyl-3-hydroxypropanoic acids and the corresponding reduced forms, monoprotected 2-alkyl-1,3-propanediols, are important chiral building blocks which have been used in the synthesis of a variety of therapeutic agents[1] and natural products.[2] The methyl substituted compounds are available in *R* or *S* form by various methods such as microbial oxidation of methylpropanoic acid,[3] yeast reduction of α-formyl propanoates[4] or asymmetric synthesis.[5] In contrast, the few methods reported for the preparation of the corresponding 2-alkylated compounds did not allow the access to these synthons in enantiomerically pure form.[6,7]

We wish to report here a simple and general method of preparation for these synthons in high enantiomeric purity based on the regioselective opening of enantiomerically pure styrene oxide followed by an oxidative cleavage of the aryl group.

Styrene oxide is a very interesting synthon which is easily available in high enantiomeric excesses both in *R* or *S* form by reduction of mandelic acid or by microbial hydrolysis.[8] The reactivity of styrene oxide with organometallic compounds has been studied some years ago. In contrast with aliphatic monosubstituted epoxides which react on the less hindered end, a mixture of primary and secondary alcohols is generally obtained. However, it has been reported that, in some cases (symmetric magnesium compound in ether,[9] trimethylaluminium,[9] n-butylcopper reagent in the presence of BF_3[10]), it was possible to isolate the primary alcohols **2** almost exclusively. In order to achieve a valuable method, it was necessary to accurately control the regioselectivity of the opening and to verify that these substitutions proceed with total inversion of configuration.

Indeed, it is well known that nucleophilic substitution in the benzylic position does not always proceed according a purely SN2 mechanism, and a partial retention of configuration was previously reported in some cases both with carbon nucleophiles such as alanes[11] and with sulfur nucleophiles.[12]

At first, we decided to investigate the reaction of the most easily available organometallic compounds: Grignard reagents. In order to accelerate the opening and to avoid the rearrangements frequently observed with these compounds, we performed the reaction in the presence of a Lewis acid. In all cases, the reaction was extremely fast and afforded one regioisomer resulting only from attack at the benzylic position (Table 1); however, due to the enhanced reactivity of epoxides in such conditions, we always observed the formation of a minor amount of halohydrins resulting from the concurrent reaction of halide ions even when the reaction was conducted in the presence of copper cyanide (Scheme 1).

Although these halohydrins were easily separable from the alcohols **2**, it was preferable, for a synthetic application, to avoid the formation of such secondary products. The direct reaction

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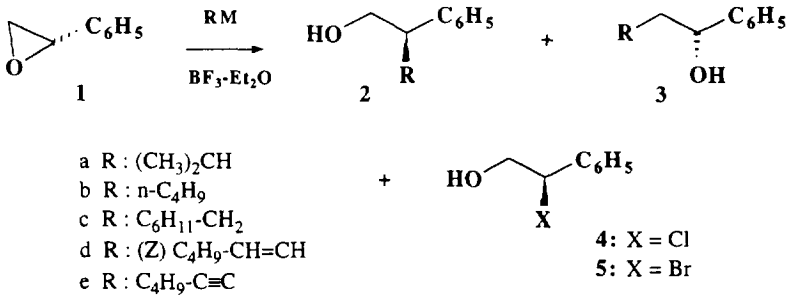
Table 1. Opening of styrene oxide by organometallic compounds in the presence of BF_3–Et_2O

Entry	R	Metal	Solvent / T °C		Yield %	
1	*i*-Pr [a]	MgCl	Et_2O / -78	**2a** 53	**3a** 3	**4** 34
2	*i*-Pr	MgBr [b]	THF / -78	**2a** 59	-	**5** 14
3	*i*-Pr	CuCNLi	THF / -78	**2a** 81	-	-
4	*n*-Bu	CuCNLi	THF / -78	**2b** 75	**3b** 1	-
5	C_6H_{11}-CH_2	CuCNLi	THF / -78	**2c** 83	-	-
6	(Z) *n*-C_4H_9-CH=CH	CuCNLi	THF / -78	**2d** 84		
7	*n*-C_4H_9-C≡C [a]	CuCNLi	THF / -78	**2e** 71	**3e** 3	

a. The reaction was achieved with racemic styrene oxide.
b. The Grignard reagent was reacted with one equivalent of CuCN before addition of **1**



Scheme 1.

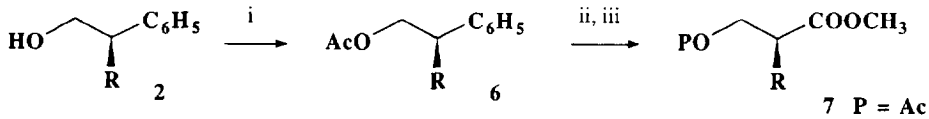
of organolithium compounds in the presence of BF_3–Et_2O being known to give a mixture of the regioisomeric alcohols **2** and **3**, we turned our attention towards copper reagents. The use of organolithium compounds in the presence of one equivalent of cuprous cyanide in THF allowed us to obtain almost exclusively the alcohols **2**. Good yields and regioselectivities were obtained in all cases even with less reactive cyanocuprates derived from vinyl or alkynyl lithium compounds.

In order to access the 2-substituted-3-hydroxy propanoates, the alcohols **2** were then converted, after protection as the acetate, into esters **7** by oxidation of the aryl group with catalytic ruthenium tetrachloride in the presence of excess of $NaIO_4$ (it may be underlined that a *t*-butyldimethylsilyl group was partially cleaved during this reaction).[13] After esterification with diazomethane, the acyl protection was removed in basic (K_2CO_3–MeOH) or acidic medium (3% acetyl chloride in MeOH) to give the required 3-hydroxy-2-alkyl propionates in nearly quantitative yield.

The enantiomeric excess of the β-hydroxy esters **8** was measured by gas chromatography directly on a chiral column or by separation of the two diastereomers obtained after reaction with (*S*)-O-acetyllactic acid chloride. In all cases, it was found better than 98% (Scheme 2).

The regioselective opening of styrene oxide by a vinylic copper reagent allowed us to achieve a very simple synthesis of methyl tropinate. Tropic acid is the biologically active moiety of atropine which is a parasympatholytic alkaloid. This acid presents a high tendency to undergo racemisation. The naturally occurring enantiomer has previously been obtained by resolution; more recently, it was also prepared by the microbial hydrolysis of a prochiral diacetate[14] and by asymmetric synthesis from iron chiral auxiliaries.[15]

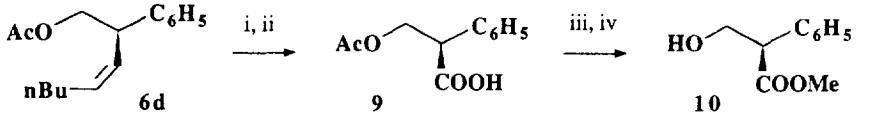
For this purpose, the acetate **6d** derived from the alcohol **2d** obtained by condensation of the (*Z*) hex-1-enyl copper with (*S*)-styrene oxide was ozonized at −78°C (Scheme 3). The crude aldehyde was immediately oxidized without purification to the acid to give, after esterification with diazomethane and



	R	7 %
a	$(CH_3)_2CH$	83
b	n-C_4H_9	73
c	C_6H_{11}-CH_2	67

Scheme 2. *Reagents and conditions:* i, Ac_2O, Et_3N, cat. DMAP; ii, $NaIO_4$, cat $RuCl_4$–xH_2O, $CCl_4/CH_3CN/H_2O$ (4/4/6), 20°C, 30 h then CH_2N_2–diethylether; iii, K_2CO_3–MeOH, 0°C, 10 mn.

cleavage of the acetate, methyl tropinate in a total yield of 57% from styrene oxide. The enantiomeric purity of this ester was found to be better than 97% by NMR in the presence of Eu(Hfe)$_3$ and comparison with the racemate. Thus, this efficient synthesis allowed us to verify the stereochemistry of the opening of styrene oxide in the presence of BF_3 and to show that the reaction occurred with complete inversion of configuration.



Scheme 3. *Reagents and conditions*: i O_3–Me_2S, −78°C, 6 mn; ii Jones' reagent (1M), 0°C, 15 mn, 80%; iii CH_2N_2, ether, 95%; iv K_2CO_3, MeOH, −5°C, 15 mn, 93%.

Experimental

Products were purified by distillation or by medium pressure liquid chromatography on a Jobin–Yvon Modulprep (Kieselgel 60H Merck) or by flash chromatography (Kieselgel 60 Merck: 230–400 Mesh; solvent: cyclohexane/AcOEt) and analyzed by VPC (BP5, SGE, 25 m capillary column) or by TLC (silica gel 60F 254). Optical rotations were measured on a Perkin–Elmer 141 polarimeter. NMR spectra were recorded on a Bruker AC at 200 MHz for ^1H and 100.56 MHz for ^{13}C NMR. $CDCl_3$ was used as solvent with TMS as internal standard. Mass spectra were recorded on a Nermag R 10–10 (fitted with a VPC-mass coupling; column: CP Sil 5, Chrompack, 40 m).

Reactions of organometallic compounds with styrene oxide

1. Reaction with magnesium cyanocuprate

1M Isopropylmagnesium bromide in diethylether (3 mL, 3 mmol) was added to a suspension of CuCN (269 mg, 3 mmol) in THF (10 mL) cooled to −40°C. The suspension was allowed to warm to −10°C and stirred for 30 min. The nearly homogeneous mixture was then cooled to −78°C then pure BF_3–Et_2O (185 µL, 1.5 mmol) and styrene oxide (120 mg, 1 mmol) were successively added. The mixture was stirred at −78°C for one hour and hydrolyzed by adding 1M HCl (5 mL) at the same temperature. After extraction with Et_2O (3×20 mL), the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give an oil which was purified by chromatography on silica gel column (cyclohexane:AcOEt 85:15) to give 97 mg of the alcohol **2a**, 5 mg of the alcohol **3a** and 28 mg of the bromhydrin **5**.

3-Methyl-2-phenyl-1-butanol ***2a.*** IR (neat) cm^{-1} ν: 3400 (OH, broad); 1050 (C–O); 700 (C_6H_5). ^1H NMR δ: 0.74 (d, 3H, *J*=6.7 Hz, CH_3CH); 1.01 (d, 3H, *J*=6.6 Hz, CH_3CH); 1.21 (s, 1H, OH);

1.85–2.06 (m, 1H, $(CH_3)_2CH$); 2.51 (ddd, 1H, J=5.0, 8.6, 8.7 Hz, CH–C_6H_5); 3.82 (dd, 1H, J=8.8, 10.8 Hz, CH_2OH); 3.94 (dd, 1H, J=5.0, 10.8 Hz, CH_2OH); 7.18–7.34 (m, 5H, C_6H_5). ^{13}C NMR δ: 20.8 (q); 20.9 (q); 29.9 (d); 55.6 (d); 65.0 (t); 126.5 (d), 128.4 (d), 128.6 (d), 141.6 (s). MS(EI) m/z: 164 (M), 133, 91. Anal. calc. for $C_{11}H_{16}O$: C, 80.50 H, 9.75; found: C, 80.47 H, 9.69.

3-Methyl-1-phenyl-1-butanol ***3a***. IR (neat) cm^{-1} ν: 3345 (OH), ^1H NMR δ: 0.96 (d, 6H, J=5.9 Hz, $(CH_3)_2CH$); 1.4–1.6 (m, 1H, $(CH_3)_2CH$); 1.65–1.76 (m, 2H, CH_2); 1.89 (s, 1H, OH); 4.76 (dd, 1H, J=8.0, 5.2, $CHOH$); 7.3–7.4 (m, 5H, C_6H_5). ^{13}C NMR δ: 22.1 (q); 23.0 (q); 24.7 (t); 48.2 (d); 72.6 (d); 125.7 (d); 127.3 (d); 128.3 (d); 145.1 (s).

2. Reactions with lithium cyanocuprates

The pentane or hexane solution of organolithium compound (26 mmol) was added to a suspension of CuCN (2.3 g, 26 mmol) in THF (40 mL) cooled to −40°C. The solution was allowed to warm to −20°C for 30 min. The homogeneous pink solution was then cooled to −80°C and pure BF_3–Et_2O (3.2 mL, 26 mmol) was slowly added. After stirring the reaction for 5 min, a solution of styrene oxide (2.4 g, 20 mmol) in THF (10 mL) was added and the resulting solution was stirred for 15 min. The reaction was quenched with a solution of 1/1 sat. aqueous NH_4Cl/10M NH_4OH (40 mL) and stirred for 1 h until the copper salts were completely dissolved. After extraction with Et_2O (3×20 mL), the organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by chromatography on a silica gel column.

(R)-3-Methyl-2-phenyl-1-butanol ***2a***. The reaction was achieved with 0.5 M isopropyllithium in pentane and (*S*) styrene oxide. After purification by chromatography on a silica gel column (cyclohexane:AcOEt 85:15), the alcohol **2a** was isolated as an oil. Yield: 81%. $[\alpha]_D^{20}$ −13.1 (c=2.06, CH_2Cl_2). ee: 99% (GC; column: Cydex B 50 m from SGE).

(R)-2-Phenyl-1-hexanol ***2b***. The same procedure was used with 1.6 M *n*-butyllithium in hexane and (*S*) styrene oxide. After purification by chromatography on a silica gel column, the alcohol **2b** was isolated as an oil. Yield: 75%. $[\alpha]_D^{20}$ −18.0 (c=3.73, CH_2Cl_2). IR (neat) cm^{-1} ν: 3320 (OH), 1060 (C–O), 800, 700 (C_6H_5). ^1H NMR[10] δ: 0.88 (t, 3H, J=6.8 Hz, CH_3CH_2); 1.1–1.4 (m, 5H, CH_2CH_2 and OH); 1.5–1.8 (m, 2H, $CHCH_2$); 2.7–2.9 (m, 1H, $CHCH_2$); 3.74 (d, 1H, J=6.1 Hz, $CHHOH$); 3.76 (d, 1H, J=6.4 Hz, $CHHOH$), 7.2–7.4 (5H, m, C_6H_5). ^{13}C NMR, δ: 13.8 (q); 22.5 (t); 29.4 (t); 31.6 (t); 48.6 (d); 67.5 (d). MS (CI/NH_3) m/z: 196 (M+18); 179 (M+1).

(R)-3-Cyclohexyl-2-phenyl-1-propanol ***2c***. The same procedure was used with cyclohexylmethyllithium 1.56 M in pentane and (*S*) styrene oxide (10 mmol). After purification by chromatography on a silica gel column (cyclohexane:AcOEt 85:15), the alcohol **2c** was isolated as a solid. Yield: 83%. ee: 98% (GC after derivatisation with O-acetyllactic chloride[16]). $[\alpha]_D^{20}$ −31.5 (c=1.59, $CHCl_3$). Mp=56°C. IR (neat) cm^{-1}: ν 3550 (OH); 1050 (C–O); 700 (C_6H_5). ^1H NMR δ: 0.8–1.9 (m, 13H, CH_2); 2.86–3.01 (1H, m, CHC_6H_5); 3.66 (dd, 1H, J=7.7, 10.7 Hz, CH_2OH); 3.74 (dd, 1H, J=5.9, 10.7 Hz, CH_2OH); 7.2–7.4 (m, 5H, C_6H_5). ^{13}C NMR δ: 26.0 (t); 26.1 (t); 26.5 (t); 32.6 (t); 34.1 (t); 34.6 (d); 39.6 (t); 45.4 (d); 67.9 (t); 126.5 (d); 128.0 (d); 128.5 (d); 142.6 (s). MS (EI) m/z: 218 (M); 187; 105; 91. Anal. calc. for $C_{15}H_{22}O$: C, 82.51 H, 10.16; found: C, 82.69 H, 10.21.

(R-Z)-2-Phenyl-3-octen-1-ol ***2d***. 1.3 M *n*-BuLi in hexane (8.5 mL, 11 mmol) was added to a solution of (Z) 1-iodohex-1-ene[17] (2.31 g, 11 mmol) in ether (20 mL) cooled to −65°C.[18] After stirring for 1 h, CuCN (985 mg, 11 mmol) was added and the mixture was allowed to warm to −20°C for 45 min. The reaction with (*S*) styrene oxide (1.20 g, 10 mmol) was then conducted as above. After purification

by chromatography on a silica gel column (cyclohexane:AcOEt 80:2), the alcohol **2d** was isolated as an oil. Yield: 84%. $[\alpha]_D^{20}$ −126.4 (c=3.16, $CHCl_3$). IR (neat) cm^{-1} ν: 3400 (OH); 1510, 1480 (C=C); 1080 and 1040 (C–O); 720 (C_6H_5). ^1H NMR δ: 0.89 (t, 3H, *J*=6.3 Hz, CH_3CH_2); 1.15–1.44 (m, 4H, CH_2CH_2); 1.52 (br s, 1H, OH); 2.10–2.15 (m, 2H, CH_2CH=C); 3.6–3.9 (m, 3H, CH_2OH, CH–C_6H_5); 5.5–5.7 (m, 2H, CH_2CH=C, CH_2CH=C*H*); 7.2–7.3 (m, 5H, C_6H_5). ^{13}C NMR δ: 13.9 (q); 22.3 (t); 27.3 (t); 31.7 (t); 46.3 (d); 66.9 (t); 125.7 (d); 126.6 (d); 127.7 (d); 128.6 (d); 128.9 (d); 133.3 (d); 141.7 (s). MS (CI/NH_3) m/z: 222 (M+18), 204 (M). Anal. calc. for $C_{14}H_{20}O$: C, 82.37 H, 9.80; found C, 82.34 H, 9.78.

2-Phenyl-3-octyn-1-ol ***2e***. 1.6 M *n*-BuLi in hexane (1.62 mL, 2.6 mmol) was added to a solution of hexyne (213 mg, 2.6 mmol) in THF (10 mL) cooled to −20°C. After stirring for 20 min, the solution was cooled to −78°C and the reaction with racemic styrene oxide (2 mmol) was conducted as described above. After chromatography (cyclohexane:AcOEt 8:2), the alcohol **2e** was isolated as an oil. Yield: 71%. IR (neat) cm^{-1} ν: 3360 (OH, broad); 1070 (C–O); 765, 715 (C_6H_5). ^1H NMR δ: 0.96 (t, 3H, *J*=7.1 Hz, CH_3CH_2); 1.3–1.6 (m, 4H, CH_2CH_2); 1.98 (s, 1H, OH); 2.30 (td, 2H, *J*=6.9, 2,1 Hz, C≡C–CH_2); 3.70–3.75 (m, 2H, $HOCH_2$); 3.8–3.9 (m, 1H, CHC_6H_5); 7.26–7.45 (m, 5H, C_6H_5). ^{13}C NMR δ: 13.5 (q); 18.4 (t); 21.9 (t); 30.9 (t); 41.4 (d); 67.8 (t); 78.3 (t); 85.2 (t); 127.1 (d); 127.8 (d); 128.4 (d); 138.5 (s). MS (CI/NH_3) m/z: 220 (M+18); 203 (M+1); 171; 130; 91. Anal. calc. for $C_{14}H_{18}O$: C, 83.18 H, 8.90; found C, 82.67 H, 8.77.

Acetylation of 2-phenyl-1-alkanols

A mixture of alcohol **2** (10 mmol), triethylamine (2.12 mL, 15 mmol), acetic anhydride (1.43 mL; 15 mmol) and DMAP (275 mg, 2.25 mmol) in anhydrous dichloromethane (30 mL) was stirred for 12 h at room temperature. After hydrolysis with water (30 mL), the aqueous phase was extracted with CH_2Cl_2 (3×30 mL), dried on $MgSO_4$ and concentrated under reduced pressure to give an oil which was purified by chromatography on a silica gel column.

(R)-1-Acetoxy-3-methyl-2-phenylbutane ***6a***. After chromatography (cyclohexane:AcOEt 95:5), the acetate was isolated as an oil in 97% yield. $[\alpha]_D^{20}$ −12.5 (c=1.05, CH_2Cl_2). IR (neat) cm^{-1} ν: 1740 (C=O); 1220 (C–O); 700 (C_6H_5). ^1H NMR δ: 0.80 (d, 3H, *J*=6.7 Hz, CH_3); 1.03 (d, 3H, *J*=6.7 Hz, CH_3); 1.9–2.1 (m, 1H, $(CH_3)_2CH$); 2.05 (s, 3H, CH_3–C=O); 2.69 (ddd, 1H, *J*=5.7, 6.7, 7.8 Hz, CH–C_6H_5); 4.34 (dd, 1H, *J*=7.8, 11.0 Hz, CHH–O); 4.40 (dd, 1H, *J*=5.7, 11.0 Hz, CHH–O); 7.1–7.4 (m, 5H, C_6H_5). ^{13}C NMR δ: 20.4 (q); 20.7 (q); 30.2 (d); 51.4 (d); 66.4 (t); 126.3 (d); 128.0 (d); 141.3 (s); 171.0 (s). MS (CI/NH_3) m/z: 224 (M+18); 207 (M+1). Anal. calc. for $C_{13}H_{18}O_2$: C, 75.74 H, 8.73; found: C, 75.70 H, 8.47.

(R)-1-Acetoxy-2-phenylhexane ***6b***. After chromatography (cyclohexane:AcOEt 95:5), the acetate was isolated as an oil in 93% yield. $[\alpha]_D^{20}$ −33.9 (c=2.2, CH_2Cl_2). IR (neat) cm^{-1} ν: 1735 (C=O); 1220 (C–O); 700 (C_6H_5). ^1H NMR δ: 0.86 (t, 3H, *J*=7.2 Hz, CH_3); 1.1–1.4 (m, 4H, 2 CH_2); 1.6–1.8 (m, 2H, CH_2); 2.02 (s, 1H, CH_3–C=O); 2.93 (m, 1H CH–C_6H_5); 4.22 (dd, 1H, *J*=1.9, 5.2 Hz, CH_2–O); 7.1–7.4 (m, 5H, C_6H_5). ^{13}C NMR δ: 13.8 (q); 20.8 (q); 22.6 (t); 29.3 (t); 32.0 (t); 44.8 (d); 68.5 (t); 126.5 (d); 127.8 (d); 128.3 (d); 142.0 (s); 171.0 (s). MS (CI/NH_3) m/z: 238 (M+18); 221 (M+1). Anal. calc. for $C_{14}H_{20}O_2$: C, 76.33 H, 9.15; found: C, 76.50 H, 9.06.

(R)-1-Acetoxy-3-cyclohexyl-2-phenylpropane ***6c***. After chromatography (cyclohexane:AcOEt 9:1), the acetate was isolated as an oil in 97% yield. $[\alpha]_D^{20}$ −25.7 (c=1.43, CH_2Cl_2). IR (neat) cm^{-1} ν: 1755 (C=O). ^1H NMR δ: 0.84–0.94 (m, 10 H, 5 CH_2); 1.4–1.6 (m, 9H, CH_2); 2.00 (s, 3H, CH_3–C=O); 3.07 (m, 1H, CHC_6H_5); 4.10–4.25 (m, 2H, CH_2O); 7.2–7.5 (m, 5H, C_6H_5). ^{13}C NMR: 20.8 (q); 25.9 (t); 26.5 (t); 32.5 (t); 34. 0 (t); 34.5 (d); 40.3 (t); 41.6 (d); 68.4 (t); 126.5 (d); 127.7 (d); 128.3 (d);

142.7 (s); 171.0 (s). MS (EI) m/z: 200 (M−60); 118; 91; 43. Anal. calc. for $C_{17}H_{24}O_2$: C, 78.42 H, 9.29; found: C, 78.51 H, 9.33.

(2R,3Z)-1-Acetoxy-2-phenyl-3-octene ***6d***. After chromatography (cyclohexane:AcOEt 9:1), the acetate was isolated as an oil in 96% yield. $[\alpha]_D^{20}$ −84.9 (c=1.98, $CHCl_3$). IR (neat) cm^{-1} ν: 1750 (C=O); 1535 (C=C); 1040 (C–O); 700 (C_6H_5). ^1H NMR δ: 0.92 (t, 3H, *J*=6.5 Hz, CH_3); 1.04–1.46 (m, 4H, CH_2); 2.03 (s, 3H, CH_3C=O); 2.1–2.2 (m, 2H, CH_2C=C); 3.96–4.04 (m, 1H, C*H*C_6H_5); 4.3–4.4 (m, 2H, C_6H_5). ^{13}C NMR δ: 13.9 (q); 20.8 (q); 22.2 (t); 27.2 (t); 31.6 (t); 42.6 (d); 67.6 (t); 126.6 (d); 127.5 (d); 128.5 (d); 141.3 (s); 127.7 (d); 132.6 (d); 170.9 (s).

Oxidative cleavage of 2-phenyl-1-alkanols

Sodium periodate (32.1 g, 150 mmol) and $RuCl_3 \cdot xH_2O$ (415 mg, 2.0 mmol,) were added to a solution of O-acetyl alcohol **6** (10 mmol) in 2/2/3 $CCl_4/CH_3CN/H_2O$ (160 mL). The mixture was vigourously stirred for 30 h, filtrated on celite and extracted with CH_2Cl_2 (4×30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was diluted in Et_2O (10 mL) and reacted for 10 min with a 1.0 M solution of diazomethane in ether (11 mL). The ether was evaporated under reduced pressure and the resulting ester was purified by chromatography on a silica gel column.

Methyl (S)-3-acetoxy-2-isopropyl-propanoate ***7a***. After purification (cyclohexane:AcOEt 85:15), the ester was isolated in 83% yield. $[\alpha]_D^{20}$ +13.9 (c=2.25, CH_2Cl_2). IR (neat) cm^{-1} ν: 1740 (C=O); 1220 (C–O). ^1H NMR δ: 0.94 (d, 3H, *J*=7.0 Hz, CH_3); 0.97 (d, 3H, *J*=7.1 Hz, CH_3); 1.87–2.04 (m, 1H, CH_3CH); 2.00 (s, 3H, CH_3–C=O); 2.50 (ddd, 1H; *J*=5.0, 7.3, 9.6 Hz, CHC=O); 3.70 (s, 3H, CH_3O); 4.19 (dd, 1H, *J*=9.4, 10.8 Hz, C*H*HO); 4.30 (dd, 1H, *J*=5.0, 10.8 Hz, CH*H*O). ^{13}C NMR δ: 20.0 (q); 20.6 (d); 28.1 (d); 51.1(d); 51.3 (q); 63.4 (t); 170.5 (s); 173.4 (s). MS (CI/NH_3): 206 (M+18); 189 (M+1); 145. Anal. calc. for $C_9H_{16}O_4$: C, 57.47 H, 8.51; found: C, 57.34 H, 8.84.

Methyl (S)-3-acetoxy-2-butyl-propanoate ***7b***. After purification (cyclohexane:AcOEt 85:15), the ester was isolated in 73% yield. $[\alpha]_D^{20}$ +7.3 (c=2.21; CH_2Cl_2). IR (neat) cm^{-1} ν: 1740 (C=O); 1230 (C–O). ^1H NMR δ: 0.90 (t, 3H, *J*=6.6 Hz, CH_3); 1.2–1.4 (m, 4H, CH_2); 1.5–1.7 (m, 2H, CH_2); 2.05 (s, 3H, CH_3–C=O); 2.6–2.8 (m, 1H, CH–C=O); 3.73 (s, 3H, OCH_3); 4.23 (dd, 2H, *J*=1.0, 5.8 Hz, O–CH_2). ^{13}C NMR δ: 13.7 (q); 20.7 (q); 22.4 (t); 28.3 (t); 29.0 (t); 44.6 (d); 51.6 (q); 64.5 (t); 170.6 (s); 174.0 (s). MS (CI/NH_3): 220 (M+18); 203 (M+1); Anal. calc. for $C_{10}H_{18}O_4$: C, 59.39 H, 8.97; found: C, 59.50 H, 8.88.

Methyl (S)-3-acetoxy-2-cyclohexylmethyl-propanoate ***7c***. After purification (cyclo-hexane:AcOEt 85:15), the ester was isolated in 67% yield. $[\alpha]_D^{20}$ −1 (c=2.18, CH_2Cl_2). IR (neat) cm^{-1} ν: 1760 (C=O); 1240 (C–O). ^1H NMR δ: 0.9–1.8 (m, 13H, CH_2 and CH); 2.05 (s, 3H, CH_3–C=O); 2.8–2.9 (m, 1H, CH–C=O); 3.72 (s, 3H, CH_3O); 4.17 (dd, 1H, *J*=6.7, 10.7 Hz, C*H*HO); 4.22 (dd, 1H, *J*=5.2, 10.7 Hz, CH*H*O). ^{13}C NMR δ: 20.7 (q); 25.9 (t); 26.2 (t); 32.7 (t); 33.2 (t); 35.1 (d); 36.2 (t); 42.1 (d); 51.6 (q); 64.9 (t); 170.6 (s); 174.3 (s). MS (EI) m/z: 243 (M+1); 211; 182; 122.

Synthesis of β-hydroxyesters ***8***

Potassium carbonate (829 mg, 6 mmol, 1.2 eq.) was added to a solution of ester **7** (5 mmol) in MeOH (10 mL) cooled to 0°C. After stirring for 10 min, the reaction was hydrolyzed with water (5 mL) and extracted with Et_2O (4×10 mL). The organic phase was dried on $MgSO_4$, concentrated under reduced pressure and purified by chromatography on a silica gel column.

Methyl (S)-3-hydroxy-2-isopropylpropanoate ***8a***. After purification (cyclohexane:AcOEt 7:3), the ester was isolated in 91% yield. $[\alpha]_D^{20}$ −8.0 (c=2.05, CH_2Cl_2). IR (neat) cm^{-1} ν: 3460 (OH); 1740 (C=O). ^1H NMR δ: 0.91 (d, 3H, *J*=6.7 Hz, CH_3); 0.95 (d, 3H, *J*=6.1 Hz, CH_3); 1.9–2.1 (m, 1H, CH_3CH); 2.39 (ddd, 1H, *J*=8.2, 4.1, 4.1 Hz, CHC=O); 2.91 (s, 1H, OH); 3.71 (s, 3H, CH_3CO); 3.76 (dd, 1H, *J*=4.1 Hz, CHHO); 3.85 (dd, 1H *J*=11.0, 8.1 Hz, CHHO). ^{13}C NMR δ: 20.1 (q); 20.4 (q); 27.6 (d); 51.3 (d); 54.2 (q); 61.4 (t); 175.5 (s). MS (EI) m/z: 147 (M+1); 128; 68; 31. Anal. calc. for $C_7H_{14}O_3$: C, 57.55 H, 9.58; found: C, 57.59 H, 9.62.

Methyl (S)-2-hydroxymethylbutylhexanoate ***8b***. After purification (cyclohexane:AcOEt 7:3), the ester was isolated in 88% yield. $[\alpha]_D^{20}$ −9.6 (c=2.53, CH_2Cl_2). IR (neat) cm^{-1} ν: 3440 (OH); 1740 (C=O). ^1H NMR δ: 0.89 (t, 3H, *J*=6.6 Hz, CH_3); 1.2–1.4 (m, 4H, CH_2); 1.4–1.7 (m, 2H, CH_2); 2.45 (s, 1H, OH); 2.59 (ddd, 1H, *J*=3.2, 5.0, 9.0 Hz, CHC=O); 3.72 (s, 3H, CH_3O); 3.7 (m, 2H, CH_2O). ^{13}C NMR δ: 13.7 (q); 22.5 (t); 28.1 (d); 29.3 (t); 47.4 (d); 51.6 (q); 63.0 (t); 175.9 (s). MS (EI) m/z: (M+1) 161. Anal. calc. for $C_8H_{16}O_3$: C, 59.98 H, 10.07; found: C, 59.84 H, 10.10.

Methyl (S)-3-hydroxy-2-cyclohexylmethylpropanoate ***8c***. After purification (cyclo-hexane:AcOEt 7:3), the ester was isolated in 90% yield. $[\alpha]_D^{20}$ −19.0 (c=2.3, CH_2Cl_2). IR (neat) cm^{-1} ν: 3480 (OH); 1740(C=O). ^1H NMR δ: 0.75–1.75 (m, 13 H, CH_2, CH); 2.20 (s, 1H, OH), 2.64–2.67 (m, 1H, CH–C=O); 3.72–3.74 (m, 1H, CH_2O); 3.73 (s, 3H, CH_3O). ^{13}C NMR: 26.0 (d); 26.3 (d); 32.9 (d); 33.1 (d); 35.2 (d); 35.8 (t); 51.6 (q); 63.4 (t); 176.2 (s). MS (EI) m/z: 182 (M−18); 122; 104. Anal. calc. for $C_{11}H_{20}O_3$: C, 57.55 H, 9.58; found: C, 57.59 H, 9.62.

(2R)-3-Acetoxy-2-phenylpropanoic acid ***9***

Ozone was bubbled for 6 min through a cooled solution of the acetate **6d** (1.2 g, 4.87 mmol) in CH_2Cl_2–MeOH 2:1 (30 mL) cooled at −78°C until the blue color persist. The ozone excess was removed with argon and dimethylsulfide (3 mL) was added. The solution was then stirred for 8 hours at room temperature and evaporated in vacuo. The residue was dissolved in ether (15 mL), washed with water (10 mL) and dried on $MgSO_4$. The solvent was evaporated to give the crude 3-acetoxy-2-phenylpropanal; yield: 881 mg (96%). ^1H NMR: δ 2.00 (s, 3H, CH_3–C=O); 3.95 (ddd, 1H, *J*=6.2, 7.1, 7.3 Hz, C_6H_5–CH); 4.37 (dd, 1H, *J*=5.8, 11.3 Hz, O–CHH); 4.67 (dd, 1H, *J*=7.9, 11.3 Hz, O–CHH); 7.2–7.5 (m, 5H, C_6H_5); 9.72 (d, 1H, *J*=1.4 Hz, CHO). The aldehyde was oxidized without purification. 1M Jones reagent (6.7 mL, 6,7 mmol) was added to an acetone solution (15 mL) of the crude aldehyde (860 mg, 5.7 mmol) cooled to 0°C. After stirring for 15 min, the solvent was evaporated under reduced pressure without warming. The resulting oil was dissolved in water (10 mL) and extracted with CH_2Cl_2 (5×10 mL). The organic phase was dried on $MgSO_4$ and chromatographed on silica gel to give 745 mg of a viscous oil. Yield: 80% from the acetate **6d**. $[\alpha]_D^{20}$ +47.4 (c=1.1, $CHCl_3$). Lit.[14]: $[\alpha]_D^{20}$ +46.1 (c=1; $CHCl_3$). IR (neat) cm^{-1} ν: 3450 (OH); 1726 (C=O). ^1H NMR δ: 2.03 (s, 3H, CH_3–C=O); 3.95 (dd, 1H, *J*=5.5, 9.5 Hz, CHC=O); 4.34 (dd, 1H, *J*=9.5, 10.9 Hz, CHHO); 4.57 (dd, 1H, *J*=9.5, 10.9 Hz, CHHO); 7.32 (s, 5H, C_6H_5); 10.7 (s br, 1H, COOH). ^{13}C NMR δ: 20.7 (q); 50.4 (d); 64.7 (t); 128.1 (d); 128.4 (d); 134.1 (s); 170.8 (s); 177.4(s). MS (CI/ NH_3) m/z: 225 (M+18); 209 (M+1). Anal. calc. for $C_{11}H_{12}O_4$: C, 63.48 H, 5.77; found: C, 63.97 H, 5.74.

(2R) Methyl tropinate ***10***

The acid **9** (624 mg, 3 mmol) was diluted in Et_2O (5 mL) and reacted for 10 min with a 1.0 M solution of diazomethane in ether (5 mL). The solvent was evaporated under reduced pressure. After purification on a silica gel column (cyclohexane:AcOEt 9:1), the O-acetoxy ester was isolated as an oil. Yield: 95%. $[\alpha]_D^{20}$ +57 (c=1.2, $CHCl_3$). IR (neat) cm^{-1} ν: 1737 (C=O); 1220; 750; 698. ^1H NMR δ: 2.06 (s, 3H, CH_3–C=O); 3.73 (s, 3H, OCH_3); 3.97 (dd, 1H, *J*=5.6, 9.4 Hz, CHC=O); 4.36 (dd, 1H, *J*=5.6, 10.9 Hz, CHHO); 4.60 (dd, 1H, *J*=9.6, 10.9 Hz, CHHO); 7.30–7.42 (m, 5H, C_6H_5). ^{13}C NMR δ: 20.3 (q); 52.7 (d); 53.2 (q); 64.7 (t); 128.1 (d); 128.3 (d); 134.1 (s); 170.8 (s); 174.2 (s).

MS (CI/ NH_3) m/z: 240 (M+18); 225 (M+1). Anal. calc. for $C_{12}H_{14}O_4$: C, 64.88 H, 6.30; found: C, 65.02 H, 6.28. Potassium carbonate (3 mmol; 1.2 eq., 415 mg) was added to a solution of the O-acetoxyester (560 mg; 2.5 mmol) in MeOH (5 mL) cooled to 0°C. After stirring for 10 min, the reaction was hydrolyzed with water (3 mL) and extracted with Et_2O (4×10 mL). The organic phase was dried on $MgSO_4$, concentrated under reduced pressure. After purification on a silica gel column (cyclo-hexane:AcOEt 7:3), methyl tropinate was isolated as an oil in 93% yield. $[\alpha]_D^{20}$ +69.9 (c=1.0, Me_2CO); Lit:[15]: *S* isomer: $[\alpha]_D^{20}$ −69.8 (c=0.87, Me_2CO). IR (neat) cm^{-1} ν: 3720 (OH); 1738 (C=O); 1042; 750; 634. ^1H NMR δ: 3.69 (s, 3H, OCH_3); 3.79–3.85 (m, 2H, C*H*H–O, CH–C=O); 4.13 (dd, 1H, *J*=7.9, 10.3 Hz, CH*H*–O); 7.27–7.39 (m, 5H, C_6H_5). ^{13}C NMR δ: 52.2 (q); 54.1 (d); 64.6 (t); 127.7 (d); 128.2 (d); 128.8 (d); 135.6 (s); 173.6 (s). MS (CI/ NH_3) m/z: 198 (M+18); 181 (M+1).

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