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Chemoenzymatic synthesis of asymmetrized bis(hydroxymethyl)propanoates (BHYMP*) as a new family of chiral building blocks

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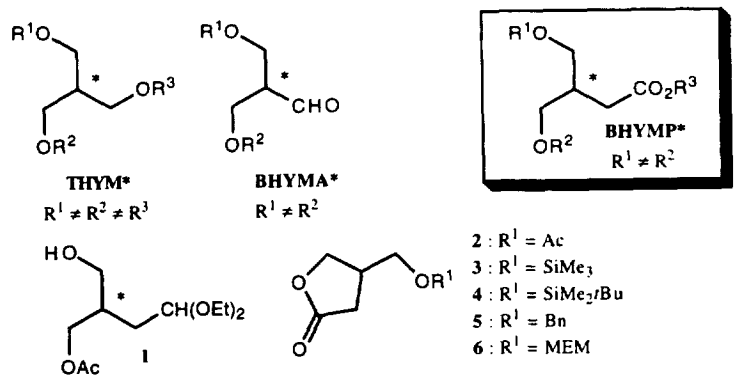
Abstract: A series of asymmetrized bis(hydroxymethyl)propanoates (BHYMP*) has been prepared in both enantiomeric forms through a chemoenzymatic methodology involving complementary diacetate monohydrolyses and diol monoacetylations catalyzed by lipases.

Small, polyfunctionalized chiral 'building blocks' are useful starting materials for the stereoselective synthesis of several biologically active substances.[2] Recently we have been particularly interested in the chemoenzymatic synthesis of C-4 polyoxygenated branched chiral building blocks like, for example, asymmetrized tris(hydroxymethyl)methane (THYM*) and bis(hydroxymethyl)acetaldehyde (BHYMA*) (Scheme 1), both characterized by three oxygenated one carbon side arms.[3] We have now focused our attention on a similar family of compounds, i.e. bis(hydroxymethyl)propanoates (BHYMP*), which have two hydroxymethyl and one (alkoxycarbonyl)methyl group bonded to the same stereogenic centre. These synthons seemed very useful to us from a synthetic point of view, thanks to the possibility of generating the ester enolate by treatment with strong bases and of functionalizing through it the α position of the ester with various electrophiles under stereocontrolled conditions. In particular, the alkylation reaction gives access to intermediates with two tertiary unfunctionalized adjacent asymmetric centers, not easily achievable in other ways.



Scheme 1.

Some examples of building blocks related to BHYMP*, such as **1**,[4] **2**,[5–7] **3**,[5] **4**,[8] **5**[6,9] and **6**[10] (Scheme 2) have been previously prepared enantioselectively, either by enzyme or microorganism catalysis,[4–6,9,10] or by non-biological techniques.[7,8] However, none of the described methodologies, which in most cases were targeted towards the corresponding lactones, seemed well suited to us for

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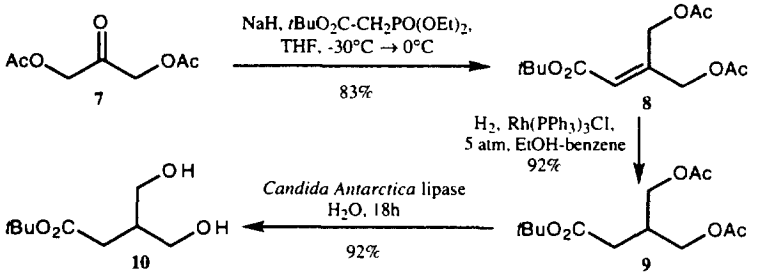
the direct obtainment of BHYMP* esters in a straightforward manner. In this paper we report a short and efficient chemoenzymatic synthesis of BHYMP* derivatives (R^3=*tert*-butyl) in both enantiomeric forms. The *tert*-butyl group was chosen because of its orthogonality with the acetate, its easy removal under acidic conditions and its stability toward nucleophiles.



Scheme 2.

First, we prepared both diacetate **9** and diol **10** starting from easily available diacetoxyacetone[11] (Scheme 2). Horner–Wadsworth–Emmons condensation with commercially available diethyl *t*-butylphosphonoacetate furnished enoate **8**. Attempts to reduce the double bond by hydrogenation on palladium on carbon or on PtO_2 gave only poor yields, because of concurrent hydrogenolysis of the C–OAc bond. This problem was overcome by using Wilkinson's catalyst, although it is usually stressed that this compound is unable to promote hydrogenation of conjugated double bonds. On the contrary, in our case, reaction took place even at 1 atm giving no hydrogenolized by-products. Nevertheless, in order to reduce the reaction times and decrease the amount of rhodium compound, we prefer to carry out the reaction at 5 atm.

Diol **10** was best prepared from **9** by hydrolysis catalyzed by recombinant *Candida antarctica* lipase in water. This enzyme was chosen for its high efficiency and low substrate selectivity (that is, monoacetate is converted to diol as easily as diacetate to monoacetate).

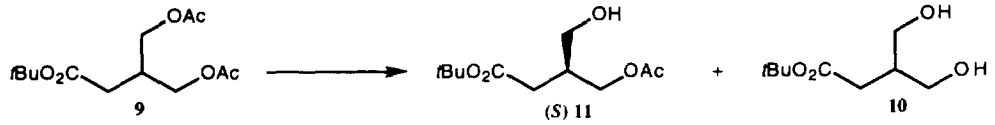
Having in hand these two substrates, we next studied their asymmetrization by enzyme mediated hydrolysis or acetylation.

Selected results of enzymatic hydrolysis of **9** are listed in Table 1. After experiencing different enzymes, two of them have been selected for further optimization, pig pancreatic lipase (PPL) and Amano P lipase from *Pseudomonas cepacia*. In water they gave comparable results, affording in each case the (*S*) enantiomer in good, but still not satisfactory e.e. (entries 1 and 4). Addition of various cosolvents led in general to an increase of e.e. This gain was particularly remarkable with PPL, especially employing water immiscible cosolvents. The best results were achieved with iPr_2O, although at partial expense of the substrate selectivity and isolated yield (cf. entry 4 with entry 11). This problem was in part overcome by lowering the substrate concentration (entry 12). Under these conditions a very high e.e. accompanied by a satisfactory yield was achieved. Other immiscible cosolvents brought about either sluggish reaction (toluene) or lower e.e.s (*iso*-octane, *n*-heptane). The use of iPr_2O was beneficial in terms of e.e. also in the case of Amano P, but in this case the reaction became particularly sluggish. In conclusion, the conditions reported in entry 12 are the best and have been used for scaling up the reaction.

We then explored the enzyme catalysed acetylation of diol **10** promoted by vinyl acetate, hoping to develop a complementary method for obtaining the (*R*) enantiomer. The results are shown in Table 2.

We first used supported PPL under the conditions recently optimized by us for highest reactivity.[12] The results obtained were satisfactory but not exceptional. As expected, the major enantiomer was, in this case, the (*R*) one. Superior results have been attained with lipase Amano P from *Pseudomonas cepacia*. In this case the reaction was remarkably faster in iPr_2O as solvent instead of neat vinyl acetate. The quite high e.e. was accompanied by an excellent isolated yield. Other enzymes were found not to be satisfactory either in terms of enantioselectivity or of substrate selectivity. It is however

Table 1. Enzyme catalyzed monohydrolysis of diacetate **9**[a]



Entry	Enzyme	Enzyme amount (mg/mmol)	Solvent	Substrate conc. (mM)	Time (min)	Conv.[b]	Yield	**9:11:10**[c]	e.e.[d] (%)
1	Amano P	143	H_2O	18.3	390	49%	69%	14 : 74 :12	82.3
2	Amano P	235	H_2O/*t*BuOH 85:15	18.3	255	46%	67%	18 : 71 :11	84.0
3	Amano P	227	H_2O/*i*Pr_2O 85:15	18.3	1365	57%	51%	14 : 57 :29	89.2
4	PPL	133	H_2O	40	360	47%	90%	9 : 91 :0	74.0
5	PPL	256	H_2O/*t*BuOH 85:15	22	380	56%	80%	3 : 82 :15	86.8
6	PPL	266	H_2O/THF 85:15	22	380	46%	69%	17 : 75 : 8	83.6
7	PPL	272	H_2O/acetone 85:15	26	330	48%	76%	12 : 81 : 7	85.0
8	PPL	192	H_2O/toluene 85:15	52	410	40%	32%	40 : 40 : 20	95.0
9	PPL	192	H_2O/*n*-heptane 85:15	52	210	60%	63%	4 : 70 : 26	91.0
10	PPL	192	H_2O/*iso*octane 85:15	52	320	63%	52%	9 : 55 : 36	77.0
11	PPL	192	H_2O/*i*Pr_2O 85:15	52	280	50%	45%	25 : 50 : 25	94.2
12	PPL	195	H_2O/*i*Pr_2O 85:15	18.3	260	52%	69%	13 : 71 : 16	97.0

[a] All reactions were carried out at 20°C. [b] Conversion is defined as the percentage of initial acetoxy groups which have been hydrolysed. [c] Determined by ^{1}H n.m.r. [d] The major enantiomer was always (*S*).

interesting to note that using lipase from *Candida antarctica* the opposite enantiomer (*S*) was produced preferentially. The inversion of enantioselectivity passing from PPL or Amano P to this enzyme has been already previously described for other substrates.[13]

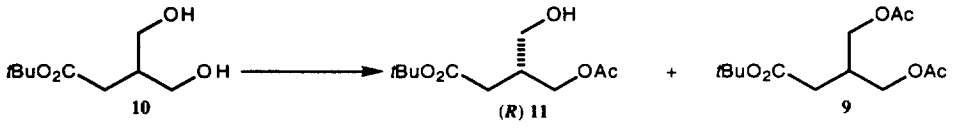
The overall yield of (*R*)-**11** from diacetate **9** (78% for 2 steps) turned out to be even better than that of the (*S*) enantiomer (69% for 1 step). Thus, also considering the easy preparation of **9**, we may assert that the developed routes are practically efficient for both enantiomers.

We then turned our attention to the elaboration of these monoacetates to give a series of related chiral building blocks (Scheme 3), with particular emphasis toward the possibility of racemization. Although Scheme 3 shows only reactions starting from (*S*)-**11**, it is obvious that all the enantiomeric compounds are available simply using (*R*)-**11**. Treatment with trifluoroacetic acid effected removal of the *t*-butyl ester affording γ-lactone (*R*)-**2**. Comparison of the $[\alpha]_D$ of this lactone with the one previously reported[5b] allowed us to establish the absolute configuration of **11**.[14]

In view of a possible use of these chiral building blocks in asymmetric synthesis, we also transformed **11** into a series of derivatives bearing, at the OH groups, protection different from Ac and, more compatible with the chemistry that we planned to develop, involving α functionalization of ester through enolate formation. An example is given by lactones **13** and **17**: these are analogues of **3–5** (Scheme 1), which have been previously employed in the synthesis of several biologically active substances, like for example A-Factor,[5a,b,d,8] I-Factor,[6] Virginiae Butanolides,[5c] Strigol,[10] Sorgolactone[10] and Maturone.[15]

Protection of **11** as the diphenyl-*tert*-butylsilyl ether gave **12**. Attempts to remove selectively the acetyl group by basic hydrolysis under various conditions surprisingly failed, because it was impossible

Table 2. Enzyme catalyzed monoacetylation of diol **10**[a]



Entry	Enzyme[b]	Enzyme amount (mg/mmol)	Solvent[c]	Substrate conc. (mM)	Time (min)	Conv.[d]	Yield	**10:11:9**[e]	e.e.[f] (%)
1	SPPL	196	VA / iPr_2O 1:3	64	375	35%	53%	31 : 68 : 1	88.0
2	SPPL	196	VA / iPr_2O 1:3	64	815	49%	86%	5 : 93 : 8	89.0
3	A6	191	VA / iPr_2O 1:3	64	1620	15%	22%	71 : 27 : 2	56.0
4	CAL	58	VA	64	50	50%	37%	26 : 48 : 26	39.0[e]
5	AY	192	VA	64	450	21%	25%	61: 36: 3	19.4
6	Amano P	115	VA	64	120	43%	73%	14 : 84 : 2	94.5
7	Amano P	125	VA	64	360	54%	79%	0 : 88 : 13	96.2
8	Amano P	152	VA / iPr_2O 6:94	64	115	52%	85%	2 : 94 : 4	97.9

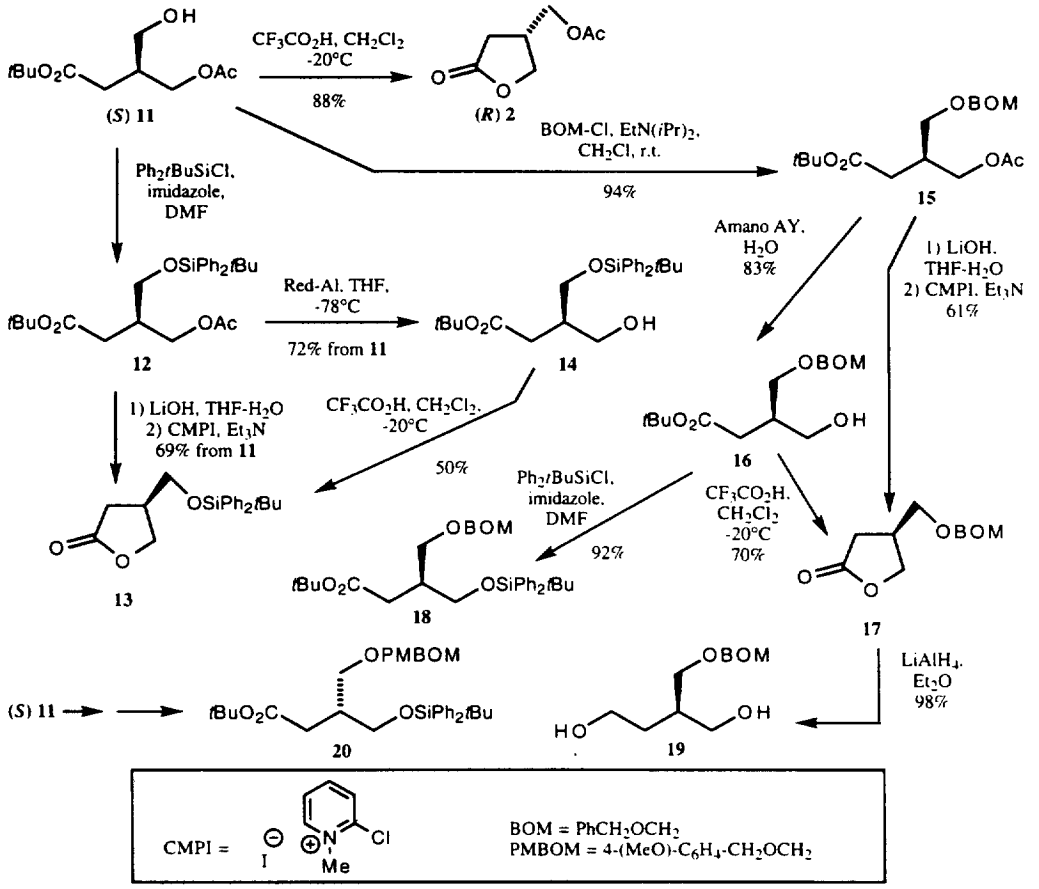
[a] All reactions were carried out at 20°C. [b] SPPL: supported PPL as described in ref. 12; A6: lipase Amano A6 (from Aspergillus Niger); CAL: Novo lipase from Candida Antarctica; AY: lipase Amano AY (from Candida Cylindracea; Amano P (lipase from Pseudomonas sp.). [c] VA = vinyl acetate. [d] Conversion is defined as the percentage of initial hydroxy groups which have been acetylated. [e] Determined by ^1H n.m.r. [f] The major enantiomer was always (*R*) except in the case of entry 4.

to suppress competitive saponification of the *t*-butyl ester. By allowing the reaction to reach completion, the corresponding γ-hydroxycarboxylate was obtained. Although spontaneous lactonization upon acidification did not take place, lactone **13** could be synthesized by using N-methyl-2-chloropyridinium iodide (MCPI) as coupling agents. Alternatively, the acetyl group has been selectively removed by reduction with Red-Al (sodium bis(methoxyethoxy)aluminium hydride) and the resulting hydroxyester **14** lactonized with CF_3CO_2H. Unfortunately both lactones obtained by the two routes were affected by a slight amount of racemization as demonstrated by the ^1H NMR in the presence of chiral shift reagents that indicated in both cases e.e.s between 80 and 85%. On the contrary, Mosher ester analysis showed the enantiomeric integrity of **14**, indicating that the problem did not lie in the silylation step or in the Red-Al reduction. Thus, we believe that the racemization is provoked by migration of the silyl group from one hydroxymethyl group to the other, catalyzed either by basic or acidic conditions.

In order to avoid this problem we turned to a protecting group unable to migrate, the benzyloxymethyl (BOM). After protection to give **15**, treatment with LiOH and MCPI, afforded lactone **17**. Alternatively, removal of the acetyl group followed by treatment with CF_3CO_2H, gave the same lactone. In both cases reduction to diol **19** followed by ^1H NMR analysis of the bis(camphanoates) demonstrated no racemization. Removal of the acetyl group in **15** was in this case best realized enzymatically. Among several enzymes tested, Amano Ay from *Candida cylindracea* turned out to be the best in terms of efficiency and yield.

We also prepared some acyclic derivatives. For example, **18** was easily prepared from **16** by silylation of the free hydroxyl. By a similar route, analogue **20** was also synthesized. We plan to employ acyclic derivatives like **14**, **16**, **18** and **20** in diastereoselective 'protecting group controlled' enolate condensation with various electrophiles to produce chiral intermediates of potential utility in the synthesis of biologically active compounds.

In conclusion, we have optimized the preparation of BHYMP* building blocks **11** and their stereoretentive transformation into useful derivatives. It is worth noting that during this work we solved various selectivity problems by using four different lipases, each one selected for the specific task.



Scheme 3.

Experimental

NMR spectra were taken in $CDCl_3$, at 200 MHz (^1H) and 20 MHz (^{13}C). Chemical shifts are reported in ppm (δ scale), coupling constants are reported in Hertz. Peak assignment in ^1H NMR spectra, was also made with the aid of double resonance experiments. In ABX systems, proton A is considered downfield and B upfield. Peak assignment in ^{13}C spectra was made with the aid of off-resonance experiments. GC–MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV and a mass temperature of approx. 167°C. Unless otherwise indicated analyses were performed with a constant He flow of 0.9 ml/min., starting at 100°C for 2 min. and then raising the temperature by 20°C/min. IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates, which were developed by the following detection methods: (A) UV; (B) dipping into a solution of $(NH_4)_4MoO_4 \cdot 4H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1 g) in H_2SO_4 (31 cc) and H_2O (469 cc) and warming; (C) dipping into 2% aqueous $KMnO_4$ and warming. The R_f were measured after an elution of 7–9 cm. Chromatographies were carried out on 220–400 mesh silica gel using the 'flash' methodology. Petroleum ether (40–60°C) is abbreviated as PE. In extractive work-up, aqueous solutions were always re-extracted three times with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen (or argon, where indicated) atmosphere. The purity of all compounds was established by TLC, ^1H NMR and GC–MS. Lipase from recombinant *Candida*

antarctica was a kind gift from Novo Nordisk. Lipases Amano P, Amano AY and Amano A6 were kindly donated by Amano. PPL was purchased from Sigma.

tert-*Butyl 4-acetoxy-3-(acetoxymethyl)but-2-enoate* ***8***

Sodium hydride (60% suspension in mineral oil) (1.192 g, 29.8 mmol) was washed three times under N_2 with dry *n*-hexane and suspended in dry THF (13 ml). After cooling to −30°C, a solution of *tert*-butyl diethylphosphonoacetate (7.199 g, 28.2 mmol) in dry THF (13 ml) was slowly added over 15 min. The reaction was allowed to warm slowly (over 1 h) to 0°C. After cooling again to −30°C, a solution of diacetoxyacetone (4.589 g, 26.35 mmol) in THF (13 ml) was added. The temperature was allowed to rise to 0°C and the mixture stirred at this temperature for 2 h. Quenching with saturated NH_4Cl, followed by extraction with Et_2O and chromatography (PE:Et_2O 1:1) gave pure **8** as a colorless oil (5.95 g, 83%). R_f 0.80 (Et_2O:PE 7:3, det. A, B, C). GC–MS: R_t 6.32 min. M/z: 216 (M^+−56, 4.4), 199 (M^+−73, 1.3); 157 (19.6), 156 (10.1), 143 (4.1), 114 (18.2), 97 (28.9), 96 (57.9), 57 (54.8), 43 (100). IR: ν_{max} 3002, 2980, 2940, 1735, 1705, 1655, 1450, 1390, 1367, 1325, 1200, 1140, 1055, 1030 cm^{-1}. ^1H NMR: δ 5.92 [1H, s, C*H*=C]; 5.22 [2H, s, CH_2OAc]; 4.70 [2H, s, CH_2OAc]; 2.12 and 2.08 [2×3H, 2s, CH_3C=O]; 1.49 [9H, s, c(CH_3)$_3$]. ^{13}C NMR: δ 170.35 and 170.10 [CH_3*C*=O]; 164.49 [*t*BuO–*C*=O]; 146.72 [*C*=CH]; 121.14 [*C*H=C]; 81.21 [*C*(CH_3)$_3$]; 63.88 and 60.95 [CH_2OAc]; 28.16 [C(CH_3)$_3$]; 20.78 [CH_3C=O].

tert-*Butyl 4-acetoxy-3-(acetoxymethyl)butanoate* ***9***

A solution of **8** (5.876 g, 21.58 mmol) in absolute ethanol (30 ml) and benzene (30 ml), was treated with (PPh_3)$_3$RhCl (423 mg, 0.46 mmol) and hydrogenated at r.t. and 5 atm for 48 h. The completion of the reaction was checked by GC. The suspension was concentrated and filtered through 50 g of 220–400 mesh silica gel packed with PE and eluted with PE:Et_2O 1:1 to give 5.98 g of a crude product, which was further purified by chromatography (PE:Et_2O 7:3 to 1:1), affording pure **9** as a slightly yellow oil (5.441 g, 92%). R_f 0.76 (Et_2O:PE 7:3, det. C). GC–MS: R_t 6.06 min. M/z: 219 (M^+−55, 0.4%), 218 (M^+−56, 0.3), 201 (4.3), 159 (37.1), 158 (3.8), 117 (24.7), 115 (5.5), 98 (21.4), 70 (6.2), 57 (57.1), 43 (100), 41 (18.9). IR: ν_{max} 3005, 2980, 2930, 1725, 1450, 1370, 1250, 1150, 1040 cm^{-1}. ^1H NMR: δ 4.09 [4H, d, CH_2OAc, J 5.7]; 2.51 [1H, heptuplet, C*H*, J 6.3]; 2.31 [2H, d, CH_2COO, J 7.1]; 2.06 [6H, s, CH_3C=O]; 1.46 [9H, s, C(CH_3)$_3$]. ^{13}C NMR: δ 170.66 (*C*=O), 80.95 [*C*(CH_3)$_3$]; 63.80 [CH_2O]; 34.64, 34.45 [CH_2CO, *C*H]; 28.71 [C(CH_3)$_3$]; 20.78 [CH_3CO].

tert-*Butyl 4-hydroxy-3-(hydroxymethyl)butanoate* ***10***

Diacetate **9** (2.02 g, 7.36 mmol) was suspended in water (360 ml) and 0.067 M pH 7 phosphate buffer (10 ml) and treated with *Candida antarctica* lipase (118 mg). The suspension was maintained at pH 7 by continuous addition of 0.5 N NaOH from an automatic burette. After 23 h the mixture was saturated with NaCl and filtered through a Celite cake, washing several times with AcOEt. The phases were separated and the organic one gave, after evaporation and chromatography (AcOEt:PE 9:1), pure **10** as a liquid. R_f 0.14 (AcOEt:PE 1:1). GC–MS: R_t 4.56 min. M/z: 160 (M^+−30, 0.6%), 135 (1.5), 134 (M^+−56, 1.3), 117 (48.0), 116 (10.3), 115 (10.8), 104 (19.3), 99 (8.7), 98 (33.4), 97 (6.4), 86 (21.8), 71 (11.2), 59 (18.8), 57 (100), 56 (14.5), 55 (10.4), 43 (20.3), 41 (37.8). ^1H NMR: δ 3.78 and 3.72 [4H, AB part of an ABX syst., CH_2OH, J_{AB} 10.5, J_{AX} 4.1, J_{BX} 5.6]; 2.40–2.15 [3H, m, C*H* and C*H*C=O]; 1.46 [9H, s, C(CH_3)$_3$]. ^{13}C NMR: δ 172.87 [*C*=O]; 81.06 [*C*(CH_3)$_3$]; 63.97 [CH_2O]; 39.8 and 34.85 [CH_2CO and *C*H]; 28.14 [C(CH_3)$_3$].

(S)-tert-*Butyl 4-acetoxy-3-(hydroxymethyl)butanoate* ***11***

Diacetate **9** (5.432 g, 19.8 mmol) was dissolved in diisopropyl ether (170 ml) and added to water (850 ml) and 0.067 M pH 7 phosphate buffer (80 ml). Crude pig pancreatic lipase (PPL) (4.33 g) was added and the resulting suspension was stirred at 20°C, while maintaining the pH constant at 7 through continuous addition of 0.5 N NaOH from an automatic burette. After consumption of 42.5 ml of NaOH, the reaction was worked out as described for the preparation of **10**. Chromatography

(PE:AcOEt 7:3 to 1: 9) gave pure (*S*)-**11** as a colorless liquid (3.20 g, 69.5%), along with recovered **9** (606 mg, 11%) and diol **10** (513 mg, 14%). The e.e. of **11**, determined by ^{1}H NMR in the presence of Eu(hfc)$_3$ (5 mg/mg **11**) by integration of the C(CH_3)$_3$ singlets was 97.0%. $[\alpha]_D$: −5.10 (c 1.9, $CHCl_3$) R_f 0.37 (Et_2O:PE 7:3), 0.50 (AcOEt:PE 1:1). GC–MS: R_t 5.38 min. M/z: 177 (M^+−55, 0.7%), 176 (M^+−56, 1.0), 159 (19.6), 146 (8.7), 117 (75.0), 116 (14.6), 115 (14.4), 98 (36.8), 86 (25.4), 70 (9.8), 61 (11.1), 59 (19.1), 57 (100), 56 (12.6), 43 (91.0), 41 (31.1). IR: ν_{max} 3620, 3500 (broad), 3020, 2980, 2930, 1720, 1450, 1390, 1368, 1222, 1150, 1040, 975, 960 cm^{-1}. ^{1}H NMR: δ 4.20–4.10 [2H, m, CH_2OAc]; 3.70–3.55 [2H, m, CH_2OH]; 2.40–2.15 [3H, m, CH_2C=O, C*H*]; 2.08 [3H, s, CH_3C=O]; 1.46 [9H, s, C(CH_3)$_3$]. ^{13}C NMR: δ 171.83, 170.90 [*C*=O]; 81.04 [*C*(CH_3)$_3$]; 64.20, 62.61 [*C*H_2O]; 37.66 [*C*H]; 34.85 [*C*H_2C=O]; 28.14 [C(*C*H_3)$_3$]; 20.88 [*C*H_3–C=O].

*(R)-*tert*-Butyl 4-acetoxy-3-(hydroxymethyl)butanoate **11***

A solution of diol **10** (502 mg, 2.64 mmol) in diisopropyl ether (40 ml), was treated with 3 Å powdered molecular sieves (30 mg). After stirring for 15 min. under N_2, vinyl acetate (2.5 ml) and Amano P lipase (400 mg) were added. The suspension was stirred at 20°C for 1 h 55 min., then filtered, washing the filter with Et_2O. The crude product was chromatographed as described for the (*S*) enantiomer, to give pure (*R*)-**11** as a colorless liquid (522 mg, 85%). E.e.: 97.9%.

*(R)-3-(Acetoxymethyl)-4-butanolide **2***

A solution of (*S*)-**11** (48.6 mg, 209 μmol) in dry CH_2Cl_2 (0.5 ml) was cooled to −20°C and treated with CF_3COOH (0.5 ml). After 1 h at 0°C and 2 h at r.t., the reaction was quenched with saturated $NaHCO_3$ and extracted with AcOEt to give, after chromatography (AcOET:PE 1:1 to 3:2) pure **2** as an oil (29 mg, 88%). R_f 0.36 (PE:AcOEt 1:1). $[\alpha]_D$ −25.8 (c 1, $CHCl_3$): (lit.:[5b] −25.3° for a sample of 89% e.e.). The other physical data were coincident with those reported.[5b]

*(R)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-butanolide **13***

(a) A solution of monoacetate (*S*)-**11** (529 mg, 2.28 mmol) in dry DMF (2.5 ml) was cooled to 0°C and treated with imidazole (392 mg, 5.76 mmol) and *tert*-butyldiphenylsilyl chloride (0.80 ml, 3.07 mmol). After stirring for 10 min. at 0°C and 4 h at r.t., the mixture was poured into saturated NH_4Cl:H_2O 1:3 and extracted with Et_2O to give, after chromatography (PE:Et_2O 8:2), compound **12** as an oil, with Ph_2tBuSiOH present as an impurity, which was very difficult to separate chromatographically (1.267 g, 118%). R_f 0.76 (PE:AcOEt 3:1, det. C). This product was taken up in THF (30 ml) and H_2O (10 ml) and treated with LiOH (218 mg, 9.12 mmol). The mixture was stirred for 48 h at r.t., quenched with a 5% (NH_4)H_2PO_4 buffer solution, extracted with AcOEt and evaporated to dryness. The residue was taken up in dry CH_2Cl_2 (25 ml) and treated with Et_3N (953 μl, 6.84 mmol) and solid N-methyl 2-chloropyridinium iodide (700 mg, 2.74 mmol). After stirring for 2 h at r.t. the mixture was poured into saturated NaCl and extracted with Et_2O to give, after evaporation and chromatography (PE:AcOEt 8:2), pure **13** as an oil (554 mg, 69%). R_f 0.51 (PE:AcOEt 3:1, det. C). $[\alpha]_D$ +11.9 (c 2, $CHCl_3$). The e.e., determined by ^{1}H NMR in the presence of Eu(hfc)$_3$, was found to be 84%.

(b) A solution of alcohol (*R*)-**14** (72 mg, 168 μmol) in dry CH_2Cl_2 (0.5 ml) was cooled to −20°C and treated with trifluoroacetic acid (0.5 ml). After stirring for 3 h at room temperature the solution was quenched with saturated $NaHCO_3$ (20 ml) and extracted with AcOEt to give, after chromatography, pure **13** (30 mg, 50%). $[\alpha]_D$ +10.3 (c 2, $CHCl_3$).

GC–MS: R_t 10.69 min. M/z: 297 (M^+−57, 100%), 267 (2.9), 253 (4.0), 249 (3.5), 219 (6.5), 199 (54.6), 189 (10.9), 181 (12.6), 167 (4.8), 161 (13.1), 141 (7.4), 139 (66.8), 135 (7.7), 123 (6.5), 117 (13.2), 115 (8.5), 104 (14.6), 91 (16.1), 77 (14.8), 55 (23.2), 45 (12.0), 41 (12.5). IR: ν_{max} 3005, 2955, 2930, 2900, 2860, 1776, 1167, 1110, 1000 cm^{-1}. ^{1}H NMR: δ 7.70–7.55 [4H, m, aromatics]; 7.47–7.30 [6H, m, aromatics]; 4.38 and 4.23 [2H, AB part of an ABX syst., CH_2–C=O, J_{AB} 9.1, J_{AX} 7.5, J_{BX} 5.2]; 3.66 [2H, d, CH_2OSi, J 5.5]; 2.84–2.62 [1H, m, C*H*]; 2.56 and 2.41 [2H, AB part of an ABX syst., J_{AB} 17.4, J_{AX} 8.7, J_{BX} 6.2]; 1.06 [9H, s, (CH_3)$_3$C]. ^{13}C NMR: δ 176.9 [*C*=O]; 135.45, 132.83,

129.9, 127.83 [aromatics], 70.52, 64.17 [CH_2O]; 37.31 [*C*H]; 30.84 [$CH_2C{=}O$]; 26.82 [$C(CH_3)_3$]; 19.25 [$C(CH_3)_3$].

*(R)-*tert*-Butyl 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxybutanoate* ***14***

A solution of crude **12** obtained as above (starting from 529 mg, 2.28 mmol of (*S*)-**11**) in dry THF (15 ml) was cooled to −78°C and treated dropwise with a 3.5 M solution of sodium bis(methoxyethoxy)aluminium hydride (Red-Al) in toluene (2.5 ml, 8.75 mmol). After stirring for 4 h and 30 min. at the same temperature, the mixture was quenched with saturated NH_4Cl. After warming to room temperature, an aqueous solution of sodium potassium tartrate was added and the mixture stirred for 30 min. and then extracted with Et_2O, to give, after the usual work-up and chromatography (PE:AcOEt 8:2) pure **14** as an oil (705 mg, 72%). R_f 0.48 (PE:AcOEt 75:25, det. C). $[\alpha]_D$ +0.9 (c 1, $CHCl_3$). GC–MS: R_t 10.842. M/z: 355 (M^+-73, 1.8%), 315 (2.9), 297 (100), 237 (30.9), 219 (7.2), 199 (57.7), 197 (8.6), 189 (8.2), 183 (9.2), 181(13.3), 161 (11.2), 139 (58.8), 135 (10.5), 123 (6.0), 117 (11.0), 115 (7.5), 105 (13.6), 91 (13.9), 77 (13.2), 59 (32.7), 57 (15.6), 55 (21.4), 45 (9.7), 41 (17.7). ^{1}H NMR: δ 7.70–7.60 [4H, m, aromatics]; 7.50–7.35 [6H, m, aromatics]; 3.81–3.62 [4H, m, CH_2O]; 2.41–2.17 [3H, m, *C*H and $CH_2C{=}O$]; 1.41 [9H, s, $OC(CH_3)_3$]; 1.06 [9H, s, $SiC(CH_3)_3$]. ^{13}C NMR: δ 172.30 [*C*=O]; 135.50, 133.18, 129.76, 127.75 [aromatics]; 80.63 [$OC(CH_3)_3$]; 65.43, 64.64 [CH_2O]; 39.92 [*C*H]; 34.79 [$CH_2C{=}O$]; 28.14, 26.92 [$C(CH_3)_3$]; 19.29 [Si–$C(CH_3)_3$].

*(S)-*tert*-Butyl 4-acetoxy-3-(((benzyloxy)methoxy)methyl)butanoate* ***15***

A solution of monoacetate (*S*)-**11** (2.042 g, 8.79 mmol) in dry CH_2Cl_2 (35 ml) was cooled to 0°C and treated sequentially with $EtN(iPr)_2$ (2.60 ml, 14.9 mmol) and redistilled benzyloxymethyl chloride (1.80 ml, 12.9 mmol). After 30 min. the cooling bath was removed and the solution stirred at r.t. for 8 h. Diethylamine (4.5 ml) was added and the solution stirred for 30 min., diluted with saturated NaCl and extracted with Et_2O. The dried (Na_2SO_4) organic phase was briefly evaporated to dryness and suddenly chromatographed (PE:Et_2O:Et_3N 60:39:1) to give pure **15** as an oil (2.90 g, 94%). R_f 0.49 (PE:Et_2O 6:4, det. A, B, C). $[\alpha]_D$ +1.1 (c 2, $CHCl_3$). GC–MS: R_t 9.27. M/z: 296 (M^+-56, 0.2%), 249 (M^+-103, 4.9), 190 (13.1), 189 (9.8), 159 (19.6), 130 (11.4), 129 (11.0), 120 (21.5), 119 (11.2), 117 (27.6), 115 (13.0), 91 (100), 57 (23.5), 43 (21.5). IR: ν_{max} 3040, 2980, 2935, 2880, 1725, 1453, 1390, 1369, 1238, 1153, 114, 1042 cm^{-1}. ^{1}H NMR: δ 7.40–7.25 [5H, m, aromatics]; 4.74 [2H, s, CH_2]; 4.58 [2H, s, CH_2]; 4.14 and 4.10 [2H, AB part of an ABX syst., CH_2OAc, J_{AB} 11.0, J_{AX} 5.9, J_{BX} 5.4]; 3.59 [2H, d, CH_2OBOM, J 5.4]; 2.57–2.23 [3H, m, *C*H and CH_2COO]; 2.04 [3H, s, $CH_3C{=}O$]; 1.45 [9H, s, $C(CH_3)_3$]. ^{13}C NMR: δ 171.22, 170.85 [*C*=O]; 137.71, 128.37, 127.76 [aromatics]; 94.68 [O–*C*–O]; 80.64 [$C(CH_3)_3$]; 69.35, 67.45, 64.34 [CH_2O]; 35.41, 34.86 [*C*H and $CH_2C{=}O$]; 28.15 [$C(CH_3)_3$]; 20.88 [$CH_3C{=}O$].

*(R)-*tert*-Butyl 3-(((benzyloxy)methoxy)methyl)-4-hydroxybutanoate* ***16***

Acetate **15** (784 mg, 2.22 mmol) was suspended in 0.1 M pH 7 buffer (K_2HPO_4–KH_2PO_4)(80 ml), warmed to 40°C and treated with lipase Amano AY (900 mg). The mixture was stirred at the same temperature until complete (24–40 h). The suspension was saturated with NaCl, filtered through a Celite cake, washing with AcOEt and the filtrate extracted with AcOEt. The crude product was chromatographed (PE:Et_2O 4:6) to give pure **16** as an oil (572 mg, 83%. R_f 0.29 (PE:Et_2O 1:1 det. B). $[\alpha]_D$ +4.35 (c 2, $CHCl_3$). GC–MS: R_t 8.86. M/z: 254 (M^+-56, 0.1%), 207 (M^+-103, 3.2); 148 (16.4), 147 (8.4), 129 (16.3), 120 (14.9), 119 (9.1), 117 (16.6), 115 (10.6), 107 (10.3), 91 (100), 85 (13.6), 59 (13.3), 57 (27.9), 41 (14.0). IR: ν_{max} 3620, 3530, 3000, 2981, 2931, 2886, 1715, 1601, 1453, 1412, 1392, 1369, 1295, 1151, 1114, 1039, 963, 907 cm^{-1}. ^{1}H NMR: δ 7.40–7.25 [5H, m, aromatics]; 4.75 [2H, s, CH_2]; 4.60 [2H, s, CH_2]; 3.75–3.57 [44H, m, CH_2O]; 2.38–2.24 [3H, m, *C*H and $CH_2C{=}O$]; 1.45 [9H, s, $C(CH_3)_3$]. ^{13}C NMR: δ 172.19 [*C*=O]; 137.70, 128.42, 127.81 [aromatics]; 94.85 [O–*C*–O]; 80.68 [$C(CH_3)_3$]; 69.63, 69.39, 64.32 [CH_2O]; 38.14 [*C*H]; 35.02 [$CH_2C{=}O$]; 28.12 [$C(CH_3)_3$].

(S)-3-(((Benzyloxy)methoxy)methyl)-4-butanolide ***17***

(a) A solution of alcohol **16** (111 mg, 358 μmol) in dry CH_2Cl_2 (1 ml) was cooled to 0°C and treated with CF_3CO_2H (1 ml). The solution was stirred for 20 min., then suddenly evaporated to dryness. The residue was taken up with *n*-heptane and re-evaporated twice in order to remove azeotropically the last traces of CF_3CO_2H. Chromatography (PE:Et_2O 1:9) gave pure **17** as an oil (59 mg, 70%).

(b) Alternatively it was prepared from **15** in 61% overall yield, by following the same procedure already described for **13** (method a). R_f 0.53 (Et_2O, det. A, B). $[\alpha]_D$ +23.0 (C 1.27, $CHCl_3$). GC–MS: R_t 7.93. M/z: 160 (M^+-76, 0.3%), 120 (29.4), 119 (9.8), 108 (12.0), 91 (100), 72 (8.4), 70 (12.8), 65 (10.4), 43 (19.7). ^{1}H NMR: δ 7.35 [5H, s, aromatics]; 4.77 [2H, s, CH_2]; 4.60 [2H, s, CH_2]; 4.41 [1H, dd, CHHOC=O, J 9.2, 7.5]; 4.15 [1H, dd, CHHOC=O, J 9.2, 5.5]; 3.62 and 3.59 [2H, AB part of an ABX syst., CH_2OBOM, JAB 9.8, J_{AX} 5.5, J_{BX} 6.4]; 2.93–2.70 [1H, m, CH]; 2.62 [1H, dd, CHH–C=O, J 17.5, 8.9]; 2.36 [1H, dd, CHH–C=O, J 17.5, 6.2].

*(S)-*tert*-Butyl 3-(((benzyloxy)methoxy)methyl)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate* ***18***

It was prepared in 92% yield from **16** following the same procedure already described for the synthesis of **12**. R_f 0.59 (PE:Et_2O 8:2). $[\alpha]_D$ −3.0 (c 2, $CHCl_3$). GC–MS: not feasible. IR: ν_{max} 3008, 2980, 2960, 2931, 2856, 1720, 1605, 1368, 1261, 1153, 1112, 1043 cm^{-1}. ^{1}H NMR 7.70–7.60 [4H, m, aromatics]; 7.45–7.25 [11H, m, aromatics]; 4.71 [2H, s, CH_2]; 4.56 [2H, s, CH_2]; 3.74–3.58 [4H, m, CH_2O]; 2.46–2.26 [3H, m, CH and CH_2–C=O]; 1.41 [9H, s, $OC(CH_3)_3$]; 1.05 [9H, s, $SiC(CH_3)_3$]. ^{13}C NMR: δ 172.01 [C=O]; 137.83, 135.52, 133.56, 129.59, 128.37, 127.82, 127.64 [aromatics]; 94.74 [O–C–O]; 80.22 [$OC(CH_3)_3$]; 69.23, 67.89, 63.49 [CH_2O]; 38.53 [CH]; 34.75 [CH_2–C=O]; 28.15, 26.93 [$C(CH_3)_3$]; 19.37 [Si–$C(CH_3)_3$].

(R)-2-(((Benzyloxy)methoxy)methyl)butane-1,4-diol ***19***

A solution of lactone **17** (31.9 mg, 135 μmol) in dry Et_2O (2 ml), was treated with $LiAlH_4$ (17 mg, 448 μmol) and stirred at r.t. for 2 h. The reaction was quenched with AcOEt (200 μl) and then saturated aqueous NH_4Cl and aqueous sodium potassium tartrate. Extraction with AcOEt gave, after the usual work-up and chromatography (AcOEt:MeOH 98:2 to 96:8) pure **19** as an oil (31.6 mg, 98%). R_f 0.29 (AcOEt, det. A, B). $[\alpha]_D$ +5.9 (c 1, $CHCl_3$). ^{1}H NMR: δ 7.42–7.28 [5H, m, aromatics]; 4.77 [2H, s, CH_2]; 4.61 [2H, s, CH_2]; 3.83–3.56 [4H, m, CH_2O]; 2.00 [1H, heptuplet, CH, J 6.0]; 1.66 [2H, q, CH_2CH_2OH, J 6.1].

This diol was converted, by reaction with (*S*) or (*R*) camphanoyl chlorides in CH_2Cl_2 in the presence of 4-dimethylaminopyridine, into both (*R*) and (*S*) camphanoates. ^{1}H NMR analysis on them showed the presence of only one diastereoisomer in either case. The e.e. was estimated to be >95% according to the detection limits.

*(R)-*tert*-Butyl 4-((*tert*-butyldiphenylsilyl)oxy)-3-((((4-methoxyphenyl)methoxy)methoxy)methyl)-butanoate* ***20***

(*R*)-**14** (307 mg, 716 μmol) was converted into (*R*)-**20** by the same procedure used for the synthesis of **15**, using *p*-methoxybenzyloxymethyl chloride[16] (PMBOM–Cl) instead of benzyloxymethyl chloride. Yield: 83%. R_f 0.67 (PE:Et_2O 1:1, det. C). ^{1}H NMR: δ 7.70–7.60 [4H, m, aromatics]; 7.55–7.30 [6H, m, aromatics]; 7.24 [2H, d, aromatics *meta* to OCH_3, J 8.6]; 6.86 [2H, d, aromatics *ortho* to OCH_3, J 8.6]; 4.68 [2H, CH_2]; 4.48 [2H, s, CH_2]; 3.80 [3H, s, OCH_3]; 3.75–3.57 [4H, m, CH_2O]; 2.46–2.25 [43H, m, CH and CH_2C=O]; 1.41 [9H, s, $OC(CH_3)_3$]; 1.05 [9H, s, $SiC(CH_3)_3$].

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