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TETRAHEDRON: *ASYMMETRY*

Asymmetrization of all-*cis*-3,5-dihydroxy-1-(methoxycarbonyl)cyclohexane and of the 4-methyl and 4-ethyl substituted homologues

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Abstract

Enantiomerically pure mono acylated derivatives of *cis*,*cis*-3,5-dihydroxy-1-(methoxycarbonyl)-cyclohexane **1**, all-*cis*-3,5-dihydroxy-4-methyl-1-(methoxycarbonyl)cyclohexane **2** and all-*cis*-3,5-dihydroxy-4-ethyl-1-(methoxycarbonyl)cyclohexane **3** were obtained upon lipase catalyzed asymmetrization. PPL-catalyzed transesterification of **1** with vinyl acetate led in high yield to the (*S*)-monoacetate (+)-**13**. With substrates **2** and **3** this process was slower and gave the (*R*)-monoacetates (−)-**14** and (−)-**15**; the best results were obtained with SAM II lipase. On the other hand, enantiotoposelective hydrolysis of their diacetates and especially dibutyrates gave useful results only for the 4-substituted substrates and produced the (*S*)-monoesters.

1. Introduction

In the context of a program directed towards enantioselective total synthesis of natural products and analogues thereof containing a cyclohexane ring, we decided to study the asymmetrization of *meso* all-*cis*-3-5-dihydroxy-1-(methoxycarbonyl)cyclohexanes **1**, **2** and **3**. Of special interest to us was the eventual synthesis of 19-*nor* vitamin D analogues in which the title compounds could be precursors for the A-ring.[1] Previously we have described the asymmetrization of **4**,[2] **5**[2] and **6**[1] and the transformation of **6** into precursor **12** for the synthesis of 19-*nor*-1α,25-dihydroxy-vitamin D_3 (**11**; R = H) (Scheme 1).

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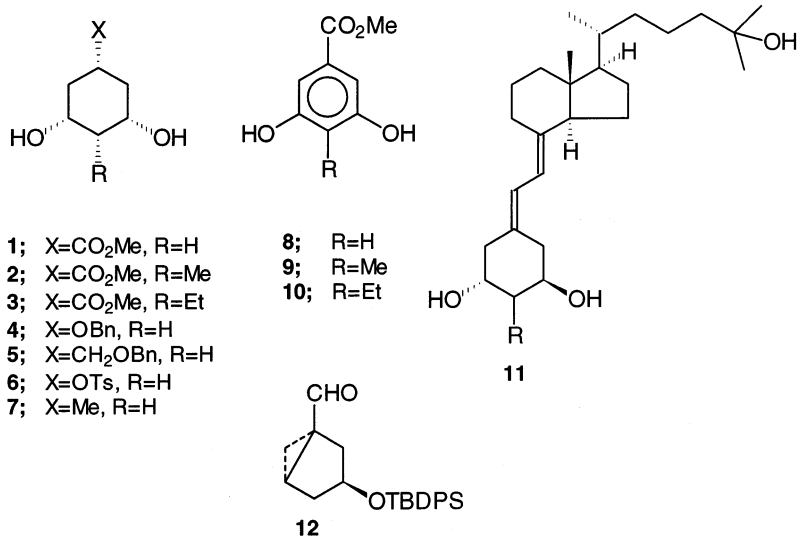


1; X=CO_2Me, R=H
2; X=CO_2Me, R=Me
3; X=CO_2Me, R=Et
4; X=OBn, R=H
5; X=CH_2OBn, R=H
6; X=OTs, R=H
7; X=Me, R=H

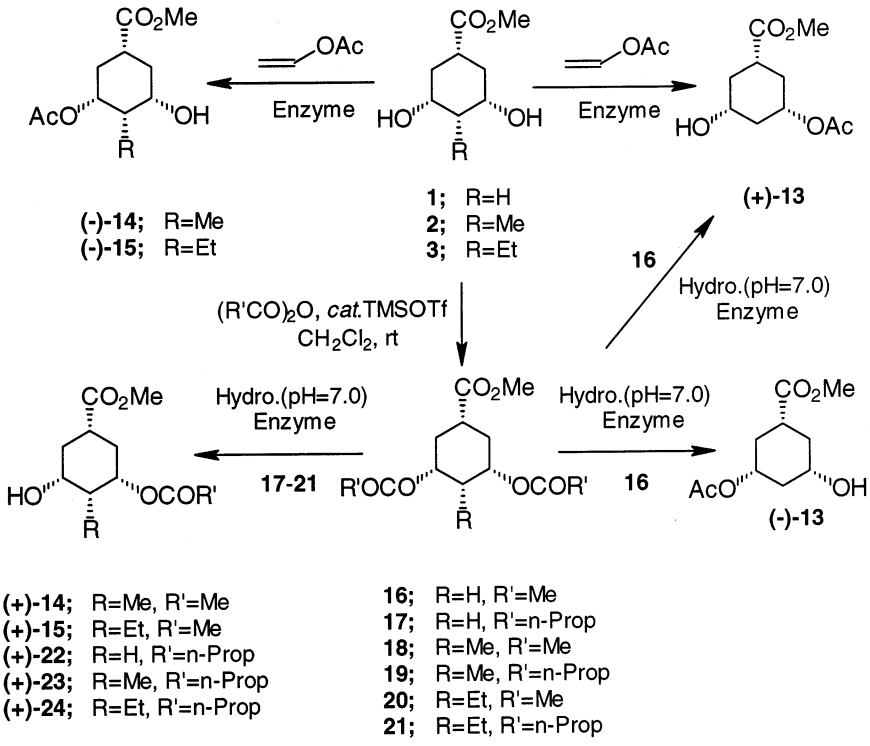
8; R=H
9; R=Me
10; R=Et

Scheme 1.

2. Results and discussion

The all-*cis* substrates **1**, **2** and **3** are readily available upon hydrogenation of the corresponding methyl benzoates **8**, **9** and **10**. The formation of *cis*,*cis*-3,5-dihydroxy-1-(methoxycarbonyl)cyclohexane **1** has already been reported by Wang and Adams[3] via Rh/Al_2O_3 catalyzed hydrogenation of 3,5-dihydroxybenzoic acid. We found that hydrogenation of the methyl esters[4] **8**, **9** and **10** is a superior method, e.g. starting from **8** essentially the same yield is obtained but only half the amount of catalyst can be used and the process is quite clean (spot to spot on TLC) allowing the recovery of circa 25–30% of the starting materials.

For the asymmetrization studies, both transesterifications of **1**, **2** and **3** (Table 1) and hydrolysis of the corresponding diacetates **16**, **18**, **20** (Table 2) and dibutyrates **17**, **19** and **21** (Table 3) were investigated (Scheme 2). Vinyl acetate mediated acylation (Table 1) of *cis*,*cis*-3,5-dihydroxy-1-(methoxycarbonyl)cyclohexane **1** led to an excellent result with PPL[5] as the lipase (Table 1, entry 2). Indeed after 24 h at room temperature enantiomerically pure monoacetate (+)-**13** was obtained in high yield, the hydroxy function on the (*S*)-stereogenic centre being acylated (vide infra). This process has been carried out on a 400 g scale. The enantiomeric excess (e.e.) was determined by subcritical fluid chromatography (SFC),[6] no enantiomer could be detected. The other enzymes[5] tested gave unsatisfactory results (entries 3–7) as substantial amounts of diacetate **16** were formed, while the enantiomeric excesses obtained for **13** were lower than for PPL. As is shown for the reaction performed with SAM II lipase, formation of **16** could, to a large extent, be suppressed (compare entries 3, 4 and 5) upon lowering the temperature. It is evident that mono-acetylation employing inexpensive PPL is the method of choice for the asymmetrization of **1**, also when compared to the enantioselective hydrolysis of the diesters **16** and **17** (vide infra). The reaction was also carried out on 10 g scale with EtOAc as solvent and 10 equiv. of vinyl acetate; the same result as shown in entry 2 was obtained.



(+)-14; R=Me, R'=Me
(+)-15; R=Et, R'=Me
(+)-22; R=H, R'=n-Prop
(+)-23; R=Me, R'=n-Prop
(+)-24; R=Et, R'=n-Prop

16; R=H, R'=Me
17; R=H, R'=n-Prop
18; R=Me, R'=Me
19; R=Me, R'=n-Prop
20; R=Et, R'=Me
21; R=Et, R'=n-Prop

Scheme 2.

Transesterification of the 4-alkyl substituted substrates **2** and **3** proceeds much slower and leads, in contrast to **1**, to the acetylation of the *R* hydroxy group (vide infra). Remarkably, PPL did not catalyze the reaction of **2** and **3** (entries 8 and 14). As can be seen from Table 1, as a general trend, the steric inhibition of the 4-ethyl substituent in **3** pushes the catalytic process to its limits (compare for instance entries 13 and 18). Nevertheless SAM II lipase catalyzed acetylation provides a practical process, as enantiopure monoacetates (–)-**14** (entry 13) and (–)-**15** (entry 18) were obtained in 92 and 67% yield, respectively.

We then turned our attention to the enantiotoposelective hydrolysis of the respective diacetates **16**, **18** and **20** (Table 2) and dibutyrates **17**, **19** and **21** (Table 3). The experiments were carried out in phosphate buffer (0.1 M) at pH 7 by continuous addition of NaOH (1 M) and monitored by a pH-stat-autotitrator. It was soon observed that the diesters **16** and **17** were poor substrates. Depending on the enzymes tested, both enantiomers of **13** were obtained starting from **16** (Table 2, entries 1–7). Only the lipases SAM II and PSL showed some selectivity (Table 2, entries 1 and 2) but unexpectedly produced (+)-**13** and (+)-**22** by hydrolysis of the (*R*)-acyloxy group, thus providing the same enantiomeric series as the transesterification of **1**.

In sharp contrast are the good to excellent selectivities obtained with several enzymes for the 4-substituted 3,5-diacyloxy-1-(methoxycarbonyl)cyclohexanes. In accordance with the general trend the hydrolyses take place at the same stereocenter (*R*), as observed for the acylation of diols **2** and **3**, thus providing an entry to both enantiomeric series. When a methyl group is present the diacetate **18** (Table 2, entries 8–13) is a poorer substrate than the dibutyrate **19** (Table 3, entries 8–13); in the latter case SAM II, PSL and CCL catalyzed hydrolysis gave

Table 1
Acylation with vinyl acetate

Entry	Subst.	Enz.[5]	t (h)	T (°C)	Ester (y %)[a]		Conv. (%)[b]	$[\alpha]_D^{20}$	% e.e.[c]
					Mono	Di			
1	**1**	PPL	24	15	(+)-**13** (31)		41	+23.4	
2	**1**	PPL	24	rt	(+)-**13** (97)		95	+23.6	>99
3	**1**	SAM II	48	35		**16** (95)	98		
4	**1**	SAM II	72	25	(+)-**13** (63)	**16** (30)	95	+14	
5	**1**	SAM II	72	15	(+)-**13** (73)	**16** (~5)	85	+14.5	
6	**1**	PSL	26	rt	(+)-**13** (33)	**16** (60)	95	+18	
7	**1**	CCL	26	rt	(+)-**13** (46)	**16** (47)	95	+22	
8	**2**	PPL	72	rt					
9	**2**	CCL	96	rt	(−)-**14** (33)		35	−17	70
10	**2**	GCL	96	rt					
11	**2**	PSL	96	rt	(−)-**14** (50)		93	−21.5	93
12	**2**	SAM II	72	rt	(−)-**14** (42)		92	−22.7	>99
13	**2**	SAM II	120	rt	(−)-**14** (92)		95	−22.5	
14	**3**	PPL	96	rt					
15	**3**	PSL	96	rt					
16	**3**	CCL	120	rt	(−)-**15** (19)		95	−46.4	
17	**3**	SAM II	96	rt	(−)-**15** (53)		92	−50.2	>99
18	**3**	SAM II	134	35	(−)-**15** (67)		91	−51	

[a] Isolated yield of pure product.
[b] Calculated upon recovery of starting material.
[c] Determined by SFC[6] for the processes leading to high specific rotations.

Table 2
Hydrolysis of diacetates **16**, **18** and **20**

Entry	Subst.	Enz.[5]	t (h)	T (°C)	Prod. (y)[a]	$[\alpha]_D^{20}$	% e.e.[b]
1	**16**	SAM II	90	rt	(+)-**13** (39)	+18.1	77
2	**16**	PSL	47	25	(+)-**13** (37)	+17.5	
3	**16**	PPL	86	30	(−)-**13** (26)	−4.3	
4	**16**	PLE	6	rt	(−)-**13** (31)	−9.7	
5	**16**	CCL	1	rt	**1**		
6	**16**	GCL	72	25	(−)-**13** (11)	−3.2	
7	**16**	CAL	27	25	(−)-**13** (25)	−4.1	
8	**18**	SAM II	46	25	(+)-**14** (49)	+19.9	88
9	**18**	PSL	44	25	(+)-**14** (72)	+19.8	
10	**18**	PPL	42	25	(−)-**14** (49)	−6.2	
11	**18**	PLE	2	rt	(+)-**14** (37)	+18.8	
12	**18**	CCL	40	25	(−)-**14** (63)	−3	
13	**18**	CAL	47	rt	(+)-**14** (54)	+12.6	
14	**20**	SAM II	70	25	(+)-**15** (38)	+47.1	
15	**20**	PSL	80	25	–	–	
16	**20**	PPL	49	25	(+)-**15** (25)	+41.1	
17	**20**	PLE	3	rt	(+)-**15** (72)	+50.4	>99
18	**20**	CCL	29	25	(+)-**15** (58)	+48	
19	**20**	CAL	42	25	(+)-**15** (76)	+48.5	

[a] Isolated yield of pure product.
[b] Determined by SFC[6] for the processes leading to high specific rotations.

Table 3
Hydrolysis of dibutyrates **17**, **19** and **21**

Entry	Subst.	Enz.[5]	t (h)	T (°C)	Prod. (y)[a]	$[\alpha]_D^{20}$	% e.e.[b]
1	**17**	SAM II	17	rt	(+)-**22** (69)	+15.9	66
2	**17**	PSL	20	25	(+)-**22** (63)	+18.2	
3	**17**	PPL	15	30	(+)-**22** (74)	+8.9	
4	**17**	PLE	5	rt	**1**		
5	**17**	CCL	3	25	(−)-**22** (31)	−3.0	
6	**17**	GCL	63	25	(−)-**22** (13)	−3.7	
7	**17**	CAL	3	25	(+)-**22** (48)	+6.5	
8	**19**	SAM II	18	25	(+)-**23** (91)	+16.5	
9	**19**	PSL	23	25	(+)-**23** (89)	+16.4	>99
10	**19**	PPL	21	25	(+)-**23** (65)	+14.5	
11	**19**	PLE	3	rt	(+)-**23** (15)	+15.2	
12	**19**	CCL	18	25	(+)-**23** (53)	+16.3	
13	**19**	CAL	10	25	(+)-**23** (89)	+12.9	
14	**21**	SAM II	69	25	(+)-**24** (88)	+44.6	>99
15	**21**	PSL	48	25	(+)-**24** (84)	+44.4	
16	**21**	PPL	22	25	(+)-**24** (49)	+33.2	87
17	**21**	PLE	2	rt	(+)-**24** (26)	+38.5	
18	**21**	CCL	23	25	(+)-**24** (78)	+44.5	
19	**21**	CAL	10	25	(+)-**24** (82)	+42.2	

[a] Isolated yield of pure product.
[b] Determined by SFC[6] for the processes leading to high specific rotations.

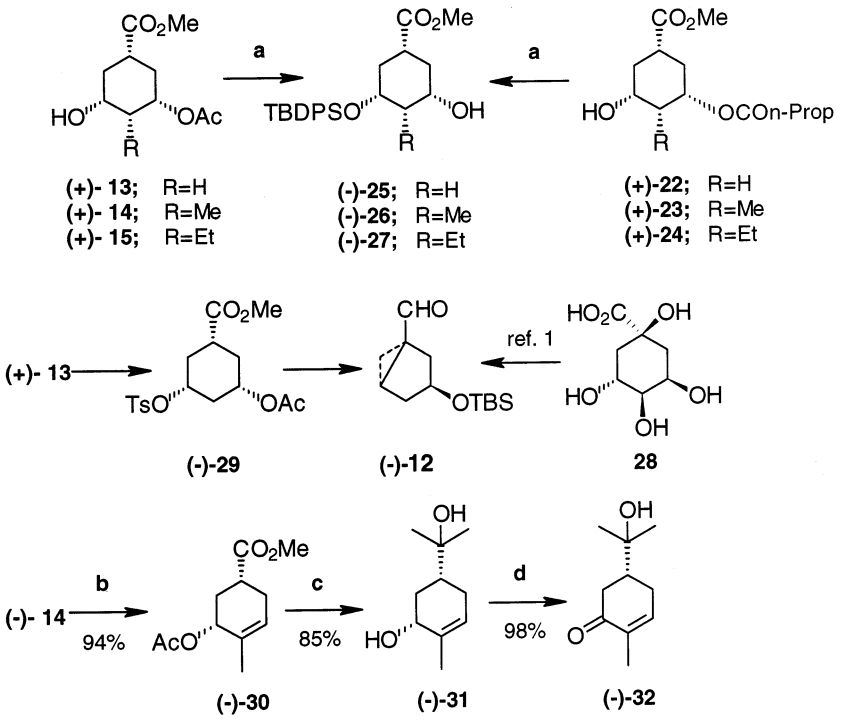
enantiopure (+)-**23** in high yield. The 4-ethyl substituted diesters **20** and **21** are the best substrates, e.g. PLE mediated mono-hydrolysis (Table 2, entry 17) is fast and completely enantiotoposelective. Similar to **19**, dibutyrate **21** is hydrolyzed to pure (+)-**24** by the same enzymes (SAM II, PSL and CCL; Table 3, entries 14, 15 and 18).

In conclusion, preparatively useful enantioselectivies were found for the acylation of diol **1** for the 4-methyl or 5-ethyl substituted homologues **2** and **3** (Table 1, entries 2, 13 and 18). In the same case of **1** the (*S*)-acetate is formed, while **2** and **3** produced the (*R*)-acetates. This is a formal discrepancy, as although, in **1** the 5-hydroxy group takes priority in the CIP rule, steric inhibition via C-2 (larger 1-carbomethoxy) being more important. In **2** and **3** the difference in substitution pattern around the hydroxy functions is more pronounced. Similar observations have previously been made in the case of the asymmetrization process of **4**, **5** and **6**.[1,2]

Also the PLE-catalyzed selective hydrolysis of diacetate **20** (Table 2, entry 17) and of dibutyrates **19** and **21**, employing SAM II, PSL and CCL (Table 3, entries 8, 9, 12, 14, 15 and 18) provide a preparatively useful entry into the enantiomeric series. On the other hand, hydrolysis of the 4-unsubstituted diesters **16** and **17** gave poor results, probably due to the similar size of the acyloxy- and the methoxycarbonyl substituents. The best ones (Tables 2 and 3, entries 1 and 2) produced, respectively, the (*R*)-alcohols (+)-**13** [as for **1** to (+)-**13**] and (+)-**22**. It is noteworthy that while 3,5-dihydroxy-4-ethyl-1-(methoxycarbonyl)cyclohexane **3** was the poor substrate in the transesterification process, the corresponding diacetate **20** and dibutyrate **21** are the better substrates in the enantiotoposelectivity hydrolysis. Seemingly the 4-ethyl

substituent in **20** and **21** provides optimum differentiation of the substitution pattern around C_3 and (or) C_5. In all cases, interference occurring from possible concomitant hydrolysis of the carbomethoxy group was not observed. It can also be noted that no selectivity could be found for either transesterification of 3,5-dihydroxy-1-methylcyclohexane **7** or hydrolysis of its diacetate.

In order to ascertain that the monobutyrates (+)-**22**, (+)-**23** and (+)-**25** belonged to the same enantiomeric series as the corresponding monoacetates (+)-**13**, (+)-**14** and (+)-**15**, the respective pairs were transformed into the TBDPS ethers (−)-**25**, (−)-**26** and (−)-**27** (Scheme 3). The absolute configuration of (+)-**13** was proven by transformation into (−)-**12** via (−)-**29** and subsequent (i) acetate hydrolysis; (ii) Mitsunobu inversion at C-3; (iii) benzoate hydrolysis and TBS ether formation; (iv) base induced cyclopropane formation; (v) reduction of the ester function. The vitamin D A-ring precursor (−)-**12** has previously been obtained from (−)-quinic acid **28**;[1] identical specific rotations were observed.[7]



Scheme 3. a: (1) TBDPSCl, Imid., DMAP, DMF, rt, (2) K_2CO_3, MeOH, rt; b: DEAD, $(Ph)_3P$, THF, rt; c: MeMgBr, THF, −78°C; d: TPAP, NMO, 4 Å MS, CH_2Cl_2, rt

The synthesis of the naturally occuring monoterpene *cis*-sobrerol (−)-**31**[8] starting from (−)-**14** proved the absolute configuration (Scheme 3). Elimination under Mitsunobu conditions afforded the substituted cyclohexene (−)-**30**, which upon treatment with MeMgBr gave *cis*-sobrerol (−)-**31** (same specific rotation).

Additional proof was obtained by oxidation of (−)-**31** to (−)-**32**, previously synthesized by Mori et al.[9] from (*R*)-carvone. Also, application of the method of Horeau[10] and of Kakisawa's

rule[11] (Fig. 1) based on Mosher's[12] method for determining the absolute configuration of secondary alcohols via the MPTA esters led to the same conclusion that indeed the acetoxy function in (–)-**14** is at the (*R*)-stereogenic center.

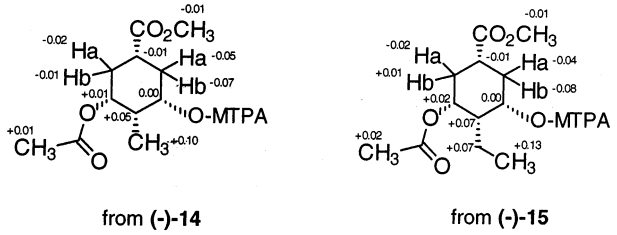


Figure 1. Absolute sterochemistry determination: $\Delta\delta$ values for the (*S*)- and (*R*)-Mosher's esters of the respective acetates (–)-**14** and (–)-**15** ($\Delta\delta = \delta_S - \delta_R$, 500 MHz)

Determination of the absolute configuration of 4-ethyl substituted (–)-**15** follows from the methods of Horeau and of Kakisawa, which with regard to the result obtained for (–)-**14** can thus be used safely. Furthermore, the behaviour of the 4-ethyl and 4-methyl homologues in subcritical fluid chromatography and in polarimetry is consistent with identical absolute configurations.

Synthetic applications of the enantiopure monoesters will be published elsewere.

3. Experimental

3.1. General remarks

All reactions were carried out under argon atmosphere with magnetic stirring. All solvents were purified or dried according to standard literature procedures. Solutions were dried over $MgSO_4$ (unless otherwise specified) and solvent evaporations were carried out in a Rotavapor at 16 mmHg. Column chromatography was performed on SiO_2. HPLC separations were performed on a Knauer 64 or a Kontron 420 delivery system with RI detection. Optical rotations were measured with a Perkin–Elmer 421 polarimeter. IR spectra were recorded on a Perkin–Elmer FTIR-1600 spectrometer, mass spectra on a HP-5988 spectrometer. The ^1H NMR spectra were recorded at 500 MHz (Brucker AN-500), the ^{13}C NMR spectra at 50 MHz (Varian Gemini-200). The chemical shifts are expressed in ppm relative to TMS and coupling constants are in Hz. Elemental analyses were carried out by ICHOR, Université Pierre et Marie Curie (Paris, France).

3.2. cis,cis-*3,5-Dihydroxy-1-(methoxycarbonyl)cyclohexane* ***1***

Methyl 3,5-dihydroxybenzoate **8** (90 g, 0.53 mol), 5% Rh/Al_2O_3 (9 g, 10%) in dry MeOH (750 mL) containing AcOH (2 mL) was added into an autoclave (1 L). The autoclave was flushed twice with hydrogen (from 130 to 40 atm). The pressure of hydrogen was put at 130 atm and the temperature was raised to 105°C during circa 2 h. In the process of raising the temperature, the pressure of hydrogen decreased. After the pressure diminished to 90 atm the hydrogen pressure was again brought to 130 atm. The hydrogenation was continued for an additional

20 h at 105°C. The catalyst was filtered off over Celite. The filtrate was concentrated and the residue was crystallized from EtOAc:isooctane (4:1) giving **1** (55 g, 59%). Circa 25% of **8** can be recuperated from the mother liquor upon crystallization from water.

R_f 0.20 (isooctane:acetone, 1:1). Crystals from isooctane/EtOAc. Mp 132–135°C. IR (KBr): 3287, 2934, 1732, 1457, 1281, 1017 cm^{-1}. ^1H NMR (500 MHz, D_2O, δ ppm): 3.73 (m, 2H), 3.72 (s, 3H), 2.53 (dt, $J=12.2$, 3.4 Hz, 1H), 2.26 (d, $J=11.30$ Hz, 1H), 2.17 (d, $J=11.7$ Hz, 2H), 1.30 (q, $J=12.0$ Hz, 2H), 1.23 (q, $J=11.4$ Hz, 1H). MS m/z (%): 156 (M^+-H_2O, 9), 137 (8), 113 (78), 97 (44), 87 (100), 55 (72).

3.3. *All*-cis-*3,5-dihydroxy-4-methyl-1-(methoxycarbonyl)cyclohexane* **2**

From **9** as described for **1** from **8**. Yield 62%. Crystals from isooctane/EtOAc. R_f 0.21 (isooctane:EtOAc, 3:2). Mp 127–128°C. IR (KBr) 3382, 2913, 1731, 1439, 1361, 1268, 1198, 1020, 739, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 3.85 (br.s, 2H), 3.32 (s, 3H), 2.61 (t, $J=5.4$ Hz, 1H), 2.21 (br.s, 2H), 1.85–1.80 (m, 4H), 1.10 (d, $J=7.1$ Hz, 3H). MS m/z (%): 189 (M^++1, 2), 170 (11), 152 (16), 127 (86), 111 (98), 95 (58), 87 (100), 67 (71), 55 (80).

3.4. *All*-cis-*3,5-dihydroxy-4-ethyl-1-(methoxycarbonyl)cyclohexane* **3**

From **10** as described for **1** from **8**. Crystals from isooctane/EtOAc. Yield 57%. R_f 0.26 (isooctane:EtOAc, 3:2). Mp 95–96°C. IR (KBr): 3395, 2956, 2854, 1722, 1433, 1267, 1011 cm^{-1}. ^1H NMR (500 MHz, MeOD, δ ppm): 3.72 (dt, $J=10.9$, 4.7 Hz, 2H), 3.66 (s, 3H), 2.42 (m, 1H), 1.86 (br.s, 1H), 1.79 (dt, $J=12.8$, 4.1 Hz, 2H), 1.59 (d, $J=9.0$ Hz, 2H), 1.46 (m, 2H), 1.02 (t, $J=7.5$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 179.3, 68.9, 52.4, 45.3, 34.9, 33.6, 21.4, 11.7. MS m/z (%): 202 (M^+, 1), 184 (11), 166 (15), 152 (14), 141 (73), 124 (28), 111 (89), 97 (29), 87 (79), 55 (100).

3.5. (*1*S,*3*S,*5*R)-*3-Acetoxy-5-hydroxy-1-(methoxycarbonyl)cyclohexane (+)-***13***

To diol **1** (412 g, 2.31 mmol) and PPL (246 g, 21 U/mg) in a 20 L round-bottom flask was added vinyl acetate (12.3 L) at rt. The resulting suspension was stirred under N_2 at rt (18–22°C) for 24 h in the dark. The residue was crystallized from *i*-$Prop_2O$ (1.4 L) yielding **13** (436.06 g). The mother liquor was evaporated and the residue purified by flash chromatography (Tol.:EtOAc, 7:3). Solvent evaporation and recrystallization from *i*-$Prop_2O$ (250 mL) gave another 61.3 g. The combined yield of (+)-**13** is 496.3 g (97.7%). R_f 0.20 (isooctane:acetone; 7:3). $[\alpha]_D^{rt}=+23.6$ (*c* 1.60, $CHCl_3$). Mp 54–55°C. IR (KBr): 3437, 2954, 1732, 1367, 1244, 1029 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.74 (dt, $J=11.4$, 4.3 Hz, 1H), 3.74 (m, 1H), 3.69 (s, 3H), 2.41 (dt, $J=12.6$, 3.5 Hz, 1H), 2.30 (m, 1H), 2.24 (m, 2H), 2.05 (s, 3H), 1.40 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 174.5, 170.7, 69.8, 67.7, 52.3, 40.5, 38.4, 37.1, 33.3, 21.5. MS m/z (%): 216 (M^+, 1), 199 (1), 156 (12), 125 (17). Anal. calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.36; H, 7.65.

3.6. (*1*R,*3*S,*4*S,*5*R)-*5-Acetoxy-3-hydroxy-4-methyl-1-(methoxycarbonyl)cyclohexane (–)-***14***

A suspension of diol **2** (0.10 g, 0.55 mmol) and SAM-II (64.3 mg, 42.5 U/mg) in vinyl acetate (4 mL) was stirred in the dark at 25–30°C. The reaction was monitored by TLC. After

completion, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography (isooctane:EtOAc, 3:2) giving (−)-**14** (0.11 g, 89%) as a colorless oil. R_f 0.39 (isooctane:EtOAc, 1:1). $[\alpha]_D^{rt} = -22.7$ (*c* 0.38, $CHCl_3$). IR (film): 3434, 1731, 1439, 1243, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.84 (dt, $J = 11.1$, 4.3 Hz, 1H), 3.82 (m, 1H), 3.69 (s, 3H), 2.45 (m, 1H), 2.32 (d, $J = 6.4$ Hz, 1H), 2.05 (s, 3H), 1.92 (dt, $J = 13.0$, 4.0 Hz, 2H), 1.77 (m, 3H), 0.96 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 174, 170.1, 71.9, 69.3, 51.7, 37.6, 37.3, 30.1, 26.9, 20.1, 5.0. MS *m*/*z* (%): 231 (M^++1, 1), 213 (1), 199 (2), 186 (4), 170 (15), 152 (21), 127 (34), 111(67), 93 (69), 87 (40), 86 (42), 43 (100).

*3.7. (1*R,*3*S,*4*S,*5*R*)-5-Acetoxy-4-ethyl-3-hydroxy-1-(methoxycarbonyl)cyclohexane (−)-**15***

From **3** as described for (−)-**14** from **2**. Colorless oil. Yield 63%. R_f 0.35 (isooctane:EtOAc, 1:1). $[\alpha]_D^{rt} = -50.2$ (*c* 0.47, $CHCl_3$). IR (film): 3421, 2958, 2360, 1733, 1437, 1239, 1027, 739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.98 (t, $J = 4.1$, 1H), 3.87 (m, 1H), 3.69 (s, 3H), 2.60 (br.s, 1H), 2.16 (m, 2H), 2.02 (s, 3H), 1.84 (m, 2H), 1.72 (br.s, 1H), 1.59 (m, 2H), 1.47 (m, 1H), 0.97 (t, $J = 7.5$, 3H). MS *m*/*z* (%): 245 (M^++1, 1), 233 (2), 206 (3), 184 (21), 166 (25), 141 (45), 125 (38), 111 (48), 95 (68), 43 (100).

3.8. cis,cis-*3,5-Diacetoxy-1-(methoxycarbonyl)cyclohexane* ***16***

To a solution of diol **1** (0.58 g, 3.333 mmol) in CH_2Cl_2 (10 mL) was added acetic anhydride (0.95 mL, 10.0 mmol) at rt, followed by a solution of TMSOTf (0.30 mL, 1 M in CH_2Cl_2). The mixture was stirred at rt for 30 min. MeOH (2.5 mL) was added and stirring was continuned for 1 h. After quenching with 5% $NaHCO_3$, the solution was washed with brine (3×5 mL), dried and concentrated. The residue was purified by chromatography (isooctane:EtOAc, 9:1) affording diacetate **16** (0.84 g, 98.8%) as a colorless oil. R_f 0.30 (isooctane:EtOAc, 4:1). IR (film): 2964, 2876, 1732, 1437, 1384, 1363, 1285, 1255, 1180, 1090, 1029, 988 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.76 (tt, $J = 11.6$, 4.2 Hz, 2H), 3.67 (s, 3H), 2.45 (tt, $J = 12.8$, 3.5 Hz, 1H), 2.29–2.26 (m, 3H), 2.03 (s, 6H), 1.47–1.38 (m, 3H). MS *m*/*z* (%): 259 (M^++1, 1), 227 (2), 215 (1), 198 (11), 185 (18), 172 (8), 157 (12), 156 (100), 125 (34), 138 (12), 113 (8).

3.9. cis,cis-*3,5-Dibutanoyloxy-1-(methoxycarbonyl)cyclohexane* ***17***

From **1** and butyric anhydride as described for **16**. Colorless oil. Yield 98%. R_f 0.32 (isooctane:EtOAc, 4:1). IR (film): 2964, 2876, 1732, 1468, 1384, 1358, 1285, 1256, 1179, 1090, 1046, 989 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.79 (m, 2H), 3.68 (s, 3H), 2.46 (m, 1H), 2.25 (m, 6H), 1.59 (m, 5H), 1.42 (m, 3H), 0.95 (t, $J = 7.4$ Hz, 6H). MS *m*/*z* (%): 313 (M^+−1, 1), 305 (5), 283 (13), 278 (4), 263 (2), 254 (2), 245 (10), 226 (95), 213 (100), 198 (18), 194 (25), 183 (12), 166 (85), 156 (16), 138 (10), 107 (10).

3.10. cis,cis-*3,5-Diacetoxy-4-methyl-1-(methoxycarbonyl)cyclohexane* ***18***

As described for **16**. Colorless oil. Yield 98%. R_f 0.25 (isooctane:EtOAc, 4:1). IR (film): 2955, 1738, 1436, 1365, 1236, 1199, 1139, 1025, 979 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.85 (dt, $J = 12.1$, 4.5 Hz, 2H), 3.68 (s, 3H), 2.46 (m, 2H), 2.05 (s, 6H), 1.98 (dt, $J = 12.8$, 4.0 Hz, 2H),

1.69 (q, $J=12.6$ Hz, 2H), 0.96 (s, 3H). MS m/z (%): 241 (M^+-31, 1), 230 (2), 199 (10), 170 (45), 153 (12), 127 (10), 111 (15), 93 (42), 43 (100).

3.11. *All*-cis-*3,5-dibutanoyloxy-4-methyl-1-(methoxycarbonyl)cyclohexane* **19**

As described for **17**. Colorless oil. Yield 97%. R_f 0.13 (isooctane:EtOAc, 9:1). IR (film): 2965, 2877, 1737, 1451, 1436, 1359, 1282, 1250, 1178, 1091, 985 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.87 (dt, $J=12.1$, 4.5 Hz, 2H), 3.68 (s, 3H), 2.47 (m, 2H), 2.27 (t, $J=7.4$ Hz, 4H), 1.97 (dt, $J=12.7$, 4.1 Hz, 2H), 1.66 (m, 6H), 0.95 (m, 9H). MS m/z (%): 297 (M^+-31, 2), 261 (1), 240 (5), 227 (8), 197 (2), 170 (38), 153 (18), 127 (8), 111 (10), 71 (100).

3.12. *All*-cis-*3,5-diacetoxy-4-ethyl-1-(methoxycarbonyl)cyclohexane* **20**

As described for **16**. Colorless oil. Yield 98%. R_f 0.28 (isooctane:EtOAc, 4:1). IR (film): 2959, 2879, 1732, 1464, 1436, 1365, 1239, 1187, 1180, 1137, 1027, 981 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.87 (dt, $J=11.1$, 4.2 Hz, 2H), 3.67 (s, 3H), 2.48 (tt, $J=11.5$, 4.4 Hz, 1H), 2.11 (t, $J=4.3$ Hz, 1H), 2.04 (s, 6H), 1.95 (dt, $J=12.9$, 4.1 Hz, 2H), 1.79 (q, $J=23.3$, 11.5 Hz, 2H), 1.54 (m, 2H), 0.96 (t, $J=7.6$ Hz, 3H). MS m/z (%): 285 (M^+-1, 1), 244 (2), 226 (1), 213 (5), 184 (20), 166 (15), 125 (25), 107 (30), 43 (100).

3.13. *All*-cis-*3,5-dibutanoyloxy-4-ethyl-1-(methoxycarbonyl)cyclohexane* **21**

As described for **17**. Colorless oil. Yield 97%. R_f 0.25 (isooctane:EtOAc, 4:1). IR (film): 2965, 2877, 1732, 1462, 1436, 1249, 1178, 1094, 1043, 988 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.89 (dt, $J=11.0$, 4.1 Hz, 2H), 3.66 (s, 3H), 2.48 (tt, $J=11.5$, 4.3 Hz, 1H), 2.26 (t, $J=7.2$ Hz, 4H), 2.09 (br.s, 1H), 1.94 (dt, $J=12.9$, 4.2 Hz, 2H), 1.77 (q, $J=11.3$ Hz, 2H), 1.64 (m, 4H), 1.53 (m, 2H), 0.94 (m, 9H). MS m/z (%): 311 (M^+-31, 1), 272 (2), 241 (5), 211 (1), 184 (45), 166 (15), 125 (10), 107 (38), 71 (100).

3.14. *(1*R,*3*S,*4*S,*5*R*)-3-Acetoxy-5-hydroxy-4-methyl-1-(methoxycarbonyl)cyclohexane (+)-***14***

To a solution of *meso*-diacetate **18** (118 mg, 0.433 mmol) in CH_3CN (3 mL) was added 27.0 mL of phosphate buffer (pH 7.00), followed by the addition of PSL (88 mg, 40 U/mg). The mixture was stirred at rt and the pH was maintained at 7.00 by addition of NaOH (1.0 M). After completion, the reaction was saturated with NaCl and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (3×10 mL), dried and concentrated. The residue was purified with HPLC (isooctane:EtOAc, 75:25) affording (+)-**14** (71 mg, 72%) as a colorless oil. R_f 0.35 (isooctane:EtOAc, 1:1). $[\alpha]_D^{rt}=+19.8$ (c 1.04, $CHCl_3$). IR (film): 3456, 2955, 1732, 1472, 1437, 1365, 1243, 1198, 1178, 1132, 1079, 1028, 981 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.83 (dt, $J=10.9$, 4.3 Hz, 1H), 3.82 (dt, $J=10.8$, 4.4 Hz, 1H), 3.69 (s, 3H), 2.46 (tt, $J=7.3$, 4.3 Hz, 1H), 2.32 (d, $J=6.4$ Hz, 1H), 2.05 (s, 3H), 1.91 (dt, $J=13.0$, 4.0 Hz, 2H), 1.81–1.71 (m, 3H), 0.96 (d, $J=7.1$ Hz, 3H). MS m/z (%): 217 (1), 199 (2), 198 (15), 185 (25), 172 (12), 157 (10), 156 (100), 138 (85), 125 (25), 113 (8), 97 (15).

3.15. (1R,3S,4S,5R)-5-Acetoxy-4-ethyl-3-hydroxy-1-(methoxycarbonyl)cyclohexane (+)-**15**

From **20** and PLE as described for (+)-**14**. Colorless oil. Yield 72%. R_f 0.35 (isooctane:EtOAc, 1:1). $[\alpha]_D^{rt}$ = +50.4 (*c* 0.83, $CHCl_3$). IR (film): 3439, 2959, 2875, 1732, 1467, 1437, 1359, 1284, 1258, 1184, 1143, 1075, 992 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.97 (t, J = 3.5 Hz, 1H), 3.87 (dt, J = 6.8, 4.0 Hz, 1H), 3.68 (s, 3H), 2.59 (t, J = 2.5 Hz, 1H), 2.14 (br.s, 2H), 2.01 (s, 3H), 1.83 (m, 2H), 1.71 (br.s, 1H), 1.58 (m, 1H), 1.45 (m, 1H), 0.96 (t, J = 7.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 176.1, 170.3, 71.6, 68.5, 52.0, 45.3, 36.5, 31.6, 29.7, 21.1, 18.2, 13.4. MS *m*/*z* (%): 244 (M^+, 1), 235 (1), 212 (12), 199 (5), 184 (20), 171 (12), 166 (42), 153 (38), 141 (100), 120 (32), 125 (85), 111(28), 107 (3).

3.16. (1S,3S,5R)-3-Butanoyloxy-5-hydroxy-1-(methoxycarbonyl)cyclohexane (+)-**22**

From **17** and PSL as described for (+)-**14**. Colorless oil. Yield 63%. R_f 0.24 (isooctane:EtOAc, 3:2). $[\alpha]_D^{rt}$ = +18.2 (*c* 0.74, $CHCl_3$). IR (film): 3465, 2959, 2878, 1732, 1463, 1436, 1365, 1240, 1197, 1178, 1082, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.75 (tt, J = 11.4, 3.9 Hz, 1H), 3.73 (tt, J = 11.1, 3.9 Hz, 1H), 3.69 (s, 3H), 2.42 (tt, J = 12.7, 3.4 Hz, 1H), 2.32–2.20 (m, 5H), 1.79 (br.s, 1H), 1.64 (dd, J = 14.8, 7.2 Hz, 2H), 1.47–1.32 (m, 3H), 0.94 (t, J = 7.4, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 174.8, 173.6, 69.8, 68.1, 52.6, 40.9, 38.8, 37.5, 36.9, 33.7, 19.1, 14.2. MS *m*/*z* (%): 245 (M^++1, 1), 226 (2), 216 (1), 200 (15), 194 (10), 183 (12), 173 (11), 169 (10), 156 (75), 143 (45), 136 (90), 125 (100), 113 (35).

3.17. (1S,3S,4R,5R)-3-Butanoyloxy-5-hydroxy-4-methyl-1-(methoxycarbonyl)cyclohexane (+)-**23**

From **19** (125 mg, 0.381 mmol) and PSL as described for (+)-**14**. Crystals from *n*-hexane/acetone. Yield 89%. R_f 0.25 (isooctane:EtOAc, 3:2). Mp 41–42°C. $[\alpha]_D^{rt}$ = +16.5 (*c* 0.79, $CHCl_3$). IR (film): 3477, 2960, 2876, 1732, 1436, 1360, 1258, 1182, 1084, 1022, 989 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.85 (dt, J = 11.1, 4.1 Hz, 1H), 3.83 (dt, J = 10.7, 4.4 Hz, 1H), 3.69 (s, 3H), 2.45 (m, 1H), 2.32 (m, 1H), 2.28 (t, J = 7.5 Hz, 2H), 1.91 (m, 2H), 1.75 (m, 2H), 1.65 (m, 3H), 0.95 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 7.5 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 174.7, 172.9, 71.8, 69.6, 52.0, 38.0, 37.7, 36.4, 30.4, 27.3, 18.5, 13.7, 6.2. MS *m*/*z* (%): 257 (M^+–1, 1), 239 (1), 214 (1), 199 (2), 170 (10), 152 (12), 139 (15), 127 (30), 110 (60), 93 (70), 71 (65). Anal. calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.16; H, 8.65.

3.18. (1S,3S,4R,5R)-3-Butanoyloxy-4-ethyl-5-hydroxy-1-(methoxycarbonyl)cyclohexane (+)-**24**

From **21** and SAM-II as described for (+)-**14**. Colorless oil. Yield 88%. R_f 0.26 (isooctane:EtOAc, 7:3). $[\alpha]_D^{rt}$ = +44.6 (*c* 1.04, $CHCl_3$). IR (film): 3476, 2963, 2876, 1732, 1461, 1436, 1357, 1240, 1182, 1092, 1027, 992, 933 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 4.99 (t, J = 3.3 Hz, 1H), 3.88 (dt, J = 6.9, 4.1 Hz, 1H), 3.68 (s, 3H), 2.60 (t, J = 3.0 Hz, 1H), 2.24 (m, 2H), 2.11 (br.s, 2H), 1.84 (m, 2H), 1.70 (br.s, 1H), 1.63 (m, 2H), 1.57 (m, 2H), 1.45 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 175.7, 172.7, 71.2, 66.4, 51.8, 45.2, 36.5, 36.1, 31.3, 29.2, 18.1, 17.8, 13.4, 13.4. MS *m*/*z* (%): 240 (M^+–31-H, 1), 201 (1), 184 (12), 165 (15), 141 (55), 125 (48), 107 (72), 87 (50), 71 (85), 43 (100). Anal. calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.57; H, 8.98.

3.19. (4R,6R)-6-Acetoxy-1-methyl-4-(methoxycarbonyl)cyclohexene (–)-30

To a stirred solution of monoacetate (–)-**14** (0.20 g, 0.869 mmol) and $(Ph)_3P$ (0.94, 3.584 mmol) in THF (10 mL) at rt was added dropwise DEAD (0.66 mL, 3.56 mmol). After stirring overnight at rt, the solution was concentrated. The residue was purified by column chromatography (pentane:Et_2O, 9:1–4:1) affording **30** (170 mg, 94%). R_f 0.41 (isooctane:Et_2O, 4:1). $[\alpha]^{rt} = -52.7$ (*c* 1.83, $CHCl_3$). IR (film): 3070, 2951, 2850, 1736, 1456, 1436, 1370, 1343, 1239, 1171, 1074, 1028, 987, 932 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 5.58 (d, $J = 1.5$, 1H), 5.35 (br.s, 1H), 3.67 (s, 3H), 2.67 (m, 1H), 2.35–2.24 (m, 3H), 2.05 (s, 3H), 1.80 (m, 1H), 1.63 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 174.7, 170.8, 132.7, 124.7, 71.1, 51.7, 37.6, 31.0, 27.3, 21.0, 19.1. MS *m*/*z* (%): 212 (M^+, 5), 199 (8), 184 (8), 170 (95), 152 (85), 139 (62), 121 (45), 111 (75), 93 (100), 77 (80).

3.20. (4R,6R)-6-Hydroxy-4-(1-hydroxyisopropyl)-1-methylcyclohexene (–)-31

To a stirred solution of (–)-**30** (75 mg, 0.354 mmol) in THF (3 mL) at −78°C was added dropwise MeMgBr solution (2.0 mL, 3.0 M in Et_2O). The resulting mixture was stirred for 6 h at −78°C, and then allowed to warm to rt overnight. The reaction was quenched with saturated NH_4Cl (3 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (3×5 mL), dried, and concentrated. The residue was purified by HPLC (isooctane:EtOAc, 55:45) affording (–)-**31** (51 mg, 85%). Crystals from $CHCl_3$. Mp 109–110°C. R_f 0.18 (isooctane:EtOAc, 1:1). $[\alpha]_D^{rt} = -20.8$ (*c* 0.29, $CHCl_3$) {lit.[8]: $[\alpha]_D = -16$}. IR (KBr): 3283, 2969, 2944, 2886, 2849, 1454, 1383, 1320, 1256, 1167, 1148, 1109, 1037, 974, 922 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 5.47 (t, $J = 1.4$ Hz, 1H), 4.16 (br.s, 1H), 2.23–2.19 (m, 1H), 2.05 (m, 1H), 1.89–1.84 (m, 1H), 1.74 (s, 3H), 1.68–1.62 (m, 1H), 1.54 (br.s, 2H), 1.32 (m, 1H), 1.19 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 136.3, 123.6, 72.2, 70.8, 43.8, 34.2, 27.3, 26.9, 26.4, 18.7. MS *m*/*z* (%): 169 (M^+-1, 4), 152 (13), 149 (4), 137 (16), 119 (11), 109 (59), 94 (57), 79 (60), 69 (34), 59 (100).

3.21. (4R)-1-Methyl-4-(1-hydroxyisopropyl)cyclohexene-6-one (–)-32

To a stirred solution of (–)-**31** (80 mg, 0.471 mmol), NMO (85 mg, 0.706 mmol) and (4 Å) molecular sieves (236 mg) in CH_2Cl_2 (6 mL) at rt was added TPAP (8.3 mg, 0.024 mmol). The resulting mixture was stirred for 2 h. After filtration on Celite and solvent evaporation, the residue was purified by HPLC (isooctane:EtOAc, 3:2) affording (–)-**32** (77 mg, 98%). R_f 0.31 (isooctane:EtOAc, 7:3). Mp 39–41°C. $[\alpha]_D^{20} = -39.7$ (*c* 0.54, EtOH) {lit.[9]: $[\alpha]_D^{24} = -42.7$ (*c* 6.94, EtOH)}. IR (film): 3443, 2975, 2927, 1661, 1452, 1434, 1369, 1300, 1146, 1113, 1059, 905, 815 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 6.75 (dd, $J = 5.7$, 1.1 Hz, 1H), 2.61–2.57 (m, 1H), 2.46–2.41 (m, 1H), 2.22 (m, 2H), 2.07–2.01 (m, 1H), 1.75 (s, 3H), 1.52 (br.s, 1H), 1.21 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 200.0, 144.8, 134.9, 71.3, 45.8, 39.4, 27.1, 26.9, 26.8, 15.4. MS *m*/*z* (%): 168 (M^+, 1), 150 (113), 138 (4), 135 (7), 123 (2), 110 (39), 95 (38), 91 (14), 82 (21), 67 (20), 59 (100).

3.22. (R)-MTPA ester of (–)-14

To a stirred solution of (–)-**14** (8.5 mg, 0.039 mmol), DMAP (2 mg) and Et_3N (15.4 μL, 0.110 mmol) in CH_2Cl_2 (4 mL) was added dropwise (*S*)-(+)-MTPACl (13.8 μL, 0.074 mmol) at rt. The

resulting mixture was stirred overnight. The solution was diluted with Et_2O (15 mL), washed with $NaHCO_3$ (2×5 mL) and brine (2×5 mL), dried and concentrated giving a residue. HPLC purification (isooctane:AcOEt, 9:1) gave the (*R*)-MTPA ester (14 mg, 89%) as a colorless oil. R_f 0.19 (isooctane:EtOAc, 4:1). $[\alpha]_D^{rt}=+36.2$ (*c* 0.56, $CHCl_3$). IR (film): 2953, 1738, 1453, 1361, 1244, 1179, 1109, 1015, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.50–7.30 (m, 5H), 5.12 (dt, $J=12.2$, 4.5 Hz, 1H), 4.88 (dt, $J=12.1$, 4.4 Hz, 1H), 3.70 (s, 3H), 3.55 (s, 3H), 2.51 (m, 2H), 2.09 (dt, $J=12.7$, 4.1 Hz, 1H), 2.05 (s, 3H), 2.01 (dt, $J=12.9$, 4.2 Hz, 1H), 1.82 (q, $J=12.6$ Hz, 1H), 1.70 ($J=12.7$ Hz, 1H), 0.85 (d, $J=7.0$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 173.5, 170.0, 165.4, 132.1, 129.6, 129.4, 128.4, 127.1, 73.8, 71.0, 55.4, 52.1, 37.5, 35.1, 26.8, 26.7, 21.0, 5.9. MS *m*/*z* (%): 415 (M^+−31, 1), 373 (1), 341 (2), 321 (1), 253 (2), 223 (2), 189 (34), 171 (28), 139 (19), 93 (45), 43 (100).

3.23. (S)-MTPA ester of (−)-**14**

From (−)-**14** and (*R*)-(−)-MTPACl. Colorless oil. Yield 90%. R_f 0.19 (isooctane:EtOAc, 4:1). $[\alpha]_D^{rt}=-26.7$ (*c* 0.19, $CHCl_3$). IR (film): 2953, 1739, 1585, 1451, 1366, 1241, 1181, 1121, 1020, 722 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.50–7.36 (m, 5H), 5.12 (dt, $J=12.1$, 4.5 Hz, 1H), 4.89 (dt, $J=11.9$, 4.6 Hz, 1H), 3.69 (s, 3H), 3.52 (s, 3H), 2.56 (m, 1H), 2.50 (tt, $J=12.9$, 3.9 Hz, 1H), 2.06 (s, 3H), 2.04 (m, 1H), 1.99 (dt, $J=12.9$, 3.9 Hz, 1H), 1.75 (m, 1H), 1.69 (m, 1H), 0.95 (d, $J=6.9$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 173.1, 170.0, 165.5, 131.9, 129.7, 129.4, 128.5, 127.4, 73.9, 71.2, 55.2, 52.1, 37.5, 35.5, 26.8, 26.5, 21.2, 6.2. MS *m*/*z* (%): 416 (M^+−31+H, 1), 373 (5), 341 (1), 321 (1), 260 (1), 247 (1), 213 (15), 189 (28), 153 (34), 139 (37), 93 (64), 43 (100).

3.24. (R)-MTPA ester of (−)-**15**

From (−)-**15** and (*S*)-(+)-MTPACl. Colorless oil. Yield 88%. R_f 0.21 (isooctane:EtOAc, 4:1). $[\alpha]_D^{rt}=+42.8$ (*c* 0.68, $CHCl_3$). IR (film): 2954, 1738, 1572, 1452, 1366, 1240, 1180, 1122, 1082, 1023, 921, 767, 722 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.50–7.39 (m, 5H), 5.09 (dt, $J=11.5$, 4.3 Hz, 1H), 4.89 (dt, $J=11.4$, 4.3 Hz, 1H), 3.67 (s, 3H), 3.55 (s, 3H), 2.50 (m, 1H), 2.12 (t, $J=4.8$ Hz, 1H), 2.07 (dt, $J=12.5$, 3.5 Hz, 1H), 2.02 (s, 3H), 1.99 (dt, $J=13.6$, 3.5 Hz, 1H), 1.80 (m, 1H), 1.77 (m, 1H), 1.42 (m, 2H), 0.74 (t, $J=7.5$ Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 173.5, 170.1, 165.6, 132.2, 129.7, 129.1, 128.5, 127.5, 74.2, 71.5, 55.5, 52.2, 43.0, 37.3, 28.0, 27.7, 21.0, 16.2, 14.3. MS *m*/*z* (%): 413 (1), 387 (4), 355 (1), 296 (2), 261 (1), 227 (10), 189 (38), 167 (35), 135 (34), 107 (85), 43 (100).

3.25. (S)-MTPA ester of (−)-**15**

From (−)-**15** and (*R*)-(−)-MTPACl. Colorless oil. Yield 90%. R_f 0.21 (isooctane:EtOAc, 4:1). $[\alpha]_D^{rt}=-23.1$ (*c* 0.82, $CHCl_3$). IR (film): 2954, 1738, 1572, 1452, 1365, 1239, 1175, 1122, 1020, 723 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.49–7.39 (m, 5H), 5.09 (dt, $J=11.4$, 4.3 Hz, 1H), 4.91 (dt, $J=11.5$, 4.3 Hz, 1H), 3.66 (s, 3H), 3.51 (s, 3H), 2.49 (tt, $J=13.2$, 4.5 Hz, 1H), 2.19 (t, $J=4.7$ Hz, 1H), 2.04 (s, 3H), 2.03 (dt, $J=11.3$, 4.5 Hz, 1H), 1.97 (dt, $J=13.1$, 3.5 Hz, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.49 (m, 2H), 0.87 (t, $J=7.5$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 173.5, 170.2, 165.8, 132.1, 129.7, 128.5, 128.2, 127.4, 74.3, 71.6, 55.3, 52.2, 43.3, 37.3, 27.9, 27.7, 21.2, 16.4, 14.5. MS *m*/*z* (%): 431 (M^+−31+2H, 1), 412 (1), 387 (4), 355 (1), 302 (1), 256 (3), 227 (9), 189 (15), 167 (14), 135 (17), 107 (49), 43 (100).

3.26. Horeau's partial resolution method for determination of the absolute configuration of (–)-**14** and (–)-**15**

To a stirred solution of (–)-**14** (17 mg, 0.076 mmol) was added dropwise 2-phenylbutyric acid anhydride (44 μL, 0.150 mmol) at rt. The resultant mixture was stirred at rt for 16 h. Then H_2O (0.2 mL) was added and the stirring was continuned for 0.5 h. The mixture was poured into aqueous NaOH solution (0.1N, 15 mL) and benzene(15 mL). The aqueous layer was separated and extracted with benzene (2×10 mL). The aqueous layer was acidified by addition of aqueous HCl (1N) and extracted with benzene (3×10 mL). The combined organic layers were dried, filtered and the volume was adjusted to 1 mL for optical measurements. The $[\alpha]_D^{rt}$ is –0.35, indicating the *S* absolute configuration at C_3. Starting from (–)-**15**, an $[\alpha]_D^{rt}$ –0.30 was found, also indicating the *S* absolute configuration at C_3.

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