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The first synthesis of both enantiomers of 2-hydroxycyclobutanone acetals by enzymatic transesterification: preparation of (*R*)-(+)-2-benzyloxycyclobutanone and its antipode ☆

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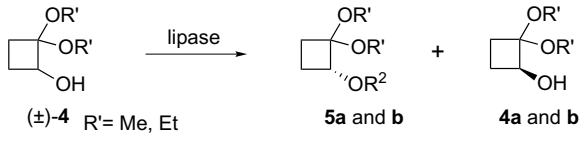
Abstract—A new practical enzymatic synthesis of (*R*)-(+)- and (*S*)-(−)-2-acetoxycyclobutanone acetals with 97–99.9% ee has been carried out via enzymatic transesterification of readily available racemic 2-hydroxycyclobutanone acetals. The absolute configuration has been established by X-ray analysis of the corresponding (*S*)-naproxenyl derivative. The first preparation of enantiomerically pure (*R*)-(+)- and (*S*)-(−)-2-benzyloxycyclobutanones was accomplished by means of protection of the hydroxy group followed by deacetalation reaction.

1. Introduction

The synthesis of optically active α-substituted cyclobutanones via asymmetric reaction has not received much attention with only a few methods for the synthesis of racemic α-substituted cyclobutanones[1–3] being described and rarely for the optically active compounds. Poor to good enantiomeric excesses have been generally obtained.[4]

Over the course of our work on the asymmetric synthesis of cyclic analogues of naturally occurring α-amino acids,[5] we have previously published the aminocyclobutane carboxylic acids **1**[6] prepared from readily available racemic α-substituted cyclobutanones **2**.[6,7] We decided in connection with our ongoing programme, to study the synthesis of optically active cyclobutanones by an enzymatic reaction, following a well-known enzyme-catalyzed transesterification.[8]

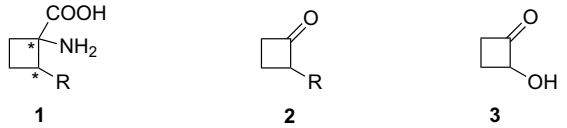
Herein starting from readily available 2-hydroxycyclobutanone (±)-**3** (acyloin) or the corresponding acetals **4**, we report on the preparation of optically active 2-hydroxycyclobutanone and derivatives **5**, by enantiomeric transesterification with various lipases in organic solvents (Scheme 1).[9]



Scheme 1.

2. Results and discussion

The racemic starting material 2-hydroxycyclobutanone **3** (acyloin) was easily prepared from the now commercially available 1,2-bis(trimethylsilyloxy)cyclobutene **6**,[10] according to Conia's procedure[11a] with water in acetone,



1 **2** **3**

☆ Part of this study was previously reported at the Organic Chemistry Symposium at Villers-sur-Mer (GECO 44, September 2003), France.

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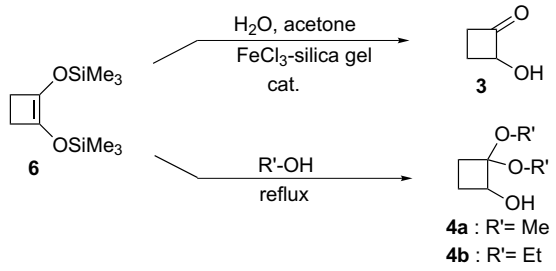
catalyzed by ferric chloride dispersed on silica gel.[12] Acetals **4** (dimethyl or diethyl) were obtained by heating compound **6**, in MeOH or EtOH, respectively (Scheme 2).[11b]



Scheme 2.

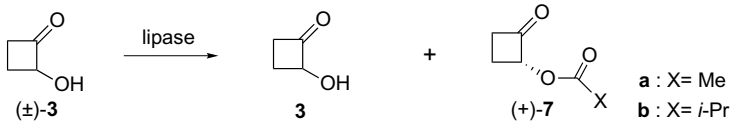
First, the resolution of 2-hydroxycyclobutanone (±)-**3** was carried out by different lipase-catalyzed enantioselective acylations (Table 1). Treatment of alcohol **3** in a mixture of anhydrous *t*-butyl methyl ether (TBME) at room temperature with 2 equiv of vinyl acetate in the presence of immobilized *Candida antarctica* lipase B (Novozym® 435, CALB - 80 mg/mmol of substrate), gave the corresponding acetate (+)-**7a** in good yields. However the enantiomeric excesses were moderate (Table 1, entries 1–3). Remaining starting material **3**, was recovered (25–45%) without any optical activity, due to rapid racemisation by comparison to the reported homologue hydroxycyclopentanone,[13] which showed an optical rotation under similar conditions.

Changing the acyl donor, to isopropenyl acetate, methyl isobutyrate or ethyl acetate, did not significantly improve either the enantiomeric excess or the yield. The acceptable enantioselectivity (61% ee) that was obtained with ethyl acetate after 24 h, decreased drastically to 8% ee over 7 days, presumably due to racemisation of ester **7a** in such a medium (Table 1, entries 5–8). However, the use of a nonpolar solvent such as cyclohexane or hexane, improved the enantiomeric excess to 83% or 89%, respectively (compare entry 3, to entries 9 and 10). In addition, we found that the enzymatic transesterification of **3** with lipase from *Pseudomonas cepacia* immobilized on Hyflo Super Cell (PSL/HSC)[14] or with lipase from *P. fluorescens* on Hyflo Super Cell (AKL/HSC), gave acetate (+)-**7a** with 62% ee or 50% ee, respectively. The absolute configuration of acetate (+)-**7a** was determined from X-ray structure of derivative as shown below.

The encouraging results obtained in the preparation of acetate (+)-**7a**, in hexane solvent (89% ee, Table 1, entry 10), prompted us to investigate the CALB-catalyzed transesterification from the readily available 2-hydroxy acetals **4a** and **4b**. Furthermore these acetals, more stable than their corresponding cyclobutanones **3**, should prevent racemisation under enzymatic reaction conditions.

Thus, hydroxy acetal **4a**, was cleanly converted into acetates (+)-**5a** and (+)-**4a** with lipase CALB in hexane in the presence of vinyl acetate with excellent enantiomeric excesses and yields (Table 2, entries 2 and 3, compared to entries 1 and 4). Silica gel column chromatographic separation of the above mixture gave (*S*)-(+)-hydroxycyclobutanone methyl acetal (+)-**4a** in 39.5% yield (ee = 99.9%) and (*R*)-(+)-2-acetoxycyclobutanone methyl acetal (+)-**5a** in 42% yield (ee ⩾ 97.6%), always with a very high enantiomeric ratio *E*.[15] However with lipase PSL/HSC, the reaction

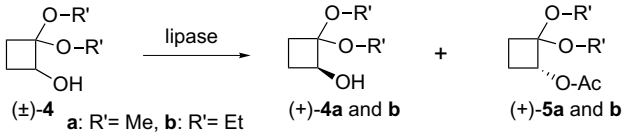
Table 1. Enzymatic acylation of acyloin **3** with various lipases



Entry	Lipase	Acyl donor	Solvent	Time	Conv. (%)[a]	Yield (%)[b]	Alcohol **3**	Ester (*R*)[f]			
							Y (%)	**7**	*Y* (%)	Ee (%)[c]	$[\alpha]_D$
1	CALB	Vinyl acetate	TBME	5.5 h	70	71	25	**7a**	46	27	+23.3
2	CALB	Vinyl acetate	TBME	3.5 h	53	86	45	**7a**	41	41	+35
3	CALB	Vinyl acetate	TBME	3.25 h	59	83	30	**7a**	53	42	+36
4	CALB	Vinyl acetate[d]	TBME	3.75 h	53	90	47	**7a**	43	38.3	+33
5	CALB	Isopropenyl acetate[d]	TBME	4 h	49	83	41	**7a**	48	30.5	+26
6	CALB	Methyl isobutyrate[d]	TBME[e]	7 days	<30	67	58	**7b**	21	12	+4.4
7	CALB	EtOAc	EtOAc[e]	24 h	30	84	58	**7a**	26	61	+52
8	CALB	EtOAc	EtOAc[e]	7 days	35	69	47	**7a**	22	8	—
9	CALB	Vinyl acetate	*c*-Hexane	3.34 h	39	76	49	**7a**	27	83	+70
10	CALB	Vinyl acetate	Hexane	2.15 h	40	57	35.8	**7a**	21.5	89	+76.5
11	PSL/HSC	Vinyl acetate	TBME[e]	11 days	<30	86	74	**7a**	11.8	62	+53.4
12	AKL/HSC	Vinyl acetate	TBME	6 h	43	69	35	**7a**	34	50	+43

[a] Conversions were measured from ^{1}H NMR spectra.
[b] Global yields were calculated from isolated yields of alcohols **3** and ester **7**.
[c] Enantiomeric excesses were measured by GC analysis using chiral column (β-cyclodextrine DM).
[d] With 1.2 equiv of acyl donor.
[e] The reaction mixture was heated at 50 °C.
[f] The absolute configuration was determined by X-ray analysis.

Table 2. Transesterification with lipase in the presence of vinyl acetate[f]



(±)-**4** **a**: R'= Me, **b**: R'= Et (+)-**4a** and **b** (+)-**5a** and **b**

Entry	4	Lipase	Solvent	Time	Conv. (%)[a]	Yield (%)[b]	Hydroxy acetal (*S*)[c]				Acetate (*R*)[c]				*E*
							4	*Y* (%)	Ee (%)	$[\alpha]_D$	5	*Y* (%)	Ee (%)	$[\alpha]_D$	
1	**4a**	CALB	Hexane	22 h	48[d]	68	(+)-**4a**	35	87	+11	(+)-**5a**	33	98.6	+12.7	405
2	**4a**	CALB	Hexane	47 h	47	79	(+)-**4a**	40	91	+11.7	(+)-**5a**	39	99.3	+14.2	910
3	**4a**	CALB	Hexane	78 h	51	82	(+)-**4a**	39.5	99.9	+12.7	(+)-**5a**	42	97.6	+13.9	810
4	**4a**	CALB	TBME	7 days	—	—	(+)-**4a**	36.4	3	—	—	—	—	—	—
5	**4a**	PSL/HSC	Hexane	6 days	—	—	**3**	30[e]	—	—	—	—	—	—	—
6	**4b**	CALB	Hexane	4 days	40	91.5	(+)-**4b**	56	64.5	+14.5	(+)-**5b**	35.5	98	+2.3	190

[a] Conversions were measured from ^{1}H NMR spectra.
[b] Global yields were calculated from isolated yields of hydroxy acetal **4** and acetate **5**.
[c] Enantiomeric excesses were measured by GC analysis using chiral column (β-cyclodextrine DM), and absolute configuration was determined by X-ray analysis.
[d] Small scale.
[e] Formation of acyloin **3** by deacetalation.
[f] Transesterifications were carried out in the presence of 2 equiv of vinyl acetate.

was very slow and only gave the corresponding deacetalation product **3** in 30% yield (Table 2, entry 5).

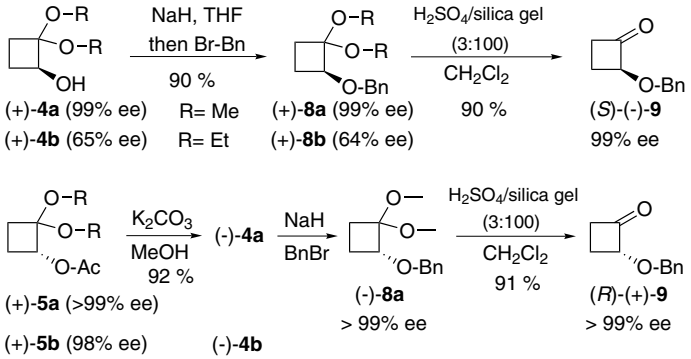
On the other hand, hydroxy ethyl acetal **4b**, was slowly converted into the corresponding acetate (+)-**5b** with excellent enantiomeric excess. However the remaining hydroxy acetal (+)-**4b** was only recovered with 64% ee (Table 2, entry 6).

The 2-hydroxy acetals (*S*)-(+)-**4a** and **4b**, on reaction with benzyl bromide in the presence of NaH gave the corresponding benzyloxy acetals (+)-**8a** and **8b** without racemisation as indicated by GC analysis on a chiral column. The deprotection of acetal (+)-**8a** with a catalytic amount of concentrated H_2SO_4 on silica gel (3/100)[16] in CH_2Cl_2, furnished for the first time optically active 2-benzyloxycyclobutanone (*S*)-(−)-**9** in excellent yield (ee > 99%). However, using much more acidic medium (concd H_2SO_4/silica gel, 20/100), resulted in partial racemisation of the expected cyclobutanone (−)-**9** (ee = 56%).[17]

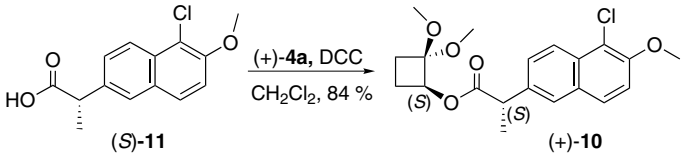
On the other hand, the base induced hydrolysis of (*R*)-(+)-**5a** (>99% ee), with K_2CO_3/MeOH[18] at 20 °C, gave 2-hydroxy acetal (−)-**4a** without racemisation. Treatment of the latter with benzyl bromide/NaH followed by deacetalation as above, furnished, via acetal (−)-**8a**, antipode 2-benzyloxycyclobutanone (*R*)-(+)-**9** without any change in enantiomeric excess (Scheme 3).

During these studies we also noticed that (+)-**4a** upon treatment with HOAc/DCC and DMAP (cat.) afforded 2-acetoxy acetal (−)-**5a** with retention of configuration. While under Mitsunobu conditions (PPh_3, DEAD, HOAc),[19] acetal (+)-**4a** did not give the desired (+)-**5a** with inversion of configuration. This well-known method[20] has previously been used to increase the 50% limit for the chemical yield of one enantiomer in conventional resolution, by direct treatment of the enzymatic reaction mixture before chromatographic separation.

Moreover, to assign for the first time the absolute configuration of the carbon bearing the hydroxy group in **4a** and **5a**, many derivatives were prepared. Only the (*S*)-5-chloro-naproxenyl derivative **10**, prepared from the (*S*)-5′-chloro-Naproxen **11**[21–23] and hydroxy acetal (+)-**4a**, gave suitable crystals (Scheme 4).



Scheme 3. Synthesis of 2-benzyloxycyclobutanone (−)-**9** and its antipodes (+)-**9**.



Scheme 4.

The X-ray crystallographic analysis[24] showed, as depicted in Figure 1, an (*S*)-configuration at the C_2 centre. Consequently the absolute configuration at C_2 of the (+)-**8a** and cyclobutanone (−)-**9** must be (*S*), while for its antipode (−)-**8a**, cyclobutanone (+)-**9** and acetate (+)-**5a**, it must be (*R*). On the other hand, deprotection of acetal (*R*)-(+)-**5a** under acidic conditions (cat. H_2SO_4, silica gel) gave the same acetoxycyclobutanone (+)-**7a**, obtained above by enzymatic reaction. Consequently its absolute configuration must also be (*R*).

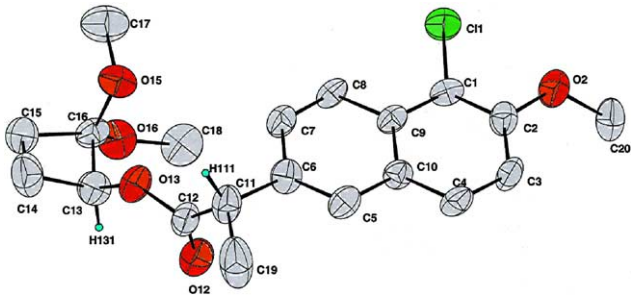


Figure 1. X-ray stereostructure of (2*S*,2′*S*)-(+)-**10**. Spheres are of fixed, arbitrary radii. Some hydrogen atoms are omitted for clarity.

These results are in agreement with the usual enantioselectivity for the (*R*)-isomer generally reported for transesterifications with *C. antarctica* lipase.[25,26]

3. Conclusion

We have developed an efficient and practical chemoenzymatic synthesis of enantiopure (*S*)-(+)-2-hydroxycyclobutanone acetal (+)-**4a** with 35–40% yield and 87–99.9% ee, and (*R*)-(+)-acetoxycyclobutanone acetal (+)-**5a** with 33–42% yield and 97.6–99.3% ee, and their antipodes (−)-**4a** and (−)-**5a**, respectively. Application in the preparation of (*R*)-(+)-2-benzyloxycyclobutanone (+)-**9** and its antipode (*S*)-(−)-**9** was also accomplished without racemisation, by means of protection and deacetalation with good yields. This approach should constitute an efficient method for preparing starting materials used in the synthesis of optically active aminocyclobutanecarboxylic acids,[6] which is currently in progress in our laboratory.

4. Experimental section

The general experimental procedures and the analytical instruments employed herein have been described in detail in a previous paper.[5a] Enantiomeric excesses were also performed on a GC chiral column Cydex B, 25 m × 0.25 mm, or β-cyclodextrine DM, 40 m × 0.25 mm, 120 °C, 1 bar). Tested lipases were as follows: lipase from *C. antarctica* SP435 (CALB, immobilized on a macroporous acrylic resin, Novo Nordisk, Denmark), lipase from *P. cepacia* (PSL, Amano) was immobilized on Hyflo Super Cell (PSL/HSC) according to Ref. 14. Lipase from *P. fluorescens* (AKL, Amano).

4.1. (±)-2-Hydroxycylobutanone, 3

Prepared following the previously reported procedure[11a] to a solution of 11.5 g (50 mmol) of 1,2-bis(trimethylsilyloxy)cyclobutene **6**[10] in 30 mL of acetone was added successively 1.8 g of water (100 mmol) and a catalytic amount (50 mg) of $FeCl_3/SiO_2$ (6/100).[12] After stirring at room temperature for 1 h and elimination of solvent, the residue was filtered through a 2-cm pad of SiO_2 eluted with ether (80 mL). After concentration we obtained 4.25 g (94% yield) as viscous oil of pure acyloin **3**, which was used in further steps without additional purification. $R_f = 0.13$ (EtOAc/pentane, 3:7); IR (neat): ν 3394 cm^{-1} (OH), 1785 (C=O), 1400, 1275, 1140, 1075, 1037; ^1H NMR ($CDCl_3$): δ 1.72–1.95 (m, 1H–C_3), 2.35–2.55 (m, 1H–C_3), 2.60–3.00 (m, 2H–C_4), 3.10 (br s, OH), 4.94 (ddt, $J = 8.4$ Hz, $J = 10.5$ Hz, $J = 2.0$ Hz, 1H–C_2); ^{13}C NMR ($CDCl_3$): δ 21.1 (C_3), 38.4 (C_4), 81.4 (C_2), 209.3 (C_1). All spectral data are identical with those previously reported.[11a]

4.2. (±)-2-Hydroxycylobutanone dimethyl acetal, 4a

Following the previously reported procedure,[11b] a solution of 11.5 g (50 mmol) of 1,2-bis(trimethylsilyloxy)cyclobutene **6** (easily prepared by acyloin condensation)[10] in 15 mL of MeOH was heated at reflux for 2 h. The solvent was removed under vacuum (pressure > 90 mbar, to prevent loss of volatile acetal) and the residue purified by flash chromatography (eluent, Et_2O/pentane, 2/8 → 5/5), to yield 5.55 g (84%) of pure α-hydroxy acetal **4a** as a colourless oil. $R_f = 0.16$ (EtOAc/pentane, 2:8), $t_R = 11.03$ min for (−)-**4a**/11.45 min for (+)-**4a** (β-cyclodextrine DM, 110 °C, 0.8 bar); IR (neat): ν 3463 cm^{-1} (OH), 2951, 1457, 1123, 1067, 1040; ^1H NMR ($CDCl_3$): δ 1.34–1.54 (m, 1H–C_3), 1.54–1.70 (m, 1H–C_3), 2.00–2.20 (m, 2H–C_4), 2.65 (br s, OH), 3.25 (s, 3H), 3.50 (s, 3H), 4.17 (t, $J = 7.6$ Hz, 1H–C_2); ^{13}C NMR ($CDCl_3$): δ 24.0 (C_3), 24.6 (C_4), 48.3 (CH_3), 49.4 (CH_3), 71.8 (C_2), 103.7 (C_1); MS (IC) m/z (%): 150 $[M+NH_4]^+$ (20), *118* (100), 103 (12). All spectral data are identical with those previously reported.[11b]

4.3. (±)-2-Hydroxycylobutanone diethyl acetal, 4b

Following the same procedure[11b] noted above, from 11.5 g (50 mmol) of 1,2-bis(trimethylsilyloxy)cyclobut-

ene **6** in 18 mL of EtOH. After heating at reflux for 2 h usual workup and flash chromatography (eluent, Et_2O/pentane, 15:85 → 30:70), 6.80 g (85%) of the diethyl acetal **4a** was obtained as a colourless oil. $R_f = 0.2$ (Et_2O/pentane, 3:7), $t_R = 9.90$ min for (−)-**4b**/10.47 min for (+)-**4b**, (β-cyclodextrine DM, 120 °C, 0.8 bar); IR (neat): ν 3569, 3450 cm^{-1} (OH), 2976, 1171, 1123, 1052; ^1H NMR ($CDCl_3$): δ 1.18 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.32–1.54 (m, 1H–C_3), 1.54–1.79 (m, 1H–C_3), 1.90–2.20 (m, 2H–C_4), 2.79 (d, $J = 11.1$ Hz, OH), 3.54 (br q, $J = 7.1$ Hz, 2H), 3.65 (br q, $J = 7.1$ Hz, 2H), 4.03–4.22 (m, 1H–C_2); ^{13}C NMR ($CDCl_3$): δ 14.9 (CH_3), 15.0 (CH_3), 24.6 (C_3), 24.7 (C_4), 56.2 (O–CH_2), 57.1 (O–CH_2), 72.0 (C_2), 103.0 (C_1); ES+MS: m/z: 183.1 $[M+Na]^+$; HR ES+ MS: m/z: calcd mass for $C_8H_{16}NaO_3$: 183.0997. Found: 183.0992.

4.4. Enzymatic transesterification: general procedure B

To 5 mmol of substituted cyclobutanol in dry 20 mL of *t*-butylmethyl ether (TBME) was added enzyme (w/w of substrate) and vinyl acetate or other acyl donors (10 mmol). TLC monitored the reaction mixture stirred at room temperature under argon. When the reaction conversion was at about 50%, the solvent was filtered off and the cake washed with ether. The concentration of solvent and flash chromatography (FC) gave the expected products with good yields and high enantiomeric excesses. The recovered enzyme was recycled.

4.4.1. (*R*)-(+)-2-Acetoxycyclobutanone, (*R*)-(+)-7a. According to procedure B: From 258 mg (3 mmol) of acyloin **3** and vinyl acetate (516 mg, 6 mmol) in the presence of *C. antarctica* lipase B (Novozym® 435, CALB) (240 mg) in hexane (15 mL). After stirring for 135 min at rt, (conversion 40%) and purification by FC (eluent: ether/pentane, 3/7 → 1/1), we isolated 83 mg (21.5 %) of acetate (+)-**7a** as a colourless oil (89% ee) and 92 mg (35.8% yield) of starting acyloin **3**.

4.4.1.1. Data for acetate (*R*)-(+)-7a. $[\alpha]_D = +77$ (*c* 1, $CHCl_3$); ee = 89%; $R_f = 0.4$ (EtOAc/pentane, 3:7), $t_R = 10.11$ min for (+)-**7a**/11.62 min for (−)-**7a** (β-cyclodextrine DM, 120 °C, 0.8 bar); IR (neat): ν 2967 cm^{-1}, 1797 (C=O), 1748 (COO), 1374, 1227, 1083; ^1H NMR ($CDCl_3$): δ 1.93–2.23 (m, 1H–C_3), 2.11 (s, 3H), 2.39–2.60 (m, 1H–C_3), 2.91 (dd, $J = 8.0$ Hz, $J = 10.0$ Hz, 2H-C_4), 5.63 (dd, $J = 9.0$ Hz, $J = 9.0$ Hz, 1H–C_2); ^{13}C NMR ($CDCl_3$): δ 19.4 (C_3), 20.3 (CH_3), 40.3 (C_4), 80.2 (C_2), 169.4 (COO), 202.8 (C=O).

All spectral data are identical with those previously reported.[11]

4.4.2. (*R*)-(+)-2-Isobutyroxycyclobutanone, (*R*)-(+)-7b. According to procedure B: From 86 mg (1 mmol) of acyloin **3** and methyl isobutyrate (122 mg, 1.2 mmol) in the presence of lipase (CALB) (86 mg) in TBME (4 mL). After stirring for 7 days at 50 °C (conversion <30%) and purification by FC (eluent: ether/pentane, 1/9 → 2/8), we obtained 33 mg (21%) as a colourless oil of isobutyrate (+)-**7b** (12% ee) and 50 mg (58% yield) of starting acyloin **3**.

4.4.2.1. Data for isobutyrate (*R*)-(+)-7b. $[\alpha]_D = +4.4$ (*c* 1, $CHCl_3$); ee = 12%; $R_f = 0.55$ (EtOAc/pentane, 3:7), $t_R = 8.98$ min for (*R*)-(+)-**7b**/9.16 min for (−)-**7b** (β-cyclodextrine DM, 130 °C, 1 bar); ^1H NMR ($CDCl_3$): δ 1.19 (d, $J = 6.8$ Hz, 3H), 1.20 (d, $J = 6.8$ Hz, 3H), 2.00–2.20 (m, 1H–C_3), 2.40–2.70 (m, 2H, H–C_3 and $H_{isopropyl}$), 2.95 (dd, $J = 8.0$ Hz, $J = 9.4$ Hz, 2H–C_4), 5.63 (dd, $J = 6.4$ Hz, $J = 7.6$ Hz, 1H–C_2); 13C NMR ($CDCl_3$): δ 18.7 ($2CH_3$), 19.5 (C_3), 34.4 (C_2'), 40.3 (C_4), 80.3 (C_2), 175.6 (COO), 203.0 (C=O); HRMS m/z: calcd mass for $C_8H_{12}O_3$: 156.0786. Found: 156.0781.

4.4.3. (*R*)-(+)-2-Acetoxycylobutanone dimethyl acetal, (*R*)-(+)-5a. According to procedure B: From 5.28 g (40 mmol) of acetal (±)-**4a**, and vinyl acetate (6.88 g, 80 mmol) in the presence of lipase (CALB) (2.75 g) in hexane (65 mL). After stirring at room temperature for 78 h (conversion 51%), and purification by FC (eluent: ether/pentane, 1:9) we isolated 2.925 g (42 %) as a colourless oil of acetate (*R*)-(+)-**5a** (97.6% ee) and 2.085 g (39.5% yield, 99.9% ee) of hydroxy acetal (*S*)-(+)-**4a** {$[\alpha]_D = +12.7$ (*c* 1, $CHCl_3$)}.

4.4.3.1. Data for acetate, (*R*)-(+)-5a. $[\alpha]_D = +13.9$ (*c* 1, $CHCl_3$); ee = 97.6%; $R_f = 0.36$ (EtOAc/pentane, 2:8), $t_R = 69.86$ min for (+)-**5a**/68.95 min for (−)-**5a**, (β-cyclodextrine DM, 75 °C, 0.75 bar); IR (neat): ν 2957 cm^{-1}, 1741 (C=O), 1241, 1058, 1040; ^1H NMR ($CDCl_3$): δ 1.68–1.87 (m, 2H), 2.13 (s, $CH_{3\ acetate}$), 2.10–2.30 (m, 2H), 3.23 (s, CH_3), 3.30 (s, CH_3), 5.02–5.15 (m, 1H–C_2); 13C NMR ($CDCl_3$): δ 21.1 (CH_3 ester), 21.4 (C_4), 26.1 (C_3), 49.1 (CH_3), 49.6 (CH_3), 72.5 (C_2), 103.9 (C_1), 170.1 (COO); MS (CI) m/z (%): 193 $[M+1+NH_4]^+$ (20), *192* $[M+NH_4]^+$ (100), 175 $[M+1]^+$ (6), 145 (92), 144 (99), 128 (99), 104 (54); ES^+ MS m/z: 197.0 $[M+Na]^+$; HR ES^+ MS m/z: calcd mass for $C_8H_{14}NaO_4$: 197.0790. Found: 197.0781.

4.4.4. (*R*)-(+)-2-Acetoxycylobutanone diethyl acetal, (*R*)-(+)-5b. According to procedure B: From 480 mg (3 mmol) of ethyl acetal (±)-**4b**, and vinyl acetate (516 mg, 6 mmol) in the presence of lipase (CALB) (250 mg) in hexane (15 mL). After stirring at 20 °C for 4 days, (conversion 40%) and purification by FC (eluent: ether/pentane, 1:9) we obtained 215 mg of acetate (*R*)-(+)-**5b** (35.5%) as a colourless oil (98% ee) and 270 mg (56% yield; 64.5% ee) of hydroxy acetal (*S*)-(+)-**4b**, $[\alpha]_D = +14.5$ (*c* 1, $CHCl_3$); $t_R = 10.47$ min (β-cyclodextrine DM, 120 °C, 0.8 bar).

4.4.4.1. Data for acetate, (*R*)-(+)-5b. $[\alpha]_D = +2.3$ $[\alpha]_{365} = +12.5$ (*c* 1, $CHCl_3$); ee = 98%; $R_f = 0.33$ (Et_2O/pentane, 3:7), $t_R = 170.65$ min for (+)-**5b**/172.43 min for

(−)-**5b** (β-cyclodextrine DM, 60 °C, 1 bar); IR (neat): ν 2977 cm^{-1}, 1742 (C=O), 1374, 1239, 1084, 1052; ^1H NMR ($CDCl_3$): δ 1.17 (t, $J = 7.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.65–1.88 (m, 2H), 2.08 (s, $CH_{3\ acetate}$), 2.10–2.23 (m, 2H), 3.37–4.62 (m, 4H), 4.97–5.10 (m, 1H–C_2); ^{13}C NMR ($CDCl_3$): δ 15.1 (CH_3), 15.4 (CH_3), 21.0 ($CH_{3\ acetate}$), 21.5 (C_4), 27.2 (C_3), 57.4 (2C, O–CH_2), 73.3 (C_2), 103.3 (C_1), 170.1 (COO); ES^+ MS m/z: 225.1 $[M+Na]^+$; HR ES^+ MS m/z: calcd mass for $C_{10}H_{18}NaO_4$: 225.1103. Found: 225.1104.

4.5. Deprotection of acetate: general procedure C

4.5.1. (*R*)-(−)-2-Hydroxycyclobutanone dimethyl acetal, (*R*)-(−)-4a. Acetate (*R*)-(+)-**5a** (2.090 mg, 12 mmol, 99.6% ee) was added to a suspension of K_2CO_3[18] (2.7 g, 2 equiv) in 20 mL of MeOH. The reaction mixture was stirred at room temperature for 4 h, then filtered over Celite and the cake washed with ether (50 mL). The organic layer was dried over $MgSO_4$, filtered and then concentrated. Flash chromatography (eluent, ether/pentane, 1:9 → 3/7) furnished 1.460 g (92 %) of hydroxy acetal (*R*)-(−)-**4a**. $[\alpha]_D = -12.5$ (c 1, $CHCl_3$); ee = 99.6% (β-cyclodextrine DM, 110 °C, 0.8 bar). All spectral data are identical with those noted above.

4.5.2. (*R*)-(−)-2-Hydroxycyclobutanone diethyl acetal, (*R*)-(−)-4b. Following procedure C: From acetate (*R*)-(+)-**5b** (101 mg, 0.5 mmol, 98% ee), K_2CO_3 (100 mg), in MeOH (3 mL) stirred at 20 °C for 2 h, we obtained after flash chromatography quantitatively the expected hydroxy (*R*)-(−)-**4b** $[\alpha]_D = -22$ (c 1, $CHCl_3$); (ee = 98%).

4.6. Benzyl protection: general procedure D

4.6.1. (*S*)-(+)-2-Benzyloxycylobutanone dimethyl acetal, (*S*)-(+)-8a. To a suspension of 630 mg (15.7 mmol) of NaH (w/w 60% in oil), washed with hexane (3 × 5 mL), was added THF (50 mL). After cooling to 0 °C, a solution of 1.24 g (9.4 mmol) of hydroxy acetal (*S*)-(+)-**4a** (99.6% ee) in THF (10 mL) was slowly added dropwise then stirred at room temperature for 30 min. The mixture was recooled to 0 °C and 1.5 mL (12.5 mmol) of benzyl bromide added and then stirred at rt for 9 h. After hydrolysis with NH_4Cl saturated solution (15 mL) and extraction with Et_2O (2 × 100 mL), the organic layer was dried over $MgSO_4$, filtered then concentrated. Purification of the residue by FC (eluent, ether/pentane, 1:9 → 3/7) afforded 1.88 g (90%) of the benzyloxy acetal (*S*)-(+)-**8a** (ee = 99.6%) as a colourless oil. $[\alpha]_D = +28.1$ and $[\alpha]_{365} = +88$ (c 1, $CHCl_3$); ee = 99.6%; $R_f = 0.56$ (EtOAc/pentane, 2:8); $t_R = 31.51$ min/32.05 min, (β-cyclodextrine DM, 150 °C, 1 bar); IR (neat): ν 2949 cm^{-1}, 1453, 1234, 1120, 1081, 1041; ^1H NMR ($CDCl_3$): δ 1.53–1.80 (m, 2H–C_3), 1.87–2.22 (m, 2H–C_4), 3.24 (s, 3H), 3.35 (s, 3H), 3.95 (m, like triplet, 1H–C_2), 4.57 (m, like AB system, $2H_{benzyl}$), 7.25–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.2 (C_3), 25.0 (C_4), 49.1 (CH_3), 49.3 (CH_3), 70.8 ($CH_{2\ benzyl}$), 78.0 (C_2), 104.5 (C_1), [6 arom. C: 127.5 (1C), 127.7 (2C), 128.1 (2C), 137.9 (1C)]; MS (CI) m/z (%): 240 $[M+NH_4]^+$ (12), 208 (18), 191 (34), *176* (100), 107 (13); HR ES^+ MS m/z: calcd mass for $C_{13}H_{18}NaO_3$: 245.1154. Found: 245.1150.

4.6.2. (*R*)-(−)-2-Benzyloxycylobutanone dimethyl acetal, (*R*)-(−)-8a. Following the procedure noted above: From NaH (2.2 mmol), THF (20 mL), hydroxy methyl acetal (*R*)-(−)-**4a** (264 mg, 2 mmol, ee = 99%), BnBr (3 mmol, 360 μL), stirred at room temperature for 10 h, we obtained after flash chromatography (eluent, ether/pentane, 1/9 → 3/7), 400 mg (90%) of pure benzyloxy acetal (*R*)-(−)-**8a** as colourless oil, $[\alpha]_D = -28$ (c 1, $CHCl_3$), ee = 99%. All spectral data are identical with those for antipode (+)-**8a**.

4.6.3. (*S*)-(+)-2-Benzyloxycylobutanone diethyl acetal, (*S*)-(+)-8b. Following the procedure used for (*S*)-(+)-**8a**: From NaH (2.2 mmol), THF (20 mL), hydroxy ethyl acetal (*S*)-(+)-**4b** (320 mg, 2 mmol, ee = 64.5%), BnBr (3 mmol, 360 μL), stirred at room temperature for 9 h, we obtained after flash chromatography (eluent, ether/pentane, 1/9 → 3/7), 450 mg (90%) of pure benzyloxy acetal (*S*)-(+)-**8b** as colourless oil. $[\alpha]_D = +11.6$ (c 1, $CHCl_3$); ee = 64%; $R_f = 0.55$ (Et_2O/pentane, 3:7); $t_R = 253.54$ min for (+)-**8b**/251.48 min for (−)-**8b** (β-cyclodextrine DM, 110 °C, 0.8 bar); IR (neat): ν 2976 cm^{-1}, 1454, 1231, 1176, 1125, 1099, 1053; ^1H NMR ($CDCl_3$): δ 1.19 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.62–1.84 (m, 2H–C_3), 1.84–2.20 (m, 2H–C_4), 3.41–3.75 (m, q, $J = 7.2$ Hz, 4H), 3.90–4.03 (m, like dt, 1H–C_2), 4.58 (m, like AB system, $2H_{benzyl}$), 7.26–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.2 (CH_3), 15.6 (CH_3), 21.4 (C_3), 26.2 (C_4), 57.3 (O–CH_2), 57.5 (O–CH_2), 70.9 ($CH_{2\ benzyl}$), 78.8 (C_2), 104.2 (C_1), [6 arom. C: 127.5 (1C), 127.7 (2C), 128.2 (2C), 138.3 (1C)]; ES^+ MS m/z: 273.1 $[M+Na]^+$; HRMS m/z: calcd mass for $[M-C_2H_4]$, $C_{13}H_{18}O_3$: 222.1256. Found: 222.1248.

4.7. Deacetalation reaction into cyclobutanone: procedure E

4.7.1. (*R*)-(+)-2-Benzyloxycyclobutanone, (*R*)-(+)-9. To a stirred suspension of silica gel (3 g) and 90 μL of concd H_2SO_4[16] in 5 mL of CH_2Cl_2, was added a solution of dimethyl acetal (*R*)-(−)-**8a** (960 mg, 4.3 mmol, ee = 99.6%) in CH_2Cl_2 (1 mL). After stirring at room temperature for 2 h (conversion 90%), the mixture was filtered and the silica gel washed with CH_2Cl_2 (20 mL). The organic layer was concentrated and then purified by flash chromatography (eluent, CH_2Cl_2) to furnish 666 mg (88%) of pure 2-benzyloxycyclobutanone (*R*)-(+)-**9** (ee > 99%) and 95 mg (10%) of starting compound (*R*)-(−)-**8a**.

4.7.1.1. Data for (*R*)-(+)-9. $[\alpha]_D = +81.2$ (c 1, $CHCl_3$); ee = 99.4%; $R_f = 0.27$ (Et_2O/pentane, 3:7), t_R = 142.15 min for (+)-**9**/143.11 min for (−)-**9**, (β-cyclodextrine DM, 110 °C/1 bar); IR (neat): ν 1786 cm^{-1} (C=O),

1455, 1167; ^{1}H NMR ($CDCl_3$): δ 1.93 (dddd, $J = 7.8$ Hz, $J = 7.3$ Hz, $J = 10.2$ Hz, $J = 21.2$ Hz, 1H–C_3), 2.29 (dddd, $J = 5.4$ Hz, $J = 8.1$ Hz, $J = 9.8$ Hz, $J = 21.2$ Hz, 1H–C_3), 2.60–2.91 (m, 2H–C_4), 4.70 (m, like AB system, $2H_{benzyl}$), 4.60–4.82 (m, 1H–C_2), 7.25 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.5 (C_3), 39.1 (C_4), 71.9 (C_2), 86.9 (C_{benzyl}), [6 arom. C: 127.9,127.95 (2C), 128.3 (2C), 137.1], 206.5 (C_1). All spectral data are identical with those reported for the racemic compound.[17]

4.7.2. (*S*)-(−)-2-Benzyloxycyclobutanone, (*S*)-(−)-9. According to procedure E: From 444 mg (2 mmol) of dimethyl acetal (*S*)-(+)-**8a** (ee = 98%), we obtained after FC 320 mg (91%) of benzyloxycyclobutanone (*S*)-(−)-**9** (ee = 98%) $[\alpha]_D = -80$ (*c* 1, $CHCl_3$); $t_R = 143.11$ min, (β-cyclodextrine DM, 110 °C/1 bar), and 22 mg of starting acetal (*S*)-(+)-**8a**. All spectral data are identical with those reported for the racemic compound.[17]

4.8. (+)-(2*S*,2′*S*)-2-[2′-(5″-Chloro-6″-methoxynaphthalen-2″-yl)propionyloxy]cyclobutanone dimethyl acetal, (+)-10

To a solution of (*S*)-(+)-5-chloro-Naproxen **11**[21] (120 mg, 0,45 mmol), (+)-2-hydroxycyclobutanone methyl acetal (+)-**4a** (57 mg, 0.43 mmol), and DMAP (cat. 7 mg) in dry CH_2Cl_2 (4 mL) was added a solution of dicyclohexylcarbodiimide (DCC), (100 mg, 048 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature with stirring for 14 h. The urea formed was filtered off, washed with CH_2Cl_2 and the organic layer concentrated under vacuum. Silica gel column chromatography (eluent, EtOAc/petrol ether, 5:95 → 3/7) gave the corresponding ester (+)-**10** (137 mg, 84% yield). Crystallisation from ether/pentane furnished nice colourless crystals. The X-ray analysis of these crystals showed an (2*S*,2′*S*) configuration.[24] $[\alpha]_D = +5.4$ (*c* 1, $CHCl_3$); mp 77.9 °C (from ether/pentane); $t_R = 213.95$ min (Cydex B, 180 °C/1.05 bar); $R_f = 0.55$ (EtOAc/pentane, 3:7); IR (neat): ν 2941 cm^{-1}, 1735 (C=O), 1630 and 1602 (Naphth), 1276, 1179, 1156, 1073; ^{1}H NMR ($CDCl_3$): δ 1.60 (d, $J = 7.2$ Hz, 3H), 1.66–1.89 (m, 2H–C_3), 2.00–2.30 (m, 2H–C_4), 3.04 (s, 3H, $OCH_{3\ acetal}$), 3.07 (s, 3H, $OCH_{3\ acetal}$), 3.94 (q, $J = 7.2$ Hz, 1H, C*H*CH_3), 4.04 (s, 3H, OCH_3), 5.00–5.13 (m, 1H–C_2), 7.01 (d, $J = 8.9$ Hz, 1H), 7.57 (dd, $J = 8.9$ Hz, $J = 1.5$ Hz, 1H), 7.68–7.79 (m, 2H), 8.16 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.1 (CH_3), 21.2 (C_3), 26.2 (C_4), 44.9 ($C_{2'}$), 49.0 ($CH_{3\ acetal}$), 49.3 ($CH_{3\ acetal}$), 56.7 (CH_3–O–Ar), 73.1 (C_2), 103.6 (C_1), [10 Naphth. C:113.7 (d), 116.5 (s), 123.6 (d), 126.1 (d), 127.4 (d), 127.6 (d), 129.3(s), 130.8 (s), 136.0 (s), 152.3 (s, $C_{6''}$)], 178.3 (s, $C_{1'}$); ES$^+$ MS *m*/*z*: 401.2 $[M+Na]^+$; HR ES$^+$ MS *m*/*z*: calcd mass for $C_{20}H_{23}ClNaO_5$: 401.1132. Found: 401.1135.

4.8.1. X-ray structure analysis of (+)-10.[24] Crystal data for (+)-(2*S*,2′*S*)-**10**: white crystal of 0.20×0.25×0.30 mm. $C_{20}H_{23}Cl_1O_5$, $M = 378.85$: orthorhombic system, space group *P* 2_1, 2_1, 2_1 (No. 19), $Z = 4$, with $a = 7.434$ (3), $b = 7.500$ (3), $c = 34.260$ (4) Å, $\alpha = \beta = \gamma = 90°$, $V = 1910.1$ (11) Å^3, $d = 1.304$ g cm^{-3}, $F(000) = 800$, $\lambda = 0.710693$ Å (Mo-Kα), $\mu = 0.227$ mm^{-1}; 5599 reflections measured ($0 \leqslant h \leqslant 10$, $0 \leqslant k \leqslant 10$, $0 \leqslant l \leqslant 48$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92[27] and refined with CRYSTALS.[27] Hydrogen atom riding, refinement converged to $R(gt) = 0.0540$ for the 1697 reflections having $I = 2\sigma(I)$, and $wR(gt) = 0.0565$, Goodness-of-Fit $S = 1.1037$, residual electron density: −0.35 and 0.35 e Å^3.

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