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Chemoenzymatic Preparation of Enantiopure Isomers of 4-Aminochroman-3-ol and 1-Amino-1,2,3,4-tetrahydronaphthalen-2-ol

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Enantiomerically pure *N*-protected *cis*-4-aminochroman-3-ol (key precursor in the synthesis of novel HIV second-generation protease inhibitors), its *trans* isomer and both *cis*- and *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol, useful chiral catalysts in organic synthesis, have been successfully prepared through a lipase-catalyzed kinetic acylation of the alcohol moiety, employing as substrates the corresponding *N*-benzyloxycarbonyl-protected derivatives. Of the biocatalysts tested, *Pseudomonas cepacea* and *Candida antarctica B* lipases showed excellent enantioselectivities in the acylation processes depending on the reaction conditions employed.

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Introduction

Vicinal amino alcohols have a well-established importance in organic and pharmaceutical chemistry. They are used as modulators of the potassium channel in cells, as intermediates in the synthesis of σ- and κ-opiate receptors and as core moieties of antiviral agents.[1] The amino alcohol structure is also found in biologically important natural products.[2]

One good example of 1,2-amino alcohols with pharmaceutical properties are the HIV type-1 protease inhibitors. These compounds, such as Indinavir and L-754394, represent a major advance in the treatment of HIV infection and AIDS.[3] However, a number of patients develop resistance to these inhibitors through viral mutations.[4] So, a second-generation of protease inhibitors has been developed with better pharmacokinetic parameters and improved activity against resistant mutants. These drugs are also 1,2-amino alcohols with a structure similar to Indinavir, but with the aminoindanol residue having been replaced by other benzo-fused 1,2-amino alcohols, as for example, the aminochromanol analogue.[5]

Several approaches have been described for the preparation of the optically pure *cis*-4-aminochroman-3-ol. Hansen et al.[6] achieved an asymmetric synthesis in seven steps in which the absolute stereochemistry of the molecule was derived from (salen)Co^{III}-catalyzed opening of methyl glycidate with phenol. The enantiomers of (±)-*cis*-aminochromanol were separated by formation of the diastereomeric salts with (*S*)-mandelic acid and selective crystallization of the mixture.[7]

On the other hand, optically pure vicinal amino alcohols have been recognized as generally useful and versatile chiral auxiliaries for the preparation of enantiopure compounds.[8] The most important applications of these compounds include the enantioselective addition of Et_2Zn to aldehydes,[9] the Diels–Alder reaction[10] and the enantioselective reduction of prochiral ketones with $BH_3{\cdot}SMe_2$.[11] (1*R*,2*S*)-1-Amino-1,2,3,4-tetrahydronaphthalen-2-ol has recently been synthesized and applied to this last reaction[12] and the (1*S*,2*S*) enantiomer has been described as a chiral auxiliary in Reformatsky-type reactions.[13]

Taking into account the importance of the enantiopure 1,2-amino alcohol structures, the main aim of this paper was to develop a biocatalytic method for the preparation of optically pure *cis*- and *trans*-1-aminochroman-2-ol and 1-amino-1,2,3,4-tetrahydronaphthalen-2-ol.

Results and Discussion

Synthesis of Substrates

Racemic *cis*-1,2-amino alcohols were synthesized according to the procedure described by Davies and co-workers (Scheme 1).[7] 4-Chromanone (**1**) and α-tetralone (**5**) were converted by Moriarty oxidation into the α-hydroxy ketones (±)-**2** and (±)-**6**, respectively.[14] Subsequent reaction with hydroxylamine hydrochloride yielded the corresponding α-hydroxy oximes (±)-**3** and (±)-**7**; *cis*-selective hydrogenation of the α-hydroxy oximes catalyzed by palladium on carbon using a methanol solution of HBr led to the corresponding bromide salts of (±)-*cis*-**4** and (±)-*cis*-**8** in good overall yields.

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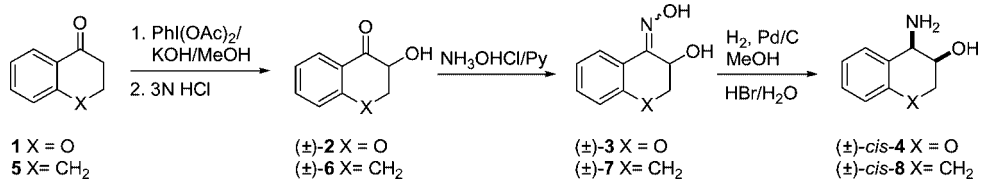
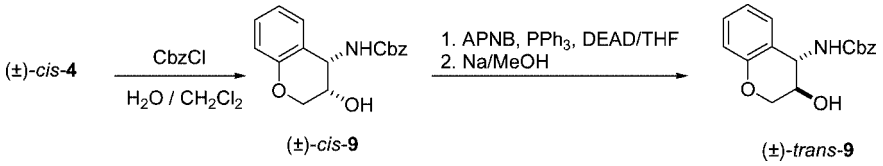
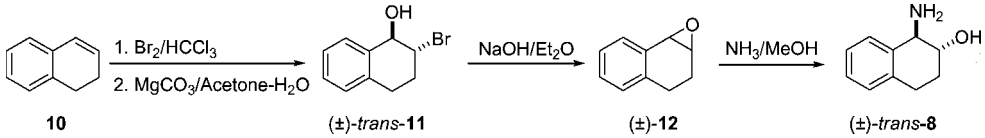


Scheme 1. Chemical synthesis of (±)-*cis*-**4** and (±)-*cis*-**8**.



Scheme 2. Synthesis of (±)-*trans*-4-(benzyloxycarbonylamino)chroman-3-ol [(±)-*trans*-**9**].



Scheme 3. Chemical procedure for the preparation of (±)-*trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol [(±)-*trans*-**8**].

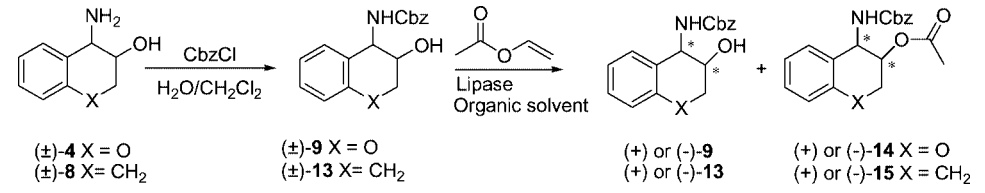
The highest yields for the preparation of racemic *trans*-4-(benzyloxycarbonylamino)chroman-3-ol [(±)-*trans*-**9**] were obtained by protection of (±)-*cis*-**4** with the benzyloxycarbonyl group[15] and Mitsunobu inversion of the *cis*-*N*-protected amino alcohol, as shown in Scheme 2. In the preparation of *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol [(±)-*trans*-**8**], a better overall yield was obtained by employing as starting material 1,2-dihydronaphathalene **10**. Epoxidation of the corresponding bromohydrin (±)-**11**[12a] and subsequent epoxide ring opening of (±)-**12** with ammonia in methanol[16] led to the desired product (±)-*trans*-**8** (Scheme 3).

Enzymatic Resolution

The *N*-(benzyloxycarbonyl) derivatives (±)-*cis*- and (±)-*trans*-**9** and -**13** were prepared in order to avoid the nonenzymatic reaction of the amino group with the acyl donor during the kinetic resolutions (Scheme 4).

Taking into account previous results obtained in the biocatalytic resolution of cyclic 1,2-amino alcohols by lipases,[17] our initial experiments were designed to find the most suitable lipase for catalyzing the acetylation of *N*-protected *cis*-4-aminochroman-3-ol (±)-*cis*-**9** in *t*BuOMe using 10 equiv. of vinyl acetate. The enzymatic processes were carried out at 30 °C. Table 1 shows the results achieved with the immobilized lipases from *Candida antarctica* (CAL-A, CAL-B and CAL-B-L2), *Pseudomonas cepacia* (PSL-C), *Candida rugosa* (CRL) and porcine pancreatic lipase (PPL). CAL-B and PSL-C exhibited the highest enantioselectivities ($E = 40$ and 63; Entries 2 and 4, respectively),[18] but moderate reaction rates. Depending on the biocatalyst employed, an opposite stereochemical preference was observed in the resolution processes. CAL-A catalyzed the acylation of the (+)-(3*R*,4*R*) enantiomer, while with the other biocatalysts, product **14** was obtained with the (–)-(3*S*,4*S*) configuration, with the (+)-(3*R*,4*R*) enantiomer of the unreacted substrate **9** remaining.

The influence of the organic solvent on the selectivity of the transesterification reaction of (±)-*cis*-**9** catalyzed by CAL-B (Entries 7–10) and PSL-C (Entries 13–16) was examined under the same reaction conditions as shown before. The best results in the CAL-B-catalyzed process were achieved with vinyl acetate or toluene as solvent. Excellent enantioselectivities ($E > 200$) and moderate reaction rates were measured (40 and 31% conversion after 96 h, respectively). Vinyl acetate was also the best solvent found for the PSL-C-catalyzed acylation, obtaining a high enantiomeric ratio ($E > 200$) with a 42% conversion after 100 h reaction time (Entry 14). Thus, by choosing the appropriate reaction conditions and biocatalyst, it is possible to isolate enantiopure (3*R*,4*R*)-**9** and (3*S*,4*S*)-**14** at conversions close to 50%.



Scheme 4. Enzymatic acetylation of *N*-protected 1,2-amino alcohols (±)-*cis*- and (±)-*trans*-**9** and -**13** employing vinyl acetate and lipases.

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Table 1. Lipase-catalyzed esterification of (±)-*cis*-**9** with vinyl acetate in organic solvents.[a]

Entry	Lipase	Solvent	T [°C]	t [h]	c [%][b]	ee_s [%][c]	ee_p [%][c]	E[d]
						(3*R*,4*R*)-**9**	(3*S*,4*S*)-**14**	
1	CAL-A[e]	*t*BuOMe	30	48	12	5	34	2
2	CAL-B	*t*BuOMe	30	24	30	40	93	40
3	CAL-B-L2	*t*BuOMe	30	24	23	21	75	9
4	PSL-C	*t*BuOMe	30	24	15	18	96	63
5	CRL	*t*BuOMe	30	24	4	1	28	2
6	PPL	*t*BuOMe	30	48	≤3	–	–	–
7	CAL-B	acetonitrile	30	48	18	21	96	60
8	CAL-B	vinyl acetate	30	96	40	67	≥99	>200
9	CAL-B	THF	30	120	43	4	3	1
10	CAL-B	toluene	30	96	31	44	≥99	>200
11	CAL-B	toluene	40	48	45	82	≥99	>200
12	CAL-B	toluene	50	248	46	40	46	4
13	PSL-C	acetonitrile	30	48	20	25	96	62
14	PSL-C	vinyl acetate	30	100	42	71	≥99	>200
15	PSL-C	THF	30	120	17	5	24	2
16	PSL-C	toluene	30	100	37	54	94	56

[a] For reaction details, see Exp. Sect. [b] Conversion, $c = ee_s/(ee_s + ee_p)$. [c] Determined by HPLC. [d] Enantiomeric ratio, $E = \ln(1-c)[(1-ee_s)]/\ln(1-c)[(1+ee_s)]$. [e] The opposite configuration of substrate and product was observed.

In order to improve the reaction rate of the CAL-B-catalyzed acetylation in toluene, the temperature was increased to 40 °C. A 45% conversion after 48 h was measured (Entry 11) with a significant enhancement of the enantioselectivity. When the resolution was carried out at 50 °C, the biocatalyst almost totally lost its selectivity, as shown in Entry 12.

The best reaction conditions found for the enzymatic resolution of (±)-*cis*-**9** were applied in the enzymatic acetylation of the non-oxygenated *N*-protected derivative (±)-*cis*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol, (±)-*cis*-**13** (Table 2). Under all the conditions tested, the (+)-(1*S*,2*R*) enantiomer of the substrate was acetylated by the biocatalysts, the alcohol with the (–)-(1*R*,2*S*) configuration remaining unaltered. As shown in Entry 1, esterification of (±)-*cis*-**13** catalyzed by CAL-B led to (–)-(1*R*,2*S*)-**13** and (+)-(1*S*,2*R*)-**15** with low conversion (14% after 48 h) and moderate enantioselectivity (E = 38) when the reaction was carried out in toluene at 40 °C. By employing vinyl acetate as the solvent and by lowering the temperature to 30 °C, the same conversion was obtained after 48 h, but a significant decrease in the selectivity was observed. In contrast, much better reaction rates and enantiomeric ratios were achieved in the acetylation reactions catalyzed by PSL-C in vinyl acetate or *t*BuOMe (E > 200 and conversions were close to 50% after 48 h, as shown in Entries 3 and 4). Note the marked effect of the organic solvent on the resolution of (±)-*cis*-**13** catalyzed by PSL-C. When using acetonitrile, toluene or 1,4-dioxane, very low enantioselectivities were measured (Entries 5–7).

After the successful resolution of *N*-protected *cis*-4-aminochroman-3-ol and *cis*-1-amino-1,2,3,4-tetrahydronaphthalen-ol, we focused our attention on the *trans* diastereoisomers (Table 3). For the *N*-protected *trans*-4-aminochroman-3-ol (±)-*trans*-**9**, resolution led to the formation of (–)-(3*R*,4*S*)-**14**, the alcohol (+)-(3*S*,4*R*)-**9** remaining. A moderate E value was achieved in the CAL-B-catalyzed acetylation in toluene at 40 °C (Entry 1). In contrast, it seemed that PSL-C was more suitable as the biocatalyst in the resolution of (±)-*trans*-**9**. When using PSL-C at 30 °C, enantiopure (3*S*,4*R*)-**9** and (3*R*,4*S*)-**14** were obtained in a process with a conversion near 50% after 24 h (Entry 2). Also with *t*BuOMe at 30 °C it was possible to achieve high enantioselectivity (E = 73), but lower than that obtained with vinyl acetate.

With (±)-*trans*-**13**, excellent results were achieved when using CAL-B as the biocatalyst in toluene or PSL-C in vinyl acetate as the solvent and acyl donor. The same enzyme enantiopreference was observed for both biocatalysts (Table 3, Entries 4 and 5). In this last reaction, a 50% con-

Table 2. Lipase-catalyzed esterification of (±)-*cis*-**13** with vinyl acetate[a] in organic solvents.

Entry	Lipase	Solvent	T [°C]	t [h]	c [%][b]	ee_s [%][c]	ee_p [%][c]	E[d]
						(1*R*,2*S*)-**13**	(1*S*,2*R*)-**15**	
1	CAL-B	toluene	40	48	14	15	94	38
2	CAL-B	vinyl acetate	30	48	15	16	85	14
3	PSL-C	vinyl acetate	30	48	42	73	≥99	>200
4	PSL-C	*t*BuOMe	30	48	45	81	≥99	>200
5	PSL-C	acetonitrile	30	72	33	37	72	9
6	PSL-C	toluene	30	72	48	45	49	4
7	PSL-C	1,4-dioxane	30	72	10	3	28	2

[a] For reaction details, see Exp. Sect. [b] Conversion, $c = ee_s/(ee_s + ee_p)$. [c] Determined by HPLC. [d] Enantiomeric ratio, $E = \ln(1-c)[(1-ee_s)]/\ln[(1-c)[(1+ee_s)]$.

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Table 3. Acetylation of (±)-*trans*-**9** and (±)-*trans*-**13** with vinyl acetate in organic solvents catalyzed by CAL-B and PSL-C.[a]

Entry	Substrate	Lipase	Solvent	T [°C]	t [h]	c [%][b]	Alcohol		Ester		E[d]
							Conf.	ee_s [%][c]	Conf.	ee_p [%][c]	
1	(±)-**9**	CAL-B	toluene	40	24	50	(3*S*,4*R*)	90	(3*R*,4*S*)	88	43
2	(±)-**9**	PSL-C	vinyl acetate	30	24	43	(3*S*,4*R*)	75	(3*R*,4*S*)	≥99	>200
3	(±)-**9**	PSL-C	*t*BuOMe	30	51	47	(3*S*,4*R*)	84	(3*R*,4*S*)	93	73
4	(±)-**13**	CAL-B	toluene	40	52	49	(1*S*,2*S*)	95	(1*R*,2*R*)	≥99	>200
5	(±)-**13**	PSL-C	vinyl acetate	30	17	50	(1*S*,2*S*)	≥99	(1*R*,2*R*)	≥99	>200
6	(±)-**13**	PSL-C	*t*BuOMe	30	72	34	(1*S*,2*S*)	13	(1*R*,2*R*)	25	2

[a] For reaction details, see Exp. Sect. [b] Conversion, $c = ee_s/(ee_s + ee_p)$. [c] Determined by HPLC. [d] Enantiomeric ratio, $E = \ln(1-c)[(1-ee_s)]/\ln(1-c)[(1+ee_s)]$.

version was achieved after 17 h and both substrate (–)-(1*S*,2*S*)-**13** and product (+)-(1*R*,2*R*)-**15** were isolated in their optically pure forms. Employing CAL-B led to lower reaction rates (c = 49% after 52 h). Both poor conversion and enantioselectivity were observed in the process catalyzed by PSL-C in *t*BuOMe, as shown in Entry 6.

Conclusions

In conclusion, we have developed an easy and efficient route to the enantiomerically pure *cis* and *trans* isomers of 4-aminochroman-3-ol and 1-amino-1,2,3,4-tetrahydronaphthalen-2-ol through lipase-catalyzed acetylation reactions. Good yields and high enantioselectivities can be achieved by the appropriate choice of biocatalyst (CAL-B and PSL-C) and reaction conditions. Taking into account the simplicity of lipase-catalyzed reactions, the applicability of this method to the synthesis of high-added-value compounds, such as chiral auxiliaries for organic synthesis and potential antiviral agents, is noteworthy.

Experimental Section

General Methods: Enzymatic reactions were carried out in a Gallenkamp incubatory orbital shaker. Immobilized *Candida antarctica* lipase B, CAL-B Novozym 435 (7300 PLU g^{-1}), was a gift from Novo Nordisk Co. *Candida antarctica* lipase B (CAL-B-L2, CHIRAZYME L-2, c-f, C3, ≥400 U g^{-1}), *Candida rugosa* lipase (CRL, CHIRAZYME L-3, >250 U mg^{-1}) and *Candida antarctica* lipase A (CAL-A, CHIRAZYME L-5, 1 kU g^{-1}) were supplied by Roche Molecular Biochemicals. Immobilized *Pseudomonas cepacia* lipase (PSL-C, 783 U g^{-1}) is available commercially from Amano Pharmaceuticals. Porcine pancreas lipase (PPL crude, 100–400 U mg^{-1}) is a product from Sigma. Chemical reagents were purchased from Aldrich, Fluka, Lancaster or Prolabo and were of the highest quality grade available. Solvents were distilled from an appropriate desiccant under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Melting points were measured with a Gallenkamp apparatus on samples in open capillary tubes and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1720-X infrared Fourier transform spectrophotometer using KBr pellets. Optical rotations were measured using a Perkin-Elmer 241 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR, ^{13}C NMR and DEPT spectra were recorded with TMS (tetramethylsilane) as the internal standard with Bruker AC-300 (^{1}H: 300.13 MHz; ^{13}C: 75.4 MHz), Bruker AC-300 DPX (^{1}H: 300.13 MHz; ^{13}C:, 75.5 MHz) and Bruker NAV-400 (^{1}H: 400.13 MHz; ^{13}C: 100.5 MHz) spectrometers. The chemical shift values (δ) are given in ppm. Mass spectra were recorded with a Hewlett-Packard 110 series spectrometer. The enantiomeric excesses were determined by chiral HPLC analysis with a Hewlett-Packard 1100 LC liquid chromatograph equipped with a CHIRALCEL OD (Daicel) or a CHIRALCEL OB-H (Daicel) chiral column.

Determination of Absolute Configurations: Optically active *cis*- and *trans*-*N*-protected amino alcohols **9** and **13** were converted into the unprotected derivatives **4** and **8** by treatment with hydrogen in the presence of Pd/C in quantitative yield. The configuration of these compounds was established by comparison of the specific rotations measured with those previously reported: (–)-(3*R*,4*R*)-**4**,[7] (–)-(1*R*,2*S*)-**8**[11a] and (–)-(1*S*,2*S*)-**8**.[19] Compound (–)-(3*S*,4*R*)-**9** was converted by a Mitsunobu inversion of the hydroxy group into the optically pure protected amino alcohol (+)-(3*R*,4*R*)-**9** and subsequently deprotected to give *cis*-(–)-(3*R*,4*R*)-**4** whose specific rotation was compared with the one previously established.[7]

Synthesis of 3-Hydroxy-2,3-dihydro-4*H*-chromen-4-one [(±)-2] and 3,4-Dihydro-2-hydroxy-2*H*-naphthalen-1-one [(±)-6]: The α-hydroxy ketones were prepared by the method described by Moriarty et al.[14] Oxidation of commercially available chroman-4-one and α-tetralone yielded (±)-**2** (yellow solid, 84% yield) and (±)-**6** (yellow oil, 90% yield), respectively.

Synthesis of the α-Hydroxy Oximes (±)-3 and (±)-7: The corresponding α-hydroxy ketones (±)-**2** and (±)-**6** (1.0 g, 1.0 equiv.) were treated with hydroxylammonium chloride (1.1 equiv.) in pyridine (35 mL) at 0 °C. The reaction mixtures were warmed to room temperature and stirred for 16 h. Pyridine was then evaporated under reduced pressure and the crude product was extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, dried and concentrated under reduced pressure to afford a yellow oil which was purified by flash chromatography (dichloromethane/ethyl acetate, 1:1) to give (±)-**3** (764.0 mg, 70% yield)[7a] or (±)-**7** (1.0 g, 92% yield).

(±)-3,4-Dihydro-2-hydroxy-2*H*-naphthalen-1-one Oxime [(±)-7]: Yellow pale oil. IR (KBr): $\tilde{\nu}$ = 3453, 1649, 1608, 1573, 1477 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.90–2.02 (m, 2 H), 2.91–2.98 (m, 2 H), 3.24 (br. s, 1 H), 5.15 (t, $^3J_{HH}$ = 5.6 Hz, 1 H), 7.14–7.27 (m, 4 H), 7.81 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 25.9 (CH_2), 29.7 (CH_2), 64.1 (CH), 124.9 (CH), 127.0 (CH), 128.6 (CH), 129.9 (CH), 132.9 (C), 140.1 (C), 155.6 (C=N) ppm. MS (ESI$^+$): *m*/*z* (%) = 200 (95) [M + Na]$^+$, 178 (10) [M + H]$^+$. HRMS: calcd. for $C_{10}H_{11}NO_2$ [M$^+$] 177.07890; found 177.08021.

Preparation of (±)-*cis*-4-(Benzyloxycarbonylamino)chroman-3-ol [(±)-*cis*-9] and (±)-*cis*-1-(Benzyloxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-2-ol [(±)-*cis*-13]: Aqueous HBr (2.5 equiv.) and a catalytic amount of 10% Pd/C were added to a solution of the

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corresponding α-hydroxy oximes (±)-*cis*-**3** or (±)-*cis*-**7** (500 mg, 1.0 equiv.) in methanol (12 mL). The mixture was stirred at room temperature for 12 h and then filtered through a Celite pad in order to remove the catalyst. The solvent was evaporated under reduced pressure and the crude free 1,2-amino alcohols (±)-*cis*-**4** or -**8** were obtained and protected without purification. Benzyl chloroformate (2.2 equiv.) was added dropwise to a biphasic system of water (12 mL) and dichloromethane (6 mL) containing the bromine salt of the amino alcohol (±)-*cis*-**4** or -**8** (500 mg, 1.0 equiv.) and Na_2CO_3 (2.2 equiv.) at 0 °C. After 4 h, the mixture was extracted with dichloromethane (3 × 15 mL). The organic phase was washed with a 5% aqueous solution of sodium hydrogencarbonate (3 × 20 mL), dried with Na_2SO_4 and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:1) to afford (±)-*cis*-**9** (542.9 mg, 65% yield) or (±)-*cis*-**13** (595.7 mg, 71% yield).

(±)-*cis*-4-(Benzyloxycarbonylamino)chroman-3-ol [(±)-*cis*-9]: White solid. M.p. 164.7–166.2 °C. IR (KBr): $\tilde{\nu}$ = 3470, 3021, 1690, 1508 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 3.94–3.99 (m, 2 H), 4.05–4.15 (m, 2 H), 4.90 (dd, $^3J_{HH}$ = 9.3 Hz, $^4J_{HH}$ = 3.9 Hz, 1 H), 5.11 (s, 2 H), 5.30 (br. s, 1 H), 6.75 (d, $^3J_{HH}$ = 8.0 Hz, 1 H), 6.85 (t, $^3J_{HH}$ = 7.5 Hz, 1 H), 7.12 (t, $^3J_{HH}$ = 7.5 Hz, 1 H), 7.31–7.42 (m, 6 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100.5 MHz): δ = 49.7 (CH), 63.8 (CH), 65.9 (CH_2), 68.1 (CH_2), 116.1 (CH), 120.7 (CH), 122.8 (C), 128.2 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 137.6 (C), 154.3 (C), 157.1 (C=O) ppm. MS (ESI): *m*/*z* (%) = 322 (100) $[M+Na]^+$, 300 (15) $[M+H]^+$. HRMS: calcd. for $C_{17}H_{17}NO_4$ $[M]^+$ 299.11521; found 299.11442.

(±)-*cis*-1-(Benzyloxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-2-ol [(±)-*cis*-13]: Yellow solid. M.p. 91.1–92.5 °C. IR (KBr): $\tilde{\nu}$ = 3473, 3031, 1695, 1509 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.92–1.97 (m, 2 H), 2.39–2.46 (br. s, 1 H), 2.73–2.81 (m, 1 H), 2.88–3.02 (m, 1 H), 4.15–4.16 (m, 1 H), 4.91–4.99 (m, 1 H), 5.15 (s, 2 H), 5.34–5.37 (m, 1 H), 7.09–7.37 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 26.4 (CH_2), 27.7 (CH_2), 54.2 (CH), 67.9 (CH_2), 69.9 (CH), 127.2 (CH), 128.4 (CH), 128.6 (C), 128.9 (CH), 129.0 (CH), 129.4 (CH), 129.8 (CH), 135.2 (C), 136.9 (C), 158.0 (C=O) ppm. MS (ESI): *m*/*z* (%) = 320 (100) $[M+Na]^+$, 298 (25) $[M+H]^+$. HRMS: calcd. for $C_{18}H_{19}NO_3$ $[M]^+$ 297.13648; found 297.13636.

(±)-*trans*-4-(Benzyloxycarbonylamino)chroman-3-ol [(±)-*trans*-9]: 4-Nitrobenzoic acid (250 mg, 1.50 mmol), triphenylphosphane (400 mg, 1.50 mmol) and diethyl azodicarboxylate (230 μL, 1.50 mmol) were added dropwise to a solution of (±)-*cis*-4-(benzyloxycarbonylamino)chroman-3-ol [(±)-*cis*-**9**] (220 mg, 0.75 mmol) in THF (10 mL). The mixture was shaken overnight and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 9:1) to afford a *p*-nitrobenzoate ester, which was hydrolyzed in situ by treatment with a 0.2 M solution of sodium methoxide (2.5 mL) in methanol (20 mL) at 0 °C. The reaction mixture was stirred for 4 h and then treated with ammonium chloride until the pH was acidic. The solvent was evaporated and ethyl acetate was added in order to precipitate the salts formed. The crude residue was filtered off and the solvent was removed under reduced pressure. The reaction mixture was purified by flash chromatography using hexane/ethyl acetate (1:1) as eluent to obtain (±)-*trans*-**9** (156.2 mg, 71% yield). White solid. M.p. 157.2–159.1 °C. IR (KBr): $\tilde{\nu}$ = 3475, 3022, 1689 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.37 (s, 1 H), 3.77–4.19 (m, 3 H), 4.95 (m, 1 H), 5.18 (s, 2 H), 6.72–7.38 (m, 9 H), 8.29 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 50.3 (CH), 65.9 (CH), 67.8 (CH_2), 67.8 (CH_2), 114.5 (CH), 120.5 (CH), 125.9 (C), 126.8 (CH), 127.1 (CH), 127.2 (CH), 128.5 (C), 129.0 (CH), 129.5 (CH), 129.8 (CH), 142.2 (C), 155.7 (C), 156.1 (C=O) ppm. MS (ESI): *m*/*z* (%) = 322 (90) $[M+Na]^+$, 300 (35) $[M+H]^+$.

(±)-*trans*-2-Bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene [(±)-*trans*-11]: Prepared from dihydronaphthalene as a white solid (2.89 g, 83% yield) according to ref.[12a]

(±)-*trans*-1,2-Epoxy-1,2,3,4-tetrahydronaphthalene [(±)-*trans*-12]: NaOH pellets (200 mg, 5.0 mmol) were added at room temperature to a solution of (±)-*trans*-**11** (1.0 g, 4.41 mmol) in diethyl ether (15 mL). The mixture was stirred for 4 h. After this time, water (10 mL) was added and the reaction mixture was extracted with diethyl ether (3 × 20 mL). The organic phases were washed with brine (2 × 25 mL), dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified on a chromatographic column using hexane/ethyl acetate (2:1) as eluent to obtain the epoxide (±)-*trans*-**12** (441.3 mg) as a colorless oil in a 68% yield. Epoxide (±)-*trans*-**12** exhibited physical and spectral properties in agreement with those reported previously.[12a]

(±)-*trans*-1-(Benzyloxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-2-ol [(±)-*trans*-13]: A solution of (±)-**12** (500 mg, 3.42 mmol) in MeOH (20 mL) was cooled to 0 °C and NH_3 was bubbled through the solution for 15 min. After this, the mixture was heated at 50 °C for 16 h. The crude product obtained containing (±)-*trans*-**8** was protected with benzyl chloroformate in CH_2Cl_2 and water as described before to give (±)-*trans*-**13** in an overall yield of 71% (722.1 mg) after purification by flash chromatography using hexane/ethyl acetate (1:1) as eluent. M.p. 102.7–104.0 °C. IR (KBr): $\tilde{\nu}$ = 3475, 3035, 1697 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.83–1.94 (m, 1 H), 2.07–2.15 (m, 1 H), 2.83–2.89 (m, 2 H), 3.42 (br. s, 1 H), 3.89 (br. s, 1 H), 4.78 (t, $^3J_{HH}$ = 7.9 Hz, 1 H), 5.10–5.15 (m, 3 H), 7.06–7.41 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 27.8 (CH_2), 29.9 (CH_2), 58.3 (CH), 68.0 (CH_2), 73.4 (CH), 127.0 (CH), 128.0 (CH), 128.4 (C), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.1 (CH), 134.9 (C), 137.0 (C), 158.0 (C=O) ppm. MS (EI): *m*/*z* (%) = 298 (20) $[M+H]^+$, 297 (94) $[M]^+$.

Chemical Acetylation of the (±)-*cis*- and -*trans*-*N*-Protected Amino Alcohols: Acetic anhydride (2.0 equiv.) was added dropwise at 0 °C to a solution of the racemic *N*-protected amino alcohols (±)-*cis*/*trans*-**9** or -**13** (50 mg, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) and pyridine (2.0 equiv.) and the mixture stirred for 8 h and washed with 1.0 N HCl (3 × 10 mL). The organic fraction was dried with Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:1) to afford the corresponding racemic esters (±)-*cis*/*trans*-**14** or -**15** (75–87% yield).

Benzyl (±)-*cis*-*N*-(3-Acetoxychroman-4-yl)carbamate [(±)-*cis*-14]: White solid. M.p. 147.8–149.6 °C. IR (KBr): $\tilde{\nu}$ = 3040, 1731, 1690 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.05 (s, 3 H), 4.21 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 3.4 Hz, 1 H), 4.25 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 3.4 Hz, 1 H) 5.19–5.28 (m, 5 H), 6.86 (d, $^3J_{HH}$ = 8.3 Hz, 1 H), 6.97 (t, $^3J_{HH}$ = 7.2 Hz, 1 H), 7.19–7.43 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 20.9 (CH_3), 47.4 (CH), 65.3 (CH), 66.6 (CH_2), 67.2 (CH_2), 116.5 (CH), 120.1 (CH), 121.2 (C), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 129.1 (CH), 136.0 (C), 154.8 (C), 156.2 (C=O), 170.3 (C=O) ppm. MS (ESI): *m*/*z* (%) = 364 (80) $[M+Na]^+$, 342 (20) $[M+H]^+$. HRMS: calcd. for $C_{19}H_{19}NO_5$ $[M]^+$ 341.12631; found 341.12901.

Benzyl (±)-*cis*-*N*-(2-Acetoxy-1,2,3,4-tetrahydronaphthyl)carbamate [(±)-*cis*-15]: White solid. M.p. 112.9–115.1 °C. IR (KBr): $\tilde{\nu}$ = 3040,

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1725, 1689 cm^{-1}. M.p. 112.0–114.1 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.01 (s, 3 H), 2.19–2.25 (m, 2 H), 2.76–2.94 (m, 2 H), 4.39–4.44 (m, 1 H), 5.06–5.27 (m, 4 H), 7.09–7.39 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 20.9 (CH_3), 26.1 (CH_2), 26.9 (CH_2), 54.0 (CH_2), 66.1 (CH), 72.3 (CH), 126.4 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 134.6 (C), 135.7 (C), 136.2 (C), 156.0 (C=O), 171.0 (C=O) ppm. MS (ESI): *m*/*z* (%) = 362 (100) $[M+Na]^+$, 340 (15) $[M+H]^+$. HRMS: calcd. for $C_{20}H_{21}NO_4$ $[M]^+$ 339.14704; found 339.14551.

Benzyl (±)-*trans*-*N*-(3-Acetoxychroman-4-yl)carbamate [(±)-*trans*-14]: White solid. M.p. 153.1–155.2 °C. IR (KBr): $\tilde{\nu}$ = 3041, 1730, 1689 cm^{-1}. M.p. 163.1–164.9 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.02 (s, 3 H), 4.18 (dd, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 3.7 Hz, 1 H), 4.35 (dd, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 3.7 Hz, 1 H), 5.09–5.28 (m, 4 H), 6.81 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 6.92 (t, $^3J_{HH}$ = 8.4 Hz, 2 H), 7.18–7.42 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 20.9 (CH_3), 48.6 (CH), 67.3 (CH), 68.7 (CH_2), 69.4 (CH_2), 117.6 (CH), 123.2 (CH), 125.4 (C), 129.1 (CH), 129.2 (CH), 129.3 (CH), 129.6 (CH), 130.3 (CH), 137.0 (C), 155.9 (C), 157.2 (C=O), 171.3 (C=O) ppm. MS (ESI): *m*/*z* (%) = 364 (80) $[M+Na]^+$, 342 (20) $[M+H]^+$.

Benzyl (±)-*trans*-*N*-(2-Acetoxy-1,2,3,4-tetrahydronaphthyl)carbamate [(±)-*trans*-15]: White solid. M.p. 103.6–105.9 °C IR (KBr): $\tilde{\nu}$ = 3038, 1728, 1692 cm^{-1}. M.p. 100.9–102.6 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.03 (s, 3 H), 2.09–2.29 (m, 2 H), 2.90–2.94 (m, 2 H), 4.95–5.26 (m, 5 H), 7.11–7.40 (9 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 20.9 (CH_3), 26.0 (CH_2), 26.5 (CH_2), 53.8 (CH_2), 66.8 (CH), 72.7 (CH), 126.5 (CH), 127.6 (CH), 128.03 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 134.6 (C), 135.8 (C), 136.4 (C), 156.3 (C=O), 170.7 (C=O) ppm. MS (ESI): *m*/*z* (%) = 362 (100) $[M+Na]^+$, 340 (5) $[M+H]^+$.

Typical Procedure for the Enzymatic Acylation of the (±)-*cis*- and -*trans*-*N*-Protected Amino Alcohols: The lipase (50 mg) and vinyl acetate (10 equiv., except when used as the solvent) were added to a solution of the racemic *N*-protected amino alcohol (±)-*cis*/*trans*-**9** or -**13** (50 mg, 1.0 equiv.) in the selected organic solvent (15 mL) at room temperature. The resulting mixture was shaken at the established temperature and at 250 r.p.m. in a rotatory shaker. The progress of the reaction was monitored by TLC using hexane/ethyl acetate (1:1) as eluent. Once the reaction was finished, the enzyme was filtered off, washed with ethyl acetate and the solvent evaporated under reduced pressure. The crude residue was then purified by flash chromatography (hexane/ethyl acetate, 1:1) to afford compounds (+)- or (–)-*cis*/*trans*-**14** or -**15** and the corresponding enantiomer of the remaining substrate (+)- or (–)-*cis*/*trans*-**9** or -**13**.

(+)-(3*R*,4*R*)-9: Determination of the *ee* by HPLC analysis: Chiralcel OD, 25 °C, hexane/2-propanol (90:10), 0.5 mL min^{-1}, t_R = 31.95 min. $[\alpha]_D^{23}$ = +48.1 (*c* = 0.78, $CHCl_3$), *ee* = 82%. (–)-(3*S*,4*S*)-**9**: t_R = 30.17 min, *ee* = 5%.

(+)-(3*S*,4*R*)-9: Determination of the *ee* by HPLC analysis: Chiralcel OD, 25 °C, hexane/2-propanol (90:10), 0.5 mL min^{-1}, t_R 35.96 min. $[\alpha]_D^{23}$ = +78.4 (*c* = 0.97, $CHCl_3$), *ee* 84%.

(–)-(1*R*,2*S*)-13: Determination of the *ee* by HPLC analysis: Chiralcel OD, 25 °C, hexane/2-propanol (90:10), 0.5 mL min^{-1}, t_R = 32.30 min. $[\alpha]_D^{23}$ = –41.9 (*c* = 0.6, MeOH), *ee* = 81%.

(–)-(1*S*,2*S*)-13: Determination of the *ee* by HPLC analysis: Chiralcel OD, 25 °C, hexane/2-propanol (90:10), 0.5 mL min^{-1}, t_R = 36.11 min. $[\alpha]_D^{23}$ = –89.0 (*c* = 0.82, $CHCl_3$), *ee* ≥ 99%.

(–)-(3*S*,4*S*)-14: Determination of the *ee* by HPLC analysis: Chiralcel OB-H, 35 °C, hexane/2-propanol (90:10), 0.7 mL min^{-1}, t_R = 35.45 min. $[\alpha]_D^{23}$ = –32.4 (*c* = 1.12, $CHCl_3$), *ee* ≥ 99%. (+)-(3*R*,4*R*)-**14**: HPLC, t_R = 37.18 min. $[\alpha]_D^{23}$ = +10.3 (*c* = 1.52, $CHCl_3$), *ee* = 34%.

(–)-(3*R*,4*S*)-14: Determination of the *ee* by HPLC analysis: Chiralcel OB-H, 35 °C, hexane/2-propanol (90:10), 0.7 mL min^{-1}, t_R = 35.45 min. $[\alpha]_D^{23}$ = –83.2 (*c* = 0.65, $CHCl_3$), *ee* ≥ 99%.

(+)-(1*S*,2*R*)-15: Determination of the *ee* by HPLC analysis: Chiralcel OD, 25 °C, hexane/2-propanol (90:10), 0.5 mL min^{-1}, t_R = 35.72 min. $[\alpha]_D^{23}$ = +28.6 (*c* = 0.75, MeOH), *ee* ≥ 99%.

(+)-(1*R*,2*R*)-15: Determination of the *ee* by HPLC analysis: Chiralcel OD, 25 °C, hexane/2-propanol (90:10), 0.5 mL min^{-1}, t_R = 28.52 min. $[\alpha]_D^{23}$ = +72.4 (*c* = 0.52, $CHCl_3$), *ee* ≥ 99%.

General Procedure for the Cleavage of the Benzyloxycarbonyl Group: Pd/C (10 mg) was added under hydrogen to a solution of *N*-protected amino alcohol *cis*/*trans*-**9** or -**13** (100 mg, 1.0 equiv.) in ethanol (3 mL) at room temperature. The progress of the reaction was monitored by TLC using hexane/ethyl acetate (1:1) as eluent. After 24 h, the resulting mixture was filtered through Celite and washed with ethanol. The solvent was then evaporated under reduced pressure to obtain the corresponding free amino alcohol *cis*/*trans*-**4** or -**8** (71–88% yield).

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