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Lipase-catalyzed resolution of chiral 1,3-amino alcohols: application in the asymmetric synthesis of (*S*)-dapoxetine

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Abstract—The enzymatic resolution of 3-amino-3-phenylpropan-1-ol derivatives has been studied through acylation processes. *Candida antarctica* lipase A (CAL-A) has been identified as the best biocatalyst for the transesterification reaction of 3-amino-3-phenyl-1-*tert*-butyldimethylsilyloxy-propan-1-ol using ethyl methoxyacetate as acylating agent and *tert*-butyl methyl ether as solvent. This enzymatic study has allowed us to obtain a valuable intermediate for the production of (*S*)-dapoxetine, which has been synthesized in good overall yield and high enantiomeric excess.

1. Introduction

Optically active 1,3-amino alcohols have found important applications in synthetic and medicinal chemistry, as they have been used as chiral auxiliaries and ligands in asymmetric synthesis.[1] In addition, they can also be used as chiral building blocks for the synthesis of many biologically active compounds.[2] Nowadays, the asymmetric synthesis of individual enantiomers is extremely important because the (*S*)- and (*R*)-isomers usually display very different pharmacological or physiological properties.[3] For example, the enantiomer (*S*)-(+)-*N*,*N*-dimethyl-α-[2-(1-naphthalenyloxy)ethyl]benzenemethanamine [(*S*)-dapoxetine, **1**, Fig. 1] is a potent serotonin re-uptake inhibitor for treating depression and other disorders as bulimia or anxiety.[4] Moreover, (*S*)-dapoxetine is currently being tested as a treatment for premature ejaculation in men,[5] however rare examples of chemical synthesis have been described in the literature.[6]

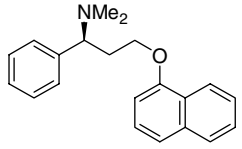

Figure 1. Structure of (*S*)-dapoxetine.

Biocatalysis is considered as an ideal tool for the preparation of enantiomerically pure compounds and has been widely exploited for the resolution of racemic mixtures in the preparation of pharmaceuticals.[7] Lipases in particular have proven to be excellent biocatalysts for application in asymmetric synthesis,[8] including the kinetic resolution of racemic alcohols, acids, esters or amines,[9] as well as the desymmetrization of prochiral compounds.[10] The resolution of racemic β-amino esters derivatives has been extensively described in the literature through enzymatic procedures,[11] however little attention has been paid to the resolution of 1,3-amino alcohols, because good bioresolutions are usually achieved with necessary protection of the amino or hydroxyl group, and migration of acyl groups normally takes place. Although recent examples have described the kinetic resolution of cyclic 1,3-aminoalcohols,[12] to the best of our knowledge there are no reports of enzymatic resolution of acyclic derivatives.

Herein we report our studies on the enzymatic kinetic resolution of 3-amino-3-phenylpropan-1-ol derivatives in terms of enzyme, acyl donor, solvent and other parameters that have influence in biocatalytic processes. Later application of a valuable intermediate obtained by this methodology will be applied in the synthesis of (*S*)-dapoxetine.

2. Results and discussion

First, we synthesized 3-amino-3-phenylpropan-1-ol **4** from benzaldehyde, a process which involves two steps: forma-

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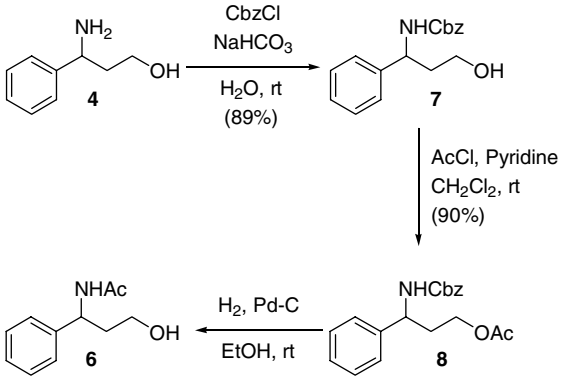
tion of 3-amino-3-phenylpropionic acid **3** following a modified procedure of the one reported by Tan and Weaver,[13] and next chemical reduction to afford the corresponding amino alcohol (Scheme 1). In this manner, benzaldehyde was reacted with malonic acid and ammonium acetate in refluxing EtOH for 12 h, obtaining **3** after filtration and final recrystallization in 68% isolated yield. 3-Amino-3-phenylpropionic acid was then reduced using $LiAlH_4$ to afford **4** in 77% yield.

At this point we decided to resolve **4** by direct enzymatic acylation of the amino group using a non-activated ester such as ethyl acetate, as acyl donor (Scheme 2).[14] For a screening test of enzymes, we selected *tert*-butyl methyl ether (TBME) as the solvent using 5 equiv of EtOAc.

Candida antarctica lipase A (CAL-A) and *Candida cylindracea* (CCL) did not show any activity, while *Chromobacterium viscosum* (CVL), *Pseudomonas cepacia* (PSL), *C. antarctica* type B (CAL-B) and lipase from porcine pancreas (PPL) showed poor enantioselectivities in the formation of diacetylated product **5** and the *N*-monoacetylated compound **6**. To explain the low enantiopreference in these processes, we decided to study the possibility of acetyl migration between the amino and the hydroxyl group. In this manner, the amino group was selectively protected as a benzyloxycarbonyl amide and the hydroxyl group was then acetylated using acetyl chloride to produce **8** (Scheme 3). The final hydrogenation reaction, catalyzed by Pd–C, was carried out, causing the migration of the acetyl group from the oxygen atom to the amino group, so that the *N*-acetylated product **6** was isolated instead of the *O*-acetylated compound. This fact can explain the poor results observed in the direct enzymatic acetylation of **4**.

Due to the low enantioselectivities achieved in the direct enzymatic acetylation of **4**, we decided to explore other routes for resolution using modified derivatives of this compound. Thus, as previously mentioned, we protected the amino group with benzyl chloroformate in dichloromethane to study the lipase-catalyzed resolution through the alcohol group of the *N*-protected derivative **7**, a strategy that was successfully employed in the enzymatic resolution of cyclic 1,3-amino alcohols in our research group (Scheme 4).[12f,h]

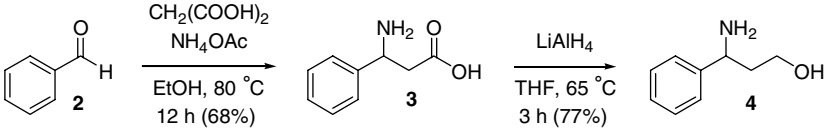


Scheme 3. Study of the acyl migration between the amino and the hydroxyl group.

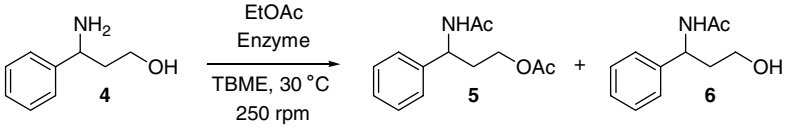
The reaction between racemic **7** and ethyl acetate was conducted using CAL-B and PSL-C as biocatalysts because they previously exhibited some grade of reactivity in the reaction with **4**, however low enantioselectivities were also observed (data not shown).

Finally we decided to protect the alcohol group as a silyl ether to later resolve the molecule by enzymatic acylation of the amino group. Initial experiments using trimethylsilyl chloride led to the formation of the corresponding *O*-silylated compound but it was impossible to recover after flash chromatography because the ether was deprotected in acidic conditions. As a result we decided to use *tert*-butyldimethylsilyl chloride (TBDMSCl) thus obtaining **9** in excellent isolated yield, which was reacted in different enzymatic conditions initially using EtOAc as acyl donor (Scheme 5).

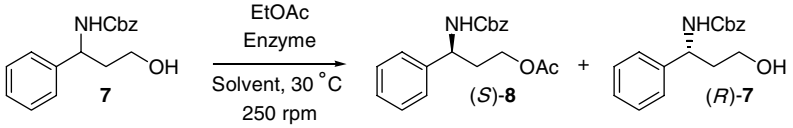
First we screened different biocatalysts in TBME using 5 equiv of EtOAc for a total molarity solution of 0.2, observing no reaction with CAL-B and PSL-C after 53 h (Table 1, entries 1 and 2), meanwhile CAL-A showed a promising $E = 37$ for a 13% conversion after 77 h (entry 3), a good starting point for the optimization of this process. This is not a surprising result as CAL-A has been identified as an ideal catalyst for the resolution of sterically hindered compounds.[15] To increase the conversion of the reaction we decided to increase the amount of acyl donor and after just 17 h, the conversion reached 15% with an



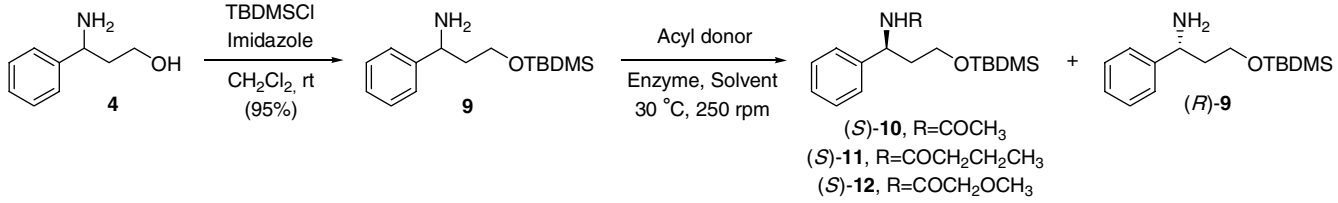
Scheme 1. Chemical synthesis of (±)-**4**.



Scheme 2. Kinetic resolution by direct enzymatic acylation of (±)-**4**.



Scheme 4. Resolution of (±)-**7** by enzymatic transesterification using EtOAc.



Scheme 5. Resolution of (±)-**9** by enzymatic acylation.

Table 1. Kinetic resolution of **9** by enzymatic acylation

Entry	Enzyme	Solvent	Molarity (M)	Acyl donor (equiv)	t (h)	ee_S (%)[a]	ee_P (%)[a]	c (%)[b]	E[c]
1	CAL-B[d]	TBME	0.2	EtOAc (5)	53	—	—	—	—
2	PSL-C[d]	TBME	0.2	EtOAc (5)	53	—	—	—	—
3	CAL-A[d]	TBME	0.2	EtOAc (5)	77	14	94	13	37
4	CAL-A[d]	—	0.2	EtOAc (50)	17	16.5	95	15	46
5	CAL-A[e]	—	0.2	EtOAc (50)	26	33	83	29	15
6	CAL-A[e]	—	0.1	EtOAc (100)	27	39	91	30	31
7	CAL-A[e]	TBME	0.1	EtOAc (50)	26	25	82	23	13
8	CAL-A[e]	TBME	0.1	EtOBu (50)	26.5	40	91	30	31
9	CAL-A[e]	TBME	0.1	EtOMac (50)	8.5	54	93	37	48

[a] Determined by HPLC.
[b] Determined by ^{1}H NMR.
[c] $E = \ln[(1-c)\times(1-ee_P)]/\ln[(1-c)\times(1+ee_P)]$.
[d] Ratio in weight enzyme: amino alcohol (0.5:1).
[e] Ratio in weight enzyme: amino alcohol (1:1).

$E = 46$ (entry 4). The use of double the amount of enzyme increased the conversion but the E value dramatically decreased (entry 5). With this amount of enzyme and using a double excess of EtOAc, the enzyme showed a similar reactivity, but the E value was much higher (entry 6).

At this point we turned our attention to the influence of the acyl donor in the enzymatic process, selecting activated esters as isopropenyl acetate or vinyl acetate, and other non-activated esters for the enzymatic resolution of **9** like ethyl butyrate (EtOBu) and ethyl methoxyacetate (EtOMac). Low enantioselectivities were achieved with activated esters, while using ethyl butyrate or ethyl methoxyacetate, conversions up to 30% were reached isolating (*S*)-**11** and (*S*)-**12** with high ee in comparison with the reaction with EtOAc (entries 7–9). The best results were obtained by employing ethyl methoxyacetate, recovering (*S*)-**12** in 93% ee and 37% yield.

On the basis of the high efficiency of EtOMac as an acyl donor, different amounts of it were attempted with the data shown in Table 2 (Scheme 6). The use of 50 equiv of acyl donor, reached after 27 h a conversion of 47% with (*S*)-**12** in 91% ee (entry 1). However, the best enantioselectivity was obtained using a lower amount of acyl donor, especially in the case of 5 equiv, isolating the final product in 96% ee with an $E = 85$ (entry 3).

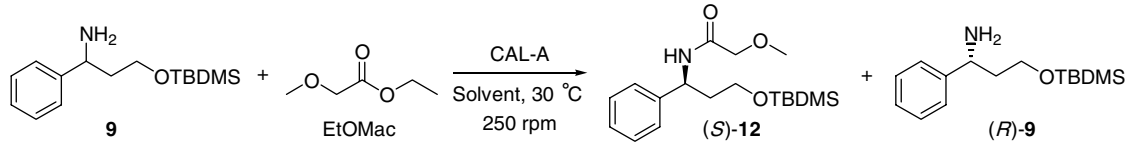
Finally, we chose different solvents observing that under the same reaction conditions, no improvements were observed using toluene, 1,4-dioxane, THF or dichloromethane instead of TBME (entries 4–8).

To end our research by finding an interesting application for the chiral building blocks obtained through enzymatic procedures, the chemical synthesis of (*S*)-dapoxetine was carried out using (*S*)-**12** in 93% ee as intermediate, which was hydrolyzed with an HCl 6 M solution to the corresponding alcohol (*S*)-**4** occurring with in situ deprotection of the silyl ether (Scheme 7). Later dimethylation of the amino group led to the formation of (*S*)-**13** in high yield. At this point, we performed the Ullmann condensation of **13** with 1-iodonaphthalene using CuI or CuCl in the presence of methyl lithium and pyridine.[16] However only the starting material was recovered. For that reason we decided to react (*S*)-**13** with mesyl chloride to activate the oxygen atom but migration of the dimethylamino and hydroxyl group occurred via an azetidinium ion, leading to the formation of (*S*)-3-(*N*,*N*-dimethylamino)-1-phenylpropan-1-ol as the major product.[17] Finally the formation of enantiomerically enriched (*S*)-dapoxetine in 72% isolated yield was possible by nucleophilic substitution under Mitsunobu conditions, using 1-naphthol in the presence of DEAD, PPh_3 and THF as solvent, without the loss of enantiomeric excess as verified by HPLC analysis.

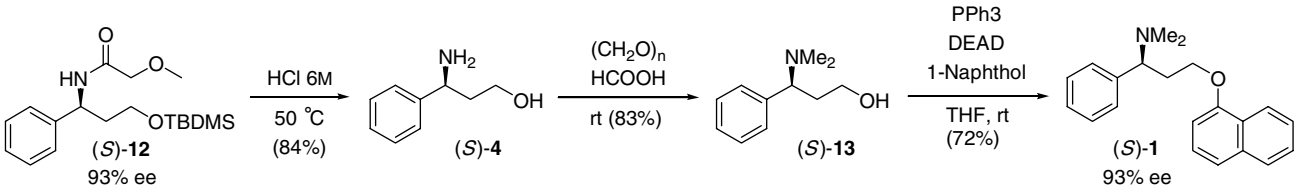
Table 2. Kinetic resolution of **9** in a solution 0.1 M with CAL-A and EtOMac at 30 °C

Entry	EtOMac (equiv)	Solvent	t (h)	ee_S (%)[a]	ee_P (%)[a]	c (%)[b]	E[c]
1	50	TBME	27	70	91	47	54
2	25	TBME	27	78.5	93	46	71
3	5	TBME	27	54	96	36	85
4	25	TBME	47	90	92	49	71
5	25	Toluene	47	37	78	32	12
6	25	1,4-Dioxane	47	3.5	49	7	3
7	25	THF	47	31	65	33	6
8	25	CH_2Cl_2	47	—	79	25	—

[a] Determined by HPLC.
[b] Determined by ^{1}H NMR.
[c] $E = \ln[(1-c)\times(1-ee_P)]/\ln[(1-c)\times(1+ee_P)]$.



Scheme 6. Enzymatic resolution of **9** using ethyl methoxyacetate, CAL-A and TBME.



Scheme 7. Synthesis of (*S*)-dapoxetine from (*S*)-**12**.

3. Conclusions

In conclusion, we have carried out an exhaustive study of the parameters that have influence in the enzymatic resolution of 3-amino-3-phenylpropan-1-ol, finding the best conditions when the oxygen atom is protected as a *tert*-butyldimethylsilyl ether and using ethyl methoxyacetate as acyl donor and TBME as solvent. The synthesis of the corresponding optically enriched intermediate (*S*)-**12** has allowed us to successfully prepare (*S*)-dapoxetine in high enantiomeric excess.

4. Experimental

4.1. General

C. antarctica lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) and *C. viscosum* lipase (CVL, 4100 U/mg) were a gift from Novo Nordisk Co. *C. antarctica* lipase type A (CAL-A, Chirazyme L-5, c-f, lyophilized, 1000 U/g using tributyrin) was acquired from Roche. Lipase from Porcine pancreas (PPL, 46 U/mg) and *C. cylindracea* lipase (CCL, 1141 U/mg) were acquired from Sigma. *P. cepacia* lipase (PSL-C, 783 U/g) was obtained from Amano Pharmaceutical Co. All other reagents were purchased from Aldrich, Acros or Sigma and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatographies were performed using silica gel 60 (230–240 mesh). Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded on using NaCl plates or KBr pellets in a Perkin–Elmer 1720-X F7. ^{1}H, ^{13}C NMR, DEPT and ^{1}H–^{13}C heteronuclear experiments were obtained using AC-200 (^{1}H, 200.13 MHz and ^{13}C, 50.3 MHz), AV-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz), DPX 300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or AV-400 (^{1}H, 400.13 MHz and ^{13}C, 100.6 MHz) spectrometers. The chemical shifts are given in delta (δ) values and the coupling constants (J) in hertz (Hz). $APCI^+$ or ESI^+ using a HP1100 chromatograph mass detector was used to record mass spectra (MS). Microanalyses were performed on a Perkin–Elmer model 2400 instrument. Measurement of the optical rotation was done on a Perkin–Elmer 241 polarimeter. High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph UV detector at 210 nm using a Daicel Chiralcel OD or OB-H column (25 cm × 4.6 mm I.D.).

4.2. 3-Amino-3-phenylpropionic acid 3

A similar procedure to the one described by Tan and Weaver was followed with some modifications.[13] Benzaldehyde (3.2 g, 30.0 mmol), ammonium acetate (3.1 g, 40.2 mmol) and malonic acid (3.1 g, 30.2 mmol) were refluxed in EtOH

(50 mL) for 12 h. The reaction mixture was cooled to room temperature and the white solid was collected by filtration washing with EtOH (25 mL) and Et_2O (25 mL). The solid was recrystallized in a mixture MeOH/H_2O (10:1) affording 3.37 g of **3** as a crystalline solid (68% isolated yield). ^1H NMR (D_2O/K_2CO_3, 300 MHz): 7.45–7.36 (m, 5H, Ar), 4.32 (t, 1H, H_3, $^3J_{HH} = 7.35$ Hz), 2.70–2.57 (m, 2H, H_2).

4.3. 3-Amino-3-phenylpropan-1-ol 4

A solution of **3** (923 mg, 5.6 mmol) in dry THF (20 mL) was cooled to 0 °C and $LiAlH_4$ (636 mg, 16.8 mmol) added in small portions. The reaction mixture was refluxed for 2 h following the disappearance of the starting material by TLC analysis. The reaction mixture was cooled to 0 °C, and the hydride excess destroyed adding H_2O dropwise. The grey mixture was extracted in EtOAc (3×20 mL) and the organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by *flash* chromatography (100% MeOH) isolating 650 mg of **4** as a white solid (77% isolated yield). R_f (100% MeOH): 0.15; mp: 76–77 °C; IR (KBr) ν 3387, 3348, 3281, 2940, 1578, 1457, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.37–7.22 (m, 5H, Ar), 4.11 (t, 1H, H_3, $^3J_{HH} = 5.59$ Hz,), 3.78 (t, 2H, H_1, $^3J_{HH} = 5.39$ Hz), 2.77 (br s, 3H, NH_2 and OH), 1.92–1.85 (m, 2H, H_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 146.0 (C_4), 128.5 (2C, $C_5+C_{5'}$), 127.0 (C_7), 125.6 (2C, $C_6+C_{6'}$), 61.7 (C_1), 56.0 (C_3), 39.6 (C_2); MS (ESI^+, *m/z*): 152 [$(M+H)^+$, 100%], 174 [$(M+Na)^+$, 9%]; Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.3; H, 8.6; N, 9.3.

4.4. 3-(Acetylamino)-3-phenylpropyl acetate 5

To a solution of **6** (57 mg, 0.4 mmol) in dry CH_2Cl_2 (0.6 mL) under a nitrogen atmosphere, was added pyridine (81 μL, 1.0 mmol). The mixture was cooled to 0 °C and acetyl chloride added dropwise (114 μL, 1.6 mmol). The reaction mixture was stirred at room temperature for 2 h and then the solvent evaporated under reduced pressure. The crude was purified by *flash* chromatography (90% EtOAc/MeOH) affording 81 mg of **5** as a white solid (87% isolated yield). R_f (90% EtOAc/MeOH): 0.37; mp: 90–91 °C; IR (KBr) ν 3311, 3060, 3029, 2972, 2923, 2839, 1732, 1650, 1547, 1426, 1370, 1242, 756, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.32–7.22 (m, 5H, Ar), 6.57 (br d, 1H, NH, $^3J_{HH} = 3.95$ Hz), 5.07 (dd, 1H, H_5, $^3J_{HH} = 15.32$ Hz, $^3J_{HH} = 7.61$ Hz), 4.10–3.93 (m, 2H, H_3), 2.12–2.01 (m, 2H, H_4), 2.00 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 170.9 (C=O), 169.4 (C=O), 141.3 (C_8), 128.6 (2C, $C_9+C_{9'}$), 127.4 (C_{11}), 126.3 (2C, $C_{10}+C_{10'}$), 61.3 (C_3), 50.5 (C_5), 34.6 (C_4), 23.1 (CH_3), 20.7 (CH_3); MS (ESI^+, *m/z*): 236 [$(M+H)^+$, 13%]; Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.3; H, 7.3; N, 5.9.

4.5. *N*-(3-Hydroxy-1-phenylpropyl)acetamide 6

To a solution of **4** (100 mg, 0.66 mmol) in a mixture of THF (1)/H_2O (1) (0.66 mL) was added $NaHCO_3$ (166 mg, 1.98 mmol) and Ac_2O (63 μL, 0.66 mmol). The mixture was stirred at room temperature during 22 h. The reaction was stopped by adding H_2O (2 mL) and the solution extracted with EtOAc (3×2 mL). The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by flash chromatography (90% EtOAc/MeOH) affording 72.5 mg of **6** as a white solid (57% isolated yield). R_f (90% EtOAc/MeOH): 0.25; mp: 128–129 °C; IR (KBr) ν 3268, 3225, 2360, 1639, 1559, 1372, 1265, 1073, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.39–7.26 (m, 5H, Ar), 6.04 (br s, 1H, NH), 5.24–5.16 (m, 1H, H_3), 3.66–3.59 (m, 2H, H_1), 3.44 (br s, 1H, OH), 2.24–2.00 (m, 4H, $1H_2+3H_9$), 1.90–1.79 (m, 1H, $1H_2$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 170.6 (C=O), 141.2 (C_4), 128.8 (2C, $C_5+C_{5'}$), 127.7 (C_7), 126.6 (2C, $C_6+C_{6'}$), 58.7 (C_1), 50.6 (C_3), 38.5 (C_2), 23.2 (C_9); MS ($APCI^+$, *m/z*): 194 [$(M+H)^+$, 100%]; Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.4; H, 7.9; N, 7.2.

4.6. Benzyl-(3-hydroxy-1-phenylpropyl)carbamate 7

To a solution of **4** (249 mg, 1.5 mmol) in H_2O (1.5 mL) was added Na_2CO_3 (126 mg, 1.5 mmol) and the mixture was cooled to 0 °C. Over the mixture was added benzyl chloroformate (211 μL, 1.5 mmol) and the reaction was stirred at room temperature for 16 h, following the progress of the reaction by TLC analysis (100% MeOH). The reaction crude was extracted with $CHCl_3$ (3×10 mL) and the organic phases were combined, dried over Na_2SO_4 and evaporated under reduce pressure. The residue was purified by flash chromatography affording 383 mg of a white solid (90% isolated yield). R_f (60% EtOAc/hexane): 0.33; mp: 44–45 °C; IR (KBr) ν 3322, 2952, 1694, 1538, 1258, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.34–7.26 (m, 10H, Ar), 5.84 (br d, 1H, NH, $^3J_{HH} = 7.89$ Hz), system AB (δ_A 5.12 δ_B 5.06, 2H, H_4, $^2J_{AB} = 19.55$ Hz), 4.95 (m, 1H, H_3), 3.74–3.68 (m, 2H, H_1), 3.32 (br s, 1H, OH), 2.08–2.01 (m, 1H, H_2), 1.91–1.83 (m, 1H, H_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 156.3 (C=O), 141.6, 136.1, 128.5, 128.3, 127.9, 127.9, 127.2, 126.1 (12C, Ar), 66.7 (C_4), 58.8 (C_1), 52.4 (C_3), 38.6 (C_2); MS (ESI^+, *m/z*): 286 [$(M+H)^+$, 13%], 308 [$(M+Na)^+$, 100%]; Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.6; H, 6.7; N, 4.9.

4.7. 3-[[(Benzyloxy)carbonyl]amino]-3-phenylpropyl acetate 8

Same procedure than **5**, except for using **7** instead of **6** as the starting material. R_f (50% EtOAc/hexane): 0.57; mp: 47–49 °C; IR (KBr) ν 3418, 2978, 1694, 1556, 1238, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.41–7.29 (m, 10H, Ar), 5.28 (d, 1H, NH, $^3J_{HH} = 8.1$ Hz), system AB (δ_A 5.14 δ_B 5.10, 2H, H_5, $/^2J_{AB}/ = 20.19$ Hz), 4.91 (m, 1H, H_4), 4.19–4.03 (m, 2H, H_2), 2.18–2.09 (m, 2H, H_3), 2.06 (s, 3H, H_1); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 170.8 (C=O), 155.5 (C=O), 136.2, 128.7, 128.7, 128.7, 128.4, 128.0, 127.6, 126.2 (12C, Ar), 66.8 (C_5), 61.2 (C_2), 52.7 (C_4), 35.2 (C_3), 20.8 (C_1); MS (ESI^+, *m/z*): 328 [$(M+H)^+$, 6%], 350 [$(M+Na)^+$, 100%]; Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.8; H, 6.5; N, 4.3.

4.8. 3-Amino-*O*-*tert*-butyldimethylsilyl-3-aryl-propan-1-ol 9

To a solution of **4** (351 mg, 1.32 mmol) in dry CH_2Cl_2 (9.6 mL) under a nitrogen atmosphere, were added imidazole (225 mg, 3.31 mmol), 4-DMAP (16 mg, 0.13 mmol) and TBDMSCl (399 mg, 2.65 mmol). The mixture was stirred overnight and the disappearance of the starting material was followed by TLC analysis (100% MeOH). The reaction was stopped by adding NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL), the organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by *flash* chromatography isolating 333 mg of **9** as a colourless oil (95% isolated yield). R_f (20% MeOH/EtOAc): 0.24; $[\alpha]_D^{20} = +7.1$ (*c* 0.55, $CHCl_3$) for 58% ee; IR (NaCl) *v* 3375, 2954, 1256, 1098, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.43–7.25 (m, 5H, Ar), 4.13 (t, 1H, H_6, $^3J_{HH} = 10.1$ Hz), 3.77–3.55 (m, 2H, H_4), 1.94–1.84 (m, 2H, H_5), 1.78 (br s, 2H, NH_2), 0.92 (s, 9H, $3H_1+3H_{1'}+3H_{1''}$), 0.06 (s, 6H, $3H_3+3H_{3'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 143.3 (C_7), 128.4 (2C, $C_8+C_{8'}$), 127.2 (C_{10}), 126.6 (2C, $C_9+C_{9'}$), 59.9 (C_4), 53.2 (C_6), 40.5 (C_5), 25.7 (3C, $C_1+C_{1'}+C_{1''}$), 18.0 (C_2), −5.6 (2C, $C_3+C_{3'}$); MS (ESI^+, *m*/*z*): 265 [$(M+H)^+$, 100%]; Anal. Calcd for $C_{15}H_{27}NOSi$: C, 67.88; H, 10.26; N, 5.28. Found: C, 67.9; H, 10.3; N, 5.4.

4.9. Enzymatic kinetic resolution of 9 by enzymatic aminolysis

In a typical procedure, to a suspension of **9** and CAL-A in TBME was added the corresponding acyl donor and the mixture shaken at 30 °C following the progress of the reaction by HPLC. After removal of the enzyme by filtration, evaporation of the solvent and ^1H NMR analysis of the crude, the residual mixture was purified by *flash* chromatography (gradient eluent 35% EtOAc/hexane to 100% EtOAc) to give (*S*)-**10**, **11** or **12** and (*R*)-**9**.

4.10. (*S*)-*N*-(*O*-*tert*-Butyldimethylsilyl-3-hydroxy-1-phenylpropyl)acetamide 10

R_f (50% EtOAc/hexane): 0.33; IR (NaCl) *v* 3286, 2926, 1738, 1651, 1552, 1257, 1098, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.31–7.21 (m, 5H, Ar), 6.96 (br d, 1H, NH, $^3J_{HH} = 7.89$ Hz), 5.18 (dd, 1H, H_6, $^3J_{HH} = 11.61$ Hz, $^3J_{HH} = 7.02$ Hz), 3.66–3.52 (m, 2H, H_4), 2.14–2.02 (m, 1H, H_5), 1.94 (s, 3H, H_{12}), 1.93–1.84 (m, 1H, H_5), 0.90 (s, 9H, $H_1+H_{1'}+H_{1''}$), 0.03 (s, 6H, $H_3+H_{3'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 160.4 (C=O), 128.9 (C_7), 128.4 (2C, $C_8+C_{8'}$), 126.9 (C_{10}), 126.2 (2C, $C_9+C_{9'}$), 60.3 (1C, C_4), 52.3 (C_6), 37.6 (C_5), 25.8 (3C, $C_1+C_{1'}+C_{1''}$), 23.4 (C_{12}), 18.3 (C_2), −5.6 (2C, $C_3+C_{3'}$); MS (ESI^+, *m*/*z*): 308 [$(M+H)^+$, 91%], 330 [$(M+Na)^+$, 56%], 637 [$(2M+Na)^+$, 100%]; Anal. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.41; H, 9.51; N, 4.56. Found: C, 66.4; H, 9.5; N, 4.6.

4.11. *N*-(*O*-*tert*-Butyldimethylsilyl-3-hydroxy-1-phenylpropyl)butanamide 11

R_f (25% EtOAc/hexane): 0.22; IR (NaCl) *v* 3288, 2929, 1644, 1548, 1257, 1104, 886 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.36–7.21 (m, 5H, Ar), 6.94 (br d, 1H, NH, $^3J_{HH} = 6.6$ Hz), 5.21 (dd, 1H, H_6, $^3J_{HH} = 11.82$ Hz, $^3J_{HH} = 6.78$ Hz), 3.69–3.54 (m, 2H, H_4), 2.21–2.06 (m, 3H, $H_{12}+1H_5$), 1.97–1.87 (m, 1H, H_5), 1.75–1.63 (m, 2H, H_{13}), 0.98–0.93 (m, 12H, $H_{14}+H_1+H_{1'}+H_{1''}$), 0.06 (s, 6H, $H_3+H_{3'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 172.0 (C=O), 141.7 (C_7), 128.3 (2C, $C_8+C_{8'}$), 126.8 (C_{10}), 126.2 (2C, $C_9+C_{9'}$), 60.3 (C_4), 52.0 (C_6), 38.9 (C_{12}), 37.7 (C_5), 25.8 (3C, $C_1+C_{1'}+C_{1''}$), 19.2 (C_{13}), 18.1 (C_2), 13.7 (C_{14}), −5.59 (2C, $C_3+C_{3'}$); MS (ESI^+, *m*/*z*): 336 [$(M+H)^+$, 226%], 358 [$(M+Na)^+$, 100%]; Anal. Calcd for $C_{19}H_{33}NO_2Si$: C, 68.01; H, 9.92; N, 4.18; N, 4.56. Found: C, 68.0; H, 9.9; N, 4.2.

4.12. *N*-(*O*-*tert*-Butyldimethylsilyl-3-hydroxy-1-phenylpropyl)methoxyacetamide 12

R_f (25% EtOAc/hexane): 0.15; $[\alpha]_D^{20} = -40.5$ (*c* 0.7, $CHCl_3$) for 93% ee; IR (NaCl) *v* 3406, 3296, 2929, 1667, 1525, 1256, 1114, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.61 (br d, 1H, NH, $^3J_{HH} = 12.1$ Hz), 7.35–7.24 (m, 5H, Ar), 5.31–5.21 (m, 1H, H_6), system AB (δ_A 3.94 δ_B 3.89, 2H, H_{12}, $/^2J_{AB}/ = 18.39$ Hz), 3.64–3.53 (m, 2H, H_4), 3.43 (s, 3H, H_{13}), 2.13–1.97 (m, 2H, H_5), 0.91 (s, 9H, $H_1+H_{1'}+H_{1''}$), 0.05 (s, 6H, $H_3+H_{3'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 168.7 (C=O), 141.5 (C_7), 128.4 (2C, $C_8+C_{8'}$), 127.0 (C_{10}), 126.3 (2C, $C_9+C_{9'}$), 72.0 (C_{12}), 60.1 (C_4), 58.9 (C_{13}), 50.9 (C_6), 38.0 (C_5), 25.8 (3C, $C_1+C_{1'}+C_{1''}$), 18.3 (C_2), −5.6 (2C, $C_3+C_{3'}$); MS (ESI^+, *m*/*z*): 338 [$(M+H)^+$, 36%], 360 [$(M+Na)^+$, 28%], 697 [$(2M+Na)^+$, 100%]; Anal. Calcd for $C_{18}H_{31}NO_3Si$: C, 64.06; H, 9.27; N, 4.15. Found: C, 64.0; H, 9.2; N, 4.2.

4.13. (*S*)-3-Amino-3-phenylpropan-1-ol 4

A solution of (*S*)-**12** (209 mg, 0.62 mmol) in an aqueous solution of HCl 6 M (6.2 mL) was stirred at 50 °C during 23 h until complete disappearance of the starting material (TLC 25% EtOAc/hexane). The solution was basified using NaOH 4 M and extracted with EtOAc (3×8 mL). The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by *flash* chromatography (100% MeOH) affording 80 mg of a white solid (84% isolated yield). $[\alpha]_D^{20} = -11.2$ (*c* 0.5, $CHCl_3$) for 93% ee.

4.14. (*S*)-3-(*N*,*N*-Dimethylamino)-3-phenylpropan-1-ol 13

To a solution of (*S*)-**4** (100 mg, 0.38 mmol) in formic acid (78 μL), was added a 30% aqueous solution of formaldehyde (157 μL, 2.10 mmol) and the mixture refluxed over 8 h. After this time the solution was acidified with HCl concd until pH = 1 and basified with NaOH 4 N. The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by flash chromatography (60% MeOH/EtOAc) affording 56 mg of a hygroscopic solid (83% isolated yield). R_f (60% MeOH/EtOAc): 0.20; $[\alpha]_D^{20} = +38.0$ (*c* 0.6, $CHCl_3$) for 93% ee; IR (NaCl) *v* 3384, 2948, 2868, 2780, 1455, 1162, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.38–7.17 (m, 5H, Ar), 3.86–3.80 (m, 2H, $2H_1$), 3.74 (dd, 1H, H_3, $^3J_{HH} = 10.49$ Hz, $^3J_{HH} = 3.77$ Hz), 2.47–2.34 (m, 1H, $1H_2$), 2.18 (s, 6H, $3H_4+3H_{4'}$), 1.71–1.62 (m, 1H, $1H_2$);

^{13}C NMR ($CDCl_3$, 75.5 MHz): 136.1 (C_5), 128.8, 127.9 (4C, C_6+$C_{6'}$+C_7+$C_{7'}$), 127.4 (C_8), 70.1(C_3), 63.4 (C_1), 41.0 (2C, C_4+$C_{4'}$), 32.1 (C_2); MS (ESI$^+$, *m*/*z*): 180 [(M+H)$^+$, 100%], 202 [(M+Na)$^+$, 12%]; Anal. Calcd for $C_{11}H_{17}NO$: C, 73.69; H, 9.56; N, 7.82. Found: C, 73.7; H, 9.6; N, 7.9.

4.15. (*S*)-Dapoxetine (1)

To a solution of (*S*)-**13** (30 mg, 0.17 mmol) in dry THF (2.4 mL) under nitrogen atmosphere was added 1-naphthol (49 mg, 0.34 mmol). The mixture was cooled to 0 °C and PPh_3 (89 mg, 0.34 mmol) and DEAD (53.5 μL, 0.34 mmol) were successively added. The solution was allowed to warm until room temperature and stirred during 15 h. The solution was evaporated and the crude purified by *flash* chromatography (gradient eluent 100% EtOAc to 10% MeOH/EtOAc) isolating 37 mg of a colourless oil (72% isolated yield). R_f (20% MeOH/EtOAc): 0.33; $[\alpha]_D^{20} = +62.5$ (*c* 0.3, $CHCl_3$) for 93% ee; IR (NaCl) *v* 2959, 2955, 1727, 1271 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.27–8.24 (m, 1H, Ar), 7.81–7.78 (m, 1H, Ar), 7.58–7.51 (m, 2H, Ar), 7.47–7.31 (m, 7H, Ar), 6.73–6.70 (m, 1H, Ar), 4.18–4.01 (m, 1H, H_1), 3.99–3.93 (m, 1H, H_1), 3.71–3.66 (m, 1H, H_3), 2.77–2.65 (m, 1H, H_2), 2.40–2.31 (m, 1H, H_2), 2.32 (s, 6H, H_4+$H_{4'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 154.5, 139.3, 134.3, 132.1, 131.9, 128.5, 128.3, 128.2, 127.3, 126.2, 125.8, 125.5, 125.0, 121.9, 119.9, 104.4 (16C, Ar), 67.6 (1C, C_3), 65.5 (1C, C_1), 42.7 (2C, C_4+$C_{4'}$), 32.9 (1C, C_2); MS (ESI$^+$, *m*/*z*): 306 [(M+H)$^+$, 100%]; Anal. Calcd for $C_{21}H_{23}NO$: C, 82.57; H, 7.60; N, 4.59. Found: C, 82.7; H, 7.7; N, 4.6.

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