A General Methodology for the Synthesis of Enantiopure 1,5-Aminoalcohols

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Dedication ((optional))

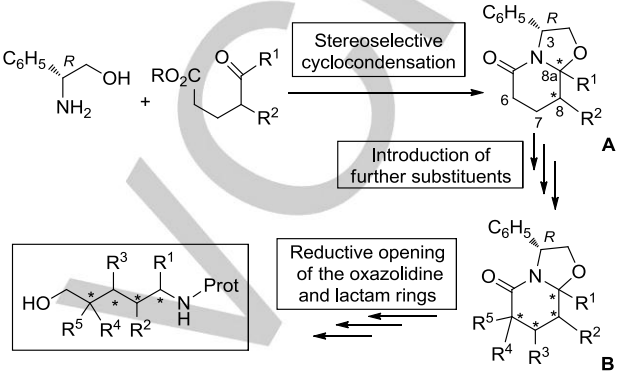
A variety of (*R*)-phenylglycinol-derived oxazolopiperidone lactams (**1**-**14**) are converted to linear-chain enantiopure aminodiols (**15**-**26**) by reduction with $LiNH_2BH_3$ in an unprecedented process involving the simultaneous reductive opening of the oxazolidine and lactam rings. The subsequent removal of the phenylethanol moiety gave enantiopure 5-amino-1-pentanols bearing substituents at the 2-, 3-, 4-, 2,2-, 2,3- 2,4- and 3,4-positions (**28**-**36**), which were isolated as the *N*-Boc derivatives.

Introduction

Functionalized nitrogen-containing small molecules are useful starting materials for the synthesis of natural products and medicinally relevant targets. Thus, the development of general procedures for the enantioselective preparation of particular types of these building blocks, enabling access to a variety of stereochemistries and substitution patterns, represents an important synthetic goal.

In previous work,[1] we have reported the stereoselective preparation of chiral non-racemic oxazolopiperidone lactams **A** by cyclocondensation of (*R*)-phenylglycinol with δ-oxoacid derivatives[2] (Scheme 1). Starting from a keto acid (R^1 = alkyl or aryl), the reaction directly installs a substituent at the angular C-8a position, whereas starting from a racemic γ-substituted δ-oxoacid derivative (R^2 = alkyl or aryl), it stereoselectively leads to enantiopure C-8 substituted lactams in a process that involves a dynamic kinetic resolution of the racemic substrate. Taking advantage of the versatile functionality and conformational rigidity of these bicyclic lactams, additional substituents can be stereoselectively introduced at the C-6 ring position by (di)alkylation reactions and at C-7 by conjugate addition to the corresponding α,β-unsaturated lactams.

With procedures available for the regio- and stereocontrolled preparation of enantiopure bicyclic lactams **B** bearing substituents at the different positions of the piperidine ring, we envisioned that the reductive cleavage of the oxazolidine and lactam rings would open a general synthetic entry to diversely substituted enantiopure 1,5-aminoalcohols. In this way, we would access a variety of related enantiopure functionalized acyclic derivatives, taking advantage of the fact that chiral centers are easier to install in conformationally rigid cyclic systems than in acyclic compounds.[3]



Scheme 1. Synthetic strategy: access to enantiopure 1,5-aminoalcohols.

Several procedures have been employed for the ring-opening of δ-lactams. Although the direct acidic or alkaline hydrolysis requires somewhat drastic reaction conditions, *N*-Boc protected lactams undergo alkaline hydrolysis or methanolysis under mild conditions.[4] There are also a few examples of the reductive cleavage of *N*-Boc and *N*-Ts piperidones using borohydride salts to give 1,5-aminoalcohols,[5] as well as of ring-opening of *N*-acyl and *N*-alkoxycarbonyl δ-lactams with Grignard reagents leading to δ-amino ketones.[6,7] For the specific case of 8a-substituted oxazolopiperidone lactams, there are also some precedents of cleavage, either by direct hydrolysis under acidic conditions to give δ-keto acid derivatives or by hydride or organometallic attack to the lactam carbonyl, followed by hydrolysis of the resulting carbinolamine. In the latter cases, the initially formed 1,5-dicarbonyl derivatives undergo *in situ* aldolization to give cyclohexenones.[2a-c] No nitrogen-containing linear-chain products are formed.

Results and Discussion

For the reductive opening of oxazolopiperidone lactams,[8] we selected lithium amidotrihydroborate ($LiNH_2BH_3$),[9] which is a highly nucleophilic reducing agent that can be easily generated by *in situ* deprotonation of the commercially available $BH_3{\cdot}NH_3$ complex.[10] Although $LiNH_2BH_3$ has been extensively used for the direct reduction of linear-chain tertiary amides to primary alcohols,[9,11,12] there are only two isolated examples of the $LiNH_2BH_3$ reduction of lactams to aminoalcohols.[13] On the other hand, the use of lithium *N,N*-dialkylaminoborohydrides ($LiNR_2BH_3$) results in the conversion of five- and six-membered *N*-alkyl lactams to the corresponding cyclic amines.[14]

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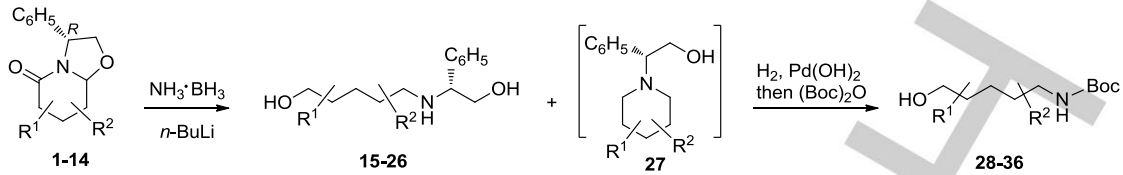
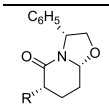
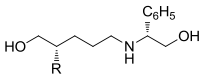
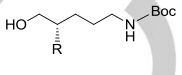
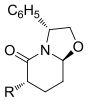
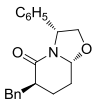
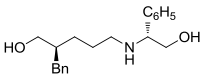
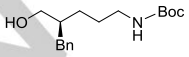
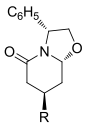
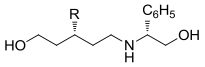
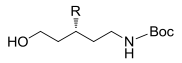
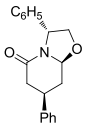
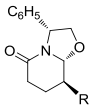
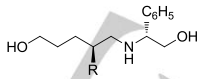
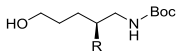
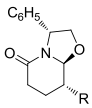
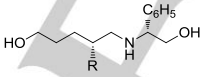
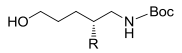
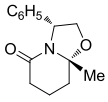
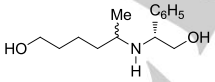
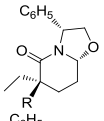
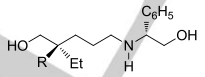
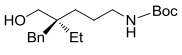
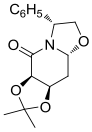
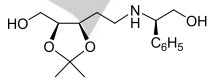
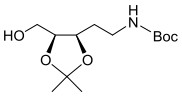
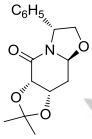
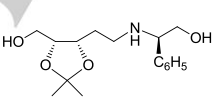
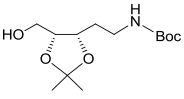
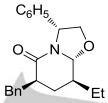
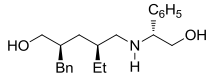
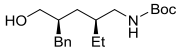
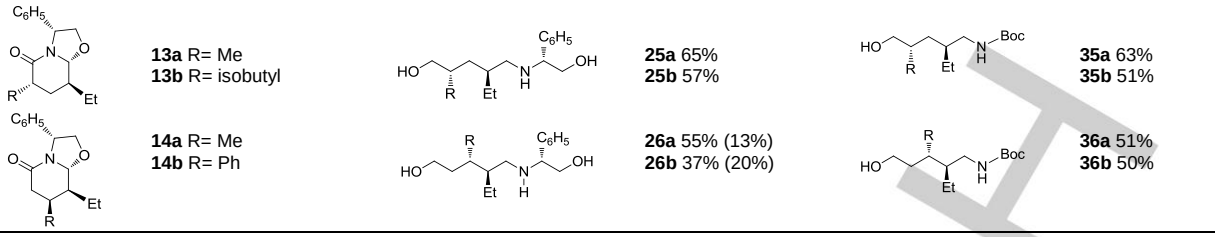
Table 1. Access to enantiopure substituted 1,5-aminoalcohols from chiral oxazolopiperidone lactams.



Starting Lactam[a]		Aminodiol, yield[b]		*N*-Boc aminoalcohol, yield	
	**1a** R= Me **1b** R= Et		**15a** 64% (6%) **15b** 65% (10%)		**28a** 48% **28b** 55%
	**2a** R= Me **2b** R= Et **2c** R= 3,5-$F_2C_6H_3CH_2$		**15a** 58% (5%) **15b** 80% (6%) **15c** 65% (12%)		**28c** 50%
	**3**		**16** 65% (5%)		**29** 60%
	**4a** R= Me **4b** R= Ph		**17a** 50% (15%) **17b** 43% (15%)		**30a** 60% **30b** 50%
	**5**		**17b** 65% (8%)		
	**6a** R= Me **6b** R= Et **6c** R= *i*-Pr **6d** R= C_6H_5 **6e** R= Bn		**18a** 75% (7%) **18b** 80% **18c** 71% (7%) **18d** 57% **18e** 70%		**31a** 70% **31b** 65% **31c** 50% **31d** 53% **31e** 51%
	**7a** R= Me **7b** R= Et		**19a** 55% (11%) **19b** 50% (9%)		*ent*-**31a** 57% *ent*-**31b** 55%
	**8**		**20** 50% (16%)		
	**9a** R= Bn **9b** R= Allyl		**21a** 69% **21b** 56% (9%)		**32** 50%
	**10**		**22** 40%		**33** 52%
	**11**		**23** 40% (12%)		*ent*-**33** 60%
	**12**		**24** 55%		**34** 55%



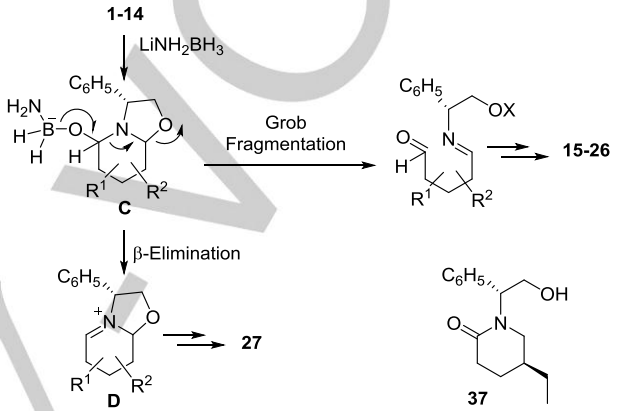
[a] For the preparation of the starting lactams, see the Experimental Section. [b] If isolated, the yields of the corresponding *N*-[(1*R*)-2-hydroxy-1-phenylethyl]piperidines (**27**) are given in brackets.

Table 1 outlines the results obtained in the $LiNH_2BH_3$ (4.3 equiv.) reduction of a variety of oxazolopiperidone lactams (**1**-**14**), either with a 3-H/8a-H *cis* or *trans* relative configuration. They include 6-, 7-, 8-, and 8a-substituted as well as 6,6-, 6,7-, 6,8-, and 7,8-disubstituted derivatives, which differ not only in the position but also in the nature of the substituents and the configuration of stereocenters on the piperidine ring. In all cases, the reduction afforded the corresponding linear-chain aminodiol (**15**-**26**), in an unprecedented process involving the reductive cleavage of both the oxazolidine and lactam rings. Minor amounts of the corresponding *N*-(2-hydroxy-1-phenylethyl)piperidines (**27**) were isolated in some cases as by-products.

The subsequent removal of the phenylethanol moiety present in the above aminodiols by hydrogenolysis, followed by treatment of the resulting primary amines with Boc_2O, led to a wide range of enantiopure *N*-Boc 5-aminopentanols (**28-36**) bearing substituents at the 2-, 3-, 4-, 2,2-, 2,3-, 2,4-, and 3,4-positions.

The formation of aminodiols **15**-**26** can be rationalized by considering that the intermediate **C**, formed after the initial hydride attack to the lactam carbonyl, undergoes a Grob-type fragmentation[15] (Scheme 2, **C**, see arrows) with cleavage of the B–O, C–N, and C–O bonds, which is facilitated by the complexation of borane species to the oxazolidine heteroatoms. A subsequent reduction of the resulting imino aldehyde would lead to **15**-**26**. Alternatively, expulsion of lithium dihydridoamino-borinate from **C** promoted by the nitrogen lone pair would give a tetrahydropyridinium species **D** that would undergo further reduction to piperidines **27**. In agreement with the above concerted mechanism leading to aminodiols **15-26**, a similar $LiNH_2BH_3$ reduction of lactam **37**, which cannot undergo Grob fragmentation, gave (76% yield) a nearly equimolecular mixture of aminodiol **18b** and the corresponding piperidine (**27**; R^1= 3*S*-Et, R^2= H).

As in the reduction of tertiary amides with related $LiNR_2BH_3$ reagents,[12] the amount of the tertiary amine by-product formed in the above $LiNH_2BH_3$ reductions may also be related with the steric requirements of the lactam. Thus, the formation of piperidines **27** was more favored in the more sterically demanding lactams, for instance, in lactams **4**, **8,** and **14** bearing a C-7 axial substituent.



Scheme 2. Proposed mechanism for the $LiNH_2BH_3$ reduction.

Conclusions

The procedure reported herein provides access to structurally diverse enantiopure 5-amino-1-pentanols bearing a variety of substitution patterns, substituents (alkyl, benzyl, aryl, protected hydroxyl), and stereochemistries. The only limitation encountered was in the reduction of 8a-substituted lactams (*e.g.*, **8**), which afforded the corresponding aminodiol **20** as a nearly equimolecular epimeric mixture.

Our approach opens the first general synthetic entry to enantiopure 5-amino-1-pentanols, functionalized nitrogen-containing building blocks that have been scarcely reported in the literature.[16] As both enantiomers of phenylglycinol are commercially available, the methodology allows the preparation of 5-aminopentanols in both enantiomeric series.

Experimental Section

General Procedures: All air sensitive manipulations were carried out under a dry argon or nitrogen atmosphere. Analytical thin-layer chromatography was performed on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located with 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography, and was carried out on SiO_2 (SDS silica gel 60 ACC, 35-75 mm, 230-240 mesh ASTM. NMR spectra were recorded at 300 or 400 MHz (^{1}H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, integrated intensity,

multiplicity, coupling constant (*J*) in hertz (Hz), and assignment (when possible). Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (*g*-HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avantar 320 FT-IR, and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured on Perkin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HRMS; LC/MSD TOF Agilent Technologies) were performed by *Centres Científics i Tecnològics* of the University of Barcelona.

(3*R*,6*R*,8a*S*)-6-(3,5-Difluorobenzyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*] pyridine (2c): LiHMDS (4.5 mL, 4.49 mmol) was added to a solution of lactam (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine[1a] (650 mg, 3.00 mmol) in anhydrous THF (34 mL), and the mixture was stirred at –78 ºC for 1 h. Then, 3,5-difluorobenzyl bromide (0.46 mL, 3.59 mmol) was added, and the mixture was stirred at –78 ºC for 8 h and at room temperature for 15 h. The reaction was quenched by the addition of NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and evaporated. The resulting residue was chromatographed (from 9:1 hexane–EtOAc to EtOAc) to afford **2c** (450 mg, 44%) as a colorless oil, its **6*S* epimer** (120 mg, 12%), and **(3*R*,8a*S*)-6,6-bis(3,5-difluorobenzyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine** (40 mg, 3%). Data for **2c**: $[\alpha]^{22}_D$ = +12.4 (*c* = 0.8, $CHCl_3$). IR (film): υ = 1649 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.46-1.55 (m, 2H, H-7, H-8), 1.81-1.86 (m, 1H, H-7), 2.30-2.36 (m, 1H, H-8), 2.60-2.65 (m, 1H, H-6), 3.02-3.10 (m, 2H, CH_2Ar), 3.68 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.49 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.88 (m, 1H, H-8a), 5.24 (t, *J* = 8.1 Hz, 1H, H-3), 6.65-6.69 (m, 3H, F-ArH), 7.17-7.20 (m, 2H, ArH), 7.26-7.37 (m, 3H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 22.1 (C-7), 27.9 (C-8), 37.5 (CH_2Ar), 43.0 (C-6), 58.5 (C-3), 72.9 (C-2), 88.7 (C-8a), 101.8 (F-Ar C-4, t, $J_{C\text{-}F}$ = 24.7 Hz), 112.2 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 16.7, 7.5 Hz), 125.7 (C-*o*), 127.5 (C-*p*), 128.8 (C-*m*), 139.2 (C-*i*), 142.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.2 Hz), 162.8 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 247.9, 13.2 Hz), 169.9 (CO) ppm; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{20}F_2NO_2$ 344.1457; found 344.1454. Data for **6*S* epimer**: $[\alpha]^{22}_D$ = –105.1 (*c* = 0.55, $CHCl_3$). IR (film): υ = 1724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.59-1.69 (m, 2H, H-7, H-8), 1.70-1.78 (m, 1H, H-7), 2.13-2.20 (m, 1H, H-8), 2.64 (m, 2H, H-6, CH_2Ar), 3.01 (m, 1H, CH_2Ar), 3.78 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 4.77 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 5.00 (m, 1H, H-8a), 5.28 (t, *J* = 7.9 Hz, 1H, H-3), 6.63 (m, 1H, F-ArH), 6.68-6.76 (m, 2H, F-ArH), 7.25-7.29 (m, 3H, ArH), 7.32-7.36 (m, 2H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 20.4 (C-7), 25.2 (C-8), 36.7 (CH_2Ar), 41.4 (C-6), 58.4 (C-3), 72.3 (C-2), 88.2 (C-8a), 101.8 (F-Ar C-4, t, $J_{C\text{-}F}$ = 25.2 Hz), 111.8 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 6.2 Hz), 126.2 (C-*o*), 127.6 (C-*p*), 128.7 (C-*m*), 139.4 (C-*i*), 143.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.3 Hz), 163.0 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 249.2, 13.3 Hz), 170.4 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{20}F_2NO_2$ 344.1457; found 344.1454. Data for **(3*R*,8a*S*)-6,6-Bis(3,5-difluorobenzyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine:** $[\alpha]^{22}_D$ = –29.6 (*c* = 1.25, $CHCl_3$). IR (film): υ = 1636 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.06-1.25 (m, 1H, H-7), 1.72-1.77 (m, 2H, H-7, H-8), 2.00-2.09 (m, 1H, H-8), 2.35 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 2.78 (d, *J* = 13.3 Hz, 1H, CH_2Ar), 3.28 (d, *J* = 13.3 Hz, 1H, CH_2Ar), 3.33 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 3.63 (dd, *J* = 9.2, 8.1 Hz, 1H, H-2), 4.37 (dd, *J* = 9.2, 8.1 Hz, 1H, H-2), 4.65 (dd, *J* = 9.0, 4.5 Hz, 1H, H-8a), 5.15 (t, *J* = 8.1 Hz, 1H, H-3), 6.47-6.51 (m, 2H, F-ArH), 6.67-6.77 (m, 1H, F-ArH), 7.05-7.09 (m, 2H, ArH), 7.31-7.44 (m, 3H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 23.8 (C-7), 25.3 (C-8), 44.4 (CH_2Ar), 44.8 (CH_2Ar), 47.6 (C-6), 59.4 (C-3), 73.1 (C-2), 88.4 (C-8a), 102.3 (F-Ar C-4, t, $J_{C\text{-}F}$ = 24.9 Hz), 102.6 (F-Ar C-4, t, $J_{C\text{-}F}$ = 25.6 Hz), 113.2 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 6.9 Hz), 113.6 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 7.0 Hz), 126.1 (C-*o*), 127.7 (C-*p*), 128.9 (C-*m*), 138.8 (C-*i*), 140.6 (F-Ar C-1, t, $J_{C\text{-}F}$ = 8.5 Hz), 141.0 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.3 Hz), 162.5 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 248.5, 12.8 Hz), 162.9 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 249.2, 13.3 Hz), 171.1 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{24}F_4NO_2$ 470.1738; found 470.1736.

(3*R*,7*R*,8a*R*)-3,7-Diphenyl-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (4b): A solution of (3*R*,7*R*,8a*R*)-6-(benzyloxycarbonyl)-5-oxo-3,7-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine[1d] (1.15 g, 2.69 mmol) in anhydrous MeOH (100 mL) containing 10% Pd–C (115 mg) was stirred under hydrogen at 25 ºC for 17 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil, which was dissolved in toluene (80 mL). The solution was heated to reflux for 3 h, cooled, and concentrated. The residue was chromatographed (1:1 hexane–EtOAc) to give pure compound **4b** (630 mg, 80%): $[\alpha]^{22}_D$ = –121.2 (*c* = 1.1, $CHCl_3$). IR (film): υ = 1655, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 2.27 (ddd, *J* = 12.9, 9.6, 5.9 Hz, 1H, H-8), 2.52 (dt, *J* = 12.9, 5.0 Hz, 1H, H-8), 2.66 (d, *J* = 5.4 Hz, 2H, H-6), 3.52 (ddd, *J* = 9.6, 5.4, 5.0 Hz, 1H, H-7), 4.02 (dd, *J* = 9.0, 1.4 Hz, 1H, H-2), 4.11 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.71 (dd, *J* = 9.3, 4.2 Hz, 1H, H-8a), 4.96 (t, *J* = 5.7, 1H, CHN), 7.22-7.37 (m, 10H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 35.2 (C-7, C-8), 36.8 (C-6), 58.7 (C-3), 73.9 (C-2), 86.0 (C-8a), 126.4 (C-*o*), 126.8 (C-*o*), 126.9 (C-*p*), 127.6 (C-*p*), 128.6 (C-*m*), 128.8 (C-*m*), 141.3 (C-*i*), 143.0 (C-*i*), 167.1 (NCO) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{20}NO_2$ 294.1489; found 294.1489.

(3*R*,7*R*,8a*S*)-3,7-Diphenyl-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (5): TFA (1.6 mL, 20.4 mmol) was added to a solution of pure lactam **4b** (630 mg, 2.15 mol) in anhydrous CH_2Cl_2 (66 mL), and the mixture was stirred at room temperature for 47 h. The resulting acidic solution was neutralized with a 2 N aqueous $NaHCO_3$ (25 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were dried and concentrated, and the residue was chromatographed (1:1 hexane–EtOAc) to give pure **5** (610 mg, 97%): $[\alpha]^{22}_D$ = –58.2 (*c* = 1.0, $CHCl_3$). IR (film): υ = 1647, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.87 (ddd, *J* = 13.3, 12.4, 9.3 Hz, 1H, H-8), 2.47 (dd, *J* = 18.0, 12.0 Hz, 1H, H-6), 2.56 (dm, 1H, H-8), 2.84 (ddd, *J* = 18.0, 5.6, 1.72 Hz, 1H, H-6), 3.20 (m, 1H, H-7), 3.84 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 4.56 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 5.20 (dd, *J* = 9.3, 4.5 Hz, 1H, H-8a), 5.32 (t, *J* = 7.9, 1H, CHN), 7.21-7.37 (m, 10H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 35.3 (C-7, C-8), 39.7 (C-6), 58.0 (C-3), 72.7 (C-2), 88.4 (C-8a), 126.1 (C-*o*), 126.4 (C-*o*), 127.0 (C-*p*), 127.6 (C-*p*), 128.7 (C-*m*), 128.8 (C-*m*), 139.3 (C-*i*), 142.4 (C-*i*), 168.1 (NCO) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{20}NO_2$ 294.1489; found 294.1496.

(3*R*,6*R*,7*R*,8a*R*)-6,7-(Isopropylidenedioxy)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (10): To a solution of (3*R*,8a*R*)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine[1d] (600 mg, 2.79 mmol) in CH_3CN (28 mL) and H_2O (0.1 mL) were added *N*-oxide-*N*-methylmorpholine (323 mg, 2.79 mmol) and OsO_4 (1.0 mL of a 2.5% in *t*-BuOH), and the mixture was stirred at room temperature for 17 h. The resulting solution was quenched with saturated aqueous $Na_2S_2O_5$ and stirred for an additional 1 h. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (8:2 EtOAc–EtOH), to give **(3*R*,6*R*,7*R*,8a*R*)-6,7-dihydroxy-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine** (390 mg, 62%): $[\alpha]^{22}_D$ = +9.31 (*c* = 0.13, EtOH). IR (film): υ = 3416, 1654, 1469 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.97-2.04 (m, 1H, H-8), 2.78 (dt, *J* = 13.3, 4.0 Hz, 1H, H-8), 2.84 (s, 1H, OH), 2.85 (s, 1H, OH), 3.93 (d, *J* = 3.2 Hz, 1H, H-6), 4.11 (dd, *J* = 9.0, 2.0 Hz, 1H, H-

2), 4.27 (dd, *J* = 9.0, 7.5 Hz, 1H, H-2), 4.46 (m, 1H, H-7), 4.89 (dd, *J* = 7.5, 2.0 Hz, 1H, H-3), 5.21 (dd, *J* = 9.8, 4.0 Hz, 1H, H-8a), 7.26-7.32 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 32.1 (C-8), 58.3 (C-3), 66.1 (C-7), 70.9 (C-6), 74.7 (C-2), 86.5 (C-8a), 126.6 (C-*o*), 127.9 (C-*p*), 128.6 (C-*m*), 140.5 (C-*i*), 167.8 (NCO) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{13}H_{16}NO_4$ 250.1074; found 250.1075. *p*-Toluenesulfonic acid (39 mg, 0.22 mmol) and dimethoxypropane (1.07 mL, 8.74 mmol) were added to a solution of the above diol (390 mg, 1.56 mmol) in CH_2Cl_2 (7.8 mL), and the mixture was stirred at room temperature overnight. Solid sodium acetate (2.9 g) was added, and the mixture was stirred for 20 minutes, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NaCl, dried, filtered, concentrated. Flash chromatography (1:1 hexane−EtOAc) of the residue gave **10** (350 mg, 77%): $[\alpha]^{22}_D$ = –48.2 (*c* = 1.05, $CHCl_3$). IR (film): υ = 1664, 1448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.37 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.94 (ddd, *J* = 13.7, 10.1, 3.7 Hz, 1H, H-8), 2.71 (dt, *J* = 13.7, 2.6 Hz, 1H, H-8), 4.11 (dd, *J* = 9.1, 0.8 Hz, 1H, H-2), 4.23 (dd, *J* = 9.1, 6.5 Hz, 1H, H-2), 4.43 (d, *J* = 6.6 Hz, 1H, H-6), 4.67-4.70 (m, 1H, H-7), 4.98 (d, *J* = 6.5 Hz, 1H, H-3), 5.11 (dd, *J* = 10.1, 2.6 Hz, 1H, H-8a), 7.23-7.34 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 23.5 (CH_3), 26.0 (CH_3), 33.6 (C-8), 58.6 (C-3), 71.4 (C-7), 73.8 (C-2), 74.5 (C-6), 84.4 (C-8a), 109.2 (*C*Me$_2$), 126.5 (C-*o*), 127.5 (C-*p*), 128.3 (C-*m*), 140.3 (C-*i*), 163.3 (NCO) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{16}H_{20}NO_4$ 290.1387; found 290.1391.

(3*R*,6*S*,8*S*,8a*R*)-8-Ethyl-6-(isobutyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*] pyridine (13b): A solution of lactam **6b**[17] (739 mg, 3.0 mol) in anhydrous THF (5 mL) was added to a cooled (–78 ºC) solution of LiHMDS (1M in THF, 4.52 mL, 4.52 mmol) in anhydrous THF (33 mL). After the solution was stirred at –78 ºC for 1h, 1-iodo-2-methylpropane (0.87 mL, 7.53 mmol) was added, and stirring was continued at –78 ºC for 6 h and at room temperature for an additional 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (from 8:2 to 1:1 hexane–EtOAc) afforded **13b** (320 mg, 35%) and its **6*R* epimer** (95 mg, 11%). Data for **13b**: $[\alpha]^{22}_D$ = –29.4 (*c* = 0.57, $CHCl_3$). IR (film): υ = 2955, 1657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.83 (d, *J* = 6.5 Hz, 3H, CH_3), 0.89 (d, *J* = 6.5 Hz, 3H, CH_3), 1.06 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.09-1.16 (m, 1H, H-7), 1.21-1.28 (m, 1H, H-8), 1.34-1.43 (m, 1H, CH$_3$C*H*$_2$), 1.64-1.74 (m, 1H, C*H*Me$_2$), 1.76-1.91 [m, 3H, CH$_3$C*H*$_2$, C*H*$_2$(CHMe$_2$)], 2.08-2.14 (ddd, *J* = 14.0, 7.0, 3.2 Hz, 1H, H-7), 2.22-2.30 (m, 1H, H-6), 4.00 (dd, *J* = 9.0, 1.1 Hz, 1H, CH_2O), 4.12 (dd, *J* = 9.0, 6.5 Hz, 1H, CH_2O), 4.50 (d, *J* = 8.8 Hz, 1H, H-8a), 4.85 (d, *J* = 6.5 Hz, 1H, CHN), 7.19-7.31 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 10.9 (*C*H$_3$CH$_2$), 21.0 (CH_3), 23.5 (CH_3), 24.1 (CH$_3$*C*H$_2$), 25.0 (*C*HMe$_2$), 30.4 (C-7), 39.4 (C-6), 40.7 (C-8), 41.0 [*C*H$_2$(CHMe$_2$)], 59.3 (C-3), 73.7 (C-2), 92.3 (C-8a), 126.4 (C-*o*), 127.3 (C-*p*), 128.4 (C-*m*), 141.8 (C-*i*), 170.0 (CO) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{19}H_{28}NO_2$ 302.2115; found 302.2116. Data for **6*R* epimer:** $[\alpha]^{22}_D$ = +8.36 (*c* = 1.1, $CHCl_3$). IR (film): υ = 2956, 1659 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.83 (d, *J* = 6.5 Hz, 3H, CH_3), 0.89 (d, *J* = 6.5 Hz, 3H, CH_3), 1.05 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.19-1.26 [m, 1H, C*H*$_2$(CHMe$_2$)], 1.32-1.43 (m, 1H, CH$_3$C*H*$_2$), 1.52-1.60 [m, 2H, H-7, C*H*$_2$(CHMe$_2$)], 1.61-1.68 (m, 1H, C*H*Me$_2$), 1.76-1.84 (m, 2H, CH$_3$C*H*$_2$, H-7), 1.87-1.96 (m, 1H, H-8), 2.30-2.36 (m, 1H, H-6), 4.01 (dd, *J* = 9.0, 1.1 Hz, 1H, CH_2O), 4.15 (dd, *J* = 9.0, 6.9 Hz, 1H, CH_2O), 4.54 (d, *J* = 8.7 Hz, 1H, H-8a), 4.89 (d, *J* = 5.9 Hz, 1H, CHN), 7.21-7.32 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.0 (*C*H$_3$CH$_2$), 21.4 (CH_3), 23.1 (CH_3), 24.7 (CH$_3$*C*H$_2$), 25.5 (*C*HMe$_2$), 29.0 (C-7), 37.6 (C-8), 38.0 (C-6), 40.8 [*C*H$_2$(CHMe$_2$)], 58.5 (C-3), 73.9 (C-2), 92.3 (C-8a), 126.2 (C-*o*), 127.3 (C-*p*), 128.4 (C-*m*), 141.7 (C-*i*), 170.8 (CO) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{19}H_{27}NNaO_2$ 324.1934; found 324.1935.

General Procedure for the Synthesis of Enantiopure Aminodiols 15-26: *n*-BuLi (1.6 M or 2.5 M solution in hexanes, 4.3 equiv.) was added to a solution of $NH_3{\cdot}BH_3$ (4.3 equiv.) in anhydrous THF at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, the mixture was added to a solution of lactam (1.0 equiv.) in anhydrous THF, and the stirring was continued at 40 ºC for 1–2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give a residue, which was purified by flash chromatography. The preparation of 4-substituted aminodiols **18a**-**e** has been reported.[3]

(*S*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-2-methyl-1-pentanol (15a). From lactam 1a: Following the general procedure, from lactam **1a**[18] (475 mg, 2.05 mmol) in THF (5.5 mL), *n*-BuLi (3.53 mL of a 2.5 M solution in hexanes, 8.84 mmol) and $NH_3{\cdot}BH_3$ (273 mg, 8.84 mmol) in THF (11 mL), a brown oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*S*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3-methylpiperidine**[19] (28 mg, 6%) and **15a** (314 mg, 64%). **From lactam 2a:** Following the general procedure, from lactam **2a**[18] (430 mg, 1.86 mmol) in THF (5 mL), *n*-BuLi (3.2 mL of a 2.5 M solution in hexanes, 8.0 mmol), and $NH_3{\cdot}BH_3$ (247 mg, 8.0 mmol) in THF (10 mL), an oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*S*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3-methylpiperidine**[19] (21 mg, 5%) and **15a** (257 mg, 58%): $[\alpha]^{22}_D$ = –50.7 (*c* = 0.76, $CHCl_3$). IR (film): υ = 3330, 1454, 1040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.88 (d, *J* = 6.7 Hz, 3H, CH_3), 1.10-1.19 (m, 1H, H-3), 1.39-1.64 (m, 4H, H-2, H-3, H-4), 2.46-2.58 (m, 2H, H-5), 3.27 (br.s, 3H, NH, OH), 3.43 (d, *J* = 6.0 Hz, 2H, H-1), 3.61 (dd, *J* = 10.9, 8.9 Hz, 1H, CH_2O), 3.72 (dd, *J*= 10.9, 4.2 Hz, 1H, CH_2O), 3.80 (dd, *J* = 8.9, 4.2 Hz, 1H, CHN), 7.25-7.37 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 16.6 (CH_3), 26.6 (C-4), 30.4 (C-3), 35.3 (C-2), 47.2 (C-5), 64.7 (CHN), 66.2 (CH_2O), 67.5 (C-1), 127.3 (C-*o*), 127.7 (C-*p*), 128.6 (C-*m*), 139.7 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{14}H_{24}NO_2$ 238.1802; found 238.1794.

(*S*)-2-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (15b). From lactam 1b: Following the general procedure, from lactam **1b**[18] (240 mg, 0.98 mmol) in THF (2.5 mL), *n*-BuLi (1.68 mL of a 2.5 M solution in hexanes, 4.21 mmol), and $NH_3{\cdot}BH_3$ (130 mg, 4.21 mmol) in THF (5 mL), a brown oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*S*)-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine**[19] (22 mg, 10%) and **15b** (159 mg, 65%). **From lactam 2b:** Following the general procedure, from lactam **2b**[18] (2.99 g, 12.2 mmol) in THF (25 mL), *n*-BuLi (21 mL of a 2.5 M solution in hexanes, 52.4 mmol), and $NH_3{\cdot}BH_3$ (1.62 g, 52.4 mmol) in THF (50 mL), an oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*S*)-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine**[19] (171 mg, 6%) and **15b** (2.45 g, 80%): $[\alpha]^{22}_D$ = –63.9 (*c* = 0.8, MeOH). IR (film): υ = 3300, 1454, 1037 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.83 (t, *J* = 7.6 Hz, 3H, CH_3), 1.22-1.38 (m, 5H, C*H*$_2$CH$_3$, H-2, H-4), 1.48 (br.s, 2H, H-3), 2.48 (m, 2H, H-5), 3.56-3.70 (m, 2H, H-1), 3.45 (dd, *J*= 10.4, 4.8 Hz, 1H, CH_2O), 3.49 (dd, *J* = 10.4, 3.6 Hz, 1H, CH_2O), 3.77 (dd, *J* = 4.8, 3.6 Hz, 1H, CHN), 7.23-7.30 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.2 (*C*H$_3$CH$_2$), 23.5 (CH$_3$*C*H$_2$), 26.4 (C-3), 27.7 (C-4), 41.5 (C-2), 47.3 (C-5), 64.3 (C-1), 64.7 (CHN), 66.3 (CH_2O), 127.3 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 139.9 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{15}H_{26}NO_2$ 252.1958; found 252.1955.

(*R*)-2-(3,5-Difluorobenzyl)-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (15c): Following the general procedure, from lactam **2c** (450 mg, 1.31 mmol) in THF (4.5 mL), *n*-BuLi (2.26 mL of a 2.5 M solution in hexanes, 5.64 mmol), and $NH_3{\cdot}BH_3$ (174 mg, 5.64 mmol) in THF (5 mL), an oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*R*)-3-(3,5-difluorobenzyl)-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine** (52 mg, 12%) and **15c** (299 mg, 65%). Data for **(*R*)-3-(3,5-Difluorobenzyl)-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine:** ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.43-1.72 (m, 4H, H-4, H-5), 1.95-2.00 (m, 1H, H-3), 2.37-2.52 (m, 2H, H-2), 2.70-2.85 (m, 2H, H-6), 2.78-2.85 (m, 2H, CH_2Ar), 3.58-3.75 (m, 2H, CH_2O), 3.93-4.00 (m, 1H, CHN), 6.60-6.67 (m, 3H, F-ArH), 7.14-7.17 (dd, *J* = 7.9, 1.9 Hz, 2H, ArH), 7.36-7.37 (m, 3H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 25.3 (C-5, d, $J_{C\text{-}F}$ = 11.7 Hz), 30.4 (C-4, d, $J_{C\text{-}F}$ = 29.7 Hz), 38.0 (C-3, d, $J_{C\text{-}F}$ = 35.8 Hz), 40.5 (CH_2Ar), 46.9 (C-6), 52.7 (C-2, d, $J_{C\text{-}F}$ = 11.7 Hz), 59.9 (CHN, d, $J_{C\text{-}F}$ = 3.1 Hz), 70.1 (CH_2O, d, $J_{C\text{-}F}$ = 17.1 Hz), 101.4 (F-Ar C-4, dd, $J_{C\text{-}F}$ = 24.8, 3.1 Hz), 111.7 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 6.9 Hz), 127.9 (C-*p*), 128.2 (C-*o*), 128.9 (C-*m*), 135.1 (C-*i*), 144.3 (F-Ar C-1, d, $J_{C\text{-}F}$ = 8.5 Hz), 162.9 (F-Ar C-3 and C-5, ddd, $J_{C\text{-}F}$ = 247.6, 13.3, 3.9 Hz) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{20}H_{23}F_2NO$ 332.1820; found 332.1820. Data for **15c**: $[\alpha]^{22}_D$ = –33.9 (*c* = 0.5, $CHCl_3$). IR (film): υ = 3353, 1625 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.26-1.31 (m, 1H, H-3), 1.35-1.43 (m, 1H, H-3), 1.45-1.53 (m, 2H, H-4), 1.72 (br.s, 1H, H-2), 2.51 (m, 3H, H-5, CH_2Ar), 2.65-2.70 (m, 1H, CH_2Ar), 3.44 (dd, *J* = 10.5, 5.2 Hz, 1H, H-1), 3.50 (dd, *J* = 10.5, 6.4 Hz, 1H, H-1), 3.55-3.68 (m, 4H, CH_2, OH, NH); 3.72 (dd, *J* = 10.8, 3.8 Hz, 1H, CH_2O); 3.80 (dd, *J* = 8.5, 3.8 Hz, 1H, CHN); 6.59-6.67 (m, 3H, F-ArH), 7.26-7.31 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 26.3 (C-3), 27.7 (C-4), 37.4 (CH_2Ar, d, $J_{C\text{-}F}$ = 9.2 Hz), 41.7 (C-2, d, $J_{C\text{-}F}$ = 6.2 Hz), 47.0 (C-5), 63.2 (C-1), 64.7 (CHN), 66.1 (CH_2O), 101.3 (F-Ar C-4, t, $J_{C\text{-}F}$ = 24.9 Hz), 111.7 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 18.7, 6.2 Hz), 127.3 (C-*o*), 127.8 (C-*p*), 128.7 (C-*m*), 139.2 (C-*i*), 144.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.3 Hz), 162.8 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 247.7, 13.3 Hz) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{20}H_{26}F_2NO_2$ 350.1926; found 350.1926.

(*S*)-2-Benzyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (16): Following the general procedure, from lactam **3**[18] (453 mg, 1.47 mmol) in THF (3 mL), *n*-BuLi (2.54 mL of a 2.5 M solution in hexanes, 6.34 mmol) and $NH_3{\cdot}BH_3$ (196 mg, 6.34 mmol) in THF (6 mL), an oil was obtained. Flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*S*)-3-benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine** (23 mg, 5%) and **16** (300 mg, 65%). Data for **(*S*)-3-benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine:** $[\alpha]^{22}_D$ = +2.1 (*c* = 0.45, $CHCl_3$). IR (film): υ = 3386, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.19-1.33 (m, 1H, H-4), 1.53-1.68 (m, 4H, H-2, H-4, H-5), 1.74-1.86 (m, 1H, H-3), 2.29-2.35 (m, 1H, H-2), 2.36 (dd, *J* = 13.5, 8.1 Hz, 1H, CH_2Ar), 2.56 (dd, *J* = 13.5, 6.5 Hz, 1H, CH_2Ar), 2.75 (m, 1H, H-6), 2.83 (m, 1H, H-6), 3.61 (dd, *J* = 10.3, 5.1 Hz, 1H, CH_2O), 3.74 (dd, *J* = 10.3, 5.1 Hz, 1H, CHN), 3.97 (t, *J* = 10.3 Hz, 1H, CH_2O), 7.09-7.38 (m, 10H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 25.4 (C-5), 30.3 (C-4), 38.2 (C-3), 40.8 (CH_2Ar), 52.8 (C-6), 52.8 (C-2), 59.8 (CH_2O), 70.1 (CHN), 125.9 (C-*p*), 127.9 (C-*p*), 128.2 (C-*o*), 128.3 (C-*o*), 129.0 (C-*m*), 129.1 (C-*m*), 135.0 (C-*i*), 140.2 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{20}H_{26}NO$ 296.2009; found 296.2010. Data for **16**: $[\alpha]^{22}_D$ = –45.3 (*c* = 1.0, $CHCl_3$). IR (film): υ = 3331, 1494, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.30-1.37 (m, 1H, H-3), 1.37-1.48 (m, 1H, H-3), 1.48-1.57 (m, 2H, H-4), 1.77 (m, 1H, H-2), 2.52 (m, 2H, H-5), 2.55 (m, 1H, CH_2Ar), 2.63 (dd, *J* = 13.6, 7.5 Hz, 1H, CH_2Ar), 2.83 (br.s, 3H, NH, OH), 3.47 (dd, *J* = 10.8, 5.3 Hz, 1H, H-1), 3.56 (dd, *J* = 10.8, 4.7 Hz, 1H, H-1), 3.59-3.62 (m, 1H, CH_2O), 3.69-3.73 (m, 1H, CH_2O), 3.76-3.78 (m, 1H, CHN), 7.13-7.19 (m, 3H, ArH), 7.24-7.37 (m, 7H, ArH) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 26.7 (C-4), 27.9 (C-3), 37.8 (CH_2Ar), 42.2 (C-2), 47.2 (C-5), 64.1 (C-1), 64.6 (CHN), 66.3 (CH_2O), 125.8 (C-*p*), 127.3 (C-*p*), 127.7 (C-*i*), 128.3 (C-*o*), 128.7 (C-*o* and C-*m*), 129.1 (C-*m*), 140.6 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{20}H_{28}NO_2$ 314.2115; found 314.2106.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-3-methyl-1-pentanol (17a): Following the general procedure, from lactam **4a**[1d] (262 mg, 1.14 mmol) in THF (2 mL), *n*-BuLi (1.95 mL of a 2.5 M solution in hexanes, 4.87 mmol), and $NH_3{\cdot}BH_3$ (150 mg, 4.87 mmol) in THF (4 mL), an oil was obtained. Flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **1-[(1*R*)-2-hydroxy-1-phenylethyl]-4-methylpiperidine** (36 mg, 15%) and **17a** (135 mg, 50%). Data for **1-[(1*R*)-2-Hydroxy-1-phenylethyl]-4-methylpiperidine:** $[\alpha]^{22}_D$ = –18.5 (*c* = 2.4, $CHCl_3$). IR (film): υ = 3414 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.87 (d, *J* = 6.0 Hz, 3H, CH_3), 1.10-1.23 (m, 1H, H-4), 1.25-1.34 (m, 2H, H-3, H-5), 1.55-1.72 (m, 3H, H-3, H-5, H-2 or H-6), 2.29 (ddd, *J* = 11.3, 11.3, 2.5 Hz, 1H, H-2 or H-6), 2.83 (m, 2H, H-2, H-6), 3.20 (br.s, 1H, OH), 3.62 (dd, *J* = 10.1, 5.2 Hz, 1H, CH_2O), 3.70 (dd, *J* = 10.1, 5.2 Hz, 1H, CHN), 3.97 (t, *J* = 10.1 Hz, 1H, CH_2O), 7.17 (m, 2H, ArH), 7.28-7.36 (m, 3H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 21.8 (CH_3), 30.8 (C-4), 34.6 and 34.9 (C-3 and C-5), 46.2 (C-2 or C-6), 52.8 (C-2 or C-6), 60.0 (CH_2O), 69.9 (CHN), 127.7 (C-*p*), 128.0 (C-*o*), 128.9 (C-*m*), 135.6 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{14}H_{22}NO$ 220.1696; found 220.1700. Data for **17a:** $[\alpha]^{22}_D$ = –51.9 (*c* = 0.84, $CHCl_3$). IR (film): υ = 3320, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.86 (d, *J* = 6.6 Hz, 3H, CH_3), 1.28-1.42 (m, 2H, H-2, H-4), 1.46-1.59 (m, 2H, H-2, H-4), 1.64-1.72 (m, 1H, H-3), 2.44-2.51 (m, 1H, H-5), 2.56-2.63 (m, 1H, H-5), 3.48 (br.s, 3H, NH, OH), 3.57-3.63 (m, 2H, H-1, CH_2O), 3.65-3.72 (m, 2H, H-1, CH_2O), 3.78 (dd, *J* = 8.9, 4.1 Hz, 1H, CHN), 7.24-7.35 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 19.8 (CH_3), 27.2 (C-3), 36.5 (C-4), 39.4 (C-2), 44.8 (C-5), 60.1 (C-1), 64.9 (CHN), 66.3 (CH_2O), 127.2 (C-*o*), 127.6 (C-*p*), 128.5 (C-*m*), 139.9 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{14}H_{24}NO_2$ 238.1802; found 238.1802.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-3-phenyl-1-pentanol (17b). From lactam 4b: Following the general procedure, from lactam **4b** (240 mg, 0.82 mmol) in THF (2.5 mL), *n*-BuLi (1.41 mL of a 2.5 M solution in hexanes, 3.52 mmol), and $NH_3{\cdot}BH_3$ (109 mg, 3.52 mmol) in THF (5 mL), an oil was obtained. Flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **1-[(1*R*)-2-hydroxy-1-phenylethyl]-4-phenylpiperidine** (35 mg, 15%) and **17b** (105 mg, 43%). **From lactam 5**: Following the general procedure, from lactam **5** (510 mg, 1.74 mmol) in THF (9 mL), *n*-BuLi (3.0 mL of a 2.5 M solution in hexanes, 7.48 mmol), and $NH_3{\cdot}BH_3$ (231 mg, 7.48 mmol) in THF (18 mL), an oil was obtained. Flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **1-[(1*R*)-2-hydroxy-1-phenylethyl]-4-phenylpiperidine** (40 mg, 8%) and **17b** (338 mg, 65%). Data for **1-[(1*R*)-2-Hydroxy-1-phenylethyl]-4-phenylpiperidine:** $[\alpha]^{22}_D$ = –6.44 (*c* = 0.26, $CHCl_3$). IR (film): υ = 3417, 1601, 1493, 1451 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.71 (dt, *J* = 12.4, 3.7 Hz, 1H, H-3 or H-5), 1.79-1.82 (m, 1H, H-4), 1.82-1.88 (m, 3H, H-3, H-5), 2.32-2.40 (m, 1H, H-2 or H-6), 2.42-2.48 (m, 1H, H-2 or H-6), 2.98-3.05 (m, 2H, H-2, H-6), 3.66 (dd, *J* = 10.4, 5.2 Hz, 1H, CH_2O), 3.76 (dd, *J* = 10.4, 5.2 Hz, 1H, CHN), 4.02 (t, *J* = 10.4 Hz, 1H, CH_2O), 7.16-7.39 (m, 10H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 33.7 and 34.1 (C-3 and C-5), 42.6 (C-4), 46.4 and 53.5 (C-2 and C-6), 60.1 (CH_2O), 70.1 (CHN), 126.1 (C-*p*), 126.7 (C-*o*), 127.9 (C-*p*), 128.1 (C-*o*), 128.4 (C-*m*), 128.9 (C- *m*), 135.5 (C-*i*), 146.1 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{19}H_{24}NO$ 282.1852; found 282.1851. Data for **17b:** $[\alpha]^{22}_D$ = –40.9 (*c* = 3.0, $CHCl_3$). IR (film): υ = 3321, 1452 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.70-1.88 (m, 4H, H-2, H-4), 2.32-2.38 (m, 1H, H-5), 2.45-2.51 (m, 1H, H-5), 2.61 (br.s, 3H, NH, OH), 2.80-2.87 (m, 1H, H-3), 3.39-3.46 (m, 1H, H-1), 3.48-3.54 (m, 2H, H-1, CH_2O), 3.62-3.66 (m, 2H, CH_2O, CHN), 7.13-7.31 (m, 10H, ArH) ppm. ^{13}C NMR

(100.6 MHz, $CDCl_3$, 25 ºC): δ = 36.1 (C-4), 39.3 (C-2), 39.8 (C-3), 44.9 (C-5), 60.5 (C-1), 64.6 (CHN), 65.9 (CH_2O), 126.4 (C-*p*), 127.2 (C-*o*), 127.5 (C-*o*), 127.8 (C-*p*), 128.4 (C-*m*), 128.5 (C-*m*), 139.4 (C-*i*), 144.4 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{26}NO_2$ 300.1958; found 300.1957.

(*R*)-5-{[1(*R*)-2-Hydroxy-1-phenylethyl]amino}-4-methyl-1-pentanol (19a): Following the general procedure, from lactam **7a**[3] (400 mg, 1.73 mmol) in THF (4 mL), *n*-BuLi (2.98 mL of a 2.5 M solution in hexanes, 7.44 mmol), and $NH_3{\cdot}BH_3$ (230 mg, 7.44 mmol) in THF (8 mL), a brown oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*R*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3-methylpiperidine**[19] (35 mg, 11%) and **19a** (225 mg, 55%) as a colorless oil: $[\alpha]^{22}_D$ = –57.4 (*c* = 0.9, MeOH). IR (film): υ = 3328, 1492, 1453, 1056 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.88 (d, *J* = 6.7 Hz, 3H, CH_3), 1.15-1.20 (m, 1H, H-2), 1.40-1.50 (m, 2H, H-2, H-3), 1.55-1.65 (m, 2H, H-3, H-4), 2.36 (m, 2H, H-5), 3.27 (br.s, 3H, OH, NH), 3.55-3.58 (m, 3H, H-1, CH_2O), 3.64 (m, 1H, CHN), 3.70 (m, 1H, CH_2O), 7.23-7.35 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 18.0 (CH_3), 29.5 (C-3), 30.5 (C-2), 32.7 (C-4), 53.5 (C-5), 62.3 (C-1), 64.8 (CHN), 66.5 (CH_2O), 127.3 (C-*o*), 127.7 (C-*p*), 128.4 (C-*m*), 140.3 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{14}H_{24}NO_2$ 238.1802; found 238.1796.

(*R*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (19b): Following the general procedure, from lactam **7b**[17] (395 mg, 1.61 mmol) in THF (3 mL), *n*-BuLi (2.77 mL of a 2.5 M solution in hexanes, 6.92 mmol), and $NH_3{\cdot}BH_3$ (214 mg, 6.92 mmol) in THF (6 mL), a brown oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*R*)-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine**[17] (35 mg, 9%) and **19b** (202 mg, 50%): $[\alpha]^{22}_D$ = –48.8 (*c* = 0.7, $CHCl_3$). IR (film): υ = 3329, 1453, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.80 (t, *J* = 7.5 Hz, 3H, CH_3), 1.28-1.35 (m, 2H, CH_3CH_2), 1.36-1.43 (m, 2H, H-3), 1.43-1.54 (m, 3H, H-2, H-4), 2.36 (dd, *J* = 11.5, 6.0 Hz, 1H, H-5), 2.48 (dd, *J* = 11.5, 5.6 Hz, 1H, H-5), 3.29 (br.s, 3H, OH, NH), 3.59 (masked signal, 1H, CH_2O), 3.60 (t, *J* = 6.4 Hz, 2H, H-1), 3.72-3.77 (m, 2H, CH_2O, CHN), 7.24-7.36 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 10.8 (CH_3), 24.5 (CH_3CH_2), 27.4 (C-3), 29.2 (C-2), 39.4 (C-4), 50.4 (C-5), 62.5 (C-1), 65.2 (CHN), 66.4 (CH_2O), 127.2 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.5 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{15}H_{26}NO_2$ 252.1958; found 252.1954.

5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-5-methyl-1-pentanol (20): Following the general procedure, from lactam **8**[20] (209 mg, 0.90 mmol) in THF (1.5 mL), *n*-BuLi (2.43 mL of a 1.6 M solution in hexanes, 3.89 mmol), and $NH_3{\cdot}BH_3$ (120 mg, 3.89 mmol) in THF (3 mL), an oil was obtained. Flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-methylpiperidine**[21] (32 mg, 16%) as a 1:1 mixture of C-2 epimers and aminodiol **20** (105 mg, 50%) as a 1:1 mixture of C-5 epimers: IR (film): υ = 3350, 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC, mixture of diastereomers): δ = 0.98 (d, *J* = 6.4 Hz, CH_3), 1.02 (d, *J* = 6.2 Hz, CH_3), 1.26-1.55 (m, H-2, H-3, H-4), 2.50-2.55 (m, H-5), 2.59-2.67 (m, H-5) 3.40 (brs, OH, NH), 3.51-3.74 (m, H-1, CH_2O), 3.87 (dd, *J* = 8.6, 4.3 Hz, 1H, CHN), 3.92 (dd, *J* = 8.5, 4.3 Hz, 1H, CHN), 7.24-7.35 (m, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 19.3, 21.2 (CH_3), 21.3, 21.8 (C-3), 32.3, 32.5 (C-2), 35.2, 37.1 (C-4), 49.6, 50.4 (C-5), 61.3, 62.1 (CHN), 61.8, 62.1 (CH_2O), 66.2, 66.4 (C-1), 126.6, 127.3 (C-*o*), 127.4, 127.6 (C-*p*), 128.6, 128.6 (C-*m*), 140.1, 140.7 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{14}H_{24}NO_2$ 238.1802; found 238.1795.

(*S*)-2-Benzyl-2-ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (21a): Following the general procedure, from lactam **9a**[22] (356 mg, 1.06 mmol) in THF (2.5 mL), *n*-BuLi (1.83 mL of a 2.5 M solution in hexanes, 4.56 mmol), and $NH_3{\cdot}BH_3$ (141 mg, 4.56 mmol) in THF (5 mL), aminoalcohol **21a** (250 mg, 69%) was obtained after flash chromatography (from EtOAc to 8:2 EtOAc–EtOH): $[\alpha]^{22}_D$ = –28.4 (*c* = 0.96, $CHCl_3$). IR (film): υ = 3384, 1601, 1494, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.89 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 1.15-1.20 (m, 2H, H-3), 1.22-1.30 (m, 2H, H-4), 1.41-1.53 (m, 2H, CH_3CH_2), 2.45-2.49 (m, 2H, H-5), 2.52 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 2.60 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 3.28 (br.s, 2H, H-1), 3.58 (dd, *J* = 11.0, 8.6, Hz, 1H, CH_2O), 3.72 (dd, *J* = 11.0, 4.4 Hz, 1H, CH_2O), 3.78 (dd, *J* = 8.6, 4.4 Hz, 1H, CHN), 7.16-7.37 (m, 10H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 7.6 (CH_3CH_2), 23.2 (CH_3CH_2), 24.8 (C-3), 30.4 (C-4), 39.9 (CH_2Ar), 41.5 (C-2), 47.9 (C-5), 64.7 (CHN), 65.4 (C-1), 66.6 (CH_2O), 125.9 (C-*p*), 127.3 (C-*o*), 127.7 (C-*p*), 127.9 (C-*o*), 128.7 (C-*m*), 130.4 (C-*m*), 138.6 (C-*i*), 140.4 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{22}H_{32}NO_2$ 342.2428; found 342.2425.

(*S*)-2-Allyl-2-ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (21b): Following the general procedure, from lactam **9b**[22] (400 mg, 1.40 mmol) in THF (2.5 mL), *n*-BuLi (2.4 mL of a 2.5 M solution in hexanes, 6.03 mmol), and $NH_3{\cdot}BH_3$ (186 mg, 6.03 mmol) in THF (5.5 mL), an oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(*S*)-3-allyl-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine** (33 mg, 9%) and **21b** (227 mg, 56%). Data for **(*S*)-3-Allyl-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine:** $[\alpha]^{22}_D$ = –19.5 (*c* = 0.5, $CHCl_3$). IR (film): υ = 3440, 1637, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.80 (t, *J* = 7.6 Hz, 3H, CH_3), 1.15-1.28 (m, 2H, CH_2), 1.31 (m, 2H, H-5), 1.60 (m, 2H, CH_2), 2.04-2.18 (m, 2H, H-4), 2.20 (m, 2H, H-2), 2.54 (br.s, 2H, H-6), 3.59-3.66 (m, 2H, CHN, CH_2O), 3.99 (t, *J* = 9.6 Hz, CH_2O), 5.03 (m, 2H, CH_2=CH), 5.70-5.80 (m, 1H, CH_2=CH), 7.15-7.35 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 7.15 (CH_3), 21.9 (CH_2), 28.3 (C-5), 33.4 (CH_2), 36.2 (C-3), 39.3 (C-4), 49.9 (C-6), 58.6 (C-2), 60.1 (CH_2O), 70.2 (CHN), 117.1 (CH_2=CH), 127.8 (C-*p*), 128.0 (C-*o*), 128.9 (C-*m*), 134.6 (CH_2=CH), 135.3 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{18}H_{28}NO$ 274.2165; found 274.2161. Data for **21b**: $[\alpha]^{22}_D$ = –34.3 (*c* = 0.8, $CHCl_3$). IR (film): υ = 3331, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.76 (t, *J*= 7.2 Hz, 3H, CH_3), 1.12-1.14 (m, 4H, CH_3CH_2, H-3), 1.40-1.45 (m, 2H, H-4), 1.89 (dd, *J* = 14.0, 7.6 Hz, 1H, CH_2=CHCH_2), 1.98 (dd, *J* = 14.0, 7.6 Hz, 1H, CH_2=CHCH_2), 2.44-2.49 (m, 2H, H-5), 3.30 (s, 2H, H-1), 3.63-3.70 (m, 2H, CH_2O), 3.82 (dd, *J* = 8.4, 4.0 Hz, 1H, CHN), 4.16 (br.s, 3H, OH, NH), 4.99 (m, 2H, CH_2=CH), 5.68-5.78 (m, 1H, CH_2=CH), 7.30 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 7.2 (CH_3CH_2), 22.4 (C-4), 25.3 (CH_3CH_2), 30.6 (C-3), 37.9 (CH_2=CHCH_2), 40.0 (C-2), 47.6 (C-5), 64.7 (CHN), 65.5 (CH_2O), 65.9 (C-1), 116.9 (CH_2=CH), 127.4 (C-*o*), 127.7 (C-*p*), 128.5 (C-*m*), 134.6 (CH_2=CH), 138.9 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{18}H_{30}NO_2$ 292.2271; found 292.2266.

(2*S*,3*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-2,3-(isopropylidenedioxy)-1-pentanol (22): Following the general procedure, from lactam **10** (245 mg, 0.85 mmol) in THF (2.5 mL), *n*-BuLi (1.46 mL of a 2.5 M solution in hexanes, 3.64 mmol), and $NH_3{\cdot}BH_3$ (112 mg, 3.64 mmol) in THF (6 mL), aminoalcohol **22** (100 mg, 40%) was obtained after flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH): $[\alpha]^{22}_D$ = –38.3 (*c* = 1.72, $CHCl_3$). IR (film): υ = 3359, 1454, 1044 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.33 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.67-1.76 (m, 1H, H-4), 1.78-1.85 (m, 1H, H-4), 2.61-2.68 (m, 1H, H-5), 2.72-2.78 (m, 1H, H-5), 3.22 (br.s, 3H, NH, OH), 3.55-3.63 (m, 3H, H-1, CH_2O), 3.71 (dd, *J* = 10.9, 4.1 Hz, 1H, CH_2O), 3.78 (dd, *J* = 8.5, 4.1 Hz, 1H, CHN), 4.11-4.15 (m, 1H, H-2), 4.17-4.22 (m, 1H, H-3), 7.27-7.37 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 25.4 (CH_3), 28.1 (CH_3), 29.0 (C-4), 44.8 (C-5), 61.3 (C-1), 64.7 (CHN), 66.3 (CH_2O), 76.1 (C-3), 77.9 (C-2), 108.0 (CMe_2),

127.2 (C-*o*), 127.7 (C-*p*), 128.6 (C-*m*), 139.8 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{16}H_{26}NO_4$ 296.1856; found 296.1848.

(2*R*,3*S*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-2,3-(isopropylidenedioxy)-1-pentanol (23): Following the general procedure, from lactam **11**[23] (420 mg, 1.45 mmol) in THF (7.5 mL), *n*-BuLi (2.5 mL of a 2.5 M solution of hexanes, 6.25 mmol), and $NH_3{\cdot}BH_3$ (193 mg, 6.25 mmol) in THF (15 mL), an oil was obtained. Flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(3*R*,4*S*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3,4-(isopropylidenedioxy)piperidine**[23] (50 mg, 12%) and **23** (172 mg, 40%): $[\alpha]^{22}_D$ = –45.9 (*c* = 2.35, $CHCl_3$). IR (film): υ = 3404, 1493 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.31 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.70-1.76 (m, 1H, H-4), 1.80-1.88 (m, 1H, H-4), 2.59-2.66 (m, 1H, H-5), 2.68-2.74 (m, 1H, H-5), 3.57-3.67 (m, 3H, H-1, CH_2O), 3.71 (dd, *J* = 11.0, 4.1 Hz, 1H, CH_2O), 3.82-3.90 (br.m, 4H, CHN, OH, NH), 4.11-4.19 (m, 2H, H-2, H-3), 7.27-7.37 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 25.3 (CH_3), 28.0 (CH_3), 28.9 (C-4), 44.5 (C-5), 61.1 (C-1), 64.8 (CHN), 66.1 (CH_2O), 75.7 (C-3), 77.7 (C-2), 108.0 (CMe_2), 127.4 (C-*o*), 127.9 (C-*p*), 128.7 (C-*m*), 138.8 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{16}H_{26}NO_4$ 296.1856; found 296.1857.

(2*S*,4*S*)-2-Benzyl-4-ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (24): Following the general procedure, from lactam **12**[18] (524 mg, 1.54 mmol) in THF (4.5 mL), *n*-BuLi (2.69 mL of a 2.5 M solution in hexanes, 6.72 mmol), and $NH_3{\cdot}BH_3$ (207 mg, 6.72 mmol) in THF (9 mL), aminoalcohol **24** (295 mg, 55%) was obtained after flash chromatography (from 7:3 hexane–EtOAc to 8:2 EtOAc–EtOH): $[\alpha]^{22}_D$ = –54.0 (*c* = 0.38, $CHCl_3$). IR (film): υ = 3338, 1494, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.74 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.14-1.23 (m, 3H, H-3, CH$_3$C*H*$_2$), 1.35-1.40 (m, 1H, H-4), 1.44-1.51 (m, 1H, H-3), 1.73-1.80 (m, 1H, H-2), 2.23 (dd, *J* = 11.6, 8.2 Hz, 1H, H-5), 2.50 (dd, *J* = 11.6, 4.0 Hz, 1H, H-5), 2.53 (dd, *J* = 13.5, 6.8 Hz, 1H, CH_2Ar), 2.67 (dd, *J* = 13.5, 7.9 Hz, 1H, CH_2Ar), 2.99 (br.s, 3H, NH, OH), 3.45 (dd, *J* = 11.5, 4.3 Hz, 1H, H-1), 3.58 (dd, *J* = 10.4, 9.2 Hz, 1H, CH_2O), 3.67 (dd, *J* = 11.5, 3.8 Hz, 1H, H-1), 3.68-3.69 (m, 1H, CH_2O), 3.71-3.76 (m, 1H, CHN), 7.15-7.19 (m, 3H, ArH), 7.24-7.37 (m, 7H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.1 (CH_3), 26.4 (CH_3CH_2), 34.0 (C-3), 37.3 (C-4), 39.1 (CH_2Ar), 41.1 (C-2), 51.6 (C-5), 63.3 (C-1), 65.1 (CHN), 66.7 (CH_2O), 125.7 (C-*o*), 127.5 (C-*p*), 128.2 (C-*m*), 128.7 (C-*p*), 129.1 (C-*m*), 140.9 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{22}H_{31}NO_2$ 342.2428; found 342.2424.

(2*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-methyl-1-pentanol (25a): Following the general procedure, from lactam **13a**[18] (525 mg, 2.03 mmol) in THF (3 mL), *n*-BuLi (3.48 mL of a 2.5 M solution in hexanes, 8.71 mmol), and $NH_3{\cdot}BH_3$ (269 mg, 8.71 mmol) in THF (6 mL), aminoalcohol **25a** (349 mg, 65%) was obtained after flash chromatography (from 1:1 hexane–EtOAc to 8:2 EtOAc–EtOH): $[\alpha]^{22}_D$ = –64.7 (*c* = 1.0, $CHCl_3$). IR (film): υ = 3319, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.81 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 1.19-1.37 (m, 4H, H-3, CH$_3$C*H*$_2$), 1.47-1.55 (m, 1H, H-4), 1.70-1.77 (m, 1H, H-2), 2.29-2.34 (m, 1H, H-5), 2.47 (dd, *J* = 11.6, 4.5 Hz, 1H, H-5), 3.42 (m, 2H, H-1), 3.50-3.75 (br.m, 3H, NH, OH), 3.58 (m, 1H, CH_2O), 3.68 (m, 1H, CH_2O), 3.75 (m, 1H, CHN), 7.24-7.35 (m, 5H ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.0 (*C*H$_3$CH$_2$), 17.0 (CH_3), 25.6 (CH_3CH_2), 32.7 (C-2), 35.5 (C-3), 36.0 (C-4), 51.1 (C-5), 65.0 (CHN), 66.5 (CH_2O), 67.6 (C-1), 127.3 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.1 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{16}H_{28}NO_2$ 266.2115; found 266.2113.

(2*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-isobutyl-1-pentanol (25b): Following the general procedure, from lactam **13b** (440 mg, 1.46 mmol) in THF (4.5 mL), *n*-BuLi (2.5 mL of a 2.5 M solution in hexanes, 6.28 mmol), and $NH_3{\cdot}BH_3$ (194 mg, 6.28 mmol) in THF (8.5 mL), aminoalcohol **25b** (254 mg, 57%) was obtained after flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH): $[\alpha]^{22}_D$ = –40.4 (*c* = 1.1, $CHCl_3$). IR (film): υ = 3330, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.83 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.86 (d, *J* = 3.1 Hz, 3H, CH_3), 0.88 (d, *J* = 3.1 Hz, 3H, CH_3), 1.03-1.14 (m, 2H, H-3, C*H*$_2$CHMe$_2$), 1.19-1.30 (m, 3H, CH$_3$C*H*$_2$, C*H*$_2$CHMe$_2$), 1.39-1.45 (m, 2H, H-3, H-4), 1.54 (br.m, 1H, H-2), 1.63 (sept, *J* = 6.7 Hz, 1H, C*H*Me$_2$), 2.23 (dd, *J* = 11.6, 7.7 Hz, 1H, H-5), 2.53 (dd, *J* = 11.6, 3.3 Hz, 1H, H-5), 3.00 (br.m, 3H, NH, OH), 3.44 (dd, *J* = 11.1, 4.8 Hz, 1H, H-1), 3.58-3.63 (m, 1H, CH_2O), 3.69-3.73 (m, 2H, H-1, CH_2O), 3.76 (dd, *J* = 8.9, 3.8 Hz, 1H, CHN), 7.26-7.37 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.4 (*C*H$_3$CH$_2$), 22.8 (CH_3), 22.9 (CH_3), 25.2 (CH), 26.7 (CH_3CH_2), 34.8 (C-3), 36.6 (C-2), 37.6 (C-4), 42.2 (*C*H$_2$CHMe$_2$), 51.6 (C-5), 64.5 (C-1), 65.0 (CHN), 66.7 (CH_2O), 127.4 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.2 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M – Boc]$^+$ calcd. for $C_{19}H_{34}NO_2$ 308.2584; found 308.2583.

(3*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-3-methyl-1-pentanol (26a): Following the general procedure, from lactam **14a**[1d] (252 mg, 0.97 mmol) in THF (3 mL), *n*-BuLi (1.67 mL of a 2.5 M solution in hexanes, 4.18 mmol), and $NH_3{\cdot}BH_3$ (129 mg, 4.18 mmol) in THF (6 mL), an oil was obtained. Flash chromatography (from 8:2 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(3*S*,4*S*)-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-4-methylpiperidine** (32 mg, 13%) and **26a** (142 mg, 55%). Data for **(3*S*,4*S*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-4-methylpiperidine:** $[\alpha]^{22}_D$ = –22.3 (*c* = 0.3, $CHCl_3$). IR (film): υ = 3330, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.73 (d, *J* = 7.2 Hz, 3H, CH_3), 0.89 (t, *J* = 7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.29 (m. 2H, CH$_3$C*H*$_2$), 1.43 (m, 1H, H-4), 1.51 (br.m, 1H, H-5), 1.58 (br.m, 1H, H-3), 1.70 (br.m, 1H, H- H-5), 2.17-2.48 (br.m, 4H, H-2 and H-6), 3.66 (m, 1H, CH_2O), 3.72 (m, NCH), 3.99 (t, J = 10.0 Hz, 1H, CH_2O), 7.18-7.37 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.9 (CH_3CH_2), 14.1 (CH_3), 22.7 (CH_3CH_2), 28.4 (C-4), 31.5 (C-5), 41.2 (C-3), and 51.0 (C-2 and C-6), 60.1 (CH_2O), 70.2 (CHN), 127.9 (C-*p*), 128.0 (C-*o*), 129.0 (C-*m*), 135.4 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{16}H_{26}NO$ 248.2009; found 248.2007. Data for **26a**: $[\alpha]^{22}_D$ = –74.4 (*c* = 0.7, $CHCl_3$). IR (film): υ = 3330, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.83-0.87 (m, 6H, 2CH$_3$), 1.16-1.22 (m, 1H, CH$_3$C*H*$_2$), 1.24-1.30 (m, 1H, H-2), 1.32-1.40 (m, 2H, H-4, CH$_3$C*H*$_2$), 1.48-1.57 (m, 1H, H-2), 1.82-1.88 (m, 1H, H-3), 2.35 (dd, *J* = 12.0, 5.3 Hz, 1H, H-5), 2.48 (dd, *J* = 12.0, 6.6 Hz, 1H, H-5), 2.54 (br.s, 3H, NH, OH), 3.53-3.61 (m, 2H, H-1, CH_2O), 3.66-3.72 (m, 2H, H-1, CH_2O), 3.73-3.75 (m, 1H, CHN), 7.27-7.37 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 12.5 (*C*H$_3$CH$_2$), 16.8 (CH_3), 22.3 (CH_3CH_2), 30.1 (C-3), 35.8 (C-2), 44.9 (C-4), 47.7 (C-5), 61.4 (C-1), 65.0 (CHN), 66.6 (CH_2O), 127.2 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 140.5 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{16}H_{28}NO_2$ 266.2115; found 266.2117.

(3*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-3-phenyl-1-pentanol (26b): Following the general procedure, from lactam **14b**[1d] (187 mg, 0.58 mmol) in THF (2 mL), *n*-BuLi (1.0 mL of a 2.5 M solution in hexanes, 2.5 mmol), and $NH_3{\cdot}BH_3$ (77 mg, 2.5 mmol) in THF (4 mL), an oil was obtained. Flash chromatography (from 7:3 hexane–EtOAc to 8:2 EtOAc–EtOH) gave **(3*S*,4*S*)-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-4-phenylpiperidine**[1d] (36 mg, 20%) and **26b** (71 mg, 37%): $[\alpha]^{22}_D$ = –87.9 (*c* = 0.75, $CHCl_3$). IR (film): υ = 3332, 3061, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.81 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$), 1.29-1.36 (m, 1H, CH$_3$C*H*$_2$), 1.51-1.57 (m, 1H, CH$_3$C*H*$_2$), 1.58-1.63 (m, 1H, H-4), 1.75-1.83 (m, 1H, H-2), 1.90-2.02 (br.m, 4H, H-2, NH, OH), 2.20 (dd, *J* = 12.0, 5.0 Hz, 1H, H-5), 2.46 (dd, *J* = 12.0, 5.3 Hz, 1H, H-5), 2.85 (br.m, 1H, H-3), 3.32-3.39 (m, 1H, H-1), 3.41-3.44 (m, 1H, CH_2O), 3.46-3.53 (m, 2H, H-1, CHN), 3.60 (dd, *J* = 10.3, 3.9 Hz, 1H, CH_2O), 7.13-7.31 (m, 10H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25

ºC): δ = 11.4 (CH_3CH_2), 22.1 (CH_3CH_2), 34.9 (C-2), 43.6 (C-3), 45.7 (C-4), 47.6 (C-5), 61.4 (C-1), 64.8 (CHN), 66.4 (CH_2O), 126.3 (C-*p*), 127.2 (C-*o*), 127.4 (C-*p*), 128.3 (C-*o*), 128.4 (C-*m*), 128.5 (C-*m*), 140.7 (C-*i*), 143.6 (C-*i*) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{21}H_{30}NO_2$ 328.2271; found 328.2269.

General Procedure for the Synthesis of Enantiopure Aminoalcohols 28-36: A solution of aminodiol (1.0 equiv.) in anhydrous MeOH containing $Pd(OH)_2$ on activated charcoal was hydrogenated at 75 °C for 22 h under 5 bar of pressure. Then, di-*tert*-butyl dicarbonate (1.2 equiv.) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography afforded the corresponding pure aminoalcohol. The preparation of 4-substituted aminopentanols **31a**-**e** has been reported. [3]

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-2-methyl-1-pentanol (28a): Following the general procedure, from a solution of aminodiol **15a** (250 mg, 1.05 mmol) in MeOH (15 mL), 20% $Pd(OH)_2$ (50 mg), and Boc_2O (276 mg, 1.26 mmol), alcohol **28a** (110 mg, 48%) was obtained as a colorless oil after column chromatography (8:2 hexane–EtOAc): $[\alpha]^{22}_D$ = –3.92 (*c* = 1.15, $CHCl_3$). IR (film): υ = 3356, 1689, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.92 (d, *J* = 6.7 Hz, 3H, CH_3), 1.08-1.18 (m, 1H, H-3), 1.44 [s and masked signal, 10H, H-3, $(CH_3)_3$], 1.49-1.51 (m, 1H, H-4), 1.55-1.58 (m, 1H, H-4), 1.60-1.65 (m, 1H, H-2), 3.11 (m, 2H, H-5), 3.46 (m, 2H, H-1), 4.54 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 16.5 (CH_3), 27.4 (C-4), 28.3 [$(CH_3)_3$], 30.0 (C-3), 35.3 (C-2), 40.6 (C-5), 67.8 (C-1), 79.0 (CMe_3), 156.1 (CO) ppm. HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd. for $C_{11}H_{24}NO_3$ 218.1751; found 218.1754.

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-2-ethyl-1-pentanol (28b): Following the general procedure, from a solution of aminodiol **15b** (250 mg, 1.0 mmol) in MeOH (17 mL), 20% $Pd(OH)_2$ (50 mg), and Boc_2O (261 mg, 1.19 mmol), alcohol **28b** (127 mg, 55%) was obtained as a colorless oil after column chromatography (8:2 hexane–EtOAc): $[\alpha]^{22}_D$ = +0.87 (*c* = 1.75, $CHCl_3$). IR (film): υ = 3449, 1670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.84 (t, *J* = 7.2 Hz, 3H, CH_3CH$_2$), 1.20-1.37 (m, 5H, CH_2CH$_3$, H-2, H-3), 1.39 [s, 9H, $(CH_3)_3$], 1.45-1.51 (m, 2H, H-4), 1.95 (br.s, 1H, OH), 2.95-2.99 (m, 2H, H-5), 3.45 (dd, *J* = 10.0, 5.6 Hz, 1H, H-1), 3.49 (dd, *J* = 10.0, 4.8 Hz, 1H, H-1), 4.20 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.0 (CH_3CH_2), 23.3 (CH_3CH_2), 27.1 (C-4), 27.3 (C-3), 28.3 [$(CH_3)_3$], 40.7 (C-5), 41.4 (C-2), 64.5 (C-1), 78.9 (CMe_3), 155.5 (CO) ppm. HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd. for $C_{12}H_{25}NNaO_3$ 254.1727; found 254.1724.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-2-(3,5-difluorobenzyl)-1-pentanol (28c): Following the general procedure, from a solution of aminodiol **15c** (299 mg, 0.86 mmol) in MeOH (15 mL), 20% $Pd(OH)_2$ (60 mg), and Boc_2O (225 mg, 1.03 mmol), alcohol **28c** (140 mg, 50%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = +1.65 (*c* = 1.0, $CHCl_3$). IR (film): υ = 3362, 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.22-1.36 (m, 2H, H-3), 1.39 [s, 9H, $(CH_3)_3$], 1.40-1.55 (m, 2H, H-4), 1.73-1.80 (m, 1H, H-2), 2.50 (dd, *J* = 13.7, 7.2 Hz, 1H, CH_2Ar), 2.66 (dd, *J* = 13.7, 7.5 Hz, 1H, CH_2Ar), 3.03 (br.m, 2H, H-5), 3.47 (m, 1H, H-1), 3.72 (m, 1H, H-1), 4.75 (br.s, 1H, NH), 6.59 (m, 1H, F-ArH), 6.65 (d, *J* = 6.0 Hz, 2H, F-ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 27.3 (C-4), 27.4 (C-3), 28.3 [$(CH_3)_3$], 37.3 (CH_2Ar, d, $J_{C\text{-}F}$ = 8.5 Hz), 40.5 (C-5), 41.7 (C-2), 65.2 (C-1), 79.2 (CMe_3), 101.2 (F-Ar C-4, t, $J_{C\text{-}F}$ = 25.7 Hz), 111.7 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 6.2 Hz), 144.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 8.5 Hz), 156.2 (CO), 162.8 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 248.4, 13.2 Hz) ppm. HRMS (ESI-TOF) *m/z* [M - C$(CH_3)_3$ + H]$^+$ calcd. for $C_{13}H_{18}F_2NO_3$ 274.1249; found 274.1249.

(*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-1-pentanol (29): Following the general procedure, from a solution of aminodiol **16** (290 mg, 0.93 mmol) in MeOH (15 mL), 20% $Pd(OH)_2$ (58 mg), and Boc_2O (242 mg, 1.11 mmol), alcohol **29** (160 mg, 60%) was obtained as a colorless oil after column (from CH_2Cl_2 to 8:2 CH_2Cl_2–EtOH): $[\alpha]^{22}_D$ = –7.3 (*c* = 0.7, $CHCl_3$). IR (film): υ = 3349, 1693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.26-1.35 (m, 1H, H-3), 1.36-1.42 (m, 1H, H-3), 1.43 [s, 9H, $(CH_3)_3$], 1.49-1.59 (m, 2H, H-4), 1.76-1.86 (m, 1H, H-2), 1.91 (br.s, 1H, OH), 2.59 (dd, *J* = 13.6, 6.8 Hz, 1H, CH_2Ar), 2.64 (dd, *J* = 13.6, 7.6 Hz, 1H, CH_2Ar), 3.02-3.14 (m, 2H, H-5), 3.49 (dd, *J* = 10.8, 5.3 Hz, 1H, H-1), 3.54 (dd, *J* = 10.8, 5.2 Hz, 1H, H-1), 4.59 (br.s, 1H, NH), 7.16-7.20 (m, 3H, ArH), 7.25-7.29 (m, 2H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 27.4 (C-4), 27.6 (C-3), 28.4 [$(CH_3)_3$], 37.6 (CH_2Ar), 40.6 (C-5), 42.1 (C-2), 64.4 (C-1), 79.1 (CMe_3), 125.9 (C-*p*), 128.3 (C-*o*), 129.1 (C-*m*), 140.5 (C-*i*), 156.1 (CO) ppm. HRMS (ESI-TOF) *m/z* [M – Boc + H]$^+$ calcd. for $C_{12}H_{20}NO$ 194.1539; found 194.1536.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-3-methyl-1-pentanol (30a): Following the general procedure, from a solution of aminodiol **17a** (140 mg, 0.59 mmol) in MeOH (16 mL), 20% $Pd(OH)_2$ (28 mg), and Boc_2O (142 mg, 0.65 mmol), alcohol **30a** (77 mg, 60%) was obtained as a colorless oil after column chromatography (8:2 hexane–EtOAc): $[\alpha]^{22}_D$ = +4.33 (*c* = 0.44, $CHCl_3$). IR (film): υ = 3349, 1686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.88 (d, *J* = 6.6 Hz, 3H, CH_3), 1.27-1.36 (m, 2H, H-2, H-4), 1.39 [s, 9H, $(CH_3)_3$], 1.43-1.50 (m, 1H, H-4), 1.54-1.66 (m, 2H, H-2, H-3), 2.41 (br.s, 1H, OH), 3.01-3.10 (m, 1H, H-5), 3.12-3.20 (m, 1H, H-5), 3.57-3.68 (m, 2H, H-1), 4.70 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 19.6 (CH_3), 26.8 (C-3), 28.3 [$(CH_3)_3$], 37.1 (C-4), 38.3 (C-5), 39.3 (C-2), 60.4 (C-1), 79.0 (CMe_3), 156.2 (CO) ppm. HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd. for $C_{11}H_{23}NNaO_3$ 240.1570; found 240.1575.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-3-phenyl-1-pentanol (30b): Following the general procedure, from a solution of aminodiol **17b** (48 mg, 0.16 mmol) in MeOH (15 mL), 20% $Pd(OH)_2$ (9.6 mg), and Boc_2O (38 mg, 0.18 mmol), alcohol **30b** (23 mg, 50%) was obtained as a colorless oil after column chromatography (hexane–EtOAc 8:2): $[\alpha]^{22}_D$ = +14.3 (*c* = 1.2, $CHCl_3$). IR (film): υ = 3350, 1689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.42 [s, 9H, $(CH_3)_3$], 1.49-1.57 (br.s, 1H, OH), 1.71-1.89 (m, 3H, H-2, H-4), 1.91-1.98 (m, 1H, H-2), 2.78 (m, 1H, H-3), 2.93-3.06 (m, 2H, H-5), 3.40-3.47 (m, 1H, H-1), 3.51-3.57 (m, 1H, H-1), 4.47 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 28.4 [$(CH_3)_3$], 36.9 (C-4), 38.8 (C-5), 39.3 (C-2), 39.7 (C-3), 60.7 (C-1), 79.1 (CMe_3), 126.5 (C-*p*), 127.5 (C-*o*), 128.6 (C-*m*), 144.1 (C-*i*), 156.0 (CO) ppm. HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd. for $C_{16}H_{25}NNaO_3$ 302.1727; found 302.1721.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-4-methyl-1-pentanol (*ent*-31a): Following the general procedure, from a solution of aminodiol **19a** (190 mg, 0.80 mmol) in MeOH (13 mL), 20% $Pd(OH)_2$ (38 mg), and Boc_2O (210 mg, 0.96 mmol), alcohol *ent*-**31a** (100 mg, 57%) was obtained as a colorless oil after column chromatography (from 9:1 to 1:1 hexane–EtOAc): $[\alpha]^{22}_D$ = +2.25 (*c* = 1.0, MeOH).

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-1-pentanol (*ent*-31b): Following the general procedure, from a solution of aminodiol **19b** (105 mg, 0.42 mmol) in MeOH (13 mL), 20% $Pd(OH)_2$ (21 mg), and Boc_2O (109 mg, 0.5 mmol), alcohol *ent*-**31b** (53 mg, 55%) was obtained as a colorless oil after column chromatography (from 9:1 to 7:3 hexane–EtOAc): $[\alpha]^{22}_D$ = +2.8 (*c* = 0.82, MeOH).

(*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-2-ethyl-1-pentanol (32): Following the general procedure, from a solution of aminodiol **21a** (200

mg, 0.59 mmol) in MeOH (16 mL), 20% $Pd(OH)_2$ (40 mg), and Boc_2O (141 mg, 0.64 mmol), alcohol **32** (96 mg, 50%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = +8.09 (*c* = 2.25, $CHCl_3$). IR (film): υ = 3365, 2935, 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.81 (t, *J* = 7.5 Hz, 3H, CH_3CH$_2$), 1.09-1.21 (m, 4H, H-3, CH$_3$CH_2), 1.37 [s, 9H, $(CH_3)_3$], 1.41-1.47 (m, 2H, H-4), 1.85 (br.s, 1H, OH), 2.50 (br.s, 2H, CH_2Ar), 2.97-3.05 (m, 2H, H-5), 3.21 (s, 2H, H-1), 4.63 (br.s, 1H, NH), 7.10-7.13 (m, 3H, ArH), 7.17-7.21 (m, 2H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 7.5 (*C*H$_3$CH$_2$), 23.7 (C-4), 25.2 (CH$_3$*C*H$_2$), 28.4 [$(CH_3)_3$], 29.7 (C-3), 40.0 (CH_2Ar), 41.1 (C-5), 41.2 (C-2), 65.6 (C-1), 79.1 (CMe_3), 125.9 (C-*p*), 127.9 (C-*o*), 130.3 (C-*m*), 138.5 (C-*i*), 156.1 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{32}NO_3$ 322.2377; found 322.2374.

(2*S*,3*R*)-5-[(*tert*-Butoxycarbonyl)amino]-2,3-(isopropylidenedioxy)-1-pentanol (33): Following the general procedure, from a solution of aminodiol **22** (82 mg, 0.28 mmol) in MeOH (14 mL), 20% $Pd(OH)_2$ (16 mg), and Boc_2O (67 mg, 0.31 mmol), alcohol **33** (40 mg, 52%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = –4.18 (*c* = 1.8, $CHCl_3$). IR (film): υ = 3368, 1695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 1.36 (s, 3H, CH_3), 1.44 [s, 9H, $(CH_3)_3$], 1.46 (s, 3H, CH_3), 1.66-1.75 (m, 2H, H-4), 2.23 (br.s, 1H, OH), 3.18-3.34 (m, 2H, H-5), 3.62 (br.m, 2H, H-1), 4.15-4.24 (m, 2H, H-2, H-3), 4.90 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 25.4 (CH_3), 28.0 (CH_3), 28.4 [$(CH_3)_3$], 29.4 (C-4), 38.4 (C-5), 61.5 (C-1), 75.3 (C-3), 77.7 (C-2), 79.3 (CMe_3), 108.2 (CMe_2), 156.0 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd. for $C_{13}H_{25}NNaO_5$ 298.1625; found 298.1626.

(2*R*,3*S*)-5-[(*tert*-Butoxycarbonyl)amino]-2,3-(isopropylidenedioxy)-1-pentanol (*ent*-33): Following the general procedure, from a solution of aminodiol **23** (150 mg, 0.51 mmol) in MeOH (13 mL), 20% $Pd(OH)_2$ (30 mg), and Boc_2O (122 mg, 0.56 mmol), alcohol *ent*-**33** (84 mg, 60%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = +4.0 (*c* = 1.8, $CHCl_3$).

(2*S*,4*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-ethyl-1-pentanol (34): Following the general procedure, from a solution of aminodiol **24** (297 mg, 0.87 mmol) in MeOH (20 mL), 20% $Pd(OH)_2$ (60 mg), and Boc_2O (209 mg, 0.96 mmol), alcohol **34** (157 mg, 55%) was obtained as a colorless oil after column chromatography (8:2 hexane–EtOAc): $[\alpha]^{22}_D$ = –14.1 (*c* = 1.4, $CHCl_3$). IR (film): υ = 3360, 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 50 ºC): δ = 0.83 (t, *J* = 7.5 Hz, 3H, CH_3CH$_2$), 1.14-1.20 (m, 1H, H-3), 1.23-1.30 (m, 2H, CH$_3$CH_2), 1.38-1.50 (m, 2H, H-3, H-4), 1.43 [s, 9H, $(CH_3)_3$], 1.88-1.94 (m, 1H, H-2), 2.55-2.69 (m, 2H, CH_2Ar), 2.99 (dt, *J* = 5.6 Hz, 1H, H-5), 3.15 (br.m, 1H, H-5), 3.44 (dd, *J* = 10.5, 5.5 Hz, 1H, H-1), 3.55 (dd, *J* = 10.5, 4.8 Hz, 1H, H-1), 4.53 (br.s, 1H, NH), 7.15-7.19 (m, 3H, ArH), 7.24-7.28 (m, 2H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 ºC): δ = 10.7 (*C*H$_3$CH$_2$), 24.9 (CH$_3$*C*H$_2$), 28.4 [$(CH_3)_3$], 33.0 (C-3), 37.7 (C-4), 38.4 (CH_2Ar), 40.4 (C-2), 43.5 (C-5), 65.0 (C-1), 79.1 (CMe_3), 125.8 (C-*p*), 128.3 (C-*o*), 129.1 (C-*m*), 140.6 (C-*i*), 156.4 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{31}NNaO_3$ 344.2196; found 344.2184.

(2*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-2-methyl-1-pentanol (35a): Following the general procedure, from a solution of aminodiol **25a** (365 mg, 1.38 mmol) in MeOH (13 mL), 20% $Pd(OH)_2$ (75 mg), and Boc_2O (330 mg, 1.51 mmol), alcohol **35a** (213 mg, 63%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = –13.7 (*c* = 1.41, $CHCl_3$). IR (film): υ = 3346, 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.89 (t, *J* = 7.5 Hz, 3H, CH_3CH$_2$), 0.91 (d, *J* = 6.7 Hz, 3H, CH_3), 1.04 (ddd, *J* = 13.9, 8.3, 5.8 Hz, 1H, H-3), 1.24-1.37 (m, 3H, H-3, CH$_3$CH_2), 1.44 [s, 9H, $(CH_3)_3$], 1.53-1.58 (m, 1H, H-4), 1.69-1.78 (m, 1H, H-2), 3.05-3.09 (m, 2H, H-5), 3.41-3.52 (m, 2H, H-1), 4.57 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 10.6 (*C*H$_3$CH$_2$), 16.9 (CH_3), 24.0 (CH$_3$*C*H$_2$), 28.4 [$(CH_3)_3$], 33.0 (C-2), 35.2 (C-3), 36.9 (C-4), 43.8 (C-5), 68.4 (C-1), 79.0 (CMe_3), 156.2 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M – Boc]^+$ calcd. for $C_8H_{20}NO$ 146.1539; found 146.1541.

(2*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-2-isobutyl-1-pentanol (35b): Following the general procedure, from a solution of aminodiol **25b** (156 mg, 0.51 mmol) in MeOH (17 mL), 20% $Pd(OH)_2$ (31 mg), and Boc_2O (122 mg, 0.56 mmol), alcohol **35b** (75 mg, 51%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = –2.47 (*c* = 1.4, $CHCl_3$). IR (film): υ = 3354, 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.88-0.93 (m, 9H, $3CH_3$), 1.03-1.10 (m, 2H, H-3, CH_2CHMe$_2$), 1.14-1.21 (m, 1H, CH_2CHMe$_2$), 1.27-1.35 (m, 2H, CH$_3$CH_2), 1.37-1.50 (m, 2H, H-3, H-4), 1.44 [s, 9H, $(CH_3)_3$], 1.60-1.70 (m, 2H, H-2, C*H*Me$_2$), 2.18 (br.s, 1H, OH), 2.99 (dt, *J* = 13.7, 5.5 Hz, 1H, H-5), 3.20-3.28 (m, 1H, H-5), 3.36-3.40 (m, 1H, H-1), 3.60 (dd, *J* = 10.5, 3.9 Hz, 1H, H-1), 4.74 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.0 (*C*H$_3$CH$_2$), 22.7 (CH_3), 23.2 (CH_3), 25.0 (CH$_3$*C*H$_2$), 25.4 (CH), 28.4 [$(CH_3)_3$], 33.6 (C-3), 35.8 (C-2), 37.5 (C-4), 41.7 (*C*H$_2$CHMe$_2$), 43.0 (C-5), 65.7 (C-1), 79.1 (CMe_3), 156.6 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{16}H_{34}NO_3$ 288.2533; found 288.2543.

(3*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-3-methyl-1-pentanol (36a): Following the general procedure, from a solution of aminodiol **26a** (101 mg, 0.38 mmol) in MeOH (13 mL), 20% $Pd(OH)_2$ (20 mg), and Boc_2O (91 mg, 0.42 mmol), alcohol **36a** (47 mg, 51%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = –1.5 (*c* = 2.6, $CHCl_3$). IR (film): υ = 3346, 1692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.88-0.94 (m, 6H, $2CH_3$), 1.15-1.22 (m, 1H, CH$_3$CH_2), 1.26-1.40 (m, 3H, CH$_3$CH_2, H-2, H-4), 1.44 [s, 9H, $(CH_3)_3$], 1.66-1.75 (m, 1H, H-2), 1.81 (m, 1H, H-3), 2.05 (br.s, 1H, OH), 2.96-3.02 (m, 1H, H-5), 3.14-3.19 (m, 1H, H-5), 3.58-3.64 (m, 1H, H-1), 3.71-3.76 (m, 1H, H-1), 4.66 (br.s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 12.4 (*C*H$_3$CH$_2$), 16.4 (CH_3), 21.1 (CH$_3$*C*H$_2$), 28.4 [$(CH_3)_3$], 28.8 (C-3), 35.6 (C-2), 41.0 (C-5), 45.9 (C-4), 61.1 (C-1), 79.2 (CMe_3), 156.5 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{13}H_{28}NO_3$ 246.2064; found 246.2067.

(3*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-3-phenyl-1-pentanol (36b): Following the general procedure, from a solution of aminodiol **26b** (110 mg, 0.34 mmol) in MeOH (15 mL), 20% $Pd(OH)_2$ (22 mg), and Boc_2O (81 mg, 0.37 mmol), alcohol **36b** (52 mg, 50%) was obtained as a colorless oil after column chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ = +5.09 (*c* = 0.6, $CHCl_3$). IR (film): υ = 3350, 1694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 ºC): δ = 0.93 (t, *J* = 7.4 Hz, 3H, CH_3CH$_2$), 1.31-1.37 (m, 1H, CH$_3$CH_2), 1.41 [s, 9H, $(CH_3)_3$], 1.43-1.52 (m, 1H, CH$_3$CH_2), 1.62-1.68 (m, 2H, H-4, OH), 1.81-1.90 (m, 1H, H-2), 2.02-2.10 (m, 1H, H-2), 2.78 (br.m, 1H, H-3), 2.82-2.87 (m, 1H, H-5), 3.09-3.15 (m, 1H, H-5), 3.32-3.38 (m, 1H, H-1), 3.49-3.55 (br.m, 1H, H-1), 4.40 (br.s, 1H, NH), 7.14-7.21 (m, 3H, ArH), 7.27-7.31 (m, 2H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.2 (*C*H$_3$CH$_2$), 21.3 (CH$_3$*C*H$_2$), 28.4 [$(CH_3)_3$], 34.5 (C-2), 41.2 (C-5), 42.7 (C-3), 45.8 (C-4), 61.0 (C-1), 79.0 (CMe_3), 126.4 (C-*p*), 128.2 (C-*o*), 128.4 (C-*m*), 142.9 (C-*i*), 156.2 (CO) ppm. HRMS (ESI-TOF) *m/z* $[M – Boc]^+$ calcd. for $C_{13}H_{22}NO$ 208.1696; found 208.1696.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C spectra of lactams **2c**, **4b**, **5**, **10**, and **13b**, aminodiols **15**-**17**, **19**-**26**, and aminoalcohols **27**-**30**, **32**-**36**.

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Keywords: Asymmetric synthesis • Lactams • Aminoalcohols • Reductive ring opening • Lithium amidotrihydroborate

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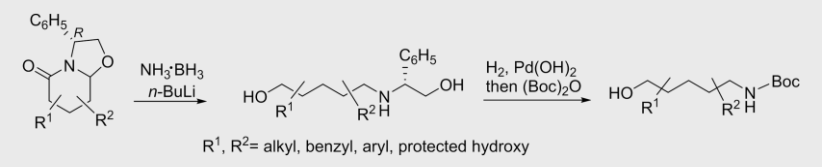

A general methodology for the generation of diversely substituted enantiopure 5-amino-1-pentanols, involving the $LiNH_2BH_3$-promoted reductive opening of (*R*)-phenylglycinol-derived oxazolopiperidone lactams as the key step

Enantiopure 1,5-Aminoalcohols

*Guillaume Guignard, Núria Llor, Aina Urbina, Joan Bosch, and Mercedes Amat**

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A General Methodology for the Synthesis of Enantiopure 1,5-Aminoalcohols