ChemPubSoc Europe

DOI: 10.1002/ejoc.201501409

EurJOC European Journal of Organic Chemistry

Full Paper

Enantiopure 1,5-Amino Alcohols

A General Method for the Synthesis of Enantiopure 1,5-Amino Alcohols

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

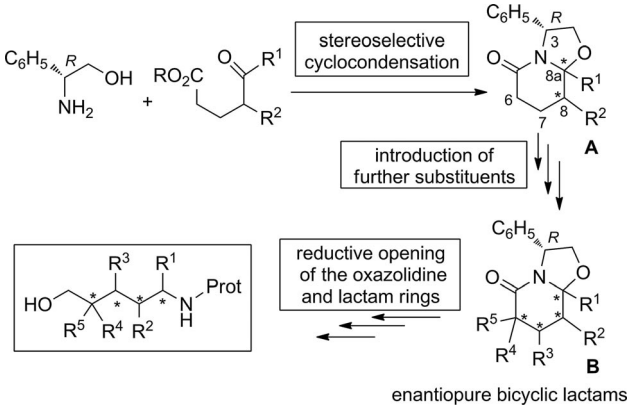
Abstract: A variety of (*R*)-phenylglycinol-derived oxazolopiperidone lactams **1**–**14** were converted to linear-chain enantiopure amino diols **15**–**26** by reduction with $LiNH_2BH_3$ in an unprecedented process involving the simultaneous reductive opening of the oxazolidine and lactam rings. 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 their *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.

We have previously[1] reported the stereoselective preparation of chiral nonracemic oxazolopiperidone lactams **A** by the cyclocondensation of (*R*)-phenylglycinol with δ-oxoacid derivatives[2] (Scheme 1). When a keto acid (R^1 = alkyl or aryl) is used as starting material, the reaction directly installs a substituent at the angular C-8a position, whereas when a racemic γ-substituted δ-oxoacid derivative (R^2 = alkyl or aryl) is used, 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 reductive cleavage of the oxazolidine and lactam rings would open up a general synthetic route to diversely substituted enantiopure 1,5-amino alcohols. 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-amino alcohols (Prot = protection group).

Several procedures have been used for the ring-opening of δ-lactams. Although direct acidic or alkaline hydrolysis requires somewhat drastic reaction conditions, *N*-Boc (*tert*-butoxycarbonyl) 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-amino alcohols,[5] as well as of the ring-opening of *N*-acyl and *N*-alkoxycarbonyl δ-lactams with Grignard reagents to give δ-amino ketones.[6,7] For the specific case of 8a-substituted oxazolopiperidone lactams, there is also some precedent for cleavage, either by direct hydrolysis under acidic conditions to give δ-keto acid derivatives, or by hydride or organometallic attack on 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–2c] No nitrogen-containing open-chain products are formed.

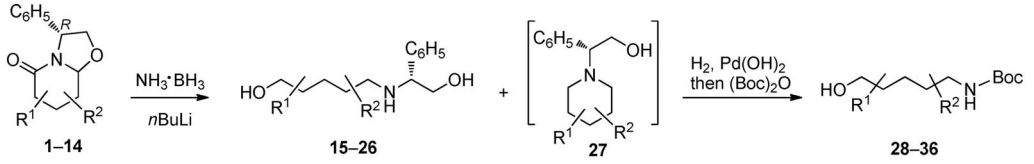
Results and Discussion

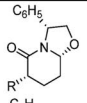
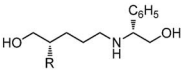
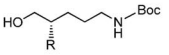
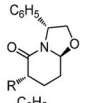
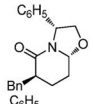
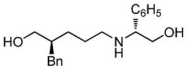
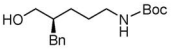
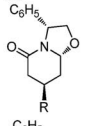
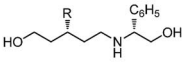
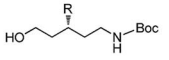
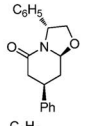
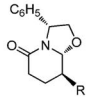
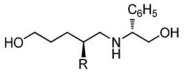
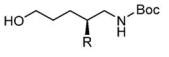
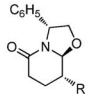
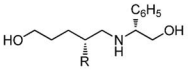
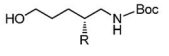
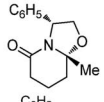
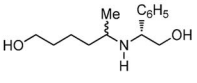
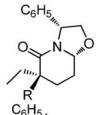
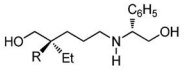
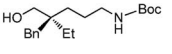
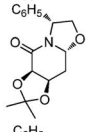
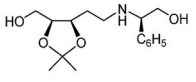
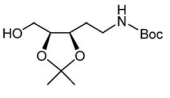
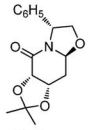
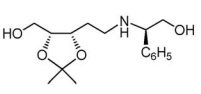
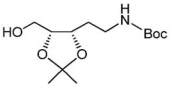
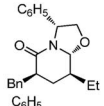
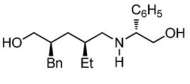
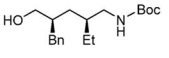
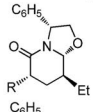
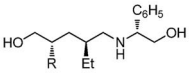
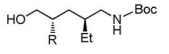
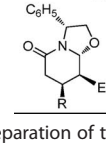
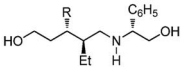
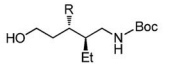
For the reductive opening of oxazolopiperidone lactams,[8] we chose to use lithium amidotrihydroborate ($LiNH_2BH_3$),[9] which

[a] *Laboratory of Organic Chemistry, Faculty of Pharmacy, and Institute of Biomedicine (IBUB), University of Barcelona, Av. Joan XXIII 27–31, 08028 Barcelona, Spain*
E-mail: amat@ub.edu
http://www.ub.edu/sintefarma/

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201501409.

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



Starting lactam[a]		Amino diol, yield[b]		*N*-Boc amino alcohol, 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%
	**13a** R = Me **13b** R = isobutyl		**25a** 65% **25b** 57%		**35a** 63% **35b** 51%
	**14a** R = Me **14b** R = Ph		**26a** 55% (13%) **26b** 37% (20%)		**36a** 51% **36b** 50%

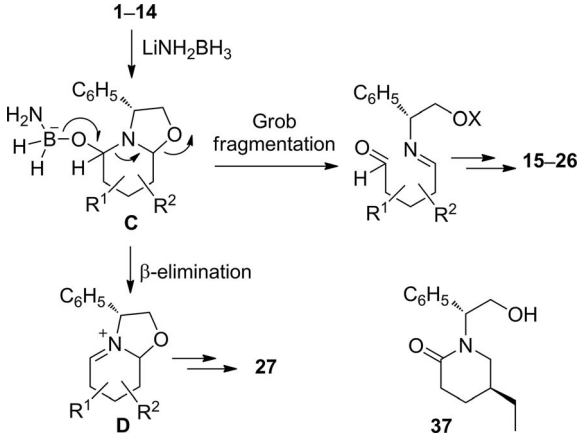
[a] For the preparation of the starting lactams, see the Exp. Section. [b] If isolated, the yields of the corresponding *N*-[(1*R*)-2-hydroxy-1-phenylethyl]piperidines **27** are given in parentheses.

is a highly nucleophilic reducing agent that can easily be generated by in situ deprotonation of the commercially available BH_3•NH_3 complex.[10] Although $LiNH_2BH_3$ has been extensively used for the direct reduction of open-chain tertiary amides to primary alcohols,[9,11,12] there are only two isolated examples of the $LiNH_2BH_3$ reduction of lactams to amino alcohols.[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 into the corresponding cyclic amines.[14]

Table 1 outlines the results obtained in the $LiNH_2BH_3$ (4.3 equiv.) reduction of a variety of oxazolopiperidone lactams **1**–**14** with 3-H and 8a-H in either a *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 that 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 gave the corresponding linear-chain amino diols **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.

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

The formation of amino diols **15**–**26** can be rationalized by considering that intermediate **C**, formed after the initial hydride attack on 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. This fragmentation is facilitated by the complexation of borane species to the oxazolidine heteroatoms. Subsequent reduction of the resulting imino aldehyde leads to **15**–**26**. Alternatively, expulsion of lithium dihydridoaminoborinate from **C** promoted by the nitrogen lone pair would give a tetrahydropyridinium species **D**, which would undergo further reduction to give piperidines **27**. In agreement with the above concerted mechanism leading to amino diols **15**–**26**, a similar $LiNH_2BH_3$ reduction of lactam **37**, which cannot undergo Grob fragmentation, gave (76 % yield) a nearly equimolecular mixture of amino diol **18b** and the corresponding piperidine (**27**; R^1 = 3*S*-Et, R^2 = H).



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

As has been seen 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 to the steric requirements of the lactam. Thus, the formation of piperidines **27** was more favored for the more sterically demanding lactams, for instance, for lactams **4**, **8**, and **14**, which bear a C-7 axial substituent.

Conclusions

The procedure reported in this paper gives access to structurally diverse enantiopure 5-amino-1-pentanols with 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 such as **8**, which gave the corresponding amino diol (i.e., **20**) as a nearly equimolecular epimeric mixture.

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

Experimental Section

General Procedures: All air-sensitive manipulations were carried out under an atmosphere of dry argon or nitrogen. Analytical thin-layer chromatography was carried out on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located with $KMnO_4$ (1 % aq.). 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 as δ values downfield from tetramethylsilane. Tetramethylsilane or residual chloroform (δ = 7.26 ppm for ^{1}H, δ = 77.0 ppm for ^{13}C) was used as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in Hertz (Hz), integrated intensity, 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 carried out with a Nicolet Avantar 320 FTIR spectrophotometer, and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured with a 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 carried out 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 the 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) at –78 °C, and the mixture was stirred at –78 °C for 1 h. Then, 3,5-difluorobenzyl bromide (0.46 mL, 3.59 mmol) was added. The mixture was stirred at –78 °C for 8 h, and then 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, and filtered, and the solvents were evaporated. The resulting residue was purified by chromatography (from hexane/EtOAc, 9:1, to EtOAc) to give **2c** (450 mg, 44 %) as a colorless oil, along with 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**: $[\alpha]_D^{22}$ = +12.4 (*c* = 0.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1649 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.46–1.55 (m, 2 H, 7-H, 8-H), 1.81–1.86 (m, 1 H, 7-H), 2.30–2.36 (m, 1 H, 8-H), 2.60–2.65 (m, 1 H, 6-H), 3.02–3.10 (m, 2 H, CH_2Ar), 3.68 (dd, *J* = 9.0, 8.1 Hz, 1 H, 2-H), 4.49 (dd, *J* = 9.0, 8.1 Hz, 1 H, 2-H), 4.88 (m, 1 H, 8a-H), 5.24 (t, *J* = 8.1 Hz, 1 H, 3-H), 6.65–6.69 (m, 3 H, F-ArH), 7.17–7.20 (m, 2 H, ArH), 7.26–7.37 (m, 3 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): 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 (t, $J_{C,F}$ = 24.7 Hz, F-Ar C-4), 112.2 (dd, $J_{C,F}$ = 16.7, 7.5 Hz, F-Ar C-2 and C-6), 125.7 (C-*o*), 127.5 (C-*p*), 128.8 (C-*m*), 139.2 (C-*i*), 142.7 (t, $J_{C,F}$ = 9.2 Hz, F-Ar C-1), 162.8 (dd, $J_{C,F}$ = 247.9, 13.2 Hz, F-Ar C-3 and C-5), 169.9 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{20}F_2NO_2$ $[M + H]^+$ 344.1457; found 344.1454.

Data for the 6*S* epimer: $[\alpha]_D^{22}$ = –105.1 (*c* = 0.55, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.59–1.69 (m, 2 H, 7-H, 8-H), 1.70–1.78 (m, 1 H, 7-H), 2.13–2.20 (m, 1 H, 8-H), 2.64 (m, 2 H, 6-H, CH_2Ar), 3.01 (m, 1 H, CH_2Ar), 3.78 (dd, *J* = 9.0, 7.9 Hz, 1 H, 2-H), 4.77 (dd, *J* = 9.0, 7.9 Hz, 1 H, 2-H), 5.00 (m, 1 H, 8a-H), 5.28 (t, *J* = 7.9 Hz, 1 H, 3-H), 6.63 (m, 1 H, F-ArH), 6.68–6.76 (m, 2 H, F-ArH), 7.25–7.29 (m, 3 H, ArH), 7.32–7.36 (m, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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 (t, $J_{C,F}$ = 25.2 Hz, F-Ar C-4), 111.8 (dd, $J_{C,F}$ = 17.9, 6.2 Hz, F-Ar C-2 and C-6), 126.2 (C-*o*), 127.6 (C-*p*), 128.7 (C-*m*), 139.4 (C-*i*), 143.7 (t, $J_{C,F}$ = 9.3 Hz, F-Ar C-1), 163.0 (dd, $J_{C,F}$ = 249.2, 13.3 Hz, F-Ar C-3 and C-5), 170.4 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{20}F_2NO_2$ $[M + H]^+$ 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: $[\alpha]_D^{22}$ = –29.6 (*c* = 1.25, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.06–1.25 (m, 1 H, 7-H), 1.72–1.77 (m, 2 H, 7-H, 8-H), 2.00–2.09 (m, 1 H, 8-H), 2.35 (d, *J* = 12.9 Hz, 1 H, CH_2Ar), 2.78 (d, *J* = 13.3 Hz, 1 H, CH_2Ar), 3.28 (d, *J* = 13.3 Hz, 1 H, CH_2Ar), 3.33 (d, *J* = 12.9 Hz, 1 H, CH_2Ar), 3.63 (dd, *J* = 9.2, 8.1 Hz, 1 H, 2-H), 4.37 (dd, *J* = 9.2, 8.1 Hz, 1 H, 2-H), 4.65 (dd, *J* = 9.0, 4.5 Hz, 1 H, 8a-H), 5.15 (t, *J* = 8.1 Hz, 1 H, 3-H), 6.47–6.51 (m, 2 H, F-ArH), 6.67–6.77 (m, 1 H, F-ArH), 7.05–7.09 (m, 2 H, ArH), 7.31–7.44 (m, 3 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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 (t, $J_{C,F}$ = 24.9 Hz, F-Ar C-4), 102.6 (t, $J_{C,F}$ = 25.6 Hz, F-Ar C-4), 113.2 (dd, $J_{C,F}$ = 17.9, 6.9 Hz, F-Ar C-2 and C-6), 113.6 (dd, $J_{C,F}$ = 17.9, 7.0 Hz, F-Ar C-2 and C-6), 126.1 (C-*o*), 127.7 (C-*p*), 128.9 (C-*m*), 138.8 (C-*i*), 140.6 (t, $J_{C,F}$ = 8.5 Hz, F-Ar C-1), 141.0 (t, $J_{C,F}$ = 9.3 Hz, F-Ar C-1), 162.5 (dd, $J_{C,F}$ = 248.5, 12.8 Hz, F-Ar C-3 and C-5), 162.9 (dd, $J_{C,F}$ = 249.2, 13.3 Hz, F-Ar C-3 and C-5), 171.1 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{27}H_{24}F_4NO_2$ $[M + H]^+$ 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 Pd/C (10 %; 115 mg) was stirred under hydrogen at 25 °C for 17 h. The catalyst was removed by filtration, and the filter residue was 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, then it was cooled and concentrated. The residue was purified by chromatography (hexane/EtOAc, 1:1) to give pure compound **4b** (630 mg, 80 %). $[\alpha]_D^{22}$ = –121.2 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1655, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 2.27 (ddd, *J* = 12.9, 9.6, 5.9 Hz, 1 H, 8-H), 2.52 (dt, *J* = 12.9, 5.0 Hz, 1 H, 8-H), 2.66 (d, *J* = 5.4 Hz, 2 H, 6-H), 3.52 (ddd, *J* = 9.6, 5.4, 5.0 Hz, 1 H, 7-H), 4.02 (dd, *J* = 9.0, 1.4 Hz, 1 H, 2-H), 4.11 (dd, *J* = 9.0, 6.8 Hz, 1 H, 2-H), 4.71 (dd, *J* = 9.3, 4.2 Hz, 1 H, 8a-H), 4.96 (t, *J* = 5.7 Hz, 1 H, CHN), 7.22–7.37 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{19}H_{20}NO_2$ $[M + H]^+$ 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 (trifluoroacetic acid; 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 $NaHCO_3$ (2 N aq.; 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 purified by chromatography (hexane/EtOAc, 1:1) to give pure **5** (610 mg, 97 %). $[\alpha]_D^{22}$ = –58.2 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1647, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.87 (ddd, *J* = 13.3, 12.4, 9.3 Hz, 1 H, 8-H), 2.47 (dd, *J* = 18.0, 12.0 Hz, 1 H, 6-H), 2.56 (dm, 1 H, 8-H), 2.84 (ddd, *J* = 18.0, 5.6, 1.72 Hz, 1 H, 6-H), 3.20 (m, 1 H, 7-H), 3.84 (dd, *J* = 9.0, 7.9 Hz, 1 H, 2-H), 4.56 (dd, *J* = 9.0, 7.9 Hz, 1 H, 2-H), 5.20 (dd, *J* = 9.3, 4.5 Hz, 1 H, 8a-H), 5.32 (t, *J* = 7.9 Hz, 1 H, CHN), 7.21–7.37 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{19}H_{20}NO_2$ $[M + H]^+$ 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): (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) was dissolved in CH_3CN (28 mL) and H_2O (0.1 mL), and *N*-methylmorpholine *N*-oxide (323 mg, 2.79 mmol) and OsO_4 (2.5 % solution in *t*BuOH; 1.0 mL) were added. The mixture was stirred at room temperature for 17 h. The resulting solution was quenched with saturated aqueous $Na_2S_2O_5$, and the mixture was 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 purified by chromatography (EtOAc/EtOH, 8:2), 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 %). $[\alpha]_D^{22}$ = +9.31 (*c* = 0.13, EtOH). IR (film): $\tilde{\nu}$ = 3416, 1654, 1469 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.97–2.04 (m, 1 H, 8-H), 2.78 (dt, *J* = 13.3, 4.0 Hz, 1 H, 8-H), 2.84 (s, 1 H, OH), 2.85 (s, 1 H, OH), 3.93 (d, *J* = 3.2 Hz, 1 H, 6-H), 4.11 (dd, *J* = 9.0, 2.0 Hz, 1 H, 2-H), 4.27 (dd, *J* = 9.0, 7.5 Hz, 1 H, 2-H), 4.46 (m, 1 H, 7-H), 4.89 (dd, *J* = 7.5, 2.0 Hz, 1 H, 3-H), 5.21 (dd, *J* = 9.8, 4.0 Hz, 1 H, 8a-H), 7.26–7.32 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 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 then added, and the mixture was stirred for 20 min. The mixture

was then 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. The residue was purified by flash chromatography (hexane/EtOAc, 1:1) to give **10** (350 mg, 77 %). $[\alpha]_D^{22}$ = –48.2 (*c* = 1.05, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1664, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.37 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.94 (ddd, *J* = 13.7, 10.1, 3.7 Hz, 1 H, 8-H), 2.71 (dt, *J* = 13.7, 2.6 Hz, 1 H, 8-H), 4.11 (dd, *J* = 9.1, 0.8 Hz, 1 H, 2-H), 4.23 (dd, *J* = 9.1, 6.5 Hz, 1 H, 2-H), 4.43 (d, *J* = 6.6 Hz, 1 H, 6-H), 4.67–4.70 (m, 1 H, 7-H), 4.98 (d, *J* = 6.5 Hz, 1 H, 3-H), 5.11 (dd, *J* = 10.1, 2.6 Hz, 1 H, 8a-H), 7.23–7.34 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{16}H_{20}NO_4$ $[M + H]^+$ 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 °C) solution of LiHMDS (1 M in THF; 4.52 mL, 4.52 mmol) in anhydrous THF (33 mL). The resulting solution was stirred at –78 °C for 1 h, then 1-iodo-2-methylpropane (0.87 mL, 7.53 mmol) was added, and stirring was continued at –78 °C for 6 h and then 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 (hexane/EtOAc, 8:2 to 1:1) gave **13b** (320 mg, 35 %), and its 6*R* epimer (95 mg, 11 %). Data for **13b**: $[\alpha]_D^{22}$ = –29.4 (*c* = 0.57, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2955, 1657 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.83 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.89 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.06 (t, *J* = 7.5 Hz, 3 H, *C*H_3CH_2), 1.09–1.16 (m, 1 H, 7-H), 1.21–1.28 (m, 1 H, 8-H), 1.34–1.43 (m, 1 H, CH_3CH_2), 1.64–1.74 (m, 1 H, *C*HMe_2), 1.76–1.91 [m, 3 H, CH_3CH_2, *C*H_2($CHMe_2$)], 2.08–2.14 (ddd, *J* = 14.0, 7.0, 3.2 Hz, 1 H, 7-H), 2.22–2.30 (m, 1 H, 6-H), 4.00 (dd, *J* = 9.0, 1.1 Hz, 1 H, CH_2O), 4.12 (dd, *J* = 9.0, 6.5 Hz, 1 H, CH_2O), 4.50 (d, *J* = 8.8 Hz, 1 H, 8a-H), 4.85 (d, *J* = 6.5 Hz, 1 H, CHN), 7.19–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 10.9 (*C*H_3CH_2), 21.0 (CH_3), 23.5 (CH_3), 24.1 (CH_3CH_2), 25.0 (*C*HMe_2), 30.4 (C-7), 39.4 (C-6), 40.7 (C-8), 41.0 [CH_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): calcd. for $C_{19}H_{28}NO_2$ $[M + H]^+$ 302.2115; found 302.2116.

Data for the 6*R* epimer: $[\alpha]_D^{22}$ = +8.36 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2956, 1659 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.83 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.89 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.05 (t, *J* = 7.5 Hz, 3 H, *C*H_3CH_2), 1.19–1.26 [m, 1 H, *C*H_2($CHMe_2$)], 1.32–1.43 (m, 1 H, CH_3CH_2), 1.52–1.60 [m, 2 H, 7-H, *C*H_2($CHMe_2$)], 1.61–1.68 (m, 1 H, *C*HMe_2), 1.76–1.84 (m, 2 H, CH_3CH_2, 7-H), 1.87–1.96 (m, 1 H, 8-H), 2.30–2.36 (m, 1 H, 6-H), 4.01 (dd, *J* = 9.0, 1.1 Hz, 1 H, CH_2O), 4.15 (dd, *J* = 9.0, 6.9 Hz, 1 H, CH_2O), 4.54 (d, *J* = 8.7 Hz, 1 H, 8a-H), 4.89 (d, *J* = 5.9 Hz, 1 H, CHN), 7.21–7.32 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 11.0 (CH_3CH_2), 21.4 (CH_3), 23.1 (CH_3), 24.7 (CH_3CH_2), 25.5 (*C*HMe_2), 29.0 (C-7), 37.6 (C-8), 38.0 (C-6), 40.8 [CH_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): calcd. for $C_{19}H_{27}NNaO_2$ $[M + H]^+$ 324.1934; found 324.1935.

General Procedure for the Synthesis of Enantiopure Amino diols 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·BH_3 (4.3 equiv.) in anhydrous THF at 0 °C, and the resulting mixture was stirred at this temperature for 10 min, and then at room temperature for 15 min. Then, the mixture was added to a solution of lactam (1.0 equiv.) in anhydrous THF, and the mixture was stirred at 40 °C 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, and the residue was purified by flash chromatography. The preparation of 4-substituted amino diols **18a**–**18e** 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 (2.5 M solution in hexanes; 3.53 mL, 8.84 mmol) and NH_3·BH_3 (273 mg, 8.84 mmol) in THF (11 mL), a brown oil was obtained. Flash chromatography (from hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) 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 (2.5 M solution in hexanes; 3.2 mL, 8.0 mmol), and NH_3·BH_3 (247 mg, 8.0 mmol) in THF (10 mL), an oil was obtained. Flash chromatography (from hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) gave (*S*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3-methylpiperidine[19] (21 mg, 5 %), and **15a** (257 mg, 58 %).

Data for **15a**: $[\alpha]_D^{22}$ = –50.7 (*c* = 0.76, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3330, 1454, 1040 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.88 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.10–1.19 (m, 1 H, 3-H), 1.39–1.64 (m, 4 H, 2-H, 3-H, 4-H), 2.46–2.58 (m, 2 H, 5-H), 3.27 (br. s, 3 H, NH, OH), 3.43 (d, *J* = 6.0 Hz, 2 H, 1-H), 3.61 (dd, *J* = 10.9, 8.9 Hz, 1 H, CH_2O), 3.72 (dd, *J* = 10.9, 4.2 Hz, 1 H, CH_2O), 3.80 (dd, *J* = 8.9, 4.2 Hz, 1 H, CHN), 7.25–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{14}H_{24}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 1.68 mL, 4.21 mmol), and NH_3·BH_3 (130 mg, 4.21 mmol) in THF (5 mL), a brown oil was obtained. Flash chromatography (from hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) 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 (2.5 M solution in hexanes; 21 mL, 52.4 mmol), and NH_3·BH_3 (1.62 g, 52.4 mmol) in THF (50 mL), an oil was obtained. Flash chromatography (from hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) gave (*S*)-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine[19] (171 mg, 6 %), and **15b** (2.45 g, 80 %).

Data for **15b**: $[\alpha]_D^{22}$ = –63.9 (*c* = 0.8, MeOH). IR (film): $\tilde{\nu}$ = 3300, 1454, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.83 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.22–1.38 (m, 5 H, *C*H_2CH_3, 2-H, 4-H), 1.48 (br. s, 2 H, 3-H), 2.48 (m, 2 H, 5-H), 3.56–3.70 (m, 2 H, 1-H), 3.45 (dd, *J* = 10.4, 4.8 Hz, 1 H, CH_2O), 3.49 (dd, *J* = 10.4, 3.6 Hz, 1 H, CH_2O), 3.77 (dd, *J* = 4.8, 3.6 Hz, 1 H, CHN), 7.23–7.30 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 11.2 (*C*H_3CH_2), 23.5 (CH_3CH_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): calcd. for $C_{15}H_{26}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 2.26 mL, 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 hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) 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 °C): δ = 1.43–1.72 (m, 4 H, 4-H, 5-H), 1.95–2.00 (m, 1 H, 3-H), 2.37–2.52 (m, 2 H, 2-H), 2.70–2.85 (m, 2 H, 6-H), 2.78–2.85 (m, 2 H, CH_2Ar), 3.58–3.75 (m, 2 H, CH_2O), 3.93–4.00 (m, 1 H, CHN), 6.60–6.67 (m, 3 H, F-ArH), 7.14–7.17 (dd, *J* = 7.9, 1.9 Hz, 2 H, ArH), 7.36–7.37 (m, 3 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 25.3 (d, $J_{C,F}$ = 11.7 Hz, C-5), 30.4 (d, $J_{C,F}$ = 29.7 Hz, C-4), 38.0 (d, $J_{C,F}$ = 35.8 Hz, C-3), 40.5 (CH_2Ar), 46.9 (C-6), 52.7 (d, $J_{C,F}$ = 11.7 Hz, C-2), 59.9 (d, $J_{C,F}$ = 3.1 Hz, CHN), 70.1 (d, $J_{C,F}$ = 17.1 Hz, CH_2O), 101.4 (dd, $J_{C,F}$ = 24.8, 3.1 Hz, F-Ar C-4), 111.7 (dd, $J_{C,F}$ = 17.9, 6.9 Hz, F-Ar C-2 and C-6), 127.9 (C-*p*), 128.2 (C-*o*), 128.9 (C-*m*), 135.1 (C-*i*), 144.3 (d, $J_{C,F}$ = 8.5 Hz, F-Ar C-1), 162.9 (ddd, $J_{C,F}$ = 247.6, 13.3, 3.9 Hz, F-Ar C-3 and C-5) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{23}F_2NO$ $[M + H]^+$ 332.1820; found 332.1820.

Data for **15c**: $[\alpha]_D^{22}$ = –33.9 (*c* = 0.5, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3353, 1625 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.26–1.31 (m, 1 H, 3-H), 1.35–1.43 (m, 1 H, 3-H), 1.45–1.53 (m, 2 H, 4-H), 1.72 (br. s, 1 H, 2-H), 2.51 (m, 3 H, 5-H, CH_2Ar), 2.65–2.70 (m, 1 H, CH_2Ar), 3.44 (dd, *J* = 10.5, 5.2 Hz, 1 H, 1-H), 3.50 (dd, *J* = 10.5, 6.4 Hz, 1 H, 1-H), 3.55–3.68 (m, 4 H, CH_2, OH, NH); 3.72 (dd, *J* = 10.8, 3.8 Hz, 1 H, CH_2O); 3.80 (dd, *J* = 8.5, 3.8 Hz, 1 H, CHN); 6.59–6.67 (m, 3 H, F-ArH), 7.26–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 26.3 (C-3), 27.7 (C-4), 37.4 (d, $J_{C,F}$ = 9.2 Hz, CH_2Ar), 41.7 (d, $J_{C,F}$ = 6.2 Hz, C-2), 47.0 (C-5), 63.2 (C-1), 64.7 (CHN), 66.1 (CH_2O), 101.3 (t, $J_{C,F}$ = 24.9 Hz, F-Ar C-4), 111.7 (dd, $J_{C,F}$ = 18.7, 6.2 Hz, F-Ar C-2 and C-6), 127.3 (C-*o*), 127.8 (C-*p*), 128.7 (C-*m*), 139.2 (C-*i*), 144.7 (t, $J_{C,F}$ = 9.3 Hz, F-Ar C-1), 162.8 (dd, $J_{C,F}$ = 247.7, 13.3 Hz, F-Ar C-3 and C-5) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{26}F_2NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 2.54 mL, 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 hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2) 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: $[\alpha]_D^{22}$ = +2.1 (*c* = 0.45, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3386, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.19–1.33 (m, 1 H, 4-H), 1.53–1.68 (m, 4 H, 2-H, 4-H, 5-H), 1.74–1.86 (m, 1 H, 3-H), 2.29–2.35 (m, 1 H, 2-H), 2.36 (dd, *J* = 13.5, 8.1 Hz, 1 H, CH_2Ar), 2.56 (dd, *J* = 13.5, 6.5 Hz, 1 H, CH_2Ar), 2.75 (m, 1 H, 6-H), 2.83 (m, 1 H, 6-H), 3.61 (dd, *J* = 10.3, 5.1 Hz, 1 H, CH_2O), 3.74 (dd, *J* = 10.3, 5.1 Hz, 1 H, CHN), 3.97 (t, *J* = 10.3 Hz, 1 H, CH_2O), 7.09–7.38 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{20}H_{26}NO$ $[M + H]^+$ 296.2009; found 296.2010.

Data for **16**: $[\alpha]_D^{22}$ = –45.3 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3331, 1494, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.30–1.37 (m, 1 H, 3-H), 1.37–1.48 (m, 1 H, 3-H), 1.48–1.57 (m, 2 H, 4-H), 1.77 (m, 1 H, 2-H), 2.52 (m, 2 H, 5-H), 2.55 (m, 1 H, CH_2Ar), 2.63 (dd, *J* = 13.6, 7.5 Hz, 1 H, CH_2Ar), 2.83 (br. s, 3 H, NH, OH), 3.47 (dd, *J* = 10.8, 5.3 Hz, 1 H, 1-H), 3.56 (dd, *J* = 10.8, 4.7 Hz, 1 H, 1-H), 3.59–3.62 (m, 1 H, CH_2O), 3.69–3.73 (m, 1 H, CH_2O), 3.76–3.78 (m, 1 H, CHN), 7.13–7.19 (m, 3 H, ArH), 7.24–7.37 (m, 7 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{20}H_{28}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 1.95 mL, 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 hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2) 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: $[\alpha]_D^{22}$ = –18.5 (*c* = 2.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3414 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.87 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.10–1.23 (m, 1 H, 4-H), 1.25–1.34 (m, 2 H, 3-H, 5-H), 1.55–1.72 (m, 3 H, 3-H, 5-H, 2-H or 6-H), 2.29 (ddd, *J* = 11.3, 11.3, 2.5 Hz, 1 H, 2-H or 6-H), 2.83 (m, 2 H, 2-H, 6-H), 3.20 (br. s, 1 H, OH), 3.62 (dd, *J* = 10.1, 5.2 Hz, 1 H, CH_2O), 3.70 (dd, *J* = 10.1, 5.2 Hz, 1 H, CHN), 3.97 (t, *J* = 10.1 Hz, 1 H, CH_2O), 7.17 (m, 2 H, ArH), 7.28–7.36 (m, 3 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{14}H_{22}NO$ $[M + H]^+$ 220.1696; found 220.1700.

Data for **17a**: $[\alpha]_D^{22}$ = –51.9 (*c* = 0.84, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3320, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.86 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.28–1.42 (m, 2 H, 2-H, 4-H), 1.46–1.59 (m, 2 H, 2-H, 4-H), 1.64–1.72 (m, 1 H, 3-H), 2.44–2.51 (m, 1 H, 5-H), 2.56–2.63 (m, 1 H, 5-H), 3.48 (br. s, 3 H, NH, OH), 3.57–3.63 (m, 2 H, 1-H, CH_2O), 3.65–3.72 (m, 2 H, 1-H, CH_2O), 3.78 (dd, *J* = 8.9, 4.1 Hz, 1 H, CHN), 7.24–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{14}H_{24}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 1.41 mL, 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 hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2) 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 (2.5 M solution in hexanes; 3.0 mL, 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 hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2) 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: $[\alpha]_D^{22}$ = –6.44 (*c* = 0.26, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3417, 1601, 1493, 1451 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.71 (dt, *J* = 12.4, 3.7 Hz, 1 H, 3-H or 5-H), 1.79–1.82 (m, 1 H, 4-H), 1.82–1.88 (m, 3 H, 3-H, 5-H), 2.32–2.40 (m, 1 H, 2-H or 6-H), 2.42–2.48 (m, 1 H, 2-H or 6-H), 2.98–3.05 (m, 2 H, 2-H, 6-H), 3.66 (dd, *J* =

10.4, 5.2 Hz, 1 H, CH_2O), 3.76 (dd, J = 10.4, 5.2 Hz, 1 H, CHN), 4.02 (t, J = 10.4 Hz, 1 H, CH_2O), 7.16–7.39 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{19}H_{24}NO$ $[M + H]^+$ 282.1852; found 282.1851.

Data for **17b**: $[\alpha]_D^{22}$ = –40.9 (c = 3.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3321, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.70–1.88 (m, 4 H, 2-H, 4-H), 2.32–2.38 (m, 1 H, 5-H), 2.45–2.51 (m, 1 H, 5-H), 2.61 (br. s, 3 H, NH, OH), 2.80–2.87 (m, 1 H, 3-H), 3.39–3.46 (m, 1 H, 1-H), 3.48–3.54 (m, 2 H, 1-H, CH_2O), 3.62–3.66 (m, 2 H, CH_2O, CHN), 7.13–7.31 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{19}H_{26}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 2.98 mL, 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 hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) gave (*R*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3-methylpiperidine[19] (35 mg, 11 %), and **19a** (225 mg, 55 %) as a colorless oil. Data for **19a**: $[\alpha]_D^{22}$ = –57.4 (c = 0.9, MeOH). IR (film): $\tilde{\nu}$ = 3328, 1492, 1453, 1056 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.88 (d, J = 6.7 Hz, 3 H, CH_3), 1.15–1.20 (m, 1 H, 2-H), 1.40–1.50 (m, 2 H, 2-H, 3-H), 1.55–1.65 (m, 2 H, 3-H, 4-H), 2.36 (m, 2 H, 5-H), 3.27 (br. s, 3 H, OH, NH), 3.55–3.58 (m, 3 H, 1-H, CH_2O), 3.64 (m, 1 H, CHN), 3.70 (m, 1 H, CH_2O), 7.23–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{14}H_{24}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 2.77 mL, 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 hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) gave (*R*)-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine[17] (35 mg, 9 %), and **19b** (202 mg, 50 %). Data for **19b**: $[\alpha]_D^{22}$ = –48.8 (c = 0.7, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3329, 1453, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.80 (t, J = 7.5 Hz, 3 H, CH_3), 1.28–1.35 (m, 2 H, CH_3CH_2), 1.36–1.43 (m, 2 H, 3-H), 1.43–1.54 (m, 3 H, 2-H, 4-H), 2.36 (dd, J = 11.5, 6.0 Hz, 1 H, 5-H), 2.48 (dd, J = 11.5, 5.6 Hz, 1 H, 5-H), 3.29 (br. s, 3 H, OH, NH), 3.59 (obscured signal, 1 H, CH_2O), 3.60 (t, J = 6.4 Hz, 2 H, 1-H), 3.72–3.77 (m, 2 H, CH_2O, CHN), 7.24–7.36 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{15}H_{26}NO_2$ $[M + H]^+$ 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 (1.6 M solution in hexanes; 2.43 mL, 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 hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2) gave 1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-methylpiperidine[21] (32 mg, 16 %) as a 1:1 mixture of C-2 epimers, and amino diol **20** (105 mg, 50 %) as a 1:1 mixture of C-5 epimers. Data for **20**: IR (film): $\tilde{\nu}$ = 3350, 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C, 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, 2-H, 3-H, 4-H), 2.50–2.55 (m, 5-H), 2.59–2.67 (m, 5-H), 3.40 (br. s, OH, NH), 3.51–3.74 (m, 1-H, CH_2O), 3.87 (dd, J = 8.6, 4.3 Hz, 1 H, CHN), 3.92 (dd, J = 8.5, 4.3 Hz, 1 H, CHN), 7.24–7.35 (m, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{14}H_{24}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 1.83 mL, 4.56 mmol), and $NH_3{\cdot}BH_3$ (141 mg, 4.56 mmol) in THF (5 mL), and after flash chromatography (from EtOAc to EtOAc/EtOH, 8:2), amino alcohol **21a** (250 mg, 69 %) was obtained. $[\alpha]_D^{22}$ = –28.4 (c = 0.96, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3384, 1601, 1494, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.89 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.15–1.20 (m, 2 H, 3-H), 1.22–1.30 (m, 2 H, 4-H), 1.41–1.53 (m, 2 H, CH_3CH_2), 2.45–2.49 (m, 2 H, 5-H), 2.52 (d, J = 13.2 Hz, 1 H, CH_2Ar), 2.60 (d, J = 13.2 Hz, 1 H, CH_2Ar), 3.28 (br. s, 2 H, 1-H), 3.58 (dd, J = 11.0, 8.6, Hz, 1 H, CH_2O), 3.72 (dd, J = 11.0, 4.4 Hz, 1 H, CH_2O), 3.78 (dd, J = 8.6, 4.4 Hz, 1 H, CHN), 7.16–7.37 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{22}H_{32}NO_2$ $[M + H]^+$ 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 (2.5 M solution in hexanes; 2.4 mL, 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 hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) 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: $[\alpha]_D^{22}$ = –19.5 (c = 0.5, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3440, 1637, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.80 (t, J = 7.6 Hz, 3 H, CH_3), 1.15–1.28 (m, 2 H, CH_2), 1.31 (m, 2 H, 5-H), 1.60 (m, 2 H, CH_2), 2.04–2.18 (m, 2 H, 4-H), 2.20 (m, 2 H, 2-H), 2.54 (br. s, 2 H, 6-H), 3.59–3.66 (m, 2 H, CHN, CH_2O), 3.99 (t, J = 9.6 Hz, CH_2O), 5.03 (m, 2 H, CH_2=CH), 5.70–5.80 (m, 1 H, CH_2=CH), 7.15–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{18}H_{28}NO$ $[M + H]^+$ 274.2165; found 274.2161.

Data for **21b**: $[\alpha]_D^{22}$ = –34.3 (c = 0.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3331, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.76 (t, J = 7.2 Hz, 3 H, CH_3), 1.12–1.14 (m, 4 H, CH_3CH_2, 3-H), 1.40–1.45 (m, 2 H, 4-H), 1.89 (dd, J = 14.0, 7.6 Hz, 1 H, CH_2=CHCH_2), 1.98 (dd, J = 14.0, 7.6 Hz, 1 H, CH_2=CHCH_2), 2.44–2.49 (m, 2 H, 5-H), 3.30 (s, 2 H, 1-H), 3.63–3.70 (m, 2 H, CH_2O), 3.82 (dd, J = 8.4, 4.0 Hz, 1 H, CHN), 4.16 (br. s, 3 H, OH, NH), 4.99 (m, 2 H, CH_2=CH), 5.68–5.78 (m, 1 H, CH_2=CH), 7.30 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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=

*C*H), 138.9 (C-*i*) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{30}NO_2$ [M + H]$^+$ 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 (2.5 M solution in hexanes; 1.46 mL, 3.64 mmol), and NH_3·BH_3 (112 mg, 3.64 mmol) in THF (6 mL), and after flash chromatography (from hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2), amino alcohol **22** (100 mg, 40 %) was obtained. $[\alpha]_D^{22}$ = –38.3 (*c* = 1.72, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3359, 1454, 1044 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.33 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.67–1.76 (m, 1 H, 4-H), 1.78–1.85 (m, 1 H, 4-H), 2.61–2.68 (m, 1 H, 5-H), 2.72–2.78 (m, 1 H, 5-H), 3.22 (br. s, 3 H, NH, OH), 3.55–3.63 (m, 3 H, 1-H, CH_2O), 3.71 (dd, *J* = 10.9, 4.1 Hz, 1 H, CH_2O), 3.78 (dd, *J* = 8.5, 4.1 Hz, 1 H, CHN), 4.11–4.15 (m, 1 H, 2-H), 4.17–4.22 (m, 1 H, 3-H), 7.27–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{16}H_{26}NO_4$ [M + H]$^+$ 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 M solution in hexanes; 2.5 mL, 6.25 mmol), and NH_3·BH_3 (193 mg, 6.25 mmol) in THF (15 mL), an oil was obtained. Flash chromatography (from hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2) 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 %). Data for **23**: $[\alpha]_D^{22}$ = –45.9 (*c* = 2.35, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3404, 1493 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.31 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.70–1.76 (m, 1 H, 4-H), 1.80–1.88 (m, 1 H, 4-H), 2.59–2.66 (m, 1 H, 5-H), 2.68–2.74 (m, 1 H, 5-H), 3.57–3.67 (m, 3 H, 1-H, CH_2O), 3.71 (dd, *J* = 11.0, 4.1 Hz, 1 H, CH_2O), 3.82–3.90 (br. m, 4 H, CHN, OH, NH), 4.11–4.19 (m, 2 H, 2-H, 3-H), 7.27–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{16}H_{26}NO_4$ [M + H]$^+$ 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 (2.5 M solution in hexanes; 2.69 mL, 6.72 mmol), and NH_3·BH_3 (207 mg, 6.72 mmol) in THF (9 mL), and after flash chromatography (from hexane/EtOAc, 7:3, to EtOAc/EtOH, 8:2), amino alcohol **24** (295 mg, 55 %) was obtained. $[\alpha]_D^{22}$ = –54.0 (*c* = 0.38, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3338, 1494, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.74 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2), 1.14–1.23 (m, 3 H, 3-H, CH_3CH_2), 1.35–1.40 (m, 1 H, 4-H), 1.44–1.51 (m, 1 H, 3-H), 1.73–1.80 (m, 1 H, 2-H), 2.23 (dd, *J* = 11.6, 8.2 Hz, 1 H, 5-H), 2.50 (dd, *J* = 11.6, 4.0 Hz, 1 H, 5-H), 2.53 (dd, *J* = 13.5, 6.8 Hz, 1 H, CH_2Ar), 2.67 (dd, *J* = 13.5, 7.9 Hz, 1 H, CH_2Ar), 2.99 (br. s, 3 H, NH, OH), 3.45 (dd, *J* = 11.5, 4.3 Hz, 1 H, 1-H), 3.58 (dd, *J* = 10.4, 9.2 Hz, 1 H, CH_2O), 3.67 (dd, *J* = 11.5, 3.8 Hz, 1 H, 1-H), 3.68–3.69 (m, 1 H, CH_2O), 3.71–3.76 (m, 1 H, CHN), 7.15–7.19 (m, 3 H, ArH), 7.24–7.37 (m, 7 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{22}H_{31}NO_2$ [M + H]$^+$ 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 (2.5 M solution in hexanes; 3.48 mL, 8.71 mmol), and NH_3·BH_3 (269 mg, 8.71 mmol) in THF (6 mL), and after flash chromatography (from hexane/EtOAc, 1:1, to EtOAc/EtOH, 8:2), amino alcohol **25a** (349 mg, 65 %) was obtained. $[\alpha]_D^{22}$ = –64.7 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3319, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.81 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2), 0.86 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.19–1.37 (m, 4 H, 3-H, CH_3CH_2), 1.47–1.55 (m, 1 H, 4-H), 1.70–1.77 (m, 1 H, 2-H), 2.29–2.34 (m, 1 H, 5-H), 2.47 (dd, *J* = 11.6, 4.5 Hz, 1 H, 5-H), 3.42 (m, 2 H, 1-H), 3.50–3.75 (br. m, 3 H, NH, OH), 3.58 (m, 1 H, CH_2O), 3.68 (m, 1 H, CH_2O), 3.75 (m, 1 H, CHN), 7.24–7.35 (m, 5 H ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 11.0 (CH_3CH_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): calcd. for $C_{16}H_{28}NO_2$ [M + H]$^+$ 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 M solution in hexanes; 2.5 mL, 6.28 mmol), and NH_3·BH_3 (194 mg, 6.28 mmol) in THF (8.5 mL), and after flash chromatography (from hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2), amino alcohol **25b** (254 mg, 57 %) was obtained. $[\alpha]_D^{22}$ = –40.4 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3330, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.83 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2), 0.86 (d, *J* = 3.1 Hz, 3 H, CH_3), 0.88 (d, *J* = 3.1 Hz, 3 H, CH_3), 1.03–1.14 (m, 2 H, 3-H, CH_2CHMe_2), 1.19–1.30 (m, 3 H, CH_3CH_2, CH_2CHMe_2), 1.39–1.45 (m, 2 H, 3-H, 4-H), 1.54 (br. m, 1 H, 2-H), 1.63 (sept, *J* = 6.7 Hz, 1 H, $CHMe_2$), 2.23 (dd, *J* = 11.6, 7.7 Hz, 1 H, 5-H), 2.53 (dd, *J* = 11.6, 3.3 Hz, 1 H, 5-H), 3.00 (br. m, 3 H, NH, OH), 3.44 (dd, *J* = 11.1, 4.8 Hz, 1 H, 1-H), 3.58–3.63 (m, 1 H, CH_2O), 3.69–3.73 (m, 2 H, 1-H, CH_2O), 3.76 (dd, *J* = 8.9, 3.8 Hz, 1 H, CHN), 7.26–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 11.4 (CH_3CH_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 (CH_2CHMe_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): calcd. for $C_{19}H_{34}NO_2$ [M – Boc]$^+$ 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 (2.5 M solution in hexanes; 1.67 mL, 4.18 mmol), and NH_3·BH_3 (129 mg, 4.18 mmol) in THF (6 mL), an oil was obtained. Flash chromatography (from hexane/EtOAc, 8:2, to EtOAc/EtOH, 8:2) 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: $[\alpha]_D^{22}$ = –22.3 (*c* = 0.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3330, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.73 (d, *J* = 7.2 Hz, 3 H, CH_3), 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2), 1.29 (m. 2 H, CH_3CH_2), 1.43 (m, 1 H, 4-H), 1.51 (br. m, 1 H, 5-H), 1.58 (br. m, 1 H, 3-H), 1.70 (br. m, 1 H, 5-H), 2.17–2.48 (br. m, 4 H, 2-H and 6-H), 3.66 (m, 1 H, CH_2O), 3.72 (m, NCH), 3.99 (t, *J* = 10.0 Hz, 1 H, CH_2O), 7.18–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{16}H_{26}NO$ [M + H]$^+$ 248.2009; found 248.2007.

Data for **26a**: $[\alpha]_D^{22}$ = –74.4 (*c* = 0.7, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3330, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.83–0.87 (m, 6 H, 2 CH_3), 1.16–1.22 (m, 1 H, CH_3CH_2), 1.24–1.30 (m, 1 H, 2-H), 1.32–1.40 (m, 2 H, 4-H, CH_3CH_2), 1.48–1.57 (m, 1 H, 2-H), 1.82–1.88 (m, 1 H, 3-H), 2.35 (dd, *J* = 12.0, 5.3 Hz, 1 H, 5-H), 2.48

(dd, J = 12.0, 6.6 Hz, 1 H, 5-H), 2.54 (br. s, 3 H, NH, OH), 3.53–3.61 (m, 2 H, 1-H, CH_2O), 3.66–3.72 (m, 2 H, 1-H, CH_2O), 3.73–3.75 (m, 1 H, CHN), 7.27–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 12.5 (CH_3CH_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): calcd. for $C_{16}H_{28}NO_2$ [M + H]$^+$ 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 (2.5 M solution in hexanes; 1.0 mL, 2.5 mmol), and NH_3·BH_3 (77 mg, 2.5 mmol) in THF (4 mL), an oil was obtained. Flash chromatography (from hexane/EtOAc, 7:3, to EtOAc/EtOH, 8:2) 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 %). Data for **26b**: $[\alpha]_D^{22}$ = –87.9 (c = 0.75, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3332, 3061, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.81 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 1.29–1.36 (m, 1 H, CH_3CH_2), 1.51–1.57 (m, 1 H, CH_3CH_2), 1.58–1.63 (m, 1 H, 4-H), 1.75–1.83 (m, 1 H, 2-H), 1.90–2.02 (br. m, 4 H, 2-H, NH, OH), 2.20 (dd, J = 12.0, 5.0 Hz, 1 H, 5-H), 2.46 (dd, J = 12.0, 5.3 Hz, 1 H, 5-H), 2.85 (br. m, 1 H, 3-H), 3.32–3.39 (m, 1 H, 1-H), 3.41–3.44 (m, 1 H, CH_2O), 3.46–3.53 (m, 2 H, 1-H, CHN), 3.60 (dd, J = 10.3, 3.9 Hz, 1 H, CH_2O), 7.13–7.31 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{21}H_{30}NO_2$ [M + H]$^+$ 328.2271; found 328.2269.

General Procedure for the Synthesis of Enantiopure Amino Alcohols 28–36: A solution of amino diol (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-*t*Bu dicarbonate (1.2 equiv.) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration, and the filter residue was washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography gave the corresponding pure amino alcohol. The preparation of 4-substituted aminopentanols **31a**–**31e** has been reported.[3]

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

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-2-ethyl-1-pentanol (28b): Following the general procedure, from a solution of amino diol **15b** (250 mg, 1.0 mmol) in MeOH (17 mL), $Pd(OH)_2$/C (20 %; 50 mg), and Boc_2O (261 mg, 1.19 mmol), alcohol **28b** (127 mg, 55 %) was obtained as a colorless oil after column chromatography (hexane/EtOAc, 8:2). $[\alpha]_D^{22}$ = +0.87 (c = 1.75, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3449, 1670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.84 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.20–1.37 (m, 5 H, CH_2CH_3, 2-H, 3-H), 1.39 [s, 9 H, $(CH_3)_3$], 1.45–1.51 (m, 2 H, 4-H), 1.95 (br. s, 1 H, OH), 2.95–2.99 (m, 2 H, 5-H), 3.45 (dd, J = 10.0, 5.6 Hz, 1 H, 1-H), 3.49 (dd, J = 10.0, 4.8 Hz, 1 H, 1-H), 4.20 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{12}H_{25}NNaO_3$ [M + Na]$^+$ 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 amino diol **15c** (299 mg, 0.86 mmol) in MeOH (15 mL), $Pd(OH)_2$/C (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = +1.65 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3362, 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.22–1.36 (m, 2 H, 3-H), 1.39 [s, 9 H, $(CH_3)_3$], 1.40–1.55 (m, 2 H, 4-H), 1.73–1.80 (m, 1 H, 2-H), 2.50 (dd, J = 13.7, 7.2 Hz, 1 H, CH_2Ar), 2.66 (dd, J = 13.7, 7.5 Hz, 1 H, CH_2Ar), 3.03 (br. m, 2 H, 5-H), 3.47 (m, 1 H, 1-H), 3.72 (m, 1 H, 1-H), 4.75 (br. s, 1 H, NH), 6.59 (m, 1 H, F-ArH), 6.65 (d, J = 6.0 Hz, 2 H, F-ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 27.3 (C-4), 27.4 (C-3), 28.3 [$(CH_3)_3$], 37.3 (d, $J_{C,F}$ = 8.5 Hz, CH_2Ar), 40.5 (C-5), 41.7 (C-2), 65.2 (C-1), 79.2 (CMe_3), 101.2 (t, $J_{C,F}$ = 25.7 Hz, F-Ar C-4), 111.7 (dd, $J_{C,F}$ = 17.9, 6.2 Hz, F-Ar C-2 and C-6), 144.7 (t, $J_{C,F}$ = 8.5 Hz, F-Ar C-1), 156.2 (CO), 162.8 (dd, $J_{C,F}$ = 248.4, 13.2 Hz, F-Ar C-3 and C-5) ppm. HRMS (ESI-TOF): calcd. for $C_{13}H_{18}F_2NO_3$ [M – $C(CH_3)_3$ + H]$^+$ 274.1249; found 274.1249.

(*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-1-pentanol (29): Following the general procedure, from a solution of amino diol **16** (290 mg, 0.93 mmol) in MeOH (15 mL), $Pd(OH)_2$/C (20 %; 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 CH_2Cl_2/EtOH, 8:2). $[\alpha]_D^{22}$ = –7.3 (c = 0.7, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3349, 1693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.26–1.35 (m, 1 H, 3-H), 1.36–1.42 (m, 1 H, 3-H), 1.43 [s, 9 H, $(CH_3)_3$], 1.49–1.59 (m, 2 H, 4-H), 1.76–1.86 (m, 1 H, 2-H), 1.91 (br. s, 1 H, OH), 2.59 (dd, J = 13.6, 6.8 Hz, 1 H, CH_2Ar), 2.64 (dd, J = 13.6, 7.6 Hz, 1 H, CH_2Ar), 3.02–3.14 (m, 2 H, 5-H), 3.49 (dd, J = 10.8, 5.3 Hz, 1 H, 1-H), 3.54 (dd, J = 10.8, 5.2 Hz, 1 H, 1-H), 4.59 (br. s, 1 H, NH), 7.16–7.20 (m, 3 H, ArH), 7.25–7.29 (m, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{12}H_{20}NO$ [M – Boc + H]$^+$ 194.1539; found 194.1536.

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

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-3-phenyl-1-pentanol (30b): Following the general procedure, from a solution of amino diol **17b** (48 mg, 0.16 mmol) in MeOH (15 mL), $Pd(OH)_2$/C (20 %; 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). $[\alpha]_D^{22}$ = +14.3 (c = 1.2, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3350,

1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.42 [s, 9 H, $(CH_3)_3$], 1.49–1.57 (br. s, 1 H, OH), 1.71–1.89 (m, 3 H, 2-H, 4-H), 1.91–1.98 (m, 1 H, 2-H), 2.78 (m, 1 H, 3-H), 2.93–3.06 (m, 2 H, 5-H), 3.40–3.47 (m, 1 H, 1-H), 3.51–3.57 (m, 1 H, 1-H), 4.47 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{16}H_{25}NNaO_3$ $[M + Na]^+$ 302.1727; found 302.1721.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-4-methyl-1-pentanol (*ent*-31a): Following the general procedure, from a solution of amino diol **19a** (190 mg, 0.80 mmol) in MeOH (13 mL), $Pd(OH)_2/C$ (20 %; 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 (hexane/EtOAc, from 9:1 to 1:1). $[\alpha]_D^{22}$ = +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 amino diol **19b** (105 mg, 0.42 mmol) in MeOH (13 mL), $Pd(OH)_2/C$ (20 %; 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 (hexane/EtOAc, from 9:1 to 7:3). $[\alpha]_D^{22}$ = +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 amino diol **21a** (200 mg, 0.59 mmol) in MeOH (16 mL), $Pd(OH)_2/C$ (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = +8.09 (*c* = 2.25, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3365, 2935, 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.81 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2), 1.09–1.21 (m, 4 H, 3-H, CH_3CH_2), 1.37 [s, 9 H, $(CH_3)_3$], 1.41–1.47 (m, 2 H, 4-H), 1.85 (br. s, 1 H, OH), 2.50 (br. s, 2 H, CH_2Ar), 2.97–3.05 (m, 2 H, 5-H), 3.21 (s, 2 H, 1-H), 4.63 (br. s, 1 H, NH), 7.10–7.13 (m, 3 H, ArH), 7.17–7.21 (m, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 7.5 (CH_3CH_2), 23.7 (C-4), 25.2 (CH_3CH_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): calcd. for $C_{19}H_{32}NO_3$ $[M + H]^+$ 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 amino diol **22** (82 mg, 0.28 mmol) in MeOH (14 mL), $Pd(OH)_2/C$ (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = –4.18 (*c* = 1.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3368, 1695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 1.36 (s, 3 H, CH_3), 1.44 [s, 9 H, $(CH_3)_3$], 1.46 (s, 3 H, CH_3), 1.66–1.75 (m, 2 H, 4-H), 2.23 (br. s, 1 H, OH), 3.18–3.34 (m, 2 H, 5-H), 3.62 (br. m, 2 H, 1-H), 4.15–4.24 (m, 2 H, 2-H, 3-H), 4.90 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): 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): calcd. for $C_{13}H_{25}NNaO_5$ $[M + Na]^+$ 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 amino diol **23** (150 mg, 0.51 mmol) in MeOH (13 mL), $Pd(OH)_2/C$ (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = +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 amino diol **24** (297 mg, 0.87 mmol) in MeOH (20 mL), $Pd(OH)_2/C$ (20 %; 60 mg), and Boc_2O (209 mg, 0.96 mmol), alcohol **34** (157 mg, 55 %) was obtained as a colorless oil after column chromatography (hexane/EtOAc, 8:2). $[\alpha]_D^{22}$ = –14.1 (*c* = 1.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3360, 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 50 °C): δ = 0.83 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2), 1.14–1.20 (m, 1 H, 3-H), 1.23–1.30 (m, 2 H, CH_3CH_2), 1.38–1.50 (m, 2 H, 3-H, 4-H), 1.43 [s, 9 H, $(CH_3)_3$], 1.88–1.94 (m, 1 H, 2-H), 2.55–2.69 (m, 2 H, CH_2Ar), 2.99 (dt, *J* = 5.6 Hz, 1 H, 5-H), 3.15 (br. m, 1 H, 5-H), 3.44 (dd, *J* = 10.5, 5.5 Hz, 1 H, 1-H), 3.55 (dd, *J* = 10.5, 4.8 Hz, 1 H, 1-H), 4.53 (br. s, 1 H, NH), 7.15–7.19 (m, 3 H, ArH), 7.24–7.28 (m, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C): δ = 10.7 (CH_3CH_2), 24.9 (CH_3CH_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): calcd. for $C_{19}H_{31}NNaO_3$ $[M + Na]^+$ 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 amino diol **25a** (365 mg, 1.38 mmol) in MeOH (13 mL), $Pd(OH)_2/C$ (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = –13.7 (*c* = 1.41, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3346, 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.89 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2), 0.91 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.04 (ddd, *J* = 13.9, 8.3, 5.8 Hz, 1 H, 3-H), 1.24–1.37 (m, 3 H, 3-H, CH_3CH_2), 1.44 [s, 9 H, $(CH_3)_3$], 1.53–1.58 (m, 1 H, 4-H), 1.69–1.78 (m, 1 H, 2-H), 3.05–3.09 (m, 2 H, 5-H), 3.41–3.52 (m, 2 H, 1-H), 4.57 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 10.6 (CH_3CH_2), 16.9 (CH_3), 24.0 (CH_3CH_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): calcd. for $C_8H_{20}NO$ $[M - Boc]^+$ 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 amino diol **25b** (156 mg, 0.51 mmol) in MeOH (17 mL), $Pd(OH)_2/C$ (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = –2.47 (*c* = 1.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3354, 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.88–0.93 (m, 9 H, 3 CH_3), 1.03–1.10 (m, 2 H, 3-H, CH_2CHMe_2), 1.14–1.21 (m, 1 H, CH_2CHMe_2), 1.27–1.35 (m, 2 H, CH_3CH_2), 1.37–1.50 (m, 2 H, 3-H, 4-H), 1.44 [s, 9 H, $(CH_3)_3$], 1.60–1.70 (m, 2 H, 2-H, $CHMe_2$), 2.18 (br. s, 1 H, OH), 2.99 (dt, *J* = 13.7, 5.5 Hz, 1 H, 5-H), 3.20–3.28 (m, 1 H, 5-H), 3.36–3.40 (m, 1 H, 1-H), 3.60 (dd, *J* = 10.5, 3.9 Hz, 1 H, 1-H), 4.74 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 11.0 (CH_3CH_2), 22.7 (CH_3), 23.2 (CH_3), 25.0 (CH_3CH_2), 25.4 (CH), 28.4 [$(CH_3)_3$], 33.6 (C-3), 35.8 (C-2), 37.5 (C-4), 41.7 (CH_2CHMe_2), 43.0 (C-5), 65.7 (C-1), 79.1 (CMe_3), 156.6 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{16}H_{34}NO_3$ $[M + H]^+$ 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 amino diol **26a** (101 mg, 0.38 mmol) in MeOH (13 mL), $Pd(OH)_2/C$ (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = –1.5 (*c* = 2.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3346, 1692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.88–0.94 (m, 6 H, 2 CH_3), 1.15–1.22 (m, 1 H, CH_3CH_2), 1.26–1.40 (m, 3 H, CH_3CH_2, 2-H, 4-H), 1.44 [s, 9 H, $(CH_3)_3$], 1.66–1.75 (m, 1 H, 2-H), 1.81 (m, 1 H, 3-H), 2.05 (br. s, 1 H, OH), 2.96–3.02 (m, 1 H, 5-H), 3.14–3.19 (m, 1 H, 5-H), 3.58–3.64 (m, 1 H, 1-H), 3.71–3.76 (m, 1 H, 1-H), 4.66 (br. s, 1 H, NH) ppm. ^{13}C NMR

(100.6 MHz, $CDCl_3$, 25 °C): δ = 12.4 (CH_3CH_2), 16.4 (CH_3), 21.1 (CH_3CH_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): calcd. for $C_{13}H_{28}NO_3$ $[M + H]^+$ 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 amino diol **26b** (110 mg, 0.34 mmol) in MeOH (15 mL), $Pd(OH)_2$/C (20 %; 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 CH_2Cl_2/Et_2O, 8:2). $[\alpha]_D^{22}$ = +5.09 (*c* = 0.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3350, 1694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C): δ = 0.93 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2), 1.31–1.37 (m, 1 H, CH_3CH_2), 1.41 [s, 9 H, $(CH_3)_3$], 1.43–1.52 (m, 1 H, CH_3CH_2), 1.62–1.68 (m, 2 H, 4-H, OH), 1.81–1.90 (m, 1 H, 2-H), 2.02–2.10 (m, 1 H, 2-H), 2.78 (br. m, 1 H, 3-H), 2.82–2.87 (m, 1 H, 5-H), 3.09–3.15 (m, 1 H, 5-H), 3.32–3.38 (m, 1 H, 1-H), 3.49–3.55 (br. m, 1 H, 1-H), 4.40 (br. s, 1 H, NH), 7.14–7.21 (m, 3 H, ArH), 7.27–7.31 (m, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 11.2 (CH_3CH_2), 21.3 (CH_3CH_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): calcd. for $C_{13}H_{22}NO$ [M – Boc]$^+$ 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**, amino diols **15–17**, **19–26**, and amino alcohols **27–30**, **32–36**.

Acknowledgments

Financial support from the Spanish Ministry of Economy and Competitiveness (MINECO) and the Fondos Europeos para el Desarrollo Regional (FEDER) (project number CTQ2012-35250) and the Generalitat de Catalunya (grant number 2014SGR-155) is gratefully acknowledged. We also acknowledge networking contribution by the COST Action CM1407.

Keywords: Synthetic methods · Asymmetric synthesis · Reduction · Ring opening · Lactams · Amino alcohols

[1] For reviews, see: a) C. Escolano, M. Amat, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 8198–8207; b) M. Amat, M. Pérez, J. Bosch, *Synlett* **2011**, 143–160; c) M. Amat, N. Llor, R. Griera, M. Pérez, J. Bosch, *Nat. Prod. Commun.* **2011**, *6*, 515–526; d) M. Amat, M. Pérez, J. Bosch, *Chem. Eur. J.* **2011**, *17*, 7724–7732.

[2] This class of lactams was first reported by Meyers. For reviews covering early work in the field, see: a) D. Romo, A. I. Meyers, *Tetrahedron* **1991**, *47*, 9503–9569; b) A. I. Meyers, G. P. Brengel, *Chem. Commun.* **1997**, 1–8; c) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843–9873.

[3] For a preliminary account of the $LiNH_2BH_3$ reduction of lactams **6**, and the use of amino diol **18a** as the starting building block in the synthesis of *Haliclona* alkaloids, see: M. Amat, G. Guignard, N. Llor, J. Bosch, *J. Org. Chem.* **2014**, *79*, 2792–2802.

[4] a) For aqueous LiOH, or NaOMe in MeOH, see: D. L. Flynn, R. E. Zelle, P. A. Grieco, *J. Org. Chem.* **1983**, *48*, 2424–2426; b) for LiOH, H_2O_2, THF, H_2O, see: J. R. Casimir, C. Didierjean, A. Aubry, M. Rodriguez, J.-P. Briand, G. Guichard, *Org. Lett.* **2000**, *2*, 895–897.

[5] a) J. Marin, A. Violette, J.-P. Briand, G. Guichard, *Eur. J. Org. Chem.* **2004**, 3027–3039; b) K. Kong, Z. Moussa, D. Romo, *Org. Lett.* **2005**, *7*, 5127–5130; c) see also: J.-J. Wang, W.-P. Hu, *J. Org. Chem.* **1999**, *64*, 5725–5727.

[6] A. Giovannini, D. Savoia, A. Umani-Ronchi, *J. Org. Chem.* **1989**, *54*, 228–234.

[7] Other carbon nucleophiles have been used in this reaction; a) for a phosphonate anion, see: K. Tchabanenko, R. M. Adlington, A. R. Cowley, J. E. Baldwin, *Org. Lett.* **2005**, *7*, 585–588; b) for lithium *tert*-butyl propiolate, see: T. N. Grant, C. L. Benson, F. G. West, *Org. Lett.* **2008**, *10*, 3985–3988.

[8] It is well known that boron- and aluminum-derived hydrides (BH_3, AlH_3, $LiAlH_4$, Red-Al) bring about the reductive opening of the oxazolidine ring and the reduction of the lactam carbonyl group to give the corresponding piperidines; see ref.[1,2]

[9] a) A. G. Myers, B. H. Yang, D. J. Kopecky, *Tetrahedron Lett.* **1996**, *37*, 3623–3626; b) A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

[10] For a one-pot procedure for the preparation of the ammonia–borane complex, see: P. V. Ramachandran, B. C. Raju, P. D. Gagare, *Org. Lett.* **2012**, *14*, 6119–6121.

[11] a) For a review, see: A. Lund, in: *Encyclopedia of Reagents for Organic Synthesis* (*EROS*) (Eds.: L. A. Paquette, P. L. Fuchs, G. A. Molander, D. Crich), Wiley, Chichester, UK, **2009**, p. 6082–6083; b) for more recent work, see: I. Paterson, F. A. Mühlthau, C. J. Cordier, M. P. Housden, P. M. Burton, O. Loiseleur, *Org. Lett.* **2009**, *11*, 353–356.

[12] In contrast, lithium (dialkylamino)borohydrides ($LiNR_2BH_3$), which are more sterically demanding than $LiNH_2BH_3$, can reduce tertiary amides to either the corresponding alcohol or to an amine, depending on the steric environments of the amide and of the amine moiety of the reductant, see: a) G. B. Fisher, J. C. Fuller, J. Harrison, C. T. Goralski, B. Singaram, *Tetrahedron Lett.* **1993**, *34*, 1091–1094; b) G. B. Fisher, J. C. Fuller, J. Harrison, S. G. Alvarez, E. R. Burkhardt, C. T. Goralski, B. Singaram, *J. Org. Chem.* **1994**, *59*, 6378–6385. For reviews, see: c) L. Pasumansky, B. Singaram, C. T. Goralski, *Aldrichim. Acta* **2005**, *38*, 62–66; d) L. Pasumansky, C. T. Goralski, B. Singaram, *Org. Process Res. Dev.* **2006**, *10*, 959–970.

[13] a) H. Abe, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **2000**, *122*, 4583–4592; b) T. Itoh, N. Yamazaki, C. Kibayashi, *Org. Lett.* **2002**, *4*, 2469–2472.

[14] J. M. Flaniken, C. J. Collins, M. Lanz, B. Singaram, *Org. Lett.* **1999**, *1*, 799–801; see also ref.[12c,12d].

[15] For reviews, see: a) C. A. Grob, P. W. Schiess, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 1–15; *Angew. Chem.* **1967**, *79*, 1–14; b) C. A. Grob, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 535–546; *Angew. Chem.* **1969**, *81*, 543–554; c) P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, UK, **1983**, p. 257–274. For related 3-aza-Grob fragmentations in the hydride reduction of lactams, see: d) J.-J. Wang, W.-P. Hu, *J. Org. Chem.* **1999**, *64*, 5725–5727; e) W.-P. Hu, J.-J. Wang, P.-C. Tsai, *J. Org. Chem.* **2000**, *65*, 4208–4209.

[16] a) H. Arai, Y. Matsushima, T. Eguchi, K. Shindo, K. Kakinuma, *Tetrahedron Lett.* **1998**, *39*, 3181–3184; b) N. Ríos-Lombardía, E. Busto, V. Gotor-Fernández, V. Gotor, *J. Org. Chem.* **2011**, *76*, 5709–5718; c) C. K. Chung, P. G. Bulger, B. Kosjek, K. M. Belyk, N. Rivera, M. E. Scott, G. R. Humphrey, J. Limanto, D. C. Bachert, K. M. Emerson, *Org. Process Res. Dev.* **2014**, *18*, 215–227.

[17] M. Amat, N. Llor, N. J. Hidalgo, J. Bosch, *Tetrahedron: Asymmetry* **1997**, *8*, 2237–2240.

[18] M. Amat, C. Escolano, O. Lozano, A. Gómez-Esqué, R. Griera, E. Molins, J. Bosch, *J. Org. Chem.* **2006**, *71*, 3804–3815.

[19] A. Castro, J. Juárez, D. Gnecco, J. L. Terán, L. Orea, S. Bernès, *Synth. Commun.* **2006**, *36*, 935–942.

[20] S. Fréville, M. Bonin, J.-P. Célérier, H.-P. Husson, G. L hommet, J.-C. Quirion, V. M. Thuy, *Tetrahedron* **1997**, *53*, 8447–8456.

[21] H. Poerwono, K. Higashiyama, T. Yamauchi, H. Takahashi, *Heterocycles* **1997**, *46*, 385–400.

[22] M. Amat, O. Lozano, C. Escolano, E. Molins, J. Bosch, *J. Org. Chem.* **2007**, *72*, 4431–4439.

[23] M. Amat, N. Llor, M. Huguet, E. Molins, E. Espinosa, J. Bosch, *Org. Lett.* **2001**, *3*, 3257–3260.

Received: November 6, 2015
Published Online: December 21, 2015