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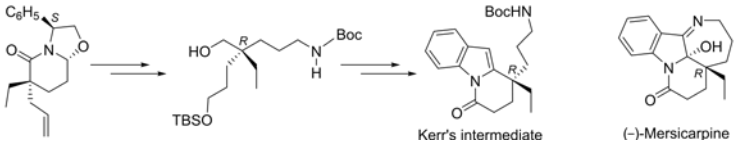

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Generation of acyclic chiral building blocks containing a quaternary stereocenter. Formal synthesis of alkaloids of the leuconolam-leuconoxine-mersicarpine group☆

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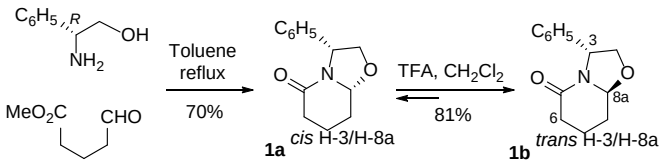
ABSTRACT

The stereocontrolled dialkylation at the carbonyl α-position of simple phenylglycinol-derived oxazolopiperidone lactams generates chiral scaffolds bearing a quaternary stereocenter, which are converted to acyclic quaternary stereocenter-containing chiral building blocks, such as 2,2-disubstituted 5-aminopentanols and 4,4-disubstituted *O*-protected 5-hydroxypentanoic acids and 5-hydroxypentanenitriles. The enantioselective synthesis of Kerr's intermediate, an advanced synthetic precursor of the alkaloids of the leuconolam-leuconoxine-mersicarpine group, is reported from one of these aminopentanols.

1. Introduction

All-carbon quaternary stereocenters[1] occur in a wide range of natural products[2] and feature in numerous semisynthetic and synthetic pharmaceutical ingredients.[3] The stereocontrolled construction of these stereogenic centers represents a considerable synthetic challenge,[4] in particular in the conformationally mobile acyclic systems.[5] A convenient way to tackle the enantioselective synthesis of complex molecules bearing quaternary stereocenters is by initially generating the quaternary carbon in a more rigid cyclic chiral scaffold, which is then converted to an acyclic linear building block via a ring-opening reaction.



Scheme 1. Generation of phenylglycinol-derived oxazolopiperidone lactams.

The easily accessible[6] phenylglycinol-derived oxazolopiperidone lactams, for instance **1** (Scheme 1), have demonstrated to be valuable chiral scaffolds. They have been extensively used to access a variety of diversely substituted enantiopure carbo- and aza(poly)cyclic natural and unnatural products, in particular complex piperidine-containing alkaloids.[7] More recently, substituted derivatives of **1** have been used to generate a variety of linear chiral building blocks, such as 5-amino-pentanols,[8] 5-hydroxypentanenitriles, and 5-hydroxypentanoic acids.[9] The procedure involves the $LiNH_2BH_3$-promoted reductive opening of the oxazolidine and lactam rings and the subsequent reductive (catalytic hydrogenation) or oxidative (*m*-CPBA or I_2/aq. NH_3) removal of the phenylethanol moiety. The synthetic value of some of these acyclic building blocks was illustrated in the total synthesis of natural products, such as haliclorensin marine alkaloids[10] and fluvirucinin B_1,[9] all of them bearing a tertiary stereocenter.

Taking into account that the stereocontrolled generation of a quaternary stereocenter at the carbonyl α-position of these lactams can be accomplished by diastereoselective enolate dialkylation,

☆ Dedicated to Prof. Nuno Maulide for his major contributions to organic synthesis.

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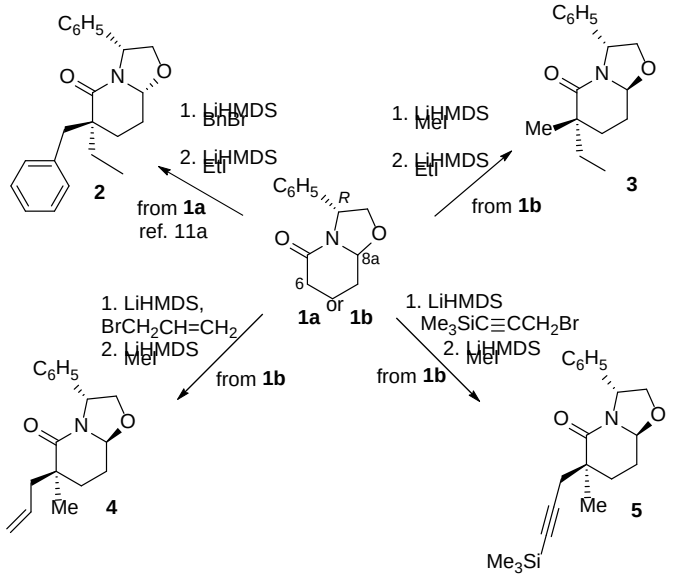


Scheme 2. Stereoselective dialkylation of oxazolopiperidone lactams**.**

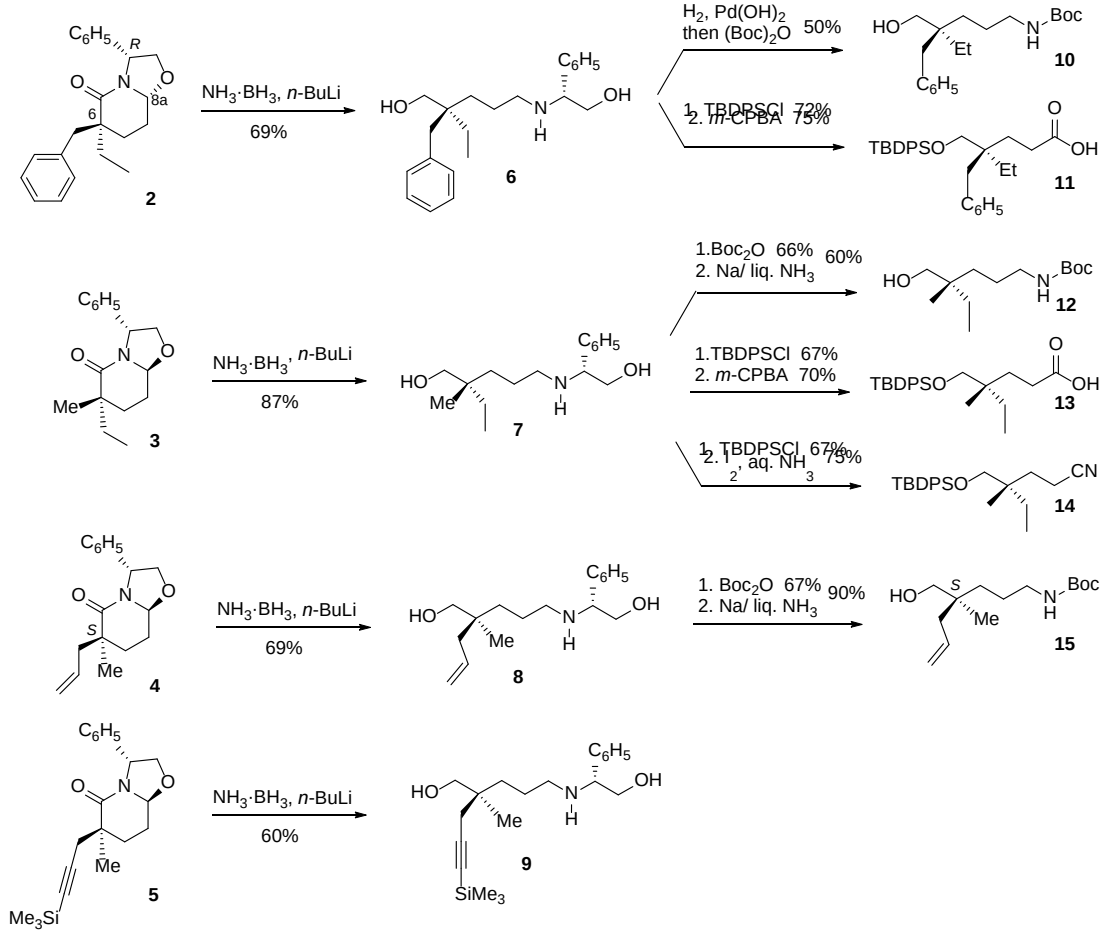
via conformationally rigid chiral tetrasubstituted enolates,[7,11] we envisaged the resulting 6,6-disubstituted lactams as convenient starting materials to access enantiopure acyclic building blocks with a quaternary stereocenter. It is known that these lactams preferentially undergo the second alkylation on the exo face of the enolate and that the degree of stereoselectivity depends upon the configuration of the C-8a stereocenter and the order of incorporation of the substituents.[11a]

We herein present the preparation of a variety of acyclic chiral building blocks (amino alcohols, hydroxy acids, hydroxy nitriles), bearing different substitution patterns (dialkyl, alkyl/benzyl, alkyl/allyl, alkyl/propargyl) at the quaternary stereocenter and illustrate the usefulness of one of them in the enantioselective synthesis of Kerr's intermediate,[12] which is an advanced synthetic intermediate of the indole alkaloids (–)-mersicarpine,[12a-f,13] (+)-melodinine E,[12a,14] and (–)-leuconoxine.[12a,15] In turn, (+)-melodinine E, has been converted to a number of related alkaloids:[13c] (–)-leuconoxine,[12a,13d,f] (–)-scholarisine G, (–)-leuconolam, (–)-leuconodine A, (+)-leuconodine F, and (–)-leuconodine C.[16]

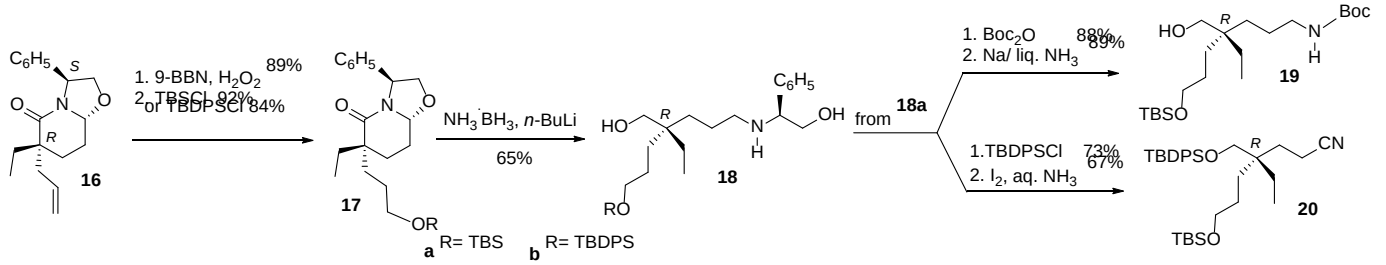
2. Results and discussion

The selected 6,6-disubstituted lactams **2**[11a] (*cis* H-3/H-8a) and **3**–**5** (*trans* H-3/H-8a) were prepared by dialkylation of the corresponding unsubstituted lactams **1a** or **1b**, with good stereofacial selectivity (95:5 to 80:20; see the Experimental Section) except in the case of **5**. In all cases, the second alkylation took place from the exo face of the lactam, i.e. cis with respect to the hydrogen at the C-8a position (Scheme 2).[17]

Treatment of lactams **2**–**5** with lithium amidotrihydroborate ($LiNH_2BH_3$),[18] generated in situ by deprotonation of the $BH_3{\cdot}NH_3$



Scheme 3. Generation of enantiopure acyclic building blocks containing a quaternary stereocenter.



Scheme 4. Synthesis of acyclic chiral building blocks en route to Kerr's intermediate.

complex with *n*-BuLi, afforded the expected amino diols **6**–**9**, all of them bearing a quaternary stereocenter. Scheme 3 outlines the synthetic transformations performed from amino diols **6**–**8**.

Removal of the benzylic substituent of **6** by catalytic hydrogenation, followed by treatment of the resulting primary amine with Boc_2O, gave the *N*-protected amino diol **10**. Interestingly, cleavage of the benzylic C–N bond can also be performed by treatment with Na/liq. NH_3, after conversion of the phenylglycinol-derived secondary amines **7** and **8** to the corresponding *N*-Boc derivatives. This methodology is compatible with the presence of an alkene functionality, for instance, in the conversion of **8** to **15**.

On the other hand, the oxidative removal of the chiral inductor of amino diols **6** and **7** was effected via the corresponding bis-TBDPS ethers, under *m*-CPBA conditions to give the *O*-protected hydroxy acids **11** and **13**, and under I_2/aq. NH_3 conditions (from **7**) to give the *O*-protected hydroxy nitrile **14**.[19]

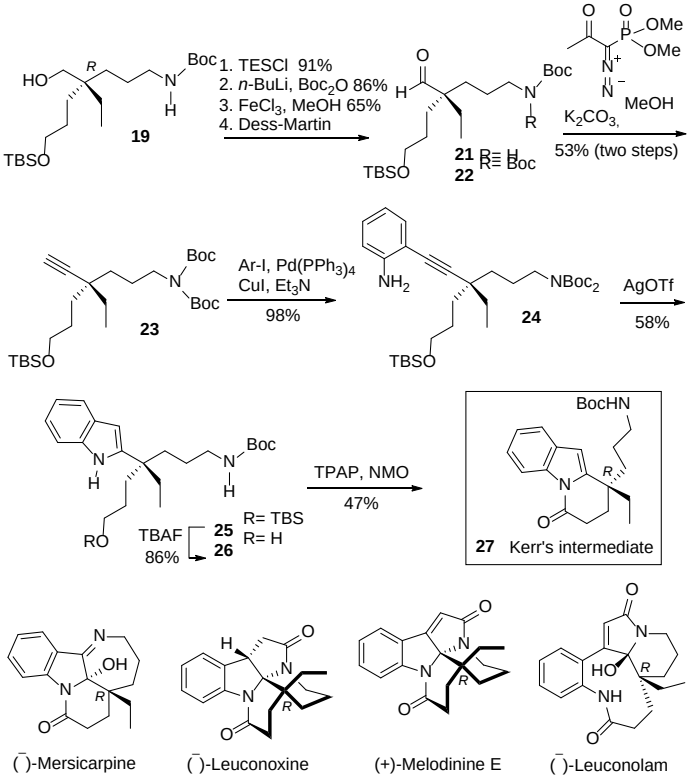
With procedures in hand for the generation of acyclic chiral building blocks containing a quaternary stereocenter, we focused our attention on the pyrido[1,2-*a*]indole derivative **27**, first reported in the racemic form by Kerr as an advanced intermediate in his synthesis of (±)–mersicarpine.[12b] This tricyclic 1-acylindole features a quaternary stereocenter with ethyl, 3- aminopropyl, and 2-indolyl substituents, and a functionalized three-carbon chain connected to the indole nitrogen.

Amino alcohol **19** and nitrile **20** were envisaged as suitable acyclic building blocks for the synthesis of the (*R*)-configurated Kerr's intermediate **27**, which is the enantiomer required to access the alkaloids of the leuconolam-leuconoxine-mersicarpine group. Compounds **19** and **20** incorporate a quaternary stereocenter with the necessary *R* configuration and the ethyl, aminopropyl, and C_3-functionalized substituents characteristic of Kerr's intermediate. They also possess a hydroxymethyl group (protected in **20**) that could be subsequently elaborated into the indole ring. After oxidation of the hydroxymethyl group and Ohira–Bestmann homologation[20] of the resulting formyl derivative to an alkyne, the indolization would be accomplished by Sonogashira coupling with 2-iodoaniline and subsequent cyclization of the resulting alkynylaniline utilizing transition-metal catalysis.

Scheme 4 depicts the generation of the acyclic intermediates **18** and the conversion of **18a** to **19** and **20** following the methodology described above, by reductive ($LiNH_2BH_3$) ring-opening of lactams **17** and subsequent reductive (Na/liq. NH_3) or oxidative (I_2/aq. NH_3) removal of the phenylethanol moiety.[21] The required lactams **17** were prepared by hydroboration/oxidation and subsequent silylation of the allyl group of the known lactam **16**, which was accessible by an allylation/alkylation sequence from the (*S*)-phenylglycinol-derived lactam *ent*-**1b**.[11a]

Contrary to our expectations,[22] treatment of bis-silyl ether **20** with 5% NaOH caused deprotection of the TBS instead of the more labile, but sterically congested TBDPS protecting group. For this reason, the application of this building block as a synthetic precursor of Kerr's intermediate was not further explored.

On the other hand, direct oxidation of **19** under a variety of conditions (Dess–Martin, Swern, PCC) unfortunately did not give the desired result, as the initially formed aldehyde **21** underwent cyclization to afford an *N*-Boc-2-hydroxypiperidine derivative.[23] Only under the milder Corey–Kim reaction conditions[24] could aldehyde **21** be isolated, although the undesired cyclization was again observed when this aldehyde was subjected to the Ohira–Bestmann homologation reaction. This problem was circumvented by blocking the nitrogen as a bis-Boc derivative, which entailed the previous protection of the free hydroxy group. Thus, after



Scheme 5. Enantioselective synthesis of Kerr's intermediate. Formal synthesis of alkaloids of the leuconolam-leuconoxine-mersicarpine group.

treatment of **19** with TESCl, reaction with Boc_2O in the presence of *n*-BuLi followed by orthogonal deprotection of the labile TES group[25] gave an *N*,*N*-diprotected amino alcohol,[26] which was

oxidized with the Dess–Martin periodinane to provide the desired aldehyde **22** (Scheme 5).

Homologation of the crude aldehyde with the Ohira–Bestmann reagent (dimethyl 1-diaza-2-oxopropylphosphonate) in the presence of K_2CO_3 and methanol generated the required terminal alkyne **23**, which was converted to alkynylaniline **24** by Pd-catalyzed Sonogashira coupling.[27] A subsequent Ag-catalyzed indolization[28] of **24** took place with concomitant deprotection of a Boc group of the bis-carbamate moiety to give the indole derivative **25** along with minor amounts of the corresponding alcohol **26**.[29] After completing the deprotection of the TBS protecting group with TBAF, treatment with a catalytic amount of tetrapropylammonium perruthenate and *N*-methyl morpholine *N*-oxide[30] brought about oxidation of the primary alcohol and cyclization on the indole nitrogen, leading to the *R* Kerr's intermediate **27**.

The synthesis of **27** constitutes the second enantioseletive synthesis of Kerr's intermediate[12a] and represents a formal enantioselective synthesis of (–)-mersicarpine, (–)-leuconoxine, (+)-melodinine E, and (–)-leuconolam.

3. Conclusion

In summary, we have developed a useful procedure for the synthesis of acyclic chiral building blocks (5-aminopentanols, 5-hydroxypentanoic acids, and 5-hidroxypentanenitriles) containing a quaternary stereocenter from enantiopure disubstituted lactams generated by enolate dialkylation of simple phenylglycinol-derived oxazolopiperidone lactams. Taking into account that these lactams allow the stereoselective introduction of a variety of substituents (alkyl, allyl, benzyl, propargyl) at the carbonyl α-position and that both enantiomers of phenylglycinol are commercially available, the procedure provides access to a number of quaternary stereocenter-bearing building blocks in both enantiomeric series. The usefulness of one of these building blocks is illustrated by the enantioselective synthesis of Kerr's intermediate, an advanced synthetic intermediate of the alkaloids of the leuconolam-leuconoxine-mersicarpine group.

4. Experimental section

4.1. General

All air sensitive reactions were performed under a dry argon or nitrogen atmosphere with dry, freshly distilled solvents using standard procedures. Evaporation of solvent was accomphished with a rotatory evaporator. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV light and a 1% $KMnO_4$ solution. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh). NMR spectra were recorded on a Varian VNMRS-400 or Mercury 400 spectrometer [400 MHz (^{1}H) and 100.6 MHz (^{13}C)], and chemical shifts are reported in δ values, in parts per million (ppm) relative to Me_4Si (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in hertz (Hz), integrated intensity, and assignment. 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 Avatar 320 FT-IR and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured on a Perlin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HMRS) were performed by Centres Científics i Tecnològics de la Universitat de Barcelona.

4.2. General procedure for the alkylation reactions

A solution of a C-6 epimeric mixture of (3*R*,8a*S*)-6-substituted-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]pyridine[31] (1 mmol) in anhydrous THF was added to a cooled solution of LiHMDS (1.0 M in THF, 3 mmol) in anhydrous THF under an argon atmosphere. After the cooled solution was stirred for 2 h, the alkylating reagent (2.9 or 3.4 mmol) was added at – 78 ºC, and stirring was continued at this temperature for an additional 3 h. The reaction was quenched by the addition of saturated aqueous NaCl at rt, and the resulting mixture was extracted with EtOAc and CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the resulting residue was chromatographed.

*4.2.1. (3R,6S,8aS)-6-Ethyl-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**3**)*

Following the general procedure, from a C-6 epimeric mixture of (3*R*,8a*S*)-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine[31] (526 mg, 2.27 mmol) in THF (6 mL, – 30 ºC), LiHMDS (6.59 mL, 6.81 mmol) in THF (25 mL), and ethyl iodide (0.55 mL, 6.81 mmol), lactam **3** (340 mg, 58%) and its **6-epi-3** diastereomer (77 mg, 13%) were obtained after flash chromatography (85:15 to 8:2 hexane-EtOAc).[32] **3**: $[\alpha]^{22}_D$ – 112.6 (*c* 1.31, MeOH); IR (film) ν 1654 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.80 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.20 (s, 3H, CH_3), 1.37-1.46 (m, 1H, C*H*$_2$CH$_3$), 1.56 (ddd, *J* = 14.0, 4.6, 3.0 Hz, 1H, H-7), 1.64-1.69 (m, 1H, H-8), 1.72-1.81 (m, 1H, CH$_3$C*H*$_2$), 1.88 (ddd, *J* = 14.0, 13.2, 2.5 Hz, 1H, H-7), 2.27 (dddd, *J* = 13.2, 4.6, 4.4, 2.7 Hz, 1H, H-8), 3.72 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.48 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 5.01 (dd, *J* = 9.2, 4.4 Hz, 1H, H-8a), 5.21 (t, *J* = 8.1 Hz, 1H, H-3), 7.22-7.27 (m, 3H, ArH), 7.30-7.34 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 8.6 (*C*H$_3$CH$_2$), 25.0 (CH_3), 25.6 (C-8), 28.2 (C-7), 33.5 (*C*H$_2$CH$_3$), 42.2 (C-6), 58.6 (C-3), 73.0 (C-2), 89.2 (C-8a), 126.0 (CH-Ar), 128.7 (CH-Ar), 127.4 (C-*p*), 139.9 (C-*i*), 174.3 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{22}NO_2$, 260.1645; found, 260.1642. **6-epi-3**: $[\alpha]^{22}_D$ – 128.5 (*c* 0.48, MeOH); IR (film) ν 1651 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.90 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 1.15 (s, 3H, CH_3), 1.54-1.74 (m, 4H, C*H*$_2$CH$_3$, H-7, H-8), 1.90-1.95 (m, 1H, H-7), 2.18-2.24 (m, 1H, H-8), 3.75 (dd, *J* = 8.8, 8.1 Hz, 1H, H-2), 4.49 (dd, *J* = 8.8, 8.1 Hz, 1H, H-2), 5.01 (dd, *J* = 8.6, 4.6 Hz, 1H, H-8a), 5.23 (t, *J* = 8.1 Hz, 1H, H-3), 7.23-7.27 (m, 3H, ArH), 7.31-7.35 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) *δ* 8.6 (*C*H$_3$CH$_2$), 25.8 (CH_3), 25.8 (C-8), 28.4 (C-7), 30.4 (*C*H$_2$CH$_3$), 41.4 (C-6), 58.3 (C-3), 72.9 (C-2), 88.8 (C-8a), 125.9 (CH-Ar), 128.8 (CH-Ar), 127.5 (C-*p*), 139.9 (C-*i*), 175.0 (NCO); HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$, 260.1645; found, 260.1646.

*4.2.2. (3R,6S,8aS)-6-Allyl-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**4**)*

Following the general procedure, from a C-6 epimeric mixture of (3*R*,8a*S*)-6-allyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine[31] (601 mg, 2.34 mmol) in THF (6.2 mL),

LiHMDS (7.0 mL, 7.0 mmol) in THF (26 mL, – 55 ºC), and methyl iodide (0.49 mL, 7.87 mmol), lactam **4** (400 mg, 63%) and its **6-epi-4** diastereomer (97 mg, 15%) were obtained after flash chromatography (9:1 to 8:2 hexane-EtOAc). **4**: $[\alpha]^{22}_D$ – 167.9 (*c* 1.04, MeOH); IR (film) ν 1641 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 1.18 (s, 3H, CH_3), 1.52-1.60 (m, 1H, H-7), 1.64-1.73 (m, 1H, H-8), 1.94 (ddd, *J* = 13.6, 4.6, 2.9 Hz, 1H, H-7), 2.16-2.22 (m, 1H, H-8), 2.34 (dd, *J* = 13.6, 7.6 Hz, 1H, C*H*$_2$CH=), 2.43 (dd, *J* = 13.6, 7.6 Hz, 1H, C*H*$_2$CH=), 3.75 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 4.49 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 5.01 (dd, *J* = 8.4, 4.6 Hz, 1H, H-8a), 5.07-5.12 (m, 2H, CH_2=), 5.23 (t, *J* = 8.0 Hz, 1H, H-3), 5.75-5.86 (m, 1H, C*H*=), 7.23-7.28 (m, 3H, ArH), 7.31-7.35 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 25.6 (C-8), 26.2 (CH_3), 28.6 (C-7). 41.3 (C-6), 42.2 (*C*H_2CH=), 58.3 (C-3), 72.9 (C-2), 88.8 (C-8a), 118.3 (CH_2=), 125.9 (CH-Ar), 128.8 (CH-Ar), 127.5 (C-*p*), 134.0 (CH=), 139.7 (C-*i*), 174.3 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_2$, 272.1645; found, 272.1642. **6-epi-4**: $[\alpha]^{22}_D$ – 65.7 (*c* 0.83, MeOH); IR (film) ν 1652 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 1.24 (s, 3H, CH_3), 1.55-1.62 (m, 1H, H-7), 1.64-1.71 (m, 1H, H-8), 1.93 (td, *J* = 13.6, 2.7 Hz, 1H, H-7), 2.11 (dd, *J* = 13.6, 8.8 Hz, 1H, C*H*$_2$CH=), 2.23-2.29 (m, 1H, H-8), 2.52 (ddt, *J* = 13.6, 6.4, 1.2 Hz, 1H, C*H*$_2$CH=), 3.72 (dd, *J* = 9.0, 8.0 Hz, 1H, H-2), 4.49 (dd, *J* = 9.0, 8.0 Hz, 1H, H-2), 4.98 (dd, *J* = 9.0, 4.6 Hz, 1H, H-8a), 5.02-5.10 (m, 2H, CH_2=), 5.21 (t, *J* = 8.0 Hz, 1H, H-3), 5.63 (dddd, *J* = 16.8, 10.4, 8.8, 6.4 Hz, 1H, CH=), 7.24-7.28 (m, 3H, ArH), 7.31-7.35 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 25.0 (CH_3), 25.4 (C-8), 28.5 (C-7), 41.8 (C-6), 45.2 (*C*H_2CH=), 58.5 (C-3), 73.0 (C-2), 89.0 (C-8a), 118.6 (CH_2=), 126.0 (CH-Ar), 128.7 (CH-Ar), 127.5 (C-*p*), 133.8 (CH=), 139.7 (C-*i*), 173.6 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_2$, 272.1645; found, 272.1643.

*4.2.3. (3R,6S,8aS)-6-Methyl-5-oxo-3-phenyl-6-[3-(trimethylsilyl)-2-propynyl]-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**5**)*

A solution of lactam **1b**[6] (1.02 g, 4.69 mmol) in anhydrous THF (12 mL) was added to a cooled solution (– 78 ºC) of LiHMDS (7.03 mL, 7.03 mmol) in anhydrous THF (39 mL). After stirring the solution at this temperature for 1 h, 3-bromo-1-(trimethylsilyl)-1-propyne (1.92 mL, 11.7 mmol) was added, and stirring was continued for 2 h. The reaction was quenched by the addition of saturated aqueous NaCl, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (9:1 to 8:2 hexane-EtOAc) of the residue afforded (3*R*,6*R*,8a*S*)-5-oxo-3-phenyl-6-[3-(trimethylsilyl)-2-propynyl]-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]pyridine (811 mg, 53%), its C-6 epimer (138 mg, 9%), and the 6,6-dialkylated lactam (91 mg , 4 %). (3*R*,6*R*,8a*S*): $[\alpha]^{22}_D$ + 23.1 (*c* 1.01, MeOH); IR (film) *v* 2174 (C≡C), 1657 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.16 [s, 9H, $(CH_3)_3$], 1.54-1.64 (m, 1H, H-8), 1.91 (dddd, *J* = 14.1, 14.1, 11.5, 2.5 Hz, 1H, H-7), 2.11-2.18 (m, 1H, H-7), 2.40-2.46 (m, 1H, H-8), 2.46-2.53 (m, 1H, H-6), 2.69-2.71 (m, 2H, CH_2C≡), 3.73 (t, *J* = 8.2 Hz, 1H, H-2), 4.52 (t, *J* = 8.2 Hz, 1H, H-2), 5.02 (dd, *J* = 9.4, 4.4 Hz, 1H, H-8a), 5.25 (t, *J* = 8.2 Hz, 1H, H-3), 7.24-7.27 (m, 3H, ArH), 7.31-7.35 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 0.1 [$(CH_3)_3$], 22.4 (C-7), 23.2 (*C*H_2C≡), 28.1 (C-8), 40.8 (C-6), 58.5 (C-3), 72.9 (C-2), 87.0 (≡*C*CH_2), 88.8 (C-8a), 103.9 (≡CSi), 125.7 (CH-Ar), 128.8 (CH-Ar), 127.5 (C-*p*), 139.3 (C-*i*), 169.7 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{26}NO_2Si$, 328.1727; found, 328.1729. (3*R*,6*S*,8a*S*): $[\alpha]^{22}_D$ – 179.3 (*c* 1.02, MeOH); IR (film) *v* 2174 (C≡C), 1655 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.15 [s, 9H, $(CH_3)_3$], 1.80-1.89 (m, 1H, H-8), 1.96-2.10 (m, 2H, H-7), 2.21-2.28 (m, 1H, H-8), 2.45 (dd, *J* = 16.9, 10.2 Hz, 1H, CH_2C≡), 2.54-2.60 (m, 1H, H-6), 2.83 (dd, *J* = 16.9, 3.6 Hz, 1H, CH_2C≡), 3.79 (dd, *J* = 8.9, 7.9 Hz, 1H, H-2), 4.47 (dd, *J* = 8.9, 7.9 Hz, 1H, H-2), 5.03 (dd, *J* = 7.8, 4.6 Hz, 1H, H-8a), 5.24 (t, *J* = 7.9 Hz, 1H, H-3), 7.24-7.28 (m, 3H, ArH), 7.32-7.3 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 0.05 [$(CH_3)_3$], 21.2 (C-7), 22.2 (*C*H_2C≡), 25.7 (C-8), 39.2 (C-6), 58.4 (C-3), 72.4 (C-2), 86.5 (≡*C*CH_2), 88.5 (C-8a), 104.9 (≡CSi), 126.3 (CH-Ar), 128.8 (CH-Ar), 127.7 (C-*p*), 139.5 (C-*i*), 170.0 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{26}NO_2Si$, 328.1727; found, 328.1731. Dialkylated lactam: $[\alpha]^{22}_D$ – 42.3 (*c* 0.63, MeOH); IR (film) *v* 2175 (C≡C), 1656 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.12 [s, 9H, $(CH_3)_3$], 0.13 [s, 9H, (C*H*$_3$)$_3$], 1.72-1.82 (m, 1H, H-8), 2.10-2.15 (m, 1H, H-7), 2.20-2.30 (m, 2H, H-7, H-8), 2.52-2.53 (m, 2H, CH_2C≡), 2.54 (d, *J* = 16.4 Hz, 1H, CH_2C≡), 2.66 (d, *J* = 16.4 Hz, 1H, CH_2C≡), 3.67 (t, *J* = 8.4 Hz, 1H, H-2), 4.46 (t, *J* = 8.4 Hz, 1H, H-2), 4.99 (dd, *J* = 9.6, 4.0 Hz, 1H, H-8a), 5.13 (t, *J* = 8.4 Hz, 1 H, H-3), 7.19-7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 0.01 [$(CH_3)_3$], 0.20 [$(CH_3)_3$], 25.0 (C-7), 26.0 (C-8), 28.7 (*C*H_2C≡), 29.7 (*C*H_2C≡), 45.0 (C-6), 59.3 (C-3), 73.0 (C-2), 87.8 (≡*C*CH_2), 88.7 (≡*C*CH_2), 89.0 (C-8a), 102.5 (≡CSi), 103.4 (≡CSi), 125.8 (CH-Ar), 128.8 (CH-Ar), 127.5 (C-*p*), 138.9 (C-*i*), 171.0 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{37}NO_2Si_2$, 439.2279; found, 439.2281.

Following the general procedure, from a C-6 epimeric mixture of the above lactams (316 mg, 0.97 mmol) in THF (2.5 mL), LiHMDS (2.91 mL, 2.91 mmol) in THF (11 mL), and methyl iodide (0.17 mL, 2.8 mmol), lactam **5** (145 mg, 43%) and its **6-epi-5** diastereomer (92 mg, 28%) were obtained after flash chromatography (hexane to 85:15 hexane-EtOAc). **5**: $[\alpha]^{22}_D$ – 163.0 (*c* 1.12, MeOH); IR (film) *v* 2174 (C≡C), 1651 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.16 [s, 9H, $(CH_3)_3$], 1.27 (s, 3H, CH_3), 1.57-1.66 (m, 1H, H-7), 1.72-1.82 (m, 1H, H-8), 2.21-2.28 (m, 2H, H-7, H-8), 2.54 (d, *J* = 17.2 Hz, 1H, CH_2C≡), 2.59 (d, *J* = 17.2 Hz, 1H, CH_2C≡), 3.75 (dd, *J* = 9.1, 8.0 Hz, 1H, H-2), 4.49 (dd, *J* = 9.1, 8.0 Hz, 1H, H-2), 5.03 (dd, *J* = 9.0, 4.2 Hz, 1H, H-8a), 5.20 (t, *J* = 8.0 Hz, 1H, H-3), 7.22-7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 0.05 [$(CH_3)_3$], 25.7 (C-8), 26.0 (CH_3), 28.6 (C-7), 28.9 (*C*H_2C≡), 41.3 (C-6), 58.4 (C-3), 72.9 (C-2), 87.6 (≡*C*CH_2), 89.0 (C-8a), 103.5 (≡CSi), 126.0 (CH-Ar), 128.8 (CH-Ar), 127.6 (C-*p*), 139.5 (C-*i*), 173.4 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{28}NO_2Si$, 342.1884; found, 342.1886. **6-epi-5:** $[\alpha]^{22}_D$ + 11.5 (*c* 1.05, MeOH); IR (film) ν 2171 (C≡C), 1635 (NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.16 [s, 9H, $(CH_3)_3$], 1.26 (s, 3H, CH_3), 1.64-1.72 (m, 1H, H-8), 1.74-1.79 (m, 1H, H-7), 2.21 (td, *J* = 14.1, 2.7 Hz, 1H, H-7), 2.29-2.34 (m, 1H, H-8), 2.37 (d, *J* = 16.8 Hz, 1H, CH_2C≡), 2.68 (d, *J* = 16.8 Hz, 1H, CH_2C≡), 3.73 (dd, *J* = 9.1, 8.0 Hz, 1H, H-2), 4.51 (dd, *J* = 9.1, 8.0 Hz, 1H, H-2), 5.01 (dd, *J* = 9.0, 4.6 Hz, 1H, H-8a), 5.20 (t, *J* = 8.0 Hz, 1H, H-3), 7.23-7.28 (m, 3H, ArH), 7.30-7.35 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 0.1 [$(CH_3)_3$], 24.7 (CH_3), 25.6 (C-8), 28.8 (C-7), 31.8 (*C*H_2C≡), 41.9 (C-6), 58.9 (C-3), 73.0 (C-2), 87.4 (≡*C*CH_2), 88.9 (C-8a), 103.5 (≡CSi), 125.8 (CH-Ar), 128.8 (CH-Ar), 127.5 (C-*p*), 139.3 (C-*i*), 172.7 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{28}NO_2Si$, 342.1884; found, 342.1888.

4.3. General procedure for $LiNH_2BH_3$-promoted opening of the oxazolopiperidone lactams

n-BuLi (1.6 M or 2.5 M in hexanes, 4.3 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (4.3 mmol) in anhydrous THF at 0 ºC, and the mixture was stirred at 0 ºC for 10 min and at rt for 15 min. The resulting mixture was added to a solution of the lactam **2**, **3**, **4** or **5** (1.0 mmol) in anhydrous THF, and stirring was continued at 40 ºC for 1 h or 2 h. The reaction mixture was quenched with H_2O, and the obtained solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated, and the residue was purified by flash chromatography.

*4.3.1. (S)-2-Benzyl-2-ethyl-5-{[(1R)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (**6**)*

Following the general procedure, from lactam **2** (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 **6** (250 mg, 69%) was obtained after flash chromatography (EtOAc to 8:2 EtOAc-EtOH):[8] $[\alpha]^{22}_D$ – 28.4 (*c* 0.96, $CHCl_3$); IR (film) *ν* 3384 (OH, NH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.89 (t, *J* = 7.0 Hz, 3H, CH_3), 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 (brs, 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); ^{13}C NMR ($CDCl_3$) δ 7.6 (CH_3), 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 (CH-Ar), 127.7 (C-*p*), 127.9 (CH-Ar), 128.7 (CH-Ar), 130.4 (CH-Ar), 138.6 (C-*i*), 140.4 (C-*i*), HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{32}NO_2$, 342.2428; found, 342.2425.

*4.3.2. (S)-2-Ethyl-5-{[(1R)-2-hydroxy-1-phenylethyl]amino}-2-methyl-1-pentanol (**7**)*

Following the general procedure, from lactam **3** (364 mg, 1.4 mmol) in THF (1.75 mL), *n*-BuLi (3.8 mL of a 1.6 M solution in hexanes, 6.02 mmol), and $NH_3{\cdot}BH_3$ (186 mg, 6.02 mmol) in THF (3.5 mL), aminoalcohol **7** (324 mg, 87%) was obtained after flash chromatography (2:8 hexane-EtOAc to 8:2 EtOAc-EtOH): $[\alpha]^{22}_D$ – 33.9 (*c* 0.99, MeOH); IR (film) ν 3346 (OH, NH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.79 (s, 3H, CH_3), 0.80 (t, *J* = 7.6 Hz, 3H, CH_3CH_2), 1.22-1.27 (m, 4H, CH_2CH_3, H-3), 1.37-1.49 (m, 2H, H-4), 2.46-2.55 (m, 2H, H-5), 2.97 (brs, 3H, OH, NH), 3.29 (d, *J* = 11.0 Hz, 1H, H-1), 3.35 (d, *J* = 11.0 Hz, 1H, H-1), 3.61 (brt, *J* = 10.4 Hz, 1H, CH_2O), 3.72 (dd, *J* = 10.4, 4.3 Hz, 1H, CH_2O), 3.79 (dd, *J* = 8.8, 4.3 Hz, 1H, CHN), 7.26-7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.8 (CH_3CH_2), 21.3 (CH_3), 23.5 (C-4), 28.8 (CH_2CH_3), 33.0 (C-3), 37.3 (C-2), 47.9 (C-5), 64.7 (CHN), 66.4 (CH_2O), 68.5 (C-1), 127.3 (CH-Ar), 128.7 (CH-Ar), 127.7 (C-*p*), 140.0 (C-*i*); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{28}NO_2$, 266.2115; found, 266.2111.

*4.3.3. (S)-2-Allyl-5-{[(1R)-2-hydroxy-1-phenylethyl]amino}-2-methyl-1-pentanol (**8**)*

Following the general procedure, from lactam **4** (464 mg, 1.71 mmol) in THF (2.2 mL), *n*-BuLi (4.6 mL of a 1.6 M solution in hexanes, 7.35 mmol), and $NH_3{\cdot}BH_3$ (227 mg, 7.35 mmol) in THF (4.5 mL), aminoalcohol **8** (326 mg, 69%) was obtained after flash chromatography (2:8 hexane-EtOAc to 9:1 EtOAc-MeOH): $[\alpha]^{22}_D$ – 41.3 (*c* 0.79, MeOH); IR (film) *ν* 3355 (OH, NH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.81 (s, 3H, CH_3), 1.21-1.33 (m, 2H, H-3), 1.41-1.53 (m, 2H, H-4), 1.99 (d, *J* = 7.2 Hz, 2H, CH_2CH=), 2.51 (t, *J* = 6.6 Hz, 2H, H-5), 3.33 (s, 2H, H-1), 3.36 (brs, 3H, NH and OH), 3.63 (dd, *J* = 10.9, 9.0 Hz, 1H, CH_2O), 3.73 (dd, *J* = 10.9, 4.1 Hz, 1H, CH_2O), 3.81 (dd, *J* = 9.0, 4.1 Hz, 1H, CHN), 5.01 (s, 1H, CH_2=), 5.04 (s, 1H, CH_2=), 5.74-5.85 (m, 1H, CH=), 7.27-7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 23.3 (C-4), 33.5 (C-3), 37.8 (C-2), 41.7 (CH_2CH=), 47.7 (C-5), 64.7 (CHN), 66.2 (CH_2O), 68.5 (C-1), 117.2 (CH_2=), 127.3 (CH-Ar), 128.7 (CH-Ar), 127.8 (C-*p*), 134.9 (*C*H=), 139.5 (C-*i*); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{28}NO_2$, 278.2115; found, 278.2108.

*4.3.4. (S)-5-{[(1R)-2-hydroxy-1-phenylethyl]-amino}-2-methyl-2-[3-(trimethylsilyl)-2-propyny1]-1-pentanol (**9**)*

Following the general procedure, from lactam **5** (312 mg, 0.91 mmol) in THF (1.15 mL), *n*-BuLi (2.44 mL of a 1.6 M solution in hexanes, 3.91 mmol), and $NH_3.BH_3$ (121 mg, 3.91 mmol) in THF (2.3 mL), aminoalcohol **9** (181 mg, 60%) was obtained after flash chromatography (2:8 hexane-EtOAc to 9:1 EtOAc-MeOH). Attempts to obtain pure compound **9** (successive chromatographic columns) were unsuccessful: IR (film) ν 3312 (OH, NH), 2172 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.13 [s, 9H, $(CH_3)_3$], 0.90 (s, 3H, CH_3), 1.27-1.50 (m, 4H, H-4 and CH_2C≡), 2.15 (t, *J* = 5.2 Hz, 2H, H-3), 2.54 (brm, 2H, H-5), 2.82 (brs, 3H, OH, NH), 3.43 (s, 2H, H-1), 3.63-3.80 (m, 3H, CH_2CHO), 7.23-7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 0.11 [$(CH_3)_3$], 14.0 (CH_3), 23.6 (C-4); 25.7 (C-3); 28.5 (CH_2C≡); 37.8 (C-2); 47.8 (C-5); 62.6 (CHN); 66.4 (CH_2O); 68.4 (C-1); 86.9 (*C*≡CH_2); 104.7 (≡CSi), 127.3 (CH-Ar), 128.7 (CH-Ar), 127.6 (C-*p*), 139.5 (C-*i*); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{34}NO_2Si$, 348.2353; found, 348.2368.

*4.4. (S)-2-Benzyl-5-[(tert-butoxycarbonyl)amino]-2-ethyl-1-pentanol (**10**)*

To a solution of aminodiol **6** (200 mg, 0.59 mmol) in anhydrous MeOH (16 mL) was added $Pd(OH)_2$ on activated charcoal. The suspension was hydrogenated at 75 ºC for 22 h under 5 bar of pressure. Then, di-*tert*-butyl dicarbonate (141 mg, 0.64 mmol) was added, and the mixture was stirred at rt 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 (CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded alcohol **10** (96 mg, 50%):[8] $[\alpha]^{22}_D$ + 8.09 (*c* 2.25, $CHCl_3$); IR (film) *ν* 3365 (OH, NH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.81 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.09-1.21 (m, 4H, H-3, CH_3CH_2), 1.37 [s, 9H, $(CH_3)_3$], 1.41-1.47 (m, 2H, H-4), 1.85 (brs, 1H, OH), 2.50 (brs, 2H, CH_2Ar), 2.97-3.05 (m, 2H, H-5), 3.21 (s, 2H, H-1), 4.63 (brs, 1H, NH), 7.10-7.13 (m, 3H, ArH), 7.17-7.21 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) 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 [$C(CH_3)_3$], 125.9 (C-*p*), 127.9 (CH-Ar), 130.3 (CH-Ar), 138.5 (C-*i*), 156.1 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{19}H_{32}NO_3$, 322.2377; found, 322.2374.

4.5. General procedure for oxidative removal of the chiral inductor under m-CPBA conditions

Step 1: Silyl chloride (2.0 or 2.5 mmol) was added to a stirring solution of the aminodiol **6** or **7** (1 mmol) and imidazole (2.5 or 3.0 mmol) in anhydrous CH_2Cl_2, and the mixture was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography gave the corresponding bis-TBDPS ether.

Step 2: A solution of the above bis-TBDPS ether (1 mmol) in CH_2Cl_2 was added to a solution of *m*-CPBA (4.2 mmol, 70% purity) in CH_2Cl_2. The mixture was stirred at reflux temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the residue was purified by flash chromatography.

*4.5.1. (S)-4-Benzyl-5-[(tert-butyldiphenylsilyl)oxy]-4-ethylpentanoic acid (**11**)*

Step 1: Operating as in the above general procedure, from aminodiol **6** (240 mg, 0.70 mmol), *tert*-butyldiphenylsilyl chloride (0.37 mL, 1.41 mmol), and imidazole (144 mg, 2.11 mmol) in refluxing anhydrous CH_2Cl_2 (6 mL), the corresponding bis-TBDPS ether was obtained (414 mg, 72%) after column chromatography (hexane to 95:5 hexane–EtOAc):[9] $[\alpha]^{22}_D$ – 5.67 (*c* 1.15, $CHCl_3$); IR (film): ν 3070 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.86 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.18 [s, 9H, (CH$_3$)$_3$], 1.19-1.26 (m, 2H, H-3), 1.27 [s, 9H, (CH$_3$)$_3$], 1.31-1.38 (m, 1H, H-2), 1.39-1.48 (m, 2H, H-2, C*H*$_2$CH$_3$), 1.53-1.64 (m, 1H, C*H*$_2$CH$_3$), 2.50-2.54 (m, 2H, H-1), 2.75 (d, *J* = 13.2 Hz, 1H, CH$_2$Ar), 2.81 (d, *J* = 13.2 Hz, 1H, CH$_2$Ar), 3.38 (d, *J* = 10.0 Hz, 1H, H-5), 3.42 (d, *J* = 10.0 Hz, 1H, H-5), 3.80-3.84 (m, 2H, CH$_2$O), 3.89 (dd, *J* = 8.0, 4.8 Hz, 1H, CHN), 7.34-7.40 (m, 10H, ArH), 7.44-7.56 (m, 12H, ArH), 7.72-7.76 (m, 4H, ArH), 7.78-7.81 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.6 (*C*H$_3$CH$_2$), 19.2 and 19.4 [*C*(CH$_3$)$_3$], 23.7 (CH$_3$*C*H$_2$), 25.4 (C-2), 26.9 and 27.1 [(CH$_3$)$_3$], 30.0 (C-3), 39.8 (CH$_2$Ar), 41.8 (C-1), 48.5 (C-4), 65.0 (CHN), 66.1 (C-5), 68.9 (CH$_2$O), 125.7 (CH-Ar), 127.2 (CH-Ar), 127.5 (CH-Ar), 127.6 (CH-Ar), 127.7 (CH-Ar), 128.2 (CH-Ar), 129.6 (CH-Ar), 129.6 (CH-Ar), 129.7 (CH-Ar), 130.5 (CH-Ar), 133.3 (C-*i*), 133.4 (C-*i*), 133.8 (C-*i*), 135.5 (CH-Ar), 135.5 (CH-Ar), 135.8 (CH-Ar), 135.9 (CH-Ar), 138.8 (C-*i*); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{54}H_{68}NO_2Si_2$, 818.4783; found, 818.4773.

Step 2: Following the general procedure, from the above bis-TBDPS ether (300 mg, 0.37 mmol) in CH_2Cl_2 (1.5 mL) and *m*-chloroperbenzoic acid (380 mg, 1.55 mmol, 70% of purity) in CH_2Cl_2 (3.5 mL), carboxylic acid **11** (130 mg, 75%) was obtained after flash chromatography (1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc):[9] $[\alpha]^{22}_D$ + 2.52 (*c* 0.65 in $CHCl_3$); IR (film) ν 3074 (OH), 1707 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.19 [s, 9H, (CH$_3$)$_3$], 1.22 (q, *J* = 7.4 Hz, 2H, CH$_3$C*H*$_2$), 1.54 (ddd, *J* = 14.0, 14.0, 5.0 Hz, 1H, H-3), 1.63 (ddd, *J* = 14.0, 14.0, 5.0 Hz, 1H, H-3), 2.06-2.14 (m, 1H, H-2), 2.18-2.27 (m, 1H, H-2), 2.66 (d, *J* = 13.0 Hz, 1H, CH$_2$Ar), 2.72 (d, *J* = 13.0 Hz, 1H, CH$_2$Ar), 3.29 (d, *J* = 10.3 Hz, 1H, H-5), 3.34 (d, *J* = 10.3 Hz, 1H, H-5), 7.18-7.25 (m, 5H, ArH), 7.40-7.49 (m, 6H, ArH), 7.69-7.72 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.4 (*C*H$_3$CH$_2$), 19.4 [*C*(CH$_3$)$_3$], 24.7 (CH$_3$*C*H$_2$), 27.2 [(CH$_3$)$_3$], 27.8 (C-3), 28.4 (C-2), 39.6 (CH$_2$Ar), 41.5 (C-4), 65.9 (C-5), 126.0 (C-*p*), 127.6 (CH-Ar), 127.7 (CH-Ar), 127.8 (CH-Ar), 129.7 (C-*p*), 129.7 (C-*p*), 130.5 (CH-Ar), 133.4 (C-*i*), 133.5 (C-*i*), 135.8 (CH-Ar), 135.9 (CH-Ar), 138.1 (C-*i*), 180.5 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{39}O_3Si$, 475.2663; found, 475.2667.

*4.5.2. (S)-5-[(tert-Butyldiphenylsilyl)oxy]-4-ethyl-4-methylpentanoic acid (**13**)*

Step 1: Operating as in the general procedure, from aminodiol **7** (706 mg, 2.66 mmol), *tert*-butyldiphenylsilyl chloride (1.76 mL, 6.65 mmol), and imidazole (453 mg, 6.65 mmol) in refluxing CH_2Cl_2 (20 mL), the corresponding bis-TBDPS ether (1.33 g, 67%) was obtained after flash chromatography (99:1 to 9:1 hexane-EtOAc): $[\alpha]^{22}_D$ −15.1 (*c* 2.15 , $CHCl_3$); ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.75 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 0.82 (s, 3H, CH$_3$), 1.04 [s, 9H, (CH$_3$)$_3$], 1.05 [s, 9H, (CH$_3$)$_3$], 1.18-1.41 (m, 6H, C*H*$_2$CH$_3$, H-2, H-3), 2.37-2.47 (m, 2H, H-1), 3.30 (d, *J* = 10.0 Hz, 1H, H-5), 3.40 (d, *J* = 10.0 Hz, 1H, H-5), 3.66-3.69 (m, 2H, CH$_2$O), 3.75-3.78 (m, 1H, CHN), 7.21 (m, 5H, ArH), 7.31-7.43 (m, 12H, ArH), 7.59-7.66 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.9 (*C*H$_3$CH$_2$), 19.2 [*C*(CH$_3$)$_3$], 19.4 [*C*(CH$_3$)$_3$], 21.7 (CH$_3$), 24.2 (C-2), 26.8 [(CH$_3$)$_3$], 26.9 [(CH$_3$)$_3$], 28.7 (*C*H$_2$CH$_3$), 33.6 (C-3), 37.8 (C-4), 48.8 (C-1), 65.2 (CHAr), 68.9 (CH$_2$O), 69.8 (C-5), 127.2 (C-*p*), 127. 5 (CH-Ar), 127.6 (CH-Ar), 128.2 (CH-Ar), 129.5 (C-*p*), 129.6 (C-*p*), 129.7 (CH-Ar), 133.3 (C-*i*), 133.5 (C-*i*), 133.9 (C-*i*), 135.6 (CH-Ar), 135.7 (CH-Ar); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{48}H_{64}NO_2Si_2$, 742.447; found, 742.4464.

Step 2: Following the general procedure, from the above bis-TBDPS ether (306 mg, 0.41 mmol) and *m*-CPBA (426 mg, 1.72 mmol, 70% purity) in CH_2Cl_2 (2 mL), carboxylic acid **13** (114.5 mg, 70%) was obtained after flash chromatography (1:1 to 1:9 hexane-CH_2Cl_2): $[\alpha]^{22}_D$ – 0.53 (*c* 1.23, MeOH); IR (film) ν 1708 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.79 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 0.84 (s, 3H, CH$_3$), 1.09 [s, 9H, (CH$_3$)$_3$], 1.28-1.37 (m, 2H, C*H*$_2$CH$_3$), 1.68 (m, 2H, H-3), 2.27 (m, 2H, H-2), 3.33 (m, 2H, H-5), 7.37-7.46 (m, 6H, ArH), 7.66-7.68 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.8 (*C*H$_3$CH$_2$), 19.4 [*C*(CH$_3$)$_3$], 21.1 (CH$_3$), 26.9 [(CH$_3$)$_3$], 28.7 (*C*H$_2$CH$_3$), 28.9 (C-2), 30.9 (C-3), 37.5 (C-4), 69.2 (C-5), 127.6 (CH-Ar), 129.6 (CH-Ar), 133.6 (C-*i*), 135.7 (CH-Ar), 180.8 (CO); HRMS (ESI-TOF) *m/z* $[M-H]^-$ calcd for $C_{24}H_{33}O_3Si$, 397.2204; found, 397.2205.

4.6. General procedure for reductive removal of the chiral inductor under Na/liq. NH$_3$ conditions

Step 1: Di-*tert*-butyl dicarbonate (1.6 or 2.0 mmol) was added at rt to a stirring solution of aminodiol **7** or **8** (1 mmol) in anhydrous MeOH, and the resulting mixture was stirred for 20 h. The solution was poured into saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give the corresponding *N*-Boc derivative, which was purified by flash chromatography.

Step 2: Liquid ammonia was condensed at –78 ºC in a three-necked flask equipped with a cold finger condenser charged with dry ice-acetone, and then a solution of the above *N*-Boc derivative (1 mmol) in ahydrous THF was added. The temperature was raised to – 33 ºC and sodium metal was added in small portions until the blue color persisted. The mixture was briefly stirred at – 33 ºC. The reaction was quenched by the addition of solid NH_4Cl until the blue color disappeared, and the mixture was stirred at rt for 4 h. The residue was digested at rt with CH_2Cl_2, and the resulting suspension was filtered through Celite®. The solution was concentrated under reduced pressure and the crude *N*-Boc aminopentanol was purified by flash chromtography.

*4.6.1. (S)-5-[(tert-Butoxycarbonyl)amino]-2-ethyl-2-methyl-1-pentanol (**12**)*

Step 1: Following the above general procedure, from aminodiol **7** (548 mg, 1.99 mmol) and Boc_2O (696 mg, 3.18 mmol) in MeOH (40 mL), the *N*-Boc derivative (500 mg, 66%) was obtained after flash chromatography (9:1 to 1:1 hexane-EtOAc): $[\alpha]^{22}_D$ − 32.4 (*c* 1.12, $CHCl_3$); IR (film) *v* 3418 (OH), 1667 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.71 (s, 3H, CH$_3$), 0.75 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 1.05 (m, 2H, H-3), 1.18 (q, *J* = 7.6 Hz, 2H, C*H*$_2$CH$_3$), 1.18 (ms, 1H, H-4), 1.38 (m, 1H, H-4), 1.48 [s, 9H, (CH$_3$)$_3$], 2.95 (m, 1H, H-5), 3.04 (m, 1H, H-5), 3.22 (d, *J* = 11.0 Hz, 1H, H-1), 3.26 (d, *J* = 11.0 Hz, 1H, H-1), 4.10 (m, 2H, CH$_2$O), 5.09 (m, 1H, CHN), 7.26-7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.8 (CH$_3$), 21.2 (*C*H$_3$CH$_2$), 23.4 (C-4), 28.4 [(CH$_3$)$_3$], 28.6 (*C*H$_2$CH$_3$) 32.8 (C-3), 37.1 (C-2), 46.4 (C-5), 61.6 (CHN), 63.2 (CH$_2$O), 68.9 (C-1), 80.2 [*C*(CH$_3$)$_3$], 127.6 (C-*p*), 128.6 (CH-Ar),

138.2 (C-*i*), 157.1 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{36}NO_4$, 366.2639; found, 366.2639.

Step 2: Following Step 2 of the general procedure, from the above *N*-Boc derivative (333 mg, 0.91 mmol) in THF (5 mL), liquid ammonia (20 mL), and sodium (stirring the blue mixture for 1 min), compound **12** (134 mg, 60%) was obtained after flash chromatography (9:1 to 8:2 hexane-EtOAc): $[\alpha]^{22}_D$ + 0.5 (*c* 1.56, $CHCl_3$); IR (film) *v* 3354 (OH, NH), 1693 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.81 (s, 3H, CH_3), 0.82 (t, *J* = 7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.21-1.31 (m, 4H, C*H*$_2$CH$_3$, H-4), 1,41 (m, 2H, H-3) 1.48 [s, 9H $(CH_3)_3$], 3.08 (m, 2H, H-5), 3.33 (d, *J* = 10.8 Hz, 1H, H-1), 3.36 (d, *J* = 10.8 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 7.9 (*C*H$_3$CH$_2$), 21.2 (CH_3), 24.1 (C-3), 28.4 [$(CH_3)_3$], 28.5 (C-4), 32.8 (*C*H$_2$CH$_3$), 37.1 (C-2), 41.4 (C-5), 69.0 (C-1), 79.1 [*C*$(CH_3)_3$], 156.1 (CO); HRMS Calcd for $C_{13}H_{28}NO_3$ $[M+H]^+$ 246.2064; found 246.2069.

*4.6.2. (S)-2-Allyl-5-[(tert-butoxycarbonyl)amino]-2-methyl-1-pentanol (**15**)*

Step 1: Following the general procedure, from aminodiol **8** (326 mg, 1.17 mmol) and Boc_2O (513 mg, 2.35 mmol) in MeOH (50 mL), the *N*-Boc derivative (298 mg, 67%) was obtained after flash chromatography (6:4 to 1:1 hexane-EtOAc): $[\alpha]^{22}_D$ – 52.8 (*c* 1.17, MeOH); IR (film) *v* 3426 (OH), 1667 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.74 (s, 3H, CH_3), 0.99-1.13 (m, 2H, H-3), 1.20-1.29 (m, 1H, H-4), 1.35-1.40 (m, 1H, H-4), 1.46 [s, 9H, $(CH_3)_3$], 1.91 (d, *J* = 7.6 Hz, 2H, C*H*$_2$CH=), 2.93 (brm, 1H, H-5), 3.05 (brm, 1H, H-5), 3.24 (s, 2H, H-1), 4.03-4.12 (m, 2H, CH_2O), 4.96-4.99 (m, 1H, CH_2=), 5.01 (s, 1H, CH_2=), 5.08 (brs, 1H, CHN), 5.67-5.78 (m, 1H, CH=), 7.24-7.27 (m, 3H, ArH), 7.30-7.34 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) *δ* 21.4 (CH_3), 23.4 (C-4), 28.4 [$(CH_3)_3$], 33.3 (C-3), 37.6 (C-2), 41.5 (*C*H$_2$CH=), 46.2 (C-5), 61.4 (CHN), 63.1 (CH_2O), 69.0 (C-1), 80.1 [*C*$(CH_3)_3$], 117.2 (CH_2=), 127.6 (CH-Ar), 128.5 (CH-Ar), 134.9 (CH=), 138.2 (C-*i*), 156.7 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{36}NO_4$, 378.2639; found, 378.2651.

Step 2: Following Step 2 of the general procedure, from the above *N*-Boc derivative (80 mg, 0.21 mmol) in THF (6 mL), liquid ammonia (20 mL), and sodium (stirring the blue mixture for 8 seconds), compound **15** (49 mg, 90%) was obtained after flash chromatography (9:1 to 8:2 hexane-EtOAc): $[\alpha]^{22}_D$ + 0.3 (*c* 1.63, MeOH); IR (film) *v* 3357 (OH, NH), 1693 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.84 (s, 3H, CH_3), 1.23-1.27 (m, 2H, H-3), 1.41-1.49 (m, 2H, H-4), 1.43 [s, 9H, $(CH_3)_3$], 1.87 (brs, 1H, NH), 2.01 (d, *J* = 7.6 Hz, 2H, C*H*$_2$CH=), 3.07 (t, *J* = 7.0 Hz, 2H, H-5), 3.34 (s, 2H, H-1), 4.59 (brs, 1H, OH), 5.03 (brs, 1H, CH_2=), 5.05-5.08 (m, 1H, CH_2=), 5.76-5.86 (m, 1H, CH=); ^{13}C NMR ($CDCl_3$) *δ* 21.5 (CH_3), 24.1 (C-4), 28.4 [$(CH_3)_3$], 33.3 (C-3), 37.7 (C-2, C-5), 41.4 (*C*H$_2$CH=), 69.3 (C-1), 79.2 [*C*$(CH_3)_3$], 117.3 (CH_2=), 134.9 (CH=), 156.1 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{28}NO_3$, 258.2063; found, 258.2064.

*4.7. (S)-5-[tert-Butyldiphenylsilyl)oxy]-4-ethyl-4-methylpentanenitrile (**14**)*

A 20% aqueous solution of NH_3 (14 mL) and iodine (875 mg, 3.43 mmol) were added to a solution of the bis-TBDPS ether derived from aminodiol **7** (320 mg, 0.43 mmol) in anhydrous THF (2 mL) at rt, and the resulting mixture was stirred at 60 ºC for 16 h. The mixture was washed with saturated aqueous Na_2SO_3 and extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the residue gave nitrile **14** (123 mg, 75%) as an oil: $[\alpha]^{22}_D$ – 2.00 (*c* 1.85, $CHCl_3$); IR (film) *v* 2246 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.78 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 0.82 (s, 3H, CH_3), 1.08 [s, 9H, $(CH_3)_3$], 1.31 (q, *J* = 7.8 Hz, 2H, C*H*$_2$CH$_3$), 1.73 (m, 2H, H-3), 2.19 (m, 2H, H-2), 3.28 (d, *J* = 10.4 Hz, 1H, H-5), 3.32 (d, *J* = 10.4 Hz, 1H, H-5), 7.39-7.47 (m, 6H, ArH), 7.63-7.66 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.7 (*C*H$_3$CH$_2$), 12.0 (C-2) 19.3 [*C*$(CH_3)_3$], 20.7 (CH_3), 26.9 [$(CH_3)_3$], 28.4 (*C*H$_2$CH$_3$), 32.3 (C-3), 37.8 (C-4), 69.8 (C-5), 120.5 (CN), 127.5 (CH-Ar), 129.8 (CH-Ar), 133.2 (C-*i)*, 135.6 (C-*m*); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{34}NOSi$, 380.2404; found, 380.2406.

*4.8. Preparation of acyclic building blocks **19** and **20***

*4.8.1. (3S,6S,8aR)-6-{3-[(tert-Butyldimethylsilyl)-oxy]propyl}-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**17a**)*

Step 1: 9-BBN (0.5 M in THF, 31.3 mL, 15.6 mmol) was added dropwise to a solution of lactam **16**[11a] (2.23 g, 7.82 mmol) in anhydrous THF (91 mL) under an argon atmosphere at 0 ºC. The ice-water bath was removed and the mixture was stirred at rt for 2 h. After cooling the mixture to 0 ºC, 3M aqueous NaOH and 30% H_2O_2 were added. Then, the mixture was allowed to slowly warm up until rt, stirred for 3 h, and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (Biotage®, 8:2 hexane-EtOAc) of the residue afforded (3*S*,6*S*,8aR)-6-(3-hydroxypropyl)-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (2.10 g, 89%) as a white crystalline solid: $[\alpha]^{22}_D$ +106.0 (*c* 1.0, MeOH); m.p. 106-108 ºC; IR (film) *v* 1644 (CO), 3507 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.78 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 1.40-1.50 (m, 1H, C*H*$_2$CH$_3$), 1.50-1.70 (m, 5H, H-8, C*H*$_2$CH$_3$, C*H*$_2$C*H*$_2$CH$_2$O), 1.70-1.84 (m, 3H, H-7, C*H*$_2$CH$_2$CH$_2$O), 2.23 (m, 1H, H-8), 2.26 (ddt, *J* = 12.4, 8.0, 4.0 Hz, 1H, H-8), 3.55-3.59 (m, 2H, C*H*$_2$O), 3.73 (dd, *J* = 9.0, 8.0, Hz, 1H, H-2), 4.46 (dd, *J* = 9.0, 8.0 Hz, 1H, H-2), 5.03 (dd, *J* = 8.8, 4.4 Hz, 1H, H-8a), 5.18 (t, *J* = 8.0 Hz, 1H, H-3), 7.24 (m, 3H, ArH), 7.31 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) *δ* 8.6 (CH_3), 25.6 (C-7), 26.5 (C-8), 27.9 (*C*H$_2$CH$_2$CH$_2$O), 32.6 (*C*H$_2$CH$_3$), 34.6 (*C*H$_2$CH$_2$O), 44.8 (C-6), 58.9 (C-3), 62.9 (CH_2O), 73.0 (C-2), 89.0 (C-8a), 126.2 (CH-Ar), 127.5 (C-*p*), 128.7 (CH-Ar), 139.7 (C-*i*), 173.8 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{26}NO_3$, 304.1907; found, 304.1908.

Step 2: Following the general procedure described in Step 1 of Section 4.5, from a solution of the above alcohol (4.02 g, 13.26 mmol) in CH_2Cl_2 (114 mL), anhydrous triethylamine (7.4 mL, 53.0 mmol), and *tert*-butyldimethylsilyl chloride (4.97 g, 33.5 mmol) at rt, lactam **17a** (5.10 g, 92%) was obtained as a colorless oil after flash chromatography (8:2 hexane-EtOAc to EtOAc): $[\alpha]^{22}_D$ + 121.0 (*c* 1.1, MeOH); IR (film) *v* 1652 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* – 0.01 [s, 6H, Si$(CH_3)_2$], 0.74 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 0.85 [s, 9H, $(CH_3)_3$], 1.32-1.48 (m, 2H, C*H*$_2$CH$_3$, C*H*$_2$CH$_2$CH$_2$O), 1.53-1.76 (m, 7H, H-7, H-8, C*H*$_2$CH$_3$, C*H*$_2$C*H*$_2$CH$_2$O), 2.17-2.23 (m, 1H, H-8), 3.54 (t, *J* = 6.4 Hz, 2H, CH_2O), 3.70 (t, *J* = 8.5 Hz, 1H, H-2), 4.43 (t, *J* = 8.5 Hz, 1H, H-2), 4.98 (dd, *J* = 8.8, 4.4 Hz, 1H, H-8a), 5.16 (t, *J* = 8.5 Hz, 1H, H-3), 7.20-7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ –5.3 [Si$(CH_3)_2$], 8.6 (*C*H$_3$CH$_2$), 18.3 [*C*$(CH_3)_3$], 25.3 (C-7), 25.9 [C(*C*H$_3$)$_3$], 26.2 (C-8), 27.9 (*C*H$_2$CH$_2$CH$_2$O), 31.9 (*C*H$_2$CH$_3$), 34.4 (*C*H$_2$CH$_2$O), 44.9 (C-6), 58.8 (C-3), 63.5 (CH_2O), 73.0 (C-2), 89.2 (C-8a), 126.2 (CH-Ar), 127.4 (C-*p*), 128.7 (CH-Ar), 139.9 (C-*i*), 173.6 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{40}NO_3Si$, 418.2772; found, 418.2774.

*4.8.2. (3S,6S,8aR)-6-{3-[(tert-Butyldiphenylsilyl)-oxy]propyl}-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**17b**)*

Following the general procedure described in Step 1 of Section 4.5, from (3*S*,6*S*,8a*R*)-6-(3-hydroxypropyl)-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (883 mg, 2.92 mmol), imidazole (297 mg, 4.36 mmol) and *tert*-butyldiphenylsilyl chloride (1.13 mL, 4.36 mmol) in CH_2Cl_2 (21 mL) at rt, lactam **17b** (1.75 g, 84%) was obtained as a colorless oil after flash chromatography (9:1 to 8:2 hexane-EtOAc) $[\alpha]^{22}_D$ + 87.3 (*c* 1.0, MeOH); IR (film) *v* 1652 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.77 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 1.04 [s, 9H, (CH$_3$)$_3$], 1.33-1.42 (dq, *J* = 14.1, 7.6 Hz, 1H, CH$_3$C*H*$_2$), 1.46-1.57 (m, 1H, C*H*$_2$CH$_2$CH$_2$O), 1.59-1.81 (m, 7H, H-7, H-8, C*H*$_2$CH$_3$, C*H*$_2$C*H*$_2$CH$_2$O), 2.19-2.25 (m, 1H, H-8), 3.63 (t, *J* = 6.4 Hz, 2H, CH$_2$O), 3.73 (dd, *J* = 9.2, 8.5 Hz, 1H, H-2), 4.46 (dd, *J* = 9.2, 8.5 Hz, 1H, H-2), 5.01 (dd, *J* = 9.2, 4.4 Hz, 1H, H-8a), 5.19 (t, *J* = 8.5 Hz, 1H, H-3), 7.21-7.43 (m, 3H, ArH), 7.64-7.66 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$) δ 8.7 (*C*H$_3$CH$_2$), 19.2 [*C*(CH$_3$)$_3$], 25.3 (C-7), 26.2 (C-8), 26.9 [(CH$_3$)$_3$], 27.7 (*C*H$_2$CH$_2$CH$_2$O), 31.9 (*C*H$_2$CH$_3$), 34.3 (*C*H$_2$CH$_2$O), 44.9 (C-6), 58.8 (C-3), 64.3 (CH$_2$O), 73.0 (C-2), 89.0 (C-8a), 126.2 (C-o), 128.7 (C-*m*), 129.5 (C-*o*), 134.0 (C-*p*),134.0 (C-*i*), 135.0 (C-*m*), 139.9 (C-*i*), 173.6 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{34}H_{44}NO_3Si$, 542.3085; found, 542.3079.

*4.8.3. (R)-2-{3-[(tert-Butyldimethylsilyl)oxy]-propyl}-5-{[(1S)-2-hydroxy-1-phenylethyl]amino}-2-ethyl-1-pentanol (**18a**)*

Following the general procedure described in Section 4.3, from lactam **17a** (396 mg, 0.95 mmol) in THF (2 mL), *n*-BuLi (2.55 mL of a 1.6 M solution in hexanes, 4.08 mmol), and $NH_3{\cdot}BH_3$ (126 mg, 4.08 mmol) in THF (4 mL), aminoalcohol **18a** (261 mg, 65%) was obtained as a colorless oil after flash chromatography (EtOAc to 9:1 EtOAc-MeOH): $[\alpha]^{22}_D$ + 3.9 (*c* 1.0, MeOH); IR (film) *v* 3355 (OH, NH); ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.05 [s, 6H, Si(CH$_3$)$_2$], 0.77 (t, *J* = 7.6 Hz, 3H, CH$_3$), 0.89 [s, 9H, (CH$_3$)$_3$], 1.17-1.25 (m, 6H, H-3, C*H*$_2$CH$_3$, C*H*$_2$CH$_2$CH$_2$O), 1.38-1.46 (m, 4H, H-4, CH$_2$C*H*$_2$CH$_2$O), 2.46-2.57 (m, 2H, H-5), 2.84 (brs, 3H, OH, NH), 3.34 (s, 2H, H-1), 3.57 (t, *J* = 6.4 Hz, 2H, CH$_2$OSi), 3.62 (brd, *J* = 10.6 Hz, 1H, C*H*$_2$OH), 3.72 (dd, *J* = 10.6, 4.4 Hz, 1H, C*H*$_2$OH), 3.79 (dd, *J* = 8.8, 4.4 Hz, 1H, CHN), 7.29-7.37 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 5.3 [Si(CH$_3$)$_2$], 7.4 (*C*H$_3$CH$_2$), 18.4 [*C*(CH$_3$)$_3$], 23.0 (C-4), 25.6 (*C*H$_2$CH$_3$), 26.0 [(CH$_3$)$_3$], 26.2(C-3), 29.0 (*C*H$_2$CH$_2$CH$_2$O), 30.9 (*C*H$_2$CH$_2$O), 39.5 (C-2), 47.9 (*C*H$_2$OSi), 63.9 (C-5), 64.7 (CHN), 65.9 (C-1), 66.4 (CH$_2$OH), 127.3 (CH-Ar), 127.8 (C-*p*), 128.7 (CH-Ar), 139.9 (C-*i*); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{46}NO_3Si$, 424.3241; found, 424.3241.

*4.8.4. (R)-2-{3-[(tert-Butyldiphenylsilyl)oxy]-propyl]}-5-{[(1S)-2-hydroxy-1-phenylethyl]amino}-2-ethyl-1-pentanol (**18b**)*

Following the general procedure described in Section 4.3, from lactam **17b** (299 mg, 0.55 mmol) in THF (2 mL), *n*-BuLi (1.45 mL of a 1.6 M solution in hexanes, 2.37 mmol), and $NH_3{\cdot}BH_3$ (73 mg, 2.37 mmol) in THF (4 mL), aminoalcohol **18b** (197 mg, 65%) was obtained as a colorless oil after flash chromatography (EtOAc to 9:1 EtOAc-MeOH): $[\alpha]^{22}_D$ + 21.6 (*c* 1.0, MeOH); IR (film) *v* 3346 (OH, NH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.77 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$), 1.05 [s, 9H, (CH$_3$)$_3$], 1.16-1.26 (m, 6H, H-3, C*H*$_2$CH$_3$, C*H*$_2$CH$_2$CH$_2$O), 1.36-1.46 (m, 4H, H-4, C*H*$_2$CH$_2$O), 2.52 (m, 2H, H-5), 2.67 (brs, 3H, OH, NH), 3.32 (s, 2H, H-1), 3.62 (m, 3H, CH$_2$OSi, CHN), 3.73-3.80 (m, 2H, C*H*$_2$OH), 7.37 (m, 11H, ArH), 7.65 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.4 (*C*H$_3$CH$_2$), 19.2 [*C*(CH$_3$)$_3$], 23.0 (C-4), 25.7 (*C*H$_2$CH$_2$CH$_2$O), 26.1 (CH$_3$C*H*$_2$), 26.9 [(CH$_3$)$_3$], 28.9 (C-3), 30.9 (*C*H$_2$CH$_2$O), 39.4 (C-2), 47.9 (C-5), 64.6 (CH$_2$OSi), 64.7 (CHN), 65.9 (C-1), 66.4 (CH$_2$OH), 127.3 (C-*p*), 127.6 (CH-Ar), 127.8 (C-*i*), 128.7 (CH-Ar), 129.5 (CH-Ar), 134.0 (C-*p*), 135.6 (CH-Ar); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{34}H_{50}NO_3Si$, 548.3554; found, 548.3549.

*4.8.5. (R)-2-{3-[(tert-Butyldimethylsilyl)oxy] propyl}-5-[(tert-butoxycarbonyl)amino]-2-ethyl-1-pentanol (**19**)*

Step 1: Following the general procedure described in Section 4.6, from aminodiol **18a** (372 mg, 0.88 mmol) and Boc_2O (307 mg, 1.41 mmol) in MeOH (35 mL), the *N*-Boc derivative (404 mg, 88%) was obtained as a colorless oil after flash chromatography (8:2 hexane-EtOAc): $[\alpha]^{22}_D$ + 39.58 (*c* 1.19, MeOH); IR (film) *v* 3421 (OH), 1669 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.05 [s, 6H, Si(CH$_3$)$_2$], 0.72 (t, *J* = 7.6 Hz, 3H, CH$_2$C*H*$_3$), 0.89 [s, 9H, SiC(CH$_3$)$_3$], 0.98-1.07 (m, 2H, C*H*$_2$CH$_2$O), 1.11-1.19 (m, 5H, H-3, H-4, C*H*$_2$CH$_2$CH$_2$O), 1.32-1.39 (m, 3H, H-4, C*H*$_2$CH$_3$), 1.45 [s, 9H, OC(CH$_3$)$_3$], 2.19 (brs, 2H, OH), 2.93 (brs, 1H, H-5), 3.04 (brs, 1H, H-5), 3.25 (s, 2H, H-1), 3.55 (dt, *J* = 4.8, 1.6 Hz, 2H, CH$_2$OSi), 4.08 (m, 2H, CH$_2$OH), 5.11 (brs, 1H, CHN), 7.26 (m, 1H, ArH), 7.26-7.36 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ –5.3 [Si(CH$_3$)$_2$], 7.3 (*C*H$_3$CH$_2$), 18.9 [Si*C*(CH$_3$)$_3$], 23.0 (C-4), 25.7 (*C*H$_2$CH$_2$CH$_2$O), 26.0 [SiC(*C*H$_3$)$_3$], 28.4 [OC(*C*H$_3$)$_3$], 29.0 (C-3), 30.5 (*C*H$_2$CH$_2$O), 39.2 (C-2), 46.2 (C-5), 61.5 (CHN), 63.2 (CH$_2$OH), 63.9 (*C*H$_2$OSi), 66.0 (C-1), 80.1 [O*C*(CH$_3$)$_3$], 127.6 (CH-Ar), 128.5 (C-*p*), (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{54}NO_5Si$, 524.3766; found, 524.3763.

Step 2: Following the general procedure described in Step 2 of Section 4.6, from the above *N*-Boc derivative (466 mg, 0.89 mmol) in THF (5 mL), liquid ammonia (20 mL), and sodium (stirring the blue mixture for 20 seconds), compound **19** (337 mg, 89%) was obtained as a colorless oil after flash chromatography (8:2 hexane-EtOAc): $[\alpha]^{22}_D$ + 8.3 (*c* 1.1, MeOH); IR (film) *v* 3420 (OH), 1668 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.05 [s, 6H, Si(CH$_3$)$_2$], 0.78 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 0.89 [s, 9H, SiC(CH$_3$)$_3$], 1.18-1.26 (m, 6H, H-3, C*H*$_2$CH$_3$, C*H*$_2$CH$_2$O), 1.44 [s, 9H, OC(CH$_3$)$_3$], 1.30-1.43 (m, 4H, H-4, C*H*$_2$CH$_2$CH$_2$O), 1.70 (brs, 1H, OH), 3.07 (t, *J* = 6.4 Hz, 2H, H-5), 3.35 (s, 2H, H-1), 3.58 (t, *J* = 6.0 Hz, 2H, CH$_2$OSi), 4.56 (brs, 1H, CH); ^{13}C NMR ($CDCl_3$) δ – 5.3 [Si(CH$_3$)$_2$], 7.4 (*C*H$_3$CH$_2$), 18.3 [Si*C*(CH$_3$)$_3$], 23.7 (C-4), 25.6 (*C*H$_2$CH$_2$CH$_2$O), 25.8 [SiC(*C*H$_3$)$_3$], 26.1 (*C*H$_2$CH$_3$), 28.5 [OC(*C*H$_3$)$_3$], 29.1 (C-3), 30.4 (*C*H$_2$CH$_2$O), 39.3 (C-2, C-5), 63.8 (CH$_2$OSi), 66.3 (C-1), 82.0 [O*C*(CH$_3$)$_3$], 152.5 (CO); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{46}NO_4Si$, 404.3191; found, 404.3198.

*4.8.6. (S)-4-{3-[(tert-Butyldimethylsilyl)oxy] propyl}-5-[(tert-butyldiphenylsilyl)oxy]-4-ethyl-pentanitrile (**20**)*

Step 1: Following the general procedure described in Section 4.5, from aminodiol **18a** (153 mg, 0.36 mmol), *tert*-butyldiphenylsilyl chloride (0.24 mL, 0.90 mmol), and imidazole (61 mg, 1.02 mmol) in refluxing CH_2Cl_2 (3 mL), the corresponding bis-TBDPS ether (236 mg, 73%) was obtained as a colorless oil after flash chromatography (Biotage®, 8:2 hexane–EtOAc): $[\alpha]^{22}_D$

+ 10.7 (*c* 1.4, $CHCl_3$); IR (film) *ν* 3335 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.05 [s, 6H, $Si(CH_3)_2$], 0.72 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 0.90 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 1.05 [s, 9H, $(CH_3)_3CSiPh_2$], 1.07 [s, 9H, $(CH_3)_3CSiPh_2$], 1.21-1.42 (m, 10H, H-2, H-3, CH_2CH_3, $CH_2CH_2CH_2O$), 1.97 (brs, NH), 2.40-2.46 (m, 2H, H-1), 3.32 (s, 2H, H-5), 3.56 (t, *J* = 6.4 Hz, 2H, CH_2CH_2OSi), 3.68 (m, 2H, CH_2CH), 3.79 (dd, *J* = 8.8, 4.4 Hz, 1H, CHN), 7.33-7.43 (m, 15H, ArH), 7.61-7.66 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$,) δ –5.3 [$Si(CH_3)_2$], 7.5 (CH_3CH_2), 18.4 [$(CH_3)_2SiC(CH_3)_3$], 19.2 [$Ph_2SiC(CH_3)_3$], 19.4 [$PhSiC(CH_3)_3$], 23.7 (CH_2CH_3), 26.0 [$MeSiC(CH_3)_3$], 26.6 ($CH_2CH_2CH_2O$, C-3), 26.7 [$(CH_3)_3CSiPh$], 27.0 [$(CH_3)_3CSiPh$], 29.4 (C-4), 31.0 (CH_2CH_2O), 39.7 (C-2), 48.7 (C-5), 64.1 (CH_2OSi), 65.1 (CHN), 66.9 (C-1), 69.0 (CH_2CH), 127.2 (C-*p*), 127.6 (CH-Ar), 127.7 (CH-Ar), 127.7 (CH-Ar), 128.1 (C-*p*), 129.5 (C-*p*), 129.6 (C-*p*), 129.7, (C-*p*), 133.3(C-*i*), 133.5 (C-*i*), 133.9(C-*i*), 135.3 (C-*i*), 135.6 (CH-Ar), 135.7 (CH-Ar), 141.0 (C-*i*); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{56}H_{82}NO_3Si_3$, 900.5597; found, 900.5589.

Step 2: Operating as described in the preparation of nitrile **14**, from a solution of the above bis-TBDPS ether (206.9 mg, 0.23 mmol) in anhydrous THF (1 mL), aqueous NH_3 (8 mL), and iodine (465 mg, 1.83 mmol), nitrile **20** (83 mg, 67%) was obtained after flash chromatography (9:1 hexane-EtOAc): $[\alpha]^{22}_D$ + 9.7 (*c* 1.0 in MeOH); IR (film) *ν* 2247 (CN); ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.03 [s, 6H, $Si(CH_3)_2$], 0.73 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 0.88 [s, 9H, $(CH_3)_3CSiMe$], 1.08 [s, 9H, $(CH_3)_3CSiPh$), 1.16-1.38 (m, 6H, CH_2CH_3, CH_2CH_2O), 1.67-1.72 (m, 2H, H-3), 2.09-2.41 (m, 2H, H-2), 3.28 (s, 2H, H-5), 3.54 (dt, *J* = 13.6, 1.6 Hz, 2H, CH_2CH_2OSi), 7.38-7.46 (m, 6H, ArH), 7.61-7.64 (4H, ArH); ^{13}C NMR ($CDCl_3$) *δ* –5.3 ($SiCH_3$), 7.2 (CH_3CH_2), 11.7 (C-2), 18.3 [$MeC(CH_3)_3$], 19.3 [$PhC(CH_3)_3$], 25.4 (CH_2CH_3), 26.0 [$MeSiC(CH_3)_3$], 26.2 ($CH_2CH_2CH_2O$), 27.0 [$(CH_3)_3CSiPh$], 28.2 (CH_2CH_2O), 30.2 (C-3), 39.8 (C-4), 63.4 (CH_2OSi), 66.4 (C-5), 120.5 (C-1), 127.8 (CH-Ar), 129.8 (C-*p*), 133.2 (C-*i*), 135.7 (CH-Ar); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{52}NO_2Si_2$, 538.3531; found, 538.3536.

4.9. Synthesis of Kerr's intermediate

*4.9.1. (R)-5-[(tert-Butoxycarbonyl)amino]-2-{3-[(tert-butyldimethylsilyl)oxy]propyl}-2-ethylpentanal (**21**)*

Dimethylsulfide (0.49 mL, 6.63 mmol) was added under an argon atmosphere to a solution of freshly recrystallized *N*-chlorosuccinimide (177 mg, 1.33 mmol) in anhydrous CH_2Cl_2 (7 mL) at – 15 ºC. After the addition was completed, a white precipitate appeared and the mixture was stirred for an additional 30 min at – 15 ºC. The temperature was lowered to – 78 ºC, and a solution of alcohol **19** (106 mg, 0.27 mmol) in anhydrous CH_2CH_2 (2 mL) was added via a cannula. After 2 h of stirring, anhydrous TEA (0.64 mL) was added, and the mixture was stirred at – 78 ºC for 1 h. The mixture was diluted with CH_2Cl_2 and quenched with H_2O. The organic layer was separated, washed with brine, dried, filtered, and concentrated to give crude aldehyde **21** (110 mg) as colorless oil. Due to its instability, further purification was not performed: ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.03 [s, 6H, $Si(CH_3)_2$], 0.78 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 0.88 [s, 9H, $SiC(CH_3)$], 1.24-1.37 (m, 6H, H-3, CH_2CH_3, CH_2CH_2O), 1.43-1.65 (m, 4H, H-4, $CH_2CH_2CH_2O$), 1.43 [s, 9H, $OC(CH_3)_3$], 3.05-3.11 (m, 2H, H-5), 3.57 (t, *J* = 6.0 Hz, 2H, CH_2OSi), 9.40 (s, 1H, H-1).

*4.9.2. (R)-5,5-bis-[(tert-Butoxycarbonyl)amino]-2-{3-[(tert-butyldimethylsilyl)oxy]propyl}-2-ethylpentanal (**22**)*

Step 1: Following Step 1 of the general procedure described in Section 4.5, from a solution of alcohol **19** (559 mg, 1.39 mmol) in CH_2Cl_2 (10 mL), imidazole (189 mg, 2.77 mmol), and chlorotriethylsilane (0.28 mL, 1.66 mmol) at rt, the *O*-TES ether (655 mg, 91%) was obtained as a colorless oil after flash chromatography (95:5 hexane-EtOAc): $[\alpha]^{22}_D$ – 1.74 (*c* 1.75, MeOH); IR (film) *ν* 1674 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.42 [s, 6H, $Si(CH_3)_2$], 0.57 [q, *J* = 7.6 Hz, 6H, $Si(CH_2CH_3)_3$]), 0.75 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 0.89 [s, 9H, $SiC(CH_3)$], 0.94 [t, *J* = 7.6 Hz, 9H, $Si(CH_2CH_3)_3$], 1.24-1.37 (m, 6H, H-3, CH_2CH_3, CH_2CH_2O), 1.43-1.65 (m, 4H, H-4, $CH_2CH_2CH_2O$), 1.43 [s, 9H, $OC(CH_3)_3$], 3.05-3.11 (m, 2H, H-5), 3.26 (s, 2H, H-1), 3.55 (t, *J* = 6.0 Hz, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ –5.3 [$Si(CH_3)_2$], 4.4 [$Si(CH_2CH_3)_3$], 6.8 [$Si(CH_2CH_3)$], 7.4 (CH_3CH_2), 1(95:5 hexane-EtOAc) 8.3 [$SiC(CH_3)_3$], 22.9 (C-4), 25.9 (CH_2CH_3), 26.0 [$SiC(CH_3)_3$], 26.6 ($CH_2CH_2CH_2O$), 28.1 [$OC(CH_3)_3$], 29.5 (C-3), 30.4 (CH_2CH_2O), 39.2 (C-2), 47.2 (C-5), 64.1 (CH_2O), 66.1 (C-1), 81.1 [$OC(CH_3)_3$], 156.1 (CO). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{60}NO_4Si_2$, 518.4055; found, 518.4049.

Step 2: *n*-BuLi (0.61 mL of a 1.6 M solution in hexanes, 1.52 mmol) was added under an argon atmosphere at 0 ºC to a solution of the above *O*-TES ether (655 mg, 1.26 mmol) in anhydrous THF (6 mL), and the resulting solution was stirred at this temperature for 15 min. Then, a solution of Boc_2O (331 mg, 1.52 mmol) in anhydrous THF (2 mL) was added, and the solution was allowed to warm slowly to rt. After stirring for 1 h, Et_2O was added (5 mL) and the solution was washed with H_2O. The organic layer was further washed with brine, dried, filtered, and concentrated. Flash chromatography (98:2 to 95:5 hexane-EtOAc) afforded the bis-*N*-Boc derivative (664 mg, 86%) as a colorless oil: $[\alpha]^{22}_D$ – 0.42 (*c* 1.2, MeOH); IR (film) *ν* 1698 (CO), 1749 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.30 [s, 6H, $Si(CH_3)_2$], 0.57 [q, *J* = 7.6 Hz, 6H, $(CH_3CH_2)_3Si$], 0.75 (t, *J* = 7.6 Hz, 3H, CH_3CH_2), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.94 [t, *J* = 7.6 Hz, 9H, $(CH_3CH_2)_3Si$], 1.12-1.25 (m, 6H, H-3, CH_2CH_3, CH_2CH_2O), 1.37-1.47 (m, 4H, H-4, $CH_2CH_2CH_2O$), 1.49 {s, 18H, $[OC(CH_3)_3]_2$}, 3.26 (s, 2H, H-2), 3.48 (t, *J* = 7.2 Hz, 2H, H-5), 3.55 (t, *J* = 6.8 Hz, 2H, CH_2OSi); ^{13}C NMR ($CDCl_3$) *δ* –5.3 [$Si(CH_3)_2$], 4.4 [$Si(CH_3CH_2)$], 6.8 [$Si(CH_2CH_3)$], 7.4 (CH_3CH_2), 18.3 [$SiC(CH_3)_3$], 22.9 (C-4), 25.9 (CH_2CH_3), 26.0 [$SiC(CH_3)_3$], 26.6 ($CH_2CH_2CH_2O$), 28.1 [$OC(CH_3)_3$], 29.5 (C-3), 30.4 (CH_2CH_2O), 39.2 (C-2), 47.2 (C-5), 64.1 (CH_2O), 66.1 (C-1), 81.1 [$OC(CH_3)_3$], 156.1 (CO); HRMS (ESI-TOF) m/z $[M-Boc]^+$ calcd for $C_{27}H_{60}NO_4Si_2$, 518.4055; found, 518.4048.

Step 3: A $6.2\cdot10^{-3}$ M solution of $FeCl_3$ in MeOH (0.27 mL, $1.7\cdot10^{-3}$ mmol) was added under an argon atmosphere to a solution of the above bis-*N*-Boc derivative (146 mg, 0.24 mmol) in anhydrous MeOH (2 mL). The mixture was stirred at rt for 1 h 45 min and filtered through silica. The solvent was evaporated, and the residue was chromatographed (8:2 to 6:4 hexane/EtOAc) to give the aminopentanol (95 mg, 65%) and the aminodiol (19 mg, 20%) derivatives as colorless oils. Aminopentanol derivative: $[\alpha]^{22}_D$ – 9.02 (c 2.2, MeOH); IR (film) *ν* 1697 (CO), 1732 (CO), 3488 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.05 [s, 6H, $Si(CH_3)_2$], 0.79 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 0.89 [s, 9H, $SiC(CH_3)$], 1.14-1.26 (m, 6H, H-3, CH_2CH_3, CH_2CH_2O), 1.37-1.50 (m, 4H, H-4, $CH_2CH_2CH_2O$), 1.50 {s, 18H, $[OC(CH_3)_3]_2$}, 3.35 (s, 2H, H-1), 3.52 (t, *J* = 7.6 Hz, 2H, H-5), 3.58 (t, *J* = 6.4 Hz, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) *δ* –5.3 [$Si(CH_3)_2$], 7.4 (CH_3CH_2), 18.3 [$SiC(CH_3)_3$], 22.7 (C-4), 25.9 (CH_2CH_3), 26.0 [$SiC(CH_3)_3$],

26.1 ($CH_2CH_2CH_2O$), 28.1 [$OC(CH_3)_3$], 29.3 (C-3), 30.1 (CH_2CH_2O), 39.3 (C-2), 47.1 (C-5), 63.9 (CH_2OSi), 66.4 (C-1), 82.0 [$OC(CH_3)_3$], 152.7 (CO); HRMS (ESI-TOF) *m/z* [M-Boc]$^+$ calcd for $C_{21}H_{46}NO_4Si_2$, 404.3191; found, 404.3196. Aminodiol derivative: $[\alpha]^{22}_D$ – 0.26 (*c* 2.2, MeOH); IR (film) ν 1696 (CO), 1731 (CO), 3427 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.77 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.11-1.29 (m, 6H, H-3, CH_2CH_3, CH_2CH_2O), 1.39-1.44 (m, 4H, H-4, $CH_2CH_2CH_2O$), 1.44 {s, 18H, $[OC(CH_3)_3]_2$}, 2.44 (brs, 2H, OH), 3.32 (s, 2H, H-1), 3.49 (t, *J* = 7.6 Hz, 2H, H-5), 3.60 (t, *J* = 6.0 Hz, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ 7.3 (CH_3CH_2), 22.5 (C-4), 25.6 ($CH_2CH_2CH_2O$), 25.9 (CH_2CH_3), 28.0 [$OC(CH_3)_3$], 29.4 (C-3), 29.7 (CH_2CH_2O), 39.3 (C-2), 47.0 (C-5), 63.2 (CH_2O), 65.7 (C-1), 82.2 [$OC(CH_3)_3$], 152.8 (CO); HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{20}H_{40}NO_6$, 390.2850; found, 390.2856.

Step 4: Dess–Martin periodinane (154 mg, 0.36 mmol) was added at rt to a solution of the above aminopentanol (73 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (2 mL) and the resulting mixture was stirred for 1 h 30 min. The solution was poured into a saturated aqueous solution (8 mL) of $Na_2S_2O_3$ and $NaHCO_3$ (1:1) and the mixture was stirred at rt for 1 h. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, filtered, and concentrated to give crude aldehyde **22** (74 mg), which was used in the next step without purification: ^{1}H NMR ($CDCl_3$) *δ* 0.02 [s, 6H, $Si(CH_3)_2$], 0.77 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.87 [s, 9H, $SiC(CH_3)_3$], 1.32-1.37 (m, 2H, H-3), 1.43 (m, 4H, CH_2CH_3, CH_2CH_2O), 1.48 {s, 18H, $OC(CH_3)_3]_2$}, 1.45-1.57 (m, 4H, H-4, $CH_2CH_2CH_2O$), 3.51-3.57 (m, 4H, H-5, CH_2O), 9.39 (s, 1H, H-1).

*4.9.3. (R)-6,6-bis-[(tert-Butoxycarbonyl)amino]-3-[(tert-butyldimethylsilyl)oxy]propyl}-3-ethyl-1-hexyne (**23**)*

Bestmann-Ohira reagent (40 µL, 0.27 mmol) and K_2CO_3 (62 mg, 0.45 mmol) were successively added at rt under an inert atmosphere to a solution of aldehyde **22** (74 mg) in anhydrous MeOH (1 mL). After stirring for 15 h, the mixture was filtered through a Celite® pad, and the organic solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed with 5% aqueous $NaHCO_3$ and brine. The organic layer was dried, filtered, and concentrated. Flash chromatography (95:5 hexane-EtOAc) of the residue gave alkyne **23** (48 mg, 53%, two steps) as a colorless oil:[29] $[\alpha]^{22}_D$ –2.5 (*c* 2.4, MeOH); IR (film) ν 1699 (CO), 1748 (CO), 3310 (H-Csp) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.04 [s, 6H, $Si(CH_3)_2$], 0.77 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 0.89 [s, 9H, $SiC(CH_3)$], 1.37-1.46 (m, 6H, H-4, CH_2CH_3, CH_2CH_2O), 1.50 {s, 18H, $[OC(CH_3)_3]_2$}, 1.55-1.70 (m, 4H, H-5, $CH_2CH_2CH_2O$), 2.07 (s, 1H, H-1), 3.57 (t, *J* = 6.4 Hz, 2H, H-6), 3.57 (t, *J* = 6.0 Hz, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) *δ* –5.3 [$Si(CH_3)_2$], 8.5 (CH_3CH_2), 18.3 [$SiC(CH_3)_3$], 24.0 (C-5), 25.9 [$SiC(CH_3)_3$], 27.7 ($CH_2CH_2CH_2O$), 28.1 [$OC(CH_3)_3$], 30.5 (CH_2CH_3), 33.8 (CH_2CH_2O), 34.7 (C-4), 38.0 (C-3), 46.6 (C-6), 63.4 (CH_2O), 69.7 (C-1), 89.8 (C-2), 82.0 [$OC(CH_3)_3$], 152.5 (CO); HRMS (ESI-TOF) *m/z* [M-2Boc+H]$^+$ calcd for $C_{17}H_{36}NOSi$, 298.2561; found, 298.2562.

*4.9.4. (R)-1-(2-Aminophenyl)-6,6-bis-[(tert-butoxycarbonyl)amino]-3-[(tert-butyldimethylsilyl)-oxy]propyl}-3-ethyl-1-hexyne (**24**)*

o-Iodoaniline (43 mg, 0.20 mmol), copper iodide (1.5 mg, 0.008 mmol), and tetrakis(triphenylphosphine)palladium (19 mg, 0.016 mmol) were added at rt under an argon atmosphere to a stirred solution of alkyne **23** (81 mg, 0.16 mmol) in anhydrous DMF (2 mL) and triethylamine (2 mL). After stirring at 80 ºC overnight, the mixture was filtered through a Celite® pad, and the organic solvent was evaporated. Flash column chromatography (98:2 to 9:1 hexane-EtOAc) of the residue gave aniline **24** (94 mg, 98%) as a yellow oil: $[\alpha]^{22}_D$ – 0.47 (*c* 1.5, MeOH); IR (film) *ν* 1695 (CO), 1738 (CO), 3377, (NH), 3478 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.04 [s, 6H, $Si(CH_3)_2$], 0.89 [s, 9H, $SiC(CH_3)$], 0.98 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.48 {s, 18H, $[OC(CH_3)_3]_2$}, 1.42-1.46 (m, 2H, CH_2CH_3), 1.46-1.56 (m, 4H, H-4, $CH_2CH_2CH_2O$), 1.57-1.60 (m, 2H, CH_2CH_2O), 1.65-1.73 (m, 2H, H-5), 3.54 (t, *J* = 7.5 Hz, 2H, H-6), 3.58 (t, *J* = 6.0 Hz, 2H, CH_2O), 6.57 (ddd, 1H, *J* = 7.2, 7.2, 0.6 Hz, H-5Ar), 6.61 (dt, 1H, *J* = 8.4, 0.6 Hz, H-3Ar), 7.05 (ddd, 1H, *J* = 8.4, 7.2, 1.6 Hz, H-4Ar), 7.20 (dd, 1H, *J* = 7.2, 1.6 Hz, H-6Ar); ^{13}C NMR ($CDCl_3$) δ –5.3 [$Si(CH_3)_2$], 8.8 (CH_3CH_2), 18.3 [$SiC(CH_3)_3$], 24.3 (C-5), 25.9 [$SiC(CH_3)_3$], 28.0 [$OC(CH_3)_3$], 28.1 (CH_2CH_2O), 30.9 (C-4), 34.2 ($CH_2CH_2CH_2O$), 35.0 (CH_2CH_3), 39.1 (C-3), 46.7 (C-6), 63.5 (CH_2O), 79.0 (C-1), 82.0 [$OC(CH_3)_3$], 100.9 (C-*i*), 100.9 (C-2), 114.0 (C-3Ar), 117.6 (C-5Ar), 128.7 (C-4Ar), 132.1 (C-6Ar), 147.5 (C-2Ar), 152.5 (CO); HRMS (ESI-TOF) *m/z* [M+Na]$^+$ calcd for $C_{33}H_{56}N_2NaO_5Si$, 611.3851; found, 611.3852.

*4.9.5. (R)-1-(tert-Butoxycarbony)lamino]-7-[(tert-butyldimethylsilyl)-oxy]-4-ethyl-4-(2-indolyl)-heptane (**25**)*

AgOTf (2.7 mg, 20% mmol) was added at rt under an argon atmosphere to a solution of aniline **24** (30 mg, 0.05 mmol) in anhydrous MeCN (1.1 mL), and the resulting mixture was stirred at reflux temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography (95:5 hexane-EtOAc) to afford indole **25** (17.4 mg, 58%) and alcohol **26** (3.4 mg, 18%) as yellow oils. **25**: $[\alpha]^{22}_D$ – 2.6 (*c* 1.2, MeOH); IR (film) *ν* 1665 (CO), 3345 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.04 [s, 6H, $Si(CH_3)_2$], 0.76 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.90 [s, 9H, $SiC(CH_3)_3$], 1.26-1.38 (m, 4H, H-2, H-3), 1.42 [s, 9H, $OC(CH_3)_3$], 1.62-1.70 (m, 2H, H-6), 1.70-1.75 (m, 4H, H-5, CH_2CH_3), 3.04 (m, 2H, H-1), 3.57 (t, *J* = 6.4 Hz, 2H, H-7), 4.42 (brs, 1H, NH), 6.26 (s, 1H, H3-ind), 7.09 (ddd, *J* = 7.6, 7.2, 1.0 Hz, 1H, H-5ind), 7.12 (ddd, *J* = 8.0, 7.6, 1.0 Hz, 1H, H6-ind), 7.30 (dd, *J* = 7.6, 1.2 Hz, 1H, H7-ind), 7.51 (dt, *J* = 7.6, 1.0 Hz, 1H, H4-ind), 8.10 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$) *δ* 7.9 (CH_3CH_2), 23.1 (C-2), 26.7 (C-3), 27.9 [$OC(CH_3)_3$], 29.2 (C-5), 32.6 (CH_2CH_3), 33.0 (C-6), 41.0 (C-4), 46.6 (C-1), 63.1 (C-7), 82.2 [$OC(CH_3)_3$], 100.3 (C3-ind), 110.5 (C7-ind), 119.4 (C4-ind), 119.8 (C5-ind), 120.9 (C6-ind), 128.3 (C3a-ind), 135.8 (C7a-ind), 144.8 (C2-ind), 152.7 (CO); HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{28}H_{49}N_2O_3$, 489.3507; found, 489.3499.

*4.9.6. (R)-7-[(tert-Butoxycarbonyl)amino]-4-ethyl-4-(2-indolyl)-1-heptanol (**26**)*

TBAF (0.16 mL, 0.16 mmol, 1.0 M in THF) was added under an inert atmosphere to a solution of indole **25** (44 mg, 0.07 mmol) in anhydrous THF (1.2 mL), and the mixture was stirred at rt for 3 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The organic extracts were washed with brine, dried, and concentrated. Flash chromatography (9:1 hexane-EtOAc) of the residue afforded alcohol **26** (24 mg, 86%) as a yellow foam: $[\alpha]^{22}_D$ – 24.2 (*c* 0.8, MeOH); IR (film) *ν* 1693 (CO), 3340 (NH, OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) *δ* 0.77 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.26-1.38 (m, 4H, H-5, H-6), 1.42 [s, 9H, $OC(CH_3)_3$], 1.49-1.77 (m, 6H, H-2, H-3, CH_2CH_3), 3.04 (m,

2H, H-7), 3.58 (t, *J* = 6.0 Hz, 2H, H-1), 4.51 (bs, 1H, NH), 6.27 (s, 1H, H3-ind), 7.04-7.13 (m, 2H, H5-ind, H6-ind), 7.30 (d, *J* = 8.0 Hz, 1H, H7-ind), 7.53 (d, *J* = 7.6 Hz, 1H, H4-ind), 8.11 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 7.9 (CH_3CH_2), 24.2 (C-6), 26.8 (C-5), 28.4 [OC(CH_3)$_3$], 29.0 (C-3), 32.4 (CH_2CH_3), 33.5 (C-2), 41.0 (masked, C-4), 41.0 (C-7), 63.0 (C-1), 79.2 [O*C*(CH_3)$_3$], 100.2 (C3-ind), 110.5 (C7-ind), 119.3 (C5-ind), 119.8 (C4-ind), 120.9 (C5-ind), 128.3 (C3a-ind), 135.9 (C7a-ind), 145.0 (C2-ind), 156.1 (CO); HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{22}H_{35}N_2O_3$, 375.2642; found, 375.2645.

*4.9.7. Kerr's intermediate: (R)-4-{3-[(tert-Butoxycarbonyl)amino]propyl}-4-ethyl-1-oxo-1,2,3,4-tetrahydropyrido[1,2-a]indole (**27**)*

Tetrapropylammonium perruthenate (1.7 mg, 0.005 mmol) was added to a solution of *N*-methylmorpholine *N*-oxide (35 mg, 0.30 mmol) and alcohol **26** (37 mg, 0.10 mmol) in anhydrous acetonitrile (2.5 mL) containing 4Å molecular sieves (60 mg). After stirring for 6 h at rt under an argon atmosphere, EtOAc (10 mL) was added and the mixture was filtered. The organic solution was washed with saturated aqueous $Na_2S_2O_3$, brine, and saturated aqueous $CuSO_4$. The organic layer was dried, filtered, and concentrated. Flash chromatography (9:1 to 8:2 hexane-EtOAc) of the residue afforded Kerr's intermediate **27** (17 mg, 47%) as a yellow oil: $[\alpha]^{22}_D$ + 5.3 (*c* 1.0 , $CHCl_3$), {lit.[12a] 74% ee; $[\alpha]^{22}_D$ +3.0 (*c* 1.0 , $CHCl_3$)}; IR (film) *v* 1693 (CO), 3340 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.43 [s, 9H, OC(CH_3)$_3$], 1.47-1.84 (m, 6H, $CH_2CH_2CH_2N$, CH_2CH_3), 1.97 (t, *J* = 6.8 Hz, 2H, H-3), 2.85 (t, *J* = 6.8 Hz, 2H, H-2), 3.11 (d, *J* = 5.6 Hz, 2H, CH_2N), 4.50 (bs, 1H, NH), 6.29 (s, 1H, CH-Ar), 7.23-7.30 (m, 2H, CH-Ar), 7.47 (d, *J* = 7.2 Hz, 1H, CH-Ar), 8.47 (d, *J* = 7.6 Hz, 1H, CH-Ar); ^{13}C NMR ($CDCl_3$) δ 8.0 (CH_3CH_2), 24.5 (CH_2CH_2N), 28.4 [OC(CH_3)$_3$], 30.0 (C-3), 30.0 (CH_3CH_2), 30.3 (C-2), 33.8 ($CH_2CH_2CH_2N$), 37.4 (C-4), 40.9 (CH_2N), 79.2 [O*C*(CH_3)$_3$], 105.1 (CH-Ar), 116.5 (CH-Ar), 119.8 (CH-Ar), 119.8 (CH-Ar), 123.9 (CH-Ar), 124.3 (C-Ar), 135.2 (C-Ar), 143.9 (C-Ar), 155.9 (OCO), 169.0 (CH_2CO); HRMS (ESI-TOF) *m/z* [M+Na]$^+$ calcd for $C_{22}H_{30}N_2NaO_3$, 393.2149; found, 393.2154.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online. Spectroscopic data of minor byproducts[32] and monocarbamates **23'** and **24'**, and copies of the ^{1}H and ^{13}C spectra of all compounds.

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