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Chiral Aminoalcohol-Derived δ-Lactams Provide Easy Access to Piperidines and Acyclic Five-Carbon Building Blocks Bearing a Tertiary and a Quaternary Stereocenter

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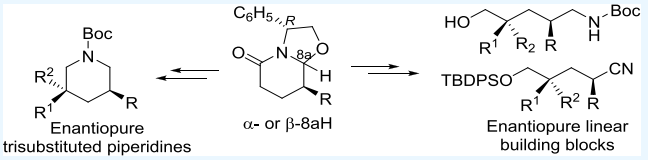
ABSTRACT: A procedure for the synthesis of enantiopure piperidines and acyclic building blocks (5-aminopentanols, *O*-protected 5-hydroxypentanenitriles) containing a tertiary and a quaternary stereocenter has been developed. Starting from a phenylglycinol- or aminoindanol-derived δ-lactam bearing an alkyl substituent at the α-position of the *N*,*O*-acetal carbon, easily accessible by a cyclocondensation reaction, the stereoselective dialkylation at the carbonyl α-position generates the quaternary stereocenter and the subsequent two-step reductive removal of the chiral inductor provides enantiopure 3,3,5-trisubstituted piperidines. Alternatively, the simultaneous reductive opening of the oxazolidine and piperidone rings of the dialkylated lactams followed by reductive or oxidative cleavage of the chiral inductor opens access to chiral 2,2,4-trisubstituted 5-amino-1-pentanols or 2,4,4-trisubstituted 5-hydroxypentanenitriles.



1. INTRODUCTION

Acyclic chiral building blocks play an important role in organic synthesis, in particular for the total synthesis of natural products and bioactive compounds. Of special interest are linear nitrogen-containing fragments possessing more than one stereocenter or an all-carbon quaternary stereocenter.[1] An effective way to access these chiral acyclic systems consists of the stereocontrolled generation of the required stereocenters from a chiral cyclic substrate,[2] taking advantage of its less conformational flexibility, and the subsequent ring-opening of the resulting substituted cyclic product.

In this context, aminoalcohol-derived oxazolopiperidone lactams have proven to be versatile chiral scaffolds for the enantioselective synthesis of a wide range of chiral molecules,[3] including those containing quaternary carbon stereocenters.[3a,4] Due to their functionality and conformational rigidity, substituents can be regio- and stereoselectively installed at the different positions of the piperidine ring to provide, after cleavage of the oxazolidine ring and removal of the aminoalcohol moiety, enantiopure piperidine derivatives bearing virtually any type of substitution pattern,[3d,e] which can be further elaborated into structurally diverse piperidine-containing alkaloids and bioactive compounds.[5] Alternatively, simultaneous opening of the oxazolidine and lactam rings provides five-carbon chiral linear building blocks,[6] which have been successfully employed in the synthesis of complex natural products.[6b,7]

Taking a further step toward greater structural and stereochemical complexity, we report herein the generation of enantiopure 3,3,5-trisubstituted piperidines and acyclic five-carbon, nitrogen-containing building blocks (1,5-aminoalcohols, 5-hydroxypentanenitriles) bearing two stereocenters, one of them quaternary, from chiral aminoalcohol-derived δ-lactams.

2. RESULTS AND DISCUSSION

Initially, we focused our attention on the dialkylation of the known phenylglycinol-derived lactam **1a**, which incorporates a methyl substituent with a well-defined configuration at the α-position of the *N*,*O*-acetal carbon. This lactam was easily accessible in 74% yield by a cyclocondensation reaction of (*R*)-phenylglycinol with methyl 4-methyl-5-oxopentanoate (**2**), in a process that involves a dynamic kinetic resolution of the racemic substrate.[7a] Treatment of a THF solution of lactam **1a** with LiHMDS at −78 °C, followed by addition of allyl bromide at the same temperature, afforded the alkylated products **3** and 6-epi-**3** in 82% yield as an 8:2 epimeric mixture[8] at the new stereogenic center (Scheme 1), in which endo isomer **3** was predominant. A similar endo facial selectivity was observed in the alkylation with methyl iodide, leading to lactams **4** (9:1 endo/exo ratio) in 70% yield.

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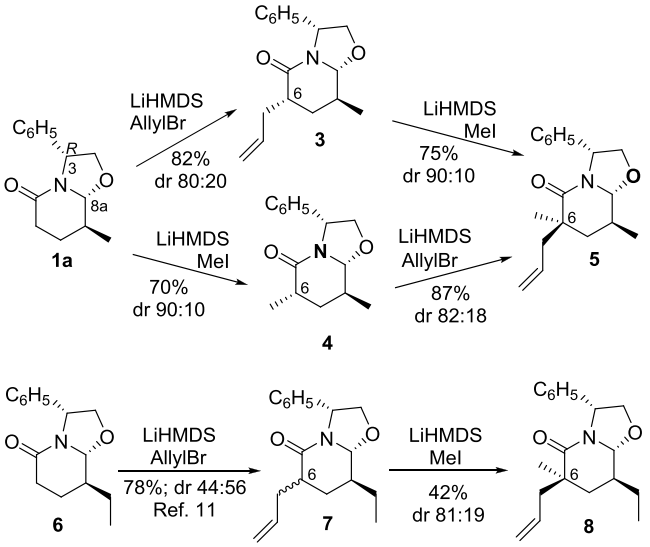
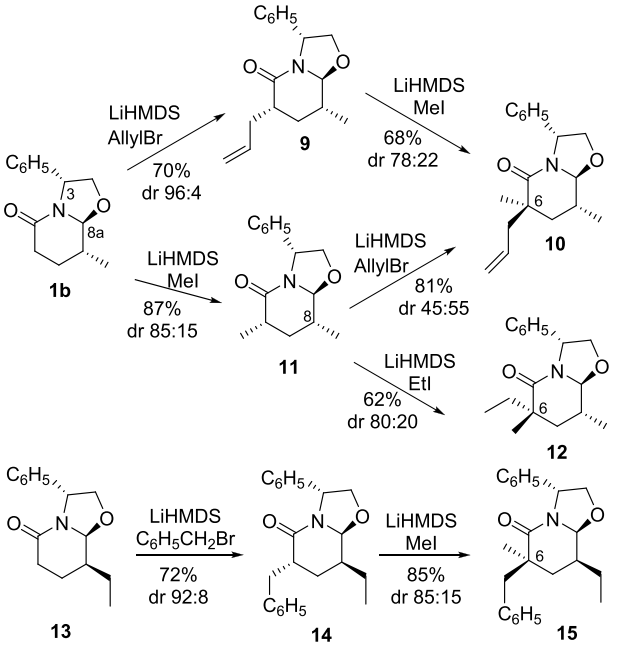
Scheme 1. Dialkylation Reactions from 3,8a-*cis* Phenylglycinol-Derived Lactams



Scheme 2. Dialkylation Reactions from 3,8a-*trans* Phenylglycinol-Derived Lactams



As could be expected,[9] in both cases, the alkylation took place predominantly from the endo face of the lactam, i.e., *trans* with respect to the hydrogen at the C-8a position. The configurational assignment of exo/endo epimers of lactams **3** and **4** was effected by ^{13}C NMR spectroscopy: the shielding of C-6 and C-8 in the endo isomers as compared with the exo (6-epi series) isomers was of diagnostic value.

The introduction of the second substituent was performed from the epimeric mixtures of the above monoalkylated lactams under the same reaction conditions used in the monoalkylation reactions (LiHMDS, −78 °C). The alkylation of **3** with methyl iodide took place in 75% yield with good endo stereofacial selectivity (dr 9:1) to give trisubstituted lactam **5** as the major product. The absolute configuration of the new quaternary stereocenter of this lactam was unambiguously established by X-ray crystallographic analysis.

Rather surprisingly, treatment of the lithium enolate of lactams **4** with allyl bromide afforded with good stereoselectivity (dr 82:18; 87% yield) the same lactam **5**, arising in this case from alkylation on the exo face of the enolate.[10] Interestingly, the two sequences afforded a dialkylated lactam with the same absolute configuration at the quaternary stereocenter. The expected endo facial selectivity was also observed in the methylation of a C-6 epimeric mixture of lactams **7** (prepared from **6** as previously described[11]), which afforded lactam **8** as the major product (dr 81:19; 42% yield).

Bearing in mind that the configuration of the C-8a stereocenter of oxazolopiperidone lactams exerts a dramatic influence on the stereoselectivity of alkylation reactions,[9] we decided to study the stereochemical outcome of dialkylation reactions from the 3,8a-*trans* phenylglycinol-derived lactam **1b**, which was prepared by epimerization of **1a** under acidic conditions (see the Supporting Information). The initial alkylation of the enolate of **1b** with allyl bromide occurred in good yield (70%) and excellent stereoselectivity (96:4 exo/endo ratio) providing almost exclusively lactam **9** (Scheme 2). A subsequent alkylation with methyl iodide took place predominantly on the exo face to give (68%) trisubstituted lactam **10** and its 6-epimer (78:22 ratio). In contrast, indicating that the order of introduction of the substituents has a dramatic influence on the stereoselectivity of the dialkylation, a sequential alkylation of **1b** with methyl iodide and allyl bromide led to a nearly equimolecular mixture of lactams **10** and 6-epi-**10** (45:55 ratio). As anticipated,[9] the initial enolate alkylation of **1b** with methyl iodide took place with exo facial selectivity (87%; 85:15 exo/endo ratio) to yield lactam **11** as the major product, although, as in the allylation of 3,8a-*cis* lactam **4**, the subsequent allylation of **11** occurred with an unexpected stereoselectivity. Nevertheless, predictably, the alkylation of **11** with ethyl iodide occurred with the same exo stereoselectivity as the methylation of **9**, affording (62% yield) trisubstituted lactams **12** and 6-epi-**12** (80:20 ratio),[12] a result similar to that observed from the 8-demethyl analogue of **11**.[7b] The same stereochemical outcome was observed in the dialkylation of the known[13] 8-ethyl substituted lactam **13**: Both the initial benzylation with benzyl bromide and the subsequent generation of the quaternary stereocenter by alkylation of the resulting substituted lactam **14** (72% yield; dr 92:8) with methyl iodide took place in good yield and exo facial selectivity to provide trisubstituted lactam **15** (85% yield; dr 85:15) as the major product.

In order to analyze the influence exerted on the stereoselectivity by the amino alcohol moiety, we then studied similar dialkylations using chiral lactam **16** derived from (1*R*,2*S*)-1-amino-2-indanol,[14] a conformationally rigid analogue of phenylglycinol. The results are outlined in Scheme 3. This lactam, in which the two H atoms at the carbons α to the nitrogen are *cis*, can be envisaged as a rigid analogue of phenylglycinol-derived lactam **1a** and was prepared in 48% yield by cyclocondensation of *cis*-1-amino-2-indanol with racemic δ-oxoester **2**. Significant amounts of the diastereomers 1-epi-**16** (19%) and 1,11a-diepi-**16** (10%) were also isolated (see the Supporting Information).

As in the case of **1a**, we studied the facial selectivity in the generation of the quaternary stereocenter by introduction of allyl and methyl substituents. When the initial alkylation of the enolate of **16** was performed with allyl tosylate, the subsequent alkylation of the resulting allyl lactam **17** (75% yield; 70:30

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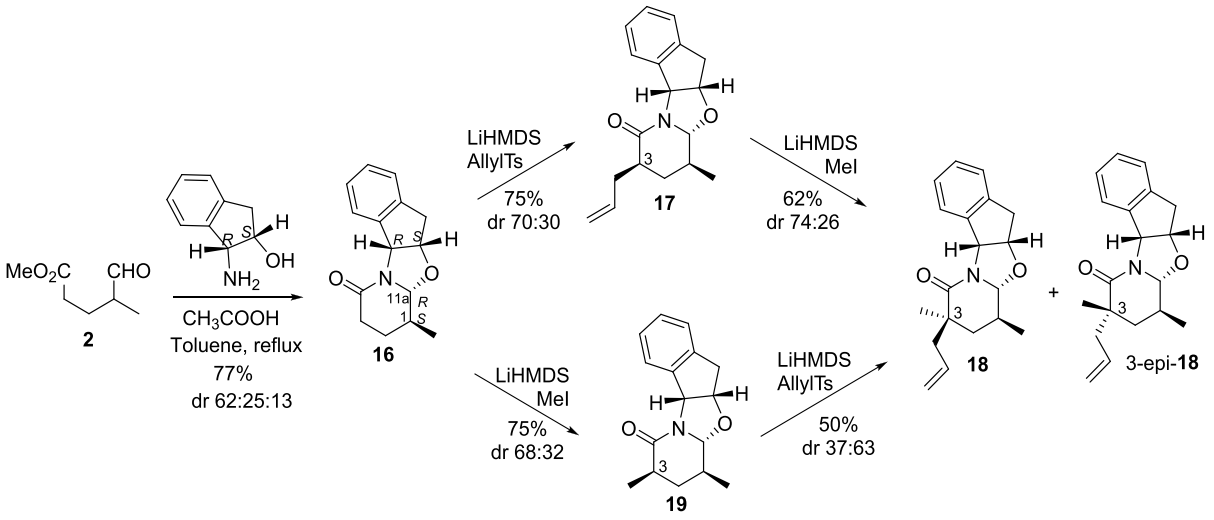
Scheme 3. Dialkylation Reactions from Aminoindanol-Derived Lactams

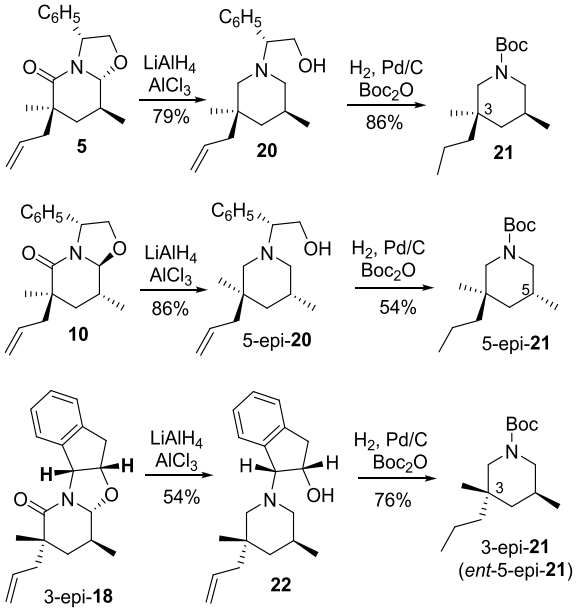


exo/endo ratio)[15,16] with methyl iodide took place with endo facial selectivity (dr 74:26) to give lactams **18** and 3-epi-**18** in 62% yield.[17] By reversing the order of introduction of the substituents, after the initial alkylation of the enolate of **16** with methyl iodide to give an epimeric mixture of **19** and 3-epi-**19** (75% yield; 68:32 exo/endo ratio),[18] the quaternary stereocenter was generated by reaction with allyl tosylate, also with endo facial selectivity (50% yield; endo/exo ratio: 63:37), to give lactam 3-epi-**18** as the major product.[19] Interestingly, by selecting the appropriate order of the alkylations, either of the two epimers at the new quaternary stereocenter can be obtained as the major product. It is worth mentioning that the dialkylation of the above aminoindanol-derived lactams takes place predominantly on the endo face, as in the dialkylations of phenylglycinol-derived lactam **1a**. However, taking into account that the stereoselectivity in both the cyclocondensation reaction leading to the aminoindanol-derived lactam **16** and the generation of the quaternary stereocenter from this lactam was lower than when operating from phenylglycinol-derived lactam **1a**, no additional studies were performed in this series.

To illustrate the potential of the procedure in providing stereochemical diversity, lactams **5** and **10** were converted to the corresponding piperidines **20** and 5-epi-**20** by treatment with alane (generated in situ from $LiAlH_4$ and $AlCl_3$), which brought about the reduction of the amide carbonyl and the reductive opening of the oxazolidine ring (Scheme 4). A subsequent debenzylation by hydrogenolysis in the presence of Boc_2O provided the respective trisubstituted piperidine **21** and its epimer at the quaternary center 5-epi-**21**. A similar two-step sequence from the tetracyclic aminoindanol-derived lactam 3-epi-**18** led to piperidine 3-epi-**21** (*ent*-5-epi-**21**). In this way, the procedure provides access to three stereoisomeric piperidines bearing a tertiary and a quaternary stereocenter. Furthermore, taking into account that both enantiomers of phenylglycinol are commercially available, by selection of the appropriate *R* or *S* enantiomer of the aminoalcohol, 3,3,5-trisubstituted piperidines are accessible in both enantiomeric series.

Finally, we decided to convert some of the above tricyclic lactams to acyclic chiral building blocks. Simultaneous reductive cleavage of both the oxazolidine and piperidone rings was satisfactorily accomplished by treatment of lactams

Scheme 4. Access to Diastereomeric Piperidines Containing Tertiary and Quaternary Stereocenters



10, 6-epi-**10**, **12**, and **15** with lithium amidotrihydroborate ($LiNH_2BH_3$),[20] generated in situ by deprotonation of the borane-ammonia complex with *n*-BuLi (Scheme 5). After protection of the secondary amino group of the resulting acyclic amino diols (**23**, 2-epi-**23** and **24**) as an *N*-Boc derivative (compounds **26**, 2-epi-**26** and **27**), the reductive removal of the benzylic substituent was performed in excellent yield by treatment with sodium in liquid NH_3 at −33 °C for short reaction times (seconds) to give the respective 5-amino-1-pentanols **28**, 2-epi-**28**, and **29**, all of them containing a tertiary and a quaternary stereocenter. As illustrated by the preparation of **28** and 2-epi-**28**, this methodology tolerates the presence of an alkene group.

Acyclic amino diols **24** and **25** were also envisaged as precursors of related five-carbon building blocks, bearing a nitrile functionality. This was achieved in two steps: protection of the hydroxy groups as TBDPS ethers (compounds **30** and **31**) followed by oxidative removal of the phenylethanol moiety

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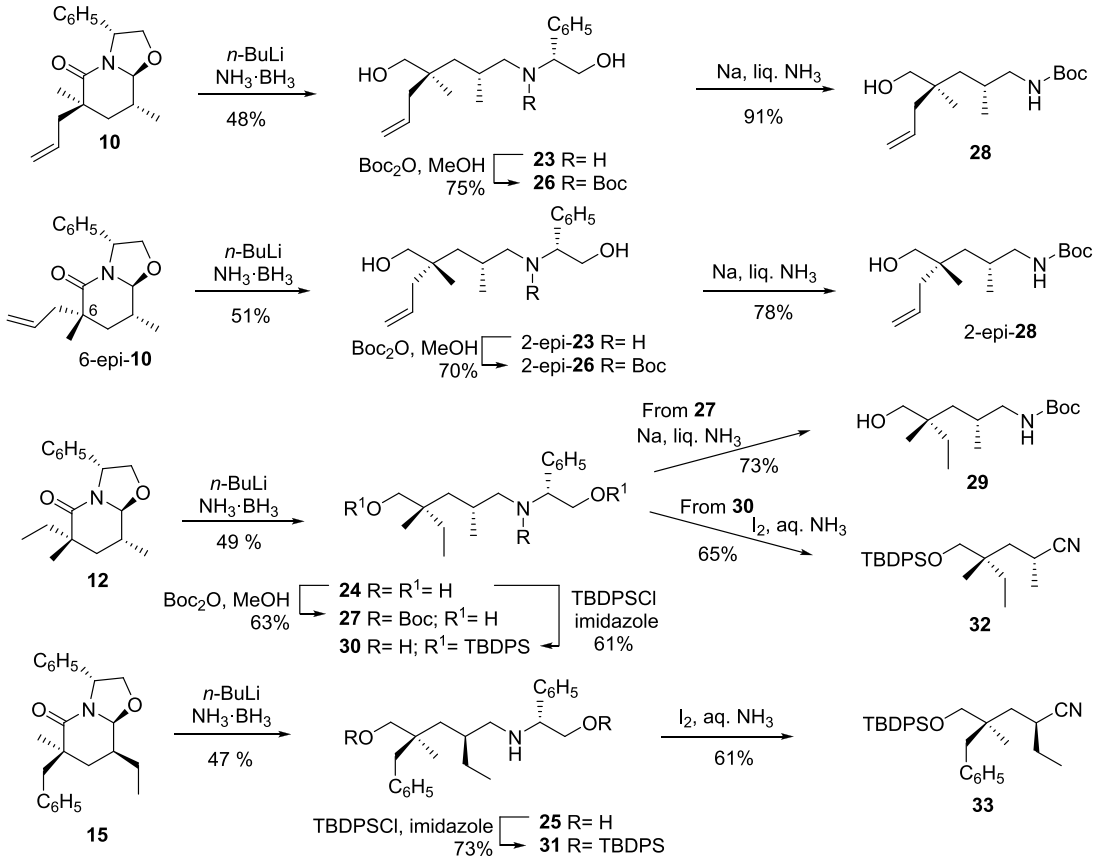
Scheme 5. Access to Acyclic Chiral Building Blocks Containing Tertiary and Quaternary Stereocenters



using molecular iodine in aqueous ammonia[21] gave the *O*-protected hydroxy nitriles **32** and **33**.

3. CONCLUSIONS

Chiral aminoalcohol-derived oxazolopiperidone lactams constitute useful starting materials for the preparation of enantiopure piperidines and linear nitrogen-containing five-carbon building blocks bearing a tertiary and a quaternary stereocenter. In the phenylglycinol series, starting from 8-substituted lactams, easily accessible by cyclocondensation reactions, the stereoselective dialkylation at the carbonyl α-position generates the quaternary stereocenter and the subsequent two-step reductive removal of the chiral inductor provides enantiopure 3,3,5-trisubstituted piperidines. The stereoselectivity of the dialkylation process mainly depends on the relative H-3/H-8a configuration of the starting lactam and the order of introduction of the two substituents. The use of aminoindanol-derived instead of phenylglycinol-derived lactams does not represent an improvement in terms of stereoselectivity and chemical yield. On the other hand, the simultaneous reductive ($LiNH_2BH_3$) opening of the oxazolidine and piperidone rings of the dialkylated lactams followed by reductive (Na, liq. NH_3) or oxidative (I_2, aq. NH_3) cleavage of the chiral inductor opens access to 5-amino-1-pentanols or *O*-protected 5-hydroxypentanenitriles also containing a tertiary and a quaternary stereocenter. By the appropriate choice of the alkylating reagents, the methodology described herein could be applied to the synthesis of a variety of related enantiopure trisubstituted piperidines and acyclic aminoalcohols and hydroxynitriles, thus significantly expanding the synthetic potential of phenylglycinol-derived oxazolopiperidone lactams.

4. EXPERIMENTAL SECTION

4.1. General Information. 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 accomplished with a rotatory evaporator. Drying of organic extracts during the workup 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). Diastereomeric ratios were calculated by ^1H NMR from the crude reaction mixtures. NMR spectra were recorded on a Varian VNMRS-400 or Mercury 400 spectrometer [400 MHz (^1H) 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 FTIR, and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured on a Perkin-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 Monoalkylation Reactions. A solution of the lactam (**1a**, **1b**, **6**, **13**, or **16**; 1

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mmol) in anhydrous THF was added to a cooled (−78 °C) solution of LiHMDS (1.0 M in THF, 1.5 mmol) in anhydrous THF under an argon atmosphere. After stirring the solution for 2 h, the alkylating reagent (2.5 mmol) was added and stirring was continued at this temperature for an additional 3 h. The reaction was quenched by the addition of saturated aqueous NaCl, 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 (SiO_2 previously washed with 9:1 hexane−Et_3N).

*4.2.1. (3R,6S,8S,8aR)-6-Allyl-8-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**3**) and Its (3R,6R,8S,8aR) Diastereomer (6-Epi-**3**).* Following the general procedure, from lactam **1a**[7a] (1.8 g, 7.8 mmol) in THF (20 mL), LiHMDS (11 mL, 11 mmol) in THF (65 mL), and allyl bromide (1.69 mL, 19.5 mmol), lactam **3** (1.38 g, 66%) and its diastereomer 6-epi-**3** (350 mg, 16%) were obtained after flash chromatography (9:1 to 1:1 hexane−EtOAc).[8] **3**: IR (film) ν 2922, 1656, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.20 (d, J = 6.4 Hz, 3H, CH_3), 1.27−1.37 (m, 1H, H-7), 1.91−1.98 (m, 1H, H-7), 1.99−2.04 (m, 1H, H-8), 2.22−2.29 (m, 1H, =CHCH_2), 2.33−2.41 (m, 1H, C-6), 2.57−2.63 (m, 1H, =CHCH_2), 4.02 (dd, J = 9.2, 1.2 Hz, 1H, H-2), 4.15 (dd, J = 9.2, 6.8 Hz, 1H, H-2), 4.42 (d, J = 8.8 Hz, 1H, H-8a), 4.89 (dd, J = 6.8, 1.2 Hz, 1H, H-3), 5.03−5.08 (m, 2H, CH_2=), 5.67−5.77 (m, 1H, CH_2=C*H*), 7.21−7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.0 (CH_3), 32.9 (C-7), 34.4 (C-8), 35.8 (=CHCH_2), 41.3 (C-6), 59.4 (C-3), 73.8 (C-2), 93.4 (C-8a), 117.2 (CH_2=), 126.4 (C-Ar), 126.4 (C-Ar), 127.5 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 135.8 (CH_2=C*H*), 141.6 (C-Ar), 168.9 (CO); $[\alpha]^{22}_D$ −4.0 (*c* 1.3, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{17}H_{22}NO_2$ 272.1645; found, 272.1644. 6-epi-**3**: IR (film) ν 2933, 1651, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.17 (d, J = 6.4 Hz, 3H, CH_3), 1.53−1.61 (m, 1H, H-7), 1.81−1.86 (m, 1H, H-7), 2.04−2.10 (m, 1H, H-8), 2.13−2.21 (m, 1H, =CHCH_2), 2.36−2.40 (m, 1H, H-6), 2.40−2.48 (m, 1H, =CHCH_2), 4.02 (d, J = 9.2 Hz, 1H, H-2), 4.15 (dd, J = 9.2, 6.8 Hz, 1H, H-2), 4.45 (d, J = 8.8 Hz, 1H, H-8a), 4.92 (d, J = 6.0 Hz, 1H, H-3), 4.99−5.03 (m, 2H, CH_2=), 5.63−5.73 (m, 1H, CH_2=C*H*), 7.22−7.33 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.8 (CH_3), 31.0 (C-7), 31.3 (C-8), 37.1 (=CHCH_2), 39.9 (C-6), 59.1 (C-3), 74.0 (C-2), 93.5 (C-8a), 117.1 (CH_2=), 126.3 (C-Ar), 126.3 (C-Ar), 127.5 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 136.2 (=*C*H), 141.6 (C-Ar), 169.7 (CO); $[\alpha]^{22}_D$ + 3.6 (*c* 1.6, $CHCl_3$); mp 73−80 °C; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{17}H_{22}NO_2$ 272.1645; found, 272.1647.

*4.2.2. (3R,6S,8S,8aR)-6,8-Dimethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**4**).* Following the general procedure, from lactam **1a**[7a] (1.89 g, 8.15 mmol) in THF (21 mL), LiHMDS (12.2 mL, 12.2 mmol) in THF (68 mL), and methyl iodide (1.3 mL, 20.4 mmol), lactam **4** (1.26 g, 63%) and its diastereomer 6-epi-**4** (140 mg, 7%) were obtained after flash chromatography (9:1 hexane−EtOAc).[10] **4**: IR (film) ν 2930, 1657, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.16 (d, J = 7.6 Hz, 3H, C6-CH_3), 1.19 (d, J = 6.8 Hz, 1H, C8-CH_3), 1.68−1.72 (m, 2H, H-7), 2.04−2.18 (m, 1H, H-8), 2.42−2.50 (m, 1H, H-6), 4.00 (dd, J = 8.8, 1.2 Hz, 1H, H-2), 4.13 (dd, J = 8.8, 6.8 Hz, 1H, H-2), 4.45 (d, J = 8.8 Hz, 1H, H-8a), 4.91 (dd, J = 6.8, 1.2 Hz, 1H, H-3), 7.21−7.33 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.9 (C8-CH_3), 18.8 (C6-CH_3), 31.0 (C-8), 34.7 (C-7), 35.2 (C-6), 58.8 (C-3), 74.0 (C-2), 93.6 (C-8a), 126.2 (C-Ar), 126.2 (C-Ar), 127.4 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 141.7 (C-Ar), 170.9 (CO); $[\alpha]^{22}_D$ −3.3 (*c* 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{15}H_{20}NO_2$ 246.1489; found, 246.1491.

*4.2.3. (3R,6S,8R,8aS)-6-Allyl-8-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**9**).* Following the general procedure, from lactam **1b** (1.5 g, 6.49 mmol; see the Supporting Information) in THF (17 mL), LiHMDS (10 mL, 10.0 mmol) in THF (60 mL), and allyl bromide (1.41 mL, 16.2 mmol), lactam **9** (1.1 g, 63%) and a 62:38 mixture of **9** and its diastereomer 6-epi-**9** (130 mg, 7%) were obtained after flash chromatography (9:1 to 1:1 hexane−EtOAc). **9**: IR (film) ν 1657 (NCO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.17 (d, J = 4.0 Hz, 3H, CH_3), 1.40 (m, 1H, H-7), 1.71 (m, 1H, H-8), 1.84 (ddd, J = 13.8, 6.4, 2.8 Hz, 1H, H-7), 2.37 (m, 1H, CH_2C-6), 2.49 (m, 1H, H-6), 2.58 (m, 1H, CH_2C-6), 3.72 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.48 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.58 (d, J = 8.0 Hz, 1H, H-8a), 5.05−5.10 (m, 2H, H_2C=), 5.25 (t, J = 8.0 Hz, 1H, H-3), 5.67−5.77 (m, 1H, CH=), 7.22−7.28 (m, 3H, ArH), 7.32−7.35 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (CH_3C-8), 31.6 (C-7), 34.5 (C-8), 36.8 (C6-CH_2), 41.6 (C-6), 58.7 (C-3), 72.8 (C-2), 93.9 (C-8a), 117.5 (CH_2=), 125.9 (C-Ar), 128.8 (C-Ar), 127.5 (C-Ar), 135.3 (CH=), 139.6 (C-Ar), 170.9 (NCO); $[\alpha]^{22}_D$ −62.78 (*c* 1.16, MeOH); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{17}H_{22}NO_2$ 272.1645; found 272.1654.

*4.2.4. (3R,6S,8R,8aS)-6,8-Dimethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**11**) and Its (3R,6R,8R,8aS) Diastereomer (6-Epi-**11**).* Following the general procedure, from lactam **1b** (1.86 g, 8.03 mmol; see the Supporting Information) in anhydrous THF (21 mL), LiHMDS (12.0 mL, 12.0 mmol) in THF (67 mL), and methyl iodide (1.25 mL, 20.1 mmol), lactam **11** (1.3 g, 66%) and a 37:63 mixture of **11** and its diastereomer 6-epi-**11** (410 mg, 21%) were obtained after flash chromatography (9:1 to 7:3 hexane−EtOAc).[12] **11**: IR (film) ν 1656 (NCO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.17 (d, J = 6.2 Hz, 3H, C8-CH_3), 1.25 (d, J = 7.0 Hz, 3H, C6-CH_3), 1.36 (m, 1H, H-7), 1.74 (m, 1H, H-8), 1.90 (ddd, J = 13.7, 6.2, 2.9 Hz, 1H, H-7), 2.45 (ddd, J = 18.4, 13.7, 7.0 Hz, 1H, H-6), 3.74 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.47 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.60 (d, J = 8.4 Hz, 1H, H-8a), 5.24 (t, J = 7.8 Hz, 1H, H-3), 7.23−7.27 (m, 3H, ArH), 7.31−7.35 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (C8-CH_3), 18.3 (C6-CH_3), 34.6 (C-8), 35.0 (C-7), 37.2 (C-6), 58.4 (C-3), 72.7 (C-2), 93.9 (C-8a), 125.9 (C-Ar), 128.8 (C-Ar), 127.5 (C-Ar), 139.7 (C-Ar), 172.1 (NCO); $[\alpha]^{22}_D$ −136.1 (*c* 1.05, MeOH); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{15}H_{20}NO_2$ 246.1489; found 246.1489.

*4.2.5. (3R,6R,8S,8aS)-6-Benzyl-8-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**14**).* Following the general procedure, from lactam **13**[13] (112 mg, 0.46 mmol) in THF (2 mL), LiHMDS (0.68 mL 0.68 mmol) in THF (3.8 mL), and benzyl bromide (0.14 mL, 1.14 mmol), lactam **14** (102 mg, 70%) and its diastereomer 6-epi-**14** (9 mg, 2%) were obtained after flash chromatography (98:2 to 9:1 hexane−EtOAc). **14**: IR (film) ν 1651 (NCO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.05−1.17 (m, 1H, CH_3CH_2), 1.52 (ddd, J = 14.4, 11.6, 2.8 Hz, 1H, H-7), 1.64 (m, 1H, CH_3CH_2), 1.81 (ddd, J = 14.4, 10.8, 4.4 Hz, 1H, H-7), 2.12 (m, 1H, H-8), 2.64 (m, 1H,

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H-6), 2.97 (dd, J = 13.5, 4.6 Hz, 1H, CH_2Ph), 3.06 (dd, J = 13.5, 8.0 Hz, 1H, CH_2Ph), 3.68 (dd, J = 9.0, 7.6 Hz, 1H, H-2), 4.39 (dd, J = 9.0, 7.6 Hz, 1H, H-2), 4.95 (d, J = 4.4 Hz, 1H, H-9), 5.18 (t, J = 7.6 Hz, H-3), 7.08−7.35 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.1 (CH_3CH_2), 16.6 (CH_2CH_3), 25.1 (C-7), 36.0 (C-8), 37.7 (CH_2Ar), 38.3 (C-6), 58.4 (C-3), 72.6 (C-2), 90.3 (C-9), 125.9 (C-Ar), 128.1 (C-Ar), 128.5 (C-Ar), 129.3 (C-Ar), 126.1 (C-Ar), 127.3 (C-Ar), 138.6 (C-Ar), 139.3 (C-Ar), 170.3 (NCO); $[\alpha]^{22}_D$ + 17.9 (c 1.19, $CHCl_3$); mp 114−116 °C; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{22}H_{26}NO_2$ $[M + H]^+$ 336.1958; found 336.1956.

*4.2.6. (1S,3R,5aR,10aS,11aR)-3-Allyl-1-methyl-4-oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo-[3,2-a]pyridine (**17**) and Its (1S,3S,5aR,10aS,11aR) Diastereomer (3-Epi-**17**).* Following the general procedure, from lactam **16** (803 mg, 3.3 mmol) in THF (8.5 mL), LiHMDS (4.95 mL, 4.95 mmol) in THF (27 mL), and allyl tosylate (1.50 mL, 8.25 mmol), lactam **17** (492 mg, 53%) and its diastereomer 3-epi-**17** (210 mg, 22%) were obtained after flash chromatography (95:5 to 1:1 hexane−EtOAc).[16] **17**: IR (film) ν 2922, 1648, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 1.02 (d, J = 6.0 Hz, 3H, CH_3), 1.46−1.54 (m, 1H, H-2), 1.65−1.70 (m, 2H, H-1, H-2), 2.17−2.25 (m, 1H, =CHCH_2), 2.43−2.46 (m, 1H, H-3), 2.57−2.63 (m, 1H, =CHCH_2), 3.20 (d, J = 2.4 Hz, 2H, H-10), 4.46 (d, J = 8.4 Hz, 1H, H-11a), 4.79 (m, 1H, H-10a), 4.99−5.03 (m, 2H, CH_2=), 5.50 (d, J = 5.2 Hz, 1H, H-5a), 5.69−5.79 (m, 1H, CH_2=CH), 7.17−7.27 (m, 3H, ArH), 7.90 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.7 (CH_3), 31.0 (C-1/2), 31.2 (C-1/2), 36.5 (C-10), 37.6 (=CHCH_2), 40.0 (C-3), 64.5 (C-5a), 81.4 (C-10a), 93.2 (C-11a), 117.1 (CH_2=), 124.8 (C-Ar), 127.4 (C-Ar), 128.2 (C-Ar), 128.4 (C-Ar), 136.3 (CH_2=CH), 140.1 (C-Ar), 141.8 (C-Ar), 170.1 (CO); $[\alpha]^{22}_D$ −12.5 (c 0.8, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{18}H_{22}NO_2$, 284.1645 found, 284.1643. 3-epi-**17**: IR (film) ν 2917, 1648, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 1.04 (d, J = 6.4 Hz, 3H, CH_3), 1.19−1.29 (q, J = 11.6 Hz, 1H, H-2), 1.63−1.71 (m, 1H, H-1), 1.84−1.90 (ddd, J = 14.0, 6.8, 3.2 Hz, 1H, H-2), 2.31−2.38 (m, 1H, =CHCH_2), 2.42−2.50 (m, 1H, H-3), 2.68−2.74 (m, 1H, =CHCH_2), 3.20 (d, J = 2.8 Hz, 2H, H-10), 4.42 (d, J = 9.2 Hz, 1H, H-11a), 4.77 (m, 1H, H-10a), 5.06−5.13 (m, 2H, CH_2=), 5.49 (d, J = 5.6 Hz, 1H, H-5a), 5.72−5.83 (m, 1H, CH_2=CH), 7.16−7.30 (m, 3H, ArH), 8.00 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.4 (CH_3), 33.0 (C-2), 34.1 (C-1), 35.9 (=CHCH_2), 36.5 (C-10), 41.1 (C-3), 64.9 (C-5a), 81.3 (C-10a), 93.1 (C-11a), 117.3 (CH_2=), 124.9 (C-Ar), 127.4 (C-Ar), 128.5 (C-Ar), 128.8 (C-Ar), 135.8 (CH_2=CH), 140.3 (C-Ar), 141.5 (C-Ar), 169.8 (CO); $[\alpha]^{22}_D$ −18.2 (c 1.3, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{18}H_{22}NO_2$, 284.1645; found, 284.1644.

*4.2.7. (1S,3R,5aR,10aS,11aR)-1,3-Dimethyl-4-oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo-[3,2-a]pyridine (**19**) and Its (1S,3S,5aR,10aS,11aR) Diastereomer (3-Epi-**19**).* Following the general procedure, from lactam **16** (470 mg, 1.93 mmol) in THF (5 mL), LiHMDS (2.9 mL, 2.9 mmol) in THF (16 mL), and methyl iodide (0.31 mL, 4.83 mmol), lactam **19** (252 mg, 51%) and its diastereomer 3-epi-**19** (119 mg, 24%) were obtained as white solids after flash chromatography (95:5 to 7:3 hexane−EtOAc). **19**: IR (film) ν 2924, 1648, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 1.09 (d, J = 6.4 Hz, 3H, C1-CH_3), 1.28 (d, J = 7.2, 3H, C3-CH_3), 1.63−1.68 (m, 2H, H-2), 1.74−1.81 (m, 1H, H-1), 2.52−2.59 (m, 1H, H-3), 3.25 (d, J = 2.8 Hz, 2H, H-10), 4.51 (d, J = 8.8 Hz, 1H, H-11a), 4.84 (m, 1H, H-10a), 5.53 (d, J = 5.6 Hz, 1H, H-5a), 7.21−7.32 (m, 3H, ArH), 7.94 (d, J = 7.6 Hz, 1H, H-5); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.8 (C1-CH_3), 19.2 (C3-CH_3), 31.0 (C-1), 34.7 (C-2), 35.4 (C-3), 36.4 (C-10), 64.4 (C-5a), 81.4 (C-10a), 93.2 (C-11a), 124.8 (C-Ar), 127.4 (C-Ar), 128.1 (C-Ar), 128.4 (C-Ar), 140.1 (C-Ar), 141.8 (C-Ar), 172.2 (CO); $[\alpha]^{22}_D$ −17.3 (c 1.0, $CHCl_3$); mp 143−147 °C; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{16}H_{20}NO_2$, 258.1489; found, 258.1486. 3-epi-**19**: IR (film) ν 2926, 1649, 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 1.04 (d, J = 6.4 Hz, 3H, C1-CH_3), 1.17−1.24 (m, 1H, H-2), 1.27 (d, J = 7.2 Hz, 3H, C3-CH_3), 1.67−1.74 (m, 1H, H-1), 1.92−1.96 (m, 1H, H-2), 2.38−2.48 (m, 1H, H-3), 3.20 (d, 2H, J = 3.2 Hz, H-10), 4.43 (d, 1H, J = 9.2 Hz, H-11a), 4.79 (m, 1H, H-10a), 5.48 (d, 1H, J = 5.6 Hz, H-5a), 7.16−7.25 (m, 3H, ArH), 8.00 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.4 (C1-CH_3), 17.1 (C3-CH_3), 34.2 (C-1), 36.4 (C-2), 36.5 (C-10), 36.7 (C-3), 64.7 (C-5a), 81.4 (C-10a), 93.3 (C-11a), 124.8 (C-Ar), 127.3 (C-Ar), 128.5 (C-Ar), 128.8 (C-Ar), 140.3 (C-Ar), 141.5 (C-Ar), 171.2 (CO). $[\alpha]^{22}_D$ −16.9 (c 1.0, $CHCl_3$); mp 115−117 °C; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{16}H_{20}NO_2$, 258.1489; found, 258.1493.

4.3. General Procedure for the Dialkylation Reactions. A solution of epimeric mixture of the lactam (**3**, **4**, **7**, **9**, **11**, **14**, **17**, or **19**; 1 mmol) in anhydrous THF was added to a cooled (−78 °C) solution of LiHMDS (1.0 M in THF, 3 or 4.2 mmol) in anhydrous THF under an argon atmosphere. The cooled solution was stirred for 2 h, the alkylating reagent (3 mmol) was added at −78 °C, and stirring was continued at this temperature for an additional 3 h. The reaction was quenched by the addition of saturated aqueous NaCl at room temperature, 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.

*4.3.1. (3R,6R,8S,8aR)-6-Allyl-6,8-dimethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**5**) and Its (3R,6S,8S,8aR) Diastereomer (6-Epi-**5**).* From lactams **3**: Following the general procedure, from a mixture of lactams **3** and 6-epi-**3** (200 mg, 0.74 mmol) in THF (4 mL), LiHMDS (2.22 mL, 2.22 mmol) in THF (6.6 mL), and methyl iodide (0.14 mL, 2.29 mmol), lactam **5** (142 mg, 68%) and its diastereomer 6-epi-**5** (15 mg, 7%) were obtained after flash chromatography (9:1 to 1:1 hexane−EtOAc). From lactams **4**: Following the general procedure, from a mixture of lactams **4** and 6-epi-4 (99 mg, 0.40 mmol) in THF (2 mL), LiHMDS (1.18 mL, 1.18 mmol) in THF (6.6 mL), and allyl bromide (0.11 mL, 1.23 mmol), lactam **5** (82 mg, 71%) and its diastereomer 6-epi-**5** (19 mg, 16%) were obtained after flash chromatography (9:1 to 1:1 hexane−EtOAc).[10] **5**: IR (film) ν 2924, 1653, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 1.10 (s, 3H, CH_3), 1.18 (d, J = 6.4 Hz, 3H, CH_3), 1.47 (dd, J = 3.6, 8.0 Hz, 1H, H-7), 1.66 (dd, J = 14.0, 14.0 Hz, 1H, H-7), 2.01−2.10 (m, 1H, =CHCH_2), 2.14 (m, 1H, H-8), 2.46−2.51 (dd, J = 6.4, 13.6 Hz, 1H, =CHCH_2), 3.99 (dd, J = 10.4, 1.2 Hz, 1H, H-2), 4.12 (dd, J = 10.4, 6.8 Hz, 1H, H-2), 4.38 (d, J = 8.8 Hz, 1H, H-8a), 4.87 (dd, J = 6.8, 1.2 Hz, 1H, H-3), 5.03−5.09 (m, 2H, =CH_2), 5.66−5.77 (m, 1H, CH_2=CH), 7.21−7.30 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.7 (C8-CH_3), 26.4 (C6-CH_3), 31.3 (C-8), 39.1

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(C-7), 42.3 (C-6), 43.9 (=CHCH$_2$), 59.2 (C-3), 73.9 (C-2), 93.6 (C-6), 118.4 (CH$_2$=), 126.2 (C-Ar), 126.2 (C-Ar), 127.4 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 134.4 (CH$_2$=CH), 141.8 (C-Ar), 171.9 (CO); $[\alpha]^{22}_D$ −6.5 (*c* 1.0, CHCl$_3$); mp 68−70 °C; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{24}NO_2$, 286.1802; found, 286.1801. 6-epi-**5**: IR (film) ν 2924, 1651, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, COSY, *g*-HSQC) δ 1.12 (s, 3H, CH$_3$), 1.14 (d, *J* = 6.4 Hz, 3H, CH$_3$), 1.34 (dd, *J* = 14.4, 13.2 Hz, 1H, H-7), 1.85 (dd, *J* = 14.4, 3.6 Hz, 1H, H-7), 2.10 (dd, *J* = 13.6, 7.6 Hz, 1H, =CHC*H*$_2$), 2.12−2.18 (m, 1H, H-8), 2.26 (dd, *J* = 13.6, 7.6 Hz, 1H, =CHC*H*$_2$), 4.04 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.15 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.42 (d, *J* = 9.2 Hz, 1H, H-8a), 4.85 (dd, *J* = 6.8, 1.2 Hz, 1H, H-3), 4.92 (m, 1H, CH$_2$=), 4.96−5.01 (m, 1H, CH$_2$=), 5.52−5.63 (m, 1H, CH$_2$=C*H*), 7.21−7.34 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 16.6 (C8-*C*H$_3$), 25.2 (C6-*C*H$_3$), 31.5 (C-8), 39.5 (C-7), 41.8 (C-6), 44.1 (=CHCH$_2$), 59.3 (C-3), 73.9 (C-2), 93.6 (C-8a), 118.2 (CH$_2$=), 126.6 (C-Ar), 126.6 (C-Ar), 127.4 (C-Ar), 128.4 (C-Ar), 128.4 (C-Ar), 133.8 (CH$_2$=CH), 141.8 (C-Ar), 172.4 (CO); $[\alpha]^{22}_D$ + 1.6 (*c* 1.0, CHCl$_3$); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{24}NO_2$, 286.1802; found, 286.1800.

*4.3.2. (3R,6R,8S,8aR)-6-Allyl-8-ethyl-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**8**).* Following the general procedure, from a mixture of lactams **7** and 6-epi-**7**[11] (274 mg, 0.96 mmol) in THF (4 mL), LiHMDS (4.12 mL, 4.12 mmol) in THF (16 mL), and methyl iodide (0.41 mL, 2.88 mmol) lactam **8** (98 mg, 34%) and its diastereomer 6-epi-**8** (23 mg, 8%) were obtained after flash chromatography (90:10 to 70:30 hexane−EtOAc). IR (film) ν 1660 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, COSY, *g*-HSQC) δ 1.07 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.09 (s, 3H, C6-CH$_3$), 1.30−1.38 (m, 1H, H-7), 1.60 (m, 2H, H-7, H-8), 1.81−1.87 (m, 1H, C*H*$_2$CH$_3$), 1.89−1.98 (m, 1H, C*H*$_2$CH$_3$), 2.07 (dd, *J* = 13.5, 8.4 Hz, 1H, =CHC*H*$_2$), 2.50 (dd, *J* = 13.5, 6.2 Hz, 1H, =CHC*H*$_2$), 3.99 (dd, *J* = 9.0, 1.3 Hz, 1H, H-2), 4.13 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.46 (d, *J* = 8.9 Hz, 1H, H-8a), 4.86 (dd, *J* = 6.8, 1.3 Hz, 1H, H-3), 5.05−5.09 (m, 2H, CH$_2$=), 5.66−5.78 (m, 1H, CH$_2$=C*H*), 7.22−7.28 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 11.1 (CH$_3$), 24.6 (*C*H$_2$CH$_3$), 26.4 (C6-*C*H$_3$), 35.9 (C-8), 37.7 (C-7), 42.0 (=CHCH$_2$), 44.4 (C-6), 59.1 (C-3), 73.9 (C-2), 92.7 (C-8a), 118.4 (CH$_2$=), 126.3 (C-Ar), 127.4 (C-Ar), 128.5 (C-Ar), 134.5 (CH$_2$=CH) 141.9 (C-Ar), 171.9 (NCO); $[\alpha]^{22}_D$ −97.5 (*c* 1.0, MeOH); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{19}H_{26}NO_2$, 300.4102; found 300.4198.

*4.3.3. (3R,6S,8R,8aS)-6-Allyl-6,8-dimethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**10**) and Its (3R,6R,8R,8aS) Diastereomer (6-Epi-**10**).* From lactams **9**: Following the general procedure, from a mixture of lactams **9** and 6-epi-**9** (547 mg, 2.02 mmol) in THF (12 mL), LiHMDS (5.86 mL, 5.86 mmol) in THF (20 mL), and methyl iodide (0.36 mL, 5.86 mmol), lactam **10** (300 mg, 52%) and a 7:93 diastereomeric mixture of lactams **10** and 6-epi-**10** (92 mg, 16%) were obtained after flash chromatography (95:5 hexane−Et$_2$O to EtOAc). From lactams **11**: Following the general procedure, from a mixture of lactams **11** and 6-epi-**11** (250 mg, 1.02 mmol) in THF (3 mL), LiHMDS (2.95 mL, 2.95 mmol) in THF (16 mL), and allyl bromide (0.28 mL, 3.07 mmol), lactam **10** (107 mg, 37%) and its diastereomer 6-*epi*-**10** (130 mg, 44%) were obtained after flash chromatography (9:1 to 1:1 hexane−EtOAc). **10**: IR (film) ν 1654 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, COSY, *g*-HSQC) δ 1.11 (d, *J* = 6.4 Hz, 3H, CH$_3$), 1.17 (s, 3H, CH$_3$), 1.37 (m, 1H, H-7), 1.78−1.86 (m, 2H, H-7, H-8), 2.37 (dd, *J* = 13.6, 7.6 Hz, 1H, C6-CH$_2$), 2.49 (dd, *J* = 13.6, 7.6 Hz, 1H, CH$_2$, C-6), 3.74 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 4.48 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 4.58 (d, *J* = 8.4 Hz, 1H, H-8a), 5.05−5.11 (m, 2H, H$_2$C=), 5.21 (t, *J* = 8.0 Hz, 1H, H-3), 5.74−5.85 (m, 1H, CH=), 7.22−7.28 (m, 3H, ArH), 7.32−7.35 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 17.1 (C8-*C*H$_3$), 26.6 (C6-*C*H$_3$), 31.8 (C-8), 37.9 (C-7), 41.9 (C6-CH$_2$), 42.8 (C-6), 58.7 (C-3), 72.9 (C-2), 93.9 (C-8a), 118.2 (CH$_2$=), 125.9 (C-Ar), 128.8 (C-Ar), 127.5 (C-Ar), 134.1 (CH=) 139.7 (C-Ar), 174.2 (NCO); $[\alpha]^{22}_D$ −160.5 (*c* 1.15, MeOH); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{24}NO_2$ 286.1802; found 286.1810. 6-epi-**10**: IR (film) ν 1655 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, COSY, *g*-HSQC) δ 1.15 (d, *J* = 6.4 Hz, 3H, CH$_3$), 1.24 (s, 3H, CH$_3$), 1.42 (dd, *J* = 13.4, 2.0 Hz, 1H, H-7), 1.73 (t, *J* = 13.2 Hz, 1H, H-7), 1.80 (m, 1H, H-8), 2.06 (dd, *J* = 13.4, 8.4 Hz, 1H, C6-*C*H$_2$), 2.49 (dd, *J* = 13.4, 8.4 Hz 1H, C6-CH$_2$), 3.70 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 4.46 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 4.55 (d, *J* = 8.0 Hz, 1H, H-8a), 5.00−5.10 (m, 2H, H$_2$C=), 5.19 (t, *J* = 8.0 Hz, 1H, H-3), 5.56−5.67 (m, 1H, CH=), 7.23−7.26 (m, 3H, ArH), 7.30−7.34 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 17.0 (C8-*C*H$_3$), 25.6 (C6-*C*H$_3$), 31.6 (C-8), 37.6 (C-7), 42.3 (C-6), 45.3 (C6-CH$_2$), 58.9 (C-3), 72.9 (C-2), 94.0 (C-8a), 118.6 (CH$_2$=), 126.0 (C-Ar), 128.6 (C-Ar), 127.4 (C-Ar), 133.7 (CH=) 139.7 (C-Ar), 173.5 (NCO); $[\alpha]^{22}_D$ −30.55 (*c* 1.29, CHCl$_3$); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{24}NO_2$ 286.1802; found 286.1810.

*4.3.4. (3R,6S,8R,8aS)-6-Ethyl-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**12**) and Its (3R,6R,8R,8aS) Diastereomer (6-Epi-**12**).* Following the general procedure, from a mixture of lactams **11** and 6-epi-**11** (1.11 g, 4.51 mmol) in THF (12 mL), LiHMDS (13.1 mL, 13.1 mmol) in THF (50 mL), and ethyl iodide (1.1 mL, 13.1 mmol), lactam **12** (614 mg, 50%) and its diastereomer 6-epi-**12** (153 mg, 12%) were obtained after flash chromatography (9:1 to 85:15 hexane−Et$_2$O).[12] **12**: IR (film) ν 1651 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, COSY, *g*-HSQC) δ 0.79 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.18 (d, *J* = 6.4 Hz, 3H, C*H*$_3$CH), 1.21 (s, 3H, CH$_3$), 1.34−1.44 (m, 2H, H-7, C*H*$_2$CH$_3$), 1.61−1.80 (m, 2H, H-7, C*H*$_2$CH$_3$), 1.80−1.88 (m, 1H, H-8), 3.72 (dd, *J* = 8.9, 8.0 Hz, 1H, H-2), 4.46 (dd, *J* = 8.9, 8.0 Hz, 1H, H-2), 4.59 (d, *J* = 8.0 Hz, 1H, H-8a), 5.19 (t, *J* = 8.0 Hz, 1H, H-3), 7.22−7.26 (m, 3H, ArH), 7.30−7.34 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 8.6 (*C*H$_3$CH$_2$), 17.2 (CH$_3$), 25.7 (*C*H$_3$CH), 31.8 (C-8), 33.7 (*C*H$_2$CH$_3$), 37.5 (C-7), 42.8 (C-6), 59.0 (C-3), 73.0 (C-2), 94.2 (C-8a), 126.1 (C-Ar), 128.7 (C-Ar), 127.5 (C-Ar), 139.8 (C-Ar), 174.3 (NCO); $[\alpha]^{22}_D$ −128.6 (*c* 0.97, MeOH); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{24}NO_2$ 274.1802; found 274.1807. 6-epi-**12**: IR (film) ν 1655 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.14 (s, 3H, CH$_3$), 1.15 (d, *J* = 5.6 Hz, 3H, C*H*$_3$CH), 1.35−1.42 (m, 1H, H-7), 1.59−1.76 (m, 2H, C*H*$_2$CH$_3$), 1.77−1.84 (m, 2H, H-7, H-8), 3.74 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 4.47 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 4.59 (d, *J* = 8.4 Hz, 1H, H-8a), 5.21 (t, *J* = 8.0 Hz, 1H, H-3), 7.23−7.27 (m, 3H, ArH), 7.31−7.35 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 8.8 (*C*H$_3$CH$_2$), 17.2 (*C*H$_3$CH), 26.2 (CH$_3$), 31.0 (*C*H$_2$CH$_3$), 32.1 (C-8), 37.9 (C-7), 42.1 (C-6), 58.6 (C-3), 72.9 (C-2), 93.9 (C-8a), 126.0 (C-Ar), 128.8 (C-Ar), 127.5 (C-Ar), 139.8 (C-Ar), 174.9 (NCO);

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$[\alpha]^{22}_{D}$ −132.2 (*c* 0.86, MeOH); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{24}NO_2$ 274.1802; found 274.1801.

*4.3.5. (3R,6S,8S,8aS)-6-Benzyl-8-ethyl-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (**15**).* Following the general procedure, from a mixture of lactams **14** and 6-epi-**14** (334 mg, 1.0 mmol) in THF (2.7 mL), LiHMDS (3.0 mL, 3.0 mmol) in THF (11.0 mL), and methyl iodide (0.19 mL, 3.0 mmol), lactam **15** (210 mg, 61%) and a 50:50 mixture of **15** an its diastereomer 6-epi-**15** (85 mg, 24%) were obtained after flash chromatography (hexane to 85:15 hexane−EtOAc). **15**: IR (film) ν 1659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (*t*, 3H, *J* = 7.2 Hz CH_3CH_2), 1.27 (s, 3H, C6-CH_3), 1.28 (m, 2H, CH_3CH_2), 1.51−1.70 (m, 2H, H-7), 2.12 (m, 1H, H-8), 2.99 (d, *J* = 13.6 Hz, 2H, C6-CH_2), 3.72 (t, *J* = 8.8 Hz, 1H, H-2), 4.36 (t, *J* = 8.8 Hz, 1H, H-2), 4.82 (d, *J* = 4.8 Hz, 1H, H-8a), 5.44 (t, *J* = 7.6 Hz, 1H, H-3) 7.25−7.45 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.0 (CH_3CH_2), 22.8 (CH_3CH_2), 25.2 (C6-CH_3), 33.4 (C-7), 34.4 (C-8), 42.0 (C-6), 44.1 (C6-CH_2), 58.2 (C-3), 70.9 (C-2), 88.2 (C-8a), 125.8 (C-Ar), 126.2 (C-Ar), 127.4 (C-Ar), 127.9 (C-Ar), 128.8 (C-Ar), 131.1 (C-Ar), 138.0 (C-Ar), 140.3 (C-Ar), 176.3 (CO); $[\alpha]^{22}_{D}$ −154.8 (*c* 0.97, MeOH); mp 110−112 °C; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{23}H_{27}NO_2$ 350.2115; found 350.2120.

*4.3.6. (1S,3R,5aR,10aS,11aR)-3-Allyl-1,3-dimethyl-4-oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo-[3,2-a]pyridine (**18**) and Its (1S,3S,5aR,10aS,11aR) Diastereomer (3-Epi-**18**).* From lactams *17*: Following the general procedure, from a mixture of lactams **17** and 3-epi-**17** (300 mg, 1.06 mmol) in THF (3 mL), LiHMDS (3.2 mL, 3.2 mmol) in THF (12 mL), and methyl iodide (0.20 mL, 3.2 mmol), lactams **18** (144 mg, 46%) and 3-epi-**18** (51 mg, 16%) were obtained as light yellow oils after flash chromatography (95:5 to 1:1 hexane−EtOAc).[17] From lactams **19**: Following the general procedure, from a mixture of lactams **19** and 3-epi-**19** (439 mg, 1.71 mmol) in THF (4.5 mL), LiHMDS (5.1 mL, 5.1 mmol) in THF (19 mL), and allyl tosylate (0.97 mL, 5.1 mmol), lactam **18** (94 mg, 19%) and its diastereomer 3-epi-**18** (158 mg, 31%) were obtained after flash chromatography (95:5 to 1:1 hexane−EtOAc).[19] **18**: IR (film) ν 2924, 1645, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.98 (d, *J* = 6.4 Hz, 3H, C1-CH_3), 1.21 (s, 3H, C3-CH_3), 1.25−1.32 (m, 1H, H-2), 1.75−1.80 (m, 2H, H-1, H-2), 2.25 (dd, *J* = 14.0, 7.6 Hz, 1H, =CHCH_2), 2.33 (dd, *J* = 14.0, 7.6 Hz, 1H, =CHCH_2), 3.20 (d, *J* = 2.8 Hz, 2H, H-10), 4.43 (d, *J* = 8.8 Hz, 1H, H-11a), 4.77−4.80 (m, 1H, H-10a), 4.96−4.97 (dm, *J* = 5.2 Hz, 1H, CH_2=), 4.99 (s, 1H, CH_2=), 5.49 (d, *J* = 5.6 Hz, 1H, H-5a), 5.64−5.74 (m, 1H, CH_2=C*H*), 7.16−7.27 (m, 3H, ArH), 7.92 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.4 (C1-CH_3), 24.9 (C3-CH_3), 31.4 (C-1), 36.4 (C-10), 39.6 (C-2), 41.8 (C-3), 44.8 (=CHCH_2), 64.6 (C-5a), 81.4 (C-10a), 93.3 (C-11a), 118.2 (CH_2=), 124.8 (C-Ar), 127.4 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 133.7 (CH_2=*C*H), 140.1 (C-Ar), 141.9 (C-Ar), 173.6 (CO); $[\alpha]^{22}_{D}$ −11.8 (*c* 1.1, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{19}H_{24}NO_2$, 298.1802; found, 298.1803. 3-epi-**18**: IR (film) ν 2928, 1651, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.02 (d, *J* = 6.4 Hz, 3H, C1-CH_3), 1.19 (s, 3H, C3-CH_3), 1.41−1.45 (m, 1H, H-2), 1.57−1.63 (m, 1H, H-2), 1.73−1.81 (m, 1H, H-1), 2.13−2.18 (dd, *J* = 13.6, 8.4 Hz, 1H, =CHCH_2), 2.59−2.64 (dd, *J* = 13.6, 6.0 Hz, 1H, =CHCH_2), 3.20 (d, *J* = 2.8 Hz, 2H, H-10), 4.39 (d, *J* = 8.8 Hz, 1H, H-11a), 4.77−4.80 (m, 1H, H-10a), 5.09−5.13 (m, 2H, =CH_2), 5.49 (d, *J* = 5.6 Hz, 1H, H-5a), 5.71−5.86 (m, 1H, CH_2=C*H*), 7.17−7.27 (m, 3H, ArH), 7.93 (d, *J* = 7.2 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.4 (C1-CH_3), 27.2 (C3-CH_3), 31.2 (C-1), 36.4 (C-10), 39.2 (C-2), 42.3 (C-3), 43.8 (=CHCH_2), 64.6 (C-5a), 81.4 (C-10a), 93.3 (C-11a), 118.4 (=CH_2), 124.9 (C-Ar), 127.5 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 134.5 (CH_2=*C*H), 140.1 (C-Ar), 141.9 (C-Ar), 173.2 (CO); $[\alpha]^{22}_{D}$ −16.5 (*c* 0.9, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{19}H_{24}NO_2$, 298.1802; found, 298.1798.

4.4. General Procedure for the Alane Reduction Reactions. $LiAlH_4$ (1 M solution in THF, 6.5 mmol) was slowly added to a cooled (0 °C) suspension of $AlCl_3$ (2 mmol) in anhydrous THF, and the mixture was stirred at room temperature for 30 min. The temperature was lowered (−78 °C), the lactam (**5**, **10**, or 3-epi-**18**; 1 mmol) was added dropwise, and the resulting suspension was stirred at −78 °C for 90 min and at room temperature for 24 h. The mixture was cooled to 0 °C, and the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried and concentrated, and the resulting residue was purified by chromatography.

*4.4.1. (3R,5S)-3-Allyl-1-[(1R)-2-hydroxy-1-phenylethyl]-3,5-dimethylpiperidine (**20**).* Following the general procedure, from lactam **5** (204 mg, 0.72 mmol), $AlCl_3$ (191 mg, 1.43 mmol), and $LiAlH_4$ (4.68 mL, 4.68 mmol) in THF (10 mL), piperidine **20** (154 mg, 79%) was obtained as a colorless oil after flash chromatography (95:5 to 8:2 hexane−EtOAc). IR (film) ν 3172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.60 (t, *J* = 12.4 Hz, 1H, H-4), 0.80 (d, *J* = 6.4 Hz, 3H, C5-CH_3), 1.06 (s, 3H, C3-CH_3), 1.37 (m, 2H, H-4, H-6), 1.76 (t, *J* = 10.8 Hz, 1H, H-2), 1.84 (d, *J* = 7.6 Hz, 2H, =CHCH_2), 1.90 (brs, 1H, OH), 1.94 (brs, 1H, H-5), 2.44 (brm, *J* = 11.2 Hz, 1H, H-6), 2.82 (brm, *J* = 10.8 Hz, 1H, H-2), 3.59−3.64 (dd, *J* = 10.4, 4.4 Hz, 1H, CH_2OH), 3.75 (brs, 1H, CHN), 3.98 (t, *J* = 10.4 Hz, 1H, CH_2OH), 4.94−5.02 (m, 2H, CH_2=), 5.71−5.82 (m, 1H, CH_2=C*H*), 7.14−7.16 (m, 2H, ArH), 7.31−7.36 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.5 (C5-CH_3), 22.6 (C3-CH_3), 27.7 (C-5), 34.0 (C-3), 44.6 (C-4), 47.5 (=CHCH_2), 56.3 (C-6), 60.0 (CHOH), 61.5 (C-2), 69.9 (CHN), 117.3 (CH_2=), 127.8 (C-Ar), 128.1 (C-Ar), 128.1 (C-Ar), 129.0 (C-Ar), 129.0 (C-Ar), 134.2 (CH_2=*C*H), 135.1 (C-Ar); $[\alpha]^{22}_{D}$ −2.0 (*c* 1.2, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{28}NO$, 274.2171; found, 274.2165.

*4.4.2. (3R,5R)-3-Allyl-1-[(1R)-2-hydroxy-1-phenylethyl]-3,5-dimethylpiperidine (5-Epi-**20**).* Following the general procedure, from lactam **10** (70 mg, 0.25 mmol), $AlCl_3$ (65 mg, 0.5 mmol), and $LiAlH_4$ (1.62 mL, 1.62 mmol) in THF (6 mL), piperidine 5-*epi*-**20** (58 mg, 86%) was obtained after flash chromatography (95:5 to 8:2 hexane−EtOAc). IR (film) ν 3385, 2952 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.55 (t, *J* = 12.0 Hz, 1H, H-4), 0.75 (d, *J* = 4.2 Hz, 3H, C3-CH_3), 0.78 (s, 3H, C5-CH_3), 1.17 (t, *J* = 12.0 Hz, 1H, H-2), 1.47 (dm, 1H, *J* = 12.0 Hz, H-4), 1.81 (m, 1H, H-5), 1.92 (d, *J* = 12.0 Hz, 1H, H-6), 2.53 (m, 2H, =CHCH_2), 2.55 (dt, *J* = 12.0, 4.2 Hz, 1H, H-6), 2.82 (dm, *J* = 8.0 Hz, 1H, H-2), 3.64 (m, 2H, ArH, CH_2OH), 4.03 (t, *J* = 8.0 Hz, 1H, CH_2OH), 5.07 (m, 2H, CH_2=), 5.82 (m, 1H, CH_2=CH), 7.16 (m, 2H, ArH), 7.34 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.6 (C5-CH_3), 26.2 (C3-CH_3), 27.2 (C-5), 34.5 (C-3), 41.3 (=CHCH_2), 44.8 (C-4), 53.7 (C-2), 60.2 (CHOH), 69.8 (CHN), 117.2 (=CH_2), 127.9 (CH_2=CH),

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129.1 (C-Ar), 128.1 (C-Ar), 135.0 (C-Ar), 135.2 (C-Ar); $[\alpha]^{22}_{D}$ −8.0 (c 0.6, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{18}H_{28}NO$, 274.2171; found, 274.2172.

*4.4.3. (3S,5S)-3-Allyl-1-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-indenyl]-3,5-dimethylpiperidine (**22**).* Following the general procedure, from lactam 3-epi-**18** (224 mg, 0.75 mmol), $AlCl_3$ (201 mg, 1.5 mmol), and $LiAlH_4$ (4.8 mL, 4.8 mmol) in THF (17 mL), piperidine **22** (116 mg, 54%) was obtained after flash chromatography (95:5 to 9:1 hexane−EtOAc). IR (film) ν 3172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.58 (m, 1H, H-4), 0.64 (s, 3H, C3-CH_3), 0.86 (d, J = 6.4 Hz, 3H, C5-CH_3), 1.51 (m, 3H, H-4, H-6), 1.96 (brs, 1H, OH), 1.96 (m, 1H, H-5), 2.14−2.19 (m, 1H, =CHCH_2), 2.35−2.42 (m, 2H, H-2, =CHCH_2), 2.80 (dd, J = 17.0, 8.8 Hz, 1H, CH_2C-Ar), 2.94−3.02 (m, 1H, H-2), 3.26 (dd, J = 17.0, 8.4 Hz, 1H, CH_2C-Ar), 4.03−4.13 (m, 1H, CHN), 4.42−4.51 (m, 1H, C*H*OH), 5.02−5.07 (m, 2H, CH_2=), 5.71−5.81 (m, 1H, CH_2=C*H*), 7.18−7.31 (m, 4H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.5 (C5-CH_3), 26.4 (C3-CH_3), 27.7 (C-5), 34.3 (C-3), 40.9 (=CH*C*H_2), 41.6 (CH_2C-Ar), 43.8 (C-4), 59.0 (C-6), 63.2 (C-2), 70.1 (CHOH), 70.2 (CHN), 117.4 (CH_2=), 124.7 (C-Ar), 125.6 (C-Ar), 126.3 (C-Ar), 126.5 (C-Ar), 128.5 (C-Ar), 134.7 (CH_2=*C*H), 141.7 (C-Ar); $[\alpha]^{22}_{D}$ −0.54 (*c* 1.3, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{19}H_{28}NO$, 286.2162; found, 286.2165.

4.5. General Procedure for the Hydrogenolysis Reactions. A solution of the piperidine (**20**, 5-epi-**20**, or **22**; 1 mmol) and di-*tert*-butyl dicarbonate (2.5 mmol) in MeOH containing Pd/C was hydrogenated at 25 °C until the disappearance of the starting material was observed by TLC. The catalyst was removed by filtration and washed with hot MeOH, and the solution was concentrated to give the *N*-Boc piperidines after flash chromatography.

*4.5.1. (3R,5S)-1-(tert-Butoxycarbonyl)-3,5-dimethyl-3-propylpiperidine (**21**).* Following the general procedure, from piperidine **20** (97 mg, 0.35 mmol), Boc_2O (252 mg, 0.88 mmol), and Pd/C (38.6 mg, 40% wt) in MeOH (8 mL), piperidine **21** (78 mg, 86%) was obtained after flash chromatography (98:2 to 9:1 hexane−EtOAc). IR (film) ν 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.81 (d, J = 6.4 Hz, 3H, C5-CH_3), 0.86 (s, 3H, C3-CH_3), 0.88 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.13 (d, J = 8.8 Hz, 2H, H-4), 1.23−1.33 (m, 2H, CH_2CH_2), 1.44 [s, 9H, $(CH_3)_3$], 1.45−1.50 (m, 2H, C3-CH_2), 1.75 (brs, 1H, H-5), 2.09 (brs, 1H, H-2 or H-6), 2.35 (brs, 1H, H-2 or H-6), 3.73 (brs, 1H, H-2 or H-6), 4.00 (brs, 1H, H-2 or H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.9 (CH_2CH_3), 16.2 (CH_2CH_2), 19.2 (C5-CH_3), 20.9 (C3-CH_3), 26.7 (C-5), 28.4 (C-(CH_3)$_3$), 34.2 (C-3), 45.4 (C3-CH_2), 44.9 (C-4), 50.9 (C-2 or C-6), 54.6 (C-2 or C-6), 79.0 [$C(CH_3)_3$], 155.0 (CO); $[\alpha]^{22}_{D}$ −8.43 (*c* 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. For $C_{15}H_{30}NO_2$, 256.2198 found, 256.2201.

*4.5.2. (3R,5R)-1-(tert-Butoxycarbonyl)-3,5-dimethyl-3-propylpiperidine (5-Epi-**21**).* Following the general procedure, from piperidine 5-epi-**20** (147 mg, 0.51 mmol), Boc_2O (279 mg, 1.28 mmol), and Pd/C (60 mg, 40% wt) in MeOH (12 mL), piperidine 5-epi-**21** (74 mg, 54%) was obtained after flash chromatography (98:2 to 9:1 hexane−EtOAc). IR (film) ν 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.81 (d, J = 6.4 Hz, 3H, C5-CH_3), 0.86 (s, 3H, C3-CH_3), 0.88 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.13 (d, J = 8.8 Hz, 2H, H-4), 1.23−1.33 (m, 2H, $CH_2CH_2CH_3$), 1.44 [s, 9H, $C(CH_3)_3$], 1.45−1.50 (m, 2H, C3-CH_2), 1.75 (brs, 1H, H-5), 2.09 (brs, 1H, H-2 or H-6), 2.35 (brs, 1H, H-2 or H-6), 3.73 (brs, 1H, H-2 or H-6), 4.00 (brs, 1H, H-2 or H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.9 (CH_2CH_3), 16.9 ($CH_2CH_2CH_3$), 19.1 (C5-CH_3), 26.4 (C3-CH_3), 25.4 (C-5), 28.4 [$C(CH_3)_3$], 34.0 (C-3), 45.8 (C-4), 47.7 ($CH_2CH_2CH_3$), 50.5 (C-2 or C-6), 53.6 (C-2 or C-6), 79.0 [$C(CH_3)_3$], 154.9 (CO); $[\alpha]^{22}_{D}$ + 6.8 (*c* 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{15}H_{30}NO_2$, 255.2198; found, 256.2281.

*4.5.3. (3S,5S)-1-(tert-Butoxycarbonyl)-3,5-dimethyl-3-propylpiperidine (3-Epi-**21**).* Following the general procedure, from piperidine **22** (50 mg, 0.18 mmol), Boc_2O (99 mg, 0.45 mmol), and Pd/C (20 mg, 40% wt) in MeOH (4 mL), piperidine 3-epi-**21** (34 mg, 76%) was obtained after flash chromatography (98:2 to 9:1 hexane−EtOAc). IR (film) ν 1696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.79 (s, 3H, C3-CH_3), 0.80 (d, J = 6.4 Hz, 3H, C5-CH_3), 0.87 (t, J = 6.0 Hz, 3H, CH_2CH_3), 1.18−1.29 (m, 2H, H-4), 1.22 (m, 4H, CH_2CH_2), 1.45 [s, 9H, $(CH_3)_3$], 1.72 (m, 1H, H-5), 2.06 (brs, 1H, H-2 or H-6), 2.28 (brs, 1H, H-2 or H-6), 3.79 (brs, 1H, H-2 or H-6), 4.10 (brs, 1H, H-2 or H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.0 (CH_2CH_3), 16.9 (CH_2CH_2), 19.1 (C5-CH_3), 25.4 (C3-CH_3), 26.4 (C-5), 28.4 [$(CH_3)_3$], 34.0 (C-3), 37.8 (C3-CH_2), 45.4 (C-4), 50.5 (C-2 or C-6), 53.6 (C-2 or C-6), 79.0 [$C(CH_3)_3$], 154.9 (CO); $[\alpha]^{22}_{D}$ −6.18 (*c* 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{15}H_{30}NO_2$, 255.2198; found, 255.2194.

4.6. General Procedure for the Reductive Cleavage of the Oxazolidine and Piperidone Rings. *n*-BuLi (4.3 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (4.3 mmol) in anhydrous THF at 0 °C, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 min. Then, the mixture was added to a solution of the lactam (**10**, 6-epi-**10**, **12**, or **15**; 1.0 mmol) in anhydrous THF, and the stirring was continued at 40 °C for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give a residue, which was purified by flash chromatography.

*4.6.1. (2R,4R)-2-Allyl-5-{[(R)-2-hydroxy-1-phenylethyl]-amino}-2,4-dimethyl-1-pentanol (**23**).* Following the general procedure, from lactam **10** (200 mg, 0.7 mmol) in THF (1 mL), *n*-BuLi (1.21 mL of a 1.6 M solution in hexanes, 3.01 mmol), and $NH_3{\cdot}BH_3$ (93 mg, 3.01 mmol) in THF (2 mL), 1,5-aminodiol **23** (98 mg, 48%) was obtained as a yellowish oil after flash chromatography (1:1 hexane−EtOAc EtOAc). IR (film) ν 3316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, J = 6.8 Hz, 3H, C4-CH_3), 0.88 (s, 3H, C2-CH_3), 1.05 (dd, J = 14.6, 2.4 Hz, 1H, H-3), 1.50−1.54 (m, 1H, H-3), 1.59 (m, 1H, H-4), 1.85−1.97 (m, 2H, C2-CH_2), 2.20 (m, 1H, H-5), 2.46 (dd, J = 12.0, 4.4 Hz, 1H, H-5), 3.19 (d, J = 11.2 Hz, 1H, H-1), 3.44 (d, J = 11.2 Hz, 1H, H-1), 3.69−3.77 (m, 3H, C*H*NH, CH_2O), 5.00−5.02 (m, 2H, CH_2=), 5.73−5.83 (m, 1H, CH=), 7.27−7.36 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.6 (C4-CH_3), 23.6 (C2-CH_3), 28.6 (C-4), 38.5 (C-2), 40.8 (C2-CH_2), 41.5 (C-3), 55.5 (C-5), 65.5 (C-Ar), 66.3 (CH_2O), 68.3 (C-1), 117.9 (CH_2=), 127.4 (C-Ar), 128.6 (C-Ar), 127.7 (C-Ar), 134.6 (-CH=), 139.8 (C-Ar); $[\alpha]^{22}_{D}$ −46.1 (*c* 1.87, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{18}H_{30}NO_2$ 292.2271; found 292.2271.

*4.6.2. (2S,4R)-2-Allyl-5-{[(R)-2-hydroxy-1-phenylethyl]-amino}-2,4-dimethyl-1-pentanol (2-Epi-**23**).* Following the general procedure, from lactam 6-epi-**10** (351 mg, 1.23 mmol) in THF (3 mL), *n*-BuLi (2.12 mL of a 2.5 M solution in

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hexane, 5.29 mmol), and $NH_3{\cdot}BH_3$ (163 mg, 5.29 mmol) in anhydrous THF (6 mL), 1,5-aminodiol 2-epi-**23** (183 mg, 51%) was obtained after flash chromatography (1:1 hexane−EtOAc to 9:1 EtOAc−MeOH). IR (film) ν 3318, 2955, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.73 (s, 3H, C2-CH_3), 0.87 (d, J = 5.8 Hz, 3H, C4-CH_3), 1.00 (dd, J = 14.2, 5.2 Hz, 1H, H-3), 1.51 (m, 1H, H-4), 1.62 (dd, 1H, J = 14.2, 3.2 Hz, H-3), 2.01 (m, 1H, =CHCH_2), 2.11 (m, 2H, H-5, =CHCH_2), 2.51 (dd, 1H, J = 11.6, 4.0 Hz, H-5), 3.21 (d, 1H, J = 11.6 Hz, H-1), 3.39 (d, 1H, J = 11.6 Hz, H-1), 3.73 (m, 3H, CH_2O, CHN), 5.05 (m, 2H, CH_2=), 5.85 (m, 1H, CH_2=C*H*), 7.26−7.36 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.0 (C2-CH_3), 22.04 (C4-CH_3), 28.9 (C-4), 38.6 (C-2), 42.0 (C-3), 45.8 (=CHCH_2), 55.9 (C-5), 65.6 (CHAr), 66.6 (CH_2O), 67.1 (C-1), 117.2 (CH_2=), 135.2 (CH_2=CH), 127.3 (C-Ar), 128.7 (C-Ar), 127.7 (C-Ar), 140.2 (C-Ar); $[\alpha]^{22}_D$ −60.9 (*c* 0.65, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd. for $C_{18}H_{30}NO_2$, 292.2271; found, 292.2276.

*4.6.3. (2S,4R)-2-Ethyl-5-{[(R)-2-hydroxy-1-phenylethyl]-amino}-2,4-dimethyl-1-pentanol (**24**).* Following the general procedure, from lactam **12** (491 mg, 1.8 mmol) in THF (2.25 mL), *n*-BuLi (4.83 mL of a 1.6 M solution in hexanes, 7.74 mmol), and $NH_3{\cdot}BH_3$ (246 mg, 7.74 mmol) in THF (4.4 mL), 1,5-aminodiol **24** (246 mg, 49%) was obtained as a colorless oil after flash chromatography (1:1 hexane−EtOAc to EtOAc). IR (film) ν 3315 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 0.70 (s, 3H, CH_3), 0.84 (t, J = 7.6 Hz, 3H, CH_3CH_2), 0.86 (d, J = 6.8 Hz, 3H, CH_3C-4), 1.01 (dd, J = 14.2, 5.6 Hz, 1H, H-3), 1.24−1.33 (m, 1H, CH_2CH_3), 1.35−1.44 (m, 1H, CH_2CH_3), 1.50−1.59 (m, 2H, H-3, H-4), 2.16 (dd, J = 12.0, 9.2 Hz, 1H, H-5), 2.52 (dd, J = 12.0, 4.0 Hz, 1H, H-5), 3.24 (d, J = 11.6 Hz, 1H, H-1), 3.40 (d, J = 11.6 Hz, 1H, H-1), 3.65−3.77 (m, 3H, CH_2CHO), 7.27−7.38 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.0 (CH_3CH_2), 19.5 (CH_3), 22.0 (CH_3CH), 28.8 (C-4), 31.4 (CH_2CH_3), 38.0 (C-2), 41.8 (C-3), 55.7 (C-5), 65.6 (C-Ar), 66.4 (CH_2O), 66.6 (C-1), 127.3 (C-Ar), 128.6 (C-Ar), 127.5 (C-Ar), 140.2 (C-Ar); $[\alpha]^{22}_D$ −44.9 (*c* 1.02, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd. for $C_{17}H_{30}NO_2$ 280.2271; found 280.2276.

*4.6.4. (2S,4S)-2-Benzyl-4-ethyl-5-{[(R)-2-hydroxy-1-phenylethyl]amino}-2-methyl-1-pentanol (**25**).* Following the general procedure, from lactam **15** (248 mg, 0.71 mmol) in THF (1 mL), *n*-BuLi (1.22 mL of a 2.5 M solution in hexane, 3.05 mmol), and $NH_3{\cdot}BH_3$ (97.1 mg, 3.05 mmol) in THF (1.7 mL), aminodiol **25** (119 mg, 47%) was obtained as a colorless oil after flash chromatography (1:1 hexane−EtOAc to EtOAc). IR (film) ν 3283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.63 (s, 3H, CH_3), 0.78 (t, J = 7.2 Hz, 3H, CH_3CH_2), 0.99 (dd, J = 14.6, 3.8 Hz, 1H, H-3), 1.11 (m, 1H, CH_3CH_2), 1.23 (m, 1H, CH_3CH_2), 1.35 (brs, 1H, H-4), 1.53 (dd, J = 14.6, 3.8 Hz, 1H, H-3), 2.02 (t, J = 11.0 Hz, 1H, H-5), 2.43 (d, J = 12.8 Hz, 1H, CH_2Ph), 2.64 (d, J = 11.0 Hz, 1H, H-5), 2.78 (d, J = 12.8 Hz, 1H, CH_2Ar), 3.14 (d, J = 12.2 Hz, 1H, H-1), 3.38 (d, J = 12.2 Hz, 1H, H-1), 3.71 (m, 2H, CH_2O), 3.82 (dd, J = 9.2, 3.6 Hz, 1H, CHAr), 7.16−7.40 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.7 (CH_3CH_2), 19.6 (CH_3), 29.1 (C-2), 34.9 (CH_2CH_3), 39.4 (C-4), 41.7 (C-3), 45.3 (CH_2Ph), 53.0 (C-5), 64.9 (C-1), 65.4 (CHAr), 66.9 (CH_2O), 125.7 (C-Ar), 127.9 (C-Ar), 128.7 (C-Ar), 130.9 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 138.8 (C-Ar), 139.5 (C-Ar); $[\alpha]^{22}_D$ −33.7 (*c* 1.25, $CHCl_3$); HRMS calcd. for $C_{23}H_{34}NO_2$ $[M + H]^+$ 356.2584; found 356.2594.

4.7. General Procedure for the Protection of the Secondary Amino Group. Di-*tert*-butyl dicarbonate (1.6 or 2.1 mmol) was added at room temperature to a stirring solution of the aminodiol (**23**, 2-epi-**23**, or **24**; 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 *N*-Boc derivative, which was purified by flash chromatography.

*4.7.1. (2R,4R)-2-Allyl-5-{N-[(tert-butoxycarbonyl)]-N-[(R)-2-hydroxy-1-phenylethyl]amino}-2,4-dimethyl-1-pentanol (**26**).* Following the general procedure, from aminodiol **23** (87 mg, 0.3 mmol) and Boc_2O (104 mg, 0.48 mmol) in MeOH (12 mL), *N*-Boc derivative **26** (88 mg, 75%) was obtained as a yellowish oil after flash chromatography (9:1 to 1:1 hexane−EtOAc). IR (film) ν 3423, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.79 (s, 3H, CH_3C-2), 0.89 (d, J = 6.8 Hz, 3H, C4-CH_3), 0.96 (dd, J = 14.4, 7.6 Hz, 1H, H-3), 1.19−1.28 (m, 1H, H-3), 1.48 [s, 9H $(CH_3)_3$], 1.73 (m, 1H, H-4) 1.93 (d, J = 7.2 Hz, 2H, C2-CH_2), 2.20 (m, 1H, H-5), 2.49 (m, 2H, OH), 2.77 (dd, J = 13.6, 5.6 Hz, 1H, H-5), 3.13 (dd, J = 14.0, 7.2 Hz, 1H, H-5), 3.24 (d, J = 10.8 Hz, 1H, H-1), 3.31 (d, J = 10.8 Hz, 1H, H-1), 4.07 (dd, J = 11.8, 5.0 Hz, 1H, CH_2O), 4.21 (dd, J = 11.8, 8.0 Hz, 1H, CH_2O), 4.86 (dd, J = 8.0, 5.0 Hz, 1H, C-Ar), 5.00−5.05 (m, 2H, CH_2=), 5.72−5.83 (m, 1H, CH=), 7.27−7.36 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.1 (C4-CH_3), 22.2 (C2-CH_3), 28.2 (C-4), 28.4 [$(CH_3)_3$], 38.3 (C-2), 40.9 (C-3), 41.8 (C2-CH_2), 54.2 (C-5), 63.5 (C-Ar), 63.8 (CH_2O), 69.4 (C-1), 80.4 [$C(CH_3)_3$] 117.3 (CH_2=), 127.6 (C-Ar), 128.5 (C-Ar), 127.6 (C-Ar), 135.0 (CH=), 138.3 (C-Ar), 157.3 (C=O); $[\alpha]^{22}_D$ + 0.9 (*c* 0.85, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd. for $C_{23}H_{38}NO_4$ 392.2795; found 392.2800.

*4.7.2. (2S,4R)-2-Allyl-5-{N-[(tert-Butoxycarbonyl)]-N-[(R)-2-hydroxy-1-phenylethyl]amino}-2,4-dimethyl-1-pentanol (2-Epi-**26**).* Following the general procedure, from aminodiol 2-epi-**23** (367 mg, 1.26 mmol) and Boc_2O (578 mg, 2.65 mmol) in MeOH (57 mL), *N*-Boc derivative 2-epi-**26** (345 mg, 70%) was obtained after flash chromatography (9:1 to 1:1 hexane−EtOAc). IR (film) ν 3418, 2973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.78 (s, 3H, C4-CH_3), 0.88 (d, J = 6.6 Hz, 3H, C2-CH_3), 0.94 (dd, J = 14.0, 7.6,Hz, 1H, H-3), 1.48 [s, 9H, $(CH_3)_3$], 1.99 (m, 3H, H-4, CH_2), 2.79 (dd, J = 14.0, 7.3 Hz, 1H, H-5), 3.09 (dd, J = 14.0, 7.8 Hz, Hz, 1H, H-5), 3.26 (d, J = 11.0 Hz, 1H, H-1), 4.05 (d, J = 11.0 Hz, 1H, H-1), 4.24 (m, 2H, CH_2O), 4.89 (dd, J = 8.9, 4.9 Hz, 1H, CHAr), 5.03 (m, 2H, CH_2=), 5.80 (m, 1H, CH=), 7.30 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.4 (C2-CH_3), 21.6 (C4-CH_3), 28.4 [$(CH_3)_3$] (C-4), 38.4 (C-2), 40.6 (C-3), 54.3 (C2-CH_2), 63.8 (C-5), 68.9 (CHAr), 80.5 (CH_2O), 117.3 (C-1), 127.5 (=CH_2), 127.6 (=CH), 128.6 (C-Ar), 135.1 (C-Ar), 138.2 (C-Ar); $[\alpha]^{22}_D$ −18.6 (*c* 1.05, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd. for $C_{23}H_{38}NO_4$, 392.2795; found, 392.2798.

*4.7.3. (2S,4R)-5-{N-[(tert-Butoxycarbonyl]-N-[(R)-2-hydroxy-1-phenylethyl]amino}-2-ethyl-2,4-dimethyl-1-pentanol (**27**).* Following the general procedure, from aminodiol **24** (98 mg, 0.35 mmol) and Boc_2O (115 mg, 0.53 mmol) in MeOH (14 mL), *N*-Boc derivative **27** (84 mg, 63%) was obtained after flash chromatography (9:1 to 1:1 hexane−EtOAc). IR (film) ν 3417, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.74 (s, 3H, C2-CH_3), 0.79 (t, J = 7.6 Hz, 3H, CH_3CH$_2$), 0.87 (d, J = 6.4 Hz, 3H, C4-CH_3), 0.93

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(m, 1H, H-3), 1.18−1.32 (m, 3H, CH_2CH$_3$, H-3), 1.48 [s, 9H (CH_3)$_3$], 1.73 (m, 1H, H-4), 2.80 (dd, J = 14.2, 7.2 Hz, 1H, H-1), 3.07 (dd, J = 14.4, 8.0 Hz, 1H, H-1), 3.25 (m, 2H, H-5), 4.07 (dd, J = 11.2, 4.8 Hz, 1H, CH_2O), 4.22 (t, J = 10.8 Hz, 1H, CH_2O), 4.91 (dd, J = 8.8, 4.4 Hz, CH-Ar), 7.26−7.30 (m, 3H, ArH), 7.32−7.36 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.9 (CH_3CH_2), 20.3 (C4-CH_3), 21.2 (C2-CH_3), 28.3 [(CH_3)$_3$], 28.4 (C-4), 30.2 (CH_2CH_3), 37.7 (C-2), 40.1 (C-3), 54.2 (C-1), 63.5 (C-Ar), 63.7 (CH_2O), 68.6 (C-5), 80.3 [C(CH_3)$_3$], 127.5 (C-Ar), 128.5 (C-Ar), 138.3 (C-Ar), 157.3 (CO); $[\alpha]^{22}_D$ −2.41 (c 2.83, $CHCl_3$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{22}H_{38}NO_4$ 380.2795; found 380.2794.

4.8. General Procedure for the Reductive Removal of the Benzylic Substituent (Warning: Ammonia Is Extremely Corrosive to the Skin, Eyes, and Mucous Membranes). Liquid ammonia was condensed at −78 °C in a three-necked flask equipped with a cold finger condenser charged with dry ice-acetone, and then a solution of the *N*-Boc derivative (**26**, 2-epi-**26**, or **27**; 1 mmol) in anhydrous THF was added. The temperature was raised to −33 °C, and sodium metal was added in small portions until the blue color persisted. The mixture was briefly stirred at −33 °C. The reaction was quenched by the addition of solid NH_4Cl until the blue color disappeared, and the mixture was stirred at room temperature 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 residue was purified by flash chromatography.

*4.8.1. (2S,4R)-5-[(tert-Butoxycarbonyl)amino]-2-ethyl-2,4-dimethyl-1-pentanol (**28**).* Following the general procedure, from the *N*-Boc derivative **26** (54 mg, 0.14 mmol) in THF (5 mL), liquid ammonia (20 mL), and sodium (stirring the blue mixture for 20 s), alcohol **28** (34 mg, 91%) was obtained as a yellowish oil after flash chromatography (hexane to 8:2 hexane−EtOAc). IR (film) ν 3364, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88 (s, 3H, C2-CH_3), 0.94 (d, J = 6.8 Hz, 3H, C4-CH_3), 1.05 (dd, J = 14.5, 6.0 Hz, 1H, H-3), 1.33 (dd, J = 14.5, 4.0 Hz, 1H, H-3), 1.43 [s, 9H (CH_3)$_3$], 1.71−1.76 (m, 1H, H-4), 2.02−2.04 (m, 2H, C2-CH_2), 2.94−3.02 (m, 2H, H-5), 3.33 (d, J = 10.8 Hz, 1H, H-1), 3.37 (d, J = 10.8 Hz, 1H, H-1) 5.03−5.08 (m, 2H, CH_2═), 5.77−5.88 (m, 1H, CH═); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6 (C4-CH_3), 22.3 (C2-CH_3), 28.4 [(CH_3)$_3$], 28.9 (C-4), 38.4 (C-2), 40.5 (C-3), 41.6 (C2-CH_2), 47.9 (C-5), 69.3 (C-1), 79.1 [C(CH_3)$_3$], 117.4 (CH_2═), 135.0 (CH═), 156.3 (CO); $[\alpha]^{22}_D$ + 7.7 (c 0.97, $CHCl_3$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{15}H_{30}NO_3$ 272.2220; found 272.2223.

*4.8.2. (2R,4R)-5-[(tert-Butoxycarbonyl)amino]-2-ethyl-2,4-dimethyl-1-pentanol (2-Epi-**28**).* Following the general procedure, from *N*-Boc derivative 2-epi-**26** (144 mg, 0.37 mmol) in THF (2.5 mL), liquid ammonia (9 mL), and sodium (stirring the blue mixture for 20 s), alcohol 2-epi-**28** (78 mg, 78%) was obtained after flash chromatography (9:1 to 8:2 hexane−EtOAc). IR (film) ν 3363, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.72 (s, 3H, C4-CH_3), 0.84 (d, J = 6.8 Hz, 3H, C2-CH_3), 0.90 (ddd, J = 10.0, 8.8, 6.0 Hz, 1H, H-3), 1.50 (dd, J = 14.0, 2.8 Hz, 1H, H-3), 1.56 (m, 1H, H-4), 2.01 (m, 1H, C2-CH_2), 2.07 (m, 2H, H-5, C2-CH_2), 2.50 (dd, J = 11.2, 2.8 Hz, 1H, H-5), 3.22 (d, J = 11.6 Hz, 1H, H-1), 3.46 (d, J = 11.6 Hz, 1H, H-1), 5.01−5.06 (m, 2H, ═CH_2), 5.79−5.90 (m, 1H, ═CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.8 (CH_3C-2), 22.2 (CH_3C-4), 28.3 (C-4), 38.6 (C-2), 42.3 (C-3), 44.0 (CH_2C-2), 55.6 (C-5), 67.0 (C-1), 117.2 (═CH_2), 135.3 (═CH); $[\alpha]^{22}_D$ + 7.74 (c 0.9, $CHCl_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{15}H_{29}NaNO_3$, 294.2117; found, 294.2149.

*4.8.3. (2S,4R)-5-[(tert-Butoxycarbonyl)amino]-2-ethyl-2,4-dimethyl-1-pentanol (**29**).* Following the general procedure, from *N*-Boc derivative **27** (56 mg, 0.15 mmol) in THF (5 mL), liquid ammonia (20 mL), and sodium (stirring the blue mixture for 90 s), alcohol **29** (28 mg, 73%) was obtained as a yellowish oil after flash chromatography (9:1 to 7:3 hexane−EtOAc). IR (film) ν 3365, 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.80 (s, 3H, C2-CH_3), 0.82 (t, J = 7.6 Hz, 3H, CH_3CH$_2$), 0.93 (d, J = 6.8 Hz, 3H, C4-CH_3), 1.00 (dd, J = 14.4, 5.6 Hz, 1H, H-3), 1.43 [s, 9H, (CH_3)$_3$], 1.65−1.73 (m, 1H, H-4), 3.32 (s, J = 11.2 Hz, 1H, H-1), 3.37 (d, J = 11.2 Hz, 1H, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.9 (CH_3CH_2), 18.4 [(CH_3)$_3$], 20.9 (C2-CH_3), 20.9 (C4-CH_3), 28.8 (C-4), 30.0 (CH_2CH_3), 37.9 (C-2), 40.2 (C-3), 48.2 (C-5), 68.4 (C-1), 79.2 [C(CH_3)$_3$], 156.4 (CO); $[\alpha]^{22}_D$ + 8.04 (c 1.17, $CHCl_3$); HRMS calcd. for $C_{14}H_{30}NO_3$ [M + H]$^+$ 260.2220; found 260.2222.

4.9. General Procedure for the Protection of Hydroxy Groups as TBDPS Ethers. *tert*-Butyldiphenylsilyl chloride (2.5 mmol) was added to a stirring solution of the aminodiol (**24** or **25**; 1 mmol) and imidazole (2.5 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 bis-TBDPS ether.

*4.9.1. (2R,4S)-5-[(tert-Butyldiphenylsilyl)oxy]-N-{(R)-2-[(tert-butyldiphenylsilyl)oxy]-1-phenylethyl}-4-ethyl-2,4-dimethyl-1-pentanamine (**30**).* Following the general procedure, from aminodiol **24** (136 mg, 0.49 mmol), *tert*-butyldiphenylsilyl chloride (0.32 mL, 1.22 mmol), and imidazole (83.1 mg, 1.22 mmol) in CH_2Cl_2 (5 mL), bis-TBDPS ether **30** (226 mg, 61%) was obtained as a colorless oil after flash chromatography (99:1 to 90:10 hexane−EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.76 (t, J = 6.8 Hz, 3H, CH_3CH$_2$), 0.86 (s, 3H, C4-CH_3), 1.06 (d, J = 6.8 Hz, 3H, C2-CH_3), 1.11 [s, 18H, C(CH_3)$_3$], 1.20 (m, 2H, H-3), 1.36 (m, 2H, CH_2CH$_3$), 1.72 (m, 1H, H-2), 2.24 (m, 1H, H-1), 2.45 (dd, J = 10.8, 4.0 Hz, 1H, H-1), 3.29 (s, 2H, H-5), 3.72 (m, 2H, CH_2O), 3.79 (m, 1H, CHAr), 7.23−7.28 (m, 5H, ArH), 7.37−7.45 (m, 12H, ArH), 7.66−7.71 (m, 8H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.1 (CH_3CH_2), 19.2 [C(CH_3)$_3$], 19.4 [C(CH_3)$_3$], 20.8 (C2-CH_3), 22.2 (C4-CH_3), 26.8 [C(CH_3)$_3$], 26.9 [(CH_3)$_3$], 28.3 (C-2), 28.8 (CH_2CH_3), 38.5 (C-4), 41.1 (C-3), 55.5 (C-1), 64.4 (C-Ar), 69.1 (CH_2O), 70.1 (C-5), 127.1 (C-Ar), 127.5 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 128.8 (C-Ar), 129.5(C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 133.3 (C-Ar), (C-Ar), 133.9 (C-Ar), 135.5 (C-Ar), 135.6 (C-Ar), 135.7 (C-Ar); $[\alpha]^{22}_D$ −16.2 (c 2.3, MeOH); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{49}H_{66}NO_2Si_2$ 756.4627; found 756.4637.

*4.9.2. (2S,4S)-5-[(tert-Butyldiphenylsilyl)oxy]-N-{(R)-2-[(tert-butyldiphenylsilyl)oxy]-1-phenylethyl}-4-benzyl-2-ethyl-4-methyl-1-pentanamine (**31**).* Following the general procedure, from aminodiol **25** (66 mg, 0.18 mmol), *tert*-butyldiphenylsilyl chloride (0.12 mL, 0.45 mmol), and imidazole (31.4 mg, 0.45 mmol) in refluxing CH_2Cl_2 (2 mL), bis-TBDPS derivative **31** (113 mg, 73%) was obtained as a colorless oil after flash chromatography (99:1 to 90:10

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hexane−EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.73 (s, 3H, CH_3), 0.83 (t, J = 7.6 Hz, 3H, CH_3CH_2), 1.06 [s, 9H, $(CH_3)_3$], 1.08 (ms, 1H, H-3) 1.12 [s, 9H, $(CH_3)_3$], 1.37−1.51 (m, 3H, H-3, CH_3CH_2), 1.53−1.59 (m, 1H, H-2), 2.26−2.36 (m, 2H, H-1), 2.59 (d, J = 13.0 Hz, 1H, CH_2Ph), 2.68 (d, J = 13.0 Hz, 1H, CH_2Ph), 3.23 (d, J = 10.0 Hz, 1H, H-5), 3.33 (d, J = 10 Hz, 1H, H-5), 3.65 (m, 3H, CHAr, CH_2O), 7.06−7.67 (m, 30H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.3 (CH_3CH_2), 19.2 [$C(CH_3)_3$], 19.4 [$C(CH_3)_3$], 21.3 (CH_3), 26.3 (CH_3CH_2), 26.8 [$(CH_3)_3$], 27.1 [$(CH_3)_3$], 35.0 (C-2), 39.8 (C-3), 39.9 (C-4), 42.8 (CH_2Ph), 52.4 (C-1), 65.8 (C-Ar), 69.1 (CH_2O), 69.4 (C-5), 125.6 (C-Ar), 127.1 (C-Ar), 127.5 (C-Ar), 127.6 (C-Ar), 128.1 (C-Ar), 129.5 (C-Ar), 129.6 (C-Ar), 130.7 (C-Ar), 135.6(C-Ar), 135.8 (C-Ar), 133.3 (C-Ar), 133.5 (C-Ar), 133.7 (C-Ar), 133.9(C-Ar), 138.8 (C-Ar), 140.1 (C-Ar); $[\alpha]^{22}_D$ −6.6 (c 1.1, $CHCl_3$); HRMS calcd. for $C_{55}H_{70}NO_2Si_2$ $[M + H]^+$ 832.4940; found 832.4941.

4.10. General Procedure for the Oxidative Removal of the Benzylic Substituent. A 20% aqueous solution of NH_3 and iodine (8 mmol) were added to a solution of the bis-TBDPS ether (**30** or **31**; 1 mmol) in anhydrous THF at room temperature, and the resulting mixture was stirred at 60 °C 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 to give the nitrile derivative after flash chromatography.

*4.10.1. (2R,4S)-5-[(tert-Butyldiphenylsilyl)oxy]-4-ethyl-2,4-dimethylpentanenitrile (**32**).* Following the general procedure, from amine **30** (115 mg, 0.152 mmol) in THF (1 mL), aqueous solution of NH_3 (5.27 mL), and iodine (309 mg, 1.22 mmol), nitrile **32** (39 mg, 65%) was obtained after flash chromatography (95:5 hexane−EtOAc). IR (film) ν 2238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.78 (t, J = 7.6 Hz, 3H, CH_3CH_2), 0.93 (s, 3H, C4-CH_3), 1.07 [s, 9H, $(CH_3)_3$], 1.31 (d, J = 7.2 Hz, 3H, C2-CH_3), 1.31 (m, 1H, CH_2CH_3), 1.44−1.53 (m, 2H, CH_2CH_3, H-3), 1.73 (dd, J = 14.4, 10.0 Hz, 1H, H-3), 2.61 (m, 1H, H-2), 3.35 (d, J = 10.4 Hz, 1H, H-5), 3.40 (d, J = 10.4 Hz, 1H, H-5), 7.37−7.46 (m, 6H, ArH), 7.63−7.65 (m, 4H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.8 (CH_3CH_2), 19.3 [$C(CH_3)_3$], 20.3 (C-2), 20.6 (C2-CH_3) 22.1 (C4-CH_3), 26.9 [$(CH_3)_3$], 27.9 (CH_2CH_3), 38.4 (C-4), 40.8 (C-3), 69.7 (C-5), 124.2 (CN), 127.6 (C-Ar), 129.7 (C-Ar), 129.7 (C-Ar), 133.3 (C-Ar), 133.4 (C-Ar), 135.6 (C-Ar), 135.7 (C-Ar); $[\alpha]^{22}_D$ −4.0 (c 1.3, $CHCl_3$); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd. for $C_{25}H_{35}NNaOSi$ 416.238; found 416.2383.

*4.10.2. (2S,4S)-4-Benzyl-5-[(tert-butyldiphenylsilyl)oxy]-2-ethyl-4-methyl-1-pentanenitrile (**33**).* Following the general procedure, from amine **31** (110 mg, 0.13 mmol) in THF (0.5 mL), aqueous solution of NH_3 (8 mL), and iodine (269 mg, 1.06 mmol), nitrile **33** (38 mg, 61%) was obtained after flash chromatography (99:1 to 95:5 hexane−EtOAc). IR (film) ν 2242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.92 (s, 3H, CH_3), 1.03 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.13 [s, 9H, $(CH_3)_3$], 1.49 (dd, J = 14.4, 2.8 Hz, 1H, H-3), 1.56 (m, 2H, CH_2CH_3), 1.65 (dd, J = 14.4, 10.4 Hz, 1H, H-3), 2.48 (m, 1H, H-2), 2.63 (d, J = 13.2 Hz, 1H CH_2Ph), 2.73 (d, J = 13.2 Hz, 1H, CH_2Ph), 3.34 (d, J = 10.2 Hz, 1H, CH_2O), 3.41 (d, J = 10.2 Hz, 1H, CH_2O), 7.09−7.67 (m, 15H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.4 (CH_3CH_2), 19.3 (C-4), 21.8 (CH_3), 27.1 [$C(CH_3)_3$], 27.7 (CH_2CH_3), 27.9 (C-2), 39.3 (C-3), 41.9 (CH_2Ph), 69.6 (C-5), 123.5 (CN), 126.2127.6, 127.7 (C-Ar), 127.9 (C-Ar), 129.7 (C-Ar), 130.5 (C-Ar), 133.3 (C-Ar), 133.7 (C-Ar), 135.7 (C-Ar), 135.8 (C-Ar); $[\alpha]^{22}_D$ −3.8 (c 0.9, $CHCl_3$); HRMS calcd. for $C_{31}H_{39}NaNOSi$ $[M + Na]^+$ 493.2698; found 493.2699.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03580.

Experimental procedure for **1b** and **16**, spectroscopic data for the compounds not included in the Experimental Section, copies of ^{1}H and ^{13}C NMR spectra of all new compounds, and complete X-ray crystallographic data for **5** and **19** (PDF)

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Notes

The authors declare no competing financial interest.

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(16) The corresponding 3,3-diallyl (10% yield) and 3-allyl-3-hydroxy (2% yield) derivatives were also isolated (see the Supporting Information).

(17) Minor amounts (11%) of the corresponding 3-allyl-3-hydroxy derivative were also isolated (see the Supporting Information).

(18) The absolute configuration of **19** was unambiguously determined by X-ray crystallographic analysis.

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