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A general synthetic route to enantiopure cis-fused perhydrocycloalka[*c*]pyridines from phenylglycinol-derived lactams

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Abstract—A synthetic route to enantiopure piperidines bearing a five-, six-, or seven-membered carbocyclic ring cis-fused on the *c* side of the heterocycle from a common phenylglycinol-derived δ-lactam is reported. Key steps are (i) a cyclocondensation reaction of (*R*)-phenylglycinol with a racemic γ-oxoester in a process that involves a dynamic kinetic resolution; (ii) a highly stereoselective conjugate addition of an organocuprate to an unsaturated δ-lactam; and (iii) a ring-closing olefin metathesis.

1. Introduction

The *cis*-perhydroisoquinoline ring system is present in a large number of bioactive natural and synthetic products. Among them, of particular interest are the indole alkaloids of the yohimbine–reserpine type[1] and the marine sponge alkaloids of the manzamine[2] and madangamine[3] groups, all of them displaying a variety of notable pharmacological activities, as well as the HIV protease inhibitors nelfinavir and saquinavir.[4] Similarly, both the lower and higher carbocyclic ring homologs of perhydroisoquinolines are ring systems also found in natural products. Thus, α-skytanthine,[5] incarvilline,[6] tecostanine,[7] and related bicyclic alkaloids are substituted cis-fused perhydrocyclopenta[*c*]pyridines whereas the *cis*-perhydrocyclohepta[*c*]pyridine framework is present in the indole alkaloids of the ervatamine group[8] (Fig. 1).

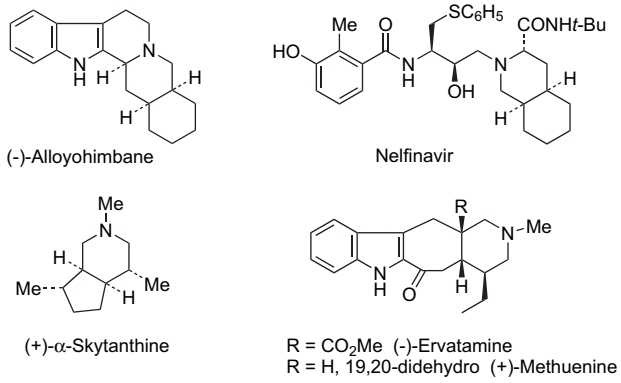

Figure 1.

2. Results and discussion

In previous work we have demonstrated that phenylglycinol-derived oxazolopiperidone lactams are exceptionally versatile building blocks for the enantioselective synthesis of structurally diverse piperidine-containing derivatives, including polysubstituted piperidines bearing virtually any type of substitution pattern, quinolizidines, indolizidines, perhydroquinolines, hexahydroisoquinolines, benzo[*a*]- and indolo[2,3-*a*]quinolizidines, as well as more complex indole alkaloids.[9,10]

In this paper we further illustrate the potential of phenylglycinol-derived oxazolopiperidone lactams in the enantioselective construction of piperidine-containing heterocycles. We present a general synthetic route to enantiopure piperidines bearing a cis-fused five-, six-, or seven-membered carbocyclic ring on the *c* side of the heterocycle.

The key steps of the synthesis are (i) a cyclocondensation reaction of (*R*)-phenylglycinol with racemic γ-substituted δ-oxoester **1**, in a process that involves a dynamic kinetic resolution;[11] (ii) a highly stereoselective conjugate addition of an appropriate organocuprate to an unsaturated lactam; (iii) the closure of the carbocyclic ring by a ring-closing

Keywords: Phenylglycinol; Oxazolopiperidone lactams; Conjugate addition; Ring-closing olefin metathesis; Dynamic kinetic resolution; Enantiopure cis-fused piperidines; Perhydroisoquinoline.
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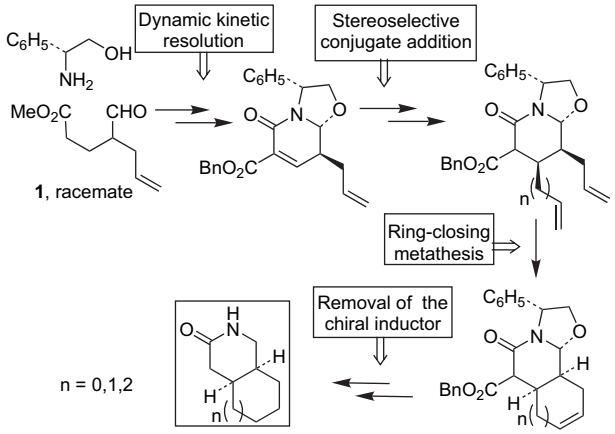
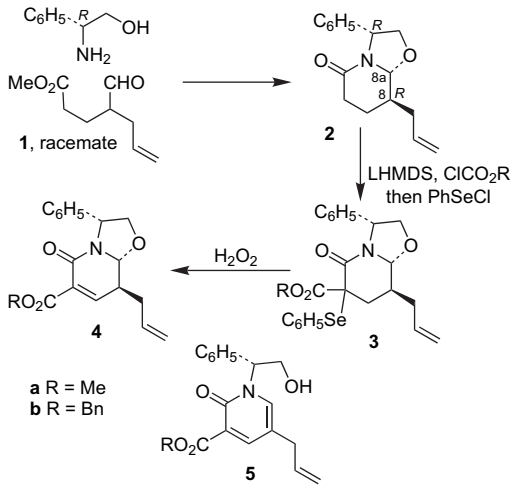
olefin metathesis;[12] and finally (iv) the reductive removal of the chiral inductor (Scheme 1).



Scheme 1. Synthetic strategy.

The starting racemic oxoester **1** was conveniently prepared in 64% yield by reaction of the piperidine enamine of 4-pentenal with methyl acrylate.[13] Cyclocondensation of **1** with (*R*)-phenylglycinol at 0 °C in the presence of anhydrous Na_2SO_4, followed by heating at 75–80 °C under vacuum (10–15 mmHg) stereoselectively afforded the enantiopure bicyclic lactam **2** in 71% yield (Scheme 2). Minor amounts (10%) of the (8*S*,8a*S*)-diastereoisomer were also isolated. This result clearly indicated that a dynamic kinetic resolution, with epimerization of the configurationally labile stereogenic center α to the aldehyde carbonyl group, had occurred during the cyclocondensation reaction.



Scheme 2. Preparation of the starting unsaturated δ-lactams.

It is known that α,β-unsaturated lactams are poor Michael acceptors.[14] The presence of an additional activating electron-withdrawing group α to the carbonyl or attached to the nitrogen is usually necessary for the success of the conjugate addition of organocuprates to unsaturated δ-lactams.[15–17] For this reason, lactam **2** was converted to the unsaturated lactams **4**, which incorporate an additional activating alkoxycarbonyl substituent in conjugation with the double bond. Thus, sequential treatment of **2** with LHMDS, methyl or benzyl chloroformate, and PhSeCl, followed by

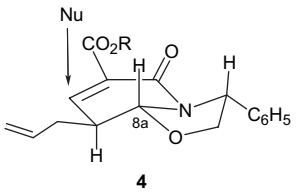
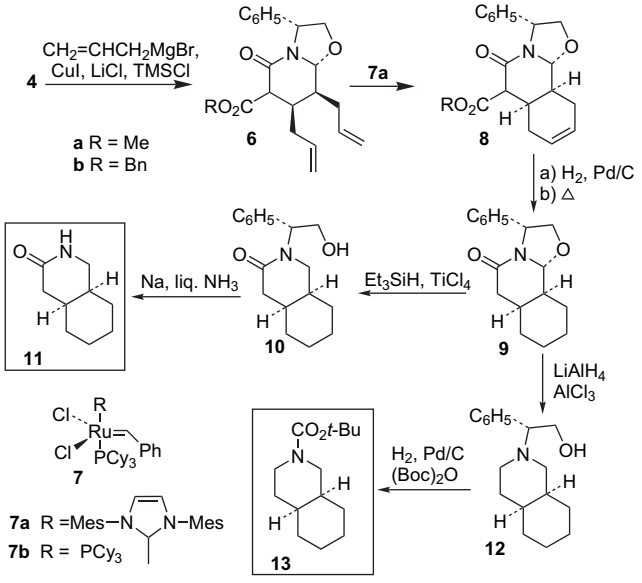


Figure 2. Stereoelectronic control in the conjugate addition.

oxidation of the resulting mixtures of selenides **3** with H_2O_2 in the presence of pyridine, afforded **4a** and **4b**, respectively, in good overall yield. Lactams **4** proved to be sensitive to both mild acid and basic conditions, affording the corresponding pyridones **5**. Consequently, they were immediately used in the next reaction without further purification.

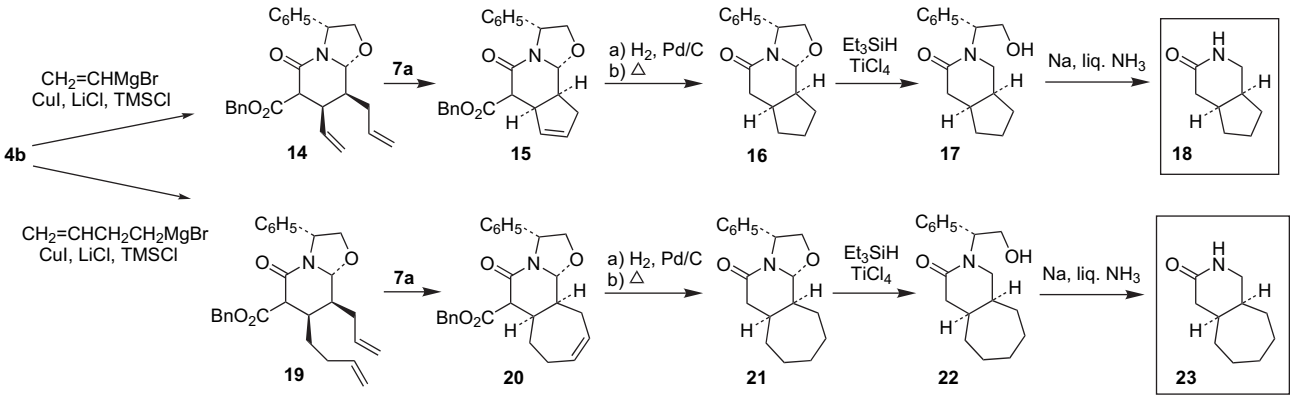
The conjugate addition of an allyl group was accomplished in excellent chemical yield and complete *exo*-facial diastereoselectivity by reacting lactams **4a** and **4b** with allylmagnesium bromide in presence of CuI, LiCl, and TMSCl.[18] The observed stereoselectivity can be explained by considering a stereoelectronically controlled[19] axial attack of the nucleophile on the electrophilic carbon of the conjugated double bond of the conformationally rigid lactams **4** (Fig. 2). The resulting *cis*-diallyl lactams **6a** and **6b** were isolated as mixtures of epimers at the isomerizable stereocenter adjacent to the ester and lactam carbonyl groups (Scheme 3).[20] However, this did not represent any inconvenience from the synthetic standpoint because the benzyloxycarbonyl substituent would be removed in a later synthetic step.



Scheme 3. Enantioselective synthesis of *cis*-perhydroisoquinolines.

The ring-closing metathesis of lactams **6a** and **6b** catalyzed by the second-generation Grubbs catalyst **7a** resulted in the closure of the carbocyclic ring to give the respective hydroisoquinolones **8a** and **8b** in excellent yield (85%). The use of the first-generation Grubbs catalyst **7b** in the reaction from **6b** was less satisfactory, hydroisoquinolone **8b** being isolated in only 66% yield after 20 h.

Catalytic hydrogenation of benzyloxycarbonyl ester **8b** using Pd–C as the catalyst brought about both the reduction



Scheme 4. Enantioselective synthesis of *cis*-perhydrocyclopenta[*c*]pyridines and *cis*-perhydrocyclohepta[*c*]pyridines.

of the carbon–carbon double bond and the debenzylation of the benzyloxycarbonyl group to give a β-keto acid, which was then decarboxylated by heating in refluxing toluene, leading to a single perhydroisoquinolone **9** in 85% overall yield.

Removal of the chiral inductor was performed in two steps. Reductive opening of the oxazolidine ring present in **9** with triethylsilane in the presence of $TiCl_4$ gave bicyclic lactam **10**, which was then debenzylated by treatment with sodium in liquid ammonia. The enantiopure *cis*-perhydroisoquinolin-3-one **11**, an advanced intermediate in the synthesis of (−)-alloyohimbane,[21] was obtained in excellent overall yield.

Alternatively, reduction of **9** with alane brought about both the reductive opening of the oxazolidine ring and the reduction of the lactam carbonyl to give the tertiary amine **12**. A final hydrogenation in the presence of $Pd(OH)_2$ and $(Boc)_2O$ led to the enantiopure *N*-protected *cis*-perhydroisoquinoline **13**.[22]

The extension of the above route to the synthesis of enantiopure piperidines cis-fused to five- and seven-membered carbocyclic rings simply required the use of an unsaturated organocuprate of suitable length, either vinyl or 3-butenyl, in the conjugate addition to the unsaturated lactam **4b** (Scheme 4). In both cases the reaction again took place with complete *exo*-facial stereoselectivity, cis with respect to the allyl substituent, leading to the corresponding lactams **14** and **19** as mixtures of epimers at the stereogenic center adjacent to the carbonyl groups.

Ring-closing metathesis of **14** led to the cis-fused cyclopenta-[*c*]piperidine derivative **15**, whereas a similar reaction from **19** gave the higher homolog **20**, bearing a seven-membered carbocyclic ring.[23] Operating as in the above perhydroisoquinoline series, tricyclic lactams **15** and **20** were converted in high overall yield to the corresponding cis-fused piperidones **18** and **23**. Thus, catalytic hydrogenation followed by decarboxylation led to **16** and **21**, respectively, as single diastereoisomers. A subsequent reductive cleavage of the C–O bond of the oxazolidine ring with Et_3SiH–$TiCl_4$, followed by removal of the phenylethanol moiety from the resulting derivatives **17** and **22** with sodium in liquid ammonia completed the synthesis.

3. Conclusion

In conclusion, starting from a common phenylglycinol-derived unsaturated δ-lactam we have developed an enantioselective synthetic route to *cis*-perhydrocycloalka[*c*]pyridines. By choosing the appropriate unsaturated organocuprate, this route provides practical and efficient access to enantiopure *cis*-perhydroisoquinolines as well as piperidines bearing a five- or seven-membered carbocyclic ring cis-fused on the *c* side of the heterocycle. The availability of both enantiomers of phenylglycinol gives access to these bicyclic derivatives in both enantiomeric series.

4. Experimental

4.1. General experimental procedures

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. NMR spectra were recorded at 300 or 400 MHz (^{1}H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography (TLC) was done on SiO_2 (silica gel 60 F_{254}), and the spots were located with aqueous potassium permanganate solution. Column chromatography was carried out using the flash chromatography technique. All non-aqueous reactions were performed under an inert atmosphere. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by the Centre D'Investigació i Desenvolupament (CSIC), Barcelona, and HRMS by the Unidade de Espectrometria de Masas, Santiago de Compostela.

4.2. Preparation of the starting unsaturated lactams 4

4.2.1. (3*R*,8*R*,8a*R*)-8-Allyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (2). A mixture of racemic aldehyde **1**[13] (4.6 g, 29 mmol), (*R*)-phenylglycinol (3.97 g, 29 mmol), and anhydrous Na_2SO_4 (17 g, 12 mmol) in Et_2O (115 mL) was stirred at 0 °C for 2 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was heated at 80 °C for 18 h under vacuum (10–15 mmHg).

Column chromatography (SiO_2 previously washed with 8:2 Et_3N–EtOAc; 1:3 EtOAc–hexane to EtOAc as eluent) of the residue afforded oxazolopiperidone **2** (5.3 g, 71%) and its (8*S*,8a*S*)-diastereoisomer **2′** (753 mg, 10%). Compound **2** (lower R_f): IR (NaCl) 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.45 (dddd, J=13.8, 13.8, 12.0, 7.2 Hz, 1H, H-7), 2.02 (m, 3H, H-7, H-8, CH_2 allyl), 2.30 (ddd, J=18.0, 12.0, 6.6 Hz, 1H, H-6), 2.42 (ddd, J=18.0, 7.2, 1.8 Hz, 1H, H-6), 2.62 (m, 1H, CH_2 allyl), 4.02 (dd, J=9.0, 1.2 Hz, 1H, H-2), 4.10 (dd, J=9.0, 6.9 Hz, 1H, H-2), 4.54 (d, J=8.7 Hz, 1H, H-8a), 4.92 (d, J=6.6 Hz, 1H, H-3), 5.12 (m, 2H, CH_2=), 5.86 (dddd, J=16.5, 10.2, 7.8, 6.0 Hz, 1H, CH=), 7.20–7.30 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.5 (C-7), 31.1 (C-6), 35.3 (CH_2), 38.9 (C-8), 58.8 (C-3), 73.5 (C-2), 91.7 (C-8a), 117.2 (CH_2=), 126.0, 128.2 (C-*o*, *m*), 127.1 (C-*p*), 134.4 (CH=), 141.2 (C-*i*), 166.9 (NCO); $[\alpha]_D^{22}$ −32.8 (*c* 1.0, EtOH). Anal. Calcd for $C_{16}H_{19}NO_2 \cdot \frac{1}{4} H_2O$: C, 73.40; H, 7.51; N, 5.35. Found: C, 73.71; H, 7.25; N, 5.41. Compound **2′** (higher R_f): IR (NaCl) 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.53 (m, 1H, H-7), 1.66 (m, 1H, H-8), 1.96 (m, 1H, H-7), 2.07 (dt, J=16.5, 8.4, 8.4 Hz, 1H, CH_2 allyl), 2.35 (ddd, J=18.6, 12.0, 6.6 Hz, 1H, H-6), 2.56 (m, 2H, H-6, CH_2 allyl), 3.76 (dd, J=9.0, 7.8 Hz, 1H, H-2), 4.48 (dd, J=9.0, 8.1 Hz, 1H, H-2), 4.71 (d, J=8.4 Hz, 1H, H-8a), 5.13 (m, 2H, CH_2=), 5.25 (t, J=7.8 Hz, 1H, H-3), 5.83 (dddd, J=16.5, 10.2, 8.1, 6.0 Hz, 1H, CH=), 7.25–7.34 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 22.8 (C-7), 31.4 (CH_2), 35.9 (C-6), 39.6 (C-8), 58.3 (C-3), 72.4 (C-2), 92.0 (C-8a), 117.4 (CH_2=), 126.0, 128.6 (C-*o*, *m*), 127.5 (C-*p*), 134.6 (CH=), 139.4 (C-*i*), 168.6 (NCO); $[\alpha]_D^{22}$ −59.9 (*c* 1.06, EtOH). Anal. Calcd for $C_{16}H_{19}NO_2 \cdot \frac{1}{4} H_2O$: C, 73.40; H, 7.51; N, 5.35. Found: C, 73.27; H, 7.25; N, 5.51.

4.2.2. (3*R*,8*S*,8a*R*)-8-Allyl-6-(methoxycarbonyl)-5-oxo-3-phenyl-6-(phenylselenyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (3a). Lithium bis(trimethylsilyl)-amide (1 M in THF, 10 mL) was slowly added at −78 °C to a solution of lactam **2** (2.0 g, 1.07 mmol) in anhydrous THF (120 mL), and the resulting mixture was stirred for 90 min. Then, methyl chloroformate (0.6 mL, 7.78 mmol) and, after 90 min of continuous stirring at −78 °C, PhSeCl (2.08 g, 10.8 mmol) were added to the solution. The resulting mixture was stirred for 1 h and poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography (1:9 EtOAc–hexane to 1:1 EtOAc–hexane) of the resulting oil afforded **3a** as a mixture of C-6 epimers (3.14 g, 86% overall yield). Compound **3a** (higher R_f epimer): IR (NaCl) 1667, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.82 (dd, J=14.0, 12.4 Hz, 1H, CH_2 allyl), 1.98 (m, 2H, H-7, H-8), 2.33 (dd, J=14.0, 2.8 Hz, 1H, CH_2 allyl), 2.41 (m, 1H, H-7), 3.58 (s, 3H, CH_3), 4.00 (dd, J=9.2, 2.0 Hz, 1H, H-2), 4.05 (dd, J=9.2, 6.8 Hz, 1H, H-2), 4.15 (d, J=8.8 Hz, 1H, H-8a), 4.87 (dd, J=6.8, 2.0 Hz, 1H, H-3), 5.03 (m, 2H, CH_2=), 5.71 (dddd, J=16.8, 10.4, 7.6, 6.4 Hz, 1H, CH=), 7.26–7.66 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 34.8 (C-7), 36.6 (CH_2), 37.7 (C-8), 53.0 (CH_3), 54.0 (C-6), 59.4 (C-3), 74.0 (C-2), 91.8 (C-8a), 117.7 (CH_2=), 126.4–138.2 (C-*o*, *m*, *p*), 133.7 (CH=), 140.5 (C-*i*), 163.3 (NCO), 170.8 (COO); $[\alpha]_D^{22}$ −99.3 (*c* 0.7, $CHCl_3$); *m*/*z* 471 (M^+, 6), 390 (68), 313 (67), 254 (50), 240 (86). HRMS calcd for $C_{24}H_{25}NO_4Se$: 471.0948, found: 471.0955. Compound **3a** (lower R_f epimer): IR (NaCl) 1656, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.98 (m, 1H, CH_2 allyl), 2.00 (dd, J=15.2, 11.6 Hz, 1H, H-7), 2.08 (dd, J=15.2, 4.0 Hz, 1H, H-7), 2.32 (m, 1H, H-8), 2.52 (m, 1H, CH_2 allyl), 3.73 (s, 3H, CH_3), 4.10 (dd, J=9.2, 1.2 Hz, 1H, H-2), 4.17 (dd, J=9.2, 6.8 Hz, 1H, H-2), 4.63 (d, J=9.2 Hz, 1H, H-8a), 4.97 (m, 3H, H-3, CH_2=), 5.59 (dddd, J=16.0, 10.0, 8.0, 6.0 Hz, 1H, CH=), 7.23–7.47 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 33.6 (C-7), 35.0 (CH_2), 36.5 (C-8), 53.3 (CH_3), 55.6 (C-6), 59.6 (C-3), 73.8 (C-2), 91.6 (C-8a), 117.8 (CH_2=), 126.8–138.3 (C-*o*, *m*, *p*), 134.0 (CH=), 140.5 (C-*i*), 162.8 (NCO), 171.0 (COO); $[\alpha]_D^{22}$ +18.46 (*c* 0.5, $CHCl_3$); *m*/*z* 471 (M^+, 26), 390 (19), 314 (18), 282 (50), 240 (53). HRMS calcd for $C_{24}H_{25}NO_4Se$: 471.0948, found: 471.0946.

4.2.3. (3*R*,8*S*,8a*R*)-8-Allyl-6-(benzyloxycarbonyl)-5-oxo-3-phenyl-6-(phenylselenyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (3b). Operating as in the above preparation of **3a**, from lactam **2** (5.39 g, 20 mmol), lithium bis(trimethylsilyl)amide (1 M in THF, 40 mL), benzyl chloroformate (6.6 mL, 20 mmol), and PhSeCl (5.7 g, 30 mmol), lactam **3b** was obtained as a mixture of C-6 epimers (8.3 g, 80% overall yield) after column chromatography (1:4 EtOAc–hexane to 1:3 EtOAc–hexane). Compound **3b** (higher R_f epimer): IR (NaCl) 1666, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.85 (dd, J=14.1, 12.6 Hz, 1H, CH_2 allyl), 1.92 (dd, J=13.5, 7.8 Hz, 1H, H-7), 1.99 (m, 1H, H-8), 2.37 (dm, J=14.1 Hz, 2H, CH_2 allyl, H-7), 3.93 (dd, J=9.0, 1.2 Hz, 1H, H-2), 3.96 (d, J=9.3 Hz, 1H, H-8a), 3.98 (dd, J=9.0, 6.0 Hz, 1H, H-2), 4.84 (dd, J=6.0, 1.2 Hz, 1H, H-3), 5.00 (br t, J=9.0 Hz, 2H, CH_2=), 5.02 (d, J=12.3 Hz, 1H, CH_2 benzyl), 5.07 (d, J=12.3 Hz, 1H, CH_2 benzyl), 5.60 (dddd, J=16.8, 10.5, 8.1, 6.0 Hz, 1H, CH=), 7.15–7.58 (m, 15H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 34.5 (C-7), 36.7 (CH_2), 37.6 (C-8), 54.7 (C-6), 59.5 (C-3), 67.6 (CH_2), 73.8 (C-2), 91.4 (C-8a), 117.6 (CH_2=), 126.2–129.5, 138.1 (C-*o*, *m*, *p*), 133.6 (CH=), 135.0, 140.3 (C-*i*), 163.0 (NCO), 169.8 (COO); $[\alpha]_D^{22}$ −75.3 (*c* 0.76, EtOH). Anal. Calcd for $C_{30}H_{29}NO_4Se$: C, 65.93; H, 5.35; N, 2.56. Found: C, 65.53; H, 5.57; N, 2.48. Compound **3b** (lower R_f epimer): IR (NaCl) 1660, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.95 (m, 1H, CH_2 allyl), 2.00 (dd, J=15.3, 4.2 Hz, 1H, H-7), 2.06 (dd, J=15.3, 4.8 Hz, 1H, H-7), 2.29 (m, 1H, H-8), 2.46 (m, 1H, CH_2 allyl), 4.05 (dd, J=9.0, 1.5 Hz, 1H, H-2), 4.12 (dd, J=9.0, 6.3 Hz, 1H, H-2), 4.54 (d, J=9.0 Hz, 1H, H-8a), 4.93 (dd, J=6.3, 1.5 Hz, 1H, H-3), 4.98 (m, 2H, CH_2=), 5.15 (d, J=12.6 Hz, 1H, CH_2 benzyl), 5.20 (d, J=12.6 Hz, 1H, CH_2 benzyl), 5.56 (dddd, J=16.8, 10.2, 8.1, 6.0 Hz, 1H, CH=), 7.15–7.40 (m, 15H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 33.5 (C-7), 34.9 (CH_2), 36.5 (C-8), 55.3 (C-6), 59.3 (C-3), 67.7 (CH_2), 73.7 (C-2), 91.3 (C-8a), 117.5 (CH_2=), 126.6–129.3, 138.1 (C-*o*, *m*, *p*), 133.9 (CH=), 135.1, 140.3 (C-*i*), 162.5 (NCO), 170.1 (COO); $[\alpha]_D^{22}$ +23.0 (*c* 1.0, EtOH). Anal. Calcd for $C_{30}H_{29}NO_4Se \cdot \frac{1}{4} H_2O$: C, 65.39; H, 5.40; N, 2.54. Found: C, 65.33; H, 5.35; N, 2.53.

4.2.4. (3*R*,8*S*,8a*R*)-8-Allyl-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (4a). Aqueous H_2O_2 (30%, 0.73 mL, 23.8 mmol) and pyridine (0.36 mL, 4.4 mmol) were added to a solution of selenides **3a** (1.6 g, 2.8 mmol) in CH_2Cl_2 (231 mL), and the resulting mixture was stirred at rt for 2 h. The two phases were separated, and the organic layer was washed with water (10×20 mL), dried, and concentrated to give crude **4a** (1.65 g) as an oil, which was kept at −30 °C and used in the next reaction without further purification: IR (NaCl) 1673, 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (dt, J=14.4, 8.7 Hz, 1H, CH_2 allyl), 2.70 (dm, J=14.4 Hz, 1H, CH_2 allyl), 2.91 (m, 1H, H-8), 3.78 (s, 3H, CH_3), 4.20 (dd, J=9.0, 2.4 Hz, 1H, H-2), 4.24 (dd, J=9.0, 6.0 Hz, 1H, H-2), 4.87 (d, J=10.5 Hz, 1H, H-8a), 5.03 (dd, J=6.0, 2.4 Hz, 1H, H-3), 5.27 (m, 2H, CH_2=), 5.86 (dddd, J=15.3, 10.8, 8.7, 5.7 Hz, 1H, CH=), 7.20–7.36 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 33.5 (CH_2), 41.2 (C-8), 52.3 (CH_3), 58.3 (C-3), 74.4 (C-2), 89.8 (C-8a), 119.0 (CH_2=), 126.8, 128.5 (C-*o*, *m*), 127.7 (C-*p*), 129.7 (C-6), 133.3 (CH=), 140.2 (C-*i*), 147.6 (C-7), 157.3 (COO), 164.3 (NCO).

4.2.5. (3*R*,8*S*,8a*R*)-8-Allyl-6-(benzyloxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (4b). Operating as described for the preparation of **4a**, from selenides **3b** (200 mg, 0.36 mmol), 30% aqueous H_2O_2 (76 μL, 2.5 mmol), and pyridine (33 μL, 0.47 mmol) in CH_2Cl_2 (26 mL), crude unsaturated lactam **4b** was obtained, kept at −30 °C, and used in the next reaction without further purification: ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 2.29 (ddd, J=14.0, 8.8, 8.0 Hz, 1H, CH_2 allyl), 2.68 (dm, J=14.0 Hz, 1H, CH_2 allyl), 2.91 (m, 1H, H-8), 4.18 (dd, J=9.2, 2.0 Hz, 1H, H-2), 4.22 (dd, J=9.2, 6.4 Hz, 1H, H-2), 4.87 (d, J=10.8 Hz, 1H, H-8a), 5.05 (dd, J=6.4, 2.0 Hz, 1H, H-3), 5.20 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.21 (masked, 2H, CH_2=), 5.26 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.83 (dddd, J=16.8, 10.8, 8.8, 6.0 Hz, 1H, CH=), 7.10–7.40 (m, 11H, ArH, H-7); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 33.6 (CH_2), 41.3 (C-8), 58.3 (C-3), 67.1 (CH_2), 74.5 (C-2), 89.9 (C-8a), 119.0 (CH_2=), 126.8–128.6 (C-*o*, *m*, *p*, C-6), 133.3 (CH=), 140.3, 135.5 (C-*i*), 147.6 (C-7), 157.3 (NCO), 163.7 (COO).

4.3. Conjugate addition reactions from unsaturated lactams 4

4.3.1. (3*R*,7*R*,8*S*,8a*R*)-7,8-Diallyl-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]-pyridine (6a). LiCl (332 mg, 7.84 mmol) was heated at 80 °C for 1 h under vacuum (10–15 mmHg) in a two-necked, 100 mL round-bottomed flask. Then, CuI (1.49 mg, 7.84 mmol) and THF (26 mL) were added at rt, and the mixture was stirred at rt for 5 min. The suspension was cooled at −78 °C, and allylmagnesium bromide (1 M in Et_2O, 7.84 mL), TMSCl (0.99 mL, 7.84 mmol), and the above crude unsaturated lactam **4a** (2.8 mmol) in THF (3 mL) were successively added. The resulting mixture was stirred at −78 °C for 18 h. The reaction was quenched with saturated aqueous NH_4Cl, and the organic layer was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (1:9 EtOAc–hexane to 3:7 EtOAc–hexane) gave **6a** (804 mg, 81% yield from **3a**) as a mixture of C-6 epimers (ratio 2:1). Compound (6*S*)-**6a** (major): IR (NaCl) 1665, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.80 (ddd, J=14.1, 12.0, 9.0 Hz, 1H, CH_2 allyl), 2.16 (dt, J=14.1, 9.3, 9.3 Hz, 1H, CH_2 allyl), 2.34 (dm, J=12.0 Hz, 1H, H-7), 2.44–2.70 (m, 3H, H-8, CH_2 allyl), 3.43 (d, J=1.5 Hz, 1H, H-6), 3.60 (s, 3H, CH_3), 4.02 (dd, J=9.3, 1.8 Hz, 1H, H-2), 4.15 (dd, J=9.3, 7.2 Hz, 1H, H-2), 4.62 (d, J=9.6 Hz, 1H, H-8a), 4.91 (dd, J=7.2, 1.8 Hz, 1H, H-3), 5.14 (m, 4H, CH_2=), 5.68 (dddd, J=15.0, 10.2, 9.0, 4.8 Hz, 1H, CH=), 5.84 (dddd, J=15.3, 9.9, 8.7, 5.1 Hz, 1H, CH=), 7.26–7.33 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 31.6, 31.8 (CH_2), 36.9 (C-7), 38.5 (C-8), 51.5 (C-6), 52.3 (CH_3), 59.6 (C-3), 73.9 (C-2), 89.4 (C-8a), 117.4, 118.5 (CH_2=), 126.4, 128.2 (C-*o*, *m*), 127.4 (C-*p*), 134.4, 134.8 (CH=), 140.5 (C-*i*), 162.3 (NCO), 170.6 (COO); *m*/*z* 355 (M^+, 1), 312 (21), 296 (13), 282 (8), 272 (8), 254 (5). Compound (6*R*)-**6a** (minor): ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 32.8, 35.9 (CH_2), 36.5 (C-7), 41.9 (C-8), 52.5 (CH_3), 53.7 (C-6), 59.2 (C-3), 73.8 (C-2), 89.8 (C-8a), 118.4, 119.6 (CH_2=), 126.7–128.5 (C-*o*, *m*, *p*), 132.8, 133.4 (CH=), 140.6 (C-*i*), 162.5 (NCO), 170.8 (COO); *m*/*z* 355 (M^+, 2), 314 (5), 272 (8), 254 (4), 176 (6), 148 (11), 128 (7), 120 (17), 119 (12), 117 (20), 105 (13), 104 (100). HRMS calcd for $C_{21}H_{25}NO_4$: 355.1783, found: 355.1779.

4.3.2. (3*R*,7*R*,8*S*,8a*R*)-7,8-Diallyl-6-(benzyloxycarbonyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]-pyridine (6b). Operating as in the preparation of **6a**, from the above crude lactam **4b** (0.36 mmol), allylmagnesium bromide (1 M solution in Et_2O, 1.04 mL), CuI (197 mg, 1.04 mmol), LiCl (45 mg, 1.04 mmol), and TMSCl (131 μL, 1.04 mmol) in THF (3 mL), lactams (6*S*)-**6b** (123 mg) and (6*R*)-**6b** (25 mg) (93% overall yield from **3b**) were obtained after column chromatography (1:4 EtOAc–hexane to 1:2 EtOAc–hexane). Compound (6*S*)-**6b** (lower R_f epimer): IR (NaCl) 1666, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.80 (ddd, J=14.1, 12.0, 8.7 Hz, 1H, CH_2 allyl), 2.16 (ddd, J=14.1, 9.6, 9.6 Hz, 1H, CH_2 allyl), 2.32 (dm, J=11.7 Hz, 1H, H-7), 2.50 (m, 2H, H-8, CH_2 allyl), 2.62 (dm, J=14.1 Hz, 1H, CH_2 allyl), 3.47 (d, J=0.9 Hz, 1H, H-6), 3.99 (dd, J=9.0, 1.8 Hz, 1H, H-2), 4.14 (dd, J=9.0, 6.9 Hz, 1H, H-2), 4.61 (d, J=9.6 Hz, 1H, H-8a), 4.91 (dd, J=6.9, 1.8 Hz, 1H, H-3), 5.02 (d, J=12.3 Hz, 1H, CH_2 benzyl), 5.09 (d, J=12.3 Hz, 1H, CH_2 benzyl), 5.13 (m, 4H, CH_2=), 5.67 (m, 2H, CH=), 7.20–7.30 (m, 10H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 31.7 (CH_2), 36.8 (C-7), 38.6 (C-8), 51.7 (C-6), 59.7 (C-3), 66.8 (CH_2), 74.0 (C-2), 89.4 (C-8a), 117.4, 118.6 (CH_2=), 126.4–128.4 (C-*o*, *m*, *p*), 134.4, 134.8 (CH=), 135.5, 140.5 (C-*i*), 162.2 (NCO), 169.9 (COO); $[\alpha]_D^{22}$ −11.3 (*c* 0.4, $CHCl_3$); *m*/*z* 431 (M^+, 1), 388 (4), 340 (7), 296 (21), 282 (11), 268 (3), 254 (5), 240 (2). HRMS calcd for $C_{27}H_{29}NO_4$: 431.2096, found: 431.2097. Compound (6*R*)-**6b** (higher R_f epimer): IR (NaCl) 1668, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.84 (m, 1H, H-8), 2.16 (m, 2H, CH_2 allyl), 2.36 (m, 1H, H-7), 2.44 (m, 2H, CH_2 allyl), 3.35 (d, J=7.6 Hz, 1H, H-6), 4.06 (dd, J=9.2, 0.8 Hz, 1H, H-2), 4.14 (dd, J=9.2, 6.4 Hz, 1H, H-2), 4.71 (d, J=9.2 Hz, 1H, H-8a), 4.92 (dd, J=6.4, 0.8 Hz, 1H, H-3), 5.05 (m, 2H, CH_2=), 5.13 (masked, 2H, CH_2=), 5.14 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.19 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.64 (dddd, J=17.6, 10.4, 7.6, 7.6 Hz, 1H, CH=), 5.85

(dddd, J=16.8, 10.0, 7.2, 7.2 Hz, 1H, CH═), 7.20–7.40 (m, 10H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 33.1, 36.1 (CH_2), 36.8 (C-7), 42.0 (C-8), 53.8 (C-6), 59.2 (C-3), 67.2 (CH_2), 73.9 (C-2), 89.9 (C-8a), 118.3, 119.6 (CH_2═), 126.7–128.6 (C-*o*, *m*, *p*), 132.9, 133.5 (CH═), 135.4, 140.7 (C-*i*), 162.7 (NCO), 170.3 (COO); $[\alpha]_D^{22}$ −53.6 (*c* 0.5, $CHCl_3$); *m*/*z* 431 (M^+, 7), 388 (6), 340 (17), 296 (13), 282 (2), 254 (7). HRMS calcd for $C_{27}H_{29}NO_4$: 431.2096, found: 431.2088.

4.3.3. (3*R*,7*R*,8*S*,8a*R*)-8-Allyl-6-(benzyloxycarbonyl)-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (14). Operating as in the preparation of **6a**, from crude lactam **4b** (prepared from 1.8 mmol of selenides **3b**), vinylmagnesium bromide (1 M solution in Et_2O, 6.84 mL), CuI (1.3 g, 6.84 mmol), LiCl (290 mg, 6.84 mmol), and TMSCl (865 μL, 6.84 mmol) in THF (40 mL), lactam **14** was obtained as a mixture of C-6 epimers (ratio 2:1, 463 mg, 62% yield from **3b**) after flash chromatography (1:4 EtOAc–hexane to 1:2 EtOAc–hexane). Compound (6*S*)-**14** (major): IR (NaCl) 1666, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 2.15 (m, 1H, CH_2 allyl), 2.47 (dt, J=10.0, 4.0, 4.0 Hz, 1H, H-8), 2.54 (m, 1H, CH_2 allyl), 3.01 (dd, J=8.0, 4.0 Hz, 1H, H-7), 3.48 (d, J=1.2 Hz, 1H, H-6), 4.00 (dd, J=9.2, 1.6 Hz, 1H, H-2), 4.13 (dd, J=9.2, 6.8 Hz, 1H, H-2), 4.56 (d, J=9.2 Hz, 1H, H-8a), 4.92 (dd, J=6.8, 1.2 Hz, 1H, H-3), 5.07 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.11 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.13–5.18 (m, 2H, CH_2═ allyl), 5.16 (d, J=17.2 Hz, 1H, CH_2═ vinyl), 5.26 (d, J=10.8 Hz, 1H, CH_2═ vinyl), 5.70 (m, 1H, CH═ allyl), 5.82 (ddd, J=17.2, 10.8, 8.0 Hz, 1H, CH═ vinyl), 7.25–7.32 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100.6) δ 31.7 (CH_2), 38.7 (C-8), 40.9 (C-7), 52.6 (C-6), 59.7 (C-3), 67.1 (CH_2), 74.0 (C-2), 89.6 (C-8a), 117.5 (CH_2═), 118.8 (CH_2═), 126.5–128.5 (C-*o*, *m*, *p*), 134.0, 134.6 (CH═), 135.4, 140.6 (C-*i*), 162.1 (NCO), 167.7 (COO); *m*/*z* 417 (M^+, 1), 326 (3), 283 (5), 282 (10), 240 (4), 148 (9), 128 (4), 120 (8), 119 (4), 118 (3), 117 (8), 108 (5), 104 (23), 91 (100). HRMS calcd for $C_{26}H_{27}NNaO_4$: 440.1832, found: 440.1843. Compound (6*R*)-**14** (minor): ^{1}H NMR (400 MHz, $CDCl_3$, selected resonances) δ 2.02 (m, 1H, CH_2 allyl), 3.10 (ddd, J=10.4, 6.4, 4.0 Hz, 1H, H-7), 3.53 (d, J=6.0 Hz, 1H, H-6), 4.07 (dd, J=9.2, 1.2 Hz, 1H, H-2), 4.15 (dd, J=9.2, 6.8 Hz, 1H, H-2), 4.68 (d, J=9.6 Hz, 1H, H-8a), 4.94 (dd, J=6.8, 1.2 Hz, 1H, H-3), 5.02 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.09 (d, J=12.4 Hz, 1H, CH_2 benzyl); ^{13}C NMR (100.6 MHz, $CDCl_3$, selected resonances) δ 32.2 (CH_2), 42.5 (C-8), 42.8 (C-7), 54.0 (C-6), 59.9 (C-3), 66.8 (CH_2), 73.8 (C-2), 89.5 (C-8a), 117.8 (CH_2═), 121.0 (CH_2═), 141.0 (C-*i*).

4.3.4. (3*R*,7*R*,8*S*,8a*R*)-8-Allyl-6-(benzyloxycarbonyl)-7-(3-butenyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (19). Operating as in the preparation of **6a**, from crude lactam **4b** (prepared from 1.8 mmol of selenides **3b**), 3-butenylmagnesium bromide[24] (5.04 mmol), CuI (960 mg, 5.04 mmol), LiCl (214 mg, 5.04 mmol), and TMSCl (636 μL, 5.04 mmol) in THF (15 mL), lactam **19** was obtained as a mixture of C-6 epimers (ratio 9:1, 557 mg, 70% yield from **3b**) after flash chromatography (1:4 EtOAc–hexane to 1.5:2 EtOAc–hexane). Compound (6*S*)-**19** (major): IR (NaCl) 1664, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 1.18 (m, 1H, CH_2), 1.71 (m, 1H, CH_2), 1.98 (ddd, J=15.6, 15.6, 8.0 Hz, 1H, CH_2), 2.29–2.10 (m, 3H, CH_2 allyl, H-7, CH_2), 2.46 (m, 1H, H-8), 2.58 (m, 1H, CH_2 allyl), 3.42 (s, 1H, H-6), 3.97 (dd, J=9.0, 1.2 Hz, 1H, H-2), 4.11 (dd, J=9.0, 6.8 Hz, 1H, H-2), 4.58 (d, J=9.2 Hz, 1H, H-8a), 4.90 (dd, J=6.8, 1.2 Hz, 1H, H-3), 4.97 (dd, J=10.4, 1.6 Hz, 1H, CH_2═), 5.04 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.08 (d, J=12.4 Hz, 1H, CH_2 benzyl), 5.02–5.11 (m, 3H, CH_2═), 5.61–5.76 (m, 2H, CH═), 7.34–7.21 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.3 (CH_2), 31.3 (CH_2), 31.5 (CH_2), 36.5 (C-7), 38.8 (C-8), 52.2 (C-6), 59.6 (C-3), 66.8 (CH_2), 73.9 (C-2), 88.4 (C-8a), 116.0, 117.3 (CH_2═), 126.3–128.4 (C-*o*, *m*, *p*), 134.5, 136.8 (CH═), 135.4, 140.5 (C-*i*), 162.3 (NCO), 169.8 (COO). Anal. Calcd for $C_{28}H_{31}O_4N\cdot\frac{1}{2}H_2O$: C, 73.98; H, 7.10; N, 3.08. Found: C, 74.14; H, 6.95; N, 3.04. Compound (6*R*)-**19** (minor): IR (NaCl) 1668, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.56 (m, 2H, CH_2), 1.83 (dddd, J=8.8, 8.8, 4.8, 4.8 Hz, 1H, H-8), 2.00 (m, 2H, CH_2), 2.27 (dddd, J=8.8, 8.8, 6.8, 5.2 Hz, 1H, H-7), 2.40 (t, J=6.4 Hz, 2H, CH_2 allyl), 3.32 (d, J=6.8 Hz, 1H, H-6), 4.06 (dd, J=9.0, 1.5 Hz, 1H, H-2), 4.14 (dd, J=9.0, 6.6 Hz, 1H, H-2), 4.70 (d, J=8.7 Hz, 1H, H-8a), 4.94 (dd, J=6.6, 1.5 Hz, 1H, H-3), 4.90–5.18 (m, 4H, CH_2═), 5.15 (d, J=12.3 Hz, 1H, CH_2 benzyl), 5.20 (d, J=12.3 Hz, 1H, CH_2 benzyl), 5.66 (m, 1H, CH═), 5.83 (ddd, J=14.8, 10.0, 7.6 Hz, 1H, CH═), 7.05–7.20 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) 29.3 (CH_2), 32.1 (CH_2), 33.7 (CH_2), 37.0 (C-7), 43.3 (C-8), 54.3 (C-6), 59.1 (C-3), 67.2 (CH_2), 73.8 (C-2), 89.9 (C-8a), 115.3, 118.2 (CH_2═), 133.8, 137.3 (CH═), 135.3, 140.7 (C-*i*), 163.8 (NCO), 170.2 (COO); *m*/*z* 445 (M^+, 2), 355 (4), 354 (15), 310 (9), 300 (3), 268 (4), 254 (3), 214 (3), 201 (6), 148 (14), 128 (6), 120 (16), 119 (7), 117 (11), 108 (7), 104 (39), 103 (8), 92 (9), 91 (100). HRMS calcd for $C_{28}H_{31}NNaO_4$: 468.2150, found: 468.2150.

4.4. Ring-closing metathesis reaction

4.4.1. (3*R*,6a*R*,10a*S*,10b*R*)-6-(Methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (8a). Second-generation Grubbs catalyst (**7a**, 57 mg) was added to a solution of lactam **6a** (300 mg, 0.84 mmol) in CH_2Cl_2 (125 mL). The mixture was stirred for 2 h at rt, concentrated, and purified by flash column chromatography (1:4 EtOAc–hexane to 2:3 EtOAc–hexane) to yield tricyclic lactam **8a** as a mixture of C-6 epimers (220 mg, 81% yield). Compound (6*R*)-**8a** (major): IR (NaCl) 1667, 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 2.00 (m, 1H, H-7), 2.20 (m, 1H, H-7), 2.43 (m, 2H, H-10), 2.50 (m, 1H, H-6a), 2.70 (m, 1H, H-10a), 3.18 (s, 1H, H-6), 3.60 (s, 1H, CH_3), 3.96 (dd, J=9.0, 1.2 Hz, 1H, H-2), 4.12 (dd, J=9.0, 6.9 Hz, 1H, H-2), 4.85 (d, J=9.9 Hz, 1H, H-10b), 4.92 (dd, J=6.9, 1.2 Hz, 1H, H-3), 5.69 (m, 2H, H-8, H-9), 7.22–7.35 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.1 (C-10), 28.0 (C-7), 32.6 (C-10a), 33.5 (C-6a), 52.2 (CH_3), 53.9 (C-6), 59.4 (C-3), 73.6 (C-2), 87.1 (C-10b), 124.4, 124.8 (C-8, C-9), 126.8, 128.0 (C-*o*, *m*), 127.2 (C-*p*), 140.6 (C-*i*), 162.0 (NCO), 170.2 (COO). Compound (6*S*)-**8a** (minor): ^{13}C NMR (75.4 MHz, $CDCl_3$, selected resonances) δ 24.7 (C-10), 32.6 (C-10a), 36.7 (C-6a), 51.8 (CH_3), 53.7 (C-6), 59.6 (C-3), 73.3 (C-2), 86.6 (C-10b), 140.9 (C-*i*), 162.4 (NCO),

169.1 (COO). Anal. Calcd for $C_{19}H_{21}O_4N\cdot\frac{1}{4}H_2O$: C, 68.76; H, 6.53; N, 4.22. Found: C, 68.82; H, 6.90; N, 4.20.

4.4.2. (3*R*,6a*R*,10a*S*,10b*R*)-6-(Benzyloxycarbonyl)-5-oxo-3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (8b). Operating as above, from lactam **6b** (575 mg, 1.33 mmol) and second-generation Grubbs catalyst (**7a**, 86 mg) in CH_2Cl_2 (190 mL), tricyclic lactam **8b** was obtained as a mixture of C-6 epimers (ratio 85:15, 455 mg, 85% yield) after column chromatography (1:4 EtOAc–hexane to 1.3:1 EtOAc–hexane). Compound (6*R*)-**8b** (major): IR (NaCl) 3030, 2915, 1736, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 2.00 (m, 1H, H-7), 2.26 (m, 1H, H-7), 2.47 (m, 2H, H-10), 2.52 (m, 1H, H-6a), 2.73 (m, 1H, H-10a), 3.24 (s, 1H, H-6), 3.97 (dd, *J*=9.0, 1.5 Hz, 1H, H-2), 4.14 (dd, *J*=9.0, 6.9 Hz, 1H, H-2), 4.86 (d, *J*=9.9 Hz, 1H, H-10b), 4.94 (dd, *J*=6.9, 1.5 Hz, 1H, H-3), 5.03 (d, *J*=12.3 Hz, 1H, CH_2 benzyl), 5.10 (d, *J*=12.3 Hz, 1H, CH_2 benzyl), 5.69 (m, 2H, H-8, H-9), 7.20–7.32 (m, 10H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.3 (C-10), 28.3 (C-7), 32.9 (C-10a), 33.7 (C-6a), 54.2 (C-6), 59.8 (C-3), 67.1 (CH_2), 73.8 (C-2), 87.3 (C-10b), 124.5, 125.0 (C-8, C-9), 126.3–128.4 (C-*o*, *m*, *p*), 135.3, 140.6 (C-*i*), 162.0 (NCO), 169.7 (COO). Compound (6*S*)-**8b** (minor): ^1H NMR (300 MHz, $CDCl_3$, selected resonances) δ 2.65 (m, 1H, H-10a), 3.58 (d, *J*=5.7 Hz, 1H, H-6), 4.02 (dd, *J*=9.0, 1.2 Hz, 1H, H-2), 4.12 (dd, *J*=9.0, 6.0 Hz, 1H, H-2), 4.91 (d, *J*=9.9 Hz, 1H, H-10b), 5.10 (d, *J*=12.3 Hz, 1H, CH_2 benzyl), 5.16 (d, *J*=12.3 Hz, 1H, CH_2 benzyl); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.9 (C-10), 29.7 (C-7), 32.6 (C-10a), 36.7 (C-6a), 53.9 (C-6), 59.7 (C-3), 66.8 (CH_2), 73.5 (C-2), 86.8 (C-10b), 124.0, 124.5 (C-8, C-9), 126.3–128.4 (C-*o*, *m*, *p*), 135.3, 141.0 (C-*i*), 162.5 (NCO), 168.6 (COO).

4.4.3. (3*R*,6a*R*,9a*S*,9b*R*)-6-(Benzyloxycarbonyl)-5-oxo-3-phenyl-2,3,5,6,6a,9,9a,9b-octahydrocylopent[*c*]oxazolo[3,2-*a*]pyridine (15). Operating as described for the preparation of **8a**, from lactam **14** (443 mg, 1.06 mmol) and second-generation Grubbs catalyst (**7a**, 50 mg) in CH_2Cl_2 (151 mL), tricyclic lactam **15** was obtained as a mixture of C-6 epimers (ratio 9:1, 366 mg, 88% yield) after column chromatography (1:2.5 EtOAc–hexane to 1:1.5 EtOAc–hexane). Compound (6*R*)-**15** (major): IR (NaCl) 1678, 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY) δ 2.49 (dm, *J*=16.2 Hz, 1H, H-9), 2.75–2.93 (m, 2H, H-9, H-9a), 3.14 (d, *J*=11.7 Hz, 1H, H-6), 3.74 (m, 1H, H-6a), 4.17 (dd, *J*=9.0, 1.5 Hz, 1H, H-2), 4.22 (dd, *J*=9.0, 6.0 Hz, 1H, H-2), 4.75 (d, *J*=8.1 Hz, 1H, H-9b), 5.00 (dd, *J*=6.0, 1.5 Hz, 1H, H-3), 5.19 (d, *J*=12.3 Hz, 1H, CH_2 benzyl), 5.09 (d, *J*=12.3 Hz, 1H, CH_2 benzyl), 5.54 (ddd, *J*=6.6, 4.5, 2.1 Hz, 1H, CH═), 5.77 (ddd, *J*=5.7, 5.4, 2.1 Hz, 1H, CH═), 7.10–7.20 (m, 10H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 35.8 (C-9), 41.7 (C-9a), 46.4 (C-6a), 53.8 (C-6), 58.5 (C-3), 67.2 (CH_2), 74.7 (C-2), 91.9 (C-9b), 126.5–128.6 (C-*o*, *m*, *p*), 130.8, 130.9 (HC═CH), 135.5, 140.1 (C-*i*), 163.9 (NCO), 168.8 (COO); mp 105–106 °C; *m*/*z* 390 (M^++1, 2), 389 (M^+, 8), 348 (4), 298 (25), 255 (10), 254 (31), 213 (7), 148 (16), 128 (7), 120 (20), 117 (14), 108 (7), 105 (8), 104 (33), 103 (9), 92 (8), 91 (100). Compound (6*R*)-**15** (minor): ^{13}C NMR (75.4 MHz, $CDCl_3$, selected resonances) δ 36.3 (C-9), 41.6 (C-9a), 46.1 (C-6a), 52.9 (C-6), 58.5 (C-3), 67.2 (CH_2), 74.0 (C-2), 131.8 (HC═CH), 135.0, 140.8 (C-*i*), 163.4 (NCO), 169.2 (COO). Anal. Calcd for $C_{24}H_{23}O_4N\cdot\frac{1}{2}H_2O$: C, 72.35; H, 6.07; N, 3.52. Found: C, 72.10; H, 5.93; N, 3.33. HRMS calcd for $C_{24}H_{23}NO_4$: 389.1627, found: 389.1623.

4.4.4. (3*R*,6a*R*,11a*S*,11b*R*)-6-(Benzyloxycarbonyl)-5-oxo-3-phenyl-2,3,5,6,6a,7,8,11,11a,11b-decahydrocyclopent[*c*]oxazolo[3,2-*a*]pyridine (20). Operating as described for the preparation of **8a**, from lactam **19** (184 mg, 0.41 mmol) and second-generation Grubbs catalyst (**7a**, 26 mg) in CH_2Cl_2 (60 mL) stirred for 4 h, tricyclic lactam **20** was obtained as a mixture of C-6 epimers (ratio 9:1, 145 mg, 85%) after column chromatography (1:3 EtOAc–hexane). Compound (6*R*)-**20** (major): IR (NaCl) 1675, 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.69 (m, 2H, H-11, H-8), 2.23 (m, 2H, H-8, H-7), 2.55 (m, 2H, H-6a, H-11), 2.60 (m, 1H, H-11a), 3.23 (d, *J*=5.6 Hz, 1H, H-6), 4.04 (dd, *J*=8.8, 1.6 Hz, 1H, H-2), 4.17 (dd, *J*=8.8, 7.2 Hz, 1H, H-2), 4.83 (d, *J*=8.4 Hz, 1H, H-11b), 4.94 (dd, *J*=7.2, 1.6 Hz, 1H, H-3), 5.11 (d, *J*=12.4 Hz, 1H, CH_2 benzyl), 5.15 (d, *J*=12.4 Hz, 1H, CH_2 benzyl), 5.71 (m, 1H, H-9), 5.77 (m, 1H, H-10), 7.23–7.34 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.2 (C-8), 28.1 (C-11), 28.5 (C-7), 39.1 (C-11a), 40.8 (C-6a), 55.2 (C-6), 59.0 (C-3), 66.9 (CH_2), 74.1 (C-2), 88.4 (C-11b), 126.3–128.4, 131.7 (C-*o*, *m*, *p*, C-9, C-10), 135.4, 140.4 (C-*i*), 163.2 (NCO), 169.6 (COO); *m*/*z* 417 (M^+, 3), 326 (7), 283 (15), 282 (47), 214 (4), 148 (9), 146 (3), 128 (6), 120 (14), 119 (5), 117 (8), 105 (6), 104 (24), 103 (8), 92 (9), 91 (100). Compound (6*S*)-**20** (minor): ^{13}C NMR (100.6 MHz, $CDCl_3$, selected resonances) δ 26.3 (C-8), 27.6 (C-11), 28.6 (C-7), 40.5 (C-11a), 41.4 (C-6a), 55.6 (C-6), 58.7 (C-3), 67.0 (CH_2), 73.8 (C-2), 89.6 (C-11b), 141.0 (C-*i*), 163.2 (NCO), 168.8 (COO). HRMS calcd for $C_{26}H_{27}NNaO_4$: 440.1837, found: 440.1832.

4.5. Catalytic hydrogenation

4.5.1. (3*R*,6a*S*,10a*S*,10b*R*)-5-Oxo-3-phenylperhydrooxazolo[2,3-*a*]isoquinoline (9). A solution of **8b** (500 mg, 1.24 mmol) in MeOH (40 mL) containing 10% Pd–C (56 mg) was hydrogenated at 25 °C for 48 h. The catalyst was removed by filtration, and the solvent was evaporated. The resulting oil was dissolved in toluene (70 mL) and the solution was heated to reflux for 12 h, cooled, and poured into brine. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. The residue was chromatographed (1:1 EtOAc–hexane) to afford compound **9** (287 mg, 85%) as a white solid: IR (NaCl) 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.40–1.80 (m, 7H), 2.10 (m, 3H, H-10a, H-6a, H-10), 2.12 (dm, *J*=18.3 Hz, 1H, H-6), 2.56 (dd, *J*=18.3, 7.2 Hz, 1H, H-6), 3.99 (dd, *J*=9.0, 1.5 Hz, 1H, H-2), 4.16 (dd, *J*=9.0, 6.9 Hz, 1H, H-2), 4.92 (d, *J*=6.0 Hz, 1H, H-3), 5.04 (d, *J*=9.6 Hz, 1H, H-10b), 7.10–7.30 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.6 (CH_2), 25.8 (CH_2), 26.0 (CH_2), 29.8 (CH_2), 33.2 (C-6a), 37.5 (C-10a), 38.5 (C-6), 59.1 (C-3), 73.7 (C-2), 86.7 (C-10b), 126.2, 128.3 (C-*o*, *m*), 127.3 (C-*p*), 141.5 (C-*i*), 166.9 (NCO); mp 126–128 °C; $[\alpha]_D^{22}$ +37.9 (*c* 0.64, $CHCl_3$). Anal. Calcd for $C_{17}H_{21}O_2N\cdot\frac{1}{4}H_2O$: C, 74.02; H, 7.86; N, 5.08. Found: C, 74.24; H, 7.82; N, 4.76.

4.5.2. (3*R*,6a*S*,9a*S*,9b*R*)-5-Oxo-3-phenylperhydrocyclopent[*c*]oxazolo[3,2-*a*]pyridine (16). Operating as above, from lactam **15** (146 mg, 0.37 mmol) and 10% Pd–C (16 mg) in MeOH (13 mL), lactam **16** was obtained (80 mg, 83%) after column chromatography (1:1.5 EtOAc–hexane): IR (NaCl) 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (m, 1H), 1.68 (m, 3H), 2.01 (m, 1H), 2.04 (d, J=17.1, 13.0 Hz, 1H, H-6), 2.52 (m, 1H), 2.54 (dd, J=17.1, 6.0 Hz, 1H, H-6), 4.12 (dd, J=9.0, 1.2 Hz, 1H, H-2), 4.24 (dd, J=9.0, 6.6 Hz, 1H, H-2), 4.70 (d, J=8.4 Hz, 1H, H-9b), 5.01 (dd, J=6.6, 1.2 Hz, 1H, H-3), 7.10–7.17 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 25.8 (CH_2), 30.0 (CH_2), 33.9 (CH_2), 35.7 (C-6a), 38.3 (C-6), 44.4 (C-9a), 58.0 (C-3), 74.6 (C-2), 92.4 (C-9b), 126.3, 128.5 (C-*o*, *m*), 127.5 (C-*p*), 140.9 (C-*i*), 168.4 (NCO); $[\alpha]_D^{22}$ +15.6 (*c* 0.5, $CHCl_3$); *m*/*z* 258 (M^+, 5), 257 (27), 256 (4), 227 (4), 189 (6), 161 (8), 149 (8), 148 (36), 147 (4), 128 (5), 120 (42), 119 (12), 118 (36), 117 (32), 105 (12), 104 (100), 103 (18), 91 (29), 90 (23). HRMS calcd for $C_{16}H_{19}NNaO_2$: 280.1308, found: 280.1309.

4.5.3. (3*R*,6a*S*,11a*S*,11b*R*)-5-Oxo-3-phenylperhydrocyclohept[*c*]oxazolo[3,2-*a*]pyridine (21). Operating as in the preparation of **9**, from lactam **20** (918 mg, 2.2 mmol) and 10% Pd–C (103 mg) in MeOH (73 mL), lactam **21** was obtained (510 mg, 81%) after column chromatography (7:3 EtOAc–hexane): IR (NaCl) 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.25–1.58 (m, 6H), 1.67–2.32 (m, 6H), 2.10 (dd, J=15.6, 12.6 Hz, 1H, H-6), 2.30 (dd, J=15.6, 4.5 Hz, 1H, H-6), 4.10 (dd, J=8.7, 1.2 Hz, 1H, H-2), 4.22 (dd, J=8.7, 6.6 Hz, 1H, H-2), 4.65 (d, J=8.1 Hz, 1H, H-11b), 5.00 (dd, J=6.6, 1.2 Hz, 1H, H-3), 7.26–7.32 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.1 (CH_2), 28.3 (CH_2), 28.9 (CH_2), 30.7 (CH_2), 33.2 (CH_2), 35.9 (C-6a), 39.6 (C-6), 44.3 (C-11a), 57.9 (C-3), 74.5 (C-2), 92.0 (C-11b), 126.2, 128.5 (C-*o*, *m*), 127.5 (C-*p*), 141.0 (C-*i*), 168.6 (NCO); $[\alpha]_D^{22}$ −5.3 (*c* 0.45, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}O_2N\cdot 3/4H_2O$: C, 72.33; H, 8.26; N, 4.69. Found: C, 72.46; H, 7.87; N, 4.48.

4.6. Removal of the chiral inductor

4.6.1. (4a*S*,8a*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-oxoperhydroisoquinoline (10). $TiCl_4$ (0.61 mL, 5.6 mmol) and Et_3SiH (0.56 mL, 3.5 mmol) were added to a solution of lactam **9** (383 mg, 1.4 mmol) in CH_2Cl_2 (25 mL), and the resulting mixture was heated at reflux for 24 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (7:3 EtOAc–hexane) to give **10** (320 mg, 81%): IR (NaCl) 3373, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.36 (m, 2H), 1.48 (m, 4H), 1.56 (m, 2H), 1.92 (m, 1H, H-8a), 2.00 (m, 1H, H-4a), 2.43 (dd, J=18.0, 6.4 Hz, 1H, H-4), 2.53 (dd, J=18.0, 6.8 Hz, 1H, H-4), 2.88 (dd, J=12.4, 5.2 Hz, 1H, H-1), 3.16 (dd, J=12.4, 7.2 Hz, 1H, H-1), 4.10 (dd, J=11.6, 9.2 Hz, 1H, H-2′), 4.14 (dd, J=11.6, 5.2 Hz, 1H, H-2′), 5.78 (dd, J=9.2, 5.2 Hz, 1H, H-1′), 7.25–7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.8 (CH_2), 26.5 (CH_2), 28.2 ($2CH_2$), 32.1 (C-4a), 32.8 (C-8a), 35.8 (C-4), 46.0 (C-1), 58.8 (C-1′), 61.7 (C-2′), 127.7 (C-*p*), 127.8, 128.6 (C-*o*, *m*), 136.8 (C-*i*), 171.4 (NCO); $[\alpha]_D^{22}$ −39.6 (*c* 1.3, $CHCl_3$); *m*/*z* 274 (M^++1, 2), 255 (28), 254 (13), 213 (29), 242 (100), 214 (11), 151 (20).

4.6.2. (4a*S*,7a*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-oxoperhydrocyclopenta[*c*]pyridine (17). Operating as above, from lactam **16** (55 mg, 0.21 mmol) in CH_2Cl_2 (5 mL), $TiCl_4$ (84 μL, 0.53 mmol), and Et_3SiH (94 μL, 0.85 mmol), lactam **17** was obtained (51 mg, 94%) after column chromatography (EtOAc) as a white solid: IR (NaCl) 1632, 3379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY) δ 1.25 (m, 2H), 1.44 (m, 1H), 1.66 (m, 2H), 1.86 (m, 1H), 2.07 (m, 1H, H-8a), 2.24 (dd, J=14.1, 9.0 Hz, 1H, H-4), 2.36 (m, 1H, H-4a), 2.54 (dd, J=14.1, 6.0 Hz, 1H, H-4), 4.90 (dd, J=13.2, 8.7 Hz, 1H, H-1), 3.06 (dd, J=13.2, 6.0 Hz, 1H, H-1), 3.14 (br s, 1H, OH), 4.02 (ddd, J=11.1, 9.0, 7.2 Hz, 1H, H-2′), 4.15 (dd, J=11.1, 4.8 Hz, 1H, H-2′), 5.68 (dd, J=9.0, 4.8 Hz, 1H, H-1′), 7.10–7.17 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.5 (CH_2), 30.9 (CH_2), 34.1 (CH_2), 35.7 (C-4a), 37.9 (C-8a), 38.1 (C-4), 46.5 (C-1), 58.3 (C-1′), 62.3 (C-2′), 127.6, 128.6 (C-*o*, *m*), 127.7 (C-*p*), 137.2 (C-*i*), 174.4 (NCO); mp 60–62 °C; $[\alpha]_D^{22}$ −10.3 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.99; H, 8.24; N, 5.27.

4.6.3. (4a*S*,9a*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-oxoperhydrocyclohepta[*c*]pyridine (22). Operating as in the preparation of **10**, from lactam **21** (95 mg, 0.233 mmol) in CH_2Cl_2 (7 mL), $TiCl_4$ (0.15 mL, 1.32 mmol), and Et_3SiH (0.13 mL, 0.83 mmol), lactam **22** was obtained (70 mg, 73%) after column chromatography (7:3 EtOAc–hexane): IR (NaCl) 3376, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.21–1.43 (m, 5H), 1.62 (m, 1H), 1.76 (m, 4H), 1.89 (m, 1H, H-9a), 2.11 (m, 1H, H-4a), 2.26 (dd, J=15.6, 10.0 Hz, 1H, H-4), 2.46 (dd, J=15.6, 5.6 Hz, 1H, H-4), 2.90 (dd, J=13.2, 6.4 Hz, 1H, H-1), 2.95 (dd, J=13.2, 9.2 Hz, 1H, H-1), 3.05 (br s, 1H, OH), 4.05 (m, 1H, H-2′), 4.14 (m, 1H, H-2′), 5.61 (t, J=4.0 Hz, 1H, H-3), 7.23–7.34 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.6 (CH_2), 27.8 (CH_2), 29.7 (CH_2), 30.2 (CH_2), 32.6 (CH_2), 35.5 (C-4a), 37.7 (C-9a), 39.5 (C-4), 48.3 (C-1), 59.0 (C-1′), 62.4 (C-2′), 127.6, 128.6 (C-*o*, *m*), 127.7 (C-*p*), 137.1 (C-*i*), 173.8 (NCO); $[\alpha]_D^{22}$ +3.3 (*c* 1.0, $CHCl_3$); *m*/*z* 288 (M^+−1, 1), 269 (7), 268 (4), 257 (14), 256 (46), 228 (3), 168 (16), 144 (3), 132 (10), 131 (5), 120 (4), 119 (4), 118 (10), 117 (10), 109 (16), 107 (14), 104 (16), 103 (21), 95 (9), 92 (10), 91 (100). HRMS calcd for $C_{18}H_{25}NNaO_2$: 310.1783, found: 310.1778.

4.6.4. (4a*S*,8a*S*)-3-Oxoperhydroisoquinoline (11). Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice–acetone were condensed 15 mL of NH_3 at −78 °C. The temperature was raised to −33 °C, and a solution of **10** (208 mg, 0.76 mmol) in THF (10 mL) was added. Then, sodium metal was added in small portions until the blue color persisted, and the mixture was stirred at −33 °C for 1 min. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and then the mixture was stirred at rt for 4 h. The resulting residue was digested at rt with EtOAc, and the suspension was filtered and concentrated. Flash chromatography (1:2 EtOAc–hexane to 60:1 EtOAc–MeOH) afforded **11** (145 mg, 89%): IR (NaCl) 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR)

δ 1.38–1.65 (m, 8H), 1.99 (m, 1H, H-8a), 2.07 (m, 1H, H-4a), 2.30 (dd, J=18.0, 6.8 Hz, 1H, H-4), 2.37 (dd, J=18.0, 6.8 Hz, 1H, H-4), 3.26 (ddd, J=12.4, 6.4, 2.4 Hz, 1H, H-1), 3.32 (ddd, J=12.4, 5.6, 2.0 Hz, 1H, H-1), 6.40 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6 (CH_2), 23.2 (CH_2), 24.3 (CH_2), 28.5 (CH_2), 32.1, 32.2 (C-4a, C-8a), 34.2 (C-4), 44.7 (C-1), 172.2 (NCO); $[\alpha]_D^{22}$ −29.2 (c 0.8, MeOH) (lit.[21a] $[\alpha]_D^{22}$ −30.9 (c 1.02, MeOH)); m/z 153 (M^+, 48), 152 (11), 136 (6), 125 (53), 110 (15). HRMS calcd for $C_9H_{15}NO$: 153.1153, found: 153.1157.

4.6.5. (4a*S*,7a*S*)-3-Oxoperhydrocyclopenta[*c*]pyridine (18). Operating as above, from lactam **17** (79 mg, 0.31 mmol) in THF (6 mL), sodium, and liquid NH_3 (10 mL) stirred at −33 °C for 1.5 min, compound **18** was obtained (41 mg, 95%) after column chromatography (EtOAc): IR (NaCl) 3238, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 1.28 (m, 1H), 1.37 (m, 1H), 1.46 (m, 1H), 1.70 (m, 1H), 1.95–1.80 (m, 2H), 2.16 (dd, J=17.2, 8.4 Hz, 1H, H-4), 2.35 (m, 1H, H-7a), 2.43 (m, 2H), 3.01 (ddd, J=13.2, 6.0, 4.0 Hz, 1H, H-1), 3.32 (ddd, J=13.2, 5.6, 4.0 Hz, 1H, H-1), 5.80 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.5 (CH_2), 30.9 (CH_2), 34.0 (CH_2), 35.9 (C-4), 36.3 (C-4a), 37.4 (C-7a), 44.4 (C-1), 174.9 (NCO); $[\alpha]_D^{22}$ −25.6 (c 0.25, $CHCl_3$); m/z 139 (M^+, 100), 131 (6), 111 (20), 110 (9), 98 (10), 97 (18), 96 (30), 84 (17), 83 (24), 82 (73), 81 (14), 80 (13). HRMS calcd for $C_8H_{13}NNaO$: 162.0895, found: 162.0890.

4.6.6. (4a*S*,9a*S*)-3-Oxoperhydrocyclohepta[*c*]pyridine (23). Operating as described above in the preparation of **11**, from **22** (110 mg, 0.31 mmol) in THF (8 mL), sodium, and liquid NH_3 (15 mL) stirred at −33 °C for 0.5 min, compound **23** was obtained (57 mg, 89%) after flash chromatography (EtOAc): IR (NaCl) 3247, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 1.42 (m, 5H), 1.75 (m, 5H), 2.14 (m, 2H), 2.17 (dd, J=19.2, 8.0 Hz, 1H, H-4), 2.36 (dd, J=19.2, 9.2 Hz, 1H, H-4), 3.08 (ddd, J=12.4, 8.0, 2.4 Hz, 1H, H-1), 3.25 (ddd, J=12.4, 5.2, 3.2 Hz, 1H, H-1), 6.40 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.5 (CH_2), 26.6 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 32.2 (CH_2), 35.2, 36.6 (C-4a, C-9a), 37.9 (C-4), 46.6 (C-1), 173.8 (NCO). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 71.42; H, 10.27; N, 8.25.

4.6.7. (4a*S*,8a*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-perhydroisoquinoline (12). $LiAlH_4$ (35 mg, 0.92 mmol) was slowly added to a suspension of $AlCl_3$ (379 mg, 2.87 mmol) in THF (47 mL) at 0 °C. After the mixture was stirred at 25 °C for 30 min and cooled to −78 °C, lactam **9** (120 mg, 0.44 mmol) in THF (1 mL) was slowly added. The stirring was continued at −78 °C for 90 min and at rt for 2 h. The mixture was cooled to 0 °C, and the reaction was quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated to give an oil, which was chromatographed (EtOAc–hexane) to afford **12** (74 mg, 65%): IR (NaCl) 3427 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 1.20–2.00 (2m, 13H), 2.34 (td, J=11.0, 3.0 Hz, 1H), 2.63 (dd, J=11.0, 3.6 Hz, 1H), 3.20 (br s, 1H), 3.60 (dd, J=8.7, 5.1 Hz, 1H, H-2′), 3.64 (dd, J=8.7, 5.1 Hz, 1H, H-1′), 3.95 (dd, J=8.7, 7.8 Hz, 1H, H-2′), 7.16–7.33 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50 °C) δ 22.4 (CH_2), 25.4 (CH_2), 27.1 (CH_2), 27.9 (CH_2), 29.9 (CH_2), 34.3, 36.3 (C-4a, C-8a), 50.7, 52.6 (C-1, C-3), 60.4 (C-2′), 70.2 (C-1′), 127.7 (C-*p*), 128.0, 128.9 (C-*o*, *m*), 136.0 (C-*i*).

4.6.8. (4a*S*,8a*S*)-2-(*tert*-Butoxycarbonyl)perhydroisoquinoline (13). A solution of **12** (70 mg, 0.27 mmol) and di-*tert*-butyl dicarbonate (67 mg, 0.3 mmol) in EtOAc (11 mL) containing 20% $Pd(OH)_2$–C (20 mg) was hydrogenated at rt for 24 h at atmospheric pressure. The catalyst was removed by filtration, and the solvent was evaporated to give an oil, which was chromatographed (1:2 EtOAc–hexane to 1:1 EtOAc–hexane) to afford **13** (52 mg, 81%): IR (NaCl) 1696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 1.20–1.80 (m, 21H), 2.90 (m, 1H), 3.02 (dd, J=13.2, 3.6 Hz, 1H, H-1), 3.65 (ddd, J=13.2, 4.5, 1.2 Hz, 1H), 3.80 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50 °C) δ 22.1 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 26.9 (CH_2), 30.0 (CH_2), 28.5 ($3CH_3$), 34.6, 36.3 (C-4a, C-8a), 43.2, 48.6 (C-1, C-3), 78.9 [$C(CH_3)_3$], 155.2 (COO); $[\alpha]_D^{22}$ −5.4 (c 1.0, $CHCl_3$).

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