A versatile synthesis of bicyclic lactams from 1,8-naphthalaldehydic acid: an extension of Meyers' method

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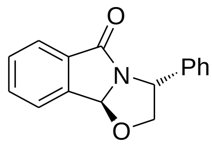
Abstract

A new and versatile approach to prepare bicyclic lactams in moderate to high yield is reported herein. This approach, based on an extension of Meyers' method, provides 6,5-, 6,6- and 6,7-fused bicyclic lactams **6a-j** from reaction of 1,8-naphthalaldehydic acid **7** with several aminoalcohols including L-serine, diamines and ethanethiol, in the absence of any catalyst. The reaction of **7** with (*R*)-phenylglycinol gave the 6,5-fused bicyclic lactam **6j** in excellent diastereoselectivity (>98:2).

Keywords: Meyers' bicyclic lactams, isoquinolinones, 1,8-naphthalaldehydic acid

Introduction

The isoindolin-1-ones (2,3-dihydro-1*H*-isoindolin-1-ones) have attracted considerable attention in recent years due to their fascinating properties and potential applications in many fields, especially in organic synthesis and medicinal chemistry. In particular, enantiopure compounds substituted at C-3, such as the chiral Meyers' bicyclic lactam type **1**, are important building blocks for the synthesis of a wide variety of natural and unnatural carbocyclic and azacyclic compounds, including simple and complex alkaloids.[1-8] Additionally, **1** has also been tested as antimicrobial agent.[9] Other bioactive 5,5-fused bicyclic lactam derivatives include the non-nucleoside HIV-reverse transcriptase inhibitor (*R*)-9b-(3-phenyl)-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one **2**,[10,11] and the 1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one derivatives (type **3**),[12] which possess antiinflamatory, analgesic, blood pressure lowering, spasmolytic, tranquilizing, and antitussive properties.[13,14] Additionally, Amat *et al.*,[15] reported that the tricyclic lactam **4** is a key intermediate in the synthesis of 1-substituted tetrahydroisoquinoline alkaloids. Further, the 7,5-fused bicyclic lactam **5** has been obtained in high diastereoselectivity.[16-18] However, in spite of their potential utility, 6,5-, 6,6- and 6,7-fused bicyclic lactams type **6** have been little studied.[19,20] Therefore, as a continuation of our program aimed at the convenient synthesis of bicyclic lactams,[21,22] we report here a versatile approach for the synthesis of bicyclic lactams **6a-j** by reaction of 1,8-naphthalaldehydic acid **7** with several aminoalcohols including L-serine methyl ester hydrochloride and (*R*)-phenylglycinol, diamines, and 2-aminoethanethiol, in the absence of any catalyst.



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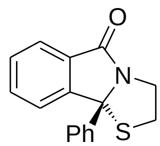

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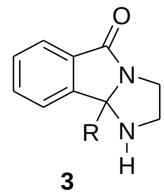

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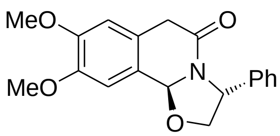

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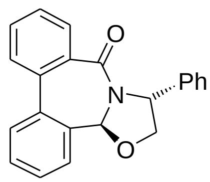

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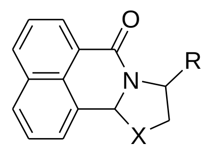


6
R = H, Ph, CO_2Me
X = O, NH, S

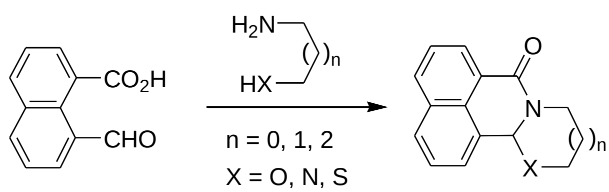
Results and discussion

Initially, we carried out the reaction of equimolecular amounts of commercially available 1,8-naphthalaldehydic acid **7** with ethanolamine in toluene at reflux for 5 h, obtaining the 5,6-fused bicyclic lactam **6a** in 92% yield (Table 1, entry 1). To establish the generality of this method for the synthesis of 6,6- and 6,7-fused bicyclic lactams, the 1,8-naphthalaldehydic acid **7** was reacted with 3-aminopropanol and 4-aminobutanol in toluene at reflux to give the expected fused bicyclic lactams **6b** and **6c** in 98 and 87% yield, respectively (Table 1, entries 2 and 3).

We next turned our attention to the synthesis of fused bicyclic lactams bearing two nitrogen atoms. After screening various conditions, we found that the reaction of 1,8-naphthalaldehydic acid **7** with ethylenediamine and 1,3-diaminopropane in toluene at room temperature provided the bicyclic lactams **6d** and **6e**, respectively, in quantitative yield (Table 1, entries 4 and 5). However, the expected product was not obtained on reaction of **7** with 1,4-diaminobutane at room temperature. Therefore, we carried out the reaction at reflux in toluene, obtaining under these conditions the 6,7-fused bicyclic lactam **6f** in 93% yield (Table 1, entry 6). Additionally, when **7** was heated with *o*-phenylenediamine in toluene at reflux the oxidized product **6g** was obtained in 23% yield (Table 1, entry 7), while the reaction at room temperature did not give the desired product. In order to obtain 6,5-fused bicyclic lactams bearing nitrogen and sulfur atoms, we found after testing various reaction conditions that the reaction of 1,8-naphthalaldehydic acid **7** with 2-aminoethanethiol in chloroform at 0 ^{o}C gave the 6,5-fused bicyclic lactam **6h** in 53% yield (Table 1, entry 8).

As part of our research program dealing with the development of new chiral 6,5-fused bicyclic lactams, the next step was to investigate the reaction of 1,8-naphthalaldehydic acid **7** with chiral aminoalcohols derivatives. In this context, we carried out the reaction of **7** with L-serine methyl ester hydrochloride in toluene at reflux, but only decomposition products were obtained, therefore we decided to use the L-serine methyl ester and ethyl acetate as solvent at reflux, obtaining under these conditions the bicyclic lactam **6i** in 66% yield and 70:30 diastereoisomeric ratio (Table 1, entry 9). Finally, we performed the reaction of **7** with (*R*)-phenylglycinol in toluene at reflux, obtaining the 6,5-fused bicyclic lactam *trans*-**6j** in 83% yield and with >98:2 diastereoisomeric ratio (Table 1, entry 10). The absolute configuration of **6j** was unambiguously determined by X-ray crystallographic analysis (Figure 1).[23]

Table 1. Preparation of fused bicyclic lactams **6a-j**



7 **6a-j**

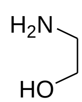
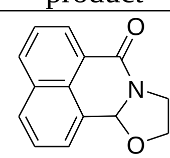
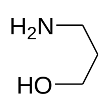
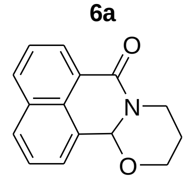
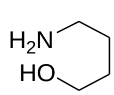
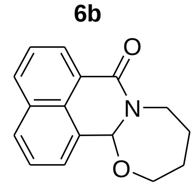
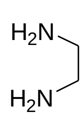
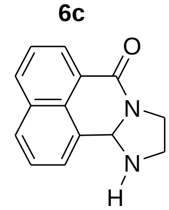
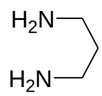
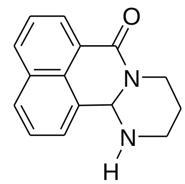
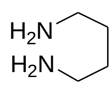
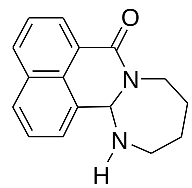
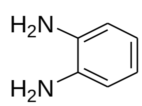
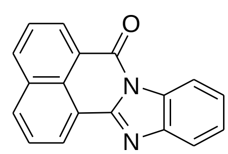
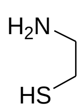
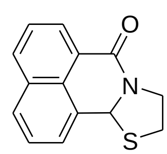
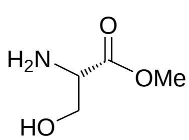
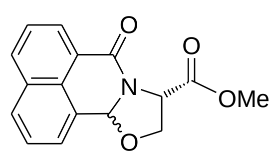
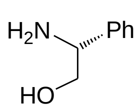
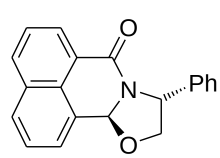
entry	amine	conditions	product	yield (%)
1		PhMe/Δ, 5 h	 **6a**	92
2		PhMe/Δ, 5 h	 **6b**	98
3		PhMe/Δ, 5 h	 **6c**	87
4		PhMe, r.t. 2 h	 **6d**	100

Table 1. Continued

entry	amine	conditions	product	yield (%)
5		PhMe, r.t. 2 h	 **6e**	100
6		PhMe/Δ, 5 h	 **6f**	93
7		PhMe/Δ, 12 h	 **6g**	23
8		$CHCl_3$, 0 ^oC	 **6h**	53
9		EtOAc/Δ, 12 h	 **6i**; 70:30 dr	66
10		PhMe/Δ, 5 h	 **6j**; >98:2 dr	83

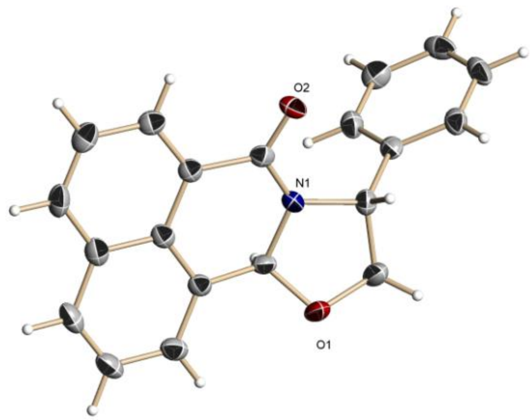
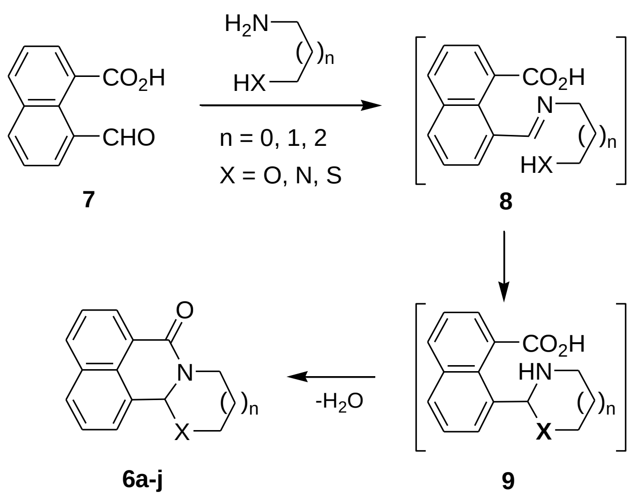


Figure 1. X-ray structure of 6,5-fused bicyclic lactam **6j**.

Based on our earlier work,[24] we propose a mechanism to explain the formation of the compounds **6a-j**, which initially involves the condensation of 1,8-naphthalaldehydic acid **7** with the amine containing an integrated nucleophilic group to give the intermediate imine **8**. Intramolecular nucleophilic attack to the imine gave the intermediate **9.** Finally, the loss of water in **9** furnished the observed fused bicyclic lactams **6a-j** (Scheme 1).



Scheme 1

In summary, we have developed an easy and efficient method for the synthesis of 6,5-, 6,6- and 6-7-fused bicyclic lactams in moderate to high yields using a simple procedure with readily available reagents and in the absence of any catalyst. Moderated diastereoselectivity was observed with L-serine methyl ester, and a high diastereoselectivity was obtained in the reaction of **7** with (*R*)-phenylglycinol.

Experimental section

All commercial materials were used as received without further purification. Melting points were registered in a Fisher-Johns apparatus. Flash chromatography was performed using 230-400 mesh Silica Flash 60 silica gel. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60 F_{254}, Merck). NMR spectra were recorded with a Varian System instrument (400 MHz for ^{1}H, and 100 MHz for ^{13}C). The spectra were recorded in $CDCl_3$ solution, using TMS as the internal reference. Chemical shifts (δ) are reported in parts per million. Multiplicities are recorded using the usual conventions. Coupling constants (*J*) are given in Hz. High resolution FAB$^+$ mass spectra (HRMS) were obtained in a JEOL HRM Station JHRMS-700.

General procedure for the synthesis of fused bicyclic lactams 6a-j

A mixture of 1,8-naphthalaldehydic acid **7** (1.0 equiv.) and amine (1.2 equiv.) in solvent (15 mL) was reacted at the appropriate temperature until the starting compound **7** has disappeared (TLC analysis; hexane/EtOAc, 4:1). Once the reaction was complete, the resultant solution was allowed to cool and the solvent was removed under reduced pressure. Further purification was performed by flash chromatography on silica gel (Hexane/EtOAc 4:1).

2,3,5,11b-Tetrahydrobenz[*de*][1,3]oxazolo[3,2-*a*]isoquinolin-5-one 6a. According to general procedure, a mixture of 1,8-naphthalaldehydic acid **7** (200 mg, 1.0 mmol), 2-aminoethanol (61.1 mg, 0.06 mL, 1.2 mmol) and toluene (15 mL) was stirred at reflux for 5 h. After chromatographic purification, the bicyclic lactam **6a** was obtained as a yellow solid (206 mg, 92%), mp 142-143 °C (lit.,[19] 142 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.67 (ddd, *J* = 11.0, 8.4, 4.4 Hz, 1H, CH_2N), 4.11 (dt, *J* = 8.0, 7.6 Hz, 1H, CH_2O), 4.26 (ddd, *J* = 8.4, 8.4, 4.4 Hz, 1H, CH_2O), 4.35 (ddd, *J* = 10.8, 10.8, 7.6 Hz, 1H, CH_2N), 6.05 (s, 1H, CHNCO), 7.57 (dd, *J* = 7.2, 6.0 Hz, 1H, H_{arom}), 7.59 (dd, *J* = 7.2, 6.4 Hz, 1H, H_{arom}) 7.71 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H, H_{arom}), 7.90 (d, *J* = 8.4 Hz, 1H, H_{arom}), 7.99 (dd, *J* = 8.8, 1.2 Hz, 1H, H_{arom}), 8.37 (dd, *J* = 7.6, 1.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.4 (CH_2N), 64.3 (CH_2O), 86.7 (CHNCO), 124.6, 125.5, 126.3, 126.4, 127.1, 127.9, 128.7, 132.2, 132.3, 161.3 (C=O). HRMS (FAB$^+$): calculated for $C_{14}H_{12}NO_2$ $[M+H]^+$, *m/z* 226.0868; found for $[M+H]^+$, *m/z* 226.0862.

2,3,4,12b-Tetrahydro-6*H*-benz[*de*][1,3]oxazino[3,2-*a*]isoquinolin-6-one 6b. According to general procedure, a mixture of 1,8-naphthalaldehydic acid **7** (200 mg, 1 mmol), 3-aminopropanol (75 mg, 0.08 mL, 1.2 mmol) and toluene (15 mL) was stirred at reflux for 5 h. After chromatographic purification, the bicyclic lactam **6b** was obtained as colorless solid (220 mg, 98%), mp 122-123 °C (lit.,[19] 126 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.66-1.71 (m, 1H, CH_2), 2.08-2.20 (m, 1H, CH_2), 3.10 (ddd, *J* = 13.0, 13.0, 2.8 Hz, 1H CH_2N), 4.14 (ddd, *J* = 12.0, 12.0, 2.4 Hz, 1H, CH_2O), 4.27-4.32 (m, 1H, CH_2O), 5.11-5.16 (m, 1H, CH_2N), 6.09 (s, 1H, CHNCO), 7.56-7.66 (m, 3H, H_{arom}), 7.91 (d, *J* = 8.0 Hz, 1H, H_{arom}), 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H, H_{arom}), 8.42 (dd, *J* = 7.2, 1.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5 (CH_2CH_2), 41.9 (CH_2N), 69.1 (CH_2O), 87.0 (CHNCO), 123.5, 126.4, 126.5, 126.7, 127.2, 127.8, 128.1, 128.8, 132.0, 132.2, 161.9 (C=O). HRMS (FAB$^+$): calculated for $C_{15}H_{14}NO_2$ $[M+H]^+$, *m/z* 240.1025; found for $[M+H]^+$, *m/z* 240.1028.

2,3,4,5,7,13b-Hexahydrobenz[*de*][1,3]oxazepino[3,2-*a*]isoquinolin-7-one 6c. According to general procedure, a mixture of 1,8-naphthalaldehydic acid **7** (200 mg, 1 mmol), 4-aminobutanol (75 mg, 0.08 mL, 1.2 mmol) and toluene (15 mL) was stirred at reflux for 5 h. After chromatographic purification, the bicyclic lactam **6c** was obtained as a colorless solid (220 mg, 87%), mp 88-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70-1.73 (m, 1H, (CH_2CH_2O)), 1.79-1.99 (m, 3H, CH_2CH_2O and CH_2CH_2N), 3.23 (t, J = 12 Hz, 1H, CH_2N), 3.59 (t, J = 11.2 Hz, 1H, CH_2O), 3.74-3.78 (m, 1H, CH_2O), 4.65 (d, J = 13.6 Hz, 1H, CH_2N), 6.18 (s, 1H, CHNCO), 7.55-7.62 (m, 2H, H_{arom}), 7.71 (d, J = 6.8 Hz, 1H, H_{arom}), 7.88 (d, J = 8.0 Hz, 1H, H_{arom}), 7.99 (d, J = 8.0 Hz, 1H, H_{arom}), 8.40 (d, J = 7.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7 (CH_2CH_2N), 29.3 (CH_2CH_2O), 45.1 (CH_2N), 64.9 (CH_2O), 86.5 (CHNCO), 123.7 (2C), 125.9, 126.2, 126.3, 127.2, 128.1, 129.9 (2C), 131.7, 162.3 (C=O). HRMS (FAB$^+$): calculated for $C_{16}H_{16}NO_2$ $[M+H]^+$, *m/z* 254.1181; found for $[M+H]^+$, *m/z* 254.1179.

1,2,3,11b-Tetrahydro-5*H*-benz[*de*]imidazo[3,2-*a*]isoquinolin-5-one 6d. According to general procedure, a mixture of 1,8-naphthalaldehydic acid **7** (200 mg, 1 mmol), ethylenediamine (72 mg, 0.08 mL, 1.2 mmol) and toluene (15 mL) was stirred at room temperature for 2 h. After chromatographic purification, the bicyclic lactam **6d** was obtained as a yellow solid (224 mg, 100%), mp 157-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (bs, 1H, NH), 3.24 (dt, J = 12.4, 8.8 Hz, 1H, CH_2NH), 3.49 (ddd, J = 11.6, 8.8, 3.0 Hz, 1H, CH_2NH), 3.59 (ddd, J = 11.6, 8.8, 3.0 Hz, 1H, CH_2N), 3.91 (dt, J = 11.6, 8.8 Hz, CH_2N), 5.53 (s, 1H, CHNCO), 7.47 (dd, J = 8.2, 7.2 Hz, 1H, H_{arom}), 7.54 (dd, J = 8.2, 7.2 Hz, 1H, H_{arom}), 7.67 (ddd, J = 6.8, 6.8, 1.4 Hz, 1H, H_{arom}), 7.79 (d, J = 8.4 Hz, 1H, H_{arom}), 7.91 (dd, J = 8.0, 1.2 Hz, 1H, H_{arom}), 8.28 (dd, J = 7.2, 1.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.4 (CH_2NH), 44.5 (CH_2N), 74.7 (CHNCO), 124.3, 125.8, 126.2, 126.5, 126.7, 127.8, 128.1, 129.1, 131.7, 132.5, 160.7 (C=O). HRMS (FAB$^+$): calculated for $C_{14}H_{13}N_2O$ $[M+H]^+$, *m/z* 225.1028; found for $[M+H]^+$, *m/z* 225.1038.

1,2,3,4,6,12b-Hexahydrobenzo[*de*]pyrimido[3,2-*a*]isoquinolin-7-one 6e. According to general procedure, a mixture of 1,8-naphthalaldehydic acid **7** (200 mg, 1 mmol), 1,3-diaminopropane (89 mg, 0.10 mL, 1.2 mmol) and toluene (15 mL) was stirred at room temperature for 2 h. After chromatographic purification, the bicyclic lactam **6e** was obtained as a colorless solid (238 mg, 100%), mp 158-160 °C (lit.,[20] 155-158 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72-1.80 (m, 3H, NH and CH_2), 2.94-3.01 (m, 1H, CH_2N), 3.16-3.24 (m, 1H, CH_2NH), 3.31-3.37 (m, 1H, CH_2NH), 5.12-5.17 (m, 1H, CH_2N), 5.64 (s, 1H, CHNCO), 7.51 (t, J = 8.0 Hz, 1H, H_{arom}), 7.54 (dd, J = 8.4, 7.2 Hz, 1H, H_{arom}), 7.69 (d, J = 7.6 Hz, 1H, H_{arom}), 7.81 (d, J = 8.0 Hz, 1H, H_{arom}), 7.92 (dd, J = 8.2, 1.2 Hz, 1H, H_{arom}), 8.34 (dd, J = 7.2, 1.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.2 (CH_2CH_2), 42.6 (CH_2N), 46.2 (CH_2NH), 72.9 (CHNCO), 123.8, 125.8, 126.3 (2C), 127.1, 127.4, 127.8, 130.4, 131.6, 132.2, 161.2 (C=O). HRMS (FAB$^+$): calculated for $C_{15}H_{14}N_2O$ $[M+H]^+$, *m/z* 239.1184; found for $[M+H]^+$, *m/z* 239.1179.

1,2,3,4,5,13b-Hexahydro-7*H*-benzo[*de*]1,3-diazepino[3,2-*a*]isoquinolin-7-one 6f. According to general procedure, a mixture of 1,8-naphthalaldehydic acid **7** (200 mg, 1 mmol), 1,4-

diaminobutane (105 mg, 0.12 mL, 1.2 mmol) and toluene (15 mL) was stirred at reflux for 5 h. After chromatographic purification, the bicyclic lactam **6f** was obtained as a colorless solid (234 mg, 93%), mp 83-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.68-1.75 (m, 2H, CH_2CH_2NH), 1.83-1.92 (m, 1H, CH_2CH_2NH), 1.99-2.10 (m, 2H, NH and CH_2CH_2NH), 2.84 (ddd, *J* = 14.3, 7.6, 3.6 Hz, 1H, CH_2NH), 3.02 (ddd, *J* = 14.3, 6.0, 3.6 Hz, 1H, CH_2NH), 3.19 (ddd, *J* = 14.2, 11.0, 3.2 Hz, 1H, CH_2N), 4.71 (dt, *J* = 14.2, 4.4 Hz, 1H, CH_2N), 5.65 (s, 1H, CHNCO), 7.54 (dd, *J* = 8.4, 8.4 Hz, 1H, H_{arom}), 7.58 (dd, *J* = 8.4, 7.2 Hz, 1H, H_{arom}), 7.74 (ddd, *J* = 6.8, 6.8, 1.2 Hz, 1H, H_{arom}), 7.83 (d, *J* = 8.4 Hz, 1H, H_{arom}), 7.97 (dd, *J* = 8.0, 1.2 Hz, 1H, H_{arom}), 8.39 (dd, *J* = 7.2, 1.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4 (CH_2CH_2N), 31.2 (CH_2CH_2NH), 44.9 (CH_2NH), 45.4 (CH_2N), 74.6 (CHNCO), 124.7, 126.1, 126.3, 126.4, 126.9, 127.5, 127.8, 131.6, 132.3, 132.5, 163.1 (C=O). HRMS (FAB$^+$): calculated for $C_{16}H_{17}N_2O$ $[M+H]^+$, *m/z* 253.1341; found for $[M+H]^+$, *m/z* 253.1350.

7*H*-Benzo[*de*]benzimidazo[3,2-*a*]isoquinolin-7-one 6g. According to general procedure, a mixture of methyl ester of 1,8-naphthalaldehydic acid (200 mg, 0.934 mmol), *o*-phenylenediamine (121 mg, 1.12 mmol) and toluene (15 mL) was stirred at reflux for 12 h. After chromatographic purification, the bicyclic lactam **6g** was obtained as a yellow solid (59 mg, 23%), mp 204-205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.46 (m, 2H, H_{arom}), 7.62-7.67 (m, 2H, H_{arom}), 7.79-7.83 (m, 1H, H_{arom}), 7.96 (dd, *J* = 8.2, 1.0 Hz, 1H, H_{arom}), 8.09 (dd, *J* = 8.2, 1.0 Hz, 1H, H_{arom}), 8.42-8.46 (m, 1H, H_{arom}), 8.59 (dd, *J* = 7.6, 1.2 Hz, 1H, H_{arom}), 8.64 (dd, *J* = 7.6, 1.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 115.8, 119.9, 120.4, 122.9, 125.2 (2C), 125.6 (2C), 126.7, 126.9 (2C), 127.1, 131.4, 131.6, 132.0, 135.2, 158.2 (C=N), 158.4 (C=O). HRMS (FAB$^+$): calculated for $C_{18}H_{11}N_2O$ $[M+H]^+$, *m/z* 271.0871; found for $[M+H]^+$, *m/z* 271.0868.

2,3,5,11b-Tetrahydrobenzo[*de*]thiazolo[3,2-*a*]isoquinolin-5-one 6h. A solution of 2-amino-ethanethiol hydrochloride (458 mg, 4 mmol) and triethylamine (303 mg, 0.42 mL, 4 mmol) in chloroform (10 mL) was stirred at 0 °C for 3 h. Subsequently, the triethylamine hydrochloride was filtered, 1,8-naphthalaldehydic acid **7** (400 mg, 2 mmol) was added, and the reaction mixture was stirred for other 3 h at 0 °C. The reaction mixture was then poured into water, and extracted twice with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure, to afford the pure bicyclic lactam **6h** as a yellow solid (257 mg, 53%), mp 127-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.14-3.24 (m, 2H, CH_2N), 3.40-3.48 (m, 1H, CH_2S), 5.08 (ddd, *J* = 12.2, 7.6, 4.6 Hz, 1H, CH_2S), 6.40 (s, 1H, CHNCO), 7.49-7.54 (m, 2H, H_{arom}), 7.59 (dd, *J* = 8.2, 7.2 Hz, 1H, H_{arom}), 7.82-7.84 (m, 1H, H_{arom}), 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H, H_{arom}), 8.37 (dd, *J* = 6.8, 1.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.2 (CH_2N), 47.2 (CH_2S), 64.4 (CHNCO), 124.3, 124.8, 126.1, 126.4, 127.1, 127.5, 127.8, 132.1, 132.5 (2C), 161.6 (C=O). HRMS (FAB$^+$): calculated for $C_{14}H_{12}NOS$ $[M+H]^+$, *m/z* 242.0640; found for $[M+H]^+$, *m/z* 242.0646.

(9*S*,9*R*)-Methyl 5-oxo[2,3,5,11b]-tetrahydrobenz[*de*]oxazolo[3,2-*a*]isoquinoline-3-carboxylate 6i. A mixture of L-serine methyl ester hydrochloride (300 mg, 1.93 mmol), Et_3N (391 mg, 0.538 mL, 3.86 mmol) and ethyl acetate (15 mL) was stirred at reflux for 1 h. The solid was filtered, and the liquor containing the L-serine methyl ester was treated with 1,8-naphthalaldehydic acid **7**

(386 mg, 1.93 mmol) and stirred at reflux for 12 h. The solvent was evaporated under reduced pressure, obtaining the crude product, which was analyzed by ^{1}H NMR spectroscopy showing a 70:30 diastereoisomeric ratio. The purification with EtOAc:hexane (8:2) gave the bicyclic lactam **6i** (473 mg, 66%) as a yellow solid, mp 97-100 °C. ^{1}H NMR 70:30 dr, asterisk denotes minor diastereoisomer peaks when it was possible to distinguish 400 MHz, $CDCl_3$) δ: 3.78* (s, 3H, CO_2CH_3), 3.81 (s, 3H, CO_2CH_3), 3.82-3.94 (m, 5H, $NCHCH_2O$), 4.08 (t, *J* = 4.8 Hz, 1H, $CHCO_2CH_3$), 6.50 (s, 1H, CHNCO), 6.59* (s, 1H, CHNCO), 7.56-7.66 (m, 4H, H_{arom}), 7.74 (d, *J* = 7.2 Hz, 1H, H_{arom}), 7.78* (d, *J* = 7.1 Hz, 1H, H_{arom}), 7.91 (d, *J* = 8.2 Hz, 2H, H_{arom}), 8.08-8.12 (m, 2H, H_{arom}), 8.36* (d, *J* = 7.1 Hz, 1H, H_{arom}), 8.40 (d, *J* = 7.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.6*, 52.9, 58.7*, 59.1, 63.2, 64.0*, 90.9, 91.3*, 120.2, 125.6*, 125.6, 125.9*, 126.5*, 126.6, 126.7, 126.8*, 128.1*, 128.4, 128.6*, 128.7, 129.1*, 129.7*, 129.9, 132.2 (2C), 132.7* 133.9 (2C), 163.9 (NC=O), 164.4*(NC=O), 173.1*(CO_2Me), 173.2 (CO_2Me). HRMS (FAB+): calculated for $C_{16}H_{14}NO_4$ [M+H]$^+$, *m/z* 284.0923; found for [M+H]$^+$, *m/z* 284.0915.

(3*R*,11b*S*)-3-Phenyl-2,3,5,11b-tetrahydrobenz[*de*][1,3]oxazolo[2,3-*a*]isoquinolin-5-one 6j. According to general procedure, a mixture of 1,8-naphthalaldehydic acid **7** (200 mg, 1.0 mmol), (*R*)-2-phenylglycinol (164 mg, 1.2 mmol) and toluene (15 mL) was reacted at reflux for 5 h. ^{1}H NMR analysis of the crude product showed a single diastereoisomer. After chromatographic purification and crystallization from Et_2O, the bicyclic lactam **6j** was obtained as plates (244 mg, 83%) mp 133-136 °C. $[\alpha]_D$ = -13.33 (c 3.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.09 (dd, *J* = 8.8, 7.2 Hz, 1H, CH_2O), 4.69 (t, *J* = 8.4 Hz, 1H, CH_2O), 5.70 (t, *J* = 7.6 Hz, 1H, CHPh), 6.34 (s, 1H, CHNCO), 7.29-7.33 (m, 1H, H_{arom}), 7.37-7.45 (m, 4H, H_{arom}), 7.60-7.65 (m, 2H, H_{arom}), 7.77 (d, *J* = 7.2 Hz, 1H, H_{arom}), 7.95 (d, *J* = 8.0 Hz, 1H, H_{arom}), 8.04 (d, *J* = 8.4 Hz, 1H, H_{arom}), 8.39 (d, *J* = 7.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 59.2 (CHPh), 72.1 (CH_2O), 87.7 (CHNCO), 124.6, 126.1, 126.3 (2C), 126.5, 126.6, 126.9, 127.2, 127.8, 127.9, 128.9, 129.2 (2C), 132.4, 132.5, 140.1, 161.9 (C=O). HRMS (FAB$^+$): calculated for $C_{20}H_{16}NO_2$ [M+H]$^+$, *m/z* 302.1181; found for [M+H]$^+$, *m/z* 302.1167.

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