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Stereoselective α-amidoalkylation of phenylglycinol-derived lactams. Synthesis of enantiopure 5,6-disubstituted 2-piperidones

Mercedes Amat,[a,*] Carmen Escolano,[a] Arantxa Gómez-Esqué,[a] Oscar Lozano,[a] Núria Llor,[a] Rosa Griera,[a] Elies Molins[b] and Joan Bosch[a]

[a]*Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain*
[b]*Institut de Ciència de Materials de Barcelona (CSIC), Campus UAB, 08193-Cerdanyola, Spain*

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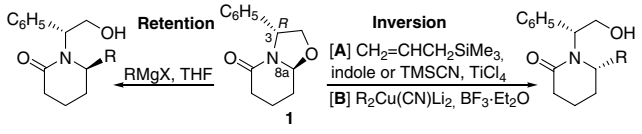
Abstract—The stereochemical outcome of α-amidoalkylation reactions of chiral nonracemic bicyclic lactams **2b** and **2c** with indole, allyltrimethylsilane, TMSCN and Grignard reagents to gain access to enantiopure 5,6-disubstituted 2-piperidones is discussed.

1. Introduction

Owing to the relevance of piperidine-containing bioactive compounds, the development of new methodologies giving access to diversely substituted enantiopure piperidines continues to be a subject of considerable interest.[1] In previous papers, we have reported the stereoselective synthesis of 6-substituted 2-piperidones by α-amidoalkylation reactions of the simple *trans* H_3–H_{8a} (*R*)-phenylglycinol-derived lactam **1**.[2] We demonstrated that carbon nucleophiles in the presence of Lewis acids, such as $TiCl_4$ and $BF_3{\cdot}Et_2O$, lead to compounds with an inversion of configuration at the C-8a stereocentre, whereas Grignard reagents afford 6-substituted 2-piperidones with retention of configuration (Scheme 1).[3] Moreover, we observed that the *cis*-epimer of lactam **1**, under the same reaction conditions, gave complex mixtures or starting materials.

Herein we report the extension of the above methodology from chiral lactams bearing a substituent at the C-8 position, that is, next to the electrophilic carbon of the oxazolidine ring.

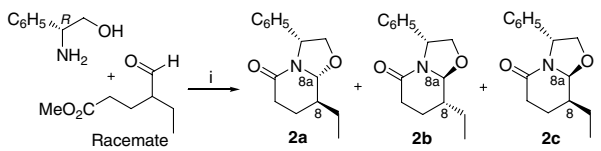


Scheme 1.

2. Results and discussion

2.1. Preparation of C-8 substituted bicyclic lactams

Cyclocondensation of (*R*)-phenylglycinol with racemic methyl 4-formylhexanoate stereoselectively afforded the *cis* H_3–H_{8a} lactam **2a**, through a process that involves dynamic kinetic resolution of the racemic substrate. Minor amounts of the *trans* H_3–H_{8a} isomer **2b** and, in some cases, its C-8a epimer **2c** were also formed.[4] Thus, when a toluene solution of methyl 4-formylhexanoate and (*R*)-phenylglycinol was heated at reflux, a 63:25:12 mixture of isomers **2a**, **2b** and **2c**, respectively, was formed. However, when an Et_2O solution of starting materials containing anhydrous Na_2SO_4 was stirred at 0 °C and the resulting mixture heated under vacuum (10–15 mm Hg) at 70 °C, lactams **2a** and **2b** were isolated in a 90:10 ratio, respectively (see Scheme 2).



Scheme 2. Reagents and conditions: (i) toluene, reflux, 18 h, 80% (**2a**/**2b**/**2c** 63:25:12) or Et_2O, anhyd Na_2SO_4, 0 °C, 1 h, then 70 °C, 10–15 mm Hg, 76% (**2a**/**2b** ratio 90:10).

* Corresponding author. Tel.: +34 93 4024540; fax: +34 93 4024539; e-mail: amat@ub.edu

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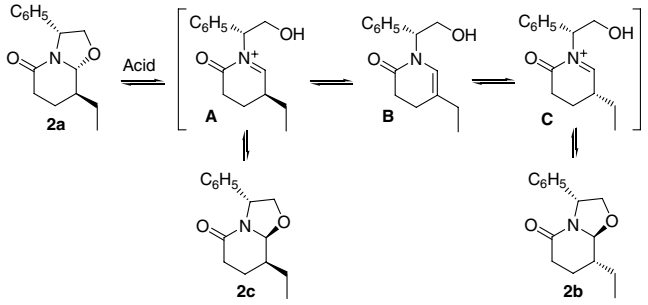
Table 1. Equilibration of lactam **2a**

Reagents and conditions	2a	2b	2c
$TiCl_4$ (2 equiv), CH_2Cl_2, 7 h, reflux	64	4	32
TFA (10 equiv), CH_2Cl_2, 24 h, reflux	60	5	35
TFA (10 equiv), CH_2Cl_2, 64 h, reflux	57	14	29
3 N MeOH–HCl, 25 h, 25 °C	28	70	2

As could be expected from previous observations,[2c] all attempts to carry out α-amidoalkylation reactions from lactam **2a** using a variety of conditions failed. In all cases, only starting material was recovered, thus confirming the reluctance of *cis* H_3–H_{8a} phenylglycinol-derived lactams to undergo α-amidoalkylation reactions.

To gain access to *trans* H_3–H_{8a} bicyclic lactams, we studied the isomerization of the major *cis*-isomer **2a** under acidic conditions (Table 1). Heating at reflux temperature a CH_2Cl_2 solution of **2a** in the presence of $TiCl_4$ or TFA for 7 or 24 h, respectively, brought about isomerization of the C-8a stereocentre, affording mixtures of **2a** and **2c** in a diastereomeric ratio of about 2:1, along with minor amounts of **2b**. When the solution of **2a** and TFA was heated for longer reaction times (64 h), an increase in the ratio of the isomer **2b** was observed. Finally, changing the acidic conditions to a 3 M HCl methanolic solution dramatically increased the ratio of isomer **2b**, which became the major product, and only trace amounts of **2c** were detected. This isomerization can be rationalized by taking into account that *trans* H_3–H_{8a} (*R*)-phenylglycinol-derived lactams, such as **2b** and **2c**, are more stable than the *cis*-isomers[5] and that, due to the conformational rigidity of the bicyclic system, the ethyl substituent is pseudoaxial in isomer **2c**, whereas in **2b** it is pseudoequatorial. Under acidic conditions, fragmentation of the C–O bond of *cis* lactam **2a** takes place, leading to acyliminium cation **A**, which, after closure of the oxazolidine ring, affords the *trans*-isomer **2c**. **A** is in equilibrium with its epimer **C** through the acyl enamine **B**. Closure of the oxazolidine ring from **C** gives the *trans*-isomer **2b** (Scheme 3).[6]



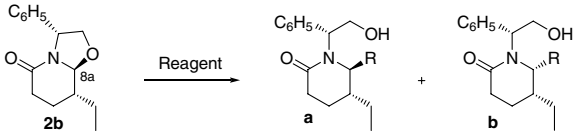
Scheme 3.

2.2. α-Amidoalkylation reactions of lactams 2b and 2c

Lactam **2b** proved to be more reluctant to undergo α-amidoalkylation than the analogous de-ethyl bicyclic lactam **1**. In fact, all attempts to carry out reactions on **2b** using higher order cyanocuprates $[R_2Cu(CN)Li_2]$ under acidic conditions failed, while the other amidoalkylations studied (Table 2) required longer reaction times or higher temperatures than those needed for **1**.

The reaction of **2b** with indole in the presence of $TiCl_4$ led exclusively to *trans*-5-ethyl-6-indolylpiperidone **3a**, in which the configuration at the C-8a position remained unchanged (entry 1). However, the addition of allyltrimethylsilane using the same Lewis acid occurred with an inversion of configuration, to afford a *cis*-5,6-disubstituted piperidone **4b** (entry 2). A similar stereochemical result was observed when trimethylsilyl cyanide was used as the nucleophile. In this case, after a longer reaction time (22 h), *cis*-isomer **5b** was obtained in moderate yield along with starting material (entry 3). In contrast, α-amidoalkylation of lactam **2b** using alkyl (entries 5 and 6), aryl (entry 7), vinyl (entry 8) or allyl (entry 9),[7] Grignard reagents took place with retention of the configuration at the C-8a stereocentre, stereoselectively affording the corresponding 5,6-*trans* isomers **a**.

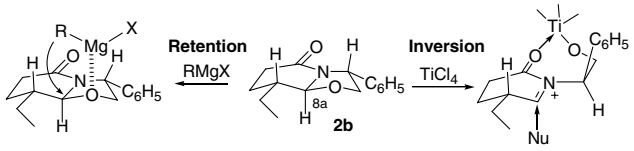
Table 2. Stereoselective α-amidoalkylation reactions from lactam **2b**



Entry	Reagents	R	Yield (%)	Product[a]
1	Indole, $TiCl_4$	3-In	77	**3a**
2	CH_2=CH–CH_2SiMe_3, $TiCl_4$	CH_2–CH=CH_2	83	**4b**
3	TMSCN, $TiCl_4$	CN	37	**5b**
4	CH_3MgCl	CH_3	76	**6a**
5	EtMgBr	CH_2CH_3	63	**7a**
6	*n*-PrMgBr	$CH_2CH_2CH_3$	66	**8a**
7	C_6H_5MgBr	C_6H_5	74	**9a**
8	CH_2=CHMgBr	CH=CH_2	43	**10a**
9	CH_2=CH–CH_2MgBr	CH_2–CH=CH_2	33[b]	**4a**

[a] **a**:**b** (or **b**:**a** for **4** and **5**) ratio >95:5.

[b] The triallylated product **4c** was isolated in 34% yield (see Section 4).



Scheme 4.

The stereochemical outcome of the above α-amidoalkylations can be explained by considering that, when a Lewis acid such as $TiCl_4$, is used (entries 2 and 3), the reaction takes place through an acyliminium species, which undergoes attack of the nucleophile from the less hindered face to give *cis*-products **b** (Scheme 4). An explanation for the opposite stereoselectivity in the reaction with indole (entry 1) is that the stereogenic centre at the 6-position in 6-(3-indolyl)-2-piperidones is configurationally labile under acidic conditions,[2a,8] ultimately leading to the thermodynamically more stable *trans*-5-ethyl-6-(3-indolyl) isomer.

In contrast, Grignard reagents coordinate with the oxygen atom of the oxazolidine ring, weakening the C–O bond. The subsequent delivery of the alkyl or aryl group on the incipient acyliminium salt takes place from the same face of the C–O bond, affording 5,6-*trans* products **a**, with retention of the configuration at the C-8a stereocentre. Consequently, the pseudoequatorial ethyl substituent in lactam **2b** does not modify the stereochemical outcome already observed in the α-amidoalkylation reactions from the de-ethyl lactam **1**.

To analyze the influence of the spatial disposition of the ethyl substituent on the stereoselectivity of the reaction, we next studied some α-amidoalkylation reactions upon lactam **2c**, the C-8 epimer of **2b**.

In accordance with the above results, the reaction of lactam **2c** with either indole or allyltrimethylsilane in the presence of $TiCl_4$ also took place with inversion of the C-8a stereocentre to give the respective *trans*-5,6-disubstituted piperidones **11b** and **12b** (Table 3; entries 1 and 2), whereas phenylmagnesium bromide afforded the *cis*-isomer **13a** (entry 3), with retention of the configuration.

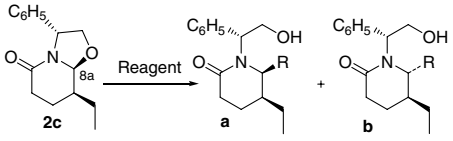
The absolute configuration of the stereogenic centre generated in the above α-amidoalkylation reactions leading to 5,6-disubstituted piperidones **3**–**13** was assigned (Table 4) by correlation of their NMR data with those reported for their respective 5-de-ethyl derivatives.[2] The configuration of **7a** was unambiguously confirmed by X-ray crystallographic analysis[9] (Fig. 1).

2.3. Synthesis of enantiopure *cis*- and *trans*-5,6-disubstituted 2-piperidones

With a method in hand for the expeditious preparation of the disubstituted lactams **3**–**13**, we undertook the removal of the chiral inductor to gain access to enantiopure N-unsubstituted *cis*- and *trans*-5,6-disubstituted-2-piperidones.

The chemoselective reduction of the 5,6-*trans* piperidones **3a**, **7a** and **9a** to the corresponding N-unsubstituted

Table 3. Stereoselective α-amidoalkylation reactions from lactam **2c**



Entry	Reagents	R	Yield (%)	Product[a]
1	Indole, $TiCl_4$	3-In	45	**11b**
2	CH_2=CH–CH_2SiMe_3, $TiCl_4$	CH_2–CH=CH_2	64	**12b**
3	C_6H_5MgBr	C_6H_5	61	**13a**

[a] **b**:**a** (or **a**:**b** for **13**) ratio >95:5.

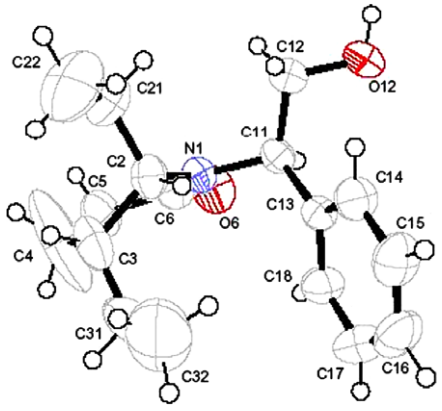
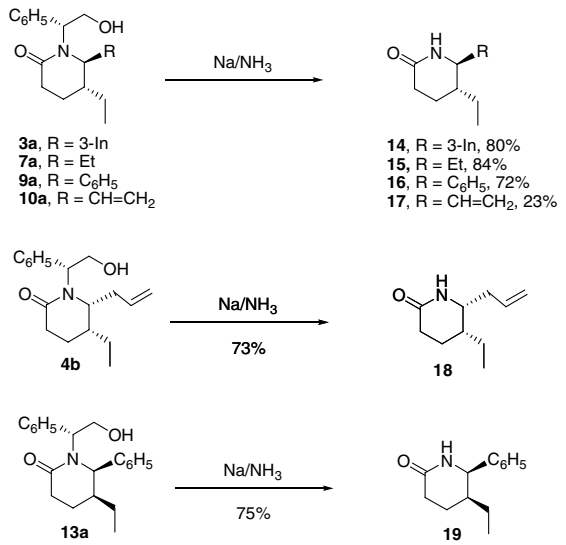


Figure 1. X-ray structure of (5*R*,6*S*)-5,6-diethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone **7a**.

Table 4. Significant ^{13}C NMR data of C-6 substituted 5-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidones **3**–**13**

	3a	**4a**	**4b**	**5b**	**6a**	**7a**	**8a**	**9a**	**10a**	**11b**	**12b**	**13a**
2	172.8	172.5	172.0	171.0	171.8	172.6	172.3	172.0	172.3	172.5	172.0	171.6
3	28.5	28.5	30.8	31.1	28.5	28.6	28.5	28.7	29.0	30.0	28.9	31.5
4	20.8	20.3	21.8	23.2	20.5	20.6	20.7	19.8	21.0	21.2	20.3	20.7
5	40.0	35.5	40.8	39.0	40.5	35.1	35.6	42.4	40.2	40.1	35.6	40.7
6	53.5	59.0	61.0	51.0	54.4	61.6	59.1	61.4	60.7	61.4	61.4	60.9
1′	59.8	63.0	67.2	60.6	61.7	63.1	62.5	60.0	60.2	68.1	66.3	59.9
2′	63.0	63.7	63.8	62.0	63.0	63.9	63.4	62.1	63.0	64.9	64.4	61.9
CH_2	23.2	24.4	25.4	25.0	24.2	24.6	24.5	23.7	23.7	23.9	24.5	24.9
CH_3	11.5	11.5	11.6	11.1	11.3	11.5	11.4	11.3	11.3	11.4	11.4	11.3



Scheme 5.

derivatives **14**, **15** and **16** was accomplished in good yields (72–84%) with Na/liq NH_3. However, under these conditions vinyl piperidone **10a** furnished the expected compound **17** in low yield, while the major product (73%) (4*R*)-4-ethyl-5-heptenamide, was formed by radical opening of the lactam ring. A similar debenzylation from the *cis*-derivatives **4b** and **13a** led to the respective *cis*-5,6-disubstituted piperidones **18** and **19** in good yields (see Scheme 5).

3. Conclusions

In conclusion, starting from racemic methyl 4-formylhexanoate and (*R*)-phenylglycinol, diversely *cis*- and *trans*-5-ethyl-6-substituted-2-piperidones have been stereoselectively prepared in enantiopure form. The key steps are a cyclocondensation of the chiral aminoalcohol with the racemic aldehyde–ester and a subsequent α-amidoalkylation. By choosing the appropriate nucleophile and reaction conditions in the latter reaction we ensured the stereocontrolled formation of a C–C bond at the C-6 position, providing access to either *cis*- or *trans*-5,6-disubstituted derivatives. The presence of the C-8 ethyl substituent has no significant effect on the stereochemical outcome of the α-amidoalkylation reaction.

4. Experimental

4.1. General

All reactions were performed under either an argon or nitrogen atmosphere with dry, freshly distilled solvents using standard procedures. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Thin-layer chromatography was carried out on SiO_2 (silica gel 60 F_{254}) or Florisil®, and the spots were located by UV and either a 1% $KMnO_4$ solution or iodine. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230–400 mesh). Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated NMR spectra were recorded in $CDCl_3$. Only noteworthy IR absorptions (cm^{-1}) are listed. Mass spectra (MS) data are reported as *m*/*z* (%). High resolution mass spectra (HMRS) were performed in Unidade de Espectrometria de Masas, Santiago de Compostela. Microanalyses were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

4.2. (5*R*,6*R*)-5-Ethyl-1-[(1*R*-2-hydroxy-1-phenylethyl]-6-(3-indolyl)-2-piperidone, 3a

Indole (858 mg, 7.32 mmol) and $TiCl_4$ (0.27 mL, 2.44 mmol) were added to a solution of **2b** (300 mg, 1.22 mmol) in CH_2Cl_2 (7 mL). The mixture was stirred at rt for 5 h. The reaction was quenched by the addition of saturated $NaHCO_3$, and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue chromatographed (SiO_2, EtOAc) to give **3a** (340 mg, 77%): IR (NaCl) 3288, 2957, 1607 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.61 (t, $J = 7.2$ Hz, 3H, CH_3CH_2), 1.12–1.29 (m, 2H, CH_3CH_2), 1.43 (m, 1H, H-4), 1.70 (m, 1H, H-5), 1.98 (m, 1H, H-4), 2.54–2.59 (m, 2H, H-3), 3.46 (br s, 1H, OH), 3.81–3.94 (m, 2H, H-2′), 4.56 (d, $J = 1.8$ Hz, 1H, H-6), 6.07 (dd, $J = 9.6$, 5.1 Hz, 1H, H-1′), 7.05–7.33 (m, 9H, HAr), 7.40 (d, $J = 8.1$ Hz, 1H, HAr), 8.79 (br s, 1H, NH); ^{13}C NMR (75.4 MHz): δ 11.5 (CH_3CH_2), 20.8 (C-4), 23.2 (CH_3CH_2), 28.5 (C-3), 40.0 (C-5), 53.5 (C-6), 59.8 (C-1′), 63.0 (C-2′), 111.6 (CHAr), 117.6 (CHAr), 117.9 (CHAr), 119.3 (CHAr), 122.0 (CHAr), 122.7 (CHAr), 124.8 (CHAr, C-3a), 128.2 (CHPh), 128.5 (2CHPh), 129.1 (2CHPh), 136.3, 136.5 (C *i*, C-7a), 172.8 (NCO); mp 180–181 °C (EtOAc–Et_2O–MeOH); $[\alpha]_D^{22} = -34.8$ (*c* 1.03, MeOH); *m*/*z* 362 (M^+, 21), 344 (50), 331 (66), 226 (100). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.84; H, 7.32; N, 7.59.

4.3. (5*R*,6*R*)-6-Allyl-5-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone, 4b

Allyltrimethylsilane (1.16 mL, 7.32 mmol) and $TiCl_4$ (0.27 mL, 2.44 mmol) were added to a solution of **2b** (300 mg, 1.22 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 23 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (Florisil®, AcOEt) to give **4b** (291 mg, 83%): IR (NaCl) 3374, 2959, 1620 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.83 (t, $J =$ 7.8 Hz, 3H, CH_3CH_2), 1.21–1.33 (m, 2H, CH_3CH_2), 1.59 (m, 1H, H-4), 1.70 (m, 1H, H-5), 1.83 (m, 1H, H-4), 2.14 (m, 1H, CH_2CH=), 2.33 (m, 1H, CH_2CH=), 2.53–2.59 (m, 2H, H-3), 3.28 (dd, $J = 9.6$, 5.4 Hz, 1H, H-6), 4.04 (dd, $J = 12.0$, 3.6 Hz, 1H, H-2′), 4.14 (dd, $J = 12.0$, 6.9 Hz, 1H, H-2′), 4.71 (dd, $J = 6.9$, 3.6 Hz, 1H, H-1′), 5.00 (br s, 1H, CH_2=), 5.04 (d, $J = 7.2$ Hz, 1H, CH_2CH=), 5.70 (m, 1H, CH_2=), 7.24–7.36 (m, 5H, HAr); ^{13}C NMR (75.4 MHz): δ 11.6 (CH_3CH_2), 21.8 (C-4), 25.4 (CH_3CH_2),

30.8 (C-3), 34.3 ($CH_2CH{=}CH_2$), 40.8 (C-5), 61.0 (C-6), 63.8 (C-2′), 67.2 (C-1′), 117.3 ($CH{=}CH_2$), 127.4 (CHAr), 127.5 (2CHAr), 128.3 (2CHAr), 135.1 ($CH{=}CH_2$), 137.1 (C *i*), 172.0 (NCO); *m*/*z* 288 (M^++1, 21), 246 (32), 216 (2), 168 (13), 126 (100); HRMS calcd for $C_{18}H_{25}NO_2$ (M^++1) 288.1963, found 288.1953.

4.4. (5*R*,6*S*)-6-Cyano-5-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone, 5b

Trimethylsilyl cyanide (0.53 mL, 4.24 mmol) and titanium tetrachloride (0.23 mL, 2.12 mmol) were added to a solution of **2b** (260 mg, 1.06 mmol) in CH_2Cl_2 (10 mL). The mixture was then refluxed for 22 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (Florisil®, 7:3 EtOAc–hexane to EtOAc) to give **5b** (107 mg, 37%) and **2b** (119 mg). Compound **5b**: IR (NaCl) 3404, 2963, 1640 cm^{-1}; ^1H NMR (400 MHz, COSY, HETCOR): δ 0.94 (t, $J = 7.6$ Hz, 3H, CH_3CH_2), 1.47 (m, 2H, CH_3CH_2), 1.74 (m, 1H, H-4), 1.91–1.98 (m, 2H, H-4, H-5), 2.55 (m, 1H, H-3), 2.71 (dd, $J = 8.0$, 1.6 Hz, 1H, H-3), 3.45 (br s, 1H, OH), 4.12 (m, 2H, H-2′), 4.31 (m, 1H, H-6), 5.56 (t, $J = 5.6$ Hz, 1H, H-1′), 7.33–7.40 (m, 5H, HAr). ^{13}C NMR (100.6 MHz): δ 11.1 (CH_3CH_2), 23.2 (C-4), 25.0 (CH_3CH_2), 31.1 (C-3), 39.0 (C-5), 51.0 (C-6), 60.6 (C-1′), 62.0 (C-2′), 116.0 (CN), 128.5 (CHAr), 128.6 (2CHAr), 128.9 (2CHAr), 135.2 (C *i*), 171.0 (NCO); $[\alpha]_D^{22} = -16.0$ (*c* 0.18, MeOH); *m*/*z* 273 (M^++H, 2), 254 (38), 241 (67), 225 (23), 214 (51), 120 (44). Anal. Calcd for $C_{16}H_{20}N_2O_2{\cdot}1/3H_2O$: C, 69.06; H, 7.48; N, 10.07. Found: C, 68.80; H, 7.50; N, 9.83. HRMS calcd for $C_{16}H_{20}N_2O_2$ 272.1525, found 272.1515.

4.5. General procedure for the reaction of lactam 2b with Grignard reagents

The Grignard reagent (6 equiv) was added to a cooled (0 °C) solution of **2b** (1 equiv) in THF (2 mL) and the mixture stirred at this temperature for 18 h. The reaction was quenched by the addition of saturated aqueous NaCl, and the mixture extracted with EtOAc. The combined extracts were dried and concentrated.

4.5.1. (5*R*,6*S*)-5-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-6-methyl-2-piperidone, 6a.

Operating as described in the general procedure, from **2b** (300 mg, 1.22 mmol) and methylmagnesium chloride (3 M in THF, 2.44 mL, 7.32 mmol) a residue was obtained. Purification by column chromatography (Florisil®, 1:1 EtOAc–hexane to EtOAc) gave **6a** (243 mg, 76%): IR (NaCl) 3380, 2960, 1618 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.66 (t, $J = 7.2$ Hz, 3H, CH_3CH_2), 1.03–1.21 (m, 2H, CH_3CH_2), 1.22 (d, $J = 6.3$ Hz, 3H, CH_3), 1.39 (m, 1H, H-5), 1.54 (m, 2H, H-4), 2.03 (m, 1H, H-4), 2.42–2.47 (m, 2H, H-3), 3.16 (m, 1H, H-6), 3.59 (br s, 1H, OH), 4.14 (dd, $J = 11.4$, 5.1 Hz, 1H, H-2′), 4.25 (dd, $J = 11.4$, 8.7 Hz, 1H, H-2′), 5.39 (dd, $J = 8.1$, 5.1 Hz, 1H, H-1′), 7.26–7.37 (m, 5H, HAr); ^{13}C NMR (75.4 MHz): δ 11.3 (CH_3CH_2), 20.5 (C-4), 22.5 (CH_3), 24.2 (CH_3CH_2), 28.5 (C-3), 40.5 (C-5), 54.4 (C-6), 61.7 (C-1′), 63.0 (C-2′), 127.4 (CHAr), 128.1 (2CHAr), 128.2 (2CHAr), 137.0 (C *i*), 171.8 (NCO); mp 109–111 °C (EtOAc–Et_2O); $[\alpha]_D^{22} = -2.9$ (*c* 0.48, MeOH); *m*/*z* 262 (M+1, 1), 243 (12), 230 (56), 216 (5). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.56; H, 8.94; N, 5.28.

4.5.2. (5*R*,6*S*)-5,6-Diethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone, 7a.

Operating as described in the general procedure, from **2b** (320 mg, 1.30 mmol) and ethylmagnesium bromide (1 M in THF, 3.90 mL, 3.90 mmol), a residue was obtained. Purification by column chromatography (SiO_2, 7:3 EtOAc–hexane to EtOAc) gave **7a** (226 mg, 63%): IR (NaCl) 3372, 2960, 1618 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.66 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 0.79 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 1.04 (m, 1H, CH_3CH_2), 1.17 (m, 1H, CH_3CH_2), 1.46–1.54 (m, 2H, CH_2CH_3), 1.55–1.60 (m, 1H, H-5), 1.68 (m, 1H, CH_2CH_3), 1.96 (m, 1H, H-4), 2.40–2.45 (m, 2H, H-3), 2.87 (app d, $J = 10.8$ Hz, 1H, H-6), 3.59 (br s, 1H, OH), 4.13 (dd, $J = 11.4$, 4.8 Hz, 1H, H-2′), 4.24 (dd, $J = 11.4$, 8.4 Hz, 1H, H-2′), 5.31 (dd, $J = 8.4$, 4.8 Hz, 1H, H-1′), 7.26–7.37 (m, 5H, HAr); ^{13}C NMR (75.4 MHz): δ 10.6 (CH_3CH_2), 11.5 (CH_3CH_2), 20.6 (C-4), 24.6 (CH_3CH_2), 27.5 (CH_2CH_3), 28.6 (C-3), 35.1 (C-5), 61.6 (C-6), 63.1 (C-1′), 63.9 (C-2′), 128.0 (CHAr), 128.2 (2CHAr), 128.4 (2CHAr), 137.0 (C *i*), 172.6 (NCO); mp 109–110 °C (EtOAc, Et_2O, MeOH); $[\alpha]_D^{22} = -48.9$ (*c* 0.27, MeOH); *m*/*z* 257 (M^+-H_2O), 244 (72), 228 (10), 216 (20), 200 (5), 126 (60). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.94; H, 9.18; N, 4.94.

4.5.3. (5*R*,6*S*)-5-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-6-propyl-2-piperidone, 8a.

Operating as described in the general procedure, from **2b** (300 mg, 1.22 mmol) and propylmagnesium chloride (2 M in Et_2O, 3.66 mL, 7.32 mmol) a residue was obtained. Purification by column chromatography (SiO_2, 7:3 EtOAc–hexane to EtOAc) gave **8a** (233 mg, 66%): IR (NaCl) 3376, 2958, 1620 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.64 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 0.84 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 0.97–1.35 (m, 4H, $2CH_3CH_2$), 1.51 (m, 1H, H-5), 1.55–1.59 (m, 3H, $CHCH_2CH_2$, H-4), 1.98 (dddd, $J = 13.8$, 13.8, 9.0, 4.8 Hz, 1H, H-4), 2.41 (dd, $J = 8.4$, 5.7 Hz, 2H, H-3), 2.98 (m, 1H, H-6), 3.96 (br s, 1H, OH), 4.13 (dd, $J = 11.4$, 5.1 Hz, 1H, H-2′), 4.25 (dd, $J = 11.4$, 8.1 Hz, 1H, H-2′), 5.35 (dd, $J = 8.1$, 5.1 Hz, 1H, H-1′), 7.26–7.34 (m, 5H, HAr); ^{13}C NMR (75.4 MHz): δ 11.4 (CH_3CH_2), 13.7 ($CH_3CH_2CH_2$), 19.3 (CH_3CH_2), 20.7 (C-4), 24.5 (CH_3CH_2), 28.5 (C-3), 35.6 (C-5), 36.7 ($CH_3CH_2CH_2$), 59.1 (C-6), 62.5 (C-1′), 63.4 (C-2′), 127.5 (CHAr), 128.2 (2CHAr), 128.3 (2CHAr), 137.0 (C *i*), 172.3 (NCO); mp 70–71 °C (EtOAc); $[\alpha]_D^{22} = -34.8$ (*c* 1.03, MeOH); *m*/*z* 271 (M^+-H_2O, 4), 258 (63), 246 (3), 216 (16), 170 (21). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.44; H, 9.35; N, 4.78.

4.5.4. (5*R*,6*R*)-5-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-6-phenyl-2-piperidone, 9a.

Operating as described in the general procedure, from **2b** (300 mg, 1.22 mmol) and phenylmagnesium bromide (1 M in THF, 7.32 mL, 7.32 mmol), a residue was obtained. Purification by column

chromatography (Florisil®, 1:1 EtOAc–hexane to EtOAc) gave **9a** (292 mg, 74%): IR (NaCl) 3385, 2958, 1618 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.58 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 1.06–1.25 (m, 2H, CH_3CH_2), 1.38–1.51 (m, 2H, H-4, H-5), 1.87 (m, 1H, H-4), 2.53–2.60 (m, 2H, H-3), 2.89 (br s, 1H, OH), 3.69 (app d, $J = 6.9$ Hz, 2H, H-2′), 4.10 (d, $J = 3.0$ Hz, 1H, H-6), 5.94 (t, $J = 7.8$ Hz, 1H, H-1′), 7.10–7.24 (m, 3H, HAr), 7.25–7.35 (m, 7H, HAr); ^{13}C NMR (75.4 MHz): δ 11.3 (CH_3CH_2), 19.8 (C-4), 23.7 (CH_3CH_2), 28.7 (C-3), 42.4 (C-5), 60.0 (C-1′), 61.4 (C-6), 62.1 (C-2′), 126.6 (2CHAr), 127.3 (CHAr), 127.9 (CHAr), 128.2 (2CHAr), 128.3 (2CHAr), 128.9 (2CHAr), 136.5 (C *i*), 142.5 (C *i*), 172.0 (NCO); *m*/*z* 305 (M^+-H_2O, 3), 292 (10), 204 (4), 117 (27), 106 (100); HRMS calcd for $C_{21}H_{26}NO_2$ 324.1963, found 324.1960.

4.5.5. (5*R*,6*S*)-5-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-6-vinyl-2-piperidone, 10a. Operating as described in the general procedure, from **2b** (500 mg, 2.04 mmol) and vinylmagnesium bromide (1 M in THF, 12.2 mL, 12.2 mmol) a residue was obtained. Purification by column chromatography (4:1 AcOEt–hexane to EtOAc) gave **10a** (240 mg, 43%): IR (NaCl) 3383, 2931, 1616 cm^{-1}; ^1H NMR (300 MHz): δ 0.58 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 0.98–1.23 (m, 2H, CH_2CH_3), 1.45 (m, 1H, H-5), 1.49 (m, 1H, H-4), 2.00 (m, 1H, H-4), 2.45 (m, 2H, H-3), 3.52 (dm, $J = 7.2$ Hz, 1H, H-6), 4.07 (dd, $J = 11.0$, 6.0 Hz, 1H, H-2′), 4.20 (dd, $J = 11.4$, 9.0 Hz, 1H, H-2′), 5.10–5.17 (m, 2H, CH=CH_2), 5.76 (dd, $J = 9.0$, 6.0 Hz, 1H, H-1′), 5.87 (ddd, $J = 17.4$, 10.5, 7.2 Hz, 1H, CH=CH_2), 7.22–7.37 (m, 5H, HAr); ^{13}C NMR (75.4 MHz): δ 11.3 (CH_3), 21.0 (C-4), 23.7 (CH_2CH_3), 29.0 (C-3), 40.2 (C-5), 60.2 (C-1′), 60.7 (C-6), 63.0 (C-2′), 116.3 (CH=CH_2), 127.8 (CHAr), 128.4 (2CHAr), 128.7 (2CHAr), 136.6 (C *i*), 140.4 (CH=CH_2), 172.3 (NCO); $[\alpha]_D^{22} = -142.2$ (*c* 0.18, MeOH); *m*/*z* 274 (M^+, 100), 256 (25), 242 (10), 154 (62); HRMS calcd for $C_{17}H_{23}NO_2$ (M^++Na) 296.162, found 296.162.

4.5.6. (5*R*,6*S*)-6-Allyl-5-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone, 4a. Operating as described in the general procedure, from **2b** (100 mg, 0.41 mmol) and allylmagnesium bromide (1 M in Et_2O, 2.45 mL, 2.45 mmol) a residue was obtained. Purification by column chromatography (Florisil®, 7:3 EtOAc–hexane to EtOAc) gave **4a** (38 mg, 33%) and (5*R*,6*S*)-2,2,6-triallyl-5-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine (**4c**; 49 mg, 34%). Compound **4a**: IR (NaCl) 3355, 2932, 1619 cm^{-1}; ^1H NMR (200 MHz): δ 0.66 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 1.02–1.33 (m, 2H, CH_3CH_2), 1.50–1.70 (m, 3H, 2H-4, H-5), 1.96–2.37 (m, 2H, CH_2CH=), 2.47 (app dd, $J = 8.4$, 5.6 Hz, 2, H-3), 3.05 (dm, $J = 10.2$ Hz, 1H, H-6), 4.16 (dd, $J = 11.5$, 4.8 Hz, 1H, H-2′), 4.28 (dd, $J = 11.5$, 8.4 Hz, 1H, H-2′), 4.98–5.14 (m, 2H, CH_2=CH), 5.34 (dd, $J = 8.4$, 4.8 Hz, 1H, H-1′), 7.26–7.40 (m, 5H, HAr); ^{13}C NMR (50.4 MHz): δ 11.5 (CH_3CH_2), 20.3 (C-4), 24.4 (CH_3CH_2), 28.5 (C-3), 35.5 (C-5), 39.3 (CH_2CH=), 59.3 (C-6), 63.0 (C-1′), 63.7 (C-2′), 117.8 (CH=CH_2), 127.6 (CHAr), 128.2 (2CHAr), 128.5 (2CHAr), 134.0 (CH=CH_2), 136.8 (C *i*), 172.5 (NCO); *m*/*z* 269 (M^+-H_2O, 1), 246 (11), 158 (3), 126 (100). Compound **4c**: IR (NaCl) 3042, 2930, 1618 cm^{-1}; ^1H NMR (300 MHz): δ 0.81 (t, $J = 7.5$ Hz, 3H CH_3CH_2), 0.89–1.40 (m, 6H), 2.05–2.21 (m, 6H), 2.58 (ddd, $J = 7.2$, 7.2, 3.0 Hz, 1H, H-6), 3.50 (dd, $J = 10.5$, 9.0 Hz, 1H, H-2′), 3.63 (dd, $J = 10.5$, 4.5 Hz, 1H, H-2′), 3.77 (dd, $J = 8.7$, 4.8 Hz, 1H, H-1′), 5.02–5.13 (m, 6H, CH_2=CH), 5.66–5.86 (m, CH_2=CH), 7.24–7.36 (m, 5H, HAr); ^{13}C NMR (75.4 MHz): δ 12.2 (CH_3), 22.4 (CH_2), 22.7 (CH_2), 35.2 (CH_2), 37.2 (CH_2), 43.1 (CH), 43.4 (CH_2), 43.6 (CH_2), 56.5 (C-6), 62.6 (C-1′), 66.6 (C-2′), 73.3 (C), 116.7 (CH=CH_2), 118.3 (CH=CH_2), 118.4 (CH=CH_2), 127.4 (3CHAr), 128.4 (2CHAr), 133.7 (2CH=CH_2), 136.5 (CH=CH_2), 141.8 (C *i*); HRMS calcd for $C_{24}H_{36}NO$ (M^++1) 354.2791, found 354.2779.

4.5.7. (5*S*,6*S*)-5-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-6-(3-indolyl)-2-piperidone, 11b. Indole (288 mg, 2.46 mmol) and titanium tetrachloride (0.10 mL, 0.82 mmol) were added to a solution of **2c** (100 mg, 0.41 mmol) in CH_2Cl_2 (5 mL). The mixture was refluxed for 3 h, $TiCl_4$ (0.1 mL, 0.91 mmol) then added, and the mixture refluxed for an additional 5 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue chromatographed (Florisil®, 1:9 EtOAc–hexane to EtOAc) to give **11b** (55 mg, 55%): IR (NaCl) 3271, 1613 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.77 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 1.26–1.38 (m, 2H, CH_3CH_2), 1.48 (dd, $J = 13.5$, 6.5 Hz, 1H, H-4), 1.93–2.00 (m, 2H, H-4, H-5), 2.62 (app t, $J = 6.3$ Hz, 2H, H-3), 3.93 (dd, $J = 12.3$, 2.7 Hz, 1H, H-2′), 4.07 (dd, $J = 12.3$, 6.6 Hz, 1H, H-2′), 4.32 (dd, $J = 6.6$, 2.7 Hz, 1H, H-1′), 4.49 (d, $J = 3.0$ Hz, 1H, H-6), 7.02–7.11 (m, 3H, HAr), 7.15–7.33 (m, 6H, HAr), 7.41 (d, $J = 7.8$ Hz, 1H, HAr), 9.01 (br s, 1H, NH); ^{13}C NMR (100.6 MHz): δ 11.4 (CH_3CH_2), 21.2 (C-4), 23.9 (CH_3CH_2), 30.0 (C-3), 40.1 (C-5), 61.4 (C-6), 64.9 (C-2′), 68.1 (C-1′), 111.8 (CHAr), 115.7 (Car), 118.2 (CHAr), 119.5 (CHAr), 122.2 (CHAr), 123.0 (CHAr), 125.3 (Car), 127.5 (CHAr), 127.7 (2CHAr), 128.4 (2CHAr), 136.8 (Car), 137.7 (Car), 172.5 (NCO); $[\alpha]_D^{22} = -5.4$ (*c* 0.11, MeOH); *m*/*z* 344 (M^+-H_2O, 81), 315 (17), 225 (21), 196 (63), 183 (68), 168 (100).

4.5.8. (5*S*,6*R*)-6-Allyl-5-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone, 12b. Operating as described in the preparation of **4b**, from **2c** (300 mg, 1.22 mmol), allyltrimethylsilane (1.16 mL, 7.32 mmol) and $TiCl_4$ (0.27 mL, 2.44 mmol) in CH_2Cl_2 (10 mL), **12b** (226 mg, 64%) and **2c** (55 mg) were obtained after purification by column chromatography (Florisil®, 1:1 EtOAc–hexane to EtOAc). Compound **12b**: IR (NaCl) 1620, 3380 cm^{-1}; ^1H NMR (300 MHz, COSY, HETCOR): δ 0.70 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 1.15 (m, 1H, CH_3CH_2), 1.27 (m, 1H, CH_3CH_2), 1.57 (m, 1H, H-4), 1.67 (m, 1H, H-5), 1.98 (m, 1H, H-4), 2.19–2.27 (m, 2H, CH_2CH=), 2.42 (dd, $J = 7.8$, 4.0 Hz, 1H, H-3), 2.44 (dd, $J = 6.9$, 4.0 Hz, 1H, H-3), 3.09 (m, 1H, H-6), 4.03 (dd, $J = 12.0$, 3.9 Hz, 1H, H-2′), 4.25 (dd, $J = 12.0$, 7.5 Hz, 1H, H-2′), 4.66 (dd, $J = 7.5$, 3.9 Hz, 1H, H-1′), 5.00 (dq, $J = 17.0$, 1.8 Hz, 1H, CH_2=), 5.07 (m, 1H, CH_2=), 5.59 (m, 1H, CH_2CH=), 7.25–7.37 (m, 5H, HAr); ^{13}C NMR (75.4 MHz): δ 11.4 (CH_3CH_2), 20.3 (C-4), 24.5 (CH_3CH_2), 28.9 (C-3), 35.6 (C-5), 38.5 (CH_2CH=),

61.4 (C-6), 64.4 (C-2′), 66.3 (C-1′), 118.0 (CH=*C*H_2), 127.8 (CHAr), 128.1 (2CHAr), 128.4 (2CHAr), 134.0 (*C*H=CH$_2$), 137.4 (C *i*), 172.0 (NCO); $[\alpha]_D^{22} = -19.6$ (*c* 10.9, MeOH). Anal. Calcd for $C_{18}H_{25}NO_2 \cdot 1/4H_2O$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.46; H, 8.80; N, 4.80. HMRS calcd for $C_{18}H_{25}NO_2$ (M^++Na) 310.177, found 310.178.

4.5.9. (5*S*,6*R*)-5-Ethyl-6-phenyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone, 13a. Operating as described in the general procedure for the reaction with Grignard reagents, from **2c** (300 mg, 1.22 mmol) and phenylmagnesium bromide (1 M in THF, 7.32 mL, 7.32 mmol), **13a** (241 mg, 61%) was obtained after purification by column chromatography (Florisil®, 1:1 EtOAc–hexane to EtOAc): IR (NaCl) 3385, 2959, 1618 cm^{-1}; ^{1}H NMR (300 MHz, COSY, HETCOR): δ 0.63 (m, 1H, CH$_3$C*H*$_2$), 0.72 (t, $J = 7.5$ Hz, 3H, C*H*$_3$CH$_2$), 1.03 (m, 1H, CH$_3$C*H*$_2$), 1.50 (m, 1H, H-5), 1.59–1.70 (m, 2H, H-4), 2.62 (ddd, $J = 18.3$, 10.5, 8.1, 1H, H-3), 2.79 (ddd, $J = 18.3$, 7.2, 0.9 Hz, 1H, H-3), 3.5 and 3.61 (2dd, $J = 11.4$, 8.4 Hz, 2H, H-2′), 4.14 (dd, $J = 4.2$, 0.6 Hz, 1H, H-6), 5.94 (d, $J = 8.4$ Hz, 1H, H-1′), 7.02–7.05 (m, 2H, HAr), 7.15–7.18 (m, 2H, HAr), 7.26–7.36 (m, 8H, HAr); ^{13}C NMR (75.4 MHz): δ 11.3 (*C*H$_3$CH$_2$), 20.7 (C-4), 24.9 (CH$_3$*C*H$_2$), 31.5 (C-3), 40.7 (C-5), 59.9 (C-1′), 60.9 (C-6), 61.9 (C-2′), 127.6 (CHAr), 127.7 (CHAr), 127.9 (2CHAr), 128.0 (2CHAr), 128.3 (2CHAr), 128.4 (2CHAr), 136.6 (C *i*), 138.1 (C *i*), 171.6 (NCO); $[\alpha]_D^{22} = -126.1$ (*c* 0.23, MeOH); mp 124–126 °C (EtOAc–Et$_2$O–MeOH); *m*/*z* 324 (M^+, 100), 306 (25), 292 (9), 204 (47); HMRS calcd for $C_{21}H_{26}NO_2$ 324.197, found 324.196.

4.6. General procedure for Na/NH$_3$ reaction

Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice–acetone, was condensed NH$_3$ at −78 °C. The temperature was raised to −33 °C, and a solution of the lactam in THF was added, followed by the addition of sodium metal in small portions until the blue color persisted. After the mixture was stirred at −33 °C for 5 min, the reaction was quenched by the addition of solid NH$_4$Cl until the blue colour disappeared. The mixture was stirred at rt for 4 h, poured into water and extracted with Et$_2$O. The combined organic extracts were dried and concentrated to give a residue, which was chromatographed.

4.6.1. (5*R*,6*R*)-5-Ethyl-6-(3-indolyl)-2-piperidone, 14. Operating as described in the general procedure, from **3a** (80 mg, 0.22 mmol) in THF (5 mL) and NH$_3$ (15 mL), a residue was obtained. Purification by column chromatography (SiO$_2$, EtOAc) afforded **14** (43 mg, 80%): IR (NaCl) 3247, 2961, 1646 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.85 (t, $J = 7.5$ Hz, 3H, C*H*$_3$CH$_2$), 1.16 (m, 1H, C*H*$_2$CH$_3$), 1.38–1.61 (m, 2H), 1.90 (m, 1H), 2.05 (m, 1H), 2.43–2.62 (m, 2H, H-3), 4.44 (d, $J = 8.7$ Hz, 1H, H-6), 5.90 (br s, 1H, NH), 7.08–7.13 (m, 2H, HAr), 7.20 (t, $J = 6.9$ Hz, 1H, HAr), 7.39 (d, $J = 8.1$ Hz, 1H, HAr) 7.59 (t, $J = 7.5$ Hz, 1H, HAr), 8.72 (br s, 1H, NH); ^{13}C NMR (75.4 MHz): δ 11.1 (*C*H$_3$CH$_2$), 24.5, 24.9 (CH$_3$*C*H$_2$, C-4), 30.9 (C-3), 40.9 (C-5), 56.0 (C-6), 111.6 (CHAr), 116.2 (Car), 119.0 (CHAr), 119.7 (CHAr), 122.3 (CHAr), 122.7 (CHAr), 125.4 (Car), 136.6 (Car), 172.2 (NCO); *m*/*z* 242 (76), 186 (72), 143 (100). HRMS calcd for $C_{15}H_{18}N_2O$, 242.1419; found 242.1411. Anal. Calcd for $C_{15}H_{18}N_2O \cdot 1/3CH_2Cl_2$: C, 68.11; H, 6.96; N, 10.36. Found: C, 67.85; H, 6.93; N, 10.11.

4.6.2. (5*R*,6*S*)-5,6-Diethyl-2-piperidone, 15. Operating as described in the general procedure, from **7a** (80 mg, 0.29 mmol) in THF (5 mL) and NH$_3$ (15 mL), a residue was obtained. Purification by column chromatography (SiO$_2$, EtOAc) afforded **15** (38 mg, 84%): IR (NaCl) 3209, 2962, 1666 cm^{-1}; ^{1}H NMR (400 MHz, COSY, HETCOR): δ 0.92 (t, $J = 7.2$ Hz, 3H, C*H*$_3$CH$_2$), 0.95 (t, $J = 7.6$ Hz, 3H, C*H*$_3$CH$_2$), 1.24 (m, 1H, CH$_3$C*H*$_2$), 1.37–1.67 (m, 5H, H-4, H-5, CH$_3$C*H*$_2$), 1.93 (m, 1H, H-4), 2.26 (ddd, $J = 18.0$, 9.6, 6.0 Hz, 1H, H-3), 2.39 (dt, $J = 18.0$, 4.8 Hz, 1H, H-3), 3.06 (dd, $J = 10.8$, 6.4 Hz, 1H, H-6), 6.36 (br s, 1H, NH); ^{13}C NMR (100.6 MHz): δ 8.9 (*C*H$_3$CH$_2$), 11.1 (*C*H$_3$CH$_2$), 23.9, 24.1, 27.2 (2CH$_3$*C*H$_2$, C-4), 30.1 (C-3), 37.5 (C-5), 58.1 (C-6), 172.7 (NCO); $[\alpha]_D^{22} = +5.0$ (*c* 0.08, MeOH).

4.6.3. (5*R*,6*R*)-5-Ethyl-6-phenyl-2-piperidone, 16. Operating as described in the general procedure, from **9a** (175 mg, 0.54 mmol) in THF (10 mL) and NH$_3$ (25 mL), a residue was obtained. Purification by column chromatography (EtOAc) afforded **16** (79 mg, 72%): IR (NaCl) 3216, 2960, 1655 cm^{-1}; ^{1}H NMR (300 MHz, COSY, HETCOR): δ 0.85 (t, $J = 7.2$ Hz, 3H, C*H*$_3$CH$_2$), 1.14 (m, 1H, CH$_3$C*H*$_2$), 1.38 (m, 1H, CH$_3$C*H*$_2$), 1.48–1.68 (m, 2H, H-4, H-5), 2.02 (m, 1H, H-4), 2.43 (m, 1H, H-3), 2.53 (m, 1H, H-3), 4.12 (d, $J = 8.7$ Hz, 1H, H-6), 5.89 (br s, 1H, NH), 7.25–7.28 (m, 2H, HAr), 7.30–7.39 (m, 3H, HAr); ^{13}C NMR (75.4 MHz): δ 10.9 (*C*H$_3$CH$_2$), 23.8 (CH$_3$*C*H$_2$), 24.4 (C-4), 30.7 (C-3), 42.2 (C-5), 62.9 (C-6), 127.1 (2CHAr), 127.9 (CHAr), 128.5 (2CHAr), 141.4 (C *i*), 172.7 (NCO); $[\alpha]_D^{22} = -10.4$ (*c* 0.27, MeOH).

4.6.4. (5*R*,6*S*)-5-Ethyl-6-vinyl-2-piperidone, 17. Operating as described in the general procedure, from **10a** (85 mg, 0.31 mmol) in THF (5 mL) and NH$_3$ (15 mL), a residue was obtained. Purification by column chromatography (EtOAc) afforded (4*R*)-4-ethyl-5-heptenamide (35 mg, 73%) and **17** (11 mg, 23%). (4*R*)-4-Ethyl-5-heptenamide: ^{1}H NMR (300 MHz): δ 0.85 (t, $J = 7.6$ Hz, 3H, C*H*$_3$CH$_2$), 1.20 (m, 1H), 1.34–1.51 (m, 2H), 1.66 (dd, $J = 6.6$, 1.8 Hz, 3H, C*H*$_3$CH=), 1.69–1.83 (m, 2H), 2.07–2.29 (m, 2H), 5.10 (m, 1H, CH=), 5.35 (m, 1H, CH=); ^{13}C NMR (50.3 MHz): δ 11.8 (CH$_3$), 18.0 (CH$_3$), 28.4 (CH$_2$), 30.7 (CH$_2$), 34.0 (CH$_2$), 44.4 (CH), 125.9 (CH), 134.7 (CH), 176.0 (NCO); *m*/*z* 155 (3), 138 (5), 126 (7), 97 (21), 59 (100). Compound **17**: ^{1}H NMR (200 MHz): δ 0.94 (t, $J = 7.2$ Hz, 3H, C*H*$_3$CH$_2$), 1.20–2.00 (m, 6H), 2.27–2.50 (m, 1H), 3.57 (m, 1H), 5.22 (m, 2H), 5.73 (ddd, $J = 17.6$, 9.8, 2.2 Hz, 1H); ^{13}C NMR (50.3 MHz): δ 11.2 (*C*H$_3$CH$_2$), 24.1 (CH$_2$), 29.8 (CH$_2$), 30.7 (CH$_2$), 39.7 (C-5), 61.4 (C-6), 118.1 (CH=*C*H$_2$), 138.5 (*C*H=CH$_2$), 172.0 (CON); *m*/*z* 153 (11), 96 (19), 69 (28), 56 (100).

4.6.5. (5*R*,6*R*)-6-Allyl-5-ethyl-2-piperidone, 18. Operating as described in the general procedure, from **4b** (280 mg,

0.97 mmol) in THF (10 mL) and NH_3 (30 mL), a residue was obtained. Purification by column chromatography (SiO_2, EtOAc) afforded **18** (118 mg, 73%): IR (NaCl) 3207, 2959, 1663 cm^{-1}; ^1H NMR (300 MHz): δ 0.95 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 1.22–1.50 (m, 2H), 1.70–1.82 (m, 3H), 2.02–2.12 (m, 1H), 2.23–2.39 (m, 3H), 3.44 (m, 1H, H-6), 5.13 (m, 1H, CH_2=), 5.19 (br s, 1H, CH_2=), 5.65–5.82 (m, 1H, CH_2CH=), 6.11 (br s, 1H, NH); ^{13}C NMR (75.4 MHz): δ (ppm): 11.4 (CH_3CH_2), 20.6 and 22.4 (C-4 and CH_3CH_2), 28.9 (C-3), 36.0 (CH_2CH=CH_2), 37.0 (C-5), 54.6 (C-6), 118.5 (CH=CH_2), 133.9 (CH=CH_2), 171.9 (NCO); mp 48–50 °C (EtOAc); $[\alpha]_D^{22} = +48.4$ (*c* 1.19, MeOH). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.35; H, 10.37; N, 8.17.

4.6.6. (5*S*,6*R*)-5-Ethyl-6-phenyl-2-piperidone, 19. Operating as described in the general procedure, from **13a** (95 mg, 0.29 mmol) in THF (5 mL) and NH_3 (15 mL), a residue was obtained. Purification by column chromatography (SiO_2, EtOAc) afforded **19** (45 mg, 75%): IR (NaCl) 2926, 1661 cm^{-1}; ^1H NMR (300 MHz): δ 0.83–0.93 (m, 4H, CH_3CH_2, CH_3CH_2), 1.11–1.24 (m, 1H, CH_3CH_2), 1.62–1.79 (m, 2H), 1.96 (m, 1H), 2.43 (m, 1H, H-3), 2.52 (dt, $J = 4.5$, 2.7 Hz, 1H, H-3), 4.65 (dd, $J = 4.5$, 2.7 Hz, 1H, H-6), 6.39 (br s, 1H, NH), 7.16–7.20 (m, 2H, HAr), 7.25–7.37 (m, 3H, HAr); ^{13}C NMR (75.4 MHz): δ 11.6 (CH_3CH_2), 21.5 and 22.3 (C-4, CH_3CH_2), 29.7 (C-3), 39.3 (C-5), 60.2 (C-6), 127.3 (2CHAr), 127.6 (CHAr), 128.1 (CHAr), 139.4 (C *i*), 171.9 (NCO); mp 75–77 °C (EtOAc); $[\alpha]_D^{22} = -75.6$ (*c* 0.53, MeOH).

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