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Stereoselective Alkylation of N-Boc-2-Pyrrolidinones and N-Boc-2-Piperidinones. Synthesis and Characterization of Disubstituted Lactams

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Abstract: Alkylation of enolates of monosubstituted N-Boc lactams **4-6** afforded *trans*-disubstituted lactams as the major isomer. In the pyrrolidinone series, 1,3-induction seems to be ruled by steric interactions and the diastereoselection is low for the alkylation of enolates with small substituents at C-5 (e.g., Me) and methyl iodide. The *trans* selectivity improves with bulkier substituents at C-2 and/or bulkier electrophiles. The formation of 3,6-*trans*-disubstituted piperidinones benefits from the axial orientation of the substituent at C-2 due to the $A^{1,3}$ strain with the N-Boc group and excellent *trans* preference is observed even in the alkylation of the lithium enolate of N-Boc-6-methyl piperidinone with methyl iodide.

Keywords: disubstituted pyrrolidinones and piperidinones, alkylation, steric and stereoelectronic effects

Substituted 5- and 6- membered lactams are synthetic precursors of N-acyliminium ions which are valuable intermediates in the total synthesis of heterocyclic nitrogen compounds and alkaloids.[1,2]

The alkylation of pyroglutamic acid derivatives has been extensively studied and good to excellent levels of *trans* selectivity were observed and correlated mainly with the bulkiness of the alkyl halides employed.[3,4,5] The use of electrophiles such as aldehydes[6], imines[7], trimethylstannylmethyl iodide[8] and Eschenmoser's salt[9] led to similar stereochemical results and steric effects were invoked to explain the *trans* selectivity.

Meyers and coworkers[10] carried out *ab initio* calculations and proposed that the nitrogen lone pair stereoelectronically stabilizes the transition state in the *trans* approach of the electrophile to the lithium enolate of 1,5-dimethyl-2-pyrrolidinone. Recently, coordination effects were proposed to contribute to the formation of *cis* products in the alkylation of pyroglutamic acid derivatives.[11]

Hanessian and coworkers[8] reported good *trans* selectivity in the alkylation of the lithium enolate of N-Boc-6-substituted-2-piperidinone. Chelation and stereoeletronic effects were proposed to rationalize the formation of non-racemic *trans*-disubstituted piperidine systems.[12,13]

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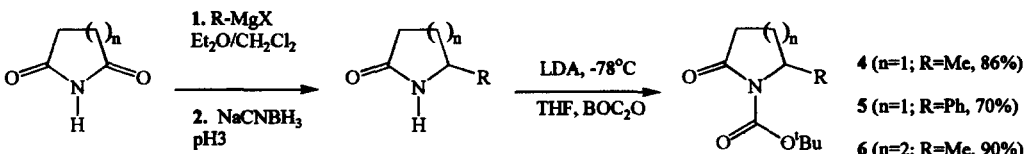
During our studies towards the total synthesis of substituted indolizidine and quinolizidine alkaloids, it became of interest to evaluate the stereochemical outcome of the alkylation of 5- and 6-monosubstituted pyrrolidinone and piperidinone, respectively, with substitutents devoid of any coordination ability. Herein, we describe the results on the alkylation of enolates of monosubstitued N-Boc-2-pyrrolidinones **4** and **5** and N-Boc-2-piperidinone **6** with methyl iodide, allyl bromide and benzyl bromide as electrophiles.

RESULTS AND DISCUSSION

N-Protected pyrrolidinones **4** and **5** and piperidinone **6** were prepared by the addition of MeMgI or PhMgBr to the corresponding imide, followed by *in situ* reduction with $NaCNBH_3$ in acidic media.[14,15] Subsequent protection of lactams **1-3** produced N-Boc-2-pyrrolidinones **4** (57% yield) and **5** (47% yield) as well as N-Boc-2-piperidinone **6** (74% yield) after three steps (Scheme 1). The formation of lactams **1-3** was achieved in reasonable yields only when dichloromethane was employed as cosolvent in the Grignard addition-reduction sequence, a protocol adapted from the procedure by Evans and coworkers.[14]

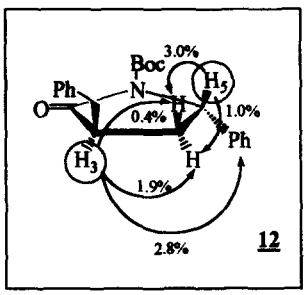


Scheme 1

Optimal experimental conditions for each lactam were standardized through variations of the nature and amounts of the base, DMPU, temperature and time (Table 1).

Whereas the alkylation of the lithium enolate of 2-pyrrolidinones **4** at –78°C and DMPU as cosolvent led to lactam **7** with low *trans:cis* ratio (58:42), lactam **8** was obtained from **5** with moderate *trans* selectivity (*trans:cis* = 86:14 – Table 1 – entries 1-2). The *trans:cis* ratio for **7** was determined by GC/MS analysis after nitrogen deprotection of the crude reaction mixture. In the case of lactam **8** the ratio was determined after isolation of the alkylation products by column chromatography on silica gel. These results revealed stronger steric influence of the bulkier phenyl substituent at C5 in lactam **5** compared to the methyl substituent in lactam **4**. Accordingly, the alkylation of 2-pyrrolidinones **4** and **5** with allyl bromide and benzyl bromide led exclusively to *trans* lactams **9-12** (Table 1 - entries 3-6).

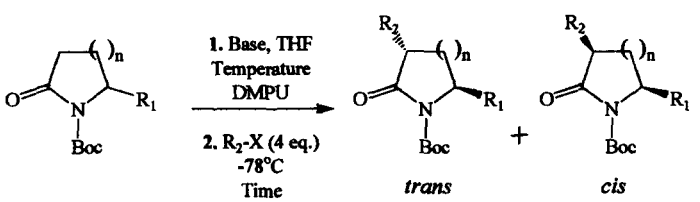
The stereochemistry of lactam 7-*trans* (major isomer) was assigned after comparison of the ^{1}H- and ^{13}C-NMR data of a 7-*trans*:7-*cis* mixture with the NMR data reported by Koskinen and coworkers for 7-*cis*.[16]



Scheme 2

The stereochemical assignment of disubstituted 2-pyrrolidinones **8-12** was performed using nOe studies, as illustrated for N-Boc-2-pyrrolidinone **12** (Scheme 2): irradiation of H3 led to a 2.8% increment in the signal of the phenyl group at C5 and a 1.9% increment in H4α. Accordingly, when H5 was irradiated a 1.0% increment in the intensity of H4α and a 3.0% increment in H4β were observed thus establishing the *trans* relationship between H3 and H5.

Table 1. Alkylation of N-Boc-2-pyrrolidinones 4 and 5 and N-Boc-2-methyl-2-piperidinone 6



Entry	R_1	R_2	n	Base (eq.)	Temp (°C)	DMPU (eq.)	Reaction time (h)	Yield (recovered reagent) (%)	Product (*trans:cis*)
1	Me	Me	1	LiHMDS(1.2)	- 78	4	2.5	58 (16)	**7** (58:42)
2	Ph	Me	1	LDA (4.0)	- 78	20	4.0	83	**8** (86:14)
3	Me	allyl	1	LDA (4.0)	- 78	20	4.0	52	**9** (>95:5)
4	Ph	allyl	1	LDA (4.0)	0	20	4.0	45 (34)	**10** (>95:5)
5	Me	Bn	1	LDA (1.2)	- 78	4	4.0	52 (13)	**11** (>95:5)
6	Ph	Bn	1	LDA (4.0)	- 78	20	4.0	60	**12** (>95:5)
7	Me	Me	2	NaHMDS(5.0)	- 78	4	0.5	77 (2)	**13** (96:4)
8	Me	allyl	2	LDA (1.1)	- 78	4	4.0	44 (26)	**14** (93:7)
9	Me	Bn	2	LDA (1.1)	- 78	4	4.0	57 (19)	**15** (>99:1)

As described by Pedregal and coworkers[3] for related systems, we have observed that H5 signals are deshielded in *trans*-2-pyrrolidinones (Table 2 - entries 1 and 3) in comparison with the corresponding *cis* products (entries 2 and 4). Additionally, H4α and H4β in *trans*-2-pyrrolidinones **7-12** usually show similar

chemical shifts ($\Delta\delta$=0 - 0.1 ppm) while for *cis*-2-pyrrolidinones **7** and **8** the difference can be larger than 1.2 ppm.

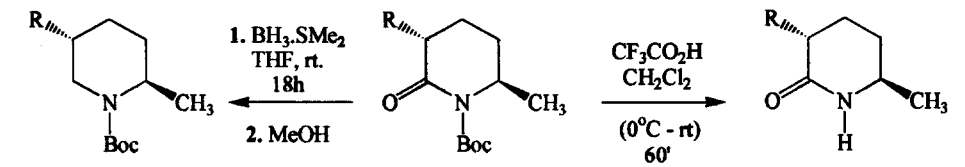
Table 2: Chemical Shifts and Coupling Constants for N-Boc-3,5 Substituted Pyrrolidinones 7-12

Entry	Product	R_1	R_2	δH_5	$\delta H_{4\alpha}$	$\delta H_{4\beta}$	^3J(H5-H4)
1	**7**-*trans*	Me	Me	4.20	1.9	1.8	6.0; 1.4
2	**7**-*cis*	Me	Me	4.03	2.4	1.3	6.2; 6.2
3	**8**-*trans*	Ph	Me	5.15	2.1	2.1	6.2; 4.0
4	**8**-*cis*	Ph	Me	4.90	2.7	1.6	9.0; 6.8
5	**9**-*trans*	Me	allyl	4.20	1.9	1.9	6.5; 1.8
6	**10**-*trans*	Ph	allyl	5.15	2.2	2.1	8.8; 1.9
7	**11**-*trans*	Me	Bn	4.13	1.9	1.7	6.2; 1.2
8	**12**-*trans*	Ph	Bn	5.04	2.2	2.0	8.8; 1.9

Comparison of ^{3}J(H5-H4α) and ^{3}J(H5-H4β) values of N-Boc-3,5-disubstituted-2-pyrrolidinone **8**-*trans* (6.2 and 4.0 Hz, respectively) and the corresponding N-deprotected 2-pyrrolidinone **8a** [^{3}J(H5-H4α) = ^{3}J(H5-H4β) = 6.0 Hz] reveals a conformational change upon nitrogen deprotection. This was assigned to the relief of the allylic $A^{1,3}$ strain in *trans*- 3-methyl-6-phenyl-2-pyrrolidinone (**8a**) which keeps the phenyl ring away from the plane of the carbamate bond in **8**-*trans*. Accordingly, nOe experiments conducted with **8**-*trans* has shown a significant correlation (5.5%) between the aromatic hydrogens and H3 (not observed in **8a**) which reveals the spacial proximity between the phenyl ring and H3 in **8**-*trans*.

In contrast with the low diastereoselection observed in the alkylation of the lithium enolate of 2-pyrrolidinone **4** with methyl iodide, the methylation of the sodium enolate of 2-piperididinone **6** afforded excellent (96:4) *trans*:*cis* ratio of lactam **13** (Table 1 – entry 7). Also, alkylation of the lithium enolate of 2-piperidinone **6** with methyl iodide carried out at –23°C showed lower diastereoselection and were accompanied by the formation of dialkylation products revealing the formation of lithium enolate of the monoalkylated piperidinone **13**. Higher selectivity was observed at –78°C but required DMPU as cosolvent in order to increase the yields. The use of LiHMDS and LDA also provided *trans*-N-Boc-2-piperidinone **13** with excellent diastereoisomeric ratio but with somewhat lower yields (*ca.* 60% yield).

The *trans:cis* ratio of the products of the alkylation of 2-piperidinone **6** was determined by GC/MS analysis of lactams **16-18** after nitrogen deprotection (Scheme 3). The *trans* stereochemistry of the major isomer was assigned after reduction with $BH_3.SMe_2$ in THF and NMR analysis (nOe experiments and/or coupling constant measurement) of N-Boc-piperidines **19-21** (Scheme 3). The ^{1}H-NMR data for piperidine **19** was also compared with previous data reported by Beak and Lee.[13]



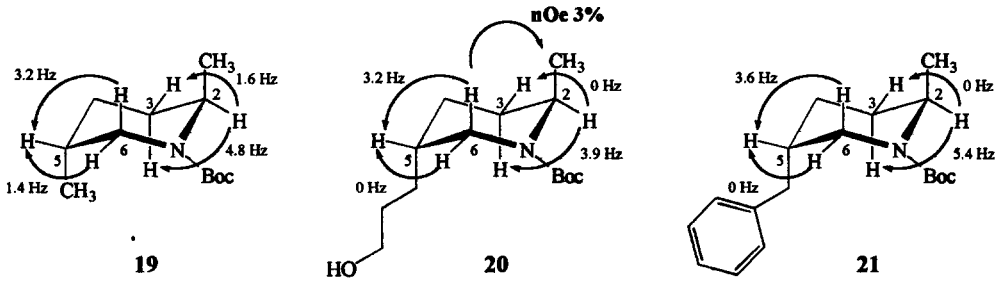
19 R=CH_3 (44%)
20 R=$(CH_2)_3OH$ (63%)
21 R=CH_2-Ph (55%)

13 R=CH_3
14 R=CH_2-CH=CH_2
15 R=CH_2-Ph

16 R=CH_3 (74%)
17 R=CH_2-CH=CH_2 (100%)
18 R=CH_2-Ph (83%)

Scheme 3

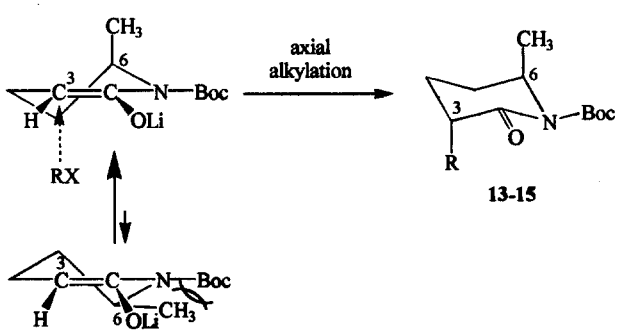
The small coupling constants between H2-H3 and H6-H5 in **19-21** and the nOe correlation between the methyl group and H6-β in **20** (Scheme 4) revealed the preferred axial orientation of the substituent in the piperidine ring.



19 **20** **21**

Scheme 4

Such conformational bias and the strong preference for the axial alkylation[17] observed for the sodium and lithium enolate of 2-piperidinone **6** may be ascribed to severe allylic $A^{1,3}$ strain due to the presence of the methyl substituent in the pseudo equatorial orientation of the half chair conformation (Scheme 5).



Scheme 5

CONCLUSION

The results described herein for the alkylation of lactams **4** and **5** reveal the preference for the formation of *trans* 3,5-disubstituted pyrrolidinones **7-12** in the absence of chelation control by the substituent at C-5. The *trans:cis* ratio was low or moderate in two cases (the methylation of the lithium enolates of 2-pyrrolidinones **4** and **5**) but preparatively useful in the other cases investigated. The stereochemical outcome of these alkylations was assigned to the steric hindrance imposed by the substituent at C5 which translate into higher *trans:cis* ratio as the sterically more demanding substituents at C5 and/or bulkier electrophiles are employed.

The alkylation of sodium and lithium enolates of 2-piperidinone **6** proved to be stereoelectronically biased in favor of the *trans* alkylation even when the sterically less demanding methyl iodide was employed. Such a preference was assigned to a conformational bias in the intermediate lithium enolate due to allylic $A^{1,3}$ interaction involving the methyl and Boc groups.

The synthetic results are being used in our laboratory for the stereoselective synthesis of substituted naturally occurring indolizidines, quinolizidines and decahydroquinolines.

EXPERIMENTAL SECTION

Material and Methods. All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) and diethyl ether were distilled from Na-benzophenone ketyl. Dichloromethane was distilled from calcium hydride. All reactions were performed under a positive argon pressure. The normal processing of organic extracts consisted of drying over $MgSO_4$, filtration and concentration with a rotary evaporator. ^{1}H-NMR and ^{13}C-NMR data were recorded on a Varian Gemini (7.0 T), Bruker AC 300P (7.0 T) or Varian Inova (11.7 T). IR spectra were obtained on Nicolet Impact 410 FT (film and KBr). Gas Chromatography (FID detector) and Gas Chromatography-Mass Spectrometry were performed using HP-5890-II and HP-GC/MS-5988 apparatus, respectively. High Resolution Mass Spectra (HRMS - EI) were measured on a VG Autospec - Micromass spectrometer. Melting points were determined on a Electrothermal 9100 apparatus and are not corrected. Chromatographic separations were performed by using 70-230 or 230-400 mesh silica gel. Elemental analyses were performed on a 2400 CHN - Perkin Elmer instrument.

General procedure for the preparation of monosubstituted lactams 4-6. Grignard reagents were prepared from 35.0 mmol of alkyl halide (methyl iodide or bromobenzene) and 40.0 mmol of magnesium turnings in diethyl ether (15 mL). A solution of succinimide or glutarimide (10 mmol) in dichloromethane (45 mL) was added at -78°C and the temperature was raised to rt. After the reaction mixture was stirred 18h at rt,

$NaCNBH_3$ (12.0 mmol) was added followed by the slow addition of a 6M HCl solution to keep pH 3-4. After 30 min for succinimide derivatives or 5h for glutarimide derivative the solution was neutralized with 10% NaOH solution and extracted with CH_2Cl_2 (5 x 20 mL). After workup, the products were separated by column chromatography on silica gel (eluent indicated for each case).

(±)- 5-methyl-2-pyrrolidinone (1). Eluent: ethyl acetate, 66% yield. Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 7.17 (s, br, 1H), 3.73 (m, 1H), 2.4-2.42 (m, 3H), 1.72 (m, 1H), 1.17 (d, ^{3}J=6.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 178.9, 50.0, 30.4, 28.8, 21.8; (lit[18]: δ 178.4, 50.1, 30.6, 29.0, 22.0;). IR (film) 3248, 2967, 2931, 1694, 1423, 1378, 1278 cm^{-1}.

(±)-5-phenyl-2-pyrrolidinone (2). Eluent: ethyl acetate; 67% yield. White solid, m.p.:103-103.5°C. ^{1}H-NMR ($CDCl_3$) δ 7.2-7.4 (m, 5H), 6.7 (s, br, 1H), 4.76 (t ,^{3}J=7.1 Hz, 1H), 2.3-2.7 (m, 3H), 1.95 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ 179.1, 142.7, 129.0, 128.0, 125.7, 58.0, 31.0, 30.1; IR (KBr pellet) 3450, 3208, 3093, 3033, 2986, 2947, 2362, 2216, 1663, 1494, 1458, 1395, 1352, 1264, 1154, 790, 757, 702, 641 cm^{-1}. Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.24; H, 6.93; N, 8.65.

(±)-6-methyl-2-piperidinone (3). Eluent: ethyl acetate/methanol: 9/1; 82% yield. White solid, m.p.:87-87.8°C (lit[19]: 87-88°C). ^{1}H-NMR ($CDCl_3$) δ 6.5 (s, br, 1H), 3.49 (m, 1H), 2.34 (m, 1H), 2.25 (m, 1H), 1.88 (m, 2H), 1.68 (m, 1H), 1.32 (m, 1H), 1.18 (d,^{3}J=6.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ (ppm) 173.1, 48.7, 31.1, 30.5, 22.7, 19.9; IR (KBr pellet) 3194, 3090, 2967, 2937, 2912, 2836, 1677, 1636, 1484, 1406, 1307, 1181, 1090, 794, 637 cm^{-1}.

General procedure for Boc protection of 2-pyrrolidinones 1 and 2 and piperidinone 3. To a solution of LDA (5.5 mmol) in THF (10 mL) stirred at -78°C was added a solution of lactams **1-3** (5.0 mmol) in THF (7 mL). After the reaction mixture was stirred at -78°C for 30 min, di-*tert*-butyl dicarbonate (5.5 mmol) was added and stirring was continued for 2h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic phases were concentrated and the products were separated by column chromatography on silica gel (eluent indicated for each case).

(±)-1-(*tert*-butoxycarbonyl)-5-methyl-2-pyrrolidinone (4). Eluent: hexane/ethyl acetate: 7/3; 86% yield. Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 4.20 (m, 1H), 2.55 (m, 1H), 2.38 (m, 1H), 2.12 (m, 1H), 1.60 (m, 1H), 1.48 (s, 9H), 1.27 (d, ^{3}J=6.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 174.56, 150.1, 82.5, 53.7, 30.9, 27.7, 24.8, 19.9; IR (film) 2978, 2934, 1785, 1752, 1713, 1367, 1310, 1155, 1026, 850, 780 cm^{-1}. Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.47; H, 8.89; N, 7.57.

(±)-1-(*tert*-butoxycarbonyl)-5-phenyl-2-pyrrolidinone (5). Eluent: hexane/ethyl acetate: 1/1; 70% yield. White solid, m.p.:97.5-98.5°C. ^{1}H-NMR ($CDCl_3$) δ 7.2-7.4 (m, 5H), 5.15 (dd, ^{3}J= 8.0 e 4.0 Hz, 1H), 2.4-2.8 (m, 3H), 1.9 (m, 1H), 1.26 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ 175.1, 149.6, 142.6, 128.8, 127.6, 125.1, 82.7, 61.4,

31.0, 27.3, 27,1; IR (KBr pellet) 3053, 3033, 2977, 2936, 1774, 1689, 1477, 1463, 1450, 1366, 1336, 1310, 1295, 1257, 1173, 1144, 1056, 853, 834, 785, 759, 715, 700 cm^{-1}. Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.56; H, 7.39; N, 5.33.

(±)-1-(*tert*-butoxycarbonyl)-6-methyl-2-piperidinone (6). Eluent: hexane/ethyl acetate 9/1; 90% yield. Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 4.29 (m, 1H), 2.4 (m, 2H), 1.6-2.0 (m, 4H), 1.53 (s, 9H), 1.27 (d, ^{3}J=6.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ (ppm) 171.4, 152.9, 82.7, 51.7, 34.2, 29.1, 27.9, 20.4, 17.2. IR (film) 2975, 2935, 1766, 1714, 1286, 1251, 1151 cm^{-1}. Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.84; H, 8.55; N, 6.27.

General procedure for the alkylation reactions on 5-substituted N-Boc-2-pyrrolidinones and N-Boc-6-methyl-2-piperidinone. To a solution of base (see Table 1) in THF (1.5 mL) stirred at temperature 1 (Table 1) was added a THF solution (1.0 mL) of the lactam (0.2 mmol). After 30 min the reaction mixture was cooled to -78°C and DMPU (see Table 1) was added. Stirring was continued for 15 min and the electrophile (0.8 mmol) was added. After the appropriate reaction time (see Table 1) the reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (4 x 5 mL). After workup, the products were separated by flash column chromatography on silica gel (eluent indicated in each case).

(3RS,5RS) and (3SR,5RS)-1-(*tert*-butoxycarbonyl)-3,5-dimethyl-2-pyrrolidinone (7). Eluent: hexane/ethyl acetate: 8/2; 58% yield of an iseparable 2:1 (*trans:cis*) mixture and 16% yield of pyrrolidinone **3** recovered. Pale yellow oil. ***7-trans:*** ^{1}H-NMR ($CDCl_3$) δ 4.18 (m, 1H), 2.70 (m, 1H), 1.75-1.95 (m, 2H), 1.54 (s, 9H), 1.30 (d, ^{3}J=6.2 Hz, 3H), 1.20 (d, ^{3}J=6.9 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 176.4, 150.5, 82.6, 51.5, 36.1, 34.1, 27.9, 19.5, 14.9. ***7-cis:*** ^{1}H-NMR ($CDCl_3$) δ 4.02 (m, 1H), 2.3-2.6 (m, 2H), 1.54 (s, 9H), 1.38 (d, ^{3}J=6.2 Hz, 3H), 1.2-1.3 (m, 1H), 1.24 (d, ^{3}J=6.9 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 177.1, 150.6, 82.6, 52.1, 37.4, 34.2 27.9, 21.8, 16.1; IR (film) 2976, 2933, 1747, 1716, 1455, 1367, 1302, 1254, 1152 cm^{-1}.

(3RS,5SR)-1-(*tert*-butoxycarbonyl)-3-methyl-5-phenyl-2-pyrrolidinone (8-*trans*). Eluent: hexane/ethyl acetate: 8/2; 71% yield. White solid, m.p.:61.5-62.5°C. ^{1}H-NMR ($CDCl_3$) δ 7.1-7.4 (m, 5H), 5.15 (dd, ^{3}J=6.2 and 4.0 Hz, 1H), 2.75 (m, 1H), 2.0-2.6 (m, 2H), 1.32 (s, 9H), 1.24 (d, ^{3}J=7.0 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 177.4, 150.0, 142.2, 128.9, 127.6, 125.0, 82.7, 59.0, 35.9, 35.8, 27.5, 14.9; IR (film) 3062, 3030, 2976, 2932, 2875, 1784, 1748, 1717, 1454, 1368, 1311, 1151, 970, 701 cm^{-1}. HRMS [M^+-$CO_2C(CH_3)_3$ +1] calcd 175.0997, found 175.0997.

(3SR,5SR)-1-(*tert*-butoxycarbonyl)-3-methyl-5-phenyl-2-pyrrolidinone (8-*cis*). Eluent: hexane/ethyl acetate: 8/2; 12% yield. White solid, m.p.:97.0-98.0°C. ^{1}H-NMR ($CDCl_3$) δ 7.2-7.4 (m, 5H), 4.89 (dd, ^{3}J=5.1 and 6.8 Hz, 1H), 2.5-2.7 (m, 2H), 1.4-1.8 (m, 2H), 1.27 (d, ^{3}J=6.6 Hz, 3H), 1.19 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ 177.5, 149.8, 128.9, 127.7, 125.6, 82.7, 60.4, 37.8, 37.2, 27.3, 15.4; IR (film) 3062, 3030, 2976, 2931,

2874, 1783, 1747, 1722, 1456, 1328, 1292, 1153, 1124, 970, 701 cm^{-1}. HRMS [M^+-$CO_2C(CH_3)_3$ +1] calcd 175.0997, found 175.0997.

(3RS,5RS)-1-(*tert*-butoxycarbonyl)-3-allyl-5-methyl-2-pyrrolidinone (9). Eluent: hexane/ethyl acetate: 9/1; 52% yield. Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 5.75 (m, 1H), 5.1 (m, 2H), 4.2 (m, 1H), 2.6-2.8 (m, 2H), 2.3 (m, 1H), 1.9 (m, 2H), 1.53 (s, 9H), 1.30 (d, ^{3}J=6.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 175.2, 150.1, 135.2, 117.2, 82.7, 51.8, 41.0, 34.5, 31.5, 27.9, 19.9; IR (film) 3077, 2977, 2931, 2875, 2854, 1783, 1748, 1713, 1642, 1456, 1367, 1332, 1317, 1302, 1278, 1255, 1156, 1096, 1040, 1006, 970, 917, 780 cm^{-1}. HRMS (M^+) calcd 239.1521, found 239.1531

(3RS,5SR)-1-(*tert*-butoxycarbonyl)-3-allyl-5-phenyl-2-pyrrolidinone (10). Eluent: hexane/ethyl acetate 8/2; 45% yield and 34% recovered reagent. White solid, m.p.:56.0-58.0°C. ^{1}H-NMR ($CDCl_3$) δ 7.1-7.4 (m, 5H), 5.75 (m, 1H), 5.0-5.15 (m, 3H), 2.79 (m, 1H), 2.65 (m, 2H); 2.2 (m, 1H), 2.05 (m, 1H), 1.31 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ 176.0, 149.8, 142.2, 134.9, 128.9, 127.5, 125.0, 117.5, 82.9, 59.2, 40.7, 34.5, 33.3, 27.6; IR (film) 3064, 3030, 3002, 2978, 2929, 1782, 1748, 1716, 1641, 1496, 1454, 1393, 1368, 1313, 1252, 1151, 1030, 1015, 999, 958, 917, 853, 799, 773, 758, 701 cm^{-1}. HRMS (M^+) calcd 301.1678, found 301.1675.

(3RS,5RS)-1-(*tert*-butoxycarbonyl)-3-benzyl-5-methyl-2-pyrrolidinone (11). Eluent: hexane/ethyl acetate: 9/1; 52% yield and 13% recovered reagent. Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 7.1-7.4 (m, 5H); 4.13 (m, 1H); 3.31 (dd, 1H, ^{3}J=13.8 e 4.0 Hz); 2.89 (m, 1H); 2.61 (dd, 1H, ^{3}J=13.8 e 10.0 Hz); 1.85 (m, 1H); 1.70 (m, 1H); 1.53 (s, 9H); 1.25 (d, 3H, ^{3}J=6.3 Hz). ^{13}C-NMR ($CDCl_3$) δ 174.8, 149.9, 138.9, 128.8, 128.4, 126.3, 82.6, 51.7, 43.4, 36.3, 31.8, 28.0, 19.8; IR (film) 3056, 3020, 2976, 2932, 2872, 1783, 1748, 1713, 1603, 1497, 1454, 1367, 1318, 1303, 1255, 1155, 1106, 1010, 847, 779, 748, 731, 701 cm^{-1}. HRMS (M^+-C_4H_8) calcd 233.10519, found 233.10511.

(3RS,5SR)-1-(*tert*-butoxycarbonyl)-3-benzyl-5-phenyl-2-pyrrolidinone (12). Eluent: hexane/ethyl acetate: 8/2; 60% yield. Pale yellow solid, m.p.:127.3-129.2°C. ^{1}H-NMR ($CDCl_3$) δ 7.1-7.4 (m, 10H); 5.04 (dd, 1H, ^{3}J=8.8 e 1.9 Hz); 3.30 (dd, ^{3}J=13.9 e 4.1 Hz, 1H); 2.95 (m, 1H); 2.71 (dd, 1H, ^{3}J=13.9 e 9.5 Hz); 2.20 (m, 1H); 1.95 (m, 1H); 1.30 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ 175.6, 149.5, 141.9, 138.6, 129.0, 128.7, 128.5, 127.4, 126.4, 124.8, 82.9, 59.2, 42.9, 36.3, 33.5, 27.7; IR (film) 3086, 3061, 3028, 2978, 2927, 2862, 1782, 1748, 1717, 1603, 1495, 1454, 1393, 1368, 1312, 1250, 1204, 1151, 1029, 947, 772, 750, 700 cm^{-1}. HRMS (M^+-C_4H_8) calcd 295.12084, found 295.12083.

(3RS,6RS)-1-(*tert*-butoxycarbonyl)-3,6-dimethyl-2-piperidinone (13). Eluent: hexane/ethyl acetate: 8/2; 77% yield and 2% recovered reagent. Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 4.16 (m, 1H), 2.45 (m, 1H), 2.00 (m, 2H), 1.6-1.4 (m, 2H), 1.49 (s, 9H), 1.22 (d, ^{3}J=6.6 Hz, 3H), 1.19 (d, ^{3}J=7.0 Hz, 3H). ^{13}C-NMR ($CDCl_3$)

δ 175.2, 153.9, 82.8, 52.3, 37.5, 28.2, 27.6, 26.3, 20.7, 17.0; IR (film) 2976, 2936, 2875, 1766, 1716, 1458, 1391, 1381, 1368, 1272, 1254, 1157 cm^{-1}. Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.36; H, 9.34; N, 6.00.

(3SR,6RS)-1-(*tert*-butoxycarbonyl)-3-allyl-6-methyl-2-piperidinone (14). Eluent: hexane/ethyl acetate: 9/1; 44% yield and 26% recovered reagent. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 5.6-5.8 (m, 1H), 5.05 (m, 2H), 4.14 (m, 1H), 2.62 (m, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 1.9-2.1 (m, 2H), 1.4-1.6 (m, 2H), 1.50 (s, 9H), 1.23 (d, ^{3}J=6.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 174.1, 153.8, 136.8, 117.2, 82.8, 52.1, 42.3, 35.7, 27.9, 27.6, 22.8, 20.7; IR (film) 3076, 2978, 2937, 2874, 1766, 1716, 1392, 1641, 1457, 1368, 1288, 1272, 1255, 1155, 915, 853 cm^{-1}. HRMS (M^+) calcd 253.1678, found 253.1677.

(3SR,6RS)-1-(*tert*-butoxycarbonyl)-3-benzyl-6-methyl-2-piperidinone (15). Eluent: hexane/ethyl acetate: 9/1; 57% yield and 19% recovered reagent. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 7.3-7.6 (m, 5H), 4.35 (m, 1H), 3.60 (q, ^{3}J=9.5 Hz, 1H), 2.80 (m, 2H), 2.20 (m, 1H), 2.00 (m, 1H), 1.75 (s, 9H), 1.65 (m, 2H), 1.44 (d, ^{3}J=6.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 173.8, 153.6, 139.5, 129.2, 128.4, 126.2, 82.9, 52.3, 44.7, 37.4, 28.2, 27.9, 22.9, 21.1; IR (film) 3085, 3061, 3026, 2977, 2935, 2872, 1765, 1732, 1714, 1603, 1496, 1454, 1392, 1368, 1287, 1272, 1255, 1152, 853, 701 cm^{-1}. Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.11; H, 8.26; N, 4.56.

General procedure for Boc deprotection reactions of 3,5-disubstituted pyrrolidinone 8-*trans* and 3,6-disubstituted 2-piperidinones 13-15. To a solution of the lactam (0.1 mmol) in CH_2Cl_2 (3 mL) stirred at 0°C was added trifluoroacetic acid (1.0 mmol). After stirring 3 h at room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic phases were concentrated and the products were separated by column chromatography on silica gel (eluent indicated for each case).

(3RS,5SR)-3-methyl-6-phenyl-2-pyrrolidinone (8a). Eluent: ethyl acetate; 73% yield. Pale yellow solid, m.p.:107.0-108.7°C. ^{1}H-NMR ($CDCl_3$) δ 7.2-7.4 (m, 5H), 6.67 (s, br, 1H), 4.75 (t, ^{3}J=6.0 Hz, 1H), 2.61 (m, 1H), 2.1-2.3 (m, 2H), 1.23 (d, ^{3}J=7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 181.6, 142.9, 129.0, 127.8, 125.6, 55.5, 39.2, 34.6, 15.6; IR (film) 3244, 3081, 3066, 2979, 2933, 2877, 1698, 1488, 1458, 1345, 1269, 763, 697 cm^{-1}. HRMS (M^+) calcd 175.0997, found 175.0997.

(3RS,6RS)-3,6-dimethyl-2-piperidinone (16). Eluent: ethyl acetate/methanol: 8/2; 74% yield. White solid, m.p.:64.0-66.0°C. ^{1}H-NMR ($CDCl_3$) δ 5.96 (s, br, 1H), 3.49 (m, 1H), 2.30 (m, 1H), 1.9-2.0 (m, 2H), 1.3-1.5 (m, 2H), 1.22 (d, ^{3}J=7.3 Hz, 3H), 1.17 (d, ^{3}J=6.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 175.7, 49.4, 35.6, 30.6, 29.0, 22.7, 16.8; IR (film) 3284, 3193, 3070, 2990, 2963, 2929, 2867, 1656, 1485, 1448, 1413, 1377, 1333, 1307, 1219, 850, 831 cm^{-1}. HRMS (M^+) calcd 127.0997, found 127.0997.

(3SR,6RS)-3-allyl-6-methyl-2-piperidinone (17). Eluent: ethyl acetate; 100% yield. White solid, m.p.:69.5-71.0°C. ^{1}H-NMR ($CDCl_3$) δ 5.6-5.8 (m, 2H), 5.10 (m, 2H), 3.47 (m, 1H), 2.70 (m, 1H), 2.30 (m, 2H), 1.95 (m, 2H), 1.2-1.5 (m, 2H), 1.17 (d, ^{3}J=6.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 173.8, 136.1, 116.8, 49.3, 40.3, 35.7, 30.7, 25.8, 23.0; IR (film) 3280, 3191, 3073, 2968, 2937, 2911, 2852, 1663, 1644, 1486, 1443, 1419, 1339, 1319, 901, 846, 640 cm^{-1}. HRMS (M^+) calcd 153.1153, found 153.1152.

(3SR,6RS)-3-benzyl-6-methyl-2-piperidinone (18). Eluent: ethyl acetate; 83% yield. White solid, m.p.:149.5-150.5°C. ^{1}H-NMR ($CDCl_3$) δ 7.4-7.6 (m, 5H), 6.1 (s, br, 1H), 3.60 (m, 2H), 2.86 (dd, ^{3}J=13.5 and 9.9 Hz, 1H), 2.65 (m, 1H), 1.9-2.1 (m, 2H), 1.4-1.7 (m, 2H), 1.35 (d, ^{3}J=6.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 173.8, 139.9, 129.3, 128.3, 126.1, 49.3, 42.5, 37.3, 30.6, 25.7, 22.9; IR (film) 3276, 3187, 3062, 3026, 2964, 2946, 2928, 2866, 1659, 1485, 1454, 1443, 1415, 1337, 1221, 845, 744 cm^{-1}. HRMS (M^+) calcd 203.1310, found 203.1310.

General procedure for the reduction of N-Boc-3,6-disubstituted 2-piperidinones 13-15. To a solution of the lactam (0.1 mmol) in THF (2 mL) stirred at 0°C was added borane dimethylsulfide complex (1.0 mmol). The reaction mixture was stirred 18 h at room temperature and then quenched with methanol (5 mL). The reaction mixture was concentrated under reduced pressure and repeatedly (4 times) dissolved in methanol (3 mL) and evaporated under reduced pressure. The product was purified by column chromatography on silica gel (eluent indicated for each case).

(2RS,5RS)-1-(*tert*-butoxycarbonyl)-2,5-dimethyl-piperidine (19). Eluent: hexane/ethyl acetate: 8/2; 36% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 4.35 (m, 1H), 3.63 (d, ^{3}J=13.4 Hz, 1H), 3.05 (dd, ^{3}J=13.4 and 3.2 Hz, 1H), 1.7-1.9 (m, 3H), 1.45 (s, 9H), 1.25 (m, 2H), 1.13 (d, ^{3}J=7.0 Hz, 3H), 0.97 (d, ^{3}J=6.9 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 155.6, 78.9, 46.2, 43.7, 28.5, 27.9, 24.9, 24.8, 16.6, 16.2; IR (film) 2966, 2933, 2861, 1692, 1475, 1454, 1415, 1363, 1337, 1310, 1261, 1245, 1182, 1155, 1078, 874 cm^{-1}. HRMS (M^+) calcd 231.1729, found 213.1725.

(2RS,5SR)-1-(*tert*-butoxycarbonyl)-2-methyl-5-allyl-piperidine (20). Eluent: hexane/ethyl acetate: 1/1; 63% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 4.33 (m, 1H), 3.80 (d, ^{3}J=13.8 Hz, 1H), 3.65 (m, 2H), 3.00 (dd, ^{3}J=13.8 and 3.4 Hz, 1H), 1.82 (m, 2H), 1.2-1.8 (m, 8H), 1.45 (s, 9H), 1.14 (d, ^{3}J=6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 155.6, 79.2, 62.9, 46.4, 41.2, 33.4, 30.9, 28.5, 26.2, 25.3, 23.9, 16.3; IR (film) 3444, 2972, 2932, 2863, 1690, 1668, 1476, 1453, 1420, 1392, 1365, 1340, 1256, 1176, 1150, 1081, 1060, 1033, 872, 768 cm^{-1}. HRMS (M^+) calcd 257.1991, found 257.2000.

(2RS,5SR)-1-(*tert*-butoxycarbonyl)-2-methyl-5-benzyl-piperidine (21). Eluent: hexane/ethyl acetate: 1/1; 55% yield. White solid, m.p.: 48.5-50.0°C. ^{1}H-NMR ($CDCl_3$) δ 7.1-7.3 (m, 5H), 4.41 (m, 1H), 3.76 (d, ^{3}J=13.7 Hz, 1H), 2.99 (dd, ^{3}J=13.7 and 3.6 Hz, 1H), 2.74 (dd, ^{3}J=13.6 and 8.3 Hz, 1H), 2.57 (dd, ^{3}J=13.6 and

7.0 Hz, 1H), 1.95 (m, 2H), 1.75 (m, 1H), 1.46 (s, 9H), 1.3-1.5 (m, 2H), 1.14 (d, ^{3}J=6.9 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 155.4, 141.1, 129.1, 128.2, 125.8, 79.1, 46.0, 41.2, 36.7, 35.5, 28.5, 25.0, 22.9, 16.0; IR (film) 3086, 3060, 3026, 2973, 2934, 2861, 1689, 1496, 1474, 1454, 1415, 1391, 1338, 1363, 1257, 1172, 1150, 1135, 1056, 1047, 1036, 739, 700 cm^{-1}. HRMS (M^+) calcd 289.2042, found 289.2041.

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