Synthesis of Functionalized Azabicycloalkane Amino Acids as Dipeptide Mimics

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Abstract: Functionalized bicyclic lactams serve as building blocks for the synthesis of conformationally constrained peptides. A route to these building blocks is described based on the stereoselective alkylation of an appropriate azabicycloalkane; all possible diastereoisomers can be obtained stereoselectively.

Key words: peptidomimetics, alkylations, lactams, bicyclic compounds, diastereoselective synthesis

The synthesis of conformationally restricted amino acids and their utilization in the synthesis of peptide conformation mimics, such as β-turn mimics, has been of considerable interest.[1] Azabicyclo[X.3.0]alkane amino acids are particularly attractive constrained dipeptide mimics because of their ability to serve as conformationally fixed surrogates of peptide turn secondary structures.[2] This has created a demand for efficient synthetic approaches towards such molecules and many methods for their synthesis have been introduced.[3–6] While studying peptide secondary structure mimics, we have synthesized several 5,5-, 6,5-, 7,5-, and 8,5-fused 1-aza-2-oxobicyclo[X.3.0]alkane amino acids[7] (Figure 1, compound **I**), that can be regarded as conformationally constrained substitutes for Xaa-Pro or Ala-Xaa dipeptide units.

The possibility of functionalizing these bicyclic lactams with lipophilic appendages is very attractive because they could improve peptide-receptor affinity by interacting with hydrophobic pockets. We have already synthesized benzyl-substituted lactams via both radical[8] or nonradical[9] approaches. However, a versatile large-scale protocol is still required, thus, we began to investigate a new synthetic method for the preparation of these bicyclic lactams. In this paper, we report a convenient method for the synthesis of *trans*- and *cis*-fused bicyclic lactams substituted with a benzyl or allyl group at the C3 position.

In a preliminary communication[10] we reported a stereoselective alkylation of a Schiff base amide enolate derived from the known lactams **1** and **2**[7a] (Figure 1). N-Deprotection and treatment with benzaldehyde gives the corresponding imines **3** and **4**, which upon treatment with a base and benzyl or allyl bromide yielded the alkyl derivatives **5–8** after reduction with $NaBH_4$ (Figure 1).

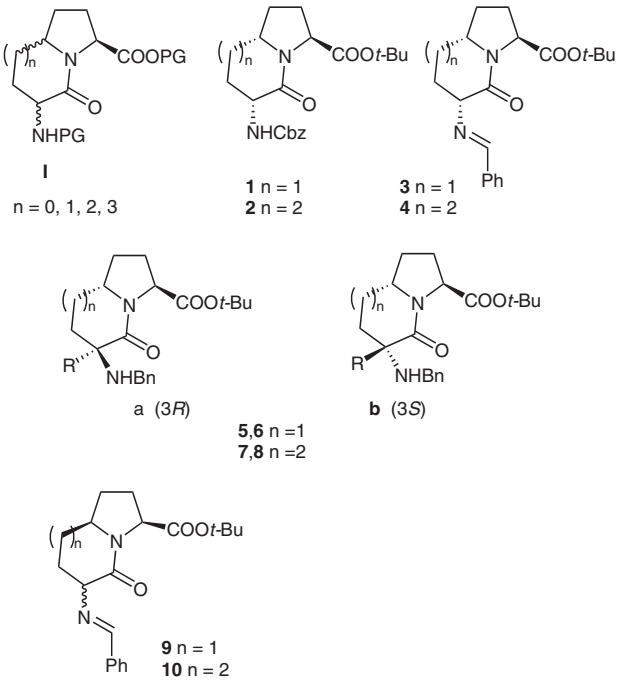

Figure 1 Bicyclic lactams.

The stereoselectivity and the yield of the reaction can be modulated using different bases or additives (Table 1). In the case of the enolate derived from **3** with LiHMDS and NaHMDS the major isomer isolated was the 3*R* isomer **5a**; the yields can be increased by adding DMPU as co-solvent. The stereoselectivity is totally reversed when a bicoordinating Lewis acid such as $MgBr_2 \cdot Et_2O$ is added to the reaction mixture. In this case the main product is the 3*S* isomer **5b**. By contrast, the benzylation of **4** affords the 3*S* isomer **7b** selectively, independently of the reaction conditions. A similar behavior can be observed with allyl bromide as the alkylating reagent.

The excellent results obtained for *trans*-fused bicyclic lactams encouraged us to extend the protocol to the *cis* series. Thus, imines **9** and **10** were obtained from the known lactams **11** and **12**, respectively, using the same procedure reported above. As observed in the *trans* series, due to the

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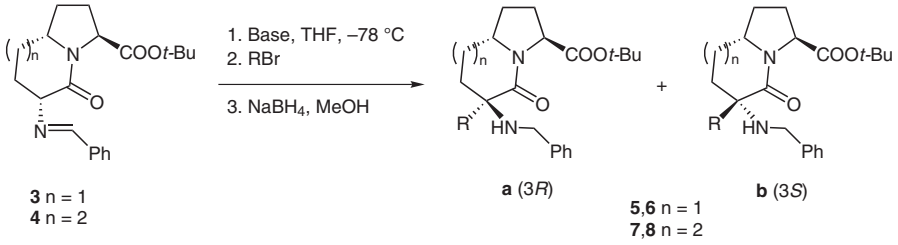
steric and electronic factors in compounds **9** and **10**, the reaction with the base was regioselective, only the proton at C3 was removed, and there was no epimerization at C9 or C10.

As shown in Table 2, the alkylation with benzyl bromide conducted with LiHMDS on imine **9**, proceeded with moderate yields but with low stereoselectivity affording the 3*S* isomer **13b** as the major product (Table 2, entry 1). It is well known that the reactivity of alkali enolates is strongly dependent on their coordination. The best results were obtained when the cation is solvated, thus, when the reaction was performed in the presence of a polar aprotic solvent such as DMPU, a slight effect on the yield and a dramatic effect on the stereoselectivity (diastereomeric ra-

Table 1 Reaction Conditions for the Alkylation of Compounds **3** and **4**



3 n = 1
4 n = 2

a (3*R*)

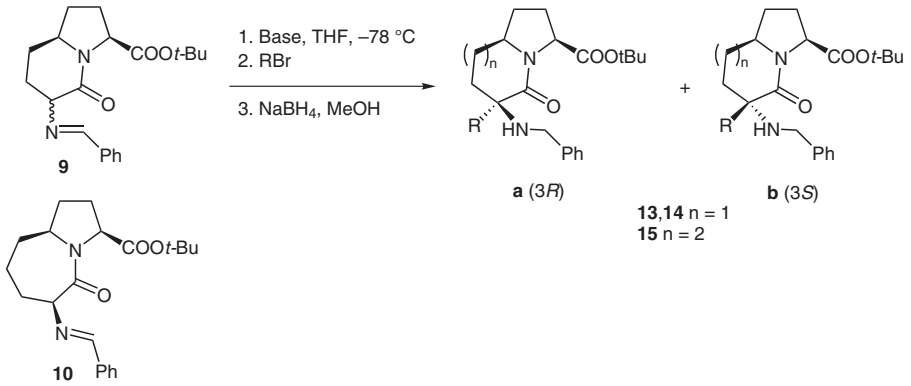
b (3*S*)

5,**6** n = 1
7,**8** n = 2

Entry	Imine	Base	T (°C)[a]	R	Products	Yield (%)	Ratio **a/b** (3*R*/3*S*)
1	**3**	LiHMDS	–78→r.t.	CH_2Ph	**5a/5b**	56	92:8[b]
2	**3**	LiHMDS/DMPU	–78→r.t.	CH_2Ph	**5a/5b**	86	82:18[b]
3	**3**	LiHMDS	–50	CH_2Ph	**5a/5b**	89	90:10[b]
4	**3**	NaHMDS	–78→r.t.	CH_2Ph	**5a/5b**	55	75:25[b]
5	**3**	NaHMDS/DMPU	–78→r.t.	CH_2Ph	**5a/5b**	81	81:19[b]
6	**3**	KHMDS	–78→r.t.	CH_2Ph	**5a/5b**	24	31:69[b]
7	**3**	LiHMDS/Mg^{2+}	–78→r.t.	CH_2Ph	**5a/5b**	43	5:95[b]
8	**3**	LiHMDS/Mg^{2+}	–50→–20	CH_2Ph	**5a/5b**	43	>2:98[b]
9	**3**	LiHMDS/Sn^{2+}	–78→r.t.	CH_2Ph	**5a/5b**	33	21:79[b]
10	**3**	LiHMDS	–78→r.t.	$CH_2CH{=}CH_2$	**6a/6b**	75	89:11[c]
11	**3**	LiHMDS	–50	$CH_2CH{=}CH_2$	**6a/6b**	90	84:16[c]
12	**3**	LiHMDS/DMPU	–78→r.t.	$CH_2CH{=}CH_2$	**6a/6b**	78	84:16[c]
13	**3**	LiHMDS/Mg^{2+}	–78→r.t.	$CH_2CH{=}CH_2$	**6a/6b**	55	7:93[c]
14	**3**	LiHMDS/Mg^{2+}	–50→–20	$CH_2CH{=}CH_2$	**6a/6b**	45	<2:>98[c]
15	**4**	LiHMDS	–78→r.t.	CH_2Ph	**7a/7b**	53	21:79[c]
16	**4**	LiHMDS	–50	CH_2Ph	**7a/7b**	82	40:60[c]
17	**4**	NaHMDS	–78→r.t.	CH_2Ph	**7a/7b**	81	10:90[c]
18	**4**	NaHMDS	–50→–20	CH_2Ph	**7a/7b**	73	20:80[c]
19	**4**	NaHMDS/DMPU	–78→r.t.	CH_2Ph	**7a/7b**	59	9:91[c]
20	**4**	LiHMDS/Mg^{2+}	–78→r.t.	CH_2Ph	**7a/7b**	68	<2:>98[c]
21	**4**	LiHMDS	–78→r.t.	$CH_2CH{=}CH_2$	**8a/8b**	67	54:46[c]
22	**4**	LiHMDS	–50	$CH_2CH{=}CH_2$	**8a/8b**	67	55:45[c]
23	**4**	LiHMDS/Mg^{2+}	–78→r.t.	$CH_2CH{=}CH_2$	**8a/8b**	20	6:94[c]

[a] Base was added at –78 °C, then bromide was added at the reported temperature.
[b] Ratio determined by ^1H NMR spectroscopy.
[c] Ratio determined by HPLC.

Table 2 Reaction Conditions for the Alkylation of Compounds **9** and **10**



Entry	Imine	Base	T (°C)[a]	R	Products	Yield (%)	Ratio **a/b** (3*R*/3*S*)
1	**9**	LiHMDS	–78→r.t.	CH_2Ph	**13a/13b**	60	39:61
2	**9**	LiHMDS/DMPU	–78→r.t.	CH_2Ph	**13a/13b**	69	17:83
3	**9**	NaHMDS	–78→r.t.	CH_2Ph	**13a/13b**	81	23:77
4	**9**	KHMDS	–78→r.t.	CH_2Ph	**13a/13b**	58	7:93
5	**9**	LiHMDS/Mg^{2+}	–78→r.t.	CH_2Ph	**13a/13b**	72	9:91
6	**9**	LiHMDS	–78→r.t.	$CH_2CH{=}CH_2$	**14a/14b**	63	10:90
7	**9**	LiHMDS/Mg^{2+}	–78→r.t.	$CH_2CH{=}CH_2$	**14a/14b**	42	<2:>98
8	**10**	LiHMDS	–78→r.t.	CH_2Ph	**15a/15b**	30	>98:<2
9	**10**	LiHMDS/Mg^{2+}	–78→r.t.	CH_2Ph	**15a/15b**	40	>99:<1

[a] Base was added at –78 °C, then bromide was added at the reported temperature.
[b] Ratio determined by ^1H NMR spectroscopy.

tio 17:83 in favor of the 3*S* stereoisomer), were observed (Table 2, entry 2).

Changing the counterion from lithium to sodium affected both the yield, which increased to 81%, and the diastereoselectivity toward the 3*S* isomer **13b** (Table 2, entry 3). When KHMDS was used as the base, a high diastereoselectivity in favor of the 3*S* isomer **13b** was observed, accompanied by only a moderate yield (Table 2, entry 4).

A dramatic effect both on the yield and on the stereoselectivity was observed when the enolate was generated with LiHMDS in the presence of a bicoordinating Lewis acid such as $MgBr_2{\cdot}Et_2O$ (Table 2, entry 5). The 3*S* isomer **13b** was obtained in 72% yield and 9:91 diastereoisomeric ratio.

In contrast to what was observed for the 6,5-fused *trans* series, the addition of a Lewis acid did not reverse the stereochemistry. This behavior could be explained by postulating that the preferred conformation of the enolate was not affected by the presence of a Lewis acid or at least was the same with or without coordinating metals. The allylation of **9** gave the same results: the presence of $MgBr_2{\cdot}Et_2O$ enhanced the diastereoisomeric ratio although with a moderate drop in yield (Table 2, entries 6 and 7). In contrast, the benzylation of **10** afforded selectively the 3*R* isomer **15a** in good yield and diastereoisomeric ratio. The only effect of the Lewis acid was to enhance the yield (Table 2, entries 8 and 9).

The stereochemical outcome of the alkylation reaction can be assigned, as in the case of the *trans* series, by invoking a pseudo-axial attack[11] onto the lowest energy conformers obtained from ab initio calculation[12] for the bicyclic intermediate enolates. The preferred conformations of the enolates derived from **9** and **10** feature a pseudo-chair conformation for the bicyclic ring (Figure 2). If pseudo-axial attack is hypothesized the products should be the 3*S* isomer **13b** and 3*R* isomer **15a**, respectively. The pure isomer **13b** was obtained by recrystallization from diethyl ether and its absolute configuration was assigned by X-ray structure analysis (Figure 3).[13]

The conformation of the fused five- and six-membered rings of isomer **13b** was determined according to the Cremer and Pople puckering analysis.[14] The conformation of the five-membered ring is very near an envelope with atom C7 as the flap [q_2 = 0.404(2) Å, φ_2 = 76.6(3)°, q_2 being the puckering amplitude and φ_2 the phase angle]. The six-membered ring adopts a conformation intermediate between envelope, with C5 as the flap, and half-chair, with C5 pointing up and C4 pointing down with respect to the mean plane of the ring [the puckering parameters in

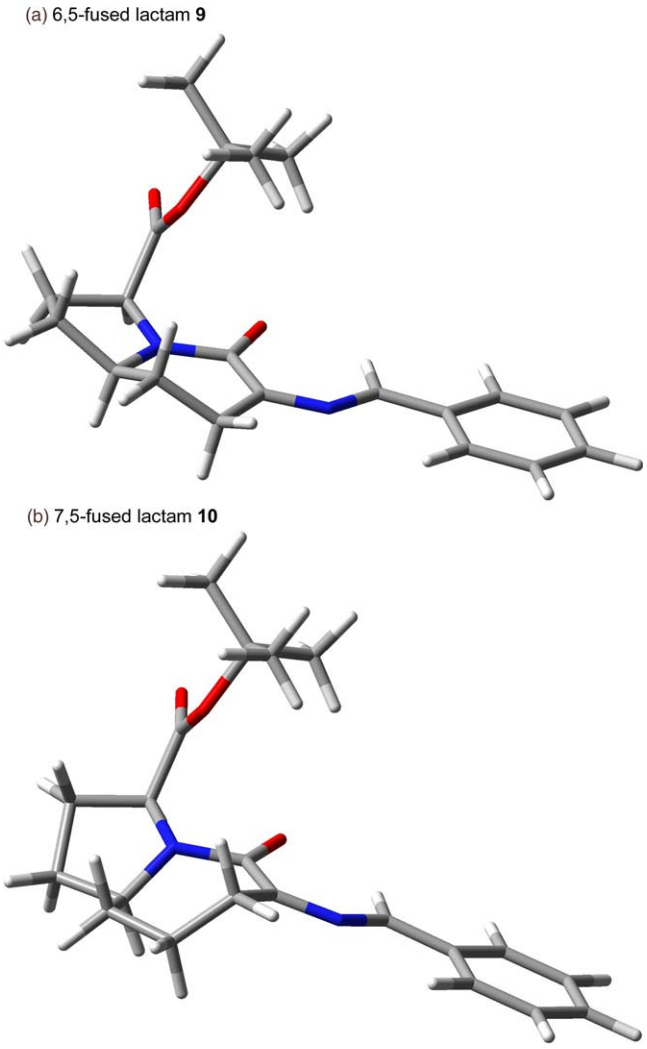


Figure 2 (a) B3LYP/6-31++G minimum energy conformation of the enolate derived from 6,5-fused lactam **9**. (b) B3LYP/6-31++G minimum energy conformation of the enolate derived from 7,5-fused lactam **10**.

this case are $Q = 0.490(2)$ Å, $c = 43.4(1)°$, $\varphi = 225.0(3)°$]. The puckering analysis on the fused rings of the (3*S*,6*S*,9*S*)-diastereoisomer previously reported,[10] which differs from **13b** only for the configuration at C6, indicated an intermediate twisted-envelope conformation and an almost perfect envelope with C2 as the flap for the five- and six-membered rings, respectively [$q_2 = 0.297(4)$ Å, $\varphi_2 = 242(1)°$; $Q = 0.469(4)$ Å, $c = 54(1)°$, $\varphi = 65(1)°$]. The conformational differences observed in the azabicyclo moiety of the two diastereoisomers, together with the different spatial disposition of the *tert*-butoxycarbonyl, benzyl, and benzylamino groups, can be ascribed to their different crystal packing.

On the basis of an absolute stereogenic center of the molecule, as shown in Figure 3, the X-ray structure of compound **13b** clearly indicated that the benzyl group is *cis* to the *tert*-butoxycarbonyl group, which implied a 3*S* configuration.

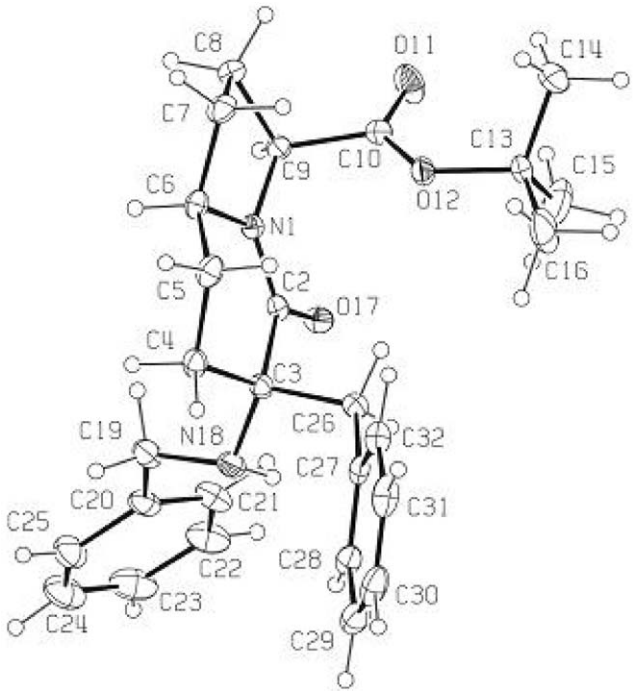


Figure 3 ORTEP plot of isomer **13b** with atom numbering scheme. Displacement ellipsoids at 30% probability level.

For compounds **14b** and **15a** the stereochemistry of the newly formed stereocenters was assigned by NOE experiments (Figure 4). In compound **14b** the NOE between the benzylamine protons and H9 result in the relative configuration 3*S* at C3. In compound **15a** a NOE between the benzyl proton, of the substituent at C3, and H7 unequivocally attributes the stereochemistry at C3 as 3*R*.

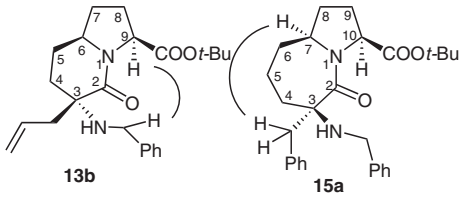


Figure 4 NOE in compounds **14b** and **15a**.

In conclusion we have found a new versatile method for the functionalization of the C3 position of azabicycloalkanes based on a stereoselective alkylation of a Schiff base amide enolate. With this method it is possible to obtain the desired functionalized azabicycloalkane by changing the base and/or adding coordinating metals to the reaction mixture.

All chemicals and solvents were of reagent grade and were used without further purification. Solvents were dried by standard procedures and reactions requiring anhydrous conditions were performed under N_2 or Ar. Optical rotations were measured in a cell of 1 dm path length and 1 mL capacity on a Perkin-Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded at 300 K on a Bruker AVANCE-400 or Bruker AC-300 or AC-200 spectrometer. Chemical shifts are expressed in ppm relative to TMS as internal standard.

MS were determined with a VG 7070 EQ-HF apparatus. TLC was carried out with precoated Merck F_{254} silica gel plates. Flash chromatography was carried out with Macherey-Nagel silica gel 60 (230–400 mesh). Elemental analyses were performed by the staff of the microanalytical laboratory of our department.

Lactams 3, 4, 9, and 10; General Procedure

A solution of NCbz-protected lactam (1.07 mmol) in MeOH (11 mL) containing 10% Pd/C (cat.) was stirred overnight under H_2. The catalyst was then removed by filtration through a pad of celite and washed with MeOH. The filtrate was concentrated to dryness under reduced pressure. The crude was dissolved in anhyd CH_2Cl_2 (11 mL) and anhyd Et_3N (299 μL, 2.14 mmol). $MgSO_4$ (64 mg) and freshly distilled benzaldehyde (217 μL, 2.14 mmol) were then added. After 24 h at r.t. the mixture was filtered through a pad of celite and washed with CH_2Cl_2. The solvent was removed under reduced pressure to a volume of 10 mL and an equal volume of hexane was added. The organic layer was washed with a sat. solution of $NaHCO_3$ (2 × 20 mL), H_2O (2 × 20 mL), and brine (2 × 20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The crude was used without further purification.

(3*R*,6*S*,9*S*)-1-Aza-2-oxo-3-benzylidenamino-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (3)

Yield: 92% (2 steps); white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 1.48–2.40 (m, 8 H), 3.75 (m, 1 H, CHN), 3.99 (m, 1 H, C*H*N=CHPh), 4.38 [dd, *J* = 8.5, 8.5 Hz, 1 H, C*H*(COO*t*-Bu)], 7.3–7.7 (m, 5 H, Ar), 8.34 (s, 1 H, N=C*H*Ph).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.0, 167.2, 163.4, 136.3, 130.9, 129.2, 128.7, 128.6, 81.6, 67.5, 60.7, 59.1, 33.1, 29.8, 28.2, 27.8, 25.3.

FAB-MS: *m*/*z* calcd for $C_{20}H_{27}N_2O_3$ [M + 1]$^+$: 343.43; found: 343.

Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.20; H, 7.66; N, 8.18.

(3*R*,7*S*,10*S*)-1-Aza-2-oxo-3-benzylidenamino-9-(*tert*-butoxycarbonyl)bicyclo[5.3.0]decane (4)

Yield: 94% (2 steps); white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*-Bu), 1.45–2.41 (m, 10 H), 4.03 (m, 1 H, CHN), 4.21 (m, 1 H, C*H*N=CHPh), 4.51 [m, 1 H, C*H*(COO*t*-Bu)], 7.37 (m, 5 H, Ar), 8.22 (s, 1 H, N=C*H*Ph).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.2, 171.6, 162.3, 136.4, 130.8, 129.2, 128.7, 128.5, 81.1, 72.9, 61.3, 58.6, 58.5, 35.1, 33.0, 32.7, 32.5, 28.2, 27.4, 27.1.

FAB-MS: *m*/*z* calcd for $C_{21}H_{29}N_2O_3$ [M + 1]$^+$: 357.21; found: 357.

Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.78; H, 7.92, N, 7.86.

(3*R*,6*R*,9*S*)-1-Aza-2-oxo-3-benzylidenamino-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (9)

Yield: 95% (2 steps); white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 1.70–2.27 (m, 8 H), 3.78 (m, 1 H, CHN), 3.97 (dd, *J* = 7.5, 7.5 Hz, 1 H, C*H*N=CHPh), 4.35 [m, 1 H, C*H*(COO*t*-Bu)], 7.41 (m, 2 H, Ar), 7.75 (m, 3 H, Ar), 8.41 (s, 1 H, N=C*H*Ph).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.3, 167.7, 164.5, 136.2, 130.9, 128.6, 128.5, 128.4, 81.3, 69.7, 60.4, 59.6, 31.8, 30.5, 28.5, 28.2, 28.1.

FAB-MS: *m*/*z* calcd for $C_{20}H_{27}N_2O_3$ [M + 1]$^+$: 343.43; found: 343.

Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.18; H, 7.64; N, 8.19.

(3*S*,6*R*,9*S*)-1-Aza-2-oxo-3-benzylidenamino-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (9)

Yield: 90% (2 steps); white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31 (s, 9 H, *t*-Bu), 1.60–2.13 (m, 8 H), 3.53 (m, 1 H, CHN), 3.95 (m, 1 H, C*H*N=CHPh), 4.23 [dd, *J* = 7.2, 1.7 Hz, 1 H, C*H*(COO*t*-Bu)], 7.35 (m, 2 H, Ar), 7.72 (m, 3 H, Ar), 8.43 (s, 1 H, N=C*H*Ph).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.2, 167.6, 163.1, 136.5, 130.7, 128.6, 128.5, 81.2, 66.5, 60.8, 59.8, 31.9, 30.0, 28.3, 27.9, 25.5.

FAB-MS: *m*/*z* calcd for $C_{20}H_{27}N_2O_3$ [M + 1]$^+$: 343.43; found: 343.

Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.16; H, 7.64; N, 8.18.

(3*S*,7*R*,10*S*)-1-Aza-2-oxo-3-benzylidenamino-9-(*tert*-butoxycarbonyl)bicyclo[5.3.0]decane (10)

Yield: 85% (2 steps); white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 1.55–2.40 (m, 10 H), 3.80 (m, 1 H, CHN), 4.12 (m, *J* = 9.8, < 1 Hz, 1 H, *t*-Bu), 4.56 (m, 1 H, C*H*N=CH), 7.40 (m, 3 H, Ar), 7.80 (m, 2 H, Ar), 8.23 (s, 1 H, N=C*H*Ph).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.1, 162.2, 134.6, 130.8, 129.9, 129.2, 128.7, 128.5, 81.3, 72.9, 61.4, 58.9, 34.8, 33.4, 32.8, 28.3, 28.2, 27.9.

FAB-MS: *m*/*z* calcd for $C_{21}H_{29}N_2O_3$ [M + 1]$^+$: 357.21; found: 357

Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.77; H, 7.93; N, 7.85.

Alkylation; General Procedure A

To a solution of imine (0.2 mmol) in anhyd THF (2 mL) under an Ar atmosphere, cooled to –78 °C, base (0.3 mmol) was added and the temperature was adjusted according to Table 1. After 20 min alkyl bromide was added and the solution was stirred for 3–5 h. H_2O (2 mL) was added and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was dissolved in MeOH (4 mL) and $NaBH_4$ (2 mmol) was added in small portions. After 15 min the solvent was evaporated under reduced pressure and the crude was purified by flash chromatography (hexane–EtOAc, 7:3).

Alkylation; General Procedure B

To a solution of imine (0.2 mmol) in anhyd THF (2 mL) and DMPU (5 mmol) under an Ar atmosphere, cooled to –78 °C, base (0.3 mmol) was added and the temperature was adjusted according to Table 1. After 20 min alkyl bromide was added and the solution was stirred for 3–5 h. H_2O (2 mL) was added and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was dissolved in MeOH (4 mL) and $NaBH_4$ (2 mmol) was added in small portions. After 15 min the solvent was evaporated under reduced pressure and the crude was purified by flash chromatography (hexane–EtOAc, 7:3).

Alkylation; General Procedure C

To a solution of imine (0.2 mmol) in anhyd THF (2 mL) under an Ar atmosphere, cooled to –78 °C, base (0.3 mmol) was added and the temperature was adjusted according to Table 1. After 20 min Lewis acid ($MgBr_2·Et_2O$ or $SnCl_2$) was added and after a further 20 min alkyl bromide was added and the solution was stirred for 3–5 h. H_2O (2 mL) was added and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was dissolved in MeOH (4 mL) and $NaBH_4$ (2 mmol) was added in small portions.

After 15 min the solvent was evaporated under reduced pressure and the crude was purified by flash chromatography (hexane–EtOAc, 7:3).

(3*R*,6*S*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-benzyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (5a)
$[\alpha]_D^{20}$ –107.1 (*c* = 1.05, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.51 (m, 1 H), 1.03 (m, 1 H), 1.49 (s, 9 H, *t*-Bu), 1.61–2.20 (m, 5 H), 2.31 (m, 1 H), 2.81 (d, *J* = 12.8 Hz, 1 H, PhCH*H*C), 3.26 (d, *J* = 12.8 Hz, 1 H, PhC*H*HC), 3.60 (m, 1 H, CHN), 3.74 (d, *J* = 11.6 Hz, 1 H, PhCH*H*NH), 3.80 (d, *J* = 11.6 Hz, 1 H, PhC*H*HNH), 4.41 [dd, *J* = 8.6, 8.6 Hz, 1 H, C*H*(COO*t*-Bu)], 7.19–7.40 (m, 10 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.7, 172.0, 140.7, 137.4, 130.4, 128.8, 128.6, 128.3, 127.1, 126.9, 81.5, 62.6, 59.9, 59.7, 48.2, 47.2, 33.5, 29.3, 28.3, 28.2, 26.6.

FAB-MS: *m*/*z* calcd for $C_{27}H_{35}N_2O_3$ [M + 1]$^+$: 435.57; found: 435.

Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.60; H, 7.88; N, 6.44.

(3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-benzyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (5b)
Mp 104–106 °C; $[\alpha]_D^{20}$ –37.0 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, *t*-Bu), 1.65–2.12 (m, 7 H), 2.26 (m, 1 H), 2.98 (d, *J* = 13.1 Hz, 1 H, PhCH*H*C), 3.23 (d, *J* = 13.1 Hz, 1 H, PhC*H*HC), 3.43 (m, 1 H, CHN), 3.72 (d, *J* = 12.0 Hz, 1 H, PhCH*H*NH), 3.84 (d, *J* = 12.0 Hz, 1 H, PhC*H*HNH), 4.41 [dd, *J* = 8.6, 8.6 Hz, 1 H, C*H*(COO*t*-Bu)], 7.20–7.37 (m, 10 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.9, 171.6, 137.0, 131.2, 128.5, 128.4, 128.2, 127.1, 126.6, 81.4, 61.0, 60.1, 59.5, 48.2, 44.7, 33.3, 30.5, 28.2, 28.1, 27.1.

FAB-MS: *m*/*z* calcd for $C_{27}H_{35}N_2O_3$ [M + 1]$^+$: 435.57; found: 435.

Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.61; H, 7.88; N, 6.45.

(3*R*,6*S*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-allyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (6a)
$[\alpha]_D^{20}$ –37.3 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 1.50 (m, 1 H), 1.76 (m, 1 H), 1.88–2.19 (m, 3 H), 2.18 (m, 1 H), 2.26–2.43 (m, 3 H), 2.54 (m, 1 H), 3.61 (m, 1 H, CHN), 3.61 (d, *J* = 11.7 Hz, 1 H, PhCH*H*NH), 3.70 (d, *J* = 11.7 Hz, 1 H, PhC*H*HNH), 4.43 [dd, *J* = 8.6, 8.6 Hz, 1 H, C*H*(COO*t*-Bu)], 5.11 (m, 2 H, CH=CH_2), 5.90 (m, 1 H, C*H*=CH_2), 7.20–7.34 (m, 5 H, Ar).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.9, 171.3, 140.4, 134.0, 129.1, 128.7, 128.3, 128.0, 126.9, 118.7, 81.3, 60.0, 59.7, 59.4, 51.1, 48.2, 45.3, 33.2, 30.4, 28.1, 28.0, 27.8.

FAB-MS: *m*/*z* calcd for $C_{23}H_{33}N_2O_3$ [M + 1]$^+$: 385.51; found: 385.

Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.85; H, 8.39; N, 7.30.

(3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-allyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (6b)
Mp 75–77 °C; $[\alpha]_D^{20}$ –71.8 (*c* = 0.99, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 1.50 (m, 1 H), 1.79 (m, 1 H), 1.88–2.19 (m, 4 H), 2.22–2.55 (m, 4 H), 3.68 (d, *J* = 11.7 Hz, 1 H, PhCH*H*NH), 3.74 (m, 1 H, CHN), 3.78 (d, *J* = 11.7 Hz, 1 H, PhC*H*HNH), 4.40 [dd, *J* = 8.6, 8.6 Hz, 1 H, C*H*(COO*t*-Bu)], 5.10 (m, 2 H, CH=CH_2), 5.87 (m, 1 H, C*H*=CH_2), 7.16–7.43 (m, 5 H, Ar).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.7, 133.4, 130.9, 128.7, 128.4, 127.1, 118.7, 111.1, 81.4, 61.6, 60.1, 59.1, 48.1, 45.3, 44.1, 33.2, 29.7, 29.2, 28.0, 26.5.

FAB-MS: *m*/*z* calcd for $C_{23}H_{33}N_2O_3$ [M + 1]$^+$: 385.51; found: 385.

Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.86; H, 8.40; N, 7.28.

(3*R*,7*R*,10*S*)-1-Aza-2-oxo-3-benzylamino-3-benzyl-9-(*tert*-butoxycarbonyl)bicyclo[5.3.0]decane (7a)
Mp 113–114 °C; $[\alpha]_D^{20}$ –20.1 (*c* = 1.06, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, *t*-Bu), 1.64–1.78 (m, 3 H), 1.78–1.96 (m, 4 H), 2.12 (m, 1 H), 2.38 (m, 2 H), 2.92 (d, *J* = 13.6 Hz, 1 H, PhCH*H*C), 3.13 (d, *J* = 13.6 Hz, 1 H, PhC*H*HC), 3.61 (d, *J* = 12.5 Hz, 1 H, PhCH*H*NH), 3.70 (d, *J* = 12.5 Hz, 1 H, PhC*H*HNH), 4.14 (m, 1 H, CHN), 4.55 [dd, 1 H, *J* = 8.4, 2.0 Hz, C*H*(COO*t*-Bu)], 7.17–7.43 (m, 10 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 174.3, 172.1, 141.8, 136.4, 131.6, 128.3, 128.2, 127.9, 126.6, 81.2, 65.8, 62.3, 57.1, 48.1, 44.6, 34.4, 32.5, 32.2, 28.2, 26.5, 22.6.

FAB-MS: *m*/*z* calcd for $C_{28}H_{37}N_2O_3$ [M + 1]$^+$: 449.60; found: 449.

Anal. Calcd for $C_{28}H_{36}N_2O_3$: C, 74.97; H, 8.09; N, 6.24. Found: C, 74.96; H, 8.08; N, 6.24.

(3*S*,7*R*,10*S*)-1-Aza-2-oxo-3-benzylamino-3-benzyl-9-(*tert*-butoxycarbonyl)bicyclo[5.3.0]decane (7b)
$[\alpha]_D^{20}$ +36.4 (*c* = 1.11, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, *t*-Bu), 1.49 (m, 3 H), 1.58–1.72 (m, 3 H), 1.80–1.97 (m, 2 H), 2.12 (m, 1 H), 2.29 (m, 1 H), 2.92 (d, *J* = 14.1 Hz, 1 H, PhCH*H*C), 3.54 (d, *J* = 14.1 Hz, 1 H, PhC*H*HC), 3.96 (d, *J* = 12.1 Hz, 1 H, PhCH*H*NH), 4.04 (d, *J* = 12.1 Hz, 1 H, PhC*H*HNH), 4.55 [dd, *J* = 8.4, 3.7 Hz, 1 H, C*H*(COO*t*-Bu)], 3.84 (m, 1 H, CHN), 7.15–7.70 (m, 10 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 174.5, 171.6, 141.0, 138.4, 131.5, 131.2, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 126.3, 81.0, 64.0, 62.7, 57.6, 47.7, 40.3, 35.7, 33.1, 32.7, 29.9, 28.3, 26.9, 23.0.

FAB-MS: *m*/*z* calcd for $C_{28}H_{37}N_2O_3$ [M + 1]$^+$: 449.60; found: 449.

Anal. Calcd for $C_{28}H_{36}N_2O_3$: C, 74.97; H, 8.09; N, 6.24. Found: C, 74.99; H, 8.10; N, 6.25.

(3*R*,7*R*,10*S*)-1-Aza-2-oxo-3-benzylamino-3-allyl-9-(*tert*-butoxycarbonyl)bicyclo[5.3.0]decane (8a)
$[\alpha]_D^{20}$ –54.0 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, *t*-Bu), 1.63–1.98 (m, 8 H), 2.12 (m, 1 H), 2.29 (m, 1 H), 2.49 (m, 1 H, CH*H*CH=CH_2), 2.58 (m, 1 H, C*H*HCH=CH_2), 3.68 (d, *J* = 11.6 Hz, 1 H, PhCH*H*-NH), 3.73 (d, *J* = 11.6 Hz, 1 H, PhC*H*HNH), 4.07 (m, 1 H, CHN), 4.53 [dd, *J* = 8.3, 3.8 Hz, 1 H, C*H*(COO*t*-Bu)], 5.14 (m, 2 H, CH=CH_2), 5.88 (m, 1 H, C*H*=CH_2), 7.26–7.42 (m, 5 H, Ar).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.8, 135.0, 128.6, 128.4, 128.3, 126.9, 118.9, 81.3, 63.1, 57.7, 48.2, 48.0, 35.2, 34.8, 32.8, 32.3, 29.9, 28.2, 26.5, 22.6.

FAB-MS: *m*/*z* calcd for $C_{24}H_{35}N_2O_3$ [M + 1]$^+$: 399.54; found: 399.

Anal. Calcd for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.34; H, 8.60; N, 7.04.

(3*S*,7*R*,10*S*)-1-Aza-2-oxo-3-benzylamino-3-allyl-9-(*tert*-butoxycarbonyl)bicyclo[5.3.0]decane (8b)
$[\alpha]_D^{20}$ +14.9 (*c* = 1.04, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, *t*-Bu), 1.44–2.34 (m, 10 H), 2.43 (dd, *J* = 14.4, 7.3 Hz, 1 H, CH*H*CH=CH_2), 2.87 (dd, *J* = 14.4, 7.3 Hz, 1 H, C*H*HCH=CH_2), 3.73 (d, *J* = 12.7 Hz, 2 H,

PhCH_2NH), 4.49 [dd, J = 8.3, 4.4 Hz, 1 H, CH(COOt-Bu)], 4.79 (m, 1 H, CHN), 5.16 (m, 2 H, CH=CH_2), 5.86 (m, 1 H, CH=CH$_2$), 7.20–7.40 (m, 5 H, Ar).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 174.4, 171.4, 141.1, 134.5, 128.7, 128.3, 126.8, 118.7, 111.4, 80.7, 67.0, 62.8, 62.5, 58.5, 57.5, 47.1, 44.7, 40.3, 35.5, 33.1, 29.7, 28.0, 26.8, 22.7.

FAB-MS: m/z calcd for $C_{24}H_{35}N_2O_3$ [M + 1]$^+$: 399.54; found: 399.

Anal. Calcd for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.35; H, 8.61; N, 7.04.

(3*R*,6*R*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-benzyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (13a)
$[\alpha]_D^{20}$ –114.7 (c = 1.02, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, t-Bu), 1.53–2.30 (m, 8 H), 2.51 (m, 1 H, CHN), 2.85 (d, J = 12.6 Hz, 1 H, PhCHHC), 3.06 (d, J = 12.6 Hz, 1 H, PhCHHC), 3.80 (s, 2 H, PhCH_2NH), 4.24 [dd, J = 7.2, 1.7 Hz, 1 H, CH(COOt-Bu)], 7.15–7.43 (m, 10 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.7, 171.7, 140.6, 136.7, 130.9, 128.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.1, 126.9, 81.4, 61.9, 59.9, 59.7, 49.1, 47.1, 31.5, 30.2, 29.9, 28.6, 28.4, 28.2, 28.1.

FAB-MS: m/z calcd for $C_{27}H_{35}N_2O_3$ [M + 1]$^+$: 435.57; found: 435.

Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.61; H, 7.88; N, 6.45.

(3*S*,6*R*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-benzyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (13b)
Mp 161–163 °C; $[\alpha]_D^{20}$ –35.5 (c = 1.06, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, t-Bu), 1.79–2.13 (m, 8 H), 2.98 (d, J = 14.0 Hz, 1 H, PhCHHC), 3.10 (d, J = 14.0 Hz, 1 H, PhCHHC), 3.57 (m, 1 H, CHN), 3.61 (d, J = 12.5 Hz, 1 H, PhCHHNH), 3.68 (d, J = 12.5 Hz, 1 H, PhCHHNH), 4.35 [dd, J = 9.0, < 1 Hz, 1 H, CH(COOt-Bu)], 7.20–7.33 (m, 10 H, Ar).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 173.1, 171.4, 140.8, 136.8, 131.2, 130.8, 128.7, 128.2, 128.1, 127.8, 126.7, 126.4, 81.1, 62.2, 60.5, 59.7, 59.0, 48.0, 44.6, 31.8, 29.7, 28.8, 28.6, 28.3, 28.0, 26.3.

FAB-MS: m/z calcd for $C_{27}H_{35}N_2O_3$ [M + 1]$^+$: 435.57; found: 435.

Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.63; H, 7.90; N, 6.44.

(3*R*,6*R*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-allyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (14a)
$[\alpha]_D^{20}$ –68.7 (c = 0.64, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, t-Bu), 1.76 (m, 1 H), 1.93–2.24 (m, 7 H), 2.39 (m, 2 H, CH_2CH=CH$_2$), 3.51 (m, 1 H, CHN), 3.72 (d, J = 11.1 Hz, 1 H, PhCHHNH), 3.78 (d, J = 11.7 Hz, 1 H, PhCHHNH), 4.36 [dd, J = 8.8, < 1 Hz, 1 H, CH(COOt-Bu)], 5.14 (m, 2 H, CH=CH_2), 5.78 (m, 1 H, CH=CH$_2$), 7.20–7.40 (m, 5 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.8, 134.2, 133.5, 128.9, 128.5, 127.0, 119.2, 81.4, 60.6, 60.4, 60.0, 49.0, 48.1, 45.7, 44.2, 31.8, 30.2, 29.9, 28.7, 28.6, 28.1, 26.8.

FAB$^+$MS: m/z calcd for $C_{23}H_{33}N_2O_3$ [M + 1]$^+$: 385.51; found: 385.

Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.85; H, 8.38; N, 7.28.

(3*S*,6*R*,9*S*)-1-Aza-2-oxo-3-benzylamino-3-allyl-9-(*tert*-butoxycarbonyl)bicyclo[4.3.0]nonane (14b)
$[\alpha]_D^{20}$ –42.9 (c = 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, t-Bu), 1.69–1.85 (m, 2 H), 1.94–2.06 (m, 5 H), 2.12 (m, 1 H), 2.54 (m, 2 H, CH_2CH=CH$_2$), 3.59 (m, 1 H, CHN), 3.62 (d, J = 12.2 Hz, 1 H, PhCHHNH), 3.70 (d, J = 12.2 Hz, 1 H, PhCHHNH), 4.37 [dd, J = 9.4, < 1 Hz, 1 H, CH(COOt-Bu)], 5.11 (m, 2 H, CH=CH_2), 6.00 (m, 1 H, CH=CH$_2$), 7.20–7.40 (m, 5 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.3, 133.6, 129.5, 129.0, 128.7, 128.6, 127.4, 119.0, 81.5, 61.5, 60.7, 60.3, 59.3, 52.3, 48.0, 43.9, 31.9, 29.9, 28.7, 28.1, 26.7.

FAB-MS: m/z calcd for $C_{23}H_{33}N_2O_3$ [M + 1]$^+$: 385.51; found: 385.

Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.83; H, 8.38; N, 7.29.

(3*R*,7*S*,10*S*)-1-Aza-2-oxo-3-benzylamino-3-benzyl-9-(*tert*-butoxycarbonyl)bicyclo[5.3.0]decane (15a)
$[\alpha]_D^{20}$ –105.5 (c = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, t-Bu), 1.47–2.42 (m, 10 H), 2.80 (d, J = 13.2 Hz, 1 H, PhCHHC), 3.06 (d, J = 13.2 Hz, 1 H, PhCHHC), 3.37 (m, 1 H, CHN), 3.67 (d, J = 11.2 Hz, 1 H, PhCHHNH), 3.73 (d, J = 11.2 Hz, 1 H, PhCHHNH), 4.39 [dd, J = 8.2, 8.0 Hz, 1 H, CH(COOt-Bu)], 7.11–7.38 (m, 10 H, Ar).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.6, 172.0, 136.6, 130.5, 128.7, 128.5, 128.3, 128.1, 127.8, 127.0, 126.9, 81.2, 66.5, 63.2, 57.1, 48.8, 45.2, 33.6, 32.7, 31.5, 31.1, 29.9, 28.1, 27.1, 22.9, 22.1.

FAB-MS: m/z calcd for $C_{28}H_{37}N_2O_3$ [M + 1]$^+$: 449.60; found: 449.

Anal. Calcd for $C_{28}H_{36}N_2O_3$: C, 74.97; H, 8.09; N, 6.24. Found: C, 74.98; H, 8.09; N, 6.25.

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