Pergamon

Tetrahedron 58 (2002) 3159–3170

TETRAHEDRON

Amino acid derived intramolecular 1,3-dipolar cycloadditions that form bridged medium ring systems with diastereoselective control

Yanbin Liu, Amy Maden and William V. Murray*

Johnson & Johnson Pharmaceutical Research and Development LLC, 1000 Route 202, Box 300, Raritan, NJ 08869, USA

Received 22 January 2002; accepted 5 March 2002

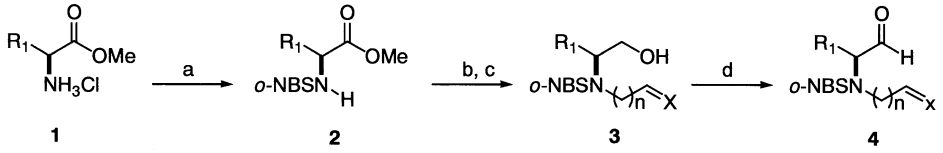
Abstract—Intramolecular nitrone cycloadditions using amino acid precursors, generate aminohydroxyazepine and amino hydroxypiperidine templates. The cycloaddition reactions yield either a [4.3.0] fused system or in most cases a [4.2.1] bridged system. The [4.2.1] bridged system allows for the stereospecific preparation of 3-amino-5-hydroxyazepines while the [4.3.0] system allows for the preparation of 3-amino-5-hydroxymethyl piperidines.

1. Introduction

Intramolecular nitrone–alkene cycloaddition reactions have received attention because they are useful methods for the formation of heterocycles of biological interest.[1–6] The key feature of the cycloadducts is that the nitrogen–oxygen bond can be readily cleaved to yield amino alcohols. Intramolecular 1,3-dipolar cycloadditions form two new rings simultaneously and generate cycloadducts in a highly regio- and stereoselective fashion.[2,7]

A number of studies using α-amino acids as chiral reactants for the synthesis of heterocyclic compounds by nitrone–alkene cycloaddition have been reported.[8–12] The approaches focused on the formation of the ring fused to the isoxazolidine nucleus, most especially the [3.3.0] fused system. The formation of 6-membered rings fused to an isoxazolidine using α-amino acids was reported by Hassner et al.[10] and Chiacchio et al.[13] In Chiacchio's study, several isoxazolidine-fused lactams were prepared from the corresponding α-amino acids.

Our interest in the synthesis of α-amino acid derived heterocycles led us to investigate the synthesis of 6-, 7- or 8-membered heterocycles utilizing intramolecular nitrone–alkene cycloaddition reactions. The stereospecific synthesis of larger heterocycles from simple α-amino acids is a synthetic challenge that could provide entry into a



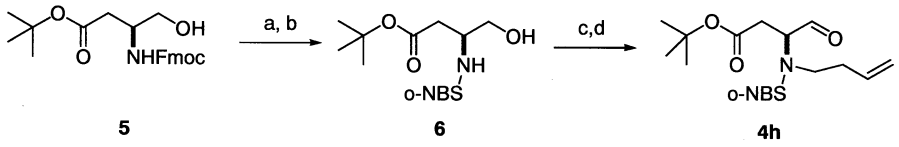
2a R_1 = Bn
2b R_1 = *iso*-propyl
2c R_1 = Me
2d R_1 = *t*-butoxymethyl

3a, 4a n = 2, R_1 = Bn, X = CH_2
3b, 4b n = 3, R_1 = Bn, X = CH_2
3c, 4c n = 2, R_1 = *iso*-propyl, X = CH_2
3d, 4d n = 2, R_1 = *iso*-propyl, X = CMe_2
3e, 4e n = 3, R_1 = *iso*-propy, X = CH_2
3f, 4f n = 2, R_1 = Me, X = CH_2
3g, 4g n = 2, R_1 = *t*-butoxymethyl, X = CH_2

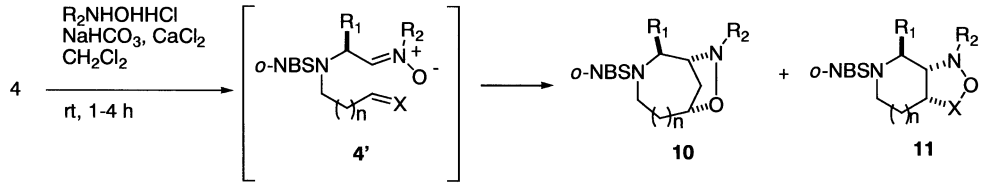
Scheme 1. Synthesis of *N*-alkylated 2-nitrobenzenesulfonamide aldehydes **4a**–**g**: (a) 2-nitrobenzenesulfonyl chloride, TEA, CH_2Cl_2, room temperature; (b) alkenyl bromide, Cs_2CO_3, 50–60°C DMF; (c) $LiAlH_4$, THF, 0°C; (d) Dess–Martin CH_2Cl_2, room temperature.

Keywords: cycloaddition; diastereoselective; isoxazolidine.
* Corresponding author. Tel.: +1-908-704-4375; fax: +1-908-722-3420; e-mail: wmurray@prdus.jnj.com

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00242-9



Scheme 2. Synthesis of aspartic acid derived aldehyde **4h**: (a) 20% piperidine in DMF; (b) 2-nitrobenzenesulfonyl chloride, TEA, CH_2Cl_2, room temperature; (c) 4-bromo-1-butene, Cs_2CO_3, 55°C DMF, 6 h; (d) Dess–Martin, CH_2Cl_2, room temperature.



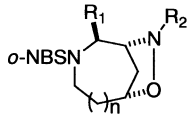
Scheme 3. Intramolecular alkene–nitrone cycloadditions.

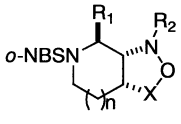
number of biologically interesting systems. Herein, we report our synthetic results toward intermediate ring heterocycles utilizing α-amino acids as precursors.

2. Results and discussion

In designing a rapid approach to alkenylaldehydes, the precursors of intramolecular nitrone–alkene cycloaddition, we needed an efficient way to *N*-protect the amino group of α-amino acids. The 2-nitrosulfonyl group proved to be a good choice for the protection of the α-amino group. The synthesis is facile and the protecting group can be removed under mild, non-racemizing conditions.[14] We also felt this approach would be potentially useful as a linker to a solid support. Commercially available α-amino acid methyl ester hydrochloride salts **1** were converted cleanly into 2-nitrobenzenesulfonamides **2a**–**d**[14] in 87–93% yields (Scheme 1). *N*-Alkylations were carried out by treatment of **2** with different alkenyl bromides in the presence of cesium carbonate at elevated temperature (50–60°C).[14] These procedures provided *N*-alkylated methyl esters as a single product in each reaction with no need for chromatographic purification. After standard work-up, these *N*-alkene methyl esters were treated with lithium aluminum hydride in THF at 0°C to afford the corresponding alcohols **3a**–**g** in 45–76% overall yields. The aspartyl alcohol derivative **3h**, was prepared from the commercially available *N*-Fmoc protected alcohol **5** (Scheme 2). Removal of the Fmoc protecting group,[15] followed by sulfonation and alkylation provided the desired alcohol **3h** in 65% overall yield.

Table 1. Products of intramolecular cycloadditions in the presence of $ZnCl_2$





Entry	*n*	X	R_1	R_2	Product	
					10, Yield (%)	**11**, Yield (%)
1	1	CH_2	Bn	Bn	**10a**, 67	0
2	1	CH_2	Bn	Me	**10b**, 64	<10[a]
3	2	CH_2	Bn	Bn	**10c**, 38	0
4	2	CH_2	Bn	Me	**10d**, 34	0
5	1	CH_2	Isopropyl	Bn	**10e**, 59	0
6	1	CH_2	Isopropyl	Me	**10f**, 63	<10[a]
7	1	CMe_2	Isopropyl	Me	0	**11b**, 52
8	2	CH_2	Isopropyl	Bn	**10g**, 30	0
9	1	CH_2	*t*BTOM[b]	Me	**10h**, 15	**11e**, 38
10	1	CH_2	*t*BTOCM[c]	Me	**10i**, 46	**11g**, 19
11	1	CH_2	*t*BTOCM	Bn	**10j**, 38	**11h**, 24
12	1	CH_2	Me	Me	Trace	**11c**, 52
13	1	CH_2	Me	Bn	0	**11d**, 36

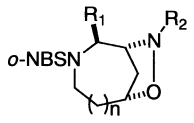
[a] Mixture of two isomers.
[b] *tert*-Butoxylmethyl.
[c] *tert*-Butoxycarbonylmethyl.

Compounds **3a**–**l** were treated with 2 equiv. of Dess–Martin periodinane in wet methylene chloride at room temperature for 10 min.[16] After aqueous work-up, the aldehydes **4a**–**h** (Schemes 1 and 2) were obtained in quantitative yields with no need for further purification. No racemization was observed by chiral HPLC.

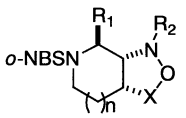
The formation of nitrones from aldehydes such as **4** could be achieved using *N*-alkylhydroxylamines such as *N*-benzylhydroxylamine and *N*-methylhydroxylamine. A mixture of the aldehyde **4a**, benzylhydroxylamine hydrochloride and sodium bicarbonate in diethyl ether was stirred overnight at room temperature in the presence of $CaCl_2$.[12,17] A polar product with the same molecular ion as the expected cyclized product was formed. ^{1}H NMR studies of the product revealed that it was the nitrone (*N*-oxide) intermediate, which was stable and could be chromatographically purified. The nitrone intermediate was refluxed overnight in benzene in the presence of $ZnCl_2$ and **10a** was then isolated in 67% yield.[11] Detailed NMR studies (^{1}H, ^{13}C, 2D-COSY, DEPT, NOESY, HMBC) have established the structure of **10a** as a bridged bicyclic [4.2.1] type product. Theoretically, the intramolecular nitrone–alkene cycloaddition reaction could give rise to two regioisomers, in which the isoxazolidine product formed either a bicyclic [4.3.0] fused system or a bridged [4.2.1] system.[1] In this case, only the bridged compound **10a** was isolated. When the (L)-valine derived starting material was used, **10e** was isolated in 59% yield as a single product.

When *N*-methylhydroxylamine rather than *N*-benzylhydroxylamine was used for nitrone formation, both the bridged compounds **10b** (64%) and **10f** (63%) were isolated

Table 2. Results of intramolecular cycloadditions without $ZnCl_2$



10



11

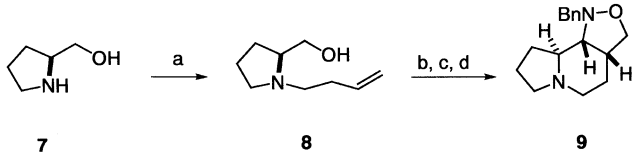
Entry	*n*	X	R_1	R_2	Product	
					10, Yield (%)	**11**, Yield (%)
1	1	CH_2	Bn	Bn	**10a**, 33	42[a]
2	1	CH_2	Bn	Me	**10b**, 30	**11a**, 51
3	1	CH_2	*t*BTOM[b]	Me	**10h**, 9	**11e**, 57
4	1	CH_2	*t*BTOM	Bn	0	**10f**, 45
5	1	CH_2	Me	Me	0	**11c**, 45
6	1	CH_2	Me	Bn	0	**11d**, 32

N-Oxide **4′** was refluxed in benzene or toluene for 15–36 h.
[a] Mixture of two isomers.
[b] *tert*-Butoxylmethyl.

as the major products. Small quantities (<10%) of two minor isomers were also isolated as an inseparable mixture (Scheme 3).

The formation of alkene–nitrone intermediates from aldehydes in ether was problematic when the alanine and serine derived aldehydes **4f** and **4g** were utilized. We observed the nitrone formation by TLC but it decomposed slowly and resulted in several unidentified products. By changing the solvent from ether to CH_2Cl_2, the alkene–nitrone formation proceeded cleanly in 1–3 h. The subsequent intramolecular cycloadditon reactions were carried out in benzene or toluene. A range of amino aldehydes were explored (Table 1).

The ease of synthesis of the bridged 7-membered ring system led us to investigate the synthesis of the bridged 8-membered ring. When aldehyde **4b** or **4e** was treated with *N*-benzylhydroxylamine or *N*-methylhydroxylamine and subsequently refluxed in toluene, the 8-membered bridged cyclized products **10c**, **d** and **g** (Table 1) were isolated as single isomers in lower yields (30–38%). No [5.3.0] fused products or other isomers were observed. Attempts to synthesize the bridged 9-membered ring where R_1 was isopropyl were unsuccessful. When R_1 was methyl or *t*-butoxylmethylene, attempts to prepare the 8-membered ring compounds were also unsuccessful and resulted in decomposition. Substitution at the terminal alkene of the aldehyde **4d** was also studied. Treatment of **4d**, a compound with geminal methyl groups on the terminal carbon, with *N*-methylhydroxylamine followed by refluxing in toluene, afforded the [4.3.0]-fused isoxazolidine **11b** as the only isolated product in 52% yield. No bridged product was observed.



7 **8** **9**

Scheme 4. Synthesis of proline derived cyclic compound **9**: (a) 4-bromo-1-butene, Cs_2CO_3, 55°C DMF, 6 h; (b) DMSO, $(COCl)_2$, −78°C; (c) BnNHOHCl, $NaHCO_3$, $CaCl_2$, CH_2Cl_2, room temperature, 4 h; (d) benzene, $ZnCl_2$, reflux, 16 h.

The cycloadditions were carried out with and without $ZnCl_2$ (Table 2). In the cases where *N*-benzylhydroxylamine was used, two major fractions were identified. The less polar product was **10a** (33% yield), the other (42%) was an inseparable isomeric mixture. When *N*-methylhydroxylamine was used, two single cyclized products were isolated, **10b** albeit in lower yield (30%), and **11a** (51% yield) a fused, bicyclic [4.3.0] product. The same reactants, in the presence of $ZnCl_2$ (entry 2 of Table 1) gave predominantly the bridged product. The serine derived aldehyde **4g** provided a higher yield of **11e** with no $ZnCl_2$ (entry 9 of Table 1 and entry 3 of Table 2). These results demonstrate that the Lewis acid $ZnCl_2$ promotes the formation of the bridged product. The ability to tune the reactivity with $ZnCl_2$ allows us entry in to both regioisomers.

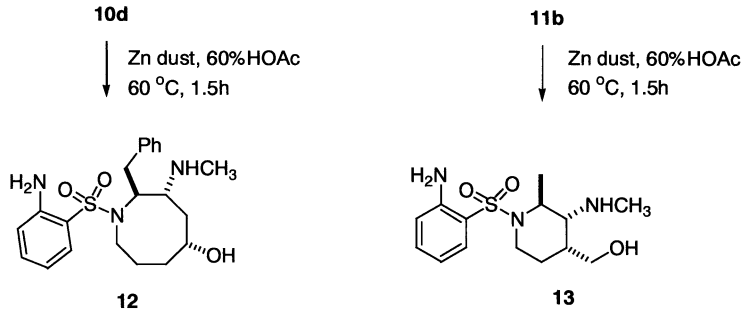
We believe that the zinc chloride increases the polarization in the dipole which increases reaction rate. It also increases the carbocation character at the more substituted carbon of the olefin in the asynchronous transition state. This leads to the carbon–carbon bond forming at the least substituted carbon of the olefin. This explains the preferential formation of bridged systems and can also explain the formation of the [4.3.0] compound **11b** when the olefin is geminally dimethylated. It is clear that the presence of zinc chloride generally favors the [4.2.1] system except in the case where the terminus of the dipolarophile is disubstituted.

We also investigated cycloaddition reaction of a constrained alkene–nitrone intermediate derived from proline. Commercially available prolinol **7** was alkylated with 4-bromo-1-butene under standard conditions to give **8** in 47% yield after distillation. While our standard Dess–Martin oxidation conditions were unsuccessful on **8**, we were able to generate the desired aldehyde from **8** by a Swern oxidation.[11,18] Treatment of the crude aldehyde with *N*-benzylhydroxyamine hydrochloride in the presence of sodium bicarbonate provided *N*-oxide intermediate. This intermediate was refluxed in benzene in the presence of zinc chloride to afford **9** in 41% overall yield for the three steps from the alcohol **8** (Scheme 4).

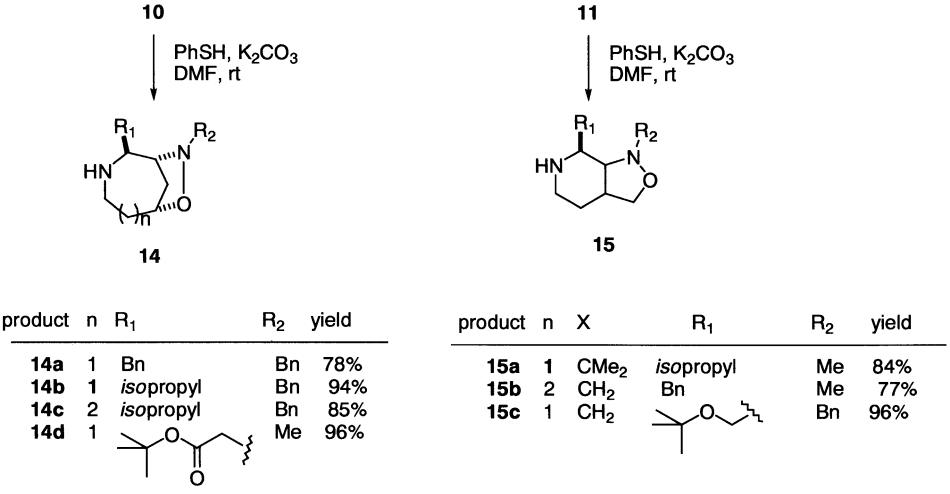
NMR studies of the cyclized product revealed that it is a 5,6,5 fused product. Alcaide et al. reported that β-lactam tethered alkene–aldehydes gave exclusively the bridged system.[19] The results from our studies demonstrated that the conformation of the proline derived alkene–nitrone favors the fused ring system formation. As the penultimate proline alkene–nitrone is a tertiary amine, it demonstrates that the cycloaddition reaction does not require the nitrogen to be tied up as the sulfonamide. Increased planarity of the nitrogen however may influence the organization of the transition state.

The cleavage of N–O bond of isoxazolidines was attempted in the presence of the sulfonamide protecting group. Treatment of **10d** or **11b** with zinc dust in 60% aqueous acetic acid at 60°C for 1.5 h provided the amino alcohol **12** or **13** good yields.[17] Under these conditions, the nitro group on the protecting group was reduced to an amino group as well (Scheme 5).

To avoid reduction of the ring nitro, we first removed the



Scheme 5. Reductive cleavage of N–O bond of isoxazolidines.



product	n	R_1	R_2	yield
14a	1	Bn	Bn	78%
14b	1	*iso*propyl	Bn	94%
14c	2	*iso*propyl	Bn	85%
14d	1		Me	96%

product	n	X	R_1	R_2	yield
15a	1	CMe_2	*iso*propyl	Me	84%
15b	2	CH_2	Bn	Me	77%
15c	1	CH_2		Bn	96%

Scheme 6. Removal of protecting groups.

sulfonyl protecting group using potassium carbonate (10 equiv.) and thiophenol (50 equiv.) in DMF at room temperature. The amines (**14a–e** and **15a–c**) were obtained in 77–96% yields. Under these conditions, all substituents at R_1, such as ester (**14d**), ether (**14e**), survived without decomposition or racemization (Scheme 6).

Treatment of **14b** and **15** with zinc dust in 60% aqueous acetic acid at 60°C provided the final amino alcohols in 78–87% yields (Scheme 7).

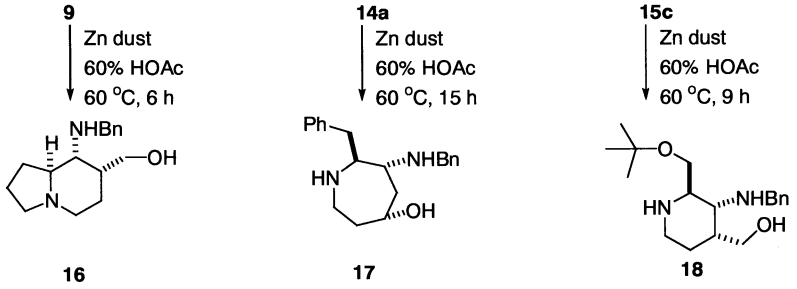
3. Conclusions

In summary, we have demonstrated a convenient and stereoselective approach to highly functionalized medium sized heterocyclic ring systems using the intramolecular alkene–nitrone cycloadditons in the presence of zinc chloride.

4. Experimental

4.1. General methods

All reactions were carried out in an atmosphere of dry nitrogen at room temperature unless otherwise stated. Reaction temperatures other than room temperature were recorded as bath temperatures unless otherwise stated. Melting points were measured on capillary melting point apparatus and uncorrected. Proton NMR spectra were recorded at 300 or 400 MHz using TMS as an internal standard. Carbon NMR were recorded at 75 or 100 MHz using chloroform-*d* as an internal standard. All other organic solvents and reagents



Scheme 7. Synthesis of heterocyclic amino alcohols.

were obtained from commercial sources and used without further purification. Organic extracts were concentrated using a rotary evaporator.

4.2. General procedure for preparation of amino acid methyl ester 2-nitrobenzenesulfonamides 2[14]

4.2.1. *N*-(2-Nitrobenzenesulfonyl)-(*S*)-phenylalanine methyl ester (2a). To a solution of (*S*)-phenylalanine methyl ester hydrochloride (2.0 g, 9.3 mmol) in CH_2Cl_2 (20 mL) was added 2-nitrobenzenesulfonyl chloride (2.2 g, 10 mmol) and triethylamine (3.2 mL, 23 mmol) at 0°C. The mixture was stirred at room temperature for 15 h and then washed with water (2×10 mL). Organic layer was separated, dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica gel eluting with 30% EtOAc in hexane afforded **2a** as a light yellow solid (2.9 g, 87%)): mp 78–80°C; ^{1}H NMR ($CDCl_3$, 400 Hz) δ 3.08 (dd, J=7.2, 14.0 Hz, 1H), 3.17 (dd, J=7.2, 14.0 Hz, 1H), 3.53 (s, 3H), 4.47 (bt, J=6.0 Hz, 1H), 6.04 (bs, 1H), 7.10–7.11 (m, 2H), 7.17–7.23 (m, 3H), 7.63–7.70 (m, 2H), 7.82–7.84 (m, 1H), 7.94–7.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 39.7, 53.0, 58.4, 126.1, 127.9, 129.2, 129.8, 130.8, 133.5, 134.1, 134.6, 135.5, 147.9, 171.4; MS calcd for $C_{16}H_{16}N_2O_6S$+Na 387, found 387.

4.2.2. *N*-(2-Nitrobenzenesulfonyl)-(*S*)-valine methyl ester (2b). The title compound was prepared from (*S*)-valine methyl ester hydrochloride (2.5 g, 14.9 mmol) and 2-nitrobenzenesulfonyl chloride (4.3 g, 19 mmol) according to the procedure for **2a** and isolated as a light brown oil (4.2 g, 89% yield): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.94 (d, J=6.9 Hz, 3H), 1.02 (d, J=6.9 Hz, 3H), 2.10–2.21 (m, 1H), 3.43 (s, 3H), 4.00 (dd, J=5.1, 9.6 Hz, 1H), 6.04 (d, J=9.9 Hz, 1H), 7.70–7.77 (m, 2H), 7.89–7.95 (m, 1H), 8.02–8.08 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 17.9, 19.4, 52.6, 62.5, 126.0, 130.8, 133.2, 134.0, 134.5, 148.0, 171.5; HRMS calcd for $C_{12}H_{16}N_2O_6S$ (MH+) 317.0812, found 317.0807.

4.2.3. *N*-(2-Nitrobenzenesulfonyl)-(*S*)-alanine methyl ester (2c). The title compound was prepared from (*S*)-alanine methyl ester hydrochloride (2.5 g, 18.0 mmol) and 2-nitrobenzenesulfonyl chloride (5.2 g, 23.3 mmol) according to the procedure for **2a** and isolated as a white solid (4.8 g, 93% yield): mp 72–74°C; ^{1}H NMR ($CDCl_3$, 400 Hz) δ 1.48 (d, J=7.2 Hz, 3H), 3.55 (s, 3H), 4.25 (q, J=7.2 Hz, 1H), 6.21 (d, J=8.4 Hz, 1H), 7.76–7.81 (m, 2H), 7.88–7.93 (m, 1H), 8.06–8.10 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 20.0, 52.9, 53.15, 126.1, 131.0, 133.7, 134.3, 134.6, 148.1, 172.5; MS calcd for $C_{10}H_{12}N_2O_6S$+Na 311, found 311.

4.2.4. *N*-(2-Nitrobenzenesulfonyl)-*O*-(*tert*-butyl)-(*S*)-serine methyl ester (2d). The title compound was prepared from *O*-(*tert*-butyl)-(*S*)-serine methyl ester hydrochloride (10 g, 47.4 mmol) and 2-nitrobenzenesulfonyl chloride (13.6 g, 61.2 mmol) according to the procedure for **2a** and isolated as a light brown oil (16.0 g, 94% yield): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.09 (s, 9H), 3.55 (s, 3H), 3.58–3.64 (m, 1H), 3.78–3.82 (m, 1H), 4.32–4.38 (m, 1H), 6.38 (d, J=9.0 Hz, 1H), 7.70–7.76 (m, 2H), 7.92–7.96 (m, 1H), 8.05–8.10 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 27.8, 53.1, 58.1, 63.2, 74.4, 126.2, 130.9, 133.7, 134.2, 135.5, 148.2, 170.6; HRMS calcd for $C_{14}H_{20}N_2O_7S$ (MH+) 361.1055, found 361.1069.

4.3. General procedure for the synthesis of 3

4.3.1. *N*-(But-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-valinol (3c). To a stirring solution of **2b** (5.0 g, 15.8 mmol) and cesium carbonate (7.7 g, 23.7 mmol) in DMF (100 mL) was added 4-bromo-1-butene (2.0 mL, 23.7 mmol) at room temperature and then stirred at 55°C for 5 h. The reaction mixture was cooled to room temperature and diluted with ether (300 mL), washed with water (2×100 mL), brine (2×100 mL) and dried over Na_2SO_4. Removal of the solvent afforded the crude product. This crude product was taken into THF (60 mL), and a solution of LAH in THF (15 mL, 15 mmol) was added dropwise at 0°C. The mixture was stirred at 0°C for 30 min, then quenched with water (1.0 mL), diluted with CH_2Cl_2 (100 mL), washed with 1N HCl (50 mL), brine (2×50 mL), dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica gel (EtOAc–hexane, 1:1) afforded **3c** as a light yellow oil (3.7 g, 68%): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.76 (d, J=6.9 Hz, 3H), 0.93 (d, J=6.9 Hz, 3H), 1.78–1.87 (m, 1H), 2.38–2.59 (m, 2H), 3.18–3.28 (m, 1H), 3.41–3.66 (m, 4H), 4.09 (m, 1H), 5.01–5.11 (m, 2H), 5.67–5.81 (m, 1H), 7.53–7.57 (m, 1H), 7.64–7.71 (m, 2H), 8.05–8.09 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 20.4, 20.6, 28.8, 35.6, 44.6, 62.3, 66.5, 117.4, 124.1, 131.4, 132.0, 133.8, 134.1, 135.2, 148.2; HRMS calcd for $C_{15}H_{22}N_2O_5S$ (MH+) 343.1341, found 343.1327.

4.3.2. *N*-(But-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-phenylalaninol (3a). The title compound was prepared from **2a** (3.00 g, 8.24 mmol), 4-bromo-1-butene (1.68 mL, 16.40 mmol) and cesium carbonate (4.00 g, 12.36 mmol) at 50°C for 5 h followed by LAH (6.20 mmol) reduction according to the procedure for **3c** and isolated as a light yellow oil (2.03 g, 63% yield): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 2.30 (t, J=5.4 Hz, 1H), 2.45–2.53 (m, 2H), 2.81 (dd, J=9.0, 13.5 Hz, 1H), 2.93 (dd, J=6.0, 13.5 Hz, 1H), 3.39–3.59 (m, 2H), 3.65–3.72 (m, 2H), 4.08–4.18 (m, 1H), 5.08–5.16 (m, 2H), 5.73–5.87 (m, 1H), 7.09–7.27 (m, 2H), 7.54–7.67 (m, 2H), 7.93–7.96 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 36.1, 37.3, 44.6, 62.4, 62.7, 117.8, 124.7, 127.2, 129.1, 129.5, 131.3, 132.4, 133.8, 134.2, 135.1, 137.9, 148.3; MS calcd for $C_{19}H_{22}N_2O_5S$+Na 413, found 413.

4.3.3. *N*-(Pent-4-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-phenylalaninol (3b). The title compound was prepared from **2a** (0.87 g, 2.39 mmol), 5-bromo-1-pentene (0.43 mL, 3.59 mmol) and cesium carbonate (1.17 g, 3.59 mmol) at 70°C for 5 h followed by LAH (2.15 mmol) reduction according to the procedure for **3c** and isolated as a light yellow oil (0.73 g, 76% yield): ^{1}H NMR ($CDCl_3$, 300 Hz) 1.82–1.90 (m, 2H), 2.02 (bs, 1H), 2.09–2.16 (m, 2H), 2.78 (dd, J=9.6, 13.5 Hz, 1H), 2.96 (dd, J=5.4, 13.5 Hz, 1H), 3.43 (dd, J=6.3, 9.9 Hz, 2H), 3.62–3.67 (m, 2H), 4.09–4.14 (m, 1H), 5.01–5.11 (m, 2H), 5.78–5.87 (m, 1H), 7.10–7.27 (m, 5H), 7.57–7.69 (m, 3H), 7.07–8.00 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 30.8, 31.6, 37.5, 44.9, 62.4, 62.8, 115.9, 124.6, 127.8, 129.1, 129.5, 131.3, 132.4, 133.83, 134.1,

137.9, 138.0, 148.3; MS calcd for $C_{20}H_{24}N_2O_5S+Na$ 427, found 427.

4.3.4. *N*-(But-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-valinol (3c). The title compound was prepared from **2c** (2.88 g, 10 mmol), 4-bromo-1-butene (2.05 mL, 20 mmol) and cesium carbonate (6.50 g, 20 mmol) at 60°C for 16 h followed by LAH (13.3 mmol) reduction according to the procedure for **3a** and isolated as a light yellow oil (2.21 g, 65 % yield): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.78 (d, J=5.1 Hz, 3H), 0.94 (d, J=5.1 Hz, 3H), 1.75–1.82 (m, 1H), 2.03–2.08 (m, 2H), 2.29–2.57 (m, 3H), 3.25–3.33 (m, 1H), 3.40–3.48 (m, 1H), 3.56–3.64 (m, 2H), 3.80–3.86 (m, 1H), 4.97–5.06 (m, 2H), 5.73–5.83 (m, 1H), 7.54–7.56 (m, 1H), 7.65–7.70 (m, 2H), 8.05–8.08 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 20.5, 20.6, 28.8, 35.7, 44.6, 62.3, 66.5, 117.4, 124.1, 131.4, 132.0, 133.8, 134.1, 135.2, 148.2; HRMS calcd for $C_{15}H_{22}N_2O_5S$ (MH+) 343.1342, found 343.1328.

4.3.5. *N*-(4-Methyl-pent-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-valinol (3d). The title compound was prepared from **2b** (4.0 g, 12.6 mmol), 5-bromo-2-methyl-2-pentene (2.56 mL, 18.9 mmol) and cesium carbonate (6.14 g, 18.9 mmol) at 60°C for 16 h followed by LAH (12.6 mmol) reduction according to the procedure for **3c** and isolated as a light yellow oil (2.1 g, 45% yield): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.79 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 1.36 (s, 3H), 1.65 (s, 3H), 1.77–1.83 (m, 1H), 2.15 (d, J= 4.2 Hz, 1H), 2.38–2.50 (m, 2H), 3.08–3.16 (m, 1H), 3.30–3.38 (m, 1H), 3.53–3.64 (m, 2H), 3.86–3.89 (m, 1H), 5.05–5.09 (m, 1H), 7.54–7.59 (m, 1H), 7.65–7.70 (m, 2H), 8.07–8.09 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 15.4, 15.9, 17.6, 18.2, 18.3, 22.8, 23.6, 26.8, 27.0, 28.1, 42.4, 60.0, 64.0, 118.0, 121.8, 129.2, 129.4, 131.3, 131.8, 132.8, 145.8; MS calcd for $C_{17}H_{26}N_2O_5S+Na$ 393, found 393.

4.3.6. *N*-(Pent-4-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-valinol (3e). The title compound was prepared from **2b** (4.0 g, 12.6 mmol), 5-bromo-1-pentene (2.2 mL, 18.9 mmol) and cesium carbonate (6.1 g, 18.9 mmol) followed by LAH (12.6 mmol) reduction according to the procedure for **3c** and isolated as a light yellow oil (4.2 g, 86% yield): ^{1}H NMR ($CDCl_3$, 400 Hz) δ 0.78 (d, J=5.1 Hz, 3H), 0.94 (d, J=5.1 Hz, 3H), 1.75–1.92 (m, 3H), 2.03–2.08 (m, 2H), 2.29–2.32 (m, 1H), 3.14–3.22 (m, 1H), 3.33–3.41 (m, 1H), 3.53–3.62 (m, 2H), 3.80–3.86 (m, 1H), 4.97–5.06 (m, 2H), 5.73–5.83 (m, 1H), 7.53–7.55 (m, 1H), 7.66–7.69 (m, 2H), 8.05–8.07 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 20.6, 20.8, 29.0, 30.4, 31.7, 44.9, 62.4, 66.6, 78.1, 115.8, 124.2, 131.4, 132.1, 133.9, 134.2, 137.9, 148.3; MS calcd for $C_{16}H_{24}N_2O_5S+Na$ 379, found 379.

4.3.7. *N*-(But-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-alaninol (3f). The title compound was prepared from **2c** (2.00 g, 6.94 mmol), 4-bromo-1-butene (1.04 mL, 10.40 mmol) and cesium carbonate (3.38 g, 10.40 mmol) followed by LAH (6.20 mmol) reduction according to the procedure for **3c** and isolated as a light brown oil (1.30 g, 66% yield): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.15 (d, J=6.9 Hz, 3H), 2.11 (bs, 1H), 2.40–2.48 (m, 2H), 3.31–3.37 (m, 2H), 3.53–3.60 (m, 1H), 4.00–4.07 (m, 1H), 5.06–5.14 (m, 2H), 5.69–5.83 (m, 1H), 7.61–7.64 (m, 1H), 7.65–7.74 (m, 2H), 8.10–8.13 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 15.5, 35.8, 43.5, 55.9, 64.3, 117.3, 124.3, 130.8, 132.1, 133.5, 134.0, 134.8, 148.1; MS calcd for $C_{13}H_{18}N_2O_5S+Na$ 337, found 337.

4.3.8. *N*-(But-3-enyl)-*O*-(*tert*-butyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-serinol (3g). The title compound was prepared from **2d** (1.5 g, 4.2 mmol), 4-bromo-1-butene (0.68 mL, 6.2 mmol) and cesium carbonate (2.0 g, 6.2 mmol) followed by LAH (3.7 mmol) reduction according to the procedure for **3c** and isolated as a light yellow oil (0.88 g, 61% yield): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.12 (s, 9H), 2.39–2.46 (m, 2H), 3.39–3.45 (m, 2H), 3.56 (d, J=5.7 Hz, 2H), 3.79 (d, J=6.3 Hz, 2H), 3.98–4.04 (m, 1H), 5.03–5.11 (m, 2H), 5.68–5.79 (m, 1H), 7.61–7.72 (m, 3H), 8.17–8.20 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 27.6, 35.8, 45.0, 60.5, 61.0, 62.6, 73.8, 117.4, 124.4, 131.0, 132.1, 133.9, 135.0, 148.6; MS calcd for $C_{17}H_{26}N_2O_6S+Na$ 409, found 409.

4.3.9. (3*S*)-3-[But-3-enyl-(2-nitro-benzenesulfonyl)-amino]-4-hydroxy-butyric acid *tert*-butyl ester (3h). (3*S*)-3-[(2-nitro-benzenesulfonyl)-amino]-4-hydroxy-butyric acid *tert*-butyl ester (6). A solution of 2-(*N*-9-fluorenylmethoxy-carbonyl-amino)-4-hydroxybutanoic acid *tert*-butyl ester (**5**) (2.5 g, 6.3 mmol) in 20% piperidine–DMF (40 mL) was stirred at room temperature for 30 min and then diluted with ether (150 mL). The resulting mixture was washed with brine (3×30 mL), dried over $MgSO_4$, concentrated and dried by vacuum pump overnight. The resulting crude amino alcohol was dissolved in CH_2Cl_2 (20 mL) and added 2-nitrobenzenesulfonyl chloride (1.4 g, 6.3 mmol) and TEA (1.8 mL, 12.6 mmol). The mixture was stirred at room temperature for 14 h, and then solvent was removed. The product was purified by column chromatography on silica gel eluting with 40% EtOAc to give **6** as a light yellow oil (1.38 g, 61%): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.37 (s, 9H), 2.36 (bs, 1H), 2.51 (d, J=6.0 Hz, 2H), 3.63 (bs, 2H), 3.86 (bs, 1H), 6.10 (bs, 1H), 7.70–7.77 (m, 2H), 7.84–7.87 (m, 1H), 8.15–8.18 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 28.3, 38.0, 53.4, 64.6, 82.3, 125.7, 131.2, 133.3, 133.9, 135.0, 148.2, 170.6; HRMS calcd for $C_{14}H_{20}N_2O_7S+Na$ 383, found 383. Compound **3h** was synthesized from **6** (0.60 g, 1.67 mmol), 4-bromo-1-butene (0.37 mL, 3.34 mmol) and cesium carbonate (0.81 g, 2.51 mmol) in DMF at 60°C for 6 h according to the procedure for **3c** and isolated **3h** as a light yellow oil (0.33 g, 78%) and starting material **6** (0.23 g). For **3h**: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.39 (s, 9H), 2.42–2.58 (m 4H), 3.32–3.43 (m, 2H), 3.71 (d, J= 6.9 Hz, 1H), 4.25–4.32 (m, 1H), 5.08–5.16 (m, 2H), 5.71–5.82 (m, 1H), 7.62–7.73 (m, 3H), 8.14–8.17 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 28.3, 35.7, 37.4, 45.1, 57.3, 63.3, 81.9, 117.7, 124.4, 131.6, 132.2, 133.5, 134.2, 134.8, 148.4, 170.2; HRMS calcd for $C_{18}H_{26}N_2O_7S+Na$ 437, found 437.

4.4. General procedure for the synthesis of aldehyde 4a–h from alcohol 3a–h

A mixture of **3** (0.27 mmol) and Dess–Martin periodinane (0.54 mmol) in water saturated CH_2Cl_2 (2.0 mL) was stirred at room temperature for 10 min and then diluted with ether (5.0 mL) and a solution of $Na_2S_2O_3$ (50% in 80% of saturated aqueous $NaHCO_3$solution) (1.0 mL). The resulting mixture was stirred at room temperature for 10 min. Ether layer was separated, and aqueous layer was extracted with

ether (5.0 mL). The combined organic layer was washed sequentially with saturated aqueous $NaHCO_3$ solution (2×5 mL), brine (2×5 mL), water (2×5 mL) and dried over $MgSO_4$. Removal of the solvent provided analytically pure aldehyde **4**.

4.4.1. *N*-(But-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-phenylalaninal (4a). Yellow syrup, 100% yield: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 2.27–2.36 (m, 2H), 2.88 (dd, J=8.7, 14.4 Hz, 1H), 3.34–3.53 (m, 3H), 4.74 (dd, J=6.6, 8.1 Hz, 1H), 5.04–5.10 (m, 2H), 5.63–5.75 (m, 1H), 7.14 (s, 5H), 7.51–7.56 (m, 2H), 7.61–7.52 (m, 1H), 7.78 (d, J=8.1 Hz, 1H), 9.70 (s, 1H).

4.4.2. *N*-(Pent-4-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-phenylalaninal (4b). White solid, 91% yield: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.59–1.69 (m, 2H), 2.02–2.09 (m, 2H), 2.86 (dd, J=8.4, 14.4 Hz, 1H), 3.31–3.48 (m, 3H), 4.73 (t, J=8.1 Hz, 1H), 4.89–5.05 (m, 2H), 5.67–5.80 (m, 1H), 7.14 (s, 5H), 7.53–7.68 (m, 3H), 7.78 (d, J=7.2 Hz, 1H), 9.70 (s, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 29.5, 30.9, 33.2, 46.0, 67.2, 116.0, 124.6, 127.1, 128.8, 129.1, 131.0, 132.0, 133.2, 133.9, 136.3, 136.9, 147.9, 199.3.

4.4.3. *N*-(But-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-valinal (4c). Yellow oil, 97% yield: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.99 (d, J=6.5 Hz, 3H), 1.18 (d, J=6.5 Hz, 3H), 2.15–2.53 (m, 3H), 3.27–3.45 (m, 2H), 4.23 (d, J=10.2 Hz, 1H), 5.05–5.10 (m, 2H), 5.64–5.77 (m, 1H), 7.61–7.66 (m, 1H), 7.71–7.75 (m, 2H), 8.08–8.11 (m, 1H), 9.76 (s, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 20.4, 20.6, 27.7, 35.3, 46.8, 72.0, 118.0, 124.6, 131.5, 132.2, 133.6, 134.2, 134.39, 148.3, 199.5.

4.4.4. *N*-(4-Methyl-pent-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-valinal (4d). Yellow solid, 94% yield: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.97 (d, J=7.2 Hz, 3H), 1.17 (d, J=7.2 Hz, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 2.14–2.40 (m, 3H), 3.12–3.34 (m, 2H), 4.20 (d, J=10.2 Hz, 1H), 4.99 (t, J=7.2 Hz, 1H), 7.60–7.65 (m, 1H), 7.69–7.75 (m, 2H), 8.06–8.11 (m, 1H), 9.74 (s, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 17.8, 20.1, 20.1, 25.6, 27.2, 29.6, 46.6, 71.5, 119.4, 124.2, 131.1, 131.7, 133.4, 133.7, 135.2, 147.9, 198.9.

4.4.5. *N*-(Pent-4-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-valinal (4e). Yellow solid, 94% yield: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.98 (d, J=6.9 Hz, 3H), 1.17 (d, J=6.9 Hz, 3H), 1.72–1.78 (m, 1H), 1.79–1.90 (m, 1H), 2.00–2.07 (m, 2H), 2.13–2.25 (m, 1H), 3.20–3.37 (m, 2H), 4.21 (d, J=10.2 Hz, 1H), 4.99–5.06 (m, 2H), 5.69–5.82 (m, 1H), 7.60–7.65 (m, 1H), 7.70–7.76 (m, 2H), 8.05–8.10 (m, 1H), 9.75 (s, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 20.2, 0.4, 27.4, 29.7, 31.2, 46.7, 71.7, 115.8, 124.3, 131.2, 131.8, 133.4, 133.9, 137.1, 148.1, 199.1.

4.4.6. *N*-(But-3-enyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-alaninal (4f). Yellow oil, 98% yield: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.42 (d, J=7.5 Hz, 3H), 1.59 (s, 1H), 2.29–2.36 (m, 2H), 3.32–3.37 (t, J=7.8 Hz, 2H), 4.60 (q, J=7.5 Hz, 1H), 5.04–5.10 (m, 2H), 5.64–5.77 (m, 1H), 7.66–7.69 (m, 1H), 7.74–7.77 (m, 2H), 8.11–8.14 (m, 1H), 9.67 (s, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 12.9 35.0, 45.7, 62.3, 118.2, 124.7, 131.4, 132.5, 133.5, 134.2, 134.5, 148.4, 200.4.

4.4.7. *N*-(But-3-enyl)-*O*-(*tert*-butyl)-*N*-(2-nitrobenzenesulfonyl)-(*S*)-serinal (4g). Yellow oil, 94% yield: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.16 (s, 9H), 2.39–2.46 (m, 2H), 3.45–3.50 (m, 2H), 3.86–4.01 (m, 2H), 4.66 (dd, J=3.6, 6.6 Hz, 1H), 5.02–5.11 (m, 2H), 5.66–5.79 (m, 1H), 7.64–7.79 (m, 3H), 8.15–8.18 (m, 1H), 9.64 (s, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 27.4, 34.9, 47.0, 59.6, 66.8, 74.2, 117.6, 124.6, 131.00, 132.1, 133.5, 134.0, 134.6, 148.4, 198.6.

4.4.8. (3*S*)-3-[But-3-enyl-(2-nitro-benzenesulfonyl)-amino]-4-oxo-butyric acid *tert*-butyl ester (4h). Yellow oil, 100%: ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.421 (s, 9H), 2.27–2.38 (m, 2H), 2.53 (dd, J=6.6, 16.8 Hz, 1H), 2.95 (dd, J=7.2, 16.8 Hz, 1H), 3.34–3.43 (m, 2H), 4.80 (t, J=6.9 Hz, 1H), 5.05–5.11 (m, 2H), 5.63–5.76 (m, 1H), 7.65–7.78 (m, 3H), 8.05–8.09 (m, 1H), 9.66 (s, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 28.6, 34.5, 35.0, 47.5, 63.5, 82.7, 118.7, 125.1, 131.8, 132.7, 133.6, 134.3, 134.8, 148.7, 169.7, 198.5.

4.4.9. *N*-(But-3-enyl)-(*S*)-prolinol (8). To a solution of (*S*)-prolinol (5.0 g, 49.5 mmol) in DMF (10 mL) was added 4-bromo-1-butene (7.6 mL, 75.0 mmol) and cesium carbonate (16.0 g, 49.5 mmol). The mixture was stirred at 60°C for 16 h. The resulting reaction mixture was cooled to room temperature and diluted with ether (150 mL), washed with saturated aqueous $NaHCO_3$ solution (2×30 mL), dried over $MgSO_4$ and concentrated. Product was purified by vacuum distillation (75–78°C, 5 mmHg) to provide **8** as a colorless oil (3.6 g, 47%): ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.68–1.78 (m, 3H), 1.81–1.92 (m, 1H), 2.19–2.29 (m, 3H), 2.31–2.37 (m, 1H), 2.55–2.61 (m, 1H), 2.74–2.81 (m, 1H), 2.88 (bs, 1H), 3.15–3.20 (m, 1H), 3.37 (dd, J=1.5, 7.8 Hz, 1H), 3.61 (dd, J=2.7, 7.8 Hz, 1H), 4.99–5.09 (m, 2H), 5.75–5.85 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 22.2, 26.3, 32.1, 52.3, 52.6, 60.3, 63.1, 114.4, 135.2; HRMS calcd for $C_9H_{17}NO$ (MH+) 156.1389, found 156.1401.

4.4.10. 1-Benzyl-decahydro-isoxazolo[4,3-*g*]indolizine (9). The title compound was synthesized from alcohol **8**. To a stirred solution of DMSO (0.35 mL, 4.98 mmol) in CH_2Cl_2 (3.0 mL) was added oxalyl chloride (0.34 mL, 3.96 mmol) at −78°C. After 10 min, a solution of **8** (0.20 g, 1.29 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise, followed by triethylamine (1.4 mL, 10.0 mmol). The mixture was warmed to room temperature (about 1 h), diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL) and dried over $MgSO_4$. Removal of solvent provided the corresponding crude aldehyde (0.14 g, 71%). The crude aldehyde was dissolved in CH_2Cl_2 (3.0 mL) and treated with *N*-benzylhydroxylamine hydrochloride (0.45 g, 2.8 mmol) and $NaHCO_3$ (0.35 g, 4.2 mmol). The mixture was stirred at room temperature for 10 h, filtered through cotton and concentrated. Residue was dissolved in benzene (60 mL) and refluxed for 16 h in the presence of $ZnCl_2$ (100 mg). Solvent was removed under vacuum, and residue was taken into CH_2Cl_2 (20 mL), washed with $NaHCO_3$ solution (10 mL×2), dried over $MgSO_4$ and concentrated.

Compound **9** was obtained by column chromatography on silica gel (5% CH_3OH in CH_2Cl_2) as a colorless oil (0.095 g, 41%): $[\alpha]=-6$ (c 0.16 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.16–1.26 (m, 2H), 1.67–1.74 (m, 2H), 1.83 (d, J=13.2 Hz, 1H), 2.01 (d, J=5.6 Hz, 1H), 2.07–2.20 (m, 4H), 2.94–2.98 (m, 1H), 3.07–3.13 (m, 2H), 3.69 (dd, J=7.6, 9.6 Hz, 1H), 3.78 (d, J=12.0 Hz, 1H), 4.12 (d, J=12.4 Hz, 1H), 4.25 (bt, J=8.8 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 20.7, 23.7, 29.6, 37.2, 54.6, 58.5, 61.7, 63.6, 67.0, 69.4, 127.6, 128.7, 129.4, 137.3; HRMS calcd for $C_{16}H_{22}N_2O$ (MH+) 259.1812, found 259.1819.

4.5. General procedure for intramolecular 1,3-dipolar reaction to synthesize cyclized compounds 9, 10 and 11

A mixture of aldehyde **4** (1.0 equiv.), *N*-substituted hydroxylamine hydrochloride (2.0 equiv.), $NaHCO_3$ (4.0 equiv.) and $CaCl_2$ (2.0 equiv.) in CH_2Cl_2 was stirred at room temperature for 2–5 h or until the disappearance of the aldehyde. The resulting suspension was filtered through cotton and solvent was removed to afford the crude *N*-oxide intermediate. The residue was dissolved in benzene or toluene and refluxed with or without the presence of $ZnCl_2$ (0.3 equiv.) for 15–36 h or until the disappearance of *N*-oxide by TLC. After removal of the solvent, residue was taken into a mixture of CH_2Cl_2–water (1:1) and organic layer was separated, dried and concentrated. The cyclized product was purified by column chromatography eluting with EtOAc–hexane (30–50%). All the yields were calculated based on correspondent alcohols (two-step yields).

4.5.1. 2,8-Dibenzyl-3-(2-nitro-benzenesulfonyl)-7-oxa-3,8-diaza-bicyclo[4.2.1]nonane (10a). White solid, 67% yield: mp 64–66°C; $[\alpha]_D^{20}=+70.6$ (c 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.64–1.79 (m, 2H), 2.22–2.41 (m, 2H), 2.73 (dd, J=6.0, 13.5 Hz, 1H), 3.12 (dd, J=9.3, 13.8 Hz, 1H), 3.46 (dd, J=5.7, 7.8 Hz, 1H), 3.60 (d, J=13.5 Hz, 1H), 3.66–3.74 (m, 1H), 3.71 (d, J=13.5 Hz, 1H), 3.86 (bd, J=15.0 Hz, 1H), 4.31–4.39 (m, 1H), 4.60 (bs, 1H), 7.05–7.14 (m, 4H), 7.26–7.35 (m, 7H), 7.51–7.63 (m, 2H), 7.79–7.82 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 35.0, 35.8, 35.9, 40.4, 61.6, 64.9, 65.0, 76.7, 124.4, 127.0, 127.8, 128.7, 128.8, 129.1, 129.5, 129.7, 131.1, 132.1, 133.7, 134.8, 137.8, 138.3, 148.2; MS calcd for $C_{26}H_{27}N_3O_5S+H$ 494, found 494. Anal. calcd for $C_{26}H_{27}N_3O_5S$: C, 63.27; H, 5.51; N, 8.51. Found: C, 63.36; H, 5.28; N, 8.20.

4.5.2. 2-Benzyl-8-methyl-3-(2-nitro-benzenesulfonyl)-7-oxa-3,8-diaza-bicyclo[4.2.1]nonane (10b). White solid, 64% yield: mp 150–152°C; $[\alpha]_D^{20}=+54.2$ (c 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ 1.68–1.69 (m, 2H), 2.34–2.52 (m, 2H), 2.42 (s, 3H), 2.60 (dd, J=7.2, 18.0 Hz, 1H), 3.14 (dd, J=8.0, 10.4 Hz, 1H), 3.23 (dd, J=14.0, 18.0 Hz, 1H), 3.54 (ddd, J=6.0, 14.4, 20.4 Hz, 1H), 3.87 (bd, J=20.4 Hz, 1H), 4.30 (dd, J=7.2, 14.0 Hz, 1H), 4.62 (bs, 1H), 7.10–7.22 (m, 5H), 7.56–7.67 (m, 3H), 7.91–7.94 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 32.1, 33.4, 33.7, 38.1, 38.1, 46.9, 59.1, 59.2, 64.8, 74.6, 122.3, 124.8, 126.6, 127.6, 128.8, 129.9, 131.7, 132.4, 135.9, 146.0; MS calcd for $C_{20}H_{23}N_3O_5S+H$ 418, found 418. Anal. calcd for $C_{20}H_{23}N_3O_5S$: C, 57.54; H, 5.56; N, 10.07. Found: C, 57.52; H, 5.17; N, 10.40.

4.5.3. 2,9-Dibenzyl-3-(2-nitro-benzenesulfonyl)-8-oxa-3,9-diaza-bicyclo[5.2.1]decane (10c). White solid, 38% yield: mp 82–84°C; $[\alpha]_D^{20}=60.5$ (c 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.66–1.77 (m, 2H), 1.92–2.08 (m, 2H), 2.39 (dd, J=3.0, 13.8 Hz, 1H), 2.58–2.69 (m, 1H), 2.81 (dd, J=9.3, 18.0 Hz, 1H), 2.92 (dd, J=6.3, 13.8 Hz, 1H), 3.09 (dd, J=4.2, 9.0 Hz, 1H), 3.28 (dd, J=10.2, 16.2 Hz, 1H), 3.55 (d, J=19.9 Hz, 1H), 3.82 (d, J=12.9 Hz, 1H), 3.96 (dd, J=6.3, 15.9 Hz, 1H), 4.48–4.53 (m, 1H), 4.58–4.65 (m, 1H), 7.06–7.54 (m, 4H), 7.17–7.28 (m, 7H), 7.38–7.52 (m, 2H), 8.11 (bd, J=7.5 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 24.8, 31.8, 33.0, 37.5, 61.4, 64.3, 73.8, 77.3, 122.9, 126.7, 127.3, 128.3, 128.7, 128.9, 129.1, 131.0, 131.9, 132.9, 133.9, 137.3, 137.4, 148.7; MS calcd for $C_{27}H_{29}N_3O_5S+Na$ 530, found 530. Anal. calcd for $C_{27}H_{29}N_3O_5S$: C, 63.89; H, 5.76; N, 8.28. Found: C, 64.21; H, 5.40; N, 8.33.

4.5.4. 2-Benzyl-9-methyl-3-(2-nitro-benzenesulfonyl)-8-oxa-3,9-diaza-bicyclo[5.2.1]decane (10d). White-off solid, 34% yield: mp 196–198°C; $[\alpha]_D^{20}=+19.6$ (c 0.69, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.67–1.81 (m, 2H), 1.95–2.06 (m, 1H), 2.13–2.20 (m, 1H), 2.36 (dd, J=3.0, 13.8 Hz, 1H), 2.45 (s, 3H), 2.61–2.72 (m, 1H), 2.80–2.94 (m, 3H), 3.26 (dd, J=10.2, 16.2 Hz, 1H), 3.93 (dd, J=6.9, 15.9 Hz, 1H), 4.51 (dd, J=6.0, 10.2 Hz, 1H), 4.56–4.61 (m, 1H), 7.11 (d, J=6.6 Hz, 2H), 7.18–7.27 (m, 3H), 7.47–7.63 (m, 3H), 8.09 (d, J=7.5 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) **δ** 24.9, 31.6, 32.4, 37.3, 45.2, 60.8, 66.3, 73.0, 77.3, 123.0, 126.6, 128.5, 128.5, 128.8, 130.7, 131.4, 132.7, 133.8, 137.2, 148.4; MS calcd for $C_{21}H_{25}N_3O_5S+H$ 432, found 432. Anal. calcd for $C_{21}H_{25}N_3O_5S$: C, 58.45, H, 5.84; N, 9.74. Found: C, 58.81; H, 5.60; N, 9.30.

4.5.5. 8-Benzyl-2-isopropyl-3-(2-nitro-benzenesulfonyl)-7-oxa-3,8-diaza-bicyclo[4.2.1]nonane (10e). White solid, 59% yield: mp 127–129°C; $[\alpha]_D^{20}=+103$ (c 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.63–1.70 (m, 2H), 2.45–2.56 (m, 3H), 3.28 (ddd, J=4.2, 11.4, 15.3 Hz, 1H), 3.57 (dd, J=6.6, 9.9 Hz, 1H), 3.74–3.86 (m, 2H), 3.83 (d, J=12.9 Hz, 1H), 3.95 (d, J=12.9 Hz, 1H), 4.61 (d, J=3.3 Hz, 1H), 7.23–7.78 (m, 5H), 7.53–7.57 (m, 1H), 7.61–7.68 (m, 2H), 7.99–8.02 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 19.3, 20.4, 26.5, 34.1, 34.2, 40.1, 64.4, 64.8, 66.1, 76.2, 123.9, 127.5, 128.41, 129.3, 130.8, 131.6, 133.5, 135.1, 137.5, 147.7; HRMS calcd for $C_{22}H_{27}N_3O_5S$ (MH+) 446.1751, found 446.1548.

4.5.6. 2-Isopropyl-8-methyl-3-(2-nitro-benzenesulfonyl)-7-oxa-3,8-diaza-bicyclo[4.2.1]nonane (10f). Light yellow syrup, 63% yield: $[\alpha]_D^{20}=+186$ (c 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 0.47 (d, J=7.0 Hz, 3H), 0.92 (d, J=6.3 Hz, 3H), 1.60–1.75 (m, 3H), 2.39–2.59 (m, 3H), 2.67 (s, 3H), 3.26 (ddd, J=3.6, 11.7, 15.3 Hz, 1H), 3.49–3.59 (m, 2H), 3.86 (d, J=15.0 Hz, 1H), 4.60 (dd, J=5.1, 6.6 Hz, 1H), 7.54–7.60 (m, 1H), 7.7.63–7.70 (m, 2H), 8.00–8.05 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 11.6, 12.7, 18.9, 25.6, 26.6, 32.2, 40.8, 58.2, 58.9, 68.4, 116.1, 123.1, 123.7, 125.6, 127.3, 139.8; HRMS calcd for $C_{16}H_{23}N_3O_5S$ (MH+) 370.1438, found 370.1449.

4.5.7. 9-Benzyl-2-isopropyl-3-(2-nitro-benzenesulfonyl)-8-oxa-3,9-diaza-bicyclo[5.2.1]decane (10g). The title

compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the presence of $ZnCl_2$ and isolated as a white solid, 30% yield: mp 167–169°C; $[\alpha]_D^{20}$=+77.0 (*c* 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 0.92 (d, *J*=6.6 Hz, 3H), 0.96 (d, *J*=6.3 Hz, 3H), 1.41–1.63 (m, 3H), 1.75–1.92 (m, 2H), 2.15 (dd, *J*=3.0, 13.8 Hz, 1H), 2.66–2.78 (m, 1H), 2.86–3.00 (m, 1H), 3.49 (dd, *J*=4.5, 9.6 Hz, 1H), 3.76 (d, *J*=12.9 Hz, 1H), 3.96 (d, *J*=15.3 Hz, 1H), 3.90–3.99 (m, 1H), 4.25 (s, 1H), 4.52–4.59 (m, 1H), 7.03 (t, *J*=7.5 Hz, 1H), 7.25–7.45 (m, 7H), 8.51 (d, *J*=8.1 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 18.6, 21.5, 26.1, 30.0, 31.7, 40.1, 60.4, 62.4, 64.4, 71.4, 120.3, 125.8, 126.8, 127.8, 128.8, 131.3, 132.0, 132.5, 136.1, 147.0; HRMS calcd for $C_{23}H_{29}N_3O_5S$ (MH+) 460.1908, found 460.1898.

4.5.8. 2-*tert*-Butoxymethyl-8-methyl-3-(2-nitro-benzenesulfonyl)-7-oxa-3,8-diaza-bicyclo[4.2.1]nonane (10h). Light yellow syrup, 17% yield: $[\alpha]_D^{20}$=+12.4 (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 0.95 9 (s, 9H), 1.60–1.74 (m, 2H), 2.39 (d, *J*=12.6 Hz, 1H), 2.49–2.58 (m, 1H), 2.97 (s, 1H), 3.14 (dd, *J*=6.9, 8.4 Hz, 1H), 3.39–3.59 (m, 3H), 3.80 (d, *J*=15.3 Hz, 1H), 3.99 (dd, *J*=6.9, 13.2 Hz, 1H), 4.59 (bt, *J*=5.7 Hz, 1H), 7.60–7.70 (m, 3H), 8.09–8.11 (m, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 27.9, 34.7, 36.4, 41.1, 49.5, 59.4, 60.0, 66.9, 73.6, 77.1, 124.7, 132.0, 132.2, 133.6, 135.5, 148.6; HRMS calcd for $C_{18}H_{27}N_3O_6S$ (MH+) 414.1700, found 414.1691.

4.5.9. [8-Methyl-3-(2-nitro-benzenesulfonyl)-7-oxa-3,8-diaza-bicyclo[4.2.1]non-2-yl]-acetic acid *tert*-butyl ester (10i). White solid, 46% yield: mp 153–155°C; $[\alpha]_D^{20}$=+48.0 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) (1.38 (s, 9H), 1.59–1.69 (m, 2H), 1.94 (dd, *J*=3.3, 16.2 Hz, 1H), 2.36 (d, *J*=12.6 Hz, 1H), 2.50–2.57 (m, 1H), 2.60 (s, 3H), 3.14 (dd, *J*=11.1, 15.9 Hz, 1H), 3.29 (ddd, *J*=3.9, 11.4, 15.3 Hz, 1H), 3.62 (dd, *J*=6.0, 8.1 Hz, 1H), 3.76 (d, *J*=15.0 Hz, 1H), 4.27–4.34 (m, 1H), 4.59–4.63 (m, 1H), 7.60–7.73 (m, 3H), 8.03–8.06 (m 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 28.0, 34.1, 34.8, 35.8, 40.1, 48.5, 55.6, 66.5, 76.2, 80.9, 124.2, 130.9, 131.7, 133.6, 133.9, 147.7, 170.2; MS calcd for $C_{19}H_{27}N_3O_7S$+Na 464, found 464. Anal. calcd for: $C_{19}H_{27}N_3O_7S$: C, 51.69; H, 6.16; N, 9.52. Found C, 52.04; H, 6.55; N, 9.90.

4.5.10. [8-Benzyl-3-(2-nitro-benzenesulfonyl)-7-oxa-3,8-diaza-bicyclo[4.2.1]non-2-yl]-acetic acid *tert*-butyl ester (10j). White solid, 38% yield: mp 142–143°C; $[\alpha]_D^{20}$=+9.00 (*c* 0.24, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.35 (s, 9H), 1.57–1.75 (m, 2H), 2.00 (dd, *J*=3.6, 16.5 Hz, 1H), 2.34–2.38 (m, 1H), 3.20–3.39 (m, 2H), 3.75–3.90 (m, 4H), 4.33–4.39 (m, 1H), 4.60 (s, 1H), 7.23–7.38 (m, 5H), 7.61–7.71 (m, 3H), 8.04–8.07 (m 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 28.2, 35.0, 35.4, 35.5, 40.4, 56.0, 64.7, 64.8, 76.4, 81.2, 124.4, 127.6, 128.5, 129.3, 131.8, 131.9, 133.8, 134.2, 137.7, 148.0, 170.5; MS calcd for $C_{25}H_{31}N_3O_7S$+Na 540, found 540. Anal. calcd for $C_{25}H_{31}N_3O_7S$: C, 58.01; H, 6.04; N, 8.12. Found C, 57.92; H, 5.99; N, 8.22.

4.5.11. 7-Benzyl-1-methyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridine (11a). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the absence of $ZnCl_2$ and isolated as a white solid (51% yield) along with **10b** (white solid, 30%): For **11a**: mp 118–120°C; $[\alpha]_D^{20}$=+135.0 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.80–1.89 (m, 2H), 2.36 (s, 3H), 2.49 (d, *J*=4.5 Hz, 1H), 2.74–2.80 (m, 1H), 2.93 (dd, *J*=10.5, 13.5 Hz, 1H), 3.22 (dd, *J*=4.5, 13.5 Hz, 1H), 3.39 (ddd, *J*=3.9, 9.9, 13.5 Hz, 1H), 3.53 (dd, *J*=2.4, 7.8 Hz, 1H), 3.80 (dt, *J*=13.5, 4.5 Hz, 1H), 4.04 (dd, *J*=6.3, 7.8 Hz, 1H), 4.21 (dd, *J*=4.8, 10.5 Hz, 1H) 7.21–7.34 (m, 5H), 7.57–7.67 (m, 3H), 8.08–8.11 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 25.6, 37.6, 39.7, 40.2, 43.4, 54.4, 66.7, 70.9, 123.7, 127.0, 128.8, 129.0, 130.5, 131.6, 133.1, 133.7, 137.5, 148.3; HRMS calcd for $C_{20}H_{23}N_3O_5S$ (MH+) 418.1438, found 418.1432.

4.5.12. 7-Isopropyl-1,3,3-trimethyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridine (11b). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the presence of $ZnCl_2$ and isolated as a white solid, 52% yield: mp 123–125°C; $[\alpha]_D^{20}$=+116 (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 0.98 (d, *J*=6.9 Hz, 3H), 1.09 (s, 3H), 1.11 (d, *J*=5.1 Hz, 3H), 1.29 (s, 3H), 1.42–1.49 (m, 1H), 1.65 (ddd, *J*=4.5, 13.2, 17.4 Hz, 1H), 1.88–2.00 (m, 1H), 2.14–2.22 (m, 1H), 2.96 (dd, *J*=2.4, 15.0 Hz, 1H), 3.62 (d, *J*=10.2 Hz, 1H), 3.90 (bd, *J*=14.4 Hz, 1H), 7.47–7.53 (m, 1H), 7.61–7.66 (m, 1H), 8.29–8.34 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 20.1, 21.5, 22.6, 23.2, 29.9, 31.0, 40.5, 45.5, 46.5, 59.8, 66.7, 81.3, 123.7, 131.5, 131.6, 133.6, 134.7, 149.1; HRMS calcd for $C_{18}H_{27}N_3O_5S$ (MH+) 398.1751, found 398.1753.

4.5.13. 1,7-Dimethyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridine (11c). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the presence of $ZnCl_2$ and isolated as a white solid (52% yield: mp 115–117°C; $[\alpha]_D^{20}$=+24.0 (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.38 (d, *J*=6.9 Hz, 3H), 1.73–1.92 (m, 2H), 2.47 (dd, *J*=1.8, 5.7 Hz, 1H), 2.59 (s, 3H), 2.66–2.74 (m, 1H), 3.29 (ddd, *J*=3.3, 11.1, 13.8 Hz, 1H), 3.54 (dd, *J*=2.1, 7.5 Hz, 1H), 3.70 (dt, *J*=13.5, 4.5 Hz, 1H), 4.04–4.14 (m, 2H), 7.59–7.69 (m, 3H), 8.16–8.21 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 19.7, 26.2, 38.4, 39.1, 44.7, 48.9, 71.2, 71.4, 124.6, 131.2, 132.2, 133.8, 134.6, 148.8; HRMS calcd for $C_{14}H_{19}N_3O_5S$ (MH+) 342.1125 found 342.1132.

4.5.14. 1-Benzyl-7-methyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridine (11d). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the presence of $ZnCl_2$ and isolated as a white solid (32% yield): mp 162–164°C; $[\alpha]_D^{20}$=111 (*c* 0.17, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.38 (d, *J*=6.9 Hz, 3H), 1.71–1.79 (m, 1H), 1.83–1.97 (m, 1H), 2.68–2.75 (m, 1H), 2.81 (dd, *J*=1.5, 5.4 Hz, 1H), 3.29 (ddd, *J*=3.0, 11.1, 13.8 Hz, 1H), 3.58 (d, *J*=7.8 Hz, 1H), 3.71 (dt, *J*=18.3, 4.8 Hz, 1H), 3.79 (d, *J*=14.1 Hz, 1H), 4.03 (dd, *J*=5.1, 7.8 Hz, 1H), 4.08 (d, *J*=14.1 Hz, 1H), 4.18 (dd, *J*=7.2, 14.1 Hz, 1H), 7.18–7.29 (m, 5H), 7.39–7.54 (m, 3H), 8.23 (d, *J*=8.1 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 18.9, 25.0, 37.4, 38.8, 48.7, 61.1, 67.9, 70.6, 123.8, 127.0, 128.1, 128.7, 130.4, 131.5, 132.8, 134.0, 137.2, 148.1; HRMS calcd for $C_{20}H_{23}N_3O_5S$ (MH+) 417.1367. Found 417.1380.

4.5.15. 7-*tert*-Butoxymethyl-1-methyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridine (11e). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the absence of $ZnCl_2$ and isolated as a yellow syrup (57% yield) along with **10h** (9% yield). For **11e**: $[\alpha]_D^{20}=+22$ (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.17 (s, 9H), 1.70–1.80 (m, 2H), 2.63 (s, 3H), 2.77 (bs, 2H), 3.43 (ddd, *J*=6.0, 8.4, 13.5 Hz, 1H), 3.52–3.55 (m, 1H), 3.57–3.66 (m, 2H), 3.68–3.76 (m, 1H), 4.01 (t, *J*=5.4 Hz, 1H), 4.11 (dd, *J*=5.7, 7.2 Hz, 1H), 7.59–7.70 (m, 3H), 8.22–8.25 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 25.7, 27.5, 38.7, 41.1, 44.0, 52.9, 64.6, 67.2, 71.1, 73.7, 124.0, 130.7, 131.7, 133.3, 133.9, 148.6; HRMS calcd for $C_{18}H_{27}N_3O_6S$ (MH+) 414.1646. Found: 414.1660.

4.5.16. 1-Benzyl-7-*tert*-butoxymethyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridine (11f). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the absence of $ZnCl_2$ and isolated as a light yellow oil (45% yield): $[\alpha]_D^{20}=+105$ (*c* 25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.20 (s, 9H), 1.73–1.83 (m, 2H), 2.75–2.80 (m, 1H), 3.17 (d, *J*=5.7 Hz, 1H), 3.45 (ddd, *J*=3.9, 10.2, 13.5 Hz, 1H), 3.55–3.69 (m, 3H), 3.72–3.80 (m, 1H), 3.83 (d, *J*=14.4 Hz, 1H), 4.05 (dd, *J*=5.1, 7.8 Hz, 1H), 4.13 (d, *J*=14.4 Hz, 1H), 4.10–4.15 (m, 1H), 7.21–7.33 (m, 5H), 7.42–7.56 9 (m, 3H), 8.31 (d, *J*=7.8 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 25.2, 27.7, 38.6, 41.2, 53.5, 61.2, 64.5, 64.8, 71.2, 73.9, 124.1, 127.4, 128.4, 128.2, 130.8, 131.8, 133.2, 134.1, 137.6, 148.7; HRMS calcd for $C_{24}H_{31}N_3O_6S$ (MH+) 490.2014, found 490.2017.

4.5.17. [1-Methyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridin-7-yl]-acetic acid *tert*-butyl ester (11g). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the presence of $ZnCl_2$ and isolated as a colorless film (19% yield) along with **10i** (46% yield). For **11g**: $[\alpha]_D^{20}=+32$ (*c* 15, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ 1.47 (s, 9H), 1.72–1.77 (m, 1H), 1.82–1.91 (m, 1H), 2.55–2.61 (m, 1H), 2.59 (s, 3H), 2.63–2.77 (m, 3H), 3.20 (ddd, *J*=2.8, 10.8, 13.6 Hz, 1H), 3.54 (dd, *J*=2.0, 7.6 Hz, 1H), 3.82 (dt, *J*=13.6, 4.4 Hz, 1H), 4.07 (dd, *J*=6.0, 7.6 Hz, 1H), 4.37 (dd, *J*=3.6, 10.4 Hz, 1H), 7.61–7.69 (m, 3H), 8.17–8.21 (m, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 25.3, 28.1, 37.7, 39.6, 39.7, 43.7, 49.2, 68.2, 70.8, 81.7, 124.0, 130.9, 131.5, 133.3, 133.5, 148.2, 169.3; HRMS calcd for $C_{19}H_{27}N_3O_7S$ (MH+) 442.1649, found 464.1652.

4.5.18. [1-Benzyl-6-(2-nitro-benzenesulfonyl)-octahydro-isoxazolo[3,4-*c*]pyridin-7-yl]-acetic acid *tert*-butyl ester (11h). The title compound was prepared from the corresponding *N*-oxide refluxing in toluene for 24 h in the presence of $ZnCl_2$ and isolated as a colorless film (24% yield) along with **10j** (38% yield). For **11h**: $[\alpha]_D^{20}=+6$ (*c* 0.14, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ 1.51 (s, 9H), 1.72–1.78 (m, 1H), 1.87–1.96 (m, 1H), 2.69–2.85 (m, 3H), 3.23 (ddd, *J*=3.2, 11.2, 14.0 Hz, 1H), 3.58 (dd, *J*=1.6, 8.0 Hz, 1H), 3.74 (d, *J*=14.4 Hz, 1H), 3.86 (dt, *J*=13.6, 4.4 Hz, 1H), 4.03 (dd, *J*=5.2, 7.6 Hz, 1H), 4.22)d, *J*=14.4 Hz, 1H), 4.55 (dd, *J*=3.2, 10.4 Hz, 1H), 7.17–7.27 (m, 5H), 7.36–7.40 (m, 1H), 7.49–7.55 (m, 2H), 8.22 (d, *J*=8.0 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 25.2, 28.4, 37.6, 39.9, 40.0, 49.9, 60.9, 66.2, 71.0, 82.0, 124.2, 127.2, 128.4, 128.8, 131.1, 131.9, 133.3, 133.8, 137.9, 148.4, 169.8; HRMS calcd for $C_{25}H_{31}N_3O_7S$ (MH+) 518.1963 found, 518.1954.

4.6. General conditions for N, O bond cleavage

A mixture of starting material (1.0 equiv.) and zinc powder (20–30 equiv.) was heated in aqueous acetic acid (60%) at 60°C for 2 h or until the disappearance of starting material. The resulting mixture was diluted with water and basified using 5 M aqueous NaOH to pH>12. The product was extracted with CH_2Cl_2. Organic layer was combined, washed with brine and dried over Na_2SO_4. Removal of solvent provided desired amino alcohols which was purified by column chromatography on silica gel (5% CHOH in $CHCl_3$).

4.6.1. 1-(2-Amino-benzenesulfonyl)-2-benzyl-3-methyl-aminoazepan-5-ol (12). The title compound was prepared from **10d** (0.0070 g, 0.016 mmol) and zinc (25 mg, 0.38 mmol) according to general procedure for N, O bond cleavage and isolated as a white solid (0.0056 g, 83%); ^1H NMR ($CDCl_3$, 300 Hz) δ 0.85–0.91 (m, 1H), 1.42–1.53 (m, 1H), 1.75–1.95 (m, 2H), 1.99–2.03 (m, 3H), 2.08 (s, 3H), 2.48–2.62 (m, 2H), 2.73 (t, *J*=10.5 Hz, 1H), 3.17–3.25 (m, 1H), 3.74–3.83 (m, 2H), 3.95–4.00 (m, 1H), 5.12 (bs, 2H), 6.75–6.83 (m, 1H), 6.99 (d, *J*=6.6 Hz, 1H), 7.18–7.35 (m, 6H), 7.68 (d, *J*=8.1 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 100 Hz) δ 24.2, 30.1, 33.2, 34.7, 37.4, 43.7 (broad), 60.0 (broad), 71.6, 118.3, 118.4, 122.3, 127.2, 129.1, 129.3, 130.4, 134.6, 138.2, 146.1; HRMS calcd for $C_{21}H_{29}N_3O_3S$ (MH+) 404.2010 found 404.2001.

4.6.2. [1-(2-Amino-benzenesulfonyl)-2-methyl-3-methyl-amino-piperidin-4-yl]-methanol (13). The title compound was prepared from **11c** (0.0080 g, 0.023 mmol) and zinc (25 mg, 0.38 mmol) according to general procedure for N, O bond cleavage and isolated as a white solid (0.005 g, 84%): mp 160–162°C; $[\alpha]_D^{20}=+75.0$ (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 Hz) δ 1.19 (d, *J*=7.2 Hz, 3H), 1.26 (s, 1H), 1.46 (d, *J*=13.5 Hz, 1H), 1.74 (d, *J*=12.9 Hz, 1H), 1.95 (ddd, *J*=5.1, 13.2, 18.3 Hz), 2.14 (s, 3H), 2.46 (s, 1H), 3.10 (td, *J*=13.2, 2.7 Hz, 1H), 3.64 (dd, *J*=2.7, 10.8 Hz, 1H), 3.79 (dd, *J*=4.5, 12.9 Hz, 1H), 3.90 (d, *J*=10.8 Hz, 1H), 4.00 (dd, *J*=6.6, 13.5 Hz, 1H), 4.87 (bs, 2H), 6.74–6.83 (m, 2H), 7.33 (t, *J*=7.5 Hz, 1H), 7.74 (d, *J*=8.1 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 14.5, 23.1, 33.6, 34.1, 38.9, 49.3, 64.1, 67.8, 117.9, 118.0, 121.6, 130.6, 134.4, 145.3; HRMS calcd for $C_{14}H_{23}N_3O_3S$ (MH+) 314.1540, found 314.1540.

4.7. General procedure for removing 2-nitrobenzenesulfonyl protecting group

A mixture of starting material (1.0 equiv.), thiophenol (50 equiv.) and K_2CO_3 (10 equiv.) in DMF was stirred at room temperature until the disappearance of the starting material (30 min to 3 h, then diluted with excess of 1N HCl and ether (equal quantity of 1N HCl). Ether layer was separated and aqueous layer was washed with ether twice. Ether layer was discarded and aqueous layer was

basified to pH 14 using 5 M NaOH. The product was extracted with ether twice. Ether layer was washed with brine and dried over Na_2SO_4. Removal of solvent provided the desire secondary amine which was purified by column chromatography on silica gel eluting with 5% CH_3OH in $CHCl_3$.

4.7.1. 2,8-Dibenzyl-7-oxa-3,8-diaza-bicyclo[4.2.1]nonane (14a). The title compound was prepared from **10a** (0.010 g, 0.020 mmol), K_2CO_3 (0.028 g, 0.20 mmol) and thiophenol (0.10 mL, 1.0 mmol) according to general procedure and isolated as a light yellow syrup (0.0049 g, 78%): $[\alpha]_D^{20}=-51.0$ (*c* 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.43–1.51 (m, 1H), 1.88–1.96 (m, 1H), 2.03 (d, *J*=12.4 Hz, 1H), 2.47–2.57 (m, 2H), 2.64–2.71 (m, 2H), 2.80 (dd, *J*=5.6, 13.2 Hz, 1H), 3.14 (d, *J*=6.0 Hz, 1H), 3.18 (d, *J*=7.6 Hz, 1H), 3.67 (d, *J*=12.8 Hz, 1H), 4.02 (d, *J*=12.8 Hz, 1H), 4.71 (dd, *J*=3.6, 9.2 Hz, 1H), 6.88–6.90 (m, 2H), 7.11–7.20 (m, 3H), 7.28–7.42 (m, 5H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 33.4, 35.8, 40.7, 44.7, 63.9, 64.3, 66.3, 77.4, 126.1, 127.7, 128.5, 128.7, 129.4, 129.9, 137.8, 140.2; HRMS calcd for $C_{20}H_{24}N_2O$ (MH+) 309.1969, found 309.1975.

4.7.2. 8-Benzyl-2-isopropyl-7-oxa-3,8-diaza-bicyclo-[4.2.1]nonane (14b). The title compound was prepared from **10e** (0.0050 g, 0.012 mmol), K_2CO_3 (0.015 g, 0.11 mmol) and thiophenol (0.065 mL, 0.60 mmol) according to general procedure and isolated as a white-off solid (0.0023 g, 78%): mp 59–61°C; $[\alpha]_D^{20}=-95.0$ (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.55 (d, *J*=6.6 Hz, 3H), 0.99 (dd, *J*=6.6 Hz, 3H), 1.57 (dt, *J*=19.2, 3.9 Hz, 1H), 1.69–1.79 (m, 1H), 1.91–2.01 (m, 1H), 2.00 (d, *J*=8.4 Hz, 1H), 2.13 (d, *J*=12.9 Hz, 1H), 2.61–2.75 (m, 2H), 3.28 (dd, *J*=6.3, 14.7 Hz, 1H), 3.55 (d, *J*=7.8 Hz, 1H),), 3.79 (d, *J*=12.3 Hz, 1H), 4.12 (d, *J*=12.3 Hz, 1H), 4.79 (dd, *J*=3.6, 8.4 Hz, 1H), 7.31–7.45 (m, 5H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 20.2, 20.7, 29.8, 30.1, 33.6, 36.0, 44.8, 63.3, 63.8, 70.8, 127.5, 128.4, 129.7, 137.5; HRMS calcd for $C_{16}H_{24}N_2O$ (MH+) 261.1969, found 261.1990.

4.7.3. 9-Benzyl-2-isopropyl-8-oxa-3,9-diaza-bicyclo-[5.2.1]decane (14c). The title compound was prepared from **10g** (0.010 g, 0.022 mmol), K_2CO_3 (0.030 g, 0.22 mmol) and thiophenol (0.112 mL, 1.0 mmol) according to general procedure and isolated as a yellow oil (0.0051 g, 85%): $[\alpha]_D^{20}=+43.0$ (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.76 (d, *J*=7.2 Hz, 3H), 0.79 (d, *J*=7.2 Hz, 3H), 1.50–1.72 (m, 4H), 1.82–1.96 (m, 2H), 2.30–2.48 (m, 3H), 2.69–2.77 (m, 1H), 2.84–2.93 (m, 1H), 3.14 (dd, *J*=3.6, 8.1 Hz, 1H), 3.75 (d, *J*=12.6 Hz, 1H), 4.06 (d, *J*=12.6 Hz, 1H), 4.58–4.65 (m, 1H), 7.22–7.37 (m, 5H);^{13}CH NMR ($CDCl_3$, 100 Hz) δ 19.5, 19.8, 25.6, 30.1, 30.9, 31.9, 45.5, 62.2, 65.7, 67.1, 127.9, 128.8, 129.6, 137.6; HRMS calcd for $C_{17}H_{26}N_2O$ (MH+) 275.2125, found 275.2132.

4.7.4. (8-Methyl-7-oxa-3,8-diaza-bicyclo[4.2.1]non-2-yl)-acetic acid *tert*-butyl ester (14d). The title compound was prepared from **10i** (0.016 g, 0.036 mmol), K_2CO_3 (0.050 g, 0.36 mmol) and thiophenol (0.075 mL, 0.73 mmol) according to general procedure and isolated as a light yellow syrup (0.0070 g, 96%): $[\alpha]_D^{20}=-12$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.49 (s, 9H), 1.83–1.93 (m, 1H), 2.19 (d, *J*=12.6 Hz, 1H), 2.56 (d, *J*=6.9 Hz, 2H), 2.64–2.79 (m, 3H), 2.66 (s, 3H), 2.97 (t, *J*=6.9 Hz, 1H), 3.15–3.21 (m, 2H), 4.71 (bd, *J*=6.0 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 28.3, 29.8, 33.1, 36.2, 40.2, 43.9, 47.9, 60.4, 68.3, 80.5, 172.1; HRMS calcd for $C_{13}H_{24}N_2O_3$ (MH+) 257.1867, found 257.1880.

4.7.5. 7-Isopropyl-1,3,3-trimethyl-octahydro-isoxazolo-[3,4-*c*]pyridine (15a). The title compound was prepared from **11b** (0.020 g, 0.050 mmol), K_2CO_3 (0.097 g, 0.50 mmol) and thiophenol (0.36 mL, 3.5 mmol) according to general procedure and isolated as a light yellow film (0.0087 g, 84%): $[\alpha]_D^{20}=+45$ (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 0.98 (d, *J*=6.6 Hz, 3H), 1.01 (d, *J*=6.6 Hz, 3H), 1.22 (s, 3H), 1.31 (s, 3H), 1.53–1.68 (m, 2H), 1.87–1.94 (m, 1H), 2.20–2.27 (m, 1H), 2.35 (dd, *J*=3.3, 7.8 Hz, 1H), 2.60–2.69 (m, 1H), 2.73 (s, 3H), 2.78–2.85 (m, 1H), 2.95 (d, *J*=3.6, 5.4 Hz, 1H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 19.2, 21.6, 23.8, 24.7, 28.7, 31.0, 40.4, 46.8, 46.9, 59.7, 67.1, 82.3; HRMS calcd for $C_{12}H_{24}N_2O$ (MH+) 213.1969, found 213.1961.

4.7.6. 7-Benzyl-1-methyl-octahydro-isoxazolo[3,4-*c*]pyridine (15b). The title compound was prepared from **11a** (0.010 g, 0.024 mmol), K_2CO_3 (0.033 g, 0.24 mmol) and thiophenol (0.13 mL, 1.2 mmol) according to general procedure and isolated as a light yellow oil (0.043 g, 77%): $[\alpha]_D^{20}=-37.0$ (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.71–1.69 (m, 2H), 1.84–1.96 (m, 1H), 2.36–2.43 (m, 1H), 2.59 (td, *J*=12.0, 3.3 Hz, 1H), 2.63–2.70 (m, 2H), 2.70 (s, 3H), 2.76–2.83 (m, 1H), 3.35 (d, *J*=13.5 Hz, 1H), 3.69 (dd, *J*=7.2, 9.3 Hz, 1H), 4.21 (dd, *J*=7.5, 9.3 Hz, 1H), 7.20–7.33 (m, 5H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 24.2, 29.7, 36.8, 40.7, 41.3, 45.5, 58.1, 68.9, 69.2, 126.4, 128.6, 129.4, 138.9; HRMS calcd for $C_{14}H_{20}N_2O$ (MH+) 233.1655, found 233.1643.

4.7.7. 1-Benzyl-7-*tert*-butoxymethyl-octahydro-isoxazolo-[3,4-*c*]pyridine (15c). The title compound was prepared from **11f** (0.040 g, 0.082 mmol), K_2CO_3 (0.11 g, 0.82 mmol) and thiophenol (0.42 mL, 4.1 mmol) according to general procedure and isolated as a light yellow oil (0.022 g, 88%): $[\alpha]_D^{20}=-14.0$ (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.05 (s, 9H), 1.74 (d, *J*=12.0 Hz, 1H), 1.81–1.93 (m, 1H), 2.02 (s, 1H), 2.60 (ddd, *J*=2.7, 7.8, 10.2 Hz, 1H), 2.72 (td, *J*=12.3, 3.3 Hz, 1H), 2.83–2.92 (m, 3H), 3.03–3.10 (m, 1H), 3.44 (dd, *J*=2.4, 8.4 Hz, 1H), 3.71 (d, *J*=12.3 Hz, 1H), 3.75 (dd, *J*=7.5, 10.2 Hz, 1H), 4.07 (d, *J*=12.3 Hz, 1H), 4.24 (dd, *J*=7.5, 9.3 Hz, 1H), 7.29–7.35 (m, 5H); ^{13}CH NMR ($CDCl_3$, 75 Hz) δ 24.3, 27.5, 36.8, 40.7, 56.2, 61.6, 61.9, 63.5, 69.3, 72.6, 127.5, 128.4, 129.5, 137.3; HRMS calcd for $C_{18}H_{28}N_2O_2$ (MH+) 305.2231, found 305.2222.

4.7.8. (8-Benzylamino-octahydro-indolizin-7-yl)-methanol (16). The title compound was prepared from **9** (0.0070 g, 0.026 mmol), zinc dust (0.025 g, 0.38 mmol) in 60% aqueous acetic acid according to general procedure for N, O bond cleavage and isolated as a colorless film (0.0055 g, 78%): $[\alpha]_D^{20}=-26$ (*c* 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.26–1.54 (m, 2H), 1.57 (dd, *J*=2.4, 13.8 Hz, 1H), 1.67–1.96 (m, 4H), 2.14–2.46 (m, 4H), 2.77–2.85 (m, 2H), 3.06 (td, *J*=8.7, 2.1 Hz, 1H), 3.55 (dd, *J*=4.2, 11.4 Hz, 1H), 3.71 (d, *J*=12.9 Hz, 1H), 4.05 (d, *J*=

12.9 Hz, 1H), 4.25 (t, J=11.1 Hz, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 20.4, 27.3, 27.9, 29.5, 33.9, 47.7, 52.0, 53.9, 61.2, 64.1, 127.2, 128.1, 128.4, 138.9; HRMS calcd for $C_{16}H_{24}N_2O$ (MH+) 261.1969, found 261.1966.

4.7.9. 7-Benzyl-6-benzylamino-azepan-4-ol (17). The title compound was prepared from **14a** (0.0070 g, 0.022 mmol), zinc dust (0.025 g, 0.38 mmol) in 60% aqueous acetic acid according to general procedure for N, O bond cleavage and isolated as a light yellow film (0.0055 g, 79%): $[\alpha]_D^{20}$=−10 (c 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.50 (dt, J=14.7, 3.0 Hz, 1H), 1.91–1.98 (m, 2H), 2.34 (dt, J=14.7, 5.1 Hz, 1H), 2.65–2.77 (m, 3H), 2.99 (bs, 3H), 3.08–3.01 (m, 2H), 3.71 (d, J=13.2 Hz, 1H), 4.00 (d, J=13.2 Hz, 1H), 4.13–4.17 (m, 1H), 7.09 (d, J=6.9 Hz, 2H), 7.19–7.35 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 36.3, 38.8, 40.8, 42.8, 53.1, 58.6, 62.9, 70.4, 126.8, 127.5, 128.8, 128.8, 128.9, 129.4, 138.9, 140.1; HRMS calcd for $C_{20}H_{26}N_2O$ (MH+) 311.2125, found 311.2122.

4.7.10. (3-Benzylamino-2-*tert*-butoxymethyl-piperidin-4-yl)-methanol (18). The title compound was prepared from **15c** (0.0050 g, 0.016 mmol), zinc dust (0.025 g, 0.38 mmol) in 60% aqueous acetic acid according to general procedure for N, O bond cleavage and isolated as a colorless film (0.0043 g, 87%): $[\alpha]_D^{20}$=+13 (c 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ 01.19 (s, 9H), 1.49–1.54 (m, 1H), 1.80–1.89 (m, 2H), 2.80–2.86 (m, 4H), 3.14–3.19 (m, 1H), 3.24 (dd, J=4.8, 8.8 Hz, 1H), 3.52 (t, J=8.4 Hz, 1H), 3.73 (dd, J=2.0, 10.8 Hz, 1H), 3.82 (s, 2H), 3.90 (dd, J=5.6, 10.4 Hz, 1H), 7.27–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 25.7, 27.9, 30.1, 36.0, 40.3, 52.4, 54.4, 59.9, 61.8, 66.9, 77.1, 127.7, 128.8, 129.0, 139.8; HRMS calcd for $C_{18}H_{30}N_2O_2$ (MH+) 307.2387, found 307.2400.

References

1. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
2. Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905–917.
3. Mulzer, J. *Org. Synth. Highlights* **1991**, 77–95.
4. Tsuge, O.; Hatta, T.; Hisano, T. *Chem. Double-Bonded Funct. Groups* **1989**, *2* (1), 345–475.
5. Padwa, A.; Schoffstal, A. M. *Adv. Cycloaddit.* **1990**, *2*, 1–89.
6. Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
7. Aurich, H. G.; Geiger, M.; Gentes, C.; Harms, K.; Koster, H. *Tetrahedron* **1998**, *54*, 3181–3196.
8. Chiacchio, U.; Casuscelli, F.; Corsaro, A.; Librando, V.; Rescifina, A.; Romeo, R.; Romeo, G. *Tetrahedron* **1995**, *51*, 5689–5700.
9. Aurich, H. G.; Frenzen, G.; Gentes, C. *Chem. Ber.* **1993**, *126*, 787–795.
10. Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W. H. *J. Org. Chem.* **1991**, *56*, 2775–2781.
11. Abiko, A.; Liu, J.; Wang, G.; Masamune, S. *Tetrahedron Lett.* **1997**, *38*, 3261–3264.
12. Uddin, M. J.; Kikuchi, M.; Takedatsu, K.; Arai, K.; Fujimoto, T.; Motoyoshiya, J.; Kakehi, A.; Iriye, R.; Shirai, H.; Yamamoto, I. *Synthesis* **2000**, *365*, 374.
13. Chiacchio, U.; Corsaro, A.; Piperno, A.; Rescifina, A.; Romeo, G.; Romeo, R. *Heterocycles* **1999**, *51*, 37–49.
14. Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *53*, 15787–15798.
15. Atherton, E.; Sheppard, R. C. *The Peptides*; Udenfriend, S., Meienhofer, J., Eds.; Academic: New York, 1987; Vol. 9, pp. 1–38.
16. Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359–1362.
17. Walts, A. E.; Roush, W. R. *Tetrahedron* **1985**, *41*, 3463–3478.
18. Takeuchi, H.; Fujimoto, T.; Hoshino, K.; Motoyoshiya, J.; Kakehi, A.; Yamamoto, I. *J. Org. Chem.* **1998**, *63*, 7172–7179.
19. Alcaide, B.; Alonso, J. M.; Aly, M. F.; Saez, E.; Martinez-alcazar, M. P.; Hernandez-Cano, F. *Tetrahedron Lett.* **1999**, *40*, 5391–5394.