Synthesis of New Chiral 4,5,6,7-Tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines from α-Amino Acid Derivatives under Mild Conditions

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Abstract: A practical and efficient regioselective synthesis of several new chiral 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines is described from α-amino acid derivatives following intramolecular 'click' reaction as the key step. The method obviates product purification; to obtain the pure triazole products, only the solvent needs to be evaporated.

Key words: pyrazine, 1,2,3-triazole, α-amino acid, click chemistry, 1,3-dipolar cycloaddition

N-Heterocyclic compounds are broadly distributed in Nature, and constitute an integral component of several amino acids, purines, pyrimidines, tetrahydropyrazines, and other natural products. Such functionalized heterocycles exhibit ability to mimic peptides, as well as their ability to reversibly bind proteins. They, therefore, provide interesting scaffolds for the preparation of diversity-oriented compound libraries for medicinal and pharmaceutical applications.[1–8] Devising simple and efficient solution- and solid-phase methods for the generation of libraries is an attractive proposition.

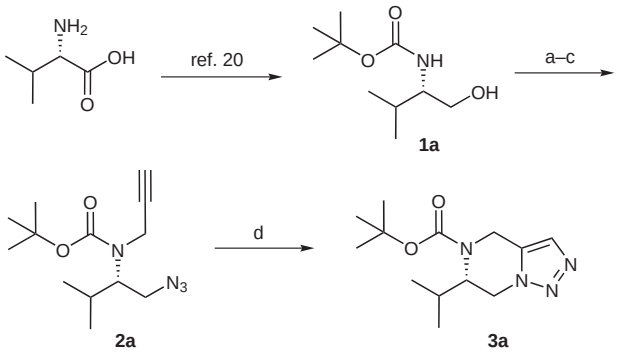
Among the large variety of novel nitrogen-containing molecules, tetrahydropyrazine derivatives are of particular interest because of their diverse biological activities and potential therapeutic applications. This core ring structure, is present in many natural products that elicit a wide array of biological effects including antitumor,[9a,b] cytotoxic,[9a,b] antidepressant,[9c] HIV protease inhibitor (crixivan),[9d,e] and drug under development.[9f] Additionally, piperazinyl-linked ciprofloxacin have been reported as potent antibacterial agents against resistant strains,[9g] dual calcium antagonists,[9h] antimalarial agents,[9i] and potent antipsychotic agents.[9j]

Similarly, the 1,2,3-triazole structural motif found in a large number of compounds possessing anti-HIV activity,[10] selective β_3-adrenergic receptor inhibition,[11] antibacterial activity,[12] potent antihistamine activity,[13] and more.[14,15] These compounds are also commercially employed as anticorrosive agents, agrochemicals, photostabilizer photographic materials, and dyes.[16] The frequent occurrence of triazoles and pyrazines in biologically active compounds, as well as the paucity of the literature for the synthesis of 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines,[17] stimulated our interest.

Several different methods, such as the intramolecular cyclization of bishydrazones or mixed hydrazones, miscellaneous oxidations, 1,3-dipolar cycloaddition between azides and alkynes, have been described for synthesis of 1,2,3-triazoles.[18] The 1,3-dipolar cycloaddition reaction is typically carried out in refluxing toluene, but labile groups may not survive these conditions. Our group has been involved in the synthesis of natural products and crucial synthetic intermediates[19] from amino acids. We wished to develop a synthetic protocol that would enable the synthesis of chiral-fused polycyclic 1,2,3-triazoles in solution/solid phase. Towards this end, we considered performing intramolecular 1,3-dipolar cycloaddition reactions on α-amino acid derived azido-alkynes. In this communication, we report an effective integration of 'click' chemistry onto α-amino acid derivatives for the synthesis of 1,2,3-triazole-fused pyrazines.

We devoted our initial efforts toward the synthesis of compound **2a** (Scheme 1) from L-valine. Boc-protected amino alcohol was prepared by following a standard literature procedure.[20] Activation of the hydroxyl group by formation of a tosylate was next achieved, in good yield, by treatment of **1a** with *p*-toluenesulfonyl chloride in pyridine at ambient temperature.

Azido compound was obtained in 92% yield by S_N2 displacement of the corresponding tosylate with sodium azide in DMF at 60 °C (Scheme 1). The alkyne functionality was then introduced by treatment with NaH and



Scheme 1 *Reagents and conditions*: (a) TsCl, pyridine, CH_2Cl_2, 0 °C to r.t., 8 h, 91%; (b) NaN_3, DMF, 60 °C, 5 h, 92%; (c) propargyl bromide, NaH, DMF, 0 °C to r.t., 4 h, 87%; (d) $CHCl_3$ or CH_2Cl_2, reflux, 4 h, 95%.

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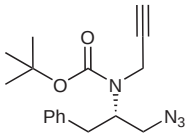
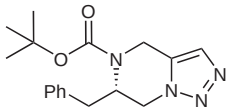
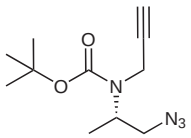
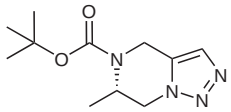
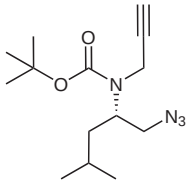
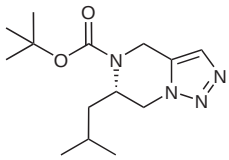
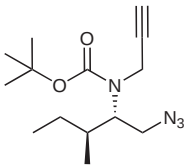
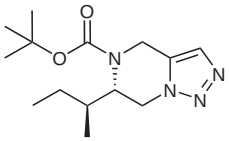
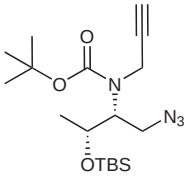
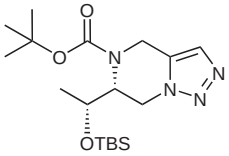
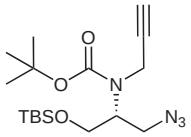
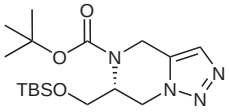
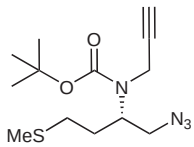
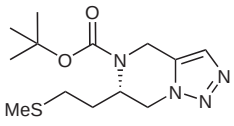
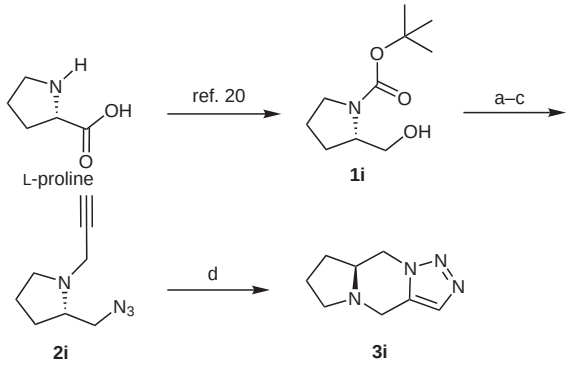
propargyl bromide in DMF. The structure of **2a** was confirmed by NMR. Compound **2a** was heated under reflux in toluene without any catalyst to convert it to 1,2,3-triazole-fused 4,5,6,7-tetrahydropyrazine moiety **3a**. Purification by silica gel column chromatography afforded the desired product **3a** in 52% yield. The low yield was attributable to the harsh conditions that led to the deprotection of the Boc group (≥110 °C).[21] We then chose $CHCl_3$ or CH_2Cl_2 as the solvent for the 1,3-dipolar cycloaddition reaction and were surprised to see complete consumption of azido-alkyne **2a** in four hours under reflux conditions. The pure product was obtained in 95% yield by simple evaporation of the solvent. At room temperature, the reaction took 72 hours for complete conversion and proceeded with the same yield. The structure of bicyclic compound **3a** was established by NMR spectroscopy. The characteristic resonances observed at δ = 128.9, 128.6, and 46.3 ppm were attributed to double bond carbon and methylene carbon adjacent to the double bond and the resonance at δ = 7.53 ppm was attributed to H-8. The structure was also confirmed by a characteristic ion at *m/z* = 267, attributable to $[M + H]^+$ in its mass spectrum (EI).[22]

This result encouraged us to verify the feasibility of using other azido-alkynes obtained from different amino acids under identical reaction conditions. As exemplified in Table 1, the reaction proceeded smoothly to completion, and the corresponding 1,2,3-triazole-fused 4,5,6,7-tetrahydropyrazine products were obtained in three to four hours with excellent yields and high purity.

Table 1 Intramolecular 1,3-Dipolar Cycloaddition Reaction under Catalyst-Free Conditions in Chloroform

	Azido-alkyne **2**	Product **3**	Time (h)	Yield (%)
2b		**3b** 	3	95
2c		**3c** 	3	94
2d		**3d** 	4	96
2e		**3e** 	3	92
2f		**3f** 	4	94
2g		**3g** 	4	95
2h		**3h** 	3	93

We then decided to extend these reaction conditions to a proline derivative in order to obtain tricyclic compound **3i**. The azido-alkyne obtained from L-proline was heated under reflux in $CHCl_3$ or CH_2Cl_2 to afford the corresponding 1,2,3-triazole-4,5,6,7-tetrahydropyrazine in 94% yield as a single product (Scheme 2). The NMR and mass spectrometry were used to establish the structure. In addition, X-ray crystallographic analysis[23–25] unambiguously confirmed the structure of **3i** (Figure 1).



Scheme 2 *Reagents and conditions*: (a) TsCl, pyridine, CH_2Cl_2, 0 °C to r.t., 8 h, 89%; (b) NaN_3, DMF, 60 °C, 5 h, 90%; (c) (i) TFA, CH_2Cl_2, 0 °C to r.t., 2 h; (ii) propargyl bromide, NaH, DMF, 0 °C to r.t., 4 h, 84% (over two steps); (d) $CHCl_3$ or CH_2Cl_2, reflux, 4 h, 94%.

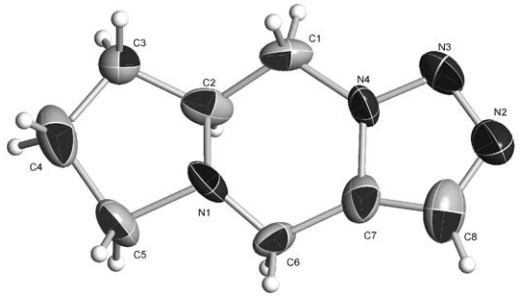


Figure 1 ORTEP diagram of compound **3i**

In conclusion, we have achieved the regioselective synthesis of several new chiral 1,2,3-triazole-fused 4,5,6,7-tetrahydropyrazine bicyclic and tricyclic compounds with excellent yield and high purity under mild reaction conditions. The method obviates product purification; one only needs evaporation of solvent to provide the pure triazole products thereby rendering the process an ideal intramolecular 'click' reaction. Further studies on the synthesis of other triazole-fused heterocylic compounds are under way and will be reported in due course.

Acknowledgment

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References and Notes

(1) Dolle, R. E.; Nelson, K. H. Jr. *J. Comb. Chem.* **1999**, *1*, 235.
(2) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195.
(3) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 1.
(4) Nicolaou, K. C.; Pfefferkorn, J. A. *Solid-Phase Synthesis of Natural Products and Natural Product-Like Libraries*, In *Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials*, Vol. 2; Nicolaou, K. C.; Hanko, R.; Hartwig, W., Eds.; Wiley-VCH: Weinheim, **2002**, 611–642.
(5) Dolle, R. E. *Solid-Phase Synthesis of Heterocyclic Systems (Heterocycles Containing One Heteroatom)*, In *Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials*, Vol. 2; Nicolaou, K. C.; Hanko, R.; Hartwig, W., Eds.; Wiley-VCH: Weinheim, **2002**, 643–684.
(6) Pernestorfer, J. In *Molecular Design and Combinatorial Chemistry. Drugs, Catalysts, Materials*, Vol. 2; Nicolaou, K. C.; Hanko, R.; Hartwig, W., Eds.; Wiley-VCH: Weinheim, **2002**, 725–742.
(7) Dörwald, F. Z. *Organic Synthesis on Solid Phase*, 2nd ed.; Wiley-VCH: Weinheim, **2002**, 1–504.
(8) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.
(9) (a) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (c) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673. (d) Rossen, K.; Weissman, S. A.; Sagar, J.; Reamer, A.; Askin, D. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 6419. (e) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443. (f) Choudhary, P.; Kumar, R.; Verma, K. *Bioorg. Med. Chem.* **2006**, *14*, 1819. (g) Upadhayaya, R. S.; Sinha, N.; Jain, S.; Kishore, N.; Chandra, R.; Arora, S. K. *Bioorg. Med. Chem.* **2004**, *12*, 2225. (h) Kimura, M.; Masuda, T.; Yamada, K.; Kobuta, N.; Kawakatsu, N.; Mitani, M.; Kishi, K.; Inazu, M.; Namiki, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1947. (i) Ryckebusch, A.; Poulain, R.; Maes, L.; Debreu-Fontaine, M.-A.; Mouray, E.; Grellier, P.; Sergheraert, C. *J. Med. Chem.* **2003**, *46*, 542. (j) Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L. Jr. *J. Med. Chem.* **1986**, *29*, 359.
(10) (a) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Carmarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (b) Velaquez, S.; Alvarez, R.; Perez, C.; Gogo, F.; De, C.; Balzarini, J.; Carmarasa, M. *J. Antiviral Chem. Chemother.* **1998**, *9*, 481.
(11) Brockunier, L. L.; Parmee, E. R.; Ok, O. H.; Candelore, M. R.; Cascieri, M. A.; Collwel, L. F.; Deng, L.; Feeney, W. P.; Forest, M.-J.; Wyvratt, M. J.; Fisher, M. H.; Weber, M. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111.
(12) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
(13) (a) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627. (b) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1983**, *26*, 251. (c) Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1986**, *29*, 2262.

(14) (a) Tullis, J. S.; VanRens, J. C.; Natchus, M. G.; Clark, M. P.; De, B.; Hsieh, L. C.; Janusz, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1665. (b) Kim, D.-K.; Kim, J.; Park, H.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401.

(15) (a) Cunha, A. C.; Figueiredo, J. M.; Tributino, J. L. M.; Miranda, A. L. P.; Castro, H. C.; Zingali, R. B.; Fraga, C. A. M.; DeSouza, M. C. B. V.; Ferreira, V. F.; Barreiro, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2051. (b) Dabak, K.; Seuer, ; Akar, A.; Anac, O. *Eur. J. Med. Chem.* **2003**, 215. (c) Tornoe, C. W.; Sanderson, S. J.; Mottram, J. C.; Coombs, G. H.; Meldal, M. *J. Comb. Chem.* **2004**, *6*, 312.

(16) (a) Dehne, H. In *Methoden der organischen Chemie (Houben–Weyl)*, Vol. E8d; Schaumann, E., Ed.; Thieme: Stuttgart, **1994**, 305–405. (b) Dehne, H. In *Methoden der organischen Chemie (Houben–Weyl)*, Vol. E8d; Schaumann, E., Ed.; Thieme: Stuttgart, **1994**, 406–478. (c) Tome, A. C. *Science of Synthesis*, Vol. 13; Storr, R. C.; Gilchrist, T. L., Eds.; Thieme: Stuttgart, **2004**, 415. (d) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*, Vol. 4; Katritzky, A. R.; Rees, C. R.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 1–126. (e) Willis, R. J.; Marlow, I. D. EP 400842, **1990**; *Chem. Abstr.* **1991**, *114*, 164247b.

(17) (a) Fuks, R.; Viehe, H. G. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**, 425–593. (b) Bastide, J.; Henri-Rousseau, O. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; Interscience Publishers: London, **1978**, 447–552.

(18) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, **1984**, 1–176. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (c) Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Betti, L.; Giannaccini, G.; Trincavelli, M. L. *Eur. J. Med. Chem.* **2002**, 565; and references therein.

(19) (a) Mohapatra, D. K.; Datta, A. *Synlett* **1996**, 1129. (b) Mohapatra, D. K.; Datta, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2527. (c) Gurjar, M. K.; Pal, S.; Mohapatra, D. K. *Heterocycles* **1999**, *50*, 109. (d) Mohapatra, D. K. *Synth. Commun.* **1999**, *29*, 4261. (e) Mohapatra, D. K.; Datta, A. *J. Org. Chem.* **1999**, *64*, 6879. (f) Karmakar, S.; Mohapatra, D. K. *Synlett* **2001**, 1326. (g) Mohapatra, D. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1851. (h) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K.; Phalgune, D. *Tetrahedron Lett.* **2002**, *43*, 1897. (i) Mohapatra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 6031. (j) Mohapatra, D. K.; Mondal, D.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 9215.

(20) McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

(21) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

(22) **Analytical and Spectral Data**
Compound **3a**: $[\alpha]_D^{25}$ –47.76 (*c* 1.2, $CHCl_3$). IR ($CHCl_3$): 3023, 1696, 1497, 1223 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.92 (d, 3 H, *J* = 6.6 Hz), 0.99 (d, 3 H, *J* = 6.5 Hz), 1.50 (s, 9 H), 1.53–1.65 (m, 1 H), 4.22 (dd, 1 H, *J* = 14.0, 4.5 Hz), 4.33 (m, 2 H), 4.76 (d, 1 H, *J* = 12.5 Hz), 5.13 (m, 1 H), 7.53 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.7, 19.5, 26.6, 27.8, 36.1, 46.3, 54.3, 55.6, 80.6, 128.6, 128.9, 153.8. ESI-MS: *m/z* = 267 $[M + H]^+$. Anal. Calcd (%) for $C_{13}H_{22}N_4O_2$: C, 58.62; H, 8.33; N, 21.04. Found: C, 58.51; H, 8.47; N, 20.88.
Compound **3c**: $[\alpha]_D^{25}$ –40.21 (*c* 1.1, $CHCl_3$). IR ($CHCl_3$): 2980, 1697, 1395, 1218, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, 3 H, *J* = 7.3 Hz), 1.51 (s, 9 H), 4.32–4.37 (m, 2 H), 4.47 (d, 1 H, *J* = 13.2 Hz), 4.92 (m, 1 H), 5.07 (d, 1 H, *J* = 17.4 Hz), 7.56 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7, 28.1, 36.1, 45.0, 50.1, 81.0, 128.9, 129.1, 153.7. ESI-MS: *m/z* = 239 $[M + H]^+$, 261 $[M + Na]^+$. Anal. Calcd (%) for $C_{11}H_{18}N_4O_2$: C, 55.45; H, 7.61; N, 23.51. Found: C, 55.67; H, 7.69; N, 23.42.
Compound **3d**: $[\alpha]_D^{25}$ –30.74 (*c* 0.95, $CHCl_3$). IR ($CHCl_3$): 3020, 1703, 1508, 1407, 1215 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, 3 H, *J* = 6.5 Hz), 0.87 (d, 3 H, *J* = 6.4 Hz), 1.06–1.12 (m, 1 H), 1.25–1.31 (m, 1 H), 1.40 (s, 9 H), 1.43–1.48 (m, 1 H), 4.12 (d, 1 H, *J* = 17.6 Hz), 4.21 (dd, 1 H, *J* = 12.8, 4.8 Hz), 4.36 (d, 1 H, *J* = 12.8 Hz), 4.72 (m, 1 H), 5.04 (d, 1 H, *J* = 17.6 Hz), 7.41 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 22.6, 24.7, 28.1, 35.9, 38.6, 47.3, 49.1, 80.9, 128.7, 128.9, 153.7. ESI-MS: *m/z* = 281 $[M + H]^+$, 303 $[M + Na]^+$. Anal. Calcd (%) for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.87; H, 8.71; N, 19.76.
Compound **3i**: $[\alpha]_D^{25}$ +98.54 (*c* 1.1, $CHCl_3$). IR ($CHCl_3$): 3020, 1508, 1409, 1215 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.61–1.69 (m, 1 H), 1.92–2.05 (m, 2 H), 2.10–2.17 (m, 1 H), 2.36 (q, 1 H, *J* = 8.8 Hz), 2.68 (m, 1 H), 3.24–3.27 (ddd, 1 H, *J* = 8.81, 7.5, 2.8 Hz), 3.38 (d, 1 H, *J* = 14.6 Hz), 3.95 (dd, 1 H, *J* = 12.5, 10.6 Hz), 4.29 (d, 1 H, *J* = 14.6 Hz), 4.68 (dd, 1 H, *J* = 12.5, 3.9 Hz), 7.42 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 27.5, 46.8, 51.2, 53.3, 59.6, 128.4, 131.8. ESI-MS: *m/z* = 165 $[M + H]^+$, 187 $[M + Na]^+$. Anal. Calcd (%) for $C_8H_{12}N_4$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.37; H, 7.11; N, 33.98.

(23) X-ray intensity data was collected on Bruker SMART APEX CCD diffractometer with graphite-monochromated (MoKα = 0.71073 Å) radiation at r.t. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (ShelxTL)[25] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

(24) Sheldrick, G. M. *SHELX-97 Program for Crystal Structure Solution and Refinement*; University of Göttingen: Germany, **1997**.

(25) Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 633496 for **3i**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(1223)336033; or e-mail: deposit@ccdc.cam.ac.uk].