Tetrahedron Letters 53 (2012) 627–631

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselective synthesis of 2-substituted 3-diarylmethylenylpiperidines

Meng-Yang Chang *, Chung-Han Lin, Tein-Wei Lee

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan

ARTICLE INFO

Article history:
Received 20 October 2011
Revised 16 November 2011
Accepted 22 November 2011
Available online 26 November 2011

Keywords:
Pipecolate
Homophenylalanine
Three-step protocol
α-Bromomethoxylation
Dehydrobromination
Cross-coupling

ABSTRACT

A simple three-step synthetic routes toward 2-substituted 3-diarylmethylenylpiperidines **7** (Y = CN) and **8** (Y = allyl) starting with 3-diarylmethylenylpiperidines **9** is described. The process was carried out by the bromomethoxylation of skeleton **9** with NBS in MeOH at reflux for 2 h, regioselective α-dehydrobromination with DBU in THF at reflux for 10 h, and $BF_3{\cdot}OEt_2$-catalyzed cross-coupling of the corresponding enamine with trimethylsilyl-based nucleophiles (TMS-Y) in DCM at rt for 2 h. α-Amino ester **18** and β-amino acid **19** are also synthesized via the simple three-step synthetic protocol.

© 2011 Elsevier Ltd. All rights reserved.

Introduction

The novel design and synthesis of conformationally multifunctionalized α-amino acids and their related derivatives (e.g., α-amino nitriles) have attracted considerable attention from both the synthetic and medicinal chemistry communities.[1,2] The high potential of the biological activities of homophenylalanine analogues is dependent on the three-dimensional orientation of the amino acid side chains.[3] As shown in Scheme 1, a number of cyclic-constrained homophenylalanine derivatives **2**–**5** have been reported.[4,5] Among these useful skeletons, compound **6** represents a C3-benzhydryl group on the skeleton of pipecolic acid. In this study, the related syntheses were carried out by a simple key three-step protocol.

Recent use of a piperidine skeleton with a C3-benzhydryl group in search of a novel neurokinin-1 receptor antagonist has focused the potential utility of the 3-diarylmethylenyl group in the design of constrained amino acid analogues.[6] Due to the potential pharmaceutical interest concerning the specific substitution patterns of pipecolate derivatives, a simple three-step protocol for the preparation of 2-pipecolinonitrile **7** and 2-allylpiperidine **8** from piperidine **9** with 3-diarylmethylenyl group was developed.

homophenylanaline (**1**)

1,2,3,4-Tetrahydroquinoline-2-carboxylic acid (Tqc, **2**)[5a]

2-Aminotetralin-2-carboxylic acid (Atc, **3**)[5b]

1-Amino-3-phenylcyclobutane-carboxylic acid (Apcc, **4**)[5c]

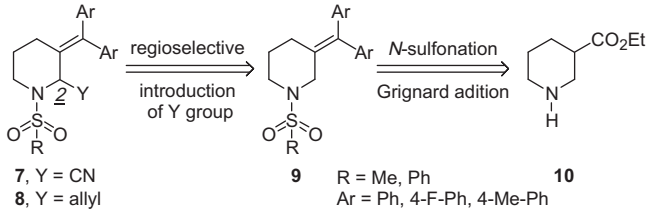
4-Phenylpipecolic acid (Ppa, **5**)[5d]

3-Benzhydrylpiperidine-2-carboxylic acid (Bpc, **6**)

Scheme 1. Structures of selected ring-utilizing conformationally constrained homophenylalanine analogues.

Results and discussion

The synthesis strategy as adopted is shown in Scheme 2. Basically, the Y group was regioselectively introduced to the C-2 position of piperidine via (i) α-bromomethoxylation of 1-sulfonyl-



7, Y = CN
8, Y = allyl

9

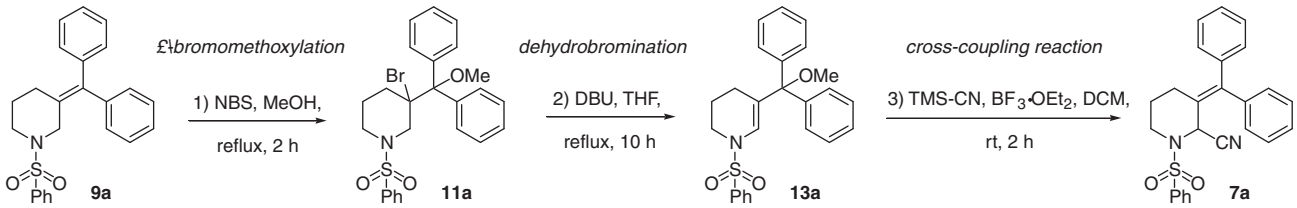
R = Me, Ph
Ar = Ph, 4-F-Ph, 4-Me-Ph

10

Scheme 2. Retrosynthetic route toward 3-diarylmethylenyl 2-pipecolinonitrile **7** and 2-allylpiperidine **8**.

E-mail addresses: mychang@kmu.edu.tw, mychang624@yahoo.com.tw (M.-Y. Chang).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.11.105

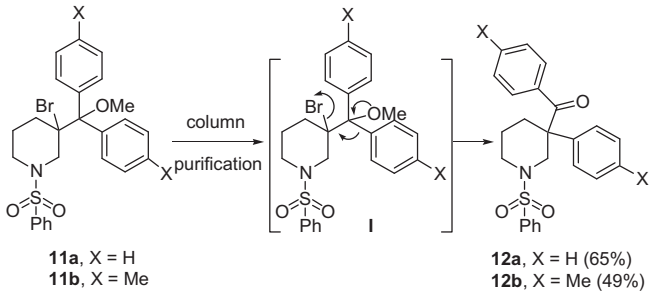


Scheme 3. Synthesis of compound **7a** from model substrate **9a**.

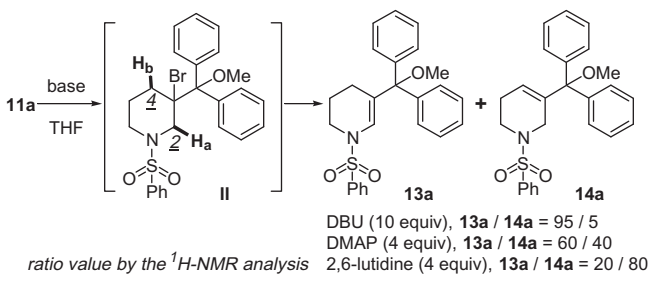
3-diarylmethylenylpiperidines **9** with NBS in MeOH, (ii) dehydrobromination with DBU in THF, and (iii) the $BF_3{\cdot}OEt_2$-catalyzed intermolecular cross-coupling of the resulting cyclic enamine with the trimethylsilyl-based nucleophiles (TMS-Y; Y = CN, allyl) in DCM. This three-step protocol provided a convenient route to the synthesis of skeleton **7** or **8** in moderate yields. The starting material **9** was easily synthesized from commercially available piperidine-3-carboxylic acid ethyl ester **10** by N-sulfonation (R = Me, Ph), Grignard addition (Ar = Ph, 4-F-Ph, 4-Me-Ph), and $BF_3{\cdot}OEt_2$-mediated dehydration.

Compounds **9a**–**e** were prepared in 56–72% yields via the three-step protocol according to the known synthesis route.[7] With skeleton **9** in hand, compound **9a** was first chosen as the model substrate for the following α-bromomethoxylation reaction (see Scheme 3). Treatment of olefin **9a** with NBS in MeOH produced a sole 1,2-methoxybromide **11a** at rt for 2 h. Compound **11a** was noticeably unstable (Equation 1), but purification on silica gel afforded α-arylketone **12a** as the major product with a 65% yield. This result showed that the phenyl group should displace the tertiary bromo group during an intramolecular rearrangement of pinacol to pinacolone via the possible intermediate **I**.[8] The rearranged product **12b** was observed (49%) during the silica-gel mediated purification procedure.

Without purification, crude compound **11a** was further studied for the regioselective dehydrobromination reaction with different bases. Under a number of conditions (e.g., prolonged time, different temperature and equivalent), we found that an excess amount of DBU (10 equiv) was the optimal base for the formation of the major enamine **13a** among some commercial tertiary amines (DBU, DMAP, 2,6-lutidine). As shown in Equation 2, when compound **11a** was reacted with DBU at reflux for 10 h, a mixture of compounds **13a** and **14a** with the approximate ratio value of 95/5 was observed. The ratio value was determined by the ^{1}H NMR analysis of vinylic proton (**13a**, δ = 7.06; **14a**, δ = 5.97). For the reaction of compound **11a** with DMAP, the ratio value of 60/40 (for **13a**/**14a**) was observed. In changing the base to 2,6-lutidine, the ratio value of **13a**/**14a** was converted into 20/80. From this phenomenon, it was thought that the ratio values of **13a**/**14a** were affected by the appropriate bases with stronger basicity and greater bulk via the regioselective hydrogen abstraction on the C2-Ha and C4-



Equation 1. Silica gel-mediated rearrangement of skeleton **11**.



Equation 2. Dehydrobromination of compound **11a**.

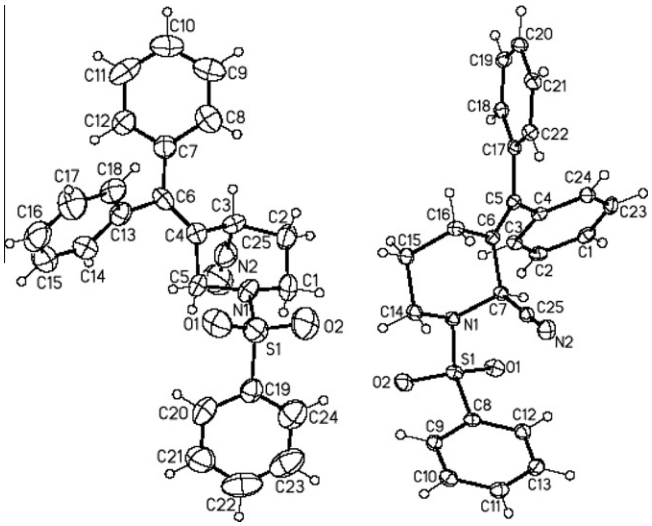
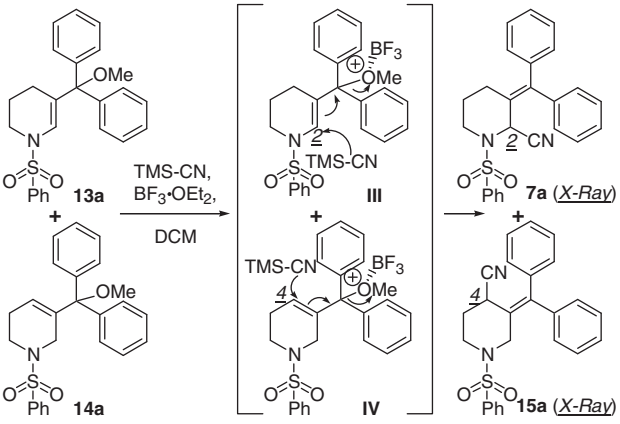


Figure 1. X-ray structures of compounds **7a** and **15a**.

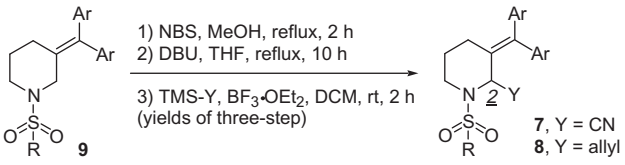


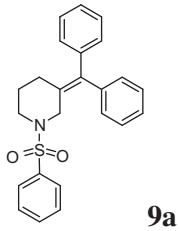
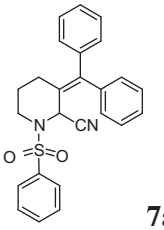
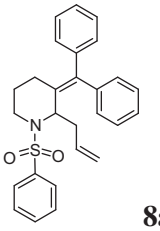
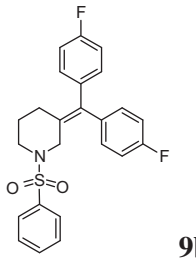
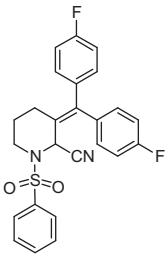
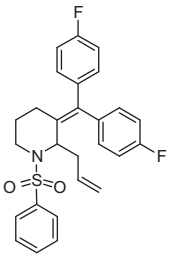
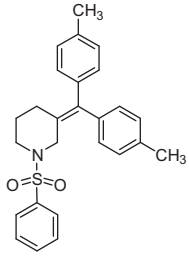
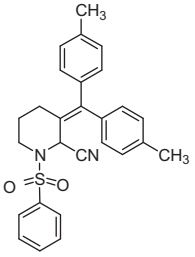
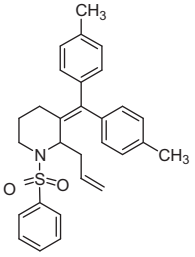
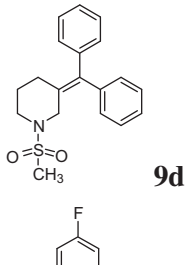
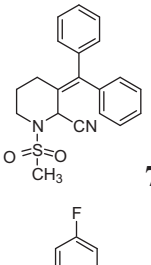
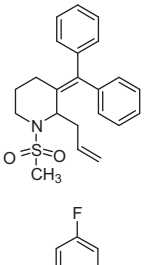
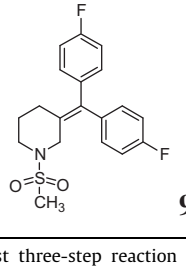
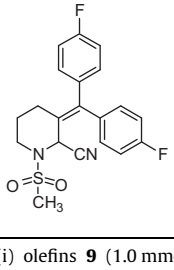
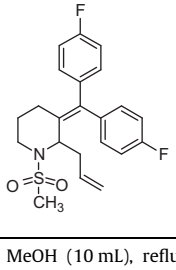
Equation 3. $BF_3{\cdot}OEt_2$-mediated cross-coupling of mixture **13a** and **14a** with TMS-CN.

Hb positions of the intermediate **II**. Attempts to separate the mixture of compounds **13a** and **14a** failed as compound **13a** was unstable under the column purification.

In the following step, two amino nitriles **7a** and **15a** were isolated from the $BF_3{\cdot}OEt_2$-mediated intramolecular cross-coupling of mixtures **13a** and **14a** (ratio value ~95/5) in a co-solvent of trimethylsilyl cyanide (TMS-CN, 3 mL) and dichloromethane (10 mL) at rt for 2 h. Between the C-2 of intermediate **III** and the C-4 of intermediate **IV**, cyanide ions formed a new bond to push off the methoxy group via the regioselective nucleophilic substitution reaction.[9] The total synthesis procedure was monitored through the TLC method until the reaction was complete. This study showed a new synthetic approach for constructing α-amino nitrile **7** and γ-amino nitrile **15** from compound **9** by the overall three-step protocol. The structures of compounds **7a** and **15a** were determined using single-crystal X-ray analysis (Fig. 1).[10] From the sim-

Table 1
Synthesis of skeletons **7** and **8**



Entry	Skeleton **9**	Skeleton **7**/Yield[a] (%)	Skeleton **8**/Yield[a,b] (%)
1	 **9a**	 **7a** / 71	 **8a** / 65
2	 **9b**	 **7b** / 63	 **8b** / 74
3	 **9c**	 **7c** / 55	 **8c** / 55
4	 **9d**	 **7d** / 62	 **8d** / 55
5	 **9e**	 **7e** / 73	 **8e** / 59

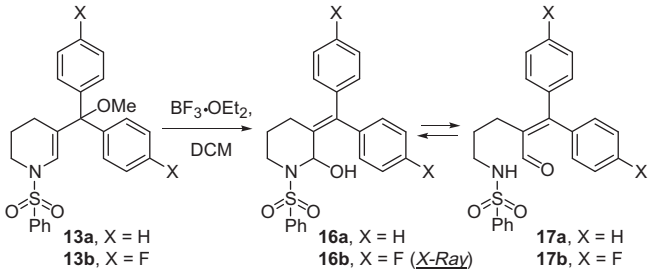
[a] For the best three-step reaction conditions: (i) olefins **9** (1.0 mmol), NBS (1.05 equiv), MeOH (10 mL), reflux, 2 h; (ii) DBU (10.0 equiv), THF (10 mL), reflux, 10 h, and (iii) $BF_3{\cdot}OEt_2$ (1 mL), TMS-Y (3 mL), DCM (10 mL), rt, 2 h.
[b] The isolated products were >95% pure as determined by ^1H NMR analysis.

ple three-step transformation (see Scheme 3), we found that the base was the key factor for the formation of compound **7a**. The overall synthetic procedure had to be monitored by TLC until the reaction was completed that day and compound **7a** was isolated in a 71% yield by only column chromatography purification on silica gel (Equation 3).

Given the above results, we envisioned that this three-step route could regioselectively introduce a CN group to the C-2 position of the piperidine skeleton by using DBU as the base. According to the protocol, treatment of compounds **9b–e** produced 2-amino nitriles **7b–e** in 55–73% yields. After changing the trimethylsilyl-based nucleophile from the cyano to the allyl group, compounds **8a–e** were also isolated in 55–74% yields (Table 1).[11]

However, when the $BF_3{\cdot}OEt_2$-promoted cross-coupling of model enamine **13a** was treated without the addition of the trimethylsilyl-based nucleophile, the equilibrium between 2-hydroxypiperidine **16a** and δ-aminoaldehyde **17a** was observed by ^1H NMR analysis (Equation 4). There was also a similar result in the reaction of enamine **13b** by $BF_3{\cdot}OEt_2$. Fortunately, the structure of compound **16b** was determined using single-crystal X-ray analysis (Fig. 2).[10]

Furthermore, the $BF_3{\cdot}OEt_2$-promoted reaction of compound **13a** with trimethylsilane converted it into the starting material **9a**.



Equation 4. $BF_3{\cdot}OEt_2$-mediated reaction of crude compounds **13a** and **13b** without addition of trimethylsilyl-based nucleophile.

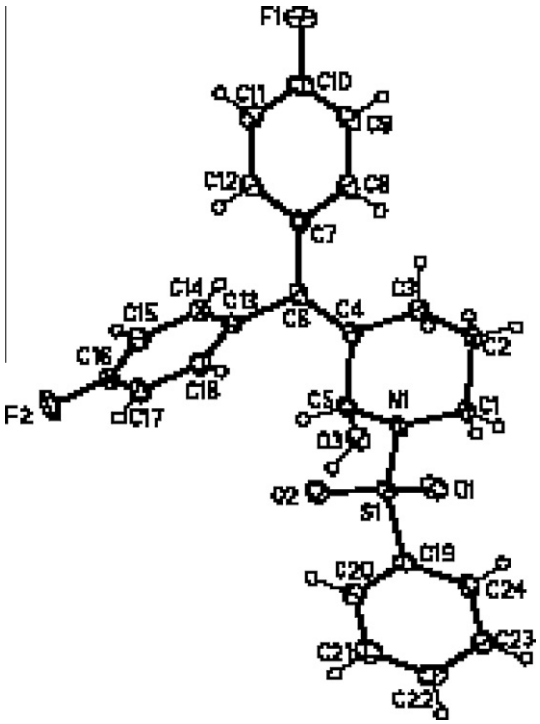
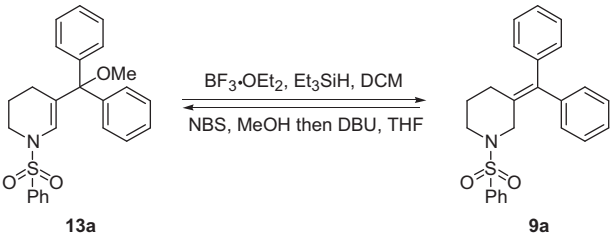
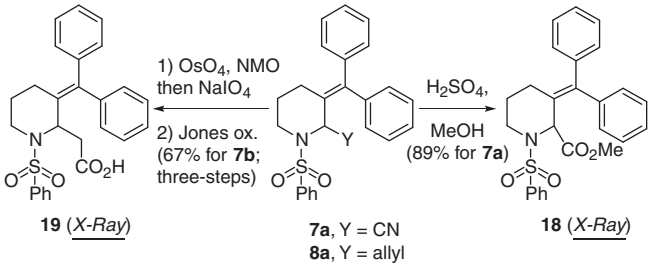


Figure 2. X-ray structure of compound **16b**.

Notably, this strategy was an interesting reversible process between compounds **13a** and **9a** (Equation 5).[12] On the basis of the three-step protocol, α-amino ester **18** and β-amino acid **19** were chosen as the next targets. Furthermore, the acid-mediated hydrolysis of 2-pipecolinonitrile **7** in methanol converted it into α-amino ester **18** in an 89% yield, as shown in Scheme 4. By the three-step protocol, compound **18** was prepared as a cyclic-constrained homophenylalanine derivative **6**, while 2-allylpiperidine **8a** was transformed to β-amino acid **19** by osymlation and subsequently followed by bond cleavage with sodium periodate and Jones oxidation in a 67% yield. The two structures, α-amino ester **18** and β-amino acid **19**, were determined using single-crystal X-ray analysis (Figs. 3 and 4).[10]



Equation 5. Interconversion of compounds **9a** and **13a**.



Scheme 4. Synthesis of α-amino ester **18** and β-amino acid **19**.

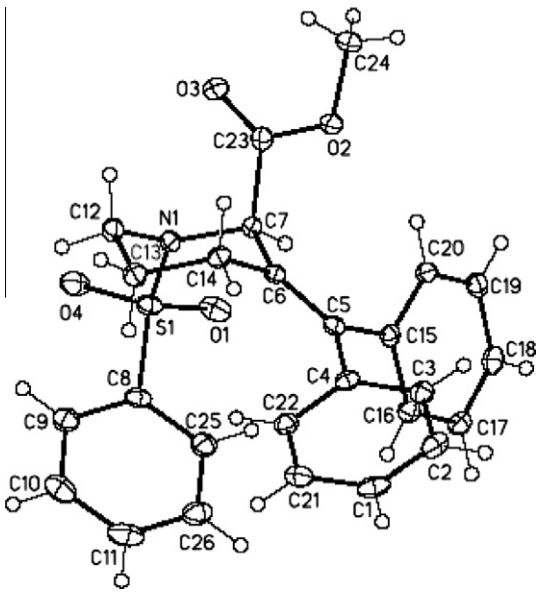


Figure 3. X-ray structure of α-amino ester **18**.

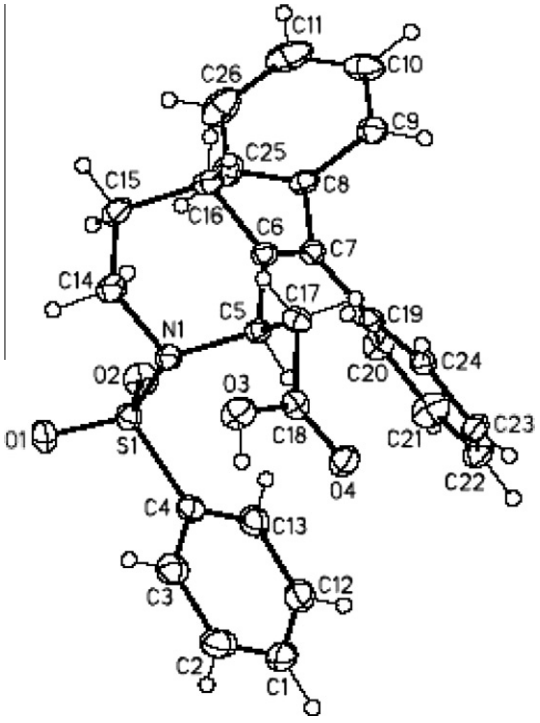


Figure 4. X-ray structure of β-amino acid **19**.

Conclusion

A synthetic methodology for producing a series of 2-substituted 3-diarylmethylenylpiperidines **7** (Y = CN) and **8** (Y = allyl) has been successfully presented using NBS-mediated α-bromomethoxylation reaction, DBU-promoted regioselective dehydrobromination reaction, and $BF_3{\cdot}OEt_2$-promoted cross-coupling reaction involving trimethylsilyl-based nucleophiles. Under the three-step protocol, α-amino ester **18** and β-amino acid **19** were also synthesized. Several structures of the target products were confirmed by X-ray crystal analysis.

Acknowledgment

The authors would like to thank the National Science Council of the Republic of China for its financial support (NSC 99-2113-M-037-006-MY3).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.105.

References and notes

1. For reviews on the synthesis of piperidine, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701; (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953; (c) Sorbera, L. A.; Serradell, N.; Bolos, J.; Rosa, E.; Bozzo, J. *Drugs Future* **2007**, *32*, 674; (d) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781; (e) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. and references cited herein.
2. (a) Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101; (b) Watanabe, L. A.; Haranaka, S.; Jose, B.; Yoshida, M.; Kato, T.; Moriguchi, M.; Soda, S.; Nishino, N. *Tetrahedron: Asymmetry* **2005**, *16*, 903. and references cited herein; (c) Carballo, R. M.; Valdomir, G.; Purino, M.; Martin, V. S.; Padron, J. I. *Eur. J. Org. Chem.* **2010**, 2304; (d) Leon, L. G.; Carballo, R. M.; Vega-Hernandez, M. C.; Martín, V. S.; Padron, J. I.; Padron, J. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2681.
3. For reviews, see: (a) Kallstrom, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601; (b) Wijdeven, M. A.; Willemsen, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2010**, 2831.
4. (a) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585; (b) Andrews, M. J. I.; Tabor, A. B. *Tetrahedron* **1999**, *55*, 11711.
5. (a) Guo, T.; Gu, H.; Hobbs, D. W.; Rokosz, L. L.; Stauffer, T. M.; Jacob, B.; Clader, J. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3010; (b) Schiller, P. W.; Weltrowska, G.; Nguyen, T. M. D.; Lemieux, C.; Chung, N. N.; Marsden, B. J.; Wilkes, B. C. *J. Med. Chem.* **1991**, *34*, 3125; (c) Wrobleski, M. L.; Reichard, G. A.; Paliwal, S.; Shah, S.; Tsui, H.-C.; Duffy, R. A.; Lachowicz, J. E.; Morgan, C. A.; Varty, G. B.; Shih, N.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3859; (d) Hijikata-Okunomiya, A.; Tamao, Y.; Kikumoto, R.; Okamoto, S. *J. Biol. Chem.* **2000**, *275*, 18995.
6. (a) Shirai, J.; Nakamura, M.; Tarui, N.; Hashimoto, T.; Ikeura, Y. *Bioorg. Med. Chem.* **2011**, *19*, 5175; (b) Kallstrom, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601.
7. (a) Chang, M.-Y.; Kung, Y.-H.; Ma, C.-C. *Tetrahedron Lett.* **2007**, *48*, 199; (b) Chang, M.-Y.; Kung, Y.-H.; Wu, T.-C. *Tetrahedron* **2007**, *63*, 3098; (c) Kieser, K. J.; Kim, D. W.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2010**, *53*, 3320.
8. (a) Chang, M.-Y.; Lee, N.-C.; Lee, M.-F.; Huang, Y.-P.; Lin, C.-H. *Tetrahedron Lett.* **2010**, *51*, 5900; (b) Chang, M.-Y.; Lee, M.-F.; Lee, N.-C.; Huang, Y.-P.; Lin, C.-H. *Tetrahedron Lett.* **2011**, *52*, 588.
9. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.
10. CCDC 846030 (**7a**), 846031 (**15a**), 844450 (**16b**), 846033 (**18**), and 846032 (**19**), and contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
11. A representative three-step synthetic transformation of skeleton **7** or **8** from olefin **9** is as follows: NBS (188 mg, 1.05 mmol) was added to a solution of olefin **9** (1.0 mmol) in methanol (10 mL) at rt. The reaction mixture was stirred at reflux for 2 h. Saturated $NaHCO_{3(aq)}$ solution (2 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, DBU (1.5 g, 10.0 mmol) was added to a solution of the resulting product in THF (10 mL) at rt. The reaction mixture was stirred at reflux for 10 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, a solution of $BF_3{\cdot}OEt_2$ (1 mL) in DCM (5 mL) was added to a stirred solution of the resulting enamine product in trimethylsilyl cyanide (3 mL) or allyltrimethylsilane (3 mL) in DCM (10 mL) at rt. The reaction mixture was stirred at rt for 15 min. Saturated $NaHCO_{3(aq)}$ solution (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 6:1–3:1) afforded skeleton **7** or **8**. Representative data for compound **7a**: HRMS (ESI, M^++1) calcd for $C_{25}H_{23}N_2O_2S$ 415.1480, found 415.1483; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76–7.73 (m, 2H), 7.65–7.61 (m, 1H), 7.56–7.51 (m, 2H), 7.43–7.25 (m, 6H), 7.19–7.16 (m, 2H), 7.07–7.05 (m, 2H), 5.70 (s, 1H), 3.99 (d, J = 12.0 Hz, 1H), 2.97 (dt, J = 3.2, 12.4 Hz, 1H), 2.68 (dq, J = 2.8, 4, 14.8 Hz, 1H), 2.28 (dt, J = 4.4, 14.8 Hz, 1H), 1.86–1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.99, 139.99, 139.40, 136.80, 133.55, 129.23 (2×), 129.10 (2×), 129.04 (2×), 128.85 (2×), 128.33 (2×), 128.29, 127.72 (2×), 126.33, 114.87, 49.07, 43.38, 29.68, 26.27, 25.77. Single-crystal X-ray diagram: crystal of compound **7a** was grown by slow diffusion of EtOAc into a solution of compound **7a** in DCM to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group P-1, a = 8.0292(3) Å, b = 11.2051(4) Å, c = 11.9519(4) Å, V = 1037.99(6) Å^3, Z = 2, d_{calcd} = 1.326 g/cm^3, F(000) = 436, 2θ range 1.75–26.52°, R indices (all data) R_1 = 0.0387, wR_2 = 0.0828. Representative data for compound **8a**: HRMS (ESI, M^++1) calcd for $C_{27}H_{28}NO_2S$ 430.1841, found 430.1841; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71–7.68 (m, 2H), 7.58–7.53 (m, 1H), 7.49–7.45 (m, 2H), 7.34–7.17 (m, 6H), 7.09–7.06 (m, 2H), 6.91–6.88 (m, 2H), 5.64–5.53 (m, 1H), 5.08–5.02 (m, 2H), 4.84 (t, J = 8.0 Hz, 1H), 3.91 (dd, J = 4.8, 14.0 Hz, 1H), 3.24 (dt, J = 3.2, 14.0 Hz, 1H), 2.62–2.55 (m, 1H), 2.49–2.40 (m, 2H), 2.16 (dt, J = 4.8, 14.0 Hz, 1H), 1.64–1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.87, 141.34, 140.87, 138.39, 134.14, 132.71, 132.12, 129.46 (2×), 129.14 (2×), 128.84 (2×), 128.17 (2×), 128.06 (2×), 127.26 (2×), 127.10, 126.72, 116.94, 55.74, 40.62, 35.73, 26.23, 25.47.
12. (a) Viti, G.; Perrotta, E.; Giannotti, D.; Nannicini, R. *Tetrahedron* **1997**, *53*, 8519; (b) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758.