Bioorganic & Medicinal Chemistry Letters 20 (2010) 5035–5038

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis of pyrrolomorphinan derivatives as κ opioid agonists

Hideaki Fujii [a], Yoshihiro Ida [a], Shinichi Hanamura [a], Yumiko Osa [a], Toru Nemoto [a], Mayumi Nakajima [b], Ko Hasebe [b], Kaoru Nakao [b], Hidenori Mochizuki [b], Hiroshi Nagase [a,*]

[a] School of Pharmacy, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan
[b] Pharmaceutical Research Laboratories, Toray Industries, Inc., 6-10-1, Tebiro, Kamakura 248-8555, Japan

ARTICLE INFO

Article history:
Received 19 June 2010
Revised 8 July 2010
Accepted 9 July 2010
Available online 13 July 2010

Keywords:
Opioid
Pyrrolomorphinan
Accessory site
Address site

ABSTRACT

We synthesized pyrrolomorphinan derivatives **6**, **7**, and **9** to examine whether the pyrrole ring would be an accessory site in the κ opioid receptor selective antagonist, nor-binaltorphimine. Derivative **6** had an α,β-unsaturated ketone substituent that strongly bound to the κ receptor. The compound with the highest κ receptor selectivity, **6e**, produced a dose-dependent antinociceptive effect in the mouse acetic acid writhing test. However, derivatives **7** and **9**, which did not have α,β-unsaturated ketone substituents, showed less κ receptor selectivity than compound **6**. Based on structure–activity relationships, we proposed that these compounds adopted active structures for κ selective agonist activity. The pyrrole ring would not function as an accessory site, but the ability of the side chain on the pyrrole ring to localize above the C-ring appeared to confer κ selective agonist activity. These results will promote the design of novel κ agonists.

Morphine is used for the management of severe pain, like that experienced in cancer or postoperatively. However, morphine also has adverse effects, including dependence, constipation, and respiratory depression. Intense efforts have been focused on obtaining an ideal analgesic without the morphine-like side-effects; however, this goal remains elusive. In 1984, a landmark investigation[1] with the irreversible μ antagonist, β-funaltrexamine, showed that morphine-like side-effects would be derived from the μ receptor, not from the δ and κ receptors. This has driven medicinal chemists to focus on the properties of δ or κ agonists. Recently, a novel, κ selective agonist, TRK-820 (nalfurafine hydrochloride),[2,3] which produced neither preferential nor aversive effects, was developed and launched in Japan as an antipruritic for hemodialysis patients. Nalfurafine hydrochloride was rationally designed from the κ selective antagonist, nor-binaltorphimine (nor-BNI),[4,5] based on the 'message-address' concept[6–8] and the 'accessory site' hypothesis.[9,10] In the drug design, a potential accessory site was removed, because it could have interfered with the induced fit necessary for eliciting agonist activity; conversely, a potential address site was retained, because it was important for opioid receptor type selectivity (Fig. 1). This led to the successful synthesis of nalfurafine. However, it remains unclear whether the pyrrole moiety could be an accessory site in nor-BNI. Clarification of the accessory site would provide useful information in the design of novel κ selective agonists or antagonists. Therefore, in this study, we synthesized the pyrrolomorphinan derivative, **1**[11–14] to examine whether the pyrrole ring could be an accessory site (Fig. 2). Herein, we report synthesis of the pyrrolomorphinan derivative **1** and its pharmacology.

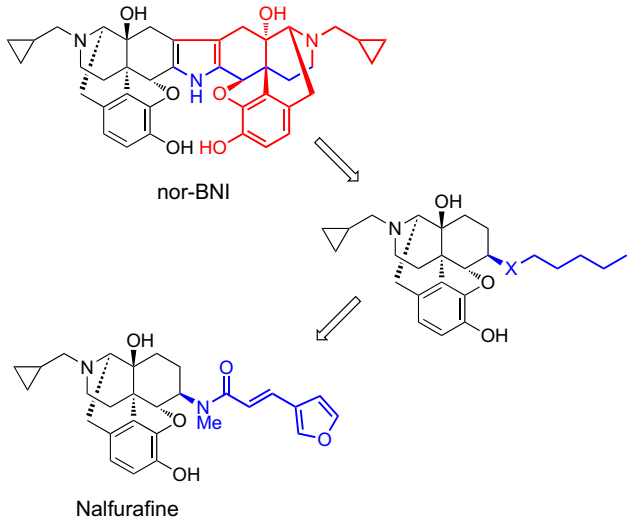


Figure 1. Drug design of κ selective agonist, nalfurafine from the κ selective antagonist, nor-BNI. A potential accessory site and a potential address site are indicated in red and blue, respectively.

Pyrrolomorphinan derivatives were synthesized from the naltrexone methyl ether (**2**)[15–17] (Scheme 1), to make variations of **6**,

Abbreviations: nor-BNI, nor-binaltorphimine; CSA, camphorsulfonic acid; KHMDS, potassium hexamethyldisilazide; SAR, structure–activity relationship.

* Corresponding author. Tel.: +81 3 5791 6372; fax: +81 3 3442 5707.
E-mail address: nagaseh@pharm.kitasato-u.ac.jp (H. Nagase).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.07.035

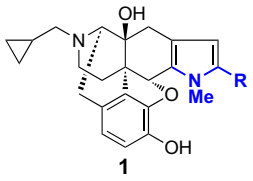
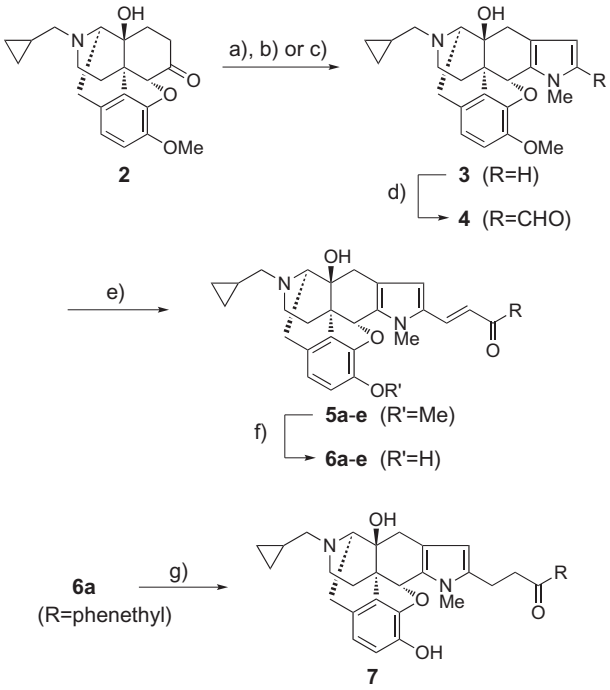
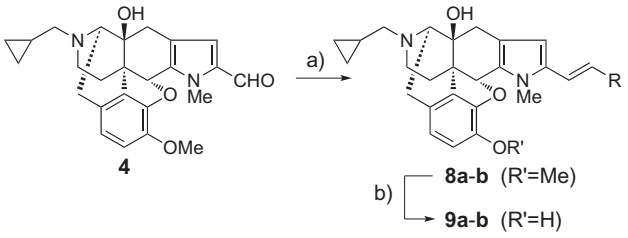


Figure 2. Synthesized pyrrolomorphinan derivative **1**. A potential address site is indicated in blue.



Scheme 1. Reagents and conditions: (a) 2,2-diethoxyethanamine, CSA, DMF, benzene, reflux, 27%; (b) NaH, MeI, DMF, rt, 81%; (c) *N*-methyl-2,2-dimethoxyethanamine, CSA, DMF, benzene, reflux, 65%; (d) $POCl_3$, DMF, 0 °C, 85%; (e) $RC(=O)CH_2P(=O)(OMe)_2$, NaH, THF, 50 °C, 28–95%; (f) BBr_3, CH_2Cl_2, rt, 31–85%; (g) H_2, 10% Pd/C, MeOH, rt, 83%.



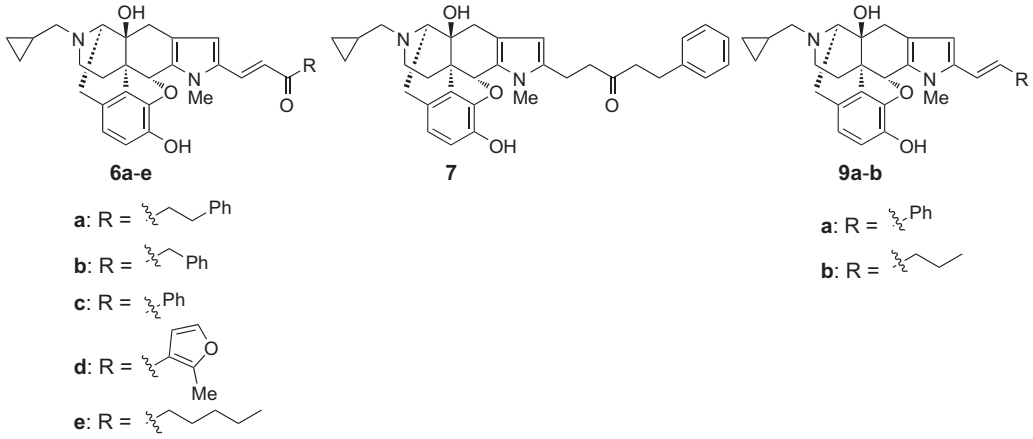
Scheme 2. Reagents and conditions: (a) RCH_2SO_2(1-phenyl-1*H*-tetrazol-5-yl), KHMDS, THF, −78 °C to rt, 86–91%; (b) BBr_3, CH_2Cl_2, rt, 61%.

which has an α,β-unsaturated ketone substituent. Treatment of **2** with 2,2-diethoxyethanamine in the presence of camphorsulfonic acid (CSA)[13] and subsequent N-methylation gave pyrrolomorphinan **3**, but the yield of this two-step procedure was low (22%). The use of *N*-methyl-2,2-dimethoxyethanamine instead of 2,2-diethoxyethanamine gave compound **3** directly from **2** and improved the yield (65%). A Vilsmeier–Haack formylation[18] of compound **3** gave the 5′-formyl derivative **4** in 85% yield, along with a 4′-formyl derivative (14%). A Horner–Wadsworth–Emmons reaction was performed on compound **4** with acylmethylphosphonate[19] to afford compounds **5a**–**e**; these were then converted to compounds **6a**–**e** by O-demethylation with BBr_3. A catalytic hydrogenation of the enone **6a** afforded compound **7**, with a saturated ketone side chain (Scheme 1). To synthesize other pyrrolomorphinan derivatives, we performed a Kocienski-modified Julia olefination[20,21] of the formyl derivative **4** and a subsequent O-demethylation. This afforded derivatives **9a**, **b** with an olefin moiety (Scheme 2).

The binding affinities of the synthesized compounds **6**, **7**, and **9** were evaluated with a competitive binding assay[22] (Table 1). All the α,β-unsaturated ketone derivatives **6a**–**e** strongly bound to the κ receptor. Among these derivatives, compound **6c** showed the strongest binding affinity, with a twofold weaker affinity than that of nalfurafine and a twofold stronger affinity than that of norBNI. Derivative **6e**, which was the most selective for the κ receptor, was evaluated for agonist activity in the mouse acetic acid writhing assay. We found that, when compound **6e** was administered subcutaneously, it induced a dose-dependent antinociceptive effect (Fig. 3) with an ED_{50} value of 5.87 mg/kg. This indicated that **6e** was a κ receptor agonist. This result suggested that the pyrrole ring in the pyrrolomorphinan derivatives could not be an accessory site. All the α,β-unsaturated ketone derivatives **6a**–**e** had a longer address site than nalfurafine; in contrast, the olefin derivative **9a** possessed an address site the same length as that in nalfurafine. Moreover, a heteroaromatic ring, like pyrrole, had been previously applied as a bioisostere with amide functionality.[23] Therefore, we expected that the olefin derivatives **9a**, **b** would bind to the κ receptor with higher selectivity and affinity than the α,β-unsaturated ketone derivatives **6a**–**e**. However, contrary to our expectation, compound **9a** was not selective for the κ receptor, and its binding affinity was eightfold weaker than that of compound **6c**.

The only structural difference between compounds **6** and **9** was the presence or absence of the ketone moiety. The selectivity for the κ receptor over the μ receptor of the saturated ketone derivative **7** was also lower than that of the corresponding α,β-unsaturated ketone derivative **6a**. These results could not be explained by the message-address concept, where the length of the address site plays an important role in receptor type selectivity. We recently reported a putative active conformation of nalfurafine;[24–26] we proposed that nalfurafine would adopt this conformation to bind to the κ receptor (Fig. 4). In the proposed active conformation, the C-ring in nalfurafine was in the boat conformation and the amide side chain (κ address) was localized above the C-ring. This hypothesis was supported both by the structure–activity relationship (SAR) in nalfurafine derivatives[24,25] and by conformational analyses[26] with the CAMDAS software program.[27] Based on the plausible active conformation of nalfurafine and the observed SAR in pyrrolomorphinan derivatives **6**, **7**, and **9** (Table 1), we developed the working hypothesis that the α,β-unsaturated ketone derivatives **6a**–**e** might adopt the active structures of **11a**–**e** to achieve κ selective agonist activity (Fig. 5). We conjectured that the α,β-unsaturated ketone **6** could adopt the structure of the iminium species **10** due to the electron withdrawing ketone functionality. In contrast, compounds **7** and **9** would not be able to adopt such iminium species, because the saturated ketone derivative **7** lacks the conjugation between the pyrrole ring and ketone moiety, and the olefin derivative **9** lacks the electron withdrawing ketone functionality. The iminium species **10a**–**e** could be converted to the plausible active structures of **11a**–**e** owing to the equilibriums between **10a**–**e** and **11a**–**e**. To confirm this working hypothesis, we attempted to trap the proposed active structures **11a**–**e** by acetylation; we used the formyl derivative **4** as a model compound. After intense investigation to optimize the acetylation conditions, **4** was treated with a solvent amount of Ac_2O in the presence of CSA (2 equiv) at 50 °C (disappearance of the starting material **4** was observed by TLC analysis). A subsequent aqueous workup gave crude compounds including compounds **13** and **14**

Table 1
Binding affinities of pyrrolomorphinan derivatives **6**, **7**, and **9** for opioid receptors[a]



Compound	K_i (κ) (nM)[b]	K_i (μ) (nM)[c]	K_i (δ) (nM)[d]	Selectivity	
				μ/κ	δ/κ
Nalfurafine	0.225	0.582	96.5	2.6	429
nor-BNI	0.861	28.2	29.3	33	34
6a	0.935	6.89	1.73	7.4	1.9
6b	1.13	6.58	2.08	5.8	1.8
6c	0.467	3.76	3.74	8.1	8.0
6d	1.15	6.20	1.47	5.4	1.3
6e	1.24	15.0	3.55	12	2.9
7	0.342	0.548	1.59	1.6	4.6
9a	3.79	1.76	ND[e]	0.5	—
9b	7.38	5.85	6.58	0.8	0.9

[a] Binding assay was carried out in duplicate using homogenate of guinea pig brain (κ: cerebellum, μ and δ: forebrain).
[b] [^{3}H] U-69593 was used.
[c] [^{3}H] DAMGO was used.
[d] [^{3}H] NTI was used.
[e] ND: The K_i value was not determined because the IC_{50} value was over 1000 nM.

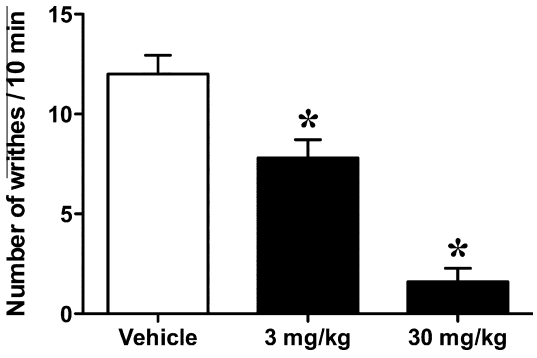


Figure 3. Antinociceptive effect of compound **6e** in the mouse acetic acid writhing test. * p <0.025 versus vehicle-treated group.

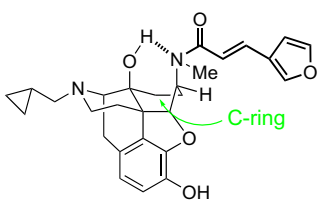


Figure 4. Proposed active conformation of nalfurafine.

(Fig. 6). IR spectra of the crude products showed a sharp band at 1761 cm^{-1}, which suggested the presence of enol acetate. In the ^{1}H NMR spectra, six singlets at 2.00, 3.80, 4.07, 5.52, 6.53, and 9.47 ppm and a doublet at 4.55 ppm were observed, consistent with the structure of compound **13**. Moreover, four characteristic signals were detected, including three singlets at 5.51, 5.99, and 7.69 ppm and a doublet at 4.52 ppm. The three singlets and a doublet would represent the 5-proton, vinylic protons of a 3-pyrroline ring, an enol acetate moiety, and a 9-methine proton, respectively. The doublet at 4.52 ppm suggested the production of compound **14**, and not compound **12**, because acylation of a 14-hydroxy group generally induces a downfield shift of the 9-methine proton signal from approximately 3.2 ppm to approximately 4.5 ppm. The mass spectrometry spectra indicated a peak at m/z = 505, which would stem from compound **15** derived from **14** by fragmentation; this also supported the structure of **14**. However, an attempt to isolate compound **14** failed, due to its instability.[28–40] These outcomes suggested that α,β-unsaturated ketone derivatives **6a**–**e** could produce the iminium species **10**, which could then be converted to the active structures **11a**–**e**. Taken together, our results suggested that the pyrrole ring in the pyrrolomorphinan derivatives **6**, **7**, and **9** would not function as an accessory site, however the κ address, that is, the side chain on the pyrrole ring localized above the C-ring may play a key role in conferring κ selective agonist activity.

In conclusion, we synthesized pyrrolomorphinan derivatives **6**, **7**, and **9** to confirm whether the pyrrole ring might be an accessory site in the κ selective antagonist, nor-BNI. We found that α, β-unsaturated ketone derivatives **6a**–**e** strongly bound to the κ receptor. Moreover, the most selective for the κ receptor, compound **6e**, produced a dose-dependent antinociceptive effect in mice. Based on the SAR analysis of the synthesized compounds, a hypothetical active structure was proposed for conferring κ

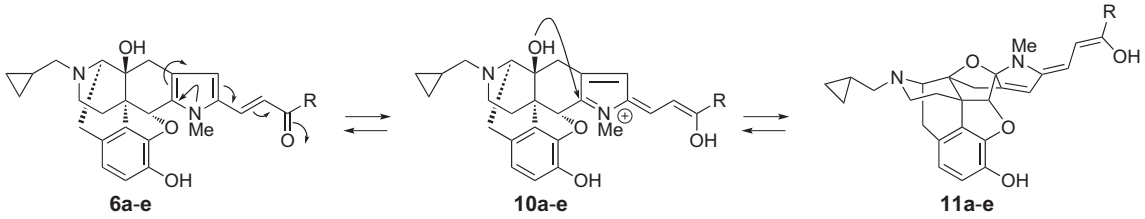


Figure 5. Hypothetical active structure **11** and plausible mechanism from **6** to **11**.

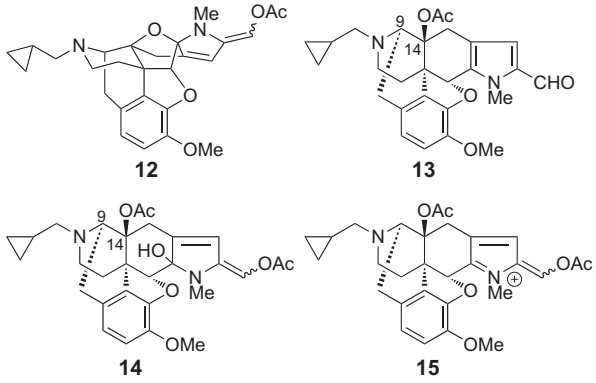


Figure 6. Structures of compounds **12**–**15**.

selective agonist activity. The pyrrole ring in the compounds could not function as an accessory site, however, the ability of the side chain on the pyrrole ring to localize above the C-ring may have played a key role in conferring κ selective agonist activity. This study provided useful information for the further design of novel κ agonists.

Acknowledgments

We acknowledge financial support from the Shorai Foundation for Science and the Uehara Memorial Foundation. We also acknowledge the Institute of Instrumental Analysis of Kitasato University, School of Pharmacy, for its facilities.

References and notes

1. DeLander, G. E.; Portoghese, P. S.; Takemori, A. E. *J. Pharmacol. Exp. Ther.* **1984**, *231*, 91.
2. Nagase, H.; Hayakawa, J.; Kawamura, K.; Kawai, K.; Takezawa, Y.; Matsuura, H.; Tajima, C.; Endo, T. *Chem. Pharm. Bull.* **1998**, *46*, 366.
3. Kawai, K.; Hayakawa, J.; Miyamoto, T.; Imamura, Y.; Yamane, S.; Wakita, H.; Fujii, H.; Kawamura, K.; Matsuura, H.; Izumimoto, N.; Kobayashi, R.; Endo, T.; Nagase, H. *Bioorg. Med. Chem.* **2008**, *16*, 9188.
4. Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. *J. Med. Chem.* **1987**, *30*, 238.
5. Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 281.
6. Portoghese, P. S.; Sultana, M.; Takemori, A. E. *J. Med. Chem.* **1990**, *33*, 1714.
7. Portoghese, P. S. *Trends Pharmacol. Sci.* **1989**, *10*, 230.
8. Portoghese, P. S. *J. Med. Chem.* **1991**, *34*, 1757.
9. Nogrady, T. In *Medicinal Chemistry A Biochemical Approach*; Oxford University Press: New York, 1985; pp 68–69.
10. Fujii, H.; Narita, M.; Mizoguchi, H.; Hirokawa, J.; Kawai, K.; Tanaka, T.; Tseng, L. F.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4241.
11. Although some pyrrolomorphinan derivatives have already been synthesized, their detailed pharmacological profiles have not yet been reported. See the Refs. 12–14.
12. Kotick, M. P.; Leland, D. L.; Polazzi, J. O. *J. Med. Chem.* **1981**, *24*, 1445.
13. Portoghese, P. S.; Nagase, H.; Lipkowski, A. W.; Larson, D. L.; Takemori, A. E. *J. Med. Chem.* **1998**, *31*, 836.
14. Schwarz, P.; Schmidhammer, H. *Heterocycles* **1994**, *39*, 35.
15. Uwai, K.; Uchiyama, H.; Sakurada, S.; Kabuto, C.; Takeshita, M. *Bioorg. Med. Chem.* **2004**, *12*, 417.
16. Nemoto, T.; Fujii, H.; Sato, N.; Nagase, H. *Tetrahedron Lett.* **2007**, *48*, 7413.
17. Nagase, H.; Watanabe, A.; Harada, M.; Nakajima, M.; Hasebe, K.; Mochizuki, H.; Yoza, K.; Fujii, H. *Org. Lett.* **2009**, *11*, 539.
18. Jones, G.; Stanforth, S. P. *Org. React.* **1997**, *49*, 1.
19. Wakita, H.; Matsumoto, K.; Yoshiwara, H.; Hosono, Y.; Hayashi, R.; Nishiyama, H.; Nagase, H. *Tetrahedron* **1999**, *55*, 2449.
20. Blakemore, P. R.; Cole, W. J.; Kocienski, P.; Morley, A. *Synlett* **1998**, 26.
21. Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.
22. Fujii, H.; Ogawa, R.; Ohata, K.; Nemoto, T.; Nakajima, M.; Hasebe, K.; Mochizuki, H.; Nagase, H. *Bioorg. Med. Chem.* **2009**, *17*, 5983.
23. Ciapetti, P.; Giethlen, B. In *The Practice of Medicinal Chemistry*; Wermth, C. G., Ed., 3rd ed.; Elsevier: Amsterdam, 2008; pp 290–342.
24. Nemoto, T.; Fujii, H.; Narita, M.; Miyoshi, K.; Nakamura, A.; Suzuki, T.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6398.
25. Nagase, H.; Watanabe, A.; Nemoto, T.; Yamaotsu, N.; Hayashida, K.; Nakajima, M.; Hasebe, K.; Nakao, K.; Mochizuki, H.; Hirono, S.; Fujii, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 121.
26. Yamaotsu, N.; Fujii, H.; Nagase, H.; Hirono, S. *Bioorg. Med. Chem.* **2010**, *18*, 4446.
27. Tsujishita, H.; Hirono, S. *J. Comput. Aided Mol. Des.* **1997**, *11*, 305.
28. Although compounds with an aminomethanol moiety are generally labile, some natural compounds are known to possess this moiety; for example, fawcettimine, yuzurimine, and vincamine, and some medicines like anoretic mazindol. See the Refs. 29 and 30.
29. Hudlický, T.; Reed, J. W. In *The Way of Synthesis, Evolution of Design and Methods for Natural Products*; Wiley-VCH: Weinheim, 2007. pp. 574, 604, and 760.
30. Bacon, E. R.; Chatterjee, S.; Williams, M. In *Comprehensive Medicinal Chemistry II*; Williams, M. Vol. Ed.; Taylor, J. B.; Triggle, D. J. Eds-in chief; Elsevier: Amsterdam, 2007; p 154.
31. Some recent examples of natural compounds that have an aminomethanol moiety include the followings. See the Refs. 32–38 for the isolation, and the Refs. 39 and 40 for the total synthesis.
32. Chen, F.-Z.; Chen, D.-L.; Chen, Q.-H.; Wang, F.-P. *J. Nat. Prod.* **2009**, *72*, 18.
33. Kubota, T.; Suzuki, T.; Ishiuchi, K.; Kuhara, T.; Kobayashi, J. *Chem. Pharm. Bull.* **2009**, *57*, 504.
34. Zhang, Y.; Di, Y.-T.; Mu, S.-Z.; Li, C.-S.; Zhang, Q.; Tan, C.-J.; Zhang, Z.; Fang, X.; Hao, X.-J. *J. Nat. Prod.* **2009**, *72*, 1325.
35. Zhang, Z.-J.; Rao, G.-W.; Hou, X.-R.; Li, C.-P.; Shan, W.-G. *Helv. Chim. Acta* **2009**, *92*, 1562.
36. Zaima, K.; Hirata, T.; Hosoya, T.; Hirasawa, Y.; Koyama, K.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Shiro, M.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1686.
37. Zhang, C.-R.; Liu, H.-B.; Dong, S.-H.; Zhu, J.-Y.; Wu, Y.; Yue, J.-M. *Org. Lett.* **2009**, *11*, 4692.
38. Hirasawa, Y.; Miyama, S.; Hosoya, T.; Kiyama, K.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Morita, H. *Org. Lett.* **2009**, *11*, 5718.
39. Zaed, A. M.; Swift, M. D.; Sutherland, A. *Org. Biomol. Chem.* **2009**, *7*, 2678.
40. Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *11*, 5554.