One-Pot Synthesis of 4,5-Biphenyl-2-pyrimidinylguanidine Derivatives

Zun-Ting Zhang,* Fei-Fei Xu, Mi-Xiang Gao, and Li Qiu

Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, and School of Chemistry and Materials Science, Shaanxi Normal University, Xi'an 710062, P.R. China

Received April 10, 2009

A simple and straightforward methodology toward the synthesis of novel 4,5-biphenyl-2-pyrimidinylguanidine compounds has been developed by one-pot reaction of biguaninde or dimethyldiguanide with isoflavones. A series of 20 new compounds was reported. All of them were characterized by FT-IR, NMR, and elemental analysis. A typical compound was determined by X-ray diffraction. A variety of substrates can participate in the process with good yields and high purities, making this methodology suitable for library synthesis in drug discovery.

Introduction

Pyrimidine and guanidine are both found widely as core structures in a large variety of compounds that exhibit important biological activity.[1−3] Given examples, pyrimidines are interesting drug targets because they are found on some nucleosides, are well-known DHFR inhibitors, and present potential antiviral, antifungal, anticancer, and antiprotozoan activity.[4] Guanidine because of its unusual structure has been applied as a catalyst[5] and in iatrology, such as antivirus, antitumor,[6] and antiplatelet.[7] Guanidine derivatives such as dimethyldiguanide hydrochloride and phenformin hydrochloride have been designed as hypoglycemic agents.[8] Combinations of both guanidine and pyrimidine moieties have been scarcely found in natural products. Tanaka et al. have synthesized 4,5-bis(4-methoxyphenyl)-2-pyrimidinylguanidine in low yield (33.7%) involving three steps.[7]

It is well-known that natural isoflavones display a wide range of biological activities.[10] For instance, soybean isoflavones have shown pharmacological effects such as antidysrhythmic,[11] antioxidant,[12] and anticardio-cerebral vascular disease.[13] Ipriflavone has been reported to be efficient in preventing and treating osteoporosis.[14] Irisolidone has shown activity as an antidiabetic.[15] It is well-known that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent which readily reacts with amidines,[16] guanidine,[9,17] carbamide,[18] or sulfocarbamide[19] to form the corresponding 2-substituted pyrimidines. We designed a route (Scheme 1) for the condensation of isoflavone **1** with biguanidines **2** to synthesize compound **3** and the dimeric structure **4**. We expect formation of **4** as a result of condensation of the guanidyl residue on **3** and a second molecule of **1**.

Herein, we report an efficient one-pot synthesis of 4,5-biphenyl-2-pyrimidinylguanidine **3** by the reaction of biguanide hydrochloride (**2a**) or dimethyldiguanide hydrochloride (**2b**) with natural isoflavone. This methodology makes the synthesis simpler and more environmentally friendly. We also proved that our method is convenient for the preparation of a wide variety of 4,5-biphenyl-2-pyrimidinylguanidines bearing different substituents on the phenyl and guanidyl units.

Results and Discussion

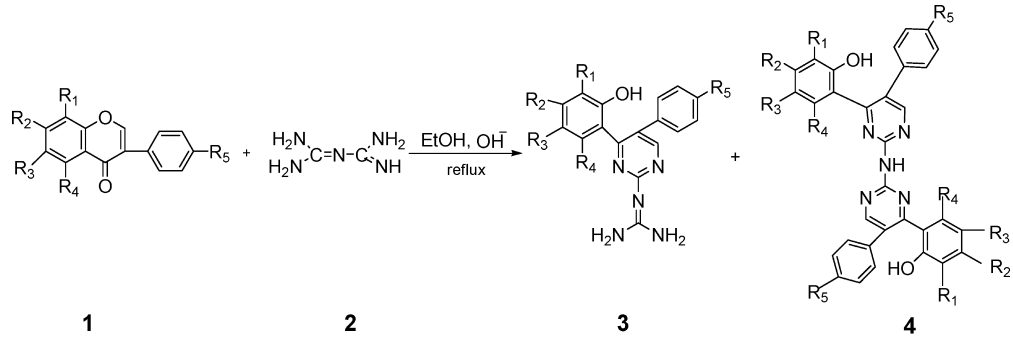
Initially, a mixture of ipriflavone **1a** (2 mmol) and biguanide hydrochloride **2a** (1 mmol) was refluxed in methanol (30 mL), and the pH was adjusted with a mass fraction of 10% aqueous solution of NaOH until pH = 12. The progress of the reaction was monitored by thin layer chromatography (TLC) until the starting **1a** disappeared. During the reaction, two new products were detected on the TLC suggesting the possible presence of the expected products of type **3** and **4**. Two products were isolated and characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. As expected, condensation of **1a** and **2a** mainly gave type **3** product 2-[4-(2-hydroxy-4-isopropoxyphenyl)-5-phenyl-2-pyrimidinyl] guanidine **3a**. However, the corresponding type **4** product was not detected and the presence of **5a** 2-amino-4-(2-hydroxy-4-isopropoxyphenyl)-5-phenylpyrimidin suggested hydrolysis of the second guanidyl fragment in **3a**.

It was reported that isoflavone may undergo ring-opening reaction when refluxing in the presence of alkali forming a 1,3-diketo intermediate **7** (Scheme 2) which at high concentration of base may eliminate formic acid to generate byproduct **6**.[20] **7** reacted with **2** and gave the product **3**. On the other hand, **5** might be a result of basic hydrolysis of the guanidyl moiety in product **3**. These assumptions and our results suggested a critical role of the concentration of base in the distribution of the obtained products. We decided to carry on optimization of the amount of base for the exclusive synthesis **3**. A mixture of **1a** (2 mmol) and **2a** (1 mmol) was refluxed in methanol (30 mL) under different pH values. Obviously, pH = 10

* To whom correspondence should be addressed. Phone: 86-29-85303940. Fax: 86-29-85307774. E-mail: zhangzt@snnu.edu.cn.

10.1021/cc900058y CCC: $40.75
Published on Web 07/21/2009

Scheme 1. Designed Cyclocondensation Route of Isoflavones with Biguanidines



R_1 =H or Br R_2 =H, OH, OCH_3, OCH_2CH_3 or $OCH(CH_3)_2$

R_3=H or OCH_3 R_4= H, OH, OCH_3 or CH_3

R_5=H, OH or OCH_3

Scheme 2. Proposed Mechanism for the Formation of **3** and Byproducts

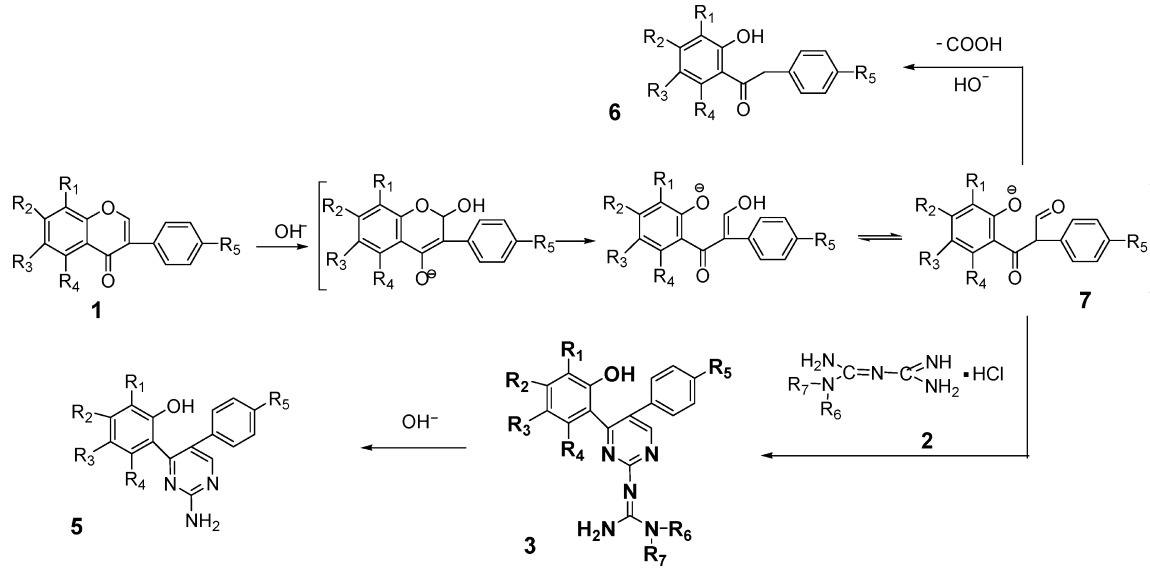


Table 1. pH Effects on the Reaction Based on **1a** Reacted with **2a** in Methanol

entry	pH	time (h)	yield (%)[a]
1	9	36	69
2	10	20	78
3	11	12	60
4	12	8	48

[a] Yields determined by column chromatography isolation.

Table 2. Optimization for the Reaction Based on **1a** and **2a** at pH 10

entry	solvent	temp (°C)	time (h)	yield (%)[a]
1	CH_3CH_2OH	60	24	72
2	CH_3CH_2OH	80	16	80
3	CH_3OH	65	20	76
4	THF	70	18	60
5	CH_3CN	82	28	62
6	$CH_3CH_2CH_2CH_2OH$	80	40	59
7	$CH_3CH_2CH_2CH_2OH$	120	32	67
8	DMF	80	60	48
9	DMF	120	19	50

[a] Yields determined by column chromatography isolation.

was the best (Table 1). On the basis of the best pH value, solvents, and temperatures, the ratio of **1a** and **2a** was optimized. The results are summarized in Tables 2 and 3.

Table 3. Optimization for the Ratios of **1a** and **2a** in Ethanol at 80 °C and pH 10

entry	n_{1a}:n_{2a}	yield (%)[a]
1	1:1	52
2	1:2	61
3	1:3	75
4	1:4	85
5	1:5	84

[a] Yields determined by column chromatography isolation.

Ethanol was found to be the best solvent at 80 °C, and the ratio of ipriflavone and biguanide was 1:4.

With the optimized reaction conditions and proven results in hand, the condensation of a variety of structurally divergent isoflavones and **2a** or **2b** were studied to illustrate this concise and general method for the synthesis of 4,5-biphenyl-2-pyrimidinylguanidines. All substrates smoothly reacted to give the corresponding 4,5-biphenyl-2-pyrimidinylguanidine in 16−48 h in excellent yields, and the results are summarized in Table 4. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. The structure was further unequivo-

Table 4. Synthesis of **3** by Reaction of Various Isoflavones and Biguanides in Ethanol at 80 °C and pH = 10

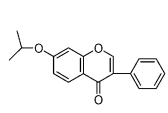
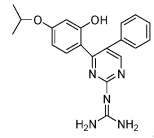
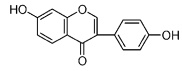
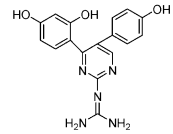
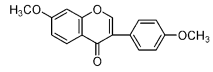
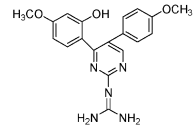
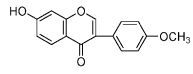
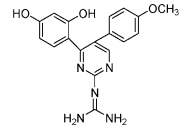
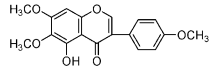
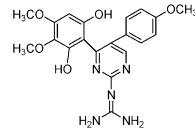
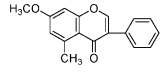
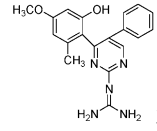
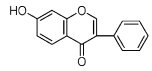
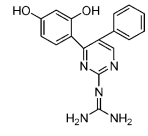
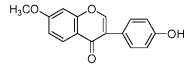
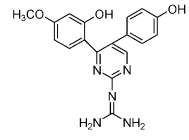
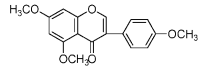
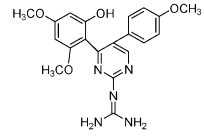
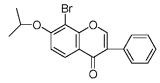
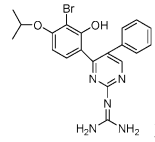
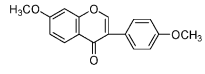
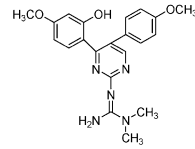
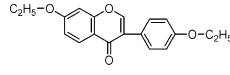
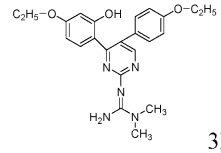
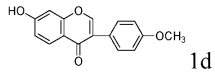
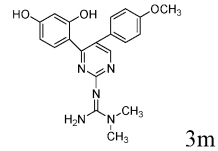
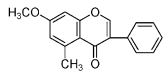
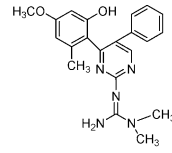
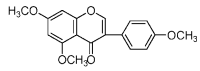
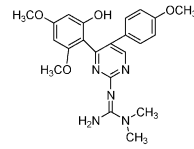
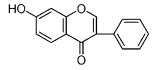
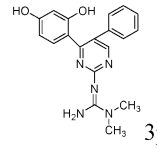
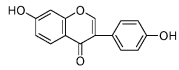
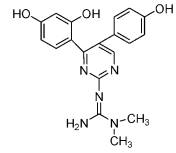
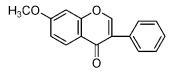
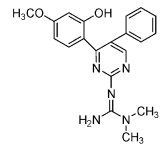
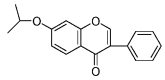
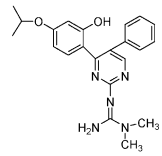
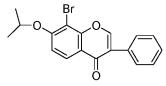
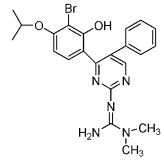
Entry	Substrate	Product	Time(h)	Yield(%)[a]
1	 1a	 3a	16	85
2	 1b	 3b	48	70
3	 1c	 3c	20	86
4	 1d	 3d	28	80
5	 1e	 3e	24	72
6	 1f	 3f	18	82
7	 1g	 3g	36	80
8	 1h	 3h	28	78
9	 1i	 3i	24	76
10	 1l	 3j	26	76
11	 1c	 3k	20	90
12	 1j	 3l	20	85

Table 4. Continued

Entry	Substrate	Product	Time(h)	Yield(%)[a]
13	 1d	 3m	28	78
14	 1f	 3n	18	80
15	 1i	 3o	24	74
16	 1g	 3p	36	70
17	 1b	 3q	48	68
18	 1k	 3r	28	72
19	 1a	 3s	16	88
20	 1l	 3t	26	74

[a] Yields determined by column chromatography isolation.

cally confirmed by single crystal X-ray diffraction of **3s** which added sharp evidence for the proposed structure (Figure 1).

The reaction has a general character since isoflavones with various substituents such as alkoxy or alkoxyphenyl groups, that have a fine conjugative effect to depress the electron density, gave good results. In contrast, the presence of more than two hydroxyl groups lowers the yields, especially when the hydroxyl is present at C-5. The hydrogen bond between the hydroxyl group and the carbonyl would prevent the occurrence of this reaction. The products of genistein (4′,5,7-trihydroxyisoflavone) and irisolidone (4′,6-dialkoxy-5,7-dihydroxyisoflavone) as the starting material were not obtained.

Conclusion

In summary, the simple workup, the excellent yield, the environmentally benign recycling of a green solvent, and the fairly mild conditions of this method offer advantages over other procedures. Moreover, this protocol should be of further interest in synthetic chemistry. On the basis of the present investigation, we are now carrying out research on the

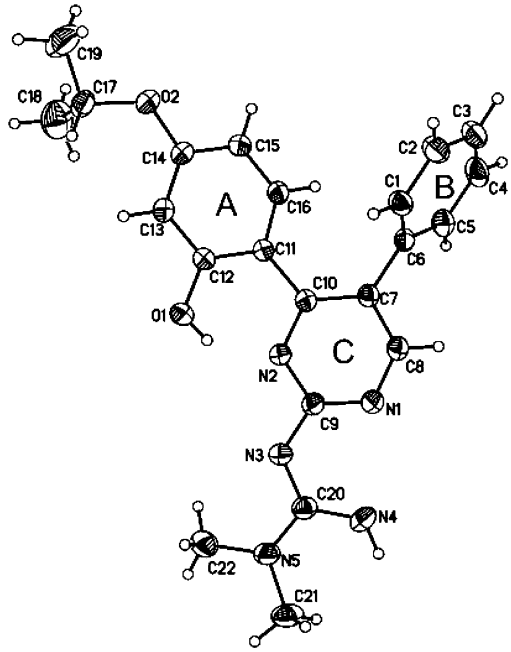


Figure 1. Single-crystal X-ray structural analysis of **3s**.

applications of 4,5-biphenyl-2-pyrimidinylguanidine in pharmacology.

Experimental Section

General Procedure for the Preparation of 4,5-Biphenyl-2-pyrimidinylguanidine (Entries 3a−3t, Table 4). The mixture of corresponding **1** (1 mmol) and biguanide hydrochloride (**2a**) or dimethyldiguanide hydrochloride (**2b**) (4 mmol) was refluxed in ethanol (30 mL), and the pH adjusted with 10% NaOH aqueous solution until pH =10. The reaction was at 80 °C for 16−48 h. All reactions were monitored by TLC, which showed the disappearance of **1** that was indicative of the reaction being complete. The reaction mixture was adjusted to neutrality with 10% HCl, and then, the solvent was removed. The crude product was purified by column chromatography on silica gel using petroleum ether−ethylacetate (1:1) to give the corresponding pure product.

2-[4-(2-Hydroxy-4-isopropoxyphenyl)-5-phenyl-2-pyrimidinyl] Guanidine (Entry 3a, Table 4). White solid. mp 278.2−279.3 °C. IR (KBr), ν (cm^{-1}): 3358, 3265, 2977, 1686, 1632, 1622, 1605, 1582, 1537, 1444, 1418, 1238, 1179, 981, 836, 769, 708, 696. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 9.91 (s, 1H), 8.45−8.67 (m, 5H), 7.25−7.32 (m, 5H), 7.00 (d, 1H, J = 8.0 Hz), 6.32−6.35 (m, 2H), 4.63 (m, 1H), 1.23 (d, 6H, J = 5.7 Hz). ^{1}H NMR (300 MHz, DMSO-δ (ppm): 8.61 (s, 1H), 7.19−7.29 (m, 5H), 6.98 (d, 1H, J = 8.4 Hz), 6.28−6.33 (m, 2H), 4.52 (m, 1H), 1.19 (d, 6H, J = 5.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6 + D_2O), δ (ppm): 163.4, 159.8, 158.6, 156.2, 155.1, 154.9, 135.8, 131.8, 129.5, 128.45, 128.40, 127.6, 116.1, 106.6, 102.8, 69.4, 21.7. Anal. Calcd for $C_{20}H_{21}N_5O_2$: C, 66.10; H, 5.82; N, 19.27. Found: C, 65.82; H, 6.15; N, 19.03.

Acknowledgment. This research was supported by the National Natural Science Foundation of China (No.: 20772076) and the Science and Technology Key Project of Education Ministry, P. R. China (No.: 107138).

Supporting Information Available. Crystallographic data for **3s** (CIF), experimental procedures, and IR, ^{1}H NMR and ^{13}C NMR spectra, elemental analysis of all compounds, and crystal and structure refinement data for **3s**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Traxler, P.; Bold, G.; Buchdunger, E.; Caravatti, G.; Furet, P.; Manley, P.; O'Reilly, T.; Wood, J.; Zimmermann, J. *Med. Res. Rev.* **2001**, *21*, 499–512. (b) Zimmermann, J.; Buchdunger, E.; Mett, H.; Meyer, T.; Lydon, N. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 187–192. (c) Ghosh, U.; Ganessunker, D.; Sattigeri, V. J.; Carlson, K. E.; Mortensen, D. J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2003**, *11*, 629–657. (d) Bennett, G. B.; Mason, R. B.; Alden, L. J.; Roach, J. B. *J. Med. Chem.* **1978**, *21*, 623–628.

(2) Berlinck, R. G. S. *Prog. Chem. Org. Nat. Prod.* **1995**, *66*, 119–295.

(3) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 337–409.

(4) Di Lucrezia, R.; Gilbert, I. H.; Floyd, C. D. *J. Comb. Chem.* **2000**, *2*, 249–253.

(5) Song, W.; Lu, X. F.; Lu, G. Y. *Chem. J. Chin. Univ.* **2006**, *27*, 460–463.

(6) Ohtani, I.; Kusumi, T.; Kakisawa, H.; et al. *J. Am. Chem. Soc.* **1992**, *114*, 8472–8479.

(7) Tanaka, A.; Motoyama, Y.; Takasugi, H. *Chem. Pharm. Bull.* **1994**, *42*, 1828–1834.

(8) Wang, R. L.; Yuan, Z. P. *Handbook of Chemical Product-Medicine*: Chemical Industrial Press: Beijing, 1998. *157.*

(9) (a) Funabiki, K.; Nakamura, H.; Matsui, M.; Shibata, K. *Synlett* **1999**, *6*, 756–758. (b) Karpov, A. S.; Merkul, E.; Rominger, F.; Muller, T. J. *J. Angew. Chem., Int. Ed.* **2005**, *44*, 6951–6956. (c) Bellur, E.; Langer, P. *Tetrahedron* **2006**, *62*, 5426–5434. (d) Sevenard, D. V.; Khomutov, O. G.; Koryakova, O. V.; Sattarova, V. V.; Kodess, M. I.; Stelten, J.; Loop, I.; Lork, E.; Pashkevich, K. I.; Roschenthaler, G. V. *Synthesis* **2000**, *12*, 1738–1748. (e) Zanatta, N.; Cortelini, M.; de, F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509–513. (f) Madruga, C.; da, C.; Clerici, E.; Martins, M. A. P.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 735–738. (g) Zanatta, N.; Fagundes, M. B.; Ellensohn, R.; Marques, M.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1998**, *35*, 451–455. (h) Soufyane, M.; Broek, S.; van den; Khamliche, L.; Mirand, C. *Heterocycl.* **1999**, *51*, 2445–2451. (i) Yu, H. B.; Huang, W. Y. *J. Fluorine Chem.* **1997**, *84*, 65–67. (j) Yu, H. B.; Huang, W. Y. *J. Fluorine Chem.* **1998**, *87*, 69–73.

(10) (a) Agullo, G.; Gamet-Payrastre, L.; Manenti, S.; Viala, C.; Remesy, C.; Chap, H.; Payrastre, B. *Biochem. Pharmacol.* **1997**, *53*, 1649–1657. (b) Wang, I. K.; Lin-Shiau, S. Y.; Lin, J. K. *Eur. J. Cancer.* **1999**, *35*, 1517–1525.

(11) Fan, L. L.; Zhao, D. H.; Zhao, M. Q.; Zeng, G. Y. *Acta Pharm. Sin.* **1985**, *20*, 647–651.

(12) (a) Tlkkanen, M. J.; Wahala, K.; Ojala, S.; Vihtna, V.; Adletcteutr, H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3106–3110. (b) Record, I. R.; Dreosti, I. E.; McInerney, J. K. *J. Nutr. Biochem.* **1995**, *6*, 481–485.

(13) (a) Potter, S. M. *J. Nutr.* **1995**, *125*, 606–611. (b) Sirtori, C. R.; Lovati, M. R.; Manzoni, C.; et al. *J. Nutr.* **1995**, *125*, 598–605. (c) Adlercreutz, H.; Goldin, B. R.; Gorbach, S. L.; et al. *J. Nutr.* **1995**, *125*, 757–770. (d) Ozaki, Y.; Yatomi, Y.; Jinnai, Y.; Kume, S. *Biochem. Pharmacol.* **1993**, *46* (3), 395–403.

(14) (a) Reginster, J. Y. L. *Bone Miner.* **1993**, *23*, 223–232. (b) Ruenitz, P. C. *Curr. Med. Chem.* **1995**, *2*, 791–802.

(15) (a) Basnet, P.; Kadota, S.; Shimizu, M.; Xu, H. X.; Namba, T. *Chem. Pharm. Bull.* **1993**, *41*, 1790–1795. (b) Ragunathan, V.; Sulochana, N. *J. Indian Chem. Soc.* **1994**, *71*, 705–706.

(16) Kenner, G. W.; Lythgoe, B.; Todd, A. R.; et al. *J. Chem. Soc.* **1943**, *87*, 388–390.
(17) (a) Burness, D. M. *J. Org. Chem.* **1956**, *21*, 97–101. (b) Xie, F. C.; Zhao, H. B.; Zhao, L. Z.; Lou, L. G.; Hu, Y. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 275–278.
(18) Sherman, W. R.; Taylor, E. C., Jr. *Org. Synth.* **1957**, *37*, 15–17.
(19) (a) Foster, H. M.; Snyder, H. R. *Org. Synth.* **1963**, *4*, 638–640. (b) Crosby, D. G.; Berthold, R. V.; Johnson, H. E. *Org. Synth.* **1963**, *43*, 68–70.
(20) Varga, M.; Batori, S.; et al. *Eur. J. Org. Chem.* **2001**, *20*, 3911–3920.

CC900058Y