Available online at www.sciencedirect.com

SciVerse ScienceDirect

Chinese Chemical Letters 23 (2012) 127–129

CHINESE CHEMICAL LETTERS

www.elsevier.com/locate/cclet

First total synthesis of (±)-sepicanin A

Jin Hui Yang *, Wen Qian Huang, Jun Shan Luo, Dong Dong Guo, Yu Heng Zhang, Hong Jun Li

State Key Laboratory Cultivation Base of Natural Gas Conversion, Ningxia University, Yinchuan 750021, China

Received 6 September 2011
Available online 21 December 2011

Abstract

A facile approach for the first total synthesis of naturally occurring geranylated flavanoids sepicanin A has been obtained with total yield 16% starting from 2,4,6-trihydroxyacetophenone after four steps. The key step was the protic acids (HCl or *p*-TsOH)-catalyzed benzopyrone formation in a *protic* polar solvent by deprotection and cyclization of chalcone in one step.

Keywords: Sepicanin A; Flavanone; Geranylated flavonoids; Total synthesis

Geranylflavonoids are a unique class of naturally products existed in various traditional medicinal plants, exhibiting a wide range of interesting physiological properties such as hypotensive [1], antifungal [2], antibacterial [3,4], and antitumor [5]. It was reported that prenylated flavanones and geranylflavanone showed a remarkably greater bioactivities than the normal flavanones [6]. So this wide range of biological properties has stimulated interest in the synthesis of naturally occurring geranylated flavonoids.

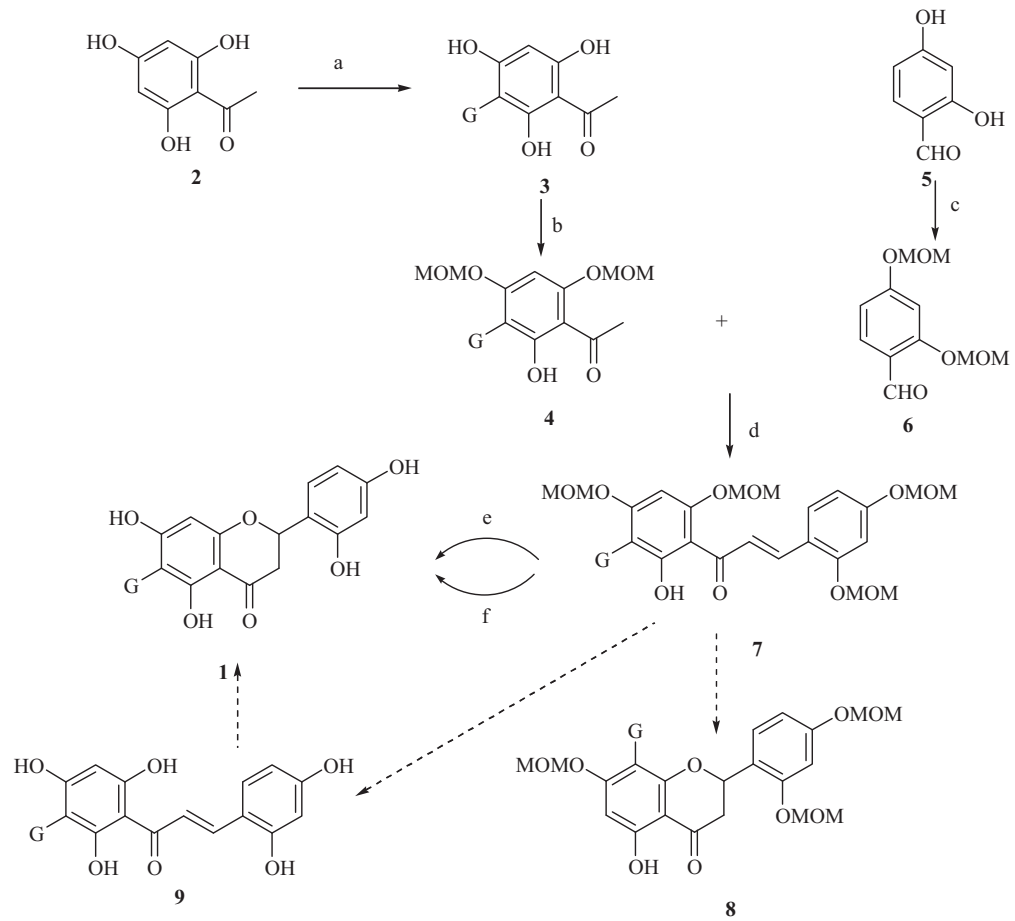
In continuation of our ongoing program on the studies of geranylated flavanoids in our laboratory [7–9], herein we report a facile and efficient approach (Scheme 1) based on the protic acids (HCl or *p*-TsOH)-mediated benzopyrone formation by cyclization chalcone in a protic polar solvent, as illustrated in the first total synthesis of the naturally occurring C-6 geranylated flavanoids, (±)-sepicanin A (**1**).

Sepicanin A (Fig. 1) had been isolated from *Artocarpus sepicanus* Diels leaves and displayed a significant selective antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with IC_{50} and MIC values of 1.4 and 2.9 μmol/L, respectively [11]. What is more, we found sepicanin A shown activity against *s. aureus* with MIC values of 6.25 μg/μL through antimicrobial testing. As far as we know, the total synthesis of sepicanin A has not been report yet. So the development of an efficient synthetic method to sepicanin A would not only have theoretical importance, but also have the potential medical prospect.

4,6-Bis[(methoxy)methoxy]-2-hydroxy-3-(1′-geranyl)acetophenone **4** was prepared from 2,4,6-trihydroxy-acetophenone **2** by the geranylation according to Huang's report [10] in 72% yield and selective bismethoxymethylation in 77% yield. Compound **6** prepared from compound **5** by standard methoxymethylation (chloromethyl methyl ether: MOMCl, potassium carbonate) in 90% yield. Compound **4** was condensed with

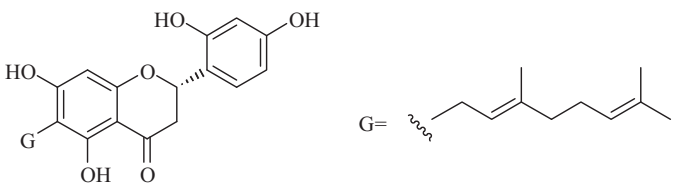
* Corresponding author.
E-mail address: yang_jh@nxu.edu.cn (J.H. Yang).

1001-8417/$ – see front matter © 2011 Published by Elsevier B.V. on behalf of Chinese Chemical Society.
doi:10.1016/j.cclet.2011.11.015



Scheme 1. Conditions and reagents: (a) geranyl bromine, anhydrous K_2CO_3, acetone, reflux, 72%; (b) CH_3OCH_2Cl, anhydrous K_2CO_3, acetone, reflux, 77%; (c) CH_3OCH_2Cl, anhydrous K_2CO_3, acetone, reflux, 90%; (d) KOH, H_2O–EtOH (v:v = 2:3), under nitrogen, 0 °C ~ r.t, 90%; (e) 3 mol/L HCl, MeOH, reflux, 1 h, 32%; (f) *p*-TsOH·H_2O (4 equiv.), MeOH, 48 h, 23%.

compound **6** in potassium hydroxide and hydrous ethanolic solution for 24 h to form the desired chalcone **7** in 90% yield. Direct cyclization chalcone **7** will result to C-8 geranylated flavanoids **8**. In order to obtain C-6 geranylated flavanoids, (±)-sepicanin A (**1**) will be synthesized from chalcone **7** by a two-step sequence: (1) demethoxymethylation; (2) cyclization. Demethoxymethylation of chalcone **7** by a treatment with 3 mol/L HCl in methanol for 1 h did not give corresponding chalcone **9** but gave cyclization product, (±)-sepicanin A (**1**) in 32% yield. Treatment of compound **7** with *p*-toluenesulfonic acid monohydrate in methanol also gave (±)-sepicanin A (**1**) in 23% yield. The synthetic (±)-sepicanin A has identical spectral data [12] with those of natural **1** [11]. It is worthy to note that flavanones—sepicanin A was gained by one step from chalcone **7**. In traditionally, it must be synthesized by two steps, one step is deprotection, other step is cyclization of chalcone.



1 Sepicanin A

Fig. 1. The structure of sepicanin A.

In summary, this paper described a concise synthetic route, and the overall yield for the entire four-step synthesis is 16%.

Acknowledgments

This work was financially supported by the National Natural Science Foundation (No. 20962016) and Ningxia Natural Science Foundation (No. NZ1006) and Program for New Century Excellent Talents in University (No. NCET-09-0860).

References

[1] T.R. Seshadri, Tetrahedron 6 (1959) 169.
[2] T.L. Meragelman, K.D. Tucker, T.G. McClord, et al. J. Nat. Prod. 68 (2005) 1790.
[3] M.J. Salvatore, A.B. Kng, A.C. Graham, et al. J. Nat. Prod. 61 (1998) 640.
[4] M.M. Rahman, A.I. Gray, P. Khondkar, et al. Pharmacol. Biol. 46 (2008) 356.
[5] K.V. Hirpara, P. Aggarwal, A.J. Mukherjee, et al. Curr. Med. Chem. 9 (2009) 138.
[6] N. Tamotsu, O. Taichi, K. Takeshi, et al. Chem. Pharm. Bull. 37 (1989) 1392.
[7] J.H. Yang, Y.M. Zhao, C.B. Ji, Chin. Chem. Lett. 19 (2008) 658.
[8] J.H. Yang, S.Z. Jiang, Y.M. Zhao, et al. Chin. Chem. Lett. 20 (2009) 1062.
[9] J.H. Yang, Y.H. Zhang, H.J. Li, et al. Chin. Chem. Lett. 21 (2010) 1267.
[10] C.S. Huang, Z. Zhang, Y.L. Li, J. Nat. Prod. 61 (1998) 1283.
[11] M.M. Radwan, R.R. Guzman, S.P. Manly, et al. Phytochem. Lett. 2 (2009) 141.
[12] Spectral data of (±)-sepicanin A: yellow powder, IR (KBr, cm^{-1}) ν: 3237, 2911, 1697, 1639, 1600, 1452, 1374, 1265, 1156, 1088, 1046, 976, 835, 756; ^1H NMR (400 MHz, acetone-d_6): δ 1.15, 1.52, 1.64 (s, 9H, 3× CH_3), 1.89–1.93 (m, 4H, CH_2), 2.58 (dd, 1H, J = 3.0, 17.2 Hz, $H_{3\beta}$), 3.03 (dd, 1H, J = 13.0, 17.2 Hz, $H_{3\alpha}$), 3.13 (d, 2H, J = 7.2 Hz, 1″-2H), 4.96 (t, 1H, J = 6.8 Hz, =CH) 5.13 (t, 1H, J = 6.8 Hz, =CH), 5.56 (dd, 1H, J = 3.0, 13.0 Hz, 2-CH), 5.90 (s, 1H, 8-H), 6.30 (dd, 1H, J = 2.0, 8.2 Hz, 5′-H), 6.33 (d, 1H, J = 2.0 Hz, 3′-H), 7.18 (d, 1H, J = 8.2 Hz, 6′-H), 12.38 (s, 1H, –OH); EIMS m/z $[M]^+$: 424 (32), 219 (100), 69 (96), 165 (86), 283 (83), 301 (47), 187 (39), 177 (31).