

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Chinese Chemical Letters 23 (2012) 1375-1377



www.elsevier.com/locate/cclet

First total synthesis of four natural prenylated flavonoids

Jin Hui Yang^{*}, Wu Biao Zuo, Dong Dong Guo, Jun Shan Luo, Wen Qian Huang

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

Received 6 September 2012 Available online 1 December 2012

Abstract

A facile approach for the first total synthesis of prenylated flavonoids, (\pm) -abyssinone-VI-4-O-methyl ether 1, (\pm) -abyssinone-IV-4'-O-methyl ether 2, (\pm) -abyssinone-V-4'-O-methyl ether 3 and (\pm) -sigmoidin E 4 has been described. The key intermediate 4-hydroxy-3,5-di-(3-methylbut-2-enyl)benzaldehyde $\mathbf{6}$ was also first synthesized that features regioselective prenylation of 4-hydroxybenzaldehyde and crystallizing with petroleum ether from the reaction mixture by freeze-out effect. © 2012 Jin Hui Yang. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.

Keywords: Prenylated flavonoid; (\pm) -Abyssinone-VI-4-O-methyl ether; (\pm) -Abyssinone-IV-4'-O-methyl ether; (\pm) -Abyssinone-V-4'-O-methyl ether ether; (\pm) -Sigmoidin E; Total synthesis

Natural flavanoids exist widely in the plant kingdom and exhibit many important biological and pharmacological activities such as antibacterial [1,2], antifungal [3], antitumor [4] and hypotensive [5].

Compounds 1-4 (Fig. 1) were all isolated from the genus *Erythrina*, compound 1 and 2 from the root bark of Erythrina mildbraedii [6], compound 3 from Erythrina abyssinica [7] and Erythrina burttii [8] and compound 4 from Erythrina sigmoidea [9]. The genus Erythrina of the family Leguminosae comprises over 110 species of trees and shrubs that are widely distributed in tropical and subtropical regions, and representative species have been used in indigenous medicine [10]. As far as we know, the total synthesis of compounds 1-4 has not been reported yet. The research on the total synthesis of compounds 1-4 does not only have theoretical importance, but have the potential medical prospect.

In continuation of our ongoing program on the studies of flavanoids [11-13], we report herein a facile synthetic approach (Scheme 1) for the synthesis of compounds 1-4.

The key step was the introduction the prenyl group to 4-hydroxybenzaldehyde 5 for the synthesis of 4-hydroxy-3,5di-(3-methylbut-2-enyl)benzaldehyde 6. The reactions of C-alkylation of phenols commonly suffer from poor yield and low selectivity. An efficient synthetic method is still in lack.

The reaction of prenylation on 4-hydroxybenzaldehyde has been reported and gave a mixture of prenylated compounds according to Robert M. Moriarty's report [14], but the synthesis of 4-hydroxy-3,5-di-(3-methylbut-2enyl)benzaldehyde 6 has not been reported. Several methods for the prenylation on the 4-hydroxybenzaldehyde 5 were tried with unsatisfactory results. The 4-hydroxy-3,5-di-(3-methylbut-2-enyl)benzaldehyde 6 was obtained in a

* Corresponding author.

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

^{1001-8417/\$-} see front matter © 2012 Jin Hui Yang, Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved. http://dx.doi.org/10.1016/j.cclet.2012.10.012



Scheme 1. Conditions and reagents: (a) isoprenyl bromide, KOH, H₂O; (b) dimethyl sulfate, anhydrous K₂CO₃, acetone, reflux; (c) KOH-H₂O-EtOH, N2; (d) EtOH, NaOAc, reflux; (e) MeOH, HCl, reflux; (f) DDQ, benzene, reflux; (g) anhydrous K2CO3, acetone, MOMCl, reflux.



(±)-abyssinone-IV-4'-O-methy elther (±)-abyssinone-V-4'-O-methy elther (\pm) -abyssinone-VI-4-O-methyl ether

Fig. 1. The structure of compounds 1-4.

relatively high yield (10.4%) by treatment of 4-hydroxybenzaldehyde **5** with isoprenyl bromide (4 equiv.) and potassium hydroxide (4 equiv.) in water. It is worthy to note that 4-hydroxy-3,5-di-(3-methylbut-2-enyl)-benzaldehyde **6** could not be separated from the mixture by direct silica gel column chromatography because of having the same polarity with an another product. It was get by a two-step sequence: (1) the mixture was separated from the reaction residue by Si gel column chromatography eluting with petroleum ether-EtOAc (10:1); (2) pure product **6** was obtained by crystallizing with petroleum ether at 0 °C for 24 h in 10.4% yield based on unrecovered starting material as a white solid.

In summary, we have synthesized (\pm) -abyssinone-VI-4-*O*-methyl ether **1**, (\pm) -abyssinone-IV-4'-*O*-methyl ether **2**, (\pm) -abyssinone-V-4'-*O*-methyl ether **3** and (\pm) -sigmoidin E **4** for the first time [15]. 4-Hydroxy-3,5-di-(3-methylbut-2-enyl)benzaldehyde was also synthesized for the first time, which would be a useful intermediate for synthesis of diprenylated flavonoids.

Acknowledgments

This work was financially supported by the National Natural Science Foundation (Nos. 21162021, 20962016), Ningxia Natural Science Foundation (No. NZ1006), Program for New Century Excellent Talents in University (No. NCET-09-0860) and the National Basic Research Program 973 of China (No. 2010CB534916).

References

- [1] M.J. Salvatore, A.B. Kng, A.C. Graham, et al. J. Nat. Prod. 61 (1998) 640.
- [2] M.M. Rahman, A.I. Gray, P. Hkondkar, et al. Pharm. Biol. 46 (2008) 356.
- [3] T.L. Meragelman, K.D. Tucker, T.G. McClord, et al. J. Nat. Prod. 68 (2005) 1790.
- [4] K.V. Hirpara, P. Aggarwal, A.J. Mukherjee, et al. Curr. Med. Chem. 9 (2009) 138.
- [5] T.R. Seshadri, Tetrahedron 6 (1959) 169.
- [6] M. Na, J. Jang, D. Njamen, et al. J. Nat. Prod. 69 (2006) 1572.
- [7] M. Moriyasu, M. Ichimaru, Y. Nishiyama, et al. J. Nat. Prod. 61 (1998) 185.
- [8] A. Yenesew, J.O. Midiwo, M. Miessner, et al. Phytochemistry 48 (1998) 1439.
- [9] R. Promsattha, M.S. Tempesta, Z.T. Fomum, et al. J. Nat. Prod. 51 (1988) 611.
- [10] B. Oliver-Bever, Medicinal Plants in Tropical West Africa, Cambridge University Press, New York, 1981, p. 100.
- [11] J.H. Yang, Y.M. Zhao, C.B. Ji, Chin. Chem. Lett. 19 (2008) 658.
- [12] J.H. Yang, S.Z. Jiang, Y.M. Zhao, et al. Chin. Chem. Lett. 20 (2009) 1062.
- [13] J.H. Yang, Y.H. Zhang, H.J. Li, et al. Chin. Chem. Lett. 21 (2010) 1267.
- [14] R.M. Moriarty, S. Grubjesic, B.C. Surve, et al. J. Med. Chem. 41 (2006) 263.
- [15] Spectral data of (±)-abyssinone-VI-4-O-methyl ether: yellow powder, mp 90–93 °C; IR (KBr): 3300, 2968, 2920, 1633, 1570, 1365, 1265, 1130 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): (13.47 (s, 1H, OH), 7.84 (d, 1H, *J* = 8.8 Hz, H-6'), 7.82 (d, 1H, *J* = 16 Hz, H-β), 7.43 (d, 1H, J = 15.6 Hz, H-a), 7.32 (s, 2H, H-2 and 6), 6.45 (dd, 1H, J = 2.4, 8.8 Hz, H-5'), 6.43 (d, 1H, J = 2.4 Hz, H-3'), 5.30 (m, 2H, H-2" and 2"'), 3.77 (s, 3H, OCH₃), 3.39 (d, 4H, *J* = 7.2 Hz, H-1" and 1"'), 1.77 (12H, s, H-4", 4"', 5" and 5"'); EIMS *m*/*z* [M⁺] 406 (31.73), 391 (3.93), 375 (7.47), 43 (100.00). HREIMS m/z [M⁺] 406.2136 (calcd. for C₂₆H₃₀O₄⁺ 406.2144). Spectral data of (±)-abyssinone-IV-4'-O-methyl ether: white powder, mp 72–73 °C; IR (KBr): 3200 (br, OH), 2970, 2920, 1650, 1600, 1460, 1370, 1270, 1125 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): (7.85 (d, 1H, J = 8.4 Hz, H-5, 7.11 (s, 2H, H-2' and 6'), 6.53 (dd, 1H, J = 2.4, 8.4 Hz, H-6), 6.45 (d, 1H, J = 2.4 Hz, H-8), 5.37 (dd, 1H, J = 2.8, 13.6 Hz, 1.6 Hz, 1 H-2), 5.29 (m, 2H, H-2" and 2"'), 5.20 (s, 1H, OH), 3.75 (s, 3H, OCH₃), 3.39 (d, 4H, J = 6.8 Hz, H-1" and 1"'), 3.04 (dd, 1H, J = 13.2, 16.8 Hz, $H-3_{ax}$, 2.79 (dd, 1H, J = 2.8, 16.8 Hz, $H-3_{eq}$), 1.75 (s, 6H, H-4'' and 4''), 1.73 (s, 6H, H-5'' and 5'''); EIMS m/z [M]⁺ 406 (59.42), 243 (55.74), 201 (40.55), 171 (52.00), 163 (38.85), 137 (100.00), 69 (93.14), 43 (50.26). HREIMS m/z [M⁺] 406.2140 (calcd. for C₂₆H₃₀O₄⁺ 406.2144). Spectral data of (±)-abyssinone-V-4'-O-methyl ether: white solid, mp 146–147 °C; IR (KBr): 3360, 2970, 2920, 1680, 1605, 1580, 1435, 1370, 1260, 1210, 1145, 1065 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): (12.06 (s, 1H, OH), 7.09 (s, 2H, H-2' and 6'), 5.99 (d, 1H, J = 2.0 Hz, ArH), 5.98 (d, 1H, J = 2.0 Hz, ArH), 5.33 (dd, 1H, J = 2.8, 13.2 Hz, H-2), 5.28 (m, 2H, H-2" and 2"'), 3.75 (s, 3H, OCH₃), 3.39 (d, 4H, J = 7.2 Hz, H-1" and 1"''), 3.10 (dd, 1H, J = 13.2, 17.2 Hz, H-3_{ax}), 2.78 (dd, 1H, J = 2.8, 17.2 Hz, H-3_{eq}), 1.75 (s, 6H, H-4" and 4"'), 1.73 (s, 6H, H-5" and 5"'); EIMS m/z [M]⁺ 422 (62.65), 391 (86.38), 243 (59.08), 179 (47.40), 153 (100.00). HREIMS m/z [M⁺] 422.2095 (calcd. for C₂₆H₃₀O₅⁺ 422.2093). Spectral data of (±)-sigmoidin E: white solid, IR (KBr): 3200 (br, OH), 2970, 2920, 1635, 1594, 1500, 1460, 1340, 1265, 1150, 1080 cm^{-1} ; ¹H NMR (CDCl₃, 400 MHz): (12.07 (s, 1H, OH), 7.02 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 Hz, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 \text{ Hz}, H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-2'), 6.31 (d, 1H, J = 2.4 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 Hz, H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), 6.92 (d, 1H, J = 2.0 \text{ Hz}), H-6'), H-6'), H-6', H-6'), H-6'), H-6', H-6'), H-6', H-6'), H-6', H-6'), H-6'), H-6', H-J = 9.6 Hz, H-4"), 5.99 (d, 1H, J = 2.0 Hz, ArH), 5.98 (d, 1H, J = 2.0 Hz, ArH), 5.64 (d, 1H, J = 9.6 Hz, H-3"), 5.29 (dd, 1H, J = 2.8, 13.2 Hz, H-2), 5.26 (m, 1H, H-2^{'''}), 3.28 (d, 2H, J = 7.6 Hz, H-1^{'''}), 3.11 (dd, 1H, J = 13.2, 17.2 Hz, H-3_{ax}), 2.76 (dd, 1H, J = 2.8, 17.2 Hz, H-3_{eq}), 1.73 (s, 6H, H-4" and 5"), 1.43 (s, 6H, H-5" and 6"); EIMS m/z [M]⁺ 406 (18.26), 391 (100.00), 239 (17.60); HREIMS m/z [M⁺] 406.1781 (calcd. for C₂₅H₂₆O₅⁺ 406.1780).