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BF_3–Et_2O mediated biogenetic type synthesis of chromanochalcones from prenylated chalcones via a regioselective cyclization reaction☆

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Abstract—In continuation of our program on synthetic chalcones, we have developed a simple and convenient method for the synthesis of chromanochalcones from prenylated chalcones in high yields by regioselective cyclization using BF_3–Et_2O.
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The benzopyran system is frequently encountered in many natural products and exhibits significant biological activity such as anti-HIV,[1a,b] antihypertensive[1c,d] and antifeedant.[1e] Several pharmaceutical compounds (Fig. 1) such as vitamin E (antioxidant),[2] clusifoliol (antitumour)[3] and troglitazone (diabetes)[4] also possess the benzopyran moiety. The relatively high incidence of the benzopyran unit in natural products is partially attributable to the numerous prenylation and cyclization reactions in many polyketide biosynthetic pathways.[5] Methods to prepare such chromans include the use of HCOOH,[6] H_2SO_4,[7] Montmorillonite KSF clay,[8] Zeolite HSZ-360[9] and $AlCl_3$/HCl.[10]

As a part of our ongoing interest in developing new antiparasitic agents, we have recently reported on the antimalarial activity of a few naturally occurring prenylated chalcones[11a] and the antileishmanial activity of chromenodihydrochalcones, that is, crotaramosmin, crotaramin and crotin[11b–d] (Fig. 1). To improve the antiparasitic activity, and we synthesized several prenylated chalcones and chromenochalcones, evaluated their antiparasitic activity and further utilized them for the synthesis of chromanochalcones in order to study the structure activity relationships.

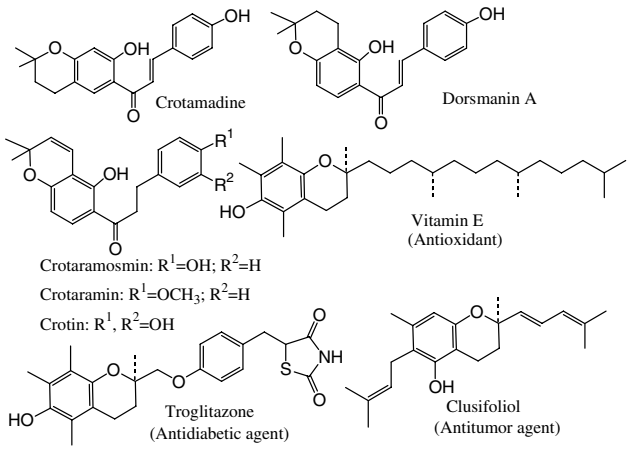

Figure 1. Crotamadine from *Crotalaria madurensis*; Dorsmanin A from *Dorstenia mannii*, crotaramosmin, crotaramin and crotin from *Crotalaria ramosissima* and biologically active compounds (vitamin E, Troglitazone and Clusifoliol) possessing a chroman ring.

Initial attempts to synthesize chromanochalcones (Scheme 1) from readily available chalcones by the following methods failed: (i) cyclization of the prenyl group of chalcone using routinely used acids such as HCOOH/H_2SO_4 led to the formation of chromanoflavanone; (ii) synthesis from chromenochalcones using several reducing agents such as Pd/C and $NaBH_4$/$NiCl_2$ failed to reduce the chromene double bond selectively and formed the fully saturated chromanodihydrochalcones; (iii)

Keywords: Chromanochalcones; Regioselective cyclization; BF_3–Et_2O; Biogenetic type synthesis.
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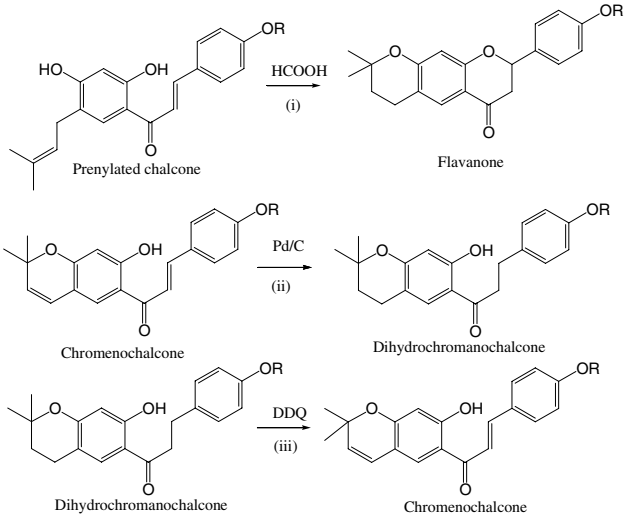


Scheme 1. (i) Cyclization of prenylated chalcone gave chromanoflavanone; (ii) hydrogenation of chromenochalcone provided chromanodidhydrochalcone; and (iii) dehydrogenation led to chromenochalcone.

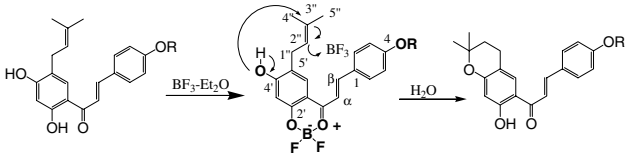
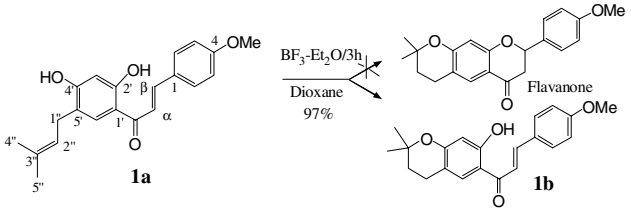
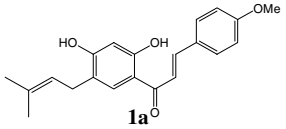
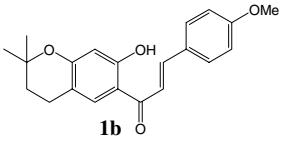
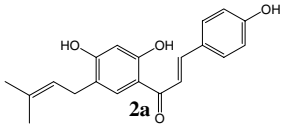
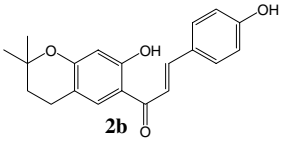
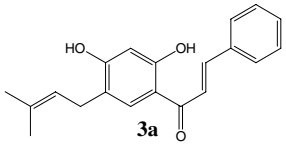
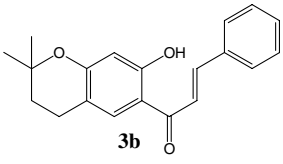
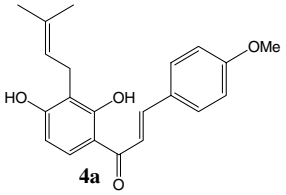
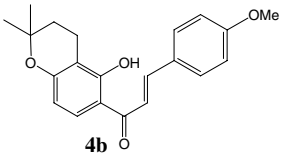
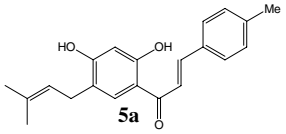
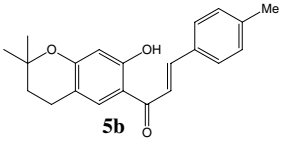
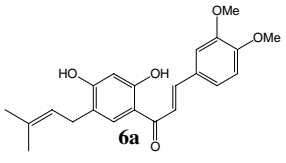
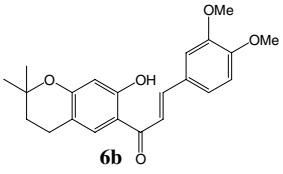


Figure 2. Possible reaction mechanism.



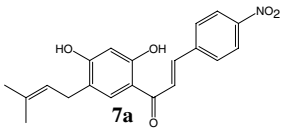
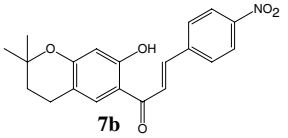
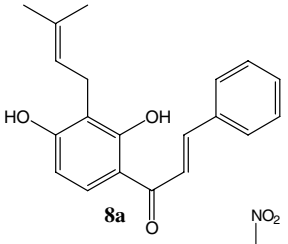
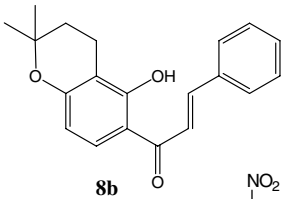
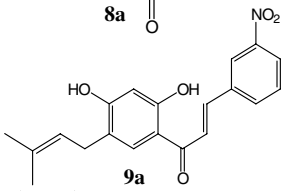
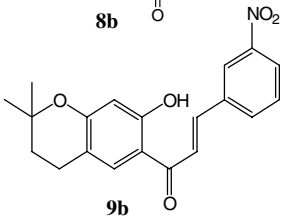
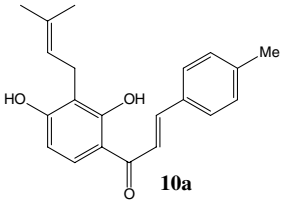
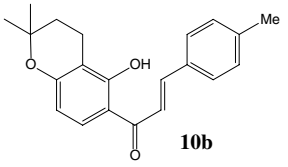
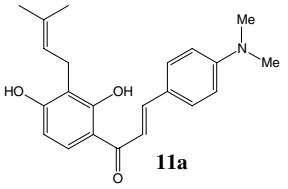
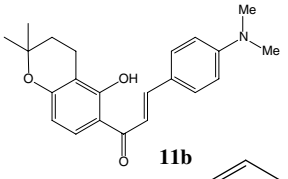
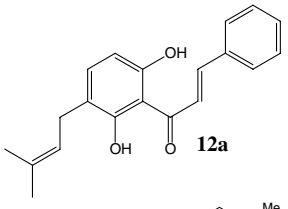
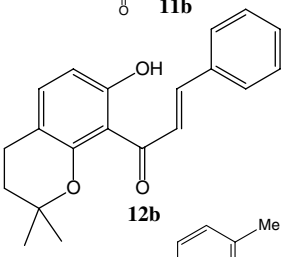
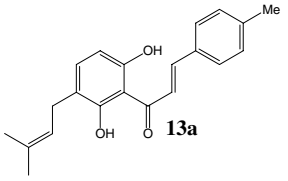
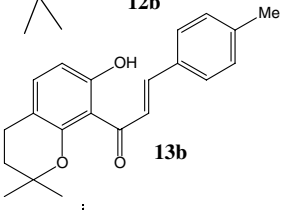
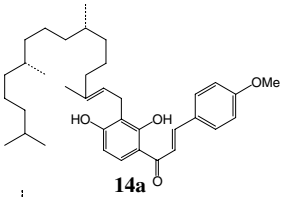
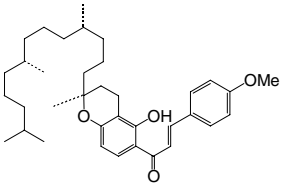
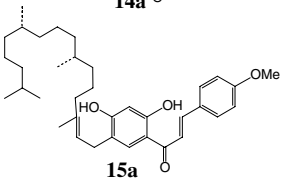
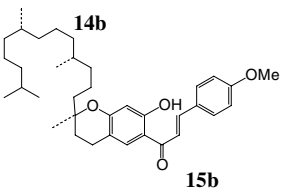
Scheme 2. Biogenetic type synthesis of chromanochalcones from prenylated chalcones using BF_3–Et_2O.

Table 1. Synthesis of chromanochalcones by regioselective cyclization of C-alkylated (prenylated and phytylated) polyhydroxychalcones using BF_3–Et_2O

Entry	Substrate	Product	Yield[a] (%)
1	 **1a**	 **1b**	97
2	 **2a**	 **2b**	94
3	 **3a**	 **3b**	98
4	 **4a**	 **4b**	89
5	 **5a**	 **5b**	96
6	 **6a**	 **6b**	95

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Product	Yield[a] (%)
7	 **7a**	 **7b**	93
8	 **8a**	 **8b**	94
9	 **9a**	 **9b**	93
10	 **10a**	 **10b**	92
11	 **11a**	 **11b**	91
12	 **12a**	 **12b**	94
13	 **13a**	 **13b**	92
14[b]	 **14a**	 **14b**	87
15[b]	 **15a**	 **15b**	95

[a] Isolated yields.
[b] Stereochemistry was not determined.

DDQ catalyzed dehydrogenation of fully saturated chromanodihydrochalcone also failed to dehydrogenate the required saturated double bond selectively and provided chromenochalcone.

A few natural chromanochalcones, which contain an α,β-unsaturated double bond and a saturated chroman ring (dihydrobenzopyran) in the same molecule, have appeared in the literature (Fig. 1: Crotamadine and Dorsmanin A).[12,13] In continuation of our efforts to synthesize chromanochalcones, we herein report the biogenetic type synthesis of chromanochalcones by regioselective cyclization of prenyl group of the prenylated chalcones using BF_3–Et_2O.

Recently, we developed a new and simple methodology for the synthesis of chalcones in high yields using BF_3–Et_2O.[14] We wanted to utilize BF_3–Et_2O for regioselective cyclization and anticipated that BF_3–Et_2O might form a complex with the chelated hydroxyl group (C-2′) and the α,β-unsaturated carbonyl group of the prenylated chalcone. This complexation prevents the formation of a flavanone. The second mole of the reagent might provide cyclization of the prenyl group to give the chromanochalcone (Fig. 2).

To investigate this possibility we carried out a cyclization reaction with the prenylated chalcone 2′,4′,-dihydroxy-4-methoxy-5′-*C*-prenylchalcone **1a** in the presence of BF_3–Et_2O. Gratifyingly, regioselective cyclization of the prenyl group occurred to give exclusively chromanochalcone **1b**, but we did not observe formation of the corresponding flavanone (Scheme 2).[15] To demonstrate the generality of the reaction we have used several prenylated chalcones **2a**–**13a** and synthesized chromanochalcones **2b**–**13b** in excellent yields (Table 1).

Several natural chalcones exist with long chain alkyl groups such as geranyl, farnesyl and phytyl. We also prepared such chalcones and succeeded to cyclize the long chain alkyl group selectively to give chromanochalcones **14b** and **15b** without the formation of the corresponding flavanones (Table 1). Recently, we demonstrated the tolerability of BF_3–Et_2O towards acid or base sensitive functional groups such as *O*-acyl and *N*-acyl groups, therefore BF_3–Et_2O can be used as a regioselective cyclizing agent in the presence of such functional groups.[14] In the case of acid or base catalyzed cyclizations, these sensitive groups undergo hydrolysis leading to deacylated compounds along with the formation of flavanone.

In summary, we have demonstrated the use of BF_3–Et_2O as a regioselective cyclizing agent for the synthesis of chromanochalcones from prenylated chalcones and long chain phytylated chalcones. Our method has several advantages over existing methods such as no side reactions (flavanone formation), high yields, simple workup, short reaction times and tolerates base or acid sensitive functional groups. This methodology can be used for the synthesis of several natural products and their analogues.

Acknowledgements

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Supplementary data

Spectral data of all the compounds associated with this article are available as supplementary data. It can be downloaded from the internet. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.124.

References and notes

1. (a) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H.; McMahon, J. B., II; Currens, M. J.; Buckheit, R. W.; Hughes, S. H., Jr.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735–2743; (b) Currens, M. J.; Mariner, J. M.; McMahon, J. B.; Boyd, M. R. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 652–661; (c) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492–504; (d) Gericke, R.; Harting, J.; Lues, I.; Schittenhelm, C. *J. Med. Chem.* **1991**, *34*, 3074–3085; (e) Srivastava, R. P.; Proksch, P. *Entomol. Gen.* **1991**, *15*, 265–274.
2. (a) Burton, G. W.; Ingold, K. U. *Ann. N.Y. Acad. Sci.* **1989**, *570*, 7–22; (b) Harada, T.; Hayashiya, T.; Wada, I.; Iwaake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527–532; (c) Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. *J. Org. Chem.* **1987**, *52*, 5495–5497.
3. (a) Seeram, N. P.; Jacobs, H.; McLean, S.; Reynolds, W. F. *Phytochemistry* **1998**, *49*, 1389–1391; (b) Tanaka, T.; Asai, F.; Iinuma, M. *Phytochemistry* **1998**, *49*, 229–232.
4. Matsumoto, K.; Miyake, S.; Yano, M.; Ueki, Y.; Tominaga, Y. *Lancet* **1997**, *350*, 1748.
5. Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953.
6. Pushpa, B.; Rameshwar, D. *Indian J. Chem.* **2002**, *41B*, 184–186.
7. Charles, D. H.; William, A. H. *J. Org. Chem.* **1940**, *5*, 212–222.
8. William, G. D.; Jeffrey, M. C.; Victor, B. *Tetrahedron Lett.* **1990**, *31*, 3241–3244.
9. Bigi, F.; Carloni, S.; Maggi, R.; Muchetti, C.; Rastelli, M.; Sartori, G. *Synthesis* **1998**, 301–304.
10. Wang, Y.; Wu, J.; Xia, P. *Synth. Commun.* **2006**, *36*, 2685–2698.
11. (a) Narender, T.; Shweta; Tanvir, K.; Rao, M. S.; Srivastava, K.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2453–2455; (b) Kumar, J. K.; Narender, T.; Rao, M. S.; Rao, P. S.; Toth, G.; Balazs, B.; Duddeck, H. *J. Braz. Chem. Soc.* **1999**, *10*, 278–280; (c) Narender, T.; Shweta; Gupta, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3913–3916; (d) Narender, T.; Tanvir, K.; Shweta; Nishi; Goyal, N.; Gupta, S. *Bioorg. Med. Chem.* **2005**, *13*, 6543–6550.
12. Ngadjui, B. T.; Abegaz, B. M.; Dongo, E.; Tamboue, H.; Fogue, K. *Phytochemistry* **1998**, *48*, 349–354.
13. Bhakuni, D. S.; Chaturvedi, R. *J. Nat. Prod.* **1984**, *47*, 585–591.
14. Narender, T.; Reddy, K. P. *Tetrahedron Lett.* **2007**, *48*, 3177–3180.

15. *Representative procedure for the preparation of chromanochalcones from prenylated chalcones*: To a stirred solution of 2′,4′,-dihydroxy-4-methoxy-5′-*C*-prenyl chalcone **1a** (500 mg, 1.4 mmol) in dry 1,4-dioxane (5 mL), was added gradually BF_3–Et_2O (0.23 mL, 1.7 mmol) at room temperature. The solution was stirred for 3 h at room temperature. After dilution with ethyl acetate (100 mL), the mixture was washed with water (3×30 mL) to discharge the colour and the BF_3–Et_2O complex. The organic solution obtained after extraction was dried over anhyd Na_2SO_4 and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford chromanochalcone **1b** (485 mg, 97%).