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Total Synthesis of (±)-Sinaiticin

Xuegong She [a], Xiaobi Jing [a], Xinfu Pan [a,*], Albert S. C. Chan [b] and Teng-Kuei Yang [c]

[a] *Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China*

[b] *Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong*

[c] *Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan*

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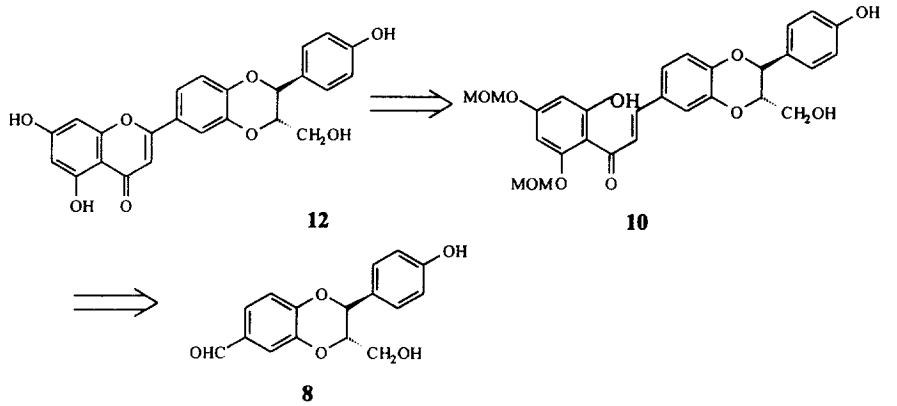
Abstract: (±)-Sinaiticin (**12**) was first synthesized from 4-hydroxybenzoaldehyde (**1**) and caffeic acid (**4**). This synthesis involves the construction of flavon ring with DDQ and the formation of 1,4-benzodioxane ring by coupling reaction in which a epimerization was taken place.

The flavonolignans, sinaiticin (**12**), was isolated from sinaticum leaves found in sinai region of Egypt.[1] This species exhibits significant inhibitory activity against the murine lymphocytic leukaemia P-388 cell line. This kind of natural products have shown a variety of bioactivities and raised synthetic chemists interesting.[2]



Scheme 1

* To whom correspondence should be addressed.

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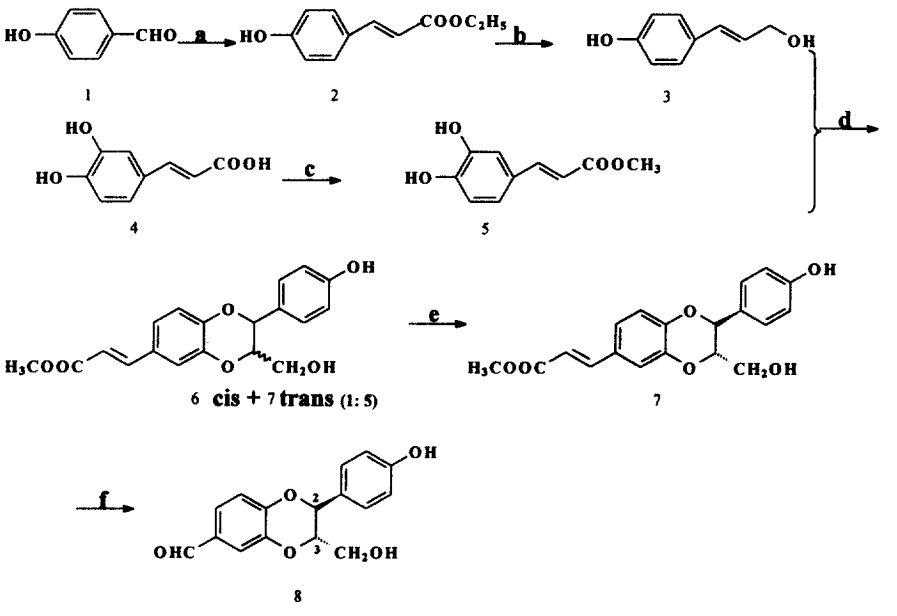
In order to verify the proposed structure, we have synthesized the titled natural product. The synthetic design is to construct the substituted benzodioxane ring first, followed by formation of flavon moiety. Retrosynthetic analysis is shown in scheme **1**.

From scheme **1**, it can be seen that compound **8** is the key intermediate in the synthesis of target molecule. Although several methods for the synthesis of benzodioxane had been reported in the literature,[3] the products were a mixture of *cis* and *trans* isomers. Herein, we wish to report the stereoselective synthesis of this type compounds in which *cis* isomer was converted to *trans* isomer by treatment with K_2CO_3.



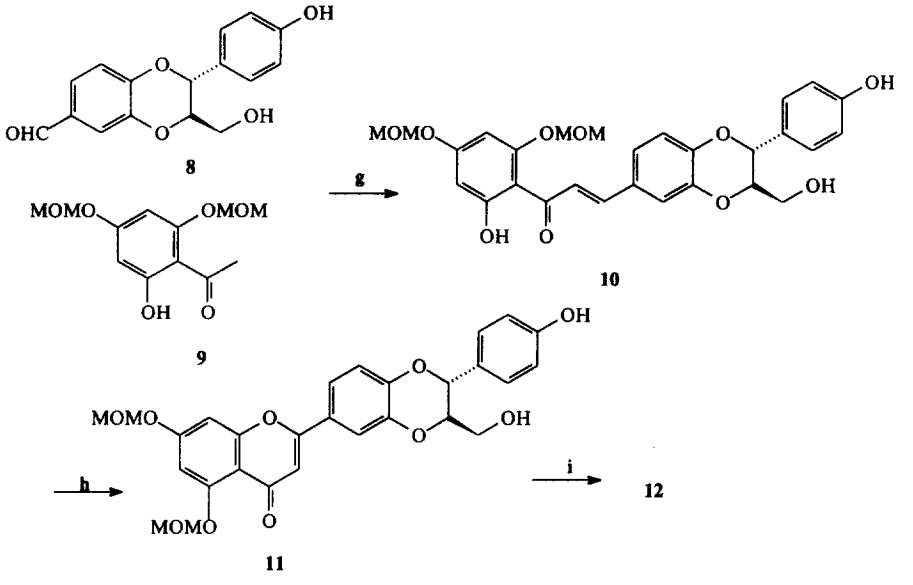
Regents and conditions: a: $HO_2CCH_2CO_2C_2H_5$, Py, Hexahydropyridine, reflux, (95%); b: $LiAlH_4$, $AlCl_3$, (90%); c: H_2SO_4, CH_3OH, reflux, (95%); d: $K_3Fe(CN)_6$, NaOAc; e: K_2CO_3, DMF, then HCl (d, e overall yield 32%);[13] f: $OsO_4/NaIO_4$,(67%.)

Scheme 2

As shown in Scheme **2**, 4-hydroxy-benzoaldehyde (**1**) reacted with monoethyl malonate to give ester (**2**) that was reduced to afford the corresponding unsaturated alcohol (**3**). **3** was coupled with **5**, which was derived from **4**, to give a mixture of isomer

6 (*cis*) and **7** (*trans*) [4] (ca. 1:5 by ^{1}HNMR), and the mixture was stirred in dry DMF with anhydrous K_2CO_3 for 1hr to yield isomer **7** exclusively. The key intermediate compound **8** was obtained by oxidition of **7** with $OsO_4/NaIO_4$.

The synthesis of sinaiticin (**12**) from **8** was accomplished as scheme **3**. Condensation of 2,4-dimethoxymethyl 6-hydroxyacetophenone (**9**)[10] with **8** in KOH-H_2O-C_2H_5OH system to provided the expected chalcone (**10**) in 95% yield. In the spectrum, the coupling constant between the signals of two vinylic protons newly appearing at 6.20 and 7.80 ppm is 16Hz, which indicates the formation of a trans double bond. Although varies unsuccessful trials were reported on the cyclization of chalcone (**10**),[5-9] we found that chalcone (**10**) reacted with DDQ in dry dioxne to afford compound **11**. The compound **11** underwent deprotection with hydrochloric acid in methanol at 70 ℃ to obtain sinaiticin (**12**) in 94% yield. All of our spectra data of siniticin (**12**) were in agreement with the literature report.[1]



Regents and conditions: g: C_2H_5OH-H_2O, KOH, rt. h: DDQ, dioxane reflux. I: 3N HCl , reflux.

Scheme 3

Advantages of the present route include the formation of the dioxane ring with *cis* isomer epimerization under the given conditions, the use of DDQ to construct the flavon ring and the utilization of mild conditions throughout. The methodology is adaptable to the synthesis of a variety of benzodioxane neolignans and flavonolignans.

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11. Date of key intermediate **8:** ^{1}H-NMR (400Hz, CD_3CN), δ 9.79 (s,1H), 6.83-7.45 `(m,7H), 5.01 (d, 8Hz, 1H), 4.12 (m, 1H), 3.62 and 3.39 (dd, 12Hz, 2.4 Hz, 2H); MS(m/z): 286 (M^+, 100), 268 (67), 232 (19), 149 (29), 107 (22); IR (KBr/V cm^{-1}): 3470, 3209, 2753, 1743, 1676, 1602.
12. Date of chalcon **10**, ^{1}H-NMR (400Hz, CD_3CN), δ 7.80 (d, 16Hz, 1H), 7.26-6.80 (m, 9H), 6.20 (d, 16Hz, 1H), 5.29 and 5.17 (s, 4H), 4.93 (dd, 8Hz, 1H), 4.08 (m, 1H),3.60 and 3.40 (dd, 12.3Hz, 2.4 Hz, 2H), 3.46 and 3.33 (s, 6H). MS (m/z): 524 (M^+ 14), 480 (25), 462 (20), 417 (7), 343 (9), 132 (39), 107 (12).
13 d. Oxidative coupling yields a ca 9:1 mixture of 2-aryl-(**6+7**) and 3-aryl-1.4-benzodioxane derivatives (*cis+trans*). e. *Trans* isomer (7)was recrystallined with methanol to afford white solid.