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Stereoselective Synthesis of 2-(4-Hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxane-6-aldehyde—The Key Intermediate of Sinaiticin

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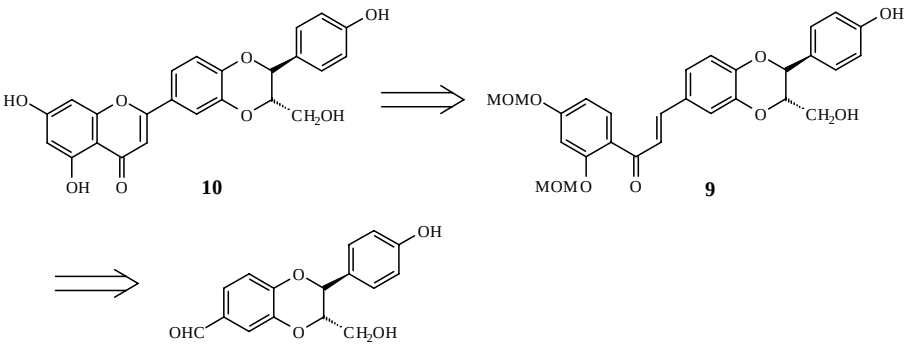
Abstract: 2-(4-Hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxane-6-aldehyde **8**, the key intermediate of sinaiticin **10**, was synthesized in 6 steps from caffeic acid **4** and 4-hydroxybenzaldehyde **1**, the coupling reaction is the key step.

Keywords: 2-(4-Hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxane-6-aldehyde, key intermediate, sinaiticin, synthesis.

Sinaiticin **10**, a flavonolignan, was isolated from *sinaiticum* leaves and had inhibitory P-388 cell activity[1]. This type of natural products have shown various bioactivity and received considerable attention from synthetic chemists [2].

We wish to report a stereoselective total synthesis of sinaiticin from readily available starting materials (**1** and **4**). Our synthetic design is based upon construction of the substituted benzodioxane ring, followed by formation of the flavanonol moiety.

Scheme 1

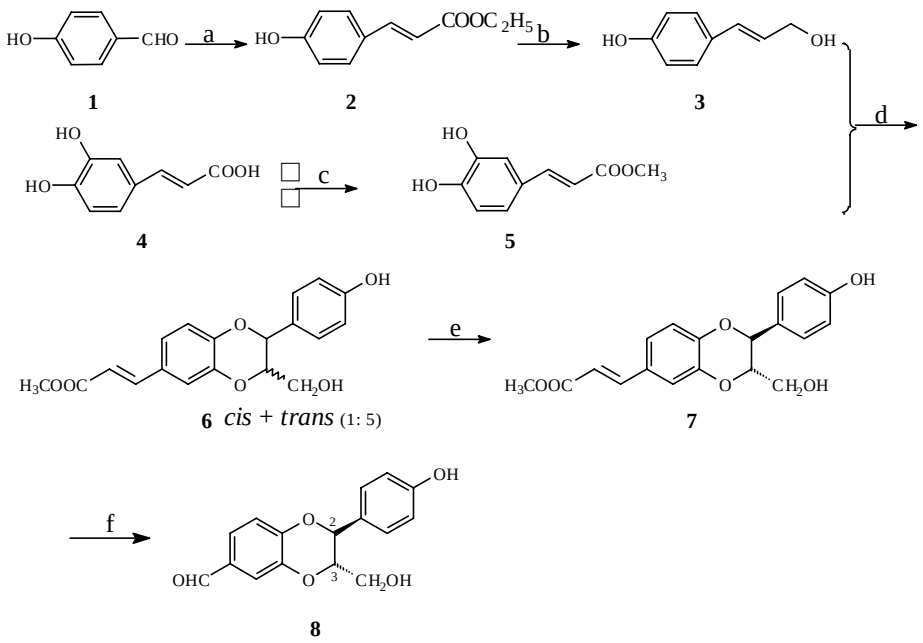


From **Scheme 1**, we can see that in this synthesis of sinaiticin, compound **8** is a key intermediate. Herein, we describe a route of stereoselective synthesis of compound **8**, in which *cis* isomer **6** was converted into *trans* **7** by treatment with K_2CO_3.

As shown in **Scheme 2**, 4-hydro-benzoaldehyde **1** reacts with mono ethyl malonate to obtain ester **2** which was reduced to afford the corresponding unsaturated alcohol **3**[3]. **3** was coupled with **5** which was derived from **4** to give a mixture of isomer **6** (*cis*) and isomer **7** (*trans*) [4] (*ca.* 1:5 by ^{1}HNMR), the mixture was stirred in dry DMF with anhydrous K_2CO_3 for 1 hr to get isomer **7** exclusively. The **7** was oxidized with

$OsO_4/NaIO_4$ to obtain key intermediat compound **8**. Synthesis of flavonolignan **10** is in progress.

Scheme 2



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%); f: $OsO_4/NaIO_4$, 67%.

Acknowledgments

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References and Notes

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5. Compound **7**: ^{1}HNMR (400Mz, CD_3CN) δ:7. 62 (d 1H 16Hz H-8'), 7. 32-6. 72 (6H Ar-H), 6. 32 (d 1H 16Hz H-7'), 4. 99 (d 1H 8Hz H-7), 4. 16 (m 1H H-8), 3. 84 (s 3H -$COCH_3$), 3. 53 and 3. 77 (dd 2H 12Hz 4Hz H-9). Ms (m/z) 342 (M^+ 45), 324 (43), 282 (25), 205 (27), 132 (76), 107 (100).
6. Compound **8**: IR (KBr):3470, 3207, 2753, 1743, 1602, 1499cm^{-1}; ^{1}HNMR (80Mz, $CDCl_3$) δ: 9. 86 (s, 1H, C**H**O), 6. 67-7. 53 (m, 7H, Ar**H**), 5. 10 (d, 1H, 8Hz, H-2), 4. 10 (m, 1H, H-3), 3. 51 and 3. 86 (dd, 2H, 12. 2Hz, 4Hz, -C**H**$_2$OH); MS (m/z): 286 (M^+,100), 268 (67), 149 (29), 107 (22).

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