Chinese Chemical Letters Vol. 14, No. 6, pp 551 – 554, 2003
http://www.imm.ac.cn/journal/ccl.html


# First Enantioselective Synthesis of Daphneticin

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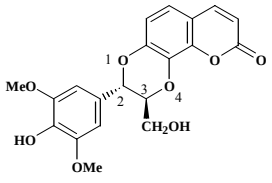
**Abstract:** An enantioselective total synthesis of chiral daphneticin is reported firstly.

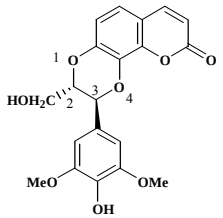
**Keywords:** Synthesis, enantioselective, coumarinolignoids, daphneticin.

Coumarinolignoids are a relatively new and rare group of natural products arising from $C_6$, $C_3$, $C_6$ units. The coumarin moieties are linked with the phenyl propanoid units through a 1,4-dioxane bridge in these molecules[1]. Because of their various biological activities, especially their cytotoxicity and antihepatotoxic activities[2], several efficient synthesises of natural coumarinolignoids have been reported[3].

Daphneticin **1** has been isolated[2] from roots and stems of *Daphne tangutica*. As a coumarinolignoid, it showed[4] cytotoxic activity *in vitro* in the Walker-256- carcino-sarcoma-ascites system. However, Cordell and Lin[5] recently published that the structure of daphneticin would be revised formula **1** by application of the selective INEPT pulse programme of the daphneticin diacetate. Although several synthesises of daphneticin were reported, it is a pity that so far chiral synthesis of daphneticin has not been reported.




**1**




**2**

In our previous work[6], a first asymmetric and regioselective synthetic approach to 1,4-benzodioxane lignans was reported. In continuation of our studies, now we wish to report an enantioselective synthesis of daphneticin **1**.

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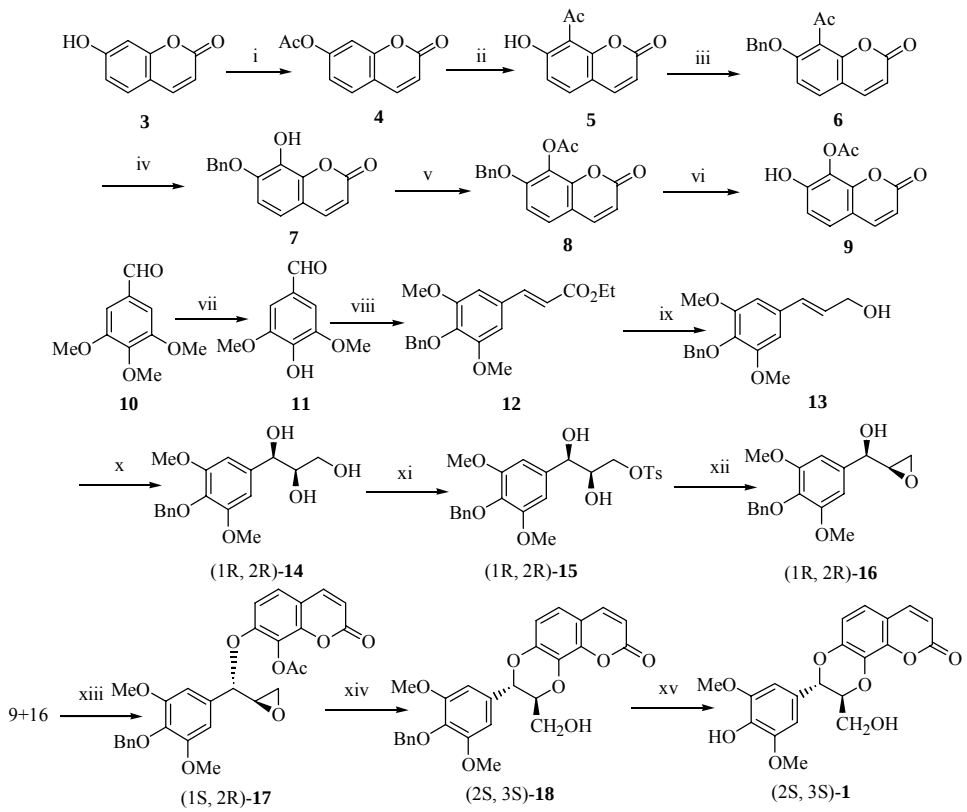
As shown in **Scheme 1**, 7-acetoxycoumarin **4** was prepared by acetylation of 7-hydroxycoumarin **3** with $Ac_2O$. Treatment of **4** with $AlCl_3$ under 160℃ gave 8-acetyl-7- hydroxycoumarin **5**[7]. Then, compound **7** was prepared by benzylation of compound **5** followed by treatment with hydrogen peroxide in alkaline dioxane solution. By acetylation, compound **7** was converted to the compound **8** that was subjected to catalytic hydrogenation yielding a debenzylation product **9**.

Treatment of compound **10** with piperidine and water gave 4-hydroxy- 3,5–dimethoxy-benzaldehyde **11**[8]. Reacted with monoethyl malonate[9] under pyridine and piperidine, aldehyde **11** was converted to an unsaturated ester[10]. Protection of the unsaturated ester with benzyl bromide afforded the benzyl ether **12** that was reduced to afford the corresponding alcohol **13**[11].

**Scheme 1**




Reagents and conditions: (i) $Ac_2O$, pyridine, r.t., 24 h, 97%; (ii) $AlCl_3$, 160°C, 2 h, 79%; (iii) BnBr, $K_2CO_3$, 24 h, 94%; (iv) $H_2O_2$, NaOH, 20 min, 94%; (v) $Ac_2O$, pyridine, r.t., 24 h, 90%; (vi) Pd/C (5%), $H_2$, EtOAc, r.t., 6 h, 92%; (vii) piperidine, $H_2O$, reflux, 48 h, 80%; (viii) 1) $CO_2HCH_2CO_2Et$, pyridine, piperidine, reflux, 6 h; 2) BnBr, $K_2CO_3$, 24 h, 80%; (ix) LAH, $AlCl_3$, THF, 0.5 h, 86%; (x) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, $H_2O$, 0°C, 20 h, 87%; (xi) TsCl, pyridine, 91%; (xii) $K_2CO_3$, MeOH, r.t., 3 h, 80%; (xiii) DIAD, $Ph_3P$, THF, r.t., 24 h, 65%; (xiv) $K_2CO_3$, MeOH, r.t., 3 h, 90%; (xv) Pd/C (5%), $H_2$, EtOAc, r.t., 6 h, 81%.

Asymmetric dihydroxylation of **13** by AD-mix-β afforded (1R, 2R)-**14** in 93% e.e.[12]. Reaction of (1R, 2R)-**14** with TsCl in pyridine provided primary tosylate (1R, 2R)-**15**. Ring closure of (1R, 2R)-**15** was promoted by potassium carbonate in methanol, generating oxirane (1R, 2R)-**16**[13]. A characterized ether (1S, 2R)-**17** was obtained by Mitsunobu reaction[14] between (1R, 2R)-**16** and compound **9**. The absolute configuration of the $C_1$-position was inversed completely by an $S_N2$-type nucleophilic displacement of 8-acetoxy-7-hydroxycoumarin in this reaction. Removal of acetyl group in (1S, 2R)-**17** followed by intramolecular cyclization with potassium carbonate in methanol afforded (2S, 3S)-**18**. In this reaction, an intramolecular nucleophilic attack at $C_2$-position of oxirane by the phenol hydroxyl in the presence of $K_2CO_3$ led to a complete inversion of the absolute configuration of the $C_2$-position and the formation of 1,4-benzodioxane[15]. The benzyl group was removed by hydrogenolysis under an atmospheric pressure of hydrogen in the presence of 5% palladized charcoal in ethyl acetate to afford (2S, 3S)-**1**[17]. In the $^1$H NMR spectrum of (2S, 3S)-**1**, H-2 resonated a doublet signal at δ 5.11 with a coupling constant (*J*=7.9 Hz) indicating a typical of *trans*-isomer and threo configuration. $^{13}$C NMR spectrum showed δ 61.4, 77.6 79.6 indicating a six-membered 2-aryl-3-hydroxymethyl-1,4-benzodioxane skeleton[16].

We have carried out the enantioselective synthesis of daphneticin (**1**) in 16.5% yield. All spectrum data were in agreement with those found in the literature[2,3c,3d]. This is the first enantioselective synthesis of coumarinolignoids.

## Acknowledgments

Support from the National Natural Science Foundation of China (No. 29972015; 20172023) is gratefully acknowledged.

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17. (2S, 3S)-Daphneticin **1**: white solid; $[\alpha]_D^{25}$ + 11 (*c* 1.40, $CHCl_3$). M.p. 229-231°C. MS (EI): 386($M^+$), 368, 353, 277, 209, 177, 167, 149, 43. $^1$H NMR (200 MHz, $D_6$-acetone): δ 3.74 (m, 2H), 3.88 (s, 6H), 4.25 (m, 1H), 5.11 (d, 1H, *J*=7.9 Hz), 6.27 (d, 1H, *J*=9.4 Hz), 6.67 (s, 2H), 7.14 (d, 1H, *J*=8.6 Hz), 7.35 (d, 1H, *J*=8.8 Hz), 7.68 (d, 1H, *J*=9.6 Hz). $^{13}$C NMR (50 MHz, $D_6$-acetone): δ 56.6, 61.4, 76.5, 78.6, 106.1, 114.6, 121.5, 125.1, 130.7, 138.9, 144.6, 145.9, 148.9, 160.5. IR (KBr/$cm^{-1}$): 3449, 1713, 1609, 1456, 1334, 1271, 1130, 1063, 835. (Found: C, 62.23; H, 4.68. $C_{20}H_{18}O_8$ requires C, 62.17; H, 4.66%).

Received 15 July, 2002