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An Efficient Synthesis of Cerbinal, a 10 π Aromatic Iridoid

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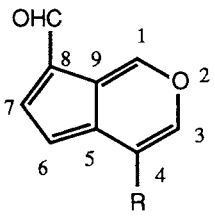
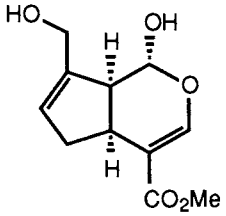
Cerbinal, an unusual iridoid with 10 π-System, was synthesized from (+)-genipin in 6 steps via dehydration of the hemiacetal and subsequent dehydrogenation with DDQ.

Cerbinal (**1**)[1] isolated from either *Cerbera manghas* L. or *Gardenia jasminoides* Ellis, has been recognized by its characteristic Δ3,5,7,9-tetraene aromatic 10 π–system. This unusual iridoid structure is also found in baldrinal (**2**)[2] and viburtinal (**3**).[3] Compound **3** has been traditionally used as a spasmolytic, while **2** was recently found to exhibit potent cytotoxicity against HTC hepatoma cells and anti-tumor activities against KREBS II ascitic tumor.[2] Those biological activities as well as an unusual iridoid structure made us investigate a synthetic scheme toward **1**, a key compound for other natural and unnatural iridoid 10 π-systems.



1: Cerbinal, R=CO_2CH_3
2: Baldrinal, R=CH_2OAc
3: Viburtinal, R=CH_3



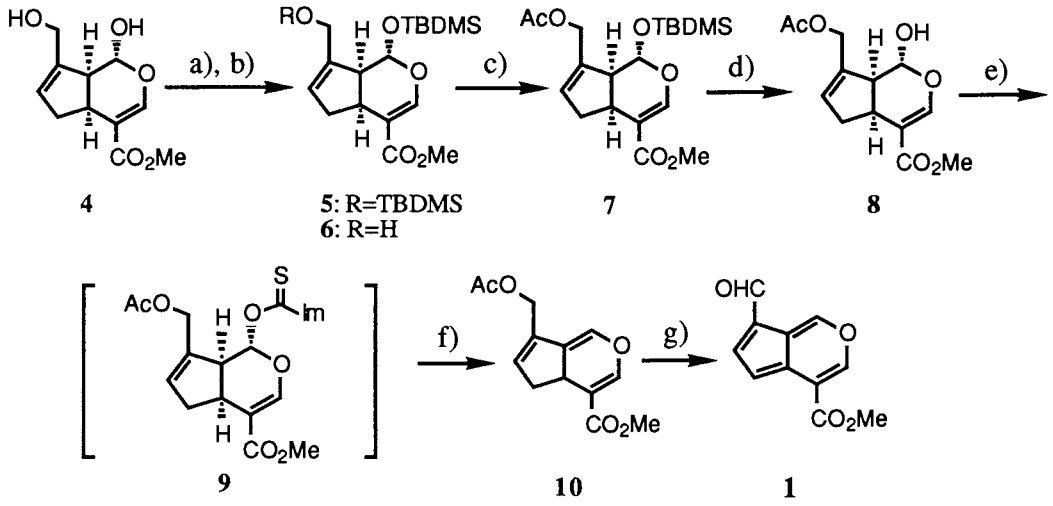
4: (+)-Genipin

In this report we would like to describe an efficient synthesis of **1** from (+)-genipin (**4**),[4,5] which could be easily obtained from the water extracts of *Gardenia jasminoides* Eills. It is anticipated that the introduction of the double bond at C1-C9 position would make the dehydrogenation of C5 and C6-H feasible to result in the formation of aromatic system.

The silylation of **4** with t-butyldimethylsilyl chloride in the presence of AgNO3 gave the disilyl ether (**5**), which was then treated with a catalytic amount of PPTS in ethanol to afford the monosilyl ether (**6**) in good yield. Acetylation of **6** followed by desilylation with n-Bu4NF in the presence of AcOH gave the hemiacetal (**8**) in excellent yield. For the subsequent dehydration, we then tried to convert the hydroxy group of **8** into several leaving groups. However it was difficult to get compounds with leaving groups on the hemiacetal carbon, because of the instability of intermediates. For example, treatment of **8** with trifluoroacetic anhydride in the presence of Et_3N and DMAP at -78 °C gave only the decomposed products. Substitution of the hydroxy group with PhS- and PhSe- groups was also unsuccessful. Either tosylate or acetate of **8** could be obtained, but eliminations of these leaving groups failed. After numerous experiments, we found that the thioimidazolide[6] underwent thermal decomposition smoothly to give the eliminated compound (**10**). Thus, treatment of **8** with

1,1'-thiocarbonyldiimdazole in benzene afforded the thioimidazolide (**9**). Since **9** was unstable for isolation, it was then heated up in refluxing benzene giving rise to the key intermediate **10**[7] in 55% yield from **8**. Upon treatment of **10** with DDQ in refluxing benzene, the expected dehydrogenation between C5-C6 and oxidation of the allylic acetate occurred to give **1** as yellow needle crystals in 55% yield. The spectral data of the synthetic **1** were in fine agreement with those published.[8]

As described above we succeeded in the efficient synthesis of **1** from (+)-genipin. This synthetic scheme would be able to apply for the synthesis of **2** and **3** as well as unnatural 10 π iridoids to investigate their structure-activity relationship in their biological activities, especially antitumor activity.



a) t-BuMe$_2$SiCl, AgNO$_3$, DMF, r.t.; b) cat. PPTS, EtOH, r.t., 92% from **4**; c) Ac$_2$O, DMAP, Et$_3$N, CH$_2$Cl$_2$, r.t., 3.5 h, 90%; d) n-Bu$_4$NF, AcOH, THF, 0 °C to r.t., 3.5 h, 96%; e) 1,1'-thiocarbonyldiimdazole, benzene, r.t., overnight; f) benzene, reflux, 4 h, 55% from **8**; g) DDQ, benzene, reflux, 2 h, 55%.

References

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7) **10** was unstable and decomposed gradually during the purification with silica gel column chromatogarphy. MS(m/e): 250(M)$^+$, 219[(M-OMe)$^+$].
8) **1**: Mp 193-194 °C (uncorrected, literature:[1] 188-189 °C); λ^{MeOH}_{max} 251, 279, 289, 330, 426 nm; Anal. Found: C, 64.41; H, 3.98%. Calcd for C$_{11}$H$_8$O$_4$: C, 64.70; H, 3.95%. ^{1}H-NMR (CDCl$_3$) δ: 4.00 (3H, s), 7.13 (1H, d, J=3.1Hz), 7.94 (1H, d, J=3.1Hz), 8.52 (1H, s), 9.17 (1H, s), 9.96 (1H, s). ^{13}C-NMR (CDCl$_3$) δ: 52.44, 96.16, 113.53, 115.12, 124.49, 125.17, 130.33, 148.02, 148.21, 164.75, 185.09.

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