Synthesis of Novel Diterpenequinone Salvicine from Ferruginol

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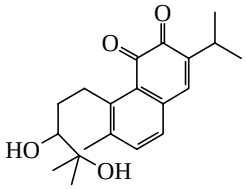
Abstract: An efficient synthetic route has developed to the antitumor compound salvicine *via* 9 steps from ferruginol. The key reaction is the rearrangement of the angular methyl group of compound **7** to 4,5-seco-5,10,-friedo-abieta diterpene **8**.

Keyword: Synthesis, rearrangement, ferruginol, salvicine.

Salvicine **1** was a novel diterpenequinone, structurally modified derivative of a natural product saprorthoquinone **2**[1]. It has been found to possess significant antitumor activity *in vitro* and *in vivo*. Its preclinical studies have been finished in our institute as a major research project for new drugs. Owing to the limited natural resources of the plant containing the leading compound **2**, now we are developing a new synthetic route to prepare **1** from the known diterpene ferruginol **3** which can be easily obtained from many medicinal plants[2,3].



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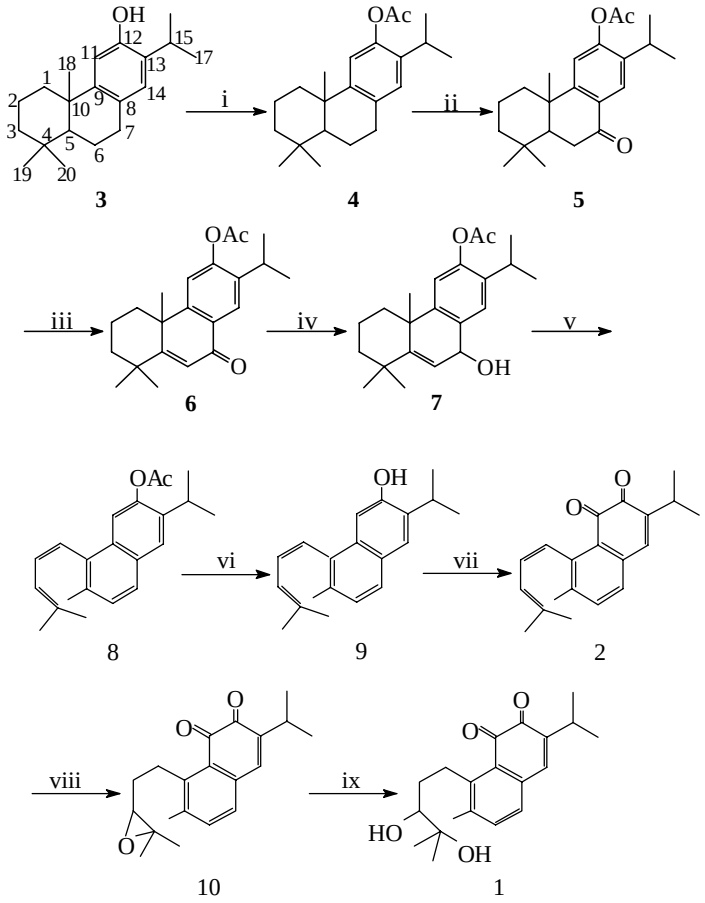
Salvicine **1** was synthesized from ferruginol **3** *via* 9 steps as shown in **Scheme 1**. The key reaction is the rearrangement of the angular methyl group of compound **7** to 4,5-seco-5,10-friedo-abieta diterpene **8**. First acetylated of ferruginol **3** with acetic anhydride in pyridine yield the compound **4**, which was then oxidized by chromium trioxide in acetic acid to give the 7-oxo compound **5**. To efficiently obtain the enone derivative **6**, we tested several conditions. Finally we found that DDQ in refluxing benzene with a catalytic amount of selenium dioxide is a better oxidation reagent which can give the expected product **6** in comparatively high yield. **6** was reduced with sodium borohydride in the presence of cerium (III) chloride heptahydrate to give the

crude 7-hydroxy compound **7**. The crude compound **7**, without further purification, was directly treated with *p*-toluenesulfonic acid monohydrate in benzene to give a 4,5-seco compound **8** in 73% yield from **6**[4]. Compound **8** was converted into the phenolic compound **9** with lithium aluminum hydride, which was oxidized with Fremy's salt and potassium dihydrogenphosphate in aqueous N,N-dimethylformamide to yield saprorthoquinone **2**[5]. The epoxide **10** was prepared by *m*-chloroperbenzoic acid epoxidation of **2** in chloroform. Hydration of **10** with water and 8% perchloric acid in tetrahydrofuran give the title compound salvicine in 65% yield.

Scheme 1



i: Ac_2O, Pyr, 10 hr, 92%;
ii: CrO_3, HOAc, 3 hr, 85% yield of **5** and 8% yield of **6**;
iii: DDQ, catalytic amount of SeO_2, refluxing benzene, 5 hr, 83%;
iv: $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH, 0℃, 0.5 hr;
v: *p*-TsOH, benzene, 1 hr, 73% yield from **6**;
vi: $LiAlH_4$, Et_2O, 0℃, 1 hr, 97%;
vii: Fremy's salt, KH_2PO_4, THF, H_2O, 56%;
viii: MCPBA, $CHCl_3$, over night, 85%; ix: 8% perchloric acid, THF, H_2O, 5 hr, 65%.

In conclusion, the antitumour compound salvicine **1** can be efficiently synthesized through this synthetic route. Previously Takashi Matsumoto *et al*.[6] had synthesized saprorthoqunone **2** *via* 12-methoxy ferruginol. A comparison of their synthetic way with ours suggested that our route was superior to theirs regarding the length of the reaction step and the overall yield of the target compounds. (We can efficiently get compound **2** in 27% yield from the starting material ferruginol *via* 7 steps, while the same compound **2** was obtained in 24% yield from 12-methoxy ferruginol through 8 steps in their synthetic route). And furthermore, the highly toxic reagents such as selenium dioxide and ethanethiol were used in much less quantity or totally avoided here.

All of the compounds were identified by IR, EIMS ^{1}H NMR (400MHz, in $CDCl_3$ with TMS as the internal standard) or by comparing with the data from literatures of known compounds.

Acknowledgment

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References and notes

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7. The spectral analytical and physical data of some compounds:
   Data of Compound **4:** mp 76-77℃; IR (KBr) 2962, 1757, 1500, 1367, 1225, 1163, 1016, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$, δppm) 0.94 and 0.96 (s, each 3H, 4-$(CH_3)_2$), 1.19 and 1.22 (d, each 3H, *J* = 7.5Hz, CH$(CH_3)_2$), 1.20 (s, 3H, 10-CH_3), 2.31 (s, 3H, 12-OAc), 2.93 (m, 1H, H-15), 6.85 (s, 1H, H-11), 6.96 (s, 1H, H-14); EIMS (*m/z*) 328 ($[M]^+$), 313, 286, 271, 243, 215, 189, 175, 149.
   Data of Compound **5:** mp 161-162℃; IR (KBr) 2962, 1755, 1682, 1610, 1491, 1367, 1271, 1209, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$, δppm) 0.91 and 0.97 (s, each 3H, 4-$(CH_3)_2$), 1.18 and 1.21 (d, each 3H, *J* = 9.0Hz, CH$(CH_3)_2$), 1.22 (s, 3H, 10-CH_3), 2.32 (s, 3H, 12-OAc), 2.96 (m, 1H, H-15), 6.96 (s, 1H, H-11), 7.97 (s, 1H, H-14); EIMS (*m/z*) 342 ($[M]^+$), 300, 285, 257, 243, 215, 201, 163.
   Data of Compound **6:** mp 168-169℃; IR (KBr) 2964, 1750, 1653, 1313, 1209, 1178, 926 cm^{-1}; ^{1}H-NMR ($CDCl_3$, δppm) 1.21 and 1.24 (d, each 3H, *J* = 6.8Hz, -CH$(CH_3)_2$), 1.24 and 1.33 (s, each 3H, 4-$(CH_3)_2$), 1.50 (s, 3H, 10-CH_3), 2.33 (s, 3H, 12-OAc), 3.00 (m, 1H, H-15),6.47 (s,1H, H-6), 7.12 (s, 1H, H-11), 8.07 (s, 1H, H-14); EIMS (*m/z*) 340 ([M]+), 325, 298, 283, 255, 229, 213.
   Data of Compound **8:** bright yellow oil; IR (KBr) 2794, 1761, 1740, 1369, 1202, 1161, 914 cm^{-1}; ^{1}H-NMR ($CDCl_3$, δppm) 1.34 (d, 6H, *J* = 7.0Hz, -CH$(CH_3)_2$), 1.61 and 1.74 (s, each 3H, 4-$(CH_3)_2$), 2.41 (s, 3H, 12-OAc), 2.32 (s, 3H, 5-CH_3), 3.09 (m, 1H, H-15), 5.33 (t, 1H, *J* = 7.0Hz, H-3), 7.25 (d, 1H, *J* = 8.5Hz, H-6), 7.59 (d, 1H, *J* = 8.5Hz, H-7), 7.65 (s, 1H, H-11),

7.71(s, 1H, H-14); EIMS (*m/z*) 324 ($[M]^+$), 282, 255, 227, 213, 198, 165.
Data of Compound **9:** bright yellow oil; ^{1}H-NMR ($CDCl_3$, δ_{ppm}) 1.34 (d, 6H, *J*=6.7Hz, -CH$(CH_3)_2$), 1.59 and 1.67 (s, each 3H, 4-$(CH_3)_2$), 2.44 (s, 3H, 5-CH_3), 3.31 (m, 1H, H-15), 5.30(t, 1H, *J* = 6.9Hz, H-3), 7.11 (d, 1H, *J* = 8.3Hz, H-6), 7.23 (s, 1H, H-11), 7.50(d, 1H, *J* = 8.3Hz, H-7), 7.56 (s, 1H, H-14).

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