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1,4-Dioxene in Organic Synthesis: An Approach to the A,B Ring System of Forskolin.

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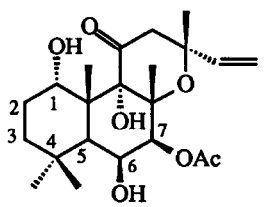
Key Words: 1,4-dioxene, forskolin, intramolecular Diels-Alder reaction, allylic hydroxylation.

Abstract: *A methodology for the introduction of C-6 and C-7 oxygenated groups in the A,B ring system of forskolin based on the use of 1,4-dioxene is reported.*

Forskolin **1**, a highly oxygenated labdane diterpene, exhibits a broad range of physiological activities through its ability to activate adenylate cyclase. The considerable therapeutic potential of this natural product combined with its highly challenging structure have served to stimulate enormous synthetic activity in a number of laboratories.[1]



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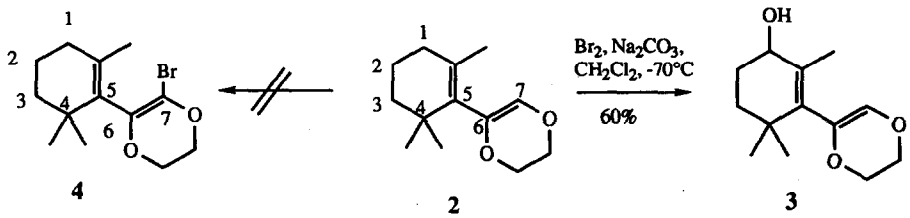
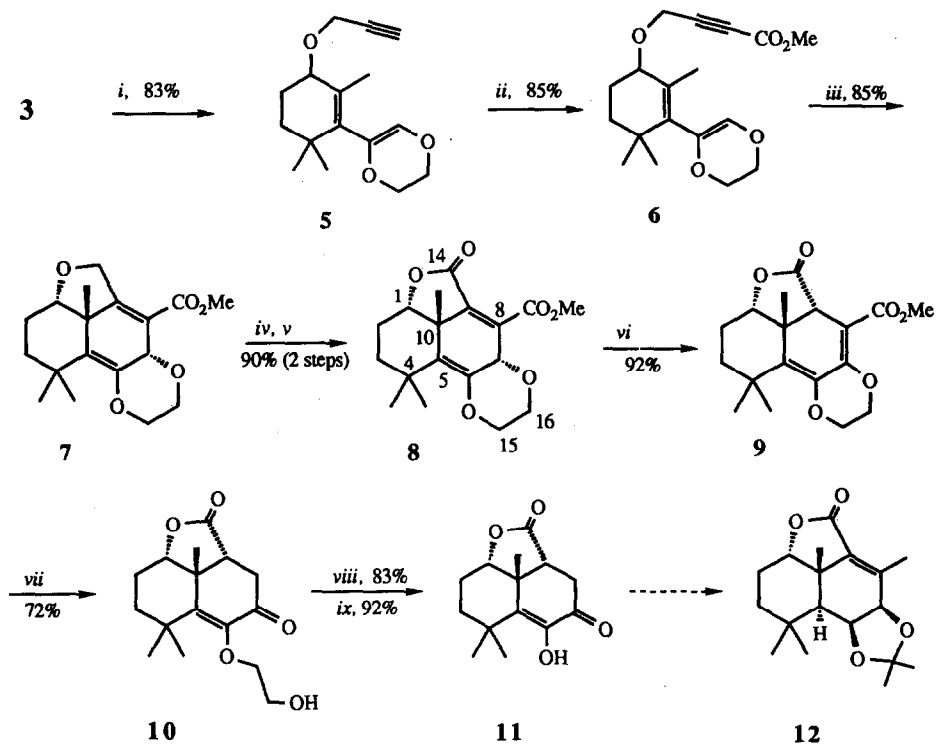
A shortcoming of most synthetic approaches to forskolin lies in the difficulty of introducing an oxygen at the sterically hindered C-6 position *after* the construction of rings A and B.[2,3] Moreover, it has been recently shown that both or either of oxygenated groups at C-6 and C-7 are critical for the activation of adenylate cyclase by forskolin.[4]

As part of our general interest in synthetic applications of 2,3-dihydro-1,4-dioxin (1,4-dioxene),[5] we have described the preparation of substituted 2-vinyl-dioxenes. In particular, 2,6,6-trimethyl-1[2-(1,4-dioxenyl)]-1-cyclohexene **2**, readily obtained from 2,2,6-trimethylcyclohexanone, appeared to be a useful intermediate in the synthesis of functionalized compounds.[6,7] We now describe the use of this oxygenated diene for the introduction of C-6 and C-7 oxygen functional groups found in the decalin system present in forskolin.

This work has been stimulated by the unexpected preparation of the allylic alcohol **3**. In fact, our initial aim was the synthesis of vinylic bromide **4** by bromination and dehydrobromination of **2**. Surprisingly, treatment of **2** with bromine (1 equiv.) in the presence of sodium carbonate (2 equiv.) in dichloromethane at -70°C afforded



Scheme 1.



Scheme 2. *Reagents and conditions:* ***i***, 60% aqueous NaOH , n-Bu_4NI (0.1 equiv.), propargylic bromide (3 equiv.); ***ii***, n-BuLi (1.5 equiv.), THF, - 70°C, then ClCOOMe (4 equiv.), - 70°C; ***iii***, 140°C, toluene, sealed tube; ***iv***, SeO_2 (2 equiv.), H_2O (2 equiv.), dioxane, reflux; ***v***, Ag_2CO_3 on Celite, benzene, reflux; ***vi***, DBU, THF, reflux; ***vii***, 70% aqueous $HClO_4$, CH_3CN, 60°C; ***viii***, Me_3SiCl (5 equiv.), NaI (5 equiv.), CH_3CN; ***ix***, Zn, NH_4Cl, EtOH, reflux.

the hydroxydiene **3**[8] in 60% yield[9] (Scheme 1).

Starting from this key intermediate, our methodology was based on an intramolecular Diels-Alder reaction first introduced by Jenkins *et al.*[10] and since widely used in synthetic approaches to forskolin. Thus, oxygens at C-6 and C-7 positions are in place *before* the formation of the A and B rings as shown in scheme 2.

Etherification of the dienol **3** gave a 83% yield of propargylic ether **5** which led to acetylenic ester **6** by treatment with n-BuLi (1.5 equiv.) at -70°C followed by methyl chloroformate (4 equiv). Ester **6** underwent an intramolecular Diels-Alder reaction on heating in toluene at 140°C in a sealed tube for 10 h to give the tetracyclic compound **7** in 85 % yield after flash chromatrography. Conversion of the adduct **7** to the lactone **8** was achieved in two steps using selenium dioxide allylic hydroxylation and subsequent oxidation of the resulting lactol with silver carbonate on Celite in refluxing benzene.[11] Initial attempts to effect direct conversion of **7** to lactone **8** using various oxidising reagents (CrO_3•DMP, CrO_3•2 Py, ...) led to mixtures and were synthetically useless.

Treatment of **8** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing THF afforded the conjugated diene ester **9**[8] in 92% yield.The stereochemistry of **9** tentatively assigned as shown in scheme 2 was based on the stereoselectivity of the intramolecular Diels-Alder cyclization and proven by X-ray crystallographic analysis.[12]

At this stage, we anticipated that conjugated diene ester **9**, which is equivalent to cyclic dienol ester would suffer hydrolysis, leading to the cleavage of dioxane ring. Rewardingly, exposure of **9** to 70% aqueous perchloric acid in acetonitrile at 60°C cleanly gave one major product (70 % yield) to which structure **10** was assigned on the basis of its spectroscopic properties.[8] This transformation is the result of the opening of the dioxane ring and a subsequent decarboxylation. As expected, the elimination of the ethylene glycol leading directly to **11** did not occur at this stage probably because formation of a cation next to the carbonyl group is unfavorable.

Consequently, the conversion of hydroxyethyl enol ether **10** to **11** was readily accomplished in two steps by iodination with chlorotrimethylsilane - sodium iodide in acetonitrile[13] followed by reductive cleavage of the oxygen carbon bond with zinc and ammonium chloride in refluxing ethanol in very good overall yield. It is worthy of note that while a similar α-diketone has been described as pure diketone form,[14] compound **11**[8] was isolated exclusively as diosphenol.

Thus, starting from the oxygenated 1,3-diene **2** prepared from easily available raw materials, 2,2,6-trimethylcyclohexanone and 1,4-dioxene, we have achieved an efficient route to the highly functionalized compound **11** which should be easily converted to the Ziegler intermediate **12**.[15]

References and Notes

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8. All new compounds exhibit satisfactory spectroscopic and analytical and/or exact mass data. Physical properties of selected compounds :

   3 : oil, IR (CCl_4) ν_{max} : 3609, 1672 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ : 5.69 (s, 1H, HC-7); 4.03-3.96 (m, 4H); 3.70 (t, 1H, J = 5 Hz, HC-1); 2.19 (br.s, 1H, OH); 1.78 (s, 3H, CH_3); 1.7-1.1 (m, 4H); 0.97 (s, 3H, CH_3); 0.93 (s, 3H, CH_3) ; ^{13}C NMR (200 MHz, $CDCl_3$) δ : 137.2 (s); 136.7 (s); 134.1 (s); 125.2 (d, 7); 69.5 (d, 1); 64.2 (t); 63.9 (t); 34.6 (t); 34.3 (s); 28.6 (q); 27.7 (t); 18.2 (q).

   9 : m.p. 218-219°C (ether-CH_2Cl_2) ; IR (CCl_4) ν_{max} : 1789, 1717, 1688 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ : 4.45 (dd, 1H, J = 8, 4 Hz, HC-1); 4.47-3.90 (m, 4H, H_2C-15 and 16); 3.91 (s, 3H, OMe); 3.46 (s, 1H, HC-9); 2.21-2.14 (m, 1H); 1.84-1.75 (m, 1H); 1.63-1.56 (m, 1H); 1.36-1.28 (m, 1H); 1.21 (s, 3H, CH_3); 1.20 (s, 3H, CH_3); 1.19 (s, 3H, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$) δ : 175.9 (s, 14); 166.0 (s, 17); 152.0 (s); 140.6 (s); 129.3 (s); 94.8 (s); 83.2 (d, 1); 65.2 (t, 15); 62.9 (t, 16); 51.5 (q, OMe); 48.8 (d, 9); 43.5 (s, 10); 34.0 (t, 2); 34.0 (s, 4); 28.1 (q); 26.5 (q); 23.2 (q); 23.0 (t, 3).

   10: m.p. 97-98°C (ether-CH_2Cl_2); IR (CCl_4) ν_{max} : 3483, 1789, 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 4.43 (dd, 1H, J = 4.4, 8.6 Hz, HC-1); 3.70 (m, 4H, H_2C-15 and 16); 3.05 (dd, 1H, J = 8, 25 Hz, HC-8); 2.74 (dd, 1H, 7.7, 25 Hz, HC-8); 2.72 (t, 1H, J = 8 Hz, HC-9); 2.40 - 1.60 (m, 4H, H_2C-2 and 3); 1.52 (s, 3H, CH_3); 1.38 (s, 3H, CH_3); 1.34 (s, 3H, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$) δ : 190.6 (s, 7); 175.8 (s, 14); 151.9 (s); 151.0 (s); 82.7 (d, 1); 73.3 (t, 16); 62.5 (t, 15); 47.1 (d, 9); 44.8 (s, 10); 35.9 (s, 4); 34.5 (d, 2); 32.0 (d, 8); 28.7 (q); 28.2 (q); 24.8 (q); 23.1 (t, 3).

   11 : m.p. 135-136°C (ether-CH_2Cl_2) ; IR (CCl_4) ν_{max} : 3397, 1789, 1676 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ : 6.65 (s, 1H, OH); 4.45 (dd, 1H, J = 9, 4 Hz, HC-1); 3.10 (dd, 1H, J = 21.4, 3.8 Hz, HC-8); 2.75 (2dd, 2H, J = 3.8, 21.4, 7.2 Hz, HC-8 and 9); 2.40-2.25 (m, 2H); 2.10-1.70 (m, 2H); 1.51 (s, CH_3); 1.36 (s, CH_3); 1.31 (s, CH_3); ^{13}C NMR (200 MHz, $CDCl_3$) δ : 189.9 (s, 7); 175.5 (s, 14); 145.5 (s); 136.2 (s); 82.9 (d, 1); 47.6 (d, 9); 43.8 (s, 10); 35.0 (s, 4); 33.9 (t, 2); 29.5 (t, 8); 27.4 (q); 25.4 (q); 25.2 (q); 23.5 (t, 3).
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