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Skeletal Rearrangement of A and B Ring of 13-Oxobaccatin Ⅲ Derivative

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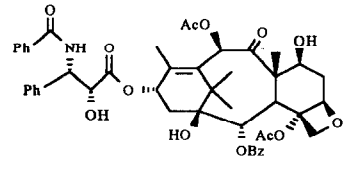
Abstract: The treatment of 13-oxo-7-triethylsilyl baccatin Ⅲ with trifluoroacetic anhydride in the presence of pyridine or with 1,8-diazabicyclo[5.4.0]undec-7-ene in refluxing chloroform produced an A ring contraction product **6** and a B ring contraction product **7** in 80% and 61% yields, respectively. © 1997 Elsevier Science Ltd.

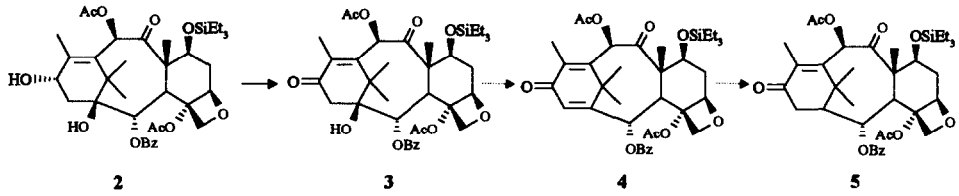
The highly oxygenated tetracyclic diterpene taxol isolated from the bark of the Pacific yew tree[1] has recently attracted much attention due to its efficacy in the treatment of various types of cancer[2], unique mechanism of action[3] as well as unusual and complex molecules[4]. Most work has focused on structure-activity relationships (SAR) studies in hopes of finding second generation taxanes with better biological properties[5]. The results of SAR investigations so far showed that the function groups at C_7, C_9, C_{10}, $C_{11\text{-}12}$[6] and $C_8\text{-}CH_3$[7] have little effect upon its biological activity, while as the side chain at C_{13} , benzoxy at C_2 and acetoxy at C_4 are essential for biological activities. However, no report had appeared on the role of the C_1 -OH group on biological activity due to the fact that C_1 deoxytaxol or deoxybaccatin derivatives are difficult to prepare. Chen's group attempted to prepare C_1 deoxybaccatin derivatives by radical deoxygenation of the $C_{1\text{-}2}$ cyclic thiocarbonate of baccatin derivatives, but led to skeleton rearrangement[8]. Kingston's group tried to make C_1 xanthate of taxol for further preparation of C_1 deoxytaxol by radical reaction but failed with benzoyl group migration from C_2 to C_1[9].



1 taxol

We have been also interested in preparing C_1 deoxytaxol. In order to overcome the difficulty mentioned above of direct radical deoxygenation, we wish to indirectly prepare C_1 deoxybaccatin derivative by the

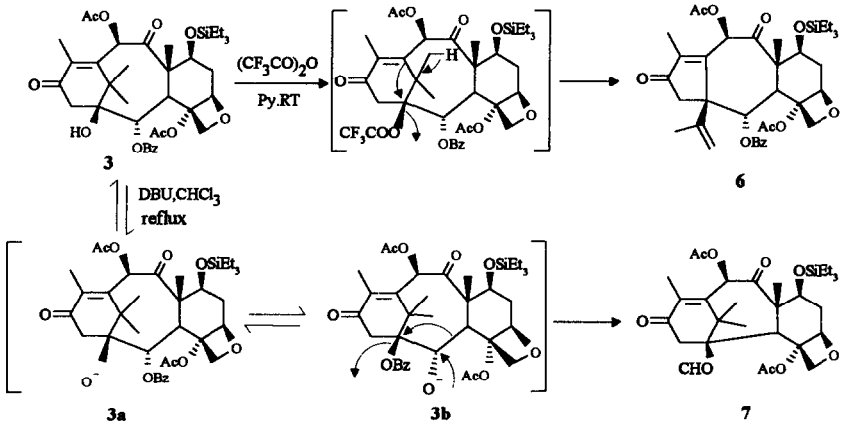
following sequence (**scheme 1**): first oxidation of C_{13} hydroxy to ketone, then β-eliminaion of C_1 hydroxy group, selective hydrogenation of the newly formed double bond and last reduction of C_{13} ketone to α-hydroxy.



2 **3** **4** **5**

Scheme 1

The treatment of compound **3**[6b] with trifluoroacetic anhydride in the medium of pyridine at room temprature afforded A ring contracted compound **6**[10](80%) without the desired dehydration product isolated. Then we turned to use 1,8-diazabicyclo[5.4.0]undec -7-ene(DBU) as base, which could make it easy to enolize the C_{13} ketone group to fulfill the β-elimination. However, DBU treatment of **3** in the refluxing $CHCl_3$ for 24hrs produced a new compound **7**[10](61%), whose ^{1}HNMR spectrum still displayed the signals of H at $C_{5,7,10,20a}$ and C_{20b} as well as six methyl signals(four methyl groups $C_{16,17,18,19}$ and two acetates), but particularly striking was the loss of the signals due to phenyl group and H at C_2. Two singlet signals(δ 10.16 and 3.56) were assigned for a aldehyde proton and H at C_3 . Infrared spectrum also showed aldehyde group (2740c m^{-1}) and FAB mass spectrum showed a molecular ion with a sodium ion at m/z 599(576+Na)$^+$. Connectivity analysis via COSY and proton-carbon correlation allowed to assign all the proton and carbon renonances[11]. All data are consistent with the assignment of structure **7** to the new compound.



3 **6** **3a** **3b** **7**

Scheme 2

From these results, we are led to propose that the formation of the A ring contracted compound **6** with the 1,2-shift rearrangement as previously reported by Kingston group[12], whereas formation of the B ring contracted compound **7** by the following consideration. Upon basic condition, there is a equilibrium between the anions **3a** and **3b**, even though it involves 2-benzoyl migration from the secondary to the tertiary position and it

would not be thermodynamically favored. However, once the very small amount of anion 3b formed, leaving benzoxy group led to 1,2-shift rearrangement to form the unexpected B ring contracted compound 7, since it is easier for the benzoxy to leave from the tertiary position than from the secondary position. This kind of 2-benzoyl migration to 1-benzoyl caused skeleton rearrangement in baccatin III derivative was first found by an Italian group[13].

Easy skeleton rearrangement of A and B ring of the 13-oxobaccatin III derivative would imply that it is rather difficult to lead to β-elimination, which produces a new double bond at $C_{1\text{-}14}$ via enolization of 13-oxobaccatin III derivative due to intense strain. Studies of dehydration at $C_{1\text{-}14}$ using alternative way for synthesis of 1-deoxytaxol derivatives is in progress.

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10. To a stirred solution of 7-triethylsilyl-13-oxobaccatin III **3** (62mg, 0.09mmol) in anhydrous pyridine (2ml), $(CF_3CO)_2O$ (0.015ml, 0.108mmol) was added dropwise at -10°C. Several minutes later, the reaction mixture was warmed to room temperature with stirring for 1h, then quenched with cold water. The mixture was extracted with EtOAc. The organic layer was washed with water, saturated aqueous $CuSO_4$, brine accordingly and dried over Na_2SO_4. The crude material was purified by chromatography on silica gel(Petroleum ether : EtOAc, 7 : 3 → 6 : 4) to yield 49mg(80%) of compound **6**.

6: white powder, m.p.152°, $[\alpha]_D^{25}$ +132° (C=0.14, $CHCl_3$), UVλ_{max}(EtOH):248, 220,212nm, IR ν_{max} (KBr): 2958, 2879, 1757, 1718, 1602, 1268, 1221, 1110, 1069, 712, ^{1}HNMR (300MHz,$CDCl_3$,TMS as reference): δ 7.82 (d, 2H, J=8.0Hz, Bz), 7.54 (t, 1H, J=7.6Hz, Bz), 7.42 (d, 2H, J=7.8Hz, Bz), 6.52 (s, 1H, H-10), 6.03 (d, 1H, J=9.2Hz, H-2), 5.12 (s, 1H, H-16), 4.95 (d, 1H, J=1.0Hz, H-16), 4.80 (d, 1H, J=8.5Hz, H-5), 4.40 (d, 1H, J=8.4Hz, H-20α), 4.38 (dd, 1H, J=9.7, 7.1Hz, H-7), 4.32 (d, 1H, J=8.3Hz, H-20β), 3.13 (d, 1H, J=9.2Hz, H-3), 2.50-2.35 (m, 1H, H-6α), 2.48 (d, 1H, J=18.6Hz, H-14α), 2.19(d, 1H, J=18.6Hz, H-14β), 2.17 (s, 3H, OAc), 1.82 (s, 3H, OAc), 1.71(s, 3H, H-17), 1.70-1.60(m, 1H, H-6β), 1.63 (s, 3H, H-19), 1.19 (s, 3H, H-18), 0.88 (t, 9H, J=8.0Hz, H-Tes), 0.54-0.48(m, 6H, H-Tes), FAB-MS (NBA+NaCl): 681$(M+1)^+$. ^{13}C NMR (100MHz, $CDCl_3$, TMS as reference): δ 210.96 (s, C-9), 199.08 (s, C-13), 172.11 (s, Ac), 170.51 (s, Ac), 163.53 (s, Bz), 148.33 (s, C-12), 145.60 (s, C-11), 137.20 (s, C-15), 132.21 (d, Bz), 130.41 (d, Bz), 116.12 (t, C-16), 84.96 (d,C-5), 79.05 (s, C-4), 74.55 (t, C-20), 72.95 (d, C-7), 71.12 (d, C-10), 70.88 (d, C-2), 63.80 (s, C-1), 56.24 (s, C-8), 44.35 (d, C-3), 42.10 (t, C-14), 38.19 (t, C-6), 22.20 (q, Ac), 21.80 (q, Ac), 20.70 (q, C-17), 11.75 (q, C-18), 9.05 (q, C-19), 6.70 (q, Tes), 5.02 (t, Tes).

To a stirred solution of 7-triethylsilyl-13-oxobaccatin III **3** (71mg, 0.10mmol) in dry chloroform (3ml), DBU(0.1ml, 0.67mmol) was added at room temperature. After stirring at room temperature for 15min, the reaction mixture was refluxed for 24h and poured into ice-water. The mixture was extracted with EtOAc. The organic layer was washed with 10% hydrochloric acid, saturated aqueous $NaHCO_3$, brine accordingly and dried over Na_2SO_4. The crude material was purified by chromatography on silica gel(Petroleum ether : EtOAc, 8 : 2 → 7 : 3) to yield 35mg(61%) of compound **7** and recovered starting material 23mg(32%). **7**: Oil, $[\alpha]_D^{25}$ +57° (C=0.23, $CHCl_3$), UV:λ_{max}(EtOH) 222,288nm, IR ν_{max} (KBr): 2950, 2879, 2820, 2720, 1760, 1740, 1710, 1705, 1679, 1218, 1110, 1054, 747, ^{1}HNMR (300MHz, $CDCl_3$, TMS as reference):10.16 (s, 1H, CHO), 6.32 (s, 1H, H-10), 4.84 (d, 1H, J=8.2Hz, H-5), 4.47 (d, 1H, J=8.6Hz, H-20α), 4.30 (dd, 1H, J=10.6, 6.1Hz, H-7), 4.29(d, 1H, J=8.3Hz, H-20β), 3.56 (s, 1H, H-3), 3.12 (d, 1H, J=2.0Hz, H-14α), 3.07 (d, 1H, J=2.0Hz, H-14β), 2.57-2.41 (m, 1H, H-6α), 2.25 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.98 (s, 3H, H-18), 2.01-1.90(m, 1H, H-6β), 1.93 (s, 3H, H-19), 1.51 (s, 3H, H-16), 1.24 (s, 3H, H-17), 0.97 (t, 9H, J=8.0Hz, Tes), 0.56 (q, 6H, J=8.0Hz, Tes), FAB-MS (NBA+NaCl):599$(M+Na)^+$, 577$(M+1)^+$, 547$(M-CHO)^+$, 516$(M-HOAc)^+$, 487$(M-CHO-HOAc)^+$, ^{13}CNMR (100MHz, $CDCl_3$, TMS as reference): 203.13 (s, C-9), 202.24 (d, CHO), 199.07 (s, C-13), 170.30 (s, Ac), 168.93 (s, Ac), 151.16 (s, C-12), 136.72 (s, C-11), 86.13 (d, C-5), 82.06 (s,C-4), 76.79 (t, C-20), 75.82 (d, C-10), 72.32 (d, C-7), 64.29 (s, C-1), 51.26 (s, C-8), 47.78 (d, C-3), 40.90 (t, C-14), 38.01 (t, C-6), 23.11 (s, Ac), 21.83 (s, Ac), 20.80 (q,C-16), 15.43 (q,C-17),14.90 (q,C-18),13.21(q, C-19), 6.76 (q, Tes), 5.05 (t, Tes).

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