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Entry into Major Groups Retaining Taxol *via* Sinenxan A

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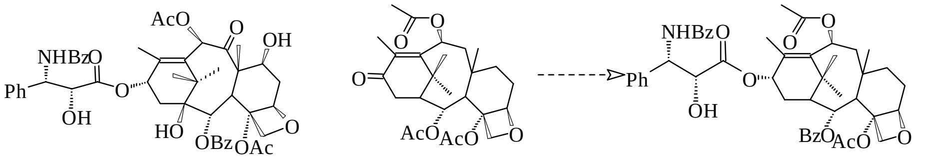
Abstract: Compound **1** as a key intermediate of 1, 7, 9-trideoxytaxol was synthesized in ten steps from a biosynthetically available taxane, Sinenxan A. The key steps in the synthesis were deoxygenation at C-14, allylic oxidation at C-13 and construction of the oxetane ring.

Keywords: Taxol, Sinenxan A, deoxygenation.

Taxol exerts its anticancer activity through a unique mechanism[1] and it has been the subject of extensive chemical and biological studies. SAR studies have revealed that the functionalities at the southern hemisphere of the molecule are important for antitumor activity, except for OH-1[2,3]. Thus synthesis of 1, 7, 9-trideoxytaxol will be very significant. Compared with taxol, Sinenxan A, a biosynthetic taxane product with good yield[4], has the same taxane skeleton. But it has no oxetane ring and 13-oxygen, which are the key moieties for anticancer activity.



taxol **1** **1, 7, 9-trideoxytaxol**

Compound **1** is considered as a secondary target of 1, 7, 9-trideoxytaxol. We started with Sinenxan A. The acetyl at C-14 was selectively removed by K_2CO_3/MeOH to give compound **2**. When **2** was treated with CS_2/NaH, then with MeI compound **3** was obtained. By radical deoxygenation and allylic oxidation[5], compound **4** and **5** could be obtained and their structure were confirmed by ^{1}HNMR, ^{13}CNMR, FABMS and 2DNMR spectra[6]. Compound **6** was obtained by hydrolysis and then selective acetylation. Treatment of **6** with OsO_4/NMO, followed by Ac_2O afforded compound **7** as the major product. Its configuration was confirmed by NOE difference spectra[10]. OH-5 was selctively protected with MsCl to give **8**. Because of acetyl transfer, 2-acetyl and 20-acetyl were removed at the same time to give compound **9**. Treatment of **9** with DBU/toluene afforded compound **10**, but when Bu_4NOAc/butone was used the oxetane ring could not be given. ^{1}HNMR

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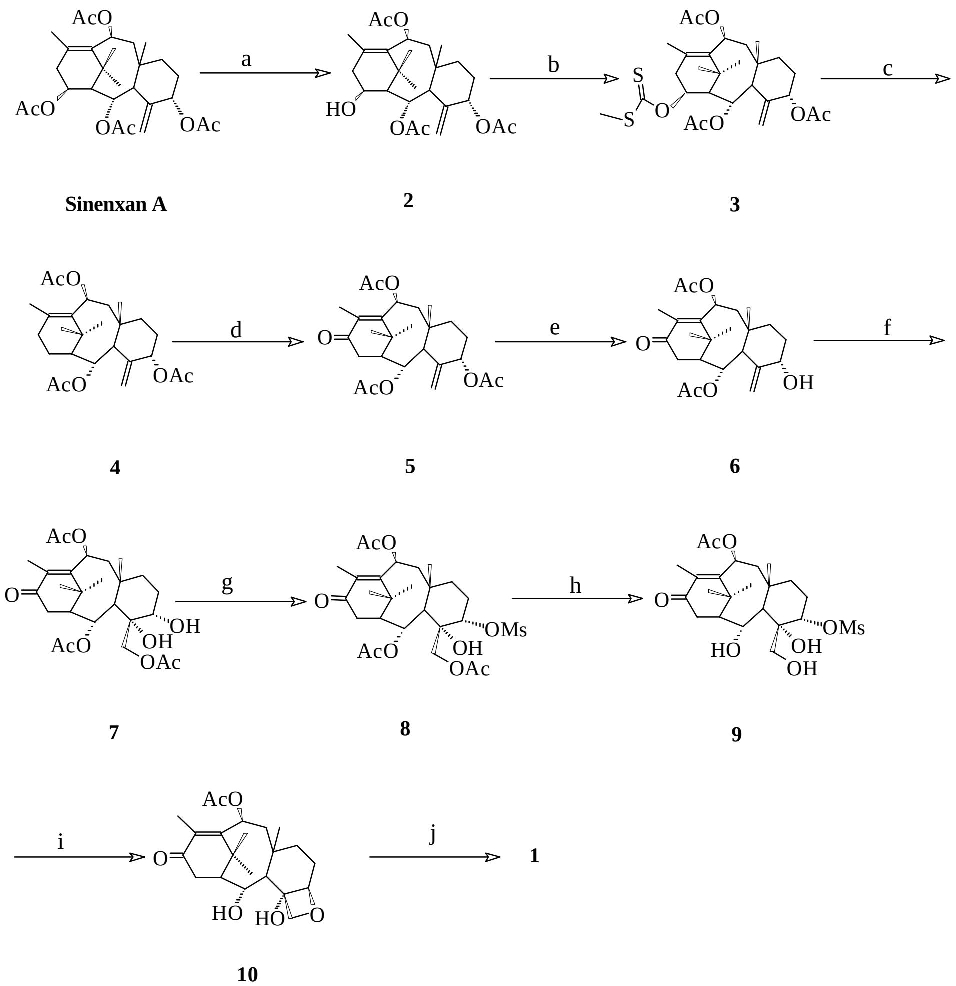
showed ^{2}J of H-20 changed from 11 Hz of **9** to 8 Hz of **10**, which indicated formation of oxetane ring. Compound **10** was very sensitive to acidic medium. If compound **10** in $CDCl_3$ which did not be processed by K_2CO_3, it was rapidly converted to **11**[8]. **11** has a characteristic coupling constant J = 10 Hz, as the same as the reference[9]. Apparently the $CDCl_3$ used here contains a traces of acidic impurities. **10** was treated with Ac_2O/DMAP to give Compound **1**. The structure of the latter was confirmed by ^{1}HNMR, ^{13}CNMR, FABMS[10].

Scheme 1 Route of synthesis of compound **1**



Reagents and conditions: a) 3 mol/L K_2CO_3/MeOH, rt., (30 - 40%); b) NaH/CS_2/THF, reflux, 24 h, then MeI, 40°C, 80 - 90%; c) Bu_3SnH/AIBN/Toluene, 80°C, 80%; d) PCC/NaOAc/celite/benzene, reflux, 65% based on 75% conversion; e) 1. 3 mol/L K_2CO_3/MeOH; 2. Ac_2O/pyridine, 50%; f) 1. OsO_4/NMO, then $NaHSO_3$; 2. Ac_2O/CH_2Cl_2/pyridine, two steps 71%; g) MsCl/pyridine, rt., 86%; h) 1 mol/L K_2CO_3/MeOH, 0°C, almost quantitative; i) DBU/toluene, 105°C, 30 - 40%; j) Ac_2O/DMAP/pyridine, rt., 70%

Compounds **1**, **3-11** were synthesized for the first time and their structures were confirmed by ^{1}HNMR, ^{13}CNMR, FABMS. The synthesis of 1, 7, 9-trideoxytaxol is underway.

Acknowledgment

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References and Notes

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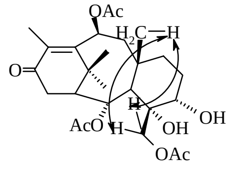
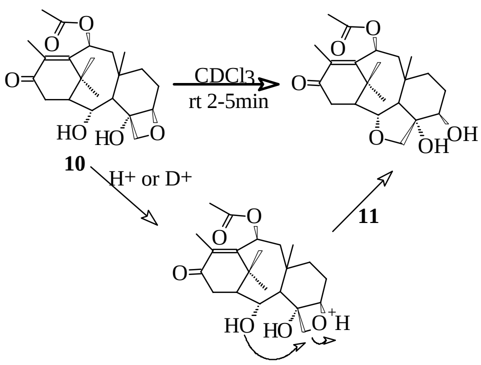
6. selected data of **5**: pale yellow solid, mp 72-74℃; ^{1}HNMR (500 MHz, $CDCl_3$, δ ppm) 6.06 (dd, 1H, J=12 Hz, 5.5 Hz, H-10), 5.46 (dd, 1H, J=2 Hz, 6.5 Hz, H-2), 5.27 (s, 1H, H-20), 5.23 (t, 1H, J=3 Hz, H-5), 4.82 (s, 1H, H-20), 3.19 (d, 1H, J=6 Hz, H-3), 2.87 (dd, 1H, J=6.7 Hz, 19.7 Hz, H-14), 2.48 (dd, 1H, J=12 Hz, 15 Hz, H-9), 2.33 (d, 1H, J=19.5 Hz, H-14), 2.20 (s, 3H, OAc-CH_3-10), 2.14 (dd, 1H, J=2 Hz, 6.7 Hz, H-1), 2.10 (s, 3H, OAc-CH_3-2), 2.06 (s, 3H, OAc-CH_3-5), 1.99 (s, 3H, CH_3-18), 2.14-1.85 (m, 1H, H-7), 1.79 (m, 3H, 2×H-6, H-9), 1.69 (s, 3H, CH_3-16), 1.21 (m, 1H, H-7), 1.13 (s, 3H, CH_3-17), 0.90 (s, 3H, CH_3-19); ^{13}CNMR (125 MHz, $CDCl_3$, δ ppm) 199.44 (13-C=O), 170.29 (OAc-C=O), 170.04 (OAc-C=O), 169.79 (OAc-C=O), 153.55 (C-20), 142.50 (C-12), 136.04 (C-11), 116.35 (C-4), 77.79 (C-10), 71.01 (C-5), 70.38 (C-2), 48.96 (C-1), 42.84 (C-15), 40.93 (C-8), 39.58 (C-14), 37.34 (C-3), 35.99 (C-6), 33.69 (C-9), 29.70 (C-7), 28.96 (C-17), 24.68 (C-16), 22.72 (C-18), 21.49 (OAc-CH_3), 21.41 (OAc-CH_3), 21.27 (OAc-CH_3), 13.76 (C-19); FABMS *m/z* 461.3(M+1).
7. selected data of **7** and NOE analysis of hydrogens at C-20**:** white solid, mp 198-200℃; ^{1}HNMR (500MHz, $CDCl_3$, δ ppm) 6.04 (dd, 1H, J=12 Hz, 5 Hz, H-10), 5.49 (dd, 1H, J=2 Hz, 5 Hz, H-2), 4.49 (d, 1H, J=11.5 Hz, H-20), 4.04 (d, 1H, J=12 Hz, H-20), 3.80 (t, J=2.7 Hz, 1H, H-5), 3.14 (d, 1H, J=19.7 Hz, H-14), 2.99 (d, 1H, J=5 Hz, H-3), 2.72 (dd, 1H, J=6.7 Hz, 19.7 Hz, H-14), 2.40 (dd, 1H, J=12.5 Hz, 15 Hz, H-9), 2.24 (s, 3H, OAc-CH_3-20), 2.17 (m, 1H, H-1), 2.12 (s, 3H, OAc-CH_3-10), 2.08 (s, 3H, OAc-CH_3-2), 2.07 (s, 3H, CH_3-18), 2.00 (m, 1H, H-7), 1.79 (m, 2H, 2×H-6), 1.68 (s, 3H, CH_3-16), 1.54 (dd, 1H, J=5.5 Hz, 15 Hz, H-9), 1.13 (s, 3H, CH_3-17), 1.07 (m, 1H, H-7), 0.89 (s, 3H, CH_3-19); ^{13}CNMR (125 MHz, $CDCl_3$, δ ppm) 200.41 (C=O-13) , 171.30 (OAc-C=O), 169.89 (OAc-C=O), 169.79 (OAc-C=O), 152.24 (C-12), 137.24 (C-11), 77.09 (C-10), 72.56 (C-4), 70.88 (C-2), 69.36 (C-5), 65.49(C-20), 48.39 (C-1), 44.23 (C-15), 41.39 (C-8), 38.21 (C-14), 37.46 (C-3), 37.34 (C-6), 35.77 (C-9), 31.01 (C-7), 24.55 (C-17), 24.51 (C-16), 24.20 (C-18), 21.59 (OAc-CH_3), 21.23 (OAc-CH_3), 20.80 (OAc-CH_3), 13.28 (C-19); FABMS *m/z* 495.3(M+1).



8. Conversion of compound 10 in $CDCl_3$:



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10. selected data of 1: colorless film; $[\alpha]_D^{30}$ +98 (c 0.50, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$, δ ppm) 5.98 (dd, 1H, J=12Hz, 5.5Hz, H-10), 5.48 (dd, 1H, J=2.5 Hz, 6 Hz, H-2), 4.93 (d, 1H, J=9 Hz, 1H, H-5), 4.50 (d, 1H, J=8 Hz, H-20), 4.18 (d, 1H, J=8 Hz, H-20), 2.87 (d, 1H, J=6.5 Hz, H-3), 2.73 (dd, 1H, J=7 Hz, 19.5 Hz, H-14), 2.51 (dd, 1H, J=12 Hz, 15 Hz, H-9), 2.31 (d, 1H, J=20.5 Hz, H-14), 2.22 (m, 1H, H-7), 2.10 (dd, 1H, J=6.5 Hz, 2.5 Hz, H-1), 2.08 (s, 3H, OAc-CH_3-10), 2.073 (s, 3H, OAc-CH_3-2), 2.04 (s, 3H, OAc-CH_3-4), 2.02 (s, 3H, CH_3-18), 1.93 (m, 2H, H-6), 1.69 (s, 3H, CH_3-16), 1.67 (dd, 1H, J=5.5 Hz, 15 Hz, H-9), 1.56 (m, 1H, H-7), 1.37 (s, 3H, CH_3-17), 1.13 (s, 3H, CH_3-19); ^{13}CNMR (125 MHz, $CDCl_3$, δ ppm) 199.03 (C=O-13), 169.91 (OAc-C=O), 169.73 (2$\times$OAc-C=O), 153.61 (C-12), 137.07 (C-11), 84.88 (C-4), 82.38 (C-5), 76.29 (C-10), 70.94 (C-20), 70.85 (C-2), 47.19 (C-1), 44.02 (C-15), 41.22 (C-8), 38.01 (C-14), 37.59 (C-3), 36.93 (C-6), 35.27 (C-9), 35.05 (C-7), 27.42 (C-17), 24.54 (C-16), 21.83 (OAc-CH_3), 21.59 (OAc-CH_3), 21.47 (C-18), 21.22 (OAc-CH_3), 13.47 (C-19); FABMS *m/z* 477.3 (M+1).

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