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Synthetic study of 1,7,9-trideoxypaclitaxel via sinenxan A

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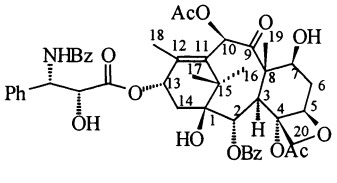
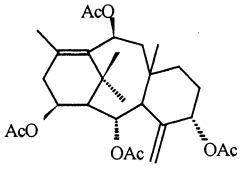
Abstract—Sinenxan A, a biosynthetic taxane, was converted into compound **9**, a key intermediate of 1,7,9-trideoxypaclitaxel. Two special steps in this transformation are worthy of note: (1) regioselective removal of *C*-5-acetyl; and (2) stereoselective reduction of the 13-carbonyl group by transannular assistance from the *C*-4-hydroxyl.

The diterpenoid paclitaxel (Taxol) which was first isolated from the bark of the western yew, *Taxus brevifolia*, has evoked much interest due to its complex molecular structure, notable antitumor activity and unique anticancer mechanism.[1,2] Paclitaxel is now approved for treatment of ovarian and breast cancers, with promise also for treatment of lung, skin, head and neck cancers. Six total syntheses of paclitaxel have been reported, but all of them are still not practical for commercial purposes. The production of paclitaxel and related compounds through semisynthesis from 10-*O*-deacetylbaccatin III has been well established.[3] Taxine B, the most abundant precursor present in the needles of *T. baccata* L., has been used to synthesize 7-deoxypaclitaxel.[4]

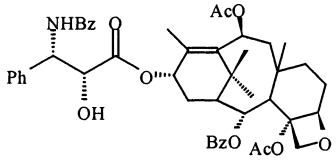


paclitaxel

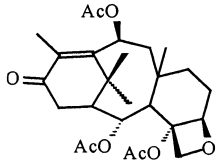


Sinenxan A

The structure–activity relationship (SAR) of paclitaxel has been intensively studied and has led to the general conclusions that modifications to the 'northern hemisphere' (C-7, C-9, and C-10) do not alter biological activity, but changes to the 'southern hemisphere' (C-4, C-2, the oxetane ring, except for OH-1) and the C-13 ester side chain can have large effects on activity.[5] Thus 1,7,9-trideoxypaclitaxel and its analogs may have potential activity as anticancer agents. Sinenxan A is readily available as a biosynthetic taxane in good yield.[6] The development of a procedure using sinenxan A as starting material for the preparation of bioactive paclitaxel analogues would be of significance. We have reported the synthesis of compound **1**,[7] but it cannot be converted to the target compound because its 13-carbonyl group could not be reduced to 13-α-OH. Here we present another route to synthesize 1,7,9-trideoxypaclitaxel analogs.



1,7,9-trideoxypaclitaxel



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In this synthetic strategy, the 13-α-OH was introduced before formation of the oxetane ring which is unstable under certain reaction conditions (Scheme 1). Thus compound **2** was prepared from sinenxan A in four steps.[7] Unfortunately compound **2** cannot be reduced to the corresponding alcohol with $NaBH_4$. There are some taxoids with a 13-carbonyl which are reduced to 13-α-hydroxyl taxanes by treatment with $NaBH_4$. We have found that most of the reducible 13-ketones have an adjacent 1-β-OH, whereas irreducible 13-ketones occur in molecules such as taxinine and compound **1**, with no 1-OH. Therefore, an adjacent hydroxyl group might be helpful to the reduction of 13-ketones. From a molecular model of compound **2**, we can see that the 5-α oxygen is spatially close to the 13-carbonyl group. We fortuitously found that the 5-*O*-acetate of **2** can be

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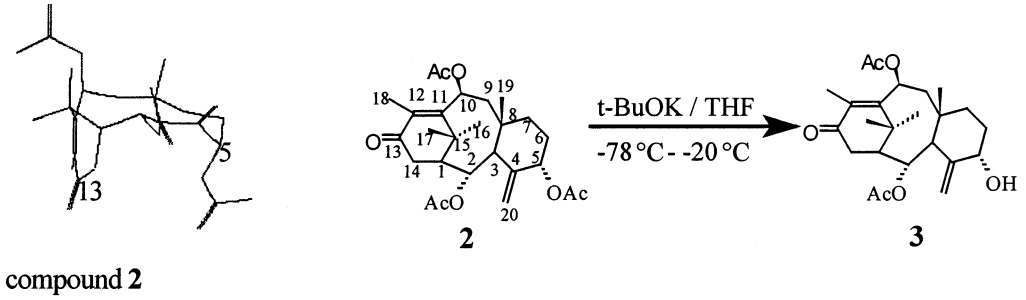
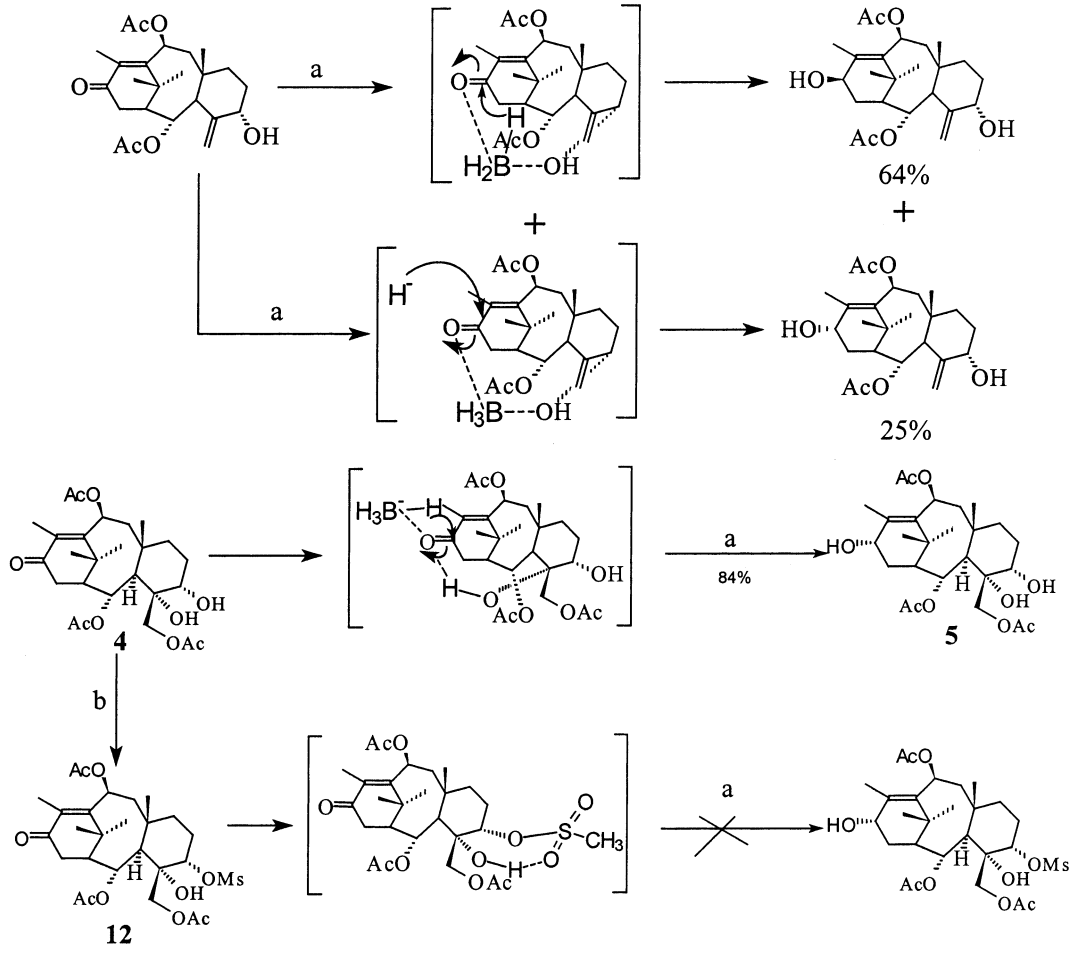
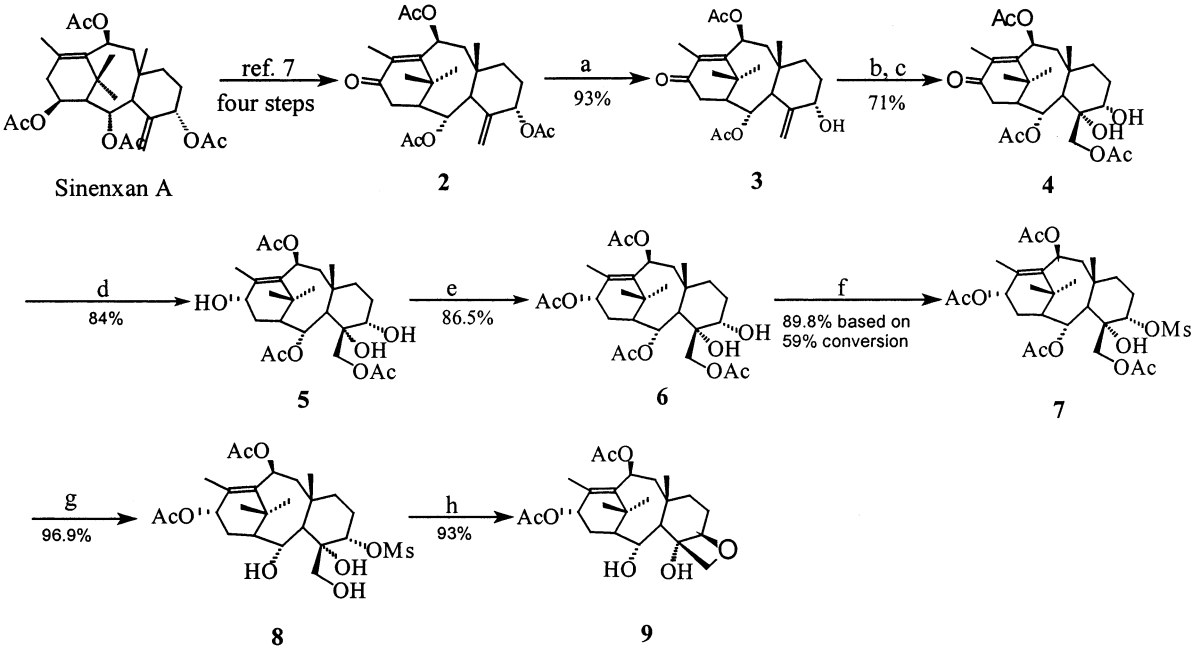
selectively cleaved by *t*-BuOK in THF to give **3** (Scheme 1). When reduced with $NaBH_4/CeCl_3{\cdot}7H_2O$, **3** gave both 13-α-OH (25%) and 13-β-OH (64%) products. As reported previously,[8] the 13-β-OH product was obtained by a normal transannular delivery. Formation of the 13-α-OH product is explained in Scheme 2. Bonding of the reagent to the C-13 ketone below the ring changes the A-ring conformation and then borohydride attacks the C-13 carbonyl from the top face to produce the 13-α-OH product. The result shows that the 13-carbonyl can be reduced with transannular assistance. Because the 4-OH is even closer than the 5-OH to the 13-carbonyl, it may help to control the stereoselectivity of 13-ketone reduction. Compound **3** was dihydroxylated with OsO_4/NMO, the resulting 20-OH product was protected with Ac_2O to leave both 4-OH and 5-OH free (compound **4**), then this was reduced under the same conditions to give a 13-α-alcohol **5** as the major product in 84% yield. Thus, it is possible that a hydrogen bond formed between the 4-hydroxy group and the 13-oxo group changes the conformation of the A-ring making the C-13-carbonyl vulnerable to the borohydride reagent. Reduction of **12** gave us indirect proof of this mechanism. When **12** was treated with $NaBH_4/CeCl_3{\cdot}7H_2O$ under the same conditions, the C-13-hydroxyl product was not obtained because the 5-mesyl of compound **12** forms a hydrogen bond with the C-4-hydroxyl group rather than with the C-13-oxo



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$; (b) MsCl, pyridine, 30–40°C.



Scheme 3. *Reagents and conditions*: (a) *t*-BuOK, THF, −20 to −78°C; (b) OsO_4, NMO, then $NaHSO_3$; (c) Ac_2O, CH_2Cl_2, pyridine; (d) $NaBH_4$, $CeCl_3{\cdot}7H_2O$; (e) Ac_2O, pyridine, DMAP; (f) MsCl, pyridine, 30–40°C; (g) K_2CO_3, MeOH, 0°C; (h) DBU, toluene, 105°C.

group. Thus, without the assistance of the 4-hydroxyl group, compound **12** cannot be reduced.

Having successfully performed the selective reduction of the C-13 carbonyl group, we developed our synthetic strategy as shown in Scheme 3. Compound **2** was treated with *t*-BuOK in anhydrous THF to give **3** in 93% yield.

Compound **3** was dihydroxylated with a catalytic amount of OsO_4 and four equivalents of NMO and then the crude product was selectively acetylated with Ac_2O in pyridine. The desired compound **4** was obtained in 71% overall yield for the two steps. Compound **5** was prepared from compound **4** using $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ in MeOH/THF in 84% yield. The configuration at C-13 was confirmed by NOE difference spectra.[9] We had tried to selectively protect the hydroxyl group at C-13 with TESCl, but in the following step, we found that it was very difficult to introduce a mesyl group at C-5 because of the steric hindrance by the huge 13-*O*-TES group. Therefore an acetyl group was chosen for protection, since the smaller acetyl at C-13 can be selectively removed with Red-Al.[2] Compound **6**, prepared from **5** by treatment with Ac_2O in pyridine, was converted into **7** by mesylation of the C-5 hydroxyl in moderate yield. We selectively removed the acetyl groups at C-20 and C-2 positions and then treated this intermediate mesylate with DBU in toluene to produce **9** in 93% yield.[10] ^1H NMR measurements showed that ^2J of H-20 changed from 11 Hz for compound **8** to 8 Hz for compound **9**, which indicated the formation of the oxetane ring. Thus, compound **9** has all the chiral centers of 1,7,9-trideoxypaclitaxel, without the amino acid side-chain. The synthesis of 1,7,9-trideoxypaclitaxel itself is underway.

In summary, we have developed a facile and practical synthetic strategy to fabricate the key framework, 7,9-dideoxy-2-debenzoyl-4-deacetyl-baccatin IV **9**. The strategy capitalized on stereoselective reduction of the 13-carbonyl group by transannular assistance from the C-4-hydroxyl group. Compound **9** was obtained in eight steps and 23% overall yield from intermediate **2**.

Acknowledgements

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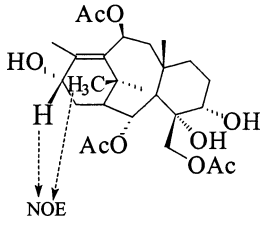
9. Spectral data of compound **5** and NOE analysis of C-13: colorless film; mp 87–89°C; $[\alpha]_D^{20}=+61$ (*c* 0.8, $CHCl_3$); HR-FABMS (Gly+NaCl) found: 519.2558, calcd: 519.2564, $C_{26}H_{40}O_9$+Na; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (dd, 1H, $J=10.7$ Hz, 6 Hz, H-10), 5.41 (dd, 1H, $J=1.8$ Hz, 4.8 Hz, H-2), 4.40 (d, 1H, $J=11.7$ Hz, H-20), 4.34 (br d, 1H, $J=8.7$ Hz, H-13), 4.02 (d, 1H, $J=11.7$ Hz, H-20), 3.95 (br s, 1H, H-5), 3.10 (d, 1H, $J=5.1$ Hz, H-3), 2.60 (dt, 1H, $J=7.8$ Hz, 15 Hz, H-14), 2.27 (dd, 1H, $J=12.6$ Hz, 15.6 Hz, H-9), 2.19–2.04 (5s+m, 14H, 4×OAc-CH_3, CH_3-18, H-14, H-7), 1.78 (m, 2H, 2×H-6), 1.67 (dd, 1H, $J=2$ Hz, 8 Hz, H-1), 1.58 (s, 3H, CH_3-16), 1.43 (dd, 1H, $J=5.5$ Hz, 15 Hz, H-9), 1.05 (m, 1H, H-7), 0.92 (s, 3H, CH_3-17), 0.86 (s, 3H, CH_3-19) ppm.



10. Spectral data of selected compounds: Compound **6**: colorless film; mp 81–83°C; $[\alpha]_D^{20}=+69$ (*c* 0.42, $CHCl_3$); FABMS *m*/*z* 561 (M+Na); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 (dd, 1H, $J=12$ Hz, 5.5 Hz, H-10), 5.59 (dd, 1H, $J=7$ Hz, 8.5 Hz, H-13), 5.41 (dd, 1H, $J=2$ Hz, 5 Hz, H-2), 4.45 (d, 1H, $J=12$ Hz, H-20), 4.06 (d, 1H, $J=12$ Hz, H-20), 3.89 (t, 1H, $J=2.7$ Hz, H-5), 3.19 (s, 1H, OH), 3.06 (d, 1H, $J=5$ Hz, H-3), 2.95 (d, 1H, $J=2$ Hz, OH), 2.62 (m, 1H, H-14), 2.30 (dd, 1H, $J=12.5$ Hz, 14.5 Hz, H-9), 2.17–2.04 (5 s, 15H, 4×OAc-CH_3, CH_3-18), 2.16 (dd, 1H, $J=3$ Hz, 15.5 Hz, H-14), 2.12–2.01 (m, 1H, H-7), 1.84–1.75 (m, 2H, 2×H-6), 1.72 (dd, 1H, $J=2$ Hz, 8 Hz, H-1), 1.62 (s, 3H, CH_3-16), 1.45 (dd, 1H, $J=5.5$ Hz, 15 Hz, H-9), 1.09 (m, 1H, H-7), 0.99 (s, 3H, CH_3-17), 0.86 (s, 3H, CH_3-19) ppm.
Compound **7**: pale yellow powder; mp 130–133°C; $[\alpha]_D^{20}=+64$ (*c* 0.33, $CHCl_3$); HR-FABMS (Gly+NaCl) found: 639.2440, calcd: 639.2445, $C_{29}H_{44}O_{12}S$+Na; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (dd, 1H, $J=12$ Hz, 5.5 Hz, H-10), 5.78 (dd, 1H, $J=7$ Hz, 8.5 Hz, H-13), 5.40 (d, 1H, $J=5$ Hz, H-2), 4.75 (s, 1H, H-5), 4.51 (d, 1H, $J=12.5$ Hz, H-20), 3.92 (d, 1H, $J=12.5$ Hz, H-20), 3.01 (s, 3H, CH_3SO_2), 2.87 (d, 1H, $J=5$ Hz, H-3), 2.42 (dt, 1H, $J=9.7$ Hz, 14.7 Hz, H-14), 2.30 (dd, 1H, $J=12.5$ Hz, 15 Hz, H-9), 2.16–1.92 (5s+m, 19H, 4×OAc-CH_3, CH_3-18, H-7, H-14, 2×H-6), 1.73 (d, 1H, $J=9$ Hz, H-1), 1.59 (s, 3H, CH_3-16), 1.42 (dd, 1H, $J=5.5$ Hz, 15 Hz, H-9), 1.26 (m, 1H, H-7), 1.03 (s, 3H, CH_3-17), 0.84 (s, 3H, CH_3-19) ppm.
Compound **9**: mp 71–73°C; $[\alpha]_D^{20}=+46$ (*c* 0.57, $CHCl_3$); HR-FABMS (Gly+NaCl) found: 459.2349, calcd: 459.2353, $C_{24}H_{36}O_7$+Na; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (dd, 1H, $J=12$ Hz, 5.5 Hz, H-10), 5.64 (d, 1H, $J=9.5$ Hz, H-13), 4.70 (d, 2H, $J=8.5$ Hz, H-5, H-20), 4.39 (d, 1H, $J=8$ Hz, H-20), 4.07 (m, 1H, H-2), 2.76 (s, 1H, OH), 2.65 (m, 2H, H-3, H-14), 2.32 (dd, 1H, $J=12.5$ Hz, 15 Hz, H-9), 2.17 (m, 2H, 2×H-6), 2.12 (s, 3H, OAc-CH_3), 2.05 (s, 3H, OAc-CH_3), 2.04–1.96 (m, 1H, H-7), 1.89 (s, 3H, CH_3-18), 1.85 (dd, 1H, $J=2.5$ Hz, 8 Hz, H-1), 1.77 (dd, 1H, $J=3$ Hz, 15.6 Hz, H-14), 1.67–1.60 (m, 1H, H-7), 1.57 (s, 3H, CH_3-16), 1.52 (dd, 1H, $J=5.5$ Hz, 15 Hz, H-9), 1.33 (s, 3H, CH_3-19), 1.01 (s, 3H, CH_3-17) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.02 (OAc-C=O), 169.67 (OAc-C=O), 138.55 (C-12), 133.92 (C-11), 87.52 (C-5), 80.327 (C-4), 77.48 (C-10), 70.46 (C-20), 70.29 (C-13), 69.83 (C-2), 49.39 (C-1), 47.64 (C-9), 44.28 (C-3), 37.16 (C-8), 36.57 (C-15), 35.69 (C-14), 33.77 (C-17), 27.49 (C-7), 27.04 (C-6), 25.07 (C-16), 22.01 (C-19), 21.35 (OAc-CH_3), 21.13 (OAc-CH_3), 15.74 (C-18) ppm.