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Semisynthesis of D-ring-modified taxoids: thietane derivatives from taxine B

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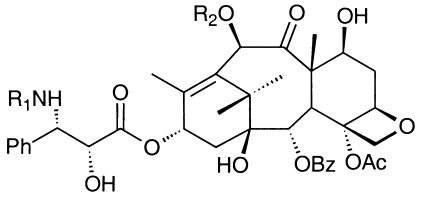
Abstract

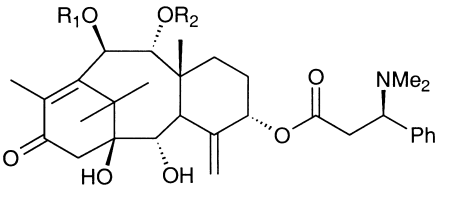
The semisynthesis of 7-deoxobaccatin III derivatives, in which the oxygen atom in ring D is substituted for a sulfur atom, is presented; the starting material is the natural taxine B and isotaxine B extracted from the needles of *Taxus baccata*.

Keywords: 7-deoxothiabaccatin III; thietane; protected taxicine I; taxine B.

Since the anticancer activity of paclitaxel **1** and docetaxel **2** is known, various studies of the chemistry and structure–activity relationships have been developed. The oxetane ring is considered as essential for biological activity but its precise role is not yet so clear.[1–3]



1 R_1 = COPh, R_2 = Ac
2 R_1 = Boc, R_2 = H



3 R_1= Ac, R_2= H
4 R_1= H, R_2 = Ac

Only a few analogues in which the oxygen atom in ring D is substituted by another heteroatom (N, S, Se) have been described[4–6] in the paclitaxel or docetaxel series. Recently, Kingston's group described the preparation of a thiapaclitaxel from paclitaxel.[6] We present the synthesis of '7-deoxothiabaccatin' derivatives from natural taxine B **3** and isotaxine B **4**. This starting material had already been used in the first synthesis of the oxetane D-ring,[7] and in the semisynthesis of deoxopaclitaxel and 7-deoxydocetaxel derivatives.[8–11]

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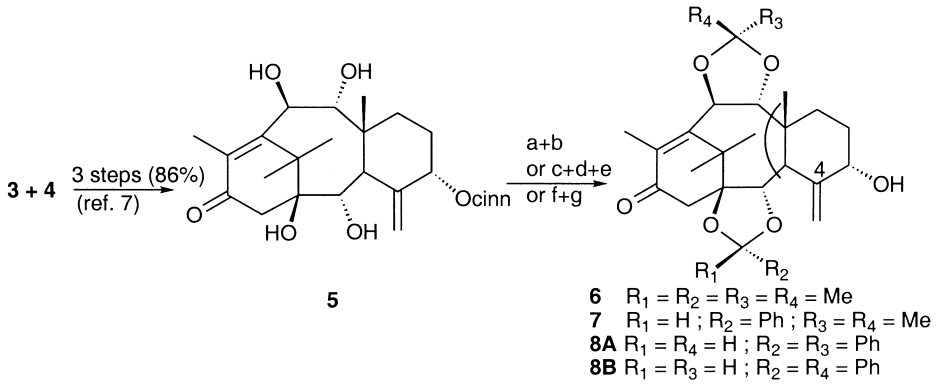
Prepared in 3 steps from taxine B and isotaxine B,[7] the starting material is the 5-cinnamoyl-taxicine I **5** (Scheme 1). Before the solvolysis of the cinnamoyl ester, the hydroxyles of **5** had to be protected: the protection–deprotection steps remain hard to manage. Three possibilities were explored: 1,2,9,10-di-*O*-isopropylidene, 1,2-*O*-benzylidene-9,10-*O*-isopropylidene and 1,2,9,10-di-*O*-benzylidene.

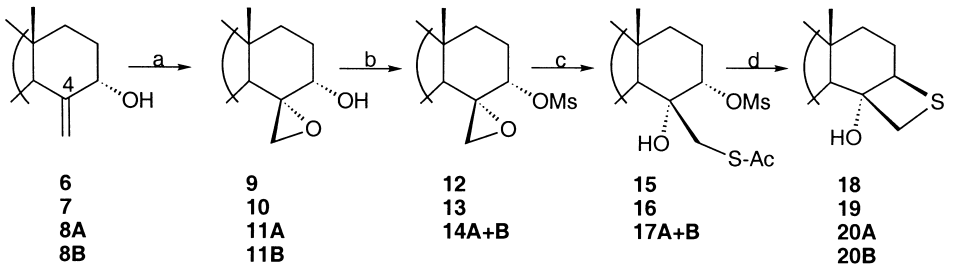


Scheme 1. Reagents and conditions: (a) $Me_2C(OMe)_2$, PTSA, THF, rt, 5 h, 64%; (b) NaOH 20N, THF, 60°C, 36 h, 90% **6**; (c) $Me_2C(OMe)_2$, PTSA, THF, rt, 3.5 h, 84%; (d) Ph $CH(OMe)_2$, PTSA, THF, 60°C, 7.5 h, 80%; (e) NaOH 20N, THF, 60°C, 22 h, 86% **7**; (f) Ph $CH(OMe)_2$, PTSA, THF, 60°C, 2.5 h, 54%; (g) NaOH 20N, THF, 60°C, 30 h, 90% **8A+8B**

After solvolysis of the cinnamoyl ester, **6**, **7**, **8A**, **8B** were obtained in good yields,[12,13] the latter two being easily separated by preparative TLC.

Various methods for preparation of the thietane heterocycle have been reported. After preliminary experiments, we chose the direct access via 5-hydroxy-4,20-epoxide derivatives. Our strategy was inspired by the Ohuchida et al. synthesis[14,15] of a thromboxane A_2 sulfur analogue: a derivative doubly substituted by the mesylate and thioacetate groups is prepared and the mesylate undergoes a nucleophilic substitution by an in situ native sulfide.

Epoxidation of the 4,(20) double bond and mesylation of the C-5 hydroxyle provided **9**, **10**, **11A**, **11B** and **12**, **13**, **14A+14B**, successively (Scheme 2).

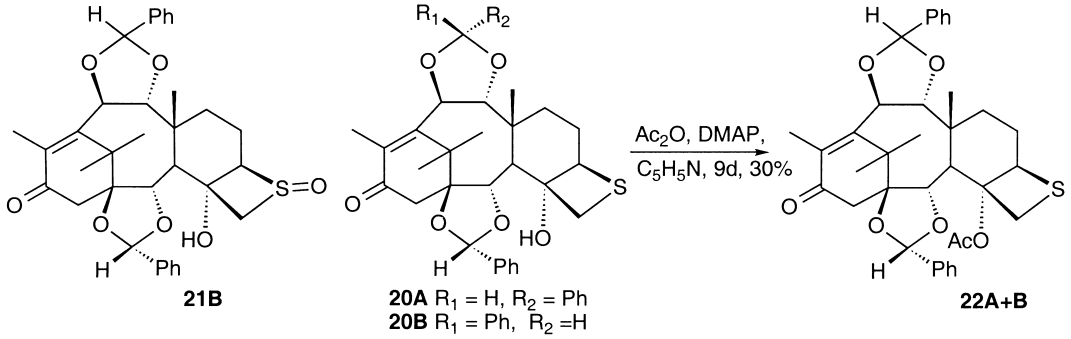


Scheme 2. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, 0°C, 0.5 h, 98% **9**, 98% **10**, 96% **11A+11B**; (b) MsCl, C_5H_5N, 0°C, 0.5 h, 74% **12**, 73% **13**, 78% **14A+14B**; (c) AcSH, NaH, DMF, 5 h, 60°C, 60% **15**, 66% **16**, 80% **17A+17B**; (d) MeONa, MeOH, 60°C, 1 h, 85% **18**, 86% **19**, 77% **20A+20B**

Attempts to transform the 4 (20)-epoxide into a thietane by using Na_2S, Li_2S (prepared in situ) or Ph_3SiSH were unsuccessful, but the treatment of **12** by thioacetic acid and NaH provided compound **15** (60% yield), while **13** and **14A+14B** provided **16** and **17A+17B**, respectively (66 and 80% yields).

The cyclisation of the intermediates **15**, **16** and **17A+17B** was carried out by treatment with NaOMe in MeOH (60°C, 1 h): the thietane derivatives **18**,[16] **19**,[17] **20A+20B**[18] were obtained with 85, 86 and 77% yields, respectively. The compounds **20A+20B** could be separated by preparative TLC; **20B** in solution was spontaneously oxidised by air oxygen to sulfoxide **21B**.[19]

It is worthy of note that several attempts to acetylate the C-4 hydroxyl group of the compounds **18** and **19** failed while the derivatives **20A+20B** could be acetylated (Ac_2O, DMAP, pyridine) to **22A+22B**[20] in 30% yield (Scheme 3).



Scheme 3.

These favourable results incited us to follow this way with other substituents or protective groups in positions 1, 2, 9 and 10 which would be more appropriate to provide the paclitaxel or docetaxel substitution pattern in these positions: these studies are in progress.

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16. Data for **18**: $C_{26}H_{38}O_6S$ ($M=478$). Amorphous. R_f: 0.6 (heptane:AcOEt, 7:3), $[\alpha]_D$ +211 (*c* 0.18, $CHCl_3$). IR ($CHCl_3$): 1679 cm^{-1} (CO). SM IC ($T=190°C$, isobutane): 479 $(MH)^+$. ^1H NMR (300 MHz) δ: 1.31 (s, 3H, Me-17), 1.36, 1.44, 1.45, 1.50 (4s, 4×3H, 4 Me-isopropylidene), 1.54 (s, 3H, Me-19), 1.56 (s, 3H, Me-16), 1.62 (d, $J=5$ Hz, 1H, H-3), 1.93 (s, 3H, Me-18), 2.24 (m, 2H, H-6), 2.63 (d, $J=19.5$ Hz, 1H, H-14), 2.96 (dd, $J=11$ and 1 Hz, 1H, H-20), 3.23 (t ép., 1H, H-5), 3.25 (d, $J=19.5$ Hz, 1H, H-14), 3.76 (d, $J=11$ Hz, H-20), 4.17 (d, $J=5$ Hz, 1H, H-2), 4.25 (d, $J=9$ Hz, 1H, H-9), 4.65 (d, $J=9$ Hz, 1H, H-10), (H-7 probably at: 1.20 and 1.98 ppm). ^{13}C NMR (75 MHz) δ: 14.15 (C-18), 18.70 (C-19), 19.90 (C-16), 26.20, 26.80, 27.10 (3×*C*H_3-isopropylidene), 27.95 (*C*H_3-isopropylidene and C-7), 30.30 (C-6), 33.55 (C-17), 40.20 (C-20), 44.60 (C-14), 48.25 (C-5), 48.55 (C-3), 75.55 (C-10), 76.55 (C-2), 81.75 (C-9), 106.80, 107.70 (2×*C*q-isopropylidene), 141.23 (C-11), 152.37 (C-12), 199.94 (C-13). SM HR (IC): $C_{26}H_{39}O_6S$, calculated: 479.2467; obtained: 479.2432.
17. Data for **19**: $C_{30}H_{38}O_6S$ ($M=526$). Amorphous. R_f: 0.7 (heptane:AcOEt, 5:5), $[\alpha]_D$ +151 (*c* 0.23, $CHCl_3$). IR ($CHCl_3$): 1679 cm^{-1} (CO). SM FAB (thioglycerol+NaCl): 549 $(MNa)^+$. ^1H NMR (250 MHz) δ: 1.22, 1.37, 1.45, 1.51, 1.57, 1.66 (6s, 6×3H, 6Me), 1.84 (d, $J=5$ Hz, 1H, H-3), 1.94 (s, 3H, Me-18), 2.28 (m, 2H, H-6), 2.67 (d, $J=19$ Hz, 1H, H-14), 2.97 (dd, $J=11$ and 1Hz, 1H, H-20a), 3.19 (t ép., 1H, H-5), 3.41 (d, $J=19$ Hz, 1H, H-14), 3.90 (d, $J=11$ Hz, 1H, H-20), 4.29 (d, $J=5$ Hz, 1H, H-2), 4.31 (d, $J=1$ Hz, 1H, H-9), 4.69 (d, $J=9$ Hz, 1H, H-10), 5.84 (s, 1H, H-benzylidene), 7.4 (m, 5H, H-Ph). SM HR (IC): $C_{30}H_{39}O_6S$, calculated: 527.2466; obtained: 527.2429.
18. The two epimers **20A** and **20B** (ratio 3:2) were separated by preparative TLC: three migrations in cyclohexane:AcOEt, 7:3. Data for **20A**: $C_{34}H_{38}O_6S$ ($M=574$). Amorphous. R_f: 0.65 (heptane:AcOEt, 5:5); $[\alpha]_D$ +165 (*c* 0.29, $CHCl_3$). UV [λ_{max} nm (ε)]: 276 (6800). IR ($CHCl_3$): 1681cm^{-1} (CO). SM IC ($T=190°C$, isobutane): 631 $(M+57)^+$, 575 $(MH)^+$. ^1H NMR (200 MHz) δ: 1.42, 1.69, 1.74 (3s, 3×3H, 3Me), 1.81 (d, $J=5$ Hz, 1H, H-3), 1.93 (s, 3H, Me-18), 2.31 (m, 2H, H-6), 2.69 (d, $J=19$ Hz, 1H, H-14), 3.00 (dd, $J=11$ and 2 Hz, 1H, H-20), 3.21 (t, $J=8$ Hz, 1H, H-5), 3.31 (s, 1H, OH), 3.41 (d, $J=19$ Hz, 1H, H-14), 3.92 (d, $J=11$ Hz, 1H, H-20), 4.33 (d, $J=5$ Hz, 1H, H-2), 4.53 (d, $J=10$ Hz, 1H, H-9), 4.86 (d, $J=10$ Hz, 1H, H-10), 5.88 (s, 1H, H-benzylidene-1,2), 6.15 (s, 1H, H-benzylidene-9,10), 7.42 (m, 5H, H-Ph), 7.44 (m, 5H, H-Ph). ^{13}C NMR (75 MHz) δ: 14.50 (C-18), 28.40 (C-7), 30.80 (C-6), 40.60 (C-20), 42.35 (C-15), 45.55 (C-14), 48.90 (C-3), 49.60 (C-5), 75.85 (C-10), 80.05 (C-2), 81.40 (C-4), 84.35 (C-9), 84.85 (C-1), 102.90 (*C*H-benzylidene-9,10), 103.20 (*C*H-benzylidene-1,2), 126.55 (4×C-Ph), 128.75 (4×C-Ph), 129.65 (2×C-Ph), 137.85 (2×C *ipso* Ph), 142.10 (C-12), 153.20 (C-11), 200.15 (C-13). Data for **20B**: $C_{34}H_{38}O_6S$ (M = 574). Amorphous. R_f: 0.62 (heptane:AcOEt, 5:5); $[\alpha]_D$ +145 (*c* 0.29, $CHCl_3$). UV [λ_{max} nm (ε)]: 273 (10200). IR: 3553 (OH), 1680 cm^{-1} (CO). SM IC ($T=200°C$, isobutane): 631 $(M+57)^+$, 575 $(MH)^+$. ^1H NMR (250 MHz) δ: 1.20–1.29 (m, 1H, H-7 or H-6), 1.36, 1.52, 1.66 (3s, 3×3H, 3Me), 1.78 (d, $J=5$ Hz, 1H, H-3), 2.01 (s, 3H, Me-18), 2.09–2.14 (m, 1H, H-7 or H-6), 2.30–2.38 (m, 2H, H-6 or H-7), 2.68 (d, $J=19$ Hz, 1H, H-14), 2.98 (d, $J=11.5$ Hz, 1H, H-20), 3.22 (dd, $J=8.5$ and 7.9 Hz, 1H, H-5), 3.30 (s, 1H, OH), 3.41 (d, $J=19$ Hz, 1H, H-14), 3.90 (d, $J=11.5$ Hz, 1H, H-20), 4.28 (d, $J=5$ Hz, 1H, H-2), 4.43 (d, $J=9.5$ Hz, 1H, H-9), 4.88 (d, $J=9.5$ Hz, 1H, H-10), 5.81 (s, 1H, H-benzylidene-1,2), 6.11 (s, 1H, H-benzylidene-9,10), 7.37–7.53 (m, 10H, H-Ph). SM HR (IC): $C_{34}H_{39}O_6S$, calculated: 575.2467; obtained: 575.2434.
19. Data for **21B**: $C_{34}H_{38}O_7S$ ($M=590$). Amorphous. R_f: 0.12 (heptane:AcOEt, 5:5); $[\alpha]_D$+100 (*c* 0.33; $CHCl_3$). SM IC ($T=210°C$, isobutane): 591 $(MH)^+$. ^1H NMR (400 MHz) δ: 1.37, 1.52, 1.59 (3s, 3×3H, 3Me), 1.94 (d, $J=5$ Hz, 1H, H-3), 2.01 (s, 3H, Me-18), 2.34 (m, 2H, H-6), 2.63 (d, $J=19$ Hz, 1H, H-14), 3.02 (dd, $J=15$ and 5 Hz, 1H, H-20), 3.16 (m, 1H, H-5), 3.52 (d, $J=19$ Hz, 1H, H-14), 4.08 (d, $J=15$ Hz, 1H, H-20), 4.12 (s, 1H, OH), 4.27 (d, $J=5$ Hz, 1H, H-2), 4.42 (d, $J=10$ Hz, 1H, H-9), 4.88 (d, $J=10$ Hz, 1H, H-10), 5.81 (s, 1H, H-benzylidene-1,2), 6.10 (s, 1H, H-benzylidene-9,10), 7.40 (m, 5H, H-Ph), 7.43 (m, 5H, H-Ph).
20. Data for **22A+22B**: $C_{36}H_{40}O_7S$ ($M=616$). Amorphous. R_f: 0.70 (heptane:AcOEt, 5:5). SM FAB (thioglycerol+NaCl): 579 $(M\text{-}AcOH+Na)^+$. ^1H NMR (300 MHz) δ: 1.26/1.30, 1.52/1.73, 1.81/1.82 (3s, 3×3H, 3Me), 1.97/2.04 (s, 3H, Me-18), 2.06 (s, 3H, Me-CO), 2.51 (s, 2H, H-14), 2.86/2.88 (d, $J=5$ Hz, 1H, H-3), 3.43/3.46 (d, $J=12.5$ Hz, 1H, H-20), 3.76/3.78 (d, $J=12.5$ Hz, 1H, H-20), 3.98–4.03 (m, 1H, H-5), 4.28/4.32 (d, $J=5$ Hz, 1H, H-2), 4.48/4.56 (d, $J=9.5$ Hz, 1H, H-9), 4.91/4.93 (d, $J=9.5$ Hz, 1H, H-10), 5.85/5.91 (s, 1H, H-benzylidene-1,2), 6.11/6.15 (s, 1H, H-benzylidene-9,10), 7.39–7.50 (m, 10H, H-Ph). SM HR (IC): $C_{36}H_{41}O_7S$, calculated: 617.2572; obtained: 617.2584.