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Synthesis of a Paclitaxel Isomer: C-2-Acetoxy-C-4-Benzoate Paclitaxel

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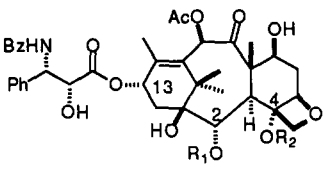
Abstract: A synthesis of the C-2-acetoxy-C-4-benzoate paclitaxel **2** is described. This analog has the substituents at C-2 and C-4 transposed. The key steps in the synthesis include the sequential use of Red-Al as reducing agent for the regioselective reduction of the C-2 benzoate and the C-4 acetoxy within the baccatin core. Iso-paclitaxel **2** was considerably less potent than paclitaxel in tubulin polymerization and in vitro cytotoxicity assays.

Since its isolation from the extract of the bark of the Pacific Yew *Taxus brevifolia* [1] and the demonstration of its antitumor activity against broad spectrum of tumors[2] including ovarian, breast and lung carcinoma, paclitaxel (TAXOL®) has become one of the most promising anticancer drugs of the decade. The cytotoxic effects of paclitaxel are believed to arise from its ability to promote tubulin polymerization and stabilize microtubule polymers thus formed, thereby blocking cell replication.[3] The continually expanding therapeutic indications of paclitaxel, coupled with its novel mode of action, have stimulated intensive research activities including structure-activity relationship (SAR) studies with the aim of designing novel paclitaxel analogs with better therapeutic indices.[4] Recently, results from extensive SAR studies on the southern part of the molecule clearly indicate that the functional groups at the C-2 and C-4 positions are critical binding elements.[5-8] For example, both the C-2 and C-4 deacylated paclitaxel analogs were devoid of biological activity. In parallel with our SAR effort directed towards the C-2 and C-4 derivatizations, we were also interested in seeking the possible correlation (if any) between in vitro activity and lipophilicity of paclitaxel analogs. Following this line of thinking, we were particularly interested in the synthesis of the C-2-acetoxy-C-4-benzoate paclitaxel **2**, simply because this analog should have similar lipophilicity to that of **1** (Figure 1). In this communication, we wish to report an efficient synthesis of iso-paclitaxel **2** and the biological activity of this analog.

Figure 1



1 R_1=Bz, R_2=Ac ***Paclitaxel***
2 R_1=Ac, R_2=Bz ***Iso-Paclitaxel***

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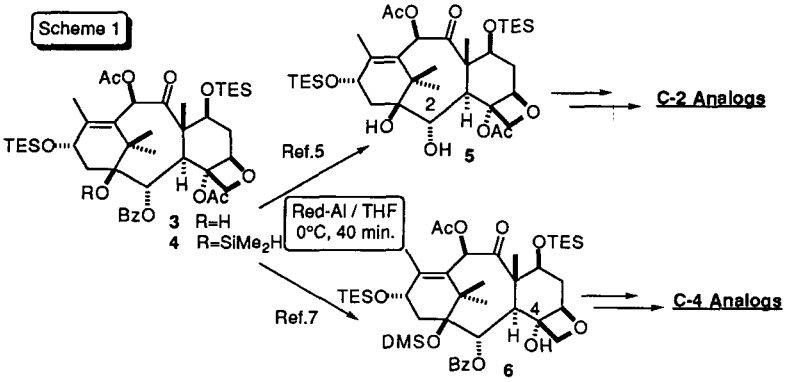
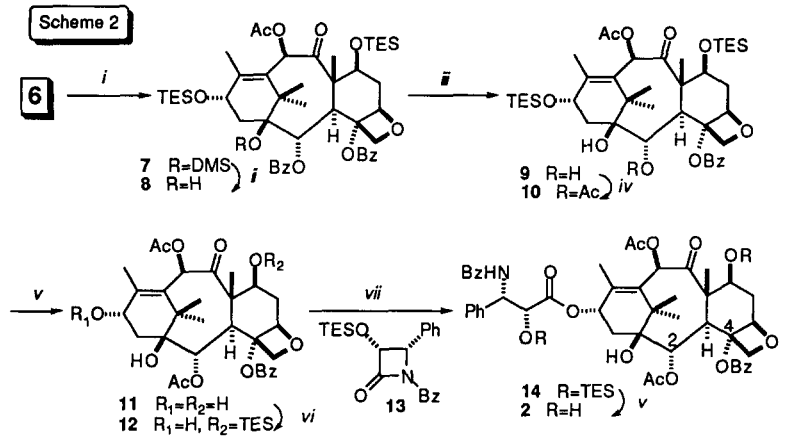
Our strategy for the synthesis of paclitaxel isomer **2** is based on the two Red-Al mediated regioselective deacylation methods previously developed in our laboratory.[5,7] As can be seen in Scheme 1, reduction of the 7,13-bisTES baccatin **3** with Red-Al afforded the C-2 deacylated baccatin **5** in 80% yield.[5] Remarkably, treatment of a fully silylated baccatin derivative **4** with Red-Al provided the C-4 deacylated baccatin **6** in 74% yield.[7] Taking advantage of these findings, we felt that combined sequential use of these two regioselective methods described here could provide a general route for the preparation of paclitaxel analogs containing modifications at the C-2 and C-4 positions (e.g., iso-paclitaxel **2**).





Reagents and Conditions: (i) LiHMDS/THF/BzCl (80%); (ii) TBAF/THF (78%); (iii) Red-Al/THF (98%); DCC/DMAP/AcOH/PhMe (95%); (v) Pyridine/48% HF/CH_3CN, **10** to **11** (57%); and **14** to **2** (77%); (vi) TESCl/imidazole/DMF (70%); LiHMDS/THF/**13** (52%).

As shown in Scheme 2, our synthesis of the target compound **2** began with benzoylation of the C-4 hydroxyl group in **6**, providing the corresponding C-4 benzoate baccatin **7**. Upon selective C-1 desilylation (0.75 equiv.TBAF/THF/0 °C), the resulting baccatin **8** was subjected to a Red-Al mediated C-2 debenzoylation, affording the desired product **9** in 76% overall yield. DCC mediated acetylation at C-2 yielded C-2-acetoxy

baccatin **10** in almost quantitative yield. Desilylation at C-7 & C-13 followed by selective resilylation at C-7 as usual led to the monosilylated derivative **12** in modest yield. Standard side chain coupling was performed using Holton/Ojima's protocols,[9,10] and provided **14**. Upon desilylation, the desired paclitaxel isomer, **2**, was obtained in 77% yield.[11,12]

It is rather interesting to note that compound **2**, having the same mass and lipophilicity as paclitaxel, was found to be totally inactive in the tubulin polymerization assay as well as in vitro cytotoxicity assay.[13] This result seems to indicate that there is no correlation between tubulin activity and lipophilicity.

Acknowledgments:

We would like to thank Dr. S. W. Mamber for performing the tubulin polymerization assay. We are also indebted to Dr. S. E. Klohr for the measurements of high-resolution mass spectra.

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® Taxol is a registered trademark of Bristol-Myers Squibb Company.

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11. ^{1}H NMR of **11** (300 MHz, $CDCl_3$): δ 8.06 - 8.03 (m, 2H), 7.66-7.47 (m, 3H), 6.33 (s, 1H), 5.39 (d, J = 7.0 Hz, 1H), 5.11 (d, J = 7.7 Hz, 1H), 4.66 (d, J = 7.9 Hz, 1H), 4.61 (m, 2H), 4.32 (d, J = 8.1 Hz, 1H), 3.92 (d, J = 6.8 Hz, 1H), 2.70- 2.59 (m, 2H), 2.23 - 1.03 (m, 20H, include. singlets at 2.23, 2.19, 2.04, 1.67, 3H each, 1.03, 6H). ^{13}C NMR of **11** (75 MHz, $CDCl_3$): δ 204.0, 171.7, 171.2, 165.3, 146.6, 133.5, 131.3, 130.3, 129.5, 128.6, 128.4, 84.4, 81.0, 79.0, 76.3, 76.1, 74.5, 72.2, 67.5, 58.6, 46.1, 42.5, 38.7, 35.5, 26.8, 21.4, 20.8, 20.7, 15.3, 9.3. HRMS (FAB) calcd. for $C_{31}H_{39}O_{11}$ (MH^+): 587.2492, found: 587.2498.

^{1}H NMR of **2** (300 MHz, $CDCl_3$): δ 8.07 - 8.00 (m, 2H), 7.67 - 7.64 (m, 2H), 7.53 - 7.23 (m, 11H), 6.85 (t, J = 7.4 Hz, 1H), 6.55 (d, J = 9.0 Hz, 1H), 6.31 (s, 1H), 5.84 (t, J = 8.8 Hz, 1H), 5.47 (d, J = 7.0 Hz, 1H), 5.04 (d, J = 7.7 Hz, 1H), 4.95 (dd, J = 1.9 Hz, J' = 9.0 Hz, 1H), 4.62 (d, J = 8.0 Hz, 1H), 4.55 (m, 1H), 4.33 (d, J = 7.9 Hz, 1H), 3.87 (d, J = 6.9 Hz, 1H), 3.57 (dd, J = 2.1 Hz, J' = 5.4 Hz, 1H), 3.05 (d, J = 5.4 Hz, 1H), 2.68 - 1.03 (m, 22H, include. singlets at 2.23, 1.84, 1.69, 1.68, 1.18, 1.04, 3H each). ^{13}C NMR of **2** (75 MHz, $CDCl_3$): δ 203.6, 173.1, 171.5, 171.2, 166.7, 165.4, 142.5, 138.3, 133.8, 132.7, 131.7, 129.9, 129.1, 128.5, 128.0, 127.9, 126.8, 84.4, 81.3, 78.9, 77.1, 76.4, 75.5, 74.6, 73.1, 72.1, 71.4, 58.5, 54.2, 45.7, 43.1, 35.4, 35.2, 26.7, 21.8, 21.5, 20.7, 14.7, 9.4. HRMS (FAB) calcd. for $C_{47}H_{52}NO_{14}$ (MH^+): 854.3389, found: 854.3421.

12. All of the new compounds described in this paper were characterized by proton NMR and high resolution mass spectra.

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