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Synthesis of a Novel C-10 Spiro-Epoxide of Paclitaxel

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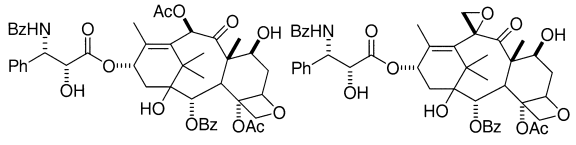
Abstract—New analogues of paclitaxel (**1a**, active constituent of Taxol®) were synthesized containing an epoxide at the C-10 position. The introduction of the epoxide was carried out by selective removal of the C10-acetate followed by protection of the C2′- and C7-hydroxyl groups. After oxidation to yield a ketone at the C10-position, this intermediate was reacted with dimethylsulfonium ylide. Deprotection and further manipulations provide the C10-spiro epoxide of paclitaxel (**1b**) and the corresponding C7-MOM ether (**1c**). © 2001 Elsevier Science Ltd. All rights reserved.

Taxol® (paclitaxel, **1a** as an active ingredient) has been found to be very beneficial in the treatment of ovarian and breast cancer as well as AIDS-related Karposi's sarcoma. Due to its unique mechanism of action and the impact it has had on these forms of cancer it is currently being studied in nonsmall cell lung cancer (NSCLC), small cell lung cancer (SCLC), and head and neck cancer.[1] It has also been the subject of numerous medicinal chemistry studies aimed at optimizing its activity and pharmacological profile through synthetic modification of the structure. Indeed a number of new paclitaxel analogues have been synthesized showing improvements in both parameters.[2]



1a paclitaxel **1b**

As part of our efforts in this area, we were interested in expanding the SAR-investigation of the C10-position. Previous studies at this position have been primarily focused on modifications of the ester group and manipulating the oxidation state of C10. Despite the amount of work carried out at this position, little attention has been paid to introducing alkyl substituents at C10. As a preliminary entry into this area we decided to synthesize **1b**. This analogue is interesting in that not only does it possess an alkyl group at C10, it also has a spiro-fused ring system, which might in theory affect the conformation of the cyclooctane ring. This modification is also interesting from another perspective in that it provides a handle for the introduction of additional functionality.

The route we envisioned for the synthesis of the C-10 epoxide of paclitaxel proceeds through the C-10 ketone **2**. Methods for the synthesis of this intermediate have previously been described.[3] Our synthesis of this intermediate, shown in Scheme 1, is similar to the literature method with a few minor variations. Thus, the C-10 acetate group was selectively removed by treatment with hydrazine at low temperature (0 °C). Following this, the C-2′ hydroxyl group was protected with the *t*-butyldimethylsilyl (TBDMS) group, followed by masking of the C-7 hydroxy group as the corresponding triethylsilyl (TES) ether. Once these positions were protected, oxidation of the C-10 position was achieved using TPAP.[4] The resulting ketone group serves as a convenient synthetic handle on which to build the C-10 epoxide.

Of the available procedures for converting a carbonyl group to the corresponding epoxide we viewed the dimethylsulfonium methylide approach to be the most readily accessible. As shown in Scheme 1, complete consumption of the starting material was achieved when 5 equiv of this reagent were used. Reaction with the ylide yielded two products having equal molecular weight. We initially assumed these to be the two possible isomeric-epoxides resulting from attack of the

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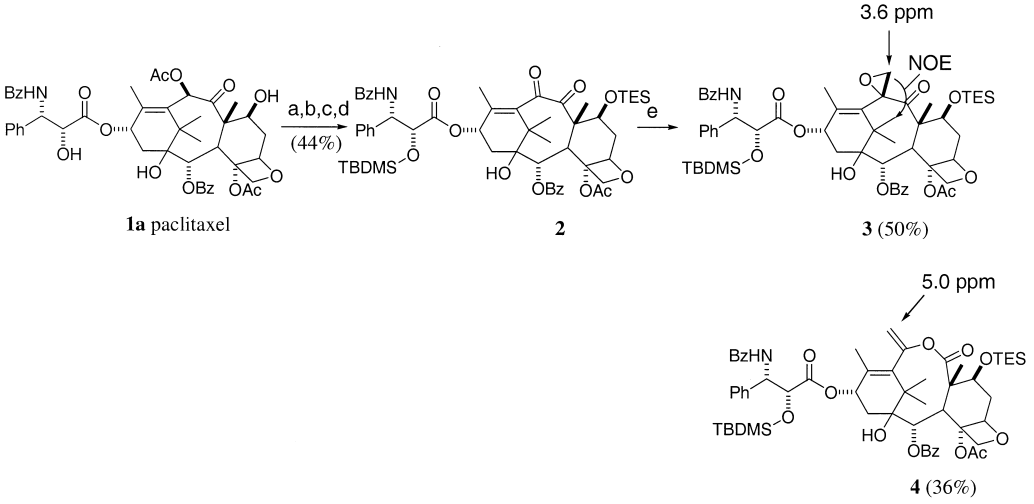
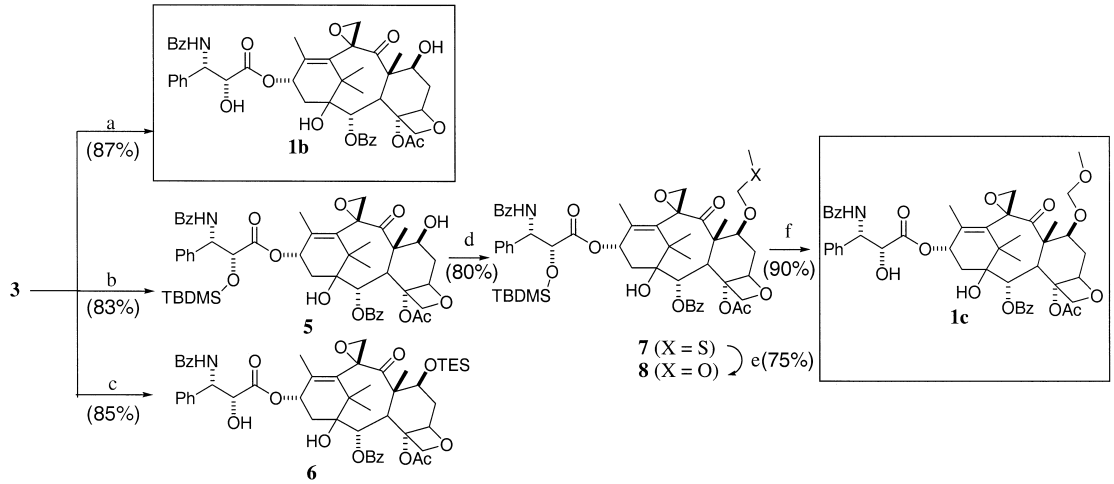
carbonyl from the α- and the β-face. However, comparison of the NMR of these two compounds was not consistent with this assumption but fit more with **3** and **4**.[5] For example, the ^{13}C NMR shift observed for the C9 carbonyl of **4** (150 ppm) is upfield compared to the signal for the same carbon atom in **3** (202 ppm) consistent with an ester rather than a ketone.[6] In addition, the ^{1}H NMR signal for the new CH_2-group of **3** was found at 3.60 ppm, while the analogous signal for **4** was at 5.0 ppm suggesting a terminal olefin.[7] This unusual by-product appears to be new in the arena of sulfur ylide chemistry, although a similar reaction has been described for bismuthonium ylides.[8] Assignment of the epoxide stereochemistry of **3** was established through the observance of an NOE signal enhancement between the bridgehead methyl group (C17) and the epoxide methylene. The high facial selectivity obtained in the epoxidation step is not surprising considering that nucleophile approach from the opposite face is sterically blocked.[9]

Subsequent manipulations of intermediate **3**, en route to **1b**, uncovered an interesting protocol for selective removal of either the C2-′ or the C7-silyl protecting group. Following a published procedure for complete desilylation of protected paclitaxel intermediates,[10] we observed incomplete removal of the C2′-TBDMS. HF•pyridine appeared to be selective for removing the triethylsilyl group since the 2′-desilylated product was not observed. Under slightly milder reaction conditions the reaction could be controlled to deliver the 7-desilylated product almost exclusively. This result was not completely unexpected since there is literature precedent for the removal of the TES protecting group in the presence of TBDMS using HF·pyridine.[11] However, we were delighted to discover that we could effect the reverse selectivity, that is to remove the TBDMS group while leaving the TES-group in place, by switching to TBAF as the desilylating agent. Thus as shown in Scheme 2, stirring **3** with 1.1 equiv of TBAF for 15 min yielded **6** almost exclusively. To the best of our knowledge this



Scheme 1. Reagents and conditions: (a) $N_2H_2 \cdot H_2O$, EtOH, 0 °C, 2 h; (b) 2.0 equiv TBDMSCl, 2.0 equiv imidazole, DMF, 0 °C, 24 h; (c) 2.2 equiv TESCl, 2.4 equiv iPr$_2$NEt, 0.4 equiv DMAP, CH_2Cl_2, −40 to 0 °C, 24 h; (d) TPAP (cat.), 1.5 equiv NMO, 4 Å sieves, CH_2Cl_2; (e) 5.0 equiv $Me_3S^+I^-$, 5.0 equiv KHMDS, THF −40 °C.



Scheme 2. (a) 10:1, 48%HF/pyridine, CH_3CN, 0 °C, 2 h; (b) 2.3:1 48%HF/pyridine, CH_3CN, 0 °C, 3 h; (c) 1.1 equiv TBAF, THF, 0 °C, 15 min; (d) 30 equiv Me_2S, 7.0 equiv Bz_2O_2, CH_3CN, 0 °C, 0.5 h; (e) 4.0 equiv I_2 4 Å sieves, MeOH, 7 h; (f) 1.5 equiv TBAF, THF, 0 °C, 0.5 h.

Table 1. In vitro activity (IC_{50}) of paclitaxel analogues (nM)

Compd	Tub. poly. ratio[a]	HCT 116	HCT VM46	A2780
1a	1	2.9	>118	3.5
1b	0.5	2.0	>121	2.5
1c	0.7	1.5	14	1.8

[a]The ratio in the tubulin polymerization assay is the potency of the analogue/the potency of paclitaxel. Ratios less than 1 reflect analogues that are more potent than paclitaxel.

appears to be the first example of TBDMS removal in the presence of a TES group.[12]

Derivatization of the C2′- and C7-positions of paclitaxel has been exploited in the past to yield prodrugs and analogues with improved activity or pharmacological properties.[13] Therefore, in order to demonstrate the utility of our selective deprotection method we decided to introduce additional modifications to the C10-epoxide analogue. Intermediate **5** was readily converted to the corresponding C7-MOM (**1c**) analogue. The two-step procedure depicted in Scheme 2 was found to afford the MOM-ether in much higher yield than reaction of the C7-hydroxyl with $MOMCl/Et_3N$.

Final products **1b** and **1c** were tested for in vitro activity against a number of cell lines.[14] IC_{50} values for HCT116, a colon carcinoma derived cell line and A2780 an ovarian cell line, are comparable to paclitaxel. Interestingly enough, when these compounds were tested against a paclitaxel-resistant cell line, HCT VM46, **1c** retained activity while **1b** was much less potent (Table 1).

A convenient method for converting the C-10 position of paclitaxel to the corresponding spiro-epoxide has been developed. The installation of the epoxide functionality using sulfonium ylide chemistry results in stereospecefic ring formation along with a unique by-product. Further manipulations at C2′ or C7 can be achieved using newly discovered methods for selective desilylation of either position. The C10-epoxide analogue of paclitaxel and the corresponding C7-MOM derivative, synthesized according to this method, were found to be equipotent to the parent in in vitro assays measuring tubulin binding and cytotoxicity tissue culture. These results suggest that epoxidation of the C10-position according to the current method is well tolerated. This would be in agreement with previous results, which showed that the C10-position can tolerate a certain degree of modification. However, it should be noted that the C10-methyl ether analogue of paclitaxel, which can be considered an acyclic version of **1b**, was found to be 6 times less potent than the parent in a previous study.[15]

References and Notes

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5. (a) ^{1}H NMR of **3** (500 MHz, $CDCl_3$) δ −0.31 (s, 3), −0.03 (s, 3), 0.56 (m, 6), 0.79 (s, 9), 0.91 (t, 9, $J=8$), 1.11 (s, 3), 1.17 (s, 3), 1.69 (s, 3), 1.77 (m, 2), 2.03 (s, 3), 2.15 (m, 1), 2,46 (m, 1), 2.49 (m, 1), 2.56 (s, 3), 3.60 (d, 1, $J=7$), 4.15 (d, 1, $J=7$), 4.20 (dd, 1, $J=8$, 60), 4.58 (m, 1), 4.66 (m, 1), 4.96 (d, 1, $J=9$), 5.71 (s, 1), 5.72 (s, 1), 6.12 (m, 1), 7.29–8.12 (m, 15). (b) ^{1}H NMR spectra for **4** (500 MHz, DMSO) δ −0.01 (s, 3), 0.03 (s, 3), 0.53 (m, 6), 0.75 (s, 9), 0.84 (t, 9, $J=8$), 0.95 (s, 3), 1.04 (s, 3), 1.45 (s, 3), 1.50 (s, 3), 1.70 (m, 2), 2.17 (m, 1), 2.34 (m, 1), 2.48 (s, 3), 3.17 (d, 1, $J=4$), 4.14 (dd, 2, $J=7$, 11), 4.48 (m, 1), 4.74 (d, 1, $J=8$), 4.88 (m, 1), 4.93 (s, 1), 5.04 (s, 1), 5.28 (d, 1, $J=4$), 5.55 (d, 1, $J=8$), 5.74 (m, 1), 7.24–7.98 (m, 15).
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14. H NMR of **1c** (300 MHz, $CDCl_3$) δ 1.14 (s, 3), 1.19 (s, 3), 1.7 (s, 3), 1.94 (s, 3), 2.04 (m, 2), 2.32 (m, 2), 2.37 (s, 3), 2.62 (d, 1, $J=7$), 2.79 (m, 1), 3.28 (s, 3), 3.68 (d, 1, $J=7$), 4.17 (m, 3), 4.30 (m, 1), 4.43 (d, 1, $J=7$), 4.77 (s, 1), 4.79 (s, 1), 4.95 (d, 1, $J=9$), 5.71 (d, 1, $J=6$), 5.81 (m, 1), 6.07 (m, 1), 7.26–8.13 (m, 15).
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