ORGANIC LETTERS

2001
Vol. 3, No. 11
1613−1615

Synthesis of 7β-Sulfur Analogues of Paclitaxel Utilizing a Novel Epimerization of the 7α-Thiol Group

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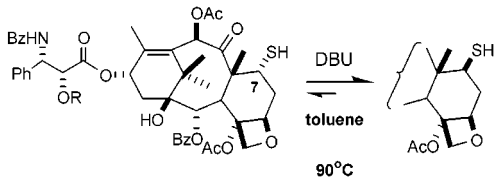
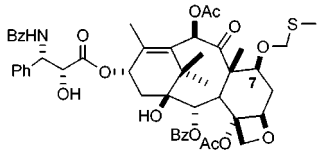
Received February 19, 2001

ABSTRACT



Paclitaxel analogues with a sulfur group at the 7β position were required for SAR studies. Attempts to generate these compounds by displacing a 7α leaving group with sulfur nucleophiles were unsuccessful. Instead, these compounds were successfully prepared from a 7β-thiol intermediate that was obtained by a base-catalyzed epimerization of the 7α-thiol derivative. The epimerization presumably proceeds through a thioaldehyde intermediate and exhibits the opposite stereochemical preference of its oxygen counterpart.

The 7-methylthiomethyl analogue **1**, BMS-184476,[1] of paclitaxel arose from an effort to identify taxanes with an expanded or improved spectrum of activity in cancer patients and is currently in Phase I clinical trials. While exploring the SAR of this compound, we wanted to examine analogues with sulfur substituents at the 7-position, in particular, the transposed isomer of **1**, **11**. Although taxanes with heteroatom substituents[2] other than oxygen at the 7 position have been described, their sulfur[3] counterparts have not been reported to date. In this Letter, we report the synthesis of 7-sulfur-substituted paclitaxel analogues and a novel epimerization reaction of the 7α-thiol group.



1 BMS-184476

To prepare 7β-sulfur analogues of paclitaxel, we first examined (Scheme 1) the reaction of intermediates bearing a 7α-leaving group with sulfur nucleophiles. The 2′-acetate derivative of the 7α-isomer of paclitaxel **3** was converted into the known mesylate derivative **4**.[2a] Attempts to displace the 7α-mesylate group of **4** with the thioacetate ion only led to the formation of the known olefin **2**.[2a] Evidently the displacement of a leaving group from the hindered 7α-position is more difficult than the competing elimination reaction. An effort to promote the displacement process by using the more reactive 7α-triflate derivative **5** was also

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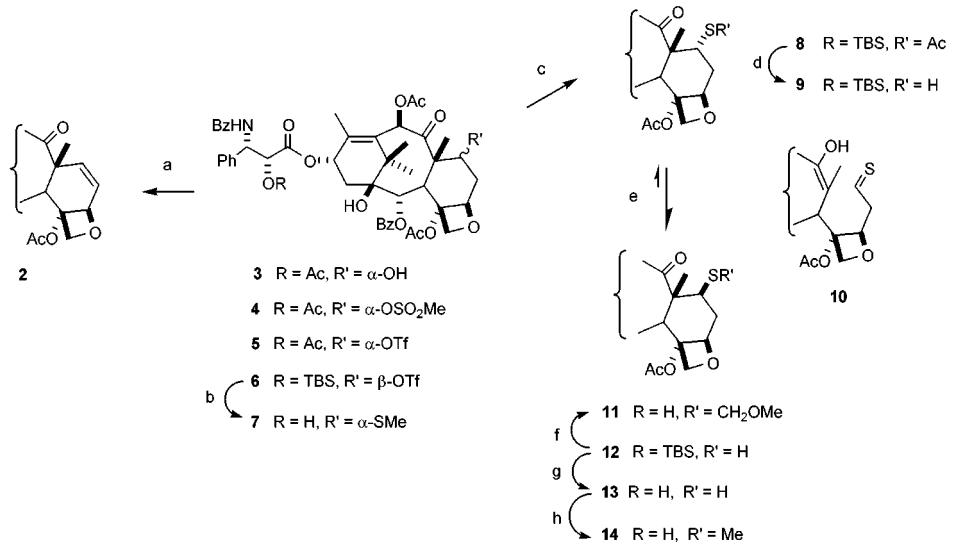
(3) The current work appears in the following: Mastalerz, H.; Kadow, J. U.S. Patent 6,017,935, 2000.

10.1021/ol015727m CCC: $20.00 © 2001 American Chemical Society
Published on Web 04/28/2001

Scheme 1[a]



[a] (a) KSAc (5 equiv), DMF, 90 °C, 19 h (yield 54%). (b) LiSMe (2.5 equiv), DMF, −10 to 0 °C, 2 h; then TBAF (1.0 M in THF, 1.1 equiv), THF, 0 °C, 20 min (overall yield 31%). (c) KSAc (10 equiv), EtOH, rt, 45 h, (yield 89%). (d) NH_3, EtOH, rt, 1 h (yield 61%). (e) DBU (2 equiv), toluene, 95 °C (yield 69%). (f) $BrCH_2OMe$ (1.1 equiv), DBU (1.5 equiv), DCM, rt, 10 min; then TBAF (1.0 M in THF, 1.1 equiv), 0 °C, 5 min (yield 52%). (g) TBAF (1.0 M in THF, 1.1 equiv), THF, 0 °C, 5 min (yield 56%). (h) MeI (1.1 equiv), DBU (1.5 equiv), DCM, rt, 5 min (yield 79%).

explored. However, none of the desired triflate derivative was obtained when the 7α-alcohol **3** was subjected to the conditions (triflic anhydride with an equivalent of DMAP in DCM at RT) that convert the isomeric 7*β*-alcohol into its triflate derivative.[2b] Attempts to force this reaction only led to the formation of complex product mixtures. The low reactivity of the 7α-alcohol group has been noted previously[4] and was attributed to its strong hydrogen bonding to the 4-acetate function.

Since the 7*β*-triflate **6** was readily available,[2b] it was examined as a precursor to 7-sulfur analogues. Reaction of **6** with sulfur nucleophiles such as LiSMe[5] and KSAc afforded respectively the 7α-sulfide **7** and the 7α-thioacetate **8**. The latter could be converted to the 7α-thiol **9** by selective hydrolysis with NH_3 in EtOH. In light of the facile interconversion of paclitaxel and 7-*epi*-paclitaxel,[6] the possibility of a related reaction of **9** was explored. It was found that **9** underwent base-catalyzed epimerization when it was heated in toluene at 90 °C in the presence of excess DBU. A 9:1 mixture (HPLC determination) of the respective *β* and α isomers **12** and **9** was obtained, and **12** was isolated in an 69% yield by chromatography. The isomer ratio did not significantly change on further heating, indicating that an equilibrium mixture had been reached. By analogy with its oxygen counterpart, this is probably an aldol-type equilibration that proceeds through the thioaldehyde intermediate **10**. Although we are not aware of other examples of this reaction, the intramolecular addition of an enol[7] or an enolate ion[8] to a transient thioaldehyde group has been postulated in other reactions. The observed thermodynamic preference for the 7*β*-thiol **12** is the opposite of what is seen with paclitaxel. In that case, the 7-*epi* isomer is favored and this has been attributed[9] to the presence of a strong hydrogen bond between the 7α-alcohol and the 4α-acetate function. The current observations are in accord with this rationale since it is known[10] that thiols form weaker hydrogen bonds than alcohols and therefore this stabilization is not available to the 7α-thiol **9**.

The 7*β*-thiol **12** could readily be S-alkylated to generate analogues of **1**. Treatment of **12** with $MeOCH_2Br$ in the presence of DBU followed by desilylation afforded **11**, the transposed isomer of **1**. Selective S-methylation of the 2′-

Table 1. In Vitro Biological Activity

compound	tubulin[a]	HCT-116[b] IC_{50} (nM)
paclitaxel	1	4.0
13	1.8	13.5
7	16	13.1
14	0.89	0.2
11	1.9	0.5
1	1.1	2.1

[a] The ratio in the tubulin polymerization assay[11] is the potency of the analogue over the potency of paclitaxel. Ratios less than 1 reflect analogues that are more potent than paclitaxel. [b] In vitro cytotoxicity assay against paclitaxel sensitive human colon tumor 116 where IC_{50} measures the drug concentration required for the inhibition of 50% cell proliferation after a 72 h incubation.[12]

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deprotected intermediate **13** gave the thioether **14** in good yield.

The 7β-thiol **13** was found to be less effective at promoting tubulin polymerization and at inhibiting the proliferation of the HCT-116 cell line than paclitaxel (Table 1). For the S-alkylated compounds, the β-isomer of the methyl sulfide **14** was significantly more cytotoxic than the α-isomer **7** and the methoxymethyl sulfide **11** was somewhat more cytotoxic than **1**. The results of further biological evaluation of these and additional 7-sulfur paclitaxel analogues will be reported elsewhere.

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Acknowledgment. We thank David Langley for his helpful insights.

Supporting Information Available: Experimental procedures and characterization data for compounds **7** to **9** and **11** to **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015727M