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First Syntheses of C-4 Methyl Ether Paclitaxel Analogs and the Unexpected Reactivity of 4-Deacetyl-4-Methyl Ether Baccatin III

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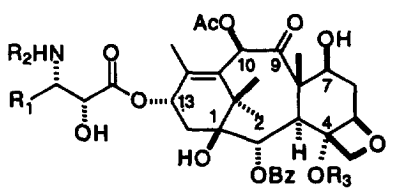
Abstract: The synthesis of three C-4 methyl ether bearing paclitaxel analogs, (2)-(4), is described. Some novel chemistry related to C-4 methyl ether baccatin III is also reported. Copyright © 1996 Elsevier Science Ltd

The clinically important anticancer drug paclitaxel (taxol®), **1**, a natural product first isolated from the bark of *Taxus brevifolia*,[1] has generated enormous research interest including structure-activity relationships (SAR) studies.[2] As a result of extensive SAR study at the diterpenoid core, we and others have shown that the functional groups on the top portion of the molecule (including C-7, C-9 and C-10) contribute relatively little to the receptor binding, whereas the functionalities on the bottom part of the molecule (*i.e.* C-2, oxetane ring and C-13 phenylisoserine side chain) are involved in the intimate interaction with the receptor[2,3]. Recently several groups have disclosed their own methodologies for the preparation of some novel C-4 derivatives. These include the synthesis of 4-deacetoxypaclitaxel,[4] 4-deoxypaclitaxel,[5] 4-aziridine carbamate bearing derivatives,[6] 4-cyclopropyl ester carrying analog[7] and a number of other C-4 analogs.[8-10] Preliminary biological evaluations of these C-4 analogs have shown that replacement of the C-4 acetoxy moiety with small aliphatic esters leads to analogs possessing eqivalent or better *in vitro* activity.[10] This promising result has stimulated our interest in further C-4 modifications. In this letter, we now report the synthesis and *in vitro* evaluation of novel 4-deacetyl-4-methyl ether paclitaxel analogs (**2-4**) and some interesting chemistry associated with 4-deacetyl-4-methyl baccatin III (**8**).

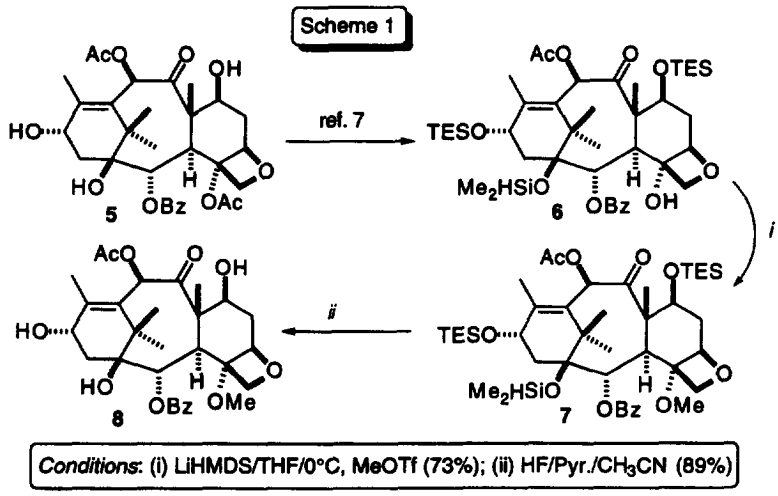


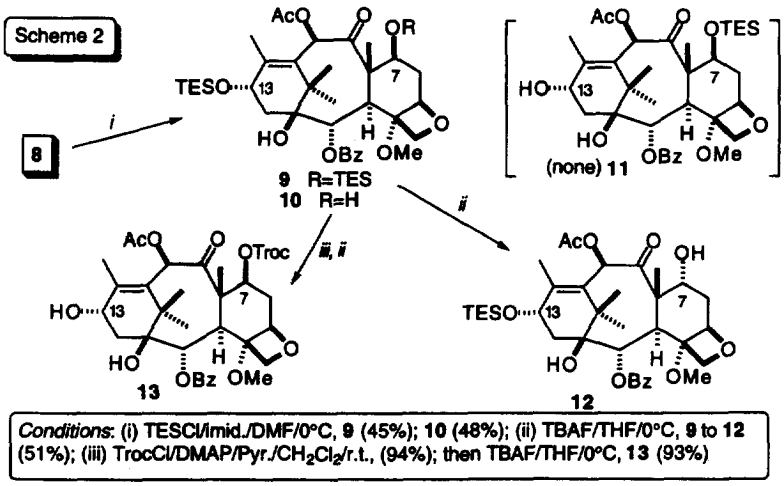
1 R_1=Ph, R_2=Bz, R_3=Ac (**Paclitaxel**)
2 R_1=Ph, R_2=Bz, R_3=Me
3 R_1=Ph, R_2=Boc, R_3=Me
4 R_1=2-Furyl, R_2=Boc, R_3=Me

The synthetic route employed for the preparation of C-4 methyl ether baccatin III, **8**, is shown in Scheme 1. The C-4 deacetyl baccatin **6** was prepared in three steps from baccatin III according to our previously published procedure.[7] The C-4 methylation was accomplished by deprotonation of **6** with LiHMDS in dry THF, and subsequent reaction with methyl triflate (MeOTf), leading to the fully silylated C-4 methyl ether baccatin derivative **7**. The C-4 methyl ether baccatin III **8** was then formed using standard desilylation conditions(HF/Pyridine).

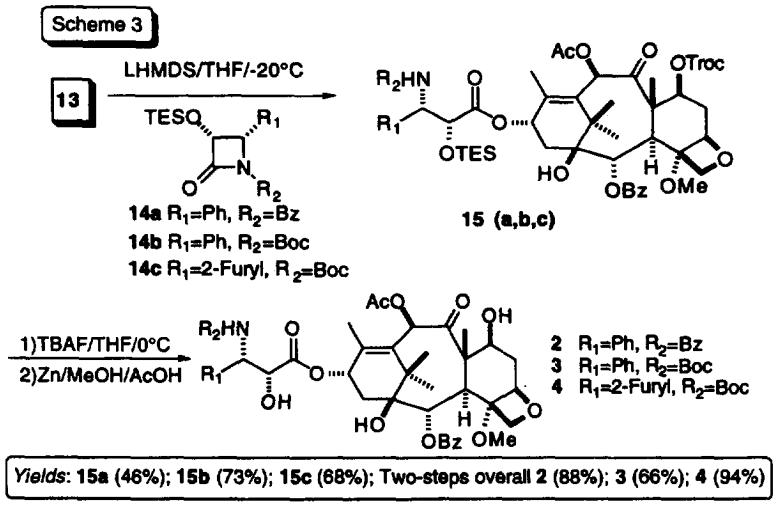
Some rather unexpected chemistry was encountered when we attempted to convert compound **8** to its C-7 silylated conterpart **11** (Scheme 2). Treatment of **8** with standard silylation reagents (4 eq. TESCl and 4 eq. imidazole in DMF at 0°C) yielded a ~1:1 ratio of the C-13 silylated baccatin **10** and the C-7,13 bisTES baccatin **9**. None of the desired C-7 mono-silylated baccatin **11** was obtained. This inversed

reactivity (C-13 > C-7 towards silylation) clearly suggests that the C-13 hydroxyl group in **8** is no longer locked in hydrogen bonding with the C-4 substituent. Thus, the allylic C-13 hydroxy group in **8** is much more reactive than its conterpart in "normal" baccatin III derivatives, such as **5**. Attempted selective removal of the C-13 silyl group in **9** led only to the baccatin derivative **12**, arising from C-7 desilylation and subsequent epimerization via a well-known sequence of retro-aldol and aldol reaction.[11] However, the C-7-Troc bearing baccatin **13** was prepared in high yield from C-13 TES protected baccatin derivative **10** via C-7 Troc protection and C-13 desilylation (Scheme 2).





As depicted in Scheme 3, coupling of 4-methyl ether containing baccatin **13** with β-lactam **14** (**a-c**)[12] was carried out smoothly according to the protocol developed by Holton and Ojima[13], affording the desired products **15** (**a-c**) in good yields. Final removal of the C-2' and C-7 protecting groups provided the target C-4 methyl ether paclitaxel derivatives (**2-4**)[14] in excellent yields.



Three C-4 methyl ether paclitaxel analogs (**2-4**) possess slightly weaker cytotoxicity as compared to paclitaxel.[15,16] This result clearly shows that removal of the carbonyl from C-4 substituent is detrimental to the biological activity, suggesting that the C-4 acyl moiety is an important element in receptor binding.

In summary, we have succeeded in the synthesis of C-4 methyl ether bearing paclitaxel analogs. The SAR information obtained from this class of C-4 derivatives has further our understanding of the role of the C-4 substituent in the drug-receptor binding, perhaps allowing us to design better paclitaxel analogs.

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(14) ^{1}H NMR (300 MHz, $CDCl_3$) of (**2**): δ 8.15-7.34 (m, 15H), 7.12 (d, J=9.1 Hz, 1H), 6.25 (s, 1H), 6.22 (m, 1H), 5.90 (d, J=8.9 Hz, 1H), 5.60 (d, J=6.2 Hz, 1H), 5.04 (dd, J=3.2 Hz, J'=9.7 Hz, 1H), 4.80 (d, J=1.8 Hz, 1H), 4.30 (AB q, J=9.1 Hz, 2H), 3.90 (dd, J=5.9 Hz, J'=11.8 Hz, 1H), 3.65 (s, 3H), 3.26 (d, J=6.2 Hz, 1H), 3.09 (dd, J=7.0 Hz, J'=15.4 Hz, 1H), 2.44 (m, 1H), 2.23-1.12 (m, 17H, incl. singlets at 2.23, 1.85, 1.65, 1.16, 1.12, 3H each). HRMS calcd. for $C_{46}H_{51}NO_{13}Na$ (MNa^+): 848.3258, found: 848.3227.
^{1}H NMR (300 MHz, $CDCl_3$) of (**3**): δ 8.10-8.07 (m, 2H), 7.60-7.33 (m, 8H), 6.25 (m, 2H), 5.62 (d, J=6.1 Hz, 1H), 5.50 (d, J=9.7 Hz, 1H), 5.39 (d, J=9.4 Hz, 1H), 5.06 (dd, J=3.3 Hz, J'=9.7 Hz, 1H), 4.65 (s, 1H), 4.30 (AB q, J=9.2 Hz, 2H), 3.93 (dd, J=6.0 Hz, J'=11.9 Hz, 1H), 3.63 (s, 3H), 3.27 (d, J=6.1 Hz, 1H), 3.07 (dd, J=6.7 Hz, J'=15.8 Hz, 1H), 2.50-1.15 (m, 27H, incl. singlets at 2.25, 1.87, 1.65, 1.21, 1.15, 3H each, 1.39, 9H). HRMS calcd. for $C_{44}H_{55}NO_{14}Na$ (MNa^+): 844.3520, found: 844.3509.
^{1}H NMR (300 MHz, $CDCl_3$) of (**4**): δ 8.10-8.07 (m, 2H), 7.60-7.44 (m, 4H), 6.41-6.36 (m, 2H), 6.28 (m, 2H), 5.62 (d, J=6.1 Hz, 1H), 5.38 (m, 2H), 5.05 (dd, J=3.3 Hz, J'=9.8 Hz, 1H), 4.73 (s, 1H), 4.29 (AB q, J=9.2 Hz, 2H), 3.92 (m, 1H), 3.56 (s, 3H), 3.26 (d, J=6.1 Hz, 1H), 3.08 (dd, J=6.9 Hz, J'=15.3 Hz, 1H), 2.44 (m, 1H), 2.25-1.15 (m, 26H, incl. singlets at 2.25, 1.93, 1.65, 1.21, 1.15, 3H each, 1.41, 9H). HRMS calcd. for $C_{42}H_{53}NO_{15}Na$ (MNa^+): 834.3313, found: 834.3332.

(15) IC_{50}(analogs)/IC_{50}(paclitaxel) values are: 17.5 for **2**; 1.1 for **3** and 1.6 for analog **4**.

(16) The *in vitro* IC_{50} measures the drug concentration required for the inhibition of cell proliferation by 50% after 72 hours incubation.

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