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SYNTHESIS OF 10-DEACETOXYTAXOL AND 10-DEOXYTAXOTERE[1]

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Abstract: 10-Deacetoxytaxol (**9**) and 10-deoxytaxotere (**10**) have been prepared from 10-deacetylbaccatin III by attachment of the C-13 side-chain and deoxygenation. 10-Deacetoxytaxol is comparable to taxol in its cytotoxicity to P-388 cells, but 10-deoxytaxotere is significantly more cytotoxic than taxol.

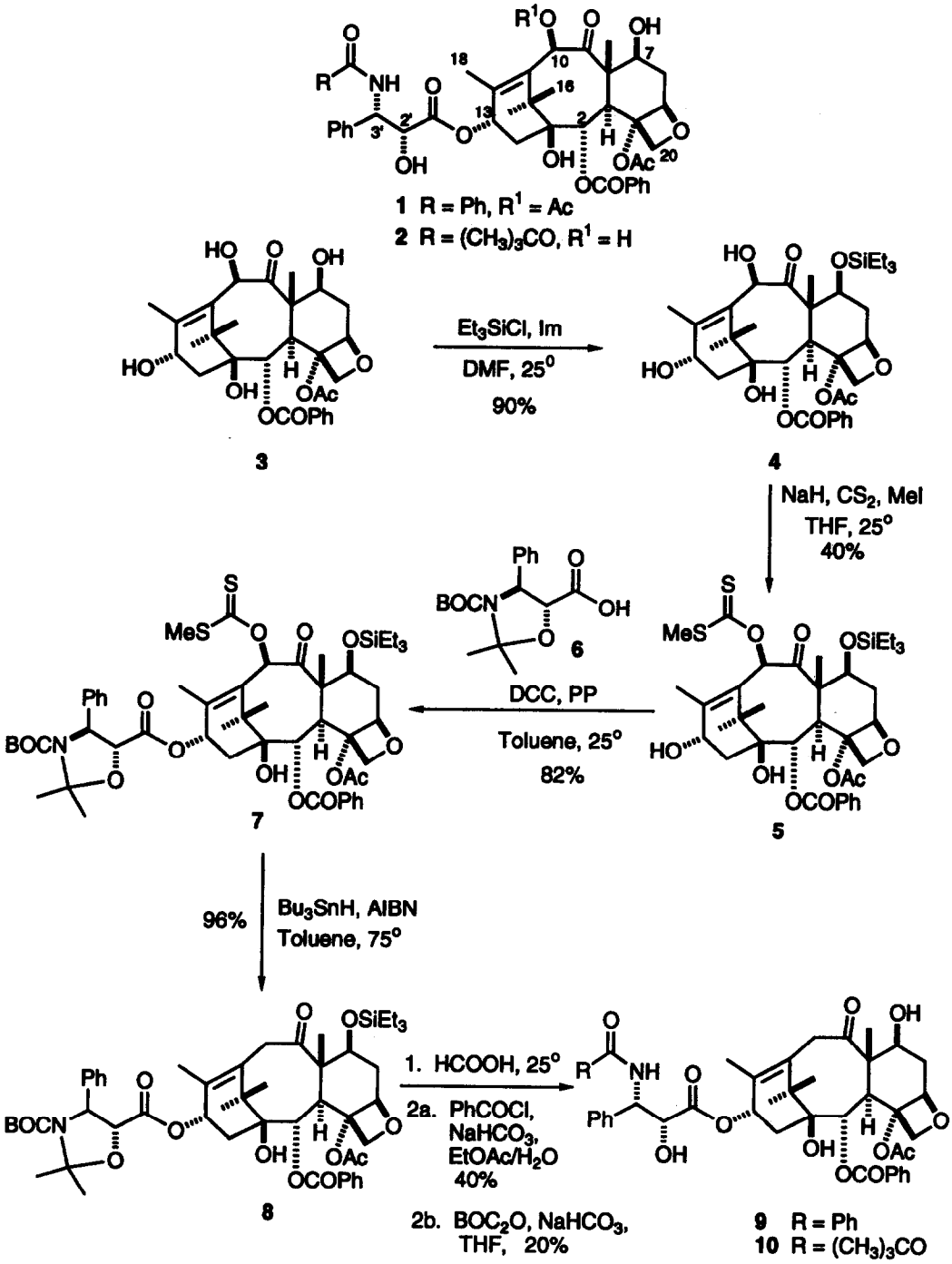
Taxol (**1**) is an unusual diterpenoid with significant clinical activity against several human cancers, including ovarian, breast, and lung cancer.[2] Since its isolation in the late 1960's by Wall and his co-workers,[3] extensive studies of its chemistry and structure-activity relationships have appeared, both from our own group[4] and from other groups,[5] and it continues to be the subject of active investigation. Various recent reviews have summarized the major findings to date.[6] The related compound taxotere™ (**2**) has also shown excellent activity both in cell culture[5a] and in animal trials.[7]

One of the questions that has so far not been addressed is that of the effect of the 10-acetoxyl group on the activity of taxol and of the 10-hydroxyl group on the activity of taxotere™. We have thus prepared 10-deacetoxytaxol and 10-deoxytaxotere, and report herein that the former is comparable to taxol in its cytotoxicity in the P-388 cell culture system, while the latter is significantly more active than taxol.

The synthetic pathway began with 10-deacetylbaccatin III (**3**), since this is now commercially available.[8] Treatment of **3** with triethylsilyl chloride and imidazole yielded 10-deacetyl-7-(triethylsilyl)baccatin III (**4**) in 90% yield. Reaction of **4** with carbon disulfide and sodium hydride in THF, followed by methyl iodide, gave 10-deacetyl-10-(S-methylxanthyl)-7-(triethylsilyl)baccatin III (**5**) in 40% yield. Compound **5** was then coupled with the protected taxol side-chain **6** (prepared from (*S*)-phenylglycine by a modification of published procedures[9]) by the use of DCC and 4-pyrrolidinopyridine (PP) in toluene at room temperature, to yield the protected xanthyl taxol **7** in 82% yield.

The key deoxygenation step was achieved cleanly through the radical deoxygenation methodology pioneered by Barton.[10] Treatment of the xanthyl derivative **7** with tributyltin hydride and AIBN gave the 10-deacetoxy derivative **8** in 96% yield. Treatment of **8** with formic acid, followed by selective N-benzoylation, gave 10-deacetoxytaxol (**9**) in 44% yield. Alternatively, treatment of **8** with formic acid followed by di-t-butyl dicarbonate yielded 10-deoxytaxotere (**10**) in 20% yield.

10-Deacetoxytaxol (**9**) had spectroscopic data fully consistent with the assigned structure. In particular, its ^{1}H-NMR spectrum showed the appearance of two methylene protons at δ 3.78 (d, *J*=16 Hz) and 3.47 (bd, *J*= 16 Hz), along with the absence of the characteristic sharp singlet for the C-10 proton of taxol at 6.27 ppm.[6d] The remaining peaks were similar to those for taxol.[11] The ^{1}H-NMR spectrum of 10-deoxytaxotere was similar to that of **9**.[12]


1 R = Ph, R1 = Ac
2 R = (CH3)3CO, R1 = H
Et3SiCl, Im
DMF, 25°
90%
3
4
NaH, CS2, MeI
THF, 25°
40%
6
DCC, PP
Toluene, 25°
82%
5
7
96%
Bu3SnH, AIBN
Toluene, 75°
8
1. HCOOH, 25°
2a. PhCOCl, NaHCO3, EtOAc/H2O
40%
2b. BOC2O, NaHCO3, THF, 20%
9 R = Ph
10 R = (CH3)3CO

The cytotoxicities of 10-deacetoxytaxol (**9**) and 10-deoxytaxotere (**10**) were determined in the P-388 cell culture system by standard methods.[13] Under these conditions taxol had an ED_{50} of 0.03 μg/mL, and 10-deacetoxytaxol also had an ED_{50} of 0.03 μg/mL. The 10-acetoxy group thus appears to make only a small contribution to the activity of taxol, and the synthesis of taxol analogues lacking this functionality would appear to be a viable approach to the preparation of synthetically accessible bioactive taxol analogues. Interestingly, the activity of 10-deoxytaxotere (**10**) in the same system was 0.0001 μg/ml, suggesting that the previously noted superior activity of taxotere in cell culture[5a] is accentuated in the 10-deoxy series.[14]

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11. Spectroscopic data for **9**: FAB mass spectrum, MH^+ *m/z* 796.3312. $C_{45}H_{50}O_{12}N$ requires 796.3333. ^{1}H-NMR ($CDCl_3$) δ 8.15 (2H, dd, *J*=1, 8, *o*-C_6H_5COO), 7.76 (2H, dd, *J*=1, 8, *o*-C_6H_5CONH), 7.4-7.7 (11H, m, Ar), 7.06 (1H, d, *J*=9, NH), 6.12 (1H, br t, *J*=9, H-13), 5.79 (1H, dd, *J*=9, 2.5, H-3'), 5.69 (1H, d, *J*=6.8, H-2), 4.94 (1H, dd, *J*=7.6, 1, H-5), 4.78 (1H, br s, H-2'), 4.31 (1H, d, *J*=8, H-20β), 4.29 (1H, m, H-7), 4.19 (1H, d, *J*=8, H-20α), 4.07 (1H, d, *J*=6.8, H-3), 3.78 (1H, d, *J*=15.9, H-10α), 3.6 (1H, br s, 2'-OH), 3.47 (1H, br d, *J*=15.9, H-10β), 2.62 (1H, m, H-6β), 2.37 (3H, s, 4-OAc), 2.30 (2H, m, H_2-14αβ), 1.66 (3H, br s, H_3-18), 1.64 (3H, s, H_3-19), 1.26 (3H, s, H_3-17), 1.18 (3H, s, H_3-16).
12. Spectroscopic data for **10**: FAB mass spectrum, MH^+ *m/z* 792.3584. $C_{43}H_{54}O_{13}N$ requires 792.3595. ^{1}H-NMR ($CDCl_3$) δ 8.10 (2H, d, *J*=7, *o*-C_6H_5COO), 7.6-7.3 (8H, m, Ar), 6.18 (1H, br t, *J*=9, H-13), 5.70 (1H, d, *J*=6.8, H-2), 5.40 (1H, d, *J*=9.5, NH), 5.27 (1H, br d, *J*=9.5, H-3'), 4.94 (1H, dd, *J*=7.5, 1, H-5), 4.62 (1H, dd, *J*=1, 5, H-2'), 4.31 (1H, d, *J*=7, H-20β), 4.28 (1H, m, H-7), 4.05 (1H, d, *J*=7, H-20α), 3.81 (1H, d, *J*=15.9, H-10α), 3.47 (1H, br d, *J*=16, H-10β), 3.35 (1H, d, *J*=5.2, 2'-OH), 2.62 (1H, m, H-6β), 2.38 (3H, s, 4-OAc), 2.32 (2H, m, H_2-14αβ), 1.72 (3H, br s, H_3-18), 1.60 (3H, s, H_3-19), 1.35 (9H, s, $(CH_3)_3C$), 1.28 (3H, s, H_3-17), 1.21 (3H, 2, H_3-16).
13. Cytotoxicities were determined by Dr. W. Lichter, University of Miami School of Medicine, using standard NCI protocols.
14. After this work was submitted, a paper describing the synthesis of **9** by an alternate route appeared: Chen, S.-H.; Fairchild, C.; Mamber, S. W.; Farina, V. *J. Org. Chem.*, **1993**, *58*, 2927-2928.

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