Pergamon

Tetrahedron Letters 40 (1999) 189–192

TETRAHEDRON
LETTERS

A Facile N-Debenzoylation of Paclitaxel: Conversion of Paclitaxel to Docetaxel

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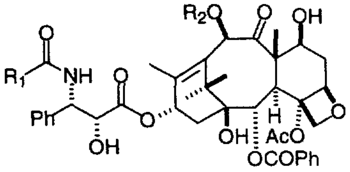
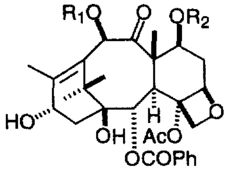
Received 22 July 1998; revised 13 October 1998; accepted 16 October 1998

Abstract: An efficient and regioselective method for the N-debenzoylation of paclitaxel has been developed, and has been applied to the conversion of paclitaxel to 10-acetyldocetaxel and to docetaxel. © 1998 Elsevier Science Ltd. All rights reserved.

Paclitaxel (Taxol® **1**) and its semisynthetic analog docetaxel (Taxotere® **2**) are among the most important new anticancer agents of this decade.[1,2] Although both paclitaxel and docetaxel can be made semisynthetically from 10-deacetylbaccatin III (10-DAB, **3**),[3] paclitaxel continues to be isolated from *Taxus brevifolia* and from other *Taxus* species,[4] and a direct method for the conversion of paclitaxel to docetaxel is thus of potential interest as an alternate source of the latter substance. Although selective cleavages of ester functions at the C-2,[5] C-4,[6] C-10,[7] and C-13[8] positions have been reported, no reports have appeared on the selective cleavage of the *N*-benzoyl amide group at the 3'-*N* position of paclitaxel. The only selective *N*-acyl cleavage that has been reported is of the *N*-tigloyl group of cephalomannine, which relies on the presence of the double bond to initiate selective reaction.[9] In our continuing studies of the chemistry of paclitaxel, we have now discovered a method for its regiospecific *N*-debenzoylation, and thus for a direct method for the conversion of paclitaxel to 10-acetyldocetaxel and thence to docetaxel.



Paclitaxel **1** R_1 = Ph, R_2 = Ac
Docetaxel **2** R_1 = ${}^tBuO$, R_2 = H



10-Deacetylbaccatin III **3** $R_1 = R_2$ = H
7-(Triethylsilyl)baccatin III **10** R_1 = Ac, R_2 = $SiEt_3$

In a previous attempt to debenzoylate the *N*-benzoyl group of paclitaxel, we prepared its 2',7,*N*-tri-*O*-(*tert*-butyloxycarbonyl) derivative.[10] This was expected to undergo selective *N*-debenzoylation, since selective deacylation of simple *N*-*tert*-butoxycarbonyl-*N*-acyl imides normally occurs under basic conditions to give *N*-

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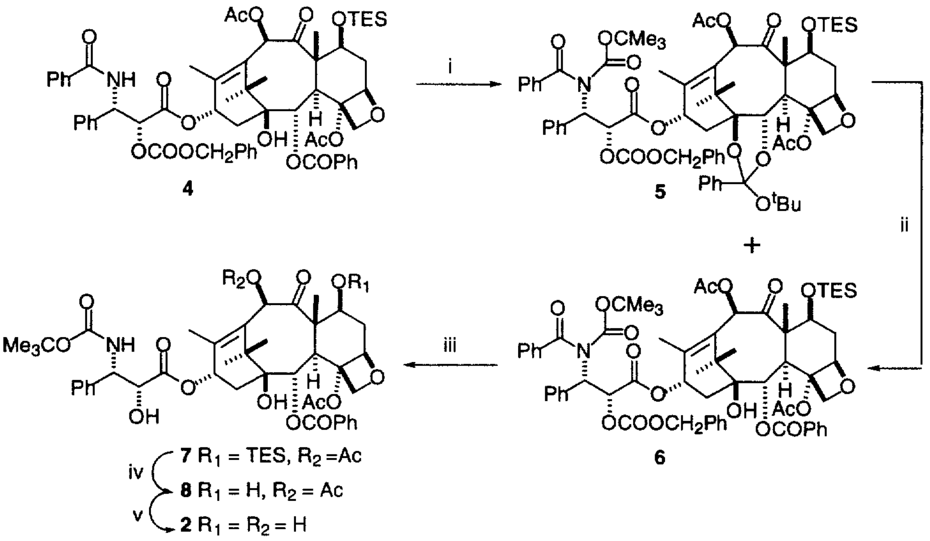
PII: S0040-4039(98)02221-7

deacyl-*N*-*tert*-butoxycarbonyl derivatives.[11] Surprisingly, it was found instead to undergo selective debenzoylation at C-2, and thus provided our first route for the synthesis of 2-acylpaclitaxel analogs.[10]

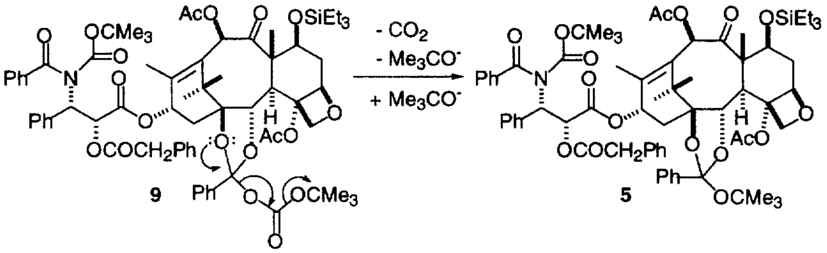
Since there appeared to be no obvious reason why selective *N*-deacylation of a suitable *N*-*tert*-butoxycarbonyl derivative of paclitaxel should not be achievable, given the right conditions, we investigated the preparation and selective cleavage of other *N*-*tert*-butoxycarbonylpaclitaxels. Treatment of paclitaxel (**1**) with benzylchloroformate and dimethylaminopyridine (DMAP) in dichloromethane, followed by addition of chlorotriethylsilane and imidazole, gave the 2',7-*O*-protected derivative **4** in 95% yield in a one-pot reaction. (Scheme).



(i) (^{t}BuOCO)$_2$O, DMAP, MeCN, rt, 24 h, **5**, 61%; **6**, 21%. (ii) $CDCl_3$, rt, 2-3 h, 98%. (iii) Mg(OMe)$_2$, MeOH, rt, 1 h, 75%. (iv) HF-Pyridine, THF, rt, 2 h, 91%. (v) H_2O_2, $NaHCO_3$, THF, rt, 16 h, 75%.

Scheme Preparation of docetaxel from paclitaxel

Treatment of **4** with di-*tert*-butyl dicarbonate and DMAP in acetonitrile led to formation of the *N*-protected compounds **5** and **6**.[12] Compound **5** was found to be very labile to acid, and it was converted to **6** on standing in the presence of slightly acidic $CHCl_3$ for 2-3 hr; the overall yield for the conversion of **4** to **6** was 86%. Our proposed mechanism for the formation of **5** from **4** is shown in the Figure. Presumably the initially formed acetal ester **9** decomposes with the loss of carbon dioxide and *tert*-butoxide ion under the experimental conditions, and the resulting oxonium ion is trapped by *tert*-butoxide ion to give **5**. The formation of similar cyclic benzylidene acetal derivatives of paclitaxel has been reported previously.[13]



Figure

Debenzoylation of **6** was achieved using magnesium methoxide in methanol[14] to give 7-*O*-triethylsilyl-10-acetyldocetaxel (**7**); In contrast to the reaction observed with LiOH,[10] selective *N*-debenzoylation could be achieved to give **7** in 72-75% isolated yield based on unrecovered starting material. The reaction requires careful monitoring to avoid the formation of the overmethanolysed product 7-*O*-triethylsilylbaccatin III (**10**); optimum conditions required the use of 20 equivalents of magnesium methoxide in MeOH at room temperature, and afforded **7** together with **10** and 10-acetyl-2-debenzoyl-7-*O*-triethylsilyldocetaxel as minor by-products. The ^{1}H NMR spectrum of compound **7** showed a downfield shift of the C-2' proton from 5.85 to 4.62 ppm and the appearance of the C-2' OH and NH doublets at 3.33 and 5.26 ppm respectively, indicating that $Mg(OMe)_2$ had methanolysed both the *N*-benzoyl and the 2'-*O*-Cbz groups in a single step. It is probable that methanolysis of the 2'-*O*-Cbz group occurs first, and that the free 2'-OH group then allows bis-complexation of magnesium ion and thus selective activation of the *N*-benzoyl group. In support of this hypothesis, only 2-*O*-debenzoylation was observed when the 2'-OH group was protected.[10]

7-Triethylsilyl-10-acetyldocetaxel **7** was deprotected using HF-pyridine to give 10-acetyldocetaxel **8** in 91% yield, identical with a sample synthesized by coupling (2*R*,3*S*)-*N*-*tert*-butoxycarbonyl-3-*O*-tri-*iso*propylsilyl-4-phenylazetidin-2-one and 7-triethylsilylbaccatin III **10**.[15] The conversion of 10-acetyldocetaxel to docetaxel **2** was carried out in 75% yield using hydrogen peroxide and sodium bicarbonate in THF as previously described.[16]

In conclusion, the method described provides a regioselective *N*-debenzoylation of paclitaxel. The method described is the first *N*-debenzoylation method reported for paclitaxel, and it is used for the conversion of paclitaxel to 10-acetyldocetaxel in 52% overall yield and for the conversion of paclitaxel to docetaxel in 39% overall yield.

Acknowledgment. Financial support by the National Cancer Institute, NIH (Grant Number CA-69571) is gratefully acknowledged, as is a gift of paclitaxel.

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12. Spectral data for compound **6**: ^{1}H NMR ($CDCl_3$, 400 MHz): 0.51-0.61 (m, 6H), 0.89-0.93 (m, 9H), 1.01 (s, 9H), 1.08 (s, 3H), 1.15 (s, 3H), 1.22-1.35 (m, 1H), 1.63 (s, 3H), 1.78-1.89 (m, 1H), 1.82 (s, 3H), 2.14 (s, 3H), 2.14-2.17 (m, 1H), 2.45-2.57 (m, 1H), 3.72 (d, J = 7.0 Hz, 1H), 4.10 (d, J = 8.0 Hz, 1H), 4.26 (d, J = 8.2 Hz, 1H), 4.41-4.46 (dd, J = 6.5 and 10.3 Hz, 1H), 4.92 (d, J = 7.9 Hz, 1H), 5.17 (s, 2H), 5.57 (d, J = 7.1 Hz, 1H), 5.84-5.91 (m, 2H), 6.12 (d, J = 11.1 Hz, 1H), 6.4 (s, 1H), 7.12-7.68 (m, 18 H), 8.07 (d, J = 7.1 Hz, 2H). ^{13}C NMR: 5.19, 5.25, 6.67, 6.74, 10.03, 14.10, 20.84, 21.12, 22.57, 34.35, 37.12, 43.06, 46.55, 58.30, 70.27, 71.56, 72.03, 74.87, 75.29, 78.74, 80.60, 83.75, 84.28, 127.74, 128.08, 128.12, 128.49, 128.54, 128.58, 128.63, 129.34, 129.64, 131.55, 133.14, 134.14, 134.57, 137.84, 140.65, 152.86, 153.64, 166.94, 169.01, 170.05, 173.26, 201.91. HRFABMS *m/z* 1208.5223 $[M+Li]^+$ ($C_{66}H_{79}NO_{18}SiLi$ requires 1208.5226).
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14. Debenzoylation reaction of **6** using $Mg(OMe)_2$: To a solution of **6** (50 mg, 0.040 mmol) in MeOH (1 mL), under argon atmosphere, was added 7% solution of $Mg(OMe)_2$ in MeOH (1.0 mL, 0.80 mmol) and the mixture stirred at room temperature for 45 min. The reaction mixture was then diluted with EtgOAc (15 mL) and the organic layer was washed with brine, water and brine again. After drying (Na_2SO_4) and concentration the residue was purified on PTLC (silica gel, 1000 μM, 35% EtOAc/hexane) to give **7** (28.2 mg, 75% yield based on 47 mg of unrecovered starting material **6**), **10** (6 mg), and 10-acetyl-2-debenzoyl-7-*O*-triethylsilyldocetaxel (2 mg). Spectral data for compound **7**: ^{1}H NMR ($CDCl_3$, 400 MHz): 0.52-0.60 (m, 6H), 0.89-0.94 (m, 9H), 1.20 (s, 3H), 1.23 (s, 3H), 1.34 (s, 9H), 1.74 (s, 3H), 1.85-1.92 (m, 2H), 1.97 (s, 3H), 2.18 (s, 3H), 2.27-2.32 (m, 1H), 2.36 (s, 3H), 2.44-2.53 (m, 1H), 3.34 (d, J = 5.3 Hz, 1H), 3.80 (d, J = 6.7 Hz, 1H), 4.16 (d, J = 8.2 Hz, 1H), 4.29 (d, J = 8.2 Hz, 1H), 4.42-4.46 (dd, J = 6.7 and 10.5 Hz, 1H), 4.62 (s, 1H), 4.92 (d, J = 8.0 Hz, 1H), 5.67 (d, J = 7.0 Hz, 1H), 6.16-6.21 (dd, J = 8.8 and 9.1 Hz, 1H), 6.44 (s, 1H), 7.29-7.39 (m, 5H), 7.48 (t, J = 7.7 Hz, 2H), 7.58 (dd, J = 7.7 and 7.3 Hz, 1H), 8.10 (d, J = 7.63 Hz, 2H). ^{13}C NMR : 5.24, 6.73, 10.02, 14.35, 20.87, 21.00, 22.66, 26.54, 28.16, 35.22, 37.21, 43.26, 58.51, 72.25, 72.43, 73.52, 74.74, 75.02, 78.72, 80.20, 81.17, 84.15, 126.72, 128.02, 128.63, 128.80, 129.12, 130.15, 133.65, 167.05, 169.18, 170.20, 201.75. HRFABMS *m/z* 970.4589 $[M+Li]^+$ ($C_{51}H_{69}NO_{15}SiLi$ requires 970.4597).
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