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New 13-aza Baccatins

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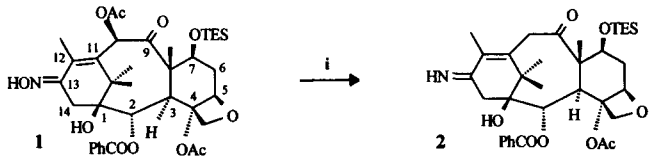
Abstract: Upon treatment of 7-triethylsilyl-10,13-dideoxy-13-imino baccatin III (**2**) subsequently with diazomethane and m-chloroperbenzoic acid a few novel derivatives, namely methylimine **3** and oximes **4** and **5**, were obtained. Interestingly, **4** is characterized by the hydroxyl at position 14.

In the course of our studies,[1] relative to the modification of the linkage at C-13 between the diterpenoid core and the side chain of paclitaxel, 7-triethylsilyl-10,13-dideoxy-13-imino baccatin III (**2**)[2] turned out to be a key intermediate for the introduction of a nitrogen atom at C-13.
Obtained[1] under Raney-nickel reductive conditions[3] from oxime **1** (Scheme 1),[4] imine **2** showed a remarkable stability that might be explained by the steric hindrance around position 13.[5]

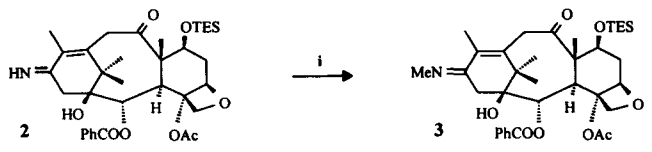
Scheme 1. Synthesis of imine **2**



Reagents: *i) W-2 Raney-nickel, 51% hydrazine hydrate, EtOH, RT, 3h, 57%.*

Imine **2** also shows an interesting reactivity which is evident from the examples described below. In particular, when treated with diazomethane in the presence of cuprous bromide, imino baccatin **2** yielded N-methyl imine **3**[6] (Scheme 2) as the major product instead of the somewhat expected aziridine,[7] a result that has little precedent in the literature.[8]

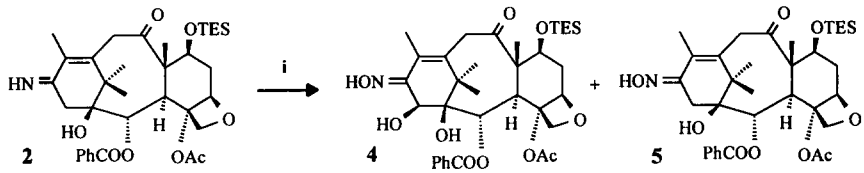
Scheme 2. Synthesis of methylimine **3**



Reagents: *i)* CH_2N_2, *diethylether, THF, CuBr, RT, 15', 62%.*

When imine **2** was reacted with meta-chloro perbenzoic acid, the two oximes **4** and **5**[9] were obtained (Scheme 3) as single stereoisomers (configuration not assigned). The formation of the oximes is favoured with respect to the corresponding oxaziridine[10] or nitrone,[11] in agreement with the few examples of oxidation of N-H ketimines reported in the literature.[12,13]

Scheme 3. Synthesis of oximes **4** and **5**



***Reagents**: i) MCPBA, CH_2Cl_2, RT, 40', 40% (4/5 ratio=3:2).*

The additional hydroxylation at position 14 in compound **4** resembles the known transformation of enols into α-hydroxy ketones upon treatment with peracids.[14] In fact the tautomeric 13-14 enamine double bond might be epoxidized and subsequently rearranged into the α–hydroxy compound in a similar fashion.[15] Isolation of **4** is particularly interesting because, apart from the 14-hydroxylated taxanes[16] derived from the natural 14β-hydroxy-10-deacetyl baccatin III,[17] to our knowledge only one 14-OH taxane has been synthesized so far by oxidizing 7-triethylsilyl,10-deacetyl baccatin III with MnO_2.[18]

The β configuration of the 14-hydroxyl, established through H-14/H-3, H-14/H-oPh NOESY cross-peaks, is in agreement with the fact that taxanes are cup-shaped and present the concavity toward the α face of the molecule.

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2. **2**: FAB-MS : 640 $(M+H)^+$ $(C_{35}\ H_{49}\ NO_8\ Si)^+$ (100). ^{1}H NMR (400MHz, $CDCl_3$) : δ 8.08 (m, 2H, oPh), 7.60 (m, 1H, pPh), 7.48 (m, 2H, mPh), 5.64 (d, J = 6.6 Hz, 1H, H-2), 4.93 (dd, J = 9.6, 2.2 Hz, 1H, H-5), 4.50 (dd, J = 6.8, 10.6 Hz, 1H, H-7), 4.31 (d, J = 8.2 Hz, 1H, H-20α), 4.12 (d, J = 8.2 Hz, 1H, H-20β), 4.07 (d, J = 6.6 Hz, 1H, H-3), 3.93 (d, J = 14.5 Hz, 1H, H-10α), 3.60 (dq, J = 14.5, 1.2 Hz, 1H, H-10β), 3.09 (d, J = 18.7 Hz, 1H, H-14α), 2.68 (d, J = 18.7 Hz, 1H, H-14β), 2.50 (ddd, J = 14.4, 9.6, 6.8 Hz, 1H, H-6α), 2.20 (s, 3H, $COCH_3$), 2.07 (d, J = 1.2 Hz, 3H, H-18), 1.86 (ddd, J = 14.4, 10.6, 2.2 Hz, 1H, H-6β), 1.59 (s, 3H, H-19), 1.19 (s, 3H, H-16), 1.13 (s, 3H, H-17), 0.95 (t, J = 7.9 Hz, 9H, $SiCH_2\underline{C}H_3$), 0.58 (m,6H, $Si\underline{C}H_2CH_3$).^{13}C-NMR (100MHz, $CDCl_3$): δ 205.5 (C-9), 175.0 (C-13), 169.9 ($\underline{C}OCH_3$), 166.9 (Ph-$\underline{C}$OO), 147.6 (C-11), 133.8 (C-pPh) 133.7 (C-12), 130.1 (C-oPh), 129.1 (C-1-Ph), 128.7 (C-mPh), 84.1 (C-5), 80.6 (C-4), 78.8 (C-1), 76.4 (C-20), 73.5 (C-2), 72.0 (C-7), 60.6 (C-8), 46.5 (C-10), 45.7 (C-3), 44.4 (C-15), 39.6 (C-14), 37.3 (C-6), 30.1 (C-17), 22.0 ($CO\underline{C}H_3$), 20.6 (C-16), 14.8 (C-18), 9.8 (C-19), 6.8 ($SiCH_2\underline{C}H_3$), 5.3 ($Si\underline{C}H_2CH_3$) [^{1}H and ^{13}C signals were assigned through the analysis of

NOESY (mixing time=0.7 s), HMQC ($^1J_{HC}$=140 Hz) and HMBC ($^1J_{HC}$ =140 Hz and $^nJ_{HC}$ =7 Hz) experiments].

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6. To a solution of imine **2** (202 mg , 0.316 mmol) in anhydrous THF (60 mL), a 0.4 M solution of diazomethane in ethyl ether (60 mL) was added under nitrogen at room temperature. After 10' CuBr (300 mg , 2.09 mmol) was added and the yellow reaction mixture became dark coloured. After dilution with ethyl ether and filtration, the reaction mixture was concentrated and purified on preparative TLC (n-hexane-ethyl acetate 1:3) to yield 128 mg (62%) of compound **3**.

   3: FAB-MS: 654 $(M+H)^+$ $(C_{36}H_{51}NO_8Si)^+$ (100). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (m, 2H, oPh), i7.62 (m, 1H, pPh), 7.49 (m, 2H, mPh), 5.67 (d, J = 6.3 Hz, 1H, H-2), 4.91 (dd, J = 9.5, 2.0 Hz, 1H, H-5), 4.54 (dd, J = 10.5, 6.8 Hz, 1H, H-7), 4.32 (d, J = 8.5 Hz, 1H, H-20α), 4.17 (d, J = 6.3 Hz, 1H, H-3), 4.12 (d, J = 8.5 Hz, 1H, H-20β), 3.96 (d, J = 14.7 Hz, 1H, H-10α), 3.56 (d, J = 14.7 Hz, 1H, H-10β), 3.31(s, 3H, NCH_3), 2.75, 2.54 (two d, J = 18.5 Hz, 2H, CH_2-14), 2.49 (ddd, J = 14.3, 9.5, 6.8 Hz, 1H, H-6α), 2.10 (s, 3H, CH_3CO), 207 (s, 3H, H-18), 1.86 (ddd, J = 14.3, 10.5, 2.0 Hz, 1H, H-6β), 1.75 (s, 1H, OH-1), 1.59 (s, 3H, H-19), 1.17 (s, 3H, H-16), 1.05 (s, 3H, H-17), 0.92 (t, J = 8.0 Hz, 9H, $SiCH_2\underline{C}H_3$), 0.60 (m, 6H, $SiC\underline{H}_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1 (C-9), 169.3 ($\underline{C}OCH_3$), 168.2 (C-13), 167.0 (Ph$\underline{C}$OO), 142.9 (C-11), 135.9 (C-12), 133.8 (C-pPh), 130.0 (C-oPh), 129.1 (C-1-Ph), 128.7 (C-mPh), 84.2 (C-5), 81.0 (C-4), 79.2 (C-1), 76.4 (C-20), 73.7 (C-2), 72.0 (C-7), 60.4 (C-8), 46.2 (C-10), 46.1 (C-3), 43.6 (C-15), 39.4 (NCH_3), 37.3 (C-6), 33.6 (C-14), 29.5 (C-17), 21.7 ($\underline{C}H_3CO$-4), 20.6 (C-16), 15.4 (C-18), 9.8 (C-19), 6.8 ($SiCH_2\underline{C}H_3$), 5.3 ($Si\underline{C}H_2CH_3$). [^{13}C signals were assigned through the analysis of gradient enhanced HSQC ($^1J_{HC}$ = 140 Hz) and gradient enhanced HMBC ($^1J_{HC}$ = 140 Hz and $^nJ_{HC}$ = 7 Hz) experiments].
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9. To a solution of imine **2** (55 mg , 0.086 mmol) in CH_2Cl_2 (3 mL) 50% MCPBA was added (52 mg, 0.151 mmol) at room temperature under nitrogen. After stirring for 40' the reaction mixture was diluted with CH_2Cl_2 (10 mL) and extracted twice with sat. $NaHCO_3$. The organic solution was washed with brine and dried over Na_2SO_4. After filtration and evaporation, the crude material was purified over

preparative TLC (n-hexane-ethyl acetate 1:1) to afford 14 mg (24%) of compound **4** and 9 mg (16%) of compound **5**.

4: FD-MS: 671 ($M^{+\bullet}$) $(C_{35}H_{49}NO_{10}Si)^{+\bullet}$. ^1H NMR (600 MHz, $CDCl_3$): δ 9.0 (bs, 1H, NOH), 8.08 (m, 2H, oPh), 7.59 (m, 1H, pPh), 7.48 (m, 2H, mPh), 5.82 (d, J = 6.8 Hz, 1H, H-2), 4.98 (d, J = 1.8 Hz, 1H, H-14), 4.90 (dd, J = 9.6, 2.1 Hz, 1H, H-5), 4.75 (d, J = 1.8 z,1H, OH-14), 4.46 (dd, J = 10.6, 6.9 Hz, 1H, H-7), 4.28 (d, J = 8.5 Hz, 1H, H-20α), 4.24 (d, J= 8.5 Hz, 1H, H-20β), 3.96 (s, 1H, OH-1), 3.92 (d, J = 14.5 Hz, 1H, H-10α), 3.89 (d, J = 6.8 Hz, 1H, H-3), 3.57 (d, J = 14.5 Hz, 1H, H-10β), 2.47 (ddd, J = 14.5, 9.6, 6.9 Hz, 1H, H-6α), 2.25 (s, 3H, CH_3CO), 2.05 (s, 3H, H-18), 1.88 (ddd, J = 14.5, 10.6, 2.1 Hz, 1H, H-6β), 1.64 (s, 3H, H-19), 1.20 (s, 3H, H-16), 1.11 (s, 3H, H-17), 0.96 (t, J = 8.0 Hz, 9H, $SiCH_2\underline{C}H_3$), 0.58 (m, 6H, $SiCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.2 (C-9), 170.1 ($\underline{C}OCH_3$), 165.7 (Ph$\underline{C}$OO), 159.1 (C-13), 146.7 (C-11), 133.3 (C-pPh), 130.0 (C-oPh), 129.7 (C-1-Ph), 128.7 (C-12), 128.5 (C-mPh), 84.1(C-5), 81.1 (C-4), 76.4 (C-20), 75.9 (C-1), 72.0, 71.9 (C-7, C-2), 63.9 (C-14), 60.8 (C-8), 46.0 (C-10), 45.3 (C-3), 43.8 (C-15), 37.3 (C-6), 31.2 (C-17), 21.8 ($\underline{C}H_3CO$), 21.3 (C-16), 15.6 (C-18), 9.8 (C-19), 6.8 ($SiCH_2\underline{C}H_3$), 5.4 ($Si\underline{C}H_2CH_3$). [^1H and ^{13}C signals were assigned through the analysis of NOESY (mixing time = 0.7 s), HMQC ($^1J_{HC}$ = 140 Hz) and HMBC ($^1J_{HC}$ = 140 Hz and $^nJ_{HC}$ = 7 Hz) experiments].

5: FD-MS: 655 ($M^{+\bullet}$) $(C_{35}H_{49}NO_9)^{+\bullet}$ ^1H NMR (400 MHz, $CDCl_3$): δ 8.2 (bs, 1H, NOH), 8.10 (m, 2H, oPh), 7.61 (m, 1H, pPh), 7.49 (m, 2H, mPh), 6.09 (dd, J = 6.5, 1.0 Hz, 1H, H-2), 4.94 (dd, J = 9.5, 2.1 Hz, 1H, H-5), 4.50 (dd, J = 10.5, 6.9 Hz, 1H, H-7), 4.32 (d, J = 8.3 Hz, 1H, H-20α), 4.12 (d, J = 8.3 Hz, 1H, H-20β), 4.01 (d, J = 6.5 Hz, 1H, H-3), 3.93 (d, J = 14.4 Hz, 1H, H-10α), 3.54 (dq, J = 14.4, 1.1 Hz, 1H, H-10β), 3.02 (d, J = 19.7 Hz, 1H, H-14α), 2.78 (dd, J = 19.7, 1.0 Hz, 1H, H-14β), 2.49 (ddd, J = 14.4, 9.5, 6.9 Hz, 1H, H-6α), 2.23 (s, 3H, CH_3CO), 2.05 (d, J = 1.1 Hz, 3H, H-18), 1.86 (ddd, J = 14.4, 10.5, 2.1 Hz, 1H, H-6β), 1.72 (s, 1H, OH-1), 1.59 (s, 3H, H-19), 1.18 (s, 3H, H-16), 1.09 (s, 3H, H-17), 0.95 (t, J = 8.0 Hz, 9H, $SiCH_2\underline{C}H_3$), 0.59 (m, 6H, $Si\underline{C}H_2CH_3$). [^1H signals were assigned through the analysis of a NOESY experiment (mixing time = 0.7 s)].

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