Chinese Chemical Letters Vol. 11, No. 6, pp. 489–492, 2000

The Chemical Reactions of 11-Hydroxycephalotaxine

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Abstract: Some of the chemical reactions of 11-hydroxycephalotaxine **1,** which were encountered during the derivation of **1** and the related compounds were reported.

Keywords: 11-Hydroxycephalotaxine, structural modification.

11-Hydroxycephalotaxine **1** is one of the three C_{11}- oxygenated alkaloids isolated from the genus *Cephalotaxus*. Only a few reports on the chemical and biological activity and derivations of **1** were found [1-3]. Some of the chemical reactions of 11-hydroxy-cephalotaxine **1**, which were encountered during the derivation of **1** and the related compounds were described in this paper.

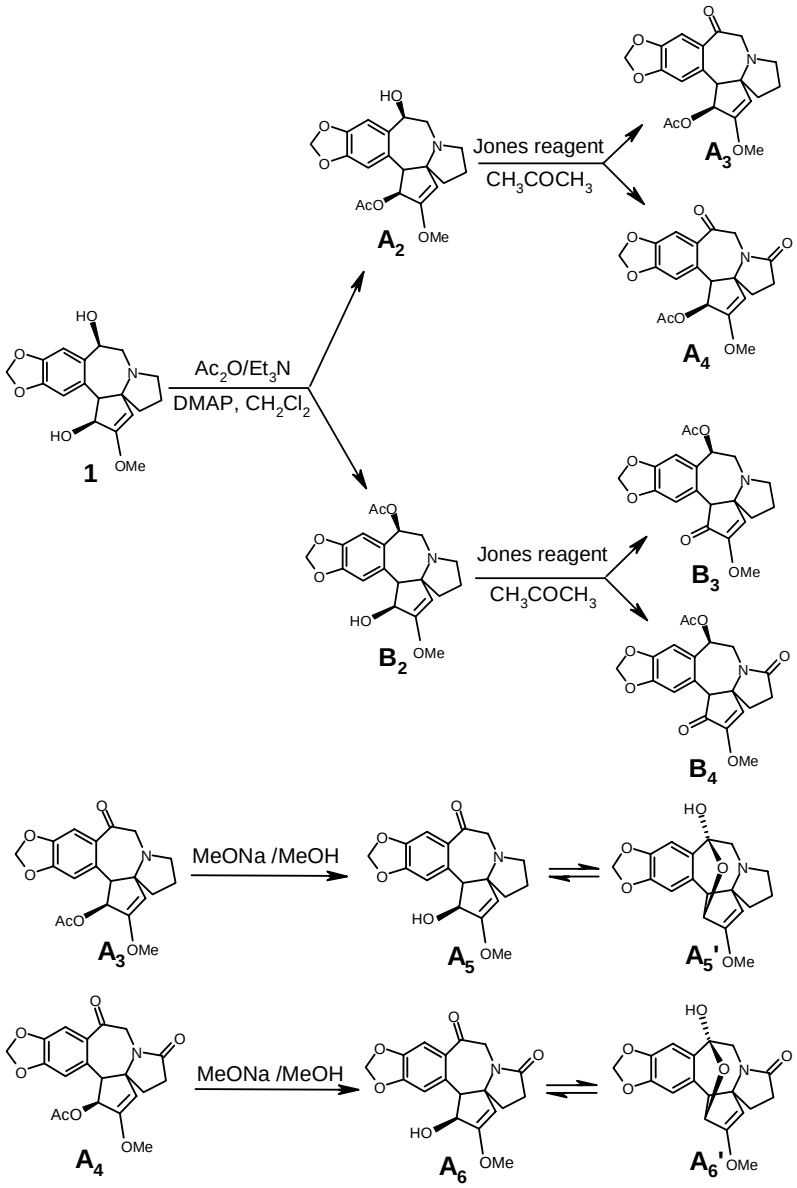
Acetylation of **1** with less than two molar of acetic anhydride formed two monoacetate $\mathbf{A_2}$ (C_3-acetate) and $\mathbf{B_2}$ (C_{11}-acetate) in favor of C_{11} acetylation due to the steric difference (**A** and **B** stand those compounds derived from C_3-OAc and C_{11}-OAc correspondingly). Compound $\mathbf{A_2}$ was obtained as colorless prism from CH_2Cl_2 , mp188～190℃; $[\alpha]_D^{15}$ -150.7, (c 0.30,$CHCl_3$); ^{1}H-NMR, 90MHz ($CDCl_3$ δ ppm), 6.86 (s, 1H, Ar-H), 6.53 (s, 1H, Ar-H), 5.89 (s, 2H, methylenedioxy), 5.76 (d, 1H, $J_{3,4}$=7Hz, H_3), 4.84 (m, 1H, H_{11}), 4.75 (s, 1H, H_1), 3.68 (s, 3H, -OCH_3), 3.60 (d, 1H, $J_{3,4}$=7Hz, H_4), 3.22 (m, 2H, H_{10}), 2.88 (m, 2H, H_8), 2.20 (brs, -OH), 2.08-1.52 (m, 4H, H_6, H_7), 1.84 (s, 3H, -OAC), Compound $\mathbf{B_2}$ was obtained as colorless prism from EtOAc, mp145～147℃; $[\alpha]_D^{15}$ -239.3, (c 0.38, $CHCl_3$); ^{1}H-NMR, 500MHz ($CDCl_3$ δ ppm), 6.78 (s, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 6.06 (dd, 1H, $J_{10a,11}$=8.4Hz, $J_{10b,11}$=7.8Hz, H_{11}), 5.95 (d, 2H, methylenedioxy), 4.66 (s, 1H, H_1), 4.57 (d, 1H, $J_{3,4}$=9Hz, H_3), 3.71 (s, 3H, -OCH_3), 3.68 (d, 1H, $J_{3,4}$=9Hz, H_4), 3.31 (dd, 1H, $J_{10a,10b}$=14.5Hz, $J_{10a,11}$=8.4Hz, H_{10a}), 3.15 (m, 1H, H_{8a}), 2.59 (dd, 1H, $J_{10a,10b}$=14.5Hz, $J_{10b,11}$=7.8Hz, H_{10b}), 2.75 (m, 1H, H_{8b}), 2.63 (brs, -OH), 2.05 (s, 3H, -OAC), 1.93 (m, 2H, H_7), 1.74 (m, 2H, H_6).

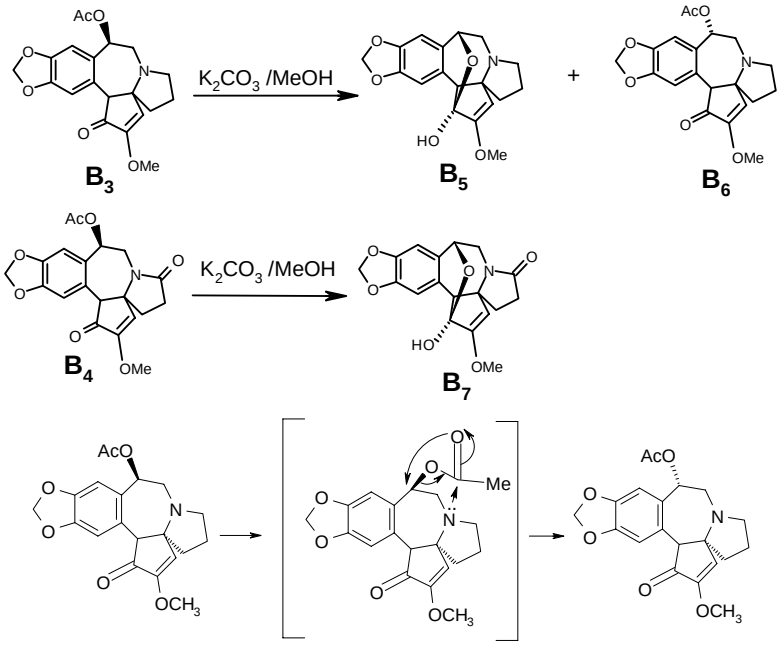
The monoacetates on treating with Jones reagent separately gave the expected ketone $\mathbf{A_3}$, ^{1}H-NMR, 500MHz ($CDCl_3$ δ ppm), 7.26 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 6.01 (d, 2H, methylenedioxy), 5.56 (d, 1H, J3.4=7.5Hz, H3), 4.67 (s, 1H, H1), 3.97 (d, 1H, J10a,10b=19Hz, H10a), 3.71 (s, 3H, -OCH3), 3.59 (d, 1H, J3.4=7.5Hz, H4), 3.52 (d, 1H, $J_{10a,10b}$=19Hz, H_{10b}), 2.83 (m, 2H, H_8), 2.10～2.00 (m, 2H, H_7), 1.74 (s, 3H, -OAC), 1.79～1.70 (m, 2H, H_6) and $\mathbf{B_3}$, mp179～182℃ (EtOAc/Pet. ether); $[\alpha]_D^{23}$ -199.1,

(c 0.21, $CHCl_3$); ^{1}H-NMR, 90MHz ($CDCl_3$ δ ppm), 6.81 (s, 1H, Ar-H), 6.76 (s, 1H, Ar-H), 6.21 (s, 1H, H_1), 5.95 (dd, 2H, methylenedioxy), 5.74 (d, 1H, $J_{10a,11}$=8Hz, H_{11}), 3.82(s, 3H, -OCH_3), 3.77 (s, 1H, H_4), 3.14(dd, 1H, $J_{10a,10b}$=14Hz, $J_{10a,11}$=8Hz, H_{10a}), 3.18～2.80 (m, 2H, H_8), 2.82 (d, 1H, $J_{10a,10b}$=14Hz, H_{10b}), 2.28～1.60 (m, 4H, H_6, H_7), 1.92 (s, 3H, -OAC), and the further oxidized product at C_8, Compound **A_4**, mp227～229℃ (EtOAc/Pet. ether); [α]$_D^{24}$ -65.2, (c 0.30,$CHCl_3$); ^{1}H-NMR, 90MHz ($CDCl_3$ δ ppm), 7.18 (s, 1H, Ar-H), 6.62 (s, 1H, Ar-H), 5.98 (s, 2H, methylenedioxy), 5.60 (d, 1H, $J_{3.4}$=7Hz, H_3), 4.68 (s, 1H, H_1), 4.61 (d, 1H, $J_{10a,10b}$=19Hz, H_{10a}), 3.85 (d, 1H, $J_{10a,10b}$=19Hz, H_{10b}), 3.72 (s, 3H, -OCH_3), 3.36 (d, 1H, $J_{3.4}$=7Hz,H_4), 2.44～2.00 (m, 4H, H_6, H_7), 1.76 (s, 3H, -OAC), and compound **B_4**, mp224～228℃ (EtOAc); [α]$_D^{21}$ -169, (c 0.34,$CHCl_3$); ^{1}H-NMR, 90MHz ($CDCl_3$ δ ppm), 6.76 (s, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 5.92 (s, 1H, H_1), 5.90 (s, 2H, methylenedioxy), 5.76 (d, 1H, $J_{11,10a}$=7.2Hz, H_{11}), 4.58 (dd, 1H, $J_{11,10a}$=7.2Hz, $J_{10a,10b}$=14Hz,H_{10a}), 3.85 (s, 3H, -OCH_3), 3.50 (s, 1H, H_4), 3.00 (d, 1H, $J_{10a,10b}$=14Hz, H_{10b}), 2.26 (brs, 4H, H_6, H_7), 1.88 (s, 3H, -OAC). The total yield of the oxidized product of **A_2** were 59% for **A_3**+**A_4** with the ratio of 1: 0.35 for **A_3**/**A_4** and for **B_2** the total yield is 37% with ratio of **B_4**/**B_3** being 1:1.34. This is evident that C_8 is less feasible than C_{11}-OH in **A** series towards Jones reagent while in **B** series the reverse is true. When Swern oxidation was applied to **B_2**, no C_8 oxidation was observed and the yield of **B_3** was almost quantitative (98%). When the ketone acetate **A_3** and **A_4** were hydrolyzed with NaOMe/MeOH separately, the expected C_3-OH, C_{11}=O (**A_5**, **A_6**), which were equilibrating with their semiketal (**A_5'**, **A_6'**) formed through the intermolecular cyclization, were formed. This was indicated in their ^{1}H-NMR and GC-MS. However, X-ray diffraction analysis of the crystal obtained from chloroform demonstrated the ketone structure. On treatment of K_2CO_3/MeOH, the ketone acetate **B_4** yielded only the cyclized product **B_7**, mp 279-282℃ (MeOH); [α]$_D^{24}$ +156.5, (c 0.23, $CHCl_3$); ^{1}H-NMR, 500MHz ($CDCl_3$ δ ppm), 6.77 (s, 1H, Ar-H), 6.71 (s, 1H, Ar-H), 5.97 (dd, 2H, methylenedioxy), 4.88 (d, 1H, $J_{11,10a}$=4.5Hz, H_{11}), 4.61 (s, 1H, H_1), 4.01 (dd, 1H, $J_{10a,10b}$=14.5Hz, $J_{10a,11}$=4.7Hz, H_{10a}), 3.82 (s, 3H, -OCH_3), 3.21 (d, 1H, $J_{10a,10b}$=14.5Hz , H_{10b}), 3.19 (s, 1H, H_4), 3.12 (s, 1H, -OH), 3.35～2.08 (m, 4H, H_6, H_7). No free ketone was obtained. Apparently the phenyl ring which conjugates with C_{11}=O somewhat stabilized the carbonyl group in **A** series. When K_2CO_3/MeOH was used as the hydrolysis medium for **B_3** two products were isolated, the cyclized product **B_5**, mp 205-206℃ (EtOAc); [α]$_D^{15}$ +18.2, (c 0.60, $CHCl_3$); ^{1}H-NMR, 500MHz ($CDCl_3$ δ ppm), 6.77 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 5.94 (s, 2H, methylenedioxy), 4.80 (m, 1H, H_{11}), 4.64 (s, 1H, H_1), 3.78 (s, 3H, -OCH_3), 3.28 (s, 1H, H_4), 3.05 (brs, 1H, -OH), 2.80 (m, 2H, H_{10}), 2.68 (m, 1H, H_{8a}), 2.43 (m, 1H, H_{8b}), 1.76 (m, 4H, H_6, H_7), and the C_{11}-α-acetyl-3-one **B_6**, ^{1}H-NMR, 500MHz ($CDCl_3$ δ ppm), 6.78 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 6.05 (s, 1H, H_1), 5.96 (d, 2H, methylenedioxy), 4.11 (d, 1H, $J_{11,10}$=8Hz,H_{11}), 3.79 (s, 3H, -OCH_3), 3.45 (s, 1H, H_4), 3.18 (brs, 1H, H_{10a}), 3.00 (brs, 1H, H_{10b}), 2.78 (s, 3H, -OAC), 2.90～2.80 (m, 2H, H_8), 2.15～1.80 (m, 4H, H_6, H_7). It means that isomerization of β-acetoxyl to α-position has taken place. The isomerization was not observed in the case of **B_4**. The different results obtained for **B_3** and **B_4** can be interpreted the participation of C_8=O as that the lone electron pair of nitrogen at position 9 of **B_3** attacked the C=O of the acetoxyl group with subsequent breaking of β-C_{11}-O and

formation of α-C_{11}-O bond consecutively. But the lone electron pair was less available in **B_4** due to the carbonyl group at position 8.

All of the above reactions were simple reactions but the steric hindrance and neighboring group participation render different products for compounds with slight deviation in structures.





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Received 19 January 2000