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Unexpected ring C enlargement of the aspidospermane skeleton

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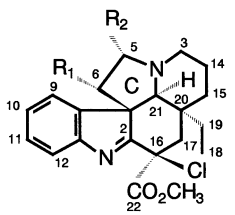
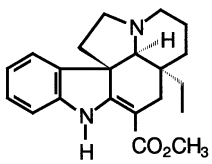
Abstract—Treatment of (–)-16-chloro-1-dehydro-5-methoxy-vincadifformine **4** with Ac_2O–pyridine led to the rearranged compound **6** through an unexpected ring C expansion. Upon reaction with dimethyl acetylenedicarboxylate, **4** provided the [2+2] cycloaddition derivative **9** but did not undergo the ring C enlargement.

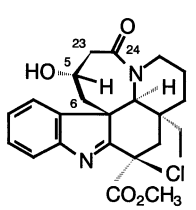
In a previous publication,[1] we reported the cytotoxicity of **1** (IC_{50} on L1210 leukemia cells 7×10^{-7} M), a semi-synthetic *Aspidosperma* alkaloid prepared from (–)-vincadifformine **2**. The C-6 bromination seemed essential for the activity since (–)-16-chloro-1-dehydrovincadifformine **3**[2] was not cytotoxic. Therefore, we carried on the study of functionalization at C-6 with acylation reactions of the carbinolamine ether **4**, a key intermediate in the preparation of **1** from **2**.[3]





1	R_1 = Br	R_2 = H	**2**
3	R_1 = H	R_2 = H	
4	R_1 = H	R_2 = OCH_3	
5	R_1 = $COCF_3$	R_2 = H	Δ 5-6

While treatment of **4** with trifluoroacetic anhydride (TFAA, pyridine, rt, 1 h) led to the expected enamino trifluoromethylketone **5**[4] (39%), replacement of TFAA by acetic anhydride (rt, 20 h) provided after standard work up of the reaction the original ring expanded derivative **6**[4] (63%). The ring C enlargement for **6** was suggested mainly by mass and NMR spectral data (molecular ion at m/z 430, lack of the acetyl singlet signal in the ^{1}H NMR spectrum). Furthermore, the IR spectrum showed a strong hydroxyl band (3400–2500 cm^{-1}) and, related to **4**, an additional carbonyl band (1705 cm^{-1}), while the ^{1}H NMR spectrum displayed at δ 4.15 ppm a pseudoquintuplet (J=5 and 6.1 Hz, 1H) characteristic of a CHOH group. The β-hydroxy lactam substructure for the ring C was supported by the occurrence in the ^{13}C NMR spectrum of a new carbonyl signal related to **4** at 174.1 ppm and was confirmed by HMBC experiments which clearly exhibited characteristic ^3J (^{1}H–^{13}C) values between C-2 at 180 ppm and H-6, H-17 and H-21. Treatment of **6** by sodium iodide in acetic acid (3 equiv. NaI, rt, 2 h) allowed for recovery of the anilinoacrylate ester chromophore and afforded compound **7** (64%), which represents a semi-synthetic ring C expanded analog of (–)-vincadifformine **2**.[4] The configuration of the carbinol carbon was inferred from the significant NOE observed in **7** between, on the one hand CHOH (3.78 ppm) and H-15a (1.85 ppm), and on the other hand H-21 (3.53 ppm) and H-15b (1.55 ppm). Inspection of molecular models proved unambiguously that an observed NOE between CHOH and one H-15 could only be consistent with an *S* configuration of the carbinol carbon.



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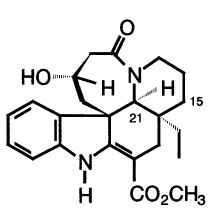

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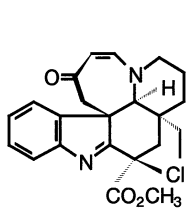

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Keywords: indole alkaloids; aspidospermane; vincadifformine; ring expansion; [2+2] cycloaddition.

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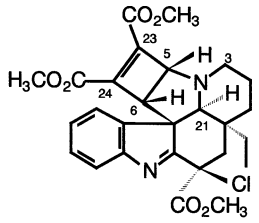
When the acylation of **4** was achieved with (acetic anhydride)-d_6, the isolated compound was, according to HREIMS, a mixture of di-, tri- and tetradeuteriated analogs of **6**. A thorough ^{1}H NMR study of this mixture proved that the C-23 position was always dideuterated (no more H-23 signal), and that other deuterium atoms were only fixed at C-6 [the CHOH signal at δ 4.15 ppm (1H) appeared as the overlapping of a singlet, a doublet and a triplet].

Mechanism of the ring C expansion (Scheme 1). The carbinolamine ether **4** was expected to react at C-6 under its enamine form as observed with TFAA or previously with BrCN.[3] However, isolation of the β-hydroxy lactam **6** did not support that hypothesis: an initial C-6 acylation followed by ring C expansion through a supposed cyclobutanone intermediate would provide the enamino ketone **8** instead of **6**. The following mechanism appears more likely: it implies a transformation of **4** into the carbinolamine,[5] which undergoes *N*-acylation and the 4–5 bond cleavage, then a cyclization of the resultant aldehyde leads to **6** by an aldol-type condensation; equilibrium of this last reaction can account for the results observed with (acetic anhydride)-d_6.

This ring expansion of **4** to **6** led us to investigate behavior of **4** towards dimethyl acetylenedicarboxylate (DMAD), an acetylenic ester known to react with enamines according to a [2+2] cycloaddition mechanism, and to provide with cyclic enamines ring expanded compounds.[6,7] Heating under vacuum a dichloromethane solution of **4** (0.1 mmol) and DMAD (0.16 mmol) (60°C, 5 min) afforded the expected compound **9** (53%).[8] Structure of **9** was deduced from the EI mass spectrum (molecular pic at m/z 512) and from NMR data, which displayed characteristic signals of the additional cyclobutene ring (^{1}H NMR: H-5 and H-6, 2d, $J=3.7$ Hz at 4.62 and 3.75 ppm; 2 CO_2CH_3, 2s at 3.88 and 3.26 ppm; ^{13}C NMR: C-5 and C-6 at 66.6 and 52.6 ppm; C-23 and C-24 at 143.2 ppm; 2 CO_2CH_3 at 162.7 and 161.5 ppm). The probable *cis* C5–C6 ring junction was confirmed by the observed NOE between H-5 and H-6 signals. Moreover, the presence of NOE between H-3a (3.42 ppm) and H-5, H-6 and between H-3b (2.70 ppm) and H-21 (3.21 ppm) on the one hand, and lack of observed NOE between H-21 and H-5, H-6 on the other hand proved stereochemistry at C-5 and C-6 to be 5*R* and 6*R*.



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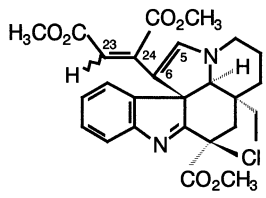

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Compound **9** was easily converted to the bright yellow derivative **10** in 66% yield by heating in methanol (reflux, 20 min).[8,9] **10** displayed the same molecular weight as **9** but UV, IR and NMR data revealed opening of the cyclobutene ring between C-5 and C-23. Contrary to **6**, **10** was not a ring C expanded derivative but appeared to be the result of the Michael addition of DMAD on the enamine of **4**. A such evolution of the [2+2] cycloaddition compound by heating in a polar solvent has already been mentioned.[6,7]

The unusual ring expansion described in this letter allowed the easy isolation of a new skeleton with a functionalized ring C, which can be potentially interesting from both chemical and biological points of view.

Acknowledgements

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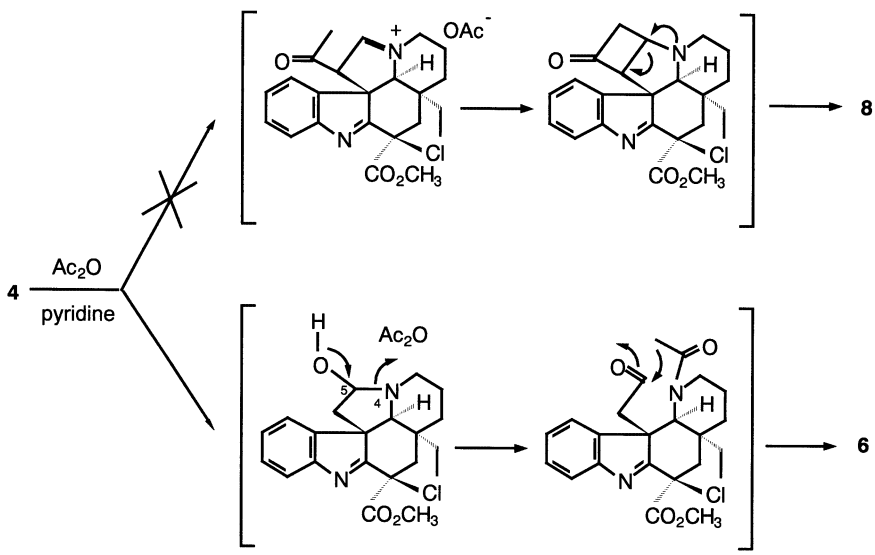

Scheme 1.

mechanism of the ring expansion. We also thank Dr. P.-H. Lambert (IdRS) for HREIMS experiments.

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4. **5**: Mp 223–225°C (MeOH); $[\alpha]_D = -111$ ($c = 0.4$, $CHCl_3$); UV (EtOH, λ_{max} nm) 228, 330; IR (cm^{-1}) 1730, 1625, 1560 (strong); ^1H NMR ($CDCl_3$, δ ppm) characteristic signals at 7.70 (s, H-5), 7.70 (d, H-12), 7.4–7.25 (m, H-9, H-10, H-11), 3.98 (s, 3H, CO_2CH_3), 3.95 (s, H-21), 0.65 (t, 3H-18); EIMS (molecular peaks at m/z 466–468).
   6: Amorphous; $[\alpha]_D = -47$ ($c = 0.3$, $CHCl_3$); UV (EtOH, λ_{max} nm) 228, 284; IR (cm^{-1}) 3400–2500, 1735 (ester), 1705 (lactam); ^1H NMR ($CDCl_3$, δ ppm) characteristic signals at 4.15 (m, $J = 6.1$ and 5 Hz, H-5), 4.00 (s, 3H, CO_2CH_3), 3.37 (s, H-21), 3.20 (dd, $J = 14$ and 6.1 Hz, H-6), 2.75 (d, $J = 5$ Hz, 2H-23), 2.07 (dd, $J = 14$ and 6.1 Hz, H-6); ^{13}C NMR ($CDCl_3$, δ ppm) 7.6 (C-18), 18.6 (C-15), 30.7 (C-19), 33.1 (C-14), 33.4 (C-23), 36.8 (C-20), 43.0 (C-6), 44.1 (C-17), 46.4 (C-3), 58.6 (C-5), 60.8 (C-7), 65.0 (C-16), 73.5 (C-21), 121.9 (C-12), 122.8 (C-9), 128.3 and 128.6 (C-10 and C-11), 146.0 (C-8), 152.0 (C-13), 170.4 ($\underline{C}O_2CH_3$), 174.1 (C-24), 180.0 (C-2); HREIMS calcd for $C_{23}H_{27}{}^{35}ClN_2O_4$ 430.1659, found 430.1658.
   7: Amorphous; $[\alpha]_D = -274$ ($c = 0.35$, $CHCl_3$); HREIMS calcd for $C_{23}H_{28}N_2O_4$ 396.2049, found 396.2045.
5. Unpublished previous works have shown that the C4–OCH_3 bond in **4** was very easy to cleave. Consequently, the carbinolamine intermediate could have been generated from **4** owing slight traces of water.
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7. Reinhoudt, D. N.; Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Harkema, S.; van Hummel, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1341–1350.
8. **9**: mp 213–215°C (MeOH); $[\alpha]_D = -33$ ($c = 0.3$, $CHCl_3$); UV (EtOH, λ_{max} nm) 226, 270; IR (cm^{-1}) 1738, 1720 (esters); ^1H and ^{13}C NMR ($CDCl_3$, δ ppm): see text; other characteristic signals at 3.99 (s, 3H, C16–CO_2CH_3), 3.21 (s, H-21) and at 170.9 (C16–$\underline{C}O_2CH_3$); HREIMS calcd for $C_{27}H_{29}{}^{35}ClN_2O_6$ 512.1714, found 512.1712.
   10: mp 250–252°C (MeOH); $[\alpha]_D = +105$ ($c = 0.4$, $CHCl_3$); UV (EtOH, λ_{max} nm) 228, 278, 379; IR (cm^{-1}) 1734 and 1694 (esters), 1551 (conjugated olefins); ^1H NMR ($CDCl_3$, δ ppm) characteristic signals at 6.82 (s, H-5), 4.00 (s, 3H, C16–CO_2CH_3), 3.92 (s, H-23), 3.89 (s, H-21), 3.86 and 3.48 (2s, 2 CO_2CH_3); ^{13}C NMR ($CDCl_3$, δ ppm) characteristic signals at 50.9, 54.0 and 54.2 (3 $CO_2\underline{C}H_3$), 77.1 (C-21), 100.6 (C-23), 107.0 (C-6), 145.1 (C-24), 148.6 (C-5); HREIMS calcd for $C_{27}H_{29}{}^{35}ClN_2O_6$ 512.1714, found 512.1732.
9. The conversion of **9** into **10** was also achieved by adsorption of **9** on silicagel then elution after 25 min.