Novel Base-Catalyzed Rearrangement of the Taxane Skeleton[1]

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Methanolysis of taxicin I esters afforded the 1,15-secotaxane **4**, the result of a vinylogous retro-aldol reaction followed by acetalization and a transannular hydride shift.

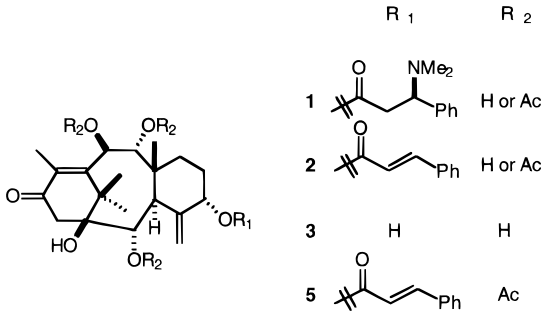
Taxine is a mixture of taxane alkaloids responsible for the poisonous properties of the yew tree.[2] It is the major constituent of the needles of the European yew,[2,3] and substantial amounts of alkaloids might also be present in other commercial sources of paclitaxel and/or paclitaxel-equivalent compounds. The use of taxine for the synthesis of antitumor taxoids is an attractive possibility to increase the pharmaceutical potential of yew biomass, an expensive commodity.[4] Indeed, taxine might be used as starting material for the synthesis of analogues of paclitaxel[5,6] or, alternatively, for the design of nonoxetane-type antitubulin taxanes like taxuspine D.[7]

Different approaches are possible for the synthesis of paclitaxel analogues from taxine, depending on the plant source and the composition of taxine obtained therefrom.[2] However, because taxine is mainly a mixture of taxanes of the $\Delta^{4(20)}$-type esterified with Winterstein acid,[2] two synthetic operations are common to all strategies, namely the modification of the C-4,C-5,C-20 functionalization and the reshuffling of the ester groups by hydrolysis and selective esterification. We report here the structure of an unusual rearrangement product obtained during the methanolysis of a mixture of cinnamates related to taxine B.

Taxine from the European yew is mainly a mixture of taxine I (**1**) derivatives with various degrees of deacetylation.[3] After conversion of Winterstein esters to their corresponding cinnamates,[8] a crude mixture of cinnamoyltaxicin I acetates (**2**) was obtained.[9] This could be converted by treatment with dilute (0.1 N) sodium methylate in MeOH−CH_2Cl_2 (1.4 :1) into the pentaol **3** (= taxicin I), an intermediate for the synthesis of 7-deoxypaclitaxel.[5,6]

Faced with the problem of scaling up and optimizing the alcoholysis reaction (ca. 70% yield), we became interested in the structure of the reaction by-products, and isolated the bisacetal **4**, slightly more polar than **3**. When the reaction was carried out in more basic conditions and without a cosolvent, **4** became the major reaction product. Thus, starting from pure 2,9,10-triacetyl-5-cinnamoyltaxicin I (**5**),[9] **4** was obtained in ca. 80% yield by treatment with 0.2 N sodium methylate in MeOH.

Compounds **3** and **4** had the same molecular formula ($C_{20}H_{30}O_6$, MS), showing loss of all ester groups. However, the NMR spectra of **4** showed an extensive reorganization of the carbon−carbon and carbon−oxygen connectivities, as confirmed by the lack of a carbonyl absorption band in the IR spectrum and the absence of UV chromophores. The ^{13}C-NMR spectrum of **4** contained 20 signals. Of these, eight could be assigned to the ring C carbons with the attached 19-methyl and 20-methylene. The functionalization of the remaining signals comprised one tetrasubstituted double bond, two tetrasubstituted acetal carbons, and three oxymethines; whereas the aliphatic region of the spectrum consisted of three methyl signals, one methylene, and one methine. Besides the signal corresponding to the ring C moiety and two allylic methyls, the ^{1}H-NMR spectrum revealed one oxymethine singlet and two ^{1}H-coupled units, resonating as an AX_3 system and an A_2-MXY spin system, Y being the signal of H-3.



The combination of these structural data to meet the requirement of the degree of unsaturation and an isoprenoid origin, led to formula **4** for the rearranged product. The carbon−carbon and carbon−hydrogen connectivities were confirmed by inspection of the long-range C−H correlations (HMBC spectrum), and Figure 1 show a mechanistic rationale for the formation of **4** from taxicin I (**3**). Thus, a vinylogous retro-aldol reaction opens ring A, giving a 1,15-secotaxane with two keto groups. The closure of a 10,13-acetal bridge brings H-9 in close proximity to the C-1 carbonyl, setting the stage for the hydride shift from C-9 to C-1, the transannular version of an α-ketol rearrangement. Formation of a C-1, C-9 acetal bridge then terminates the reaction. An alternative vinylogous retro-aldol reaction, involving the C-9, C-10 bond, triggers the well-known rearragement of taxinine (the C-1 deoxy analogue of **5**) to anhydrotaxininol.[10]

The reactions involved in the formation of **4** are both precedented in taxane chemistry. Thus, the fragmentation of the C-1/C-15 bond had already been observed,

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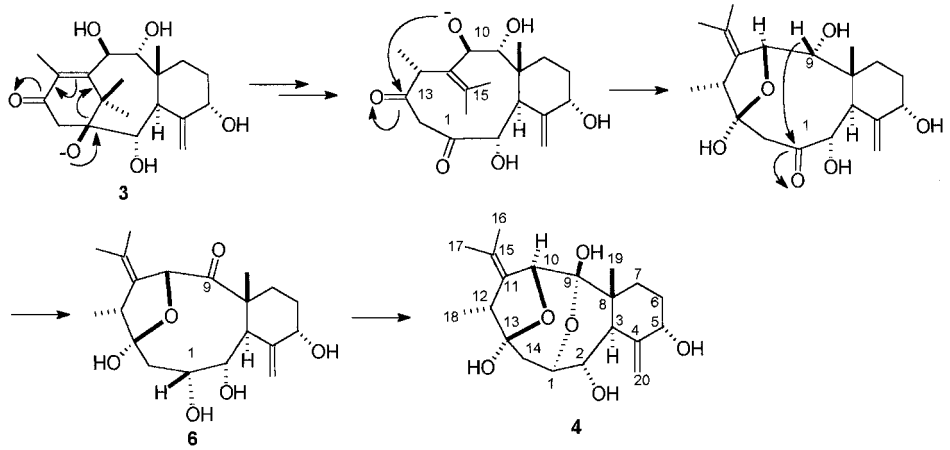

Figure 1. Formation of **4** from taxicin I (**3**).

under acidic conditions, in a baccatin VI derivative,[11] and a long-range hydride shift was reported in two synthetic taxane model compounds.[12,13] It is interesting to note that both the formation of a 13-cation in compounds of the 1,13-dihydroxy type and the formation of a 1-alcoholate in compounds of the 1-hydroxy-13-oxo type, result in the formation of cyclodecane derivatives of the 1,15-secotaxane type. Formation of a C-1 cation triggers instead the rearrangement to 11 (15 → 1) abeotaxanes (brevifoliol-type compounds).[14]

The stereochemistry of **4** was established by ROE measurements. Especially diagnostic were the correlations H-1/H-12, H-10/H-14α, and H-18/H-14α. The NMR spectra of **4** showed no evidence for the presence of carbonyl tautomers. Surprisingly, an attempt to trap the 9-oxo tautomer as the 1,2-acetonide (Me_2CO, H_2SO_4) gave the 1,2-diol itself (**6**). This compound showed an unexpected stability, allowing its chromatographic purification and full spectroscopical characterization.

The novel ring expansion reported here adds to the growing inventory of rearrangements and isomerizations triggered by a vinylogous retro-aldol reaction. Other notable examples are the rearrangement of taxinine to anhydrotaxininol, the first rearrangement reported for the taxane skeleton,[10] and the isomerization of phorbol to 4α-phorbol.[15]

Experimental Section

General Experimental Procedures. Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter. IR spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer. CIMS were taken on a Finnigan-MAT 4610 quadrupole instrument. ^{1}H- and ^{13}C-NMR spectra were taken on a Bruker AM-500 spectrometer (500.14 and 125.77 MHz, respectively), with TMS as reference. Si gel 60 (70−230 mesh, Merck) was used for column chromatography.

Synthesis of 4. To a solution of 2,9,10-triacetyl-5-cinnamoyltaxicin I (**5**) (100 mg, 0.16 mmol) in anhydrous MeOH (3 mL), a 0.5 N solution of sodium methoxide in MeOH (2 mL) was added dropwise at 0 °C. After stirring overnight at +4 °C under nitrogen atmosphere, the reaction was worked up by addition of saturated ammonium chloride (5 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography [hexane−EtOAc (5:5 and then 3:7) as eluent) to give 46 mg (79%) **4** as a white powder: mp 128−130 °C; $[\alpha]^{25}_D$ −99° (*c* 0.5, MeOH); IR (KBr) 3420, 1445, 1377, 1075, 1022 cm^{-1}; ^{1}H NMR (500.14 MHz, $CDCl_3$, TMS as reference) δ 5.23 (1H, br s, H-20a), 5.00 (1H, br s, H-20b), 4.83 (1H, s, H-10), 4.23 (1H, br s, H-5), 4.09 (1H, dd, J = 7.4,11.8 Hz, H-2), 3.68 (1H, t, J = 7.4 Hz, H-1), 3.03 (1H, d, J = 12.1 Hz, H-3), 2.86 (1H, q, J = 7.4 Hz, H-12), 2.73 (1H, dd, J = 14.7, 7.4 Hz, H-14α), 2.20 (1H, dd, J = 13.6, 5.1 Hz, H-7α), 2.20 (1H, dd, J = 15.4, 1.8 Hz, H-14*β*), 1.80 (2H, m, H- 6α,*β*), 1.74 (3H, s, H-16), 1.68 (3H, d, J = 1.5 Hz, H-17), 1.40 (1H, br d, J = 15.1 Hz, H-7*β*), 1.28 (3H, d, *J* = 7.4 Hz, H-18), 1.06 (3H, s, H-19); ^{13}C NMR (125.77 MHz, $CDCl_3$, TMS as reference) δ 146.6 (s, C-4), 130.7 (s, C-11), 134.2 (s, C-15), 112.1 (t, C-20), 110.4 (s, C-9), 100.9 (s, C-13), 83.0 (d, C-10), 76.7 (d, C-1), 73.1 (d, C-5), 70.0 (d, C-2), 48.2 (d, C-12), 44.9 (s, C-8), 44.4 (d, C-3), 41.1 (t, C-14), 29.8 (t, C-7), 29.6 (t, C-6), 22.4 (q, C-16), 20.9 (q, C-17), 16.4 (q, C-18), 15.5 (q, C-19); CIMS (NH_3) *m*/*z* $[M]^+$ 384 $[C_{20}H_{30}O_6 + NH_4]^+$ (100).

Synthesis of 6. To a solution of **4** (100 mg, 0.27 mmol) in anhydrous Me_2CO (500 μL) 1 drop of H_2SO_4 was added at 0 °C, and the reaction was kept at 4 °C for 24 h. The reaction was worked up by the addition of H_2O (1 mL), neutralized with saturated $NaHCO_3$, and extracted with EtOAc (3 × 1 mL). After removal of the solvent, the residue was purified by column chromatography (hexane−EtOAc 6:4 as eluent) to give 31 mg (31%) of **6** as a white powder: mp 246−248 °C; $[\alpha]^{25}_D$ −68° (*c* 0.4, MeOH); IR (KBr) 3432, 1688, 1300, 1075, 1038, 911 cm^{-1}; ^{1}H NMR (500.14 MHz, $CDCl_3$, TMS as reference) δ 5.58 (1H, br s, H-20a), 5.13 (1H, br s, H-20b), 5.13 (1H, d, *J* = 7.0 Hz, 1-OH), 4.98 (1H, p, *J* = 7.0 Hz, H-1), 4.67 (1H, s, H-10), 4.30 (1H, d, *J* = 2.2 Hz, 5-OH), 4.12 (1H, br q, *J* = 3.3 Hz, H-5), 3.99 (1H, t, *J* = 5.9 Hz, H-2), 3.36 (1H, d, *J* = 5.9 Hz, H-3), 2.64 (1H, br q, *J* = 7.0 Hz, H-12), 2.53 (1H, m, H-7*β*), 2.27 (1H, dd, *J* = 11.5, 6.6 Hz, H-14α), 1.95 (1H, dd, *J* = 8.5, 11.5 Hz, H-14*β*), 1.75 (3H, br s, H-16), 1.73 (2H, m, H-6α,*β*), 1.69 (3H, s, H-17), 1.42 (3H, s, H-19), 1.12 (3H, d, *J* = 7.0 Hz, H-18), 0.97 (1H, dt, *J* = 3.3, 1.4 Hz, H-7α); ^{13}C NMR (125 MHz, $CDCl_3$, TMS as reference) δ 213.0 (s, C-9), 146.3 (s, C-4), 133.2 (s, C-11), 127.7 (s, C-15), 113.2 (t, C-20), 112.6 (s, C-13), 85.0 (d, C-2), 80.0 (d, C-10), 72.4 (d, C-1), 72.0 (d, C-5), 52.4 (d, C-3), 50.8 (s,

C-8), 40.1 (t, C-14), 39.4 (d, C-12), 31.5 (t, C-7), 28.8 (t, C-6), 22.9 (q, C-16), 20.1 (q, C-17), 14.2 (q, C-19), 12.9 (q, C-18).

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