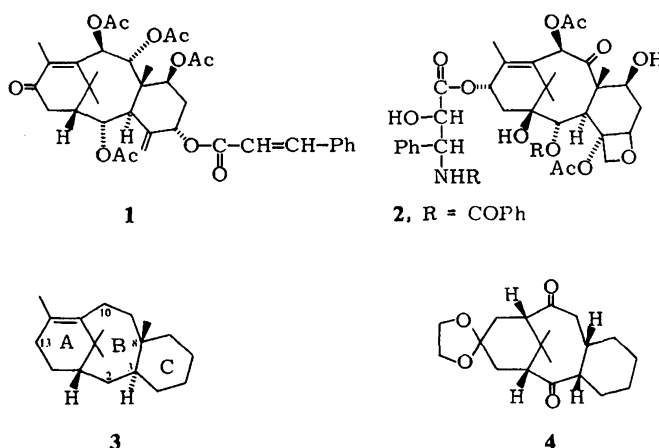


A Novel Entry to the Taxane Structural Unit**

By Harribert Neh, Siegfried Blechert*, Wolfgang Schnick, and Martin Jansen

Taxanes, such as, e.g., taxinin B **1** or taxol **2**, are unusual hydroxylated diterpenes which occur in plants of the family Taxaceae, to which the yew tree (*Taxus baccata* L.) belongs^[1]. The antileukemic and antitumoral activities of some taxanes^[1] and the problems encountered in the synthesis of the unusual tricyclic carbon skeleton **3** have aroused increasing interest in recent years^[3]. According to in vitro experiments^[4], less substituted taxane derivatives could also be biologically active. For this reason it appeared to us that the synthesis of a tricyclic taxane skeleton with functional groups in ring A and ring B which should be readily convertible into hydroxy groups might prove rewarding. We report here on a stereoselective route to the tricycle **4**.

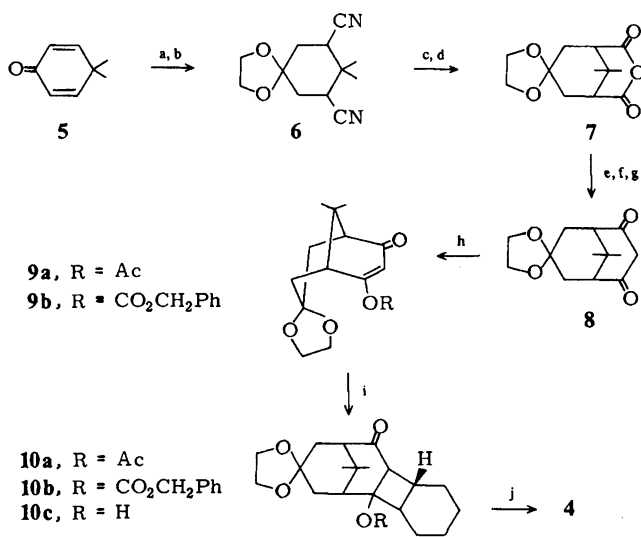


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A problem in the synthesis of the taxane framework is the formation of the eight-membered ring. This has previously been achieved by way of intramolecular Diels-Alder reactions, but this approach involved an aromatic ring C^[5] or simply dispensed of the bulky geminal dimethyl group^[6]. For preparation of the central ring, we used the de Mayo reaction^[7,8]. The key step of our reaction sequence 5→4 (Scheme 1) is the stereoselective [2+2]-photocycloaddition of cyclohexenes to the bicycle 9, since in this way the configuration at C-8 of the taxane framework is fixed. A C-8- α -ring coupling should be possible by a β -*exo* attack of the cyclohexene. As directing substituent we chose a ketal, which we expected would, according to model considerations, favor the formation of a β -adduct.



Scheme 1. a) KCN, NH₄Cl, (DMF)/H₂O, 68% yield; b) HOCH₂CH₂OH, *p*-toluenesulfonic acid, benzene, 83% yield; c) KOH, H₂O₂/H₂O, 3 d reflux, yield 88%; d) dicyclohexylcarbodiimide, CH₂Cl₂, 91% yield; e) MeLi, -60°C, 55% yield; f) CH₂N₂, 95% yield; g) KH, xylene, reflux, 85% yield; h) Ac₂O/NaOAc, 96% yield or ClCO₂CH₂Ph, CH₂Cl₂, aq. NaHCO₃, 86% yield; i) cyclohexene/CH₂Cl₂, hv, -78°C, 10a: 56% yield + 15% educt, 10b: 65% yield + 30% educt; j) 0.5N KOH/EtOH, 15 h, 56% yield.

Our strategy for the synthesis of the 1,3-diketone 8 enabled us to investigate intramolecular photocycloadditions also, since substituted 1,3-diketones can be synthesized from the anhydride 7 by reactions with alkyllithium compounds other than MeLi. Irradiation of the enol acetate 9a (500 W Hg high-pressure lamp (Pyrex filter), 4 h,

-78°C) in a 4:1 mixture of dichloromethane/cyclohexene led to 10a, which, however, was less suited for the ring-opening, since elimination readily takes place with formation of cyclobutene. The benzyl carbonate 10b, which is obtainable in 65% yield (30% recovered educt) from 9b after chromatography can, on the other hand, be converted quantitatively by hydrogenolysis (H₂, Pd/C) into the alcohol 10c. The very slow retroaldol cleavage leading to formation of 4 (15 h, 0.5N ethanolic KOH solution) is remarkable. After chromatography on silica gel, during which larger losses occur, the diketone 4 is obtained in 56% yield (m.p. 129–130°C, crystallization from petroleum ether). The configuration at C-3 and C-8 could not be determined unequivocally on the basis of the NMR data^[9] in the case of the strongly strained tricycle 4; however, this could only be established by X-ray structure analysis^[10].

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[9] Supplementary ¹H-NMR data (400 MHz, CDCl₃): δ = 3.8–4.2 (ketal-H, m), 3.71 (H _{α} -9, t, *J* = 12.2 Hz), 3.41 (H-3, t d, *J* = 5.0 and 1.2 Hz), 2.98 (H _{α} -14, ddd, *J* = 12.8, 4.8, and 1.8 Hz), 2.48 (H-11, d (br.), *J* = 7.5 Hz), 2.32 (H _{β} -12, dd, *J* = 16.2 and 7.8 Hz), 2.05–2.13 (H _{β} -14, H-1, H-8, m), 2.01 (H _{α} -12, dd (br.), *J* = 16 and 2 Hz), 1.97 (H _{β} -9, ddd, *J* = 12.4, 6.0, and 1.8 Hz), 1.75 (1 H, m), 1.67 (1 H, m), 1.1–1.5 (6 H, m), 1.31 (3 H, s), 1.45 (3 H, s).
[10] 4 = C₁₉H₂₈O₄, *M_r* = 320.4; *a* = 6.737, *b* = 9.971, *c* = 14.114 Å, α = 69.37, β = 83.98, γ = 86.04, *V* = 881.9 Å³, *Z* = 2, space group P1̄. Data collection: Siemens AED2 diffractometer, MoK α radiation, graphite monochromator, scan width 1.2°, ω -scan, 8080 measured reflections in the range 3.1° < 2 θ < 50.0°, 1723 symmetry independent reflections with *F* > 3 σ (*F*), solution of structure by direct methods. Anisotropic refinement of all atoms other than hydrogen, hydrogen atoms isotropic, *R* = 0.0624 for 208 free parameters, *R_w* = 0.0467, *W* = 2.833/[σ^2 (*F*)]. Further details of the crystal structure are available on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 51050, the names of the authors, and the journal citation.

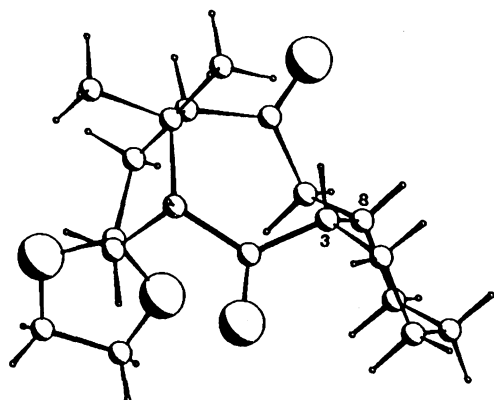


Fig. 1. Structure of a molecule of 4 in the crystal (PLUTO-PLOT).