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STUDIES DIRECTED TOWARDS THE SYNTHESIS OF TAXANE DITERPENES: A REMARKABLE REARRANGEMENT[1]

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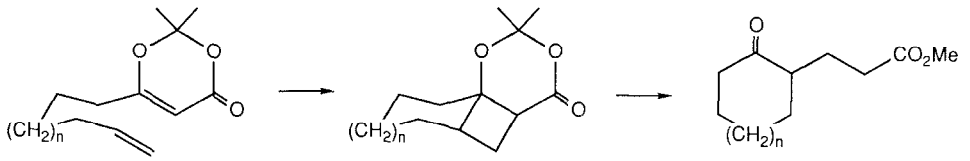
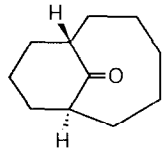
Abstract: Acid-catalyzed fragmentation of the intramolecular dioxolenone photocycloaddition product 9 leads not to 10, the desired taxane skeleton, but instead to the remarkable rearrangement product 11.

We have recently described the application of the intramolecular dioxolenone photocycloaddition,[5] i.e, 1→3 (Scheme I), to the synthesis of the bicyclo[5.3.1]undecane ring system, 4,[6] an important structural feature of the taxane diterpenes, of which taxol, 5,[7] has been found to exhibit significant antitumor properties.[8] In the course of the application of this methodology to the construction of the taxane skeleton, we have discovered a remarkable rearrangement reaction, which is the subject of this Letter.

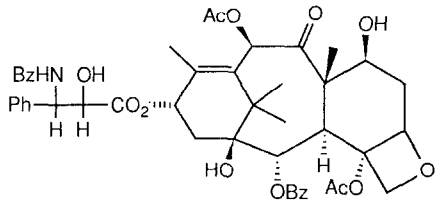
SCHEME I



1 2 3 (n = 1, 2, 3)



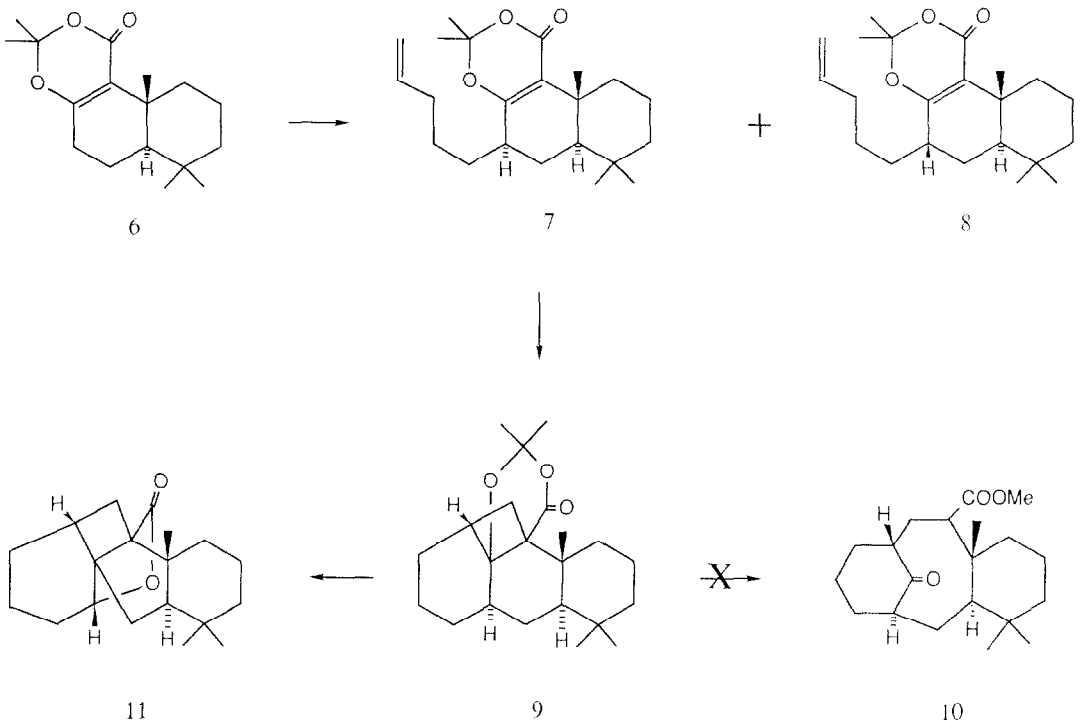
4



5

The substrate for the intramolecular dioxolenone cycloaddition was prepared as outlined in Scheme II[9]. Alkylation of the dianion of tert-butyl acetoacetate with geranyl bromide,[10] followed by cyclization to the bicyclic ketoester ($SnCl_4$, wet dichloromethane)[11] and dioxolenone formation (acetone, acetic anhydride, sulfuric acid, 0°C, 18h) gave 6 in 20% overall yield. Treatment of the anion of 6 with 4-pentenyl iodide (LDA, THF, -78°C) furnished the alkylated dioxolenones 7 and 8 in 80% yield as a 1:1 mixture of diastereomers at the newly formed stereocenter, which could be separated by HPLC.

SCHEME II



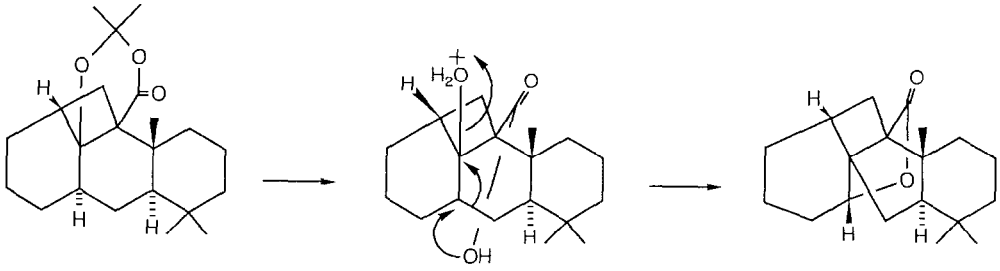
While irradiation of 8 (10% acetone/acetonitrile, 450 W Hanovia lamp, pyrex filter) gave a mixture of products, epimer 7, under identical conditions, afforded a single photoadduct whose structure, 9, was determined by X-ray.[4] As we have observed in our earlier work,[6] the stereochemistry of the fusion of the newly formed six and four membered rings is trans,

so that this compound would be expected to unravel to a trans-bridged (inside-outside) bicyclo[5.3.1]undecane ring system. However, when 9 was submitted to the usual fragmentation conditions (p-toluenesulfonic acid in refluxing methanol) we obtained none of the expected tricyclic ketoester 10 but instead the lactone 11[12] (85% yield), the structure of which was also determined by X-ray.[4]

We suggest that the driving force for this rearrangement is the relief of considerable strain energy in going from the trans-fused [4.2.0] fragment in 9 to the cis-[4.2.0] bicyclooctane in 11. MM2 calculations[13] show a ca. 5 kcal/mol difference in strain energy between 9 and 11.

The mechanism for this reaction presumably involves dioxolanone hydrolysis to a hydroxy acid, displacement of the protonated hydroxyl by contraction of the six-membered ring to a five-membered ring, and capture of the secondary carbonium ion by the carboxylic acid to form the γ-lactone, as outlined in Scheme III.

SCHEME III



Further studies in the photochemistry of 8 and the control of the stereochemistry of the introduction of the appendage, 6→8, with the correct relative stereochemistry for the synthesis of the taxanes, are currently underway and will be reported on in due course.

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Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599).

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2. Recipient of a Merck Grant for Faculty Development, 1985-1986.

3. National Institutes of Health Predoctoral Trainee (GM07148).

4. Author to whom correspondence regarding the X-ray structures of 9 and 11 should be addressed. Full details will be reported in the full paper.

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12. Spectral data for 7: ^{1}H-NMR (500 MHz, $CDCl_3$): 0.89 (s, 3H), 0.97 (s, 3H), 1.07 (m, 2H), 1.18 (s, 3H), 1.25-1.75 (m, 12H), 1.90 (q, 1H), 2.17 (bd, 1H), 2.40 (m, 2H), 4.14 (bs, 1H); IR ($CHCl_3$): 2930, 1740 cm^{-1}; MS (EI): 288, 273, 243, 220, 205, 193, 175, 164, 151, 123.

13. Calculated using the Gajewski/Gilbert modification of the Allinger MM2 program (#395, Quantum Chemistry Program Exchange, Indiana University), which is commercially available through Serena Software, Bloomington, IN.

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