Stereoselective Synthesis of the Tricyclic Skeleton of the Taxane Diterpenes. The First C-Silylation of a Ketone Enolate†

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Summary: The application of the intramolecular dioxenone photocycloaddition to the efficient synthesis of the tricyclic skeleton of the taxane diterpenes, with complete control of the relative stereochemical relationship between the two six-membered rings (A and C), is described. The first example of C-silylation of a ketone (cyclooctanone B-ring) enolate is reported, and the origins of this remarkable reactivity are discussed.

Sir: The taxane diterpenes,[4] such as taxol, **1**,[5] possess both unique molecular structures and a potent array of biological activities.[6] Taxol has been shown to exhibit in vivo activity against P-388, P-1534, and L-1210 mouse leukemias, and CX-1 colon, LX-1 lung, and MX-1 breast xenografts.[7] Considerable effort has been directed toward the synthesis of this fascinating group of compounds.[8] We report herein that the intramolecular dioxenone photocycloaddition[9] leads to the efficient synthesis of the tricyclic skeleton of the taxane diterpenes, with complete control of the relative stereochemical relationship between the two six-membered rings (A and C). We also note that silylation of the enolate derived from the tricyclic taxane ketone **8** leads to *the first example of C-silylation of a ketone enolate.*[10]

The synthesis of the requisite photosubstrate is outlined in Scheme I.[11] Conjugate addition of di-4-pentenylcopper magnesium bromide to enone **2**,[12] followed by trapping of the resulting enolate with methyl cyanoformate,[13] led to the exclusive formation of **3** in 79% yield, in which axial addition of cuprate to the rigid bicyclic enone resulted in the establishment of the desired C-1/C-3 (taxane numbering) relative stereochemical relationship. Exchange of **3** with *p*-methoxybenzyl alcohol provided the *p*-methoxybenzyl keto ester **4** in quantitative yield, which on treatment with trifluoroacetic anhydride and trifluoroacetic acid in acetone led to the formation of the photosubstrate, **5**, in 41% yield. Irradiation of **5** (7.6 mM in 1:9 acetone–acetonitrile, medium-pressure Hg lamp, Pyrex filter) gave a unique photoadduct in 77% yield as a white solid (mp 133–134 °C), whose structure was established as the cis-fused photoadduct **6**[14] by single-crystal X-ray analysis.[15] Reaction of **6** with 2 N potassium hydroxide in methanol and treatment of the resulting keto acid **7** with ethereal diazomethane led to the formation of the keto ester **8** and its C-15 epimer (3:1 ratio) in quantitative yield.[16] Recrystallization of **8** from ethyl acetate/petroleum ether provided a sample (mp 93–95 °C) suitable for X-ray analysis,[17] which confirmed the presence of the taxane skeleton with the correct C-1/C-3 relative stereochemical relationship between the two six-membered rings (A and C).

We next examined the further functionalization of the central eight-membered (B) ring of the taxane skeleton. Attempted formation of the silyl enol ether of ketone **8** by reaction of **8** with lithium diisopropyl amide at −78 °C,

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(2) Fellow of the National Institutes of Health Predoctoral Training Program (GM07183).

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(4) Lythgoe, B. *The Alkaloids*; Manske, R. H. E., Ed.; Academic Press: New York, 1968; Vol. X, p 597. Nakanishi, K.; Et al. *Natural Products Chemistry*; Kodansha-Academic: Tokyo, 1974; Vol. I, p 281. Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(5) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P. McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(6) For leading references on the effect of taxol on microtubule assembly, see: Manfredi, J. J.; Fant, J.; Horwitz, S. B. *Eur. J. Cell Biol.* **1986**, *42*, 126. Solari, A. J.; Duschak, V. G. *Micro. Sc. Electron. Bio. Cel.* **1985**, *9*, 163. Bhattacharyya, B.; Ghoschaudhuri, G.; Maity, S.; Biswas, B. B. *Ann. N. Y. Acad. Sci.* **1986**, *466*, 791. Horwitz, S. B.; Lothstein, L.; Manfredi, J. J.; Melcado, W.; Parness, J.; Roy, S. N.; Schiff, P. B.; Sorbara, L.; Zeheb, R. *Ann. N. Y. Acad. Sci.* **1986**, *466*, 733. Wallin, M.; Nordh, J.; Deinum, J. *Biochim. Biophys. Acta* **1986**, *880*, 189.

(7) For leading references, see: Riondel, J.; Jacrot, M.; Picot, F.; Beriel, H.; Mouriquand, C.; Potier, P. *Cancer Chemother. Pharmacol.* **1986**, *17*, 137. Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83. Hamel, E.; Lin, C. M.; Johns, D. G. *Cancer Treat. Rep.* **1982**, *66*, 1381. Suffness, M.; Douros, J. D. *Methods Cancer Res.* **1979**, *16*, 73. Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219. Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.

(8) For very recent work, see: (a) Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4143. (b) Shea, K. J.; Haffner, C. D. *Tetrahedron Lett.* **1988**, 1367. (c) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, 2221. (d) Pettersson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, 2753. (e) Kraus, G. A.; Thomas, P. J.; Hon, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1849. (f) Berkowitz, W. F.; Amarasekara, A. S.; Perumattam, J. J. *J. Org. Chem.* **1987**, *52*, 1119. (g) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1540. (h) Swindell, C. S.; Patel, B. P.; deSolms, S. J. *J. Org. Chem.* **1987**, *52*, 2346. (i) Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. For an exhaustive list of work prior to 1987, see: Winkler, J.; Hey, J.; Darling, S. *Tetrahedron Lett.* **1986**, 5959. Winkler, J.; Hey, J.; Williard, P. *J. Am. Chem. Soc.* **1986**, *108*, 6425. Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, 5275 and references cited therein.

(9) For examples of the use of the intramolecular dioxenone photocycloaddition reaction, see: (a) Winkler, J.; Hey, J.; Williard, P. *J. Am. Chem. Soc.* **1986**, *108*, 6425. (b) Winkler, J.; Hey, J.; Darling, S. *Tetrahedron Lett.* **1986**, 5959. (c) Winkler, J.; Hey, J.; Hannon, F.; Williard, P. *Heterocycles* **1987**, *25*, 55. (d) Winkler, J.; Henegar, K.; Williard, P. *J. Am. Chem. Soc.* **1987**, *109*, 2850. (e) Winkler, J.; Hey, J.; Williard, P. *Tetrahedron Lett.* **1988**, 4691. For the first intermolecular photocycloaddition of dioxenones, see: Baldwin, S.; Wilkinson, J. *J. Am. Chem. Soc.* **1980**, *102*, 3634.

(10) For earlier unsuccessful attempts to prepare α-silyl ketones by direct silylation of ketone enolates, see: Sato, S.; Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* **1983**, 3855. Larson, G. L.; Fuentes, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 2418. After the completion of our work, a related kinetic C-silylation was reported by Professor Robert Holton (Florida State University) at the Central Regional ACS Meeting, Cleveland, OH (June 1, 1989); Paper no. 286.

(11) All new compounds were characterized by full spectroscopic (NMR, IR, MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

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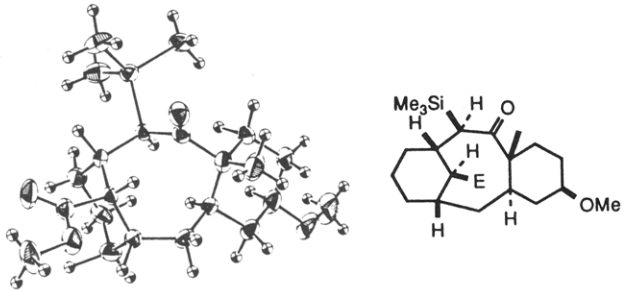
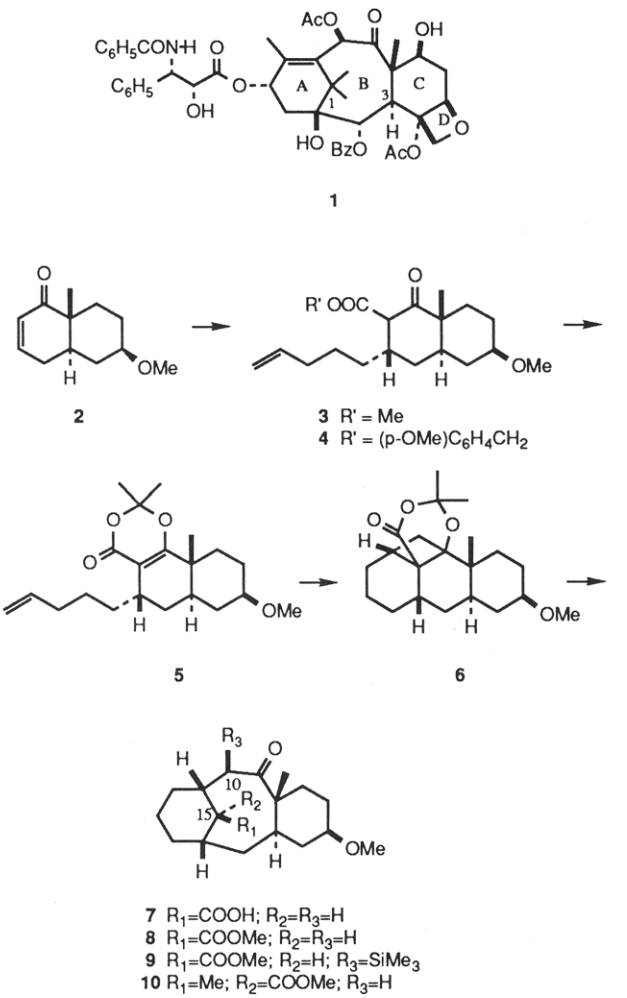


Figure 1. ORTEP plot for the X-ray structure of α-silyl ketone **9**.

Scheme I



followed by treatment with an excess of trimethylsilyl chloride, led to the exclusive formation of *the C-silylated ketone*, **9** (m.p. 144–145 °C), in 97% yield, the structure of which was confirmed by X-ray analysis (see Figure 1).[18]

We attribute the unprecedented C-silylation of **8** to the unusually congested environment at the center of the taxane nucleus. The dihedral angle formed by the C_{10}–$H_{(C-10)}$ bond and the C–O bond of the carbonyl in the conjugate base of **8** should be 0° or 180° for a planar ketone enolate. However, the value calculated by MM2[19] for that dihedral angle is 25°, suggesting the presence of substantial α-keto carbanion character in the conjugate base of **8**, which, as a consequence of the conformation of the eight-membered ring, cannot effectively resonate into the adjacent carbonyl. The unique geometry of the tricyclic taxane skeleton also precludes the well-known Brook rearrangement[20] of **9** to the corresponding silyl enol ether. Only unchanged starting material was recovered upon heating **9** to 150 °C for 18 h, suggesting that the activation barrier for the Brook rearrangement, which proceeds by a concerted four-centered mechanism,[20] was too high for the isomerization to be observed in taxane **9**, even at elevated temperatures.

However, the factors which prevent formation of a fully delocalized ketone enolate do not impede the introduction of the second substituent at C-15. Generation of the dianion of **9** with 2 equiv of lithium diisopropyl amide, followed by reaction with methyl iodide at −78 °C, and basic workup (to hydrolyze the carbon–silicon bond) led to the formation of **10** in 56% yield, in which the relative stereochemistry has been assigned as shown in Scheme I, based on approach of the methyl electrophile from the less hindered β-face of **9**.

The efficient construction of the taxane skeleton described herein attests to the utility of the intramolecular dioxenone photocycloaddition–fragmentation reaction for the construction of structurally complex carbocyclic ring systems. Studies directed toward the synthesis of the naturally occurring taxanes using this methodology are currently in progress in our laboratory.

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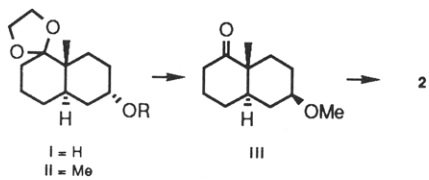
(12) Enone **2** was prepared from the known ketal i [Brown, E.; Ragault, M. *Tetrahedron Supp.* **1981**, *37*, 61] by (1) protection of the alcohol (KH, MeI, Et_2O) to give methyl ether ii, (2) deketalization (1 M aqueous HCl, THF) to give ketone iii, and (3) bromination (Br_2, AcOH) and dehydrobromination ($CaCO_3$, *N,N*-dimethylacetamide; Agami, C.; Fadlallah, M.; Levisalles, J. *Tetrahedron* **1981**, *37*, 909) in 74% overall yield from i.



(13) Mander, L.; Sethi, S. *Tetrahedron Lett.* **1983**, 5425. Henegar, K.; Winkler, J. *Tetrahedron Lett.* **1987**, 1051.

(14) The stereochemical outcome of the intramolecular dioxenone photocycloaddition of **5** differs strikingly from our earlier results in this area (ref 8a and 8b), in which the photoproducts were exclusively trans-fused. The factors which lead to this dramatic change in stereoselectivity are currently under investigation in our laboratory, and our results will be reported in a separate publication.

(15) All X-ray data were collected on Rigaku AFC5R diffractometer. Photoadduct **6** crystallized in the monoclinic $P21/n$ space group. The unit cell parameters were determined to be a = 9.426 (3) Å, b = 12.293 (3) Å, c = 16.979 (3) Å, and β = 98.08 (2)°; R = 0.063, R_w = 0.076.

(16) Keto ester **8** could be obtained as a single diastereomer by reaction of the mixture of **8** and its C-15 epimer with 2 N aqueous KOH in methanol, followed by treatment of the resulting **7** with ethereal diazomethane (see supplementary material).

(17) Keto ester **8** crystallized in the monoclinic Pc space group. The unit cell parameters were determined to be a = 10.927 (2) Å, b = 7.001 (2) Å, c = 11.598 (3) Å, and β = 91.27 (2)°; R = 0.049, R_w = 0.060.

(18) The α-silyl ketone **9** crystallized in the monoclinic $P21/n$ space group. The unit cell parameters were determined to be a = 10.022 (6) Å, b = 18.44 (1) Å, c = 12.139 (8) Å, and β = 96.98 (5)°; R = 0.058, R_w = 0.067.

(19) Calculated using PCMODEL, 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.

(20) Brook, A. G.; McRae, P. M.; Limburg, W. W. *J. Am. Chem. Soc.* **1967**, *89*, 5493. Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

(CA40250, and GM 07183 for a training grant to C.L.M.), the Alfred P. Sloan Foundation, American Cyanamid, Merck, Sharp and Dohme, and Glaxo. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599). P.J.S. would like to acknowlege financial support from the Robert A. Welch Foundation.

Supplementary Material Available: Experimental procedures and spectral data for ii, iii (footnote 11), and 2–10 (8 pages). Ordering information is given on any current masthead page.

Solvolytic Cyclization of 4,15-Anhydroverrucarol. A Facile Trichothecene–10,13-Cyclotrichothecene Rearrangement

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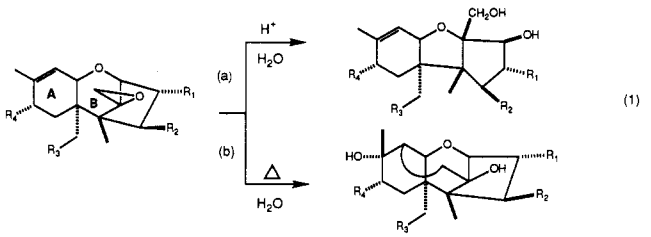
Summary: The conformation of the trichothecene ring system has been altered appreciably by introduction of an oxygen bridge between C4 and C15, which results in the C9,C10 double bond participating in the spontaneous solvolysis of the spiro epoxide group.

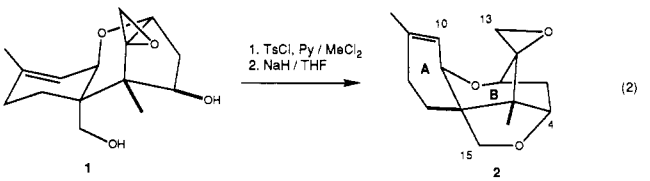
Sir: The trichothecene complex of antibiotics has attracted attention in recent years, principally due to their role as mycotoxins.[1] These sesquiterpenes exhibit a broad range of biological activity,[2] in addition to undergoing a variety of interesting chemical transformations.[3] Although the 12,13-epoxide group is very unreactive toward external nucleophiles,[4] this spiro epoxide is subject to two types of intramolecular nucleophilic ring-opening reactions, involving (1) participation by O_1 of the B-ring and (2) participation of the 9,10-double bond in the A-ring (eq 1a and 1b, respectively).[5] The former rearrangement leads to the



(1)

biologically inactive apotrichothecenes and occurs under acid conditions.[6] Rearrangement to the 10,13-cyclotrichothecenes (eq 1b), which occurs under neutral conditions, is far less commonly observed.[6,7] Herein, we report kinetic data for a 10,13-cyclotrichothecene rearrangement (eq 1b) that reveal that this reaction takes place via a solvolytic (or S_CN)[8] pathway, which to our knowledge is unprecedented for a methylene epoxide, though it does occur with suitably activated epoxides (e.g., *p*-methoxystyrene epoxide).[9]

Because the 10,13-cyclotrichothecene rearrangement requires that the 9,10 double bond become proximate to C-13, the course of events for the rearrangement should be highly dependent on the conformational bias of the tetrahydropyran ring (ring B), i.e., C-10 must come within bonding distance of C-13, which occurs only when ring B goes into a boat form. We have synthesized a bridged ether (**2**), whose conformational mobility differs markedly from normal trichothecenes, with the idea that this compound will differ significantly in its chemical behavior from normal trichothecenes. The 4,15-cyclic ether **2** was prepared in overall 40% yield (eq 2) from verrucarol (**1**), a trichothecene available from the hydrolysis of macrocyclic trichothecenes.[10] Ether **2** can readily assume the B-ring boat conformation and thus should readily undergo the 10,13-cyclotrichothecene rearrangement.



(2)

Molecular mechanics calculations MM2 (Macro Model System 1.5, W. C. Still, Columbia University) indicate that for verrucarol (**1**), the chair form of the B-ring is more stable by ca. 6 kcal/mol over that of the boat form. Somewhat surprisingly, these same calculations show that the boat form of the 4,15-cyclic ether **2** is more stable than the chair form by ca. 2 kcal/mol. This dramatic change in equilibrium appears to be due, in part, to the loss of nonbonding interactions between the C-15 group and the underside of the B/C-rings when C-15 is locked to C-4 by the oxygen bridge. This shift in equilibrium to favor the boat form of the B-ring is demonstrated by the reactivity of **2**. For example, care must be taken in the isolation of **2** since it reacts readily with water *under neutral or basic* conditions to give the 10,13-cyclotrichothecene **3a**, whose

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(1) *Developments in Food Science: Trichothecenes: Chemical, Biological, and Toxicological Aspects*; Ueno, Y., Ed.; Elsevier: New York, 1983; Vol. 4.
(2) (a) Bamburg, J. R. *Prog. Mol. Subcell. Biol.* **1983**, *8*, 41. (b) Snyder, A. P. *J. Food Protect.* **1986**, *49*, 544. (c) *Trichothecene Mycotoxicosis: Pathophysicological Effects*; Beasley, V. R., Ed.; CRC Press: Boca Raton, FL, 1988; Vol. I and II.
(3) Grove, J. F. *Nat. Prod. Rep.* **1988**, 187.
(4) Roush, W. R.; Russo-Rodriguez, S. J. *J. Org. Chem.* **1985**, *50*, 5465.
(5) Grove, M. D.; Burmeister, H. R.; Taylor, S. L.; Weisleder, D.; Plattner, R. D. *J. Agric. Food Chem.* **1984**, *32*, 541.
(6) Grove, J. F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 647.
(7) Gutzwiller, J.; Mauli, R. M.; Sigg, H. P.; Tamm, C. *Helv. Chim. Acta* **1964**, *47*, 2234.
(8) Stork, G.; Schoofs, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 5081.
(9) Ukachukwu, V. C.; Whalen, D. L. *Tetrahedron Lett.* **1988**, *29*, 293, and references therein.
(10) Jarvis, B. B.; Yatawara, C. S.; Greene, S. L.; Vrudhula, V. M. *Appl. Environ. Microbiol.* **1984**, *48*, 673.

0022-3263/89/1954-4493$01.50/0