Serendipitous Synthesis of a Cyclopropane-Containing Taxol Analog via Anchimeric Participation of an Unactivated Angular Methyl Group

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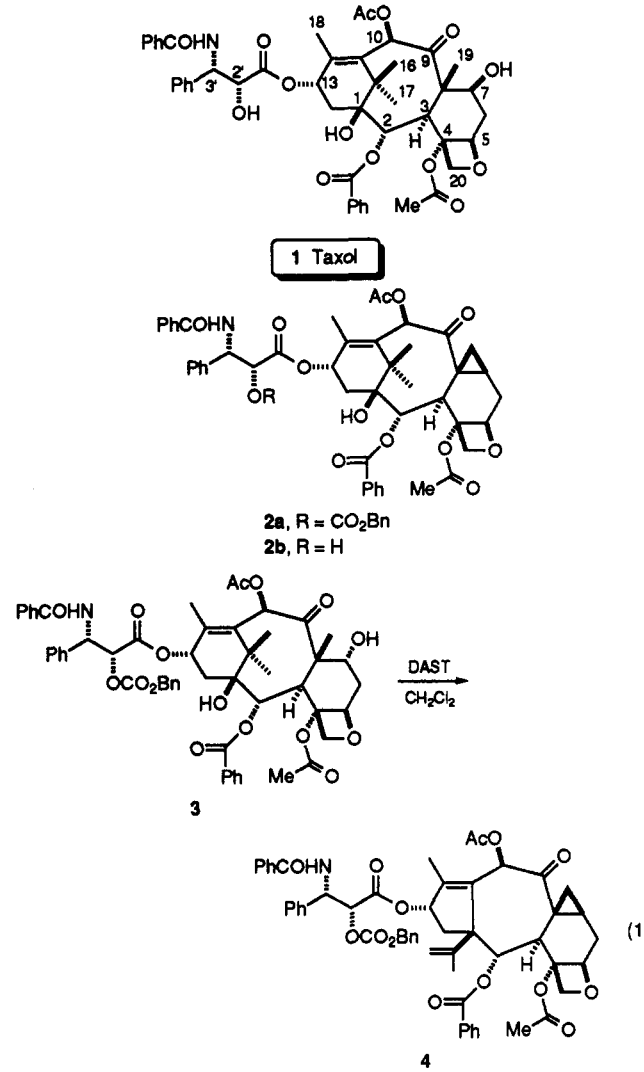
Summary: Treatment of a 7-*epi* taxol derivative with DAST in dichloromethane led to an unexpected reaction involving participation of the C-19 methyl group and clean formation of a cyclopropane ring.

The anticancer drug taxol, 1, is showing excellent clinical activity,[1] and this observation has recently sparked further investigations in the chemistry of this exciting diterpenoid,[2] aimed at a more complete definition of the structure–activity relationship (SAR) in this area. In connection with our own studies on the chemistry of taxol,[3] we have focused our attention, *inter alia*, on modifications at C-7. What little is known about the SAR at this position suggests that the hydroxyl group does not play an essential role in target recognition. In an attempt to synthesize new C-7 taxol analogs, we treated 7-*epi* taxol[4] derivative 3 with DAST (eq 1, Scheme I).[5]

A single product was isolated typically in 80–90% yield. The mass spectrum indicated the loss of 2 equiv of water. Contraction of ring A, as previously reported by Kingston,[3] was evident upon inspection of the ^{1}H-NMR spectrum. This failed to show any further olefinic proton, but particularly striking was the loss of the signal due to the C_{19} methyl group. This was apparently replaced by an aliphatic methylene group. Standard connectivity analysis by COSY and proton–carbon correlation indicated that the structure contained a cyclopropane ring,[6] and all our data are consistent with 4 as the reaction product.

Rearrangement reactions are sometimes observed in DAST fluorinations, as the hydroxyl group is strongly activated and the products can be rationalized as arising from carbonium ion intermediates. Thus, dehydration and/or 1,2-shifts,[7] ether formation,[8] allylic or homoallylic rearrangements,[9] Friedel–Crafts alkylation,[10] and norbornyl cation rearrangements[11] have been observed.

Scheme I



From these precedents, we are led to propose that the formation of the cyclopropane ring occurs (Scheme II) by activation of the C-7 hydroxyl group, with backside displacement by the angular methyl group to afford, *via* protonated cyclopropane intermediate 6,[12] the observed

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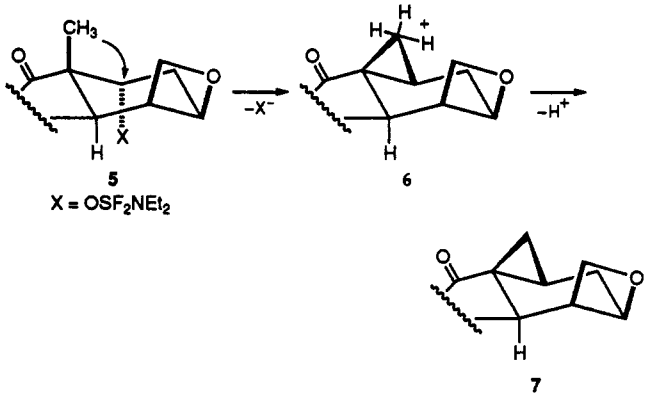
(2) Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1.
(3) Preceding contributions: Farina, V.; Huang S. *Tetrahedron Lett.* **1992**, *33*, 3979. Chen, S. H.; Combs, C. M.; Hill, S. E.; Farina, V.; Doyle, T. W. *Tetrahedron Lett.* **1992**, *33*, 7679.
(4) Huang, C. H. O.; Kingston, D. G. I.; Magri, N. F.; Samaranayake, G.; Boettner, F. E. *J. Nat. Prod.* **1986**, *49*, 665.
(5) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(6) Especially diagnostic were the values of the one-bond C–H coupling constants for 4: C_{19} (δ 22.4) had J_{C-H} = 163.0 Hz and C_7 (δ 30.3) had J_{C-H} = 163.2 Hz. These values are typical for cyclopropanes. See: Breitmeier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: New York, 1987.
(7) (a) Biollaz, M.; Kalvoda, J. *Helv. Chim. Acta* **1977**, *60*, 2703. (b) Green, M. J.; Shue, H. J.; Tanabe, M.; Yasuda, D. M.; McPhail, A. T.; Onan, K. D. *J. Chem. Soc., Chem. Commun.* **1977**, 611. (c) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090. (d) Rozen, S.; Faust, Y.; Ben-Yakov, H. *Tetrahedron Lett.* **1979**, *20*, 1823. (e) Street, I. P.; Withers, S. G. *Can. J. Chem.* **1986**, *64*, 1400. (f) El-Laghdach, A.; Echarri, R.; Matheu, M. I.; Barrena, M. I.; Castillon, S.; Garcia, J. *J. Org. Chem.* **1991**, *56*, 4556. (g) Pankiewicz, K. W.; Krzeminski, J.; Ciszewski, L. A.; Ren, W. Y.; Watanabe, K. A. *J. Org. Chem.* **1992**, *57*, 553.
(8) (a) Johnson, A. L. *J. Org. Chem.* **1982**, *47*, 5220. (b) Cai, S.; Hakomori, S.; Toyokuni, T. *J. Org. Chem.* **1992**, *57*, 3431.
(9) (a) Kobayashi, T.; Maeda, M.; Komatsu, H.; Kojima, M. *Chem. Pharm. Bull.* **1982**, *30*, 3082. (b) Bannai, K.; Toru, T.; Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Hazato, A.; Kurozumi, S. *Tetrahedron* **1983**, *39*, 3807.
(10) Napolitano, E.; Fiaschi, R.; Hanson, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1330.
(11) MacLeod, A. M.; Herbert, R.; Hoogsteen, K. *J. Chem. Soc., Chem. Commun.* **1990**, 100. For an excellent review on the use of DAST, including a more complete list of side reactions, see: Hudlicky, M. *Org. React.* **1988**, *35*, 513.
(12) For a recent report on corner- vs edge-protonated cyclopropanes, see: Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1990**, *55*, 4137 and references cited therein.

0022-3263/93/1958-4520$04.00/0

Scheme II



product. Intermediacy of a carbonium ion at C-7 is also possible, although in this case one would expect a more complex mixture.[13] The occurrence of a carbene was also considered, but it is very unlikely given the spectrum of reactivity observed with DAST. Final clarification must await further studies.

The present reaction has well-studied *enzymatic* counterparts in the production of cycloartenol from squalene,[14] and in the biosynthesis of cyclopropanated sesquiterpenes.[15] The formation of small amounts of cyclopropanes from the decomposition of aliphatic diazonium salts is usually explained, in analogy with our rationale, by invoking corner-protonated cyclopropanes as intermediates.[16] We believe several factors may contribute to the unprecedented success of this cyclopropane formation: (1) S_N2 reaction by fluoride in **5** is severely hindered by the C_{19} methyl group. (2) Such a methyl group is almost exactly antiperiplanar to the departing leaving group at C_7; i.e., the geometry is ideal for C_{19} participation. (3) Participation of a vicinal methyl group usually manifests itself in a 1,2 Wagner–Meerwein shift. It is likely that the shift is initiated but cannot be completed because cleavage of the C_8–C_{19} bond would place a positive charge at C_8, α to the C_9 carbonyl.[17] This reaction is therefore unlikely to be general or easy to duplicate in a simpler system.[18]

In connection with our taxol SAR studies, we were interested in avoiding A-ring contraction, which usually leads to loss of biological activity.[19] When we carried out the DAST reaction under controlled conditions (only 2–4 equiv of DAST at rt and careful HPLC monitoring of the reaction) a second cyclopropane-containing product, **2a**, was isolated (by preparative HPLC) in modest yield. Catalytic hydrogenation then gave **2b**, which was shown to be almost as potent as taxol in a number of biological assays.[20] This implies that modifications in the C_7/C_{19} region do not drastically affect binding of taxol to its microtubule binding site. In addition, the serendipitous preparation of **2a** offers an unexpected handle for further manipulation at the difficult position 19 of the taxol skeleton.

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Supplementary Material Available: Experimental details and ^1H NMR spectra of **2a** and **2b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) DAST treatment on derivatives bearing the 7β configuration indeed led to more complex mixtures (Chen, S. H. Unpublished observations).

(14) Clayton, R. B. In *Aspects of Terpenoid Chemistry and Biochemistry*; Goodwin, T. W., Ed.; Academic Press: New York, 1971; p 1.

(15) Cane, D. E.; Sohng, J. K.; Williard, P. G. *J. Org. Chem.* **1992**, *57*, 844.

(16) Jurewicz, A. T.; Friedman, L. *J. Am. Chem. Soc.* **1967**, *89*, 149 and references cited therein.

(17) A carbonyl group retards a-carbonium ion formation by a factor of 10^7–10^8; see: (a) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938. (b) Creary, X. *J. Am. Chem. Soc.* **1981**, *103*, 2463. (c) Takeuchi, K.; Yoshida, M.; Ohga, Y.; Tsugeno, A.; Kitagawa, T. *J. Org. Chem.* **1990**, *55*, 6063.

(18) We have been unable to observe cyclopropane formation in a number of conformationally constrained model systems. Full details will appear in due course.

(19) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114.

(20) For example, the *in vitro* IC_{50} in a human colon cancer cell line (HCT116) for **2b** was 0.008 mM (taxol 0.004 mM). Further details will be published separately. We thank Dr. C. Fairchild for this determination.