present work measures a value closer to a kinetic acidity than a thermodynamic pK_a, it is surprising that acetaldehyde might be in the acidity range of phenylacetone. However, there is increasing evidence[8,11] that relative C–H acidity rankings determined with classical bases do not hold for "naked fluoride". As seen in the present work, this base can be much stronger than might be expected.

Acknowledgment. We are grateful to Dr. J.-P. Senet for useful discussions and contributions. We also thank SNPE of France for the funds used to perform this research.

(11) Note ease of deprotonating $C_6H_5C{\equiv}CH$ (pK_a 28.8 vs 26.5 for acetone[10]) with F^- (Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 805).

Stereoselective Construction of the Taxinine AB System through a Novel Tandem Aldol–Payne Rearrangement Annulation

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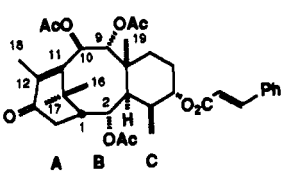
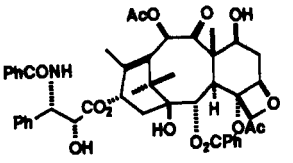
Received November 13, 1989

Summary: The construction of the fully functionalized AB portion of taxinine through a series of stereoselective operations on the eight-membered ring including annulation of the A ring through a novel tandem aldolization–Payne rearrangement process is described.

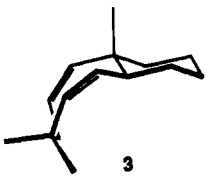
Sir: One view of the synthesis of the taxane diterpenes[1] (e.g. taxinine,[2] **1**, and taxol,[3] **2**) is that it should provide an exercise in the stereocontrolled manipulation of the eight-membered ring. Our A-ring annulation strategy for addressing this challenge has relied on two notions: (1) that the requisite bicyclo[6.4.0] BC intermediates possessing trans ring fusion stereochemistry and (at least) C-9–C-10 unsaturation assume conformations[4] (**3**) appropriate for α stereocontrol at relevant sites; and (2) that the taxane skeleton will tolerate the reversible relocation of C-11–C-12 unsaturation (or its structurally close relative) to C-10–C-11, an idea well founded in Lythgoe's seminal structural work.[5] Herein we report the selective introduction of oxygenation at three taxane B-ring sites culminating in the construction of the taxinine AB substructure (**4**) through a single-operation A-ring annulation process, which triggers elaboration of the B ring.



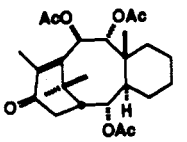
1



2



3



4

Photoproduct **5**[6] (Scheme I) was converted through Rubottom type oxidation[7] to silyloxy ketone **6**, and thence through our five-step fragmentation protocol[6] to enone **7**. Preparation of the dilithio dianion derived from **7** and its alkylation[8] produced **8** with all AB carbons in place and with correct C-1 α stereochemistry. Dehydration of the secondary formamide function in **8** to give a keto isocyanide and its dissolving metal reduction[6] installed concomitantly in **9** the angular methyl substituent and the C-2 α hydroxyl. The facility with which isocyanides suffer reductive cleavage by metal–liquid ammonia reagents is crucial to maintenance of the allylic silyloxy group in this step. Both the reduction of the C-2 carbonyl and the alkylation which precedes it are completely stereoselective within the limits of conventional FT NMR procedures.[9] Further conversion of **9** into **10** seemed to require the initial three-step sequence illustrated; preliminary attempts to hydrolyze directly side chain enol ether containing substances led to their decomposition while intermediate acid treatment closed the methyl acetal ring and provided a useful hydrolytic substrate. Although one-step deprotection of intermediates like **9** should be possible, the relative acid stability of their derived cyclic acetals and the internal protection thereby afforded the C-2 hydroxyl have important implications for the elaboration of taxinine C-ring functionality at the corresponding stage of its synthesis.

Pivotal intermediate **10** could be converted to taxane skeleta of increasing complexity (Scheme II). Its hydro-

(1) For references to taxane structural and synthesis studies through early 1987, see: Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275. For more recent taxane synthesis reports, see: Benchick-le-Hocine, M.; Do Khac, D.; Fetizon, M.; Hanna, I.; Zeghdoudi, R. *Synth. Commun.* **1987**, *17*, 913. Berkowitz, W. F.; Perumattam, J.; Amarasekara, A. *J. Org. Chem.* **1987**, *52*, 1119. Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1540. Kraus, G. A.; Thomas, P. J.; Hon, Y.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 1849. Lin, J.; Nikaido, M. M.; Clark, G. *J. Org. Chem.* **1987**, *52*, 3745. Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4143. Shea, K. J.; Haffner, C. D. *Tetrahedron Lett.* **1988**, *29*, 1367. Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558. Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4711. Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4722. Winkler, J. D.; Lee, C.-S.; Rubo, L.; Muller, C. L.; Squattrito, P. J. *J. Org. Chem.* **1989**, *54*, 4491. Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277.

(2) Dukes, M.; Eyre, D. H.; Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. C* **1967**, 448.

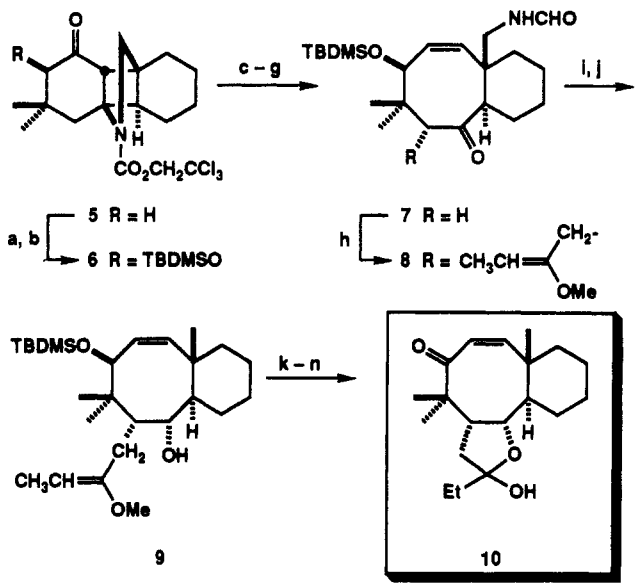
(3) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(4) Our initial conclusions regarding the preferred conformation for this hydrocarbon model as reported in an earlier publication (Swindell, C. S.; deSolms, S. J. *Tetrahedron Lett.* **1984**, *25*, 3801.) were led astray by a faulty MM2 calculation. We thank Professor R. Alder, University of Bristol, for pointing this out to us. Since that time, both we and Wender (Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451) have confirmed that conformations like **3** apply.

(5) Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. C* **1966**, 1933.

0022-3263/90/1955-0003$02.50/0

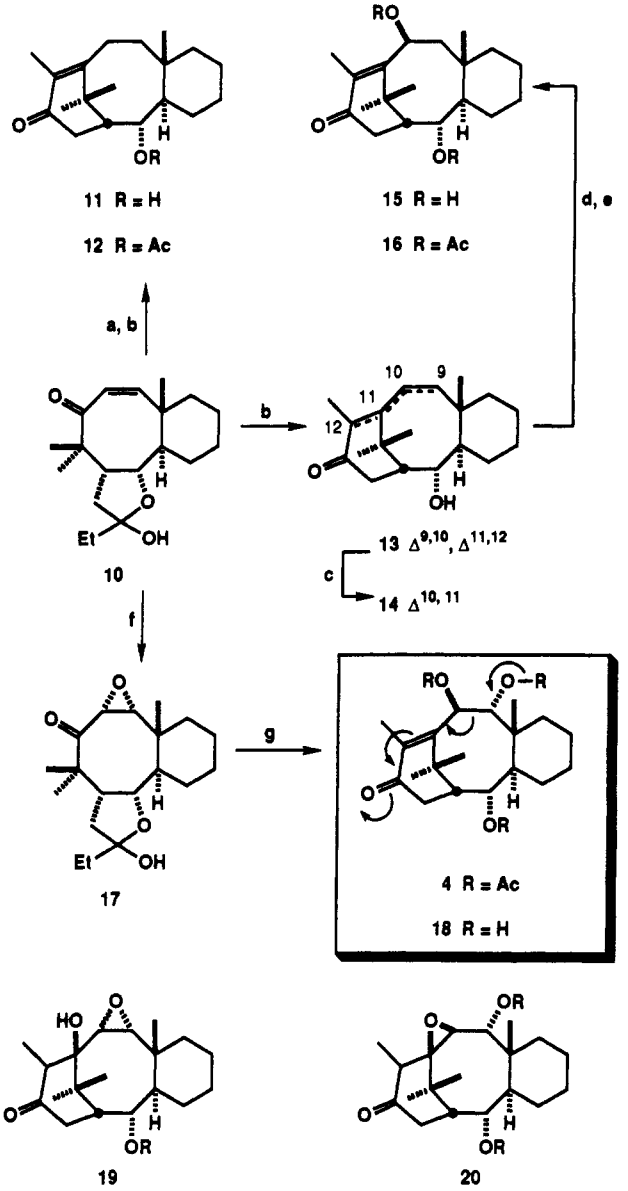
Scheme I[a]



[a] (a) TBDMSOTf, Et_3N; (b) MCPBA (90:10, 79% for two steps); (c) K-Selectride (94:6; 87%); (d) MsCl, Et_3N; (e) Zn; (f) AcOH, H_2O; (g) AcOCHO, py (61% from alcohol); (h) 2 LDA, then $CH_3CH{=}C(OMe)CH_2I$ (84%); (i) MsCl, py; (j) Na, liquid NH_3, NH_4Cl (66% for two steps); (k) Bu_4NF (94%); (l) AcOH, H_2O; (m) HCl, H_2O (81% for two steps); (n) MnO_2 (76%).

genation followed by base treatment to provide **11** confirmed that the taxane skeleton could be completed through aldol chemistry.[10] Similarly, **10** produced **13**,[11] which afforded a model for the examination of the A-ring enone deconjugation–reconjugation process. Dissolving metal reduction of **13** with kinetically controlled protonation of the dienolate[12] so produced gave β,γ-enone **14**. Its epoxidation and subsequent base treatment created C-2, C-10 functionalized **15**. Stereochemical control in the epoxidation step derives both from cyclooctene olefin α face shielding in the boat–chair conformation of **14**, and avoidance of inside–outside AB stereochemistry characteristic of the alternative epoxide. Finally, nucleophilic epoxidation of **10**, a transformation less stereoselective than those prior at C-1 and C-2, enabled a tandem aldolization–Payne rearrangement–epoxy ketone isomerization (**17** → **19** → **20** → **4**) to assemble in one operation the taxinine AB substructure. The reduction in the yield of **4** observed when the latter step was carried out on the mixture of epoxide diastereomers is consistent with the

Scheme II[a]



[a] (a) H_2, Pd–C (82%); (b) KO*t*-Bu (85–90%); (c) Li, liquid NH_3, NH_4Cl (61%); (d) MCPBA (62%); (e) DBU (47%); (f) *t*-BuOOH, Triton B (80:20; 74%); (g) DBU, LiCl, Ac_2O, THF, 20–40 °C (70%).

derivation of **4** from diastereomer **17** only. Since subjection of **17** to conventional basic aqueous Payne rearrangement conditions[13] (no acylating agent) led to its destruction without accumulation of **18**, it seems likely that the vinylogous retro-aldol cleavage at C-9–C-10 known to occur in such structures[14] intervened under these conditions. The nonaqueous Payne rearrangement[15] is compatible with acylative C-9 hydroxyl capture, thus circumventing this process. Substances **4**, **12**, and **16** exhibited ^1H NMR phenomena for methyl groups and H-2, H-9, and H-10, as appropriate, commensurate with the spectral behavior of taxinine.[16] In addition, the NOE relationships involving

(6) Swindell, C. S.; Patel, B. P.; deSolms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 2346.

(7) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. Corey, E. J.; Hidetsura, C.; Rücker, C.; Hua, D. M. *Tetrahedron Lett.* **1981**, *22*, 3455.

(8) The iodo enol ether A-ring progenitor was prepared as a mixture of *E* and *Z* isomers from α-ketobutyric acid by sequential esterification, ketalization, acid-catalyzed methanol elimination, and lithium aluminum hydride reduction. The allylic alcohol so prepared was further converted to the chloride by treatment with methyllithium, then tosyl chloride–lithium chloride. The chloride was stable to storage at −20 °C; it was converted to the unstable iodide by reaction with sodium iodide in acetone immediately prior to use.

(9) C-2 reduction of enones like **7** lacking a C-1 substituent proceeds with no stereoselectivity. Conformational anchoring of the lower B ring of the keto isocyanide derived from **8** by C-1 α substitution appears necessary for the anticipated stereoselectivity to be expressed.

(10) For a related bridgehead enone synthesis, see: House, H. O.; Sieloff, R. F.; Lee, T. V.; DeTar, M. B. *J. Org. Chem.* **1980**, *45*, 1800.

(11) For a related substance, see: Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.

(12) Schaub, R. E.; Weiss, M. J. *Chem. Ind.* **1961**, 2003. Dastur, K. P. *Tetrahedron Lett.* **1973**, 4333.

(13) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(14) Yamamoto, Y.; Uyeo, S.; Ueda, K. *Chem. Pharm. Bull. (Tokyo)* **1964**, *12*, 386. Uyeo, S.; Ueda, K.; Yamamoto, Y. *Yakugaku Zasshi* **1966**, *86*, 1172.

(15) Bulman Page, P. C.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1988**, 356.

(16) Woods, M. C.; Nakanishi, K.; Bhacca, N. S. *Tetrahedron* **1966**, *22*, 243.

Me-16 and H-2 (4, 12, and 16), Me-16 and H-9 (4), and Me-18 and H-10 (4 and 16) are fully consistent with those detected by Nakanishi.[17] The characteristic A-ring enone UV spectral λ_{max} (unusually high) and ϵ (unusually low) values for 4, 11, and 15 are compatible with available data[18] as well.

In conclusion, we note that the sequence leading to 4 proceeds with an economy of steps and functional group protection and concludes with a new annulation process, one whose generality we intend to explore. A conceptually similar tandem approach to the AB system of the more medicinally significant taxol might offer hope for its preparation with reasonable brevity.

Acknowledgment. Support by PHS Grant no. CA 41349 awarded by the National Cancer Institute, DHHS is gratefully acknowledged. The acquisition of a GC/MS system was made possible by grants from the Camille and Henry Dreyfus Foundation and the PQ Corporation, and of a high-field NMR spectrometer by grants from the W. M. Keck Foundation and Merck & Co., Inc.

Supplementary Material Available: Procedure for the transformation of 17 into 4, complete spectral and combustion analytical data for 4, 11, and 15, a chart of characteristic ^{1}H NMR chemical shifts and coupling constants for taxinine, 4, 12, and 16, and copies of ^{1}H NMR spectra and NOE difference spectra for 4, 12, and 16 (11 pages). Ordering information is given on any current masthead page.

(17) Woods, M. C.; Chiang, H.-C.; Nakadaira, Y.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 522.

(18) For appropriate reference data, see that on compound VII (R = H) in: Kukes, M.; Eyre, D. H.; Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. C* **1967**, 448.

Aureolic Acid Antibiotics: A Simple Method for 2-Deoxy-β-glycosidation

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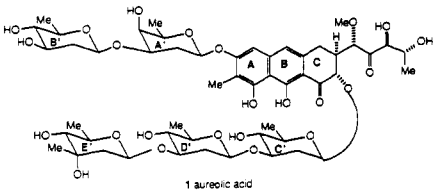
Received November 13, 1989

Summary: The phenylbis(phenylthio)sulfonium salt 8 electrophilically activates glycals for glycosyl transfer to form, in most cases, β-glycosides.

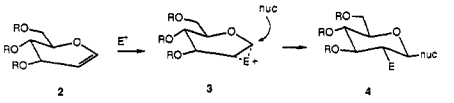
Sir: A problem of current interest to the organic chemistry community is the synthesis of 2-deoxy-β-glycosides, which are constituents of antibiotics such as the calicheamicins,[1] esperamicins,[2] benzanthrins,[3] and the aureolic acids 1 including its relatives, the chromomycins and the olivomycins, all of which are highly toxic antibiotics that also have antitumor properties.[4,5]



The specific requirements for an aureolic acid synthesis are that the procedure(s) work with phenols and acyloins under conditions where the acid- and base-sensitive aglycons can survive.[6,7] Of the 13 different methods recently reported,[8] we favored schemes where glycals 2 were ste-

Scheme I

(a) mechanism of electrophilic initiation of glycosyl transfer



(b) formation of E^+ in Ogawa's method

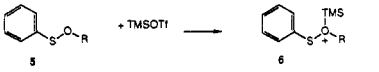


Table I. Glycosyl Transfers to Methanol

entry	glycal	reagent	β/α[a]	yield, %	$[\alpha]^{25}_D$ ($CHCl_3$) for β, deg
a	**9a**	8	3.7/1	83	
b	**9a**	7	1.3/1	75	
c	**9b**	8	2/1	62[b]	+5.4
d	**9c**	8	2/1	80	
e	**9d**	8	2/1	76[c]	-48.2
f	**9e**	8	2.7/1	86[d]	-31.2[e]
g	**9f**	8	1/10	80	
h	**9g**	8	12/1	92	

[a] Ratios determined by separation and isolation except for entries a-d. [b] In addition 2α-(phenylthio)-1α-isomer was obtained in 10% yield. [c] During workup, the 4,6-benzylidene of the glucal was partially cleaved. [d] During workup, the 4,6-isopropylidene of the glucal was completely cleaved. [e] Optical rotation for the 4,6-dihydroxyglucoside.

(1) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198.

(2) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci.* **1989**, *86*, 2.

(3) Rasmussen, R. R.; Nuss, M. E.; Scherr, M. H.; Mueller, S. I.; McAlpine, J. B.; Mitscher, L. A. *J. Antibiot.* **1986**, *39*, 1515.

(4) (a) A complete discussion of the isolation, structure proof, and biological activity of these materials to 1979, requiring several revisions in structure and stereochemistry: Remers, W. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol. 1, Ch. 3. (b) An update on isolations: Skarbeck, J. D.; Speedie, M. K. In "Antitumor Antibiotics of the Aureolic Acid Group Chromomycin A_3, Mithramycin A, and Olivomycin A"; Aszalos, A., Ed.; *Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*; CRC Press: New York, 1981; Ch. 5. (c) Most recent isolations: Yoshimura, Y.; Koenuma, M.; Matsumoto, K.; Tori, K.; Terui, Y. *J. Antibiot.* **1988**, *41*, 53. (d) Definitive saccharide assignments: Thiem, J.; Meyer, B. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1331. Thiem, J.; Meyer, B. *Tetrahedron* **1981**, *37*, 551.

(5) A review of the synthetic chemistry in the field through 1987: Franck, R. W.; Weinreb, S. M. In *Studies in Natural Product Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1989; pp 173-208.

(6) Recent papers: (a) Dodd, J. H.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811-1812. (b) Franck, R. W.; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455-2457. (c) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575-7577. (d) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (e) Thiem, J.; Schottmer, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 555-557. Reviews: (f) Reference 5 (g) Thiem, J. *Topics in Current Chemistry, Carbohydrate Chemistry*; Springer Verlag: New York, 1988.

(7) In an unpublished thesis from Professor Thiem's lab, there is described the Koenigs-Knorr coupling of a 2-deoxy-2α-bromosaccharide with an olivin derivative and a 21% yield of β-glycoside product was obtained. Schneider, G. *Untersuchung uber den Aufbau Modifizierter Aureolsauren*, dissertation der Universitat Hamburg, 1985.

0022-3263/90/1955-0005$02.50/0