Studies toward a Synthesis of Epothilone A: Use of Hydropyran Templates for the Management of Acyclic Stereochemical Relationships

Dongfang Meng,[†,‡] Erik J. Sorensen,[†] Peter Bertinato,[†] and Samuel J. Danishefsky*[,†,‡]

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021, and Department of Chemistry, Columbia University, Havemeyer Hall, New York, New York 10027

Received August 30, 1996

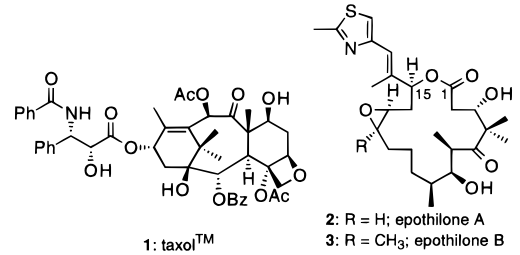
Taxol has been approved for chemotherapeutic clinical application against ovarian carcinomas. It is also undergoing extensive evaluation for other indications. While taxol is not a curative agent, it is already a useful chemotherapeutic resource.[1]

The best indications arising from tissue culture and *in vitro* experiments are that taxol functions by inhibition of cellular mitosis through binding to and stabilization of microtubule assemblies.[2] Presumably, this property is pertinent to the human patient.

Unfortunately, taxol is far from an ideal drug. Thus, difficulties with respect to formulation and susceptibility to multiple drug resistance (MDR) complicate its applicability.[3] At the present writing, no major improvements in drug performance have been realized from any substantially modified analogs of taxol or its close relative, taxotere.[4]

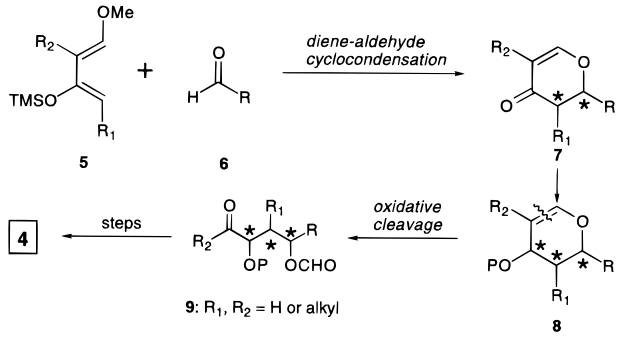
New agents that function by microtubule stabilization are clearly of great interest.[2] In this connection, there has already been considerable attention directed toward the bacterial-derived metabolites epothilone A (**2**) and B (**3**), which were first identified as antifungal cytotoxic agents by Höefle *et al.*[5a,b] and subsequently encountered by a group based at the Merck corporation.[6] The report of the Merck scientists on the epothilones indicated that they are powerful cytotoxic agents that seem to function through stabilization of microtubules by binding to taxol-binding domains. Given the possibilities that these agents themselves, or appropriately modified derivatives, might function as alternatives to taxol, attention from the standpoint of organic synthesis is warranted.

Augmenting the biological rationale for such a venture are the chemical incentives associated with several novel structural features of the epothilones. Thus, the presence of a thiazole moiety, as well as a *cis* epoxide and geminal dimethyl groups are among the issues to be addressed. Not the least intriguing feature is the array of three contiguous methylene groups that serves to insulate the two functional domains of the molecules. This achiral "spacer element" actually complicates prospects for continuous chirality transfer and seems to call for a strategy of merging two stereochemically committed substructures. Herein, we direct our attention to a synthesis of compound **4**, confident that, in principle, such a structure could be converted to the epothilones themselves, and to related screening candidates.



1: taxol™ **2**: R = H; epothilone A **3**: R = CH_3; epothilone B

The identification of compound **4** as a synthetic intermediate provided an opportunity to illustrate the power of hydropyran matrices in addressing problems associated with the control of stereochemistry in acyclic intermediates. Some years ago, we described the synthesis of dihydropyrones through what amounts to overall cyclocondensation of suitably active dienes and aldehydic heterodienophiles.[7]



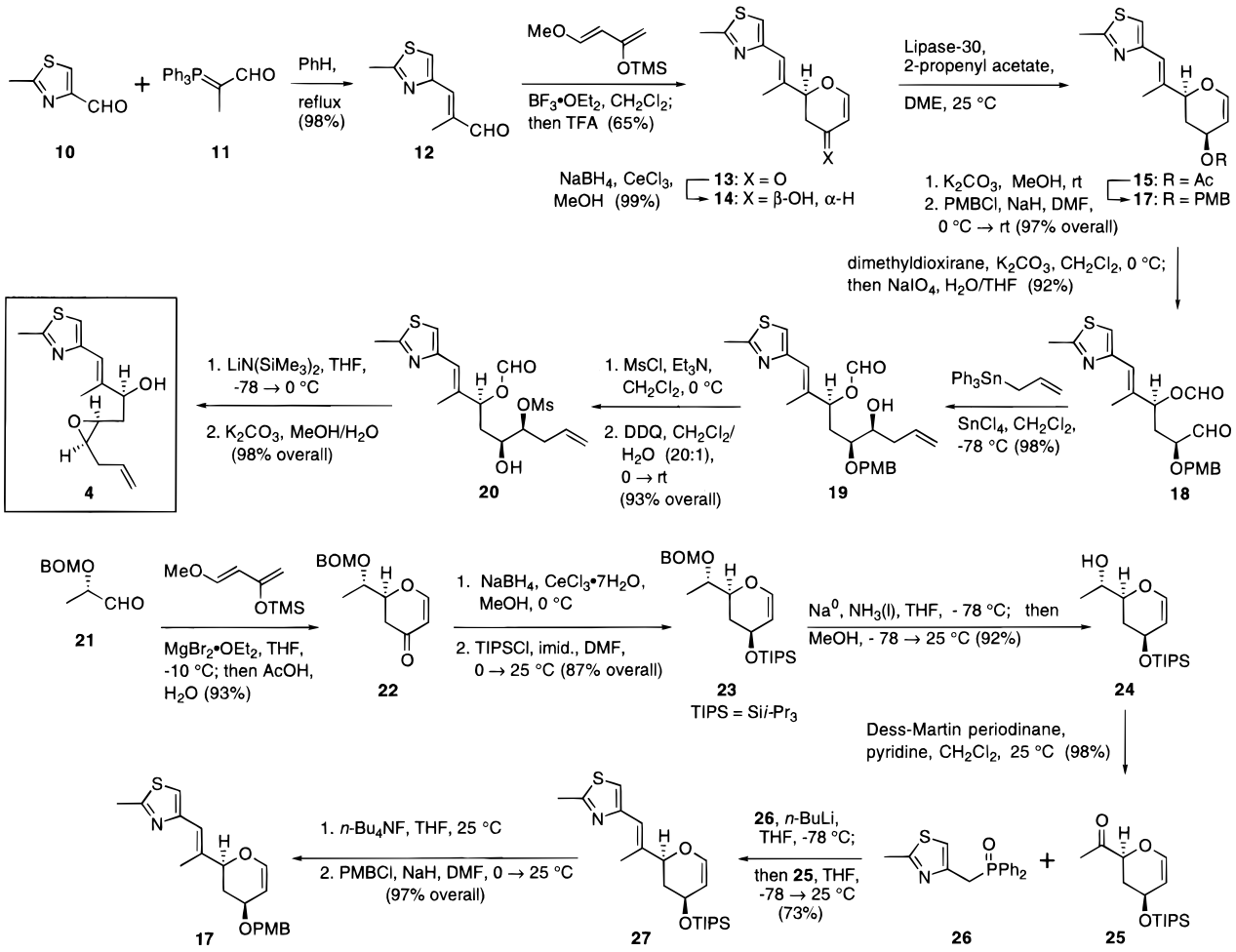
High margins of stereoselectivity can be realized in assembling such matrices (*cf.* **5** + **6** → **7**). Moreover, the hydropyran platforms service various stereoselective reactions (see formalism **7** → **8**). Furthermore, the products of these reactions are amenable to ring-opening schemes, resulting in the expression of acyclic fragments with defined stereochemical relationships (*cf.* **8** → **9**).[8]

We describe the application of two such routes for the synthesis of compound **4**. Route 1, which does not *per se* involve control over the issue of absolute configuration, commences with the known aldehyde **10**.[9] Homologation, as shown, provided enal **12**. Cyclocondensation of **12** with the known diene,[10] under BF_3 catalysis, led to racemic dihydropyrone **13**. Luche reduction[11] of **13** provided compound **14**. At this point we were well positioned to take advantage of our previously introduced lipase methodology for resolution of glycal derivatives through enzymatically mediated kinetic resolution.[12] Thus, carbinol **14** was treated with lipase 30 and isopropenyl acetate (following the prescriptions of Wong),[13] and

† Sloan-Kettering Institute for Cancer Research.
‡ Columbia University.

(1) Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M. *Taxane Anticancer Agents*; American Cancer Society: San Diego, 1995.
(2) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature (London)* **1979**, *277*, 665.
(3) Landino, L. M.; Macdonald, T. L. In *The Chemistry and Pharmacology of Taxol® and its Derivatives*; Farin, V., Ed.; Elsevier: New York, 1995; Chapter 7, p 301.
(4) Gueritte-Voegelein, F.; Guenard, D.; Dubois, J.; Wahl, A.; Marder, R.; Muller, R.; Lund, M.; Bricard, L.; Potier, P. In *Taxane Anticancer Agents*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; American Cancer Society: San Diego, 1995; Chapter 14, p 189.
(5) (a) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560. (b) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567.
(6) Bollag, D. M.; McQueney, P. A. Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.
(7) Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59.
(8) Danishefsky, S. J. *Chemtracts* **1989**, *2*, 273.
(9) (a) Shafiee, A.; Mazloumi, A.; Cohen, V. I. *J. Heterocycl. Chem.* **1979**, *16*, 1563. (b) Schafiee, A.; Shahocini, S. *J. Heterocycl. Chem.* **1989**, *26*, 1627.
(10) Danishefsky, S. J.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(11) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

S0022-3263(96)01673-8 CCC: $12.00



the reaction was stopped after *ca.* 48% conversion, providing acetate **15** in addition to the enantiomerically related free glycal **16**. Compound **15** was further advanced to the *p*-methoxybenzyl (PMB)-protected system **17**. At this juncture, reaction of **17** with dimethyldioxirane[14] generated an intermediate (presumably the corresponding glycal epoxide) that, upon treatment with sodium metaperiodate, gave rise to aldehyde formate **18**. Lewis acid-promoted allylation of **18** afforded carbinol **19** in which the formate ester had nicely survived. Unfortunately, **19** was accompanied by its *anti* stereoisomer (not shown here) (4:1). Although this 4:1 mixture of diastereomers was obtained in an excellent yield of 98%, it was not possible to obtain the desired stereoisomer **19** in pure form at this stage. Mesylation of the secondary alcohol, followed by deprotection (see **19** → **20**) and cyclization, as indicated, gave compound **4**, a substance that could be separated from the stereoisomeric *trans* epoxide.

Needless to say, in this synthesis, only *ca.* half of the dihydropyrone was secured through the process of kinetic resolution. While, in theory, several of our synthetic strategems contemplate the possible use of each enantiomer of **15** to reach epothilone itself, we sought to implement another route to allow for full enantiomeric convergence. The logic of this route is that the chirality of a "dummy" stereogenic center is communicated to the emerging pyran following previously established principles of tunable diastereoselection in the cyclocondensation reaction.[7,8] We proceeded as follows. Cyclocondensation of lactaldehyde derivative **21**[15] with the indicated diene, under ostensible chelation control, afforded **22**. The side chain ether could then be converted to the methyl ketone **25** as shown (see **22** → **23** → **24** → **25**). Finally, an Emmons condensation of **25** with the phosphine oxide **26**[16] as shown in Scheme 4 afforded compound **27** as a single geometrical isomer. A straightforward protecting group adjustment then afforded the previously encountered **17**. This route cogently illustrates the concept of stereochemical imprinting through a carbon center that eventually emerges in planar form after conferring enantioselection to subsequently derived stereocenters. The use of the dihydropyrone-based logic for securing the stereochemical elements of the epothilones, as well as the identification of a possible strategy for macrocyclization will be described in the paper that follows.

Acknowledgment. This work was supported by NIH Grant No. CA 28824. Postdoctoral Fellowships are gratefully acknowledged by E.J.S. (NSF, CHE-9504805) and P.B. (NIH, CA 62948).

Supporting Information Available: Experimental procedures and spectroscopic data for the compounds illustrated in the reactions (compounds **12**−**15**, **17**−**20**, **4**, and **22**−**27**) (9 pages).

JO961673W

(12) (a) Berkowitz, D. B.; Danishefsky, S. J. *Tetrahedron Lett.* **1991**, *32*, 5497. (b) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518.

(13) Hsu, S.-H.; Wu, S.-S.; Wang, Y.-F.; Wong., C.-H. *Tetrahedron Lett.* **1990**, *31*, 6403.

(14) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1381.

(15) Heathcock, C. H.; Young, S. D.; Hagen J. P.; Pirrung, M. C. White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.

(16) The known 2-methyl-4-chloromethylthiazole (see: Marzoni, G. *J. Heterocycl. Chem.* **1986**, *23*, 577) was transformed to **26** (*cf.* Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414.