

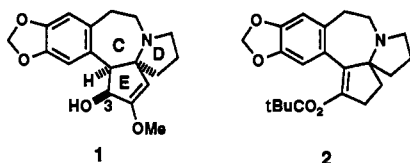
## A Cephalotaxine Synthesis Founded on a Mechanistically Interesting, Quasi-biomimetic Strategy

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Interest in the synthesis of cephalotaxine (**1**) and its C-3 hydroxyl esters has remained high ever since the isolation and structural analysis of these alkaloids in the 1960s.<sup>1</sup> Reasons for



this reside in the anticancer properties reported for several members of this family<sup>2</sup> and the unique, deceptively simple, structural features found in their pentacyclic skeleton. Cephalotaxine, the parent member of this alkaloid class, has been the target of previous synthetic efforts<sup>3</sup> which to date have yielded six total syntheses.<sup>4,5</sup> Our early preparative efforts in this area focused on a cephalotaxine synthetic strategy which employs SET-promoted photocyclization of an *N*-silylmethylallyl-iminium salt to construct the spirocyclic DE unit.<sup>6</sup> These studies demonstrated that the methodology could be used to prepare the potential cephalotaxine precursor **2**.<sup>6b</sup> However, in ensuing work, we observed an, at first, disappointing and, then, enlightening result which led to the design of the efficient and quasi-biomimetic cephalotaxine synthesis strategy described below.

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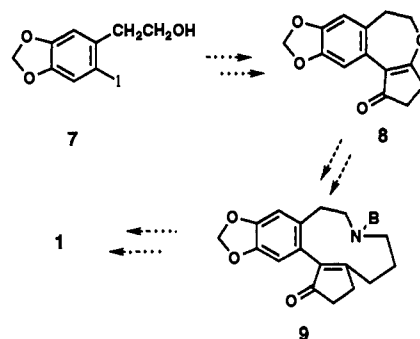
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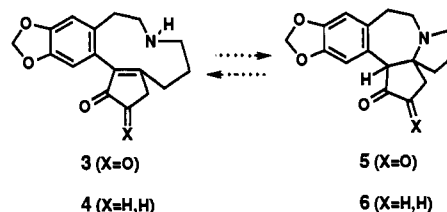
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### Scheme 1



This cephalotaxine synthetic design is based on a transannular cyclization reaction of the endione **3** to produce the pentacyclic dione **5**. The proposal that this process would be successful and that it would lead to significant simplification of the synthetic task derived from our observation that deacylation of the enol ester **2** (NaOMe, MeOH, 25 °C) gives the macrocyclic enone **4**, which is the predominant (*ca.* 10:1) isomer in a dynamic equilibrium with **6**. In contrast, desmethylcephalotaxinone **5**



(which actually exists in its  $\Delta^{3,4}$ -diosphenol form) does not appear to equilibrate to produce its ring-opened endione isomer **3**.<sup>7</sup> We believe that these phenomena are a consequence of thermodynamics and not kinetics and that the instability of **3** is caused by an unfavorable cyclopentendione dipole interaction which cannot be compensated by forming an antiaromatic five-membered ring diosphenol form. Since **5** has served as the penultimate intermediate in several cephalotaxine syntheses and since its potential precursor **3** appeared accessible by a short and uncomplicated route, we believed that a strategy based on the transannular cyclization process would be efficient. Finally, cephalotaxine pentacyclic ring formation in the conversion of **3**  $\rightarrow$  **5** would mimic the key ring-building step in the proposed biosynthesis of members of this alkaloid family.<sup>8</sup> These intriguing issues and proposals stimulated the effort described below which has culminated in a novel and efficient synthesis of cephalotaxine.

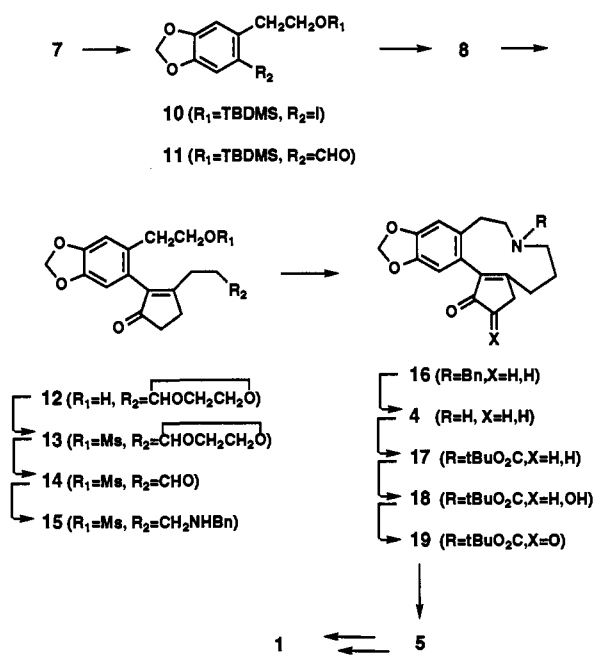
The general design (Scheme 1) emanating from the above reasoning employs the known<sup>5c</sup> iodopiperonyl ethanol derivative **7** as the starting point of the synthesis (Scheme 2). Conversion of **7** to tetracyclic enol ether **8** provides an intermediate in which the remaining aminopropylene D-ring fragment and E-ring enone functionality found in **9** can be installed by use of Grignard addition chemistry. Preparation of **8** takes advantage of the Kuwajima method<sup>9</sup> for 2-arylcyclopentan-1,3-dione synthesis. Accordingly, hydroxyl protection **7**  $\rightarrow$  **10** (*tert*-butyldimethylsilyl chloride (TBDMSCl), DIEA, DMF, 100%) followed by met-

(7) Fuchs (ref 5f) observed that the 11-hydroxy derivative of **5** undergoes partial eliminative ring opening in its conversion to its the  $\Delta^{1,2}$ -methyl enol ether.

(8) (a) The proposed (ref 8b) biosynthetic pathway involves transannular cyclization of a macrocyclic amino cyclohexadienone intermediate followed by E-ring contraction to produce cephalotaxine. (b) Parry, R. J.; Schwab, I. M. *J. Am. Chem. Soc.* **1975**, *97*, 2556. Parry, R. J.; Chang, M. N. T.; Schwab, J. M.; Foxman, B. M. *J. Am. Chem. Soc.* **1980**, *102*, 1099. Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K. *J. Org. Chem.* **1978**, *43*, 4465.

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Scheme 2



allation (*n*BuLi,  $-78^\circ\text{C}$ ) and formylation (DMF, 84%) gives the aldehyde **11**, which is transformed to **8** by sequential aldol condensation with 1,2-*bis*(trimethylsiloxy)cyclobutene ( $\text{BF}_3\cdot\text{Et}_2\text{O}$ , THF,  $-78^\circ\text{C}$ ) and acid-catalyzed pinacol rearrangement (TFA, MeOH, 90%). The final step is accompanied by fortuitous TBDMS deprotection and cyclic enol ether formation.

Installation of the three-carbon unit of the target is then carried out by use of Stork's<sup>10</sup> enone synthesis method involving addition to **8** of the Grignard derived from the ethylene glycol acetal of  $\beta$ -bromopropanal<sup>11</sup> to produce on workup with aqueous  $\text{NH}_4\text{Cl}$  the enone alcohol **12** (82%). Mesylation of the alcohol function **12**  $\rightarrow$  **13** ( $\text{MsCl}$ , TEA,  $\text{CH}_2\text{Cl}_2$ , 100%) followed by acetal hydrolysis **13**  $\rightarrow$  **14** (10% HCl, acetone, 92%), reductive amination **14**  $\rightarrow$  **15** ( $\text{BnNH}_2\text{-HCl}$ ,  $\text{NaCNBH}_3$ , NaOAc, THF), and cyclization (DIEA, MeCN,  $65^\circ\text{C}$ , 64% two steps) then yields the macrocyclic amino enone **16**. It is interesting to note that NMR analysis of the intermediate **16** shows that it does not exist to a detectable extent in its ring-closed, spirocyclic form. This is consistent with our observations on **4** and with those made by Fuchs<sup>12</sup> in model studies probing aspects of an early, unsuccessful cephalotaxine synthesis strategy.

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In order to shield the amine function in **16** from the ensuing oxidation chemistry and to demonstrate that the macrocyclic amino enone **4** can be prepared in a more efficient manner than originally described,<sup>6b</sup> this substance was debenzylated ( $\text{H}_2$ , Pd-C, *i*PrOH, 83%) and the resulting secondary amine **4** was converted to its tBOC derivative **17** ( $(\text{tBOC})_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , 100%). Among the various  $\alpha$ -oxidation procedures attempted, the Davis oxaziridine method<sup>13</sup> was found to be superior. Thus,  $\alpha'$ -enolate generation from **17** (LDA, THF,  $-78^\circ\text{C}$ ) followed by oxygenation with [(-)-camphor-10-ylsulfonyl]oxaziridine<sup>13</sup> yields (78%) the  $\alpha$ -hydroxy enone **18**.<sup>14</sup> The *N*-tBOC endione **19** is derived from **18** by Swern oxidation (DMSO, TFAA, TEA,  $\text{CH}_2\text{Cl}_2$ ,  $-78 \rightarrow 0^\circ\text{C}$ ). In the fashion proposed, *N*-deprotection of **19** (TMSOTf,  $\text{CH}_2\text{Cl}_2$ , 50% two steps) occurs cleanly to generate desmethylcephalotaxinone **5** by a route involving initial formation and cyclization of the macrocyclic amine endione **3**. The physical and spectroscopic properties of **5** prepared in this manner (13 steps from **7** in an unoptimized 12% overall yield) precisely match those previously reported.<sup>15</sup> Finally, **5** is converted to cephalotaxine by the modified<sup>5f</sup> Weinreb<sup>5a</sup> procedure. Here again, the synthetic material was identical in all respects to a commercial (Sigma) sample of the cephalotaxine.

In summary, the strategic foundation of the cephalotaxine synthetic sequence described above arose from mechanistic thoughts about the driving force for the key transannular cyclization process. As proposed, the existence of desmethylcephalotaxinone in its ring-closed form is a consequence of thermodynamics. In this regard, it is not yet known whether this substance can undergo ring opening to reversibly form the amino endione which, as suggested by Fuchs,<sup>5f</sup> might<sup>14</sup> have an adverse impact on attempts at nonracemic syntheses of cephalotaxine which proceed *via* the intermediacy of this substance.

**Acknowledgment.** We express our appreciation to David Labaree, whose thoughts contributed to the success of this study, and to the NIH (GM-27251) for their financial support.

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(14) Several observations suggest that ring opening of nonracemic desmethylcephalotaxinone might not in itself cause racemization since macrocyclic amino enones or endiones related to **16**–**19** may be chiral/resolvable substances. For example,  $^1\text{H}$  NMR analysis of the *N*-benzyl enone **16** shows that it remains chiral over the temperature range  $25$ – $135^\circ\text{C}$ . Also, two isomers of the  $\alpha'$ -hydroxy derivative are formed when **16** is subjected to the Davis LDA/(-)CSA oxidation procedure, and although these substances have yet to be separated, they can be enriched in separate fractions upon silica gel chromatography. Finally, the  $^1\text{H}$  NMR spectra of **17**–**19** reveal the presence of diastereotopic sets of methylene protons, indicative of a slowly interconverting center of chirality in each substance. The sources of these stereochemical phenomena are biphenyl-like centers of chirality resulting from hindered rotation about the bond connecting the aryl and cyclopentenone rings on which we have previously commented (ref 6a).

(15) We thank Professor Fuchs for providing us with copies of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **5**.