dation of the *R* enantiomer took place,[1] with the less reactive ternary complex as the only available template (eq 4).

For certain substrates, additional H_2DIPT (up to 1.5 equiv total) was beneficial.[2] A probable explanation is that the unreacted $Ti(O^iPr)_4$ in equation 2 constitutes an alternative site for (*R*)-HA in cases of incomplete formation of the ternary complex. An additional 0.5 equiv of H_2DIPT would preclude this. This might also be avoided if, as eq 2 suggests, only the 1.5 equiv of $Ti(O^iPr)_4$ actually required for the oxidative resolution were used. On the other hand, eq 1 suggests that no chemical transformation of HA would be needed if a method of isolating the free (*S*)-HA could be found, with subsequent release of the (*R*)-HA by the standard workup.[2] Indeed, careful gel permeation chromatography of the *rac*-HDMAC mixture (Bio-rad Biobeads SX-8/CH_2Cl_2) was accompanied by some decomposition of the ternary species (H_2DIPT was detected in the early fractions) but provided a 25% yield of (*S*)-HDMAC in 75% ee[2] in the later fractions. Further work in this vein is currently underway.

Thus, it is the complexation, not the oxidation, which is enantioselective. The (*R,R*)-DIPT-based Katsuki-Sharpless complex will give well-defined complexes with α,*N*-disubstituted and α,*N*,*N*-trisubstituted β-amino alcohols related to *l*-ephedrine. With the proven generality and the predictable enantioselectivity of the oxidative resolution (13 successful examples of *N*,*N*,α-trisubstituted β-amino alcohols including HDMAC[2,9]), probably extendable also to substrates with α-substituents as small as methyl and/or with only secondary amino groups, this reaction could be used to reliably assign the absolute stereochemistries of homochiral materials, even on a very small scale, according to which tartrate antipode will give signals fitting the patterns of Table I.

Acknowledgment. The author is grateful to Mr. Benjamin Fieldhouse for the work with HEPY, to Mr. Stephen Bianchet for the gel permeation work, and to the Natural Sciences and Engineering Research Council of Canada for financial support.

Supplementary Material Available: General procedure for the preparation of NMR samples, NMR peak listings with assignments, and ^1H and ^{13}C spectra (13 pages). Ordering information is given on any current masthead page.

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A Straightforward Route to Functionalized Intermediates Containing the CD Substructure of Taxol

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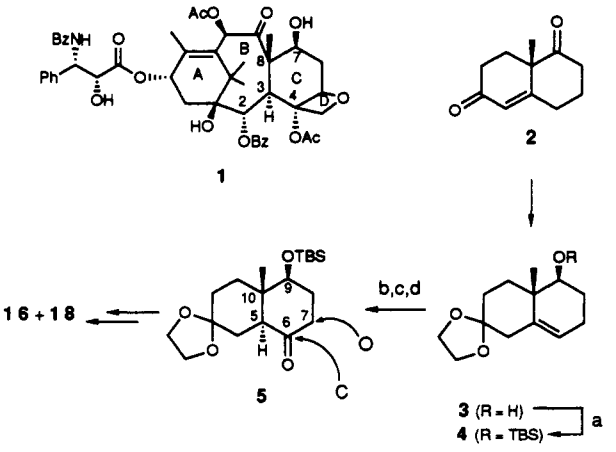
Received March 9, 1992

Summary: The Wieland-Miescher ketone lends itself to conversion, in a few steps, to intermediates which could well be useful for a synthesis of taxol (1) and analogs thereof.

The chemistry and pharmacology of the potent anticancer diterpenoid taxol (1; Scheme I)[1] have been reviewed extensively.[2] After isolation from the yew tree, *Taxus brevifolia*, taxol is only available in limited quantities. The therapeutic promise of this compound for the treatment of certain cancers, combined with its limited availability, have made it the subject of intensive synthetic and hemisynthetic study.[2]

We began by taking note of the possibility that the commercially available Wieland-Miescher ketone **2**[3] might be exploited to secure much of the functionality required for embarking upon a synthesis of taxol. The relationship of the angular methyl group and its vicinal ketone in **2** bear obvious homology with the corresponding C-7,8 region of **1**. Moreover, transformations reported by Heathcock[4] provide access to **3** which by modest adaptation allowed for the preparation of **5**. Thus, the equatorial secondary alcohol of **3**[5] was readily converted to **4**.[6] Hydroboration and oxidation analogous to the reported protocol gave a mixture of diastereomeric alcohols. Tetrapropylammonium perruthenate catalyzed oxidation[7] of this

Scheme I[a]



[a] Conditions: (a) TBSOTf/2,6-lutidine/CH_2Cl_2/0 °C; 97%; (b) (i) BH_3-THF, (ii) H_2O_2/NaOH; (c) 6 mol % TPAP/NMO/powdered 4-Å molecular sieves/CH_2Cl_2; (d) NaOMe/MeOH; 62% from **4**.

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(2) (a) Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465. (b) Blechert, S.; Guenard, D. *Taxus* Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, pp 195-238. (c) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (d) Chabner, B. A. *Princ. Prac. Oncol.* **1991**, *5*, 1.
(3) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215.
(4) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
(5) (a) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 2680. (b) Ward, D. E.; Rhee C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517.
(6) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

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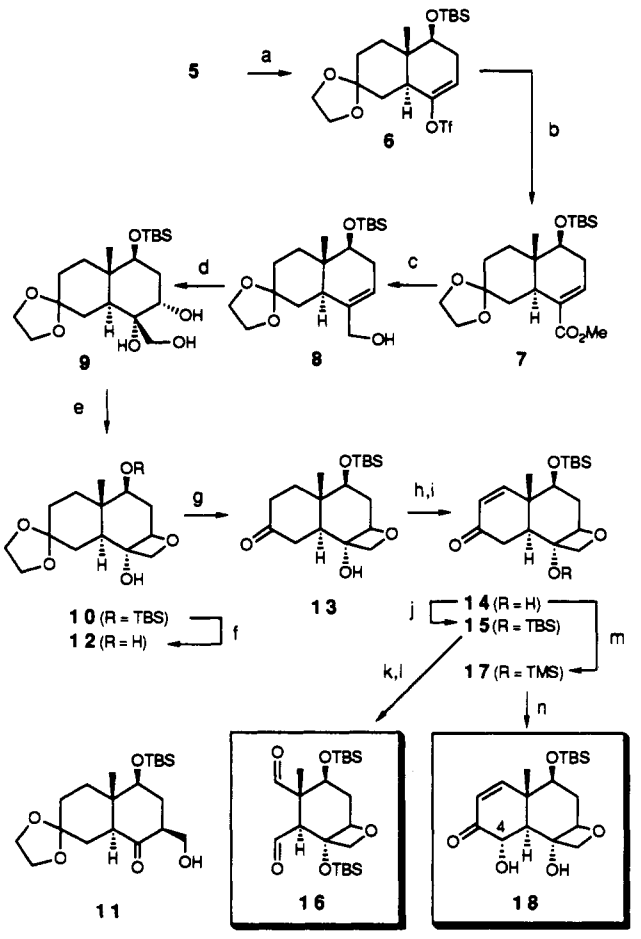
Scheme II[a]



[a] Conditions: (a) (i) KHMDS/THF/−78 °C/30 min, (ii) $PhNTf_2$/−78 °C/1 h; 81%; (b) DMF/3 equiv of Hünig's base/40 equiv of anhyd MeOH/8 mol % $Pd(OAc)_2$/16 mol % Ph_3P/2 psi CO/4 h; 73%; (c) DIBAH/hexanes/−78 °C; 99%; (d) 5 mol % OsO_4/NMO/acetone/H_2O; flash chromatography; 66%; (e) (i) TMSCl/pyr/CH_2Cl_2/−78 °C to rt, (ii) Tf_2O/−78 °C to rt, (iii) ethylene glycol/40 °C/12 h; 69% overall; (f) TBAF/THF/reflux/10 h; 93%; (g) 1 equiv collidium tosylate/acetone–H_2O (12:1)/reflux/120 h; 84%; (h) (i) 2 equiv of LDA/THF/−78 °C/1.5 h, (ii) 2.3 equiv of TMSCl/−78 °C to rt; (i) (i) 1.1 equiv of $Pd(OAc)_2$/MeCN/reflux, (ii) MeOH/K_2CO_3; 77% from **13**; (j) TBSCl/imidazole/DMF/80 °C; 57%; (k) (i) LDA/THF/−78 °C, (ii) TMSCl/−78 °C to rt; (l) (i) O_3/CH_2Cl_2/−78 °C, (ii) Ph_3P/−78 °C to rt; 36% from **15**; (m) TMSCl/pyr/CH_2Cl_2; 88%; (n) (i) KHMDS/THF/−78 °C, (ii) 2-(phenylsulfonyl)-3-phenyloxaziridine, (iii) H_2O/−78 °C to rt; 77%.

mixture gave the *cis*- and *trans*-fused ketones which converged to the *trans*-**5** after base-catalyzed equilibration. It is seen that carbons, 5, 9, and 10 of **5**[8] might be the progenitors of carbons 3, 7, and 8 of **1**. While we elected to commence our exploratory phase with racemic **2** the ready availability of its 10*S* enantiomer[9] could prove to be of great value toward the ultimate goal of synthesizing **1**.

Critical to the success of the plan would be the installation of the oxetane ring across carbons 6 and 7 of **5** by introduction of both a one-carbon fragment at C-6 and oxygenation at C-7. In this paper we describe the synthesis of intermediates **16** and **18**, which have potential for the synthesis of **1** and analogs thereof.

For the purpose of one-carbon homologation, ketone **5** was converted to the enol triflate **6** by O-sulfonylation of its potassium enolate with *N*-phenyltrifluoromethanesulfonimide (Scheme II).[10] Palladium-catalyzed carbomethoxylation[11] of **6** yielded the unsaturated ester **7**, which was readily reduced with DIBAH to the corresponding allylic alcohol **8**. Osmylation of **8** under catalytic conditions yielded a 4:1 diastereomeric ratio of triols, with **9** as the major product.

Triol **9** was converted in one pot to oxetane **10**. Selective silylation of the primary alcohol was achieved by careful treatment with TMSCl/pyridine in CH_2Cl_2 (−78 °C to rt). When silylation (as monitored by TLC) was complete, the solution was cooled back to −78 °C and treated with trifluoromethanesulfonic anhydride. TLC analysis of the solution after warming to room temperature (1 h) indicated that the secondary alcohol had been converted to its triflate. While fluoride treatment of the siloxy triflate tended to promote the migration of the hydroxymethyl function to give **11**, it was observed that alcohol-induced desilylation yielded principally oxetane **10**. The best result was achieved through the use of excess ethylene glycol as a desilylating agent (analysis of the crude ^1H NMR spectrum indicated a *ca.* 6:1 ratio of **10**:**11**). The desired oxetane **10** was isolated in 69% overall yield from triol **9**. Removal of the TBS ether with tetrabutylammonium fluoride gave diol **12**.[12] *It will be noted that compounds **10** and **12**[13] are the first synthesized subunits containing the full complement of oxygens corresponding to the CD section of taxol.*

We next sought to expose appendages which might be useful for the introduction of rings A and B. To this end, the ketal of **10** was removed under mildly acidic conditions (collidinium tosylate) which maintain the integrity of both the TBS ether and the oxetane ring. Ketone **13** was subsequently converted to the corresponding enone **14** by reaction of its silyl enol ether[14] with $Pd(OAc)_2$.[15] The tertiary alcohol of **14** was protected as the TBS ether, though only under forcing conditions (excess TBSCl/DMF/imidazole/80 °C/12 h) to give **15**. Degradation of **15** to dialdehyde **16** was accomplished by ozonolysis of the corresponding silyl dienol ether, albeit in only 36% isolated yield at this writing.

With a view to obtaining the needed oxygenation at C-2, and in the interest of exploring alternative degradative pathways, we have briefly studied the oxidation of the

(7) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. (b) See also: Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(8) Designations are in accordance with steroid numbering.

(9) (a) See: Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis* **1977**, 167 and references therein. (b) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1985**, *63*, 26. (c) Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett.* **1983**, *24*, 3175. (d) Toda, F.; Tanaka, K. *Tetrahedron Lett* **1988**, *29*, 551.

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(11) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(12) The structure of **12** has been confirmed by a single-crystal X-ray determination. Details will be disclosed in a subsequent publication.

(13) Potier and co-workers have recently published a method for oxetane closure similar to that developed independently in these laboratories. See: (a) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823. This work did not provide for the inclusion of the C-7 oxygen of **1**. For complimentary hydroxyoxetane methods, see: (b) Berkowitz, W. F.; Amarasekara, A. S.; Perumattam, J. J. *J. Org. Chem.* **1987**, *52*, 1119. (c) Lin, J.; Nikaido, M. M.; Clark, G. *J. Org. Chem.* **1987**, *52*, 3745.

(14) The free tertiary hydroxyl served, as the lithium alcoholate, to direct the lithium enolate formation to the regiochemically desired position. (When the alcohol was silylated, a significant amount of the undesired enone was formed.) The lithio dianion was subsequently trapped with excess TMSCl to give the disilyl enol ether. During the course the subsequent oxidation, the majority of the tertiary silyl ether was concomitantly removed. After consumption of starting material (TLC), MeOH and K_2CO_3 were added to complete the desilylation process to give **14** along with an unidentified minor component.

(15) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543.

enone system. The tertiary alcohol of 14 was readily converted to the corresponding TMS ether 17. The potassium dienolate of 17 was generated with potassium *bis*(trimethylsilyl)amide and subsequently treated with the Davis oxaziridine[16] to give diol 18 after aqueous workup.[17] Formally, C-4 of 18 can be viewed as corresponding in stereochemistry to C-2 of 1. However, the preservation of this stereogenicity throughout the steps leading to 1 could prove to be particularly challenging.

We are currently attempting to extend the findings, described herein, in programs directed toward the total syntheses of taxol and potentially useful analogs thereof.

Acknowledgment. We thank V. Parmakovich and B. Sporer from the Department of Chemistry of Columbia University for mass spectral analyses.

Supplementary Material Available: Procedures and spectral data (^1H and ^{13}C NMR, IR, HRMS) for compounds 4-18 (47 pages). This material is contained in many 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.

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(17) Aqueous workup readily removes the TMS ether. Flash chromatography using a 20-40% EtOAc in CH_2Cl_2 gradient elution was needed to remove the *N*-phenylsulfonamide byproduct.

Autocatalysis during the Reduction of Tetra-*n*-propylammonium Perruthenate by 2-Propanol

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Received January 2, 1992

Summary: A kinetic study has revealed that the reaction between tetra-*n*-propylammonium perruthenate and 2-propanol in methylene chloride solutions is strongly autocatalytic.

Tetraalkylammonium perruthenates are particularly good oxidants for the conversion of primary alcohols to aldehydes or secondary alcohols to ketones under nonaqueous conditions. Griffith and Ley[1] have demonstrated that excellent yields are obtained in most cases, that a variety of functional groups (double bonds, amines, ethers, etc.) may be present during the reaction, and that the reactions are particularly facile. In this paper, we wish to report on kinetic experiments that reveal why these reactions are so rapid.

Under appropriate conditions the rates of the reactions may be followed visually by noting the appearance of a dark green/black product or determined precisely by monitoring spectral changes associated with the reduction of perruthenate. Although the product has the appearance and general spectroscopic properties of a colloid[2] its final absorbance conforms to Beer's Law.[3] The colloidal nature of the product is also consistent with the observation that a fine, black solid precipitates from the solution after about 72 h.

From a consideration of the spectra of the reactant, tetra-*n*-propylammonium perruthenate, and the product of the reaction, presumably ruthenium dioxide, it can be seen (Figure 1) that the largest spectral change occurs at approximately 270 nm. At this wavelength the extinction coefficient for tetra-*n*-propylammonium perruthenate is 1080 ± 10 cm^{-1} M^{-1} while that for the product is 3680 ± 160 cm^{-1} M^{-1}. When the absorbance at 270 nm is plotted against time as in Figure 2, a sigmoidal curve typical of autocatalytic reactions results.[4] A plot of dA/dt against time (Figure 3) is typical of other autocatalytic reactions such as the oxidation of glycine and other reductants by permanganate.[5,6] The rate, initially slow, accelerates sharply as the concentration of the product builds up and then decreases near the end of the reaction because of a reduction in the concentration of the reactants giving what is commonly referred to as a "bell-shaped curve". The sharpness of the curve in Figure 3 indicates that the reaction under consideration is strongly autocatalytic.

Similar results were obtained with other primary and secondary alcohols such as 2-butanol, 1-methoxy-2-propanol and 2-phenylethanol.

The catalytic nature of the product of this reaction was further demonstrated in an experiment where additional tetra-*n*-propylammonium perruthenate was added after all of the oxidant originally present had been reduced by excess 2-propanol. As shown by the curve reproduced in Figure 4, the reaction immediately resumed at an accelerated rate. However, after 72 h a product precipitated giving a transparent solution that no longer exhibited catalysis in the initial stages of the reaction.

In analogy with autocatalytic permanganate oxidations, where the catalyst is known to be colloidal manganese dioxide,[7] it seems reasonable to expect that the product responsible for the autocatalytic nature of these reactions is colloidal ruthenium dioxide which is known to be the product formed when perruthenate is reduced by organic reductants.[8] Partial confirmation of this possibility was obtained from the observation that RuO_2 produced by the reduction of RuO_4 with an excess of 2-propanol in methylene chloride[9] also caused the rate of reaction between tetra-*n*-propylammonium perruthenate and 2-propanol to

(1) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(2) Between 300 and 500 nm the absorbance of the solution is inversely proportional to λ^4 as required by the Rayleigh Law for light scattering by a colloid. See: Moore, W. J. *Physical Chemistry*, 4th ed.; Prentice-Hall: Englewood Cliffs, 1972; p 934.

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