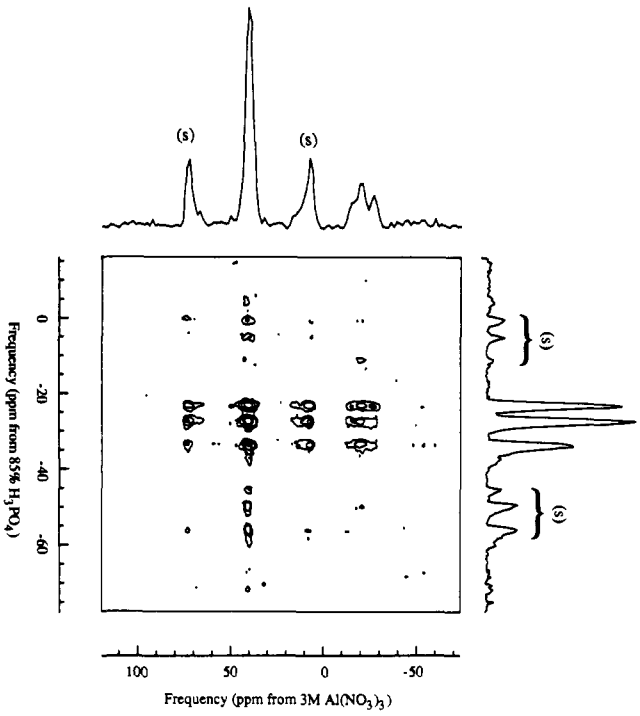

Figure 2. Two-dimensional heteronuclear correlation spectrum of ^{27}Al and ^{31}P in VPI-5. The data were accumulated as described in the text with 640 scans from each of 256 cross-polarization experiments with an incremental increase in the ^{27}Al evolution time of 12.5 μs.

for the use of heteronuclear correlations for further investigations of local microstructure in solids.

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A New and Practical Approach to the Synthesis of Taxol and Taxol Analogues: The Pinene Path

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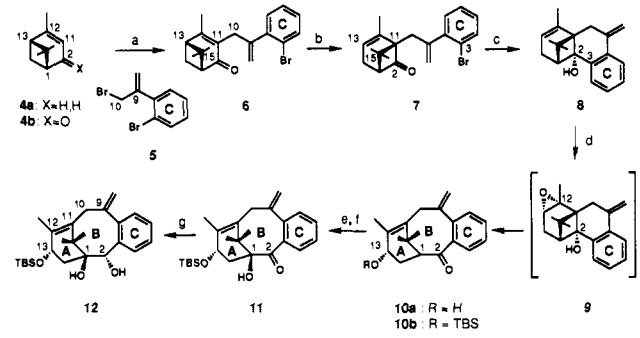
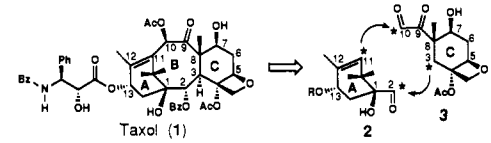
The natural product taxol (**1**) has shown remarkable potential in recent clinical trials for the treatment of breast and ovarian cancer.[1,2] Unfortunately, the limited supply of taxol from its currently approved source,[3-6] the Pacific yew tree, has hampered the development of this promising chemotherapeutic lead. To alleviate this supply problem, an impressive range of science is being investigated; major efforts to secure taxol, its analogues, and possible precursors include botanical,[5] cell culture,[7] biosynthetic, and synthetic[8] approaches. We describe here a new and practical synthetic route to tricyclic analogues of taxol that could serve in the synthesis of taxol itself. The underlying strategy allows for the preparative and routine formation of analogues and potential precursors of taxol in the correct enantiomeric form in a uniquely concise sequence based on an abundant and inexpensive starting material, pinene (**4a**).

Scheme I[a]



[a] (a) KOtBu, DME, 0 °C (50-60%). (b) $h\nu$, C_6H_{12} (85%). (c) *t*-BuLi, TMEDA, THF, -78 °C (67%). (d) i. $Ti(OiPr)_4$, tBuOOH, CH_2Cl_2, 0 °C; ii. DABCO, CH_3CN reflux (50-60% overall). (e) TBSCl, imid., DMF, 60 °C (98%). (f) KOtBu, O_2, DMSO, THF, 60 °C (80%). (g) Na, EtOH, Et_2O, 0 °C (60%).

Our approach to this problem was guided by the goal of producing a practical synthesis of taxol that could also be used to make analogues as needed to elucidate the novel mode of action of taxol at the molecular level[9] and to develop second generation drugs. It was reasoned that this goal could best be realized through the convergence of variable A and C ring precursors (e.g., **2** and **3**) in a process that produces the taxane B ring, affording overall access to systematically varied ABC tricycles. Toward these ends, a novel and flexible strategy was fashioned around the use of α-pinene, a constituent of pine and a major component of industrial solvents such as turpentine. Available in either enantiomeric form and possessing 10 of the 20 carbons of the taxol core, pinene was viewed as a superb building block for a variety of approaches to the taxanes.



Our first objective in the elaboration of pinene (**4a**) focused on the attachment of a suitable C ring precursor to its C11 center (Scheme I).[10] For this purpose, the readily available air-oxidation product of pinene,[11] verbenone (**4b**), was seen to possess a carbonyl group ideally situated for bond formation at C11 through the use

(1) For a review of the clinical biology of taxol, see: Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247.
(2) For recent clinical results, see: Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *J. Natl. Cancer Inst.* **1991**, *83*, 1797.
(3) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
(4) For environmental and supply reasons, extraction of taxol from the Pacific yew is expected to be phased out in the next few years. Replacement sources are under evaluation.
(5) Witherup, K. M.; Look, S. A.; Stasko, M. W.; Ghiorzi, T. J.; Muschik, G. M.; Cragg, G. M. *J. Nat. Prod.* **1990**, *53*, 1249.
(6) Vidensek, N.; Lim, P.; Campbell, A.; Carlson, C. *J. Nat. Prod.* **1990**, *53*, 1609.
(7) Christen, A. A.; Bland, J.; Gibson, D. M. *Proc. Am. Assoc. Cancer Res.* **1989**, *30*, 566, A2252.
(8) Over 30 groups have made impressive contributions to the literature on the synthesis of taxanes. These include the following: Berkowitz, Blechert, Clark, Fetizon, Frejd, Funk, Gadwood, Ghosh, Greene, Holton, Hua, Hudlicky, Inouye, Jenkins, Kato, Kende, Kitagawa, Kraus, Kuwajima, Lange, Martin, Oishi, Paquette, Pattenden, Potier, Sakan, Shea, Snider, Swindell, Trost, Wender, Winkler, Yadav, Yamada, Zucker. For reviews, see: (a) Snapper, M. L. Ph.D. Dissertation, Stanford University, Stanford, CA, 1990. (b) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465.
(9) (a) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561. (b) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.
(10) The numbering used in this paper refers to the corresponding centers of taxol. This sequence has been performed in both enantiomeric series.
(11) Kizlink, J.; Hronec, M.; Cvengrosova, Z.; Kuruc, L.; Kriz, M.; Oblozinsky, A.; Ilavsky, J. Czech CS 258 634, 1986; *Chem. Abstr.* **1989**, *111*, 214768r.

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of practical enolate chemistry. In accord with this analysis, treatment of (*R*)-(+)-verbenone[10] with KO-*t*-Bu in DME at 0 °C followed by addition of dibromide **5**,[12] which for the purposes of this study serves as a *representative* C ring precursor,[13] yielded the C11 alkylated product **6** (50–60%).[14] Subsequent reorganization of the pinene nucleus of **6**, requiring a 1,3-alkyl shift of C15 from C13 to C11, was inspired by the pioneering photochemical studies on the conversion of verbenone to chrysanthenone.[15] With the alkylated verbenone **6**, this photoinduced shift occurred quickly and efficiently (degassed cyclohexane/Hanovia/Pyrex/20 min), providing the desired rearrangement product **7** in 85% isolated yield.

The next stage of our plan, involving the addition of C3 to the carbonyl group of **7**, was designed to exploit the relative ease of intramolecularly forming a six-membered ring, which as a consequence of its fusion to a strained four-membered ring was expected to fragment to the eight-membered B ring of the taxanes. In accord with this plan, tetracyclic alcohol **8** was formed in 67% yield when bromide **7** was treated with *t*-BuLi. It is noteworthy that while the aryllithium intermediate in this process adds readily to the C2 carbonyl the more reactive *t*-BuLi does not, owing in part to steric congestion at C2 and the facility of lithium–halogen exchange. Epoxidation of alcohol **8** using Ti(O-*i*-Pr)$_4$/*t*-BuOOH at 0 °C resulted in the completely stereocontrolled formation of the epoxide **9** in 60–70% yield, thereby setting the necessary stereochemistry at C13 for eventual attachment of taxol-like side chains. Due to the lability of this epoxide, it was directly treated with DABCO to effect fragmentation to the desired tricycle **10a** in 80% yield.[16] In analogy with the observations of Shea and co-workers,[17] tricycle **10a** exists at 25 °C as a 9:1 mixture of two slowly interconverting atropoisomers.

At this point all that remained to complete the A ring functionality required for taxol was incorporation of the bridgehead hydroxyl group at C1. While oxygenation of a bridgehead enolate represented a potentially practical solution to this goal, computer modeling indicated that only in the minor atropoisomer of **10a** is the C1 hydrogen suitably aligned for enolate formation. However, at higher temperatures (60 °C) where isomer interconversion is rapid, complete hydrogen–deuterium exchange at C1 was expected and indeed observed when the ether derivative **10b** was treated with $NaOCD_3$ in CD_3OD. Moreover, when this ether (**10b**) was treated with KO-*t*-Bu in THF at 60 °C in the presence of DMSO and O_2 gas for 30 min, formation of the desired bridgehead hydroxyl product **11** was accomplished in 80% isolated yield. The final task in converting all 10 carbons of pinene to the corresponding functionalized carbons of the taxol nucleus was achieved through thermodynamically controlled reduction of **11** (Na/EtOH/Et_2O/0 °C), affording diol **12** in 60% yield.[18]

In summary, a new and versatile strategy has been described that offers promise for the synthesis of taxol and is currently being used for the practical formation of taxol analogues[19] as required for molecular mode of action and drug development studies. In the current example, the tricyclic core of the taxanes is assembled with enantiomeric control in five steps from pinene and further elaborated to produce the complete functionality and stereochemistry of the taxol A ring and strategically located and differentiated functionality at other key sites in three additional steps. This sequence is sufficiently straightforward to be conducted on a large scale; current runs have started with 1–2 mol but could be readily increased. More generally, this process demonstrates how the 10 carbons of pinene can be incorporated into the 20-carbon taxol core with control of absolute and relative stereochemistry and substitution. Moreover, this chemistry can be extended to widely varied and functionalized aromatic and nonaromatic C ring precursors. These studies will be reported in due course.

Acknowledgment. This research was supported by grants from the National Institutes of Health (CA31845) and Bristol-Myers Squibb. T.P.M. is grateful to the National Science Foundation for predoctoral fellowship support in the first phase of this work in 1989. The authors are especially indebted to Drs. S. Broder, B. Chabner, and M. Suffness of the NIH and Dr. T. Doyle of BMS for invaluable discussions on taxol clinical and supply studies.

Supplementary Material Available: Listings of ^{1}H NMR, ^{13}C NMR, FTIR, and high-resolution mass spectroscopic and/or elemental analysis data for **6–8**, **10a,b**, **11**, and **12** (5 pages). Ordering information is given on any current masthead page.

(12) Compound **5** was prepared on a multimole scale in two steps from methyl 2-bromobenzoate (i. MeMgBr addition at 0 °C, followed by distillative dehydration of the carbinol product over $KHSO_4$ (93%) (see Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 829). ii. Allylic bromination with NBS/$(PhCOO)_2$) (83%)).

(13) This reaction has been conducted on a multimole scale. We have also achieved related alkylations of verbenone with a wide range of aromatic and nonaromatic C ring precursors. Methods for condensation with aldehydes and esters have also been developed. T. Glass, T. Mucciaro, T. Ohkuma, B. Peschke, A. Shuker, J. Sutton, L. Wessjohann, Stanford University, unpublished results, 1989 to the present.

(14) All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and HRMS or elemental analysis.

(15) (a) Hurst, J. J.; Whitham, G. H. *J. Chem. Soc.* **1960**, 2864. (b) Erman, W. F. *J. Am. Chem. Soc.* **1967**, *89*, 3828.

(16) The structure of the TBS ether (**10b**) has been confirmed by an X-ray crystal structure determination performed by Dr. Qi Gao of Bristol-Myers Squibb. Details will be provided in a separate publication.

(17) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953.

(18) Reduction of **11** with LAH (ether, 0 °C) provided the C2 epimer of **12** (92%). The stereochemical assignments are fully in accord with theoretical expectations and supported by side-by-side comparisons of anisotropic shifting of the methyl groups observed in the NMR spectra of the acetonides of **12** and of its C2 epimer.

(19) Jim Sutton, Stanford University, unpublished results, 1991. The side chain was synthesized by the method of Denis et al. (Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957) and attached by the method of Swindell et al. (Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1991**, *34*, 1176).

CASSCF Calculations Find That a D_{8h} Geometry Is the Transition State for Double-Bond Shifting in Cyclooctatetraene

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NMR studies have found that in cyclooctatetraene (COT)[1] the barrier to double-bond shifting is approximately 14 kcal/mol.[2,3b] Additional dynamic NMR experiments on monosubstituted derivatives of COT found the barrier to bond shifting to be 3–4 kcal/mol higher than the barrier to ring inversion.[3,4] With the assumption that the transition states for both processes have planar geometries, the difference in barrier heights represents the energy required to delocalize the double bonds in going from the D_{4h} transition state for ring inversion to the D_{8h} transition state for bond shifting (Figure 1).[3]

The assumption that bond shifting in COT requires a planar ring has recently been questioned.[5,6] Paquette and co-workers[5]

(1) Reviews: Paquette, L. A. *Tetrahedron* **1975**, *31*, 2855. Fray, G. I.; Saxton, R. G. The *Chemistry of Cyclooctatetraene and Its Derivatives*; Cambridge University Press: New York, 1978.

(2) Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 671. Slightly lower values have been reported for COT in liquid crystals (Naor, R.; Luz, Z. *J. Chem. Phys.* **1982**, *76*, 5662) and for fluoro-COT (Gwynn, D. E.; Whitesides, G. M.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 2862).

(3) (a) Anet, F. A. L.; Bourn, A. J.; Lin, Y. S. *J. Am. Chem. Soc.* **1964**, *86*, 3576. (b) Oth, J. F. M. *Pure Appl. Chem.* **1971**, *25*, 573.

(4) Steric effects in substituted COTs tend to increase the barrier heights for both bond shifting and ring inversion and in multiply substituted COT derivatives steric effects also reduce the difference between the two barrier heights. Review: Paquette, L. A. *Pure Appl. Chem.* **1982**, *54*, 987.

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