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STEREOSELECTIVE SYNTHESIS OF A SYNTHON FOR THE A-RING OF TAXOL FROM R-(+)-VERBENONE

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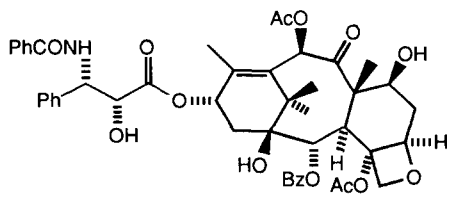
Summary: The efficient conversion of R-(+)-verbenone to bicyclic lactone **6**, a potentially useful intermediate for the synthesis of taxanes, is described. The introduction of C-1 (taxane numbering) oxygen functionality is also reported, thereby completing the synthesis of the A-ring subunit of taxol.

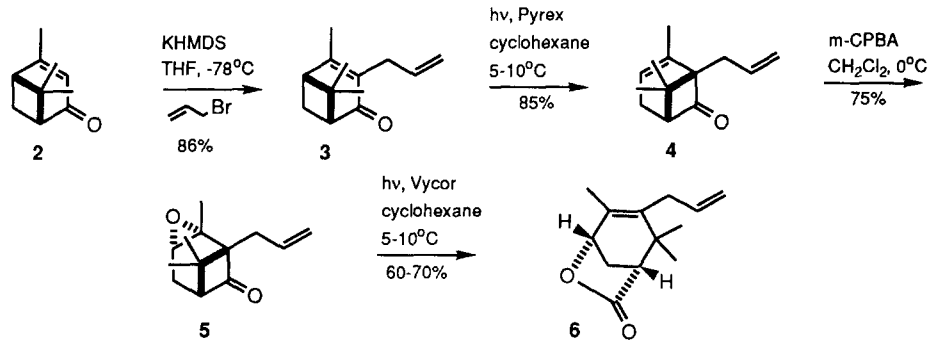
According to the National Cancer Institute, the naturally occurring diterpene ester taxol, **1**, is the most promising natural product lead in cancer chemotherapy in the last decade, with extremely promising activity against intractable ovarian cancer and other tumor systems.[2] Taxol is the only plant product known to promote the assembly of microtubules and inhibit the tubulin disassembly process,[3] and therefore appears to be the prototype of a new class of cancer chemotherapeutic agents as well as an important tool in cell research. Because taxol is isolated in exceedingly low yield by extracting the bark of the Pacific yew tree,[4] a massive harvesting program has recently been undertaken to make available sufficient quantities to permit further clinical trials. However, the ecological ramifications of this harvesting program make it very undesirable. The unique mode of action of taxol, coupled with its extreme scarcity, have resulted in a prodigious effort directed towards both semi- and total synthesis of **1**, which have recently culminated in the first two reported total syntheses of taxol.[5,6] However, work continues around the world in an effort to achieve a practical, efficient laboratory synthesis of taxol that will significantly increase the supply of this important drug, as well as making available taxol analogs for the study of structure-activity relationships. Towards that end, we report herein a very efficient procedure for the preparation of the A-ring subunit of taxol from R-(+)-verbenone, **2**,[7,8] a particularly attractive starting point, since it possesses the correct absolute stereochemistry for taxol synthesis, as well as containing all the necessary carbons for the elaboration of A ring substructures.



1

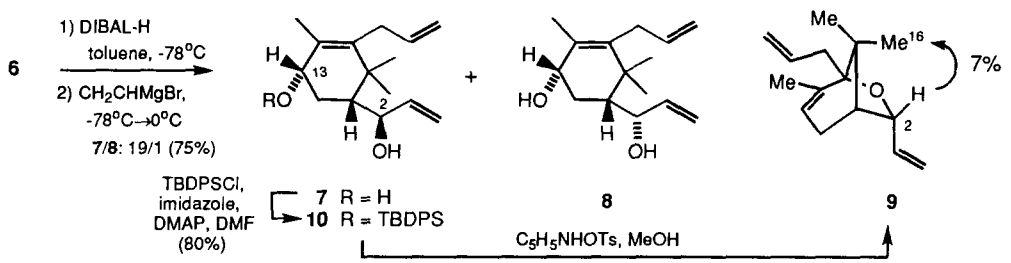
Deprotonation of (R)-(+)-verbenone, **2**, with KHMDS in THF at -78 °C, followed by the addition of allyl bromide gave the α-allylated product **3** (Scheme I). Irradiation of **3**, based on the work of Hurst and Whitham,[9] led to the formation of the rearranged cyclobutanone, **4**.

Scheme I



The requisite C-13 oxygen functionality of taxol was introduced via regioselective and stereoselective epoxidation of **4** from the least hindered face (away from the geminal dimethyl group) of the more highly substituted alkene to give **5**. Based on the pioneering work of Agosta and Murray,[10] the β,γ-ketoepoxide **5** underwent a second photochemically mediated rearrangement to yield the γ-lactone, **6**.

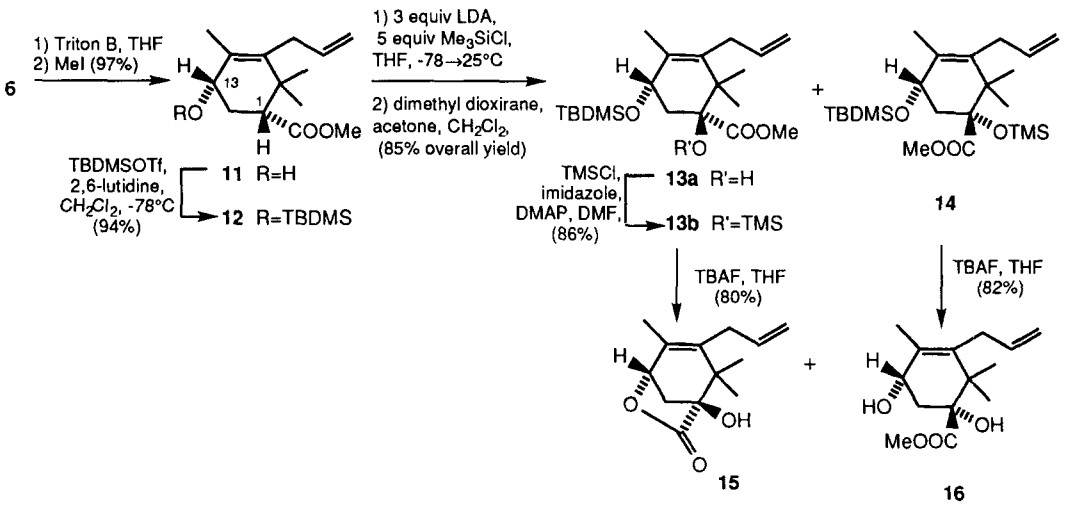
Scheme II



The versatility of the lactone as an intermediate for elaboration of the A-ring and the construction of taxanes was demonstrated by the subsequent transformations outlined in Schemes II and III. Treatment of **6** with DIBAL gave a lactol intermediate, which on *in situ*[11] reaction with vinyl Grignard led to the stereoselective formation of **7** (19:1 ratio of diols **7** and **8**) with the requisite C-2 and C-13 oxygen functionalities of taxol in place.[12] nOe analysis of the rearranged product **9** (obtained on exposure of **7** to pyridinium tosylate in methanol) revealed a 7% enhancement from the C-2 methine to the C-16 methyl group (as shown in **9**), establishing the C-2β alcohol stereochemistry in **9**, and therefore in **7**. The differentiation of the two hydroxyl groups in **7** could be achieved by selective reaction of the C-13 hydroxyl with TBDPSCl which led to the formation of **10**.

Alternatively, transesterification of lactone **6** gave the corresponding hydroxyester **11** (Scheme III). While lactone opening was initially problematic (i.e., reaction of **6** with sodium methoxide in methanol led to the formation of 40% of the desired hydroxy ester along with 53% recovered lactone), it was eventually found that treatment of **6** with Triton B,[13] followed by alkylation of the resulting quaternary ammonium carboxylate with MeI, furnished the desired hydroxyester **11** in 97% yield (Scheme III). The hydroxy ester could also be obtained in 82% yield by treatment of **6** with sodium hydroxide in methanol, followed by CH_2N_2 esterification.

Scheme III



To complete the synthesis of a fully functionalized A-ring unit, it was next necessary to introduce C-1 oxygen functionality. Towards that end, protection of the C-13 hydroxyl group of **11** gave silyl ether **12**. Dimethyl dioxirane[14] oxidation of the derived silyl ketene acetal led to the formation of a 2.3:1 ratio of the C-1 epimeric esters **13** (obtained as a 1:1 mixture of alcohol **13a** and trimethylsilyl ether **13b**) and **14**. The stereochemistry of **13** and **14** could be established by treatment of the separated C-1 epimers with tetrabutylammonium fluoride. Desilylation of both **13a** and **13b** (the C-1β oxygenated products) resulted in the formation of the same lactone **15**, whereas desilylation of **14** gave the monocyclic dihydroxyester **16**.[15] The modest facial selectivity observed in the reaction of the silyl ketene acetal derived from **12** can be understood as a function of the pseudoequatorial orientation of the C-13 *t*-butyldimethylsilyloxy substituent.

In conclusion, the practical and efficient transformation of **2** to **6** and ultimately to **15** underscores the utility of this R-(+)-verbenone approach to the synthesis of the fully functionalized A-ring moiety of the taxane diterpenes. The application of this methodology to the synthesis of taxol and novel analogs is currently underway in our laboratory.

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[15]All new compounds were characterized by full spectroscopic (NMR, IR, high resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials. Spectral data for hydroxylactone **15**: ^{1}H NMR ($CDCl_3$, 500 MHz): 5.65 (m, 1 H), 4.99 (m, 1 H), 4.94 (m, 1 H), 4.54 (d, J = 5.5, 1 H), 2.83 [(s, 1 H) superimposed on 2.77 (m, AB of the ABX system, 2 H)], 2.43 (d, J = 11.0 Hz, 1 H), 2.31 (dd, J = 11.0, 5.5 Hz, 1 H), 1.56 (s, 3 H), 1.15 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): 179.0, 140.1, 135.1, 131.0, 115.6, 78.7, 78.4, 43.9, 39.1, 32.0, 21.0, 20.8, 18.3 ppm; FT-IR (film, cm^{-1}): 3472 (br), 2978, 2940, 1769, 1637, 1470, 1278, 1127, 918; exact mass calculated for $C_{13}H_{18}O_3$ (M^+ + H): 223.1334, found 223.1339.

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