The Pinene Path to Taxanes. 4. Approaches to Taxol and Taxol Analogs through Elaboration of Aromatic C-Ring Precursors

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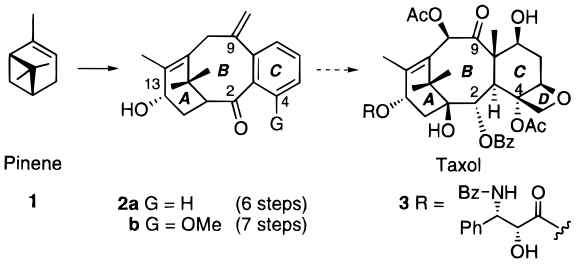
The chemotherapeutic agent Taxol (**3**, Scheme 1), originally obtained from Pacific yew tree bark, has shown remarkable promise in the treatment of both breast and ovarian cancer.[2] As part of our ongoing research in this area, we have developed a strategy for the synthesis of taxanes based on pinene (**1**),[3] which provides concise, enantiomerically controlled access to the tricarbocyclic taxane core (e.g., **2a** in six steps), structural analogs, and taxol itself.[4] A recently introduced C9−C10 linker variant of this strategy has also provided tricycle **2b** in only seven steps from pinene (**1**).[5] Herein we describe the next phase of this program, the elaboration of **2b** toward both taxol and its analogs entailing concise solutions for the functionalization of the B and C rings.

The elaboration of **2b** began with protection of its C13 hydroxyl group as the TBS ether (**4**, Scheme 2). It is a noteworthy consequence of the striking interconnectedness of functional group reactivities in this structural series that **4** failed to undergo C1 deprotonation and oxidation under conditions in which the closely related silyl ether derivative of **2a** reacted readily.[3] At the core of this reactivity difference is the C4 substituent (H vs MeO), which restricts **4** to a conformation in which the C1−CH bond is improperly aligned with the C2 carbonyl for deprotonation. Removal of this conformational constraint through saturation of the C9 center was found to resolve this problem, as demonstrated by the highly efficient conversion of the hydroboration product **5** (with *t*-BuOK/DMSO/O_2 in THF at −25 °C) to the C1-oxidized product **6** in 96% yield. The primary alcohol of **6** was subsequently converted to the C9 ketone **7** (82%) by oxidation with Dess−Martin's periodinane[6] to an aldehyde (84%) followed by oxidative decarbonylation using *t*-BuOK/DMSO/O_2.

Scheme 1



Further elaboration of diketone **7** was initially accomplished by Birch reduction. However, complications with over-reduction of the aromatic ring prompted our selection of the C2 monoketone **8** in order to achieve better control over this reduction. For this purpose, ketone **8** (mp 149−150 °C) was prepared by double reduction of **7** with sodium, followed by selective protection of the C9 alcohol and reoxidation of the C2 alcohol (53% yield over three steps). When **8** was treated with K/NH_3/THF, the α- and *β*-C3-stereoisomers **9a** and **9b**/**9c** were obtained in a ratio that was dependent on the reaction conditions and workup. Although it was possible to obtain either C3 epimer, compounds possessing the *β*-CH configuration were selected for study since they were expected to afford greater stereocontrol over the introduction of groups at C8 and to be amenable to epimerization at a later synthetic stage. Ketone **8** was therefore selectively reduced to the *β*-CH derivatives **9b** and **9c** (77% yield, along with a trace of **9a**). Silyl ether **9b** was readily converted to **9c** upon treatment with acid.

Access to our multipurpose analog precursor, enone **13**, entailed initial reduction of the C2 ketone of **9c** with Na in NH_3/THF to the desired C2 alcohol stereoisomer **10** (85% yield). Subsequent treatment of **10** with triphosgene provided the carbonate **11** (99% yield), which when exposed to phenyllithium yielded the C2 benzoate **12** (68% yield).[7] Oxidation of the C9 alcohol using Dess−Martin periodinane gave enone **13** (mp 175−176 °C) in 95% yield.

Enone **13** serves as a potentially general precursor to various classes of taxol analogs. For example, access to 7-deoxy analogs, many of which have similar biological activity to taxol,[8] requires introduction of a *β*-C8 methyl group. This alkylation was achieved by reduction of **13** with Li/NH_3 in THF followed by methyl iodide treatment, affording the desired C8 methylated compound **16a** (30%) along with material arising from further reductive methylation of the C2 benzoate, **16b** (27%). Similarly, 7,8-

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(2) Taxol is the registered trademark for the molecule with generic name paclitaxel. For a recent review of synthetic studies from over 35 groups, see: (a) Wender, P. A.; Natchus, M. G.; Shuker, A. J. In *TAXOL® Science and Applications*; Suffness, M., Ed.; CRC Press: New York, 1995; pp 123−187. For overviews of other aspects of taxol research, see: (b) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G., Chen, T., Ojima, I., Vyas, D., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. For total syntheses of Taxol, see: (c) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597−1598, 1599−1600. (d) Nicolaou, K. C.; Yang, Z.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. (e) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, J. *J. Am. Chem. Soc.* **1996**, *118*, 2843−2859 and references cited therein.

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(4) Presented in part at the ACS Western Regional Meeting, Oct 18−21, 1995, ORGN. 129. For an overview of our strategy see: Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Ohkuma, T.; Peschke, B.; Rawlins, D. B.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K.; Wessjohann, L. A. In ref 2b, pp 326−339.

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(7) This method of incorporating the C2-benzoate was used successfully in all of the reported syntheses of taxol.[2c−e] A similar reaction was reported in an early phorbol synthesis from these laboratories: Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957−8958.

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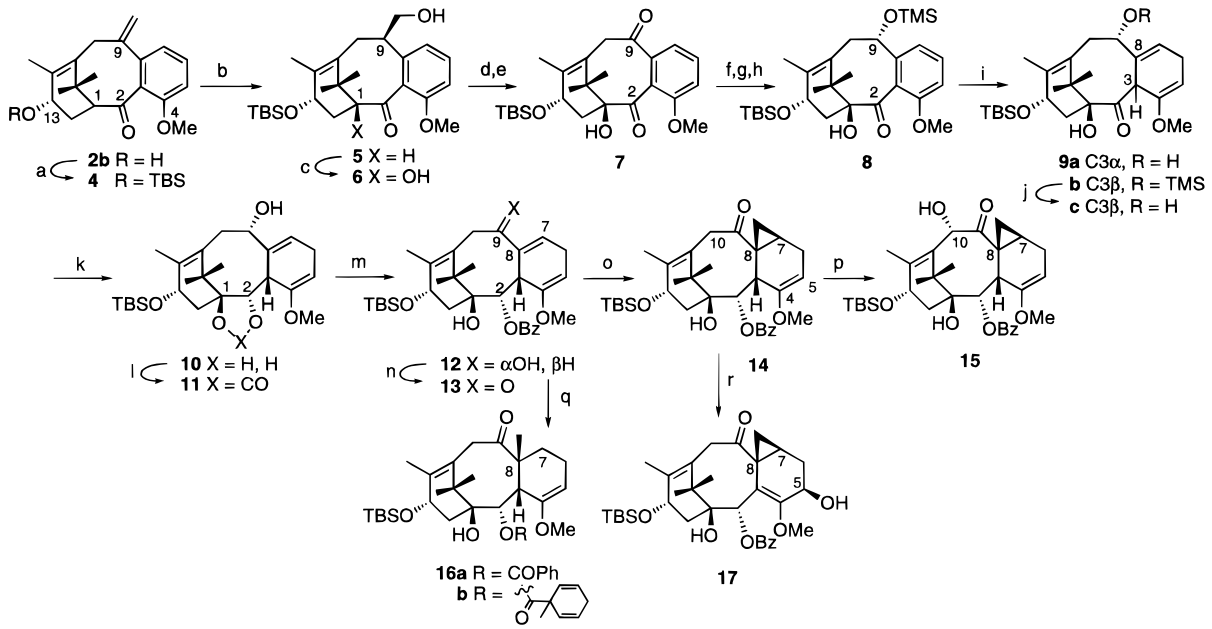
Scheme 2[a]



[a] Reagents: (a) TBSCl, imidazole, DMF, 60 °C (91%); (b) (i) 9-BBN, THF, reflux, (ii) 6 N NaOH, 30% H_2O_2, reflux (66%); (c) *t*-BuOK, O_2, DMSO, THF, −25 °C (96%); (d) Dess−Martin periodinane, CH_2Cl_2 (84%); (e) *t*-BuOK, O_2, DMSO, THF, −30 °C (84%); (f) Na, EtOH, wet Et_2O, 0 °C; (g) TMSCl, Et_3N, CH_2Cl_2; (h) Dess−Martin periodinane, CH_2Cl_2 (53%, three steps); (i) (i) K, NH_3, THF, −78 °C, (ii) isoprene, (iii) NH_4Cl (aq) (**9a** trace, **9b** 58%, **9c** 19%); (j) AcOH, MeOH (69%); (k) Na, NH_3, THF, −78 °C (85%); (l) triphosgene, CH_2Cl_2, pyridine (99%); (m) PhLi, THF, −78 °C (68%); (n) Dess−Martin periodinane, CH_2Cl_2 (95%); (o) $(CH_3)_3S(O)I$, NaH, THF, DMSO, 45 °C (69%); (p) (i) KHMDS, THF, −78 °C, (ii) 2-(phenylsulfonyl)-3-phenyloxaziridine, −78 °C (52%); (q) (i) Li, NH_3, THF, −78 °C, (ii) CH_3I (**16a** 30%, **16b** 27%); (r) acetone, Oxone, $NaHCO_3$, CH_2Cl_2, 18-C-6, 0 °C (37).

cyclopropyltaxol analogs that exhibit comparable activity to taxol[9] are also potentially derivable from enone **13**. Key to accessing this class is the cyclopropanation of **13**, which was found to proceed with dimethylsulfoxonium methylide in THF/DMSO[10] to afford compound **14** (173−176 °C)[11] in 69% yield. Further modification of **14**, as required for structure−activity studies in this series, was realized by selective oxidation of the C4−C5 enol ether with dimethyldioxirane, giving ketone **17** and setting the functionality required for oxetane formation.[12] Alternatively, selective introduction of C10 oxygenation was accomplished by treatment of **14** with KHMDS at −78 °C followed by the addition of Davis' oxaziridine,[13] affording hydroxy ketone **15** in 52% yield.

In summary, the advanced taxoid precursor **13** has been synthesized in 21 steps from commercially available pinene (**1**). Several developments figured significantly in this latest advance in the pinene path strategy. Elimination of the adverse conformational influence imparted by the C4 methoxy group in **4** was achieved by saturation of the C9 center, thereby allowing for efficient access to C1 oxidized intermediates. The C2 carbonyl of **8** was shown to provide control over the reduction of the aromatic ring while allowing retention of C9 oxidation. The stereochemistry of this reduction was demonstrated in turn to control reduction at C2 and stereoselective introduction of groups at C8, a new development in the elaboration of taxane tricycles. Finally, the strategy preserves in differentiated form a ketone oxidation level at C9 and C4 allowing for selective introduction of substituents at C8 and oxidation at positions C10 and C5 as required to access various taxol analogs as well as taxol itself. Studies on these advanced intermediates will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for **4**−**17** (9 pages).

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