Heteroatomic Modulation of Oxyanionic Cope Rearrangement Rates. Consequences on Competing Nucleophilic Cleavage of an Oxetane Ring in Precursors to Paclitaxel

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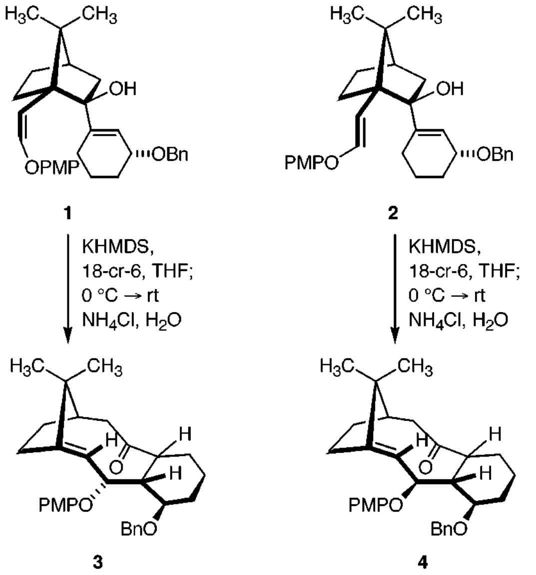
The condensation of alkenyl and cycloalkenyl organometallic reagents with bridgehead vinyl camphor derivatives and subsequent oxyanionic rearrangement of these divinyl carbinols,[1,2] hold considerable promise for the synthesis of taxoids. Earlier work from our laboratory along these lines has culminated in a total synthesis of taxusin.[3] The heightened oxygenation levels present in paclitaxel require that a number of these additional substituents be incorporated early in the synthetic scheme.[4] Instructive examples are given by **1** and **2**, where the absolute configuration at C-2 is controlled directly by the geometry of the enol ether double bond. Thus, **1** leads only to **3**, while **2** affords exclusively **4**.[5]



During the course of an extension of this study, which included possible use of a vinyl sulfide as an oxygen surrogate,[6] we had occasion to make direct comparison of the response of **9** and **10** to charge-accelerated structural rearrangement (Scheme 1).

Both ketonic precursors are available by chemoselective homologation of **5**[4a] with the appropriate Wittig reagent.[7,8] In the coupling reactions of **6** and **7** with enantiopure (*Z*)-vinyl iodide **8**,[9] halogen−metal exchange was accomplished with *n*-butyllithium. The steric control associated with this process distinctively relegates nucleophilic addition to the endo surface and gives rise to **9** and **10** in good yield. When samples of **10** were subjected to the action of potassium hexamethyldisilazide and 18-crown-6 in THF at −78 °C, complete conversion to an isomeric ketone ($\nu = 1692$ cm^{-1}) was seen to occur in less than 5 min. This compound is formulated to be **12** (85% isolated) on the strength of its ^{1}H and ^{13}C NMR signals and selected NOE experiments (see formula).

When **9** was treated in comparable fashion, rearrangement did not occur at a useful rate until the reaction temperature reached ca. 0 °C.[10] Very modest literature precedent exists for widely divergent kinetic effects on oxyanionic sigmatropy attributable to heteroatomic influences.[11,13] The heightened reactivity of **10** can be attributed to lessened steric interactions in the relevant transition state brought on by the increased length of a C−S bond relative to one of the C−O type. Electronic effects resulting from the disparity in electronegativety between S and O as well as the carbanion and radical stabilization capacity of S could also be contributory. This new finding provided us with an opportunity to probe its potential in synthesis.

Toward this end, **6** and **13** were brought into reaction with the (*Z*)-alkenyllithium derived from **14**.[14] In both instances, coupling occurred with an efficiency in excess of 80% (Scheme 2). At this point, the vinyl sulfide **16** was carried on to **18** without event. As before, the rearrangement was complete within a few minutes following admixing of the reagents at −78 °C. Without doubt, the change in the structural features of the heavily substituted side chain to one containing an oxetane ring had an effect neither on the reactivity characteristics of the system nor on the product outcome.

Notably, however, the scenario was radically different for vinyl ether **15**. Exposure of **15** to the same strongly basic conditions resulted in its rapid consumption at a rate comparable to that exhibited by **16**! The spectral data for this new compound revealed it to be isomeric with the starting carbinol but indicated also that it was neither a ketone nor structurally related to **11**, **12**, or **18**. In view of the widely recognized principle that alkoxides generated in the presence of 18-crown-6 find themselves relatively dissociated from their potassium counterions and consequently in a highly reactive state, we reasoned that an alternative pathway involving S_N2 attack at the oxetane ring may well have occurred. Molecular models revealed that proximity

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(1) (a) Zeng, Q.; Bailey, S.; Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 137 and references cited therein.

(2) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.

(3) (a) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203. (b) Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.

(4) (a) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 889. (b) Paquette, L. A.; Su, Z.; Bailey, S.; Montgomery, F. J. *J. Org. Chem.* **1995**, *60*, 897. (c) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849. (d) Paquette, L. A.; Montgomery, F. J.; Wang, T.-Z. *J. Org. Chem.* **1995**, *60*, 7857.

(5) Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 6874.

(6) Johnston, J. N.; Tsui, H.-C.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 129.

(7) (a) Marino, J. P.; Kaneko, T. *Tetrahedron Lett.* **1973**, 3975. (b) Vlattas, I.; Lee, A. O. *Tetrahedron Lett.* **1974**, 4451. (c) Muthukrishnan, R.; Schlosser, M. *Helv. Chim. Acta* **1976**, *59*, 13.

(8) Prepared by reaction of the phosphonium salt (Schönauer, K.; Zbiral, E. *Tetrahedron Lett.* **1983**, *24*, 573) with KHMDS in ether at 0 °C.

(9) Vinyl iodide **8** was prepared from D-mannitol by a route closely allied to one already detailed: Paquette, L. A.; Zeng, Q.; Tsui, H.-C.; Johnston, J. N. Submitted for publication.

(10) Since **11** and **12** have the same bridgehead olefin geometry and exo-directed (β) oxygenated side chains, the rate differences are clearly not related to the operation of both chair and boat pathways.

(11) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242.

(12) (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.

(13) It will be noted that **11** and **12** belong to different atropisomeric series. In line with earlier discoveries realized in this laboratory, this phenomenon is related to reaction temperature.

(14) Vinyl iodide **14** was prepared in several steps from D-glucose. The details of this synthetic sequence will appear elsewhere.

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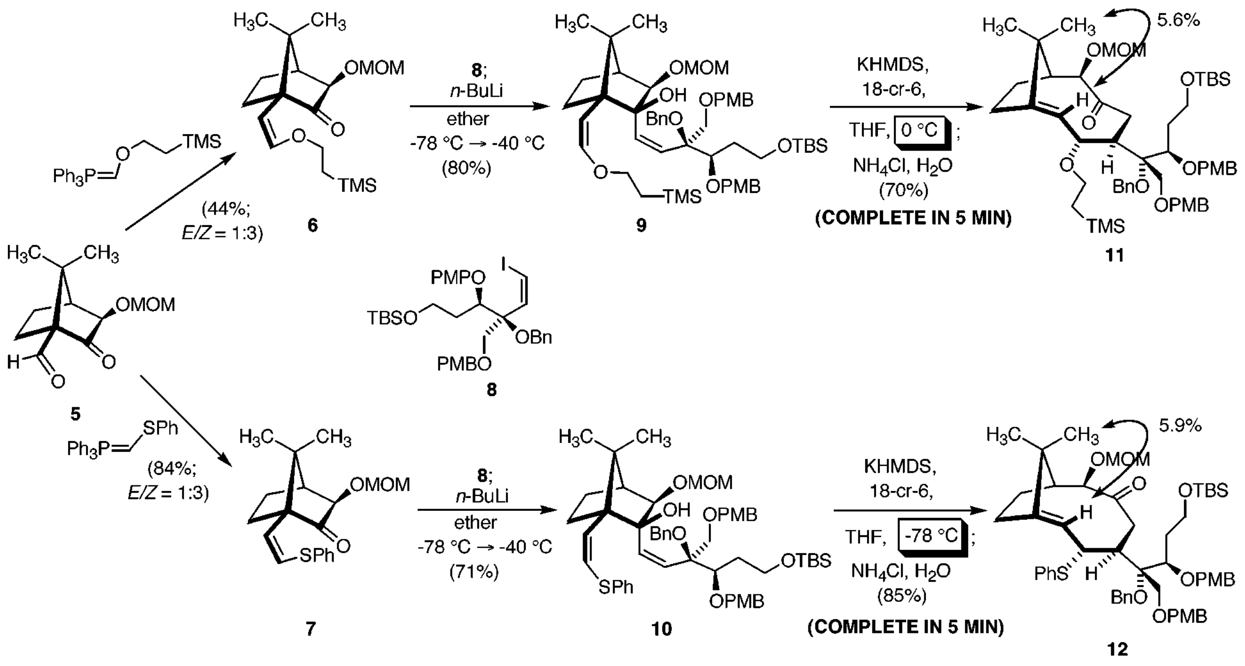
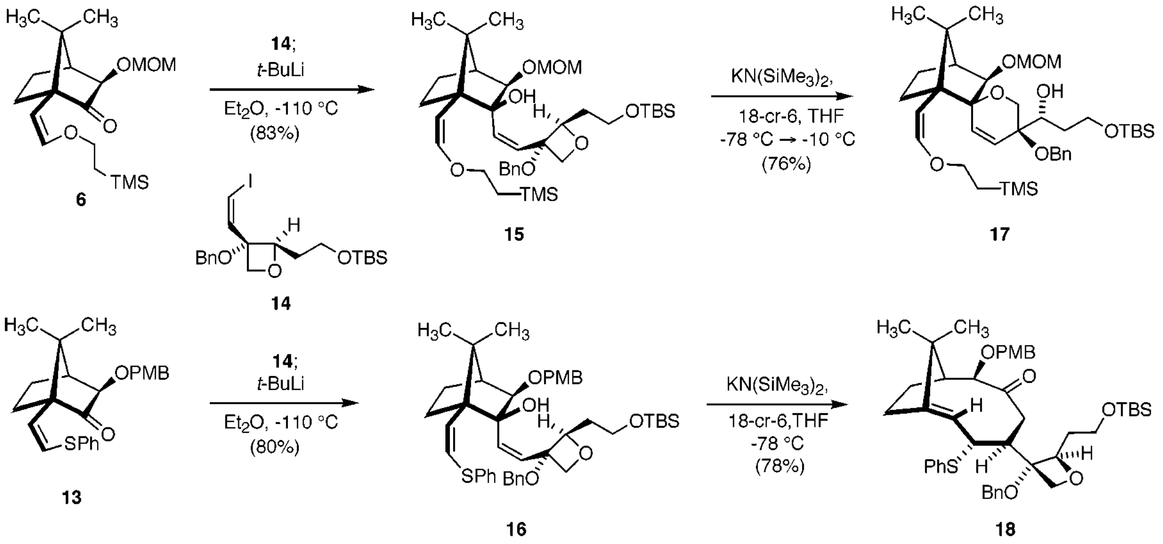
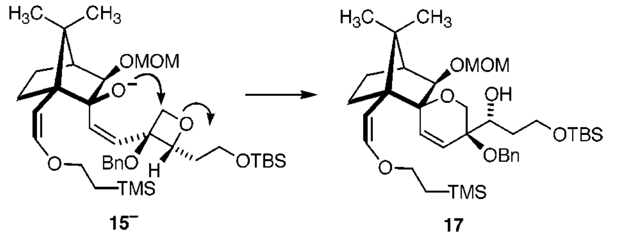
Scheme 1



Scheme 2



Scheme 3



effects and orientational alignments for backside attack on either C–O bond were quite suitable. Since the 300 MHz ^{1}H NMR spectrum did not completely resolve matters, its oxidation was effected with TPAP since one mechanistic option would give rise to an aldehyde and the other to a ketone. The distinctive spectral characteristics exhibited by **19** unequivocally define it to have arisen by intramolecular cleavage of the oxetane at its less substituted C–O bond with formation of **17** (Scheme 3).

The highly divergent response to deprotonation exhibited by **15** and **16** is remarkable in that it is brought about entirely by a simple OR → SR transposition. These results are considered to provide the first unambiguous glimpse of a subtle way in which [3.3] sigmatropic transpositions can be modulated. The extremely selective nature of the processes described here supports the contention that mechanistic diversity is capable of being sharply delineated.

In the context of paclitaxel synthesis, the facts are presently clear. Any intent to carry a fully functionalized oxetane ring from the outset to arrival at the target along this oxy-Cope pathway must be matched with the use of sulfur-containing norbornanones such as **7** and **13**. Failure to do so will likely result in an early rerouting.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (7 pages).

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