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Use of a Lithiolactone in the Enantioselective Constructions of A/C seco-B and of A/B seco-C *pro*Taxol Systems

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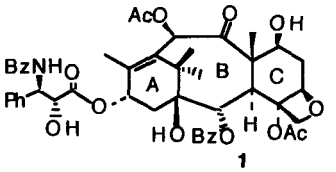
Abstract: *We show that an unusual lithiolactone system is a useful starting point for the construction of various intermediates to the taxol structure.* © 1997 Elsevier Science Ltd.

The arcane interactions within the two dimensional representation of taxol[1] (**1**) have stimulated much novel chemistry.[2] We show here that a taxol A-C system bearing functionality which might



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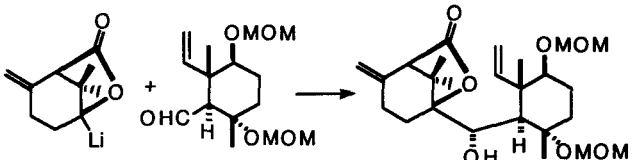
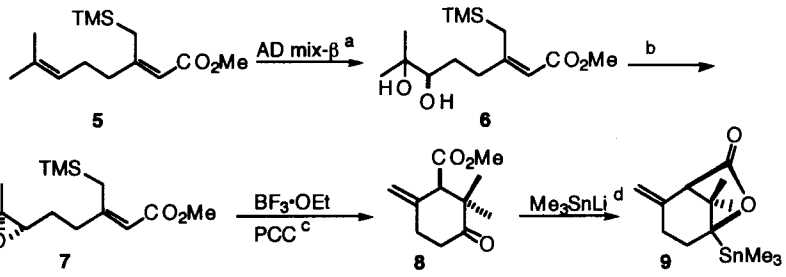
serve for the eventual closure of the B ring can be assembled by the addition of lithiolactone **2** to the ring C aldehyde **3**. Our expectation that the proper enantiomer of lithiolactone **2** should be readily available, as its precursor **9**, provided the incentive for attempting this novel and, a priori, somewhat unlikely sequence. As it developed, this coupling proved feasible and, in some cases, leads directly to the correct epimer of the C-2 hydroxyl, as shown in **4**.



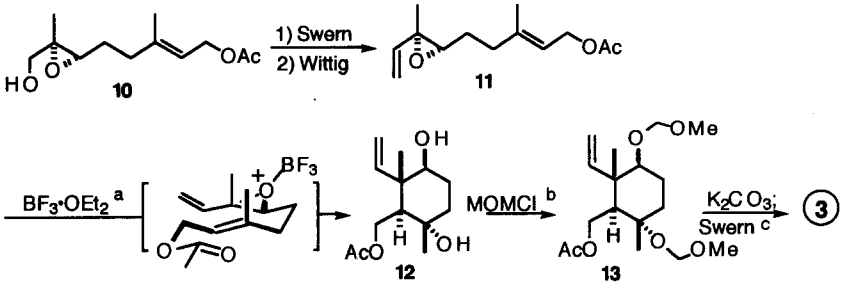
2 **3** **4**

We first describe the synthesis of the precursor of lithiolactone **2**, stannyl lactone **9**. The readily available trimethylsilyl derivative **5**[3] of methyl geranate was submitted to enantioselective cis dihydroxylation,[4] followed by conversion of **6** to the derived epoxide **7**. The latter, following a well known route to compounds of the desired type[5], upon BF_3-catalyzed cyclization, followed by oxidation of the resulting methylenecyclohexanol, gave ketoester **8**, enantiomerically pure after recrystallization from hexane (mp 69.5-70.2 °C; $[\alpha]^{25}_D$ +285). Addition of trimethylstannyllithium[6] then gave the required trimethylstannyllactone **9** (mp 91.0 °C, $[\alpha]^{25}_D$ +93.0).



Key: (a) aq. t-BuOH, $MeSO_2NH_2$, 0 ° C, 26 h; 76%. (b) MsCl, Et_3N, -40 °C to -20 °C, 1 h; then DBU, 0 °C; 80%. (c) CH_2Cl_2, room temp., 10 h; 80%. (d) Et_2O, -78 °C, 3.5 h; 73%.

We expected that an enantioselective construction of the ring C aldehyde **3** could be based on a concerted acid-catalyzed cyclization[7] of vinyl epoxide **11**. The vinyl group should not only facilitate such a process,[8] it also is a potential participant in an eventual closure of ring B. Synthesis of **11** was easily accomplished, starting with the known (-)epoxide **10**,[9] by Swern oxidation and Wittig methylenation.



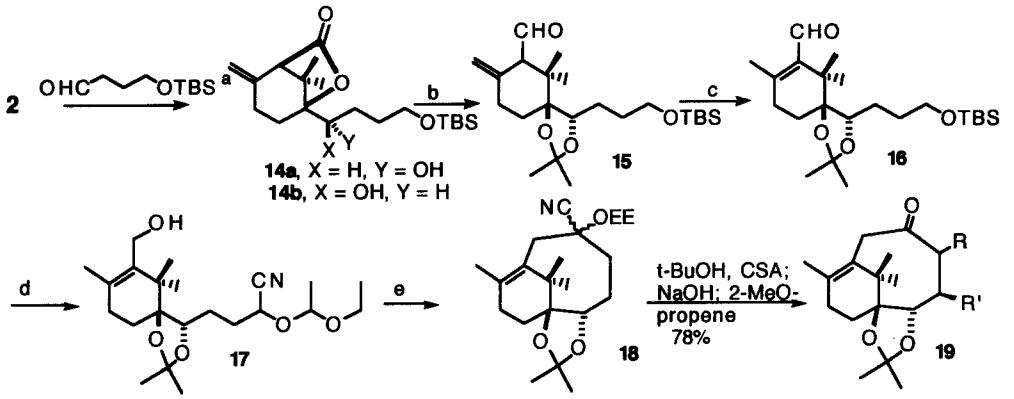
Key: (a) CH_2Cl_2, -60°C to -15 °C; 40%. (b) i-Pr_2NEt, CH_2Cl_2, room temp., 12 h; 92%. (c) 73%.

In the event, treatment of **11** with BF_3 resulted in the formation of the cyclized acetoxydiol **12**, obtained in ~40% yield after purification by chromatography.[10] It is notable that the four asymmetric centers of **12** are generated in only 3 steps from epoxide **10**. Final conversion to ring C aldehyde **3** only required protection of the two free hydroxyls in **12** as the bis-methoxymethyl ether **13**, hydrolysis of the acetate, and Swern oxidation.

Low temperature coupling of the lithio derivative **2** (from **9**) with ring C aldehyde **3** gave (55% yield) the hoped for secondary alcohol **4** *as a single isomer*, which proved to have the correct taxol C-2 stereochemistry.[11]

The successful A-C coupling represented by structure **4** established the feasibility of the lithiolactone route to B-seco systems capable, in principle, of elaboration to taxol itself. It is particularly noteworthy that this route allows the assembly of *the 7 asymmetric centers of* **4** *stereselectively, as well as enantioselectively.*

Reduction of the lactone system of **4** (LAH) released the C1-C2 glycol sytem which, however, proved very difficult to protect. We assumed that the difficulty was related to the presence of the heavily substituted ring C area of **4**. It was clear, in any case, that such protection, required before one could attend to the closure of ring B, should be much easier to achieve before the construction of ring C. This altered sequence of synthesis objectives proved effective and we now describe the construction of **19**, R=H, from lithioactone **2**.



Key: (a) THF, -90 °C; 49% 15a, 37% 15b. (b) i. DiBAL; CSA (cat.), toluene, -78 °C . ii. 2-methoxypropene, CH_2Cl_2, 0 °C; 96% (2 steps). (c) DBU, benzene, 70 °C; 72%. (d) i. $NaBH_4$-$CeCl_3$; ii. TBDPSCl, imidazole; iii. TBAF; 80% (3 steps); iv. Dess-Martin; 92%; v. TMSCN; HCl; ethyl vinyl ether; vi. TBAF; 79% (2 steps). (e) i. MsCl, LiCl, DMF; ii. NaHMDS, THF, 60 °C; 72%.

In the event, addition of lithiolactone **2** to the TBS derivative of 4-hydroxybutanal gave an easily separated *mixture* of secondary alcohol epimers **14a,b**.[12] This not unexpected lack of selectivity was corrected by oxidation of the unwanted **14b** to its ketone, which was then stereoselectively reduced with DIBAL to a lactol which now had the *correct* C-2 stereochemistry.[13] The latent 1,2-glycol system in this lactol and in that directly obtained from **14a** could now be protected, in quantitative yield, by reaction with 2-methoxypropene. This formed the isopropylidene ketal and released the latent β,γ-methylenic aldehyde **15** which could then be conjugated to **16** by treatment with DBU. Minor changes, involving selective protection and adjustment of oxidation states, led to the protected cyanohydrin **17**, now ready for the planned closure of the cyclooctane ring B. We had planned to use the protected cyanohydrin method[14] for the closure step and were gratified to find that base mediated cyclization of the primary chloride from **17**[15] did indeed result in the desired closure, in 72% yield, of the cyclooctane ring to form **18**, the immediate precursor of our target, *pro*-taxol ketone **19**, R = R' = H.

Elaboration of this construction to taxol itself requires the construction of a structure **19** in which R = Me and R' = a substituent suitable for the closure of ring C, and for the installation of the oxetane ring. This has been done, and will be reported shortly.[16]

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References and Notes.

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(1) Taxol is a registered trademark for the substance also known under the generic name paclitaxel.
(2) For a relatively recent review, see Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew Chem. Int. Ed. Engl.* **1994**,*33*, 15. For the most recent synthesis, and references to others, see Wender, P. A. et al. *J. Am. Chem. Soc.* **1997**, *119*, 2757.
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(8) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852, and numerous earlier and later papers of the Johnson group, have established the value of *allylic* hydroxyls as initiators in concerted cationic olefin cyclizations.
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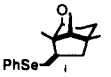
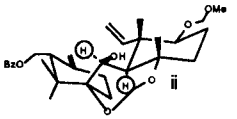
(10)The stereochemistry of **12** was confirmed by conversion to the bis cyclic ether **I.**



(11) This may involve lithium chelation between the aldehyde carbonyl and the MOM group at C-9 (taxol numbering). The structure follows from the very small coupling constant (J=1.2) between the circled hydrogens in ii below ("Macromodel"). Substance ii was made by reduction of **4** (LAH), monobenzoylation, and formation of the 7-membered formaldehyde acetal (CSA, acetone 5 days; r.t). We thank Dr. Richard Hsung of this Laboratory for his help in obtaining some of the nmr data which established this structure.



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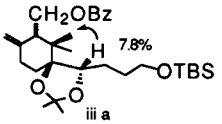
(12) The stereochemistry of the C-2 OH was established from *noe* determinations on the acetonides derived from**14a**,b. (LAH; BzCl; 2-methoxypropene). One of the two isomers (iiia below, from aldehyde **15** by reduction and benzoylation) showed *noe* enhancement (7.8%) of one of the gem dimethyls on the cyclohexane ring upon irradiation of the C-2 hydrogen. Models clearly show that that isomer and, thus, **14a** have the desired C-2 configuration shown in iiia .



iii a

(13) We thank Dr. Kei Manabe in these Laboratories for this finding which suggests that reduction of the lactone precedes the C2 ketone reduction which then takes place intramolecularly.
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