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Ireland-Claisen Rearrangement for the Stereoselective Formation of the C_2-C_3 Bond in Taxanes

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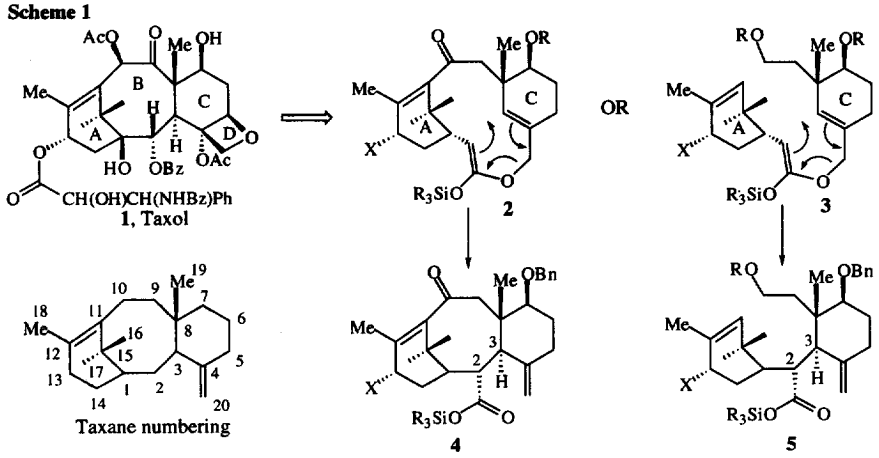
Abstract: *Ireland-Claisen rearrangement of the ester 21 gave 22 with the correct C_3 stereochemistry.*

Research on the synthesis of the antitumor diterpene taxol® **1**[1] has produced an wide variety of strategies for the construction of the core structure,[2] and to-date six total syntheses have been reported.[3a-f] Our recent studies in this area have focused on the strategy depicted in **Scheme 1** involving the synthesis of the A- and C-rings, **2** and **3** respectively, and their subsequent connection to form the central B-ring.[4] While the Ireland-Claisen rearrangement reaction[5] has been used by Funk to contract a 10-membered lactone B-ring precursor into the central 8-membered B-ring, the strategy did not accommodate the *gem*-methyl group in the A-ring.[6]

Scheme 1



Since we have ready access to A- and C- ring components in an enantioenriched form[7,4] we considered two possible Ireland-Claisen rearrangements to form the C_2-C_3 bond. The 12-membered ring ketene acetal **2** rearrangement to give **4**, and the acyclic version **3** that can produce **5**. In order to test these two possibilities the appropriate lactone **16**, **Scheme 2** and ester **21**, **Scheme 3** were synthesized. Classical Arndt-Eistert homologation of **6**[7] gave **7**, which was converted into **8** , followed by bromine-lithium exchange and addition of **9**, resulted in **10**. Dess-Martin (D-M) oxidation[8] of **10** gave **11** which was converted into the acid **12**. During this sequence of reactions the sulfide was oxidized to the sulfoxide. Exposure of the allylic sulfoxide

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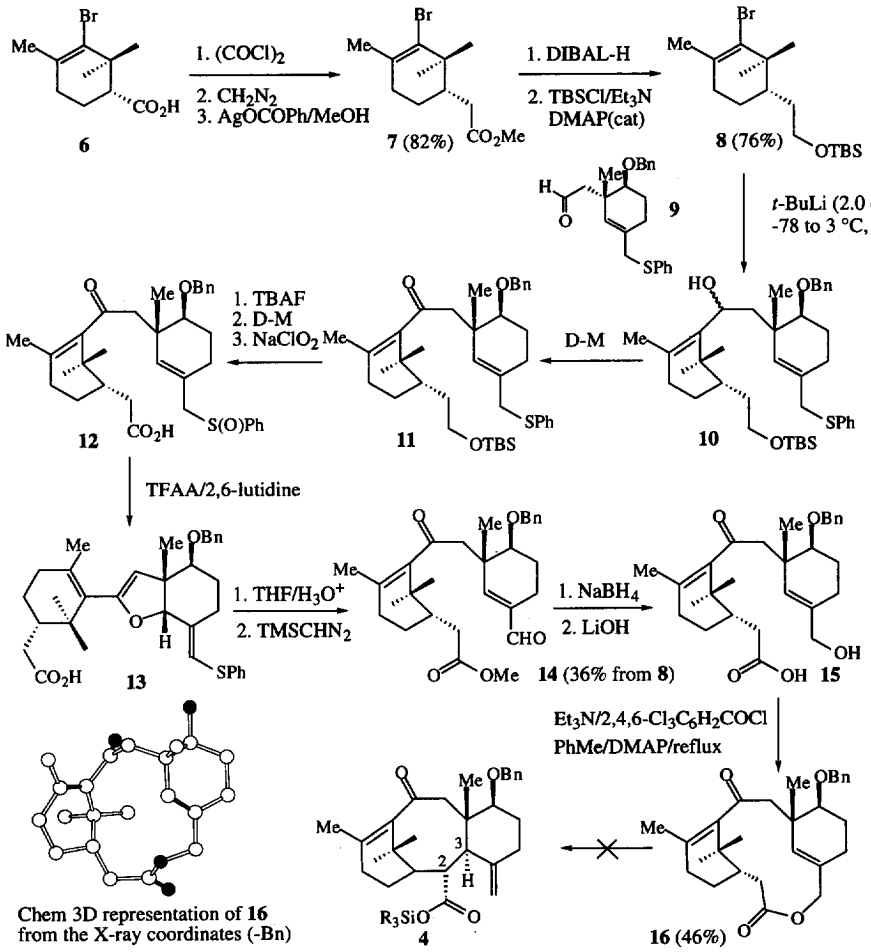
12 to Pummerer reaction conditions (TFAA) resulted in the dihydrofuran **13**. Presumably the intermediate vinyl sulfonium ion has been trapped by the C_{10} carbonyl group, which after proton loss provides **13**. Treatment of **13** with aqueous acid followed by $TMSCHN_2$ gave **14**, which on reduction and hydrolysis provided **15**. Macrolactonization of **15** using the Yamaguchi procedure[9] gave **16** (46%), which variable temperature ^1H NMR showed slow conformational equilibration of two major conformers. The structure of **16** was confirmed by X-ray analysis. Exposure of **16** to the standard Ireland-Claisen reaction procedures that work in the case of **21** (**Scheme 3**), only gave **15**. Even if large excesses of $LiNPr^i_2$ and TBSCl are used (to also form the C_{10} enol ether) the same result is obtained. It appears that the transition state from **2** to **4** is too strained, and fragmentation to the ketene takes place, resulting in **15** on work-up. Consequently, it was decided to explore the Ireland-Claisen strategy on the ester **21** which should not suffer the same transannular strain present in the lactone substrate.

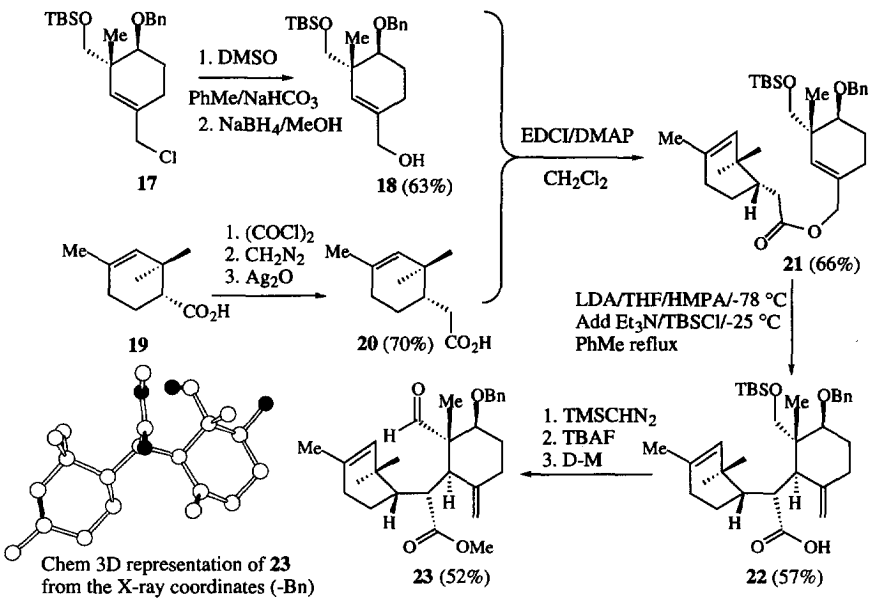
Scheme 2



Chem 3D representation of **16** from the X-ray coordinates (-Bn)

Kornblum oxidation[10] of **17**[7], followed by reduction gave **18**, **Scheme 3**. Attempts to displace the allylic chloride **17** with other oxygen nucleophiles such as superoxide gave very poor results. The racemic version of **19** was resolved *via* its S-(-)-α-methylbenzylamide derivative[7] and hydrolyzed to give **19**.[11] Arndt-Eistert homologation of **19** provided **20**, which was coupled to **18** resulting in the ester **21**. Exposure of **21** to standard Ireland-Claisen reaction conditions gave **22** as the only detectable stereoisomer. It was converted into **23** whose structure was established by X-ray crystallography. As expected, the newly formed C_2-C_3 bond has the correct absolute stereochemistry as in taxol.

Scheme 3



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References and Footnotes

1. Paclitaxel is the generic name for Taxol, which is now a registered trademark. For the isolation and structure see: Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2327.

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11. The absolute stereochemistry of **19** was deduced from an X-ray structure of its S-(-)-α-methylbenzylamide derivative.