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Pinacol Closure of Oxygenated Taxane Skeleta at C-1–C-2 with Stereoinduction by Oxygen Substituents at C-9 and C-10

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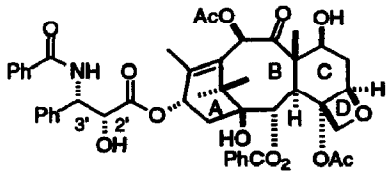
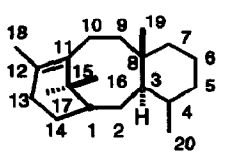
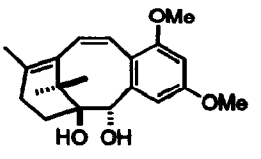
Abstract: The treatment of keto aldehydes **4** and **5** with low-valent Ti results in stereoselective intramolecular pinacol couplings that lead to optically active oxygenated taxane skeleta **2** and **3**.

Despite succumbing recently to the impressive total synthesis programs of the Holton[1] and Nicolaou[2] groups, taxol[3] is likely to remain an important total synthesis objective.[4] It is noteworthy that much of the ongoing effort directed at the synthesis of taxol involves convergent strategies that focus on closure of the eight-membered B-ring. For example, a pinacol closure of the taxol C-9–C-10 bond formed one of the key steps in the total synthesis by Nicolaou, *et al.*,[2,5] and model studies disclosed by Kende[6] and Kuwajima[7] have exploited bond connection at C-9–C-10 to form tricyclic taxane skeleta, as well. Likewise, installations of the adjacent C-10–C-11 bond in sequences reported by Kishi[8] and Danishefsky[9] have produced tricyclic taxane models. We recently reported[10] a conceptually related strategy focused on C-1–C-2 bond formation that led to **1** through a stereoselective pinacol cyclization of the appropriate bicyclic 1,2-*seco*-keto aldehyde. Herein we summarize the results of additional investigations that indicate more elaborate pinacol coupling substrates bearing oxygen substituents at C-9 and C-10 required by the natural taxane targets to undergo efficient cyclizations at C-1–C-2, as well. The configurations of the oxygen substituents at C-9 and, to a much lesser degree, at C-10 induce the newly created stereogenic C-1 and C-2 sites in **2** and **3** to which these processes lead.



TAXOL





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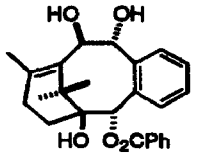

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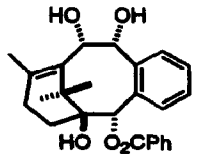

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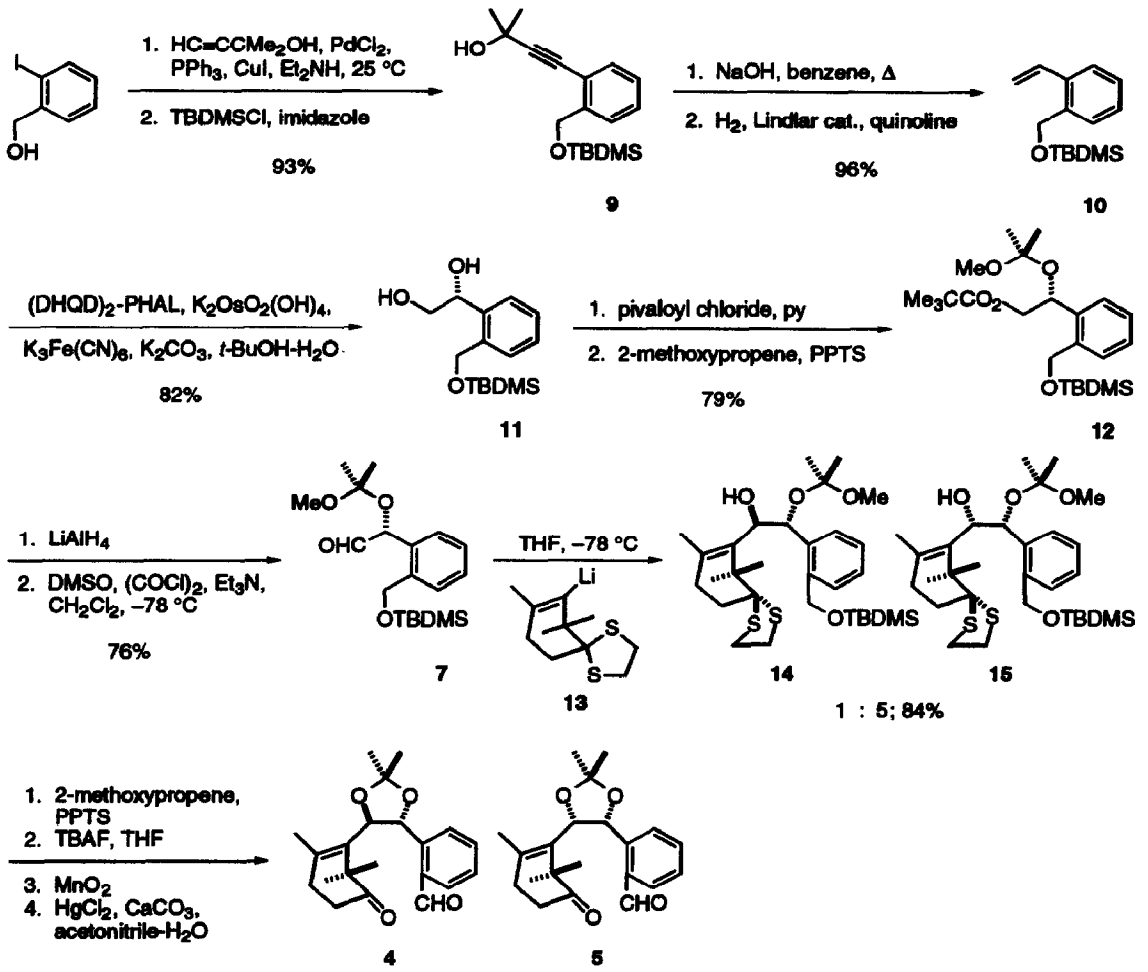
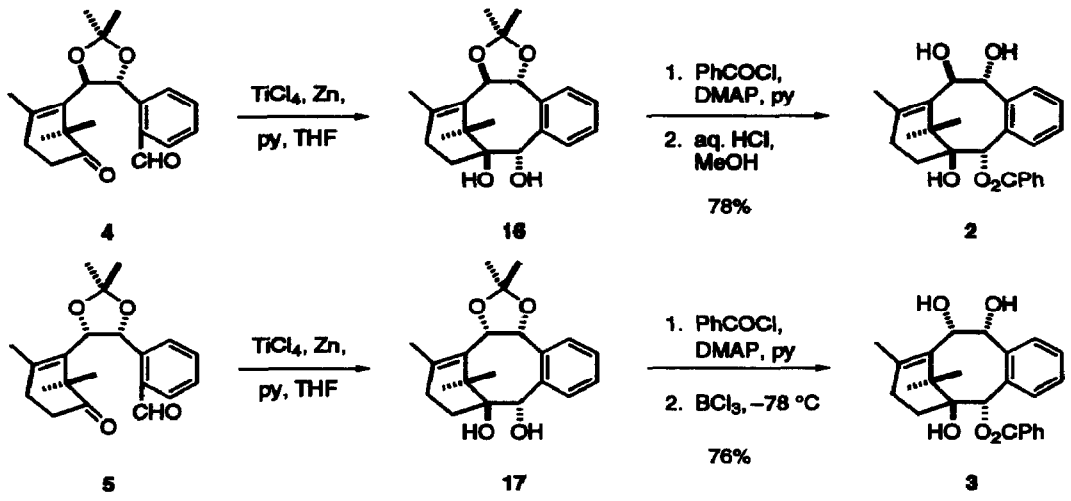


Scheme 1

The preliminary phase of the present work was directed at the construction of optically active 1,2-*seco*-keto aldehydes **4** and **5** from chiral, enantiomerically enriched C-ring fragment **7** and achiral A-ring fragment **13** (**Scheme 1**). Aldehyde **7** arose from a sequence that began with commercially available *o*-iodobenzyl alcohol. Its Pd-induced coupling with commercially available 1,1-dimethylpropargyl alcohol and subsequent protection of the primary hydroxyl gave **9**. Hydroxide ion-mediated deprotection of the terminal acetylene followed, which led to complex mixtures when the benzylic hydroxyl was not masked. Subsequent Lindlar reduction produced **10**. Styrene **10** was process into **7** through a five-step sequence initiated by Sharpless asymmetric dihydroxylation,[11] which gave **11** in 82% ee. Manipulation of protecting groups then afforded **12**, and then **7** after a final Swern oxidation. The vinyl iodide precursor to **13** was readily prepared from the corresponding dioxolane vinyl iodide[12] by treatment with ethanedithiol and BF_3-OEt_2 in methylene chloride at ambient temperature (quantitative). Its subjection to lithium-iodine exchange (*t*-BuLi, THF, −78 °C) led to **13**, and subsequent addition of **7** created (formally) chelation-controlled product **14** and (formally) Cram-Felkin



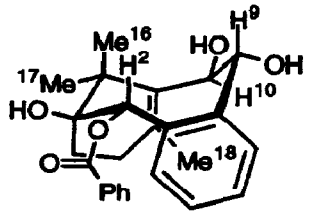
4 16 2

5 17 3

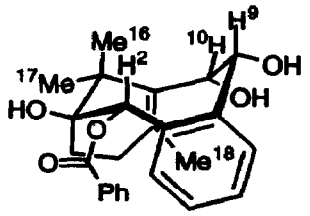
Scheme 2

product **15**. The predominant formation of either stereoisomer (or related substances) should be amenable to optimization. Whereas some flexibility existed in converting **14** and **15** into **4** and **5**, respectively, the optimal procedure involved deprotection-oxidation at the primary benzylic site before unmasking the A-ring carbonyl. Thus were **14** and **15** separately taken forward in overall yields of 50-60%.

Subjection of **4** to modified Mukaiyama pinacol coupling conditions[13] converted it (**Scheme 2**) in 69% total yield into **16** (75% of the product mixture) and two minor diastereomers (25% of the product mixture), which were not further characterized. Benzoylation of **16** and cleavage of the acetonide then delivered **2**. Likewise, pinacol coupling carried out on **5** led in 91% yield to **17** as the sole stereoisomer detectable. Conventional acid-catalyzed acetonide hydrolysis applied in the conversion of **17** into **3** caused decomposition of starting material and/or product, thus leading to the use of BCl_3 for efficient cleavage. Tricycle **2** exhibited spectral parameters consistent with those reported for this substance by Nicolaou.[5b] In particular, the ^1H NMR signal for the Me-18 group (0.64 δ) that is highly shielded by the aromatic C-ring is a characteristic signature of the endo conformation of **2**,[14] and the NOE relationships connecting Me-16, H-2, and H-9, and Me-18 and H-10 detected for its precursor **16** are characteristic of the indicated B-ring stereochemistry (see conformational structure **A** below).[15] Pinacol product **3** also exhibited a highly shielded Me-18 ^1H NMR signal (0.81 δ), NOE relationships between Me-16, H-2, H-9, and H-10, and the absence of an observable NOE involving Me-18 and H-10.[16] These spectral features are consistent with its endo conformation and B-ring



A = 2



B = 3

stereochemistry (see conformational structure **B**).

We speculated that, in the least energetic endo, boat-chair transition structure conformations anticipated for these pinacol cyclizations, the (maximally equatorial) C-9 and C-10 oxygen groups would control stereochemistry at the newly created C-1 and C-2 sites, the latter being expected to form with equatorially disposed oxygen groups (cf. **A** and **B**).[17] The above results indicate the C-9 oxygen group to exert a much higher degree of control, consistent with the pseudo A-values for substituents at these boat-chair conformer positions.[18] Whether other processes that establish the taxane framework through B-ring closure exhibit this type of transition structure conformational preference and stereoselectivity will depend on their mechanistic and stereochemical details.[19] However, the pinacol couplings investigated herein show considerable promise for delivering tricyclic taxane synthesis intermediates stereoselectively functionalized at the problematic B-ring sites.

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