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SYNTHESIS OF STEREODEFINED *Z*-VINYL IODIDES FROM CARBOHYDRATES AS A PRELUDE TO C/D RING ASSEMBLY IN TAXANES

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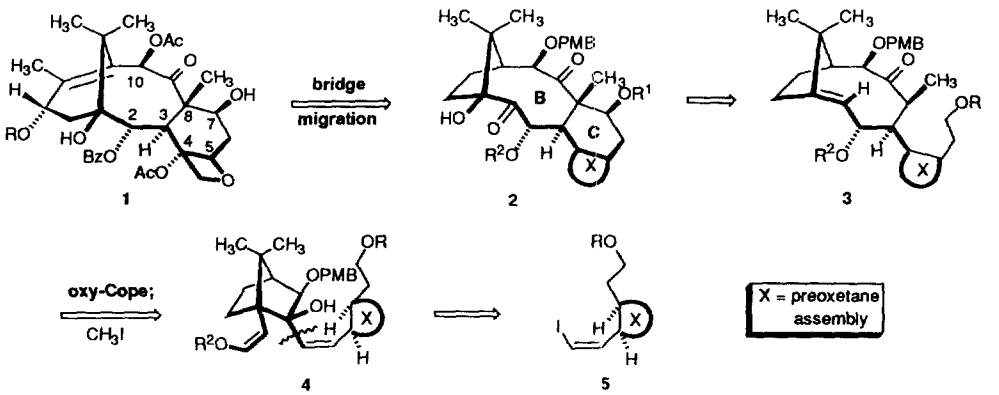
Abstract: *D*-Mannitol has been transformed into **10** and **14**, while *D*-glucose has served as precursor to **20**. In the latter example, key steps include stereocontrolled vinylation, oxidative fragmentation of the tetrahydrofuran-2,3-diol, oxetane ring closure, and highly stereoselective iodoolefination.

Keywords: carbohydrates, alkenyl halides, Wittig reactions, oxetanes

A key feature of our global approach to taxanes is the utilization of *D*-camphor as the template for construction of the entire western sector.[1] An economic means for achieving the overall synthetic agenda is to elaborate the eastern sector starting from equally inexpensive carbohydrate precursors. For paclitaxel and related compounds (**1**), this tactic requires an intrinsic ability to craft the oxetane ring rapidly and in its proper absolute configuration. Retrosynthetic analysis of these objectives (Scheme 1) suggested that a variety of "preoxetane

Scheme 1



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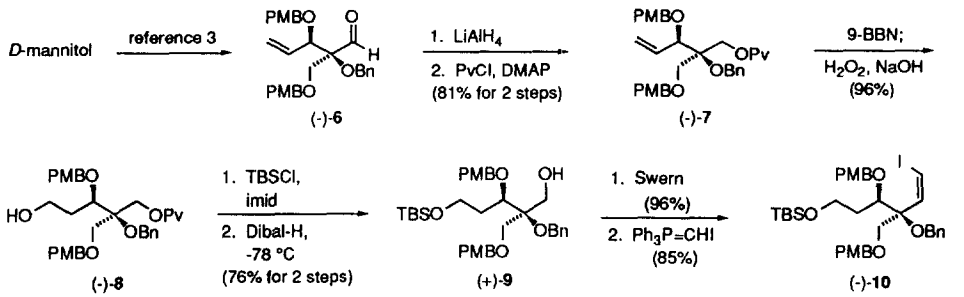
assemblies" are possible. All of these share in common the *Z*-vinyl iodide substructure defined in **5**, such that endo coupling to a functionalized norbornanone and ensuing anionic oxy-Cope rearrangement simultaneously sets correct stereochemistry at C-2, 3, 8, and 10 (taxane numbering). Herein we describe our successful effort to prepare three very useful candidate nucleophiles, including a fully elaborated vinyl oxetane.[2]

In the first instance, aldehyde **6** was generated from *D*-mannitol by known chemistry,[3] subjected to hydride reduction, and esterified to furnish pivalate **7** (Scheme 2). Following hydroboration to install the β-hydroxyethyl side chain required for ultimate aldol cyclization as in **3** → **2**, the terminal hydroxyl in (-)-**8** was protected in advance of Dibal-H reduction that afforded (+)-**9**. Subsequent Swern oxidation and Wittig condensation with (iodomethylene)triphenylphosphorane[4] produced the homologated *Z*-vinyl iodide **10**.

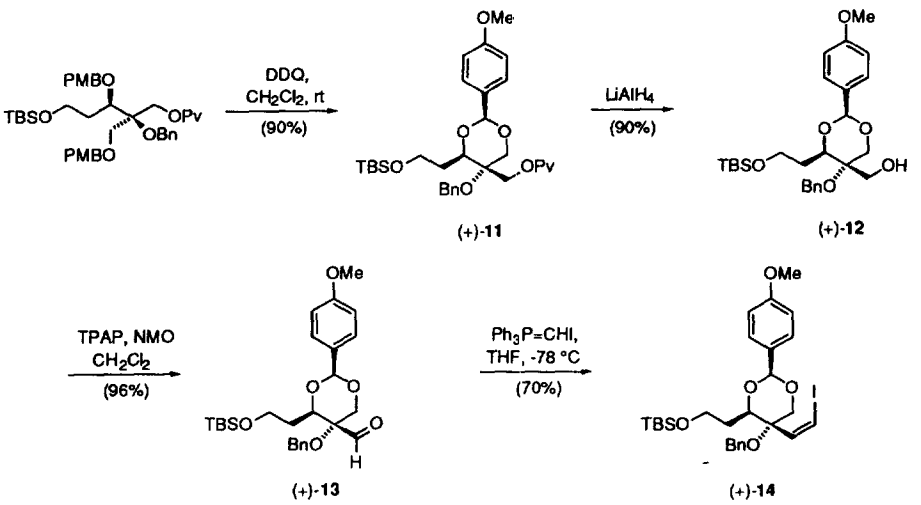
Scheme 2



A rationale for the substitution pattern in (-)-**10** has its basis in anticipated acyclic stereocontrol during the C-ring-forming step (**3** → **2**). In light of the intricacies associated with this important intramolecular maneuver,[3b,5] it could prove desirable to have a broader selection of nucleophilic building blocks at one's disposal. For this reason, we elected to pursue the development of a companion route to a cyclized variant of **10** as outlined in Scheme 3.

In our hands, the desired conformational restriction was realized directly upon oxidation of TBS-protected **8** with DDQ. Although we have not established which *p*-methoxybenzyl group is retained under these conditions, formation of acetal **11** is seen to occur rapidly and in an efficient manner. It will be recognized that all five oxygens that form an integral part of the functional group array are now suitably differentiated. The pivalate was therefore reductively cleaved, and the resulting alcohol was oxidized and transformed into the targeted substrate (+)-**14** without event.

Scheme 3

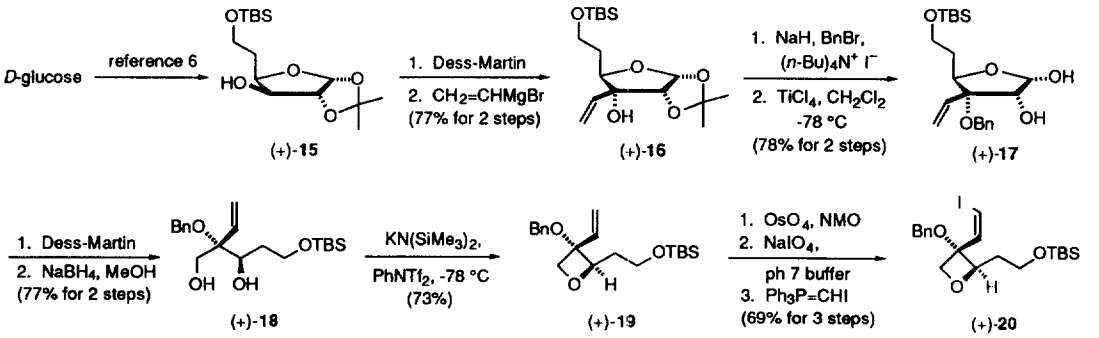


For obvious reasons, the allure of introducing the oxetane ring directly from the point of convergency could not be resisted. This tactic would be the most convergent of all, as no synthetic steps would need to be expended later to generate this strained heterocyclic unit. Consequently, advantage was taken of the ease with which *D*-glucose can be transformed into the furanose carbinol **15**.[6] Oxidation to the ketone was followed by the addition of vinylmagnesium bromide. The expectation that attack would occur in a substrate-controlled manner with avoidance of the steric congestion offered by the acetonide was confirmed by NOE analysis. These uncomplicated maneuvers allowed for regiocontrolled benzylation of the tertiary hydroxyl group in (+)-**16** in advance of acetonide hydrolysis with titanium tetrachloride at -78 °C to give (+)-**17**.

We had defined this lactol as an interim goal while recognizing the existing need to excise C-2 with concomitant cleavage of its tetrahydrofuran core. For this purpose, **17** was oxidized with the Dess-Martin periodinane,[7] thereby producing the aldehydo formate. This intermediate was directly reduced with sodium borohydride to give (+)-**18** in 77% overall yield. With this diol in hand, it proved an easy matter to activate the primary hydroxyl as the triflate and to engage the flanking OH group in neighboring group participation. This effort successfully delivered oxetane **19** in 73% yield. The previously described methodology was then exploited to generate (+)-**20**.[8]

The present study has demonstrated that the heavily functionalized *Z*-vinyl iodides **10**, **14**, and **20** can be elaborated in enantiopure form starting with *D*-mannitol or *D*-glucose. These substrates have been shown elsewhere to enter smoothly into lithium-halogen exchange, a critical step, to function as reliable nucleophiles in 1,2-additions to carbonyl compounds, and

Scheme 4



to participate stereoselectively in charge-accelerated [3,3] sigmatropic processes.[2] It is expected that these and related building blocks will see more extended use in synthesis.

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References and Notes

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(8) All new compounds described herein exhibited IR, ^{1}H NMR, ^{13}C NMR, and MS spectra/combustion data in satisfactory agreement with the assigned structures.