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SYNTHESIS OF A C-1 EPI TAXININE INTERMEDIATE USING THE TYPE 2 INTRAMOLECULAR DIELS-ALDER APPROACH

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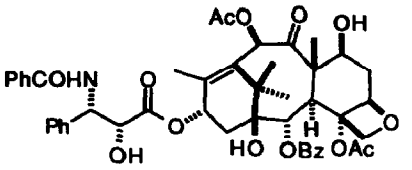
Summary: *A highly functionalized type 2 intramolecular Diels-Alder precursor, suited for use in the synthesis of taxane natural products, has been prepared. Its stereoselective preparation and cyclization to an epi-tricyclic taxane intermediate are described.*

The unprecedented success of taxol, **1**,[1,2] as a chemotherapeutic agent for the treatment of advanced ovarian cancer has made this molecule an attractive target for organic synthesis.[3] We have previously described the type 2 intramolecular Diels-Alder approach to the synthesis of the tricyclo[9.3.1.$0^{3,8}$]pentadecene ring system.[4] We report herein our findings based on the use of a highly functionalized Diels-Alder precursor possessing the C8-C10 (taxane numbering) stereocenters found in the taxane natural products, e.g., taxinine, **2**.



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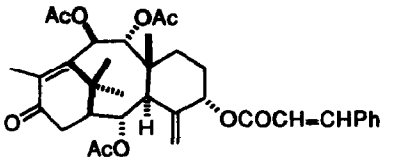


2

Allylic alcohol **3**[5] was coupled with benzyloxyacetic acid **4** (DCC, DMAP) to afford the glycolate ester **5**[6] in 85% yield (Scheme I). Enolization (KHMDS, THF, -78°C, 1 min) followed by trapping with trimethylsilyl chloride generated the silylketene acetal which when warmed to 23°C smoothly underwent a glycolate Ireland-Claisen rearrangement[7] to give, after hydrolysis and esterification with diazomethane, the desired α-benzyloxy ester **6** and diastereomer **7** in a ratio of 3.0:1 (500 MHz ^{1}H NMR). The C8-C9 relative stereochemistry of the major product was verified by X-ray analysis of the carboxylic acid.[8] Reduction of the esters (DIBALH, $PhCH_3$, 0 °C) followed by silica gel chromatography resulted in isolation of primary alcohol **8** in 65% yield. Swern oxidation[9] proceeded to give the α-benzyloxy aldehyde **9** in 79% yield.

Appendage of the diene moiety and generation of the C10 stereocenter was accomplished by treatment of the aldehyde with the dienylcerium reagent[10] derived from bromodiene **10**[4] ((i) t-butyllithium, Et_2O, 0 °C, (ii) $CeCl_3$, -78 °C). The diene alcohol **11** was isolated along with the allenyl alcohol **12** as an inseparable 5.4:1 mixture. The stereochemistry at C10 of the diene product was established by X-ray analysis of a later intermediate (vide infra). No evidence of the C10 epimers of either compound was observed in the 500 MHz ^{1}H NMR spectrum of the reaction mixture. The high level of stereoselectivity can be rationalized by invoking a chelation controlled addition of the organometallic reagent to the α-alkoxy aldehyde. Protection of the alcohols (benzyl bromide, NaH, DME, 83 °C, 29h) followed by chromatography gave the bis-benzylether **13** in 73% yield from aldehyde **9**. X-ray analysis[8] of **13** verified the product as having the same relative stereochemistry at C8, C9, and C10 as taxinine. A

judicious choice of protecting groups at this stage in the synthesis would allow selective deprotection and oxidation at C9, a critical transformation in our synthesis of taxol. For the current scheme it was desirable to minimize the number of differing protecting groups so the C-10 hydroxyl was also protected as the benzyl ether.

Conversion of the vinyl bromide to the cycloaddition precursor was carried out as follows. Metal-halogen exchange (t-butyllithium, Et_2O, -78 °C) followed by reaction with acrolein afforded a 1.5:1 diastereomeric mixture of secondary alcohols. These could be separated, but it was more expedient to oxidize the mixture directly. Thus, the alcohols were combined with $BaMnO_4$ in refluxing benzene for 2.5 h to give the trienone **14** in 48% yield for the two steps.

The key cycloaddition was affected by heating a toluene solution of the trienone at 205 °C (sealed tube) for 18 h. The cycloadduct **15** was isolated along with an inseparable impurity in 44% yield after chromatography. A single diastereomer was observed in the ^1H NMR spectrum of the reaction product. However, NOE studies to determine the relative configuration of the newly created stereocenter were inconclusive.

Inspection of molecular models reveals that the stereoisomer with the same relative configuration (bridge syn to the angular methyl group) as that found in the natural products exists in a folded (endo) conformation. The C1 epimer exists in an extended (exo) form.[11] MM2 calculations[12] support this notion, and identify the endo-syn conformation as being 7.4 kcal/mole lower in energy than the exo-anti. It was hoped that the difference in the calculated ground state tree energies of the two might be manifested, at least in part, in the relative transition state energies, thereby giving rise to the formation of the desired diastereomer. A related report by Jenkins also supported this analysis.[13] Absolute proof of the structure of the cycloadduct came from reduction of the carbonyl group. Treatment of the ketone with DIBALH at 0 °C afforded a single alcohol diastereomer **16** in 73% yield. X-ray analysis of the crystalline product verified the *anti* relationship between the bridge and the C19 methyl group (Figure 1).[14]

The cyclization of enone **14** in the exo mode was unexpected based on previous results utilizing the type 2 intramolecular Diels-Alder reaction to generate the taxane ring system.[4] It becomes even more interesting in light of the lower calculated ground state energy of the endo-syn isomer.

The chemistry described here may provide a general entry into a novel class of interesting taxol analogs, i.e., the C1-epi derivatives. We are currently pursuing this lead and are investigating the factors involved in determining the stereochemical outcome of the key Diels-Alder reaction.

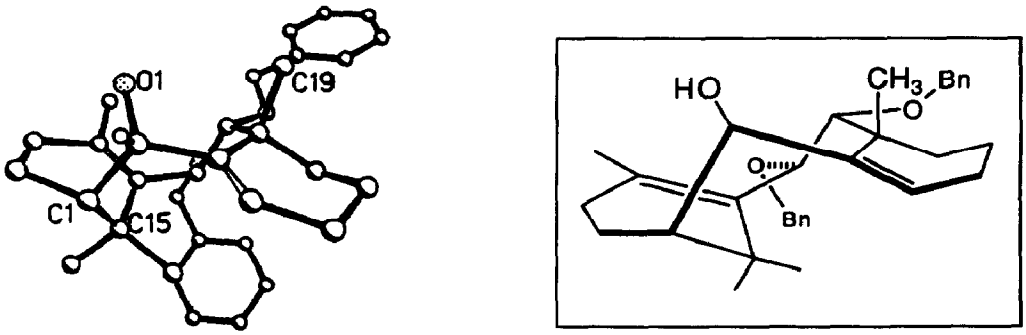
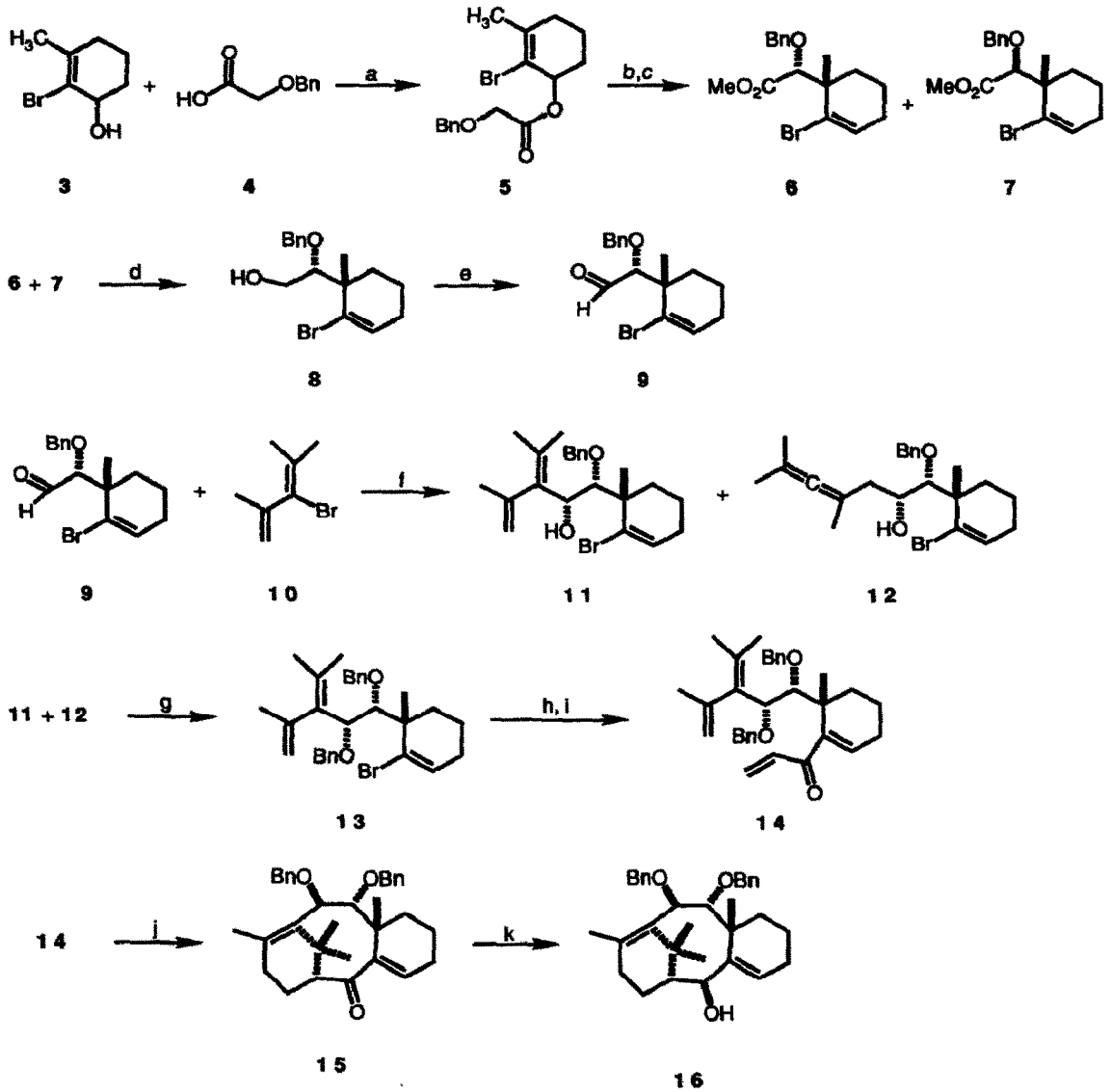


Figure 1. X-ray structure of exo -16.

SCHEME I[a]



[a] (a) DCC, DMAP, CH_2Cl_2, 85%; (b) i) KHMDS, TMSCl, THF, -78 °C - 23 °C, ii) H_3O^+; (c) CH_2N_2, 67% from **5**; (d) i) DIBALH, 0 °C, ii) Silica gel chromatography, 65%; (e) $(ClCO)_2$, DMSO, NEt_3, CH_2Cl_2, 79%; (f) i) t-BuLi, 0 °C, Et_2O, ii) $CeCl_3$, -78 °C, then **9**; (g) BnBr, NaH, DME, 73% from **9**; (h) t-BuLi, -78 °C, then acrolein; (i) $BaMnO_4$, Celite, C_6H_6, 48% from **13**; (j) $PhCH_3$ (0.007M), 205 °C, 18h, 44%; (k) DIBALH, 0 °C, 73%.

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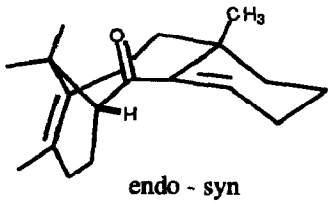
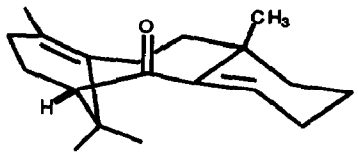
11. Endo - syn and exo - anti conformations of the carbon skeletons:



endo - syn



exo - anti

12. Macromodel, version 3.0, Columbia University, 1990.
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14. Crystal data for **16**: The crystals belong to the monoclinic system with unit cell parameters at 163K: a = 11.37(8) Å, b = 8.909(6) Å, c = 26.709(3) Å, b = 98.21(8)°, and V = 2679.8(6) $Å^3$. The space group is $P2_1/c$ with Z = 4 formula units/unit cell and D(calc.) = 1.06 Mg/m^3. Intensity data (4039 total) were collected on a Syntex $P2_1$ diffractometer employing a Siemens R3m/V system using monochromatized MoKα radiation (l = 0.710730 Å) via a q-2q scan technique. Those 2775 reflections with $|F_0| > 3.0s(|F_0|)$ were considered observed. The structure was solved by direct methods and refined by full-matrix least-squares techniques. Hydrogen atoms were included using a riding model with d(C-H) = 0.96Å, d(O-H) = 0.85 Å and U(iso) = 0.08 Å. At convergence, R_F = 5.7%, R_{wF} = 7.0% and GOF = 1.54. A final difference-Fourier synthesis showed no significant features.

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