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An Intramolecular Diels-Alder Approach to Tricyclic Taxoid Skeletons#

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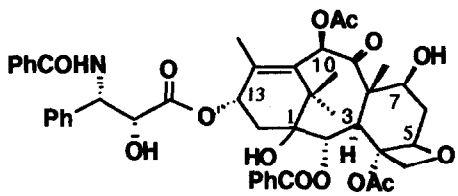
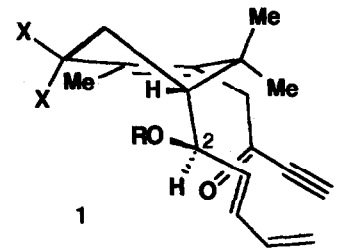
Abstract: A direct, intramolecular cycloaddition route to functionalized tricyclic taxanes is described. This will facilitate the preparation of potentially useful analogues and ultimately the total synthesis of taxol. The cyclohexenone **2** is converted as illustrated to the trimethylcyclohexene **9** to which the diene and acetylenic side chains are attached by sequential nucleophilic additions. Removal of the trimethylsilyl protecting group and Dess-Martin oxidation afforded the triene **13**. Microwave assisted thermal cyclization generated the tricyclic ketone **14** stereoselectively whose structure was further established by conversion to the aromatic system **15** upon treatment with DDQ.

Recently the potent antitumor agent taxol has elicited considerable attention due to the synthetic challenge presented by its rare ring system,[1] its therapeutic promise and novel mode of action,[2,3] and scarcity of supply.[4,5] Consequently a variety of synthetic approaches to the carbocyclic nucleus are under active investigation[6,7,8] in order to prepare medicinally interesting analogs and ultimately taxol itself. We wish to report a convergent, intramolecular Diels-Alder route to the functionalized tricyclo[9.3.1.$0^{3,8}$]pentadecene skeleton in which the C_2 epimer controls the adduct stereochemistry.



Taxol



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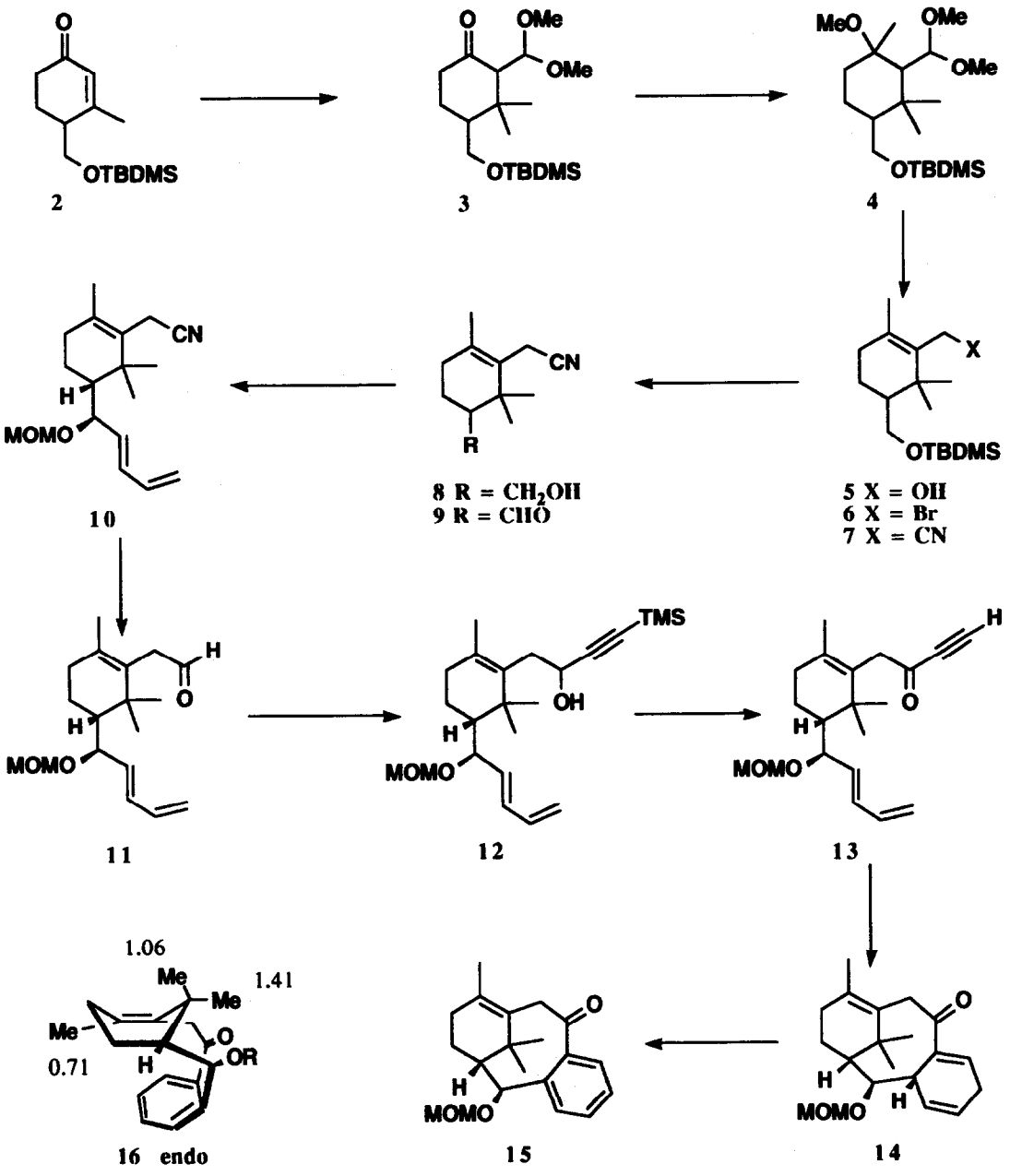
Retrosynthetically this requires the disconnection of a modified ring C cyclohexene to the intermediate **1** in which the endo transition state, with the dienophile anti to the C_2 substituent, should be preferred. However this simplistic approach has several potential complications due to the known difficulty of forming congested cyclooctanes via [4 + 2] cycloadditions[9,10,11] and the structural requirement that the diene side chain adopt an axial orientation to ensure the close proximity of the reactive components as required for the transition state. Previously it has been assumed that a rigid geometry is necessary to accomplish this. In a related case, a one carbon bridge between the C_{13} center and C_{17} methyl group was employed in a bicyclo[2.2.2]octene system to overcome these entropic problems.[12,13] However, the conformer population in cyclohexenes is known to vary with the substitution pattern[14,15] and the potential 1,3 diaxial interaction (X = H_2) should not cause difficulty provided the reactive conformer comprises a reasonable percentage of the equilibrium mixture at the temperature

selected. Molecular mechanics calculations[16] indicated that 1,2,3,3,4-pentamethylcyclohexene preferred a conformation with minimal 1,3-methyl-hydrogen interference. Furthermore this nonbonded interaction will disappear entirely if a carbonyl (X = O) or enol ether were employed. Thus additional ring constructions should not be required to access the transition state geometry. To encourage cycloaddition the rotational parameters were minimized by using an acetylenic dienophile. The validity of this analysis has been demonstrated below by the synthesis of the tricyclic taxane nucleus **14** and the related aromatic system **15**.

Conjugate addition to the cyclohexenone **2**[17] (MeMgBr, CuI, 0°C, 0.5 h) followed by condensation with trimethyl orthoformate in the presence of $BF_3{\cdot}Et_2O$ installed the gem dimethyl function and the acetal in **3** (59%). Addition of methyllithium followed by oxygen alkylation with methyl iodide to form **4** set the stage for acetal cleavage (TMSCl, NaI, CH_2Cl_2), methoxide elimination (MeONa, MeOH, 68°C) and reduction ($NaBH_4$, $CeCl_3$, 70%) to the alcohol **5**.[18] Chain extension was accomplished by cyanide displacement (NaCN, methyl pyrrolidinone, 75%) of the primary bromide **6** (Ph_3PBr_2, Et_3N, CH_2Cl_2, -78°C, 1h) followed by removal of the silyl protecting group (*n*-Bu_4NF, THF, 21°C, 3h, 98%) and oxidation (DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, 94%) of the resulting primary alcohol **8** to the aldehyde **9**. The diene unit was prepared by exchange of 1,3-(*E*)-butadiene-1-tributylstannane[19] with *n*-BuLi and added to the aldehyde **9** (THF, -78°C, 0.5 h, 96%). The resulting secondary alcohol (6:1 diastereomer ratio) was protected as a methoxymethyl ether (MOMCl, $(i\text{Pr})_2\text{EtN}$, CH_2Cl_2, 90%) to afford **10**. X-ray analysis of a derivative of the major diastereomer established the C_1, C_2 stereochemistry (taxol numbering).[20] Diisobutyl aluminum hydride reduction of the nitrile **10** provided the aldehyde **11** which was treated with lithium trimethylsilylacetylide (HCCTMS, *n*-BuLi, THF, -78°C, 95%) to form alcohol **12**. The final steps to the triene **13** were surprisingly challenging. It was important to remove the trimethylsilyl group (KOH, MeOH, CH_2Cl_2, 21°C, 99%) at the alcohol stage, while only the Dess-Martin periodinane oxidation method,[21] of several examined, generated the required ketone in reasonable yield (55%).

Cyclization of ketone **13** was effected by heating in a sealed glass tube in a modified microwave oven[22] (0.05 M toluene solution, 1% mol equiv. hydroquinone, 10 h, 35-40%) to afford the tricyclic system **14** stereoselectively. The major adduct arose via the preferred endo transition state in which the nonbonded interactions were minimized due to the alignment of the dienophile under the triene remote from the MOM substituent as illustrated in **1**. This pattern of π-facial selectivity was consistent with related intermolecular cycloadditions involving acetylenes and acyclic dienes.[23] The structural assignment was further established on the basis of the ^1H NMR spectrum, in which the C_3 proton appeared at δ 2.95 as a doublet of doublets (J = 5.6, 9.6 Hz) due to coupling with the adjacent allylic C_4 and secondary C_2 hydrogens.[24] Unfortunately it was not possible to catalyze the cycloaddition with Lewis acids, due to the ease with which the cyclohexene double bond migrated into conjugation with the acetylenic ketone. This accounted for the uncyclized material in the thermal reaction. It is anticipated, that current research with the C_{13} ketone in place (taxol numbering), will suppress this tendency and lead to improved yields. Confirmation of the tricyclo[9.3.1.$0^{3,8}$]pentadecatriene skeleton was provided by the conversion of **14**, upon treatment with DDQ, in refluxing benzene to the aromatic ketone **15**. In keeping with related literature examples this material existed as a mixture of exo and endo isomers (~1:1)[25] in which the vinyl methyl signal appeared at 0.71 (endo, **16**) or 1.76 (exo) depending upon the orientation of the benzene ring.

An important feature of taxol itself is the C_{13} oxygen side chain. Previous studies, including our own, have established that the requisite oxygen may be installed by allylic oxidation[7,26] and recently the C_1 oxygen was introduced from the C_2 ketone enolate.[8,27]



In conclusion, a carefully designed [4 + 2] cycloaddition strategy with an acetylenic dienophile can be employed to generate the substituted taxane nucleus directly, with good stereochemical control, in a convergent manner from a functionalized cyclohexene substrate. We are currently extending these results toward the total

synthesis of taxol and the preparation of therapeutically promising analogs, using more highly oxygenated precursors, in which the C_{13} ketone and 'natural' C_2 epimer are expected to facilitate and control the cyclization.

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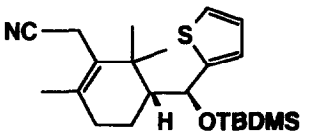

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Dedicated to the memory of our colleague Jean-Louis Roustan, deceased September 28, 1992.

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