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A stereoselective intramolecular Diels–Alder strategy for the tricyclo[9.3.1.0^{3,8}]pentadecane core of aromatic C-ring taxanes

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Abstract—A stereoselective Lewis acid-catalyzed and chelation controlled intramolecular Diels–Alder entry into the tricyclo[9.3.1.0^{3,8}]pentadecane core of aromatic C-ring taxanes is described. The approach affords an efficient, high yield, access to aromatic C-ring taxanes variably functionalized at the C2, C4, C5, and C9 positions.

Paclitaxel **1** (Taxol®), Docetaxel **2** (Taxotere®) (Fig. 1) and related taxane diterpenoids continue to elicit international attention. This is a consequence of their proven chemotherapeutic utility and their attraction as challenging synthetic targets.[1] Six total syntheses of Taxol® have been reported.[2] Novel strategies continue to be developed for construction of the unique taxane tricyclo[9.3.1.0^{3,8}]-pentadecane nucleus, and the synthesis of structurally simplified analogs. Consequently methods for the rapid assembly of the core structure for the eventual preparation of improved therapeutic analogues are still required.

Despite the diminished cytotoxicity of aromatic C-ring taxanes such as those prepared by Nicolaou (**3a**–**c**)[3] and Danishefsky (**4a**–**b**),[4] structures in this class remain attractive candidates for synthesis. In particular, the multi-drug resistance (MDR) reversing activity of an aromatic C-ring taxane observed by Kuwajima (**5**)[5] warrants further study, and aromatic C-ring taxane scaffolds with judiciously selected substituents positioned to accommodate current taxoid structure–activity relationship (SAR) data may show cyctotoxic activity.[6]

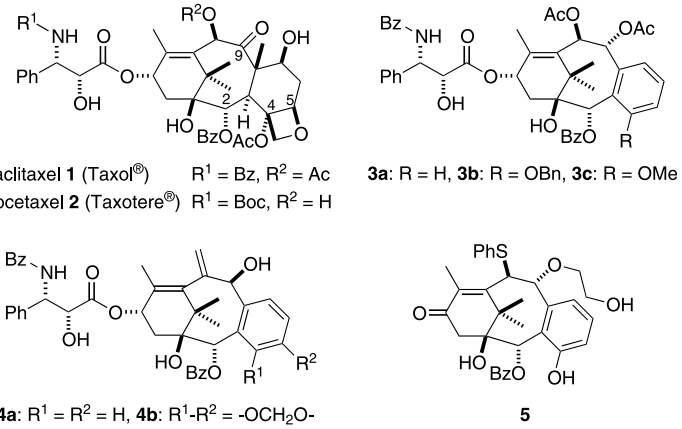

Figure 1. Taxol®/Taxoetere® and biologically significant aromatic C-ring taxanes.

Keywords: taxanes; intramolecular Diels–Alder; Lewis acid; stereoselective.

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Several groups have reported the preparation of differentially substituted aromatic C-ring taxanes as simplified targets to demonstrate various B-ring construction methods and subsequent functional group manipulation.[7] Shea[8] and Malacria[9] have described efficient type II intramolecular Diels–Alder (IMDA)[10] strategies to the AB-ring system. However, these routes afford aromatic C-ring taxanes that are not readily amenable for the introduction of therapeutically meaningful substituents after ABC-ring assembly. We have developed an extension of our ongoing taxane research,[11] that utilizes a concise AB-ring cycloaddition protocol[12] to highly oxygenated aromatic C-ring taxanes.

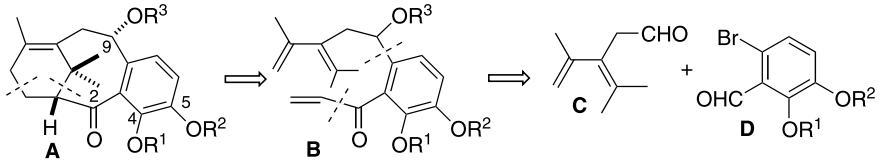
SAR data for Taxol® have established that the C2 benzoate and C4 acetate on the molecule's 'southern' perimeter are crucial for activity. In contrast, the 'northern' perimeter substituents C7 hydroxyl and C10 acetate can be omitted without compromising efficacy.[1] Although not essential, the C9 hydroxyl increases activity slightly, and acts as a handle for resolvable derivatives[3a] or solubilizing groups.[13] In addition, Snyder suggested the C4–C5 oxetane ring is not obligatory but a replacement hydrogen bond acceptor is desirable. In addition, the 'structural stiffness' imparted in benzannulated skeletons is beneficial to 'maintain Taxol®-like protein polymerization activity'.[6a]

Despite the elegance of previous syntheses, the diene and aromatic C-ring components selected do not easily allow installation of the critical substituents (or potential mimics) at the C4, C5, and C9 positions. In order to address this deficiency and retain the advantage of rapid cycloaddition AB-ring assembly, we elected to employ diene aldehyde **C** as a source of the future C9 oxygen, and to incorporate the requisite C4 and C5 oxygens into aryl bromide **D** (Scheme 1). It was anticipated, that addition of bromide **D** to **C** and subsequent elaboration to triene **B**, would permit the Lewis acid catalyzed and chelation controlled IMDA closure of the AB-ring system to afford the aromatic C-ring taxane **A** as a single diastereomer.

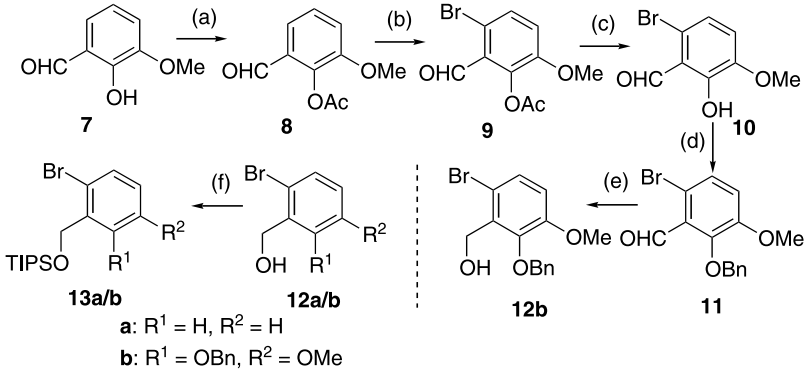
Diene aldehyde **6** (i.e. **C**) was readily prepared in multigram quantities, and 45% overall yield as previously reported from 2,3-dimethyl-2-butene (four steps, 45%).[11] An established sequence (four steps, 86%) afforded bromobenzaldehyde **9** from *o*-vanillin **7** (Scheme 2).[14] The initial bromination of benzaldehyde **8** yielded **9**, and acetate cleavage afforded bromophenol **10**.

Protection of bromophenol **10** as its benzyl ether **11** was selected to allow the eventual facile deprotection via hydrogenolysis following AB-ring closure to the aromatic C-ring taxane core.[2] Reduction of bromobenzaldehyde **11** gave the bromobenzyl alcohol **12b**, which was quantitatively protected as its triisopropylsilyl ether to furnish aryl bromide **13b**. The aryl bromide **13a** was prepared separately from 2-bromobenzyl alcohol **12a**.

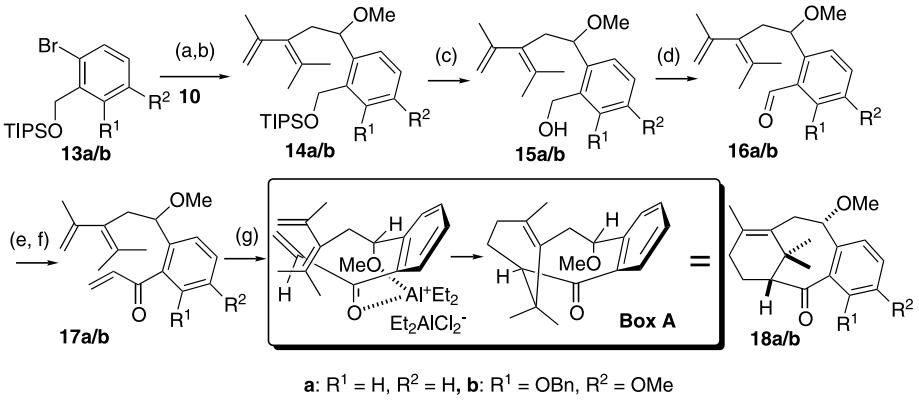
In order to establish the optimal conditions, the entire synthetic sequence leading to the formation of aromatic C-ring taxane **18a** was performed initially with aryl bromide **13a**, and then repeated with aryl bromide **13b** to generate the aromatic C-ring taxane **18b** (Scheme 3). Lithium–halogen exchange enabled coupling of aryl bromides **13a**/**b** with diene aldehyde **6** (**C**, Scheme 1). The resulting alcohols (not illustrated) were methylated to provide intermediates **14a**/**b**. Attempts to obtain trienes **17a**/**b** directly by coupling the diene aldehyde **6**



Scheme 1. Retrosynthetic strategy for differentially substituted aromatic C-ring taxanes



Scheme 2. *Reagents and conditions*: (a) Ac_2O, DMAP (cat.), Et_3N, CH_2Cl_2, rt, 2 h, 95%; (b) KBr, Br_2, H_2O, rt (22°C), 10 h, 98%; (c) $NaHCO_3$, MeOH/H_2O (2:1), rt, 5 h, 96%; (d) BnCl, MeOH, K_2CO_3, 65°C, 5 h, 96%; (e) $NaBH_4$, MeOH, rt, 2 h, 86%; (f) TIPSCl, imidazole, CH_2Cl_2, rt, 18 h, 98%.



Scheme 3. *Reagents and conditions*: (a) (i) ^{t}BuLi, THF, −78°C, 30 min (ii) **6**, −78 to 0°C, 2 h, 76%; (b) NaH, MeI, THF, rt, 18 h, 95%; (c) TBAF, THF, rt, 2 h, 92%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 89%; (e) CH_2=CHMgCl, Et_2O, −78 to 0°C, 2 h, 97%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 80%; (g) Et_2AlCl, CH_2Cl_2, −78 to 0°C, 5 min, 72%.

and an aryl bromide substituted with the C1–C2 alkene dieneophile resulted in complex mixtures. Subsequent deprotection of silyl ethers **14a**/**b** with tetrabutylammonium fluoride (TBAF) afforded benzyl alcohols **15a**/**b** in 92% yield. Prolonged exposure of silyl ether **14b** to TBAF promoted the elimination of methanol between the C9 and C10 positions, thus deprotection was carefully monitored to minimize formation of the undesired olefin. The benzyl alcohols **15a**/**b** were readily oxidized to benzaldehydes **16a**/**b** using Dess–Martin periodinane. Subsequent generation of the hydroxy-trienes (not illustrated) with vinyl magnesium bromide followed by an additional oxidation of the benzyl alcohols afforded the desired Diels–Alder precursors **17a**/**b**. Under conditions previously developed in the Fallis group,[12] Lewis acid catalyzed and chelation controlled IMDA cyclization of **17a**/**b** afforded aromatic C-ring taxanes **18a**/**b** as single diastereomers.

The stereochemistry of aromatic C-ring taxanes **18a**/**b** was assigned, as established earlier, based on the previously obtained crystal structure of a related AB-ring compound prepared under identical Lewis acid catalyzed IMDA conditions.[12] The observed stereoselectivity arises from the chelation control provided by complexation of the Lewis-acid between the C2 carbonyl and C9 methoxy substituents as illustrated in Box A (R's deleted for clarity). This geometric arrangement mimics a 'cycloheptene like' ring and appears to be particularly favorable, as this orientation may also be partially stabilized by association with the aromatic ring to facilitate achievement of the *endo* transition state. Related chelation effects have been shown to control the selectivity of both intermolecular[15] and intramolecular cycloadditions[16] mediated by Lewis acids. The aromatic C-ring taxanes **18a**/**b** exist as the *endo* atropoisomers based on the chemical shifts of the three A-ring methyl groups (0.70, 1.09, 1.34 ppm for **18a** and 0.82, 1.08, 1.32 ppm for **18b**).[17,18]

Overall, this Lewis acid-catalyzed and chelation controlled stereoselective IMDA strategy provides a concise route for the preparation of aromatic C-ring taxanes variably substituted at the C2, C4, C5, and C9 positions. This approach allowed the construction of a single diastereomer of the substituted aromatic C ring taxanes **18a**/**b**[19] in seven steps and greater than 40% overall yield from the combination of diene aldehyde **6** and aryl bromides **13a**/**b**. Additional investigations into the stereoselective reduction of the C2 ketone, esterification of the resulting C2 hydroxyl,[1] and alteration protecting group manipulation for the C4, C5, and C9 hydroxyls are in progress in order to access appropriately functionalized, biologically active aromatic C-ring taxanes.

Acknowledgements

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19. Spectra **18b**: IR (thin film) ν 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.82 (s, 3H), 1.08 (s, 3H), 1.32 (s, 3H), 1.60 (m, 1H), 1.85 (m, 2H), 2.18 (m, 1H), 2.44 (dd, $J=12.4$, 10.7 Hz, 1H), 2.63 (d, $J=7.3$ Hz, 1H), 2.72 (dd, $J=10.4$, 6.3 Hz, 1H), 3.38 (s, 3H), 3.85 (s, 3H), 4.27 (dd, $J=10.6$, 6.4 Hz, 1H), 4.59 (d, $J=10.2$ Hz, 1H), 5.02 (d, $J=10.3$ Hz, 1H), 6.80 (d, $J=8.5$ Hz, 1H), 7.23 (d, $J=8.5$ Hz, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6, 20.8, 25.2, 27.9, 28.5, 37.0, 37.5, 55.8, 58.1, 63.7, 80.6, 110.9, 114.0 120.8, 127.9, 128.3, 128.4×2, 129.2, 130.6, 135.3, 137.4, 138.7, 142.0, 151.2, 213.0; HRMS (EI) m/z calcd for $C_{27}H_{32}O_4=420.2301$, found 420.2299.