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SYNTHESIS OF A TAXININE ANALOG VIA THE INTRAMOLECULAR DIELS-ALDER CYCLOADDITION

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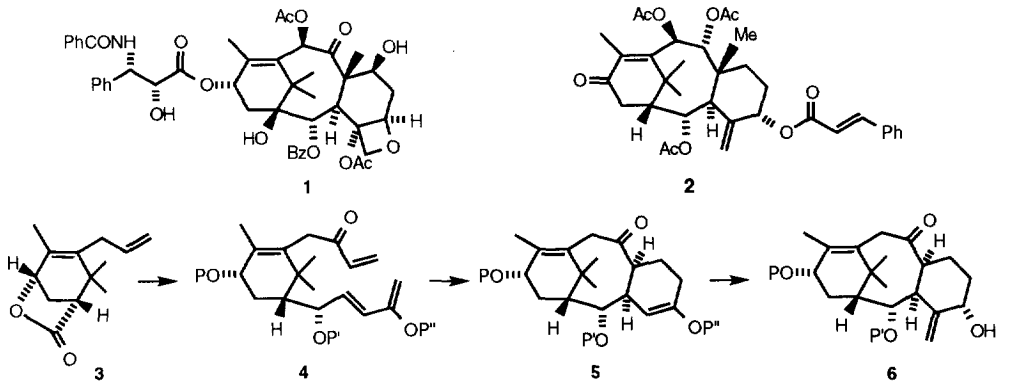
Abstract: The synthesis of the tricyclic ring system of the taxane diterpenes via an A→ABC intramolecular Diels-Alder construction, and the elaboration of the cycloadduct **13** to taxinine analog **17** are described.

The discovery of taxol (paclitaxel) **1** (Scheme I) has been an important breakthrough in cancer chemotherapy.[1] It is the only plant product known to promote the formation of microtubules and to interfere with their disassembly by binding to β-tubulin.[2] Its remarkable clinical efficacy against breast and ovarian cancer, coupled with its entirely novel mechanism of action, have resulted in a prodigious effort directed towards both semi- and total synthesis of **1**,[3] which have recently culminated in the first three reported total syntheses of taxol.[4-6]

Scheme I



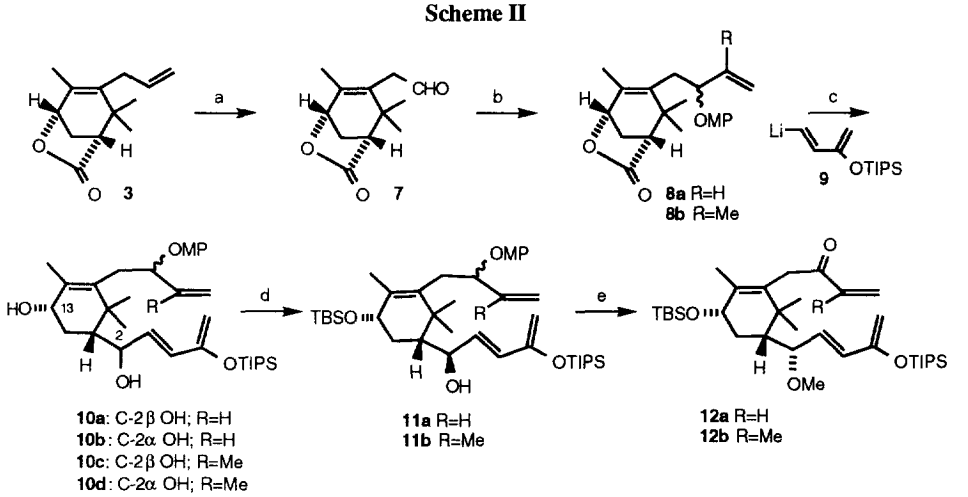
We have recently disclosed a verbenone-based route for the stereoselective synthesis of A-ring synthon **3**.[7] We report herein the transformation of **3** to intramolecular Diels-Alder substrate **4**, and the subsequent transformation of the derived cycloadduct **5** to **6**, a highly functionalized analog of taxinine, **2**, as outlined in Schemes II and III.[8]

Oxidation of the terminal alkene of **3** via dihydroxylation (cat. OsO_4) and cleavage of the resulting diol ($NaIO_4$) resulted in the formation of aldehyde **7**. Addition of either vinyl or isopropenyl Grignard to **7**

and protection of the resulting alcohol with 2-methoxypropene afforded acetal **8a** and **8b**, respectively (MP=2-methoxypropyl). Lactone opening was achieved using the procedure of Danishefsky.[9] Reaction of **8a** (R=H) with DIBAL-H followed by treatment of the lactol intermediate with vinyl lithium **9**, obtained on reaction of the corresponding stannane[10] with n-BuLi, gave alcohols **10a** and **10b**, as a 5:1 ratio of C-2 β and α epimers, respectively (taxol numbering). Comparable selectivities were observed in the formation of **10c** and **10d** from **8b** (R=Me).

Selective protection of the C-13 hydroxyl of **10a** led to the formation of **11a**. We have found that C-2β stereochemistry of **11a** could be cleanly inverted to the C-2α oxygen stereochemistry found in the taxanes. Oxidation of **11a** to the corresponding ketone, followed by carbonyl reduction with L-Selectride, resulted in the exclusive formation of the C-2α alcohol, via addition of hydride to the ketone derived from **11a** with the same facial selectivity as that observed on addition of **9** to the aldehyde derived from **8**. Methylation of the C-2α alcohol, followed by C-9 deprotection and oxidation provided the intramolecular Diels-Alder substrate **12a**. The isopropenyl dienophile **12b** was prepared in the same manner from **10c**.

Scheme II

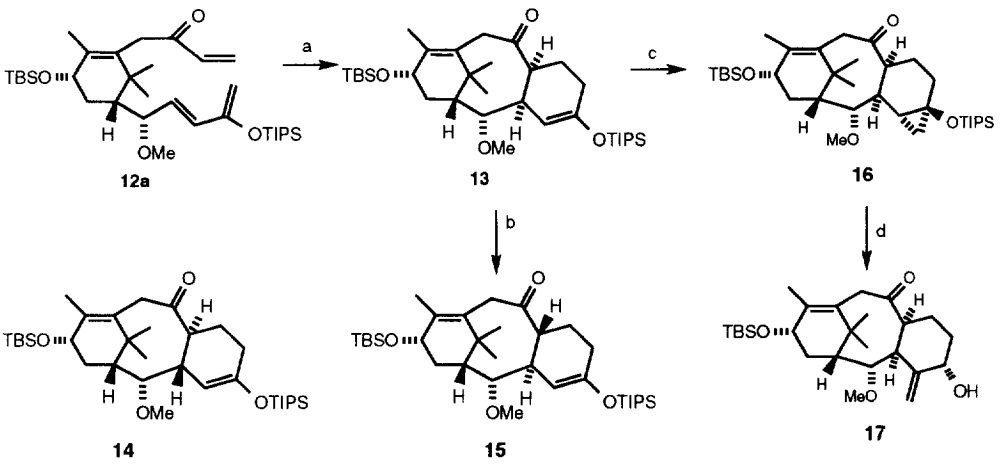


a)1) 2mol % OsO_4/H_2O,NMO, Acetone : water (8:1);2) $NaIO_4$,0°C, 30 mins, THF:H_2O (1:1), 70%; b) 1) CH_2=CHMgBr, ether, -78°C, 61 %; 2)2-methoxy propene, cat. PpTs, 0°C, 93%; c) DIBAL, tol, -78°C, 1h; R'Li, 18h, 60%; d) TBSOTf, 2,6-lutidine, -78°C, 68%; e)1) Dess-Martin periodinane, CH_2Cl_2, 93%,2) L-Selectride, THF, -78°C, 89%,3) NaHMDS/THF, 0°C, MeI, 95%,4) cat. PpTs, MeOH-Et_2O (1:1),0°C, 98%, 5) Dess-Martin periodinane, CH_2Cl_2, 91%.

While cycloaddition of the isopropenyl dienophile **12b** could not be achieved under a variety of reaction conditions, heating **12a** to 140°C in a sealed tube under scrupulously degassed conditions for 110h led to a 95% yield of 7:2:0.5 mixture of diastereomers **13**, **14**, and **15**, of which **13** was the major adduct (Scheme III). The stereochemical relationships was established by a combination of X-ray crystallographic, NMR spectroscopic analysis and chemical correlation. Epimerization of **13** led to a 56:44 mixture of **13** and the *trans*-fused product **15**.

We have converted **13** to **17** (Scheme III), an analog of taxinine, **2** (Scheme I).[11] Direct methylenation of **13** with Eschenmoser's salt,[12] or reaction of **13** with a variety of formaldehyde equivalents was not successful. However, cyclopropanation of **13** gave **16**, via reaction from the sterically less hindered convex α-face of the silyl enol ether. Treatment of **16** with Zeise's dimer, based on work by Ryu *et al.*, provided stereoselectively the C-5α allylic ether corresponding to **17**, the stereochemistry of which is established by migration of the C-4β hydrogen in **16**.[13] The C-5 TIPS ether was selectively deprotected to give **17**, the stereochemistry of which was unequivocally established by X-ray crystallographic analysis.

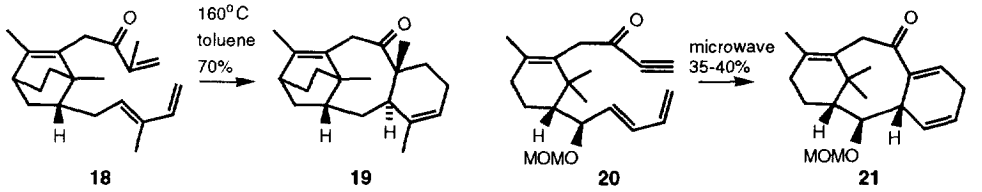
Scheme III



a) Toluene, 140°C, 110h, 95% overall; b) 2.5% NaOMe/MeOH, reflux, 20h; c) Et_2Zn, ICH_2Cl, 1,2-dichloroethane, 0°C, 100%;d)1)$Pt[(CH_2{=}CH_2)Cl_2]_2$, 5 mol%, CH_2Cl_2, 80%; 2) TBAF (10 eq.), 0°C, 7h, 60%

The construction of this cis-fused C-ring analog of taxol via intramolecular Diels-Alder cycloaddition that we have described here stands in striking contrast to related reports by Sakan[8a] and Fallis[8b] (Scheme IV). Sakan reported that cycloaddition of **18** leads to the exclusive formation of **19**, containing both the C-8 angular methyl group and the trans B/C ring fusion, although the bicyclooctane framework of **19** cannot be readily transformed to the geminal dimethyl-substituted A ring of taxol. In the more recent report by Fallis, cycloaddition of **20** occurred only to give **21** with the acetylenic dienophile under microwave irradiation and in modest yield. In the present study, we have demonstrated that the cycloaddition of **4** generates the tricyclic ring system of the taxanes in excellent yield, without recourse to either a bicyclooctane A ring construct or the sterically undemanding acetylenic dienophile. This reaction leads to the establishment of oxygen functionalities at C-2, C-5, C-9 and C-13, as well as a $\Delta^{4,5}$ enol ether to facilitate introduction of the oxetane ring. Further studies on the introduction of the C-8 methyl group and the establishment of the trans-B/C ring fusion in this system are currently underway, and our results will be reported in due course.

Scheme IV



18 **19** **20** **21**

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10 Hydrostannylation of (±)-2-butynol, oxidation of the major (*E*)-isomer and subsequent treatment with LHMDS / TIPSOTf afforded the stannylated diene, from which **9** is derived on reaction with n-BuLi.

11 All new compounds were characterized by full spectroscopic (NMR, IR, high resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials. Spectral data for allylic alcohol **17:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.96 (d, J 1.7 Hz, 1H), 4.95 (d, J 1.6 Hz, 1H), 4.6 (br unresolved multiplet, 1H), 4.02 (br m, 1H), 3.90 (br m, 1H), 3.55 (d, J 15.6 Hz, 1H), 3.24 (m partly hidden, 1H), 3.22 (s, 3H), 3.14 (dd, J 6.8, 2.6 Hz, 1H), 2.27-2.42 (m, 3H), 2.1 (m, 1H), 1.98 (dd, J 8.9, 1.9 Hz, 1H), 1.9 (s, 3H), 1.71 (dd, J 15.3, 6.1 Hz, 1H), 1.60 (m, 2H), 1.1 (m, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 0.93 (s, 9H), 0.11 (s, 3H) and 0.09 (s, 3H).; ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 209.9, 153.7, 137.0, 130.7, 106.2, 79.5, 71.3, 68.0, 57.1, 57.0, 49.0, 47.3, 42.5, 37.8, 35.1, 31.3, 29.1, 26.6, 26.0, 23.0, 18.1, 15.5, -4.2, -5.1. FT-IR (film, cm^{-1}): 3508, 2923, 2851, 1681, 1470, 1360, 1253, 1086, 1067, 1035, 1001.; exact mass calculated for $C_{26}H_{44}SiO_4$ ($M+NH_4^+$): 466.3352; found: 466.3359.

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