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Utilization of the Versatility of Sulfur in C–C Bond Formation and Cleavage: Synthesis of ABC Taxoid Skeletons

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A practical and convenient five-step protocol is described to access the ABC ring system of Taxol by utilizing the versatility of the sulfur atom in its various oxidation states viz., condensation/Pummerer cyclization/coupling/annulation/fragmentation.

Introduction

Taxol®, the best-selling anti-cancer drug, has attracted the attention of organic chemists, biologists, medicinal chemists and pharmacologists for the past two decades owing to its unique structural framework, unique mechanism of action towards cancer tumor cells, limited supplies, and difficulties in the formulation of the drug (Figure 1).[1] Taxol®, a tetracyclic diterpenoid was isolated from the bark of a slow-growing Pacific yew tree (*Taxus brevifolia*), and its structure was elucidated by Wall and Wani.[2] Tremendous efforts towards its synthesis have been made during the last two decades by organic chemists, which have so far resulted in six elegant and successful total syntheses of this molecule.[3]

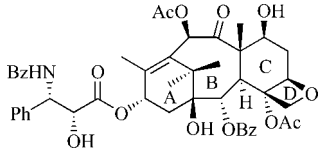
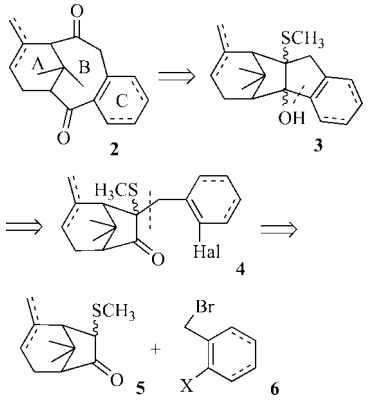


Figure 1. Taxol® (**1**).

The main challenge in the Taxol® synthesis lies in the construction of the sterically congested central eight-membered B-ring, bridgehead double bond and dense pattern of oxygenated functionality present at the periphery of the molecule. In this context, we have devised a novel sulfur-assisted synthetic protocol to access fused medium-sized rings, and to test our idea we chose Taxol®. Thus, the 6-8-6 ABC ring system **2** of Taxol® was envisioned to arise from the tetracyclic intermediate **3** (Scheme 1). The key precursor could be constructed by intramolecular ring annulation of compound **4**, which in turn could be derived by alkylation of the bicyclic system **5**. We report herein our successful preliminary results for the preparation of the ABC ring taxane skeleton by a lead tetraacetate mediated oxidative fragmentation reaction of **3** as the key step.[4] This indirect method of construction of the central eight-membered B-ring circumvents the well-known problem of the high degree of ring strain and the transannular interactions associated with cyclooctane annulations.[5]



Scheme 1. Retrosynthesis.

Results and Discussion

The bicyclic system **5** was prepared as follows (Scheme 2). A-ring ester **7** was prepared in 75% yield by classical Diels–Alder strategy[6] using 2,4-dimethyl-1,3-pentadiene and methyl acrylate. The A-ring ester **7** was acylated

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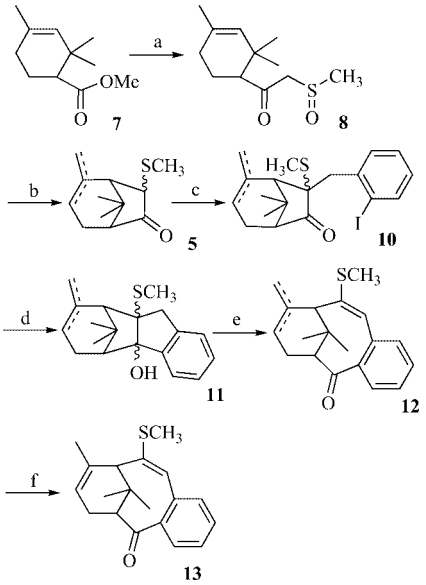
with dimsylsodium[7] to form β-oxo sulfoxide **8** in 70% yield. Pummerer reaction[8] on β-oxo sulfoxide **8** furnished the bicyclic ring system **5** as inseparable diastereomeric and regioisomeric mixture in 60% yield. The formation of **5** as a mixture of four isomers during the Pummerer cyclization of **8** was surprising in view of the fact that in a similar substrate lacking the two geminal methyl groups, the formation of a single bicyclic isomer with an exocyclic double bond and *endo*-oriented $-SCH_3$ group was reported.[8] Thus, formation of four isomers in our case may be attributed to steric hindrance by the two geminal methyl groups. Although a mixture of isomers was obtained, it was decided to carry forward with them since the steoreogenic center would be destroyed subsequently as delineated in the retrosynthesis (Scheme 1), whereas the olefinic isomers could be easily equilibrated to a single isomer (vide infra).



Scheme 2. Synthesis of the C-aromatic ABC taxane system: a) dimsylsodium, THF, 0 °C to room temp., 70%; b) $(CF_3CO)_2O$, dichloromethane, 50 °C, 3 h, 60%; c) i. NaH, THF, 0 °C, 1 h, ii. *o*-iodobenzyl bromide (**9**), THF, 0 °C to room temp., 70%; d) *n*BuLi, THF, –78 °C, 3 h, 80%; e) $Pb(OAc)_4$, $PhCH_3$/AcOH (4:1), 0 °C, 6 h, 75%; f) $RhCl_3 \cdot 3H_2O$, EtOH, 80 °C, 24 h, 80%.

The bicyclic system **5** was alkylated with *o*-iodobenzyl bromide (**9**) to afford **10** in 70% yield (Scheme 2).

The key tetracyclic intermediate **11** was prepared by intramolecular metal/halogen exchange methodology.[9] Thus, addition of *n*BuLi to **10** afforded the tetracyclic compound **11** in 80% yield.[10] Having secured the requisite 6-5-5-6 skeleton, the next task was to unmask the eight-membered ring to access the 6-8-6 skeleton. This could be readily achieved by cleaving the bond shared by the two five-membered rings bearing heteroatoms as the handle. The obvious choice of accomplishing the cleavage of the vicinal thioether alcohol was a photo-induced electron transfer.[11] However, in our hands the photochemical cleavage of **11** was unsuccessful and the starting material remained unchanged. Having failed to cleave the bond photochemically, the next option available was the lead tetraacetate (LTA) mediated cleavage as reported by Trost[12] in a norbornane system. To the best of our knowledge this elegant methodology remained largely unexplored and was never used for the synthesis of any medium- to large-sized ring. Therefore, we decided to exploit this methodology for the synthesis of the cyclooctane ring by fragmentation of the tetracyclic compound **11**. Accordingly, compound **11** was subjected to treatment with LTA. The IR, ^1H NMR and ^{13}C NMR spectra of **12** support the formation of a fragmented product and the GC-MS data reveal two peaks in an almost 1:1 ratio, each having the same $[M^+]$ peak in its mass spectrum with similar fragmentation patterns.

Though success was achieved in obtaining the ABC skeleton of the taxane system **12**, it was obtained as an inseparable mixture of *exo* and *endo* double bond isomers. The next task was to isomerize the double bond. Amongst the array of known methods for olefin isomerization, the one involving rhodium trichloride[13] appeared best suited to our needs. Therefore, compound **12** was isomerized with a catalytic amount of rhodium trichloride to deliver the thermodynamically more stable *endo* olefin **13** in 80% yield. The ^1H NMR, ^{13}C NMR and GCMS spectroscopic data clearly reveal the formation of the C-aromatic ABC ring system **13** of Taxol®. Further, single-crystal X-ray crystallography of compound **13** provided the unambiguous evidence and vindicated the assigned structure (Figure 2).[14]

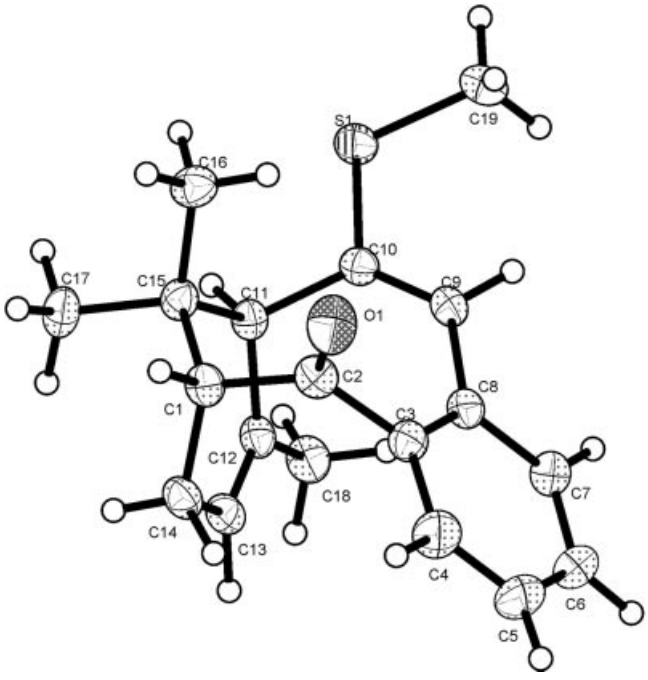
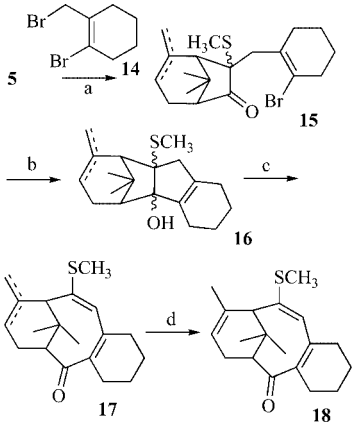


Figure 2. ORTEP view of **13**.

After successful synthesis of the C-aromatic ABC skeleton, we focused our attention towards the synthesis of more advanced taxoids. To this end, a C-alicyclic ABC skeleton of the taxane system was the immediate target.

Therefore, we needed the appropriate alicyclic C-ring unit **14** which was readily prepared from cyclohexanone according to a reported procedure.[15] Having secured the 1-

bromo-2-(bromomethyl)cyclohex-1-ene (**14**), it was coupled with the bicyclic ring system **5** to obtain **15** in 70% yield (Scheme 3). The next step, a five-membered ring annulation was carried out by using the metal/halogen exchange methodology. Thus, addition of *s*BuLi to **15** delightfully afforded the tetracyclic compound **16** in 60% yield. The IR, ^{1}H NMR, ^{13}C NMR spectra support the assigned structure. The GC-MS data of **16** reveal two major and two minor peaks (5.0:1.0:1.8:10.0) whose corresponding mass spectral analysis exhibits similar fragmentation patterns with the same molecular ion peak at *m*/*z* = 304. After having successfully achieved the five-membered ring annulation to form the 6-5-5-6 fused system, the next task was to unmask the eight-membered ring which was achieved by LTA to afford the fragmented product **17** in 75% yield. The IR, ^{1}H NMR and ^{13}C NMR spectroscopic data support the assigned structure. Here too, GC-MS data reveal that the C-alicyclic ABC taxane system **17** exists as a mixture (1:1) of *exo*/*endo* double-bond isomers. Therefore, **17** was isomerized with catalytic amounts of rhodium trichloride and *para*-toluenesulfonic acid to furnish **18** in 80% yield.[16] The ^{1}H NMR, ^{13}C NMR spectroscopic data support the assigned structure **18**. Further, the structure was unambiguously assigned by X-ray crystallography (Figure 3).[17]



Scheme 3. Synthesis of the C-alicyclic ABC taxane system: a) i. NaH, THF, 0 °C, 1 h; ii. **14**, THF, 0 °C (1 h) to room temp. (8 h), 70%; b) *s*BuLi, THF, –100 °C, 3 h, 60%; c) $Pb(OAc)_4$, $PhCH_3$/AcOH (4:1), 0 °C, 6 h, 75%; d) $RhCl_3 \cdot 3H_2O$, *p*-toluenesulfonic acid, EtOH, 80 °C, 24 h, 80%.

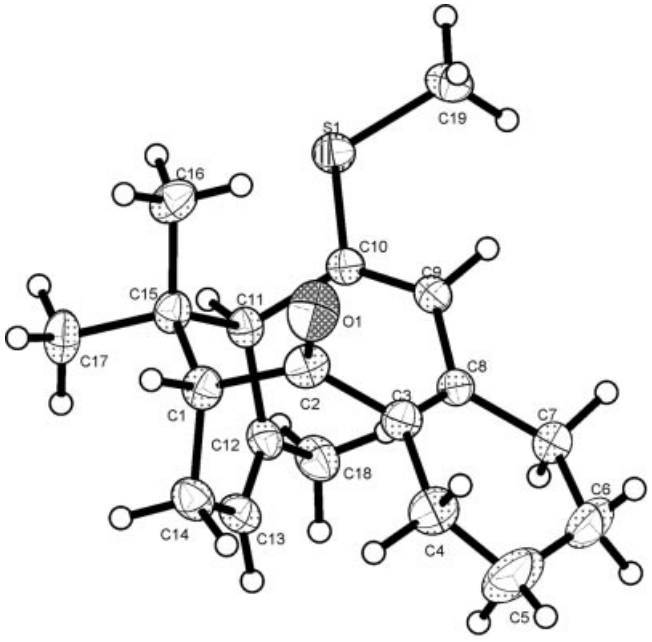


Figure 3. ORTEP view of **18**.

Conclusions

We have demonstrated a concise, simple, practical and convenient route to access the C-aromatic as well as the C-alicyclic ABC ring system of Taxol® with differentiated carbonyl groups for further elaborations, using cheap and readily available starting materials. No functional group protection/deprotection steps were required in the synthetic sequence. The salient feature of this protocol is the versatile role played by sulfur, in C–C bond formation as well as in cleavage, in its various oxidation state viz., (i) sulfoxide-stabilized anion in the C–C bond formation to furnish the β-oxo sulfoxide, (ii) sulfoxide-mediated intramolecular Pummerer cyclization forming the bicyclic compound (C-10–C-11 bond), (iii) as α-oxo sulfide, stabilizing the enolate, in forming the coupled product during alkylation (C-9–C-10 bond), and (iv) pivotal lead tetraacetate cleavage of the β-methyl sulfide alcohol (C-2–C-10 bond) leading to the formation of the vinyl sulfide group (masked ketone). Literally, sulfur acted as a vehicle for vital formations and fragmentations of C–C bonds to deliver the ABC ring skeleton of Taxol®. We believe that this practical five-step protocol, i.e. condensation/Pummerer cyclization/coupling/annulation/fragmentation will deliver a large number of advanced taxoids as well as fused ring systems whose further elaboration may lead to complex fused natural products. The success of the above protocol will provide impetus for the synthesis of the more complicated CD ring system and its conversion to more advanced taxoids. The work in this direction is in progress in our laboratory and will be communicated in due course.

Supporting Information (see footnote on the first page of this article): Experimental procedures, full spectroscopic data of all new compounds along with ^{1}H NMR, ^{13}C NMR, DEPT and GC-mass spectra.

Acknowledgments

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[14] CCDC-633193 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[16] After refluxing **17** in ethanol in the presence of $RhCl_3$ for 3 d, it was observed that the isomerization was incomplete. Surprisingly, the addition of a catalytic amount of *p*-toluenesulfonic acid accelerated the isomerization. See ref.[13]

[17] CCDC-633194 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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