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A new route for the construction of the AB-ring core of Taxol

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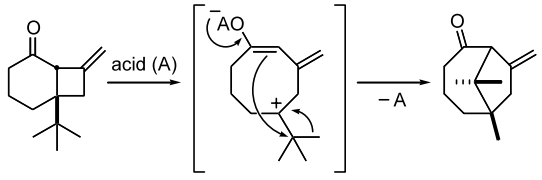
Abstract—A new method for the construction of the AB-ring core of Taxol was developed utilizing a new skeletal transformation protocol as a pivotal step. The acid-catalyzed rearrangement of the cyclopentenone–allene photoadduct gave a bridged seven-membered ketone, which was easily transformed, using the intramolecular Suzuki reaction and the oxidative cleavage of the vicinal diol, to the bicyclic diketone.

Taxol **1** is one of the most powerful, naturally occurring antitumor reagents known, and is widely and routinely used in the treatment of breast, lung, and ovarian cancers[1] (Fig. 1). Due to its therapeutic potential and its limited availability, enormous efforts have been directed towards the chemical synthesis of Taxol in the past decade, and this remains one of the most challenging targets for synthetic chemists because of its unique structural features.[2] The construction of the AB-ring core of Taxol, which involves bicyclo[5.3.1]undecane moiety consisting of a ten-membered ring bridged by one carbon, has been nonpractical yet. As a solution to the problem, some efficient methods for the construction of bicycloundecanes have recently developed.[3] We report here an new route for the construction of the AB-ring core.

We have already reported an efficient method for the construction of bicyclo[4.2.1]nonanones by the acid-catalyzed rearrangement of 6-substituted bicyclo[4.2.0]octanones (Eq. (1)), and demonstrated its utility in the total synthesis of (±)-tetramethylmediterraneol B.[4] The skeletal rearrangement of cyclobutyl ketones, which are easily derived from the photocycloaddition of cyclohexen-2-one with alkenes, proved to be an efficient route to bridged eight-membered ring compounds.[4a] We envisioned a use of this rearrangement for the construction of a bridged bicyclic system corresponding to the AB-ring core of Taxol.



(1)

Our strategy for preparing the AB-ring core of Taxol **1** was based on the initial construction of the isoprorylidene bridge of AB-ring. Thus, the skeletal rearrangement of the 5-4 fused ketone **6** would result in the formation of bicyclo[3.2.1]octanone **5** having an isopropylidene bridge (Scheme 1). A subsequent functional group elaboration, based on the *exo*-methylene group of **5**, including an increase in the number of carbon atoms and a ring-expansion, would lead to the AB-ring core of **1**.

The irradiation of cyclopentenone **7**, which is readily synthesized from 6-methyl-5-hepten-2-one,[5] with allene in CH_2Cl_2 at −78°C gave the head-to-head adduct **6** in 84% yield, along with the head-to-tail adduct in 12%

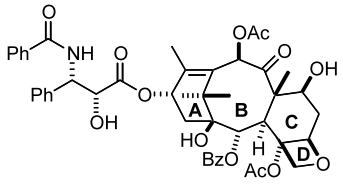


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Figure 1.

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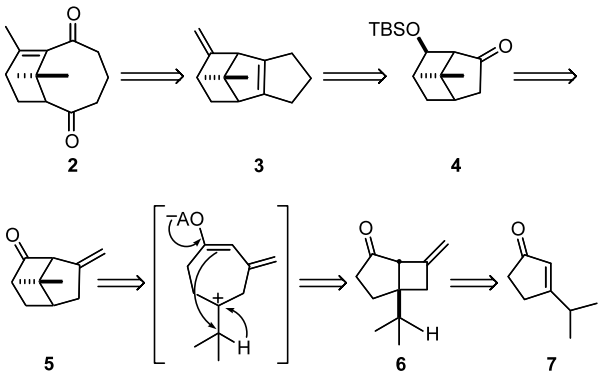
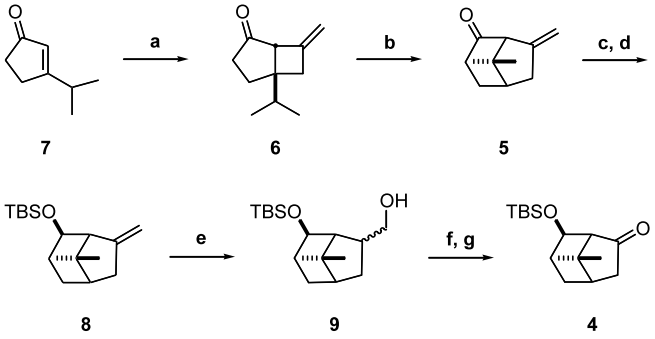


Scheme 1. Retrosynthetic analysis of the AB-ring core of Taxol.

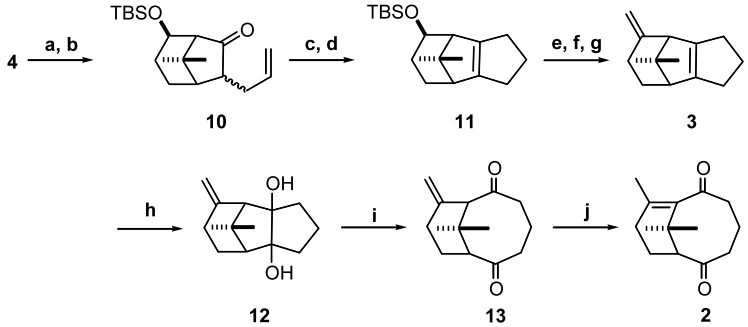


Scheme 2. *Reagents and conditions*: (a) *hv*, allene, CH_2Cl_2, −78°C, head-to-head adduct **6**, 84% (head-to-tail adduct, 12%); (b) $TiCl_4$, CH_2Cl_2, rt, 78%; (c) DIBALH, Et_2O, −78°C, 98%; (d) TBSCl, imidazole, DMF, rt, quant.; (e) BH_3–THF, rt; H_2O, NaOH, H_2O_2, rt, 97%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0°C; (g) O_2, *t*-BuOK, THF/DMSO (4/1), −20°C, 92% (two steps).

yield (Scheme 2).[6] The rearrangement of ketone **6** with $TiCl_4$ (5 equiv.) proceeded at room temperature to give bicyclo[3.2.1]heptanone **5** in 78% yield. For this rearrangement, the use of other acid catalysts, such as H_2SO_4, $AlCl_3$, and BCl_3, resulted in lower yield. The diastereoselective reduction of ketone **5** with DIBALH and protection of the resulting hydroxy group afforded the bridged bicyclic olefin **8** in quantitative yield. The olefin **8** was hydroborated and subsequently oxidized to form alcohols **9** as a diastereomeric mixture (88/12). The alcohols **9** were converted to ketone **4** in 92% yield, via a Swern oxidation and subsequent oxidative cleavage with oxygen.[7]

Allylation of ketone **4** with excess LDA and allyl iodide in THF/HMPA gave a mixture of *C*-allylated ketone **10** and the *C*,*O*-bis-allylated compound, which, on treatment with acetic acid gave ketone **10** as a diastereomeric mixture (88/12) in 98% yield based on a 91% conversion (Scheme 3). Triflation of the allylketone **10** with KHMDS and $PhNTf_2$ in THF gave the triflate in 99% yield based on an 80% conversion, and hydroboration of the triflate with 9-BBN followed by palladium-catalyzed intramolecular Suzuki–Miyaura coupling afforded the tricyclic olefin **11** in 85% yield.[8] The diene **3** was obtained in three steps utilizing the oxygen functional group in **11**, removal of the silyl group, catalytic oxidation with TPAP,[9] and Wittig olefination. The osmium-catalyzed dihydroxylation[10] of diene **3** gave diol **12** as a single diastereomer with the *exo*-methylene group intact in 94% overall yield from **11**. The 1,2-glycol unit of diol **12** was oxidatively cleaved with $Pb(OAc)_4$ to quantitatively give diketone **13** corresponding to the AB-ring system of the Taxanes. The target diketone **2** was obtained by isomerization of diketone **13** in 94% yield based on a 97% conversion under basic conditions which consisted of *t*-BuOK (2.0 equiv.) in DMSO/DMF (1/1) at −10°C.[11]

In summary, we report on the development of an efficient route to the bridged bicyclic compound **2** corresponding to the AB-ring core of Taxol **1**, which was obtained in 42% in 16 steps from **7**. Compound **2** possesses the framework included in the family of highly bioactive Taxanes, and the present route establishes its applicability to the chemical synthesis of all of them, including derivatives thereof.



Scheme 3. *Reagents and conditions*: (a) LDA, HMPA, allyliodide, THF, −78 to 0°C; (b) AcOH, THF, H_2O, rt, 98% based on 91% conversion (two steps); (c) KHMDS, $PhNTf_2$, THF, −78°C, 99% based on 80% conversion; (d) 9-BBN, THF, rt; H_2O, K_3PO_4, $Pd(PPh_3)_4$, dioxane, 80°C, 85%; (e) TBAF, THF, rt, quant.; (f) TPAP, NMO, CH_2Cl_2, rt, quant.; (g) PPh_3CH_3Br, $NaNH_2$, toluene, reflux; (h) OsO_4 (cat.), $K_3Fe(CN)_6$, K_2CO_3, $MsNH_2$, quinuclidine, *t*-BuOH/H_2O, rt, 94% (two steps); (i) $Pb(OAc)_4$, benzene, rt, quant.; (j) *t*-BuOK, DMSO/DMF (1/1), −10°C, 94% based on 97% conversion.

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