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# New Efficient Construction of the ABC Core of the Taxoids via a Sequence of Consecutive Cobalt(I)-Mediated [2 + 2 + 2] and [4 + 2] Cyclizations

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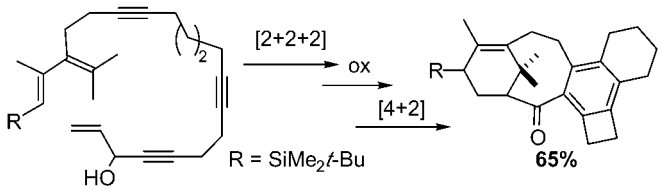
## ABSTRACT




**A new and efficient sequence of two consecutive cyclizations, a cobalt(I)-mediated [2 + 2 + 2] cyclotrimerization and a Diels–Alder reaction, is proposed to allow the formation of the ABC core of the taxoids in 65% overall yield, starting from an acyclic polyunsaturated precursor.**

In the past 10 years, taxane diterpenoids have been among the most difficult challenges for synthetic chemists both because of their unusual and unique structural features and their considerable therapeutic potential.[1] Thus, the synthesis of taxoids is reliant on the development of new methodologies, and as a consequence, an impressive range of synthetic designs have been published toward syntheses of taxol and its analogues, with six of them succeeding in the total synthesis of taxol itself.[2]

As part of our ongoing research based on metal-catalyzed or radical cyclization cascades aimed at the elaboration of the basic skeletons of natural products,[3] we have developed a short and efficient two-step synthesis of the ABC core of the taxoids from an acyclic polyunsaturated precursor. This approach presents the novelty to potentially allow a powerful entry to a myriad of taxane analogues. In our retrosynthetic plan, we envisoned a new combination of a cobalt(I)-mediated cyclotrimerization[4] and a [4 + 2] reaction to reach the compound **1** that presents an aryl C-ring, an all carbon D-ring, and an additional six-membered ring (Scheme 1). Indeed, **1** could be obtained from the intramolecular Diels−Alder substrate **2**. Such a cyclization has been already

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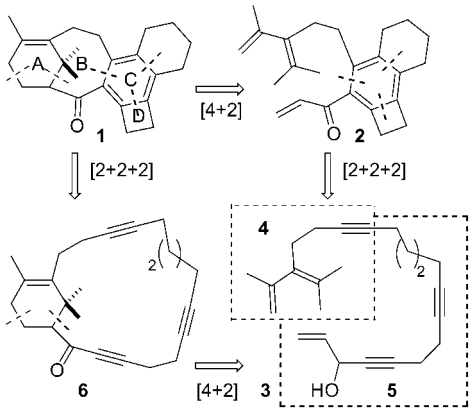
**Scheme 1.** Retrosynthesis for the ABC Core of Taxoids

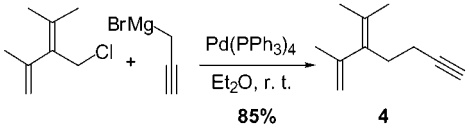



successfully used in several approaches of the AB ring system of the taxoids.[5] The benzocyclobutene moiety of **2** could arise from the [2 + 2 + 2] cyclization of the three alkynes of the precursor **3**. The alkyl tether between both unsaturated moieties **4** and **5** should ensure the chemoselectivity of the [2 + 2 + 2] cyclization. It is noteworthy that the benzocyclobutene moiety that could be formed presents a hexasubstituted aromatic ring, which is usually quite difficult to attain.

Looking at the Scheme 1, it seems obvious that the compound **1** could be obtained via the opposite pathway [4 + 2]/[2 + 2 + 2]. Indeed, we disclosed already that the sequence [4 + 2] and Co(I)-mediated cyclization allowed the construction of the AB taxane ring.[6] Herein, we present our efforts devoted to the elaboration of **1** via the sequence [2 + 2 + 2]/[4 + 2] reactions.

The dienyne moiety **4** of the precursor **3** was prepared,[6] on the basis of work of Shea, from 2,4-dimethyl-3-(chloromethyl)-1,3-pentadiene[5a] as outlined in Scheme 2.

**Scheme 2**




The precursor **3** was obtained following Scheme 3. Indeed, the monoalkylation of the 1,5-hexadiyne with acrolein provided the allylic alcohol **7** in 60% yield, which was protected as tetrahydropyranyl ether **8**.

Then, the corresponding lithium acetylide was alkylated with 4-iodo-(*tert*-butyldimethysilyloxy)butane[7] to afford **9**

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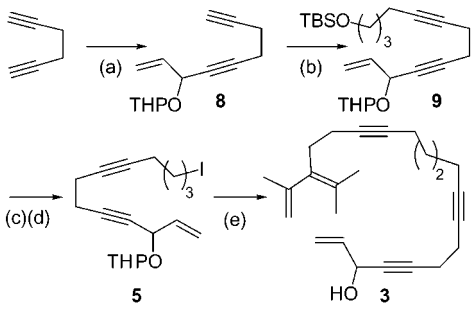
**Scheme 3.** Preparation of the Precursor **3**[a]

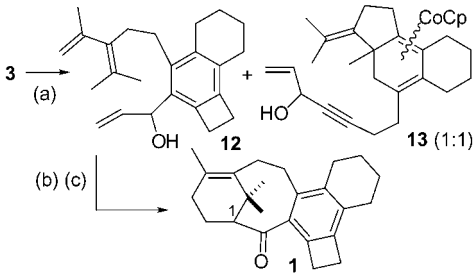



[a] (a) (1) *n*-BuLi, THF, −78 °C, acrolein −78° to 25 °C, **7**: 60%; (2) cat. PTSA, dihydropyrane, $CH_2Cl_2$, **8**: 96%. (b) *n*-BuLi, THF, −78 °C, $I(CH_2)_4OSiMe_2t$-Bu, HMPA, −78° to 25 °C, **9**: 71%. (c) *n*-$Bu_4NF$, THF, rt, **10**: quant. (d) (1) TsCl, $Et_3N$, cat. DMAP, $CH_2Cl_2$, 0 °C; (2) NaI, DMF, 50 °C, **5**: 65%. (e) (1) **4**, *n*-BuLi, HMPA, THF, −78 °C, 2 h, **11**: 79%; (2) cat. PTSA, MeOH, **3**: 90%.

in 71% yield. After deprotection, the resulting alcohol was transformed into the iodide **5**. Alkylation of the latter with the lithium acetylide derived from **4**, followed by an acid hydrolysis of the ether, gave the precursor **3** in 90% yield.

Exposure of **3** to $\eta^5$-cyclopentadienyldicarbonyl cobalt [$CpCo(CO)_2$] in boiling xylenes for 6 h under irradiation led to the corresponding benzocyclobutene **12** in 18% yield (Scheme 4). Surprisingly, the major compound of the [2 +

**Scheme 4.** Cobalt-Mediated and [4 + 2] Cyclizations of **3**[a]




[a] (a) $CpCo(CO)_2$ (1 equiv), xylenes, *hν*, Δ. (b) $BaMnO_4$/Celite, benzene, Δ, **2**: 30%. (c) $Et_2O{\cdot}BF_3$, toluene, − 40 °C, **1**: 95%.

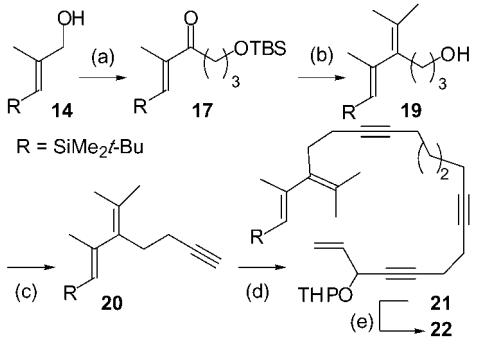
2 + 2] cyclization is a 1:1 mixture of diastereomeric tricyclic cobalt complexes **13** (37%) resulting from the diastereoselective cyclization of two alkynes and the terminal double bond.[8] Besides, 30% of starting material remained unchanged. Attempts to avoid the participation of the double bond in the cyclization by a temporary protection of the dienic system failed.

Nevertheless, **12** was oxidized[5a] and the resulting enonediene **2** was converted in the presence of $Et_2O{\cdot}BF_3$ in toluene into the AB ring system and therefore to **1** in 95% yield. Thus, the formation of **1** validates our strategy for the taxoids framework.

(8) Decomplexation of the (1:1) mixture of **13** with Cu(II) salts led to the free ligand as only one diastereomer.

However, to circumvent the cyclization of the enediyne, we decided to introduced a bulky *t*-BuMe$_2$Si substituent at the terminal position of the double bond. The requisite polyunsaturated precursor **21** or **22** was obtained as before by the coupling between the dienyne **20** and the enediyne **5** (see Scheme 5). The starting allylic alcohol **14** was prepared

**Scheme 5.** Preparation of the Precursors **21** and **22**[a]

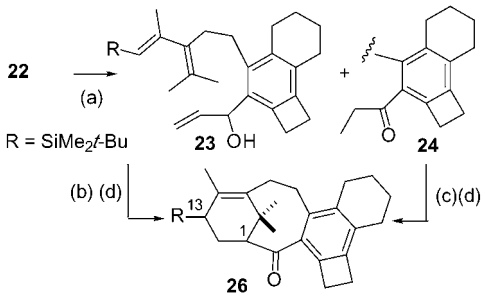



[a] (a) (1) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, −78 °C to rt, **15**: quant; (2) *t*-BuLi, *t*-BuMe$_2$SiO(CH$_2$)$_3$I, **16**: 90%; (3) Swern ox., **17**: quant. (b) (1) *n*-BuLi, Me$_2$C(SePh)$_2$, THF, −78 °C; (2) $SOCl_2$, $NEt_3$, $CH_2Cl_2$, **18**: 77%; (3) *n*-Bu$_4$NF, THF, rt, **19**: 83%. (c) (1) $SO_3$·pyridine, $NEt_3$, DMSO, $CH_2Cl_2$; (2) MeCOC(N$_2$)P(O)(OMe)$_2$, $K_2CO_3$, MeOH, **20**: 63%. (d) **5**, *n*-BuLi, HMPA, THF, −78 °C, **21**: 33%. (e) cat. PTSA, MeOH, **22**: quant.

following a procedure described by our laboratory.[9] Consecutive Swern oxidation, addition of the aldehyde to the lithio derivative of 3-(*tert*-butyldimethylsilyloxy)-1-iodopropane and Swern oxidation led to the enone **17** in 55% overall yield. Subsequent olefination[10] and deprotection afforded the dienol **19** and after its oxidation,[11] the aldehyde was transformed by chain extension[12] to the dienyne **20**. Then, the sequence—alkylation/deprotection—furnished the precursors **21** and **22**.

When **21** was exposed to the cobalt mediator, we were pleased to observe in 92% yield the formation of the corresponding benzocyclobutene, but whatever the conditions used, we were unable to hydrolyze the tetrahydropyranyl ether. In the same conditions, **22** led to a mixture of the benzocyclobutenes **23** and **24** in 50% and 37% yield, respectively (Scheme 6). Compound **24** arose from a (1,3)

**Scheme 6.** [2 + 2 + 2] and [4 + 2] Cyclizations of **22**[a]




[a] (a) cat. CpCo(CO)$_2$, xylenes, *hν*, Δ. (b) IBX, DMSO, rt, **25**: 76%. (c) (1) LDA, PhSeBr, THF; (2) $NaIO_4$, $NaHCO_3$, MeOH/$H_2O$, **25**: 81%. (d) $Et_2O$·$BF_3$, $CHCl_3$, −78 °C, **26**: 95%.

migration of the double bond leading to the enol ether. However, the dienophilic alkene was easily introduced via selenation−oxidation. After oxidation[13] of **23**, the resulting enone **25** was exposed to 5 equiv of $BF_3$·$Et_2O$ in chloroform to afford **26** in 95% yield as only one diastereomer. Molecular models reveal that only the *endo* approach is possible and according to the chemical shifts of the three methyls (1.33, 1.12, 0.77 ppm), the conformation of the cycloadduct is probably the *endo* conformer as compared to those described by Shea.[14]

In summary, the formation of the pentacyclic structure **26**, including the ABC core of the taxoids, in 65% overall yield, starting from the acyclic polyunsaturated precursor **22** represents a new illustration of the remarkable synthetic potential of the combination of the cobalt(I)-[2 + 2 + 2] cyclization with a [4 + 2] reaction. It is noteworthy that the silylated group strategically located at C-13 in **26** could be easily oxidized, by changing the nature of the substituents, into a hydroxyl goup, precursor of the lateral chain. In addition, either **1** or **26** exhibits only one stereogenic center C-1, which could be controlled during the Diels−Alder reaction by employing chiral catalysts. Finally, it should be noted that the all carbon D ring has never been tested. These studies are under investigation and will be reported in due course.

**Supporting Information Available:** Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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