

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

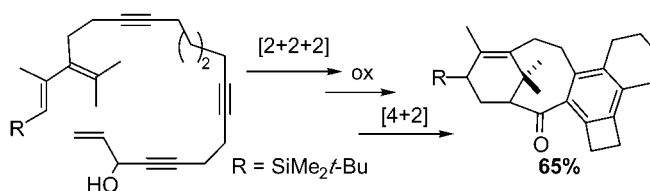
Marc Petit, Gaëlle Chouraqui, Phannarath Phansavath, Corinne Aubert,^{*,†} and Max Malacria^{*}

Université Pierre et Marie Curie (Paris 6), Laboratoire de Chimie Organique de Synthèse associé au CNRS, Tour 44-54, 2ème étage, Case 229, 4 place Jussieu 75252, Paris Cedex 05, France

malacria@ccr.jussieu.fr.

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ABSTRACT



A new and efficient sequence of two consecutive cyclizations, a cobalt(I)-mediated [2 + 2 + 2] cyclootrimerization 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 envisioned a new combination of a cobalt(I)-mediated cyclootrimerization⁴ 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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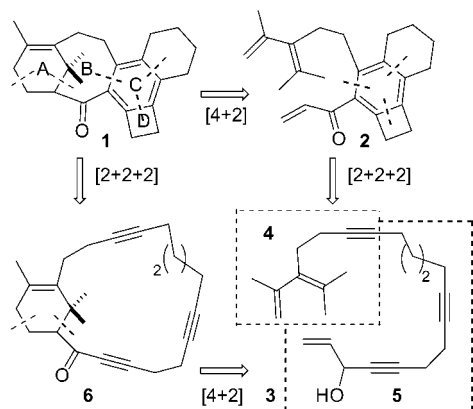
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[†] E-mail: aubert@ccr.jussieu.fr.

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Scheme 1. Retrosynthesis for the ABC Core of Taxoids

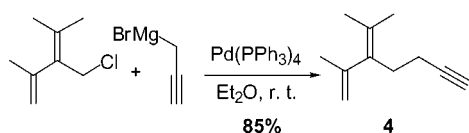


successfully used in several approaches of the AB ring system of the taxoids.⁵ The benzocyclobutene moiety of **2** could arise from the [2 + 2 + 2] cyclization of the three alkynes of the precursor **3**. The alkyl tether between both unsaturated moieties **4** and **5** should ensure the chemoselectivity 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.

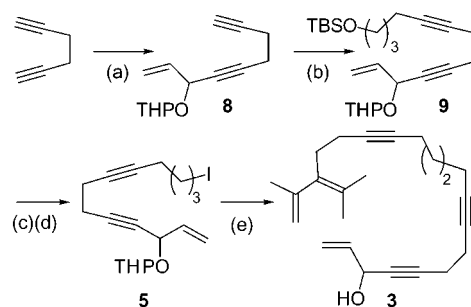
Scheme 2



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*-butyldimethylsilyloxy)butane⁷ to afford **9**

Scheme 3. Preparation of the Precursor **3**^a

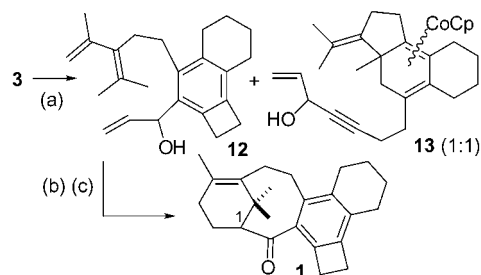


^a (a) (1) *n*-BuLi, THF, -78°C , acrolein -78° to 25°C , **7**: 60%; (2) cat. PTSA, dihydropyran, CH_2Cl_2 , **8**: 96%. (b) *n*-BuLi, THF, -78°C , $\text{I}(\text{CH}_2)_4\text{OSiMe}_2t\text{-Bu}$, HMPA, -78° to 25°C , **9**: 71%. (c) *n*-Bu₄NF, THF, rt, **10**: quant. (d) (1) TsCl, Et₃N, cat. DMAP, 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 η^5 -cyclopentadienyldicarbonyl cobalt [$\text{CpCo}(\text{CO})_2$] 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) $\text{CpCo}(\text{CO})_2$ (1 equiv), xylenes, $h\nu$, Δ . (b) $\text{BaMnO}_4/\text{Celite}$, benzene, Δ , **2**: 30%. (c) $\text{Et}_2\text{O}\cdot\text{BF}_3$, 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 enone-diene **2** was converted in the presence of $\text{Et}_2\text{O}\cdot\text{BF}_3$ 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.

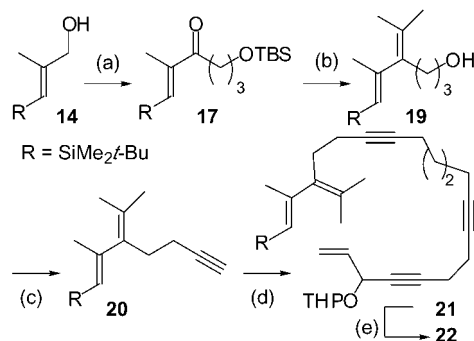
(8) Decomplexation of the (1:1) mixture of **13** with Cu(II) salts led to the free ligand as only one diastereomer.

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However, to circumvent the cyclization of the enediyne, we decided to introduce a bulky *t*-BuMe₂Si 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



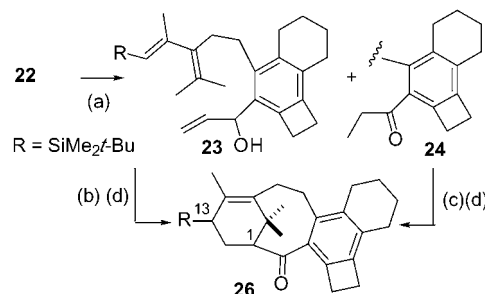
^a (a) (1) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, -78 °C to rt, **15**: quant; (2) *t*-BuLi, *t*-BuMe₂SiO(CH₂)₃I, **16**: 90%; (3) Swern ox., **17**: quant. (b) (1) *n*-BuLi, Me₂C(SePh)₂, THF, -78 °C; (2) SOCl₂, NEt₃, CH₂Cl₂, **18**: 77%; (3) *n*-Bu₄NF, THF, rt, **19**: 83%. (c) (1) SO₃·pyridine, NEt₃, DMSO, CH₂Cl₂; (2) MeCOC(N₂)P(O)(OMe)₂, K₂CO₃, 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 olefination¹⁰ and deprotection afforded the dienol **19** and after its oxidation,¹¹ the aldehyde was transformed by chain extension¹² 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) NaIO₄, NaHCO₃, MeOH/H₂O, **25**: 81%. (d) Et₂O·BF₃, CHCl₃, -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 oxidation¹³ of **23**, the resulting enone **25** was exposed to 5 equiv of BF₃·Et₂O 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 group, 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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