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The [4+2], [2+2] Strategy for the Construction of the AB Taxane Ring System

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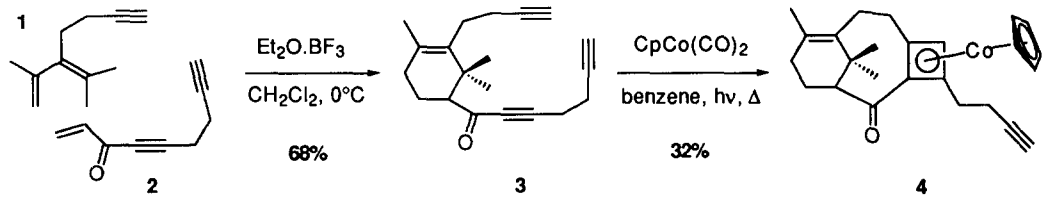
Abstract : The construction of the AB taxane ring system through a [4+2] reaction and Co(I)-[2+2] cyclization is presented. For the first time, $CpCo(CO)_2$ catalyzes the ring closure of strained polyunsaturated triynic compound into eight-membered ring.

In recent years, taxane diterpenoids have been most challenging synthetic targets for the organic chemists because of their unique structural features as well as their considerable therapeutic potential.[1] As a consequence, an impressive range of synthetic designs have been published towards syntheses of taxol and its analogues,[2] with four of them succeeding in the total synthesis of taxol itself.[3]

In connection with our synthetic studies on tetracyclic diterpenes and sesquiterpenes based on transition metal-catalyzed[4] or radical cyclizations cascades,[5] we have envisioned different approaches to the ABCD taxane framework by using as key steps in these strategies, [4+2] cycloaddition reactions and cobalt(I)-mediated cyclotrimerizations.[6]

In this communication, we disclose the construction of the AB taxane ring system through this tandem strategy and report an unexpected cobalt(I)-mediated cyclization from the very strained polyunsaturated cyclohexenetriyne **3** to an even more sterically congested eight-membered B ring and crowded [6.8.4] fused tricyclic system **4** (Scheme 1).



Scheme 1

The dieneyne **1** was prepared from 2,4-dimethyl-3-(chloromethyl)-1,3-pentadiene[7] as outlined in Equation 1 (Scheme 2).

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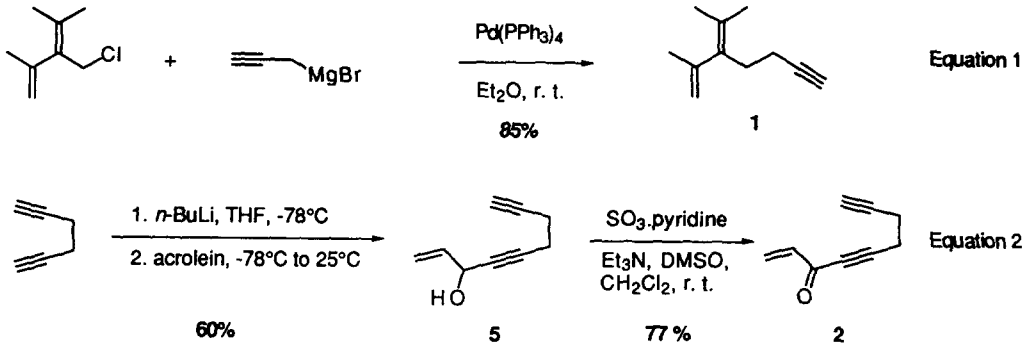
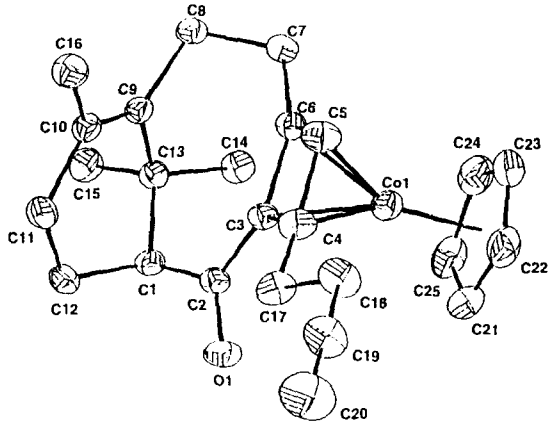


Scheme 2

By using a palladium zerovalent catalysis, the coupling reaction of the chlorodiene with the Grignard reagent derived from propargyl bromide led to **1** in 85 % yield. The dienophile **2** was obtained following Equation 2 (Scheme 2). The monoalkylation of the 1,5-hexadiyne with acrolein provided the allylic alcohol **5** in 60 % yield, accompanied by the dialkylated compound (10-15 %). Alcohol **5** was subsequently oxidized with the SO_3.pyridine reagent[8] to afford the enediynone **2** in 77 % yield.

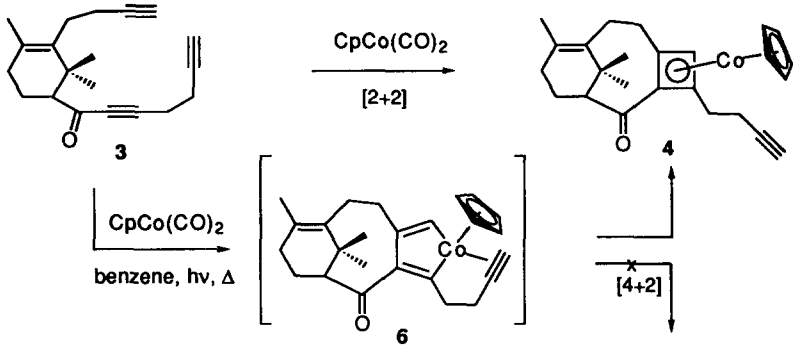
The intermolecular Diels-Alder cycloaddition of **1** with **2** proceeded with $BF_3.Et_2O$ catalysis at 0°C in CH_2Cl_2 to give cyclohexene **3** in 68 % yield. Exposure of the latter to a stoichiometric amount of $CpCo(CO)_2$ (η^5-cyclopentadienyldicarbonyl cobalt) under irradiation either in refluxing benzene or toluene furnished the red crystalline compound **4** as only one diastereomer in 32 % yield.[9] The tricyclo[8.2.1^{3,7}.0^{1,10}] tridecane structure in which the cyclobutadiene is complexed to the cobalt was unambiguously established by a single crystal X-ray analysis.



Scheme 3

The ORTEP representation (Scheme 3) shows that the cobalt moiety can only be placed on the less crowded face of the molecule, explaining the observed diastereoselectivity. It is interesting to note that this tricyclic [6.8.4] compound is photolytically and thermally quite inert and stable under oxidative conditions as well.

Although the obtention of cobaltacyclobutadienes has been observed in the case of the cyclization of diynic compounds[10] or when the third unsaturation could not be incorporated on the metallacyclopentadiene,[11] the formation of compound **4** remains surprising. Two pathways can be invoked to explain the formation of such a product (Scheme 4). The first one would involve a cobalt(I)-mediated [2+2] cycloaddition, which would furnish directly the complexed cyclobutadiene. In the second one, after coordination of the two triple bonds with the cobalt complex, the oxidative addition leads to the cobaltacyclopentadiene **6**. This presumed intermediate metallacycle would then prefer valence tautomerization to **4** rather than incorporation of the appended alkyne unit, probably for electronic reasons due to the presence of the carbonyl group conjugated with the cobaltacyclopentadienyl moiety.



Scheme 4

In order to determine the factors governing these tautomerization *versus* incorporation processes, we have investigated the cobalt(I)-mediated cyclizations of cyclohexenetriynes in which the carbonyl group is replaced by different functionnalities. These results illustrating the dramatic influence of the substitution in that position will be presented in a forthcoming paper.

In summary, these preliminary results show for the first time that cobalt(I) species mediate the ring closure of strained polyunsaturated compounds into an eight-membered ring. More importantly, the sequence : [4+2] reaction and Co(I)-cyclization allows the construction of the AB taxane ring system.

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9. Preparation of **3** : At 0°C, to a solution of **1** (160 mg, 1.08 mmol) and **2** (171 mg, 1.3 mmol) in CH_2Cl_2 (1.3 mL) was added $Et_2O.BF_3$ (160 µL, 1.3 mmol). After being stirred 5 min, the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (petroleum ether/ether = 9/1) to afford **3** (206 mg, 0.73 mmol, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.59 (t, *J* = 7.1 Hz, 2H), 2.51 (dd, *J* = 11.2, 3.0 Hz, 1H), 2.45 (td, *J* = 7.1, 2.6 Hz, 2H), 2.33-2.16 (m, 5H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.99-1.94 (m, 2H), 1.94-1.86 (m, 1H), 1.82-1.76 (m, 1H), 1.63 (s, 3H), 1.18 (s, 3H), 1.03 (s, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.1, 135.3, 128.2, 92.0, 84.3, 82.5, 81.5, 69.9, 68.2, 59.5, 37.9, 30.9, 27.7, 27.0, 22.8, 21.6, 19.8, 19.0, 18.9, 17.6 ; IR (CH_2Cl_2) 3300, 2970, 2210, 1650 cm^{-1}. Anal. Calcd. for $C_{20}H_{24}O$: C, 85.67 ; H, 8.63. Found : C, 85.58 ; H, 8.69.
Preparation of **4** : To a boiling solution of **3** (100 mg, 0.36 mmol) in benzene (36 mL), degassed by three freeze-pump-thaw cycles, was added $CpCo(CO)_2$ (45 µL, 0.36 mmol). The mixture was irradiated (light from a projector lamp; ELW 300 W, 50% of its power) and refluxed for 30 min. After completion, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (petroleum ether/ether = 9/1) to give **4** (46 mg, 0.12 mmol, 32%). Red crystals : mp 115°C ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.78 (s, 5H), 4.05 (s, 1H), 2.97-2.89 (m, 1H), 2.66-2.55 (m, 2H), 2.40-2.03 (m, 8H), 1.94 (t, J = 2.6 Hz, 1H), 1.85-1.78 (m, 2H), 1.48 (s, 3H), 1.44 (s, 3H), 1.05 (s, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 213.8, 136.3, 128.2, 84.3, 82.8, 80.6, 75.3, 69.8, 68.5, 64.1, 61.0, 34.4, 29.7, 28.4, 28.1, 27.1, 26.9, 25.5, 24.8, 20.1, 18.8 ; IR (CH_2Cl_2) 3300, 2920, 2610, 1460, 1350, 1200, 750, 660 cm^{-1}. Anal. Calcd. for $C_{25}H_{29}OCo$: C, 74.24 ; H, 7.23. Found : C, 74.13 ; H, 7.30. MS (*m/z*) 405 (MH^+), 180, 74.
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