Versatile Synthesis of Bicyclo[9.3.1]pentadecatriene for New Bicyclic Taxoids

Satoshi Shibuya and Minoru Isobe*

Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

Fax +81-52-789-4111

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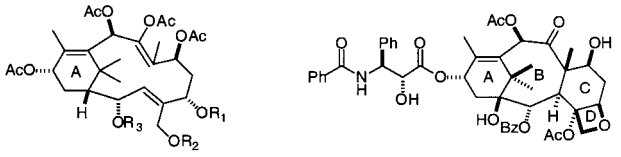
Abstract: A common carbon skeleton bicyclo[9.3.1]pentadecatriene of taxachitrienes was synthesized in its des-methyl form in short steps. The key step was Nicholas-Hosomi type reaction in the acidic cyclization between ene-yne biscobalthexacarbonyl complex electrophile with allyltrimethylsilane nucleophile. Decomplexation of the biscobalthexacarbonyl was achieved with a tin hydride and NBS in 1,4-cyclohexadiene solvent.

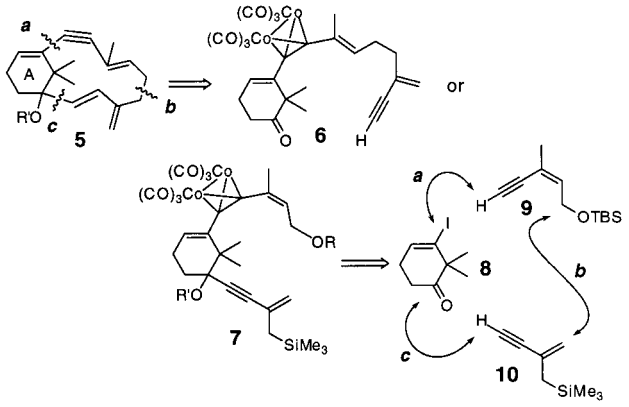
Drug development toward antitumor agents has been continued as an activity of organic synthesis. Recently several new bicyclic taxoids diterpenoids (**1**, **2**[1] and **3**[2]) were found from the needles of *Taxus chinensis*, or *Taxus canadensis*, respectively. These have been proposed as the biogenetic precursor for taxanes. We became interested in the synthesis of this class of compounds (**1**, **2** and **3**) having bicyclo[9.3.1]pentadecatriene. It has a similarity of the carbon framework with taxol[3] (**4**) to which five total syntheses have been achieved.[4] All of these compounds possess the same A ring having *gem*-dimethylcyclohexene, but the former bicyclic compounds have the double bond with less strain energy at the bridge head position because of fused ring with 12 membered ring rather than the 8 membered ring in taxol. This paper deals with a versatile synthesis of a common framework bicyclo[9.3.1]pentadecatriene of **1**, **2** and **3**.



Taxachitriene A (**1**) : R_1=H, R_2=R_3=Ac
Taxachitriene B (**2**) : R_1=Ac, R_2=R_3=H
Canadensene (**3**) : R_1=R_2=H, R_3=Ac

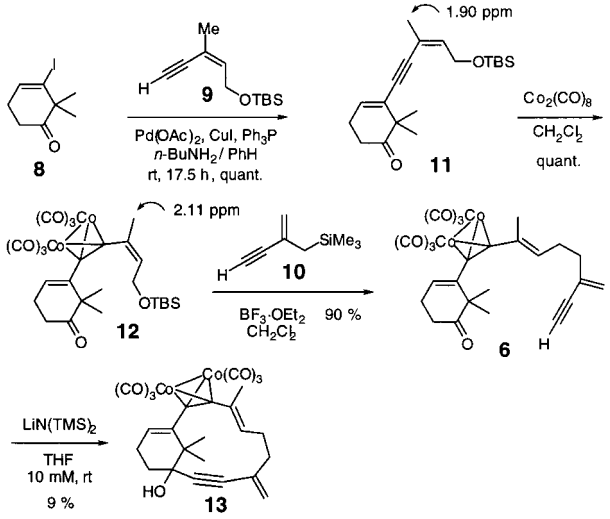
Taxol (**4**)

Retrosynthesis of the target framework **5** (des-methyl at the olefinic position of A ring) is summarized in Scheme 1. Disconnection of the C-C bonds at the 3 positions (***a***, ***b*** and ***c***) should lead us two routes for 3 components coupling strategy, to which we decided first to connect bond ***a***. Two alternative coupling orders at ***b*** or ***c*** should give two possible synthetic intermediates **6** and **7**, respectively. In these cases an acetylene biscobalthexacarbonyl complex is to be involved for putting the reaction centers as close as possible to each other (Fig 1, in Scheme 3). All of the 3 building blocks (**8**, **9** and **10**) were synthesized from commercially available compounds in a few steps, respectively.[5]



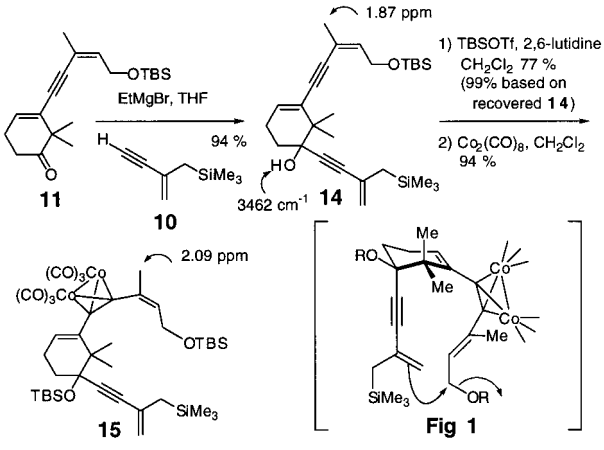
Scheme 1

One of the routes via intermediate **6** is summarized in Scheme 2. An ene-yne coupling between the vinyl iodide **8** and acetylene **9** was facilitated by palladium as catalyst under Sonogashira condition[6] to give **11**. Addition of biscobaltoctacarbonyl to this conjugate yne-diene provided deep red color complex **12** which was further treated with $BF_3{\cdot}OEt_2$ for coupling with the third building block **10** under Nicholas effect and Hosomi-Sakurai condition.[7,8,] The final cyclization of the acetylene-ketone **6** with basic condition showed only 9 % yield at best as an extremely poor result. This result suggested a thermodynamic limitation of the intramolecular yne-one addition reaction for the 12-membered ring cyclization.



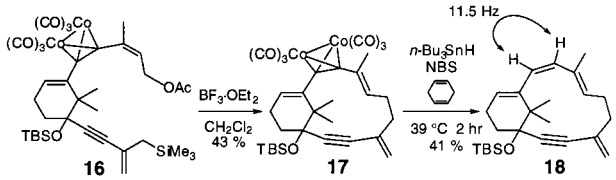
Scheme 2

We have examined an alternative ***b*** route of cyclization through intermediate **7** (equivalent to **15** in Scheme 3). Intermolecular addition of the magnesium acetylide of **10** to the ketone **11** afforded the adduct **14**. The *tert*-propargylic alcohol was protected as TBS ether, and one of the two acetylene groups was selectively converted into the corresponding biscobalthexacarbonyl complex under the usual way to provide **15**.[9]



Scheme 3

The cyclization reaction of **15** was the most crucial step in this synthesis; thus, simple addition of Lewis acid in dichloromethane as solvent provided very poor yield of **17**. A variety of possible conditions for this cyclization were examined; e.g. usage of a resin (Amberlyst 15E) having strong protonic acid nature and diluted conditions afforded the cyclized product **17** in 58 % yield, but poor reproducibility. Finally we found that careful addition of BF_3•OEt_2 into a 0.001M solution of **16**[10] in dichloromethane at -78 °C and then warmed to 0 °C for 40 min afforded **17** in 43 % yield with reproducibility. Decomplexation[11] of the product **17** was achieved by heating its solution containing *n*-Bu_3SnH and a catalytic amount of NBS[12] in 1,4-cyclohexadiene at 39 °C for 2 h. The product **18**[13] as isolated in 40-45% yield.



As a summary we examined two cyclization reactions for the desmethyl carbon framework of taxachitrienes, and only one of the two routes exhibited a reasonable result in the 12-membered cyclization. Decomplexation of the biscobalthexacarbonyl was achieved under new condition to provide the tetra-ene-yne bicyclo[9.3.1]pentadecatriene. Overall reaction from **8** to **18** was 13 % in 8 steps.

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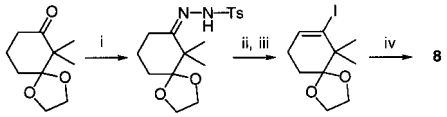
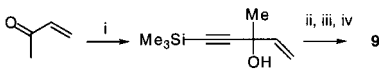
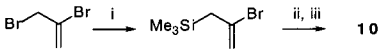
(5) Preparation of starting material **8**, **9** and **10**:
(a) A-ring **8** was synthesized from mono ketal of 2,2-dimethyl 1,3-cyclohexadione in 4 steps.



(i) H_2NNHTs / MeOH, 87 %; (ii) *n*-BuLi, *n*-Bu_3SnCl / THF-TMEDA (5:1); (iii) I_2 / Et_2O, 77 % in 2 steps; (iv) 3N HCl-THF (1:1), 97 %.
(b) Allylic alcohol **9** was synthesized from metyhl vinyl ketone in 4 steps.



(i) Me_3Si-≡-Li / THF, 31 %; (ii) K_2CO_3 / MeOH; (iii) 10 % H_2SO_4; (iv) TBSCl, imidazole / DMF, 53 % in 3 steps.
(c) Terminal acetylene **10** was synthesized from 2,3-dibromopropene in 3 steps.



(i) Me_3SiLi, CuI / HMPA, 42 %; (ii) Me_3Si-≡-H, $Pd(OAc)_2$, Ph_3P, CuI, *n*-$BuNH_2$ / THF, 95 %; (iii) K_2CO_3 / MeOH, 93 %.

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(9) When a methyl group was present on the olefin of the 6-membered ring, the cobalt complex did not form at this position.

(10) Precursor **16** was synthesized from TBS ether of **14** in 3 steps. (i) Amberlyst 15E / MeOH, 83 %; (ii) Ac_2O, pyridine, 93 %; (iii) $Co_2(CO)_8$ / CH_2Cl_2, quant.

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(12) In previous report (ref.11), we used a large excess of *n*-Bu_3SnH (10-12 equiv.) in benzene solvent at 65 °C for 2 h. NBS promoted this decomplexation, which was effective to reduce the amount of *n*-Bu_3SnH and to lower the reaction temperature. We used 3 equiv. of *n*-Bu_3SnH and 0.2 equiv. of NBS.

(13) Compound **18**: IR (KBr, film) ν_{max} 2956, 2929, 2856, 1249 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.20 (3H, s, $SiCH_3$), 0.22 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.11 (3H, s, $C(CH_3)_2$), 1.16 (3H, s, $C(CH_3)_2$), 1.64 (3H, d, *J* = 1.5 Hz, $C(CH_3)$=CH), 1.71-1.79 (1H, m, CH_2), 2.01-2.18 (3H, m, CH_2), 2.21-2.40 (4H, m, CH_2 ×2), 5.19 (1H, d, *J* = 2.1 Hz, C=CHH), 5.20 (1H, tq, *J* = 6.5, 1.5 Hz, $C(CH_3)$=CH), 5.23 (1H, d, *J* = 2.1 Hz, C=CHH), 5.78 (1H, d, *J* = 11.5 Hz, CH=C-CH=CH), 5.83-5.93 (2H, m, CH=C-CH=CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.1, -2.9, 17.0, 18.3, 21.9, 24.3, 24.8, 25.8, 29.8, 32.3, 38.4, 43.5, 74.2, 86.2, 93.4, 120.1, 122.5, 127.8, 128.9, 131.2, 132.4, 134.4, 142.0. MS (EI) *m/z* 382 (M^+), 367 (M-15). HRMS (EI) calcd for $C_{25}H_{38}OSi$: 382.2692, found 382.2712.