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Unexpected Rearrangement During Biomimetic Entry Toward a Taxane Skeleton

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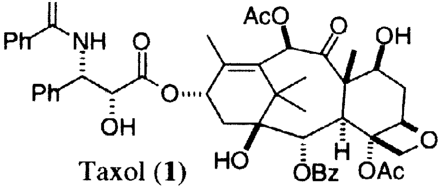
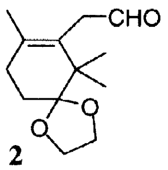
Abstract: Bicyclo[9.3.1]pentadecatriene derivative **4** which corresponds to a precursor of taxol in a biomimetic entry was constructed by means of $TiCl_4$-Zn promoted McMurry cyclization and Mitsunobu inversion. Treatment of **4** with mercuric triflate afforded an unexpected rearrangement-transannular cyclization product **5**.

Taxol (**1**) is a diterpene derivative employed as a significant clinical application against human cancers such as breast, ovarian, and lung cancer.[1, 2] Since the supply of taxol is a serious problem, numerous synthetic studies have been carried out and several groups have accomplished total syntheses.[3-6] We have developed an efficient olefin cyclization agent, mercuric triflate $Hg(OTf)_2$, and applied it for the syntheses of a variety of carbocyclic terpenoids.[7-13] We have been interested in the synthetic application of $Hg(OTf)_2$ for the construction of a taxane skeleton according to a biomimetic entry.[14-19] In a previous communication from this laboratory, it was demonstrated that the A-ring synthone **2** could be efficiently synthesized by $Hg(OTf)_2$ induced cyclization of homogeranyl acetate as the key step.[20] We would like to describe herein the conventional introduction of the side chain moiety and McMurry cyclization of the derived keto aldehyde **3** to give diols with a bicyclo[9.3.1]pentadecatriene skeleton. Transannular cyclization of selected 2α-*p*-nitrobenzoate **4** with $Hg(OTf)_2$ was examined and a rearranged organomercuric product **5** was isolated. The mechanism of the totally unexpected rearrangement is also proposed.



Taxol (**1**)



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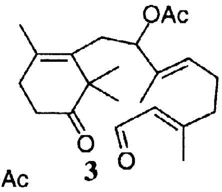

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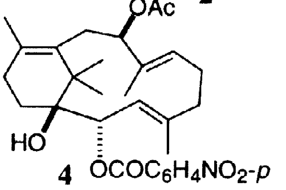

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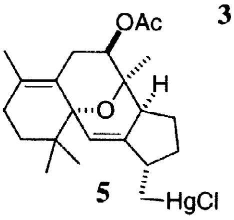

5

Lithium acetylide derived from **6** with *n*-BuLi was trapped by methyl iodide to give **7**. The acetylene **7** was treated with 3 eq of $Cp_2Zr(H)Cl$[21] in benzene at 40 °C for 12 h, and followed by an addition of iodine to give vinyl iodide **8** in 68% yield containing a small amount of a regioisomer (at least 25:1 on the basis of 600 MHz ^1H NMR). The vinyl lithium reagent was generated by the reaction of **8** with n-C_4H_9Li in hexane,[22] and treated with aldehyde **2** at -50 °C for 25 min affording alcohol **9** in 90% yield. After protection of the hydroxyl group as an acetate, ketal as well as TBS groups were simultaneously hydrolyzed under acidic

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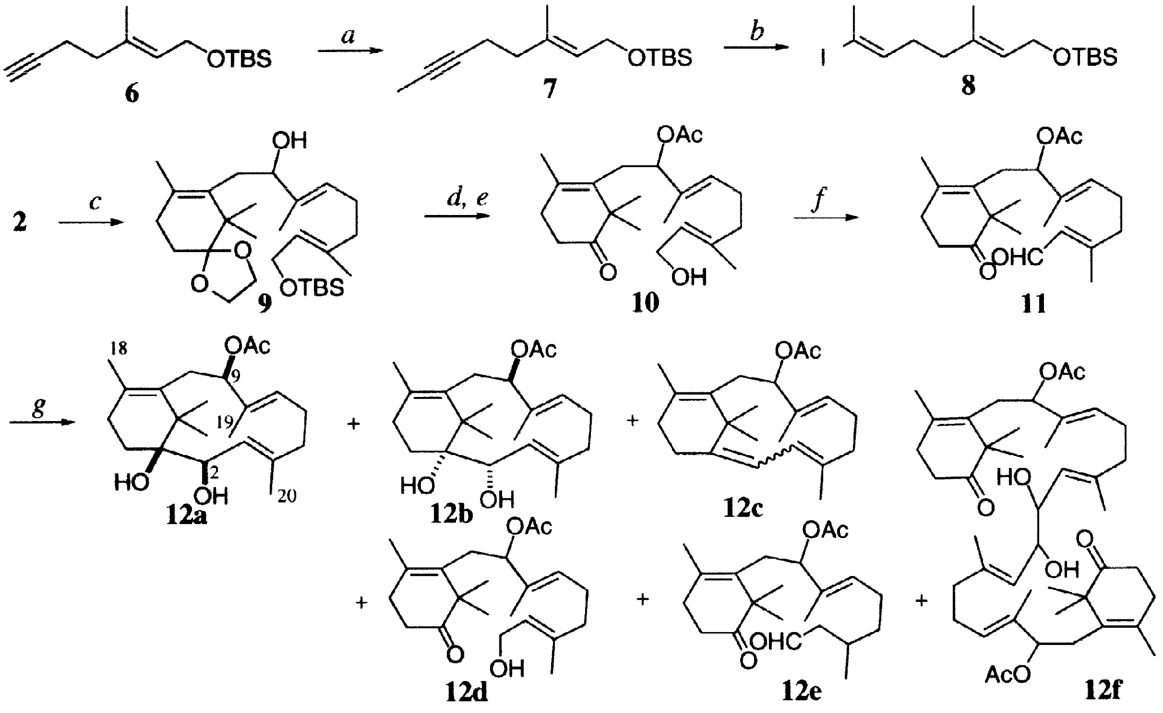
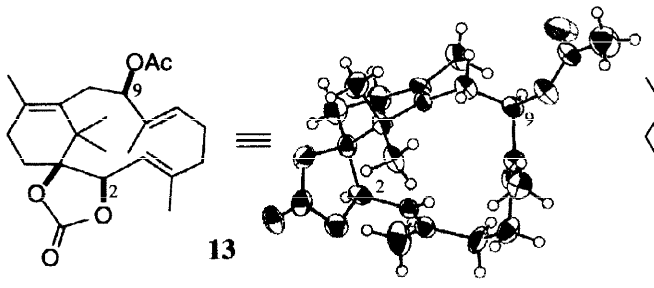
conditions to give **10** in quantitative yield in two steps. Swern oxidation of the alcohol **10** afforded keto aldehyde **11** in 94% yield. To a diluted solution of a low-valent titanium reagent prepared from $TiCl_4$ (20 eq) and Zn (60 eq) in super-dried benzene/THF[23] (5:1, 0.017M) in the presence of pyridine (20 eq),[24] a diluted solution of **11** in the same solvent (0.0028 M) was dropwise added using a syringe drive over a period of 12 h at 0 °C. After stirring for an additional 30 min, the reaction was quenched by the addition of saturated $NaHCO_3$ solution. Cyclization products **12a** and **12b** were obtained in 60% yield as a mixture of diastereomers after column chromatography on silica gel along with a tetraene **12c** (7%), a keto alcohol **12d** (8%), a 1,4-reduction product **12e** (3%), and dimers **12f** (5%). The mixture of diastereomers was separated by HPLC (Develosil-60-5 column, CH_2Cl_2/EtOAc/*i*-PrOH 15:1:0.1) to give minor product **12a** and major product **12b** in 1:2.3 ratio. The minor **12a** was converted into the crystalline carbonate **13** (mp 214-216 °C) by the treatment with triphosgene in pyridine/CH_2Cl_2 in 75% yield. Single crystal X-ray diffraction study of **13** defined the stereochemistry of **12a** to be 1, 2, 9 cis arrangement.[25] The stereochemistry of the major product **12b** was established by careful NMR experiment to be 1,2-cis and 2,9-trans arrangement.

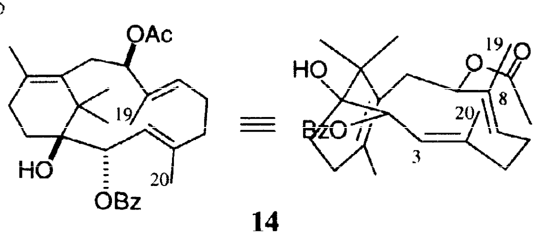


a *n*-BuLi/THF then CH_3I, 100%; *b* $Cp_2Zr(H)Cl$ (3 eq)/PhH, 40 °C, 12 h, then I_2, 68%; *c* **8** (1.2 eq)/*n*-BuLi (1.2 eq)/hexane, -50 °C, 25 min, 90%; *d* Ac_2O/Pyridine, 100%; *e* AcOH/H_2O (2:1), 25 °C, 11 h, 100%; *f* $(COCl)_2$/ DMSO/CH_2Cl_2, -78 °C, 23 h and then Et_3N, 94%; *g* $TiCl_4$ (20 eq)/Zn (60 eq)/Pyridine (20 eq)/PhH-THF (5:1), **11** in THF-PhH (final concentration 0.64×10^{-3} M), 0 °C, 12 h (addition by syringe drive) and additional 30 min, then aq $NaHCO_3$

To achieve the biomimetic transannular cyclization leading to correct B/C ring arrangement of taxol, the precursor must take a conformation of 19-methyl up and 20-methyl up. According to the conformation analysis by MATERIA-CONFLEX[26] calculation as well as MacroModel study, bicyclo[9.3.1]pentadecatriene with 2α and 9β oxygen functionalities favors the up/up conformation in more than 98%. For example 2α-benzoyloxy-9β-acetoxy derivative **14** takes the up/up conformation in 99.03% and its C-3 and C-8 distance is 3.84Å. Thus, we examined Mitsunobu inversion of the minor cyclization product **12a**. Upon treatment of **12a** with *p*-nitrobenzoic acid in the presence of tributylphosphine and DEAD in CH_2Cl_2[27] inverted *p*-nitrobenzoate **4** was obtained in 59% yield. Treatment of **4** with $Hg(OTf)_2$ (1.2 eq) in CH_3CN in the presence of tetramethylurea (1.2 eq) at room temperature[28] for 5.5 h afforded the sole organomercuric product in 22% yield. NMR and mass spectrum suggested this product is a transannular cyclized organomercuric compound without a benzoate moiety, however, the structure analysis by NMR is not an easy task. Therefore, single crystals were prepared from hexane and dichloromethane (mp 165-166 °C), and the structure was established by the single crystal X-ray diffraction analysis to be **5**.[29, 30]

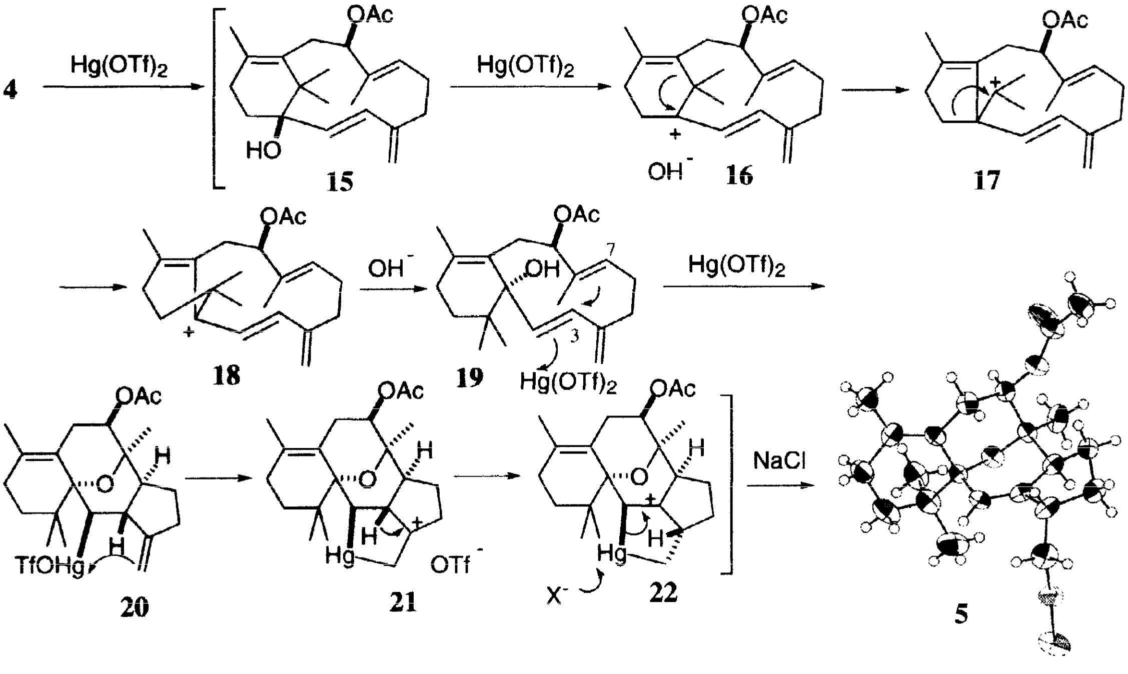


13



14

This unexpected rearrangement can be explained as follows. The nitrobenzoic acid moiety will be eliminated at an early stage by the action of $Hg(OTf)_2$ as a Lewis acid to give tetraene **15**. Removal of the hydroxy moiety generates stable dienyl cation **16** and successive 1, 2-shifts of the C-C bond produces sterically less-congested cation **18**. The alcohol **19** will be formed by hydroxylation. Organomerculation of **19** at C-2 leads to transannular cyclization between C-3 and C-7 followed by etherification to produce **20**. Intramolecular organomerculation gives **21** and the following hydride shift generates **22**. Final rearrangement product **5** should be formed by a nucleophilic attack to Hg creating the 2, 3 double bond.



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23. After closing the reaction system, suspension of Zn in solvent (benzene/THF 5:1) was heated at reflux through molecular sieves using an apparatus developed in this laboratory on the occasion of thermal glycosylation (see Nishizawa, M.; Kan, Y.; Yamada, H. *Tetrahedron Lett.* **1988**, *29*, 4597-4598, Nishizawa, M.; Garcia, D. M.; Yamada, H. *Synlett*, **1992**, 797-799) under argon atmosphere for 3 h prior to the addition of $TiCl_4$ and pyridine. A solution of keto aldehyde **11** in the same solvent was also dried by the same operation separately.
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25. The crystal of carbonate **13** was triclinic $P\bar{1}$, a = 9.105 Å, b = 9.368 Å, c = 13.087 Å, α = 106.38°, β = 94.46°, γ = 98.41°, Z = 2, V = 1051.1 $Å^3$, and D_{calc} = 1.227 Mgm^{-3}. Cu *K*-alpha radiation was employed and the final *R* value was 0.062 for 3148 reflections.
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28. Any reaction dose not take place at lower temperature.
29. Spectral data of **5** are follows. ^{1}H NMR (600 MHz in $CDCl_3$): δ 0.91 (3H, s), 0.97 (3H, s), 1.10 (1H, dddd, J = 6.0, 9.6, 12.4, 15.4 Hz), 1.23 (3H, s), 1.32 (1H, ddd, J = 1.2, 6.0, 12.4 Hz), 1.57 (3H, s), 1.67 (1H, ddd, J = 6.0, 13.0, 13.5 Hz), 1.79 (1H, m), 1.83 (1H, m), 1.92 (1H, dq, J = 6.0, 6.3 Hz), 2.02 (1H, dd, J = 12.5, 13.5 Hz), 2.04 (3H, s), 2.13 (1H, m), 2.18 (1H, m), 2.24 (1H, dd, J = 5.5, 11.5 Hz), 2.32 (1H, dd, J = 7.1, 11.5 Hz), 2.15 (1H, ddd, J = 2.5, 6.0, 9.9 Hz), 2.65 (1H, dd, J = 5.8, 13.5 Hz), 2.97 (1H, m), 4.72 (1H, dd, J = 5.8, 12.5 Hz), 5.43 (1H, t, J = 2.5 Hz);^{13}C-NMR (150 MHz in $CDCl_3$): δ 18.9 (q), 21.3 (q), 21.7 (q), 25.1 (q), 26.8 (t), 28.1 (q), 28.2 (t), 29.3 (t), 33.4 (t), 35.0 (s), 36.4 (t), 40.7 (t), 40.8 (d), 47.8 (d), 72.3 (s), 77.7 (s), 77.9 (d), 120.5 (d), 127.2 (s), 127.6 (s), 146.5 (s), 170.1 (s); HRMS (CI): *m/z* 580.1641 (M^+), calcd for $C_{22}H_{31}O_3HgCl$ 580.1668; FT-IR (film): ν 2922, 2857, 1740, 1453, 1373, 1236, 1034 cm^{-1}.
30. The crystal of **5** was monoclinic $P2_1/a$, a = 15.566 Å, b = 11.202 Å, c = 13.085 Å, β = 105.02°, V = 2203.67 $Å^3$, Z = 4, and D_{calc} = 1.746 Mgm^{-3}. Cu *K*-alpha radiation was employed and the final *R* value was 0.079 for 3054 reflections.