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Synthesis of C-Aromatic Taxinine Derivatives

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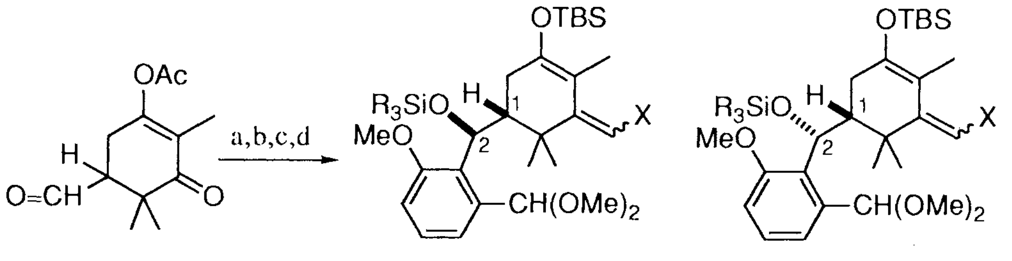
An oxygenated substituent at the 2-position (taxane numbering) plays a critical role to determine the endo/exo cyclization into the 8-membered ring system involved in the taxane skeleton, and the aromatic taxinine derivative was prepared from the corresponding 2α,9β,10α-exo cyclized compound through thermal exo-to-endo isomerization and a Lewis acid induced inversion on the C-9 and C-10 sites.

Owing to the remarkable structural feature as well as significant biological activities exhibited by taxol, a taxane family has attracted much attention in synthetic organic chemistry.[1] In the previous paper, we reported a direct 8-membered ring cyclization to form endo tricarbocycles through aldol-like coupling between a dienol ether and an acetal.[2] To extend this methodology for taxinine synthesis, we investigated the cyclization reaction of 2-oxygenated derivatives (taxane numbering). The 2-oxygenated cyclization precursors were prepared as shown in Eq. 1. Treatment of the aldehyde **1**[3] with the nucleophilic reagent corresponding to C-ring gave a mixture of diastereomers in 88% yield (ca. 3:1 ratio). While the stereochemistry of these adducts was unclear at this stage, the major isomer was later proven to be Cram-type adduct, and the minor to be *anti*-Cram type one by further conversion to the taxane-like skeleton (*vide infra*). The mixture of diastereomers was converted to **2a** (70%), **2b** (58%), **3a** (67%), and **3b** (35%)[4] by the following four steps; 1) exchange of the acetyl group with the TBS group, 2) separation of the diastereomers, 3) silylation of the 2-hydroxy group, and 4) Peterson olefination.



(1)

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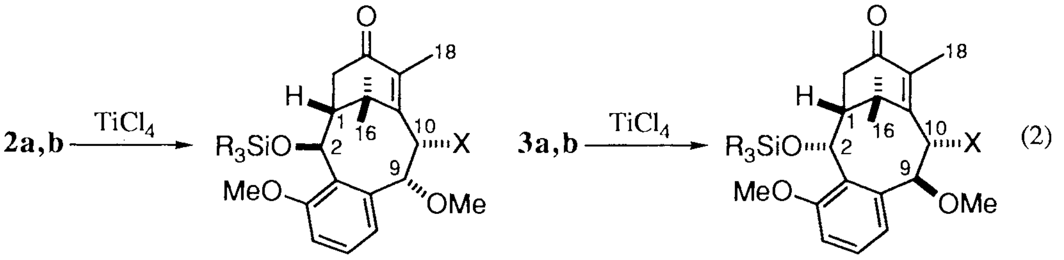
2a (X = H, R = Me)
2b (X = OMe, R = Et)

3a (X = H, R = Me)
3b (X = OMe, R = Et)

a) (2-Dimethoxymethyl-6-methoxy)phenyllithium/$CeCl_3$. b) Pyrrolidine, TBS-Cl/Et_3N, and Separation. c) TMS-Cl or TES-Cl/Et_3N. d) For **2a** and **3a**: TMS-CH_2Li/t-BuOK. For **2b** and **3b**: TMS-CH(OMe)Li/t-BuOK.

Under the influence of $TiCl_4$ in CH_2Cl_2 at low temperature, **2a,b** and **3a,b** underwent cyclization to give the corresponding tricarbocyclic products in moderate to good yields. However, in contrast to strong endo preference observed in the cyclization of 2-unsubstituted substrates,[2)] it was found that the endo/exo conformation of the cyclization product critically depends on the stereochemistry of the 2-siloxy group. While **2a** formed the endo cyclization product **4a** with 9α-substituent, **3a** afforded the exo cyclization product **5a** with 9β-methoxy group. Similarly, the cyclization reaction of **2b** gave 9α,10α-endo **4b**, whereas **3b**[5)] produced the 9β,10α-exo product **5b** (48%) together with small amounts of 9α,10β-endo (16%) and 9α,10α-endo isomers (8%). Conformation as well as stereochemistry of each product were determined by ^1H NMR.[6)] The structures of **4b**[7)] and **5b** were also confirmed by X-ray crystallographic analyses.



Endo

4a (X = H, R = Me): 51%
4b (X = OMe, R = Et): 76%

Exo

5a (X = H, R = Me): 30%
5b (X = OMe, R = Et): 48%

Remarkable directing effect of the siloxy group is probably due to its steric repulsion with *o*-MeO group. On cyclization of **3a**, for example, TS-1 which leads to the formation of endo tricarbocycle is greatly disfavored as shown in Fig. 1, and the cyclization preferentially proceeds through TS-2 to give exo **5a**. Stereochemistry of the C-9 methoxy group seems to be controlled by steric repulsion of MeO of $CH=O^+Me$ with the *o*-substituent.[2)]

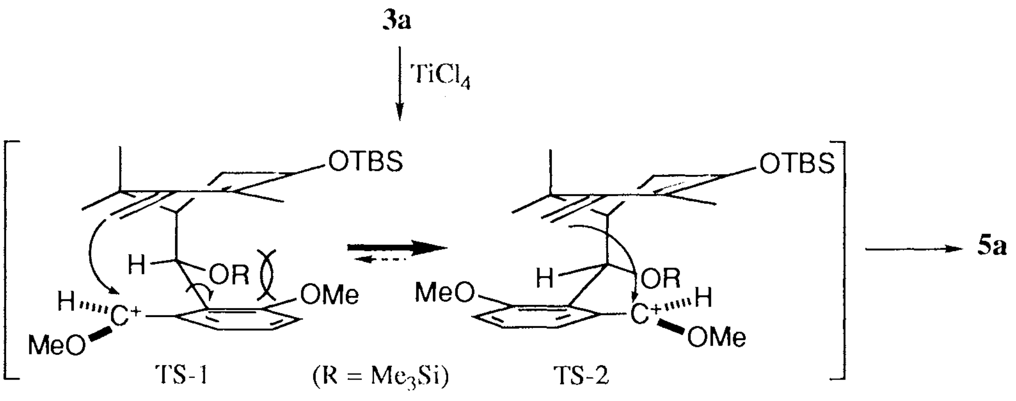
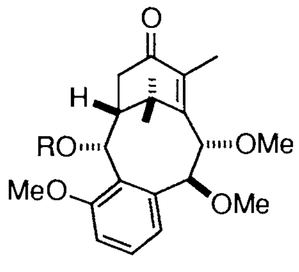


Fig. 1.

In order to explore a synthetic route to C-aromatic taxinine (2α,9α,10β-endo) derivatives, exo-to-endo isomerization of **5b** and inversion at C-9 and C-10 sites have been examined. The exo/endo equilibration took place at higher reaction temperature: A mixture of **5b** and **6b** was obtained in a ratio of 66:34[8)] by heating the former in toluene for 12 h. Further, 2-unprotected **5c** (R = H; 2α,9β,10α-exo) underwent almost complete isomerization to the desired endo isomer **6c** after heating for 30 min (Eq. 3). The exo/endo energy barrier between **5** and **6** in each case appears to be quite large enough to allow the isolation of each pure isomer at room temperature. A dramatic difference observed on **6b** and **6c** is attributable to a hydrogen bonding of OH with the methoxy group in the latter which may bring about a large additional stabilization.[9]

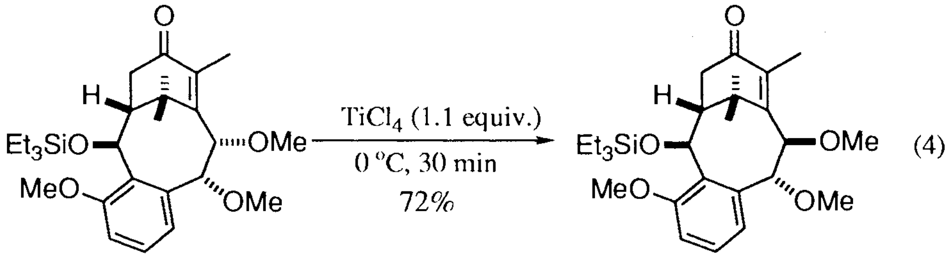


5b (exo:R = Et_3Si)
6b (endo:R = Et_3Si)
5c (exo:R = H)
6c (endo:R = H)

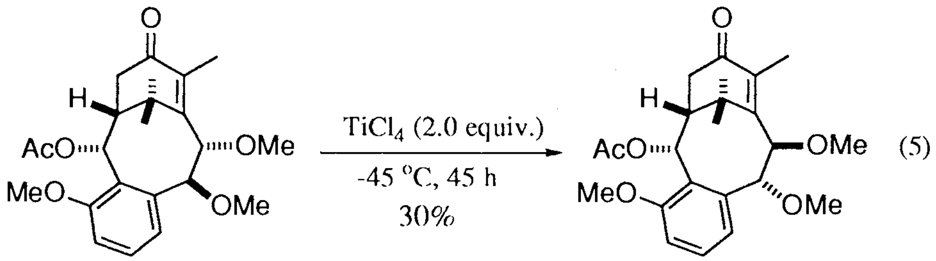
$$\textbf{Exo} \underset{\Delta}{\overset{\text{Toluene}}{\rightleftharpoons}} \textbf{Endo} \qquad (3)$$

R	**5**(exo):**6**(endo)
Et_3Si	66:34
H	3:97

A Lewis acid mediated isomerization at C-10 could be effected cleanly with **4b**, which, on treating with $TiCl_4$ at relatively higher temperature, gave **7b**[10] in good yield. In contrast, **6b** underwent selective removal of the silyl group, not isomerization, to give **6c** and its C-9 epimer, but use of the acetate **6d** gave the desired **7d**[11] (30% yield) together with its C-10 epimer (6% yield) at lower temperature for longer reaction period.



4b (endo) **7b** (endo)



6d (endo) **7d** (endo)

Thus, the present results have disclosed several interesting features of aromatic taxane chemistry and have allowed us to prepare the C-aromatic taxinine derivative **7d** and the 2-epimer **7b**.

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References

1) Review: C. S. Swindell, *Org. Prep. Proced. Int.*, **23**, 465 (1991).

2) Y. Horiguchi, T. Furukawa, and I. Kuwajima, *J. Am. Chem. Soc.*, **111**, 8277 (1989). T. Furukawa, K. Morihira, Y. Horiguchi, and I. Kuwajima, *Tetrahedron*, **48**, 6975 (1992).

3) The aldehyde **1** was prepared in 43% overall yield by the following 8-step procedures; (1) addition reaction of lithiated THP-propargyl ether to propionaldehyde, (2) partial reduction of the triple bond with H_2/Lindlar catalyst, (3) Swern oxidation, (4) conjugate addition of lithiated isobutyric ester, (5) Dieckmann-like cyclization with t-BuOK, (6) acetylation with Ac_2O/Et_3N, (7) removal of THP group with *p*-TsOH/MeOH, and (8) Swern oxidation.

4) The yields were based on amounts of the corresponding isomer in the diastereomeric mixture used.

5) While the cyclization of **2a**, **2b**, and **3a** proceeded at -78 °C within 30 min, a longer reaction period at higher temperature was required to complete the reaction of **3b**; -78 °C (45 min) and -23 °C (2 h).

6) Owing to C-aromatic ring, the 18-methyl group of the endo and the 16-methyl group of the exo isomer appear at higher fields in the ^{1}H NMR spectra: K. J. Shea and J. W. Gilman, *Tetrahedron Lett.*, **25**, 2451 (1984). In the present case, these groups appear as follows. **4a**: (270 MHz, $CDCl_3$) δ at 1.67 (C-16), 0.85 ppm (C-18). **4b**: 1.67 (C-16), 1.00 ppm (C-18). **5a**: 0.20 (C-16), 1.90 ppm (C-18). **5b**: 0.10 (C-16), 2.04 ppm (C-18). Further, protons on C(9) and C(10) appear as follows; **4b**: 5.90 (J = 5.5 Hz), 4.66 (J = 5.5 Hz). **5b**: 5.23 (J = 9.3 Hz), 3.99 (J = 9.3 Hz).

7) Y. Sakai, Y. Kojima, Y. Ohashi, K. Morihira, T. Furukawa, Y. Horiguchi, and I. Kuwajima, *Acta Crystallogr., Sect. C*, **47**, 2700 (1991).

8) This value seems to be reasonable because the exo isomer **5b** is estimated to be ca. 0.39 kcal/mol more stable than the endo isomer **6b** by MM2 calculation (CaChe program).

9) The molecular modeling shows OH of **6c** is closely situated to make the hydrogen bonding with the *o*-MeO group , whereas those of **5c** are too far each other.

10) The key ^{1}H NMR signals of **7b**: (270 MHz, $CDCl_3$) δ 0.97 (s, 3H, 18-Me), 1.80 (s, 3H, 16-Me), 4.44 (d, J = 9.2 Hz, 1H, C(10)-H), 5.75 (d, J = 5.2 Hz, 1H, C(2)-H), 5.82 (d, J = 9.2 Hz, 1H, C(9)-H).

11) The key ^{1}H NMR signals of **7d**: (270 MHz, $CDCl_3$) δ 0.96 (s, 3H, 18-Me), 1.71 (s, 3H, 16-Me), 4.42 (d, J = 9.0 Hz, 1H, C(10)-H), 4.92 (d, J = 9.0 Hz, 1H, C(9)-H), 6.17 (s, 1H, C(2)-H).

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