An Asymmetric Synthesis of the Fully Functionalized AB Ring System of 12-Demethyltaxol *via* Successive Stereoselective Allylation and Intramolecular Aldol Reactions

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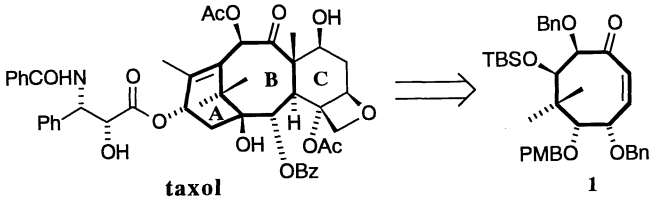
Optically active 9-*t*-butyldiphenylsiloxy-11,11-dimethyl-5-methoxymethoxy-1,2,6-tribenzyloxybicyclo[5.3.1]undec-3,7-diene (**12**) was synthesized from diketone **9** *via* an intramolecular aldol reaction. The diketone **9** was synthesized from 7-*t*-butyldimethylsiloxy-4,8-dibenzyloxy-6,6-dimethyl-5-*p*-methoxybenzyloxy-2-cycloocten-1-one (**1**) by way of a two-step sequence using diastereoselective allylation with allylmagnesium bromide followed by Wacker oxidation.

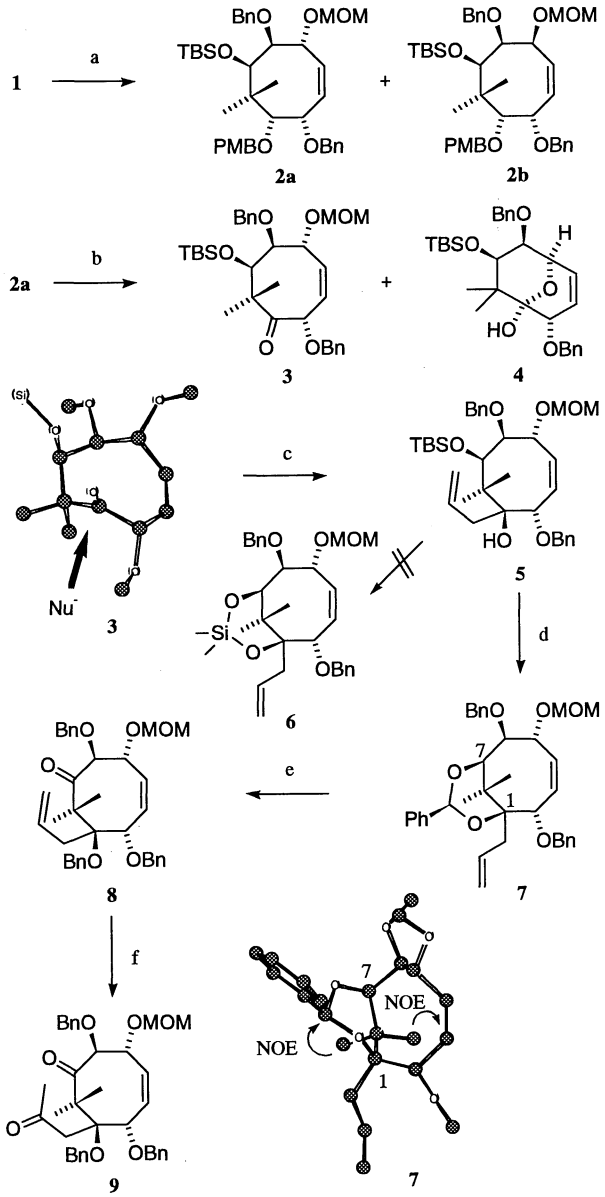
In previous communications, a stereoselective synthesis of optically active 8-membered ring enone **1**, a potential synthetic intermediate for taxol, including a novel synthetic strategy towards taxol was described.[1,2] Furthermore, the synthesis of AB ring model of taxol was achieved *via* allylation of a 8-membered ring compound followed by intramolecular aldol condensation.[3] Now, an asymmetric synthesis of the fully functionalized AB ring system of 12-demethyltaxol is described as a part of a total synthesis of taxol.



Scheme 1.

Since 8-membered ring enone **1** is a mixture of two slowly interconverting conformational isomers as shown in previous communication,[2] its transformation to a conformationally rigid derivative was first examined. When **1** was treated with DIBAL in CH_2Cl_2, a mixture of two diastereomers was obtained in 70% yield with moderate stereoselectivity (75 / 25). Interestingly, the ^1H NMR of the methoxymethyl ether of **2a** derived from the major stereoisomer shows that it has only one conformation at room temperature in $CDCl_3$, whereas the other stereoisomer **2b** has broadened spectra. Calculation of the ground state energy of **2a** by MM2 suggests that it has lesser transannular strain than stereoisomer **2b**.[4] Therefore, it was planned to utilize **2a** as a starting substrate for constructing the AB ring system of taxol. By screening several reducing reagents, a highly stereoselective reduction was found when L-Selectride was used in THF at -45 °C (98%, α-alcohol only). β,γ-Unsaturated ketone **3** was obtained by DDQ oxidation of **2a** followed by oxidation using Dess-Martin periodinane.[5] When the oxidation was carried out by Swern's procedure, on the other hand, bicyclic hemiketal **4** was produced as a by-product. The relative stereochemistry of **3** was assigned from the ^1H NMR of the transformed product **4**.

In the model study, it was revealed that successive allylation and Wacker oxidation of the 8-membered ring ketone were most



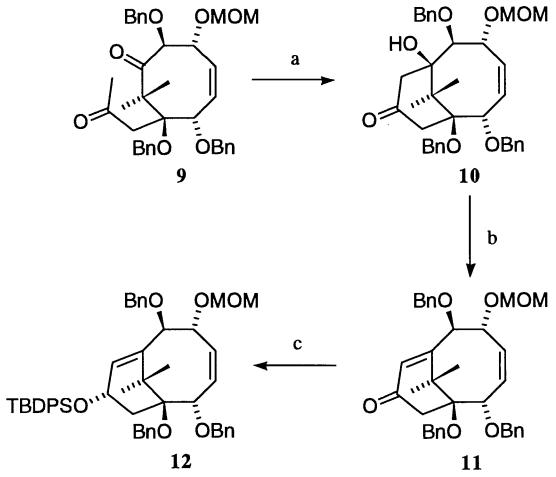
a) L-Selectride, THF, -78 °C to -45 °C (98%); MOMCl, i-Pr_2NEt, DMAP, CH_2Cl_2, 40 °C (95%); b) DDQ, H_2O, CH_2Cl_2, r.t. (99%); Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t. (96%, **3** only); c) allylMgBr, Et_2O, -78 °C to -45 °C (82%); d) TBAF, THF, r.t. (100%); $PhCH(OMe)_2$,CSA, benzene, azeotrope (100%); e) DIBAL, CH_2Cl_2, -23 °C to 0 °C (87%); PDC, CH_2Cl_2, r.t. (100%); f) $PdCl_2$, CuCl, O_2, H_2O, DMF, r.t. (84%).

Scheme 2.

effective for construction of the AB ring skeleton of taxol.[3] Conformational analysis of β,γ-unsaturated ketone **3** by ^{1}H NMR and MM2 calculation showed that **3** has the chair-boat form as shown in Scheme 2, and therefore it was anticipated that the desired α-face selective allylation would take place smoothly. In actual fact, allylation of **3** with allylmagnesium bromide afforded homoallyl alcohol **5** in high yield with good diastereoselectivity (98%, α-face / β-face = 84 / 16). Deprotection of silyl ether **5** gave the cis-diol in quantitative yield, however, the cyclic silyl ether **6** was not obtained under the conditions used in the model synthesis of the AB ring system.[3] On the other hand, treatment of the cis-diol with benzaldehyde dimethylacetal in the presence of a catalytic amount of camphorsulfonic acid afforded a single benzylidene derivative **7** in quantitative yield under standard reaction conditions.[6] The ^{1}H NMR of **7** and MM2 calculation of the conformation indicate that **7** has a rigid bicyclic structure as shown in Scheme 2. Comparing the environments of the oxygen atoms at the C-1 and C-7 positions, the C-1 oxygen atom is located inside of the 8-membered ring skeleton of **7**. Therefore, it was considered that reductive cleavage of the bond between C-7 and oxygen would take place chemoselectively in the presence of Lewis acid because the oxygen atom at the C-1 position is effectively shielded.[7] As expected, the desired reductive cleavage of the benzylidene derivative **7** proceeded with almost perfect chemoselectivity to give secondary alcohol in 87% yield. γ,δ-Unsaturated ketone **8** was obtained in high yield by oxidation of the alcohol with PDC, and diketone **9**, a precursor of the AB ring system of 12-demethyltaxol, was prepared by successive Wacker oxidation according to the same procedure examined in the model synthesis.[3]

Next, intramolecular aldol condensation of the diketone **9** was tried in order to produce the desired α,β-unsaturated ketone **11** directly from **9** under ordinary reaction conditions. However, in the case of substrate **9**, the corresponding aldol **10** was unexpectedly isolated on treatment with LHMDS and HMPA combined system. The aldol **10** was stable at room temperature and spontaneous dehydration of **10** did not proceed at all. On the other hand, facile dehydration of **10** was achieved using Burgess' reagent to afford **11** in high yield.[8] Successive reduction of **11** by DIBAL, and silylation by *t*-butyldiphenylsilyl triflate in pyridine produced the desired silyl ether **12**, which corresponds to the fully functionalized AB ring system of 12-demethyltaxol.[9]

It is noteworthy that optically active **12** was synthesized in high yield from 8-membered ring enone **1** *via* successive highly stereoselective allylation and intramolecular aldol reactions. Further studies on the effective synthesis of the ABC ring system of taxol using the bicyclic compound **12** are now in progress.



a) LHMDS, THF, -100 °C to -78 °C; then HMPA, -35 °C (92% based on 40% conversion); b) Burgess' reagent, benzene, 50 °C (84%); c) DIBAL, CH_2Cl_2, 0 °C (100%); TBDPSOTf, pyridine, 0 °C (66%).

Scheme 3.

References and Notes

1 T. Mukaiyama, I. Shiina, K. Sakata, T. Emura, K. Seto, and M. Saitoh, *Chem. Lett.*, **1995**, 179.

2 I. Shiina, K. Uoto, N. Mori, T. Kosugi, and T. Mukaiyama, *Chem. Lett.*, **1995**, 181.

3 T. Mukaiyama, I. Shiina, K. Kimura, Y. Akiyama, and H. Iwadare, *Chem. Lett.*, **1995**, 229, in which a similar way to construct A ring on BC ring system of taxinine via intramolecular aldol-type reaction by Swindell was shown.

4 All calculations were performed using the Chem3D Plus molecular mechanics program ver. 3.1.2. Some atoms are omitted for clarity in Scheme 2.

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6 **7**; $[\alpha]_D^{28}$ -83.8° (c. 3.43, PhH); ^{1}H NMR ($CDCl_3$) δ = 1.14 (3H, s), 1.33 (3H, s), 2.58 (1H, dd, J = 7.9, 14.9 Hz), 2.80 (1H, dd, J = 5.9, 14.9 Hz), 3.35 (3H, s), 3.61 (1H, dd, J = 1.1, 9.9 Hz), 4.07 (1H, dd, J = 0, 1.1 Hz), 4.35 (1H, d, J = 11.9 Hz), 4.42 (1H, d, J = 11.9 Hz), 4.64 (1H, d, J = 11.9 Hz), 4.71 (1H, d, J = 6.6 Hz), 4.79 (1H, d, J = 6.6 Hz), 4.86 (1H, dd, J = 5.6, 9.9 Hz), 4.87 (1H, d, J = 11.9 Hz), 4.95 - 5.08 (3H, m), 5.64 - 5.76 (2H, m), 6.03 (1H, d, J = 0 Hz), 6.05 - 6.20 (1H, m), 7.21 - 7.54 (15H, m).

7 S. Takano, M. Akiyama, S. Sato, and K. Ogasawara, *Chem. Lett.*, **1983**, 1593; S. L. Schreiber, Z. Wang, and G. Schulte, *Tetrahedron Lett.*, **29**, 4085 (1988); N. R. Curtis, A. B. Holmes, and M. G. Looney, *Tetrahedron Lett.*, **33**, 671 (1992).

8 E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Org. Chem.*, **38**, 26 (1973).

9 **12**; $[\alpha]_D^{29}$ +28.8° (c. 1.09, PhH); ^{1}H NMR ($CDCl_3$) δ = 0.84 (3H, s), 1.09 (9H, s), 1.41 (3H, s), 2.25 (2H, d, J = 6.6 Hz), 3.40 (3H, s), 3.90 (1H, d, J = 8.9 Hz), 4.18 (1H, dd, J = 1.7, 7.3 Hz), 4.33 (1H, d, J = 11.5 Hz), 4.40 (1H, d, J = 11.9 Hz), 4.50 (1H, d, J = 12.5 Hz), 4.56 (1H, d, J = 11.5 Hz), 4.57 (1H, d, J = 11.9 Hz), 4.66 (1H, ddd, J = 1.7, 6.6, 8.9 Hz), 4.72 (1H, dt, J = 0, 6.6 Hz), 4.73 (1H, d, J = 6.7 Hz), 4.85 (1H, d, J = 6.7 Hz), 4.88 (1H, d, J = 12.5 Hz), 5.27 (1H, d, J = 0 Hz), 5.45 (1H, ddd, J = 1.7, 7.3, 12.2 Hz), 5.75 (1H, ddd, J = 1.7, 6.6, 12.2 Hz), 7.15 - 7.45 (25H, m); ^{13}C NMR ($CDCl_3$) δ = 19.05 (CH_3), 19.14 (C, ^{t}Bu), 26.99 (CH_3*3), 27.62 (CH_3), 34.56 (CH_2), 42.72 (C), 55.38 (CH_3), 66.08 (CH), 68.16 (CH_2), 71.16 (CH_2), 72.02 (CH_2), 78.15 (CH), 81.06 (C), 82.41 (CH), 92.09 (CH), 96.12 (CH_2), 126.49 (CH), 126.58 (CH), 127.30 (CH), 127.39 (CH), 127.64 (CH), 127.92 (CH), 127.96 (CH), 128.12 (CH), 128.21 (CH), 129.70 (CH), 133.91 (CH), 133.98 (CH), 134.20 (C), 135.80 (CH), 135.83 (CH), 137.72 (CH), 138.49 (C), 138.53 (C), 139.44 (C), 139.89 (CH), 141.19 (C).