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The synthesis of the CD ring of paclitaxel

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Abstract—We have developed a practical synthetic route to the CD ring of paclitaxel. Unsaturated ester **8** was stereo- and regioselectively isomerized to **9**. Stereoselective introduction of hydroxy groups and oxetane formation provided potential intermediate **4**, which was coupled to an A ring moiety.

An approach ACD→ABCD is a particularly attractive route for the synthesis of paclitaxel (**1**) due to high convergency.[1] As described in the preceding paper, we have developed a Ti-mediated radical cyclization of epoxyalkenes, providing both the A and C ring synthons.[2] Here we wish to report the synthesis of the CD ring and the coupling reaction of the A and CD moieties as part of our strategy for an ACD→ABCD route (Fig. 1).

We reported the stereoselective synthesis of enal **7** by radical cyclization of an epoxy geraniol derivative. If one can isomerize this α,β-unsaturated derivative **7** to either *endo*-β,γ-unsaturated **5** or *exo*-β,γ-unsaturated **6**, selectively, with formation of the *trans* stereochemistry between the C8-Me and C3-H,[3] it could be converted to CD ring **4**. We wish to report the synthesis of the CD ring synthon **4** and its coupling reaction with the A ring moiety **3** in order to synthesize **2**, which is poised for intramolecular alkylation to form the B ring.[4]

Our first attempt to isomerize the alkene was carried out on enal **7a** (R = MEM). Isomerization by way of the formation of a metal enamine, followed by protonation failed. Therefore, enal **7a** was converted to ester **8a** (R = MEM) by oxidation ($NaClO_2$/*t*-BuOH/water) and methylation (MeI/K_2CO_3/DMF). **8a** was treated with lithium diisopropylamide (LDA) and the resulting enolate was quenched with acid. As shown in Table 1 (entries 1 and 2), alkene isomerization was observed to provide **9a** (R = MEM) in 30–35% yield and starting material **8a** was mostly recovered under those conditions. To avoid the existence of other proton sources, i.e. diisopropylamine formed in situ, we trapped the ester enolate with TMSCl. Only a single silyl ketene acetal **10** was selectively obtained (detected by ^1H NMR).[5] **10** was hydrolyzed by acid treatment, as shown in Table 1 (entries 3–6).[6] When protonation was carried out with camphorsulfonic acid in THF, the best diastereoselectivity (88%) was obtained (entry 3). This stereoselection is explained by the axial attack of the proton at the α-position of the enol ether **10**. We next investigated the protonation of **8b** (R = BOM), which was prepared with higher diastereomeric ratio via radical cyclization in the preceding paper. Similarly, **9b**

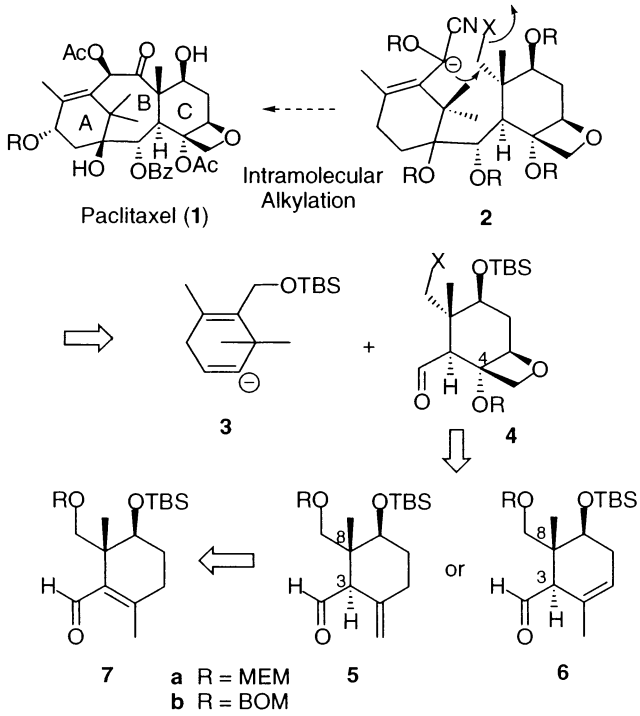

Figure 1. Strategy of the synthesis of paclitaxel.

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Table 1. The isomerization of **8** to **9** by dienolate formation and protonation

Entry	Substrate	Conditions	Yield (%)	Ratio (**9**: 3-*epi* **9**)[a]
1	**8a**	LDA (4 equiv.), THF, −78°C; NH_4Cl solid	35	[b]
2	**8a**	LDA (4 equiv.), THF, −78°C; 1 M HCl	30	[b]
3	**8a**	(1) LDA (4 equiv.), THF, −78°C; TMSCl, (2) CSA, THF	80	88:12
4	**8a**	(1) LDA (4 equiv.), THF, −78°C; TMSCl, (2) CSA, CH_2Cl_2	50	80:20
5	**8a**	(1) LDA (4 equiv.), THF, −78°C; TMSCl, (2) 1 M HCl, THF	70	56:44
6	**8a**	(1) LDA (4 equiv.), THF, −78°C; TMSCl, (2) TBAF, THF	20	50:50
7	**8b**	(1) LDA (4 equiv.), THF, −78°C; TMSCl, (2) CSA, THF	85	88:12

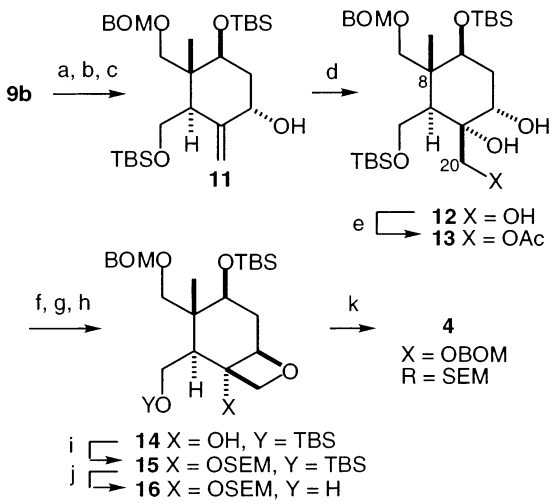
[a] The ratio was determined by HPLC.
[b] The ratio was not determined.

(R = BOM) was obtained in 85% yield with 88% diastereoselectivity (entry 7). Interestingly, none of the *endo*-alkene was obtained in these reactions. Presumably, LDA coordinates to the ester carbonyl to abstract the adjacent hydrogen of a vinylmethyl group rather than that of the distal methylene position (Scheme 1).

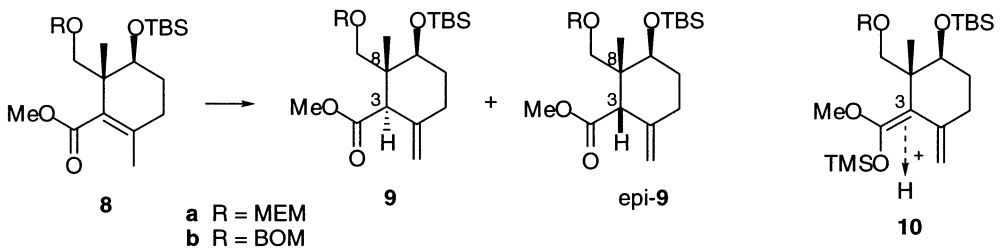
The synthesis of the CD ring proceeds as follows: Reduction of methyl ester **9b** with lithium aluminum hydride, protection of the resulting alcohol with TBS, and allylic oxidation with selenium dioxide provided **11**, stereoselectively (51%, three steps).[7,8] Oxidation of the *exo*-alkene of **11** with a catalytic amount of OsO_4 under the usual conditions[7] (NMO, acetone–water or *t*-BuOH–water) afforded triol **12** in modest yield (37–42%). However, we found the addition of DABCO in this catalytic dihydroxylation increased the yield to 52% and use of quinuclidine afforded **12** in up to 60% yield.[9]

According to the reported procedure,[10,11] selective acetylation of the primary alcohol of **12** provided mono acetate **13** in 90% yield. The NOE observed between the C8-Me and C20-CH_2-OAc showed that dihydroxylation proceeded from the bottom face. Mesylation of the secondary alcohol, hydrolysis of the acetyl group, and DBU treatment in refluxing toluene afforded oxetane **14** in 75% overall yield (three steps).[10,11] Protection of the hindered tertiary alcohol with TMSOTf, BOMCl, and EVE failed. However, protection with SEMCl provided the desired ether **15** in 64% yield. Deprotection of the primary TBS ether with HF·Py led to **16** in 65% yield, whereas other reagents (AcOH/THF/water or PPTS/MeOH) only gave deprotection of the SEM group. Oxidation of the primary alcohol **16** provided the desired aldehyde **4** (X = OBOM, R = SEM) corresponding to the precursor of the CD ring of paclitaxel (Scheme 2).[12]

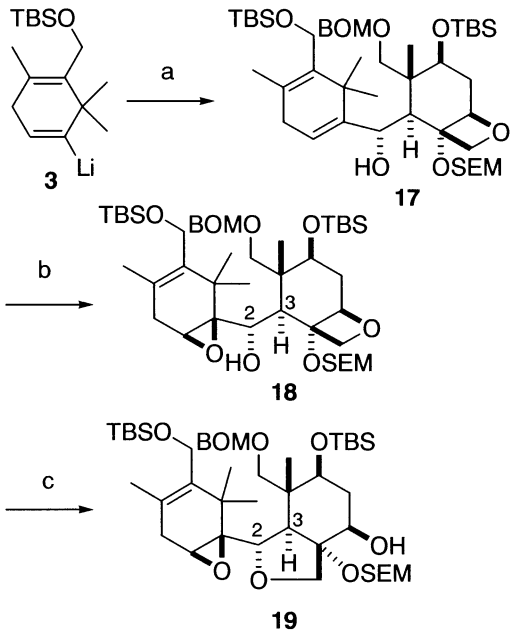
The coupling reaction of aldehyde **4** with an anion **3**[13,14] proceeded at −78°C to furnish alcohol **17** as a single diastereomer,[15] which underwent hydroxy-directed epoxidation leading to a single product **18**. The stereochemistry at the 2 position of **18** was assigned based on the small coupling constant between the C2-H and C3-H.[16] Treatment with $LiAlH_4$ did not provide the expected ring opening of the epoxide.[17] Rather etherification accompanied by oxetane cleavage leading to **19** predominated (Scheme 3).[18,19]



Scheme 2. Synthesis of CD ring **4**. (a) $LiAlH_4$, ether; (b) TBSCl, imidazole, DMF; (c) SeO_2, TBHP, salicylic acid, hexane, three steps 51%; (d) OsO_4, NMO, quinuclidine, *t*-BuOH, H_2O, 60%; (e) AcCl, DMAP, CH_2Cl_2, 90%; (f) MsCl, DMAP, CH_2Cl_2; (g) K_2CO_3, MeOH, H_2O; (h) DBU, toluene, three steps 75%; (i) SEMCl, DIEA, TBAI, 64%; (j) HF-Py, 65%; (k) TPAP, NMO, CH_2Cl_2, 75%.



Scheme 1. Stereo- and regioselective isomerization of α,β-unsaturated ester **8**.



Scheme 3. Coupling of **4** with a ring moiety. (a) **4** in THF, −78°C (61%); (b) $VO(acac)_2$, TBHP, CH_2Cl_2 (65%); (c) $LiAlH_4$, ether, reflux (70%).

We have demonstrated the stereoselective isomerization of α,β-unsaturated ester **8** to β-methylene ester **9**, the synthesis of the CD ring moiety **4**, and successful coupling of aldehyde **4** with the A ring **3**. Further study toward the direct formation of the B ring in the synthesis of paclitaxel will be reported in due course from our laboratory.

References

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5. The stereochemistry of **10** formed in this lithiation is probably *E* because acid treatment provided β-trimethylsilylmethyl-α,β-unsaturated ester in some cases.
6. To determine the stereochemistries, **9** and its epimer were converted to enal **5** and its epimer, respectively. The NOE between C3-H and C7-H was found in the major product, determined as **5** and it was also observed between CHO and C7-H in its epimer.
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12. Spectra data of **4**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 0.9–1.0 (m, 2H), 1.17 (s, 3H), 2.00 (ddd, 1H, J=4.0, 10.2, 14.8 Hz), 2.27 (ddd, 1H, J=5.6, 8.7, 14.8 Hz), 3.10 (bs, 1H), 3.51 (d, 1H, J=9.9 Hz), 3.61 (d, 1H, J=8.3 Hz), 3.66 (d, 1H, J=9.6 Hz), 3.67 (d, 1H, J=7.9 Hz), 3.86 (dd, 1H, J=5.6, 9.9 Hz), 4.54 (d, 1H, J=11.6 Hz), 4.64 (d, 1H, J=11.6 Hz), 4.7–4.9 (m, 7H), 7.3–7.4 (m, 5H), 9.85 (d, 1H, J=1.65 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 201.9 (d), 128.6 (d), 127.9 (d), 127.9 (d), 95.1 (t), 90.4 (t), 84.3 (d), 77.7 (t), 71.5 (t), 70.0 (t), 68.7 (d), 65.7 (t), 55.8 (d), 42.5 (s), 35.0 (t), 25.9 (q), 18.2 (t), 18.1 (t), 13.4 (q), −1.4 (q), −3.9 (q), −4.9 (q); IR (neat) 2890, 2830, 2800, 1701, 1455, 1375, 1240, 1155, 1094, 1046, 859, 834, 764 cm^{-1}; MS (ESI-TOF) 598.4 $[M+NH_4]^+$.
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15. Coupling reaction without protection of the tertiary alcohol at the 4 position did not provide a 1,2-adduct.
16. Calculation of coupling constants by Carplus equation based on conformational analysis using MM2 (macromodel 6.0, Monte Carlo) suggested $J_{2,3}$=0.4 Hz for the desired isomer and 2.9 Hz for the other. The observed J value was <1.0 Hz in **18**.
17. See also, Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K., Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634–644.
18. Spectra data of **19**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.036 (s, 3H), 0.059 (s, 3H), 0.067 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 0.91 (s, 3H), 0.84–1.00 (m, 2H), 1.33 (s, 3H), 1.36 (s, 3H), 1.61 (s, 3H), 1.76 (ddd, 1H, J=10.9, 11.2, 12.9 Hz), 1.93–2.01 (m, 1H), 2.29 (bs, 3H), 3.07 (bs, 1H), 3.23 (d, 1H, J=9.6 Hz), 3.37 (d, 1H, J=9.6 Hz), 3.60 (dt, 1H, J=9.9, 10.9 Hz), 3.74 (dt, 1H, J=9.9, 10.9 Hz), 3.85 (dd, 1H, J=3.3, 10.9 Hz), 3.90 (d, 1H, J=10.9 Hz), 3.97–4.06 (m, 1H), 4.11 (d, 1H, J=10.9 Hz), 4.13 (bs, 2H), 4.56 (d, 1H, J=12.2 Hz), 4.65 (d, 1H, J=12.2 Hz), 4.68 (d, 1H, J=6.6 Hz), 4.70 (d, 1H, J=8.2 Hz), 4.74 (bs, 1H), 4.75 (d, 1H, J=6.6 Hz), 4.87 (d, 1H, J=8.2 Hz), 7.26–7.39 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.4 (q), −5.3 (q), −4.8 (q), −3.7 (q), −1.4 (q), 14.3 (q), 18.1 (s), 18.40 (t), 18.43 (s), 19.7 (q), 22.0 (q), 24.9 (q),

26.0 (q), 26.1 (q), 32.1 (t), 33.8 (t), 39.7 (s), 42.6 (s), 46.1 (d), 54.6 (d), 59.1 (t), 65.2 (s), 66.0 (t), 69.9 (d), 70.1 (t), 70.6 (d), 72.7 (t), 77.3 (s), 82.0 (d), 89.7 (t), 89.8 (t), 95.6 (t), 124.5 (s), 127.6 (d), 127.8 (d), 128.5 (d), 135.0 (s), 137.8 (s).

19. Partial opening of the oxetane ring forming a tetrahydrofuran ring was reported in 7-silylated deacetyl Baccatin III. See, Wahl, A.; Guéritte-Voegelein, G.; Guénard, D.; Le Goff, M.-T.; Potier, P. *Tetrahedron* **1992**, *48*, 6965–6974.