A Novel Highly Stereoselective Synthesis of the *A*-ring of Taxol *via* Two Aldol Reactions

Yu Ding* and Xiang-Rong Jiang

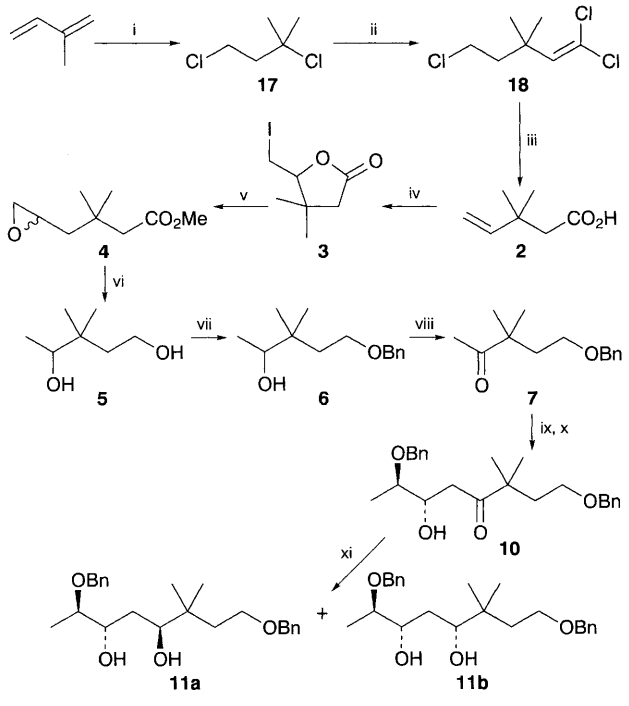
Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Lu, Shanghai 200032, China

An efficient, scalable route to the Taxol *A*-ring synthon is described; high stereoselectivity and regioselectivity are achieved by means of an intermolecular Aldol addition and an intramolecular Aldol condensation.

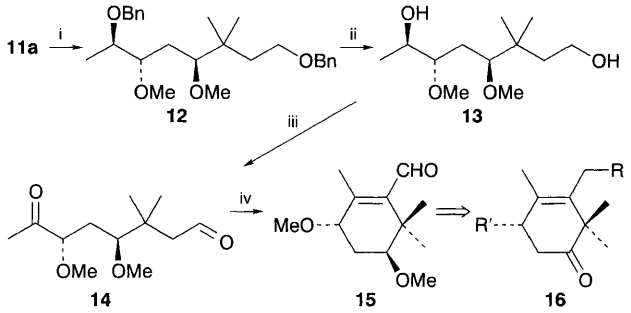
Efficient routes to taxane diterpenoids[1] have recently been described. The convergent synthesis of Taxol being pursued in this laboratory entails construction of *A* and *C/D* ring moieties followed by their coupling with the formation of the *ABC* ring system. Despite a lot of syntheses of *A*-ring and the successful total synthesis of Taxol by Holton *et al.* and Nicolaou *et al.*[2] there still remains much room for development. Here, we report an elegant stereocontrolled formation of the *A*-ring *via* an intermolecular Aldol addition and an intramolecular Aldol condensation.

In Scheme 1, **2** was prepared readily on a large scale.[3] The carboxylic acid **2**, when treated with potassium iodide/iodine in sodium hydrogen carbonate solution, was transformed into the iodolactone **3** in quantitative yield. Methanolysis of the iodolactone proceeded smoothly with concomitant loss of iodide and formation of the corresponding epoxide **4** in quantitative yield. The expoxide **4** was reduced to the diol **5** with LAH in diethyl ether in 92% yield. The primary alcohol in diol **5** was selectively protected as its benzyl ether **6** by treating with NaH and then $PhCH_2Cl$ in dry Me_2SO in 80% yield. Then, **6** underwent Swern oxidation to give C-4 ketone **7** in 93% yield. Before the key Aldol reaction, ketone **7** was converted in quantitative yield to the silyl enol ether **9**, which then reacted with 2-benzyloxyl propioaldehyde **8**[4] by treating with $TiCl_4$ in anhydrous CH_2Cl_2 at −78 °C for 3 h to give only the *erythro* product **10**.† Its stereochemistry was deduced from the Felkin rule[5] and indicated by H-6 and H-7 coupling constant (*J* 4.67 Hz, *erythro*) from its decoupling spectrum. Protection of the C-4 carbonyl group in compound **10** is troublesome. Attempts to protect the C-4 carbonyl group by several methods was unsuccessful. Finally, ketone **10** was converted into diol **11a**, **11b** by LAH reduction in *ca.* 1 : 1 ratio and 90% total yield. Diol **11a/11b** could be separated easily by flash chromatography. Because the hydroxy group at C-4 is oxidized into the carbonyl group finally (see compound **16** in Scheme 2), both isomers (**11a/11b**) could be used for synthesis of *A*-ring, but only the synthetic route starting from **11a** is shown in Scheme 2. Their relative stereochemistry was determined by 2D-NOESY of their isopropylidene derivatives.

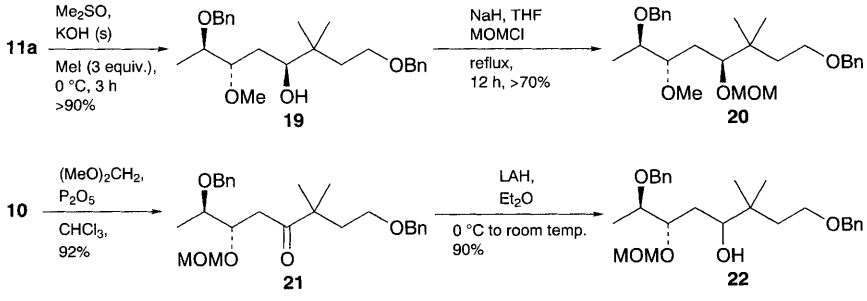
As shown in Scheme 2, when diol **11a** was treated with NaH, MeI (2.5 equiv.) in DMF at room temp. for 3 h, compound **12** was obtained in 90% yield. However, when diol **11a** (or **11b**)



Scheme 1 *Reagents and conditions*: i, HCl, >90%; ii, $CH_2{=}CH_2$, $AlCl_3$, −15 °C, 91%; iii, NaOH, Me_2SO, $(CH_2OH)_2$, 180 °C, 76%; iv $NaHCO_3$ 5%, KI, I_2, H_2O, room temp., overnight, crude 100%; v, K_2CO_3, MeOH, room temp. overnight, crude 100%; vi, LAH, Et_2O, room temp., 92%; vii, Me_2SO, NaH, BnCl, room temp. 80%; viii, Swern oxidation, 90%; ix, LDA, THF, −78 °C; TMCS, 100%; x, $TiCl_4$, CH_2Cl_2, −78 °C, 97%; xi, LAH, Et_2O, room temp. 1 h, 90%



Scheme 2 *Reagents and conditions*: i, DMF, NaH, MeI (2.5 eq), room temp. 92%; ii, Pd/C 5%, EtOH, 92%; iii, Swern oxidation, crude 100%; iv, piperidine, HOAc, benzene, reflux, 1 h, 65%



Scheme 3 (MOM = methoxymethyl)

was treated with KOH(s), MeI (3 equiv.) in Me_2SO at 0 °C for 4 h **19** was obtained exclusively in 91% yield (Scheme 3).‡ Compound **12** was then converted to its diol **13** by hydrogenation over Pd/C(5%) in anhydrous ethanol in 92% yield. Swern oxidation of diol **13** afforded compound **14**, and the crude product **14** was directly transformed to compound **15**§ with high regioselectivity with piperidine, HOAc in benzene under refluxing[6] in overall 65% yield. **15** can be used for the construction of the *B*-ring.

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Footnotes

† Compound **10**: IR (film): 3600–3100, 2900, 1700, 1450, 1360, 1080, 740, 690 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz): 1.12 (6 H, s), 1.13 (3 H, d, J 6.3 Hz), 1.88 (2 H, m), 2.46 (1 H, br s), 2.67 (2 H, m), 3.46 (3 H, m), 4.0 (1 H, m), 4.40 (2 H, s), 4.42 (1 H, d, 11.9 Hz), 4.60 (1 H, d, 11.9 Hz), 7.28 (10 H, m); MS (*m/z*): 385 ($M^+ + 1$), 367 ($M^+ + 1 - H_2O$); HRMS: 383.2188 (calc. 383.2222).

‡ Compounds **20** and **22** could be obtained in excellent yields as shown in Scheme 3.

Compound **20**: IR (film): 2900, 1450, 1360, 1260, 1100, 1060, 730, 690 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz): 0.90 (6 H, br s), 1.18 (3 H, d, 6.4 Hz), 1.54 (2 H, m), 1.82 (2 H, m), 3.36 (3 H, s), 3.40 (3 H, s), 3.45 (1 H, m), 3.56 (3 H, m), 3.70 (1 H, m) 4.50 (3 H, m), 4.65 (2 H, m), 4.76 (1 H, dd), 7.32 (10 H, m); MS (*m/z*): (M = 444), 430 ($M^+ + 1 - CH_3$).

§ Compound **15**: IR (film). 2850, 1700, 1680, 1450, 1350, 1180, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.20 (3 H, s), 1.22 (3 H, s), 1.30 (3 H, s), 2.18 (2 H, m), 2.71 (1 H, dd, 12.0, *J* 3.7 Hz), 2.85 (1 H, dd, 11.8, *J* 4.4 Hz), 3.38 (3 H, s), 3.46 (3 H, s), 9.98 (1 H, d, 4.9 Hz); MS (*m/z*): 211 ($M^+ - 1$), 197 ($M^+ - CH_3$); HRMS ($M^+ - CH_3$): 197.1177 (calc. 197.1170).

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