A New Method for Synthesis of 7-Deoxytaxane Analogues by Hydrogenation of Δ⁶,⁷-Taxane Derivatives

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A new method for the synthesis of 7-deoxytaxane analogues has been established through hydrogenation of Δ⁶,⁷-taxane derivatives. Among several catalysts examined, Pd–C was found to be a most effective catalyst for the preparation of target compound.

Key words 7-deoxytaxane analogue; hydrogenation; new efficient method

Paclitaxel (1, Taxol®) and docetaxel (2, Taxotere®) are currently considered to be some of the most important drugs used in cancer chemotherapy. Since their discovery, structure–activity relationships of taxane analogues have been extensively studied, and these studies have established that the C-13 side chain, the ester groups at C-2 and C-4, and the rigid core are essential for biological activity. In contrast, it was shown that the C-7 hydroxyl group was not essential for antitumor activity and that modifications of this moiety could lead to improvements in the cytotoxicity against drug-resistant cancer cell lines. On the basis of these findings, we focused on the 7-deoxytaxane analogues and thus have established a new method for the synthesis of these compounds.

Chemistry

Some groups have already reported the synthesis of 7-deoxytaxane analogues by employing the Barton deoxygenation procedure or the electrochemical reduction of 7α-iodo docetaxel, however, those yields were relatively low. In our previous paper, we achieved the synthesis of 7-deoxytaxane analogue in satisfactory yield, but still using the organotin reagent. To avoid using the toxic organotin reagent, we planned to prepare the 7-deoxytaxane analogues by hydrogenation of Δ⁶,⁷-taxanes. Application of a modified Johnson’s protocol (Tf₂O/DMAP/DMF) for the attempted triflation of 10-deacetylbaccatin III (3) was found to provide 10-O-formyl-10-deacetylbaccatin III (4) unexpectedly. Treatment of 4 with triflic anhydride in a mixture of pyridine and CH₂Cl₂ afforded 10-O-formyl-7-O-triflate 5. After removal of the formyl group at the C-10 position with Me₂NH in THF, the resulting compound was treated with DBU to generate the key intermediate 6,7-dehydro-10-deacetyl-baccatin III 6 (Chart 1).

With this olefin 6, hydrogenation using various catalysts were carried out (Table 1). With PtO₂, both the phenyl ring at C-2 and 6,7-double bond were smoothly reduced to afford 8 in high yield (entry 1). As with PtO₂, the hydrogenation of 6 over Pt–C (100 wt%) generated 8 in good yield (entry 3). By using Rh–Al₂O₃ (50 wt%), the target compound 7 was obtained along with unreacted 6 (entry 4). When the amount of the catalyst was increased, however, hydrogenation of aromatic nuclei occurred to provide a mixture of 7 and 8 (entry 5). Therefore, it might be possible to obtain the target compound 7 by controlling the amount of Rh–Al₂O₃ and the reaction time. In contrast to the above catalysts, Pd–C was found effective to produce the target compound 7 selectively (entry 6). Moreover, the hydrogenation of 6 with this catalyst proceeded smoothly without reducing the aromatic nuclei and/or decomposing of starting material, irrespective of an increase in the amount of catalyst and/or decomposition of starting material, irrespective of an increase in the amount of catalyst and elongation of the reaction time (entries 7, 8, 9) and was successfully applied to the direct scale up (entry 10). By the use of Pd(OH)₂, the target compound 7 was obtained as a major product, together with an unknown byproduct (entry 11).

We recently reported the synthesis of novel 9β-dihydro-9,10-O-acetal taxane analogues. Potier et al. had already prepared 9α-dihydro-9,10-O-isopropylidene-7-deoxydocetaxel from natural taxine B and isotaxine B, and its cytotoxicity was reported to be the same as that of docetaxel. On the other hand, our novel analogues, 9β-isomer, showed stronger activity against several tumor cell lines than did docetaxel. Therefore, we applied this newly developed method to the synthesis of their 7-deoxy analogues. 9,10-O-
Acetonide (9)(10) was treated with triflic anhydride in CH₂Cl₂ in the presence of DMAP, elimination of 7-O-triflate occurred to afford the 6,7-olefin (10). Attempts to reduce the 6,7-double bond of (10) by using Pd–C or Rh–Al₂O₃, however, resulted in the decomposition of the starting material (Chart 2). Highly strained architecture of (10) in which the cyclic acetate at C-9/C-10 causes angle distortion may be responsible for this unfavorable reaction. Though an efficient method to obtain the target compound (11) has not been developed, the hydrogenation of other oxo-taxane analogues is presently under investigation.

In conclusion, we have developed a new method for the synthesis of 7-deoxytaxane analogues. Although the applicability should be limited, we believe that this synthetic method should provide efficient and practical routes to obtain 7-deoxytaxane analogues.

Experimental

All chemicals and solvents used in the synthesis were reagent-grade products and were used without additional purification. The following abbreviations are used for the solvent and reagent names: ethyl acetate (AcOEt), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), triflic anhydride (Tf₂O). Melting points were obtained on a Yanaco micro melting point apparatus and are uncorrected. NMR spectra were obtained on a JEOL EX-400 spectrometer, with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm, δ units). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained on a Hitachi 270-30 spectrometer with KBr disks. Elementary analysis was carried out with a Perkin-Elmer Model 240C elemental analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter. Mass spectra were recorded on a JEOL JMS-HX-100, AX505W, JMS-D300 or JMS-700 spectrometer. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography.

Table 1. Hydrogenation of (6) Using Several Catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale (g)</th>
<th>Catalyst (Amount)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>Pd(OH)&lt;sub&gt;2&lt;/sub&gt; (50 wt%)</td>
<td>AcOEt</td>
<td>1.5</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>Pt–C (50 wt%)</td>
<td>EtOH</td>
<td>14</td>
<td>7 and 8 (5:6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>Pd–C (100 wt%)</td>
<td>EtOH</td>
<td>41</td>
<td>8</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>Rh–Al₂O₃ (50 wt%)</td>
<td>EtOH</td>
<td>1.5</td>
<td>6 and 7 (1:3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>Rh–Al₂O₃ (100 wt%)</td>
<td>EtOH</td>
<td>2</td>
<td>7</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>Pd–C (50 wt%)</td>
<td>EtOH</td>
<td>14</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>Pd–C (100 wt%)</td>
<td>EtOH</td>
<td>14</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>0.1</td>
<td>Pd–C (100 wt%)</td>
<td>EtOH</td>
<td>62</td>
<td>7</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>0.1</td>
<td>Pd–C (50 wt%)</td>
<td>AcOEt</td>
<td>45</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
<td>Pd–C (100 wt%)</td>
<td>AcOEt</td>
<td>24</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>Pd(OH)&lt;sub&gt;2&lt;/sub&gt; (50 wt%)</td>
<td>AcOEt</td>
<td>15</td>
<td>7</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield.  
<sup>b</sup> Ratios determined by <sup>1</sup>H-NMR analysis of the crude mixture.  
<sup>c</sup> 7 was obtained as a mixture of unknown by-product.
give the title compound (11.5 g) as a white solid, which contained a small amount of pyridine and was used for the next reaction without further purification. ¹H-NMR (CDCl₃) δ: 1.06 (3H, s), 1.20 (3H, s), 1.61 (1H, br s), 1.88 (3H, s), 2.05—2.40 (4H, m), 2.25 (3H, s), 2.31 (3H, s), 2.80—2.95 (1H, m), 4.01 (1H, d, J = 7.1 Hz), 4.16 (1H, d, J = 8.5 Hz), 4.35 (1H, d, J = 8.5 Hz), 4.80—4.90 (1H, br s), 4.95 (1H, d, J = 8.8 Hz), 5.53 (1H, dd, J = 7.8, 10.3 Hz), 5.69 (1H, d, J = 7.1 Hz), 6.73 (1H, s), 7.50 (2H, d, J = 7.8 Hz), 7.63 (1H, t, J = 7.8 Hz), 8.10 (2H, d, J = 7.8 Hz), 8.20 (1H, s); FAB-MS (m/z): 705 (M + H)⁺.

(15S,25R,35S,45R,75S,85R,10R,13S)-4-Acetoxy-2-benzoyloxy-5,20-epoxy-9-oxo-1,10,13-trihydroxytax-11-diene (6) To a solution of 5 (11.5 g) in THF (115 ml) was added Me₂NH (2.0 ml in THF, 12.3 ml, 24.5 mmol), and the mixture was stirred at room temperature for 1.5 h. After adding ethyl formate (2.0 ml, 24.5 mmol) to the reaction mixture, the mixture was stirred at the same temperature for further 15 min. The reaction mixture was concentrated under reduced pressure and the residue was suspended in a mixture of THF (5 ml) and 1,4-dioxane (50 ml). To this suspension was added DBU (5 ml), and the mixture was stirred at 100°C for 30 min. The reaction mixture was poured into a cold mixture of 1N HCl and AcOEt. The layers were separated and the aqueous layer was extracted with AcOEt. The mixture of THF (5 ml) and 1,4-dioxane (50 ml) was added to the reaction mixture, the resulting mixture was stirred at room temperature for 1.5 h, and the mixture was then filtered to give the title compound (90 mg, 89%) as a white powder, mp 137—140°C. ¹H-NMR (CDCl₃) δ: 1.10 (3H, s), 1.13 (3H, s), 1.66 (1H, br s), 1.92 (3H, s), 1.95—2.35 (3H, m), 2.00 (3H, d, J = 1.0 Hz), 2.31 (3H, s), 4.18 (1H, d, J = 6.5 Hz), 4.23 (1H, d, J = 1.5 Hz), 4.30 (1H, d, J = 8.3 Hz), 4.43 (1H, d, J = 8.3 Hz), 4.82—4.93 (1H, br s), 5.02 (1H, s), 5.10 (1H, d, J = 5.4 Hz), 5.76 (1H, d, J = 9.8 Hz), 5.81 (1H, d, J = 6.5 Hz), 6.04 (1H, dd, J = 5.4, 9.8 Hz), 7.49 (2H, t, J = 7.8 Hz), 7.62 (1H, t, J = 7.8 Hz), 8.14 (2H, d, J = 7.8 Hz); FAB-MS (m/z): 527 (M + H)⁺; Anal. Calcd for C₂₉H₃₇O₉: C, 65.03; H, 6.59. Found: C, 65.07; H, 6.64; IR: 3461, 2975, 1725, 1689, 1482 cm⁻¹.

References and Notes