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Synthesis of Taxoids 3. A Novel and Efficient Method for Preparation of Taxoids by Employing *cis*-Glycidic Acid.

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Abstract: A novel route for the synthesis of docetaxel (**2**) using esterification of (2*R*,3*R*)-glycidic acid with 7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetylbaccatin III is described. Subsequent stereo- and regio-selective conversion afforded **2** and related novel compounds.

Keywords: taxoids; stereocontrol; epoxides; esterification

Paclitaxel (Taxol, **1**)[1] and a semisynthetic analogue, docetaxel (Taxotere, **2**)[2], are regarded as most promising anticancer agents, especially for the treatment of ovarian, breast, and lung cancer.[3,1b] However, they also have some drawbacks such as undesired side effects and multidrug resistance. To overcome these problems, a number of paclitaxel analogues were semisynthetically prepared from 10-deacetylbaccatin III (**3**) which is extracted from renewable yew leaves. Extensive studies on structure activity relationships (SAR) of paclitaxel analogues revealed that C-13 side chains are extremely important for the outstanding antitumor activity.[3] However, the taxane skeleton has a very folded structure in which the hydroxyl group at C-13 is in a hindered position and, furthermore, it can form a hydrogen bond with the 4α acetyl group.[4a,1b] Therefore, such circumstances hamper introduction of C-13 side chains. Consequently, a few approaches were established for the efficient conversion of 10-deacetylbaccatin III to paclitaxel analogues.[4,5]

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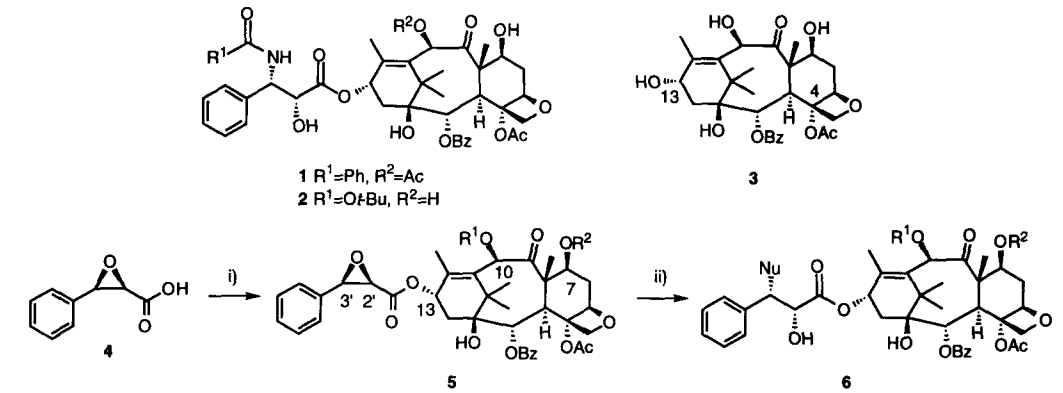
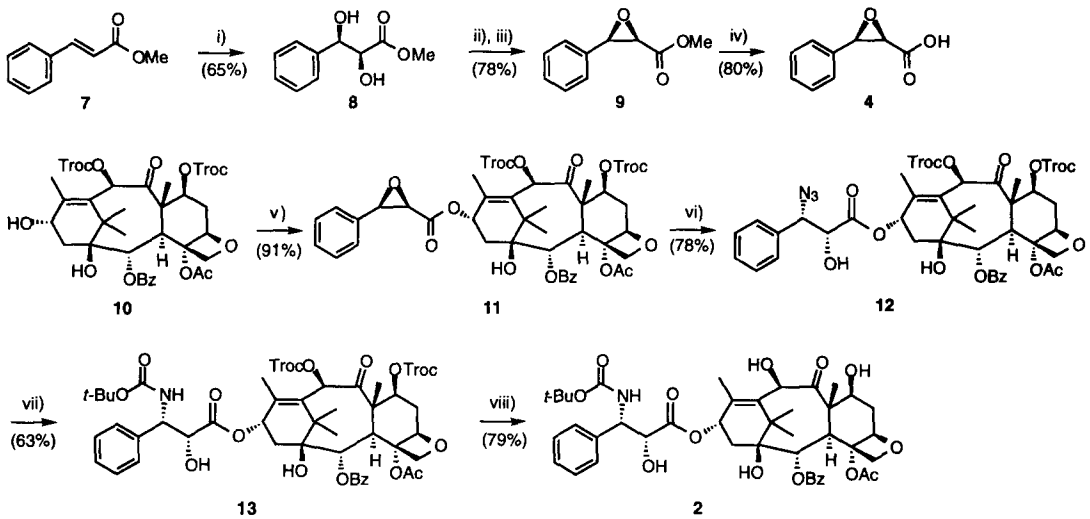


Reagents: (i) 7,10-protected baccatin III; (ii) nucleophile (Nu:)

Scheme 1.

In the course of our continuous studies on taxoids[6], we would like to disclose herein an improved synthesis of paclitaxel analogues as shown in Scheme 1. We have been interested in the reactivity of epoxides, since we had found that tin reagents worked as an excellent catalyst for *cis*-opening of the glycidic esters.[7] Moreover, recently, highly stereo- and regio-selective nucleophilic reactions on C-3 of glycidic esters have been reported.[8] In addition, the glycidic acid **4** would be expected to have relatively less steric hindrance such as to enable it to react with the hydroxyl group at C-13.

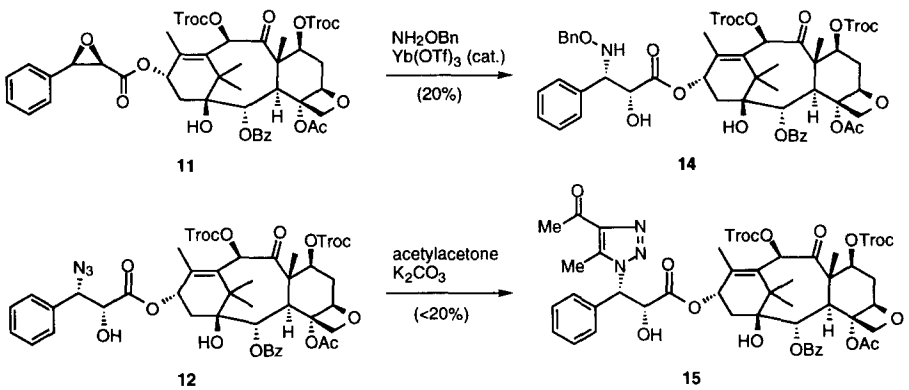


Reagents and conditions: (i) AD-mix-β, *t*-BuOH, H_2O, r.t., 18 h; (ii) TsCl, Et_3N, CH_2Cl_2, 0 °C, 38 h; (iii) K_2CO_3, H_2O, DMF, r.t., 24 h (iv) LiOH, MeOH, H_2O, r.t., 1 h; (v) **4** (1.5 eq.), DCC, DMAP, toluene, 80 °C, 1 h; (vi) NaN_3, HCO_2Me, MeOH, H_2O, 50 °C, 40 h; (vii) PPh_3, Boc_2O, K_2CO_3, CH_2Cl_2, H_2O, r.t., 19 h; (viii) Zn, AcOH, MeOH, 60 °C, 40 min.

Scheme 2.

(2*R*,3*R*)-Glycidic acid **4** was prepared in a highly stereoselective manner as shown in Scheme 2. Methyl cinnamate **7** was subjected to the Sharpless AD process (AD-ß) to give enantiopure (2*S*,3*R*)-diol **8** in 65%. The diol **8** was regioselectively converted to the α-tosylate, which was treated with K_2CO_3 in aqueous DMF to afford **9**[9] in moderate yield, which on hydrolysis using LiOH, gave **4**.

We have described an efficient synthesis of docetaxel by employing glycidic acid **4** in Scheme 2. The critical coupling reaction of 7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetyl baccatin III **10**[5a] with 1.5 equivalents of **4** and DCC (1.5 eq) in the presence of DMAP (1 eq) in toluene at 80 °C afforded the 13-*O*-acylated compound **11**[10] in 91% yield. Here, we established an efficient esterification. Even at room temperature, the reaction proceeded smoothly and gave **11** in moderate yield (71%). Then, the epoxide **11** reacted with NaN_3 in aqueous MeOH in the presence of methyl formate at 50 °C to give azide derivative **12**[10,11] in good yield. Unfortunately, the catalytic hydrogenation of **12** using Pd-C in the presence of di-*tert*-butyl dicarbonate (Boc_2O) gave **13** in low yield together with undesired compounds. Among the various reactions, the iminophosphorane method was found to be the best. Compound **12** was treated with PPh_3 in the presence of Boc_2O, K_2CO_3 and a small amount of water in CH_2Cl_2 to give **13** in 63%. The final reductive deprotection was performed with zinc powder in acetic acid and MeOH to yield **2** in 79%.



Scheme 3.

Furthermore, novel compounds the synthesis of which could not be considered by previous methods[5], can easily be prepared from the novel synthetic intermediates (**11**,**12**); 3'-hydroxylamine derivatives (**14**) were synthesized from **11**[12] and 3'-triazole derivatives (**15**) were synthesized from **12**[13], respectively, details of which and related compounds will be disclosed in the near future.

In summary, we have accomplished a novel and efficient synthesis of taxoids, which can eliminate the annoying protection-deprotection steps on the 2',3' amino alcohol moiety. The synthetic intermediates (**11**,**12**) will be converted to novel C-13 side chain derivatives, which are expected to expand SAR of paclitaxel analogues.

References and Notes

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10) All new compounds gave satisfactory analytical data. Spectroscopic data of selected new compounds. **11**: IR (nujol) ν_{max} 3500, 1760, 1730, 1460, 1380, 1250, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-8.04 (m, 2H, Ar-H), 7.64 (m, 1H, Ar-H), 7.30-7.53 (m, 7H, Ar-H), 6.19 (s, 1H, 10-H), 6.03 (m, 1H, 13-H), 5.63 (d, J = 7.0 Hz, 1H, 2-H), 5.55 (dd, J = 7.0, 10.7 Hz, 1H, 7-H), 4.97 (m, 1H, 5-H), 4.92 (d, J = 11.8 Hz, 1H, Troc), 4.76 (s, 2H, Troc), 4.60 (d, J = 11.8 Hz, 1H, Troc), 4.33 (d, J = 4.5 Hz, 1H, 3'-H), 4.30 (d, J = 8.7 Hz, 1H, 20-H), 4.14 (d, J = 8.7 Hz, 1H, 20-H), 3.97 (d, J = 4.5 Hz, 1H, 2'-H), 3.87 (d, J = 7.0 Hz, 1H, 3-H), 2.63 (m, 1H, 6-H), 2.39 (s, 3H, Ac), 1.95-2.11 (m, 3H, 14-2H and 6-H), 1.83 (s, 6H, 12-Me and 8-Me), 1.58 (s, 1H, D_2O exchangeable, 1-OH), 1.14 (s, 6H, 15-Me); Mass (FAB) *m/z* 1039 (MH^+, 1), 1041 (MH^++2, 2), 1043 (MH^++4, 2). **12**: IR (nujol) ν_{max} 3480, 2110, 1760, 1730, 1460, 1380, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-8.09 (m, 2H, Ar-H), 7.64 (m, 1H, Ar-H), 7.34-7.54 (m, 7H, Ar-H), 6.27 (s, 1H, 10-H), 6.22 (m, 1H, 13-H), 5.68 (d, J = 6.9 Hz, 1H, 2-H), 5.56 (dd, J = 7.2, 10.6 Hz, 1H, 7-H), 5.01 (d, J = 3.7 Hz, 1H, 3'-H), 4.95 (m, 1H, 5-H), 4.92 (d, J = 11.8 Hz, 1H, Troc), 4.78 (s, 2H, Troc), 4.60 (d, J = 11.8 Hz, 1H, Troc), 4.44 (dd, J = 3.7, 8.4 Hz, 1H, 2'-H), 4.32 (d, J = 8.5 Hz, 1H, 20-H), 4.16 (d, J = 8.5 Hz, 1H, 20-H), 3.90 (d, J = 6.9 Hz, 1H, 3-H), 3.12 (d, J = 8.4 Hz, 1H, D_2O exchangeable, 2'-OH), 2.63 (m, 1H, 6-H), 2.30 (s, 3H, Ac), 2.01-2.19 (m, 3H, 14-2H and 6-H), 2.09 (s, 3H, 12-Me), 1.86 (s, 3H, 8-Me), 1.70 (s, 1H, D_2O exchangeable, 1-OH), 1.27 (s, 3H, 15-Me), 1.20 (s, 3H, 15-Me); Mass (FAB) *m/z* 1082 (MH^+, 1), 1084 (MH^++2, 2), 1086 (MH^++4, 2).
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