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Synthesis of Taxoids 4. Novel and Versatile Methods for Preparation of New Taxoids by Employing *cis*- or *trans*-Phenyl Glycidic Acid.

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Abstract: A novel route to the synthesis of docetaxel using esterification of (2*R*,3*R*)- or (2*R*,3*S*)-glycidic acid with 7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetyl-baccatin III is described. Related novel taxoids which have new side chains were synthesized from these synthetic intermediates.

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.[1b,3] 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 the C-13 side chains are extremely important for the outstanding antitumor activity.[3] However, 10-deacetylbaccatin III 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.[1b,4] Therefore, such circumstances hamper introduction of C-13 side chains into the taxane skeleton. Consequently, only limited approaches have been established for the efficient conversion of 10-deacetylbaccatin III to paclitaxel analogues: i) coupling of a suitable ß-lactam[5] or ii) direct acylation by protected oxazolidinecarboxylic acid.[6] However, these processes afforded only 3'-nitrogen substituted compounds[3a] that proved to prevent more extensive studies on SAR of paclitaxel analogues.

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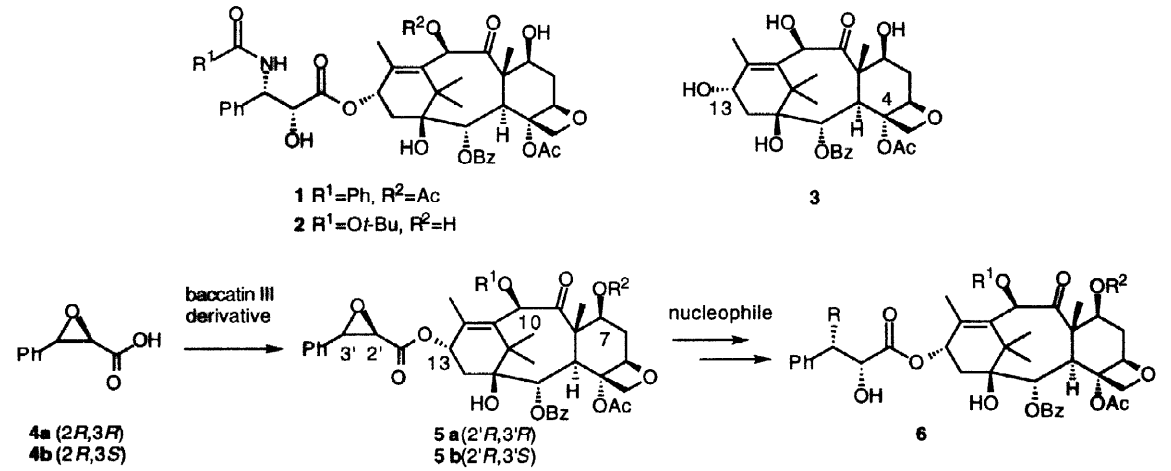
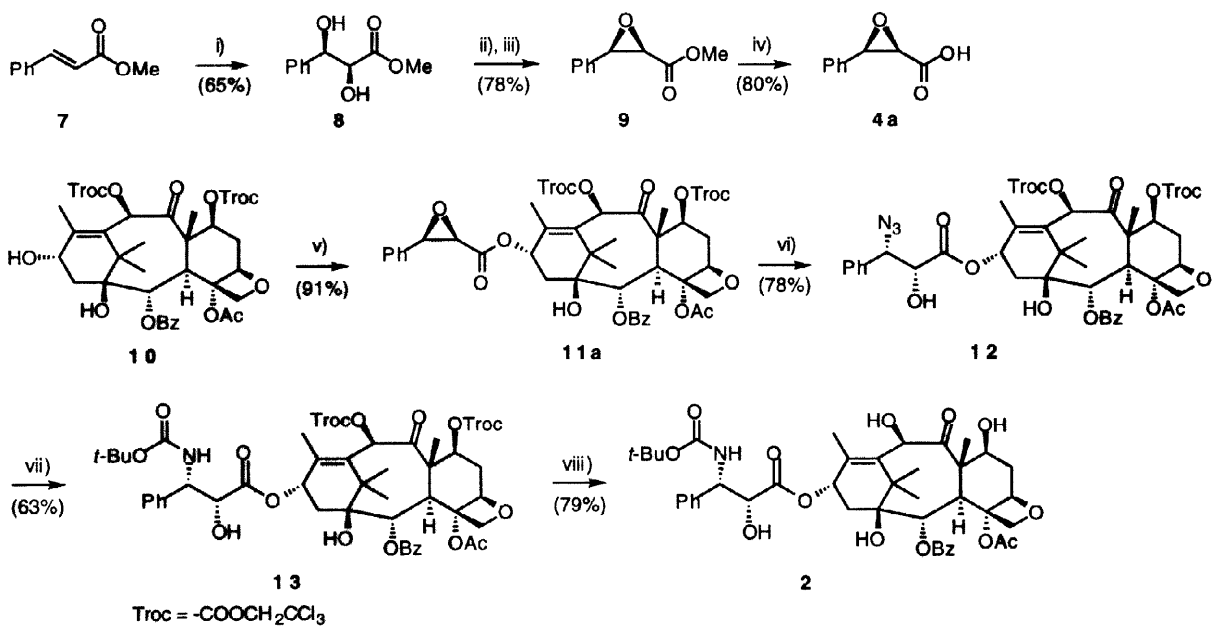


Scheme 1.

In the course of our continuous studies on taxoids[7], we would like to report an improved synthesis of known taxoids such as docetaxel and versatile synthetic methods for novel taxoids, the syntheses of which could not be considered by previous methods.[5,6] We have been eager to utilize the epoxy carbonyl group as a reactive intermediate in organic synthesis, since we had found that tin reagents worked as an excellent catalyst for *cis*-opening of the epoxide ring in glycidic esters.[8] We envisaged that the glycidic acids **4** would have relatively less steric hindrance such as to enable it to react with the hydroxyl group at C-13. Therefore, we investigated the synthesis of taxoids using esterification of the glycidic acids **4** with a baccatin III derivative as shown in Scheme 1.

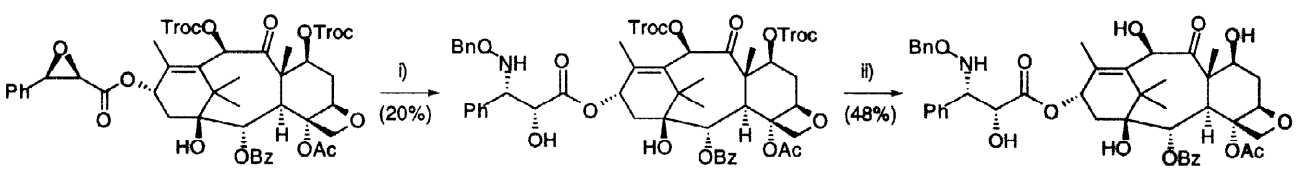


Reagents and conditions: (i) AD-mix-ß, *t*-BuOH, H_2O, r.t., 18 h; (ii) TsCl, Et_3N, CH_2Cl_2, 0 °C, 38 h; (iii) K_2CO_3, H_2O, DMF, r.t., 24 h (iv) LiOH, MeOH, H_2O, r.t., 1 h; (v) **4a** (1.5 eq.), DCC, DMAP, toluene, 80 °C, 1 h; (vi) NaN_3, HCO_2Me, MeOH, H_2O, 50 °C, 40 h; (vii) PPh_3, Boc_2O, K_2CO_3,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

Scheme 2.

First of all, we describe an efficient conversion of a 10-deacetylbaccatin III derivative into docetaxel **2** which could be converted to paclitaxel[9], by employing (2*R*,3*R*)-phenyl glycidic acid **4a** as shown in Scheme 2.[7c] Methyl cinnamate **7** was subjected to the Sharpless AD process (AD-ß) to give enantiopure (2*S*,3*R*)-diol **8** in 65% yield. Diol **8** was regioselectively converted to the α- tosylate, which was treated with K_2CO_3 in aqueous DMF to afford **9**[10] in moderate yield which, on hydrolysis using LiOH, gave **4a**.

The critical coupling reaction of 7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetylbaccatin III **10**[6] with 1.5 equivalents of **4a** and dicyclohexylcarbodiimide (DCC) (1.5 eq.) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) (1 eq.) in toluene at 80 °C afforded the 13-*O*-acylated compound **11a** in 91% yield. Here, we found that the glycidic acid **4a** is an efficient substrate for the esterification. Even at room temperature, the reaction proceeded smoothly and gave **11a** in moderate yield (71%). Then, the epoxide **11a** reacted with NaN_3 in aqueous MeOH in the presence of methyl formate at 50 °C to give azide derivative **12** in 78% yield. The azide **12** was also prepared as follows: the epoxide **11a** was reacted with tri-*n*-butyltinazide in the precence of ZnI_2 at 50 °C to give **12** in 67% 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, $KHCO_3$ and a small amount of water in CH_2Cl_2 to give **13** in 63%. The final reductive deprotection[6,9] was performed with zinc powder in acetic acid and MeOH to yield **2** in 79%.



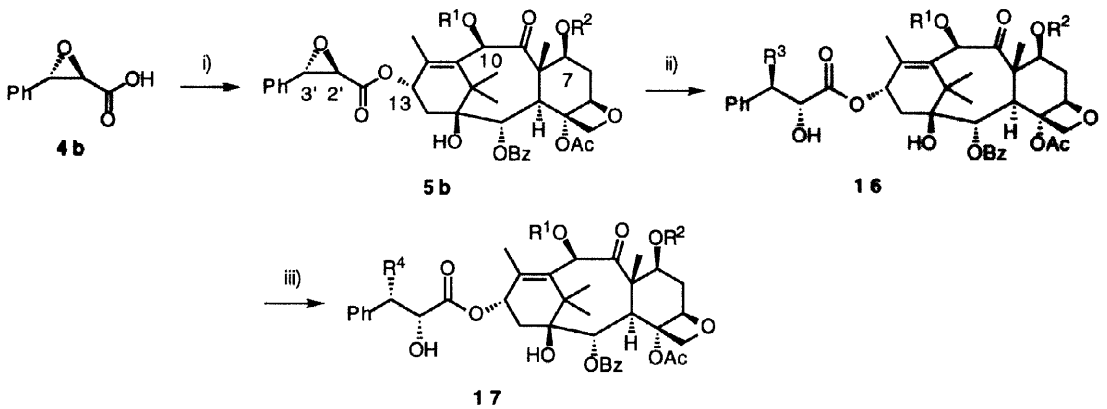
11a **14** **15**

Reagents and conditions: (i) NH_2OBn, $Yb(OTf)_3$ (cat.), CH_2Cl_2, 60 °C, 6d; (ii) Zn, AcOH, MeOH, 60 °C, 30 min.

Scheme3.

Furthermore, the novel synthetic intermediate **11a** was reacted with *O*-benzylhydroxylamine in the presence of a catalytic amount of $Yb(OTf)_3$[11] to give 3'-hydroxylamine derivative **14**. The deprotection step afforded a novel taxoid **15**, the synthesis of which could not be attained by previous methods.[5,6] However, the epoxide **11a** did not react with ordinary nucleophiles such as thiols.

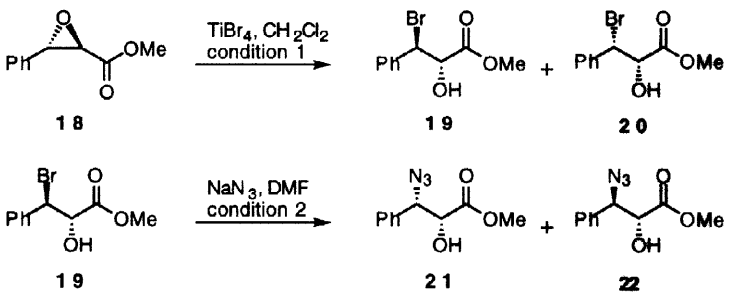
Therefore, next we examined the esterification of **10** by employing *trans*-glycidate, whose reactivity was higher than that of *cis*-glycidate.[8] We describe an improved synthesis of a known taxoid such as docetaxel and novel taxoids using (2*R*,3*S*)-*trans*-glycidic acid **4b** which was more readily obtained than *cis*-glycidic acid **4a**, by Darzen's reaction of benzaldehyde, followed by enzyme-mediated enantioselective transesterification[12a] and hydrolysis. The



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

Scheme 4.

trans-glycidate **5b** and docetaxel **2** have the same 2'*R*,3'*S* stereochemistry, so it is neccessary to accomplish a totally stereo-retained conversion of C-3' to convert **2**. We designed successive nucleophilic ring-opening and substitution, as shown in Scheme 4. When R^3 of the intermediate **16** is a good leaving group, it might be possible to synthesize not only docetaxel but also novel taxoids effectively.



Bromination of **18**

condition 1	additive	yield*(%)	**19** / **20****
-78 °C, 15 min	—	99	5 / 8
-78 °C, 3 h then -10 °C, 1 h	HMPA***	82	>20 / 1

Reaction of **19** with NaN_3

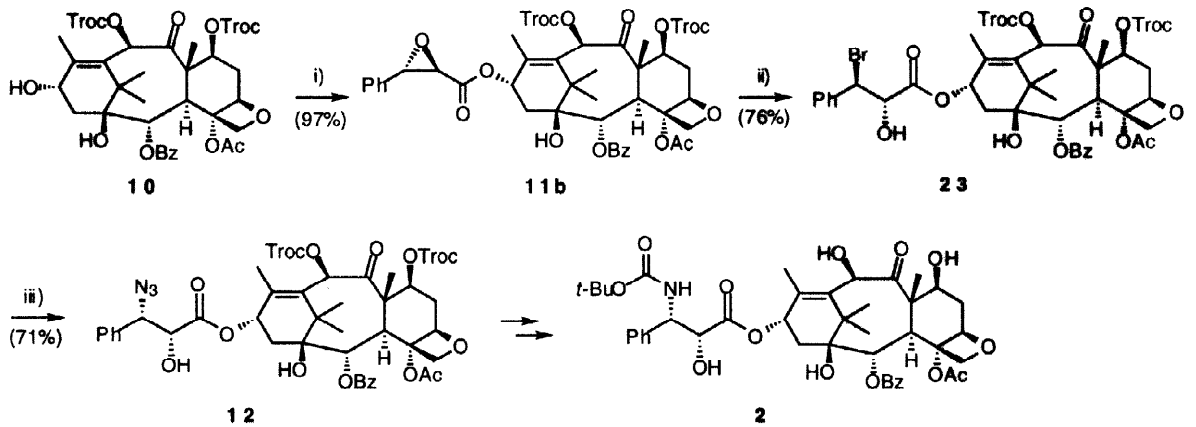
condition 2	additive	yield*(%)	**21** / **22****
70 °C, 20 h	—	67	5 / 2
0 °C, 31 h	15-crown-5****	88	>20 / 1

* Isolated yield. ** Ratio was determined by 300Mz ^{1}H-NMR spectrum.
*** HMPA-CH_2Cl_2 (1:10). **** Catalytic amount of 15-crown-5 was added.

Table 1.

First, we investigated the conversion of glycidate **18**[12] to azide **21** as a model study shown in Table 1. Stereoselctive bromination of **18** was acheived by the use of $TiBr_4$ in the presence of hexamethylphosphoramide (HMPA). Without HMPA, the reaction proceeded in a poorly stereocontrolled manner. Unfortunately, in our experimentation the reaction of the bromohydrine **19** and NaN_3 in DMF afforded an appreciable amount of stereoisomer **22** together with the desired product **21**. The formation of **22** might involve the step through the epoxide **18** as a reactive intermediate. Therefore, in order to increase the nucleophilicity of the azide anion, a catalytic amount of a crown ether was added to the

reaction mixture. Under these conditions the reaction proceeded smoothly and gave **21** predominantly. The assignment of the stereochemistry of the four compounds (**19**, **20**, **21**, **22**) was determined by the proton coupling constant at C-2 and C-3 on ^{1}H-NMR spectra.[13]



10 **11b** **23**

12 **2**

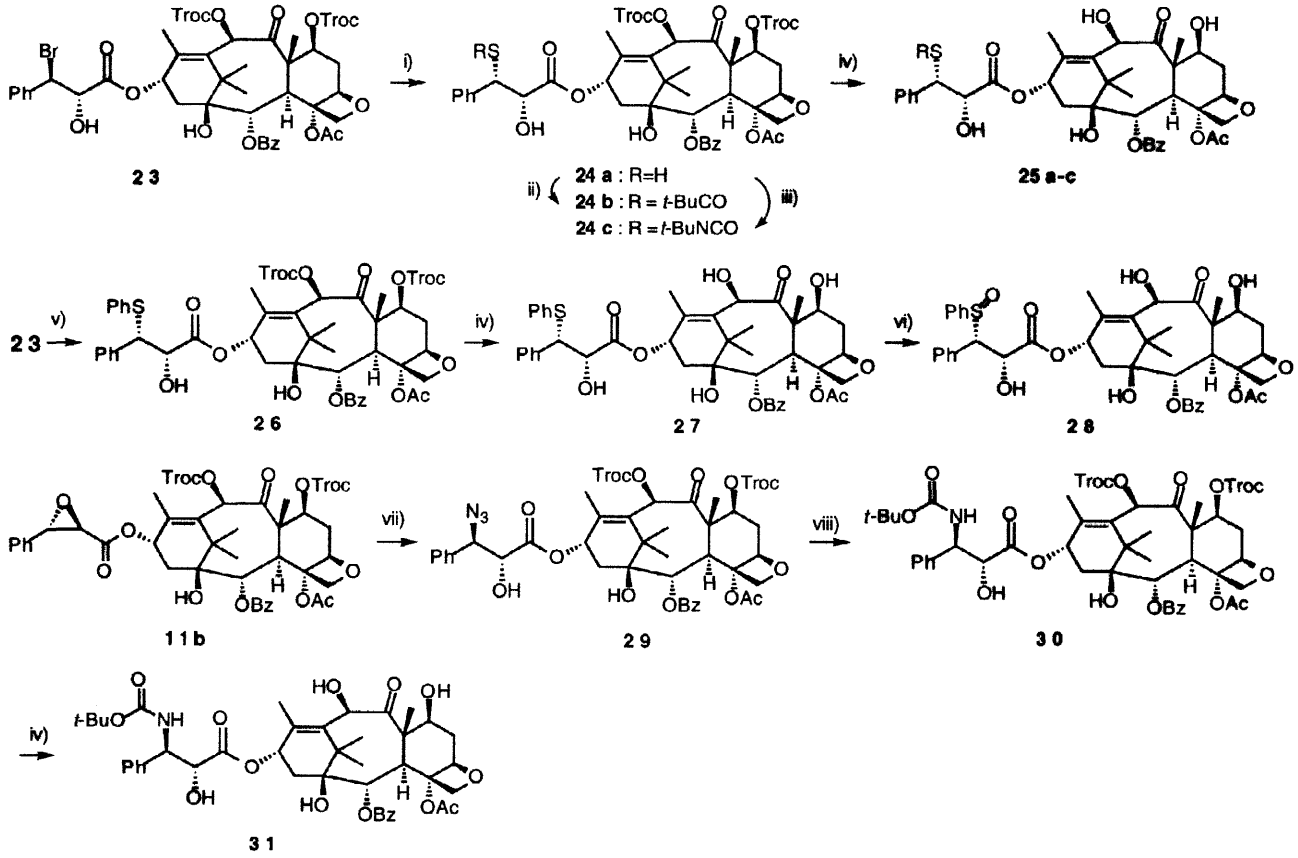
Reagents and conditions: (i) **4b** (2 eq.), DCC, DMAP, toluene, r.t., 10 min; (ii) $TiBr_4$, HMPA, CH_2Cl_2, 0 °C, 18 h; (iii) NaN_3, 15-crown-5, DMF, 0 °C, 24 h.

Scheme 5.

Next, we describe an efficient synthesis of docetaxel by employing *trans*-glycidic acid **4b** (Scheme 5). The coupling reaction of a baccatin III derivative (**10**) and 2 equivalents of **4b** in toluene with DCC (2.1 eq.) and DMAP (0.5 eq.) at room temperature proceeded smoothly and gave 13-*O*-acylated compound (**11b**) in almost quantitative yield. Surprisingly, **10** was completely consumed within 10 minutes at room temperature. Then, the epoxide **11b** was reacted with $TiBr_4$ in CH_2Cl_2 in the presence of HMPA at 0 °C to give bromohydrin **23** in a highly stereo- and regio-selective manner. Stereoselective azidation of the bromohydrin **23** was acheived by the use of NaN_3 in DMF in the presence of a catalytic amount of 15-crown-5 at 0 °C to give **12** in 71% together with the recyclable epoxide **11b** in 10%. The azide **12** is easily converted to docetaxel; hence we established a novel synthesis of docetaxel in only 9 steps.

Furthermore, novel compounds, the synthesis of which could not be considered by previous methods,[5,6] can easily be prepared from novel and reactive synthetic intermediates (**11b**, **23**). Nucleophilic substitution of the bromohydrin **23** with thiolate anions afforded thiol **24a** and phenyl thioether **26**, which were readily converted to various 3'-thio-derivatives (**25a~c**, **27**, **28**). The epoxide **11b** reacted with NaN_3 to give azide derivative **29**, which was converted to 3'-epi-docetaxel (**31**) which can not be obtained by conventional methods.[14]

In conclusion, we have accomplished a novel and efficient synthesis of docetaxel by employing *cis*- or *trans*-glycidic acids, which eliminates the annoying protection-deprotection steps on the 2',3'-aminoalcohol moiety. The synthetic intermediates (**11a**, **11b**, **23**) are converted to novel C-13 side chain derivatives, which are expected to expand the SAR of paclitaxel analogues.



Reagents and conditions: (i) NaSH, 15-crown-5 (0.1 eq.), DMF, -45 °C, 2 h, 79%; (ii) *t*-BuCOCl, Et_3N, CH_2Cl_2, -78 °C, 30 min, 100%; (iii) *t*-BuNCO, Et_3N, CH_2Cl_2, 0 °C, 30 min, 94%; (iv) Zn, AcOH, MeOH, 50–60 °C, 20–60 min, 75–94%; (v) PhSH, NaH, DMF, -10 °C, 30 min, 92%; (vi) 3-chloroperoxybenzoic acid (*m*CPBA), $CHCl_3$, 0 °C–r.t., 2 h, 53%; (vii) NaN_3, HCO_2Me, MeOH, H_2O, 45 °C, 3.5 h, 92%; (viii) PPh_3, Boc_2O, $KHCO_3$, CH_2Cl_2, H_2O, r.t., 22 h, 86%.

Scheme 6.

Experimental section

General. Melting points were determined with a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a Horiba SEPA-200 high sensitive polarimeter. IR spectra were obtained with an Analect FT-IR spectrophotometer. ^{1}H-NMR were measured with a Varian Gemini-300 spectrometer. The fast atom bombardment (FAB) mass spectra (MS) were obtained using 5 keV Xe atoms to ionize samples from dithiothreitol / dithioerythritol / 3-nitrobenzyl alcohol, or dithiothreitol / dithioerythritol / 3-nitrobenzyl alcohol / NaCl as the matrix with a Hitachi RMu-6 or a JEOL JMS-HX 100 mass spectrometer. High-resolution electrospray ionization (HRESI) mass spectra were obtained using 0.1% AcOH / MeOH (3:7) as the mobile phase at a flow rate of 0.1 ml/min with a JEOL JMS-700T MStation introduced by a Hewlett packard HPLC model 1100 system. Chromatography was performed using pre-coated Merck silica gel 60 GF_{254} plates, and Katayama silica gel 60 K230 (230-430 mesh) powder. In general, reactions were carried out in dry solvents under argon atmosphere.

(2*R*,3*R*)-3-Phenyloxiranecarboxylic acid (4a). To an ice-cooled solution of methyl (2*R*,3*R*)-3-phenyloxiranecarboxylate (**9**)[10] (1.78 g, 10.0 mmol) in MeOH (50 ml) was added LiOH•H_2O (504 mg, 12 mmol) in H_2O (25 ml) dropwise and the reaction mixture was stirred at room temperature for 1 h. MeOH was removed and to the residue was added 5% aqueous citric acid at 0 °C to adjust pH 3-4. The product was extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. To the residue was added hexane and stirred. The precipitate was collected by filtration and dried to give a white solid **4a** (1.32 g, 8.0 mmol, 80%): mp 82-83 °C; ^{1}H-NMR ($CDCl_3$) δ 8.17

(brs, 1H, D_2O exchangeable, COOH), 7.10-7.42 (m, 5H, Ar-H), 4.31 (d, J = 4.7 Hz, 1H, 3-H), 3.83 (d, J = 4.7 Hz, 1H, 2-H); MS (FAB) *m/z* 165 (MH^+); IR (nujol) ν_{max} 3140, 1750, 1720, 1460, 1200 cm^{-1}.

Coupling reaction of 7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetyl baccatin III (10) with 4a. To a solution of **10**[9] (1.07 g, 1.19 mmol) and **4a** (295 mg, 1.80 mmol) in toluene (50 ml) was added DCC (393 mg, 1.90 mmol) and DMAP (73 mg, 0.60 mmol). The mixture was stirred at 80 ℃ for 1 h and cooled to room temperature. The precipitate was filtered off. The resulting solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate / hexane 1:3-2:3) to give a colorless foam **11a** (1.13 g, 1.08 mmol, 91%): $[\alpha]^{25}_D$ +5° (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$) 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); MS (FAB) *m/z* 1039 (MH^+, 1), 1041 (MH^++2, 2), 1043 (MH^++4, 2); HRMS (ESI) *m/z* 1097.0858 ([M-H+AcOH]$^-$, $C_{42}H_{47}O_{18}Cl_6$ requires 1097.0894); IR (nujol) ν_{max} 3500, 1760, 1730, 1460, 1380, 1250, 1060 cm^{-1}.

Reaction of 11a with sodium azide. To a solution of **11a** (104 mg, 0.100 mmol) in MeOH-H_2O (8:1, 3 ml) was added HCO_2Me (0.3 ml) and NaN_3 (195 mg, 3.0 mmol) and the reaction mixture was stirred at 50 ℃ for 40 h. The mixture was poured into ice-water and extracted with ethyl acetate. The organic layers were washed with 5% aqueous citric acid and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was separated by preparative TLC (ethyl acetate / $CHCl_3$ 1:20) to give a colorless foam **12** (84 mg, 0.77 mmol, 78%): $[\alpha]^{25}_D$ -10° (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$) 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); MS (FAB) *m/z* 1082 (MH^+, 1), 1084 (MH^++2, 2), 1086 (MH^++4, 2); IR (nujol) ν_{max} 3480, 2110, 1760, 1730, 1460, 1380, 1250 cm^{-1}.

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)docetaxel (13). To a solution of **12** (109 mg, 0.10 mmol) and Boc_2O (45 mg, 0.21 mmol) in CH_2Cl_2 (4 ml) was added $KHCO_3$ (50 mg, 0.50 mmol), H_2O (2 drops) and PPh_3 (54 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 19 h. The mixture was diluted with $CHCl_3$ and the organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 1:3) to give a colorless amorphous solid **13** (74 mg, 0.06 mmol, 63%). The spectroscopic data was identified by published one.[9] : $[\alpha]^{25}_D$ -29° (*c* 0.50, EtOH); HRMS (ESI) *m/z* 1214.1750 ([M-H+AcOH]$^-$, $C_{51}H_{58}O_{20}NCl_6$ requires 1214.1683)

Typical procedure for the zinc reduction of 7,10-bis-*O*-2,2,2-trichloroethoxycarbonyl-compounds (13,14,24,26,30). To a solution of **24b** (160 mg, 0.14 mmol) in MeOH (3 ml) and AcOH (0.6 ml) was added Zn (271 mg, 4.1 mmol). The mixture was stirred at 60 ℃ for 20 min and cooled to room temperature. The insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, and the organic layer was washed with cold 1% aqueous HCl, cold aqueous $NaHCO_3$, and brine, and dried over (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 2:1) to give a colorless amorphous solid **25b** (105 mg, 0.13 mmol, 94%).

2 (79%): colorless crystal; R_f = 0.2 (ethyl acetate / hexane 4:1); the spectroscopic data was identified by published one.[9] ; $[\alpha]^{25}_D$ -38° (*c* 0.74, EtOH); lit.[10] $[\alpha]_D$ -36° (*c* 0.74, EtOH); HRMS (ESI) *m/z* 806.3391 ([M-H]$^-$, $C_{43}H_{52}O_{14}N$ requires 806.3388)

15 (48%): colorless amorphous solid; R_f = 0.1 (ethyl acetate / hexane 3:2); ^{1}H NMR ($CDCl_3$) δ 8.05-8.09 (m, 2H, Ar-H), 7.64 (m, 1H, Ar-H), 7.24-7.54 (m, 12H, Ar-H), 6.18 (brs, 1H, D_2O exchangeable, 3'-NH), 5.89 (m, 1H, 13-H), 5.63 (d, J = 7.0 Hz, 1H, 2-H), 5.15 (s, 1H, 10-H), 4.92 (m, 1H, 5-H), 4.68 (d, J = 11.1 Hz, 1H, 3'-$PhCH_2$), 4.64 (d, J = 11.1 Hz, 1H, 3'-$PhCH_2$), 4.60 (m, 1H, 3'-H), 4.43 (dd, J = 2.8, 6.9 Hz, 1H, 2'-H), 4.29 (d, J = 8.3 Hz, 1H, 20-H), 4.13-4.19 (m, 3H, 7-H and D_2O exchangeable, 10-OH and 20-H),

3.85 (d, J = 7.0 Hz, 1H, 3-H), 3.40 (d, J = 6.9 Hz, 1H, D_2O exchangeable, 2'-OH), 2.57 (m, 1H, 6-H), 2.26 (s, 3H, Ac), 1.83-2.12 (m, 3H, 14-2H and 6-H), 1.83 (d, J = 1.3 Hz, 3H, 12-Me), 1.74 (s, 3H, 8-Me), 1.59 (brs, 2H, D_2O exchangeable, 1-OH and 7-OH), 1.25 (s, 3H, 15-Me), 1.09 (s, 3H, 15-Me); MS (FAB) *m/z* 836 ($M+Na^+$); IR (nujol) ν_{max} 3500, 1730, 1460, 1375, 1240 cm^{-1}.

25a (75%): colorless amorphous solid; R_f = 0.2 (ethyl acetate / hexane 2:1); ^1H NMR ($CDCl_3$) δ 8.05-8.09 (m, 2H, Ar-H), 7.23-7.67 (m, 8H, Ar-H), 6.13 (m, 1H, 13-H), 5.66 (d, J = 7.0 Hz, 1H, 2-H), 5.20 (d, J = 1.7 Hz, 1H, 10-H), 4.94 (dd, J = 1.9, 9.5 Hz, 1H, 5-H), 4.59 (dd, J = 4.2, 7.6 Hz, 1H, 3'-H), 4.48 (dd, J = 4.2, 7.9 Hz, 1H, 2'-H), 4.31 (d, J = 8.4 Hz, 1H, 20-H), 4.24 (m, 1H, 7-H), 4.17 (d, J = 8.4 Hz, 1H, 20-H), 4.17 (d, J = 1.7 Hz, 1H, D_2O exchangeable, 10-OH), 3.90 (d, J = 7.0 Hz, 1H, 3-H), 3.35 (d, J = 7.6 Hz, 1H, D_2O exchangeable, 3'-SH), 2.59 (m, 1H, 6-H), 2.30 (d, J = 7.9 Hz, 1H, D_2O exchangeable, 2'-OH), 2.29 (s, 3H, Ac), 2.02-2.12 (m, 2H, 14-H), 1.96 (d, J = 1.3 Hz, 3H, 12-Me), 1.84 (m, 1H, 6-H), 1.75 (s, 3H, 8-Me), 1.64 (s, 1H, D_2O exchangeable, 1-OH), 1.42 (d, J = 7.8 Hz, 1H, D_2O exchangeable, 7-OH), 1.22 (s, 3H, 15-Me), 1.12 (s, 3H, 15-Me); MS (FAB) *m/z* 725 (MH^+); IR (nujol) ν_{max} 3440, 1700, 1460, 1375 cm^{-1}.

25b (94%): colorless amorphous solid; R_f = 0.3 (ethyl acetate / hexane 2:1); ^1H NMR ($CDCl_3$) δ 8.12-8.15 (m, 2H, Ar-H), 7.26-7.66 (m, 8H, Ar-H), 6.13 (m, 1H, 13-H), 5.67 (d, J = 7.2 Hz, 1H, 2-H), 5.19 (d, J = 1.8 Hz, 1H, 10-H), 5.13 (d, J = 3.2 Hz, 1H, 3'-H), 4.94 (dd, J = 1.9, 9.5 Hz, 1H, 5-H), 4.69 (dd, J = 3.2, 7.6 Hz, 1H, 2'-H), 4.32 (d, J = 8.1 Hz, 1H, 20-H), 4.24 (m, 1H, 7-H), 4.20 (d, J = 8.1 Hz, 1H, 20-H), 4.18 (d, J = 1.8 Hz, 1H, D_2O exchangeable, 10-OH), 3.91 (d, J = 7.0 Hz, 1H, 3-H), 3.40 (d, J = 7.6 Hz, 1H, D_2O exchangeable, 2'-OH), 2.58 (m, 1H, 6-H), 2.37 (s, 3H, Ac), 2.29 (dd, J = 8.8, 15.6 Hz, 1H, 14-H), 2.15 (dd, J = 9.5, 15.6 Hz, 1H, 14-H), 1.89 (d, J = 1.3 Hz, 3H, 12-Me), 1.84 (m, 1H, 6-H), 1.75 (s, 3H, 8-Me), 1.63 (s, 1H, D_2O exchangeable, 1-OH), 1.45 (d, J = 7.8 Hz, 1H, D_2O exchangeable, 7-OH), 1.23 (s, 3H, 15-Me), 1.16 (s, 9H, *t*-Bu), 1.13 (s, 3H, 15-Me); MS (FAB) *m/z* 809 (MH^+); IR (nujol) ν_{max} 3440, 1730, 1450, 1370, 1240 cm^{-1}.

25c (90%): colorless amorphous solid; R_f = 0.3 (ethyl acetate / hexane 2:1); ^1H NMR ($CDCl_3$) δ 8.12-8.15 (m, 2H, Ar-H), 7.26-7.66 (m, 8H, Ar-H), 6.18 (m, 1H, 13-H), 5.67 (d, J = 7.1 Hz, 1H, 2-H), 5.20 (d, J = 1.7 Hz, 1H, 10-H), 5.17 (brs, 1H, 3'-SCONH), 5.06 (d, J = 3.5 Hz, 1H, 3'-H), 4.95 (dd, J = 1.9, 9.3 Hz, 1H, 5-H), 4.69 (dd, J = 3.5, 7.8 Hz, 1H, 2'-H), 4.33 (d, J = 8.1 Hz, 1H, 20-H), 4.24 (m, 1H, 7-H), 4.18 (d, J = 8.1 Hz, 1H, 20-H), 4.18 (d, J = 1.7 Hz, 1H, D_2O exchangeable, 10-OH), 3.92 (d, J = 7.1 Hz, 1H, 3-H), 3.77 (d, J = 7.8 Hz, 1H, D_2O exchangeable, 2'-OH), 2.58 (m, 1H, 6-H), 2.37 (s, 3H, Ac), 2.29 (dd, J = 9.2, 15.6 Hz, 1H, 14-H), 2.15 (dd, J = 9.1, 15.6 Hz, 1H, 14-H), 1.90 (d, J = 1.3 Hz, 3H, 12-Me), 1.84 (m, 1H, 6-H), 1.74 (s, 3H, 8-Me), 1.61 (s, 1H, D_2O exchangeable, 1-OH), 1.45 (d, J = 7.8 Hz, 1H, D_2O exchangeable, 7-OH), 1.21 (s, 9H, *t*-Bu), 1.22 (s, 3H, 15-Me), 1.12 (s, 3H, 15-Me); MS (FAB) *m/z* 846 ($M+Na^+$); IR (nujol) ν_{max} 3420, 1735, 1700, 1455, 1375, 1245 cm^{-1}.

27 (78%): colorless amorphous solid; R_f = 0.1 (ethyl acetate / hexane 1:1); ^1H NMR ($CDCl_3$) δ 8.04-8.08 (m, 2H, Ar-H), 7.16-7.67 (m, 13H, Ar-H), 5.94 (m, 1H, 13-H), 5.63 (d, J = 7.1 Hz, 1H, 2-H), 5.19 (d, J = 1.7 Hz, 1H, 10-H), 4.93 (m, 1H, 5-H), 4.61-4.68 (m, 2H, 2'-H and 3'-H), 4.28 (d, J = 8.1 Hz, 1H, 20-H), 4.22 (m, 1H, 7-H), 4.18 (d, J = 1.7 Hz, 1H, D_2O exchangeable, 10-OH), 4.17 (d, J = 8.1 Hz, 1H, 20-H), 3.87 (d, J = 7.1 Hz, 1H, 3-H), 3.42 (m, 1H, D_2O exchangeable, 2'-OH), 2.52 (m, 1H, 6-H), 2.26 (s, 3H, Ac), 2.03 (m, 1H, 14-H), 1.92 (d, J = 1.3 Hz, 3H, 12-Me), 1.79-1.91 (m, 2H, 6-H and 14-H), 1.74 (s, 3H, 8-Me), 1.60 (s, 1H, D_2O exchangeable, 1-OH), 1.51 (d, J = 7.8 Hz, 1H, D_2O exchangeable, 7-OH), 1.18 (s, 3H, 15-Me), 1.10 (s, 3H, 15-Me); MS (FAB) *m/z* 801 (MH^+); IR (nujol) ν_{max} 3450, 1735, 1720, 1700, 1460, 1375, 1245 cm^{-1}.

31 (86%): colorless amorphous solid; R_f = 0.25 (ethyl acetate / hexane 2:1); ^1H NMR ($CDCl_3$) δ 8.07-8.10 (m, 2H, Ar-H), 7.23-7.69 (m, 8H, Ar-H), 5.99 (m, 1H, 13-H), 5.67 (brs, 1H, 3'-NH), 5.66 (d, J = 7.0 Hz, 1H, 2-H), 5.16 (m, 1H, 3'-H), 5.15 (s, 1H, 10-H), 4.93 (m, 1H, 5-H), 4.65 (dd, J = 3.1, 8.4 Hz, 1H, 2'-H), 4.32 (d, J = 8.3 Hz, 1H, 20-H), 4.12-4.26 (m, 3H, 7-H and D_2O exchangeable, 10-OH and 20-H), 3.87 (d, J = 7.0 Hz, 1H, 3-H), 3.05 (d, J = 8.4 Hz, 1H, D_2O exchangeable, 2'-OH), 2.59 (m, 1H, 6-H), 2.32 (s, 3H, Ac), 2.13-2.25 (m, 2H, 14-H), 1.83 (m, 1H, 6-H), 1.74 (s, 3H, 12-Me), 1.70 (s, 1H, D_2O exchangeable, 1-OH), 1.58 (s, 3H, 8-Me), 1.45 (s, 9H, *t*-Bu), 1.17 (s, 3H, 15-Me), 1.11 (s, 3H, 15-Me); MS (FAB) *m/z* 808 (MH^+); IR (nujol) ν_{max} 3400, 1740, 1720, 1240 cm^{-1}.

Reaction of 11a with *O*-benzylhydroxylamine. In a sealed tube $Yb(OTf)_3$ (74 mg, 0.12 mmol) and NH_2OBn (296 mg, 2.40 mmol) were added to a solution of **11a** (312 mg, 0.30 mmol) in CH_2Cl_2 (20 ml) and the reaction mixture was stirred at 60 °C for 6 d. The reaction mixture was diluted with $CHCl_3$ and the organic layers were washed with water and brine, and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was

purified by preparative TLC (ethyl acetate / $CHCl_3$ 1:20) to give a colorless foam **14** (70 mg, 0.60 mmol, 20%): ^{1}H NMR ($CDCl_3$) δ 8.04-8.09 (m, 2H, Ar-H), 7.65 (m, 1H, Ar-H), 7.21-7.55 (m, 12H, Ar-H), 6.21 (brs, 1H, D_2O exchangeable, 3'-NH), 6.17 (s, 1H, 10-H), 5.86 (m, 1H, 13-H), 5.64 (d, J= 7.0 Hz, 1H, 2-H), 5.51 (dd, J= 7.0, 10.7 Hz, 1H, 7-H), 4.94 (m, 1H, 5-H), 4.91 (d, J = 11.7 Hz, 1H, Troc), 4.83 (d, J = 11.8 Hz, 1H, Troc), 4.75 (d, J= 11.8 Hz, 1H, Troc), 4.67 (s, 2H, 3'-PhCH_2), 4.66 (m, 1H, 3'-H), 4.60 (d, J = 11.7 Hz, 1H, Troc), 4.46 (dd, J= 2.8, 6.8 Hz, 1H, 2'-H), 4.31 (d, J = 8.4 Hz, 1H, 20-H), 4.16 (d, J = 8.4 Hz, 1H, 20-H), 3.83 (d, J = 7.0 Hz, 1H, 3-H), 3.43 (d, J = 6.8 Hz, 1H, D_2O exchangeable, 2'-OH), 2.61 (m, 1H, 6-H), 2.29 (s, 3H, Ac), 1.95-2.12 (m, 3H, 14-2H and 6-H), 1.88 (d, J= 1.3 Hz, 3H, 12-Me), 1.84 (s, 3H, 8-Me), 1.51 (s, 1H, D_2O exchangeable, 1-OH), 1.15 (s, 3H, 15-Me), 1.11 (s, 3H, 15-Me); MS (FAB) *m/z* 1184 ($M+Na^+$, 1), 1041 ($M+Na^+$+2, 2.3), 1184 ($M+Na^+$+4, 2); IR (nujol) ν_{max} 3440, 1760, 1720, 1460, 1375, 1240 cm^{-1}.

Methyl (2*R*,3*S*)-3-bromo-2-hydroxy-3-phenylpropionate (19). To a solution of methyl (2*R*,3*S*)-3-phenyl-oxiranecarboxylate (**18**)[12] (167 mg, 0.94 mmol) in CH_2Cl_2 (5 ml) and HMPA (0.5 ml) was added $TiBr_4$ (380 mg, 1.03 mmol) at -78 ℃. The mixture was stirred at -78 ℃ for 3 h and at -10 ℃ for 1 h. To the mixture was added water and extracted with $CHCl_3$. The organic layers were washed with water (twice), and brine, and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 1:4) to give a colorless oil **19** (200 mg, 0.77 mmol, 82%). The ratio of **19/20** was determined by ^{1}H NMR analysis of crude product. The comparison of **19** with **20** was described as follow.
19 : ^{1}H NMR ($CDCl_3$) δ 7.42-7.47 (m, 2H, Ar-H), 7.30-7.35 (m, 3H, Ar-H), 5.27 (d, J = 4.5 Hz, 1H, 3-H), 4.71 (dd, J = 4.5, 6.6 Hz, 1H, 2-H), 3.74 (s, 3H, CO_2 Me), 2.97 (d, J = 6.6 Hz, 1H, D_2O exchangeable, 2-OH); MS (FAB) *m/z* 259 (MH^+, 1), 261 (MH^++2, 1); IR (nujol) ν_{max} 3500, 3380, 1735, 1715, 1450, 1100 cm^{-1}.
20 : ^{1}H NMR ($CDCl_3$) δ 7.50-7.63 (m, 2H, Ar-H), 7.30-7.39 (m, 3H, Ar-H), 5.39 (d, J = 2.5 Hz, 1H, 3-H), 4.49 (m, 1H, 2-H), 3.86 (s, 3H, CO_2 Me), 3.33 (brd, J = 7.3 Hz, 1H, D_2O exchangeable, 2-OH)

Methyl (2*R*,3*R*)-3-azide-2-hydroxy-3-phenylpropionate (21). To a solution of **19** (90 mg, 0.35 mmol) in DMF (5 ml) was added 15-crown-5 (8 mg, 0.04 mmol) and NaN_3 (226 mg, 3.5 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 31 h, and to the reaction mixture was added water and extracted with ethyl acetate. The organic layers were washed with brine, and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 1:5) to give a colorless oil **21** (68 mg, 0.31 mmol, 88%). The ratio of **21/22** was determined by ^{1}H NMR analysis of crude product. The comparison of **21** with **22** was described as follow.
21 : ^{1}H NMR ($CDCl_3$) δ 7.30-7.50 (m, 5H, Ar-H), 4.87 (d, J = 2.9 Hz, 1H, 3-H), 4.39 (dd, J = 2.9, 6.8 Hz, 1H, 2-H), 3.84 (s, 3H, CO_2 Me), 3.08 (d, J = 6.8 Hz, 1H, D_2O exchangeable, 2-OH); MS (FAB) *m/z* 222 (MH^+); IR (nujol) ν_{max} 3480, 2060, 1740, 1450 cm^{-1}.
22 : ^{1}H NMR ($CDCl_3$) δ 7.30-7.50 (m, 5H, Ar-H), 4.88 (d, J = 4.4 Hz, 1H, 3-H), 4.54 (dd, J = 4.4, 6.2 Hz, 1H, 2-H), 3.73 (s, 3H, CO_2 Me), 2.93 (d, J = 6.2 Hz, 1H, D_2O exchangeable, 2-OH)

(2*R*,3*S*)-3-Phenyloxiranecarboxylic acid (4b). To an ice-cooled solution of methyl (2*R*,3*S*)-3-phenyl-oxiranecarboxylate (**18**) (1.95 g, 10.9 mmol) in THF (60 ml) was added 1N aqueous NaOH (21.8 ml, 21.8 mmol) dropwise and the reaction mixture was stirred at room temperature for 20 min. The mixture was diluted with water and washed with Et_2O. To the ice-cooled aqueous layers was added toluene and 1N aqueous HCl (21.3 ml, 21.3 mmol) dropwise. The mixture was extracted with toluene and dried over Na_2SO_4 and concentrated *in vacuo* to give a colorless amorphous solid **4b** (1.79 g, 10.9 mmol, 100%). The crude product **4b** was immediately used for next reaction without more purification.

Coupling reaction of 7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetylbaccatin III (10) with 4b. To a solution of **10** (4.92 g, 5.49 mmol) and **4b** (1.79 g, 10.9 mmol) in toluene (83 ml) was added dicyclohexylcarbodiimide (2.38 g, 11.5 mmol) and 4-*N*,*N*-dimethylaminopyridine (342 mg, 2.8 mmol). The reaction mixture was stirred at room temperature for 10 min. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate / toluene 1:15) to give a colorless foam **11b** (5.55 g, 5.33 mmol, 97%): $[\alpha]^{25}_D$ -74° (*c* 0.49, EtOH); ^{1}H NMR ($CDCl_3$) δ 8.05-8.10 (m, 2H, Ar-H), 7.30-7.66 (m, 8H, Ar-H), 6.31 (m, 1H, 13-H), 6.27 (s, 1H, 10-H), 5.69 (d, J= 7.0 Hz, 1H, 2-H), 5.57 (dd, J= 7.1, 10.7 Hz, 1H, 7-H), 4.94 (m, 1H, 5-H), 4.92 (d, J= 11.8 Hz, 1H, Troc), 4.79 (s, 2H, Troc), 4.61 (d, J= 11.8 Hz, 1H, Troc), 4.32 (d, J= 8.4 Hz, 1H, 20-H), 4.22 (d, J= 1.7 Hz, 1H, 3'-H), 4.16 (d, J= 8.4 Hz, 1H, 20-H), 3.92 (d, J= 7.0 Hz, 1H, 3-H), 3.64 (d, J= 1.7 Hz, 1H, 2'-H), 2.63 (m, 1H, 6-H), 2.20-2.41 (m, 2H, 14-H), 2.22 (s, 3H, Ac), 2.09 (s, 3H, 12-Me), 2.07 (m, 1H, 6-H), 1.86 (s, 3H, 8-Me), 1.73 (s, 1H, D_2O exchangeable, 1-OH), 1.28 (s, 3H, 15-Me), 1.21 (s, 3H, 15-Me); MS (FAB) *m/z* 1039 (MH^+, 1), 1041 (MH^++2, 2), 1043 (MH^++4, 2); HRMS (ESI) *m/z* 1097.0908 ([M-H+AcOH]$^-$, $C_{42}H_{47}O_{18}Cl_6$ requires

1097.0894); IR (nujol) ν_{max} 3520, 1760, 1730, 1250, 1160 cm^{-1}.

Bromination of 11b. To a solution of **11b** (2.70 g, 2.59 mmol) in CH_2Cl_2 (50 ml) and HMPA (5 ml) was added $TiBr_4$ (2.80 g, 7.62 mmol) at 0 ℃ and the reaction mixture was stirred at 0 ℃ for 18 h. To the mixture was added water and extracted with $CHCl_3$. The organic layers were washed with water, and brine, and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 1:2) to give a colorless foam **23** (2.22 g, 1.98 mmol, 76%): $[\alpha]^{25}_D$ -45° (*c* 0.50, EtOH); ^1H NMR ($CDCl_3$) δ 8.05-8.10 (m, 2H, Ar-H), 7.64 (m, 1H, Ar-H), 7.37-7.53 (m, 7H, Ar-H), 6.21 (s, 1H, 10-H), 6.17 (m, 1H, 13-H), 5.68 (d, *J* = 7.0 Hz, 1H, 2-H), 5.53 (dd, *J* = 7.2, 10.6 Hz, 1H, 7-H), 5.27 (d, *J* = 6.2 Hz, 1H, 3'-H), 4.97 (m, 1H, 5-H), 4.91 (d, *J* = 11.8 Hz, 1H, Troc), 4.48 (dd, *J* = 6.2, 7.5 Hz, 1H, 2'-H), 4.77 (s, 2H, Troc), 4.60 (d, *J* = 11.8 Hz, 1H, Troc), 4.34 (d, *J* = 8.4 Hz, 1H, 20-H), 4.16 (d, *J* = 8.4 Hz, 1H, 20-H), 3.90 (d, *J* = 7.0 Hz, 1H, 3-H), 2.99 (d, *J* = 7.5 Hz, 1H, D_2O exchangeable, 2'-OH), 2.63 (m, 1H, 6-H), 2.39 (s, 3H, Ac), 2.02-2.33 (m, 3H, 14-2H and 6-H), 1.85 (s, 3H, 8-Me), 1.81 (d, *J* = 1.2 Hz, 3H, 12-H), 1.74 (s, 1H, D_2O exchangeable, 1-OH), 1.25 (s, 3H, 15-Me), 1.19 (s, 3H, 15-Me); MS (FAB) *m/z* 1119 (MH^+, 0.7), 1121 (MH^++2, 1.5), 1123 (MH^++4, 2), 1125 (MH^++6, 1.2) ; HRMS (ESI) *m/z* 1116.9951 ($[M-H]^-$, $C_{44}H_{44}O_{16}Cl_6Br$ requires 1116.9944); IR (nujol) ν_{max} 3440, 1760, 1720, 1460, 1380, 1250 cm^{-1}.

Reaction of 23 with sodium azide. To a solution of **23** (112 mg, 0.100 mmol) in DMF (2 ml) was added 15-crown-5 (111 mg, 0.50 mmol) and NaN_3 (33 mg, 0.50 mmol) at -10 ℃. The mixture was stirred at 0 ℃ for 18 h. To the mixture was added water and extracted with ethyl acetate. The organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was separated by preparative TLC (ethyl acetate / hexane 2:3) to give a colorless foam **12** (77 mg, 0.71 mmol, 71%).

Reaction of 23 with sodium mercaptan. To a solution of **23** (1.00 g, 0.89 mmol) and 15-crown-5 (20 mg, 0.09 mmol) in DMF (7 ml) was added 70% NaSH (100 mg, 1.2 mmol) at -45 ℃. The mixture was stirred at -45 ℃ for 2 h. To the mixture was added water and extracted with ethyl acetate. The organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 2:3) to give a colorless foam **24a** (755 mg, 0.70 mmol, 79%): ^1H NMR ($CDCl_3$) δ 8.05-8.08 (m, 2H, Ar-H), 7.25-7.67 (m, 8H, Ar-H), 6.25 (s, 1H, 10-H), 6.16 (m, 1H, 13-H), 5.67 (d, *J* = 6.9 Hz, 1H, 2-H), 5.55 (dd, *J* = 7.2, 10.6 Hz, 1H, 7-H), 4.96 (brd, *J* = 7.9 Hz, 1H, 5-H), 4.91 (d, *J* = 11.8 Hz, 1H, Troc), 4.79 (d, *J* = 11.8 Hz, 1H, Troc), 4.76 (d, *J* = 11.8 Hz, 1H, Troc), 4.60 (d, *J* = 11.8 Hz, 1H, Troc), 4.62 (dd, *J* = 4.1, 7.3 Hz, 1H, 3'-H), 4.50 (dd, *J* = 4.1, 8.1 Hz, 1H, 2'-H), 4.32 (d, *J* = 8.4 Hz, 1H, 20-H), 4.17 (d, *J* = 8.4 Hz, 1H, 20-H), 3.89 (d, *J* = 6.9 Hz, 1H, 3-H), 3.44 (d, *J* = 7.3 Hz, 1H, D_2O exchangeable, 3'-SH), 2.58-2.69 (m, 2H, 6-H and 14-H), 2.33 (s, 3H, Ac), 2.30 (d, *J* = 8.1 Hz, 1H, D_2O exchangeable, 2'-OH), 2.01-2.14 (m, 2H, 6-H and 14-H), 2.06 (d, *J* = 1.3 Hz, 3H, 12-H), 1.86 (s, 3H, 8-Me), 1.71 (s, 1H, D_2O exchangeable, 1-OH), 1.26 (s, 3H, 15-Me), 1.19 (s, 3H, 15-Me); MS (FAB) *m/z* 1095 ($M+Na^+$, 1), 1097 ($M+Na^+$+2, 2), 1099 ($M+Na^+$+4, 2); IR (nujol) ν_{max} 3480, 2560, 1760, 1730, 1460, 1370 cm^{-1}.

Reaction of 24a with trimetylacetyl chloride. To a solution of **24a** (160 mg, 0.15 mmol) in CH_2Cl_2 (3 ml) was added Et_3N (17 mg, 0.17 mmol) and trimetylacetyl chloride (19 mg, 0.16 mmol) at -78 ℃. The reaction mixture was stirred at -78 ℃ for 30 min. To the mixture was added water and extracted with ethyl acetate (twice). The organic layers were washed with brine, and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 1:3) to give a colorless foam **24b** (173 mg, 0.15 mmol, 100%): ^1H NMR ($CDCl_3$) δ 8.11-8.15 (m, 2H, Ar-H), 7.28-7.67 (m, 8H, Ar-H), 6.24 (s, 1H, 10-H), 6.13 (m, 1H, 13-H), 5.69 (d, *J* = 7.0 Hz, 1H, 2-H), 5.55 (dd, *J* = 7.0, 10.7 Hz, 1H, 7-H), 5.12 (d, *J* = 3.0 Hz, 1H, 3'-H), 4.95 (m, 1H, 5-H), 4.90 (d, *J* = 11.8 Hz, 1H, Troc), 4.77 (s, 2H, Troc), 4.71 (dd, *J* = 3.0, 7.8 Hz, 1H, 2'-H), 4.60 (d, *J* = 11.8 Hz, 1H, Troc), 4.34 (d, *J* = 8.2 Hz, 1H, 20-H), 4.18 (d, *J* = 8.2 Hz, 1H, 20-H), 3.91 (d, *J* = 7.0 Hz, 1H, 3-H), 3.39 (d, *J* = 7.8 Hz, 1H, D_2O exchangeable, 2'-OH), 2.60 (m, 1H, 6-H), 2.38 (s, 3H, Ac), 2.23-2.33 (m, 2H, 14-H), 2.05 (m, 1H, 6-H), 1.98 (d, *J* = 1.3 Hz, 3H, 12-H), 1.86 (s, 3H, 8-Me), 1.67 (s, 1H, D_2O exchangeable, 1-OH), 1.26 (s, 3H, 15-Me), 1.20 (s, 3H, 15-Me), 1.17 (s, 9H, *t*-Bu); MS (FAB) *m/z* 1179 ($M+Na^+$, 1) , 1181 ($M+Na^+$+2, 2), 1183 ($M+Na^+$+4, 2); IR (nujol) ν_{max} 3490, 1760, 1730, 1680, 1455, 1375, 1245 cm^{-1}.

Reaction of 24a with *t*-butyl isocyanate. To a solution of **24a** (150 mg, 0.14 mmol) in CH_2Cl_2 (2 ml) was added Et_3N (17 mg, 0.17 mmol) and *t*-butyl isocyanate (18 mg, 0.18 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 30 min. To the mixture was added water and extracted with ethyl acetate. The organic layers were washed with water, 10% aqueous citric acid and brine, and dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 1:2) to give a colorless amorphous solid **24c** (154 mg, 0.13 mmol, 94%): ^1H NMR ($CDCl_3$) δ 8.11-8.15 (m, 2H, Ar-H), 7.26-7.67

(m, 8H, Ar-H), 6.24 (s, 1H, 10-H), 6.19 (m, 1H, 13-H), 5.69 (d, J = 7.0 Hz, 1H, 2-H), 5.55 (dd, J = 7.3, 10.7 Hz, 1H, 7-H), 5.08 (brs, 1H, 3'-SCONH), 5.03 (d, J = 3.3 Hz, 1H, 3'-H), 4.96 (dd, J = 0.9, 9.2 Hz, 1H, 5-H), 4.90 (d, J = 11.8 Hz, 1H, Troc), 4.79 (d, J = 11.8 Hz, 1H, Troc), 4.75 (d, J = 11.8 Hz, 1H, Troc), 4.72 (dd, J = 3.3, 7.9 Hz, 1H, 2'-H), 4.60 (d, J = 11.8 Hz, 1H, Troc), 4.34 (d, J = 8.1 Hz, 1H, 20-H), 4.17 (d, J = 8.1 Hz, 1H, 20-H), 3.92 (d, J = 7.0 Hz, 1H, 3-H), 3.75 (d, J = 7.9 Hz, 1H, D_2O exchangeable, 2'-OH), 2.62 (m, 1H, 6-H), 2.38 (s, 3H, Ac), 2.20-2.35 (m, 2H, 14-H), 2.05 (m, 1H, 6-H), 1.99 (d, J = 1.3 Hz, 3H, 12-H), 1.85 (s, 3H, 8-Me), 1.64 (s, 1H, D_2O exchangeable, 1-OH), 1.26 (s, 3H, 15-Me), 1.22 (s, 9H, t-Bu), 1.19 (s, 3H, 15-Me); MS (FAB) m/z 1194 ($M+Na^+$, 1), 1196 ($M+Na^+$+2, 2), 1198 ($M+Na^+$+4, 2); IR (nujol) ν_{max} 3500, 3360, 1760, 1730, 1450, 1375, 1245 cm^{-1}.

Reaction of 23 with thiophenol. To a solution of PhSH (107 mg, 0.97 mmol) in DMF (3 ml) was added NaH (13 mg, 0.54 mmol) at 0 °C, and stirred for 30 min. To the mixture was added **23** (545 mg, 0.49 mmol) in DMF (7 ml) at -10 °C, and the reaction mixture was stirred at -10 °C for 30 min. The mixture was poured into ice-water and extracted with ethyl acetate. The organic layers were washed with water and brine, and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / hexane 1:2) to give a colorless foam **26** (515 mg, 0.45 mmol, 92%): ^1H NMR ($CDCl_3$) δ 8.03-8.09 (m, 2H, Ar-H), 7.16-7.69 (m, 13H, Ar-H), 6.23 (s, 1H, 10-H), 5.98 (m, 1H, 13-H), 5.65 (d, J = 7.0 Hz, 1H, 2-H), 5.54 (dd, J = 7.3, 10.7 Hz, 1H, 7-H), 4.95 (m, 1H, 5-H), 4.91 (d, J = 11.8 Hz, 1H, Troc), 4.77 (s, 2H, Troc), 4.64-4.69 (m, 2H, 2'-H and 3'-H), 4.60 (d, J = 11.8 Hz, 1H, Troc), 4.31 (d, J = 8.1 Hz, 1H, 20-H), 4.16 (d, J = 8.1 Hz, 1H, 20-H), 3.86 (d, J = 7.0 Hz, 1H, 3-H), 3.45 (m, 1H, D_2O exchangeable, 2'-OH), 2.63 (m, 1H, 6-H), 2.29 (s, 3H, Ac), 1.98-2.08 (m, 3H, 14-2H and 6-H), 2.02 (d, J = 1.3 Hz, 3H, 12-H), 1.85 (s, 3H, 8-Me), 1.63 (s, 1H, D_2O exchangeable, 1-OH), 1.22 (s, 3H, 15-Me), 1.18 (s, 3H, 15-Me); MS (FAB) m/z 1149 (MH^+, 1), 1151 (MH^++2, 2), 1153 ($M+Na^+$+4, 1.5); IR (nujol) ν_{max} 3500, 1760, 1725, 1455, 1375, 1245 cm^{-1}.

Reaction of 27 with 3-chloroperoxybenzoic acid (*m*CPBA). To a solution of **27** (104 mg, 0.13 mmol) in $CHCl_3$ (10 ml) was added *m*CPBA (22 mg, 0.13 mmol) at 0 °C, and stirred at room temperature for 2 h. The mixture was diluted with $CHCl_3$ and washed with saturated agueous $NaHCO_3$ and brine, and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was separated by preparative TLC (ethyl acetate / hexane 2:1) to give a colorless amorphous solid **28** (56 mg, 0.07 mmol, 53%): ^1H NMR ($CDCl_3$) δ 8.05-8.10 (m, 2H, Ar-H), 7.63 (m, 1H, Ar-H), 7.12-7.54 (m, 12H, Ar-H), 6.08 (m, 1H, 13-H), 5.67 (d, J = 7.2 Hz, 1H, 2-H), 5.23 (d, J = 1.8 Hz, 1H, 10-H), 5.02 (dd, J = 4.2, 4.4 Hz, 1H, 2'-H), 4.97 (m, 1H, 5-H), 4.57 (d, J = 4.2 Hz, 1H, D_2O exchangeable, 2'-OH), 4.43 (d, J = 4.4 Hz, 1H, 3'-H), 4.32 (d, J = 8.7 Hz, 1H, 20-H), 4.26 (m, 1H, 7-H), 4.19 (d, J = 8.7 Hz, 1H, 20-H), 4.15 (d, J = 1.8 Hz, 1H, D_2O exchangeable, 10-OH), 3.96 (d, J = 7.2 Hz, 1H, 3-H), 2.61 (m, 1H, 6-H), 2.36 (s, 3H, Ac), 2.09-2.26 (m, 2H, 14H), 2.01 (d, J = 1.3 Hz, 3H, 12-Me), 1.85 (m, 1H, 6-H), 1.76 (s, 3H, 8-Me), 1.63 (s, 1H, D_2O exchangeable, 1-OH), 1.45 (s, 1H, D_2O exchangeable, 7-OH), 1.20 (s, 3H, 15-Me), 1.12 (s, 3H, 15-Me); Mass (FAB) m/z 817 (MH^+); IR (nujol) ν_{max} 3440, 1720, 1460, 1375, 1270, 1245 cm^{-1}.

Reaction of 11b with sodium azide. To a solution of **11b** (1.23 g, 1.18 mmol) in MeOH-H_2O (8:1, 30 ml) was added HCO_2Me (5 ml) and NaN_3 (767 mg, 11.8 mmol). The reaction mixture was stirred at 45 °C for 3.5 h. The mixture was poured into ice-water and was extracted with ethyl acetate. The organic layers were washed with 5% aqueous citric acid and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / toluene 1:9) to give a colorless foam **29** (1.17 g, 1.08 mmol, 92%): ^1H NMR ($CDCl_3$) δ 8.04-8.10 (m, 2H, Ar-H), 7.12-7.68 (m, 8H, Ar-H), 6.19 (s, 1H, 10-H), 6.12 (m, 1H, 13-H), 5.66 (d, J = 6.9 Hz, 1H, 2-H), 5.50 (dd, J = 7.1, 10.7 Hz, 1H, 7-H), 4.96 (d, J = 5.1 Hz, 1H, 3'-H), 4.96 (m, 1H, 5-H), 4.90 (d, J = 11.7 Hz, 1H, Troc), 4.77 (s, 2H, Troc), 4.59 (d, J = 11.8 Hz, 1H, Troc), 4.54 (dd, J = 5.1, 7.5 Hz, 1H, 2'-H), 4.31 (d, J = 8.4 Hz, 1H, 20-H), 4.15 (d, J = 8.4 Hz, 1H, 20-H), 3.85 (d, J = 6.9 Hz, 1H, 3-H), 2.93 (d, J = 7.5 Hz, 1H, D_2O exchangeable, 2'-OH), 2.61 (m, 1H, 6-H), 2.24 (s, 3H, Ac), 2.10-2.34 (m, 2H, 14-2H), 2.05 (m, 1H, 6-H), 1.84 (s, 3H, 12-Me), 1.76 (s, 3H, 8-Me), 1.70 (s, 1H, D_2O exchangeable, 1-OH), 1.24 (s, 3H, 15-Me), 1.18 (s, 3H, 15-Me); MS (FAB) m/z 1082 (MH^+, 1), 1084 (MH^++2, 2), 1086 (MH^++4, 2); IR (nujol) ν_{max} 3520, 2120, 1760, 1750, 1720, 1240 cm^{-1}.

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-3'-epi-docetaxel (30). To a solution of **29** (163 mg, 0.15 mmol) and Boc_2O (116 mg, 0.53 mmol) in CH_2Cl_2 (5 ml) was added H_2O (5 drops), PPh_3 (79 mg, 0.30 mmol), and $KHCO_3$ (75 mg, 0.75 mmol). The reaction mixture was stirred at room temperature for 22 h. The mixture was diluted with $CHCl_3$ and the organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate / toluene 1:4) to give a colorless foam **30** (149 mg, 1.13 mmol, 86%): ^1H NMR ($CDCl_3$) δ 8.06-8.12 (m, 2H, Ar-H), 7.66 (m, 1H, Ar-H), 7.23-7.58 (m, 7H, Ar-H), 6.18 (s, 1H, 10-H), 5.99 (m, 1H, 13-H), 5.67 (d, J = 6.6 Hz,

1H, 2-H), 5.65 (m, 1H, 3'-H), 5.50 (dd, J = 7.3, 10.6 Hz, 1H, 7-H), 5.16 (brs, 1H, 3'-NH), 4.94 (m, 1H, 5-H), 4.89 (d, J = 11.8 Hz, 1H, Troc), 4.76 (s, 2H, Troc), 4.67 (dd, J = 3.0, 7.9 Hz, 1H, 2'-H), 4.58 (d, J = 11.8 Hz, 1H, Troc), 4.33 (d, J = 8.8 Hz, 1H, 20-H), 4.16 (d, J = 8.8 Hz, 1H, 20-H), 3.85 (d, J = 6.6 Hz, 1H, 3-H), 3.03 (d, J = 7.9 Hz, 1H, D_2O exchangeable, 2'-OH), 2.62 (m, 1H, 6-H), 2.35 (s, 3H, Ac), 2.10-2.40 (m, 2H, 14-2H), 2.01 (m, 1H, 6-H), 1.84 (s, 3H, 12-Me), 1.73 (s, 3H, 8-Me), 1.70 (s, 1H, D_2O exchangeable, 1-OH), 1.45 (s, 9H, t-Bu), 1.21 (s, 3H, 15-Me), 1.18 (s, 3H, 15-Me); MS (FAB) m/z 1156 (MH^+, 1), 1158 (MH^++2, 2), 1160 (MH^++4, 2); IR (nujol) ν_{max} 3400, 1760, 1720, 1245 cm^{-1}.

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