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The Synthesis and Biological Activity of 9- and 2′-cAMP 7-Deoxypaclitaxel Analogues from 5-Cinnamoyltriacetyltaxicin-I

Qian Cheng,* Takayuki Oritani and Tohru Horiguchi

Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

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Abstract—The synthesis and biological activity of new 7-deoxypaclitaxel analogues **3** and **4** in which the hydroxy group at C-2′ of the side-chain, C-9 and C-10 in the B-ring are substituted by cAMP and benozoyloxy group respectively are presented. These derivatives have been first synthesized from a natural taxoid 5-cinnamoyltriacetyltaxicin-I **5** and tested in vitro for cytotoxicity against three human tumor cell lines. The biologically tested results indicate **3** having more potent cytotoxicity and **4** having a remarkably reduced cytotoxicity as well as **33** having no much effect on cytotoxicity against all human tumor cell lines tested in comparison to that of paclitaxel.

Introduction

The diterpenoid paclitaxel (Taxol® **1**), originally isolated from the Pacific yew tree *Taxus brevifolia*,[1] is a powerful therapeutic drug for cancer chemotherapy[2] and exhibits remarkably high cytotoxicity and strong antitumor activity against different types of cancer that are resistant to existing anticancer drugs.[3] Its outstanding results of clinical studies have led to be approved for treatment of advanced ovarian and breast cancers,[4,5] and it is currently in clinical trials for treatment of lung, skin, and head and neck cancers with encouraging results.[2,6] Over the past two decades, structural complexity, important biological activity and novel mechanism of action[7] of paclitaxel have stimulated extensive chemical, biological and medicinal research,[8] and a number of research groups have attempted to synthesize it and its improved analogues for clinical use. Up to now, six total syntheses of paclitaxel have been achieved.[9] Among many studies of structural modifications of paclitaxel, numerous analogues have been prepared by contractions and changes to A-ring,[10] B-ring,[11] C-ring,[12] the oxetane ring,[13] and the side chain[14] which have led to the discovery of the biologically potent taxoid docetaxol[15] (Taxotere® **2**) in the semisynthesis of paclitaxel from 10-deacetylbaccatin III.

From a large number of the structure-activity relationship (SAR) studies of paclitaxel, it is known that the function group at C-7, C-9, C-10, and double bond in the northern hemisphere have no significant effect on activity, while the benzoyloxy and acetoxy at C-2 and C-4 respectively plus the oxetane ring in the southern hemisphere, and the side chain at C-13 are essential for activity.[8,11,14,16] However, only a few modifications of C-9 such as dihydrogenation and decarboxylation have been reported.[17] Further chemical and SAR studies of C-9 have appeared recently in the literature. The mechanism of action studies indicate that the anticancer activity of paclitaxel is believed to be mediated by a combination of its primary action on microtubule assembly and secondarily by inhibiting DNA synthesis and promoting DNA fragmentation of the cell.[18] These actions are found to be related with a nucleotide, such as GTP and ATP,[19] which can be converted from GMP and AMP via GDP and ADP in the organism. In addition, twin drugs combining two biologically active components into a single molecule have been applied in numerous domains of medicinal chemistry.[20] With this in mind and the known SAR studies in which show 7-deoxylation having no significant effect on activity, we thus expected to explore the possibility of taxoid combined with the nucleotide for the synthesis of the new taxoids **3** and **4** possessing anticancer activity or other biological activity, and the additional knowledge for SAR of paclitaxel.

Although the semisyntheses of 7-deoxypaclitaxel analogues have been reported,[21] all investigations have been carried out using taxine B and isotaxine B[22] as starting materials. To our knowledge no attention to date has been paid to 5-cinnamoyltriacetyltaxicin-I **5**,[23] which is an available taxoid existing in the needles of different *Taxus* species, as a precursor for the synthesis of either paclitaxel or its analogues. In this paper, we describe our efforts on the synthesis and biological activity of new 7-deoxypaclitaxel analogues **3** and **4** from **5** (Scheme 1).

Keywords: biologically active compounds; taxoids; phosphoric acid and derivatives.

* Corresponding author. Fax: 81+(022)-717-8783;
e-mail: chengq@biochem.tohoku.ac.jp

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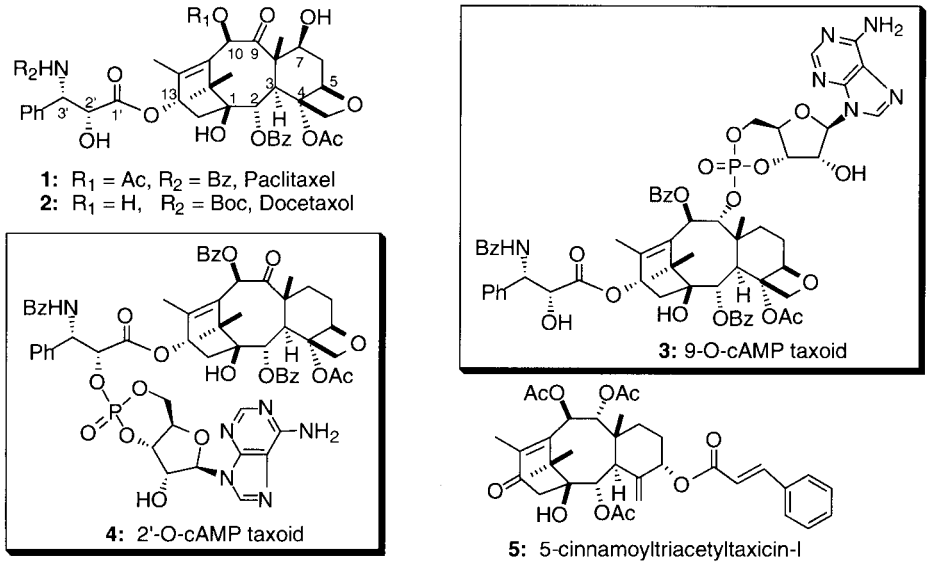
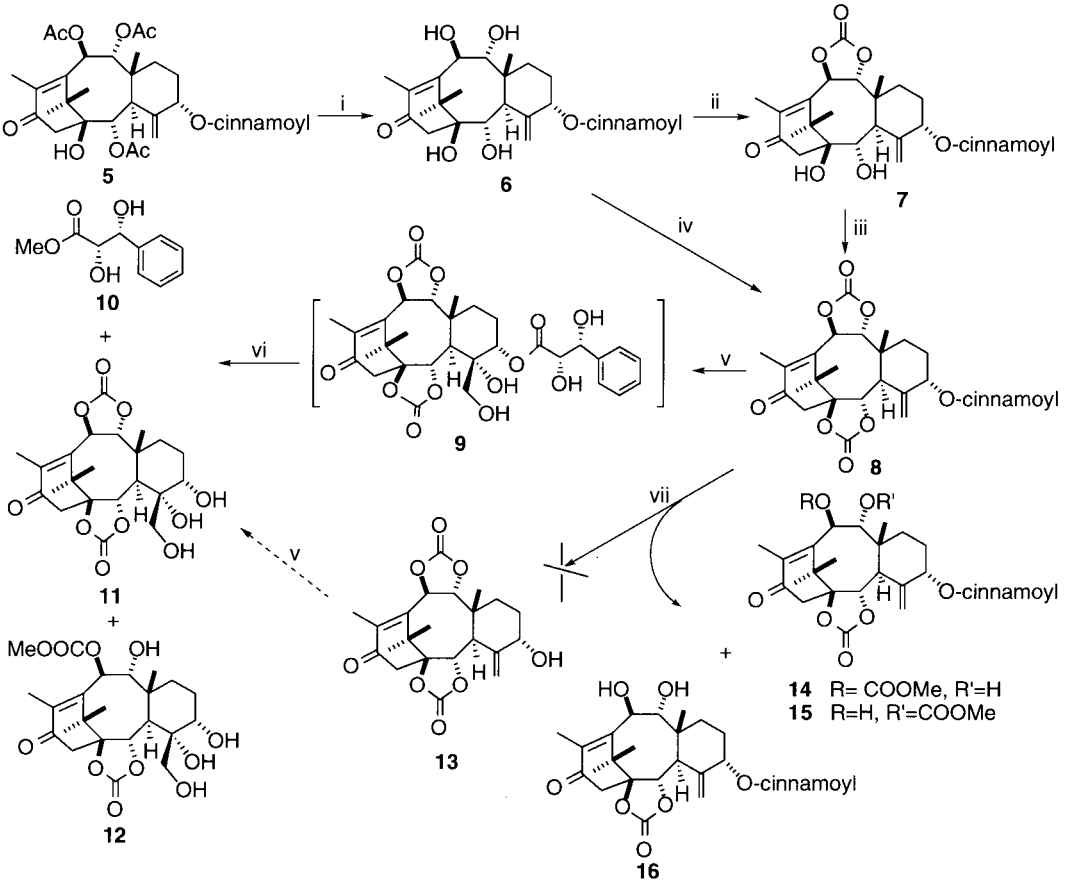


Scheme 1.

Results and Discussion

As the synthetic protocol is depicted in Scheme 2, the 5-cinnamoyltriacetyltaxicin-I **5**, easily isolated from the needles of Japanese yew *T. cuspidata*, underwent deacetylation to give a polyalcohol **6** at 0°C in the presence of $NaOCH_3$.[21a] Attempted protection of the polyalcohol **6** with triphosgene (2 equiv.) and Et_3N (4 equiv.) in CH_2Cl_2 at rt yielded a sole reaction product 9,10-cyclic carbonate alcohol **7** in 90% yield. But the compound **7** was further protected with

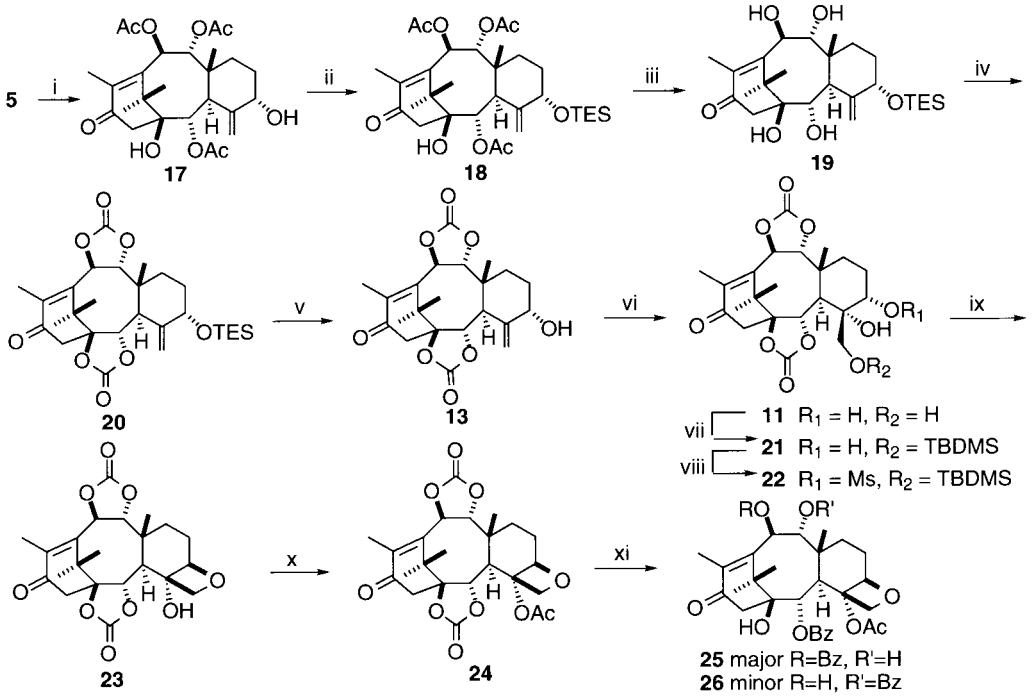


Scheme 2. Reagents and conditions: (i) $NaOCH_3$, CH_3OH-CH_2Cl_2, 0°C, 86%; (ii) $(Cl_3CO)_2CO$ (2 equiv.), Et_3N (4 equiv.), CH_2Cl_2, rt, 90%; (iii) $(Cl_3CO)_2CO$ (2 equiv.), CH_2Cl_2-pyridine (2:1), 0°C, 91%; (iv) $(Cl_3CO)_2CO$ (5 equiv.), CH_2Cl_2-pyridine (2:1), 0°C, 86%; (v) OsO_4, NMO, THF-H_2O (2:1), rt, 85%; (vi) 10% KOAc, CH_3OH, reflux, 0.5 h, **11** (36%), **12** (45%); (vii) K_2CO_3 or $NaHCO_3$, CH_3OH, 0°C, overall yield 83%.

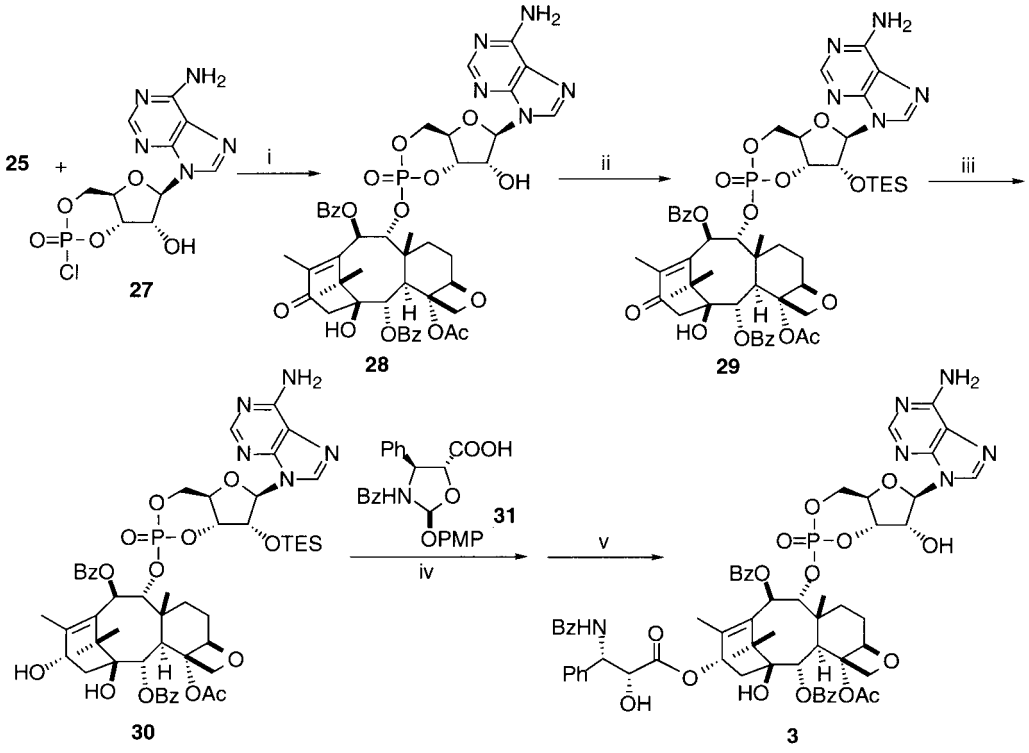
triphosgene (2 equiv.) in CH_2Cl_2-pyridine (v/v 2:1) at 0°C leading to a 1:2,9:10-dicyclic carbonate **8**, which could be prepared in 86% yield directly from the polyalcohol **6** under similar conditions using triphosgene (5 equiv.). Following the previously reported methods by Saicic,[21d] osmylation of **8** with OsO_4 (2.5% in*t*-BuOH) in the presence of 4-methylmorpholine *N*-oxide generated an intermediate **9**, which was followed by treatment with methanolic 10% KOAc under reflux to afford the desired triol **11** in 36% yield and the 9-hydroxy tetraol **12** in 45% yield together with an optically pure (2*S*, 3*R*)-(−)-methyl-2,3-dihydroxy-3-phenylpropionate **10** which was determined by NMR and optical rotation data in comparison to those of its commercial sample. The stereochemistry of **11** was established by a NOESY experiment. The NOESY correlations of H_3-19 (δ_H 1.17, s) to H_2-20 (δ_H 4.03 and 3.54, d, J=10.8 Hz), and H-20a to H-5β (δ_H 3.69, t, J=3.0 Hz) and H-6β (δ_H 1.72, m) demonstrated **11** possessing the β-orientation of the 4-hydroxymethylene group located at C-4. The similar stereochemistry of **12** was established by the NOESY correlations of H_3-19 (δ_H 1.11, s) to H_2-20 (δ_H 4.04 and 3.54, d, J=10.5 Hz), and H-20a to H-5β (δ_H 3.63, t, J=3.0 Hz) and H-6β (δ_H 1.65, m).

Alternatively, attempted conversion of **8** into a precursor **13** for the direct preparation of **11** using either K_2CO_3 or $NaHCO_3$ at 0°C even with NaOAc/NH_2OH.HCl system in MeOH–H_2O under reflux, all induced the methanolysis of the 9,10-cyclic carbonate generating two separable isomers **14** and **15** in 4:1 ratio and the 9,10-deprotected diol **16**[24] which were determined by their ^{1}H NMR, ^{13}C NMR data (see Experimental) and 2D NMR (^{1}H-^{1}H COSY and HMBC) studies. The hydrolysis of the cinnamate ester did not take place under these conditions. The above demonstrated that the key intermediate triol **11** which is a direct precursor for construction of the oxetane ring could be successfully prepared from **5**, but the yield was in comparatively low (overall yield 22.6% from **5**) due to the low selectivity in the hydrolysis of the cinnamate ester in the last step.

In order to explore an effective access to the triol **11** from **5**, the second synthetic protocol for the preparation of **11** via the intermediate **13** (Scheme 3) was employed. First selective removal of the cinnamate ester according to the known method[25] gave a 5-hydroxytriacetyltaxicin-I **17**, subsequent protection of the 5-hydroxy group by chlorotriethylsilane, deacetylation, and further protection with triphosgene afforded the protected taxoid **20**. Deprotection of **20** with a solution of tetrabutylammonium fluoride (1.0 M in THF) led to **13** in quantitative yield which subsequently was osmylated with OsO_4/NMO to furnish successfully only the triol **11** in 83% yield as the reaction product. It was worthy to note that this route was longer than the first, but the overall yield (33%) of **11** prepared from **5** via **13** was higher than that of the first route. Construction of the oxetane ring **23** was achieved in overall yield 60% from **11** following the previously established methods.[21] Acetylation of **23** with acetic anhydride catalyzed by DMAP[9a] in CH_2Cl_2 gave **24**, which subsequently was treated with phenyllithium in THF at −78°C to furnish two separable isomers **25** and **26** in 4:1 ratio. The structure and stereochemistry of **25** and **26** were determined by ^{1}H NMR, ^{13}C NMR, and 2D NMR experiments. The ^{1}H NMR data of **25** showed two downfield signals at δ_H 6.45 (d, J=9.4 Hz) and δ_H 5.62 (d, J=7.0 Hz) assigned to be the H-10 and H-2,



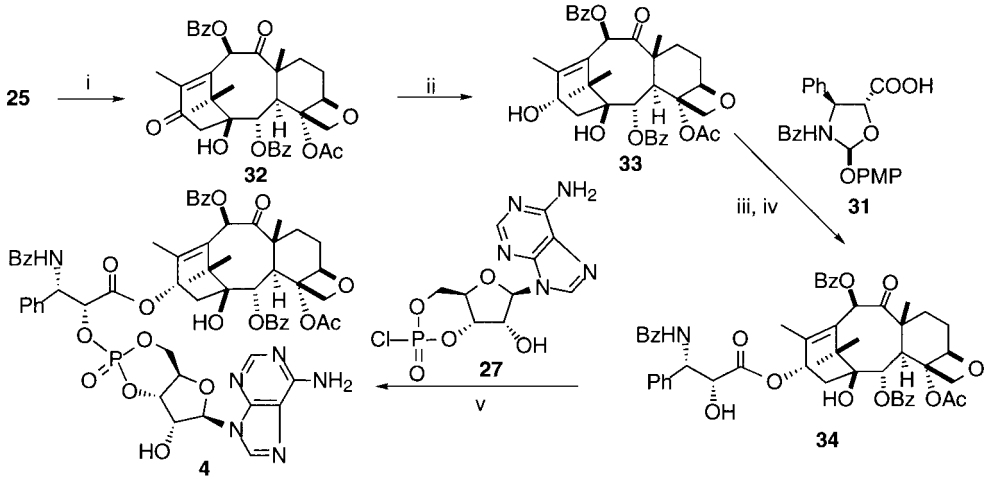
Scheme 3. Reagents and conditions: (i) NH_2OH.HCl, NaOAc, EtOH-H_2O, reflux, 70%; (ii) TESC1 (10 equiv.), pyridine, rt, 81%; (iii) $NaOCH_3$, CH_3OH-CH_2Cl_2, 0°C, 81%; (iv) $(Cl_3CO)_2CO$ (5 equiv.), CH_2Cl_2-pyridine (v/v 2:1), 0°C, 88%; (v) TBAF/THF, rt, 100%; (vi) OsO_4, NMO, THF-H_2O (2:1), rt, 83%; (vii) TBDMSCl, imidazole, DMF, rt, 95%; (viii) MsCl, pyridine, rt, 83%; (ix) a: TBAF, THF, rt, b: TBAOAc, butanone, reflux, 76%; (x) Ac_2O, DMAP, rt, 93%; (xi) PhLi, THF, -78°C, **25** (64%), **26** (15%).



Scheme 4. Reagents and conditions: (i) DMAP, DMF, rt, 84%; (ii) TESCl, imidazole, DMAP, rt, 89%; (iii) $NaBH_4$, CH_3OH, rt, 77%; (iv) DCC, DMAP, toluene, 75°C, (v) TFA, H_2O, 0°C to rt, 74% from **30**.

respectively by ^1H-^1H COSY indicating the presence of a benzoyloxy group at C-10 and C-2. This was confirmed by the HMBC correlations of H-10 and H-2 to their respective quaternary carbon (C═O) at δ_c 166.8 (Bz-10) and δ_c 168.7 (Bz-2). Whereas a upfield signal at δ_H 4.19 (dd, J=9.4, 3.4 Hz) was assigned to H-9 and a hydroxy (δ_H 2.65, d, J=3.4 Hz) was located at C-9 by means of ^1H-^1H COSY, which were confirmed by the H-9 showing doublet signal and the absence of the signal of 9-hydroxy in the D_2O exchanged ^1H NMR experiment. In comparison to the NMR data of **25**, those of **26** showed two downfield signals at δ_H 6.37 (d, J=9.1 Hz) and δ_H 5.63 (d, J=6.8 Hz) assigned to be the H-9 and H-2 respectively, and an upfield signal at δ_H 5.12 (dd, J=9.1, 4.0 Hz) assigned to be the H-10 by ^1H-^1H COSY. These implied a benzoyloxy group connected to C-9 and C-2 respectively and a hydroxy located at C-10, which were confirmed by the HMBC correlations of H-9 and H-2 to their respective quaternary carbon (C═O) at δ_c 166.3 (Bz-9) and δ_c 168.2 (Bz-2), and the H-10 showing only doublet signal in the D_2O exchanged ^1H NMR experiment. Compound **25** was regarded as the key intermediate for the synthesis of 9- and 2′-cAMP coupling 7-deoxypaclitaxel analogues **3** and **4**.

Our strategy for preparation of the 9-cAMP-7-deoxypaclitaxel **3** has been realized as shown in Scheme 4.



Scheme 5. Reagents and conditions: (i) TPAP, NMO, CH_2Cl_2, 70%; (ii) $NaBH_4$. CH_3OH, rt, 74%; (iii) DCC, DMAP, toluene, 75°C; (iv) TFA, H_2O, 0°C, 78%; (v) DMAP, DMF, rt, 78%.

Though direct coupling of **25** with (−)-adenosine 3′, 5′-cyclic monophosphate was unsuccessful, it was found that 9-cAMP taxoid **28** was prepared in 84% yield by a coupling of (−)-adenosine 3′, 5′-cyclic phosphate chloride **27** derived from acid (−)-adenosine 3′, 5′-cyclic monophosphate in the presence of DMAP at rt.[26] In order to avoid occuring coupling between **31** and the 2′-hydroxy of cAMP in esterification, the 9-cAMP taxoid **28** was first treated with TESC1 followed by selective reduction using $NaBH_4$[9a] to afford the desired 13α-hydroxy-9-cAMP taxoid **30**. Finally, the 9-cAMP-7-deoxypaclitaxel **3** was accomplished in overall yield 74% through esterification of **30** with **31** followed by acidic hydrolysis.[9f,27]

Recently, studies on C-2′ and C-7 paclitaxel phosphates used as phosphatase-activated prodrugs of paclitaxel have been reported.[28] This result has prompted us to attempt to synthesize the 2′-cAMP paclitaxel analogue **4** (Scheme 5). Oxidation of **25** with tetrapropylammonium perruthenate and 4-methylmorpholine *N*-oxide[29] gave a ketone **32** which underwent selective reduction to afford the desired 13α-hydroxy taxoid **33** in 74% yield. Esterification of **33** with **31** followed by acidic hydrolysis yielded a 10-*O*-benzoyl-7-deoxypaclitaxel **34** in 78% yield. Finally, attachment of cAMP at C-2′ giving the desired 2′-cAMP-7-deoxypaclitaxel **4** was achieved in 78% yield through a combination of **34** with (−)-adenosine 3′, 5′-cyclic phosphate chloride **27** in the presence of DMAP.

The biological results tested in vitro presented in Table 1 show the substitution of 9-hydroxy by cAMP **3** having more potent cytotoxicity against three human tumor cell lines (MCF-7, SK-OV3 and WIDR) in comparison with paclitaxel. On the other hand, the substitution of 2′-hydroxy by cAMP **4** exhibits less cytotoxicity against all human tumor cell lines than paclitaxel. The reason that **4** shows only weak activity against human tumor cell lines is not clear yet, but it is probably attributed to the absence of a free hydroxy group at C-2′ of the side chain in accordance with the known SAR studies of paclitaxel in which it is shown that the free hydroxy at C-2′ is necessary for activity.[14] In addition, the 10-benzoyloxy-7-dexoypaclitaxel **34** shows a unremarkable decrease of cytotoxicity compared to paclitaxel, this is consistent with the previously reported SAR studies of paclitaxel in which the hydroxy and acetyl groups at 7- and 10-positions respectively might be removed without significant loss of activity.[16] Biological tests of **3** and **4** for tubulin-assembly assay and used as phosphatase-activated prodrugs for cytotoxicity assay in vivo are in progress.

Table 1. Biological cytotoxicity of 7-deoxypaclitaxel analogues **3**, **4** and **34**

Compound	Cytotoxicity against tumor cell (ED_{50}/ED_{50})[a–c]		
	MCF-7 (breast)	SK-OV3 (ovarian)	WIDR (colon)
3	0.41	0.53	0.30
4	5.42	6.47	4.86
34	0.93	0.95	0.89
paclitaxel **1**	1.00	1.00	1.00

[a] ED_{50} is the concentration which produces 50% inhibition of proliferation after 72 h of incubation.
[b] Ratio of ED_{50} relative to paclitaxel is 1.00.
[c] MCF-7: human breast cancer; SK-OV3: human ovarian cancer; WIDR: human colon cancer.

Experimental

All commercially available reagents were used without further purification. All anhydrous reactions were performed in the oven-dried glassware under nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone, and dichloromethane was refluxed and distilled from CaH_2 under nitrogen. Chromatography was carried out on a Merck silica gel 60 (230–400 mesh). Preparative TLC was performed on Merck silica gel 60 F_{254} plates (0.85 mm thickness). ^1H NMR, ^{13}C NMR and 2D NMR were performed on Varian Unity INOVA 500 and 600 spectrometers in $CDCl_3$ except notes using TMS as an internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). Optical rotation was recorded by a Horiba SEPA-300 polarimeter. HRMS(EI) and HRMS(FAB) were measured by a JEOL JMS-700 spectrometer.

2,9,10-Trideacetyl-5-*O*-cinnamoyltaxicin-I (6). To a solution of 2,9,10-triacetyl-5-*O*-cinnamoyltaxicin-I **5** (1.5 g, 2.78 mmol) in CH_2Cl_2–CH_3OH (120 ml, v/v 1:1) was added a solution of $NaOCH_3$ (0.18 g, 3.33 mmol) in CH_3OH (2 ml). The reaction mixture was stirred at 0°C under nitrogen for 24 h (the reaction was monitored by TLC), subsequently acidified with glacial acetic acid and concentrated. Water (25 ml) was added to the above residue. This resulting solution was extracted with CH_2Cl_2 (150 ml) and the organic layer was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (ethyl acetate:hexane=1:1 v/v) to give 1.18 g (86%) of **6** as a white solid which proved to be identical to the previously described compound.[21b]

9:10 Cyclic carbonate-2,9,10-trideacetyl-5-*O*-cinnamoyltaxicin-I (7). To an ice-cooled solution of **6** (50 mg, 0.1 mmol) in CH_2Cl_2 (3 ml) containing Et_3N (0.12 ml, 0.4 mmol) was added triphosgene (60 mg, 0.2 mmol). The reaction mixture was stirred for 4 h at rt under nitrogen. The saturated aqueous $NaHCO_3$ (5 ml) was added and the resulting solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate:hexane=1:1 v/v) to give 47 mg (90%) of **7** as a white solid. mp: 234–235°C, ^1H NMR (500 MHz) δ: 7.72 (m, 2H), 7.66 (d, 1H, *J*=16.0 Hz), 7.45 (m, 3H), 6.28 (d, 1H, *J*=16.0 Hz), 5.65 (d, 1H, *J*=11.5 Hz), 55.5 (s, 1H), 5.45 (s, 1H), 5.36 (t, 1H, *J*=3.0 Hz), 5.02 (d, 1H, *J*=11.5 Hz), 4.04 (t, 1H, *J*=7.0 Hz), 3.07 (d, 1H, *J*=7.0 Hz), 2.75 (d, 1H, *J*=20.0 Hz), 2.70 (d, 1H, *J*=20.0 Hz), 2.60 (d, 1H, *J*=7.0 Hz, OH), 2.19 (s, 3H), 2.07 (m, 1H), 1.83 (dddd, 1H, *J*=14.5, 11.5, 5.0, 3.0 Hz), 1.71 (m, H), 1.59 (m, 1H), 1.58 (s, 3H), 1.42 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (125 MHz) δ: 198.4 (s), 166.0 (s), 153.4 (s), 149.6 (s), 146.4 (d), 142.9 (s), 141.7 (s), 134.1 (s), 130.7 (d), 129.0 (d), 128.4 (d), 118.5 (d), 116.9 (t), 84.9 (d), 79.1 (s), 78.7 (d), 77.6

(d), 71.6 (d), 45.6 (d), 44.0 (t), 42.4 (s), 41.1 (s), 34.4 (q), 28.6 (t), 27.0 (t), 20.6 (q), 17.1 (q), 14.3 (q). HRMS (EI) Calcd for $C_{30}H_{34}O_8$ (M^+) 522.2252, found 522.2247.

1:2, 9:10 Cyclic carbonate-2,9,10-trideacetyl-5-*O*-cinnamoyltaxicin-I (8). *Pathway A* (from **7**): To an ice-cooled solution of **7** (26 mg, 0.05 mmol) in CH_2Cl_2-pyridine (v/v 2:1, 1.5 ml) was added triphosgene (30 mg, 0.1 mmol). The reaction mixture was stirred for 30 min at 0°C under nitrogen, and saturated aqueous $NaHCO_3$ (1 ml) was added and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate:hexane=1:1 v/v) to give 25 mg (91%) of **8** as a white solid. *Pathway B* (from **6**): To an ice-cooled solution of **6** (50 mg, 0.1 mmol) in CH_2Cl_2-pyridine (v/v 2:1, 3 ml) was added triphosgene (148 mg, 0.5 mmol). The reaction mixture was stirred for 30 min at 0°C under nitrogen, and saturated aqueous $NaHCO_3$ (3 ml) was added and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel to give 47.5 mg (86%) of **8**. mp: 253–255°C, ^{1}H NMR (600 MHz) δ:7.69 (m, 2H), 7.66 (d, 1H, J=16.0 Hz), 7.45 (m, 3H), 6.19 (d, 1H, J=16.0 Hz), 5.62 (d, 1H, J=11.5 Hz), 5.56 (d, 1H, J=1.5 Hz), 5.46 (s, 1H), 5.40 (t, 1H, J=3.0 Hz), 4.85 (d, 1H, J=11.5 Hz), 4.83 (d, 1H, J=6.0 Hz), 3.11 (brd, 1H), 3.02 (d, 1H, J=19.5 Hz), 2.97 (d, 1H, J=19.5 Hz), 2.24 (s, 3H), 2.08 (m, 1H), 1.86 (dddd, 1H, J=13.5, 11.5, 5.0, 3.0 Hz), 1.76 (ddd, 1H, J=13.5, 5.0, 2.0 Hz), 1.65 (s, 3H), 1.54 (dd, 1H, J=13.5, 5.0 Hz), 1.48 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (125 MHz) δ: 195.0 (s), 165.6 (s), 154.4 (s), 152.6 (s), 151.7 (s), 146.6 (d), 146.1 (s), 137.7 (s), 134.0 (s), 130.7 (d), 129.0 (d), 128.4 (d), 119.3 (t), 116.6 (d), 89.1 (s), 85.1 (d), 79.0 (d), 78.5 (d), 76.7 (d), 42.3 (d), 42.2 (t), 40.9 (s), 40.8 (s), 33.0 (q), 27.3 (t), 26.4 (t), 20.0 (q), 16.9 (q), 15.1 (q). HRMS (EI) Calcd for $C_{31}H_{32}O_9$ (M^+) 548.2044, found 548.2031.

1:2, 9:10 Cyclic carbonate-2,9,10-trideacetyl-4,20,2′,3′-tetrahydro-4α,20,2′,3′-tetrahydroxy-5-*O*-cinnamoyltaxicin-I (9). To a solution of **8** (45 mg, 0.082 mmol) in THF–H_2O (v/v 2:1, 3 ml) was added *N*-methylmorpholine *N*-oxide (15 mg, 0.113 mmol) and a solution of OsO_4 (2.5% in *t*-BuOH, 0.14 ml). After stirring for 20 h at rt, florisil (20 mg), water (0.7 ml) and $Na_2O_4S_2$ (6 mg) were added. The resulting mixture was stirred for an additional 10 min and filtered. The filtrate was treated with saturated aqueous NH_4Cl (5 ml) and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 43 mg (85%) of **9** as a colorless oil which was allowed to be used for next step without further purification. ^{1}H NMR (500 MHz) δ: 7.42–7.27 (m, 5H), 5.57 (d, 1H, J=11.5 Hz), 5.27 (t, 1H, J=3.0 Hz), 5.05 (d, 1H, J=3.0 Hz), 4.78 (d, 1H, J=11.5 Hz), 4.74 (d, 1H, J=4.8 Hz), 4.39 (d, 1H, J=3.0 Hz), 4.05 (d, 1H, J=10.8 Hz), 3.91 (brs, 1H, OH*), 3.85 (d, 1H, J=19.2 Hz), 3.56 (d, 1H, J=10.8 Hz), 3.11 (brs, 1H, OH*), 2.88 (d, 1H, J=19.2 Hz), 2.78 (d, 1H, J=4.8 Hz), 2.73 and 2.69 (brs, 2H, 2OH*), 2.17 (s, 3H), 1.99 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.63 (s, 3H), 1.54 (m, 1H), 1.46 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (125 MHz) δ: 196.8 (s), 173.1 (s), 154.3 (s), 152.7 (s), 150.1 (s), 139.8 (s), 136.7 (s), 128.7 (d), 128.1 (d), 126.4 (d), 89.1 (s), 84.2 (d), 82.3 (s), 79.8 (d), 78.7 (d), 77.2 (d), 74.5 (d), 74.2 (d), 62.4 (t), 44.2 (s), 43.7 (d), 41.6 (t), 40.1 (s), 32.5 (q), 27.2 (t), 26.7 (t), 20.4 (q), 17.9 (q), 14.5 (q). (*exchangeable by D_2O).

Hydrolysis of 9 to 10, 11 and 12

A solution of **9** (40 mg) and KOAc (0.3 g, about 10%) in CH_3OH (3 ml) was refluxed for 30 min and water (1 ml) was added. The reaction mixture was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed by preparative TLC (ethyl acetate: hexane=2:1 v/v) to give 10 mg (83%) of **10** as a white solid, 11 mg (36%) of **11** and 14 mg (45%) of **12**.

Methyl (2*S*, 3*R*)-(−)-2,3-dihydroxy-3-phenylpropionate (10). mp: 85–87°C, $[\alpha]_D^{22}$=−10.5° (c=0.7, $CHCl_3$), $[\alpha]_D^{21}$=−10° (c=1.0, $CHCl_3$) in Aldrich Products Catalogue. ^{1}H NMR (500 MHz) δ: 7.39–7.26 (m, 5H), 5.04 (d, 1H, J=3.0 Hz), 4.39 (d, 1H, J=3.0 Hz), 3.83 (s, 3H), 3.11 (brs, 1H, OH), 2.74 (brs, 1H, OH). ^{13}C NMR (125 MHz) δ: 173.1 (s), 139.8 (s), 128.5 (d), 128.1 (d), 126.1 (d), 74.6 (d), 74.3 (d), 52.9 (d).

1:2, 9:10 Cyclic carbonate-2,9,10-trideacetyl-4,20-dihydro-4α,20-dihydroxytaxicin-I (11). A colorless oil. $[\alpha]_D^{23}$=+178° (c=0.3, $CHCl_3$). ^{1}H NMR (600 MHz) δ: 5.53 (d, 1H, J=11.4 Hz), 4.79 (d, 1H, J=11.4 Hz), 4.71 (d, 1H, J=4.8 Hz), 4.03 (d, 1H, J=10.8 Hz), 3.95 (d, 1H, J=19.2 Hz), 3.94 (brs, 1H, OH*), 3.69 (t, 1H, J=3.0 Hz), 3.54 (d, 1H, J=10.8 Hz), 2.86 (d, 1H, J=19.2 Hz), 2.71 and 2.63 (brs, 2H, 2OH*), 2.60 (d, 1H, J=4.8 Hz), 2.14 (s, 3H), 1.96 (ddd, 1H, J=14.4, 6.0, 3.0 Hz), 1.72 (m, 1H), 1.65 (m, 1H), 1.61 (s, 3H), 1.52 (m, 1H), 1.45 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (150 MHz) δ: 196.4 (s), 152.6 (s), 151.2 (s), 147.8 (s), 145.0 (s), 89.2 (s), 84.7 (d), 83.9 (s), 79.9 (d), 78.4 (d), 70.4 (d), 62.0 (t), 41.4 (s), 40.8 (d), 39.7 (t), 32.8 (s), 29.7 (q), 23.4 (t), 23.0 (t), 20.3 (q), 18.5 (q), 14.8 (q). HRMS (FAB) Calcd for $C_{22}H_{29}O_{10}$ (MH^+) 453.1759, found 453.1754. (*exchangeable by D_2O).

1:2 Cyclic carbonate-2,9,10-trideacetyl-10-*O*-methoxycarbonate-4,20-dihydro-4α,20-dihydroxytaxicin-I (12). A colorless oil. $[\alpha]_D^{23}$=+225° (c=0.4, $CHCl_3$). ^{1}H NMR (600 MHz) δ: 5.73 (d, 1H, J=9.6 Hz), 4.69 (d, 1H, J=4.8 Hz), 4.04 (d, 1H, J=10.5 Hz), 4.03 (dd, 1H, J=9.6, 3.4 Hz), 3.99 (d, 1H, J=19.2 Hz), 3.92 (brs, 1H, OH*), 3.83 (s, 3H), 3.63 (t, 1H, J=3.0 Hz), 3.54 (d, 1H, J=10.5 Hz), 3.09 (s, 1H, OH*), 2.90 (d, 1H, J=4.8 Hz), 2.81 (d, 1H, J=19.2 Hz), 2.68 (d, 1H, J=3.4 Hz, OH*), 2.58 (brs, 1H, OH*), 2.22 (s, 3H), 1.90 (m, 1H), 1.72 (m, 1H), 1.65 (m, 1H), 1.54 (s, 3H), 1.50 (dd, 1H, J=13.8, 4.2 Hz), 1.33 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (150 MHz) δ: 197.8 (s), 156.6 (s), 154.8 (s), 148.8 (s), 143.4 (s), 89.1 (s), 82.9 (s), 80.3 (d), 79.6 (d), 75.7 (d), 70.7 (d), 62.5 (t), 55.4 (q), 43.7 (s), 41.6 (d), 41.4 (t), 41.0 (s), 32.3 (q), 23.7 (t), 23.2 (t), 20.3 (q), 19.2 (q), 13.9 (q). HRMS (FAB) Calcd for $C_{23}H_{32}O_{11}Na$ $(M+Na)^+$ 507.1840, found 507.1829. (*exchangeable by D_2O).

Hydrolysis of 8 to 14, 15 and 16

To a solution of **8** (28 mg, 0.051 mmol) in CH_3OH (1 ml) was added a solution of K_2CO_3 (69 mg, 0.5 mmol) in CH_3OH (1 ml). The reaction mixture was stirred for 12 h at 0°C and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed by preparative TLC (ethyl acetate:hexane=1:1 v/v) to give 12 mg (40%) of **14**, 3 mg (10%) of **15**, and 6 mg (23%) of **16** as white amorphous solids.

1:2 Cyclic carbonate-2,9,10-trideacetyl-10-*O*-methoxycarbonate-5-*O*-cinnamoyltaxicin-I (14). ^{1}H NMR (600 MHz) δ: 7.74 (m, 2H), 7.66 (d, 1H, *J*=16.0 Hz), 7.45 (m, 3H), 6.31 (d, 1H, *J*=16.0 Hz), 5.75 (d, 1H, *J*=9.0 Hz), 5.53 (d, 1H, *J*=1.2 Hz), 5.37 (s, 1H), 5.36 (t, 1H, *J*=3.0 Hz), 4.81 (d, 1H, *J*=5.4 Hz), 4.16 (dd, 1H, *J*=9.0, 3.6 Hz), 3.84 (s, 3H), 3.36 (brd, 1H), 2.96 (high, s, 2H), 2.69 (d, 1H, *J*=3.6 Hz, OH), 2.32 (s, 3H), 2.02 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.57 (s, 3H), 1.48 (dd, 1H, *J*=13.8, 4.8 Hz), 1.35 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (125 MHz) δ: 196.4 (s), 166.0 (s), 154.9 (s), 152.5 (s), 150.4 (s), 146.0 (d), 142.1 (s), 139.8 (s), 134.2 (s), 130.4 (d), 128.9 (d), 128.4 (d), 118.3 (t), 117.3 (d), 88.7 (s), 79.8 (d), 79.4 (d), 77.4 (d), 76.0 (d), 55.4 (q), 44.9 (s), 43.1 (d), 41.1 (t), 40.9 (s), 32.5 (q), 27.7 (t), 25.9 (t), 20.2 (q), 17.7 (q), 14.4 (q). HRMS (FAB) Calcd for $C_{32}H_{37}O_{10}$ (MH^+) 581.2384, found 581.2376.

1:2 Cyclic carbonate-2,9,10-trideacetyl-9-*O*-methoxycarbonate-5-*O*-cinnamoyltaxicin-I (15). ^{1}H NMR (600 MHz) δ: 7.73 (m, 2H), 7.65 (d, 1H, *J*=16.0 Hz), 7.42 (m, 3H), 6.30 (d, 1H, *J*=16.0 Hz), 5.56 (d, 1H, *J*=1.2 Hz), 5.39 (s, 1H), 5.38 (d, 1H, *J*=9.0 Hz), 5.34 (t, 1H, *J*=3.0 Hz), 5.13 (dd, 1H, *J*=9.0, 4.2 Hz), 4.92 (d, 1H, *J*=6.0 Hz), 3.88 (s, 3H), 3.37 (brd, 1H), 2.98 (d, 1H, *J*=19.2 Hz), 2.95 (d, 1H, *J*=19.2 Hz), 2.49 (d, 1H, *J*=4.2 Hz, OH), 2.15 (s, 3H), 2.02 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.76 (s, 3H), 1.46 (dd, 1H, *J*=13.8, 4.8 Hz), 1.43 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (125 MHz) δ: 196.7 (s), 165.9 (s), 156.1 (s), 153.7 (s), 152.4 (s), 146.1 (d), 139.7 (s), 139.4 (s), 134.3 (s), 130.5 (d), 129.0 (d), 128.4 (d), 118.8 (t), 117.2 (d), 88.9 (s), 83.2 (d), 79.2 (d), 77.2 (d), 71.6 (d), 55.6 (q), 44.7 (s), 43.2 (d), 41.2 (t), 41.0 (s), 32.9 (q), 27.4 (t), 26.9 (t), 19.9 (q), 17.3 (q), 14.5 (q). HRMS (FAB) Calcd for $C_{32}H_{37}O_{10}$ (MH^+) 581.2384, found 581.2380.

1:2 Cyclic carbonate-2,9,10-trideacetyl-5-*O*-cinnamoyltaxicin-I (16). ^{1}H NMR (600 MHz) δ: 7.73 (m, 2H), 7.65 (d, 1H, *J*=16.0 Hz), 7.44 (m, 3H), 6.32 (d, 1H, *J*=16.0 Hz), 5.52 (d, 1H, *J*=1.2 Hz), 5.35 (s, 1H), 5.34 (t, 1H, *J*=3.0 Hz), 4.93 (d, 1H, *J*=9.0 Hz), 4.85 (d, 1H, *J*=5.4 Hz), 4.02 (d, 1H, *J*=9.0 Hz), 3.36 (brd, 1H), 2.95 (high s, 2H), 2.94 (s, 1H, OH*), 2.92 (s, 1H, OH*), 2.15 (s, 3H), 2.00 (m, 1H), 1.88 (m, 1H), 1.79 (dddd, 1H, *J*=13.8, 11.4, 4.8, 3.0 Hz), 1.65 (s, 3H), 1.44 (dd, 1H, *J*=13.8, 4.8 Hz), 1.41 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz) δ: 196.9 (s), 166.0 (s), 154.9 (s), 152.8 (s), 145.9 (d), 140.0 (s), 139.6 (s), 134.3 (s), 130.5 (d), 128.9 (d), 128.4 (d), 118.1 (t), 117.4 (d), 89.1 (s), 79.3 (d), 78.2 (d), 77.5 (d), 73.3 (d), 44.5 (s), 43.1 (d), 41.2 (t), 41.1 (s), 32.8 (q), 27.7 (t), 26.0 (t), 20.2 (q), 17.7 (q), 14.2 (q). HRMS (FAB) Calcd for $C_{30}H_{35}O_8$ (MH^+) 523.2330, found 523.2326. (*exchangeable by D_2O).

5-Hydroxytriacetyltaxicin-I (17). To a solution of 5-cinnamoyltriacetyltaxicin-I (2.5 g, 4.0 mmol) and hydroxylamine hydrochloride (2.5 g, 36 mmol) in EtOH (250 ml), NaOAc (5.0 g, 61 mmol) in H_2O (250 ml) was added and the reaction mixture was heated at 80°C for 24 h. The reaction mixture was cooled to rt, diluted with H_2O, and extracted with $CHCl_3$. The combined organic phase was dried over $MgSO_4$. After removal of the solvent, the resulting product was purified by column on silica gel (ethyl acetate: hexane=1:1 v/v) to give 1.42 g (70%) of **17** which proved to be identical to the previously described compound.[30]

5-*O*-Triethylsilyltriacetyltaxicin-I (18). To a solution of **17** (1.23 g, 2.5 mmol) in pyridine (5 ml) at 0°C was added chlorotriethylsilane (4.2 ml, 25 mmol). The reaction mixture was stirred for 40 min at rt, and saturated aqueous $NaHCO_3$ was added at 0°C. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $CuSO_4$, water, brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel (ethyl acetate:hexane=1:2 v/v) to give 1.23 g (81%) of **18** as a white amorphous solid. ^{1}H NMR (500 MHz) δ: 6.16 (d, 1H, *J*=10.5 Hz), 5.89 (d, 1H, *J*=10.5 Hz), 5.62 (d, 1H, *J*=6.5 Hz), 5.21 (s, 1H), 4.78 (s, 1H), 4.20 (t, 1H, *J*=3.0 Hz), 3.68 (d, 1H, *J*=6.5 Hz), 2.84 (d, 1H, *J*=19.8 Hz), 2.62 (d, 1H, *J*=19.8 Hz), 2.24 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.84 (m, 1H), 1.76 (m, 1H), 1.69 (s, 3H), 1.65–1.58 (m, 2H), 1.23 (s, 3H), 0.93 (s, 3H), 0.90 (m, 9H), 0.50–0.65 (m, 6H). HRMS (FAB) Calcd for $C_{32}H_{50}O_9SiNa$ $(M+Na)^+$ 629.3119, found 629.3117.

2,9,10-Detriacetyl-5-*O*-triethylsilyltaxicin-I (19). Following the procedure for preparation of **6**, using **18** (1.212 g, 2.0 mmol) gave 778 mg (81%) of **19** as white amorphous solid after chromatography on silica gel (ethyl acetate: hexane=2:1 v/v). ^{1}H NMR (500 MHz) δ: 5.19 (s, 1H), 4.93 (d, 1H, *J*=9.0 Hz), 4.77 (s, 1H), 4.18 (t, 1H, *J*=3.0 Hz), 4.16 (d, 1H, *J*=9.0 Hz), 4.05 (d, 1H, *J*=6.5 Hz), 3.52 (s, 1H, OH*), 3.36 (d, 1H, *J*=6.5 Hz), 2.69 (high, s, 2H), 2.47 (brs, 2H, 2OH*), 2.18 (s, 3H), 2.00–1.95 (m, 2H), 1.80–1.73 (m, 2H), 1.62 (s, 3H), 1.37 (s, 3H), 1.17 (s, 3H), 0.89–0.92 (m, 9H), 0.53–0.70 (m, 6H). (*exchangeable by D_2O).

1:2, 9:10 Cyclic carbonate-2,9,10-trideacetyl-5-*O*-triethylsilyltaxicin-I (20). Following the procedure for preparation of **8**, using **19** (720 mg, 1.5 mmol), triphosgene (2.22 g, 7.5 mmol) in CH_2Cl_2–pyridine (v/v 2:1) gave 702 mg (88%) of **20** as white amorphous solid after chromatography on silica gel (ethyl acetate:hexane=1:1 v/v). ^{1}H NMR (600 MHz) δ: 5.60 (d, 1H, *J*=11.0 Hz), 5.24 (s, 1H), 4.87 (d, 1H, *J*=11.0 Hz), 4.80 (s, 1H), 4.83 (d, 1H, *J*=6.0 Hz), 4.16 (t, 1H, *J*=3.0 Hz), 3.07 (d, 1H, *J*=6.0 Hz), 3.00 (d, 1H, *J*=19.5 Hz), 2.96 (d, 1H, *J*=19.5 Hz), 2.19 (s, 3H), 2.02 (m, 1H), 1.87 (dddd, 1H, *J*=13.6, 11.5, 5.0, 3.0 Hz), 1.75 (ddd, 1H, *J*=13.6, 5.0, 2.4 Hz), 1.66 (s, 3H), 1.56 (dd, 1H, *J*=13.6, 5.0 Hz), 1.49 (s, 3H), 1.21 (s, 3H), 0.89–0.91 (m, 9H), 0.50–0.70 (m, 6H).

^{13}C NMR (125 MHz) δ: 196.5 (s), 154.7 (s), 152.8 (s), 150.2 (s), 145.8 (s), 139.6 (s), 116.7 (t), 89.0 (s), 84.9 (d), 79.1 (d), 78.3 (d), 74.5 (d), 43.7 (d), 42.7 (t), 42.5 (s), 38.9 (s), 32.4 (q), 27.4 (t), 26.5 (t), 20.1 (q), 17.2 (q), 14.7 (q), 6.9 (q) and 4.7 (t). HRMS (FAB) Calcd for $C_{28}H_{40}O_8SiNa$ $(M+Na)^+$ 555.2388, found 555.2381.

1:2, 9:10 Cyclic carbonate-2,9,10-trideacetyl-5-hydroxy-taxicin-I (13). To a solution of **20** (532 mg, 1.0 mmol) in THF (5 ml) was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 2 ml). The reaction mixture was stirred for 1 h at rt. EtOAc (50 ml) was added and the organic layers were washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silica gel (ethyl acetate:hexane=1:1 v/v) to give 418 mg of **13** in quantitative yield as a white amorphous solid. $[\alpha]_D^{23}=+236^\circ$ (c=0.05, $CHCl_3$). ^{1}H NMR (500 MHz) δ: 5.61 (d, 1H, J=11.4 Hz), 5.17 (s, 1H), 4.89 (d, 1H, J=11.4 Hz), 4.84 (d, 1H, J=5.5 Hz), 4.65 (s, 1H), 4.09 (brt, 1H), 3.35 (d, 1H, J=5.5 Hz), 2.98 (d, 1H, J=19.5 Hz), 2.94 (d, 1H, J=19.5 Hz), 2.18 (s, 3H), 1.94 (m, 1H), 1.75 (m, 1H), 1.66 (m, 1H), 1.64 (s, 3H), 1.55 (m, 1H), 1.47 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (125 MHz) δ: 196.8 (s), 154.4 (s), 152.6 (s), 149.6 (s), 146.8 (s), 140.2 (s), 116.4 (t), 89.1 (s), 84.6 (d), 78.9 (d), 78.4 (d), 76.5 (d), 43.2 (s), 42.8 (d), 42.6 (t), 39.4 (s), 33.2 (q), 27.9 (t), 26.3 (t), 19.8 (q), 17.0 (q), 14.5 (q). HRMS (FAB) Calcd for $C_{22}H_{27}O_8$ (MH^+) 419.1704, found 419.1699.

Osmylation of 13 to 11

Following the procedure for preparation of **9**, using **13** (397 mg, 0.95 mmol), NMO (174 mg, 1.3 mmol), OsO_4 (2.5% in *t*-BuOH, 1.62 ml), florisil (231 mg), water (1.5 ml), and $Na_2O_4S_2$ (70 mg) gave 356 mg (83%) of **11** after chromatography on silica gel (ethyl acetate: hexane=2:1 v/v) which proved to be identical to the previously described compound.

Silylation and mesylation of 11 to 22 via 21

1:2, 9:10 Cyclic carbonate-2,9,10-trideacety1-4,20-dihydro-4α,20-dihydroxy-20-*O*-tertbutyldimethylsilyltaxicin-I (21). A solution of imidazole (735 mg, 10.8 mmol) and *tert*-butyldimethylsilyl chloride (678 mg, 4.5 mmol) in dry DMF (5 ml) was stirred for 15 min at rt. The triol **11** (339 mg, 0.75 mmol) was subsequently added and stirred for an additional 3 h. The reaction mixture was diluted with a solution of 10% citric acid in water (30 ml) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate:hexane=1:2 v/v) to give 403 mg (95%) of **21** as a colorless oil. ^{1}H NMR (500 MHz) δ: 5.51 (d, 1H, J=11.4 Hz), 4.81 (d, 1H, J=11.4 Hz), 4.68 (d, 1H, J=4.8 Hz), 4.17 (d, 1H, J=10.5 Hz), 3.92 (d, 1H, J=19.2 Hz), 3.64 (t, 1H, J=3.0 Hz), 3.58 (s, 1H, OH), 3.56 (d, 1H, J=10.5 Hz), 2.87 (d, 1H, J=19.2 Hz), 2.71 (s, 1H, OH), 2.62 (d, 1H, J=4.8 Hz), 2.15 (s, 3H), 1.95 (m, 1H), 1.74 (m, 1H), 1.65 (m, 1H), 1.60 (s, 3H), 1.54 (m, 1H), 1.43 (s, 3H), 1.12 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

1:2, 9:10 Cyclic carbonate-2,9,10-trideacetyl-4,20-dihydro-4α,20-dihydroxy-5-*O*-mesyl-20-*O*-tertbutyldimethylsilyltaxicin-I (22). To a solution of the above silylated compound **21** (402 mg, 0.71 mmol) in pyridine (5 ml) at 0°C was added MsCl (0.36 ml). The reaction mixture was stirred for 20 h at rt, and CH_2Cl_2 (50 ml) was added. The resulting solution was washed with a solution of 10% citric acid in water (25 ml), saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (ethyl acetate:hexane=1:2 v/v) to give 361 mg (83%) of **22** as a white solid. mp: 87–89°C. ^{1}H NMR (500 MHz) δ: 5.56 (d, 1H, J=11.5 Hz), 4.86 (brs, 1H), 4.79 (d, 1H, J=11.5 Hz), 4.70 (d, 1H, J=5.0 Hz), 4.15 (d, 1H, J=10.5 Hz), 3.77 (d, 1H, J=19.2 Hz), 3.54 (d, 1H, J=10.5 Hz), 3.42 (s, 1H, OH), 2.97 (s, 3H), 2.82 (d, 1H, J=19.2 Hz), 2.66 (d, 1H, J=5.0 Hz), 2.13 (s, 3H), 1.99 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.66 (s, 3H), 1.57 (m, 1H), 1.44 (s, 3H), 1.13 (s, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz) δ: 197.4 (s), 154.3 (s), 152.6 (s), 151.5 (s), 140.7 (s), 88.7 (s), 84.2 (d), 80.5 (s), 79.8 (d), 79.2 (d), 75.4 (d), 64.1 (t), 44.5 (s), 43.4 (d), 42.1 (t), 40.4 (s), 39.0 (q), 33.9 (q), 27.0 (t), 26.4 (t), 25.7 (q), 25.7 (q), 25.6 (q), 20.2 (q), 18.7 (q), 18.6 (s), 14.3 (q), −3.1 (q), −3.2 (q). HRMS (FAB) Calcd for $C_{29}H_{44}O_{12}SiNa$ $(M+Na)^+$ 635.2497, found 635.2493.

1:2, 9:10 Cyclic carbonate-2,4,9,10,13-pentadeacetyl-7-deacetoxy-13-oxo baccatine IV (23). To a solution of **22** (337 mg, 0.55 mmol) in THF (5 ml) was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 2 ml). The reaction mixture was stirred for 1 h at rt. EtOAc (50 ml) was added and the organic layers were washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in butanone (8 ml) and tetrabutylammonium acetate (1.46 g, 4.86 mmol) was added. The mixture was refluxed for 20 h and diluted with EtOAc (35 ml). The resulting solution was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate:hexane=1:2 v/v) to give 181 mg (76%) of **23** as a white amorphous solid. $[\alpha]_D^{25}=+191^\circ$ (c=0.1, $CHCl_3$). ^{1}H NMR (600 MHz) δ: 5.54 (d, 1H, J=11.4 Hz), 4.82 (dd, 1H, J=9.4, 2.5 Hz), 4.80 (d, 1H, J=11.4 Hz), 4.74 (d, 1H, J=4.8 Hz), 4.57 (dd, 1H, J=8.4, 1.2 Hz), 4.32 (d, 1H, J=8.4 Hz), 3.01 (d, 1H, J=19.0 Hz), 2.75 (d, 1H, J=19.0 Hz), 2.57 (dd, 1H, J=4.8, 1.2 Hz), 2.53 (s, 1H, OH-4), 2.07 (m, 1H), 1.94 (s, 3H), 1.90 (dddd, 1H, J=13.8, 11.5, 5.0, 2.5 Hz), 1.78 (m, 1H), 1.67 (s, 3H), 1.58 (dd, J=13.8, 5.0 Hz), 1.38 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (125 MHz) δ: 198.6 (s), 154.7 (s), 153.2 (s), 151.8 (s), 141.7 (s), 87.8 (s), 86.4 (d), 83.8 (d), 80.6 (t), 79.8 (d), 79.2 (d), 75.7 (s), 45.6 (d), 44.2 (s), 42.7 (t), 39.2 (s), 32.4 (q), 27.2 (t), 26.5 (t), 19.9 (q), 17.3 (q), 14.2 (q). HRMS (EI) Calcd for $C_{22}H_{26}O_9$ (M^+) 434.1575, found 434.1566.

1:2, 9:10 Cyclic carbonate-2,9,10,13-tetradeacetyl-7-deacetoxy-13-oxo baccatine IV (24). A solution of **23** (175 mg, 0.4 mmol) and 4-(dimethylamino)pyridine (DMAP, 729 mg, 6.0 mmol) in CH_2Cl_2 (5 ml) was treated with acetic anhydride (0.3 ml, 3.2 mmol), and stirred at rt for 5 h. The reaction mixture was diluted with EtOAc

(30 ml), washed with 1N aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate:hexane=1:3 v/v) to give 177 mg (93%) of **24** as a white amorphous solid. $[\alpha]_D^{25}=+203°$ (c=0.4, $CHCl_3$). ^1H NMR (500 MHz) δ: 5.51 (d, 1H, J=11.4 Hz), 4.94 (dd, 1H, J=9.4, 2.5 Hz), 4.81 (d, 1H, J=11.4 Hz), 4.72 (d, 1H, J=5.0 Hz), 4.34 (brd, 1H), 4.21 (d, 1H, J=8.4 Hz), 2.76 (d, 1H, J=19.2 Hz), 2.68 (d, 1H, J=19.2 Hz), 2.54 (brd, 1H), 2.29 (m, 1H), 2.25 (s, 3H), 1.96 (s, 3H), 1.95 (dddd, 1H, J=13.8, 11.5, 5.2, 2.5 Hz), 1.79 (ddd, 1H, J=13.8, 11.5, 5.2 Hz), 1.68 (s, 3H), 1.56 (dd, J=13.8, 5.2 Hz), 1.39 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (125 MHz) δ: 196.9 (s), 170.5 (s), 154.4 (s), 152.9 (s), 151.2 (s), 140.6 (s), 88.6 (s), 86.6 (d), 83.5 (d), 81.2 (s), 79.6 (d), 78.9 (d), 76.8 (t), 42.9 (s), 42.7 (t), 41.7 (d), 39.5 (s), 33.4 (q), 27.4 (t), 26.6 (t), 22.8 (q), 20.1 (q), 16.8 (q), 14.5 (q). HRMS (FAB) Calcd for $C_{24}H_{29}O_{10}$ (MH^+) 477.1759, found 477.1752.

Preparation of 25 and 26 from 24

A solution of **24** (167 mg, 0.35 mmol) in THF (10 ml) at −78°C under nitrogen was treated with PhLi (1.8 M in cyclohexane–ether, v/v 7:3, 1.94 ml, 3.5 mmol) and stirred at −78°C for 20 min. The reaction was quenched with saturated aqueous NH_4Cl (1.5 ml), and the resulting mixture was allowed to warm to rt. After dilution with EtOAc, the organic was separated, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed twice by preparative TLC (ethyl acetate:hexane=1:1 v/v) to give 142 mg (64%) of **25** and 33 mg (15%) of **26** as white solids.

9-Hydroxy-2,10-dibenzoyl-2,9,10,13-tetradeacetyl-7-deacetoxy-13-oxo baccatine IV (25). mp: 144–146°C. $[\alpha]_D^{25}=+127°$ (c=0.2, $CHCl_3$). ^1H NMR (500 MHz) δ: 8.12 (d, 2H, J=7.6 Hz), 8.10 (d, 2H, J=7.6 Hz), 7.60 (t, 1H, J=7.6 Hz), 7.59 (t, 1H, J=7.6 Hz), 7.49 (m, 2H), 7.47 (m, 2H), 6.45 (d, 1H, J=9.4 Hz), 5.62 (d, 1H, J=7.0 Hz), 4.97 (d, 1H, J=9.2 Hz), 4.33 (d, 1H, J=8.3 Hz), 4.21 (d, 1H, J=8.3 Hz), 4.19 (dd, 1H, J=9.4, 3.4 Hz), 3.85 (d, 1H, J=7.0 Hz), 2.78 (d, 1H, J=19.5 Hz), 2.67 (d, 1H, J=19.5 Hz), 2.65 (d, 1H, J=3.4, OH Hz), 2.28 (m, 1H), 2.25 (s, 3H), 2.18 (s, 3H), 1.96 (ddd, 1H, J=13.6, 11.5, 5.2 Hz), 1.78 (ddd, 1H, J=13.6, 11.5, 5.2 Hz), 1.69 (s, 3H), 1.57 (dd, 1H, J=13.6, 5.2 Hz), 1.39 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (125 MHz) δ: 197.2 (s), 170.5 (s), 168.7 (s), 166.8 (s), 151.6 (s), 140.5 (s), 133.9 (d), 133.7 (d), 130.2 (d), 129.9 (d), 129.1 (s), 129.0 (s), 128.7 (d), 128.7 (d), 86.5 (d), 81.7 (s), 81.4 (s), 77.5 (d), 76.7 (t), 76.1 (d), 75.0 (d), 43.0 (s), 41.8 (d), 41.3 (t), 40.1 (s), 33.2 (q), 27.5 (t), 26.8 (t), 22.6 (q), 20.6 (q), 17.2 (q), 14.3 (q). HRMS (FAB) Calcd for $C_{36}H_{41}O_{10}$ (MH^+) 633.2697, found 633.2689.

10-Hydroxy-2,9-dibenzoyl-2,9,10,13-tetradeacetyl-7-deacetoxy-13-oxo baccatine IV (26). mp: 137–139°C. $[\alpha]_D^{25}=+97°$ (c=0.08, $CHCl_3$). ^1H NMR (500 MHz) δ: 8.10 (m, 4H), 7.60 (m, 2H), 7.49–7.47 (m, 4H), 6.37 (d, 1H, J=9.1 Hz), 5.63 (d, 1H, J=6.8 Hz), 5.12 (dd, 1H, J=9.1, 4.0 Hz), 4.99 (d, 1H, J=9.2 Hz), 4.34 (d, 1H, J= 8.4 Hz), 4.23 (d, 1H, J=8.4 Hz), 3.78 (d, 1H, J=6.8 Hz), 2.98 (d, 1H, J=19.5 Hz), 2.89 (d, 1H, J=19.5 Hz), 2.50 (d, 1H, J=4.0 Hz, OH), 2.27 (m, 1H), 2.23 (s, 3H), 2.17 (s, 3H), 1.98 (ddd, 1H, J=13.6, 11.5, 5.2 Hz), 1.84 (ddd, 1H, J=13.6, 11.5, 5.2 Hz), 1.67 (s, 3H), 1.61 (dd, 1H, J=13.6, 5.2 Hz), 1.39 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (125 MHz) δ: 196.9 (s), 170.5 (s), 169.2 (s), 166.3 (s), 150.7 (s), 139.6 (s), 133.9 (d), 133.6 (d), 130.1 (d), 130.1 (d), 129.2 (s), 129.0 (s), 128.8 (d), 128.7 (d), 86.7 (d), 81.6 (s), 81.1 (s), 79.8 (d), 76.9 (t), 75.3 (d), 71.4 (d), 44.5 (s), 41.9 (d), 41.2 (t), 40.2 (s), 31.4 (q), 27.3 (t), 26.7 (t), 22.8 (q), 20.4 (q), 17.5 (q), 14.4 (q). HRMS (FAB) Calcd for $C_{36}H_{41}O_{10}$ (MH^+) 633.2697, found 633.2691.

Coupling of 25 with cAMP-Cl 27 to 28

A solution of cAMP-Cl **27** (51 mg, 0.152 mmol), 4-(dimethylamino)pyridine (DMAP, 83 mg, 0.456 mmol), and **25** (48 mg, 0.076 mmol) in DMF (3 ml) was stirred for 6 h at rt. A solution of saturated aqueous $NaHCO_3$ was added, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed by preparative TLC (methanol: chloroform=1:1 v/v) to give 60 mg (84%) of **28** as a white solid. mp: 296–298° (dec.). $[\alpha]_D^{25}=+7.8°$ (c=0.7, CH_3OH). ^1H NMR (500 MHz, CD_3OD+D_2O) δ: 8.21 (s, 1H), 8.14 (s, 1H), 8.13 (d, 2H, J=7.6 Hz), 8.09 (d, 2H, J=7.5 Hz), 7.61 (t, 1H, J=7.5 Hz), 7.59 (t, 1H, J= 7.6 Hz), 7.49 (m, 2H), 7.47 (m, 2H), 6.54 (d, 1H, J= 9.8 Hz), 6.11 (d, 1H, J=9.8 Hz), 6.09 (d, 1H, J=0.9 Hz), 5.62 (d, 1H, J=6.5 Hz), 4.95 (d, 1H, J=9.0 Hz), 4.75 (dd, 1H, J=8.9, 5.2 Hz), 4.71 (dd, 1H, J=5.2, 0.9 Hz), 4.60 (dd, 1H, J=9.7, 4.8 Hz), 4.39 (dd, 1H, J=10.7, 9.7 Hz), 4.37 (ddd, 1H, J=10.7, 8.9, 4.8 Hz), 4.34 (d, 1H, J=8.1 Hz), 4.17 (d, 1H, J=8.1 Hz), 3.76 (d, 1H, J=6.5 Hz), 2.89 (d, 1H, J=19.4 Hz), 2.70 (d, 1H, J=19.4 Hz), 2.24 (s, 3H), 2.23 (m, 1H), 2.15 (s, 3H), 1.98 (m, 1H), 1.83 (ddd, 1H, J=13.8, 11.5, 5.2 Hz), 1.72 (s, 3H), 1.59 (m, 1H), 1.51 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (125 MHz) δ: 197.4 (s), 170.4 (s), 167.8 (s), 167.2 (s), 156.2 (s), 153.8 (d), 150.3 (s), 149.1 (s), 140.8 (d), 140.3 (s), 133.6 (d), 133.4 (d), 130.2 (d), 130.0 (d), 129.2 (s), 129.1 (s), 128.7 (d), 128.6 (d), 119.5 (s), 92.7 (d), 86.3 (d), 82.1 (s), 81.4 (s), 78.6 (d), 78.5 (d), 77.5 (d), 77.0 (t), 75.1 (d), 73.5 (d), 72.9 (d), 68.5 (t), 44.2 (s), 41.9 (d), 41.7 (t), 40.1 (s), 33.2 (q), 27.6 (t), 26.9 (t), 22.7 (q), 19.8 (q), 17.4 (q), 14.3 (q). HRMS (FAB) Calcd for $C_{46}H_{50}O_{15}N_5PNa$ $(M+Na)^+$ 966.2935, found 966.2927.

Silylation of 28 to 29

A solution of imidazole (62 mg, 0.9 mmol), chlorotriethylsilane (0.1 ml, 0.6 mmol), and DMAP (11 mg, 0.06 mmol) in dry DMF (2.5 ml) was stirred for 10 min at rt. The compound **28** (57 mg, 0.06 mmol) was subsequently added and stirred for an additional 4 h. The reaction mixture was neutralized (about pH=6–7) with a solution of 10% citric acid in water and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by chromatographed by preparative TLC (methanol:chloroform=1:1 v/v) to give 56 mg (89%) of **29** as a white solid. mp: >300°C (dec.). $[\alpha]_D^{25}=+15.3°$ (c=0.08, CH_3OH). ^1H NMR (500 MHz, CD_3OD+D_2O) δ: 8.20 (s, 1H), 8.14 (s, 1H), 8.13 (d, 2H,

J=7.6 Hz), 8.09 (d, 2H, J=7.6 Hz), 7.60–7.59 (m, 2H), 7.49 (m, 2H), 7.47 (m, 2H), 6.54 (d, 1H, J=9.8 Hz), 6.10 (d, 1H, J=0.9 Hz), 6.09 (d, 1H, J=9.8 Hz), 5.63 (d, 1H, J=6.6 Hz), 4.96 (d, 1H, J=9.0 Hz), 4.77 (dd, 1H, J=9.0, 5.2 Hz), 4.73 (dd, 1H, J=5.2, 0.9 Hz), 4.60 (dd, 1H, J=9.7, 4.8 Hz), 4.39 (dd, 1H, J=10.5, 9.7 Hz), 4.37 (ddd, 1H, J=10.5, 9.0, 4.8 Hz), 4.34 (d, 1H, J=8.1 Hz), 4.18 (d, 1H, J=8.1 Hz), 3.74 (d, 1H, J=6.6 Hz), 2.88 (d, 1H, J=19.4 Hz), 2.69 (d, 1H, J=19.4 Hz), 2.24 (s, 3H), 2.23 (m, 1H), 2.16 (s, 3H), 1.98 (ddd, 1H, J=13.8, 11.5, 5.1 Hz), 1.82 (ddd, 1H, J=13.8, 11.5, 5.1 Hz), 1.71 (s, 3H), 1.59 (dd, 1H, J=13.8, 5.1 Hz), 1.50 (s, 3H), 1.39 (s, 3H), 0.89–0.92 (m, 9H), 0.53–0.72 (m, 6H). ^{13}C NMR (125 MHz) δ: 197.5 (s), 170.3 (s), 167.7 (s), 167.4 (s), 156.3 (s), 153.9 (d), 151.1 (s), 148.9 (s), 140.9 (d), 139.8 (s), 133.7 (d), 133.5 (d), 130.0 (d), 129.9 (d), 129.0 (s), 128.9 (s), 128.7 (d), 128.6 (d), 119.7 (s), 93.2 (d), 88.5 (s), 86.2 (d), 82.5 (s), 78.7 (d), 78.5 (d), 77.6 (d), 76.8 (t), 74.9 (d), 74.8 (d), 73.2 (d), 68.5 (t), 43.9 (s), 42.3 (d), 41.7 (t), 40.5 (s), 32.8 (q), 27.4 (t), 27.0 (t), 22.6 (q), 20.1 (q), 17.6 (q), 14.5 (q), 6.9 (q), 4.6 (t). HRMS (FAB) Calcd for $C_{52}H_{64}O_{15}N_5PSiNa$ $(M+Na)^+$ 1080.3799, found 1080.3786.

Reduction of 29 to 30

A solution of **29** (53 mg, 0.05 mmol) in CH_3OH (5 ml) was treated with an excess of $NaBH_4$ (15 mg, 0.4 mmol) for 3 h at rt. The reaction was quenched with aqueous NH_4Cl (2 ml), and the resulting mixture was stirred for 15 min. After dilution with water, the reaction mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by preparative TLC (methanol:chloroform=1:1 v/v) to give 41 mg (77%) of **30** as a white solid. mp: 276–79°C. $[\alpha]_D^{25}=-27°$ (c=0.2, CH_3OH). ^{1}H NMR (600 MHz, CD_3OD+D_2O) δ: 8.20 (s, 1H), 8.14 (s, 1H), 8.12 (d, 2H, J=7.6 Hz), 8.09 (d, 2H, J=7.6 Hz), 7.61 (t, 1H, J=7.6 Hz), 7.59 (t, 1H, J=7.6 Hz), 7.49 (m, 2H), 7.47 (m, 2H), 6.51 (d, 1H, J=9.8 Hz), 6.10 (d, 1H, J=0.9 Hz), 6.08 (d, 1H, J=9.8 Hz), 5.62 (d, 1H, J=5.5 Hz), 4.94 (d, 1H, J=9.0 Hz), 4.77 (dd, 1H, J=9.0, 5.2 Hz), 4.72 (dd, 1H, J=5.2, 0.9 Hz), 4.61 (dd, 1H, J=9.7, 4.8 Hz), 4.39 (dd, 1H, J=10.5, 9.7 Hz), 4.37 (ddd, 1H, J=10.5, 9.0, 4.8 Hz), 4.31 (d, 1H, J=8.2 Hz), 4.15 (d, 1H, J=8.2 Hz), 3.83 (m, 1H), 3.73 (d, J=5.5 Hz), 2.32 (dd, 1H, J=15.2, 9.0 Hz), 2.29 (m, 1H), 2.24 (s, 3H), 2.17 (s, 3H), 2.13 (dd, 1H, J=15.2, 8.0 Hz), 2.01 (m, 1H), 1.82 (m, 1H), 1.63 (s, 3H), 1.57 (dd, 1H, J=13.8, 5.2 Hz), 1.44 (s, 3H), 1.09 (s, 3H), 0.88–0.91 (m, 9H), 0.56–0.75 (m, 6H). ^{13}C NMR (125 MHz) δ: 170.4 (s), 168.4 (s), 167.6 (s), 156.3 (s), 154.0 (d), 140.8 (d), 140.7 (s), 135.6 (s), 133.6 (d), 133.4 (d), 130.1 (d), 129.8 (d), 129.1 (s), 128.9 (s), 128.7 (d), 128.6 (d), 119.6 (s), 93.3 (d), 85.9 (d), 82.4 (s), 78.7 (s), 78.6 (d), 78.4 (d), 77.1 (d), 76.8 (t), 74.8 (d), 74.6 (d), 73.2 (d), 69.8 (d), 68.7 (t), 44.2 (s), 42.3 (s), 42.1 (d), 37.2 (t), 29.3 (q), 27.5 (t), 26.6 (t), 22.6 (q), 20.6 (q), 17.4 (q), 15.8 (q), 6.8 (q), 4.7 (t). HRMS (FAB) Calcd for $C_{52}H_{66}O_{15}$-N_5PSiNa $(M+Na)^+$ 1082.3956, found 1082.3949.

Coupling of 30 with the side chain acid 31 leads to compound 3

To a solution of carboxylic acid **31** (85 mg, 0.21 mmol), **30** (37 mg, 0.035 mmol) and DMAP (10 mg, 0.071 mmol) in toluene (2 ml) was added DCC (43 mg, 0.21 mmol) at rt. The reaction mixture was stirred at 75°C for 1.5 h by slow evaporation of the solvent. The residue was chromatographed by preparative TLC to give the protected compound which was further treated with trifluoroacetic acid (1.0 ml) and water (0.1 ml) at rt. The reaction mixture first was stirred at 0°C for 20 min and then at rt for an additional 20 min. EtOAc and saturated aqueous $NaHCO_3$ were added at 0°C, and separated. The organic layer was washed with water, brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by preparative TLC (1% NH_4OH in methanol:chloroform=3.2 v/v) to give 31 mg (74%) of **3** as a white solid. mp: >300°C (dec.). $[\alpha]_D^{25}=-45°$ (c=0.03, CH_3OH). ^{1}H NMR (600 MHz, CD_3OD+D_2O) δ: 8.22 (s, 1H), 8.15 (dd, 2H, J=8.4, 1.3 Hz), 8.14 (s, 1H), 8.13 (d, 2H, J=7.6 Hz), 7.83 (dd, 2H, J=8.4, 1.2 Hz), 7.62 (m, 1H), 7.60 (t, 1H, J=7.6 Hz), 7.55 (m, 1H), 7.51 (m, 2H), 7.48 (m, 2H), 7.47–7.44 (m, 4H), 7.35 (m, 2H), 7.27 (m, 1H), 6.53 (d, 1H, J=9.8 Hz), 6.13 (t, 1H, J=8.5 Hz), 9.11 (d, 1H, J=1.0 Hz), 6.09 (d, 1H, J=9.8 Hz), 5.72 (d, 1H, J=5.7 Hz), 5.62 (d, 1H, J=3.0 Hz), 4.95 (d, 1H, J=8.7 Hz), 4.76 (dd, 1H, J=9.0, 5.3 Hz), 4.71 (dd, 1H, J=5.3, 1.0 Hz), 4.59 (dd, 1H, J=9.6, 5.0 Hz), 4.55 (d, 1H, J=3.0 Hz), 4.40 (dd, 1H, J=10.5, 9.6 Hz), 4.37 (ddd, 1H, J=10.5, 9.0, 5.0 Hz), 4.34 (d, 1H, J=8.5 Hz), 4.17 (d, 1H, J=8.5 Hz), 3.04 (d, 1H, J=5.7 Hz), 2.36 (dd, 1H, J=15.1, 8.5 Hz), 2.25 (s, 3H), 2.18 (m, 1H), 2.16 (dd, 1H, J=15.1, 8.5 Hz), 1.94 (m, 1H), 1.86 (s, 3H), 1.82 (m, 1H), 1.64 (s, 3H), 1.58 (dd, 1H, J=14.5, 4.8 Hz), 1.31 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (150 MHz) δ: 172.6 (s), 170.4 (s), 167.6 (s), 167.1 (s), 166.9 (s), 156.4 (s), 153.9 (d), 149.3 (s), 142.4 (s), 141.1 (d), 138.3 (s), 133.8 (s), 133.7 (d), 133.6 (s), 133.6 (d), 131.9 (d), 130.1 (d), 130.0 (d), 129.1 (s), 129.1 (s), 129.0 (d), 128.7 (d), 128.7 (d), 128.6 (d), 128.3 (d), 127.1 (d), 127.0 (d), 119.6 (s), 92.8 (d), 86.0 (d), 82.4 (s), 79.2 (s), 78.6 (d), 78.4 (d), 76.7 (d), 76.6 (t), 74.9 (d), 73.7 (d), 73.2 (d), 73.1 (d), 72.5 (d), 68.9 (t), 55.8 (d), 43.8 (s), 43.1 (s), 42.0 (d), 35.8 (t), 27.3 (t), 27.0 (q), 26.8 (t), 22.5 (q), 21.7 (q), 17.6 (q), 14.8 (q). HRMS (FAB) Calcd for $C_{62}H_{65}O_{17}N_6PNa$ $(M+Na)^+$ 1219.4037, found 1219.4029.

Oxidation of 25 to 32

To a solution of **25** (63 mg, 0.1 mmol) in CH_2Cl_2 (3.0 mL) was added 4-methylmorpholine *N*-oxide (34 mg, 0.3 mmol), molecular sieves 4A (activated 24 mg) and tetrapropylammonium perruthenate (10 mg, 0.03 mmol) at 0°C. The reaction mixture was stirred at rt for 3 h and diluted with EtOAc at 0°C. After filtration of the resulting mixture through a short pad of silica gel and evaporation of the solvent, the residue was chromatographed by preparative TLC (ethyl acetate-hexane 1:1 v/v) to give 44 mg (70%) of **32** as a white solid. mp: 166–168°C. $[\alpha]_D^{25}=-8°$ (c=0.12, CH_3OH). ^{1}H NMR (500 MHz) δ: 8.09 (m, 4H), 7.64 (t, 1H, J=7.2 Hz), 7.59 (t, 1H, J=7.2 Hz), 7.48–7.47 (m, 4H), 6.72 (s, 1H), 5.68 (d, 1H, J=7.0 Hz), 4.93 (dd, 1H, J=9.4, 2.3 Hz), 4.35 (d, 1H, J=8.5 Hz), 4.17 (d, 1H, J=8.5 Hz), 3.89 (d, 1H, J=7.0 Hz), 3.01 (d, 1H, J=19.8 Hz), 2.66 (d, 1H, J=19.8 Hz), 2.25 (s, 3H), 2.17 (s, 3H), 2.12 (m, 1H), 1.96 (m, 1H), 1.82 (m, 1H), 1.74 (s, 3H), 1.64 (m, 1H), 1.22 (s, 3H), 1.17 (s, 3H). ^{13}C NMR

(125 MHz) δ: 204.5 (s), 197.8 (s), 170.3 (s), 167.6 (s), 167.2 (s), 152.8 (s), 140.4 (s), 134.1 (d), 133.7 (d), 130.2 (d), 129.9 (d), 129.1 (s), 128.9 (s), 128.3 (d), 128.0 (d), 84.6 (d), 81.4 (s), 79.6 (s), 77.8 (d), 76.7 (t), 74.8 (d), 53.7 (s), 44.8 (t), 43.2 (s), 42.7 (d), 34.5 (t), 32.7 (q), 27.1 (t), 22.1 (q), 18.9 (q), 14.7 (q), 13.8 (q). HRMS (FAB) Calcd for $C_{36}H_{39}O_{10}$ (MH^+) 631.5408, found 631.5406.

Reduction of 32 to 33

Following the procedure for preparation of **30**, using **32** (41 mg, 0.065 mmol) gave 31 mg (74%) of **33** as a white amorphous solid after chromatography by preparative TLC (ethyl acetate-hexane 3:2 v/v). $[\alpha]_D^{25}=-39°$ (c=0.05, CH_3OH). ^1H NMR (500 MHz) δ: 8.12 (d, 2H, J=7.8 Hz), 8.10 (d, 2H, J=7.8 Hz), 7.60 (t, 1H, J=7.8 Hz), 7.59 (t, 1H, J=7.8 Hz), 7.48–7.47 (m, 4H), 6.64 (s, 1H), 5.62 (d, 1H, J=7.0 Hz), 4.96 (dd, 1H, J=9.4, 2.3 Hz), 4.87 (m, 1H), 4.32 (d, 1H, J=8.5 Hz), 4.15 (d, 1H, J=8.5 Hz), 3.84 (d, 1H, J=7.0 Hz), 2.57 (brs, 1H, OH-13), 2.36–2.35 (m, 2H), 2.26 (s, 3H), 2.18 (dd, 1H, J=15.3, 7.6 Hz), 2.07 (d, 3H, J=1.1 Hz), 1.95 (dddd, 1H, J=14.0, 11.6, 5.5, 2.3 Hz), 1.88 (ddd, 1H, J=14.0, 11.6, 5.5 Hz), 1.74 (s, 3H), 1.58 (dd, 1H, J=14.0, 5.5 Hz), 1.15 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (125 MHz) δ: 206.8 (s), 170.4 (s), 168.2 (s), 167.5 (s), 145.7 (s), 133.9 (d), 133.7 (d), 131.9 (s), 130.1 (d), 130.0 (d), 129.2 (s), 129.1 (s), 128.5 (d), 128.3 (d), 85.2 (d), 81.2 (s), 80.1 (s), 78.1 (d), 76.8 (t), 74.9 (d), 68.7 (d), 53.3 (s), 43.1 (d), 41.8 (s), 38.9 (t), 34.7 (t), 27.2 (q), 26.8 (t), 22.4 (q), 20.5 (q), 15.2 (q), 14.6 (q). HRMS (FAB) Calcd for $C_{36}H_{41}O_{10}$ (MH^+) 633.2697, found 633.2693.

Coupling of 33 with the side chain acid 31 leads to 34

Following the procedure for preparation of **3**, using **33** (30 mg, 0.047 mmol), carboxylic acid **31** (114 mg, 0.282 mmol), DMAP (13 mg, 0.094 mmol), DCC (58 mg, 0.282 mmol), and TFA (1.0 ml containing 0.1 ml of H_2O) gave 32.4 mg (78%) of **34** as a white solid after chromatography by preparative TLC (ethyl acetate-hexane 3:1 v/v). mp: 196–198°C. $[\alpha]_D^{25}=-62°$ (c=0.03, CH_3OH). ^1H NMR (500 MHz) δ: 8.16 (dd, 2H, J=8.3, 1.3 Hz), 8.12 (d, 2H, J=7.6 Hz), 7.71 (dd, 2H, J=8.4, 1.2 Hz), 7.63 (t, 1H, J=7.2 Hz), 7.59 (t, 1H, J=7.6 Hz), 7.51–7.50 (m, 3H), 7.48–7.44 (m, 6H), 7.31 (m, 2H), 7.29 (m, 1H), 6.93 (d, 1H, J=9.0 Hz, NH), 6.72 (s, 1H), 6.25 (dd, 1H, J=9.2, 8.8 Hz), 5.98 (dd, 1H, J=9.0, 2.6 Hz), 5.67 (d, 1H, J=7.2 Hz), 4.96 (dd, 1H, J=9.5, 2.3 Hz), 4.59 (dd, 1H, J=4.0, 2.6 Hz), 4.33 (d, 1H, J=8.4 Hz), 4.19 (d, 1H, J=8.4 Hz), 3.75 (d, 1H, J=7.2 Hz), 3.56 (d, 1H, J=4.0 Hz, OH-2′), 2.38 (dd, 1H, J=15.5, 9.2 Hz), 2.35 (m, 1H), 2.26 (dd, 1H, J=15.5, 8.8 Hz), 2.25 (s, 3H), 2.03 (s, 3H), 1.93–1.89 (m, 2H), 1.72 (s, 3H), 1.57 (dd, 1H, J=14.0, 5.6 Hz), 1.23 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (125 MHz) δ: 206.8 (s), 172.4 (s), 170.5 (s), 167.8 (s), 167.5 (s), 167.1 (s), 145.2 (s), 138.5 (s), 133.7 (d), 133.6 (s), 133.4 (d), 132.3 (s), 132.1 (d), 130.1 (d), 129.9 (d), 129.1 (s), 128.9 (d), 128.8 (d), 128.7 (d), 128.6 (d), 128.4 (d), 128.4 (d), 127.0 (d), 126.9 (d), 84.9 (d), 80.2 (s), 79.8 (s), 78.4 (d), 76.8 (t), 74.9 (d), 73.7 (d), 72.6 (d), 55.6 (d), 53.6 (s), 43.7 (d), 42.0 (s), 39.2 (t), 34.2 (t), 27.4 (q), 26.9 (t), 22.2 (q), 21.0 (q), 15.6 (q), 14.8 (q). HRMS (FAB) Calcd for $C_{52}H_{53}O_{12}NNa$ $(M+Na)^+$ 906.3462, found 906.3453.

Esterification of 34 with cAMP-Cl 27 leads to compound 4

Following the procedure for preparation of **28**, using cAMP-Cl **27** (20 mg, 0.06 mmol), 4-(dimethylamino)pyridine (DMAP, 33 mg, 0.18 mmol), and **34** (27 mg, 0.03 mmol) gave 28 mg (78%) of **4** as a white solid. mp: >300°C (dec.). $[\alpha]_D^{25}=-96°$ (c=0.01, CH_3OH). ^1H NMR (600 MHz, CD_3OD) δ: 8.23 (s, 1H), 8.15 (s, 1H), 8.14 (d, 2H, J=7.6 Hz), 8.12 (d, 2H, J=7.6 Hz), 7.74 (dd, 2H, J=8.4, 1.2 Hz), 7.62 (t, 1H, J=7.6 Hz), 7.60 (t, 1H, J=7.6 Hz), 7.50 (m, 3H), 7.48–7.43 (m, 6H), 7.31–7.29 (m, 3H), 6.87 (d, 1H, J=9.0 Hz), 6.69 (s, 1H), 6.27 (t, 1H, J=8.9 Hz), 6.08 (d, 1H, J=1.0 Hz), 6.02 (dd, 1H, J=9.0, 3.0 Hz), 5.66 (d, 1H, J=7.2 Hz), 4.94 (dd, 1H, J=9.4, 2.3 Hz), 4.76 (dd, 1H, J=9.0, 5.3 Hz), 4.70 (dd, 1H, J=5.3, 1.0 Hz), 4.68 (d, 1H, J=3.0 Hz), 4.60 (dd, 1H, J=9.6, 5.0 Hz), 4.39 (dd, 1H, J=10.5, 9.6 Hz), 4.36 (d, 1H, J=8.5 Hz), 4.35 (ddd, 1H, J=10.5, 9.0, 5.0 Hz), 4.15 (d, 1H, J=8.5 Hz), 3.78 (d, 1H, J=7.2 Hz), 2.37 (dd, 1H, J=15.4, 8.9 Hz), 2.36 (m, 1H), 2.26 (s, 3H), 2.23 (dd, 1H, J=15.4, 8.9 Hz), 2.05 (s, 3H), 1.95 (m, 1H), 1.86 (m, 1H), 1.73 (s, 3H), 1.59 (dd, 1H, J=14.1, 5.8 Hz), 1.21 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (150 MHz) δ: 207.2 (s), 172.8 (s), 170.5 (s), 168.2 (s), 167.6 (s), 167.3 (s), 156.3 (s), 154.0 (d), 149.3 (s), 145.9 (s), 140.9 (d), 137.6 (s), 133.7 (d), 133.5 (s), 133.3 (d), 132.7 (s), 132.2 (d), 130.0 (d), 129.9 (d), 129.2 (s), 129.0 (d), 128.9 (d), 128.7 (d), 128.6 (d), 128.5 (d), 128.3 (d), 127.0 (d), 126.7 (d), 119.8 (s), 92.6 (d), 85.1 (d), 81.3 (s), 80.6 (s), 79.8 (d), 78.7 (d), 78.6 (d), 76.8 (t), 74.9 (d), 73.8 (d), 73.2 (d), 73.1 (d), 68.9 (d), 57.2 (d), 53.3 (s), 43.2 (d), 42.3 (s), 39.6 (t), 34.6 (t), 27.5 (q), 26.8 (t), 22.4 (q), 20.8 (q), 15.3 (q), 14.5 (q). HRMS (FAB) Calcd for $C_{62}H_{63}O_{17}N_6PNa$ $(M+Na)^+$ 1217.3881, found 1217.3879.

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