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Synthesis of novel thiol taxoids based on the 7,10-di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III: both the *syn* and *anti* 10-deacetyl-2′-deoxy-2′-mercaptopaclitaxels

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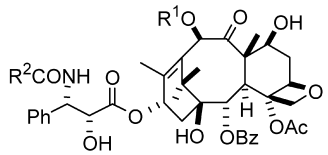
Abstract—Two new kinds of docetaxel compound, with a mercapto group instead of the hydroxyl on the C13 side chain (both *syn* and *anti*), via the 7,10-di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III route, were synthesized. The uses of *trans* and *cis* oxazoline compounds, and their stereoselective ring-opening reactions with thiolacetic acid, were proved to be key steps.

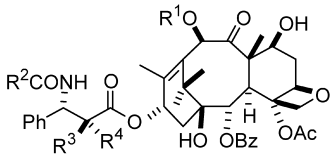
1. Introduction

The complex natural product paclitaxel (Taxol®) **1**, first isolated from *Taxus brevifolia*,[1] is a member of a large family of taxane diterpenoids.[2] Paclitaxel has excellent clinical activity against ovarian and breast cancers, and also shows promising results in the treatment of other cancers.[3] Extensive studies on the structure activity relationship (SAR) have been explored. It is already well known that a free hydroxyl group at the C-2′ position on the C-13 side chain is crucial for microtubule binding[4] and may play as a hydrogen bond donor.[5] In light of this hypothesis, the introduction of thiol functionality, which is more acidic instead of hydroxyl onto the C-13 side chain, would be of great interest for the study about the taxoid binding site on microtubules and for the development of new compounds bearing more desirable properties than paclitaxel. In our previous report,[6] the syntheses of new kinds of thiol surrogates of paclitaxel on the C-13 side chain instead of the C-2′ hydroxyl group **3a/3b** were demonstrated by means of 7-triethylsilyl baccatin III. Here, another kind of 2′ mercapto taxoids is reported, with a free hydroxyl on the C-10 position **4a/4b**, utilizing the 7,10-di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III (7,10-diTroc DAB) **5** approach. As a matter of fact, the 7,10-diTroc DAB proved to be another important synthetic intermediate for the semi-synthesis of many taxoids compounds,[7] as did the 7-TES-baccatin III. One example is the docetaxel **2**, a semisynthetic analog of paclitaxel. Meanwhile, simultaneous modification methods, on different positions in the taxoids structure, recently emerged[4a,8] and have begun to appear as an important tool in the search for new taxoid analogues bearing better physical, chemical and biological properties, especially when parallel[9] and



Paclitaxel **1** R^1= Ac R^2 = Ph

Docetaxel **2** R^1= H R^2 = ^{t}BuO



2′-Deoxy-2′-Mercaptopaclitaxel **3b** R^1= Ac R^2 = Ph R^3 = H, R^4 = SH
2′-Deoxy-2′-*epi*-Mercaptopaclitaxel **3** R^1= Ac R^2 = Ph R^3 = SH, R^4 = H
10-Deacetyl-2′-Deoxy-2′-Mercaptopaclitaxel **4a**
R^1= H R^2 = Ph R^3=H R^4=SH
10-Deacetyl-2′-deoxy-2′-*epi*-Mercaptopaclitaxel **4b**
R^1= H R^2 = Ph R^3=SH R^4=H

Keywords: Taxol; Oxazoline; Mercapto taxoid.
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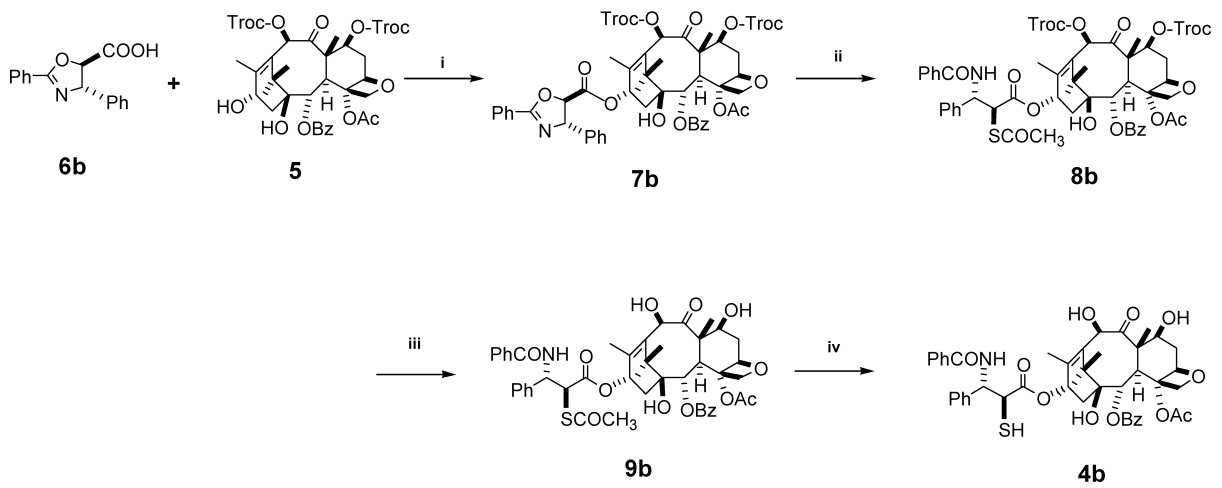


Scheme 1. (i) DCC, 4-Pyrrolidinopyridine, toluene, rt, 2 h, 92%. (ii) Thiolacetic acid, dioxane, 70 °C, 12 h, 72%. (iii) Zn dust, MeOH/HAc (1:1), 60 °C, 2 h, 77%. (iv) LiOH, MeOH/H_2O, rt, 2 h, 68%.

combinatorial synthesis[10] were used for quick and convenient scans. In these cases, the thiol taxoid analogues, bearing two free hydroxyl groups at the 7 and 10 sites, would be interesting precursors for this kind of application, as the different reactivity of the two hydroxy groups are well known.

2. Results and discussion

The methodology applied to the synthesis of **4b** involved in a similar pathway, as described in our previous paper,[6a] with the *trans*-oxazoline carboxylic acids, **6b**, and 7,10-diTroc DAB, **5**,[7f] serving as starting materials, as shown in Scheme 1.

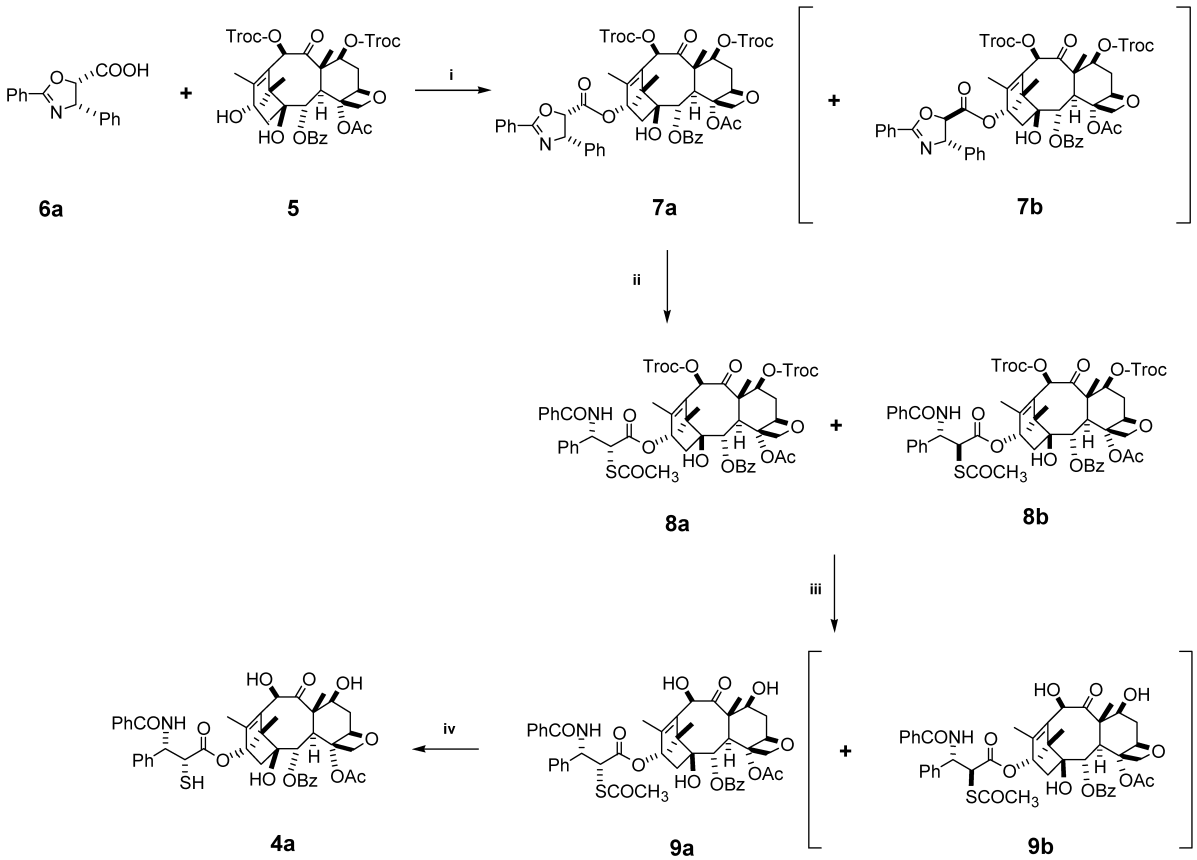
Thus, the excess (3.5 equiv.) *trans*- (4*S*, 5*R*)-2,4-diphenyl-oxazoline-5-carboxylic acid **6b**, which was generated by hydrolysis from the corresponding methyl ester,[11] was coupled with **5** in the presence of DCC and 4-pyrrolidino-pyridine to afford a new kind of oxazoline intermediate **7b**, which was fully characterized with a yield of 92%. First, the HRMS spectrum revealed a characteristic [M+H+4] molecular ion peak, showing the existence of six chlorine atoms. With the aid of 2D NMR experiments, the complete assignments of **7** could be made. First, the $^1H-^{13}C$ HMQC 2D NMR clearly showed the positions of the pairs of H20α,β, H6α,β and H14α,β, and the four alkyl methyl groups, at 1.20, 1.25, 1.85 and 2.02 ppm, respectively. Then, the two doublet peaks, at 4.94 and 5.60 ppm with a coupling constant of 7.0 Hz in ^1H NMR spectrum, were consistent with a *trans* oxazoline structure,[12] and correlated only with each other. As proved previously,[6a] the small amount of *cis* oxazoline ester mixed with the *trans* isomer did not affect the purity of the coupling product. The $^1H-^1H$ COSY 2D NMR revealed two correlated 7-Troc methylene protons, at 4.60 and 4.90 ppm, doublet (J=11.8 Hz) and the two correlated 10-Troc methylene protons, at 4.76 ppm, triplet (J=12.2 Hz). Other protons, such as H2 and H3 at 5.70 and 3.93 ppm, respectively, both doublet, J=7.0 Hz, correlated with each other, H7, at 5.58 ppm, multiplet, and correlated with the H6α and H6β, at 2.62 and 2.06 ppm, respectively and H5, at 4.93 ppm, multiplet, and correlated with the H6α only, were consistent with the desired structure.

A ring-opening reaction, with thiolacetic acid in a dilute 1,4-dioxane solution, was performed at 70 °C for 12 h to give the *anti* C-13 side chain product of **8b**. The disappearance of the two oxazoline ring proton peaks, and the appearance of the amide peak at 8.07 ppm (doublet, J=7.9 Hz), the H3′ at 5.71 ppm (doublet–doublet, J=4.07, 9.26 Hz), the H2′ at 4.82 ppm (doublet, J=4.10 Hz) and the C2′ thioacetyl group at 2.44 ppm, in the ^1H NMR spectrum demonstrated the formation of the *anti* C-13 side chain.

The two Troc groups, at the 7 and 10 positions, were then simultaneously removed by means of the zinc dust method in a mixture of methanol and acetic acid (1:1) at 60 °C to give **9b**.[7e] The ^1H NMR spectrum clearly showed the loss of the two Troc groups. Also, the H10 shifted from 6.07 ppm to, a relatively high field, 5.03 ppm due to the loss of the strong electron-withdrawing neighboring group, as did the H7 proton from 5.43 to 4.12 ppm. The HRMS spectrum further confirmed the removal of Troc groups as shown by a molecular ion peak of 870 ($[M+H]^+$).

Finally, the selective removal of the *S*-acetyl group from the side chain of **9b** was achieved under aqueous basic conditions. However, potassium bicarbonate, which was used in the paclitaxel case, was obviously not enough to completely cleave the *S*-acetyl group this time. Even with the excess amount of base used, there will always be some un-reacted starting material as with the use of potassium carbonate. Maybe the free C10 hydroxyl group accounted for the phenomenon of the increased acidity. Then, an equivalent amount of lithium hydroxide was used to afford **4b**. Surprisingly, no epimerization appeared to happen at the C2′ position, namely, no *syn* amide peak was found at around 7.0 ppm, which always accompanied the main product in the paclitaxel case.

Unlike the straightforward process for the *trans* isomer, with the synthesis of the *cis* oxazoline, **6a**, the problem of epimerization was again encountered, as in the case with 7-TES-baccatin III[6b] (Scheme 2). That is, when 3.5 equiv. of **6a** were coupled to **5**, only 38% of the *cis* oxazoline derivative **7a** was obtained, with more than half undergoing the C-5′ configuration inversion pathway to afford **7b**, with a



Scheme 2. (i) DCC, 4-Pyrrolidinopyridine, toluene, rt, 2 h, **7a** (38%), **7b** (52%). (ii) Thiolacetic acid, dioxane, 70 °C, 12 h, 80 °C, 12 h, 95 °C, 12 h, **8a/8b**, 72%. (iii) Zn dust, MeOH/HAc (1:1), 60 °C, 2 h, **9a** (52.2%), **9b** (18%). (iv) LiOH, MeOH/H_2O, rt, 2 h, 58%.

yield of 52%, which was even worse than in the case employing 7-TES-baccatin III. Maybe this could be attributed to the more bulky Troc groups, which might further compress the space around the C-13 hydroxyl group. From a chemical point of view, the formation of an enol should be the intermediate process of the configuration inversion.[6b] However, the separation of **7a** and **7b** was easier than that of their TES counterparts, as the abundance of the *cis* derivative was clearly lower than that of **7b** on the TLC plate. The two peaks at 5.8 and 5.41 ppm, with a coupling constant of 10.6 Hz in the ^{1}H NMR spectrum of **7a** confirmed the *cis* structure,[12] while **7b** was identical in every respect with the *trans* sample. One of the obvious differences in the ^{1}H NMR spectrum of **7a** was that the H13 occurred at 5.56 ppm, compared to 6.24 ppm with **7b**, which proved by the correlation with the H14α and H14β in the ^{1}H–^{1}H COSY 2D NMR analysis. Another difference was the exchange of the chemical shifts between the protons on the C4 acetyl group (2.04–2.24 ppm) and the two C14 protons (2.25–2.42 to 1.92–2.02 ppm).

The ring-opening reaction with thiol acetic acid inherited the bad configuration inversion behavior of the *cis* oxazoline structure. Even though the temperature applied to the reaction vial was carefully controlled, the product was a mixture with the **8a**:**8b** ratio 3.2:1 (confirmed by ^{1}H NMR), while the amide peak at 6.87 ppm revealed the *syn* side chain. Again, the pressure from the two bulky Troc groups has caused greater instability of **8a** than in the TES counterpart (in which a *cis*/*trans* ratio of 35:1 was received), with another enolation process occurring in the reaction procedure. Therefore, it would be easier for the activated molecular species to carry sufficient energy to overcome the energy barrier to directly undergo the C5′ configuration inversion pathway.[6b] In that case, the temperature used for the 7-TES-baccatin model seemed to be not suitable for the di-Troc conditions. No further optimization of the process has been made in this paper.

The two isomers could be separated after removing of the Troc groups using zinc dust to obtain both **9a** and **9b**, which could be distinguished by the chemical shift features of the amides at 6.84 and 8.17 ppm for **9a** and **9b**, respectively. Removal of the *S*-acetyl group by an equivalent amount of lithium hydroxide in aqueous methanol solution of **9a** afforded **4a**, with the evidence of the disappearance of the doublet peak at 4.8 ppm on the ^{1}H NMR and HRMS. On this occasion, a small amount of **4b** accompanied the **4a**.

3. Conclusions

In conclusion, two new kinds of docetaxel compound with a mercapto group instead of a hydroxyl on the C13 side chain (both *syn* and *anti*), via the 7,10-di-(2,2,2-trichloroethyl-oxycarbonyl)-10-deacetylbaccatin III route, were synthesized. The uses of *trans* and *cis* oxazoline compounds, and their stereoselective ring-opening reactions with thiolacetic acid, were proved to be key steps. This kind of thiol taxoids, bearing two free hydroxyl functional groups,

will be useful in the search for new taxoid analogues, with better physical, chemical and biological properties, using combinatorial or parallel syntheses.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. (4*S*,5*R*) and (4*S*,5*S*) 2,4-diphenyloxazoline-5-carboxylic acids were synthesized by the literature procedure.[11] 7,10-Di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III **5** was prepared by the literature method from 10-deacetylbaccatin III.[7f] Toluene and dioxane were freshly distilled over sodium-benzophenone ketyl. Solvents for re-crystallization were purified by standard methods before use. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM; Merck). Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with a 0.25 mm thickness. Preparative TLC was performed with Merck 60 F_{254} plates with a 1 mm thickness.

Melting points were measured with Büchi 530 melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded using Bruker Avance 500 or 600 spectrometers with TMS as internal standard. Chemical shifts were expressed in ppm and coupling constants (*J*) in Hz. ^{13}C NMR were recorded using Bruker Avance 300 or 600 spectrometers. Infrared spectra were recorded on JASCO FTIR-200 Spectrometer. Mass spectra were obtained using JEOL JMS AX505WA or JMS-600 Mstation spectrometers. Elemental analyses were performed using EA 1110 (CHNS-O) (Thermo Finnigan, Italy). Optical rotations were measured using JASCO 3100 polarimeter.

4.1.1. Compound 7b. A solution of DCC (130 mg, 0.63 mmol) in dry toluene (10 mL) was added to a suspension of 7,10-diTroc-10-deacetylbaccatin III **5** (187 mg, 0.21 mmol), *trans*-carboxylic acid **6b** (168 mg, 0.63 mmol) and catalytic amount of 4-pyrrolidinopyridine in 10 mL of dry toluene at 0 °C under N_2 while stirring. After 10 min at 0 °C, the reaction mixture was stirred for another 2 h at room temperature (the reaction was monitored by TLC, EtOAc/hexane=1:2), then passed through a short silica gel plug (~5 g) and further eluted with 50 mL of EtOAc. The combined eluent was concentrated to dry under reduced pressure. A mixture of EtOAc and hexane (20:20 mL) was added to the residue and the suspension was filtered through a cotton plug. The filtration was concentrated again. Careful purification of the residue by flash chromatography twice (EtOAc/hexane, 1:3) afforded the desired product **7b** (220 mg, 0.19 mmol, 92%) as a white solid. An analytical sample was obtained by re-crystallization (EtOAc/hexane) as white fluffy needles: mp 214–6 °C (dec.); $[\alpha]_D^{10}=-41.1°$ (*c*=0.50, $CHCl_3$); IR (KBr) 3573, 3016, 2958, 1764, 1732, 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.20 (s, 3H), 1.74 (s, 1H), 1.85 (s, 3H), 2.02–2.08 (m, 8H), 2.25–2.29 (m, 1H), 2.38–2.42 (m, 1H), 2.62–2.68 (m, 1H), 3.93 (d, *J*=7.0 Hz, 1H), 4.15 (d, *J*=8.5 Hz, 1H), 4.30 (d, *J*=8.6 Hz, 1H), 4.59 (d, *J*=11.8 Hz, 1H), 4.76 (t, *J*=12.1 Hz, 2H), 4.86 (d, *J*=11.8 Hz, 1H), 4.94 (m, 2H), 5.56 (m, 2H), 5.60 (d, *J*=7.3 Hz, 1H), 5.69 (d, *J*=7.0 Hz,1H), 6.24–6.28 (m, 2H), 7.37–7.65(m, 11H), 8.06 (d, *J*=7.9 Hz, 2H), 8.18 (d, *J*=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 11.00, 14.94, 21.18, 21.84, 26.63, 33.47, 35.87, 43.35, 47.23, 56.46, 71.95, 74.54, 75.11, 76.50, 76.63, 77.38, 77.68, 79.25, 79.30, 80.82, 83.74, 83.94, 94.45, 126.66, 127.05, 128.59, 128.96, 129.07, 129.31, 130.33, 132.50, 132.57, 134.16, 141.04, 142.60, 153.38, 153.48, 164.00, 167.16, 170.24, 170.32, 200.87; HRMS (FAB) *m*/*z*=1144.1240 $[M+H+2]^+$, Calcd for $C_{51}H_{50}Cl_6NO_{16}$(1142.1244. Anal. Calcd for $C_{51}H_{49}Cl_6NO_{16}$: C, 53.51; H, 4.32; N, 1.22; Found: C, 53.59; H, 4.44; N, 1.20.

4.1.2. (2′*S*,3′*S*) 3′-*N*-Benzoylamino-2′-deoxy-2′-thioacetyl-7,10-di-(2,2,2-trichloroethyloxycarbonyl)paclitaxel 8b. Compound **7b** (100 mg, 0.087 mmol), thiolacetic acid (1.0 mL) and dioxane (3.0 mL) were added in an 8 mL pressure vial at room temperature. The vial was then closed tightly with a Teflon disk lid, and was heated at 70 °C for 12 h. After concentration under reduced pressure, the sticky yellowish oil was purified by flash chromatography (EtOAc/hexane, 1:3) to get **8b** (76.8 mg, 0.063 mmol, 72%) as a white solid. An analytical sample was obtained by re-crystallization (EtOAc/hexane) as white crystals: mp 173–5 °C; $[\alpha]_D^{16}=-71.2°$ (*c*=0.506, $CHCl_3$); IR (KBr) 3417, 3019, 2955, 1767, 1738, 1663, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.13 (s, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 1.76 (s, 1H), 1.80 (s, 3H), 2.00–2.04 (m, 1H), 2.12–2.21 (m, 2H), 2.32 (s, 3H), 2.44 (s, 3H), 2.59–2.64 (m, 1H), 3.78 (d, *J*=7.0 Hz, 1H), 4.11 (d, *J*=8.6 Hz, 1H), 4.31 (d, *J*=8.6 Hz, 1H), 4.59 (d, *J*=11.8 Hz, 1H), 4.75 (t, *J*=12.0 Hz, 2H), 4.82 (d, *J*=4.1 Hz, 1H), 4.88 (d, *J*=11.8 Hz, 1H), 4.93 (d, *J*=8.9 Hz, 1H), 5.43–5.46 (dd, *J*=7.2, 10.6 Hz, 1H), 5.62 (d, *J*=7.0 Hz, 1H), 5.71 (dd, *J*=4.1, 9.3 Hz, 1H), 6.07 (m, 2H), 7.36–7.63 (m, 11H), 7.89 (m, 2H), 8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.73, 13.59, 21.03, 21.93, 26.24, 30.40, 33.18, 35.08, 43.06, 50.04, 54.42, 56.09, 71.78, 74.25, 76.21, 76.25, 77.12, 77.38, 78.82, 78.94, 80.46, 83.69, 126.12, 127.12, 128.66, 128.70, 128.77, 128.95, 129.27, 130.15, 131.81, 131.97, 133.89, 137.78, 142.13, 153.00, 153.15, 166.90, 170.09, 171.21, 192.41, 200.62; HRMS (FAB) *m*/*z*=1220.1223 $[M+H+2]^+$, Calcd for $C_{53}H_{54}Cl_6NO_{17}S$=1218.1231. Anal. Calcd for $C_{53}H_{53}Cl_6NO_{17}S$: C, 52.14; H, 4.38; N, 1.15; S, 2.63; Found: C, 52.16; H, 4.46; N, 1.12; S, 2.42.

4.1.3. (2′*S*,3′*S*) 10-Deacetyl-2′-deoxy-2′-*epi*-acetylmercaptopaclitaxel 9b. Zinc dust (100 mg) was added in one portion to a vigorously stirred solution of **8b** (75 mg, 0.0615 mmol) in a mixture of 2 mL MeOH and 2 mL acetic acid at 60 °C under N_2. After 2 h, the reaction mixture was cooled down, then passed through a cotton plug and eluted with EtOAc (20 mL). The eluent was concentrated to dry and the residue was re-dissolved in a mixture of EtOAc and brine (45 mL:15 mL). The organic layer was then dried over anhydrous sodium sulfate. After concentration in vacuo, the crude product was purified by flash chromatography (EtOAc/hexane=1:1) to afford product **9b** (41 mg, 0.047 mmol, 77%) as a white solid: mp 164–6 °C; $[\alpha]_D^{11}=-85.1°$ (*c*=0.77, $CHCl_3$); IR (KBr) 3368, 2941,

2833, 1732, 1646, 1548 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.06 (s, 3H), 1.08 (s, 3H), 1.15 (s, 3H), 1.68 (s, 1H), 1.69 (s, 3H), 1.78–1.85 (m, 1H), 2.08–2.20 (m, 2H), 2.28 (s, 3H), 2.43 (s, 3H), 2.53–2.59 (m, 1H), 3.77 (d, J=7.1 Hz, 1H), 4.11–4.15 (m, 3H), 4.29 (d, J=8.5 Hz, 1H), 4.78 (d, J=4.0 Hz, 1H), 4.92 (d, J=8.2 Hz, 1H), 5.0 (s, 1H), 5.60 (d, J=7.1 Hz, 1H), 5.69 (dd, J=3.9, 9.3 Hz, 1H), 6.05 (t, J=8.6 Hz, 1H), 7.29–7.62 (m, 11H), 7.90 (d, J=7.4 Hz, 2H), 8.06 (d, J=7.5 Hz, 2H), 8.16 (d, J=9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.11, 13.57, 20.87, 22.23, 26.58, 30.67, 35.66, 37.13, 43.23, 46.65, 50.29, 54.80, 57.75, 72.11, 72.29, 74.62, 75.13, 76.77, 79.22, 81.02, 84.40, 126.46, 127.40, 128.75, 128.92, 129.03, 129.41, 129.44, 130.40, 132.21, 134.03, 134.05, 135.92, 138.16, 138.42, 167.23, 167.27, 170.16, 171.45, 192.73, 211.54; HRMS (FAB) m/z=870.3159 $[M+H]^+$, Calcd for $C_{47}H_{52}NO_{13}S$=870.3145.

4.1.4. (2′*S*,3′*S*) 10-Deacetyl-2′-deoxy-2′-*epi*-mercaptopaclitaxel 4b. A solution of $LiOH{\cdot}H_2O$ (1.56 mg, 0.037 mmol) in 0.2 mL water (degassed before used) was added dropwise to a stirred solution of **9b** (32 mg 0.037 mmol) in 2 mL MeOH at room temperature during 30 min under N_2. After addition, the reaction was continued for another 1.5 h. A mixture of $CHCl_3$ and water (15 mL:15 mL) was added. The mixture was acidified by 2 or 3 drops of 1 N HCl to pH 1–2. The aqueous layer was extracted with $CHCl_3$ (3×15 mL) and the combined organic layer was washed with brine (10 mL) and then dried over anhydrous sodium sulfate. After concentration in vacuo, the crude product was purified by preparative TLC ($CHCl_3$/MeOH=20:1) in dark place to afford final product **4b** (20.8 mg, 0.025 mmol, 68%) as a white solid: mp 206–8 °C (dec.); $[\alpha]_D^{13}$=+11.7° (c=0.40, MeOH); IR (KBr) 3465, 2986, 2927, 1726, 1663, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.08 (s, 3H), 1.11 (s, 3H), 1.16 (s, 3H), 1.63 (s, 1H), 1.72 (s, 3H), 1.79–1.84 (m, 1H), 2.00–2.04 (m, 2H), 2.2–2.22 (m, 2H), 2.36 (s, 3H), 2.53–2.59 (m, 2H), 3.80 (d, J=8.3 Hz, 1H), 3.85 (dd, J=4.3, 13.1 Hz, 1H), 4.13–4.15 (m, 3H), 4.30 (d, J=10.1 Hz, 1H), 4.93 (d, J=7.1 Hz, 1H), 5.05 (s, 1H), 5.63 (d, J=8.5 Hz, 1H), 5.77 (dd, J=4.2, 11.3 Hz, 1H), 6.05 (m, 1H), 7.29–7.63 (m, 11H), 7.94 (d, J=8.8 Hz, 2H), 8.06 (d, J=8.8 Hz, 2H), 8.18 (d, J=11.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.17, 14.02, 14.51, 23.08, 23.21, 26.76, 29.63, 30.09, 35.72, 43.34, 45.06, 46.90, 57.99, 71.73, 72.39, 74.85, 75.08, 76.49, 76.98, 79.19, 81.37, 84.43, 126.52, 127.51, 128.88, 129.11, 129.21, 129.48, 129.56, 130.45, 132.45, 167.40, 170.02, 173.32, 211.61; HRMS (FAB) m/z=828.3065 $[M+H]^+$, Calcd for $C_{45}H_{50}NO_{12}S$=828.3196.

4.1.5. Compound 7a. A solution of DCC (464 mg, 2.25 mmol) in dry toluene (20 mL) was added to a suspension of 7,10-diTroc-10-deacetylbaccatin III **5** (570 mg, 0.636 mmol), *cis*-carboxylic acid **6a** (600 mg, 2.25 mmol) and catalytic amount of 4-pyrrolidinopyridine in 30 mL of dry toluene at 0 °C under N_2 while stirring. After 10 min at 0 °C, the reaction mixture was stirred for another 3 h at room temperature (the reaction was monitored by TLC, EtOAc/hexane=1:2), then passed through a short silica gel plug (~5 g) and further eluted with 50 mL of EtOAc. The combined eluent was concentrated to dry under reduced pressure. A 1:1 mixture of EtOAc and hexane (40 mL) was added to the residue and the suspension was filtered through a cotton plug. The filtration was concentrated again. Careful purification of the residue by flash chromatography twice (EtOAc/hexane, 1:3) afforded **7b** (378 mg, 0.33 mmol, 52%) as a white solid (proved by ^{1}H NMR) and **7a** (276 mg, 0.24 mmol, 38%) as a white solid: mp 174–6 °C; $[\alpha]_D^{16}$=−53.4° (c=1.14, $CHCl_3$); IR (KBr) 3526, 3043, 2974, 1759, 1728, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.09 (s, 3H), 1.11 (s, 3H), 1.58 (s, 1H), 1.59 (s, 3H), 1.81 (s, 3H), 1.92 (m, 1H), 2.01 (m, 1H), 2.04 (m, 1H), 2.24 (s, 3H), 2.59–2.64 (m, 1H), 3.75 (d, J=6.9 Hz, 1H), 4.13 (d, J=8.5 Hz, 1H), 4.27 (d, J=8.5 Hz, 1H), 4.60 (d, J=11.8 Hz, 1H), 4.74–4.79 (dd, J=15.1, 11.8 Hz, 2H), 4.90 (d, J=11.8 Hz, 1H), 4.92–4.94 (m, 1H), 5.43 (d, J=10.5 Hz, 1H), 5.48–5.51 (dd, J=10.7, 7.2 Hz, 1H), 5.60 (t, J=8.1 Hz, 1H), 5.61 (d, J=7.0 Hz, 1H), 5.79 (d, J=10.5 Hz, 1H), 6.13 (s, 1H), 7.25–7.65 (m, 11H), 8.04 (d, J=7.3 Hz, 2H), 8.11 (d, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.95, 14.57, 21.23, 22.59, 26.51, 33.48, 36.12, 43.15, 47.07, 56.36, 71.86, 73.97, 74.40, 76.47, 76.60, 77.40, 77.68, 79.10, 79.29, 80.94, 81.62, 83.84, 94.46, 126.76, 128.46, 128.89, 128.95, 129.05, 129.13, 129.30, 130.30, 131.84, 132.53, 134.13, 136.59, 142.50, 153.40, 153.46, 164.78, 167.02, 168.25, 169.90, 200.87; HRMS (FAB) m/z=1144.1240 $[M+H+2]^+$, Calcd for $C_{51}H_{50}Cl_6NO_{16}$=1142.1244. Anal. Calcd for $C_{51}H_{49}Cl_6NO_{16}$: C, 53.51; H, 4.32; N, 1.22; Found: C, 53.93; H, 4.40; N, 1.02.

4.1.6. (2′*R*,3′*S*) 3′-*N*-Benzolamino-2′-deoxy-2′-thiolacetyl-7,10-di-(2,2,2-trichloroethyloxycarbonyl)paclitaxel 8a. Compound **7a** (270 mg, 0.236 mmol), thiolacetic acid (1.3 mL) and dioxane (4.0 mL) were added in an 8 mL pressure vial at room temperature. The vial was then closed tightly with a Teflon disk lid, and was heated stepwise at 70 °C for 12 h, 80 °C 12 h and 95 °C 12 h. After concentration under reduced pressure, the sticky oil was purified by flash chromatography (EtOAc/hexane, 1:3) to get **8a** (207 mg, 0.17 mmol, 72() as a white solid, which mixtured with *trans*- diastereoisomer **8b** (the ratio of *cis*/*trans* is 3.2:1 as shown by ^{1}H NMR): mp 181–3 °C; $[\alpha]_D^{16}$=+6.3° (c=1.77, $CHCl_3$); IR (KBr) 3415, 3010, 2953, 1768, 1732, 1679, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.14 (s, 3H), 1.18 (s, 3H), 1.58 (s, 1H), 1.80 (s, 3H), 1.89 (s, 3H), 2.00–2.06 (m, 1H), 2.13–2.44 (m, 2H), 2.31 (s, 3H), 2.46 (s, 3H), 2.59–2.62 (m, 1H), 3.82 (d, J=6.9 Hz, 1H), 4.12 (m, 1H), 4.28 (d, J=8.5 Hz, 1H), 4.57 (d, J=11.7 Hz, 1H), 4.74 (m, 3H), 4.89 (d, J=11.8 Hz, 1H), 4.93 (d, J=9.3 Hz, 1H), 5.52 (d, J=8.1 Hz, 1H), 5.60 (d, J=7.0 Hz, 1H), 5.72 (m, 1H), 6.05 (m, 1H), 6.20 (s, 1H), 6.87 (d, J=8.7 Hz, 1H), 7.31–8.10 (m, 15H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.68, 14.48, 20.84, 22.25, 26.23, 30.49, 33.13, 34.91, 42.97, 46.80, 49.04, 55.77, 56.10, 70.90, 74.10, 76.07, 77.21, 78.78, 78.87, 80.29, 83.66, 94.15, 126.50, 127.21, 128.63, 129.28, 130.04, 131.94, 132.08, 133.54, 134.84, 139.13, 142.04, 153.05, 166.46, 166.75, 168.40, 169.97, 195.50, 200.56; HRMS (FAB) m/z=1220.1223 $[M+H+2]^+$, Calcd for $C_{53}H_{54}Cl_6NO_{17}S$=1218.1231.

4.1.7. (2′*R*,3′*S*) 10-Deacetyl-2′-deoxy-2′-acetylmercaptopaclitaxel 9a. Zinc dust (250 mg) was added in one portion to a vigorously stirred solution of **8a/8b** (195 mg, 0.16 mmol) in a mixture of 3 mL MeOH and 3 mL acetic

acid at 62 °C under N_2. After 2 h, the reaction mixture was cooled down, then passed through a cotton plug and eluted with EtOAc (20 mL). The eluent was concentrated to dry and the residue was re-dissolved in a mixture of EtOAc and brine (60:15 mL). The organic layer was then dried over anhydrous sodium sulfate. After concentration in vacuo, the crude product was purified by preparative TLC (EtOAc/hexane=1:1) to afford *trans* product **9a** (24 mg, 0.028 mmol, 18%) and *cis*-product **9a** (73 mg, 0.084 mmol, 52.5%) as a white solid: mp 168–70 °C; $[\alpha]_D^{14}$=+9.62° (*c*=0.21, $CHCl_3$); IR (KBr) 3374, 2942, 2832, 1726, 1647, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.07 (s, 3H), 1.13 (s, 3H), 1.54 (br, 2H), 1.72 (s, 3H), 1.79 (s, 3H), 1.88–1.92 (m, 2H), 2.10–2.47 (m, 1H), 2.30 (s, 3H), 2.44 (s, 3H), 2.55 (m, 1H), 3.83 (d, *J*=7.1 Hz, 1H), 4.13 (s, 1H), 4.17 (d, *J*=8.5 Hz, 1H), 4.19 (br, 1H), 4.26 (d, *J*=8.5 Hz, 1H), 4.75 (d, *J*=10.5 Hz, 1H), 4.92 (d, *J*=8.2 Hz, 1H), 5.13 (s, 1H), 5.60 (d, *J*=7.1 Hz, 1H), 5.73 (t, *J*=9.7 Hz, 1H), 6.03 (t, *J*=8.8 Hz, 1H), 6.85 (t *J*=8.7 Hz, 1H), 7.33–7.72 (m, 11H), 7.72 (d, *J*=7.5 Hz, 2H), 8.02 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (DMSO, 150 MHz) δ 9.81, 13.56, 20.81, 22.37, 26.51, 30.20, 42.85, 45.91, 52.56, 70.73, 70.76, 73.57, 74.81, 75.34, 76.87, 80.15, 83.79, 127.45, 127.74, 128.09, 128.35, 128.50, 128.67, 129.47, 130.06, 131.54, 134.15, 135.57, 136.83, 139.27, 165.21, 166.23, 166.31, 169.49, 170.69, 192.56, 209.28; HRMS (FAB) *m*/*z*=870.3150 $[M+H]^+$, Calcd for $C_{47}H_{52}NO_{13}S$=870.3145. Anal. Calcd for $C_{47}H_{51}NO_{13}S$: C, 64.90; H, 5.91; N, 1.61; S, 3.68; Found: C, 64.60; H, 6.40; N, 1.46; S, 3.20.

4.1.8. (2′*R*,3′*S*) 10-Deacetyl-2′-deoxy-2′-mercapto-paclitaxel 4a. A solution of $LiOH{\cdot}H_2O$ (2.69 mg, 0.064 mmol) in 0.2 mL water (degassed before used) was added dropwise to a stirred solution of **9a** (55.6 mg 0.064 mmol) in 2 mL MeOH at room temperature under N_2. After addition, the reaction was continued for another 1.5 h. A mixture of $CHCl_3$ and water (15 mL:15 mL) was added. The mixture was acidified by 2 or 3 drops of 1 N HCl to pH 1–2. The aqueous layer was extracted with $CHCl_3$ (3×15 mL) and the combined organic layer was washed with brine (10 mL) and then dried over anhydrous sodium sulfate. After concentration in vacuum, the crude product was purified by preparative TLC ($CHCl_3$/MeOH=20:1) in dark place to afford final product **4a** (31 mg, 0.037 mmol, 57.8%) as a white solid: mp 198–200 °C; $[\alpha]_D^{12}$=−3.38° (*c*=0.308, MeOH); IR (KBr) 3417, 2947, 2854, 1731, 1633, 1528 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.08 (s, 3H), 1.14 (s, 3H), 1.24–1.31 (m, 2H), 1.52 (s, 3H), 1.70 (s, 1H), 1.73 (s, 3H), 1.82 (m, 1H), 2.04 (m, 1H), 2.21 (m, 1H), 2.27 (d, *J*=5.8 Hz, 1H), 2.56–2.60 (m, 1H), 3.86 (d, *J*=7.0 Hz, 1H), 4.02 (t, *J*=8.6 Hz, 1H), 4.16 (d, *J*=8.5 Hz, 1H), 4.20 (m, 2H), 4.29 (d, *J*=8.5 Hz, 1H), 4.95 (d, *J*=9.4 Hz, 1H), 5.19 (s, 1H), 5.64 (d, *J*=7.0 Hz, 1H), 5.66 (t, *J*=8.0 Hz, 1H), 6.04 (t, *J*=8.6 Hz, 1H), 7.05 (m, 1H), 7.28–7.62 (m, 11H), 7.80 (d, *J*=7.4 Hz, 2H), 8.06 (d, *J*=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.15, 14.71, 20.94, 22.80, 26.68, 29.46, 31.18, 36.00, 37.22, 43.24, 46.66, 47.28, 56.01, 57.82, 71.87, 72.22, 74.67, 75.08, 76.78, 79.21, 81.20, 84.34, 127.30, 127.40, 128.70, 128.93, 129.02, 129.22, 129.47, 130.36, 132.23, 124.02, 134.22, 136.01, 138.74, 138.95, 167.20, 167.41, 170.13, 171.10, 211.68; HRMS (FAB) *m*/*z*=828.3008 $[M+H]^+$, Calcd for $C_{45}H_{50}NO_{12}S$=828.3196.

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