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Synthesis of novel thiol surrogate of Taxol®: 2′-deoxy-2′-mercaptopaclitaxel

Xin Qi,[a,b] Sang-Hyeup Lee,[b] Juyoung Yoon[c,*] and Yoon-Sik Lee[b,*]

[a]*School of Chemical Engineering, Dalian University of Technology, Dalian 116012, People's Republic of China*
[b]*School of Chemical Engineering, Seoul National University, Seoul 151-742, South Korea*
[c]*Department of Chemistry, Ewha Womans University, 11-1 Daehyun-Dong, Seodaemun-Ku, Seoul 120-750, South Korea*

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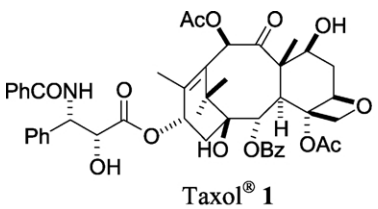
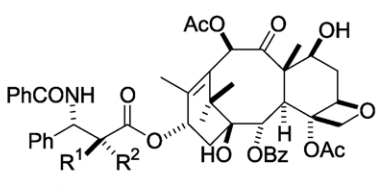
Abstract—Paclitaxel analogues with a thiol group in place of the hydroxyl group on the C-13 side chain constitute an interesting avenue of research for the study of new taxoid compounds. A synthetic route for the preparation of the exact thiol surrogate product of Taxol® by coupling (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid with 7-triethylsilyl baccatin III, followed by ring-opening of the oxazoline intermediate with thiolacetic acid is described.

1. Introduction

The complex natural paclitaxel (Taxol®) **1**, originally isolated from *Taxus brevifolia*, is a powerful therapeutic drug for cancer chemotherapy.[1] Paclitaxel has excellent clinical activity against ovarian and breast cancers, and shows encouraging results for other types of cancers.[2] In contrast to other common anticancer drugs, paclitaxel elicits its biological activity through a unique mechanism, i.e. it inhibits cell replication in the mitotic phase of the cell cycle by promoting tubulin assembly and stabilizing the microtubules formed, which induces cell death.[3] Extensive studies on the structure activity relationship of paclitaxel have been performed for the purpose of elucidating its unique mechanism and designing better analogues, which exert even more effective bioactivity. Although the mechanism of action on the molecular level is still uncertain, it is already well known that the free hydroxyl group at the 2′ position on the C-13 side chain is crucial for microtubule binding[4] and may act as a hydrogen bond donor.[5] In light of this hypothesis, the introduction of thiol functionality, which is more acidic than the hydroxyl group, onto the C-13 side chain **2a** or **2b**, would be of great interest for obtaining information about the taxoid binding site on the microtubules and for the development of new compounds having more desirable properties than paclitaxel. In our earlier report,[6] we demonstrated the first synthetic way of introducing a free thiol functional group onto the C-13 side chain instead of the hydroxyl group, via an oxazoline ring opening procedure with thiolacetic acid. However, only the 2′-epi-mercaptopaclitaxel **2b** had been obtained since the inversion of the configuration at the C-5 position (5*R* to 2′*S*) of the *trans*-oxazoline ring during the ring-opening process. Herein, we report the synthesis of the exact thiol surrogate product of Taxol® by coupling (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid with 7-triethylsilyl baccatin III, followed by ring-opening of the oxazoline intermediate with thiolacetic acid.



Taxol® **1**



2'-deoxy-2'-mercaptotaxol $R_1 = H, R_2 = SH$ **2a**
2'-deoxy-2'-epi-mercaptotaxol $R_1 = SH, R_2 = H$ **2b**

Keywords: Taxol; Mercaptopaclitaxel; Oxazoline.
* Corresponding authors. Tel.: +82-2-3277-2400; fax: +82-2-3277-2384 (J.Y.); tel.: +82-2-880-7073; fax: +82-2-888-1604 (Y.-S.L.); e-mail addresses: jyoon@ewha.ac.kr; yslee@snu.ac.kr

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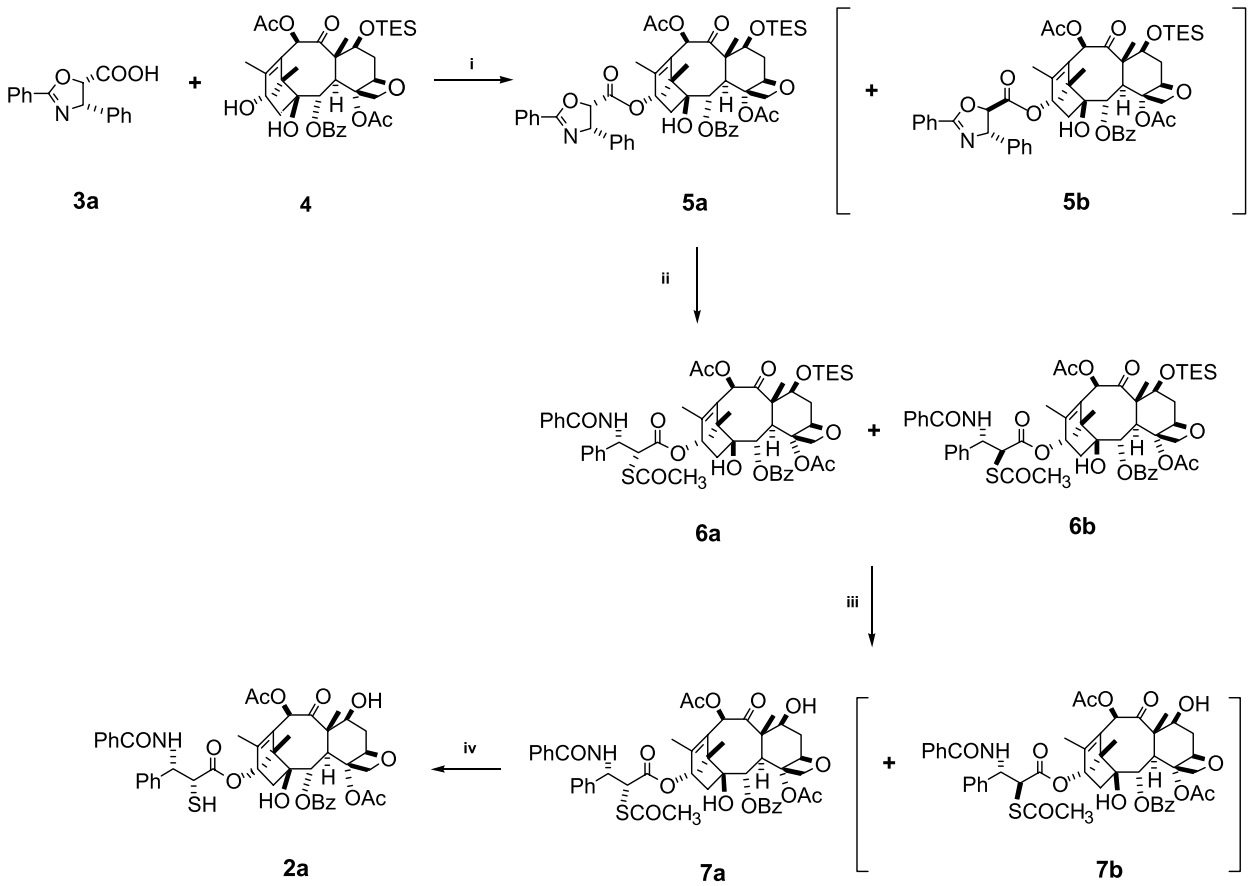


Scheme 1. (i) DCC, 4-Pyrrolidinopyridine, toluene, rt, 2 h, 42% (**5a**) and 50% (**5b**). (ii) Thiolacetic acid, dioxane, 70 °C, 12 h, 80 °C, 12 h, 95 °C, 12 h, 71%. (iii) HF/pyridine (70:30), THF, rt, 5 h, 82%. (iv) LiOH, MeOH–H_2O, rt, 2 h, 65%.

2. Results and discussion

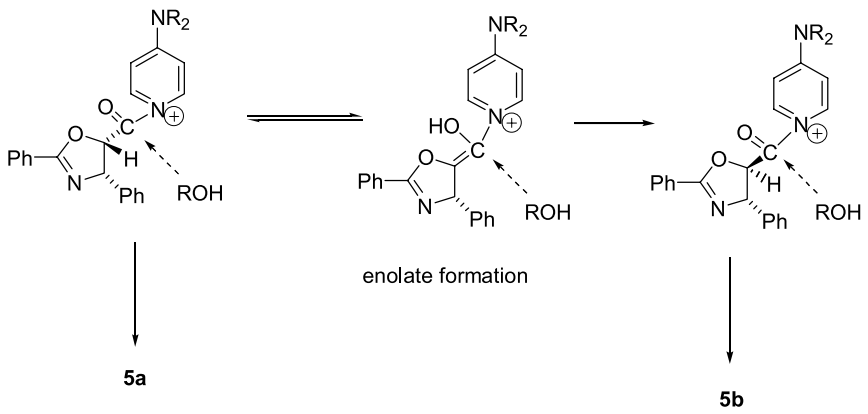
The (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid **3a** was prepared by the literature method.[7] Although the general procedure applied to the synthesis of **2a** involved a similar methodology to that of its counterpart **2b**, as shown in Scheme 1, epimerization occurred during the coupling and ring-opening process of the *cis* structure, which has never happened in the *trans* case,[6] nor in those cases where the simple oxazoline derivatives (both *cis* and *trans*) were involved.[7] Therefore, more attention should be paid to the control of the reaction conditions and the separation procedure.

Thus, when the enantiomerically pure **3a** was coupled to 7-TES-baccatin III **4**,[8] less than half (42% yield) of the *cis*-oxazoline configuration **5a** remained, and nearly half (50% yield) underwent configuration inversion at C5′ leading to the formation of **5b**. Both of the two products were fully characterized. While the ^{1}H NMR spectrum of **5b** was exactly the same as that of the authentic sample, the peaks at 5.78 and 5.41 ppm with a coupling constant of 10.6 Hz corresponding to **5a** were consistent with the corresponding *cis*-oxazoline feature.[9]

This important difference between the coupling products is thought to arise from the repulsions that the *cis* and *trans* structures received from the baccatin skeleton when coupling occurred. For the *cis*-oxazoline carboxylic acid **3a**, the C4 phenyl group lies on the same side as the carboxylic acid group, which directly faces the baccatin skeleton as the C5 carbonyl approaches the C-13 hydroxyl group, which is hidden in the concavity of the baccatin backbone.[10] In this case, the phenyl group has to overcome the steric hindrance and, to some extent, squeeze into a restricted space, which leads to a strong repulsion force being created, which assists portion of the activated reaction species to bring about C5 configuration inversion to afford the formation of **5b**. From the chemical point of view, we believed that the formation of an enol structure (Scheme 2) might be the transitional process for these over-activated reactive species. After the back-migration of the proton to form a more stable configuration (*trans*), the coupling with the C13 hydroxyl of the baccatin afforded **5b**. On the other hand, the C4 phenyl of the *trans* oxazoline acid **3b** likely encounters little counteraction from the baccatin motif, since the phenyl group is facing the opposite direction to the C-5 carboxylic group and is stretched out and away from the concavity of the baccatin backbone during the course of the coupling reaction.

Furthermore, the conformation adopted by the 4′-phenyl group within the *cis* derivative **5a** led to a different, i.e. higher energy ground state of this coupling product. This instability is demonstrated once again in the subsequent ring opening reaction with thiolacetic acid.

The ring-opening product was always a mixture of **6a** and



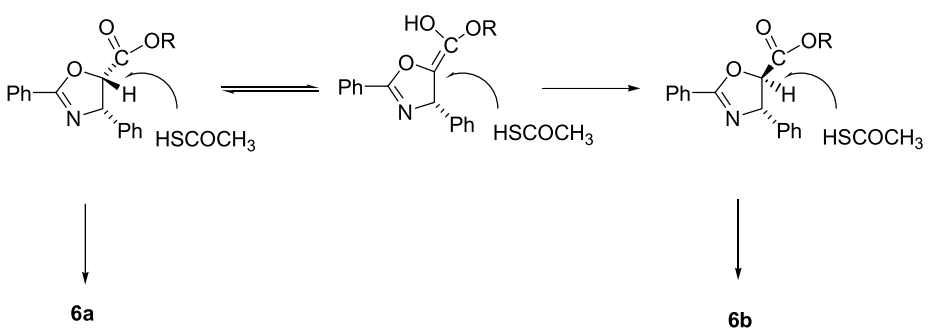
Scheme 2. The possible enol formation during the coupling reaction.

6b. When the reaction temperature was set to 95 °C from the outset, serious epimerization occurred leading to a 1/2.4 ratio of **6a/6b**. As different carefully controlled temperatures were applied, the ratio varied, and the best result was achieved when a stepwise heating model of 70, 80 and finally 95 °C was used and the **6a/6b** ratio in this case was 35:1 (all confirmed by ^{1}H NMR). In our early work with simple alcohol derivatives such as *para*-methoxybenzyl alcohol (PMB), no epimerization occurred, even if the reaction mixture was heated directly to 95 °C and held there for 1.5 days. Therefore, the steric repulsion within the **5a** structure must again account for the various degrees of inversion observed. The pressure acting in the outward direction on the 4′-phenyl group (vide infra) caused the *cis* configuration to be unstable, namely to have a relatively higher energy ground state compared to the simple alcohol derivatives as well as its isomer **5b**. Therefore, the total energy barrier including both energy from ground state to the normal active transition state and from the latter to the crest, which must be surpassed for configuration inversion from the unstable *cis* to the stable *trans* configuration, is relatively lower and easier to reach for activated molecules. Here, the enolation at C5 occurred again (Scheme 3). Once a high reaction temperature is applied, a large portion of the activated molecules will possess enough energy to overcome the above-mentioned lowered energy barrier, thus enabling them to directly follow the inversion pathway and to afford the stable product **5b**. In this case, the key factor is to control the temperature during the reaction procedure, in order to restrict the activated species to within the proper energetic state range, which theoretically lies between the crest and the normal energy barrier.

^{1}H NMR revealed the *cis* structure of **6a** with the amide peak at 6.88 ppm. Fortunately, the diastereoisomeric mixture could easily be separated when the 7-triethylsilyl group were removed by HF/py (70:30), to obtain the pure **7a** and a small amount of **7b**. The basic deprotection approach of the *S*-acetyl group was utilized again to afford the final **2a**, which, similar to its diastereoisomer **7b**, was always formed accompanied by a small amount of **2b**. However, the basicity of potassium bicarbonate was insufficient to fulfil this task, as it did in the case of **7b**. Lithium hydroxide proved to be suitable and an equal number of equivalent of base was used.

With the aid of 2D NMR experiments, the complete assignments of **7a**, the precursor of **2a**, were able to be made. The peak at 6.82 ppm corresponding to the amide group, along with the well-separated peaks as 6.22 ppm (H10) and 6.03 ppm (H3′), 4.36 ppm (H7) and 4.26 ppm (H20α), confirmed the *syn* C-13 side chain, which was distinct from the data of the *anti* **7b**. The two cross peaks due to the vicinal coupling of $H_2$14 with H13 (t, 6.04 ppm) proved that the two protons at around 1.85 ppm must belong to H6β and one of the H14, respectively, which was confirmed by the cross peak from the geminal coupling between the two protons of H6.

The cytotoxicity of the two mercapto taxoids was evaluated using the sulphorhodamine B assay (SRB), unfortunately, both compounds were essentially inactive. We assume that this unexpected result may have come from the formation of the disulfide in situ during the routine assay process when DMSO was used as the solvent. It is well known that



Scheme 3. The possible enol formation during the ring opening reaction.

dimethyl sulfoxide (DMSO) is a good oxidant for the formation of disulfide from thiol functionality at ambient temperature and under a wide range of pH values.[11] Therefore, considering the anticipated role of the free thiol in the cytotoxicity of paclitaxel, the result mentioned above was understandable. The addition of dithiothreitol (DDT) revealed no effect, and further attempts to overcome this problem are currently in progress.

3. Conclusions

In conclusion, we described the synthesis of the exact thiol surrogate product of Taxol® by coupling (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid with 7-triethylsilyl baccatin III, followed by ring-opening of the oxazoline intermediate with thiolacetic acid, which allows the introduction of the sulfur-containing group onto the side chain. Since we have shown the ring-opening reactions of the oxazoline intermediates,[9] our approach can be used for the syntheses of taxol derivatives bearing various C-13 side chains.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. (4*S*, 5*S*)-2,4-Diphenyloxazoline-5-carboxylic acid **3a** was synthesized by the literature procedure.[7] 7-Triethylsilylbaccatin III **4** was prepared by the literature method from 10-deacetylbaccatin III.[8] THF, 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 JEOL JNM-LA 300 or Bruker Avance 500 spectrometers with TMS as internal standard. Chemical shifts were expressed in ppm and coupling constants (*J*) in Hz. ^{13}C NMR were recorded using JEOL JNM-LA 300, Bruker Avance 300 or 500 spectrometers. Infrared spectra were recorded on JASCO FTIR-200 Spectrometer. Mass spectra were obtained using JEOL JMS AX505WA or JMS-700 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 5a. A solution of DCC (620 mg, 3.00 mmol) in dry toluene (20 mL) was added to a suspension of 7-TES-baccatin III **4** (500 mg, 0.71 mmol), *cis*-carboxylic acid **3a** (792 mg, 2.96 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 2 h at room temperature. (The reaction was monitored by TLC, EtOAc/hexane, 1:2) The reaction mixture was then passed through a short silica gel plug (~5 g) and further eluted with 100 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 oxazoline ring inversion product **5b** (which was proved by ^{1}H NMR) as a white solid (337 mg, 0.354 mmol, 50%) and the desired product **5a** as a white solid (283 mg, 0.30 mmol, 42%). An analytical sample of **5a** was obtained by re-crystallization (distilled EtOAc/hexane) as white needles: mp 210–211 °C; $[\alpha]_D^{15}=-71.7°$ (c=0.547, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.55 (m, 6H), 0.91 (t, J=7.9 Hz, 9H), 1.01 (s, 3H), 1.15 (s, 3H), 1.48 (s, 3H), 1.65 (s, 3H), 1.83–1.83 (m, 1H), 2.01–2.04 (m, 2H), 2.16 (s, 3H), 2.28 (s, 3H), 2.47–2.57 (m, 1H), 3.65 (d, J=7.1 Hz, 1H), 4.11 (d, J=8.4 Hz, 1H), 4.26 (d, J=8.2 Hz, 1H), 4.50 (dd, J=6.8, 10.6 Hz, 1H), 4.91 (d, J=8.2 Hz, 1H), 5.41 (d, J=10.6 Hz, 1H), 5.53–5.56 (m, 1H), 5.60 (d, J=7.0 Hz, 1H), 5.78 (d, J=10.4 Hz, 1H), 6.32 (s, 1H), 7.21–7.65 (m, 11H), 8.04–8.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.17, 6.66, 9.88, 13.72, 20.72, 20.81, 22.02, 22.39, 26.27, 27.62, 35.78, 37.07, 42.87, 46.62, 58.26, 68.34, 71.86, 72.09, 73.61, 74.62, 74.83, 76.29, 78.60, 80.92, 81.18, 83.97, 126.40, 128.24, 128.65, 129.17, 129.91, 132.08, 133.22, 133.54, 136.18, 139.54, 164.31, 166.71, 167.93, 168.98, 169.28, 201.59; HRMS (FAB) m/z=950.4147 $[M+H]^+$, calcd for $C_{53}H_{64}NO_{13}Si$=950.4129. Anal. calcd for $C_{53}H_{63}NO_{13}Si$: C, 67.00; H, 6.68; N, 1.47; found: C, 67.08; H, 6.74; N, 1.50.

4.1.2. 2′-Deoxy-2′-thioacetoxy-7-triethylsilylpaclitaxel 6a. Compound **5a** (220 mg, 0.231 mmol), thiolacetic acid (1.5 mL) and dioxane (4.5 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 for 12 h and then 95 °C for 12 h. After concentration under reduced pressure, the sticky yellowish oil was purified twice by flash chromatography (EtOAc/hexane, 1:3) to get **6a** as a white solid (168 mg, 0.164 mmol, 71%), which proved to be a mixture with **6b** by ^{1}H NMR. An analytical sample of **6a** was obtained by re-crystallization (distilled EtOAc/hexane) as white flakes: mp 160–162 °C; $[\alpha]_D^{28}=-3.84°$ (c=0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.52–0.59 (m, 6H), 0.90 (t, J=7.8 Hz, 9H), 1.11 (s, 3H), 1.17 (s, 3H), 1.65 (s, 3H), 1.69–1.74 (m, 1H), 1.82–1.93 (m, 2H), 1.86 (s, 3H), 2.16 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 2.45–2.55 (m, 1H), 3.70 (d, J=7.0 Hz, 1H), 4.09 (m, 1H), 4.25 (d, J=8.4 Hz, 1H), 4.38–4.43 (dd, J=10.6, 6.8 Hz, 1H), 4.73 (d, J=12.4 Hz, 1H), 4.90 (d, J=8.1 Hz, 1H), 5.59 (d, J=7.1 Hz, 1H), 5.74 (m, 1H), 6.02 (m, 1H), 6.37 (s, 1H), 6.88 (d, J=9.0 Hz, 1H), 7.22–7.74 (m, 13H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.23, 6.71, 10.01, 14.02, 20.81, 21.06, 22.57, 26.44, 30.49, 34.82, 37.14, 43.12, 46.63, 51.15, 55.33, 58.36, 71.16, 72.10, 74.81, 78.83, 80.86, 84.15, 126.14, 126.91, 127.09, 127.28, 128.54, 128.68, 128.89, 129.28, 130.06, 131.87, 133.56, 133.74, 138.78, 140.02, 166.42, 166.92, 168.74, 169.14, 169.76, 196.17, 201.61; HRMS (FAB) m/z=1048.3943

$[M+Na]^+$, calcd for $C_{55}H_{67}NO_{14}SSi\,Na$=1048.3931. Anal. calcd for $C_{55}H_{67}NO_{14}SSi$: C, 64.37; H, 6.58; N, 1.36; S, 3.12; found: C, 64.22; H, 6.63; N, 1.34; S, 3.12.

4.1.3. 2′-Deoxy-2′-thioacetoxypaclitaxel 7a. To a vigorous stirred solution of compound **6a** accompanied by **6b** (140 mg, 0.136 mmol) in dry THF (10 mL) was added 1.4 mL of hydrogen fluoride–pyridine (70:30) at 0 °C under N_2. After 10 min stirring at 0 °C, the reaction mixture was then stirred for another 5 h at room temperature. Water (10 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (4×20 mL). The combined organic layer was washed subsequently with dilute aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash chromatography (EtOAc/hexane, 1:1) afforded small amount of **7b** and the corresponding product **7a** as a white solid (100 mg, 0.11 mmol, 82%). An analytical sample was obtained by re-crystallization (distilled EtOAc/hexane) as white crystalline: mp 181–183 °C; $[\alpha]_D^{13}=-10.7°$ (c=0.77, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 3H), 1.17 (s, 3H), 1.58 (s, 1H), 1.59 (s, 1H), 1.64 (s, 3H), 1.70–1.76 (m, 3H), 1.76 (s, 1H), 1.83–1.94 (m, 2H), 2.22 (s, 3H), 2.31 (s, 3H), 2.44 (s, 3H), 2.50–2.56 (m, 1H), 3.70 (d, J=7.0 Hz, 1H), 4.12 (d, J=8.5 Hz, 1H), 4.26 (d, J=8.4 Hz, 1H), 4.36–4.40 (m, 1H), 4.75 (d, J=10.7 Hz, 1H), 4.93 (m, 1H), 5.58 (d, J=7.1 Hz, 1H), 5.73 (dd, J=9.0, 10.5 Hz, 1H), 6.03 (dd, J=7.9, 9.0 Hz, 1H), 6.21 (s, 1H), 6.82 (d, J=8.8 Hz, 1H), 7.23 (m, 2H), 7.36 (t, J=7.6 Hz, 2H), 7.42–7.46 (m, 4H), 7.50–7.55 (m, 2H), 7.65 (t, J=7.5 Hz, 1H), 7.72 (d, J=7.2 Hz, 2H), 8.03 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.92, 15.17, 21.22, 22.22, 22.97, 30.91, 35.47, 35.88, 43.44, 45.93, 51.59, 55.61, 58.89, 71.51, 72.52, 75.36, 75.83, 76.73, 79.56, 81.29, 84.81, 127.33, 127.66, 129.02, 129.14, 129.36, 129.62, 130.49, 132.35, 133.25, 133.95, 134.24, 139.16, 142.79, 166.88, 167.32, 169.19, 170.28, 171.67, 196.38, 204.03; HRMS (FAB) m/z=934.3083 $[M+Na]^+$, calcd for $C_{49}H_{53}NO_{14}SNa$=934.3070. Anal. calcd for $C_{49}H_{53}NO_{14}S$: C, 64.53; H, 5.86; N, 1.54; S, 3.52; found: C, 64.51; H, 5.99; N, 1.49; S, 3.45.

4.1.4. 2′-Deoxy-2′-mercaptopaclitaxel 2a. To a solution of **7a** (40 mg, 0.044 mmol) in MeOH (2 mL, degassed) was added dropwise a solution of $LiOH{\cdot}H_2O$ (1.85 mg, 0.044 mmol) in H_2O (0.2 mL, degassed) during 0.5 h at room temperature under N_2 with vigorous stirring. After another 30 min, the reaction mixture was poured into a mixture of $CHCl_3$–H_2O (15:15 mL), and was acidified with two or three drops of 1 N HCl to pH 1–2. The water layer was extracted with $CHCl_3$ (3×10 mL), and the combined organic layer was washed with water (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (2% MeOH/$CHCl_3$) in dark place to afford final product **2a** as a white solid (25 mg, 0.029 mmol, 65%); mp 214–216 °C (dec.); $[\alpha]_D^{15}=-17.6°$ (c=1.00, MeOH); IR (KBr) 3463, 2984, 2937, 2552, 1721, 1642, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (s, 3H), 1.18 (s, 3H), 1.65 (s, 3H), 1.74 (s, 1H), 1.85 (m, 1H), 1.88 (s, 3H), 2.03–2.09 (m, 3H), 2.20 (s, 3H), 2.22 (s, 3H), 2.50–2.55 (m, 2H), 3.74 (d, J=7.0 Hz, 1H), 4.05–4.11 (m, 1H), 4.13 (d, J=8.4 Hz, 1H), 4.24 (d, J=8.4 Hz, 1H), 4.39 (m, 1H), 4.91 (d, J=8.0 Hz, 1H), 5.62 (d, J=7.1 Hz, 1H), 5.66 (t, J=7.8 Hz, 1H), 6.13 (t, J=8.7 Hz, 1H), 6.26 (s, 1H), 7.05 (d, J=8.0 Hz, 1H), 7.31–7.63 (m, 11H), 7.79 (d, J=7.7 Hz, 2H), 8.02 (d, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.95, 15.32, 21.23, 22.27, 22.95, 27.15, 35.90, 43.50, 46.00, 47.48, 56.20, 58.91, 71.80, 72.54, 75.37, 75.89, 79.59, 81.39, 84.76, 127.45, 127.51, 128.86, 129.06, 129.14, 129.38, 129.51, 130.50, 132.36, 133.24, 134.17, 134.38, 138.99, 142.91, 167.32, 167.62, 170.26, 171.36, 171.65, 204.06; HRMS (FAB) m/z=892.2986 $[M+Na]^+$, calcd for $C_{47}H_{51}NO_{13}SNa$=892.2965.

Acknowledgements

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References and notes

1. For recent review, see: Kingston, D. G. I. *Chem. Commun.* **2001**, 867.
2. Ojima, I.; Bounaud, P.; Ahern, D. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1189.
3. Schiff, P. B.; Fant, J.; Horwtz, S. B. *Nature* **1979**, *277*, 665.
4. (a) Baloglu, E.; Hoch, J. M.; Chatterjee, S. K.; Ravindra, R.; Bane, S.; Kingston, D. G. I. *Bioorg. Med. Chem.* **2003**, *11*, 1557. (b) Lożyński, M.; Rusińska-Roszak, D. *Tetrahedron Lett.* **1995**, *36*, 8849. (c) Jiménez-Barbero, J. A.; Souto, A. A.; Abal, M.; Barasoain, I.; Evangelio, J. A.; Acuña, A. U.; Andreu, J. M.; Amat-Guerri, F. *Bioorg. Med. Chem.* **1998**, *6*, 1857. (d) Kant, J.; Huang, S.; Wong, H.; Fairchild, C.; Vyas, D.; Farina, V. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2471. (e) Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160.
5. Moyna, G.; Williams, H. J.; Scott, A. I. *Synth. Commun.* **1997**, *27*, 1561.
6. Qi, X.; Lee, S.-H.; Yoon, J.; Lee, Y.-S. *Tetrahedron* **2003**, *59*, 7409.
7. Lee, S.-H.; Qi, X.; Yoon, J.; Nakamura, K.; Lee, Y.-S. *Tetrahedron* **2002**, *58*, 2777.
8. Kant, J.; O'Keeffe, W. S.; Chen, S. H.; Farina, V.; Fairchild, C.; Johnston, K.; Kadow, J. F.; Long, B. H.; Vyas, D. *Tetrahedron Lett.* **1994**, *35*, 5543.
9. Lee, S.-H.; Yoon, J.; Nakamura, K.; Lee, Y.-S. *Org. Lett.* **2000**, *2*, 1243. Another approach regarding to the preparation of **5a** with Taxol® as starting material, was reported by Cabri via a ring cyclization process by triflic anhydride, see: Cabri, W. *Tetrahedron Lett.* **1996**, *37*, 4785.
10. Denis, J. N.; Greene, A. W.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
11. Tam, J. P.; Wu, C.-R.; Liu, W.; Zhang, J.-W. *J. Am. Chem. Soc.* **1991**, *113*, 6657.