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Synthesis of novel taxoid analogue containing sulfur group on C-13 side-chain: 2′-deoxy-2′-*epi*-mercaptopaclitaxel

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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 2′-deoxy-2′-*epi*-mercaptopaclitaxel with high *ee* has been developed. The key step is the regio-controlled ring-opening reaction of the *trans*-oxazoline derivative with thiolacetic acid, which allows the introduction of the sulfur-containing group onto the side-chain.

1. Introduction

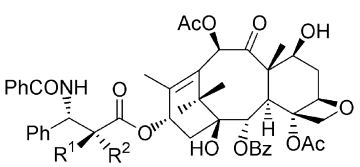
Paclitaxel (taxol®) **1**, a complex diterpenoid natural product first isolated from the bark of the western yew tree, *Taxus brevifolia*, has proved to be one of the most important new anticancer agents to appear during last decade.[1] In contrast with other common anticancer drugs, paclitaxel inhibits cell replication in the mitotic phase of the cell cycle by promoting tubulin assembly and stabilizing the microtubules formed, thus inducing cell death.[2] Although numerous efforts have been made to determine its structure–activity relationship and elucidate its unique mechanism, the specific roles of its various functional groups on the molecular level remain unclear.[1–3] Some research studies have shown that the 2′-hydroxyl functionality plays a crucial role in its biological activity by interacting directly with a protein residue in the paclitaxel–microtuble complex,[4] perhaps acting as a hydrogen bond donor.[5] In light of this hypothesis, the synthesis of the 2′-sulfur analogue (**2a** or **2b**) (Fig. 1) would be of great interest for the investigation of paclitaxel binding site on the microtubules, and thus for the development of new compounds with more desirable properties than paclitaxel itself. Although the synthesis of the 7β-sulfur analogue of paclitaxel was recently reported,[6] to our knowledge, the synthesis of taxoid compounds bearing thiol group at the C-13 side-chain has not yet been demonstrated to date.

We report herein the preparation of 2′-deoxy-2′-*epi*-mercaptopaclitaxel **2b** through the coupling of (4*S*,5*R*)-2,4-diphenyloxazoline-5-carboxylic acid **3** with suitably protected baccatin III **4**, followed by the ring-opening reaction of the oxazoline intermediate with thiolacetic acid as a key step.

2. Results and discussion

Recently we reported the asymmetric syntheses of both *syn* and *anti*, suitably protected β-phenylisocysteine.[7] However, the direct coupling of *S*-acetyl-*N*-benzoyl-phenylisocysteine with 7-(triethylsilyl)baccatin III **4** was unsuccessful, presumably because of the congested location of the C-13 hydroxy group. Thus, we decided to use an oxazoline derivative for the coupling reaction.

Among the available hands of attaching a β-phenylisoserine side-chain onto the C-13 hydroxy group of the baccatin III moiety, the coupling of oxazoline derivatives with the corresponding baccatin compound constitutes an attractive



1 R^1 = H, R^2 = OH
2a R^1 = H, R^2 = SH
2b R^1 = SH, R^2 = H

Figure. 1. Structures of paclitaxel and 2′-deoxy-2′-mercaptopaclitaxels.

Keywords: taxol; mercaptopaclitaxel; oxazoline.
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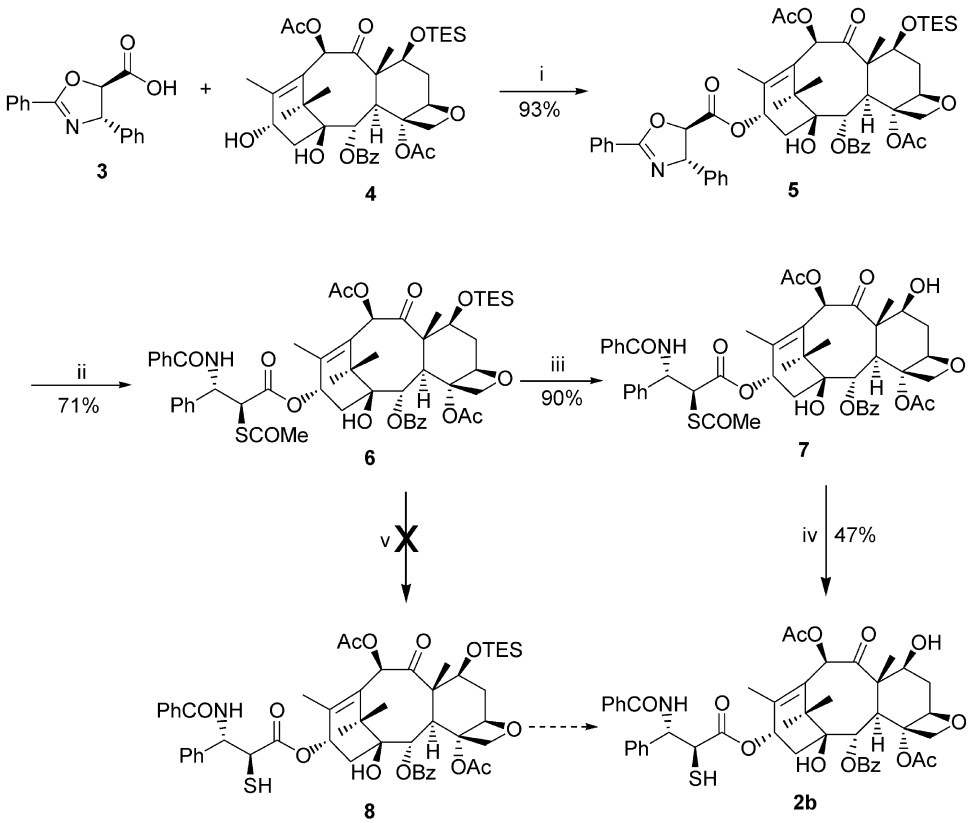
alternative, and this is followed by simple hydrolysis, to obtain the desired taxol with good yield.[8] However, unlike the hydrolysis procedure with dilute hydrochloric acid producing no change at the C-5 configuration of the oxazoline ring (5*R*→2′*R*), complete inversion at the C-5 configuration (5*R*→2*S* or 5*S*→2*R*) was observed during the ring-opening reaction of oxazoline derivatives with thiolacetic acid in our previous experiments.[7,9] Thus, the methodology applied to the preparation of 2′-deoxy-2′-*epi*-mercaptopaclitaxel **2b** involved the coupling of (4*S*,5*R*)-2,4-diphenyloxazoline-5-carboxylic acid **3** with 7-(triethylsilyl)baccatin III **4** first, then ring-opening with thiolacetic acid to generate the sulfur-containing side-chain, followed by two subsequent deprotection steps, as shown in Scheme 1.

(4*S*,5*R*)-2,4-Diphenyloxazoline-5-carboxylic acid **3**, generated from the corresponding methyl ester by hydrolysis,[7] was coupled to 7-(triethylsilyl)baccatin III **4**[10] in the presence of DCC and 4-pyrrolidinopyridine, as shown by Kingston,[8] giving the coupling product **5**. Excess carboxylic acid **3** (3.5 equiv. in our methods) was used to ensure the complete conversion of the baccatin compound. Although this *trans*-oxazoline derivative **3** should in fact be mixed with a small amount of its *cis*-isomer [(4*S*,5*R*):(4*S*,5*S*)=25:1, in the form of methyl esters[7]], the resulting coupling product was quite pure based on the ^{1}H NMR spectrum. This is likely due in part to the difference of steric hindrance between the *trans*- and *cis*- structures, when they approached the C-13 hydroxy group hidden in the concavity of the baccatin skeleton,[11] and also because of the epimerization of the *cis*-oxazoline methyl ester when hydrolyzing methyl ester with lithium hydroxide, which leads to there being less of the *cis*-isomer actually present in the hydrolysis product.[7] The ring-opening reaction of coupling product **5** with thiolacetic acid was performed at relatively simple conditions (70°C and 12 h) to afford compound **6** (2′*S*,3′*S*) with the thioacetyl group introduced at the 2′-position, without any of the (2′*R*,3′*S*)-isomer being produced. Dilute rather than neat thiolacetic acid was used during this process to help reduce the possibility of acid-catalyzed cleavage of the 7-triethylsilyl group.[12] The 7-triethylsilyl group was then removed by means of hydrogen fluoride–pyridine in dry THF to afford compound **7** using the method described in the literature.[13] The *S*-acetyl group on the side-chain was able to be selectively removed under aqueous basic conditions, based on the differences in reactivity between the thioester and other ester groups in the structure. However, it was found that the final product **2b** (2′*S*,3′*S*) was always accompanied by a small amount of its diastereoisomer **2a** (2′*R*,3′*S*) based on its ^{1}H NMR spectrum.[14] This small amount of epimerization can probably be attributed to the acidic thiol geminal 2′-methane, under the basic reaction conditions, whose acidity is enhanced by the presence of the adjacent ester bond. Four kinds of bases such as LiOH, K_2CO_3, $KHCO_3$ and $NH_3{\cdot}H_2O$ were examined. Among them, $KHCO_3$ proved to be the best, whereas LiOH was too strong and resulted in the hydrolysis of other ester bonds of the taxane and in more severe epimerization. The use of a less than stoichiometric amount of $KHCO_3$ and the slow addition of the base solution were adopted in order to obtain the best result. In our experiment, a ratio of 9:1 (**2b/2a**) was obtained when 0.9 equiv. of $KHCO_3$ was used.[14]



Scheme 1. Preparation of 2′-deoxy-2′-*epi*-mercaptopaclitaxel **2b**. (i) DCC, 4-pyrrolidinopyridine, toluene, rt, 1 h. (ii) Thiolacetic acid, dioxane, 70°C, 12 h. (iii) HF–pyridine (70:30), THF, rt, 5 h. (iv) $KHCO_3$, MeOH–H_2O, rt, 2 h. (v) $KHCO_3$, K_2CO_3 or LiOH, MeOH–H_2O, rt.

Another route was also explored from **6** to **8**, and then **2b**, as shown in Scheme 1, but attempts to obtain the desired product **8** were unsuccessful. Surprisingly, the *S*-acetyl group was tolerated under $KHCO_3$ or K_2CO_3 conditions, and a mixture of several products was obtained from starting material **6** when LiOH was employed. It would appear that the low reactivity observed can be attributed to the existence of the protective 7-triethylsilyl group. Similar observations were reported by another research group regarding the removal of the 10-acetyl group.[15]

3. Conclusions

In conclusion, we have stereoselectively synthesized 2′-deoxy-2′-*epi*-mercaptopaclitaxel through the coupling of (4*S*,5*R*)-2,4-diphenyloxazoline-5-carboxylic acid with suitably protected baccatin III, followed by the ring-opening reaction of the oxazoline intermediate with thiolacetic acid as a key step. 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. 7-(Triethylsilyl)baccatin III **4** was prepared from 10-deacetylbaccatin III using the method described in the literature.[9] (4*S*,5*R*)-2,4-Diphenyloxazoline-5-carboxylic acid **3** was synthesized by the procedure described in the literature.[7] THF, toluene and dioxane were freshly distilled over sodium-benzophenone ketyl. The $CHCl_3$ and MeOH were distilled from CaH_2. 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 thickness of 0.25 mm. Preparative TLC was performed using Merck 60 F_{254} plates with a thickness of 1 mm.

Melting points were measured using a 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 the 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 600 spectrometers. Infrared spectra were recorded on a JASCO FTIR-200 Spectrometer. Mass spectra were obtained using JEOL JMS AX505WA or JMS-700 Mstation spectrometers. Optical rotations were measured using a JASCO 3100 polarimeter.

4.1.1. Compound 5. A solution of DCC (134 mg, 0.651 mmol) in dry toluene (10 mL) was added to a suspension of 7-(triethylsilyl)baccatin III **4** (130 mg, 0.186 mmol), carboxylic acid **3** (174 mg, 0.651 mmol) and a catalytic amount of 4-pyrrolidinopyridine in 5 mL of dry toluene at 0°C under N_2 while stirring. After 10 min, the reaction mixture was stirred for a further 1 h at room temperature. The reaction mixture was then passed through a short silica gel plug (~5 g) and further eluted with 50 mL of EtOAc. The combined eluent was concentrated under reduced pressure. A 1:1 mixture of EtOAc and hexane (20 mL) was added to the residue and the suspension was filtered through a cotton plug. The filtrate was concentrated again. Purification of the residue by flash chromatography (EtOAc–hexane, 1:3) afforded **5** as a pale yellow solid (164 mg, 0.173 mmol, 93%). An analytical sample was obtained by recrystallization (distilled EtOAc–hexane) as white needles: mp 211–212°C; $[\alpha]_D^{20}=-49.9°$ (*c*=1.00, $CHCl_3$); IR (KBr) 3471, 2958, 2873, 1753, 1726, 1710, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (m, 6H), 0.91 (t, *J*=8.1, 7.7 Hz, 9H), 1.19 (s, 3H), 1.23 (s, 3H), 1.69 (s, 3H), 1.77 (s, 1H), 1.84–1.93 (m, 1H), 1.99 (s, 3H), 2.07 (s, 3H), 2.16 (s, 3H), 2.10–2.42 (m, 2H), 2.49–2.60 (m, 1H), 3.83 (d, *J*=7.1 Hz, 1H), 4.14 (d, *J*=8.2 Hz, 1H), 4.29 (d, *J*=8.2 Hz, 1H), 4.50 (dd, *J*=6.8, 10.3 Hz, 1H), 4.94 (d, *J*=6.6 Hz, 2H), 5.60 (d, *J*=6.4 Hz, 1H), 5.68 (d, *J*=7.0 Hz, 1H), 6.18 (m, 1H), 6.42 (s, 1H), 7.36–7.64 (m, 11H), 8.07 (d, *J*=7.1 Hz, 2H), 8.24 (d, *J*=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.20, 6.65, 9.93, 14.43, 20.72, 21.61, 26.47, 35.54, 43.09, 46.90, 58.38, 71.84, 72.23, 74.74, 74.89, 76.32, 77.21, 78.88, 80.80, 83.28, 84.11, 126.37, 126.62, 128.18, 128.50, 128.80, 128.92, 128.96, 129.23, 129.25, 129.98, 123.03, 133.63, 133.98, 139.73, 140.72, 166.86, 169.04, 169.76, 170.08, 201.58; HRMS (FAB) *m*/*z*=972.3966 $[M+Na]^+$, calcd for $C_{53}H_{63}NO_{13}SiNa$=972.3949.

4.1.2. 2′-Deoxy-2′-*epi*-acetylmercapto-7-(triethylsilyl)paclitaxel 6. Compound **5** (140 mg, 0.147 mmol), thiolacetic acid (1 mL) and dioxane (3 mL) were added in a 6 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 afford **6** as a white solid (107 mg, 0.105 mmol, 71%); mp 165–167°C; $[\alpha]_D^{15}=-97.8°$ (*c*=0.532, $CHCl_3$); IR (KBr) 3483, 3425, 3300, 3026, 2952, 2873, 1747, 1726, 1710, 1663, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.49–0.63 (m, 6H), 0.93 (t, *J*=8.0, 7.9 Hz, 9H), 1.12 (s, 3H), 1.15 (s, 3H), 1.17 (s, 3H), 1.64 (s, 3H), 1.69 (s, 1H), 1.81–1.90 (m, 1H), 2.03–2.28 (m, 2H), 2.15 (s, 3H), 2.33 (s, 3H), 2.44 (s, 3H), 2.39–2.56 (m, 1H), 3.64 (d, *J*=7.0 Hz, 1H), 4.09 (d, *J*=8.4 Hz, 1H), 4.30 (d, *J*=8.0 Hz, 1H), 4.35 (m, 1H), 4.86 (d, *J*=3.8 Hz, 1H), 4.93 (d, *J*=10.0 Hz, 1H), 5.61 (d, *J*=6.9 Hz, 1H), 5.73 (dd, *J*=3.6, 9.3 Hz, 1H), 6.06 (m, 1H), 6.27 (s, 1H), 7.39–7.64 (m, 11H), 7.92 (m, 2H), 8.08 (m, 2H), 8.20 (d, *J*=9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.29, 6.75, 9.98, 20.81, 20.91, 22.11, 26.44, 30.38, 34.91, 37.14, 43.18, 46.82, 49.83, 54.46, 58.40, 72.11, 72.21, 74.80, 75.00, 76.45, 77.26, 78.75, 80.85, 84.21, 126.18, 127.12, 128.35, 128.60, 128.75, 129.20, 130.14, 131.93, 133.63, 133.70, 133.81, 127.80, 139.58, 166.92, 167.04, 169.12, 169.77, 171.44, 192.37, 201.65; HRMS (FAB) *m*/*z*=1026.4130 $[M+H]^+$, calcd for $C_{55}H_{68}NO_{14}SSi$=1026.4111.

4.1.3. 2′-Deoxy-2′-*epi*-acetylmercaptopaclitaxel 7. To a solution of compound **6** (90 mg, 0.088 mmol) in dry THF (9 mL) was added HF–pyridine (70:30) at 0°C. After

10 min, the reaction mixture was then stirred for a further 5 h at room temperature. Water (10 mL) was added to quench the reaction and the mixture was extracted with EtOAc (4×20 mL). The combined organic layer was subsequently washed with 5% aqueous $NaHCO_3$ (30 mL) and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash chromatography (EtOAc–hexane, 1:1) afforded the corresponding product **7** as a white solid (72 mg, 0.079 mmol, 90%); mp 180–182°C; $[\alpha]_D^{18}=-98.9°$ (c=0.431, $CHCl_3$); IR (KBr) 3536, 3515, 3415, 2984, 2947, 1715, 1678, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 3H), 1.08 (s, 3H), 1.18 (s, 3H), 1.63 (s, 3H), 1.69 (s, 1H), 1.80–1.88 (m, 1H), 2.05–2.41 (m, 3H), 2.22 (s, 3H), 2.32 (s, 3H), 2.44 (s, 3H), 2.44–2.59 (m, 1H), 3.65 (d, J=7.0 Hz, 1H), 4.11 (d, J=8.2 Hz, 1H), 4.30 (d, J=8.6 Hz, 1H), 4.34 (m, 1H), 4.81 (d, J=3.9 Hz, 1H), 4.94 (d, J=8.4 Hz, 1H), 5.60 (d, J=7.1 Hz, 1H), 5.72 (dd, J=4.0, 9.3 Hz, 1H), 6.08 (m, 1H), 6.10 (s, 1H), 7.33–7.65 (m, 11H), 7.90 (m, 2H), 8.08 (m, 2H), 8.14 (d, J=9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.80, 21.78, 22.05, 24.70, 26.61, 28.46, 29.29, 29.66, 30.35, 34.84, 35.19, 35.42, 71.93, 71.97, 74.99, 75.43, 76.32, 77.20, 79.16, 80.76, 84.39, 126.09, 127.09, 128.60, 128.73, 129.08, 129.17, 130.12, 131.94, 132.82, 133.74, 137.82, 141.88, 166.84, 166.97, 169.89, 171.15, 171.33, 192.33, 203.57; HRMS (FAB) m/z=912.3265 $[M+H]^+$, calcd for $C_{49}H_{54}NO_{14}S$=912.3250.

4.1.4. 2′-Deoxy-2′-*epi*-mercaptopaclitaxel 2b. To a solution of **7** (40 mg, 0.044 mmol) in MeOH (3 mL) was added dropwise a solution of $KHCO_3$ (4.0 mg, 0.040 mmol) in H_2O (0.2 mL) over a period of 1.5 h at room temperature under N_2 with vigorous stirring. After another 30 min the reaction mixture was poured into a 1:1 mixture of $CHCl_3$–H_2O (30 mL), and acidified with 2–3 drops of 1N HCl to pH 1–2. The organic layer was collected, and the water layer was extracted with $CHCl_3$ (3×10 mL). 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 (EtOAc–hexane, 1:1) in a dark place, followed by flash chromatography with a small silica gel column wound with aluminum foil (EtOAc–hexane, 1:2, containing 0.5% MeOH, all distilled and degassed under N_2 before use) to afford final product **2b** (mixed with 10% **2a** as shown by ^1H NMR) as a white solid (16.3 mg, 0.019 mmol, 47%); mp 149–151°C; $[\alpha]_D^{25}=-26.0°$ (c=0.500, distilled EtOAc); IR (KBr) 3489, 3415, 2952, 2926, 2852, 2558, 1726, 1663, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.64 (s, 3H), 1.74 (s, 1H), 1.82–1.89 (m, 1H), 2.03–2.43 (m, 3H), 2.21 (s, 3H), 2.37 (s, 3H), 2.49–2.56 (m, 1H), 2.54 (d, J=11.2 Hz, 1H), 3.68 (d, J=6.9 Hz, 1H), 3.89 (dd, J=3.8, 11.1 Hz, 1H), 4.13 (d, J=8.6 Hz, 1H), 4.30 (d, J=8.2 Hz, 1H), 4.32 (m, 1H), 4.94 (d, J=8.0 Hz, 1H), 5.62 (d, J=7.0 Hz, 1H), 5.78 (dd, J=3.8, 9.5 Hz, 1H), 6.07 (m, 1H), 6.13 (s, 1H), 7.30–7.63 (m, 11H), 7.94 (m, 2H), 8.06 (m, 2H), 8.16 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 9.45, 14.09, 20.82, 21.49, 22.79, 26.66, 35.10, 35.53, 43.04, 44.55, 45.64, 56.53, 58.55, 71.19, 72.12, 74.81, 75.49, 76.38, 78.98, 81.02, 84.32, 126.06, 127.03, 127.09, 128.50, 128.64, 128.69, 128.80, 128.96, 129.02, 129.15, 130.05, 132.07, 132.99, 133.58, 133.81, 138.51, 141.78, 166.98, 167.01, 169.66, 171.16, 172.91, 203.51; HRMS (FAB) m/z=892.2977 $[M+Na]^+$, calcd for $C_{47}H_{51}NO_{13}SNa$=892.2965.

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