Synthesis of Novel 2-O,3′-N-Linked Macrocyclic Taxoids with Variable Ring Size

Olivier Querolle,[a] Joëlle Dubois,*[a] Sylviane Thoret,[a] Christophe Dupont,[a][‡] Françoise Guéritte,[a] and Daniel Guénard[a]

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A series of macrocyclic taxoids was prepared by connecting the 2-OH and 3′-NH moieties with aliphatic chains to mimic the docetaxel solid-state conformation. The synthesis was achieved by acylation of both positions with various bromoalkanoic acids, and ring closure was carried out with sodium sulfide. Nine 19- to 27-membered macrocyclic taxoids were obtained and evaluated as inhibitors of microtubule disassembly as well as for their cytoxicity.

Introduction

Paclitaxel (Taxol®) (**1a**) and docetaxel (Taxotere®) (**1b**) (Figure 1) are very useful anticancer drugs in the treatment of breast, ovarian, and non-small-cell lung cancers.[1] These compounds block cell-cycle progression during mitosis by binding to microtubules and stabilizing them against disassembly.[2] The structure of tubulin has recently been determined by electron crystallography on zinc-induced sheets of tubulin stabilized with paclitaxel.[3] The 3.7 Å resolution allowed visualization of the location of the paclitaxel binding site but not a complete determination of the ligand conformation. Several studies have led to propose three conformations that could interact with tubulin. The so-called "polar" conformer, with 2-O-benzoyl and 3′-phenyl groups exhibiting hydrophobic collapse, and the "nonpolar" form where the 2-O and 3′-NH-substituents are in hydrophobic interaction, were first proposed on the basis of NMR spectra[4,5] and X-ray crystal structures.[6,7] Then, refinement at 3.5 Å of the previous αβ-tubulin model[8] led to propose an intermediate conformation, in which the phenyl ring of the 2-benzoyl group is almost equidistant from both hydrophobic groups at the 3′-position (T-shaped structure).[9]

Syntheses of analogues with built-in conformational restrictions have been designed to investigate the bound conformation of taxoids on tubulin. Most published studies have involved compounds mimicking the "polar" conformation, with bridges linking the 2-O-benzoyl and 3′-phenyl groups.[10,11] Recently, two analogues have been described in which the ester group at C-4 is linked with the 3′-phenyl group to model the "T-shaped" conformer.[12] A few of these analogues were still able to interact with tubulin but they were less active than paclitaxel. For example three of the 17- and 18-membered macrocyclic taxoids described by Ojima et al.[11] showed relative activities of 19, 21, and 36% as compared to paclitaxel whereas the 4,3′-linked macrocycles reported by Kingston et al.[12] (19- and 21-membered rings) were 10- and 30-fold less active than paclitaxel. Recently, the first derivatives mimicking the "nonpolar" conformer with bridges linking the 3′-NH moiety to the 2-position were described but their activity on tubulin was not reported.[13]

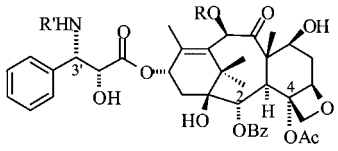

Figure 1. Structure of paclitaxel (Taxol®) (**1a**: R = Ac; R′ = Bz) and docetaxel (Taxotere®) (**1b**: R = H; R′ = Boc)

In the course of our study on the bioactive conformation of docetaxel, we designed new conformationally restricted taxoids mimicking the "nonpolar" conformation, which is found in the docetaxel crystal structure. Therefore, we synthesized macrocyclic taxoids with bridges linking the 3′-NH moiety to the 2-position. The macrocycle that best fitted the crystal conformation of docetaxel was calculated by molecular modeling to be a 19-membered ring. To account for the "T-shaped" conformer calculated from the crystallographic density, we decided to vary the size of the macrocycle and to correlate it with the activity on cold-induced microtubule disassembly. To synthesize these macrocyclic taxoids, we chose to effect ring-closure by the classical addition of sulfide to α,ω-dibromo derivatives.[14] The large vari-

[a] ICSN-CNRS,
Avenue de la Terrasse, 91198 Gif sur Yvette Cedex, France
Fax: (internat.) + 33-1/69077247
E-mail: joelle.dubois@icsn.cnrs-gif.fr
[‡] Present address: Orga-Link,
2, route de la Noue, 91193 Gif sur Yvette Cedex, France
E-mail: contact@orga-link.com

ety of bromoalkanoic acids commercially available allowed us to prepare several taxoid precursors bearing two bromoalkyl chains at the 2-O and 3′-N-positions.

We describe here a short and efficient synthesis of a series of eight novel macrocyclic taxoids **2** bearing 19- to 27-membered rings (Figure 2). We also discuss their biological evaluation in relation to their macrocyclic ring size and their restricted conformation.

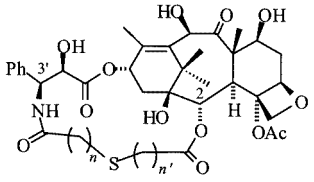

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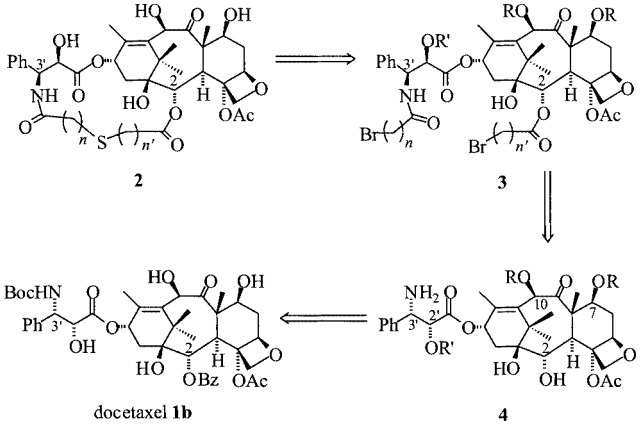
Figure 2. New C-2,3′-N-macrocyclic taxoids

Results and Discussion

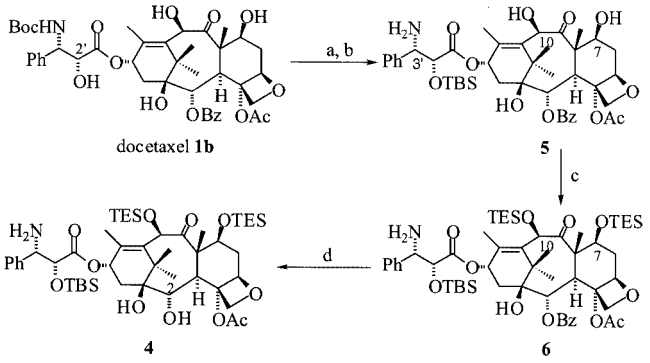
The retrosynthetic analysis of the target macrocyclic taxoids **2** is shown in Scheme 1. As described in this scheme, compound **2** can be obtained by addition of sodium sulfide to the ω,ω′-dibromotaxoid precursor **3**, which can be synthesized from the 2-OH/3′-NH_2 taxoid **4**. The deacylated derivative **4** could be obtained from docetaxel (**1b**) after suitable protection of the 2′-, 7-, and 10-hydroxy groups, which are not involved in the transformation.



Scheme 1. Retrosynthesis of compound **2**

Preparation of 2-Debenzoyl-2′-OTBS-3′-(de-*tert*-butoxycarbonyl)-7,10-diTES-docetaxel (4)

It was important to design the most rapid and efficient synthesis for compound **4**, starting from docetaxel. The hydroxy group in 2′-position was first protected with the bulky *tert*-butyldimethylsilyl group to prevent hydrolysis of the ester group at C-13 during further debenzoylation.[15] The Boc group was removed by addition of trifluoroacetic acid at 0 °C before protection of the 7- and 10-hydroxy groups. We chose triethylsilyl as the protective group for these alcohols but had to substitute another solvent for DMF, which is often used as the solvent in this reaction, because of the potential formylation of the free amino group in the 3′-position. The best yield in this protection step was obtained in a solution of dichloromethane and acetonitrile (50:50, v/v) using chlorotriethylsilane in the presence of imidazole. Among the reagents described for deacylation of the 2-position,[15−18] Red-Al was the most efficient and reproducible. In summary, compound **4** was obtained in four steps from docetaxel (**1b**) with an overall yield of 24%. (Scheme 2)

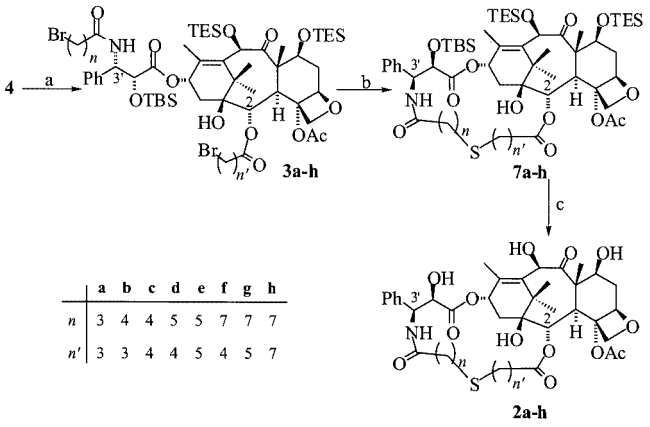


Scheme 2. a) TBSCl, imidazole, DMF, room temp. (87%); b) TFA, CH_2Cl_2, 0 °C (87%); c) TESCl, imidazole, CH_3CN/CH_2Cl_2, 60 °C (58%); d) Red-Al, THF, 0 °C (54%)

Synthesis of Macrocyclic Taxoids 2

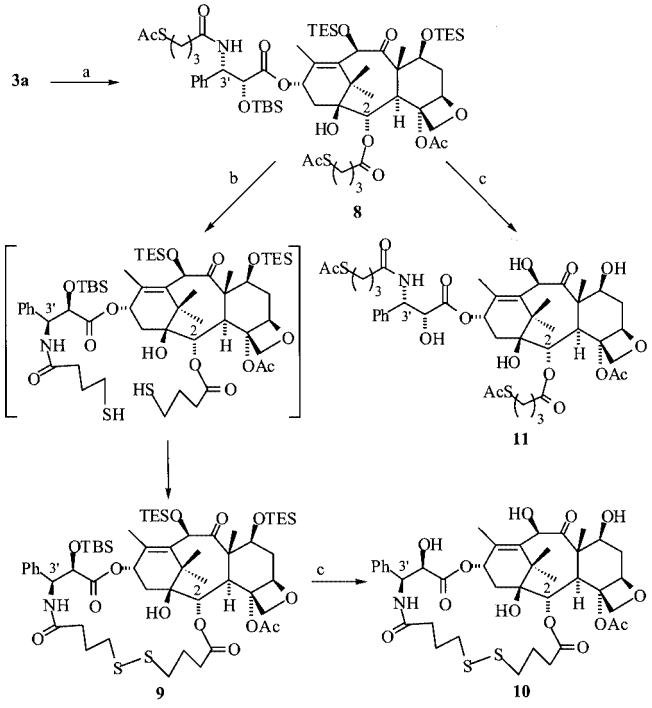
The introduction of the bromoalkyl chains on **4** was performed by acylation of 2-OH and 3′-NH_2 with $Br[CH_2]_nCOOH$ (n = 3, 4, 5, or 7). Taking advantage of the great difference in reactivity between the amino group in 3′-position and the hydroxy group in 2-position, different alkyl chains could be added in the two positions. In this way, acylation of the amine was realized with only 2 equiv. of the bromo acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP). Then, addition in the same pot of a large excess of another bromo acid and of the coupling reagents allowed the esterification of the 2-hydroxy group. For compounds **3** with $n = n'$, a large amount of the appropriate bromo acid was added at one time to perform both acylations together. Compounds **3a**−**h** were thus synthesized in medium to good yield (45−90%; Scheme 3). Macrocyclization was carried out by adding sodium sulfide in anhydrous acetone. As previously described,[14] high dilution was not necessary for ring-closure, but the solvent was critical and the acetone needed to be freshly distilled to obtain macrocyclic taxoids with acceptable yields. Final deprotection of the silyl groups at the 2′-, 7-, and 10-positions was easily achieved by HF/

pyridine to afford macrocyclic taxoids **2a**−**h** with 19- to 27-membered rings (Scheme 3).



Scheme 3. a) $Br[CH_2]_nCOOH$ (2 equiv.), DCC, DMAP, toluene, room temp. 2.5 h, then $Br[CH_2]_{n'}COOH$ (15 equiv.), DCC, DMAP, toluene, room temp. 2 h; b) Na_2S, acetone, room temp. 1 h; c) HF/pyridine, 0 °C, 3 h

In the model of paclitaxel bound to tubulin described by Snyder et al.[9] the imidazole ring of His 229 is located between the 2-benzoyl and the 3′-benzamido rings. Therefore, the presence of a macrocycle at that position could prevent interaction with tubulin and it was important to be able to compare the bioactivity of a macrocyclic taxoid with its noncyclic analogue. We chose to do this comparison only for $n = n' = 3$ and so we designed the synthesis of the noncyclic analogue of **2a**. Deprotection of the silyl groups on compound **3a** did not lead to the desired derivative because of the bromide reactivity. Therefore, we considered the synthesis of a derivative bearing a thiol group at the end of both alkyl chains (Scheme 4). The sulfur atoms were introduced as thioacetyl moieties by nucleophilic substitution of the bromides by potassium thioacetate leading to **8** in good yield. Unfortunately, hydrolysis of the acetyl groups of compound **8** only afforded the macrocyclic taxoid **9** bearing a disulfide bond, coming from oxidation in situ of the expected ω,ω′-dithiotaxoid. The tendency of this dithiol to be oxidized to a disulfide macrocyclic compound prompted us to use the dithioacetyl derivative as the reference for the noncyclic analogue. Then, the silyl groups of **8** and **9** were removed to afford compounds **10** and **11** corresponding to a 20-membered ring macrocyclic taxoid and its noncyclic analogue.



Scheme 4. a) KSAc, DMF, room temp. (84%); b) Na_2CO_3, MeOH, room temp. (33%); c) HF/pyridine, CH_3CN, 0 °C (**10**: 42%; **11**: 64%)

Biological Activities

Macrocyclic taxoids **2a**−**h**, **10**, and **11** were evaluated for their inhibition of cold-induced microtubule disassembly[19] and for their cytotoxicity against the KB cell line.[20] The results are reported in Table 1.

Table 1. Biological evaluation of macrocyclic taxoids **2a**−**h**, **10**, and **11**

Compound	n	n'	Ring size	Microtubule disassembly inhibitory activity IC_{50}/IC_{50}(paclitaxel)[a]	Cytotoxicity against the KB cell line IC_{50} [μM][b]
2a	3	3	19	inactive	45
2b	4	3	20	inactive	21
2c	4	4	21	42	15
2d	5	4	22	inactive	65
2e	5	5	23	inactive	6
2f	7	4	24	inactive	26
2g	7	5	25	80	3.5
2h	7	7	27	inactive	4.6
10	3	3	20	23	15
11	3	3	noncyclic	18	5.5

[a] IC_{50} is the concentration that inhibits 50% of the rate of microtubule disassembly. The ratio IC_{50}/IC_{50}(paclitaxel) gives the activity with respect to paclitaxel. IC_{50}(paclitaxel) = 1 μM. [b] IC_{50} measures the drug concentration required for the inhibition of 50% cell proliferation after 72 h incubation. IC_{50}(docetaxel) = 0.001 μM.

The cytotoxicity of all compounds is very low compared to that of docetaxel and does not appear to follow the tubulin activity. In the taxoid series, a few derivatives have already been reported to be inactive towards tubulin but still cytotoxic.[21−23] This may be due to a different cellular mode of action, which deserves further investigation.

Only three macrocyclic taxoids (**2c**, **2g**, and **10**) show an interaction with microtubules, and they are much less active than paclitaxel. The small difference in bioactivity between macrocyclic taxoid **10** and its noncyclic analogue **11** suggests that the presence of the macrocycle is not the main factor responsible for the low interaction with tubulin. This could instead be due to the presence of the heteroatoms in the tether linking the taxane skeleton to the side chain. It is worth noting that the disulfide taxoid **10** bearing a 20-membered ring is the most active compound of this series, whereas the sulfide 20-membered ring analogue **2b** is completely inactive towards tubulin. This discrepancy could be explained by the differences in length and geometry between C−S and S−S bonds or by a particular interaction of the disulfide bond with the protein. The low but positive interaction of the 25-membered ring taxoid **2g** with microtubules is difficult to explain unless, in this particular case, the larger ring induces a greater mobility of the macrocycle that allows it to approach the binding site.

Conclusion

We have synthesized nine new macrocyclic taxoids **2a**−**h** and **10** designed to model the "nonpolar" conformation observed in the crystal structure of docetaxel. The easy ring-closure method by nucleophilic substitution of ω,ω′-dibromotaxoids with sodium sulfide afforded a series of 19- to 27-membered ring sulfides. Although less active than paclitaxel and docetaxel, all the compounds were cytotoxic against the KB cell line even when they do not interact with microtubules, suggesting another cellular mode of action for these products. These results show that information on the active conformation can only be obtained from the tubulin activity. Although the results are disappointing in terms of bioactivity, the information that tubulin recognized taxoids **2c** and **10**, bearing 21- and 20-membered rings, respectively, is valuable, since it shows that these compounds can adopt a conformation close to the bioactive one. It should be noted that a couple of the 2-O,3′-N-linked macrocyclic taxoids bearing a 19- or a 20-membered ring[13] have shown higher cytotoxicity than taxoids **2c** and **10**, but no tubulin activity was reported for these compounds. The low antitubulin activity of the sulfur-containing compounds **2c** and **10** is not due to the presence of the macrocycle, as proved by the similar activities of the disulfide compound **10** and its noncyclic analogue **11**. Since we suspected that the presence of the sulfur atom was detrimental to the activity, we have designed new macrocyclic taxoids without any heteroatom on the macrocycle ring in order to increase the interaction with tubulin and consequently to approach the real active conformation of taxoids. We shall report the results of this study in the near future.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 300. Chemical shifts are given as δ values and are referenced to the residual solvent proton or carbon peak, i.e. chloroform [δ(C^1HCl_3) = 7.27 ppm and δ($^{13}CHCl_3$) = 77.14 ppm]. For compounds **2a**−**h**, **3a**−**h**, and **7a**−**h** all NMR spectra are very similar. The only modifications are the added acyl chains, so only the first compound of each series is fully described. For the following ones, only the NMR characteristics of the chains are reported. Mass spectra were obtained with an AQA Navigator ThermoQuest®. High-resolution mass spectra were performed with a Voyager-DE STR (PerSeptive Biosystems®) with gentisic acid as matrix and paclitaxel and docetaxel as internal standards. Merck silica gel 60 (40−63 μm) was used for flash chromatography. All chemicals were purchased from Fluka, Aldrich or Acros and were used without further purification unless indicated otherwise. Solvents were purchased from SDS. Toluene and THF were dried and distilled before use. Standard workup means extraction with a suitable solvent (EtOAc unless otherwise specified), washing the extract with H_2O or brine, drying with Na_2SO_4, and concentration under reduced pressure. Docetaxel (**1b**) was a gift from Alain Commerçon (Aventis−Pharma). Microtubular proteins were purified from bovine brain as described previously.[24]

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-(de-*tert*-butoxycarbonyl)docetaxel (5)

a) 2′-*O*-(*tert*-Butyldimethylsilyl)docetaxel: Imidazole (2 g, 29.4 mmol) and *tert*-butyldimethylsilyl chloride (3.8 g, 25.2 mmol) in DMF (16 mL) were stirred at room temperature for 45 min. Then, docetaxel (**1b**) (2 g, 2.48 mmol) in DMF (16 mL) was added and the reaction mixture was stirred for 4 h at room temperature. After workup with CH_2Cl_2, the residue was purified on silica gel (CH_2Cl_2/MeOH, 96:4) to afford pure 2′-*O*-(*tert*-butyldimethylsilyl)-docetaxel (2 g, 87%) as an amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.30 (s, 3 H, CH_3Si), −0.11 (s, 3 H, CH_3Si), 0.74 [s, 9 H, $(CH_3)_3$CSi], 1.13 (s, 3 H, 16-H_3), 1.27 (s, 3 H, 17-H_3), 1.30 [s, 9 H, 3 CH_3, Boc], 1.75 (s, 3 H, 19-H_3), 1.88 (m, 1 H, 6-Hβ), 1.91 (s, 3 H, 18-H_3), 2.14 (m, 1 H, 14-H), 2.40 (m, 1 H, 14-H), 2.56 (s, 3 H, CH_3, OAc), 2.62 (m, 1 H, 6-Hα), 3.94 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 3-H), 4.27 (qAB, $^2J_{H,H}$ = 8 Hz, 2 H, 20-H_2), 4.26 (dd, $^3J_{H,H}$ = 6.6, $^3J'_{H,H}$ = 10.5 Hz, 1 H, 7-H), 4.52 (br. s, 1 H, 2′-H), 4.98 (br. d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 5-H), 5.21 (s, 1 H, 10-H), 5.3 (br. d, $^3J_{H,H}$ = 9 Hz, 1 H, 3′-H), 5.48 (d, $^3J_{H,H}$ = 9 Hz; 1 H, 3′-NH), 5.69 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 2-H), 6.32 (t, $^3J_{H,H}$ = 8.8 Hz, 1 H, 13-H), 7.30 (m, 5 H, CH, 3′-Ph), 7.49 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, *m*-CH, 2-OBz), 7.59 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, *p*-CH, 2-OBz), 8.12 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H, *o*-CH, 2-OBz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −6.0 and −5.5 [$(CH_3)_2$Si], 10.1 (C-19), 14.4 (C-18), 21.3 (C-16), 23.0 (*C*H_3, OAc), 25.6 [$(CH_3)_3$CSi], 26.5 (C-17), 28.3 (*C*H_3, Boc), 35.9 (C-14), 37.0 (C-6), 43.3 (C-15), 46.5 (C-3), 56.9 (C-3′), 57.7 (C-8), 71.3 (C-13), 72.0 (C-7), 74.5 (C-10), 75.2 (C-2), 75.8 (C-2′), 76.9 (C-20), 79.2 (C-1), 80.1 (C, Boc), 81.2 (C-4), 84.4 (C-5), 126.6, 127.8, and 128.7 (C, 3′-Ph), 129.4 (*m*-C, 2-OBz), 130.3 (*o*-C, 2-OBz), 133.7 (*p*-C, 2-OBz), 135.7 (C-11), 139.2 (C-12 and *i*-C, 3′-Ph), 155.3 (CO, Boc), 167.2 (CO, Bz), 170.1 (CO, Ac), 171.5 (C-1′), 211.4 (C-9) ppm. MS (ESI$^+$): *m*/*z* = 944 [M + Na^+].

b) 2′-*O*-(*tert*-Butyldimethylsilyl)-3′-(de-*tert*-butoxycarbonyld)docetaxel (5): 2′-*O*-(*tert*-Butyldimethylsilyl)docetaxel (2 g, 2.17 mmol) in

CH_2Cl_2 (30 mL) was stirred at 0 °C for 20 min before dropwise addition of trifluoroacetic acid (10 mL, 25% total volume). The reaction mixture was stirred for 45 min at 0 °C before careful neutralization with sodium hydrogen carbonate. After standard workup, the residue was precipitated with a mixture of heptane/EtOAc (45:55) to afford pure **5** (1.1 g). Additional pure **5** (385 mg) was obtained by purification of the filtrate on silica gel (CH_2Cl_2/MeOH, 95:5). Compound **5** was thus obtained as an amorphous solid in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.50 (s, 3 H, CH_3Si), 0.0 (s, 3 H, CH_3Si), 0.86 [s, 9 H, $(CH_3)_3CSi$], 1.04 (s, 3 H, 16-H_3), 1.14 (s, 3 H, 17-H_3), 1.64 (m, 1 H, 14-H), 1.65 (s, 3 H, 19-H_3), 1.78 (m, 1 H, 6-Hβ), 1.79 (s, 3 H, 18-H_3), 1.94 (m, 1 H, 14-H), 2.33 (s, 3 H, CH_3, OAc), 2.48 (m, 1 H, 6-Hα), 3.77 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 3-H), 4.05−4.32 (m, 5 H, 20-H_2, 7-H, 2′-H, 3′-H), 4.90 (br. d, $^3J_{H,H}$ = 7.9 Hz, 1 H, 5-H), 5.13 (s, 1 H, 10-H), 5.56 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 2-H), 6.05 (t, $^3J_{H,H}$ = 9 Hz, 1 H, 13-H), 7.24−7.35 (m, 5 H, CH, 3′-Ph), 7.49 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, *m*-CH, 2-OBz), 7.61 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, *p*-CH, 2-OBz), 8.01 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H, *o*-CH, 2-OBz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.2 and −5.5 [$(CH_3)_2Si$], −4.6 [$C(CH_3)_3Si$], 9.9 (C-19), 14.6 (C-18), 20.8 (C-16), 22.8 (CH_3, OAc), 25.6 [$(CH_3)_3CSi$], 26.3 (C-17), 35.2 (C-14), 36.6 (C-6), 43.0 (C-15), 46.2 (C-3), 57.5 (C-3′), 59.4 (C-8), 70.9 (C-13), 71.6(C-7), 74.3 (C-10), 75.0 (C-2), 75.8 (C-2′), 76.9 (C-20), 78.2 (C-1), 81.0 (C-4), 84.3 (C-5), 127.3, 128.2 and 128.5 (*o*-, *m*-, *p*-C, 3′-Ph), 129.4 (*m*-C, 2-OBz), 130.0 (*o*-C, 2-OBz), 133.7 (*p*-C, 2-OBz), 135.5 (C-11), 139.0 (*i*-C, 3′-Ph), 139.2 (C-12), 166.8 (CO, Bz), 169.9 (CO, Ac), 172.1 (C-1′), 211.2 (C-9) ppm. MS (ESI$^+$): *m*/*z* = 822 [M + H$^+$].

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-(de-*tert*-butoxycarbonyl)-7,10-bis-(triethylsilyl)docetaxel (6): Compound **5** (1.4 g, 1.7 mmol) was heated at 60 °C in CH_3CN/CH_2Cl_2 (50:50, 30 mL) for 40 min. Meanwhile, imidazole (4 g, 58.7 mmol) and chlorotriethylsilane (8.5 mL, 62.3 mmol) were also heated at 60 °C in CH_3CN/CH_2Cl_2 (50:50, 20 mL) and both solutions were mixed quickly and stirred at 60 °C for 1.5 h. After standard workup, the crude product was purified on silica gel (heptane/EtOAc, 60:40) to afford pure **6** (1.03 g, 58%) as an amorphous white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, CH_3Si), 0.06 (s, 3 H, CH_3Si), 0.60 [m, 12 H, 2 $(CH_3CH_2)_3Si$], 0.90−1.05 [m, 27 H, $(CH_3)_3CSi$ and 2 $(CH_3CH_2)_3Si$], 1.15 (s, 3 H, 16-H_3), 1.18 (s, 3 H, 17-H_3), 1.62 (m, 1 H, 14-H), 1.64 (s, 3 H, 19-H_3), 1.78 (s, 3 H, 18-H_3), 1.80−2.01 (m, 2 H, 6-Hβ and 14-H), 2.34 (s, 3 H, CH_3, OAc), 2.52 (m, 1 H, 6-Hα), 3.76 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 3-H), 4.18 and 4.27 (qAB, $^2J_{H,H}$ = 8.3 Hz, 2 H, 20-H_2), 4.26 (d, $^3J_{H,H}$ = 6 Hz, 1 H, 2′-H), 4.30 (d, $^3J_{H,H}$ = 6 Hz, 1 H, 3′-H), 4.36 (dd, $^3J_{H,H}$ = 6.5, $^3J'_{H,H}$ = 10.5 Hz, 1 H, 7-H), 4.89 (br. d, $^3J_{H,H}$ = 8.3 Hz, 1 H, 5-H), 5.12 (s, 1 H, 10-H), 5.60 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 2-H), 6.01 (t, $^3J_{H,H}$ = 8.8 Hz, 1 H, 13-H), 7.28−7.42 (m, 5 H, CH, 3′-Ph), 7.51 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, *m*-CH, 2-OBz), 7.64 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, *p*-CH, 2-OBz), 8.04 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H, *o*-CH, 2-OBz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.1 and −4.8 [$(CH_3)_2Si$], 5.4 and 6.1 (CH_2Si), 7.0 and 7.1 (CH_3CH_2Si), 10.5 (C-19), 14.2 (C-18), 20.6 (C-16), 23.1 (CH_3, OAc), 25.8 [$(CH_3)_3CSi$], 26.5 (C-17), 35.0 (C-14), 37.4 (C-6), 43.2 (C-15), 46.8 (C-3), 58.4 (C-3′), 59.6 (C-8), 71.2 (C-13), 72.8 (C-7), 75.2 (C-2), 75.5 (C-10), 77.3 (C-2′), 78.5 (C-20), 78.9 (C-1), 81.2 (C-4), 84.2 (C-5), 127.5, 128.2 and 128.4 (*o*-, *m*-, *p*-C, 3′-Ph), 128.6 (*m*-C, Bz), 129.6 (*i*-C, Bz), 130.2 (*o*-C, Bz), 133.7 (*p*-C, Bz), 134.7 (C-11), 137.6 (C-12), 140.1 (*i*-C, 3′-Ph), 167.1 (CO, Bz), 169.9 (CO, Ac), 172.1(C-1′), 205.4 (C-9) ppm. MS (ESI$^+$): *m*/*z* = 1050 [M + H$^+$], 1072 [M + Na$^+$], 1088 [M + K$^+$].

2-Debenzoyl-2′-*O*-(*tert*-butyldimethylsilyl)-3′-(de-*tert*-butoxycarbonyl)-7,10-bis(triethylsilyl)docetaxel (4):[25] Red-Al (0.89 mL of a 0.7 M solution in THF, 0.62 mmol) was added at 0 °C to a THF solution (2.1 mL) of **6** (330 mg, 0.31 mmol), previously cooled to 0 °C for 15 min. The reaction mixture was stirred at 0 °C for 30 min and the reaction was stopped by careful addition of a saturated K^+/Na^+ tartrate solution. After standard workup, the residue was purified by silica-gel chromatography (CH_2Cl_2/MeOH, 97:3) to afford **4** (160 mg, 54%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.14 (s, 3 H, CH_3Si), −0.01 (s, 3 H, CH_3Si), 0.43−0.70 (m, 12 H, CH_2Si), 0.86 [s, 9 H, $(CH_3)_3CSi$], 0.93−1.08 [m, 18 H, 2 $(CH_3CH_2)_3Si$], 1.07 (s, 3 H, 16-H_3), 1.20 (s, 3 H, 17-H_3), 1.61 (s, 3 H, 19-H_3), 1.74 (s, 3 H, 18-H_3), 1.77 (m, 1 H, 14-H), 1.81−1.99 (m, 2 H, 6-Hβ and 14-H), 2.28 (s, 3 H, CH_3, OAc), 2.52 (m, 1 H, 6-Hα), 3.41 (d, $^3J_{H,H}$ = 6.7 Hz, 1 H, 3-H), 3.86 (d, $^3J_{H,H}$ = 6.7 Hz, 1 H, 2-H), 4.22 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 3′-H), 4.28 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2′-H), 4.32 (dd, $^3J_{H,H}$ = 6.6, $^3J'_{H,H}$ = 10.6 Hz, 1 H, 7-H), 4.58 (qAB, $^2J_{H,H}$ = 9.1 Hz, 2 H, 20-H_2), 4.90 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 5-H), 5.07 (s, 1 H, 10-H), 6.09 (t, $^3J_{H,H}$ = 8.8 Hz, 1 H, 13-H), 7.27−7.42 (m, 5 H, CH, 3′-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.3 and −4.9 [$(CH_3)_2Si$], 5.3 and 6.1 (CH_2Si), 7.0 and 7.1 (CH_3CH_2Si), 10.8 (C-19), 14.0 (C-18), 20.7 (C-16), 23.1 (CH_3, OAc), 25.8 [$(CH_3)_3CSi$], 26.3 (C-17), 35.5 (C-14), 37.5 (C-6), 42.8 (C-15), 46.7 (C-3), 58.4 (C-3′), 59.3 (C-8), 71.5 (C-13), 72.9 (C-7), 74.6 (C-2), 75.6 (C-10), 77.7 (C-2′), 78.2 (C-20), 78.5 (C-1), 82.5 (C-4), 83.8 (C-5), 127.1, 127.2, 128.0 and 128.6 (*o*-, *m*-, *p*-C, 3′-Ph), 134.4 (C-11), 137.7 (C-12), 141.4 (*i*-C, 3′-Ph), 169.6 (CO, Ac), 172.4 (C-1′), 206.1 (C-9) ppm. MS (ESI$^+$): *m*/*z* = 946 [M + H$^+$].

General Procedure for the Synthesis of Compounds 3a−h

Method A (for *n* = *n*′: 3a, c, e, h): Bromoalkanoic acid ($Br[CH_2]_nCO_2H$, 16.5 equiv.) was added dropwise to a toluene solution of **4** (1 equiv., 13 mM), DCC (16.5 equiv.) and DMAP (16.5 equiv.). The reaction mixture was stirred at room temperature for 1.5 h.

Method B (for *n* ≠ *n*′: 3b, d, f, g): Bromoalkanoic acid ($Br[CH_2]_nCO_2H$, 2 equiv.) was added dropwise to a toluene solution of **4** (1 equiv., 0.16 M initial concentration), DCC (2 equiv.), and DMAP (2 equiv.). The reaction mixture was stirred at room temperature for 2.5 h. Then, a toluene solution of DCC (15 equiv.), DMAP (15 equiv.), and another bromoalkanoic acid ($Br[CH_2]_{n'}CO_2H$, 15 equiv., 0.26 M final concentration) was added and the reaction mixture was stirred for an additional 2 h. Workup was the same for both methods. The reaction mixture was filtered through silica gel and the crude product was rapidly eluted with the purification solvent. After standard workup, the residue was purified by silica-gel chromatography.

3a (*n* = *n*′ = 3): Application of Method A on **4** (130 mg, 0.137 mmol) with 4-bromobutanoic acid, and purification with heptane/EtOAc (60:40) afforded **3a** (102 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.27 (s, 3 H, CH_3Si), −0.11 (s, 3 H, CH_3Si), 0.54−0.69 [m, 12 H, 2 $(CH_3CH_2)_3Si$], 0.80 [s, 9 H, $(CH_3)_3CSi$], 0.89−1.02 [m, 18 H, 2 $(CH_3CH_2)_3Si$], 1.17 (s, 3 H, 16-H_3), 1.21 (s, 3 H, 17-H_3), 1.63 (s, 3 H, 19-H_3), 1.81 (s, 3 H, 18-H_3), 1.92 (m, 1 H, 6β-H), 2.05−2.28 (m, 6 H, 14-H_2 and 2 $CH_2CH_2CH_2$), 2.42 (s, 3 H, CH_3, OAc), 2.43−2.66 (m, 5 H, 6-Hα, CH_2CON and CH_2COO), 3.49 (m, 4 H, 2 CH_2Br), 3.75 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 3-H), 4.20 and 4.49 (qAB, $^2J_{H,H}$ = 8 Hz, 2 H, 20-H_2), 4.35 (dd, $^3J_{H,H}$ = 6.6 Hz and $^3J'_{H,H}$ = 10.5 Hz, 1 H, 7-H), 4.49 (br. s, 1 H, 2′-H), 4.93 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-H), 5.13 (s, 1 H, 10-H), 5.43 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 2-H), 5.46 (br. d, $^3J_{H,H}$ = 9 Hz, 1 H, 3′-H), 6.15 (t, $^3J_{H,H}$ = 9 Hz, 1 H, 13-H), 6.47 (d, $^3J_{H,H}$ = 9 Hz, 1 H, NH), 7.21−7.43 (m, 5 H, 5 CH, 3′-Ph) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$): δ = −5.6 and −5.3 (CH_3Si), 5.4 and 6.1 (CH_3CH_2Si), 7.1 (CH_3CH_2Si), 10.5 (C-19), 13.9 (C-18), 20.7 (C-16), 23.3 (CH_3, OAc), 25.7 [$(CH_3)_3CSi$], 26.7 (C-17), 27.7 and 28.3 ($CH_2CH_2CH_2$), 32.8 (CH_2Br and CH_2COO), 33.4 (CH_2Br), 34.4 (CH_2CON), 35.4 (C-14), 37.4 (C-6), 43.4 (C-15), 46.6 (C-3), 55.5 (C-3′), 58.5 (C-8), 72.1 (C-13), 72.8 (C-7), 75.0 (C-2), 75.3 (C-10), 75.5 (C-2′), 77.2 (C-20), 78.8 (C-1), 81.2 (C-4), 84.3 (C-5), 126.7, 128.1, and 128.8 (*o*-, *m*-, *p*-C, 3′-Ph), 134.4 (C-11), 138.0 (C-12), 138.6 (*i*-C, 3′-Ph), 170.1 (CO, Ac), 171.4 (C-1′), 171.8 (2-OCO), 173.5 (3′-NHCO), 205.4 (C-9) ppm. MS (ESI^+): *m*/*z* = 1266 [M + Na^+].

3b (*n* = 4, *n*′ = 3): Application of Method B on **4** (150 mg, 0.159 mmol) with 4- and 5-bromopentanoic acids, and purification with CH_2Cl_2/acetone (95:5) afforded **3b** (146 mg, 73%); NMR ^1H (300 MHz, $CDCl_3$): δ = 1.74−1.94 (m, 5 H, $BrCH_2CH_2CH_2CH_2CON$ and 6-Hβ), 1.95−2.05 (m, 2 H, $BrCH_2CH_2CH_2CO$), 2.32 (m, 2 H, CH_2CON), 2.43−2.66 (m, 3 H, 6-Hα and CH_2COO), 3.38−3.60 (m, 4 H, 2 CH_2Br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (CH_2), 27.7 (CH_2), 32.0 (CH_2), 32.8 ($BrCH_2$), 33.0 (CH_2COO), 33.4 ($BrCH_2$), 35.5 (CH_2CON), 172.0 (COO), 173.5 (CON) ppm. MS (ESI^+): *m*/*z* = 1280 [M + Na^+].

3c (*n* = *n*′ = 4): Application of Method A on **4** (150 mg, 0.159 mmol) with 4-bromopentanoic acid, and purification with heptane/EtOAc (75:25) afforded **3c** (183 mg, 91%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.72−1.98 (m, 9 H, 2 $BrCH_2CH_2CH_2CH_2CO$ and 6-Hβ), 2.34 (m, 2 H, CH_2CON), 2.42−2.56 (m, 3 H, 6-Hα and CH_2COO), 3.35−3.50 (m, 4 H, 2 CH_2Br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0 (CH_2), 24.8 (CH_2), 32.0 (CH_2), 32.8 (CH_2), 33.4 ($BrCH_2$), 33.9 ($BrCH_2$), 34.7 (CH_2COO), 35.4 (CH_2CON), 171.9(COO), 174.2 (CON) ppm. MS (ESI^+): *m*/*z* = 1294 [M + Na^+].

3d (*n* = 5, *n*′ = 4): Application of Method B on **4** (150 mg, 0.159 mmol) with 4- and 5-bromohexanoic acids, and purification with CH_2Cl_2/acetone (98:2) afforded **3d** (152 mg, 75%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (m, 2 H, $CH_2CH_2CH_2$), 1.66 (m, 2 H, $CH_2CH_2CH_2$), 1.80−2.00 (m, 7 H, 3 $CH_2CH_2CH_2$ and 6-Hβ), 2.32 (m, 2 H, CH_2CON), 2.41−2.57 (m, 3 H, 6-Hα and CH_2COO), 3.37−3.50 (m, 4 H, 2 CH_2Br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (CH_2), 24.9 (CH_2), 27.8 (CH_2), 31.8 (CH_2), 32.5 (CH_2), 33.5 ($BrCH_2$), 33.9 ($BrCH_2$ and CH_2COO), 36.3 (CH_2CON), 172.3 (COO), 174.2 (CON) ppm. MS (ESI^+): *m*/*z* = 1308 [M + Na^+].

3e (*n* = *n*′ = 5): Application of Method A on **4** (50 mg, 0.053 mmol) with 4-bromohexanoic acid, and purification with heptane/EtOAc (50:50) afforded **3e** (58 mg, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20−1.26 (m, 4 H, 2 $CH_2CH_2CH_2$), 1.58−1.74 (m, 4 H, 2 $CH_2CH_2CH_2$), 1.76−1.94 (m, 5 H, 2 $BrCH_2CH_2CH_2$ and 6-Hβ), 2.30 (m, 2 H, CH_2CON), 2.35−2.41 (m, 3 H, 6-Hα and CH_2COO), 3.33−3.44 (m, 4 H, 2 CH_2Br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (CH_2), 24.5 (CH_2), 24.8 (CH_2), 27.7 (CH_2), 27.8 (CH_2), 32.7 (CH_2), 33.6 ($BrCH_2$), 33.7 ($BrCH_2$), 35.5 (CH_2COO), 36.2 (CH_2CON), 172.3(COO), 174.5 (CON) ppm. MS (ESI^+): *m*/*z* = 1322 [M + Na^+].

3f (*n* = 7, *n*′ = 4): Application of Method B on **4** (150 mg, 0.159 mmol) with 4- and 5-bromooctanoic acids, and purification with CH_2Cl_2/acetone (95:5) afforded **3f** (90 mg, 43%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22−1.49 (m, 6 H, 3 $CH_2CH_2CH_2$), 1.66 (m, 2 H, $CH_2CH_2CH_2$), 1.79−1.89 (m, 4 H, 2 $CH_2CH_2CH_2$), 1.89−2.02 (m, 3 H, $CH_2CH_2CH_2$ and 6-Hβ), 2.27 (m, 2 H, CH_2CON), 2.30−2.57 (m, 3 H, 6-Hα and CH_2COO), 3.38 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH_2Br), 3.45 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH_2Br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (CH_2), 28.0 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 31.8 (CH_2), 32.8 (CH_2), 33.4 ($BrCH_2$), 33.9 ($BrCH_2$ and CH_2COO), 36.2 (CH_2CON), 172.6 (COO), 174.2 (CON) ppm. MS (ESI^+): *m*/*z* = 1336 [M + Na^+].

3g (*n* = 7, *n*′ = 5): Application of Method B on **4** (116 mg, 0.123 mmol) with 4- and 5-bromooctanoic acids, and purification with heptane/EtOAc (85:15) afforded **3g** (91 mg, 56%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23−1.47 (m, 6 H, 3 $CH_2CH_2CH_2$), 1.49−1.74 (m, 6 H, 3 $CH_2CH_2CH_2$), 1.79−1.96 (m, 5 H, 2 $CH_2CH_2CH_2$ and 6-Hβ), 2.24−2.39 (m, 3 H, CH_2CON and CHCOO), 2.41−2.60 (m, 2 H, 6-Hα and CHCOO), 3.35−3.44 (m, 4 H, CH_2Br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (CH_2), 27.7 (CH_2), 28.0 (CH_2), 29.1 (CH_2), 32.5 (CH_2), 32.8 (CH_2), 33.6 ($BrCH_2$), 33.9 ($BrCH_2$), 35.2 (CH_2COO), 36.6 (CH_2CON), 172.6 (COO), 174.5 (CON) ppm. MS (ESI^+): *m*/*z* = 1350 [M + Na^+].

3h (*n* = *n*′ = 7): Application of Method A on **4** (150 mg, 0.159 mmol) with 4-bromohexanoic acid, and purification with heptane/EtOAc (80:20) afforded **3h** (148 mg, 69%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23−1.40 (m, 12 H, 6 $CH_2CH_2CH_2$), 1.61−1.75 (m, 4 H, 2 $CH_2CH_2CH_2$), 1.75−2.00 (m, 5 H, 2 $BrCH_2CH_2CH_2$ and 6-Hβ), 2.22−2.42 (m, 4 H, CH_2CON and CH_2COO), 3.23−3.49 (m, 4 H, CH_2Br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (CH_2), 25.3(CH_2), 28.0 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 32.7 (CH_2), 33.9 ($BrCH_2$), 35.8 (CH_2COO), 36.6 (CH_2CON), 172.7 (COO), 174.8 (CON) ppm. MS (ESI^+): *m*/*z* = 1378 [M + Na^+].

General Procedure for Ring Closure (Compounds 7a−h): Anhydrous sodium sulfide (Na_2S, 1.05 equiv.) was added to a dry acetone solution of compound **3a−h** (1 equiv., 12 mM) and the reaction mixture was stirred at room temperature for 1 h. After standard workup, the residue was purified by silica-gel chromatography (CH_2Cl_2/acetone, 95:5) unless otherwise specified.

7a (*n* = *n*′ = 3): Ring closure of **3a** (100 mg, 0.080 mmol) afforded **7a** (45 mg, 50%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = −0.36 (s, 3 H, CH_3Si), −0.12 (s, 3 H, CH_3Si), 0.55−0.79 [m, 12 H, 2 $(CH_3CH_2)_3Si$], 0.70 [s, 9 H, $(CH_3)_3CSi$], 0.95−1.02 [m, 18 H, 2 $(CH_3CH_2)_3Si$], 1.15 (s, 3 H, 16-H_3), 1.25 (s, 3 H, 17-H_3), 1.63 (s, 3 H, 19-H_3), 1.65 (m, 2 H, $CH_2CH_2CH_2$), 1.87 (s, 3 H, 18-H_3), 1.81−2.20 (m, 5 H, 6-Hβ, 14-H_2, and $CH_2CH_2CH_2$), 2.30−2.69 (m, 9 H, 2 CH_2S, 6-Hα, CH_2CON, and CH_2COO), 2.52 (s, 3 H, CH_3, OAc), 3.74 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 3-H), 4.17 (qAB, $^2J_{H,H}$ = 8 Hz, 1 H, 20-H), 4.32−4.49 (m, 2 H, 7-H and 20-H), 4.52 (br. s, 1 H, 2′-H), 4.89 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 5-H), 5.11 (s, 1 H, 10-H), 5.41 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 2-H), 5.52 (br. d, $^3J_{H,H}$ = 9.1 Hz, 1 H, 3′-H), 6.29 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, NH), 6.37 (t, $^3J_{H,H}$ = 8.8 Hz, 1 H, 13-H), 7.15−7.39 (m, 5 H, 5 CH, 3′-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −6.1 and −5.4 (CH_3Si), 5.4 and 6.1 (CH_3CH_2Si), 7.0 and 7.1 (CH_3CH_2Si), 10.7 (C-19), 13.7 (C-18), 21.3 (C-16), 23.4 (CH_3OAc), 25.5 [$(CH_3)_3CSi$], 25.9 ($CH_2CH_2CH_2$), 26.8 (C-17), 30.6 and 30.9 (CH_2S), 33.6 (CH_2COO), 35.2 (CH_2CON), 35.8 (C-14), 37.3 (C-6), 43.4 (C-15), 46.8 (C-3), 54.8 (C-3′), 58.3 (C-8), 70.7 (C-13), 72.6 (C-7), 75.1 and 75.2 (C-2, C-10, and C-2′), 77.2 (C-20), 79.7 (C-1), 80.8 (C-4), 84.4 (C-5), 126.5, 127.8, and 128.6 (*o*-, *m*-, *p*-C, 3′-Ph), 134.0 (C-11), 137.6 (C-12), 138.3 (*i*-C, 3′-Ph), 170.1 (CO, Ac), 171.2 (C-1′), 171.6 (2-OCO), 174.2 (3′-NHCO), 205.2 (C-9). MS (ESI^+): *m*/*z* = 1138 [M + Na^+].

7b (*n* = 4, *n*′ = 3): Ring closure of **3b** (120 mg, 0.095 mmol) afforded **7b** (55 mg, 51%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41−1.76 (m, 4 H,

$SCH_2CH_2CH_2CH_2CON$), 1.85−2.03 (m, 3 H, $SCH_2CH_2CH_2CO$ and 6-Hβ), 2.27 (m, 1 H, CHCON), 2.35−2.47 (m, 3 H, CHCON and CH_2COO), 2.50−2.71 (m, 5 H, 6-Hα and 2 CH_2S) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (CH_2), 25.2 (CH_2), 28.9 (CH_2), 30.5 (SCH_2), 32.1 (SCH_2), 34.4 (CH_2COO), 34.7 (CH_2CON), 172.0 (COO), 174.2 (CON) ppm. MS (ESI^+): *m*/*z* = 1152 [M + Na^+].

7c (*n* = *n*′ = 4): Ring closure of **3c** (100 mg, 0.079 mmol) afforded **7c** (47 mg, 52%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45−1.80 (m, 8 H, 2 $SCH_2CH_2CH_2CH_2CO$), 2.30 (m, 2 H, CHCON and CHCOO), 2.36−2.49 (m, 4 H, CHCON, CHCOO, and 2 $SCHCH_2$), 2.49−2.70 (m, 3 H, 6-Hα and 2 $SCHCH_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5 (CH_2), 24.5 (CH_2), 28.2 (CH_2), 28.5 (CH_2), 30.1 (SCH_2), 31.3 (SCH_2), 34.5 (CH_2COO), 34.7 (CH_2CON), 171.9(COO), 174.2 (CON) ppm. MS (ESI^+): *m*/*z* = 1166 [M + Na^+].

7d (*n* = 5, *n*′ = 4): Ring closure of **3d** (120 mg, 0.093 mmol) afforded **7d** (75 mg, 69%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (m, 2 H, $CH_2CH_2CH_2$), 1.54−1.76 (m, 8 H, 4 $CH_2CH_2CH_2$), 2.24−2.45 (m, 4 H, CH_2CON and CH_2COO), 2.47−2.60 (m, 5 H, 2 SCH_2 and 6-Hα) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (CH_2), 24.4 (CH_2), 27.2 (CH_2), 28.7 (CH_2), 30.6 (SCH_2), 31.2 (SCH_2), 34.6 (CH_2COO), 35.4 (CH_2CON), 172.2 (COO), 174.5 (CON) ppm. MS (ESI^+): *m*/*z* = 1180 [M + Na^+].

7e (*n* = *n*′ = 5): Ring closure of **3e** (50 mg, 0.038 mmol) afforded **7e** (20 mg, 44%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08−1.43 (m, 4 H, 2 $CH_2CH_2CH_2$), 1.43−1.88 (m, 8 H, 2 $CH_2CH_2CH_2$), 2.23−2.45 (m, 4 H, CH_2CON and CH_2COO), 2.45−2.58 (m, 5 H, 2 SCH_2 and 6-Hα) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5 (CH_2), 25.0 (CH_2), 27.6 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 31.1 (SCH_2), 31.6 (SCH_2), 34.4 (CH_2COO), 35.5 (CH_2CON), 172.2 (COO), 174.8 (CON) ppm. MS (ESI^+): *m*/*z* = 1194 [M + Na^+].

7f (*n* = 7, *n*′ = 4): Ring closure of **3f** (50 mg, 0.038 mmol) afforded **7f** (26 mg, 58%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12−1.42 (m, 6 H, 3 $CH_2CH_2CH_2$), 1.49−1.78 (m, 6 H, 3 $CH_2CH_2CH_2$), 1.72−2.01 (m, 3 H, 6-Hβ and $CH_2CH_2CH_2$), 2.21−2.47 (m, 4 H, CH_2CON and CH_2COO), 2.47−2.60 (m, 5 H, SCH_2 and 6-Hα) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (CH_2), 24.5 (CH_2), 27.0 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 30.9 (SCH_2), 31.4 (SCH_2), 34.4 (CH_2COO), 35.9 (CH_2CON), 171.6 (COO), 172.3 (CON) ppm. MS (ESI^+): *m*/*z* = 1208 [M + Na^+].

7g (*n* = 7, *n*′ = 5): Ring closure of **3g** (73 mg, 0.055 mmol) afforded **7g** (29 mg, 44%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20−1.41 (m, 6 H, 3 $CH_2CH_2CH_2$), 1.41−1.58 (m, 8 H, 4 $CH_2CH_2CH_2$), 1.64 (m, 2 H, $CH_2CH_2CH_2$), 2.26−2.41 (m, 4 H, CH_2CON and CH_2COO), 2.45−2.57 (m, 5 H, SCH_2 and 6-Hα) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (CH_2), 24.8 (CH_2), 27.6 (CH_2), 27.8 (CH_2), 28.0 (CH_2), 28.8 (CH_2), 29.4 (CH_2), 31.9 (SCH_2), 34.5 (CH_2COO), 36.0 (CH_2CON), 172.4 (COO), 174.7 (CON) ppm. MS (ESI^+): *m*/*z* = 1222 [M + Na^+].

7h (*n* = *n*′ = 7): Ring closure of **3h** (83 mg, 0.061 mmol) afforded **7h** (30 mg, 40%) as a white amorphous solid [purification was performed with CH_2Cl_2/acetone (96:4) as solvent]. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22−1.36 (m, 12 H, 6 $CH_2CH_2CH_2$), 1.36−1.73 (m, 8 H, 4 $CH_2CH_2CH_2$), 2.23−2.58 (m, 9 H, 2 SCH_2, 6-Hα, CH_2CON, and CH_2COO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (CH_2), 25.2 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 28.5 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 31.5 (S-CH_2), 31.7 (S-CH_2), 34.7 (CH_2-COO), 36.1 (CH_2-CON), 172.5 (COO), 175.0 (CON) ppm. MS (ESI^+): *m*/*z* = 1250 [M + Na^+].

General Procedure for Removal of the Silyl Groups: HF/pyridine (70:30, 40 equiv.) was added dropwise at 0 °C to a solution of **7a−h** (1 equiv., 30 mM) in pyridine/acetonitrile (7:93), and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate solution. After standard workup, the crude extract was purified by silica-gel chromatography (CH_2Cl_2/acetone, 95:5).

2a (*n* = *n*′ = 3): Removal of the silyl groups of **7a** (10 mg, 0.009 mmol) afforded **2a** (3.6 mg, 52%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, 16-H_3), 1.27 (s, 3 H, 17-H_3), 1.73 (s, 3 H, 19-H_3), 1.77−1.91 (m, 2 H, 6-Hβ and CH_2CHCH_2S), 1.94 (s, 3 H, 18-H_3), 1.97−2.15 (m, 2 H, 14-H and CH_2CHCH_2S), 2.18−2.28 (m, 1 H, 14-H), 2.29−2.44 (m, 2 H, CHCON and CHCOO), 2.51 (s, 3 H, CH_3, OAc), 2.48−2.75 (m, 5 H, CHCON, CHCOO, 6-Hα and CH_2S), 3.83 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 3-H), 4.16−4.32 (m, 2 H, 7-H and 20-H), 4.49 (d, $^3J_{H,H}$ = 8 Hz, 1 H, 20-H), 4.72 (br. s, 1 H, 2′-H), 4.95 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, 5-H), 5.16 (s, 1 H, 10-H), 5.46 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 2-H), 5.87 (br. d, 1 H, $^3J_{H,H}$ = 9.3 Hz, 3′-H), 6.14 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, NH), 6.48 (t, $^3J_{H,H}$ = 9 Hz, 1 H, 13-H), 7.29−7.47 (m, 5 H, 5 CH, 3′-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.1 (C-19), 13.8 (C-18), 21.5 (C-16), 22.9 (CH_3, OAc), 25.5 and 25.7 ($CH_2CH_2CH_2S$), 26.6 (C-17), 30.3 and 30.7 (CH_2S), 33.3 (CH_2CO), 35.1 (C-14), 36.2 (C-6 and CH_2CON), 43.2 (C-15), 46.3 (C-3), 55.7 (C-3′), 57.5 (C-8), 71.1 (C-13), 71.5 (C-7), 72.9 (C-2′), 73.9 (C-2), 75.1 (C-10), 77.6 (C-20), 79.4 (C-1), 80.7 (C-4), 84.8 (C-5), 126.6, 127.7 and 128.7 (*o*-, *m*-, *p*-C, 3′-Ph), 135.5 (C-11), 138.4 (C-12 and *i*-C, 3′-Ph), 171.1 (CO, Ac), 171.9 (2-OCO), 172.6 (C-1′), 174.1 (CON), 210.9 (C-9) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{39}H_{51}NO_{13}S$ + Na^+] 796.2979, found 796.2988 (Δ = −1.1 ppm).

2b (*n* = 4, *n*′ = 3): Removal of the silyl groups of **7b** (44 mg, 0.039 mmol) afforded **2b** (16 mg, 54%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.80−1.94 (m, 5 H, $SCH_2CH_2CH_2CH_2CON$ and 6-Hβ), 1.95−2.15 (m, 3 H, $SCH_2CH_2CH_2CO$ and 14-H), 2.36 (m, 2 H, CH_2CON), 2.45−2.73 (m, 7 H, CH_2COO, 6-Hα and 2 CH_2S) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0 (CH_2), 25.1 (CH_2), 28.8 (CH_2), 30.5 (SCH_2), 31.9 (SCH_2), 34.4 (CH_2COO), 34.6 (CH_2CON), 173.3 (COO), 174.1 (CON) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{40}H_{53}NO_{13}S$ + Na^+] 810.3135, found 810.3138 (Δ = −0.4 ppm).

2c (*n* = *n*′ = 4): Removal of the silyl groups of **7c** (20 mg, 0.017 mmol) afforded **2c** (8.4 mg, 60%) as a white amorphous solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.56−1.87 (m, 9 H, 2 $SCH_2CH_2CH_2CH_2CO$ and 6-Hβ), 2.11−2.38 (m, 6 H, 14-H_2, CH_2CON, and CH_2COO), 2.38−2.71(m, 5 H, 6-Hα and 2 SCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (CH_2), 24.5 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 31.0 (SCH_2), 31.9 (SCH_2), 34.7 (CH_2COO), 34.8 (CH_2CON), 173.4 (COO), 174.1 (CON) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{41}H_{55}NO_{13}S$ + Na^+] 824.3292, found 824.3284 (Δ = 1.0 ppm).

2d (*n* = 5, *n*′ = 4): Removal of the silyl groups of **7d** (40 mg, 0.035 mmol) afforded **2d** (14 mg, 50%) as a white amorphous solid [purification was performed with CH_2Cl_2/acetone (97:3) as solvent]. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (m, 2 H, $CH_2CH_2CH_2$), 1.60−1.76 (m, 4 H, 2 $CH_2CH_2CH_2$), 1.76−1.89 (m, 5 H, 2 $CH_2CH_2CH_2$ and 6-Hβ), 2.15−2.30 (m, 6 H, CH_2CON, CH_2COO, and 14-H_2), 2.48−2.66 (m, 5 H, 2 SCH_2 and 6-Hα) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5 (CH_2), 24.6 (CH_2), 27.2 (CH_2), 28.7 (CH_2), 31.4 (SCH_2), 31.7 (SCH_2), 34.9 (*C*H_2COO), 35.7 (*C*H_2CON), 173.1 (COO), 174.3 (CON) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{42}H_{57}NO_{13}S$ + Na^+] 838.3448, found 838.3469 (Δ = −2.5 ppm).

2e (*n* = *n*′ = 5): Removal of the silyl groups of **7e** (18 mg, 0.015 mmol) afforded **2e** (7.1 mg, 57%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37−1.60 (m, 4 H, CH_2CH_2CH$_2$), 1.60−1.97 (m, 9 H, 2 CH$_2$CH_2CH_2 and 6-Hβ), 2.27−2.70 (m, 9 H, CH_2CON, 2 SCH_2, 6-Hα, and CH_2COO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5 (CH_2), 25.5 (CH_2), 27.0 (CH_2), 28.2 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 31.9 (SCH_2), 32.1 (SCH_2), 34.9 (*C*H_2COO), 35.9 (*C*H_2CON), 173.2 (COO), 173.9 (CON) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{43}H_{59}NO_{13}S$ + Na^+] 852.3605, found 852.3617 (Δ = −1.4 ppm).

2f (*n* = 7, *n*′ = 4): Removal of the silyl groups of **7f** (26 mg, 0.022 mmol) afforded **2f** (10.5 mg, 57%) as a white amorphous solid [purification was performed with CH_2Cl_2/acetone (97:3) as solvent]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29−1.48 (m, 6 H, 3 CH$_2$CH_2CH$_2$), 1.50−1.93 (m, 9 H, 4 CH$_2$CH_2CH$_2$ and 6-Hβ), 2.08−2.43 (m, 6 H, 14-H_2, CH_2CON, and CH_2COO), 2.43−2.64 (m, 5 H, SCH_2 and 6-Hα) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (CH_2), 24.8 (CH_2), 27.3 (CH_2), 27.5 (CH_2), 27.8 (CH_2), 28.0 (CH_2), 28.6 (CH_2), 31.5 (SCH_2), 32.0 (SCH_2), 34.7 (*C*H_2COO), 36.2 (*C*H_2CON), 172.9 (COO), 174.2 (CON) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{44}H_{61}NO_{13}S$ + Na^+] 866.3761, found 866.3766 (Δ = −0.5 ppm).

2g (*n* = 7, *n*′ = 5): Removal of the silyl groups of **7g** (20 mg, 0.017 mmol) afforded **2g** (7.6 mg, 53%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19−1.42 (m, 6 H, 3 CH$_2$CH_2CH$_2$), 1.43−1.79 (m, 10 H, 5 CH$_2$CH_2CH$_2$), 2.26−2.36 (m, 4 H, CH_2CON and CH_2COO), 2.37−2.55 (m, 5 H, 2 SCH_2 and 6-Hα) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5 (CH_2), 25.0 (CH_2), 27.9 (CH_2), 28.7(CH_2), 29.4 (CH_2), 29.9 (CH_2), 32.1 (SCH_2), 34.8 (*C*H_2COO), 36.2 (*C*H_2CON), 173.1 (COO), 174.5 (CON) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{45}H_{63}NO_{13}S$ + Na^+] 880.3918, found 880.3895 (Δ = 2.5 ppm).

2h (*n* = *n*′ = 7): Removal of the silyl groups of **7h** (20 mg, 0.016 mmol) afforded **2h** (7.4 mg, 53%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28−1.49 (m, 12 H, 3 CH_2CH_2CH$_2$), 1.50−1.90 (m, 9 H, 4 CH$_2$CH_2CH_2 and 6-Hβ), 2.10−2.31 (m, 4 H, 14-H_2 and CH_2CON),2.33−2.63 (m, 7 H, 2 SCH_2, 6-Hα, and CH_2COO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (CH_2), 25.3 (CH_2), 27.8 (CH_2), 28.3 (CH_2), 28.5 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 31.9 (SCH_2), 34.9 (*C*H_2COO), 36.3 (*C*H_2CON), 173.2 (COO), 174.8 (CON) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{47}H_{67}NO_{13}S$ + Na^+] 908.4231, found 908.4248 (Δ = −1.9 ppm).

Synthesis of the Dithioacetyl Derivative 8: Potassium thioacetate (30 mg, 0.26 mmol) was added to a solution of **3a** (150 mg, 0.12 mmol) in dry DMF (2.95 mL) and the solution was stirred for 3 h at room temperature. After standard workup, the residue was purified by silica-gel chromatography (heptane/EtOAc, 75:25) to afford **8** (124 mg, 83%) as a yellowish amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.30 (s, 3 H, CH_3Si), −0.11 (s, 3 H, CH_3Si), 0.61 [m, 12 H, 2 (CH_3CH_2)$_3$Si], 0.78 [s, 9 H, (CH_3)$_3$CSi], 0.96 [m, 18 H, 2 (CH_3CH_2)$_3$Si], 1.16 (s, 3 H, 16-H_3), 1.18 (s, 3 H, 17-H_3), 1.62 (s, 3 H, 19-H_3), 1.80 (s, 3 H, 18-H_3), 1.91 (m, 5 H, 6-Hβ and 2 CH$_2$CH_2CH$_2$S), 2.19 (m, 2 H, 14-H_2), 2.30−2.32 (s, 6 H, 2 CH_3COS), 2.37−2.44 (m, 4 H, CH_2COO and CH_2CON), 2.41 (s, 3 H, CH_3, OAc), 2.49 (m, 1 H, 6-Hα), 2.94 (m, 4 H, 2 CH_2S), 3.72 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 3-H), 4.20 and 4.44 (qAB, $^2J_{H,H}$ = 8 Hz, 2 H, 20-H_2), 4.34 (dd, $^3J_{H,H}$ = 6.6 Hz and $^3J'_{H,H}$ = 10.6 Hz, 1 H, 7-H), 4.48 (d, $^3J_{H,H}$ = 1.5 Hz, 1 H, 2′-H), 4.92 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, 5-H), 5.11 (s, 1 H, 10-H), 5.44 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 2-H), 5.47 (dd, $^3J_{H,H}$ = 9 Hz and $^3J'_{H,H}$ = 1.5 Hz, 1 H, 3′-H), 6.13 (t, $^3J_{H,H}$ = 9 Hz, 1 H, 13-H), 6.59 (d, $^3J_{H,H}$ = 9 Hz, 1 H, NH), 7.31 (m, 5 H, 5 CH, 3′-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.7 and −5.3 (CH_3Si), 5.3 and 6.1 [2 (CH_3CH_2)$_3$Si], 7.0 and 7.1 [2 (CH_3CH_2)$_3$Si], 10.5 (C-19), 13.9 (C-18), 20.8 (C-16), 23.3 (CH_3, OAc), 24.8 ($CH_2CH_2CH_2S$), 25.6 [(CH_3)$_3$CSi], 26.6 (C-17), 28.3 and 28.4 ($CH_2CH_2CH_2S$), 30.7 (*C*H_3COS), 33.5 (2-OCO*C*H_2), 34.9 (*C*H_2CON), 35.5 (C-14), 37.4 (C-6), 43.4 (C-15), 46.5 (C-3), 55.4 (C-3′), 58.4 (C-8), 72.1 (C-13), 72.7 (C-7), 74.9 (C-2), 75.2 (C-2′), 75.4 (C-10), 76.9 (C-20), 78.5 (C-1), 81.1 (C-4), 84.3 (C-5), 126.7, 128.0 and 128.7 (*o*-, *m*-, *p*-C, 3′-Ph), 134.2 (C-11), 138.0 (C-12), 138.6 (*i*-C, 3′-Ph), 170.1 (CO, Ac), 171.6 (C-1′), 171.7 (2-OCO), 173.5 (3′-NHCO), 195.6 and 196.1 (COS), 205.4 (C-9). MS (ESI^+): *m*/*z* = 1257 [M + Na^+].

Synthesis of the Disulfide Derivative 9: Sodium carbonate was added to a solution of **8** (30 mg, 0.024 mmol) in MeOH (0.56 mL) and the solution was stirred for 3 h at room temperature. After standard workup, the residue was purified by silica-gel chromatography (heptane/EtOAc, 50:50) to afford **9** (9.4 mg, 34%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.35 (s, 3 H, CH_3Si), −0.09 (s, 3 H, CH_3Si), 0.56 [m, 12 H, 2 (CH_3CH_2)$_3$Si], 0.72 [s, 9 H, (CH_3)$_3$CSi], 0.99 [m, 18 H, 2 (CH_3CH_2)$_3$Si], 1.16 (s, 3 H, 16-H_3), 1.26 (s, 3 H, 17-H_3), 1.63 (s, 3 H, 19-H_3), 1.86 (s, 3 H, 18-H_3), 1.79−2.27 (m, 7 H, 6-Hβ, 14-H_2, and 2 CH$_2$CH_2CH$_2$S), 2.30−2.60 (m, 5 H, 6-Hα, CH_2COO, and CH_2CON), 2.52 (s, 3 H, CH_3, OAc), 2.66−2.92 (m, 4 H, 2 CH_2S), 3.76 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 3-H), 4.18 and 4.41 (qAB, $^2J_{H,H}$ = 8 Hz, 2 H, 20-H_2), 4.40 (m, 1 H, 7-H), 4.54 (br. s, 1 H, 2′-H), 4.9 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, 5-H), 5.12 (s, 1 H, 10-H), 5.40 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 2-H), 5.61 (br. d, $^3J_{H,H}$ = 9 Hz, 1 H, 3′-H), 6.33 (d, $^3J_{H,H}$ = 9 Hz, 1 H, NH), 6.40 (t, $^3J_{H,H}$ = 8.5 Hz, 1 H, 13-H), 7.15−7.42 (m, 5 H, 5 CH, 3′-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −6.1 and −5.4 (CH_3Si), 5.3 and 5.9 (CH_3CH_2Si), 6.8 and 6.9 (*C*H_3CH_2Si), 10.6 (C-19), 13.6 (C-18), 21.1 (C-16), 23.3 (CH_3, OAc), 25.3 ($CH_2CH_2CH_2S$), 25.4 [(CH_3)$_3$CSi], 26.7 (C-17), 33.6 (2-OCO*C*H_2), 34.7 (*C*H_2CON), 35.6 (C-14), 37.2 (C-6), 38.9 (CH_2S), 43.3 (C-15), 46.6 (C-3), 54.7(C-3′), 58.2 (C-8), 70.8 (C-13), 72.6 (C-7), 74.8 (C-2), 75.1 (C-2′ and C-10), 77.3 (C-20), 79.4 (C-1), 80.8 (C-4), 84.2 (C-5), 126.4, 127.6, and 128.5 (*o*-, *m*-, *p*-C, 3′-Ph), 133.8 (C-11), 137.6 (C-12), 138.1 (*i*-C, 3′-Ph), 170.7 (CO, Ac), 171.2 (C-1′), 171.5 (2-OCO), 173.7 (3′-NHCO′), 205.1 (C-9) ppm. MS (ESI^+): *m*/*z* = 1170 [M + Na^+].

Synthesis of Macrocyclic Taxoid 10: Removal of the silyl protecting groups of **9** (20 mg, 0.017 mmol) was carried out according to the general procedure but the solution was stirred for an additional 3 h at room temperature. After standard workup, the residue was purified by silica-gel chromatography (CH_2Cl_2/MeOH, 9:1) to afford pure **10** (6.5 mg, 42%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (s, 3 H, 16-H_3), 1.26 (s, 3 H, 17-H_3), 1.71 (s, 3 H, 19-H_3), 1.87 (m, 1 H, 6-Hβ), 1.91 (s, 3 H, 18-H_3), 1.98−2.31 (m, 6 H, 14-H_2 and 2 CH$_2$CH_2CH$_2$S), 2.32−2.43 (m, 4 H, CH_2COO and CH_2CON), 2.46 (s, 3 H, CH_3, OAc), 2.55 (m, 1 H, 6-Hα), 2.84 (m, 4 H, 2 CH_2S), 3.83 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 3-H), 4.20 and 4.48 (qAB, $^2J_{H,H}$ = 8.2 Hz, 2 H, 20-H_2), 4.24 (dd, $^3J_{H,H}$ = 6.4 Hz and $^3J'_{H,H}$ = 11.4 Hz, 1 H, 7-H), 4.73 (br. s, 1 H, 2′-H), 4.96 (d, $^3J_{H,H}$ = 9 Hz, 1 H, 5-H), 5.15 (s, 1 H, 10-H), 5.41 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 2-H), 5.58 (br. d, 1 H, $^3J_{H,H}$ = 9 Hz, 3′-H), 6.28 (d, $^3J_{H,H}$ = 9 Hz, 1 H, NH), 6.47 (t, $^3J_{H,H}$ = 9 Hz, 1 H,

13-H), 7.31−7.43 (m, 5 H, 5 CH, 3′-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.4 (C-19), 14.2 (C-18), 21.5 (C-16), 22.6 (CH_3, OAc), 25.4 ($CH_2CH_2CH_2S$), 26.7 (C-17), 33.8 (2-OCOCH_2), 34.9 (CH_2CON), 36.0 (C-14), 36.8 (C-6), 38.9 and 39.0 (CH_2S), 43.2 (C-15), 46.3 (C-3), 55.3 (C-3′), 57.5 (C-8), 71.8 (C-13), 72.4 (C-7), 72.7 (C-2), 74.2 (C-2′), 74.7 (C-10), 77.3 (C-20), 79.6 (C-1), 80.6 (C-4), 84.4 (C-5), 126.7, 128.1, and 128.9 (*o*-, *m*-, *p*-C, 3′-Ph), 135.1 (C-11), 138.1 (C-12), 138.3 (*i*-C, 3′-Ph), 170.8 (CO, Ac), 171.6 (C-1′), 173.2 (2-OCO), 173.8 (3′-NHCO), 211.5 (C-9) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{39}H_{51}NO_{13}S_2$ + Na^+] 828.2700, found 828.2734 (Δ = −4.1 ppm).

Synthesis of Taxoid 11: Removal of the silyl protecting groups of **8** (30 mg, 0.024 mmol) was carried out according to the general procedure but the solution was stirred for an additional 3 h at 0 °C. After standard workup, the residue was purified by silica-gel chromatography (CH_2Cl_2/MeOH, 95:5) to afford pure **11** (13.7 mg, 64%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 3 H, 16-H_3), 1.21 (s, 3 H, 17-H_3), 1.70 (s, 3 H, 19-H_3), 1.80 (s, 3 H, 18-H_3), 1.80−2.00 (m, 5 H, 6-Hβ and 2 $CH_2CH_2CH_2S$), 2.12−2.65 (m, 7 H, 14-H_2, 6-Hα, CH_2COO, and CH_2CON), 2.23 (s, 3 H, CH_3, OAc), 2.34 (s, 6 H, 2 CH_3COS), 2.94−3.03 (m, 4 H, 2 CH_2S), 3.76 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 3-H), 4.17 (m, 1 H, 7-H), 4.20 and 4.44 (qAB, $^2J_{H,H}$ = 8 Hz, 2 H, 20-H_2), 4.63 (d, $^3J_{H,H}$ = 2.1 Hz, 1 H, 2′-H), 4.93 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, 5-H), 5.17 (s, 1 H, 10-H), 5.45 (d, $^3J_{H,H}$ = 7 Hz, 1 H, 2-H), 5.54 (dd, $^3J_{H,H}$ = 9 Hz and $^3J'_{H,H}$ = 2.1 Hz, 1 H, 3′-H), 6.16 (t, $^3J_{H,H}$ = 9.9 Hz, 1 H, 13-H), 6.58 (d, $^3J_{H,H}$ = 9 Hz, 1 H, NH), 7.31−7.46 (m, 5 H, CH, 3′-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.9 (C-19), 14.4 (C-18), 20.7 (C-16), 22.7 (CH_3, OAc), 24.8 ($CH_2CH_2CH_2S$), 26.6 (C-17), 28.3 ($CH_2CH_2CH_2S$), 30.8 (CH_3COS), 33.5 (2-OCOCH_2), 34.9 (CH_2CON), 35.8 (C-14), 37.0 (C-6), 43.2 (C-15), 46.3 (C-3), 55.8 (C-3′), 57.7 (C-8), 71.9 (C-13), 72.7 (C-7), 73.1 (C-2), 74.6 (C-2′ and C-10), 78.2 (C-20), 78.4 (C-1), 81.0 (C-4), 84.4 (C-5), 127.2, 128.3, and 129.0 (*o*-, *m*-, *p*-C, 3′-Ph), 136.2 (C-11), 138.3 (C-12 and *i*-C, 3′-Ph), 170.3 (CO, Ac), 171.8 (C-1′), 173.1 (2-OCO), 173.4 (3′-NHCO), 196.1and 197.0 (COS), 211.5 (C-9) ppm. HRMS (MALDI-TOF): *m*/*z* calcd. for [$C_{43}H_{57}NO_{15}S_2$ + Na^+] 914.3067, found 914.3079 (Δ = −1.3 ppm).

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[25] Larger amounts of compound **4** have been prepared by OrgaLink.

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