Semisynthesis of D-Ring Modified Taxoids: Novel Thia Derivatives of Docetaxel

Ludovic Mercklé, Joëlle Dubois,* Estelle Place, Sylviane Thoret, Françoise Guéritte, Daniel Guénard, Christiane Poupat, Alain Ahond, and Pierre Potier

Institut de Chimie des Substances Naturelles, CNRS 91198 Gif sur Yvette Cedex, France

joelle.dubois@icsn.cnrs-gif.fr

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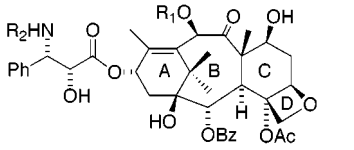
Two novel 5(20)-thia analogues of docetaxel have been synthesized from 10-deacetylbaccatin III or taxine B and isotaxine B. The key step of these syntheses is the concomitant thietane ring formation and acetylation of the tertiary alcohol at C-4. Both compounds are less cytotoxic than docetaxel but have divergent activity on microtubule disassembly.

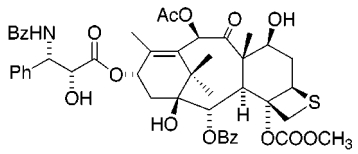
Introduction

Paclitaxel (Taxol, **1a**)[1] and docetaxel (Taxotere, **1b**)[2] are anticancer drugs[3] of the taxoid series, which inhibit cell growth by interacting with microtubules.[4] Since their discovery, structure−activity relationships have been extensively studied in order to determine the minimal structural requirements to maintain microtubule binding.[5] These studies have established that the C-13 side chain, the ester groups at C-2 and C-4, and the rigid core to which all these moieties are attached are essential for biological activity.



Paclitaxel (Taxol®) **1a** R_1=Ac, R_2=Bz
Docetaxel(Taxotere®) **1b** R_1=H, R_2=Boc

The role of the oxetane ring, which is still unclear, has been one of our main interests over the past few years. Two hypotheses can be proposed to explain the importance of the D-ring in the interaction with microtubules. It might either act to rigidify ring C and enforce a favorable conformation of the side chain at C-13 and acyl groups at C-2 and C-4 or be directly involved in the interaction with microtubules via its oxygen atom. In the paclitaxel-β-tubulin binding site, observed in the electron crystallographic structure of tubulin,[6] the oxygen of the oxetane ring can be involved in a hydrogen bond with Thr276.[7] Thus, replacement of this atom by sulfur, which is unable to undergo hydrogen bonding, would give information on the presence of such a hydrogen bond between tubulin and the taxoid and, if it exists, on its contribution to the binding. While we were preparing the thietane analogues of docetaxel, the synthesis of a 5(20)-thiapaclitaxel analogue **2** was published.[8] In this case, formation of the thietane ring led to a C-4 hydroxyl group that was totally unreactive toward acetylation. The authors thus introduced a C-4 methoxycarbonyl group instead of the usual C-4 acetyl moiety. This lack of reactivity of the C-4 hydroxyl group toward acetylation was also observed in thia derivatives of 7-deoxybaccatin III[9] in which only the dibenzylidene derivative **3** could be acetylated (Ac_2O, DMAP, pyridine) in moderate yield.



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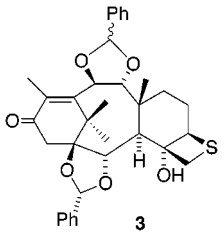

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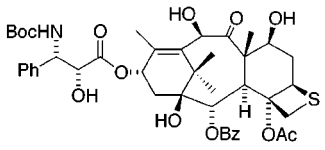
As part of our studies on the synthesis of D-ring modified taxoids,[9−11] we wish to present here an efficient method to synthesize the thietane ring with concomitant C-4 acetylation. Full synthesis of 5(20)-thiadocetaxel (**4**) and its 7-deoxy analogue **5** will be described along with their biological activities.



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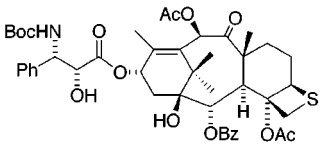

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(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.
(2) For a review, see: Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160−167.
(3) Guénard, D.; Guéritte-Voegelein, F.; Lavelle, F. *Curr. Pharm. Design* **1995**, *1*, 95−112.
(4) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665−667.
(5) For general reviews on taxoid chemistry, see: (a) *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: New York, 1995. (b) *Taxane Anticancer Agents: Basic Science and Current Status;* Georg, I. G., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series No. 583; American Chemical Society: Washington DC, 1995. (c) *The Chemistry and Pharmacology of Taxol® and its Derivatives*; Farina, V. Ed.; Elsevier: New York, 1995.
(6) Nogales, E.; Wolf, S.; Downing, K. H. *Nature* **1998**, *391*, 199−203.
(7) Wang, M.; Cornett, B.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.* **2000**, *65*, 1059−1068.
(8) Gunatilaka, A. A. L.; Ramdayal, F. D., Sarragiotto, M. H.; Kingston, D. G. I.; Sackett, D. L.; Hamel, E. *J. Org. Chem.* **1999**, *64*, 2694−2703.
(9) Payré, C.; Al Mourabit, A.; Mercklé, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron Lett.* **2000**, *41*, 4891−4894.
(10) Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **1997**, *62*, 6631−6637.
(11) Dubois, J.; Thoret, S.; Guéritte, F.; Guénard, D. *Tetrahedron Lett.* **2000**, *41*, 3331−3334.

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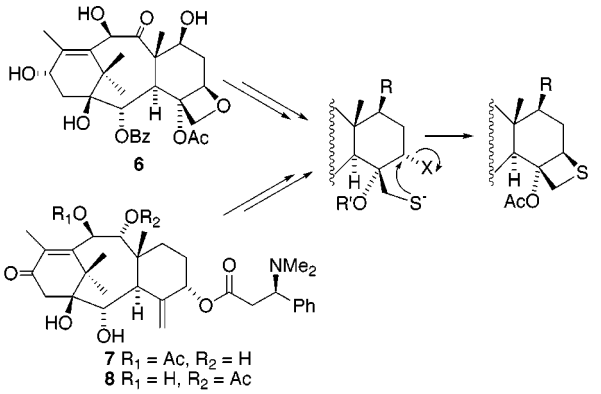
Scheme 1



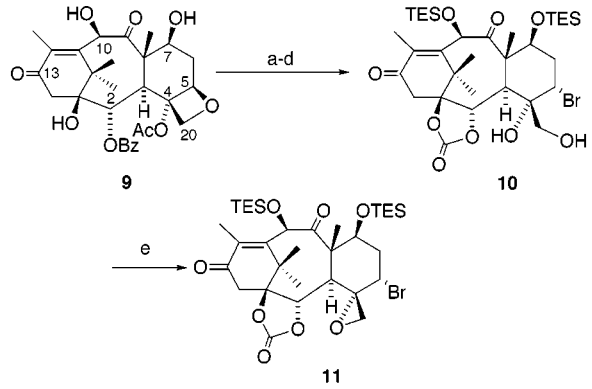
To synthesize the D-ring modified docetaxel analogues, two synthetic pathways were considered. In the first, the oxetane ring of 10-deacetylbaccatin III (**6**) is opened and a new ring closure is realized after suitable transformations. In the second, the C-4 exocyclic double bond of taxine B (**7**) and isotaxine B (**8**) is correctly functionalized to allow further D-ring formation. The starting materials, 10-deacetylbaccatin III (**6**), taxine B (**7**), and isotaxine B (**8**), were obtained from the leaves of the European yew tree *Taxus baccata* L. in significant yield (up to 1 g/kg for **6** and commonly 3−5 g/kg for **7** and **8**).[12] Our approach to thietane ring formation was identical to the general strategy we have developed for the construction of the D-ring in taxoids:[13] introduction of a leaving group at C-5 and a sulfur functionality at C-20 allowing ring closure by intramolecular nucleophilic substitution (Scheme 1).

Results and Discussion

The introduction of the leaving group at C-5 of 10-deacetylbaccatin III (**6**) was realized as previously described.[10] After suitable protection of the various hydroxyl groups of 13-oxo-10-deacetylbaccatin III (**9**)[14] and oxetane ring opening with tetraethylammonium bromide, several attempts were made to introduce a sulfur group on C-20 of compound **10**. Classical methods for direct introduction of sulfur were ineffective, and as for the synthesis of 5(20)-deoxydocetaxel,[11] substitution by means of a sulfonate using Na_2S or a thioacetate only led to C-4,C-20 epoxide formation. Finally, compound **11** was synthesized directly from **10** as previously described[11] (Scheme 2) to continue the synthesis according to Payré et al.[9]

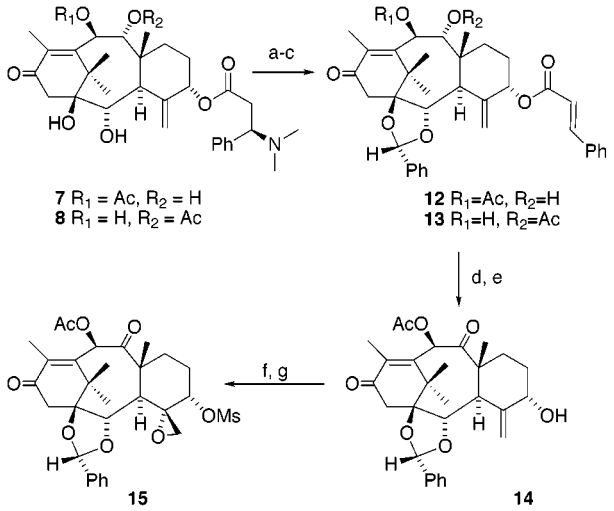
The mixture of **12**−**13**,[15] obtained from taxine B (**7**) and isotaxine B (**8**) by a previously published method,[13] was converted into the single 9-keto compound by Jones oxidation.[16] Because of the presence of the acetyl group in position 10, solvolysis of the cinnamoyl ester could not be carried out with 20 N NaOH as had been done in the first synthesis of D-ring modified taxoids;[9] hydroxylamine sulfate, a reagent reported to produce deacylation of a

Scheme 2[a]



[a] Reagents: (a) TESCl, imidazole, DMF, rt (69%); (b) Red-Al (4 equiv), THF, 0 °C (59%); (c) $(CCl_3O)_2CO$, CH_2Cl_2−pyridine (85−15), −15 °C (93%); (d) Et_4NBr, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt (63%); (e) PBu_3, DEAD, DMF, rt (72%).

Scheme 3[a]



[a] Reagents: (a) MeI, THF, rt (100%); (b) K_2CO_3 2%, EtOH, 95%, rt (91%); (c) $(MeO)_2CHPh$, PTSA, THF, rt (60%); (d) CrO_3, H_2SO_4, acetone, rt (66%); (e) $NH_2OH{\cdot}H_2SO_4$, Et_3N, THF−EtOH−H_2O (1:1:1), 80 °C (50%); (f) *m*-CPBA, CH_2Cl_2, 0 °C (94%); (g) MsCl, pyridine, 0 °C (73%).

5-*O*-cinnamoyl moiety in the presence of acetate groups,[17] was thus used successfully. The resulting compound **14** was then epoxidized and a leaving group was introduced by mesylating the C-5 hydroxyl function to afford compound **15** (Scheme 3).

Formation of the Thietane Ring. When an attempt was made to open the 4(20)-epoxide of **11** with sodium thioacetate according to the described conditions,[9] the expected C-20 thioacetate was not obtained. Instead, a new compound **16** was formed, but in very low yield (17%). To simplify the procedure, potassium thioacetate was used instead of sodium thioacetate which must be generated in situ by the action of NaH on thioacetic acid. The new product **16** was then obtained in higher yield (76%), again without formation of the C-20 thioacetyl derivative. The same reaction conditions applied to **15** also led to a new compound **17** in an acceptable yield (55%) (Scheme 4).

(12) Poupat, C.; Hook, I.; Guéritte, F.; Ahond, A.; Guénard, D.; Adeline, M.-T.; Wang, X.-P.; Dempsey, D.; Breuillet, S.; Potier, P. *Planta Med.* **2000**, *66*, 580−584.

(13) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823−9838.

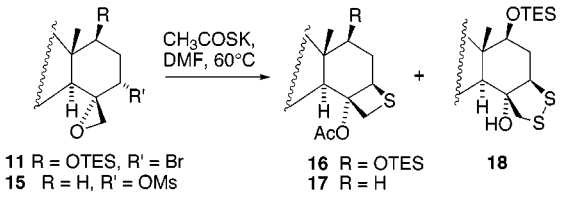
(14) Marder, R.; Dubois, J.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron* **1995**, *51*, 1985−1994.

(15) Poujol, H. Ph.D. Thesis, Paris XI-Orsay University, 1996.

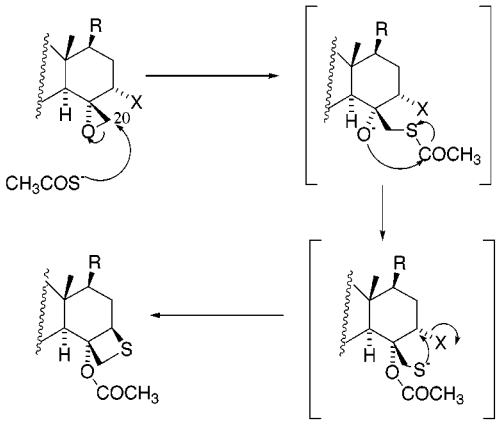
(16) Poujol, H.; Ahond, A.; Al Mourabit, A.; Chiaroni, A.; Poupat, C.; Riche, C.; Potier, P. *Tetrahedron* **1997**, *53*, 5169−5184.

(17) (a) Bathini, Y.; Micetich, R. G.; Daneshtalab, M. *Synth. Commun.* **1994**, *24*, 1513−1517. (b) Fenoglio, I.; Nano, G. M.; Vander Velde, D. G.; Appendino, G. *Tetrahedron Lett.* **1996**, *37*, 3203−3206.

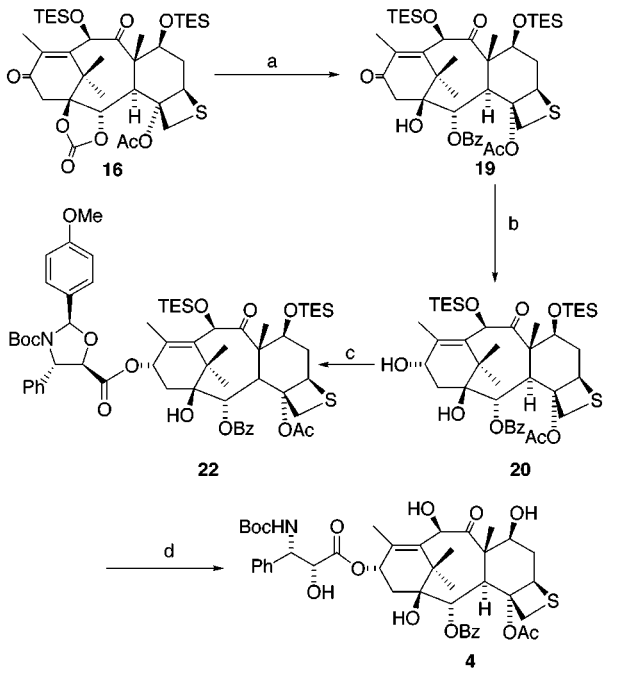
Scheme 4



Scheme 5



Scheme 6[a]



[a] Reagents: (a) PhLi, THF, −72 °C (74%); (b) $NaBH_4$, EtOH/THF (20:80), rt (21%); (c) **21**, DCC, DMAP, toluene, rt (85%); (d) PTSA, MeOH, rt (52%).

The new derivatives of 10-deacetylbaccatin III and taxine B-isotaxine B, **16** and **17,** respectively, showed similar NMR spectra indicating the formation of the thietane ring together with the presence of an acetyl group at C-4. This was further proved by mass spectrometric analysis. The formation of these compounds may be explained by the following sequence of reactions: epoxide opening by nucleophilic attack of thioacetate at C-20, transacetylation from the C-20 to the C-4 position and nucleophilic substitution of the C-5 bromide or mesylate by the C-20 thiolate thus formed (Scheme 5).

This method afforded directly the expected thietane ring together with the acetyl group at C-4 previously shown to be difficult to obtain.[8,9] This intramolecular approach proved to be very efficient and could be applied to the formation of other heterocycles.

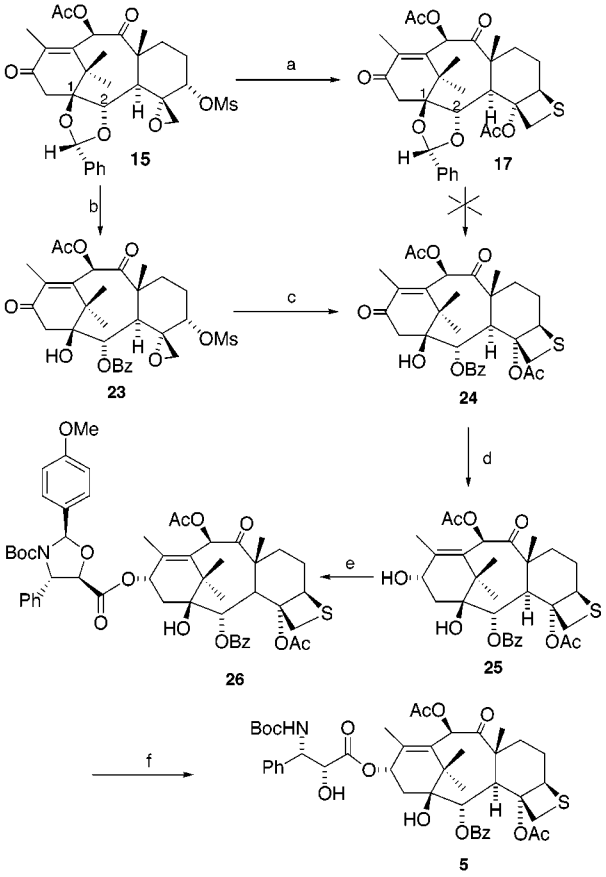
In the 10-deacetylbaccatin III series, an additional product (compound **18**) was also obtained whose proportion increased with the quantity of potassium thioacetate used while **16** became the minor product of the reaction. Spectroscopic data (NMR and mass spectrometry) were in agreement with the structure depicted for **18**. The formation of this compound may be explained by intermolecular nucleophilic attack of thioacetate at C-5. However, it must be noted that intermolecular substitution at C-5 has never been observed during the course of our studies on the modification of the oxetane ring, probably because of the steric hindrance caused by the C-19 methyl and the C-20 methylene groups in an axial position. The formation of a cyclic disulfide derivative together with a thietane ring has already been observed by Gunatilaka et al.[8] in the taxoid series and also by Hirota et al.[18] in nucleosides. The mechanism proposed by the latter for the formation of the disulfide goes through a nucleophilic attack of the thietane ring by another thiolate followed by oxidative coupling of the resulting dithiol. This mechanism may also provide a plausible explanation for the formation of **18**.

Synthesis of 5(20)-Thiadocetaxel and Its 7-Deoxy Analogue. The synthesis of 5(20)-thiadocetaxel **4** was then completed using the following steps (Scheme 6). First, the C-1,C-2 carbonate of **16** was readily opened by phenyllithium in acceptable yield (**19**, 74%) without affecting the C-13 ketone. Reduction of the latter with $NaBH_4$ then afforded the C-13α isomer **20**, but in poor yield compared to that obtained with the parent compounds bearing an oxetane, an azetidine, or a cyclopropyl D-ring. Modifications of the reaction conditions (reagents: boranes or aluminum hydrides, solvent, temperature) did not lead to any improvement. The best conditions were those employed for the syntheses of aza-[10] and deoxydocetaxel[11] and which afforded the desired compound **20** in 21% along with 44% of unreacted **19**. The great difference in reactivity toward reducing agents between 13-oxo-10-deacetylbaccatin III and 13-oxo-5(20)thia-10-deacetylbaccatin III is difficult to explain since no modifications were observed in the environment of the ketone at position 13 in the crystal structure of **19** (unpublished data). The main difference between these two compounds was the decreased solubility of **19** in protic solvents. Esterification at C-13 of **20** was then realized with the 2-(4-OMe)phenyl-1,3-oxazolidine derivative of *N*-Boc-phenylisoserine **21**, DCC and DMAP in toluene at room temperature leading to compound **22** in good yield (85%). Finally, deprotection of **22** with *p*-toluenesulfonic acid in methanol afforded the desired compound **4** (52% yield).

To complete the synthesis of 7-deoxy-10-acetyl-5(20)-thiadocetaxel **5** (Scheme 7), the first step was the transformation of the 1,2-benzylidene acetal of **17** into a 2-benzoyl group. Unfortunately, the hydroxyl functions in positions 1 and 2 of **17** could not be deprotected with tBuOOH and $CuCl_2$ without concomitant oxidation of the

(18) Hirota, K.; Kitade, Y.; Tomishi, M.; De Clerk, E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2233−2241.

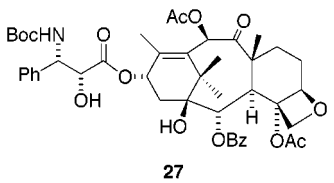
Scheme 7[a]



[a] Reagents: (a) CH_3COSK, DMF, 60 °C (55%); (b) tBuOOH, $CuCl_2$, toluene, rt (56%); (c) CH_3COSK, DMF, 60 °C (12%); (d) $NaBH_4$, THF−MeOH (6:1), 0 °C (60%); (e) **21**, DCC, DMAP, toluene, rt (78%); (f) PTSA, MeOH, rt (97%).

sulfur atom. The reaction was thus performed on **15** before thietane ring formation. Treatment of this new derivative **23** with potassium thioacetate provided the thietane **24** in poor yield (12%) but the following steps of reduction, esterification, and final deprotection led to the final compound **5** with satisfactory yields.

Biological Activities. Compounds **4** and **5** were evaluated for their effects in vitro on the cold-induced disassembly process of microtubules into tubulin[19] and on the growth of KB cells.[20] The activity of 7-deoxy-10-acetyl-5(20)-thiadocetaxel **5** was compared to its parent compound 7-deoxy-10-acetyl-docetaxel **27**.[21]



Though less active than docetaxel, its thia analogue **4** retained good activity on microtubule disassembly whereas the 7-deoxy thia analogue **5** showed no significant inhibition (Table 1). On the other hand, both compounds **4** and **5** were still active on KB cells but showed a much lower cytotoxicity than their parent compounds **1b** and **27**, respectively. In the taxoid series, a few derivatives have already been reported to be inactive on tubulin but still cytotoxic.[22,23] In the case of the 7- and 10-*O*-acyl derivatives,[23] this lack of reactivity toward tubulin was hypothesized to be due to increased hydrophobicity. For this reason, the chromatographic hydrophobic index φ_0 of both compounds **4** and **5** was calculated as previously described;[23] the resulting values, $\varphi_0 = 70.5$ and 83, respectively, could not account for their contrasting activities.[24] Suspecting a different cellular mode of action of compound **5**, its effect on the cell cycle, studied by flow cytometry, turned out to be similar to paclitaxel (arrest in G2/M stage) but to a very much lower extent. The reasons for these divergent activities on microtubule disassembly between **4** and **5** are as yet unclear.

Table 1. Results of Biological Evaluation of 5(20)-Thiadocetaxel Analogues

compd	microtubule disassembly inhibitory activity[a] IC_{50}/IC_{50}(paclitaxel)	cytotoxicity against KB cell line[b] IC_{50} (nM)
1a	1	1.2
1b	0.5	0.6
4	2	650
5	not significant	200
27	0.8	0.2

[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. [b] IC_{50} measures the drug concentration required for the inhibition of 50% cell proliferation after 72 h incubation.

Molecular modeling of thiadocetaxel **4** showed that, while the elongated C−S bond (vs C−O) leads to a slightly more strained D-ring, there are no dramatic changes in the overall conformation of the molecule compared to docetaxel. The main differences reside on the charge on the heteroatom of the D-ring (+0.05 on the sulfur of compound **4** and −0.265 on the oxygen of docetaxel) and the bulkiness of sulfur. The docking of the structures of docetaxel and thiadocetaxel onto the paclitaxel binding site of tubulin was also realized, showing that the distances between the hydroxyl group of Thr276 and oxygen or sulfur of the D-ring are 2.76 and 2.24 Å, respectively, while the more bulky sulfur atom creates a steric hindrance at that position. Thus, in the case of the thia derivatives, there would be no possibility of hydrogen bonding between the hydroxyl group of Thr276 on β-tubulin and the heteroatom of the D-ring as previously proposed.[7] The tubulin−taxoid complex would then be less stabilized, thereby explaining the activity decrease which was observed.

In conclusion, the syntheses of 5,20-thiadocetaxel **4** and of its 7-deoxy analogue **5** confirm the prediction of an activity decrease when the oxygen of the D-ring is replaced by a sulfur atom. Though the difference in activity between docetaxel and compound **4** on microtubule disassembly is weak (only 4×), supporting the hypothesis of the loss of a hydrogen bond, the lack of activity of **5** on microtubule disassembly does not allow

(19) Lataste, H.; Sénihl, V.; Wright, M.; Guénard, D.; Potier, P. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 4090−4094.
(20) Da Silva, A. D.; Machado, A. S.; Tempête, C.; Robert-Gero, M. *Eur. J. Med. Chem.* **1994**, *29*, 149−152.
(21) Poujol, H.; Al Mourabit, A.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1997**, *53*, 12575−12594.
(22) Cheng, Q.; Oritani, T.; Horiguchi, T.; Yamada, T.; Mong, Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 517−521.
(23) Guénard, D.; Thoret, S.; Dubois, J.; Adeline, M.-T.; Wang, Q.; Guéritte, F. *Bioorg. Med. Chem.* **2000**, *8*, 145−156.
(24) φ_0 (docetaxel) = 64, φ_0 (**27**) = 76.6, and for the cytotoxic 7- or 10-*O*-acyl derivatives[23] inactive on microtubule disassembly, $\varphi_0 > 100$.

us a definite conclusion as to the reality of such an interaction.

Experimental Section

General Methods. All chemicals were purchased from Fluka or Aldrich and were used without further purification unless indicated otherwise. Solvents were purchased from SDS. Toluene was distilled before use. General methods were the same as previously described.[25] Standard workup means extraction with a suitable solvent (CH_2Cl_2 unless otherwise specified), washing the extract with H_2O or brine, drying over Na_2SO_4 or $MgSO_4$, and evaporation under reduced pressure. 10-Deacetylbaccatin III (DAB) (**6**), taxine B (**7**), and isotaxine B (**8**) were extracted from *Taxus baccata* needles, and the acid side chain of docetaxel **21** was a gift from Alain Commerçon (Aventis Pharma). Microtubular proteins were purified from bovine brain as previously described.[26] Molecular modeling studies were realized using Sybyl software from Tripos with the MMFF94 force field.

2-Debenzoyl-4-deacetyl-5α-bromo-7,10-di(triethylsilyl)-20-hydroxy-13-oxo-D-seco-DAB 1,2 carbonate (10). (a) To a solution of **13-oxo-10-deacetylbaccatin III** (**9**) (1.7 g, 3.16 mmol) in 130 mL of dry DMF was added imidazole (1.72 mg, 25.2 mmol, 8 equiv). Then triethylsilyl chloride (3.18 mL, 18.9 mmol, 6 equiv) was added dropwise at room temperature. The solution was stirred for 15 h. After removal of the solvent, 100 mL of AcOEt and 70 mL of water were added. After standard workup, the residue was purified on silica gel (heptane/AcOEt 80:20) to yield pure **7,10-di(triethylsilyl)-13-oxo-DAB** (1.67 g, 69%) as an amorphous solid: IR ($CHCl_3$) 1725, 1671, 1601, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (12H, m), 1.00 (18H, m), 1.21 (3H, s), 1.29 (3H, s), 1.58 (3H, s), 1.92 (1H, m), 2.05 (3H, s), 2.20 (3H, s), 2.56 (1H, m), 2.64 (1H, d, J = 19.6 Hz), 2.93 (1H, d, J = 19.6 Hz), 3.94 (1H, d, J = 6.6 Hz), 4.13 (1H, d, J = 8.8 Hz), 4.33 (1H, d, J = 8.8 Hz), 4.43 (1H, dd, J = 10.3 Hz, J' = 7.4 Hz), 4.90 (1H, bd, J = 8.1 Hz), 5.38 (1H, s), 5.69 (1H, d, J = 6.6 Hz), 7.48, 7.63, 8.08 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.3, 6.2, 6.9, 7.1, 10.0, 13.5, 17.8, 21.9, 33.1, 37.5, 42.5, 43.6, 46.3, 59.6, 73.0, 73.2, 76.5, 77.0, 78.7, 80.7, 83.9, 128.8, 129.1, 130.2, 134.0, 136.1, 158.5, 167.0, 170.3, 199.0, 204.0; MS (FAB^+) m/z 793 (MNa^+).

(b) Red-Al (3.5 M in toluene, 2.1 mL, 7.2 mmol, 4 equiv) was added at 0 °C to a THF solution (11.6 mL) of **7,10-di-(triethylsilyl)-13-oxo-DAB** (1.38 g, 1.8 mmol). The solution was stirred at 0 °C for 20 min, and the reaction was stopped by careful addition of 4 mL of a saturated K^+,Na^+ tartrate solution. After standard workup with AcOEt, the residue was purified by silica gel chromatography (heptane/AcOEt 60:40) to afford **2-debenzoyl-4-deacetyl-7,10-di(triethylsilyl)-13-oxo-DAB** (666 mg, 59%) as an amorphous solid: IR ($CHCl_3$) 3592, 1721, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (12H, m), 0.99 (18H, m), 1.26 (3H,s), 1.27 (3H, s), 1.73 (3H, s), 1.95 (1H, m), 2.06 (3H, s), 2.52 (1H, m), 2.74 (1H, d, J = 5.2 Hz), 2.80 (1H, d, J = 19.1 Hz), 3.66 (1H, d, J = 19.1 Hz), 4.10 (1H, dd, J = 7.4 Hz, J' = 10.3 Hz), 4.46 (1H, d, J = 8.1 Hz), 4.49 (1H, d, J = 5.2 Hz), 4.62 (1H, d, J = 8.1 Hz), 4.80 (1H, dd, J = 2.9 Hz, J' = 9.6 Hz), 5.31 (1H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 5.3, 6.2, 6.9, 7.0, 10.3, 13.4, 18.0, 32.6, 37.6, 43.1, 43.4, 51.2, 59.1, 73.2, 73.8, 75.1, 76.8, 78.1, 82.0, 85.3, 134.4, 135.1, 158.2, 200.5, 205.0; MS (FAB^+) m/z 647 (MNa^+).

(c) A solution of **2-debenzoyl-4-deacetyl-7,10-di(triethylsilyl)-13-oxo-DAB** (360 mg, 0.58 mmol) in 8.4 mL of a mixture CH_2Cl_2/pyridine (85/15) was cooled to −18 °C. Triphosgene (274 mg, 0.92 mmol, 1.6 equiv) was then added, and the solution was stirred for 20 min at −18 °C. The reaction was stopped by addition of a saturated sodium bicarbonate solution. After standard workup, the residue was purified on silica gel (heptane/AcOEt 75:25) to yield pure **2-debenzoyl-4-deacetyl-7,10-di(triethylsilyl)-13-oxo-DAB 1**, **2 carbonate** (348 mg, 93%) as an amorphous white solid: IR ($CHCl_3$) 1806, 1720, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (12H, m), 0.98 (18H, m), 1.27 (3H, s), 1.32 (3H, s), 1.67 (3H, s), 1.95 (1H, m), 2.06 (3H, s), 2.52 (1H, m), 2.74 (1H, d, J = 5.2 Hz), 2.80 (1H, d, J = 19.1 Hz), 3.66 (1H, d, J = 19.1 Hz), 4.10 (1H, dd, J = 10.3 Hz, J' = 7.4 Hz), 4.46 (1H, d, J = 8.1 Hz), 4.49 (1H, d, J = 5.2 Hz), 4.62 (1H, d, J = 8.1 Hz), 4.80 (1H, dd, J = 9.6 Hz, J' = 2.9 Hz), 5.31 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.2, 6.0, 6.8, 7.0, 10.3, 14.2, 18.7, 31.6, 38.0, 40.5, 41.9, 47.6, 60.6, 72.9, 73.3, 78.0, 80.1, 80.5, 87.5, 88.9, 137.9, 153.1, 155.0, 197.9, 204.7; MS (FAB^+) m/z 657 (MLi^+).

(d) Et_4NBr (362 mg, 1.72 mmol, 3.5 equiv) and $BF_3{\cdot}OEt_2$ (0.91 mL, 0.74 mmol, 1.5 equiv) were added to a solution of **2-debenzoyl-4-deacetyl-7,10-di(triethylsilyl)-13-oxo-DAB 1**, **2 carbonate** (320 mg, 0.49 mmol) in 300 mL dry CH_2Cl_2. The solution was stirred at room temperature for 45 min and then hydrolyzed. After standard workup, the residue was purified on silica gel (CH_2Cl_2/Et_2O 80:20) to yield pure **10** (226 mg, 63%) as a white amorphous solid: IR ($CHCl_3$) 3510, 1805, 1717, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.64 (12H, m), 0.99 (18H, m), 1.23 (3H, s), 1.32 (3H, s), 1.79 (3H, s), 2.23 (1H, m), 2.28 (3H, s), 2.38 (1H, m), 2.88 (1H, d, J = 19.1 Hz), 3.02 (1H, sl), 3.56 (1H, s), 3.72 (1H, dl, J = 9.4 Hz), 3.62 (1H, d, J = 4.4 Hz), 3.97 (1H, d, J = 19.1 Hz), 4.09 (1H, d, J = 9.4 Hz), 4.35 (1H, d, J = 4.4 Hz), 4.48 (1H, dd, J = 10.3 Hz, J' = 4.4 Hz), 4.68 (1H, t, J = 2.2 Hz), 5.47 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.2, 5.9, 6.9, 13.3, 15.0, 18.7, 31.9, 37.3, 41.0, 42.1, 44.6, 60.7, 62.6, 62.7, 70.2, 73.8, 77.6, 81.0, 89.2, 139.1, 153.0, 154.8, 197.5, 204.1; MS (FAB^+) m/z 753−755 (MNa^+).

2-Debenzoyl-4-deacetyl-4(20)-epoxy-5α-bromo-7,10-di-(triethylsilyl)-13-oxo-D-seco-DAB 1,2 carbonate (11). Tributylphosphine (140 μL, 0.57 mmol, 2 equiv) and diethyl azodicarboxylate (89 μL, 0.57 mmol, 2 equiv) were added to a solution of **10** (209 mg, 0.29 mmol) in 2 mL of dry DMF. The solution was stirred at room temperature for 44 h. After removal of the solvent and standard workup, the residue was purified on silica gel (heptane/AcOEt 80:20) to yield pure **11** (147 mg, 72%) as a white amorphous solid along with starting material **10** (25 mg, 12%). Compound **11**: IR ($CHCl_3$) 3029, 1809, 1720, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.67 (12H, m), 1.03 (18H, m), 1.26 (3H, s), 1.27 (3H, s), 1.36 (3H, s), 2.38 (3H, s), 2.45 (2H, m), 2.90 (1H, d, J = 5.2 Hz), 2.92 (1H, d, J = 19.9 Hz), 3.20 (1H, d, J = 19.9 Hz), 3.60 (1H, d, J = 5.2 Hz), 3.89 (1H, t, J = 3.7 Hz), 3.95 (1H, d, J = 4.4 Hz), 4.19 (1H, d, J = 4.4 Hz), 4.55 (1H, dd, J = 11.0 Hz, J' = 5.2 Hz), 5.50 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.1, 6.0, 7.0, 11.8, 15.3, 18.8, 31.8, 38.7, 39.6, 41.2, 42.1, 56.4, 58.6, 60.5, 63.2, 70.2, 77.6, 79.7, 88.2, 139.2, 152.9, 154.3, 196.6, 204.2; MS (FAB^+) m/z 719−721 (MLi^+).

The compounds **12** and **13** were prepared from taxine B (**7**) and isotaxine B (**8**) according to the described procedure[13,15] (**a**−**c**).

1,2-*O*-Benzylidene-9-oxo-10-acetyltaxicine I (14). (d) To a dry acetone solution (10 mL) of compounds **12** and **13** (112 mg, 1.79 mmol) was added Jones reagent (1 equiv of CrO_3). The solution was stirred for 10 min at room temperature and quenched with water. After standard workup, the residue was purified by preparative TLC (heptane/AcOEt 5:5) to afford **1,2-*O*-benzylidene-9-oxo-10-acetyl-5-cinnamoyltaxicine I** (74 mg, 66%) as an amorphous solid: $[\alpha]^{20}_D$ +74.5 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 1745, 1711, 1678, 1638 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (6H, s), 1.33 (3H, s), 1.46−2.24 (4H, m), 2.26 (3H, s), 2.31 (3H, s), 2.86 (2H, s), 3.83 (1H, d, J = 5.0 Hz), 3.96 (1H, d, J = 5.1 Hz), 5.30 (1H, s), 5.42 (1H, bs), 5.72 (1H, s), 5.75 (1H, bs), 6.41 (1H, d, J = 15.9 Hz), 6.75 (1H, s), 7.35−7.49 (8H, m), 7.68 (1H, d, J = 16.0 Hz), 7.72−7.76 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 15.7, 18.6, 21.0, 27.8, 31.7, 32.6, 42.5, 45.0, 45.3, 57.2, 76.7, 77.2, 81.6, 83.8, 103.2, 117.7, 118.7, 126.8, 128.1, 128.5, 128.6, 128.7, 129.1, 129.6, 130.6, 134.5, 137.3, 140.4, 140.5, 146.0, 151.0, 166.1, 169.5, 199.7, 204.3; MS (CI^+) m/z 625 (MH^+).

(e) To a solution of **1,2-*O*-benzylidene-9-oxo-10-acetyl-5-cinnamoyltaxicine I** (662 mg, 1.06 mmol) in 30 mL of dry THF was added $NH_2OH{-}H_2SO_4$ (347 mg, 2.11 mmol, 2 equiv) in 30 mL of EtOH and 30 mL of H_2O. The solution was stirred,

(25) Marder-Karsenti, R.; Dubois, J.; Chiaroni, A.; Riche, C.; Guénard, D.; Guéritte, F.; Potier, P. *Tetrahedron* **1998**, *54*, 15833−15844.

(26) Dubois, J.; Le Goff, M. T.; Guéritte-Voegelein, F.; Guénard, D.; Tollon, Y.; Wright, M. *Bioorg. Med. Chem.* **1995**, *3*, 1357−1368.

and Et_3N (0.295 mL, 2.11 mmol, 2 equiv) was added. The solution was heated for 8 h at 80 °C, and 8 equiv of NH_2OH-H_2SO_4, and Et_3N were added. The solution was stirred for an additional 12 h. After standard workup, the residue was purified by flash chromatography on silica gel (heptane/AcOEt 8:2) to afford **14** (260 mg, 50%) as an amorphous solid along with starting material **1,2-*O*-benzylidene-9-oxo-10-acetyl-5-cinnamoyltaxicine I** (36 mg, 6%). Compound **14**: $[\alpha]^{20}_D$ −51.0 (*c* 0.88, $CHCl_3$); IR ($CHCl_3$) 3594, 1749, 1710, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.28 (3H, s), 1.29 (3H, s), 1.32−1.41 (2H, m), 1.82 (2H, m), 2.25 (6H, s), 2.71 (2H, d, J = 19 Hz), 2.79 (1H, d, J = 19 Hz), 3.92 (1H, d, J = 5 Hz), 4.03 (1H, d, J = 4.9 Hz), 4.21 (1H, bs), 5.09 (1H, bs), 5.61 (1H, bs), 5.70 (1H, s), 6.77 (1H, s), 7.35−7.44 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 15.5, 18.7, 21.0, 29.8, 31.1, 32.3, 42.5, 42.6, 45.4, 57.7, 75.1, 76.6, 82.3, 84.6, 103.1, 115.3, 126.8, 128.6, 129.6, 137.6, 141.1, 145.6, 149.8, 169.7, 200.2, 205.1; MS(CI^+) *m*/*z* 495 (MH^+); HRMS (CI^+) calcd for $C_{29}H_{35}O_7$ (MH^+) *m*/*z* 495.2382, found 495.2393.

1,2-*O*-Benzylidene-9-oxo-10-acetyl-4α(20)-epoxy-5-mesyltaxicine I (15). (f) To a dry CH_2Cl_2 solution (100 mL) of compound **14** (5.23 g, 10.6 mmol) cooled to 0 °C was added *m*-CPBA (2.74 g, 15.9 mmol, 1.5 equiv). The solution was stirred for 30 min at 0 °C and quenched by a 10% solution of Na_2SO_3. After standard workup, the residue was purified by flash chromatography on silica gel (heptane/AcOEt 7:3) to afford **1,2-*O*-benzylidene-9-oxo-10-acetyl-4α(20)-epoxytaxicine I** (5.10 g, 94%) as an amorphous solid: $[\alpha]^{20}_D$ −23.0 (*c* 1.79, $CHCl_3$); IR ($CHCl_3$) 3589, 1748, 1712, and 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.26 (3H, s), 1.35 (3H, s), 1.37−1.45 (2H, m), 1.92 (2H, m), 2.25 (3H, s), 2.26 (3H, s), 2.56 (1H, d, J = 4.8 Hz), 2.70 (1H, d, J = 19.8 Hz), 3.10 (1H, d, J = 19.7 Hz), 3.23 (1H, t, J = 2.8 Hz), 3.57 (1H, d, J = 5 Hz), 3.74 (1H, d, J = 3.9 Hz), 3.9 (1H, d, J = 4 Hz), 5.61 (1H, s), 6.75 (1H, s), 7.33−7.47 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 16.0, 18.8, 21.0, 27.1, 30.0, 32.1, 38.3, 42.9, 45.0, 52.9, 57.5, 62.7, 74.4, 76.6, 82.0, 103.6, 127.1, 128.6, 129.6, 137.6, 141.9, 149.9, 169.7, 200.5, 204.7; MS (FAB^+) *m*/*z* 533 (MNa^+); HRMS (CI^+) calcd for $C_{29}H_{35}O_8$ (MH^+) *m*/*z* 511.2331, found 511.2304.

(g) To a solution of **1,2-*O*-benzylidene-9-oxo-10-acetyl-4α(20)-epoxytaxicine I** (242 mg, 47.4 mmol) in dry pyridine cooled at 0 °C was added dropwise mesyl chloride (0.550 mL, 7.15 mmol, 15 equiv). The solution was stirred for 30 min at 0 °C. After standard workup, the residue was purified by preparative TLC (CH_2Cl_2/MeOH 98:2) to yield **15** (204 mg, 73%) as an amorphous solid: $[\alpha]^{20}_D$ −15.5 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 1749, 1715, 1679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, s), 1.27 (3H, s), 1.35 (3H, s), 1.51−2.19 (4H, m), 2.23 (3H, s), 2.27 (3H, s), 2.62 (1H, d, J = 4.9 Hz), 2.74 (1H, d, J = 19.8 Hz), 2.98 (1H, d, J = 19.8 Hz), 3.08 (3H, s), 3.57 (1H, d, J = 4.85 Hz), 3.71 (1H, bs), 4.23 (1H, bs), 5.59 (1H, s), 6.71 (1H, s), 7.35−7.42 (5H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.6, 16.1, 18.6, 20.9, 27.9, 29.9, 32.3, 39.1, 39.5, 42.9, 44.7, 52.2, 57.0, 59.6, 76.6, 81.5, 84.1, 86.1, 103.7, 126.9, 128.6, 129.7, 137.1, 142.2, 151.2, 169.4, 199.6, 203.6; MS (CI^+) *m*/*z* 589 (MH^+).

2-Debenzoyl-7,10-di(triethylsilyl)-5(20)-deoxy-5(20)-sulfanyl-13-oxo-DAB 1,2-Carbonate (16) and 2-Debenzoyl-7,10-di(triethylsilyl)-5(20)-deoxy-5(20)-dithia-13-oxo-DAB 1,2 Carbonate (18). To a solution of **11** (103 mg, 0.14 mmol) in 4 mL of dry DMF was added potassium thioacetate (33 mg, 0.29 mmol, 2 equiv). The solution was stirred at 60 °C for 8 h. After removal of the solvent and standard workup in ethyl acetate, the residue was purified by preparative TLC (heptane/AcOEt 70:30) to yield pure **16** (78 mg, 76%) along with compound **18** (9.8 mg, 10%) as white amorphous solids. With a large excess of potassium thioacetate (321 mg, 28 mmol, 20 equiv) and **11** (102 mg, 0.14 mmol) in 5 mL of dry DMF over 4 h at 65 °C, the major product was **18** (53.1 mg, 54%) and the minor was **16** (22 mg, 22%). Compound **16**: IR ($CHCl_3$) 1811, 1720, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (12H, m), 0.98 (18H, m), 1.26 (3H, s), 1.30 (3H, s), 1.83 (3H, s), 2.10 (3H, s), 2.13 (3H, s), 2.16 (1H,m), 2.62 (1H, m), 2.65 (1H, d, J = 19.9 Hz), 2.90 (1H, d, J = 19.9 Hz), 3.42 (1H, d, J = 12.5 Hz), 3.58 (1H, d, J = 12.5 Hz), 3.62 (1H, d, J = 5.2 Hz), 3.98 (1H, dd, J = 5.2 Hz, J' = 10.3 Hz), 4.34 (1H, dd, J = 5.9 Hz, J' = 10.3 Hz), 4.42 (1H, d, J = 5.2 Hz), 5.34 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.15, 6.02, 6.83, 7.03, 12.08, 14.29, 18.48, 22.65, 31.82, 35.35, 40.62, 41.58, 42.03, 45.29, 61.14, 72.55, 77.91, 80.38, 87.17, 88.79, 138.18, 152.31, 154.74, 171.04, 196.08, 204.38; MS (FAB^+) *m*/*z* 715 (MLi^+); HRMS (CI^+) calcd for $C_{35}H_{57}O_9Si_2S(MH^+)$ *m*/*z* 709.3262, found 709.3234. Compound **18**: IR ($CHCl_3$) 1811, 1720, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.61 (12H, m), 0.96 (18H, m), 1.25 (3H, s), 1.29 (3H, s), 1.32 (3H, s), 2.08 (3H, s), 2.14 (1H,m), 2.36 (1H, m), 2.80 (1H, d, J = 19.4 Hz), 3.14 (1H, dd, J = 5.9 Hz, J' = 12.8 Hz), 3.19 (1H, d, J = 4.7 Hz), 3.32 (2H, qAB, J = 13.9 Hz), 3.85 (1H, d, J = 19.4 Hz), 4.07 (1H, dd, J = 4.5 Hz, J' = 11.3 Hz), 4.36 (1H, d, J = 4.5 Hz), 5.39 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0, 5.9, 6.8, 7.0, 11.4, 14.3, 18.5, 31.6, 34.9, 40.5, 42.1, 47.9, 48.3, 62.1, 64.4, 73.3, 77.5, 80.5, 85.3, 88.7, 137.8, 152.4, 154.2, 197.8, 204.2; MS (FAB^+) *m*/*z* 705 (MLi^+); HRMS (FAB^+) calcd for $C_{33}H_{54}O_8LiSi_2S_2$ (MLi^+) *m*/*z* 705.2958, found 705.2960.

2-Debenzoyl-1,2-*O*-benzylidene-7-deoxy-5(20)-deoxy-5(20)-sulfanyl-13-oxobaccatin III (17). To a dry DMF solution (10 mL) of **15** (33 mg, 56.1 μmol) was added potassium thioacetate (64 mg, 561 μmol, 10 equiv). The solution was stirred at 60 °C for 1 week, and the DMF was evaporated under reduced pressure. After standard workup, the residue was purified on preparative TLC (CH_2Cl_2/MeOH 98:2) to afford **17** (17 mg, 55%) as an amorphous solid along with starting material **15** (6 mg, 20%). Compound **17**: $[\alpha]^{20}_D$ −13.0 (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 1747, 1729, 1717, and 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.26 (3H, s), 1.65 (2H, m), 1.85 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 2.24 (3H, s), 2.57 (2H, s), 3.43 (1H, d, J = 12 Hz), 3.61 (1H, d, J = 5 Hz), 3.75 (1H, d, J = 12 Hz), 3.95 (1H, d, J = 5 Hz), 4.02 (1H, dd, J = 3.5 Hz, J' = 6 Hz), 5.83 (1H, s), 6.53 (1H, s), 7.35−7.50 (5H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.3, 16.4, 18.5, 20.9, 22.7, 31, 32.2, 33.8, 36.4, 41.9, 42.7, 44.1, 44.5, 55.3, 76.6, 81.2, 83.5, 89.3, 102.8, 126.2, 128.5, 129.3, 138.2, 141.5, 150.9, 169.4, 170.8, 198.7, 204.8; MS (CI^+) *m*/*z* 569 (MH^+).

7,10-Di(triethylsilyl)-5(20)-deoxy-5(20)-sulfanyl-13-oxo-DAB (19). To a dry THF solution (3 mL) of **16** (73 mg, 0.10 mmol) cooled to −72 °C was added under argon a hexane solution of phenyllithium (2 M, 0.36 mL, 0.72 mmol, 7 equiv). The solution was stirred for 1 h at −72 °C and then poured into a mixture of CH_2Cl_2 and of saturated NH_4Cl solution and stirred for 1 min at room temperature. After standard workup, the residue was purified on preparative TLC (heptane/AcOEt 75:25) to yield **19** (59 mg, 74%) as a white crystalline solid: mp 196−198d °C; IR ($CHCl_3$) 1723, 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (12H, m), 0.98 (18H, m), 1.20 (3H, s), 1.26 (3H, s), 1.80 (3H, s), 2.02 (3H, s), 2.07 (1H,m), 2.11 (3H, s), 2.42 (1H, m), 2.49 (1H, d, J = 19.9 Hz), 2.74 (1H, d, J = 19.9 Hz), 3.00 (1H, d, J = 11.8 Hz), 3.23 (1H, d, J = 11.8 Hz), 3.34 (1H, s), 3.67 (1H, d, J = 6.6 Hz), 3.87 (1H, dd, J = 5.9 Hz, J' = 10.3 Hz), 4.18 (1H, dd, J = 5.9 Hz, J' = 11.8 Hz), 5.31 (1H, s), 5.67 (1H, d, J = 6.6 Hz), 7.50 (2H, t, J = 7.4 Hz), 7.62 (1H, t, J = 7.4 Hz), 8.08 (2H, d, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.3, 6.2, 6.9, 7.1, 11.7, 13.5, 17.9, 22.8, 33.2, 36.2, 40.5, 42.5, 42.7, 43.3, 47.9, 59.9, 73.0, 73.5, 77.0, 79.6, 88.5, 128.9, 129.4, 130.2, 133.9, 136.2, 153.6, 166.9, 170.6, 198.6, 204.1; MS (L-SIMS$^+$) *m*/*z* 793 (MLi^+).

7,10-Di(triethylsilyl)-5(20)-deoxy-5(20)-sulfanyl-DAB (20). To a THF solution (2 mL) of **19** (53 mg, 68 μmol) was added $NaBH_4$ (18 mg, 475 μmol, 7 equiv) in 0.44 mL of EtOH. The solution was stirred at room temperature for 4 h. After standard workup with ethyl acetate, the residue was purified on preparative TLC (heptane/AcOEt 60:40) to yield **20** (11.2 mg, 21%) as a white amorphous solid along with starting material **19** (23.2 mg, 44%). Compound **20**: IR ($CHCl_3$) 3577, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (12H, m), 0.99 (18H, m), 1.20 (3H, s), 1.26 (3H, s), 1.78 (3H, s), 2.10 (3H, s), 2.23(1H, m), 2.29 (2H, m), 2.37 (3H, s), 2.46 (1H,m), 3.11 (1H, d, J = 11.8 Hz), 3.41 (1H, d, J = 11.8 Hz), 3.93 (1H, d, J = 7.4 Hz), 4.00 (1H, dd, J = 5.9 Hz, J' = 10.3 Hz), 4.29 (1H, dd, J = 5.9 Hz, J' = 11.8 Hz), 4.81 (1H, dd, J = 8.8 Hz, J' = 15.4 Hz),

5.31 (1H, s), 5.59 (1H, d, $J = 7.4$ Hz), 7.47 (2H, t, $J = 7.4$ Hz), 7.58 (1H, t, $J = 7.4$ Hz), 8.09 (2H, d, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.4, 6.2, 7.0, 7.1, 12.2, 14.7, 19.7, 23.8, 26.7, 36.5, 39.6, 40.6, 42.8, 42.9, 49.0, 59.2, 68.3, 73.2, 75.2, 76.1, 79.0, 89.9, 128.8, 129.9, 130.2, 133.6, 136.4, 138.1, 167.1, 172.7, 205.8; MS (L-SIMS$^+$) *m/z* 811 (MNa^+).

5(20)-Deoxy-5(20)-sulfanyl-7,10-di(triethylsilyl)-13-[[(4*S*,5*R*)-2-(4-methoxyphenyl)-3-(*tert*-butyloxycarbonyl)-4-phenyl-1,3-oxazolidin-5yl]carbonyl]-DAB (22). To a toluene solution (3 mL) of **20** (30 mg, 38 μmol) were added 4-DMAP (7.8 mg, 63 μmol, 1.7 equiv), DCC (23.6 mg, 110 μmol, 3 equiv), and **21** (47.9 mg, 120 μmol, 3.2 equiv). The solution was stirred for 1.5 h at room temperature. After standard workup, the residue was purified on preparative TLC (heptane/AcOEt 70:30) to yield **22** (38 mg, 85%) as a white amorphous solid: IR ($CHCl_3$) 1704, 1613, 1515, 1456, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (12H, m), 0.96 (18H, m), 1.00 (9H, s) 1.17 (3H, s), 1.19 (3H, s), 1.53 (3H, s), 1.73 (6H, s), 2.06 (3H, m), 2.49 (1H, m), 3.04 (1H, d, $J = 11.8$ Hz), 3.29 (1H, d, $J = 11.8$ Hz), 3.75 (1H, d, $J = 7.4$ Hz), 3.81 (3H, s), 3.98 (1H, dd, $J = 5.9$ Hz, $J' = 10.3$ Hz), 4.23 (1H, dd, $J = 5.9$ Hz, $J' = 11.8$ Hz), 4.61 (1H, d, $J = 4.4$ Hz), 5.09 (1H, s), 5.32 (1H, bd, $J = 4.4$ Hz), 5.58 (1H, d, $J = 7.4$ Hz), 6.10 (1H, m), 6.66 (1H, bs), 6.93 (2H, d, $J = 7.4$ Hz), 7.43 (11H, m), 8.02 (2H, d, $J = 7.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 5.4, 6.2, 7.0, 7.1, 12.3, 13.7, 20.6, 22.4, 26.7, 28.0, 35.7 36.2, 40.3, 42.9, 43.0, 48.9, 55.3, 64.0, 71.8, 73.0, 75.4, 75.5, 79.5, 80.9, 83.6, 88.5, 92.7, 113.9, 126.7, 128.3, 128.7, 128.9, 129.1, 130.2, 133.7, 134.7, 136.9, 151.8, 160.5, 167.2, 169.7, 169.9, 205.3; MS (L-SIMS$^+$) *m/z* 1176 (MLi^+).

5(20)-Deoxy-5(20)-sulfanyldocetaxel (4). To a MeOH solution (3 mL) of **22** (38 mg, 32 μmol) was added PTSA (18.6 mg, 98 μmol, 3.1 equiv). The solution was stirred at room temperature for 2.5 h and quenched by an excess ethyl acetate. After standard workup, the residue was purified on preparative TLC (CH_2Cl_2/MeOH 95:5) to yield **4** (13.9 mg, 52%) as a white amorphous solid: IR ($CHCl_3$) 3440, 1715, 1494, 1453 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.21 (3H, s), 1.37 (9H, s), 1.78 (1H, m), 1.85 (3H, s), 1.86 (3H, s), 2.17 (1H, m), 2.30 (1H, m), 2.39 (3H, s), 2.33 (1H, m), 3.12 (1H, d, $J = 11.6$ Hz), 3.41 (1H, d, $J = 11.6$ Hz), 3.94 (1H, d, $J = 6.9$ Hz), 4.07 (2H, m), 4.66 (1H, bs), 5.23 (1H, s), 5.31 (1H, bd, $J = 9.2$ Hz), 5.59 (1H, d, $J = 9.2$ Hz), 5.64 (1H, d, $J = 6.9$ Hz), 6.16 (1H, t, $J = 6.9$ Hz), 7.33, 7.40, 7.41 (5H, m), 7.50 (2H, t, $J = 7.9$ Hz), 7.62 (1H, t, $J = 7.9$ Hz), 8.09 (2H, d, $J = 7.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 14.1, 20.5, 23.2, 26.4, 28.1, 35.9, 36.2, 39.6, 42.9, 43.0, 48.5, 58.1, 71.7, 71.7, 73.9, 74.4, 75.3, 78.5, 89.0, 126.7, 127.8, 128.6, 129.8, 130.1, 133.5, 135.3, 138.5, 155.8, 166.9, 170.8, 172.4, 210.9; MS (L-SIMS$^+$) *m/z* 846 (MNa^+); HRMS (FAB$^+$) calcd for $C_{43}H_{53}NO_{13}SNa$ (MNa^+) *m/z* 846.3149, found 846.3135.

2-Benzoyl-9-oxo-10-acetyl-4α(20)-epoxy-5-mesyltaxicine I (23). To a solution of **15** (2.05 g, 3.49 mmol) in dry toluene were added over a period of 3 weeks $CuCl_2$ (4.69 g, 34.9 mmol, 10 equiv) and tBuOOH (15.1 mL, 157 mmol, 45 equiv). The reaction was quenched with water, and copper salts were filtered. After standard workup, the residue was purified by flash chromatography on silica gel (heptane/AcOEt 9:1, 8:2, and 7:3) to afford **23** (1.19 g, 56%) as an amorphous solid: $[\alpha]^{20}_D$ −23.0 (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) 3337, 1749, 1719, and 1676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, s), 1.26 (3H, s), 1.35 (3H, s), 2.26 (3H, s), 2.29 (3H, s), 2.52 (1H, d, $J = 4$ Hz), 2.75 (1H, d, $J = 19.6$ Hz), 2.94 (1H, d, $J = 4$ Hz), 3.13 (3H, s), 3.19 (1H, d, $J = 19.5$ Hz), 4.03 (1H, d, $J = 4.5$ Hz), 4.15 (1H, bs), 5.46 (1H, d, $J = 4.6$ Hz), 6.78 (1H, s), 7.47 (2H, t, $J = 7.8$ Hz), 7.62 (1H, bt, $J = 7.35$ Hz), 8.06 (2H, dd, $J = 1.2$ Hz, $J' = 7.2$ Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.3, 15.9, 17.9, 20.9, 27.5, 30.9, 32.9, 39.1, 40.9, 43.7, 44.0, 51.6, 56.5, 60.4, 74.3, 75.9, 77.4, 86.9, 128.8, 128.9, 130.3, 134.1, 141.8, 152.1, 166.7, 169.4, 198.7, 202.8; MS (CI$^+$) *m/z* 605 (MH^+).

7-Deoxy-5(20)-deoxy-5(20)-sulfanyl-13-oxobaccatin III (24). To a solution of **23** (135 mg, 2.24 mmol) in 20 mL of dry DMF was added potassium thioacetate (52 mg, 0.46 mmol, 2 equiv). The solution was stirred at 60 °C for 17 h, and the DMF was evaporated under reduced pressure. After standard workup, the residue was purified by preparative TLC (CH_2Cl_2/MeOH 98:2) to afford **24** (15 mg, 12%) as an amorphous solid: $[\alpha]^{20}_D$ −6.5 (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 3413, 1747, 1718, and 1677 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.21 (3H, s), 1.80 (3H, s), 2.10 (3H, s), 2.23 (3H, s), 2.27 (3H, s), 2.65 (1H, d, $J = 19.95$ Hz), 2.97 (1H, d, $J = 19.9$ Hz), 3.17 (1H, d, $J = 11.6$ Hz), 3.40 (1H, d, $J = 11.7$ Hz), 4.04 (1H, t, $J = 7.8$ Hz), 4.06 (1H, d, $J = 6.85$ Hz), 5.72 (1H, d, $J = 6.85$ Hz), 6.51 (1H, s), 7.50 (2H, bt, $J = 7.45$ Hz), 7.63 (1H, bt, $J = 7.35$ Hz), 8.09 (2H, bd, $J = 7.15$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 17.4, 19.0, 20.9, 22.8, 29.8, 32.9, 35.1, 36.3, 43.0, 43.2, 44.9, 45.0, 53.7, 74.3, 75.4, 78.9, 89.0, 128.9, 129.3, 130.2, 134.0, 140.9, 152.1, 167.0, 169.4, 170.4, 197.8, 204.3; MS (CI$^+$) *m/z* 585 (MH^+).

7-Deoxy-5(20)-deoxy-5(20)-sulfanylbaccatin III (25). To a solution of **24** (43 mg, 74 μmol) in dry THF (0.6 mL) and dry MeOH (0.1 mL) cooled at 0 °C was added $NaBH_4$ (15 mg, 400 μmol, 5 equiv). The solution was stirred at 0 °C for 2 h. After standard workup, the residue was purified by preparative TLC (heptane/AcOEt 3:7) to afford **25** (28 mg, 60%) as an amorphous solid along with starting material **24** (10 mg, 21%). Compound **25**: $[\alpha]^{20}_D$ −45.5 (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) 1734, 1711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, s), 1.10 (3H, s), 1.83 (3H, s), 2.11 (3H, d, $J = 1.25$ Hz), 2.22 (3H, s), 2.37 (3H, s), 3.15 (1H, d, $J = 11.55$ Hz), 3.44 (1H, d, $J = 11.6$ Hz), 3.99 (1H, d, $J = 7$ Hz), 4.02 (1H, t, $J = 8.1$ Hz), 4.82 (1H, m), 5.63 (1H, d, $J = 7$ Hz), 6.42(1H, s), 7.51 (2H, bt, $J = 7.35$ Hz), 7.61 (1H, bt, $J = 7.45$ Hz), 8.11 (2H, bd, $J = 7.25$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 17.5, 21.0, 23.7, 26.5, 30.0, 35.7, 36.6, 40.0, 42.6, 45.4, 46.0, 53.2, 68.3, 75.0, 76.1, 79.1, 90.3, 128.8, 129.8, 130.2, 132.0, 133.7, 145.1, 167.1, 170.0, 172.4, 206.3; MS (CI$^+$) *m/z* 509 ($MH^+ - AcOH - H_2O$).

5(20)-Deoxy-5(20)-sulfanyl-7-deoxy-13-[[(4*S*,5*R*)-2-(4-methoxyphenyl)-3-(*tert*-butyloxycarbonyl)-4-phenyl-1,3-oxazolidin-5yl]carbonyl]baccatin III (26). To a solution of **25** (10 mg, 17 μmol), compound **21** (14 mg, 34 μmol, 2 equiv), and DCC (16 mg, 77 μmol, 4.5 equiv) in dry toluene (1 mL) was added 4-DMAP (3 mg, 26 μmol, 1.5 equiv). The solution was stirred at 80 °C for 3 h. After standard workup, the residue was purified by preparative TLC (heptane/AcOEt 1:1) to afford **26** (13 mg, 78%) as an amorphous solid: $[\alpha]^{20}_D$ −44.5 (*c* 0.48, $CHCl_3$); IR ($CHCl_3$) 3405, 1734, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.09 (3H, s), 1.20 (3H, s), 1.64 (3H, s), 1.76 (6H, s), 2.01−2.16 (3H, m), 2.21 (3H, s), 3.09 (1H, d, $J = 11.55$ Hz), 3.38 (1H, d, $J = 11.6$ Hz), 3.77 (1H, d, $J = 7.3$ Hz), 3.81 (3H,s), 3.97 (1H, t, $J = 8.65$ Hz), 4.61 (1H, d, $J = 5.65$ Hz), 5.35 (1H, bs), 5.6 (1H, d, $J = 7.3$ Hz), 6.11(1H, bt, $J = 7.35$ Hz), 6.33 (1H, s), 6.35 (1H, br s), 6.92 (2H, d, $J = 8.7$ Hz), 7.42 (5H, m), 7.43 (2H, d, $J = 8.95$ Hz), 7.50 (2H, bt, $J = 7.45$ Hz), 7.63 (1H, bt, $J = 7.45$ Hz), 8.03 (2H, br d, $J = 8.45$ Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.2, 17.2, 20.9, 21.8, 22.4, 26.4, 27.9, 30.3, 36.2, 36.4, 37.5, 42.8, 44.9, 45.8, 52.9, 55.5, 64.1, 71.6, 74.3, 76.2, 79.6, 80.9, 89.1, 92.7, 114.0, 126.7, 128.3, 128.8, 129.1, 129.7, 130.2, 132.6, 133.8, 141.4, 151.6, 160.5, 167.2, 169.5, 169.7, 170.0, 206.4; MS (ESI$^+$) *m/z* 990 (MNa^+).

7-Deoxy-10-acetyl-5(20)-deoxy-5(20)-sulfanyldocetaxel (5). To a dry MeOH solution (0.1 mL) of **26** (10 mg, 10 μmol) cooled to 0 °C was added a 0.012 M solution of PTSA (0.88 mL, 10 μmol, 1 equiv) in MeOH. The solution was stirred at 0 °C for 10 min and at room temperature for 3 h. The residue was purified by preparative TLC (heptane/AcOEt 1:1) to afford **5** (9 mg, 97%) as an amorphous solid: $[\alpha]^{20}_D$ −41.5 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3438, 1733, 1713, 1647 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.22 (3H, s), 1.35 (9H, s), 1.84 (6H, s), 2.22 (3H, s), 2.40 (3H, s), 3.14 (1H, d, $J = 11.55$ Hz), 3.43 (1H, d, $J = 11.55$ Hz), 3.53 (1H, bs), 3.86 (1H, d, $J = 7.1$ Hz), 4.04 (1H, t, $J = 8.1$ Hz), 4.66 (1H, bs), 5.32 (1H, bs), 5.47 (1H, d, $J = 9.55$ Hz), 5.66 (1H, d, $J = 7.2$ Hz), 6.18 (1H, bt, $J = 8.25$ Hz), 6.41 (1H, s), 7.39 (5H, m), 7.5 (2H, bt, $J = 7.3$ Hz), 7.61 (1H, bt, $J = 7.35$ Hz), 8.11 (2H, bd, $J = 7.2$ Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.7, 17.4, 20,1, 21.6, 23.5, 26.5, 28.3, 29.8, 30.1, 36.1, 36.1, 36.7, 42.9, 45.0, 46.0, 53.1, 56.1, 72.1, 74.0, 74.4, 76.1, 79.3, 80.2, 89.7, 126.9, 128.1, 128.9, 129.4, 130.3, 133.0, 133.8, 138.7, 141.0, 155.3, 167.2, 169.8, 170.7,

172.5, 206.1; MS (ESI$^+$) *m*/*z* 872 (MNa$^+$); HRMS (FAB$^+$) calcd for $C_{45}H_{56}NO_{13}S$ (MH$^+$) *m*/*z* 850.3431, found 850.3472.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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