Synthesis and Biological Evaluation of D-Ring-Modified Taxanes:[1] 5(20)-Azadocetaxel Analogs

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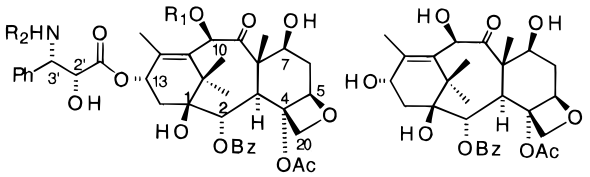
Two 5(20)-aza analogs of docetaxel, *N*-20-benzyl-5(20)-azadocetaxel (**5**) and 5(20)-azadocetaxel (**6**), have been synthesized from 10-deacetylbaccatin III. The key steps of this synthesis involved the direct introduction of a C-5 leaving group while ring opening and the intramolecular nucleophilic attack of the C-20 amino group at C-5. Both compounds were inactive on the *in vitro* cytotoxic assay, and only the azadocetaxel **6** retains an antitubulin activity, but 16 times less than docetaxel.

Since its isolation from the bark of the pacific yew tree, *Taxus brevifolia*, at the end of the 1960's,[2] paclitaxel (Taxol, **1a**) has been extensively studied and is now clinically used in ovarian and breast cancer chemotherapy. This diterpenoid and related compounds possess an original mechanism of action on microtubules[3] and constitute a new class of antimitotic agents. The isolation of 10-deacetylbaccatin III (**2**) from the needles of the European yew tree, *Taxus baccata* L.,[4] permitted the first semisynthesis of paclitaxel[4b,5] and the discovery of docetaxel (Taxotere, **1b**),[5] a clinically active agent, now used against breast and non-small-cell lung cancers.

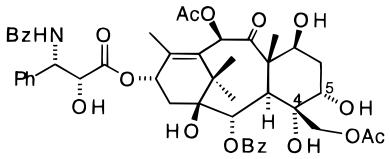


Paclitaxel (Taxol®) **1a** R_1=Ac, R_2=Bz **2**

Docetaxel (Taxotere®) **1b** R_1=H, R_2=Boc

The availability of significant amounts of **2** secured the long term supply of these anticancer drugs and facilitated semisynthetic studies directed at the elucidation of the paclitaxel pharmacophore. The number of analogs which have been synthesized by different groups contributed to the structure−activity relationship (SAR) studies.[6] Thus, the C-13 phenylisoserine side chain and the C-2 and C-4 esters have been determined to be crucial for biological activity.

Based on the inactivity of D-secotaxol derivatives like **3**,[7] it has also been reported that the oxetane ring was essential for interaction with microtubules and cytotoxicity. This observation seemed unsatisfactory because these compounds lacked the C-4 acetate group, known to be important for activity.[8] Furthermore they possessed a C-5α hydroxyl moiety instead of a *β*-oxygen.



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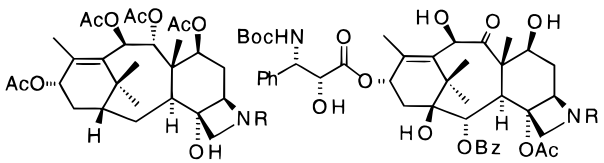
The oxetane ring might either act to rigidify ring C and point the C-4 acetoxy group in the appropriate direction for binding or be directly involved in the interaction with microtubules by its oxygen atom. Thus, replacement of this atom by another heteroatom or by a methylene group might distinguish between conformational and electronic contributions. We first decided to replace the oxetane by an azetidine ring. While progressing in our work, the synthesis of azetidine derivatives **4** was described.[9] But these compounds lacked the C-1 and C-2 functionalities, the presence of the latter, at least, being very important for the biological activity. Thus, in order to evaluate the influence of the azetidine ring on antitubulin activity, real docetaxel or paclitaxel analogs were needed.



4 R=H or R=Ac **5** R=Bn **6** R=H

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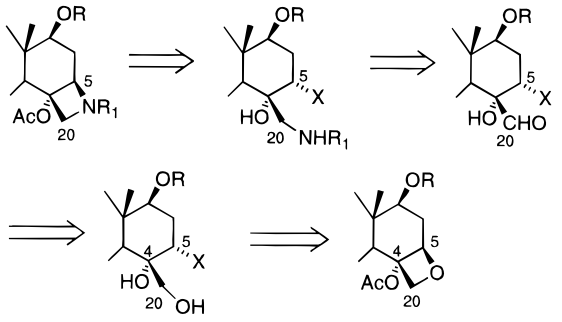
Scheme 1



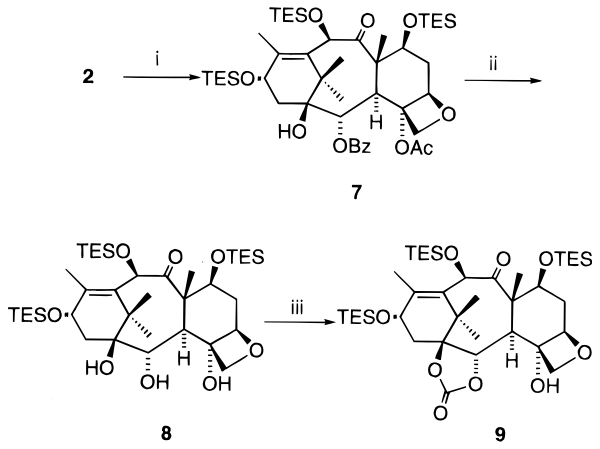
R and R_1 = protective groups

As part of our SAR work, we wish to present herein the synthesis and antitubulin activity evaluation of 5(20)-azadocetaxel analogs **5** and **6**.

Our strategy (Scheme 1) was based on the work of Ettouatti et al. for the construction of the oxetane ring.[10] For the azetidine ring closure, a C-5α leaving group and a C-20 amino moiety were needed. This functionality could be introduced by reductive amination of the C-20 aldehyde obtained by oxidation of the corresponding alcohol. The C-20 hydroxyl group might proceed from oxetane ring opening, the C-5α leaving group being introduced simultaneously as was done by Holton et al.[11] in their Taxol total synthesis.

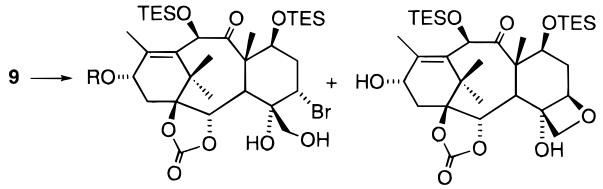
The mechanism of the oxetane ring opening catalyzed by Lewis acids involves the intramolecular participation of the C-4 acetyl group leading to the formation of an orthoester between C-4, C-5, and C-20. The hydrolysis of this orthoester afforded the C-5 and C-20 acetoxy derivatives.[12,13] These undesired acetylations can be avoided by using a C-4 hydroxyl derivative rather than the C-4 acetoxy analog. To avoid intramolecular transacylations between C-1, C-2, and C-20 oxygen and eventual A-ring contraction during acid-catalyzed opening of the oxetane,[13] the protection by a C-1,C-2 cyclic carbonate was required. As previously reported in paclitaxel total syntheses,[14] this protective group has additional advantages: it facilitates the introduction of the C-4 acetyl function and can be easily transformed to the C-2 benzoate derivative. Because of side reactions during formation of the cyclic carbonate, all the other hydroxyl groups have to be protected. Thus, Lewis acid-promoted opening of the oxetane ring was studied on compound **9**. Its synthesis is depicted in Scheme 2.

Scheme 2[a]



[a] Conditions: (i) TESCl/imidazole/DMF/rt, 48 h, 86%; (ii) Red-Al (12 equiv)/THF/0 °C, 86%; (iii) $(CCl_3O)_2CO/CH_2Cl_2$−pyridine (85-15)/−15 °C, 92%.

Scheme 3



Starting from 10-deacetylbaccatin III (**2**), the C-7, C-10, and C-13 hydroxyl groups were protected by chlorotriethylsilane with imidazole in DMF. Complete protection of the three alcohols required long reaction time (48 h to yield **7** in 86% yield), the C-10 OH being sluggishly silylated. Though Red-Al was described to selectively deacylate the C-2 position when the C-13 hydroxyl group was protected,[15] a large excess of Red-Al (12 equiv) removed both C-2 and C-4 acyl groups yielding **8** in 86% yield. Similar results have been obtained by Georg et al. on paclitaxel with tBuOK and KOH as deacylating reagents.[16] Formation of the C-1,C-2 cyclic carbonate was easily achieved by addition of triphosgene to yield **9** in 92% yield.

Results on the opening of the oxetane ring promoted by Lewis acid (Scheme 3) are summarized in Table 1. Bromotrimethylsilane was described to open cyclic ethers and to introduce a bromide and a trimethylsilyl ether.[17] In our hands, no additional silyl ether was observed. On the contrary, partial desilylation at C-13 was always observed along with oxetane ring opening (entries 1−3) likely due to the relative acidity of the reaction mixture. Boron trifluoride etherate/iodide ion was described as a mild ether-cleaving reagent.[18] In order to correlate with the previous experiments using bromotrimethylsilane, bromide was used instead of iodide. Among the different

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Table 1. Lewis Acid Promoted Oxetane Ring Opening

		products (%)			
entry	conditions[a]	**9**	**10**	**11**	**12**
1	TMSBr (1 equiv), 0 °C, 15 min	18	20	40	
2	TMSBr (1 equiv), 0 °C, 35 min		17	57	
3	TMSBr (5 equiv), rt, 40 min			15	*b*
4	$BF_3{\cdot}OEt_2$ (0.9 equiv), Et_4NBr (3 equiv), rt, 3 min		35	25	30
5	$BF_3{\cdot}OEt_2$ (1.8 equiv), Et_4NBr (3 equiv), rt, 5 min		23	40	
6	$SnCl_4$ (1 equiv), Et_4NBr (1.5 equiv), rt, 2 h	66			9
7	BBr_3 (1 equiv), Et_4NBr (3 equiv), 0 °C, 5 min			*b*	
8	$BF_3{\cdot}OEt_2$ (1 equiv), NaBr (3.5 equiv), rt, 5 min			*b*	

[a] All experiments were conducted in dry CH_2Cl_2. [b] Formation of very polar compounds not identified.

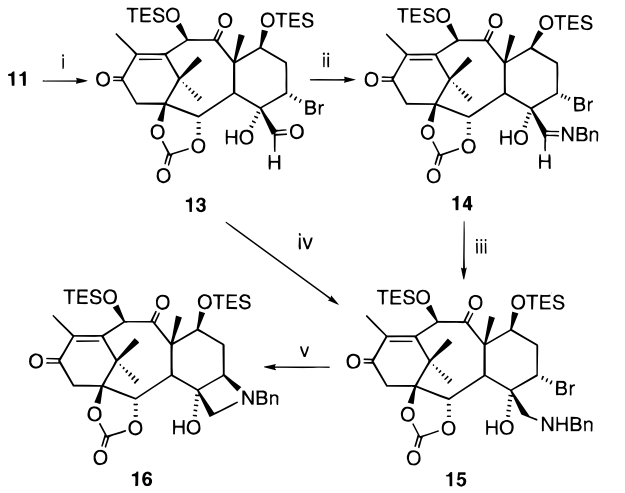
bromide ions (entries 4 and 8) and Lewis acids (entries 4, 6, and 7) used, the best results were obtained with Et_4NBr and boron trifluoride etherate. Greater amounts of this later reagent increased desilylation (entry 5), and variation in the amount of bromide ion had little influence on the opening rate (data not shown). Increasing reaction times only allowed additional removal of silyl ethers. This side reaction could not be avoided by lower temperature but was minimized by using dry methylene chloride as the solvent for this reaction. Acetonitrile, ethyl ether, and DMF gave predominantly desilylated compounds (data not shown).

Under those different conditions, the oxetane ring was always opened with the same regioselectivity, with the bromide being introduced at the C-5 α-position. In the literature both reagents (TMSBr or $BF_3{\cdot}OEt_2/Et_4NBr$) were known to yield the less hindered bromide.[17,18] Our results, as well as those of Holton with TMSCl,[11] could be explained by the steric hindrance at the C-20 position due to the presence of the C-4 hydroxyl group on the α-face and the C-19 methyl group on the *β*-face.

Two derivatives bearing a C-5α leaving group and a free C-20 hydroxyl group (**10** and **11**) were thus available. Though the subsequent steps of the synthesis, *i.e.*, oxidation, reductive amination, and azetidine ring formation, have been realized on compound **10**[19] and optimized to 54% overall yield, further acetylation and selective removal of the C-13 protective group appeared troublesome. Indeed, the C-4 OH was known to be hard to acylate[20] especially when a bulky group such as triethylsilyl was in the C-13 position. Moreover, preliminary studies on 7,10,13-tris(triethylsilyl) derivatives showed that the C-13 protective group could best be removed by HF/pyridine complex. Because of the sensitivity of the azetidine ring toward mineral acids,[21] starting from the triprotected derivative **10** did not appear suitable and we chose to continue the synthesis on compound **11**.

We needed a small C-13 protective group that would be removed under mild conditions in the presence of the triethylsilyl ethers and the cyclic carbonate. Transformation of the C-13 hydroxyl moiety into a ketone seemed to us of valuable interest, since it could be easily reduced to the starting hydroxyl group[22] and would not trouble acetylation.

Scheme 4[a]



[a] Conditions: (i) TFAA/DMSO in toluene then Et_3N, −60 °C, **13** (82%); (ii) $BnNH_2$ (4 equiv), $ZnCl_2$ (1 equiv) in CH_3CN, rt, **14** (27% isolated yield); (iii) $NaBH_3CN$ (3.5 equiv), AcOH, MeOH, 0 °C, **15** (61%); (iv) $BnNH_2$ (4 equiv), $ZnCl_2$ (1.1 equiv) in CH_3CN, rt then $NaBH_3CN$ (3.5 equiv), AcOH, 0 °C; (v) CH_2Cl_2, rt, **16** (56% from **13**).

Scheme 4 summarizes the synthetic route to the azetidine derivative **16**. Dess−Martin periodinane[23] first gave the desired compound, but the reaction was not reproducible and yields were only moderate (no more than 50%). On the contrary to results of Fenoglio et al.,[9] Swern oxidation was totally ineffective. Finally, compound **13** was obtained in good yield using trifluoroacetic anhydride-activated DMSO[24] in toluene, both C-13 and C-20 alcohol being oxidized simultaneously. Reductive amination on **13** was achieved with benzylamine and $NaBH_3CN$ under acidic conditions. This reaction could not be realized in one step as usually described.[25] The imine **14** was obtained in acetonitrile with an excess of amine, and the yield was improved by addition of $ZnCl_2$ (it would serve as dehydrating agent as it was described with $TiCl_4$ in the same type of reaction[26]). The C-13 ketone was unreactive toward benzylamine at room temperature. This was predictable from recent results on the oximation of this ketone that could only be realized at elevated temperature.[20b,27] Compound **14** was isolated before reduction, but amine **15** was obtained in a better yield by direct reduction of the reaction mixture with sodium cyanoborohydride under acidic conditions. The azetidine ring closure occurred spontaneously in methylene chloride at room temperature. Thus, compound **15** led to the aza derivative **16**. The overall yield of this synthetic pathway could only be improved by carrying

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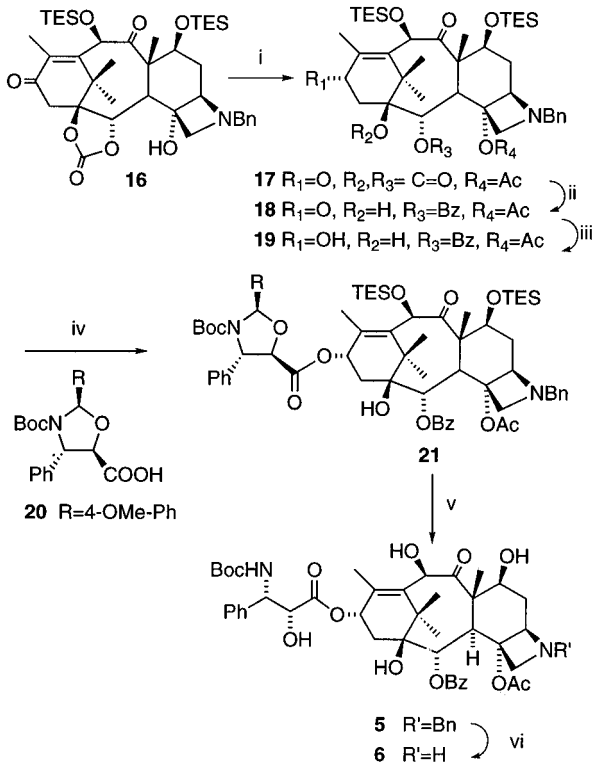
Scheme 5



[a] Conditions: (i) DMAP (20 equiv), Ac_2O (25 equiv), CH_2Cl_2, rt, **17** (71%); (ii) PhLi (5 equiv), THF, −72 °C, **18** (91%); (iii) $NaBH_4$ (14 equiv), EtOH/THF (1/3), rt, **19** (74%); (iv) **20** (3 equiv), DCO (3 equiv), DMAP (1.5 equiv), toluene, rt, **21** (99%); (v) PTSA, (3 equiv), MeOH, rt, **5** (72%); (vi) H_2, Pd/C, MeOH, rt, **6** (61%).

out the reaction without isolating neither the imine **14** nor the amine **15**.

Afterwards, the following steps of the synthesis (Scheme 5) were uneventful. Acetylation of compound **16** was achieved at room temperature, affording **17** in 70% yield. As previously described,[28] the C-1,C-2 carbonate was readily opened by phenyllithium in excellent yield (**18**, 90%) without affecting the C-13 ketone. This function was then reduced with $NaBH_4$ to afford the C-13α isomer **19** in 70% yield. Esterification was realized with the 2-(4-OMe)phenyl-1,3-oxazolidine of *N*-Boc-phenylisoserine (**20**),[29] DCC, and DMAP in toluene at room temperature in excellent yield (**21**, 99%). Deprotection of **21** with PTSA in MeOH afforded **5**, which was fully deprotected by hydrogenolysis to afford **6**, the azetidine isostere of the oxetane ring of docetaxel.

The activity of compounds **5** and **6** was evaluated *in vitro* on the disassembly process of microtubules into tubulin[30] and on the cytotoxicity against KB cell line.[31]

As shown in Table 2, the replacement of the oxetane oxygen atom by a nitrogen greatly affects the interaction with microtubules. Compound **6** is 16 times less active than docetaxel, and compound **5** is inactive. It is worthy

Table 2. Results of Biological Evaluation of 5(20)-Azadocetaxel Analogs

compd	microtubule disassembly inhibitory activity[a] IC_{50}/IC_{50}(paclitaxel)	cytotoxicity against KB cell line[b] IC_{50} (nM)
1a	1	6
1b	0.5	3.2
5	inactive[c]	inactive
6	8	inactive

[a] IC_{50} is the concentration required to inhibit 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. [c] Only 15% inhibition at 75 μM.

to note that molecular modeling studies and examination of related examples from the Cambridge Data Bank show that the azetidine ring induces almost the same constraint on the C-ring than the oxetane, even if its structural parameters are very slightly different. Moreover, the replacement of an oxygen by a nitrogen should only bring small electronic modifications in this area of the molecule. Indeed, the pyramidal N-inversion can easily take place, the two isomers being very similar in energy as shown by molecular modeling analysis. Thus, in order to explain the large difference of activity between docetaxel (**2**) and its aza analog **6**, we can suppose the involvement of a specific interaction of the heteroatom with the protein, probably troubled by the presence of the hydrogen of the amine. The total inactivity of compound **5** supports the hypothesis of a sterically restricted binding site for this part of the molecule. But, an ether has been replaced by an amine, a more basic function likely protonated at biological pH, so we cannot rule out the hypothesis of a charge repulsion at the binding site. Preliminary studies on the *N*-acetyl derivative of **6**, a nonprotonable amide devoid of antitubulin activity (data not shown), are not in favor of this latest hypothesis. Additional studies of other small amide derivatives are under current investigation and will be reported in due time.

In summary, 5(20)-aza derivatives of docetaxel (**5** and **6**) have been prepared from 10-deacetylbaccatin III. These are the first tetracyclic docetaxel analogs bearing a modified D-ring. The key steps of this synthesis were the direct introduction of a C-5 leaving group while the ring was opened and the intramolecular nucleophilic attack of the C-20 amino group at C-5. This strategy can be applied to the preparation of other modified D-ring analogs that could also help to determine the precise role of the oxetane ring in the interaction of taxoids with microtubules.

Experimental Section

General Methods. General methods were the same as previously described.[32] Standard workup means extraction with a suitable solvant (CH_2Cl_2 unless otherwise specified), washing the extract with H_2O or brine, drying over Na_2SO_4, and evaporation in vacuo. 10-Deacetylbaccatin III was extracted from *T. baccata* leaves,[4a] and the docetaxel acid side chain **22** was a gift from Rhône-Poulenc Rorer S.A. Microtubular proteins were purified from bovine brain as previously described.[33] Molecular modeling studies were performed using MacroModel on a Silicon Graphics 4D/35 workstation.

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Preparation of Compound 7. To a solution of **2** (4.6 g, 8.5 mmol) in 13 mL of dry DMF was added imidazole (1.85 g, 27 mmol, 3.2 equiv). Then triethylsilyl chloride (7 mL, 42.5 mmol, 5 equiv) was added dropwise at room temperature. The solution was stirred for 48 h. After removal of the solvant, 100 mL of AcOEt and 75 mL of water were added. After standard workup the residue was purified on silica gel (heptane/AcOEt: 95/5) to yield pure **7** (6.5 g, 86%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.62 (18H, m), 1.01 (27H, m), 1.12 (3H, s), 1.20 (3H, s), 1.65 (3H, s), 1.80 (1H, m), 1.99 (3H, s), 2.17 (2H, m, 2H), 2.29 (3H, s), 2.51 (1H, m), 3.87 (1H, d, J = 7 Hz), 4.14 (1H, d, J = 8 Hz), 4.30 (1H, d, J = 8 Hz), 4.42 (1H, dd, J = 11 Hz, J' = 7 Hz), 4.93 (1H, m), 4.95 (1H, m), 5.20 (1H, s), 5.62 (1H, d, J = 7 Hz), 7.45, 7.59, 8.10 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0, 5.4, 5.9, 7.0, 7.1, 10.8, 14.8, 20.9, 22.6, 26.6, 37.6, 40.1, 43.2, 47.0, 60.0, 68.5, 72.8, 75.6, 75.9, 76.8, 79.7, 80.9, 84.2, 128.7, 129.8, 130.2, 133.6, 136.6, 139.6, 167.3, 170.1, 205.8; IR ($CHCl_3$) 1725 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 203.2 (1727), 214 (1727), 240.4 (6933), 270.4 (1550) nm; MS (FAB$^+$) m/z 909 (MNa^+).

Preparation of Compound 8. To a THF solution (50 mL) of **7** (5 g, 5.6 mmol) was added Red-Al (3.5 M) in toluene (21 mL, 73.5 mmol, 13 equiv) at 0 °C. The solution was stirred at 0 °C for 25 min, and the reaction was stopped by careful addition of 15 mL of a saturated potassium−sodium tartrate solution. After standard workup with AcOEt the residue was purified by silica gel chromatography (cyclohexane/AcOEt: 70/30) to afford **8** (3.6 g, 86%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.71 (18H, m), 1.03 (27H, m), 1.11 (3H, s), 1.56 (3H, s), 1.92 (3H, s), 2.02 (1H, m), 2.18 (1H, m), 2.48 (1H, m), 2.50 (1H, m), 3.26 (1H, s), 3.28 (1H, d, J = 6 Hz), 3.48 (1H, d, J = 11 Hz), 3.78 (1H, dd, J = 11 Hz, J' = 6 Hz), 4.02 (1H, dd, J = 11 Hz, J' = 6 Hz), 4.19 (1H, s), 4.40 (1H, d, J = 8 Hz), 4.62 (1H, m), 4.67 (1H, dd, J = 9.5 Hz, J' = 4 Hz), 4.75 (1H, d, J = 8 Hz), 5.26 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.3, 5.8, 6.6, 7.4, 7.5, 10.6, 17.9, 18.4, 30.6, 38.4, 39.2, 41.8, 51.8, 59.6, 70.8, 74.0, 74.2, 76.4, 77.1, 77.6, 80.5, 86.8, 135.7, 141.3, 206.6; IR ($CHCl_3$) 3493, 1712, 1593 cm^{-1}; MS (FAB$^+$) m/z 763 (MNa^+).

Preparation of Compound 9. A solution of **8** (1.18 g, 1.6 mmol) in 20 mL of a mixture of CH_2Cl_2/pyridine (85/15) was cooled to −15 °C. Then triphosgene (0.85 g, 2.9 mmol, 1.8 equiv) was added, and the solution was stirred for 15 min at −15 °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: 85/15) to yield pure **9** (1 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (18H, m), 0.98 (27H, m), 1.03 (3H, s), 1.10 (3H, s), 1.55 (3H, s), 1.91 (4H, m), 2.43 (2H, m), 2.57 (1H, m), 3.02 (1H, d, J = 5 Hz), 4.07 (1H, dd, J = 11 Hz, J' = 7 Hz), 4.25 (1H, d, J = 5 Hz), 4.42 (1H, d, J = 8 Hz), 4.48 (1H, d, J = 8 Hz), 4.53 (1H, m), 4.70 (1H, dd, J = 10 Hz, J' = 1 Hz), 5.14 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.5, 5.7, 6.7, 6.7, 9.9, 17.3, 18.5, 28.1, 35.7, 37.8, 40.3, 18.7, 60.3, 68.9, 73.4, 73.5, 77.3, 78.5, 80.4, 87.3, 89.8, 137.2, 139.3, 153.2, 206.1; IR ($CHCl_3$) 3700, 1800, 1712, 1600 cm^{-1}; MS (FAB$^+$) m/z 789 (MNa^+).

Oxetane Ring Opening. Experimental conditions are described in Table 1. Dry CH_2Cl_2 and freshly distilled BF_3·OEt_2 were required. As a typical procedure entry 5 is described:

To a solution of **9** (155 mg, 0.2 mmol) in 10 mL dry of CH_2Cl_2 were added Et_4NBr (127 mg, 0.6 mmol, 3 equiv) and BF_3·OEt_2 (22 μL, 0.18 mmol, 0.9 equiv). The solution was stirred at room temperature for 3 min and then hydrolyzed. After standard workup, the residue was purified on preparative TLC (heptane/AcOEt/MeOH: 50/50/2) to yield pure **10** (60 mg, 35%) along with **11** (37 mg, 25%) and **12** (40 mg, 30%).

Compound 10: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (18H, m), 0.94 (27H, m), 1.08 (3H, s), 1.12 (3H, s), 1.17 (3H, s), 2.08 (3H, s), 2.14 (1H, m), 2.26 (1H, m), 2.34 (1H, dd, J = 15 Hz, J' = 9 Hz), 2.88 (1H, dd, J = 15 Hz, J' = 5 Hz), 2.95 (1H, s), 3.58 (1H, d, J = 12 Hz), 3.68 (1H, d, J = 5 Hz), 4.18 (1H, d, J = 12 Hz), 4.21 (1H, d, J = 5 Hz), 4.39 (1H, dd, J = 10 Hz, J' = 4 Hz), 4.80 (1H, m), 4.88 (1H, bs), 5.28 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0, 5.2, 5.8, 6.9, 7.0, 13.3, 17.1, 19.5, 26.8, 37.1, 37.4, 40.9, 46.5, 61.4, 62.3, 63.2, 68.4, 70.0, 74.9, 76.7, 82.1, 91.0, 135.0, 142.8, 153.4, 205.7; IR ($CHCl_3$) 3495, 1798, 1718 cm^{-1}; MS (FAB$^+$) m/z 869−871 (MNa^+); HRMS calcd for $C_{39}H_{71}O_9Si_3BrNa$ (MNa^+) 869.4039, found 869.3455.

Compound 11: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.49, 0.55 (12H, m), 0.90 (18H, m), 1.05 (3H, s), 1.09 (3H, s), 1.13 (3H, s), 2.14 (1H, m), 2.23 (3H, s), 2.32 (1H, m), 2.59 (1H, dd, J = 16 Hz, J' = 9 Hz), 2.88 (1H, dd, J = 16 Hz, J' = 4 Hz), 3.01 (1H, bs), 3.59 (1H, d, J = 11 Hz), 3.69 (1H, d, J = 5 Hz), 3.81 (1H, s), 4.11 (1H, d, J = 11 Hz), 4.21 (1H, d, J = 5 Hz), 4.41 (1H, dd, J = 11 Hz, J' =4 Hz), 4.65 (2H, m), 5.28 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.1, 5.8, 6.9, 13.2, 17.1, 19.1, 27.4, 36.1, 37.2, 40.8, 45.8, 61.2, 61.9, 62.7, 68.4, 70.0, 74.0, 76.9, 81.9, 91.6, 135.8, 142.5, 154.0, 205.7; IR ($CHCl_3$) 3518, 1787, 1706 cm^{-1}; MS (FAB$^+$) m/z 755−757 (MNa^+), 677 (M − Br + Na^+).

Compound 12: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (12H, m), 0.98 (18H, m), 1.12 (3H, s), 1.18 (3H, s), 1.60 (3H, s), 1.96 (1H, m), 2.05 (3H, s), 2.53 (1H, m), 2.62 (2H, m), 3.16 (1H, d, J = 5 Hz), 3.49 (1H, s), 4.15 (1H, dd, J = 11 Hz, J' = 7 Hz), 4.39 (1H, d, J = 5 Hz), 4.50 (1H, d, J = 8 Hz), 4.62 (1H, d, J = 8 Hz), 4.62 (1H, m), 4.85 (1H, dd, J = 10 Hz, J' = 1 Hz), 5.21 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.3, 6.1, 7.0, 7.2, 10.4, 17.4, 18.9, 28.5, 35.3, 38.0, 40.7, 48.2, 60.4, 68.2, 72.7, 74.5, 77.8, 79.7, 80.9, 87.9, 91.2, 137.0, 140.8, 154.1, 206.5; IR ($CHCl_3$) 3362, 1806, 1725 cm^{-1} MS (CI) m/z 653 (M + H)$^+$, 635 (M − H_2O + H)$^+$.

Preparation of Compound 13. A dry toluene solution (6 mL) of DMSO (1.22 mL, 17 mmol) was added dropwise at −70 °C to a toluene solution (6 mL) of TFAA (1.8 mL, 13 mmol). After stirring at −65 °C for 15 min, a toluene solution (12 mL) of **11** (633 mg, 0.86 mmol) was added dropwise, and the solution was stirred between −60 and −50 °C for 45 min. Then Et_3N (2.4 mL, 17 mmol) was added dropwise, and the solution was stirred below −40 °C for 15 min. The reaction was stopped by addition of water (5 mL), and the solution was allowed to warm up. After standard extraction the residue was purified on silica gel (heptane/AcOEt: 82/18) to yield **13** (520 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (12H, m), 0.90 (18H, m), 1.13 (3H, s), 1.19 (3H, s), 1.28 (3H, s), 2.22 (3H, s), 2.28 (2H, m), 2.66 (1H, d, J = 19 Hz), 3.25 (1H, s), 3.61 (1H, d, J = 19 Hz), 3.62 (1H, d, J = 5 Hz), 4.40 (1H, dd, J = 11Hz, J' = 4 Hz), 4.43 (1H, d, J = 5 Hz), 4.81 (1H, t, J = 3 Hz), 5.41 (1H, s), 9.78 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.4, 6.1, 7.1, 7.2, 13.3, 15.4, 19.0, 32.2, 37.6, 41.2, 42.5, 45.3, 56.7, 62.4, 70.3, 77.5, 78.1, 80.8, 89.2, 139.7, 151.9, 155.2, 195.8, 197.4, 204.0; IR ($CHCl_3$) 1806, 1720, 1685 cm^{-1}; MS (LSIMS$^+$) m/z 751−753 (MNa^+).

Preparation of Compound 14. To a CH_3CN solution (2 mL) of **13** (59 mg, 81 μmol) were added $ZnCl_2$ (11 mg, 81 μmol) and benzylamine (35 μL, 32 μmol). The solution was stirred at room temperature for 6 h. After standard workup, the residue was purified on preparative TLC (CH_2Cl_2/acetone: 97/3) to yield **14** (18 mg, 27%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (6H, m), 0.65 (6H, m), 0.94 (18H, m), 1.17 (3H, s), 1.26 (3H, s), 1.38 (3H, s), 2.31 (3H, s), 2.31 (2H, m), 2.89 (1H, d, J = 19 Hz), 3.71 (1H, d, J = 5 Hz), 3.84 (1H, d, J = 19 Hz), 4.42 (1H, d, J = 5 Hz), 4.50 (1H, dd, J = 4 Hz, J' = 10 Hz), 4.68 (2H, qAB, J = 14 Hz), 5.10 (1H, t, J = 3 Hz), 5.48 (1H, s), 7.32 (5H, m), 8.16 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.1, 5.9, 6.9, 13.2, 15.1, 18.6, 31.9, 37.4, 41.0, 42.2, 44.9, 59.8, 62.6, 64.2, 70.4, 74.7, 77.6, 80.9, 88.9, 127.6, 128.1, 128.8, 137.5, 139.4, 152.5, 154.7, 163.3, 194.4, 204.3; IR ($CHCl_3$) 1810, 1717, 1685, 1605 cm^{-1}; MS (LSIMS$^+$) m/z 818−820 (MH^+).

Preparation of Compound 15. To a CH_3CN solution (3 mL) of **14** (49 mg, 60 μmol) were added AcOH and $NaBH_3CN$ (12.5 mg, 0.2 mmol, 3.3 equiv). The solution was stirred at 0 °C for 2 h and then hydrolyzed with saturated $NaHCO_3$. After standard workup, the residue was purified by preparative TLC (CH_2Cl_2/acetone: 97/3) to yield **15** (20 mg, 40%) along with **16** (9.7 mg, 22%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.53 (6H, m), 0.64 (6H, m, 6H), 0.98 (18H, m), 1.22 (6H, s), 1.31 (3H, s), 2.08 (1H, m), 2.23 (1H, m), 2.27 (3H, s), 2.62 (1H, d, J = 13 Hz), 2.80 (1H, d, J = 19 Hz), 3.25 (1H, d, J = 13 Hz), 3.66 (1H, d, J = 5 Hz), 3.85 (2H, qAB, J = 13 Hz), 4.03 (1H, t, J = 2 Hz), 4.14 (1H, d, J = 19 Hz), 4.30 (1H, d, J = 5 Hz), 4.46 (1H, dd, J = 4 Hz, J' = 10 Hz), 5.44 (1H, s), 7.29 (5H, m); ^{13}C NMR

(62.5 MHz, $CDCl_3$) δ 5.1, 5.8, 6.8, 6.9, 13.5, 15.0, 18.7, 31.7, 36.9, 41.1, 42.0, 44.2, 51.4, 54.3, 62.7, 63.0, 70.1, 71.1, 77.7, 81.1, 88.9, 127.9, 128.4, 128.8, 138.6, 139.1, 153.0, 154.1, 197.7, 204.7; IR ($CHCl_3$) 3402, 1802, 1715, 1682 cm^{-1}; MS (LSIMS$^+$) *m/z* 820−822 (MH^+), 740 (MH^+ of **16**).

Preparation of Compound 16 from 13. To a CH_3CN solution (5 mL) of **13** (108 mg, 0.15 mmol) were added benzylamine (70 μL, 0.64 mmol, 4 equiv) and zinc chloride (21.6 mg, 0.16 mmol, 1.1 equiv). The solution was stirred overnight at room temperature. The solution was cooled to 0 °C, and 0.9 mL of acetic acid and $NaBH_3CN$ (29.3 mg, 0.47 mmol, 3.1 equiv) were added. The solution was stirred at 0 °C for 30 min and then hydrolyzed by saturated $NaHCO_3$. After standard workup, the residue was allowed to stand at room temperature in CH_2Cl_2 for 2 days and then was purified on silica gel (CH_2Cl_2/acetone: 97/3) to yield **16** (62 mg, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47 (6H, m), 0.65 (6H, m), 0.95 (18H, m), 1.26 (3H, s), 1.31 (3H, s), 1.62 (1H, m), 1.79 (3H, s), 2.04 (3H, s), 2.17 (1H, s), 2.62 (1H, d, J = 5 Hz), 2.78 (1H, d, J = 19 Hz), 2.92 (1H, d, J = 11 Hz), 3.26 (1H, bd, J = 8.5 Hz), 3.61 (1H, d, J = 19 Hz), 3.74 (2H, qAB, J = 13 Hz), 3.88 (1H, d, J = 11 Hz), 4.02 (1H, dd, J = 7 Hz, J' = 10 Hz), 4.45 (1H, d, J = 5 Hz), 5.29 (1H, s), 7.29 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.2, 6.0, 6.9, 7.0, 10.1, 14.6, 18.2, 31.6, 38.0, 40.7, 41.8, 48.8, 60.8, 62.5, 64.7, 70.5, 73.8, 78.8, 81.0, 89.0, 127.2, 128.2, 128.9, 137.7, 138.0, 153.3, 154.8, 198.1, 205.4; IR ($CHCl_3$) 1800, 1712, 1687 cm^{-1}; MS (LSIMS$^+$) *m/z* 740 (MH^+), 712 (MH^+ − carbonate).

Preparation of Compound 17. To a CH_2Cl_2 solution (8 mL) of **16** (60 mg, 81 μmol) were added 4-DMAP (200 mg, 1.6 mmol, 20 equiv) and acetic anhydride (190 μL, 2 mmol, 25 equiv). The solution was stirred for 3 h at room temperature and then hydrolyzed by aqueous $NaHCO_3$. After standard workup, the residue was purified by preparative TLC (heptane/AcOE: 70/30) to yield **17** (46 mg, 71%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.47 (6H, m), 0.65 (6H, m), 0.94 (18H, m), 1.25 (3H, s), 1.29 (3H, s), 1.52 (1H, m), 1.87 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.28 (1H, m), 2.83 (2H, qAB, J = 19 Hz), 3.14 (1H, d, J = 11 Hz), 3.39 (1H, bd, J = 9 Hz), 3.42 (1H, d, J = 5 Hz), 3.68 (2H, qAB, J = 11 Hz), 3.73 (1H, d, J = 11 Hz), 4.34 (1H, dd, J = 8 Hz, J' = 10 Hz), 4.45 (1H, d, J = 5 Hz), 5.31 (1H, s), 7.32 (5H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 5.1, 6.0, 6.8, 7.0, 9.9, 14.3, 18.5, 22.1, 31.8, 38.2, 40.1, 41.6, 43.8, 61.0, 61.4, 62.7, 68.4, 73.0, 77.6, 77.9, 80.5, 88.7, 127.4, 128.4, 128.9, 137.6, 138.0, 152.7, 155.6, 170.4, 196.6, 204.9; IR ($CHCl_3$) 1806, 1722, 1686 cm^{-1}; MS (LSIMS$^+$) *m/z* 782 (MH^+).

Preparation of Compound 18. To a dry THF solution (3 mL) of **17** (30 mg, 39 μmol) cooled to −72 °C was added under argon a hexane solution of phenyllithium (1.6 M, 120 μL, 192 μmol, 4.8 equiv). The solution was stirred for 30 min at −72 °C and then poured on a mixture of CH_2Cl_2 and saturated ammonium chloride and stirred for 1 min at room temperature. After standard workup, the residue was purified on preparative TLC (heptane/AcOEt: 70/30) to yield **18** (30 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51 (6H, q, J = 7 Hz), 0.76 (6H, q, J = 7 Hz), 0.96 (9H, t, J = 7 Hz), 1.09 (9H, t, J = 7 Hz), 1.26 (3H, s), 1.34 (3H, s), 1.50 (1H, m), 1.86 (3H, s), 2.11 (3H, s), 2.22 (3H, s), 2.24 (1H, m), 2.67 (1H, d, J = 19 Hz), 2.98 (1H, d, J = 11 Hz), 2.99 (1H, d, J = 19 Hz), 3.45 (1H, bd, J = 9 Hz), 3.46 (1H, d, J = 11 Hz), 3.48 (1H, d, J = 13 Hz), 3.71 (1H, d, J = 13 Hz), 3.84 (1H, d, J = 7 Hz), 4.41 (1H, dd, J = 7 Hz, J' = 10 Hz), 5.42 (1H, s), 5.74 (1H, d, J = 7 Hz), 7.26 (5H, m), 7.56 (2H, t, J = 7 Hz), 7.69 (1H, t, J = 7 Hz), 8.16 (2H, d, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.3, 6.2, 6.9, 7.1, 9.9, 13.5, 17.9, 22.3, 33.1, 38.0, 42.6, 43.5, 46.9, 59.1, 61.6, 62.6, 73.5, 73.9, 76.9, 79.1, 127.5, 128.6, 129.0, 129.2, 129.9, 130.5, 133.9, 136.2, 138.1, 158.2, 167.3, 170.0, 199.2, 204.7; IR ($CHCl_3$) 1725, 1667 cm^{-1}; MS (LSIMS$^+$) *m/z* 860 (MH^+).

Preparation of Compound 19. To a THF/EtOH solution (22/78, 7.7 mL) of **18** (30 mg, 35 μmol) was added $NaBH_4$ (18 mg, 480 μmol, 14 equiv). The solution was stirred at room temperature overnight. After standard workup, the residue was purified on preparative TLC (heptane/AcOEt: 60/40) to yield **19** (22.5 mg, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.44 (6H, q, J = 7 Hz), 0.75 (6H, m), 0.87 (9H, t, J = 7 Hz), 1.01 (9H, t, J = 7 Hz), 1.05 (3H, s), 1.18 (3H, s), 1.48 (1H, m), 1.80 (3H, s), 1.98 (3H, s), 2.15 (1H, m), 2.23 (2H, m), 2.25 (3H, s), 2.90 (1H, d, J = 11 Hz), 3.48 (1H, bd, J = 9 Hz), 3.52 (1H, d, J = 11 Hz), 3.52 (1H, d, J = 13 Hz), 3.65 (1H, d, J = 13 Hz), 3.77 (1H, d, J = 7 Hz), 4.36 (1H, dd, J = 7 Hz, J' = 10 Hz), 4.81 (1H, m, 1H), 5.18 (1H, s), 5.59 (1H, d, J = 7 Hz), 7.18 (5H, m), 7.49 (2H, t, J = 7 Hz), 7.60 (1H, t, J = 7 Hz), 8.15 (2H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.7, 6.5, 7.4, 7.4, 10.5, 15.1, 20.0, 23.6, 27.2, 38.4, 39.1, 43.1, 48.1, 59.4, 62.3, 63.0, 68.5, 68.8, 74.3, 75.8, 76.3, 79.5, 79.8, 127.5, 128.6, 128.9, 129.2, 130.5, 130.6, 133.7, 137.1, 138.0, 138.3, 167.8, 171.2, 206.9; IR ($CHCl_3$) 1718 cm^{-1}; MS (LSIMS$^+$) *m/z* 862 (MH^+).

Preparation of Compound 21. To a toluene solution (4 mL) of **19** (30 mg, 35 μmol) were added 4-DMAP (6.5 mg, 53 μmol, 1.5 equiv), DCC (21.3 mg, 103 μmol, 3 equiv), and **20** (45 mg, 113 μmol, 3.2 equiv). The solution was stirred for 40 min at room temperature. After standard workup the residue was purified on preparative TLC (heptane/AcOEt: 70/30) to yield **21** (43 mg, 99%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.42 (6H, q, J = 7 Hz), 0.60 (6H, m), 0.87 (9H, t, J = 7 Hz), 0.98 (9H, m), 1.06 (9H, s), 1.16 (3H, s), 1.18 (3H, s), 1.46 (4H, m), 1.61 (3H, s), 1.73 (3H, s), 2.09 (3H, m), 2.81 (1H, d, J = 11 Hz), 3.29 (1H, bd, J = 9 Hz), 3.35 (1H, d, J = 11 Hz), 3.36 (1H, d, J = 13 Hz), 3.57 (1H, d, J = 7 Hz), 3.60 (1H, d, J = 13 Hz), 3.81 (3H, s), 4.23 (1H, dd, J = 7, 10 Hz), 4.60 (1H, d, J = 5 Hz), 5.04 (1H, s), 5.40 (1H, bd, J = 5 Hz), 5.58 (1H, d, J = 7 Hz), 6.09 (1H, m), 6.42 (1H, m), 6.92 (2H, d, J = 9 Hz), 7.14 (2H, m), 7.42 (10H, m), 7.50 (2H, t, J = 7 Hz), 7.62 (1H, t, J = 7 Hz), 8.05 (2H, d, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.3, 6.2, 7.0, 7.2, 10.2, 13.4, 20.5, 22.1, 26.5, 27.9, 35.5, 37.9, 43.1, 47.4, 55.3, 58.7, 61.8, 62.6, 63.9, 68.4, 71.9, 73.6, 75.2, 75.6, 79.1, 79.5, 80.9, 83.6, 92.7, 113.9, 126.6, 127.1, 128.0, 128.2, 128.3, 128.5, 128.8, 129.0, 130.0, 130.2, 133.4, 134.1, 137.4, 137.8, 137.39, 137.8, 160.5, 167.2, 169.6, 169.7, 205.9; IR ($CHCl_3$) 1717, 1707 cm^{-1}; MS (LSIMS$^+$) *m/z* 1243 (MH^+).

Preparation of Compound 5. To a MeOH solution (3 mL) of **21** (43 mg, 35 μmol) was added APTS (20 mg, 0.1 mmol, 3 equiv). The solution was stirred at room temperature for 5 h and then diluted with an excess of ethyl acetate. After standard workup, the residue was purified on preparative TLC (CH_2Cl_2/MeOH: 95/5) to yield **5** (22 mg, 72%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (3H, s), 1.22 (3H, s), 1.34 (9H, s), 1.47 (1H, m), 1.82 (3H, s), 1.90 (3H, s), 2.24 (2H, m), 2.29 (3H, s), 2.33 (1H, m), 2.91 (1H, d, J = 11 Hz), 3.43 (1H, bd, J = 9 Hz), 3.47 (1H, d, J = 11 Hz), 3.56 (2H, qAB, J = 12 Hz), 3.79 (1H, d, J = 7 Hz), 4.15 (1H, dd, J = 7 Hz, J' = 10 Hz), 4.62 (1H, bs), 5.19 (1H, s), 5.28 (1H, bd, J = 9 Hz), 5.50 (1H, d, J = 9 Hz), 5.65 (1H, d, J = 7 Hz), 6.19 (1H, bt, J = 8 Hz), 7.09, 7.21, 7.32 (5H, m), 7.39 (5H, m), 7.50 (2H, t, J = 7 Hz), 7.62 (1H, t, J = 7 Hz), 8.11 (2H, d, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 14.5, 20.6, 23.0, 27.6, 28.3, 35.9, 37.6, 43.1, 46.9, 58.1, 58.5, 61.8, 62.2, 68.4, 72.5, 73.0, 74.0, 74.6, 75.4, 79.2, 79.3, 80.2, 126.9, 127.3, 128.0, 128.4, 128.7, 128.7, 128.8, 129.7, 130.3, 133.5, 137.5, 135.9, 137.2, 155.4, 167.3, 170.9, 176.7, 212.0; IR ($CHCl_3$) 1718 cm^{-1}; MS (LSIMS$^+$) *m/z* 897 (MH^+), 919 (MNa^+); HRMS calcd for $C_{50}H_{61}N_2O_{13}$ (MH^+) 897.4174, found 897.4182.

Preparation of Compound 6. A MeOH solution (3 mL) of **5** (22 mg, 24 μmol) with traces of acetic acid was stirred over Pd on 10% charcoal (12 mg) under hydrogen for 5 h. The solution was filtered on Celite, and the Celite was washed several times with MeOH and CH_2Cl_2. After concentration the residue was purified on preparative TLC (CH_2Cl_2/MeOH: 90/10) to yield **6** (12 mg, 61%): ^{1}H NMR (250 MHz, $CDCl_3$ + CD_3OD) δ 1.10 (3H, s), 1.21 (3H, s), 1.32 (9H, s), 1.68 (3H, s), 1.71 (1H, m), 1.75 (3H, s), 2.21 (2H, m), 2.32 (3H, s), 2.42 (1H, m), 3.48 (2H, qAB, J = 12 Hz), 3.82 (1H, d, J = 7 Hz), 4.09 (1H, dd, J = 6 Hz, J' = 11 Hz), 3.43 (1H, dd, J = 4 Hz, J' =10 Hz), 4.57 (1H, bs, 1H), 5.16 (2H, m), 5.61 (1H, d, J = 7 Hz), 5.89 (1H, d, J = 9 Hz), 6.15 (1H, bt, J = 8 Hz), 7.35 (5H, m), 7.47 (2H, t, J = 7 Hz), 7.59 (1H, t, J = 7 Hz), 8.07 (2H, d, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 10.7, 14.6, 20.7, 23.1, 26.5, 28.3, 36.0, 38.6, 43.1, 46.7, 55.1, 56.2, 57.9, 61.3,

72.5, 73.9, 74.7, 75.2, 79.0, 80.0, 83.2, 126.9, 128.1, 128.8, 128.9, 129.6, 130.3, 135.9, 133.7, 138.5, 155.4, 167.2, 170.5, 172.0, 212.0; IR ($CHCl_3$) 1719 cm^{-1}; MS (LSIMS$^+$) *m*/*z* 829 (MNa^+), 807 (MH^+), 548 (MNa^+ − side chain); HRMS calcd for $C_{43}H_{55}N_2O_{13}$ (MH^+) 807.3704, found 807.3724.

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Supporting Information Available: ^1H NMR (300 or 250 MHz) spectra for compounds **5**−**13**, **16**−**19**, and **21** and full lisiting of NMR data, accompanied by subjective peak assignments, for compounds **5**−**19** and **21** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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