Semisynthesis of 7-Deoxypaclitaxel Derivatives Devoid of an Oxetane D-Ring, Starting from Taxine B

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Keywords: Antitumor agents / Natural products / Paclitaxel / Structure-activity relationships / Taxine B

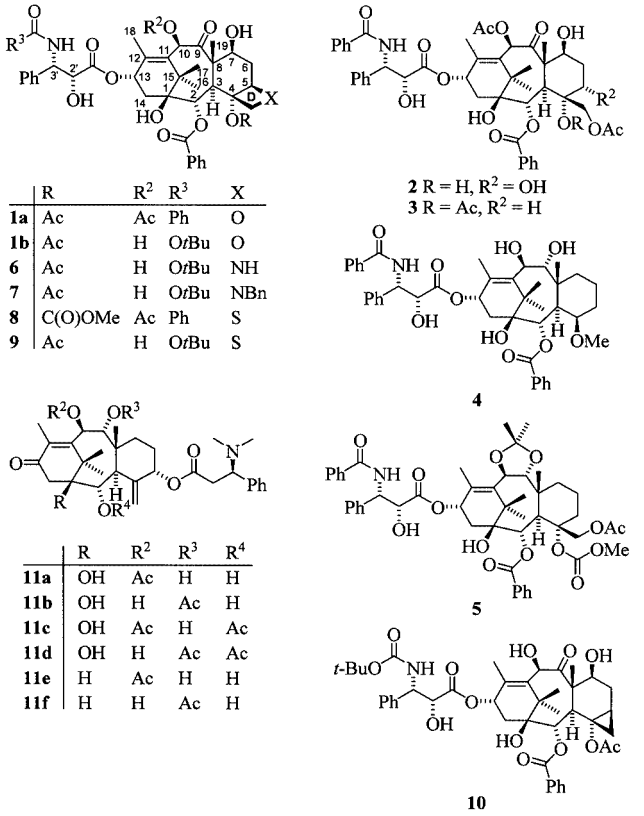
Six 7-deoxypaclitaxel derivatives have been prepared from taxine B; they contribute to understanding of the effect of the oxetane D-ring in paclitaxel on the cytotoxic activity of paclitaxel. Three of these analogues each contain a double bond instead of a D-ring at the C-4 position, while two others each contain a three-membered ring in place of the oxetane ring. Both the C-4 double bond and the small D-ring in these paclitaxel derivatives were intended to act as substitutes for the paclitaxel oxetane D-ring and were expected to impose on the taxane skeleton and the pendant groups a kind of rigidity and conformation similar to that produced by the oxetane ring in paclitaxel. All the derivatives demonstrated considerably reduced in vitro cytotoxic activity – relative to paclitaxel – against a panel of seven well-characterized human tumor cell lines. The general picture coming out of the structure-activity relationships of the paclitaxel derivatives reported here is that the presence of an oxygen atom at a spatial position resembling that of the oxygen atom in the oxetane ring of paclitaxel is important if a paclitaxel derivative is to retain considerable cytotoxic activity.

Introduction

Paclitaxel (**1a**, see Figure 1) is a natural diterpene first reported by Wani and co-workers[1] in 1971 following its isolation in the 1960s from an extract of the bark of the Pacific yew *Taxus brevifolia*, and is considered to be one of the most effective anticancer agents known to date. Paclitaxel has been approved by the United States Food and Drug Administration (FDA) for the treatment of patients suffering from breast cancer, ovarian cancer, non-small cell lung cancer, and AIDS-related Kaposi's sarcoma.[2]

Thanks to its high cytotoxic activity and unique mechanism of action, based on stabilization of microtubules and suppression of microtubule dynamics with consequent induction of apoptosis, but also because of its poor water solubility and induction of multidrug resistance, paclitaxel has become the subject of extensive structure-activity relationship (SAR) studies. These should eventually result in the development of new paclitaxel derivatives with improved pharmacological properties, ideally retaining strong cytotoxic activity against multidrug-resistant tumors.

The contribution of the oxetane D-ring to the biological activity of paclitaxel is not yet fully understood. With respect to microtubule binding, the oxetane D-ring in paclitaxel is believed to serve two functions.[3,4] The oxetane ring oxygen atom may have a stabilizing dipolar or hydrogen-bonding interaction with an amino acid residue facing the paclitaxel binding pocket on β-tubulin,[5] one of the building blocks of a microtubule. Alternatively, the rigid oxetane ring may force the molecule to adopt the biologically active



	R	R^2	R^3	X
1a	Ac	Ac	Ph	O
1b	Ac	H	O*t*Bu	O
6	Ac	H	O*t*Bu	NH
7	Ac	H	O*t*Bu	NBn
8	C(O)OMe	Ac	Ph	S
9	Ac	H	O*t*Bu	S

	R	R^2	R^3	R^4
11a	OH	Ac	H	H
11b	OH	H	Ac	H
11c	OH	Ac	H	Ac
11d	OH	H	Ac	Ac
11e	H	Ac	H	H
11f	H	H	Ac	H

Figure 1. Structures of paclitaxel (**1a**), docetaxel (**1b**), paclitaxel analogues **2**–**10**, and taxines **11a**–**11f**

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conformation and thus position the essential groups in the desired spatial orientation through its rigidifying effect on the whole taxane skeleton.

Previously prepared flexible paclitaxel derivatives with at least one oxygen atom at about the same spatial position as the oxetane ring oxygen atom in paclitaxel, which include taxanes **2**,[6,7] **3**,[8] **4**,[9] and **5**,[9] all exhibited strongly reduced in vitro cytotoxic activities. This may be due to the absence of an apolar 4α-substituent able to mimic the essential 4α-acetoxy group in paclitaxel and/or because of unfavorable steric interactions between the 4β-acetoxymethyl or 4β-methoxy group and the receptor on β-tubulin.[8] The increased flexibility of these taxanes, as well as the slightly different spatial position of the oxygen atom(s) of the 4β-substituent with respect to that of the oxetane ring oxygen atom in paclitaxel, may also contribute to the observed reduced cytotoxicities.

Rigid D-ring-modified paclitaxel derivatives **6** and **7**, each containing an azetidine D-ring, proved inactive in an in vitro cytotoxicity assay.[10] The strongly reduced cytotoxicity of **7** was explained in terms of unfavorable steric interactions between the *N*-benzyl group and the receptor on β-tubulin, while the low cytotoxic activity of **6** was attributed to protonation of the basic nitrogen under physiological conditions.[10]

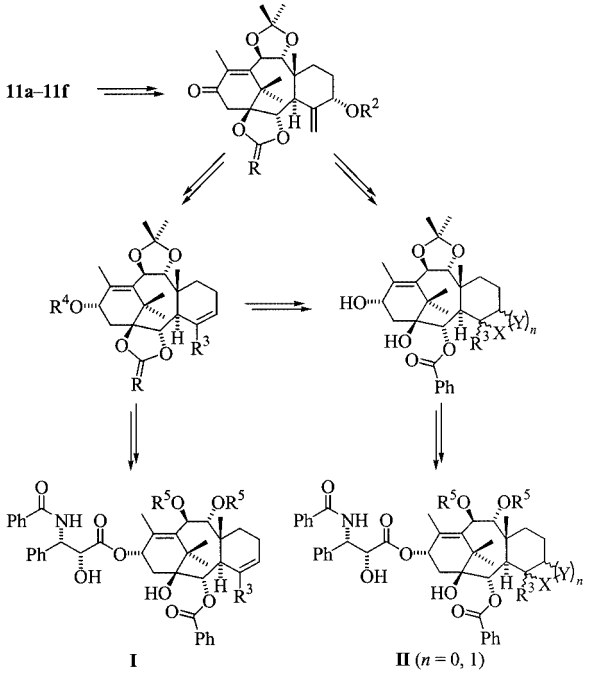
Rigid D-ring-modified derivatives **8**[11] and **9**,[12] each containing a thietane D-ring, also demonstrated strongly reduced in vitro cytotoxicities, attributed to unfavorable steric interactions between the receptor and the thietane ring, which is bulkier than the oxetane ring due to the elongated C−S bond and the relatively large sulfur atom. This may also further weaken hydrogen bonding between the sulfur atom and an amino acid residue, perhaps a threonine residue,[3] in β-tubulin.[12]

5(20)-Deoxydocetaxel[13] (**10**) displayed only twofold reduced tubulin disassembly activity relative to docetaxel, but was nevertheless shown to exhibit strongly reduced cytotoxic activity.[14] This seems to indicate that the presence of a suitably positioned oxygen atom is of considerable importance.

It follows from the above that it is not possible to use these previously prepared, oxetane ring-free paclitaxel derivatives to discriminate completely between the proposed rigidifying function and the hydrogen bond acceptor function of the oxetane ring as the decisive contributor to the cytotoxicity of paclitaxel. More SAR data are therefore needed in order to identify the structural moiety at C-4/C-5 required for cytotoxic activity to be retained.

Here we wish to report the semisynthesis of some 7-deoxypaclitaxel analogues that do not contain an oxetane D-ring. This semisynthesis starts from taxine, an alkaloid mixture obtained in 0.5−1% yield by acid extraction of dried leaves of the European yew *Taxus baccata*. Taxine B (**11a**) and the related taxines **11b**−**11f** constitute the major proportion (ca. 40%) of this alkaloid mixture.[15] Although the structures of taxines **11a**−**11f** are quite distinct from that of paclitaxel, several groups have used them to prepare 7-deoxypaclitaxel and derivatives.[9,16−21] These derivatives all lack a hydroxy group at C-7 and sometimes have a substitution pattern at C-9 and C-10 that differs from that of paclitaxel. SAR studies have shown, however, that variations at these positions usually affect cytotoxic activity only marginally.[22]

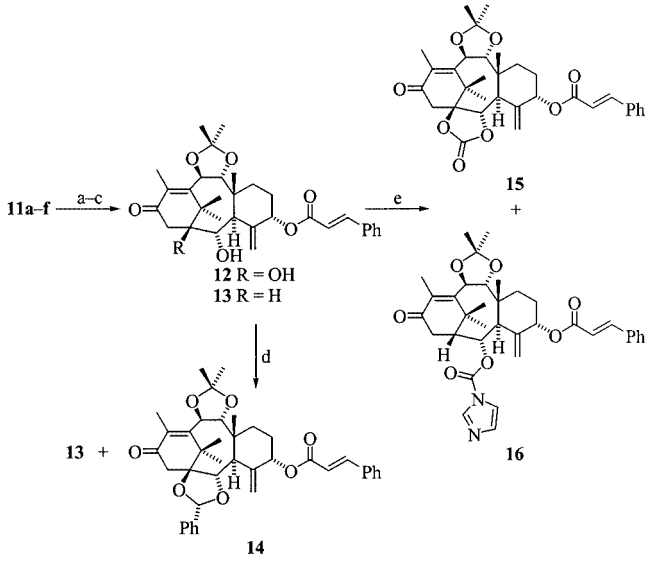
We believed that taxine should be a convenient starting material with which to prepare 7-deoxypaclitaxel derivatives of general structures **I** and **II** by the general route depicted in Scheme 1. The route towards paclitaxel derivatives **I** involves a net migration of the exocyclic double bond attached to the C-ring to an endocyclic position with the concomitant introduction of a suitable C-4 substituent, while the small D-ring in paclitaxel derivatives **II** could be introduced either by a cycloaddition approach involving a suitable intermediate taxane with an endocyclic C-4 double bond or by an intramolecular substitution process.



Scheme 1. General scheme for the preparation of paclitaxel derivatives **I** and **II**

Results and Discussion

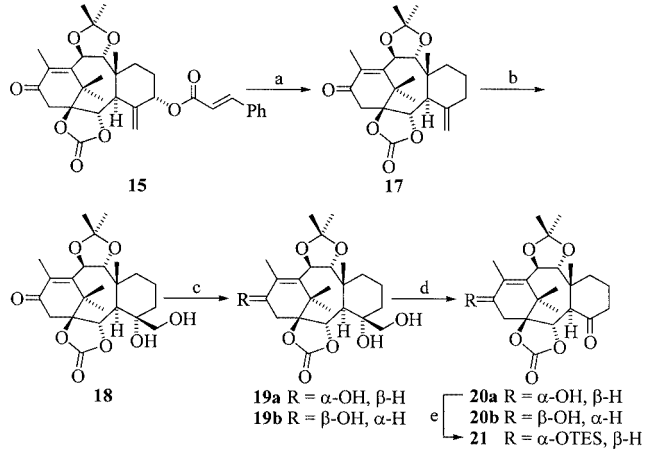
The crude alkaloid mixture from *T. baccata*, containing taxines **11a**−**11f**, was converted into a mixture of taxanes **12** and **13** in three steps (Scheme 2) as described previously.[9] Depending on the reaction conditions required in the remaining steps to the desired 7-deoxypaclitaxel derivatives, the two vicinal hydroxy groups at C-1 and C-2 in **12** were protected either as a benzaldehyde-derived acetal or as a carbonate, giving taxanes **14** and **15**, respectively. On treatment of the mixture of **12** and **13** with carbonyldiimidazole, **13** was converted into **16**. On treatment with benzaldehyde dimethyl acetal, though, **13** remained unchanged.



Scheme 2. Conversion of taxines **11** into **13** and **14**, and into **15** and **16**; reagents and conditions: (a)−(d) ref.[9]; (e) CDI, butanone, reflux, 3 h, **15**: 86%, **16**: 9%

Attempts to prepare paclitaxel derivatives **I** from **14** and **15** by a single-step isomerization of the exocyclic double bond in **14**, **15**, and their analogues (e.g., by a base-catalyzed or palladium-catalyzed isomerization process) proved unsuccessful.[23] A route towards paclitaxel derivatives **I** involving an intermediate taxane with a C-4 oxo group was therefore developed. Conversion of this oxo group into an enol acetate moiety would provide a suitable intermediate that could be converted into taxanes **I**.

Starting from **15**, we prepared intermediate **21**, containing a C-4 oxo group, by the route depicted in Scheme 3. The C-5 cinnamate side chain in **15** was removed by palladium-catalyzed hydrogenolysis with formate as the hydride donor, as described previously for **14**.[9] The reaction proceeded at virtually the same rate as the reaction with **14**, demonstrating the independence of the reaction rate of the size of the C-2 substituent.



Scheme 3. Preparation of key intermediate **21** from **15**; reagents and conditions: (a) HCOOH, NEt_3, $Pd(dba)_2$, PPh_3, THF, reflux, 2 d, 97%; (b) OsO_4, NMO, THF/H_2O, 5 d, 91%; (c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 30 min; (d) $NaIO_4$, THF/H_2O, 3 h, **20a**: 49% (2 steps), **20b**: 12% (2 steps); (e) TESCl, imidazole, DMF, 4 h, 86%

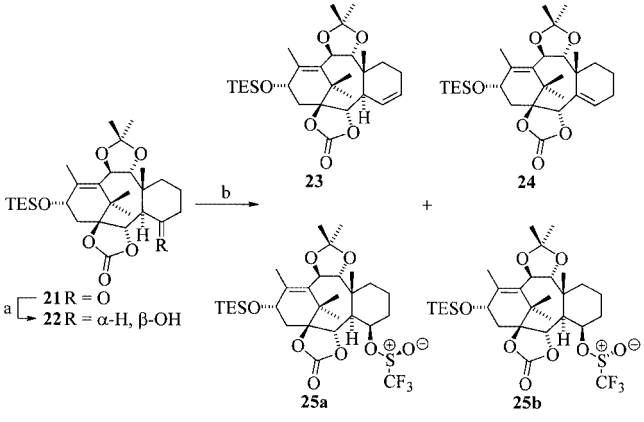
Diastereoselective dihydroxylation of **17** with osmium tetroxide afforded **18** in high yield. The configuration at C-4 in **18** was established from NOE data. Reduction of the C-13 carbonyl group was carried out with sodium borohydride in the presence of cerium(III) chloride, which afforded a 4:1 mixture of epimers **19a** and **19b**. When the reaction was carried out without cerium(III) chloride, the **19a/19b** ratio changed to 1:10. Coordination of the transition metal complex to the 4α-hydroxy group is believed to block the approach of sodium borohydride towards the 13-carbonyl group from the concave face of the molecule and thus favor the formation of **19a**.

The crude mixture of **19a** and **19b** was oxidized with sodium periodate to afford **20a** and **20b**, which were easily separable by column chromatography. The C-13 hydroxy group in **20a** was protected with a triethylsilyl group, which gave **21**.

Attempts to enolize the C-4 carbonyl moiety and to trap the enolate with an acetyl group all failed to give the desired enol acetate. The only products isolated when a strong base was used were products resulting from *C*-acetylation. Attempts to create a methyl enol ether moiety at C-4 were also unsuccessful.

We therefore settled for the preparation of paclitaxel derivatives with a cyclohexene C-ring containing a C-4 alkyl substituent. These were to be accessible from **21** by treatment of **21** with an alkyllithium reagent and subsequent dehydration. As 4-deacetoxypaclitaxel has been shown to exhibit considerable cytotoxicity,[24] albeit significantly less than paclitaxel, the preparation of a rigid paclitaxel derivative with a cyclohexene C-ring and no C-4 substituent was also considered useful.

Reduction of the C-4 carbonyl group in **21** with sodium borohydride proceeded with complete facial selectivity and provided **22** in quantitative yield (Scheme 4). The complete facial selectivity most probably results from the upward orientation of the carbonyl oxygen atom with respect to the mean plane of the C-ring, causing shielding of the β-face of the double bond by the C-8 methyl group.



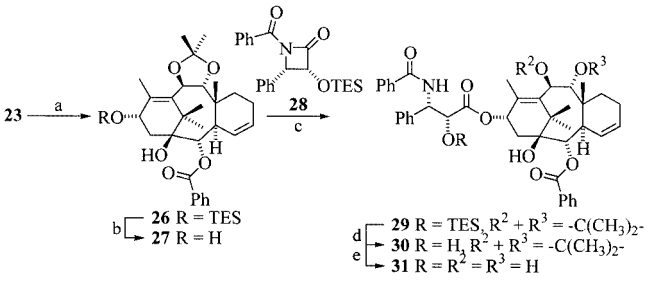
Scheme 4. Preparation of compounds **23**, **24**, **25a**, and **25b** from **21**; reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 30 min; (b) (I) $(CF_3SO_2)O$, pyridine, CH_2Cl_2, 2 d, **23/24** (1:10 mixture): 34%, **25a/25b**: 16% and 4%, or (II) CF_3SO_2Cl, DMAP, CH_2Cl_2, 2 d, **23/24** (9:1 mixture): 31%, **25a/25b**: 17% and 4%

As dehydration of **22** under acidic conditions might be accompanied by deprotection of some hydroxy groups and/or rearrangements, conversion of the secondary C-4 hydroxy group into a suitable leaving group was undertaken so that elimination could be achieved under mildly basic conditions.

Conversion of the C-4 hydroxy group in **22** into a methylsulfonyloxy group proved unsuccessful under common conditions. In contrast, treatment of **22** with trifluoromethanesulfonic anhydride and pyridine in dichloromethane afforded four products. Two of these, compounds **23** and **24**, were obtained as a 1:10 mixture in 34% overall yield. The other two products turned out to be the stereoisomeric trifluoromethanesulfinates **25a** and **25b**. The less polar of the two epimers was isolated in 16% yield, while the other was isolated in only 4% yield. The formation of **25a** and **25b** from **22** must be a consequence of partial reduction of trifluoromethanesulfonic anhydride by pyridine,[25,26] although no evidence was obtained for this.

The same products were obtained when **22** was treated with trifluoromethanesulfonyl chloride and 4-(dimethylamino)pyridine (DMAP) in dichloromethane. Compounds **23** and **24**, however, were now obtained in a 9:1 ratio in 31% overall yield, while **25a** and **25b** were obtained in about the same yields as in the reaction with trifluoromethanesulfonic anhydride. An increase in the reaction temperature from room temperature to 40 °C increased the relative amounts of **25a** and **25b** with respect to the amount of the mixture of **23** and **24**. A decrease in the reaction temperature to 4 °C suppressed the formation of **25a** and **25b**, but did not increase the yield of the mixture of **23** and **24**, nor did it alter the ratio between **23** and **24**. Furthermore, the reaction proceeded extremely slowly at this temperature.

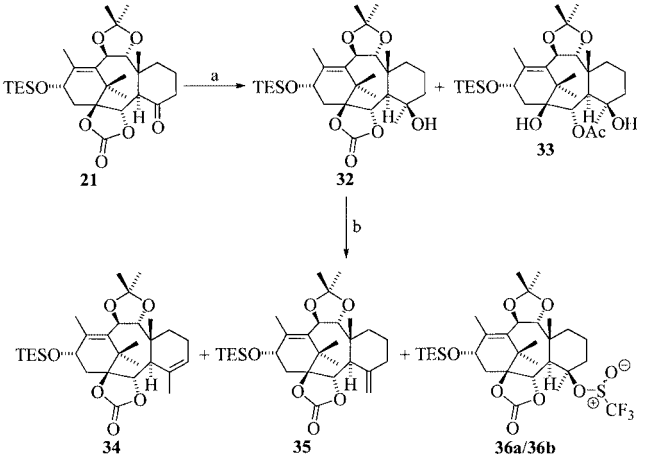
As **23** proved to be inseparable from **24** by chromatographic means, the 9:1 mixture of **23** and **24** obtained from treatment of **22** with trifluoromethanesulfonyl chloride and DMAP was used in the next step towards the paclitaxel derivatives **30** and **31** (Scheme 5). As separation of the corresponding isomers also proved impossible after this step, and after all following steps as well, compounds **26**−**27** and **29**−**31** were obtained contaminated with their respective isomers.



Scheme 5. Preparation of paclitaxel derivatives **30** and **31** from **23**; reagents and conditions: (a) PhLi, THF, −78 °C, 30 min, 100%; (b) TBAF, THF, 5 min, 95%; (c) **28**, NaHMDS, THF, −78 °C, 20 min, 84%; (d) TBAF, THF, 5 min, 92%; (e) PTSA, MeOH, 3 h, 80%

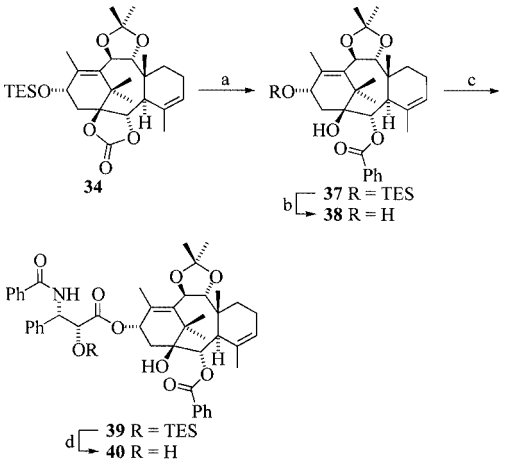
Regioselective opening of the carbonate moiety in **23** with phenyllithium gave **26**. Desilylation of the C-13 hydroxy group was followed by attachment of the paclitaxel side chain to the C-13 hydroxy group in **27** through coupling with β-lactam **28** under strongly basic conditions. Desilylation of the C-2′ hydroxy group in **29** gave **30**. Deprotection of the hydroxy groups at C-9 and C-10 under acidic conditions afforded paclitaxel derivative **31**.

A paclitaxel derivative analogous to **30** but with a C-4 methyl group was prepared from **21** by a route similar to that used to prepare **30**, except that **21** was treated in the first step with methyllithium rather than sodium borohydride. This gave the desired **32**, along with some **33** (Scheme 6). The configuration at C-4 in **32**, and thus in **33**, was established from NOE data. Treatment of **32** with trifluoromethanesulfonyl chloride and DMAP in dichloromethane afforded a 10:1 mixture of **34/35** in 19% overall yield, together with compounds **36a** and **36b**, each in approximately 30% yield. The reaction proceeded only at the same rate as the corresponding reaction of **22** when the amount of trifluoromethanesulfonyl chloride was increased tenfold, indicative of increased steric hindrance at the site of reaction. This may also explain the lower yields of **34** and **35** and the relatively high yields of side products **36a** and **36b**. Most noticeably, elimination to give a C-3 double bond, which would result in the formation of a taxane analogous to **24**, did not occur in this case. AM1 gas-phase calculations indicate the taxane analogous to **24** to be considerably more stable than **34** and **35**, and so it is conceivable that the C-3 proton cannot be abstracted, resulting in the exclusive formation of **34** and **35**.

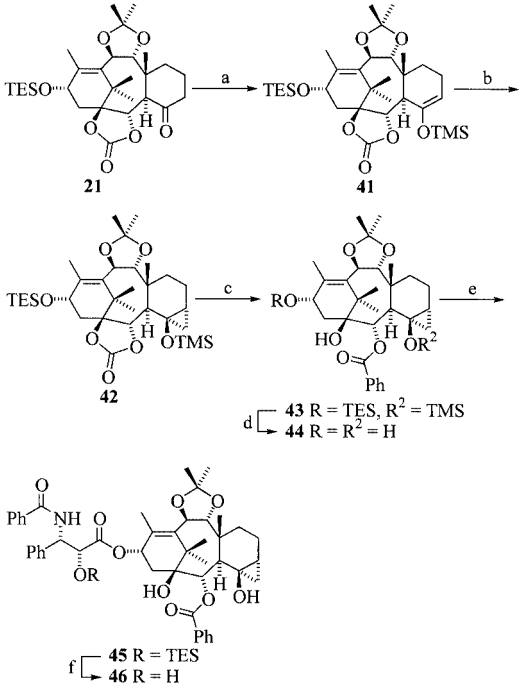


Scheme 6. Conversion of **21** into a mixture of **34** and **35**, **36a**, and **36b**; reagents and conditions: (a) MeLi, THF, −78 °C, 15 min, **32**: 82%, **33**: 4%; (b) CF_3SO_2Cl, DMAP, CH_2Cl_2, 2 d, **34/35** (10:1 mixture): 19%, **36a/36b**: 32% and 29%

As **34** proved to be inseparable from **35** by column chromatography, the 10:1 mixture of **34** and **35** was used to prepare paclitaxel derivative **40** by the reaction sequence depicted in Scheme 7, meaning that compounds **37**−**40** were obtained slightly contaminated with their respective isomers. Opening of the carbonate moiety in **34** gave **37**, which



Scheme 7. Preparation of paclitaxel analogue **40** from **34**; reagents and conditions: (a) PhLi, THF, −78 °C, 30 min, 80%; (b) TBAF, THF, 5 min, 84%; (c) **28**, NaHMDS, THF, −78 °C, 20 min, 66%; (d) TBAF, THF, 5 min, 79%



Scheme 8. Preparation of paclitaxel analogue **46** from **21**; reagents and conditions: (a) LDA, TMSCl, THF, −78 °C → −20 °C, 1 h, 92%; (b) CH_2I_2, Zn/Cu, Et_2O/DME, 50 °C, 60 h, 58%; (c) PhLi, THF, −78 °C, 2.5 h, 86%; (d) TBAF, THF, 30 min, 58%; (e) **28**, NaHMDS, THF, −78 °C, 45 min, 45%; (f) TBAF, THF, 5 min, 76%

was deprotected with tetrabutylammonium fluoride (TBAF). Coupling of **28** to the C-13 hydroxy group in **38** gave **39**, which was converted into **40** by fluoride-mediated deprotection.

The preparation of paclitaxel analogues **II**, each containing a small, non-oxetane D-ring, seemed achievable through an intermediate taxane with an endocyclic C-4 double bond, as pointed out in Scheme 1. D-rings could then be introduced by means of [2 + 2] or [2 + 1] cycloadditions to this double bond. Since enol ether double bonds are generally more reactive than alkyl-substituted double bonds towards cycloaddition reactions with electron-deficient cycloaddition partners, we set out to prepare a taxane with an enol ether moiety at C-4.

Although the introduction of an enol acetate or methyl enol ether moiety at C-4 had proven unsuccessful when starting from **21** (vide supra), an attempt was made to trap the enolate of **21** with trimethylsilyl chloride, trapping of the enolate of a similar taxane by trimethylsilyl chloride having been reported before.[27−29] Silyl enol ether formation was indeed achieved by treatment of **21** with lithium diisopropylamide and trimethylsilyl chloride in THF at −78 °C. Taxane **41** was obtained in high yield (Scheme 8).

[2 + 2] Cycloadditions at atmospheric pressure between **41** and dichloroketene, prepared in situ from dichloroacetyl chloride and triethylamine, and also between **41** and ketene, did not yield any cycloadduct. Similarly, cycloadditions between **41** and tetracyanoethylene at pressures of up to 3 kbar in different solvents all failed to give the desired cycloadduct. At pressures above 3 kbar the starting material slowly decomposed.

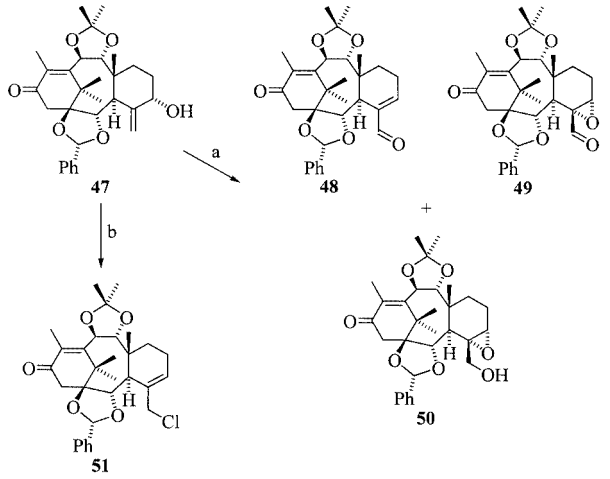
The reaction between **41** and Simmons−Smith carbene proceeded slowly in refluxing ether and afforded one main product, identified as **42**. The configuration at C-4 was established from NOE correlations observed for **43**, obtained from **42** on treatment with phenyllithium in THF at −78 °C. NOE correlations of the proton on C-20 and *cis* to 5-H both with 5-H and with the methyl protons of the trimethylsilyloxy group and correlations of the proton on C-20 and *trans* to 5-H both with 3-H and with 14α-H clearly indicated an (*R*) configuration at C-4. Although the cyclopropane ring protrudes from the α face of the C-ring whereas the oxetane D-ring in paclitaxel protrudes from the β face, cytotoxicity data from paclitaxel derivatives derived from **43** could still afford valuable SAR data as they could provide insight into the effect on cytotoxicity of a different kind of rigidity exerted by the presence of a small D-ring, especially since the hydrogen bond acceptor properties of the oxetane ring might be taken over by the 4β-hydroxy group.

Conversion of **43** into the paclitaxel derivative **46** was accomplished in three steps. Desilylation of the C-4 and C-13 hydroxy groups in **43** was accomplished with TBAF and afforded **44** in 58% yield. Coupling of β-lactam **28** to the C-13 hydroxy group in **44** afforded **45** in only 45% yield. The low yields of these steps are due to partial decomposition, possibly as a consequence of base-promoted rearrangement of the cyclopropanol moiety. Deprotection of **45** with TBAF smoothly afforded paclitaxel derivative **46**.

A route to a paclitaxel derivative similar to **46**, but with an epoxide D-ring rather than a cyclopropane D-ring, was unexpectedly found when **47** was oxidized with pyridinium chlorochromate (PCC) with the intent to create an *outer,outer* heterodiene moiety incorporating C-4 and C-5. Such a moiety should enable the construction of rigid five- and six-membered D-rings through a cycloaddition approach. A related taxane bearing such a heterodiene moiety

was reported to dimerize by [4 + 2] cycloaddition, which indicates that such a heterodiene moiety should be reactive towards alkenes.[30]

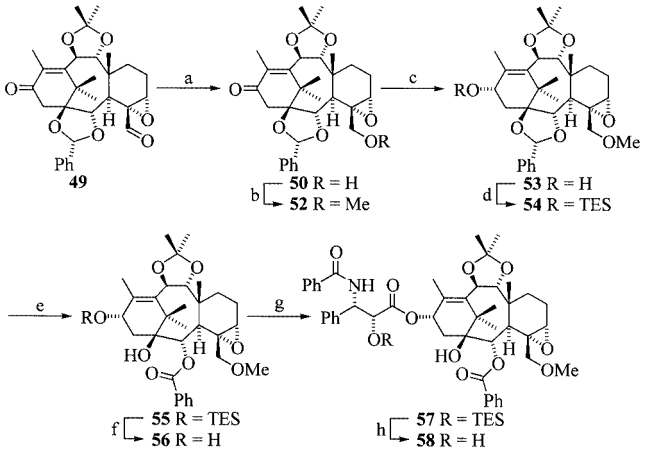
PCC oxidation of **47**, prepared from **14** by hydrolysis,[9,21] did not afford the desired product resulting from straightforward oxidation, but instead gave taxanes **48**, **49**, and **50** (Scheme 9). Taxane **50** was completely converted into **49** when the reaction time exceeded 3 h and excess PCC was used. The formation of these products must be a result of complexation of chromium(VI) to the allylic C-5 hydroxy group, followed by a sigmatropic rearrangement. Oxidation then affords **48**, while epoxidation, which most probably occurs through intramolecular oxygen transfer from the chromium atom to the double bond, followed by hydrolysis and/or oxidation affords **49** and **50**.[31] The configuration at C-4 in **49** and **50** was established from the NOE data of the methyl ether of **50**.



Scheme 9. Conversion of **47** into **48**−**50** and **51** by PCC oxidation and Swern oxidation, respectively; reagents and conditions: (a) PCC, CH_2Cl_2, 3.5 h, **48**: 5%, **49**: 43%, **50**: 2%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −50 °C, 10 min, then **47**, −10 °C, 20 min, then Et_3N, −10 °C → room temp., 40 min, 21%

While oxidation with Collin's reagent gave similar results, no reaction took place with activated manganese oxide or tetrapropylammonium perruthenate. Swern oxidation gave **51** as the main product, albeit in low yield. Compound **51** is probably formed by an S_N2'-type substitution of the activated C-5 hydroxide group by chloride.

The aldehyde group in **49** was reduced with sodium borohydride, which gave **50** (Scheme 10). Conversion of the primary hydroxy group in **50** into a methoxy group was carried out with excess methyl iodide and sodium hydride. Stereoselective reduction of the C-13 carbonyl group in **52** with sodium borohydride in the presence of cerium(III) chloride gave **53** in good yield. After protection of the C-13 hydroxy group with a triethylsilyl group, giving **54**, the acetal moiety was oxidatively opened by means of a palladium(II)-mediated reaction with *tert*-butyl hydroperoxide. Fluoride-assisted desilylation of **55** gave **56**, which was then coupled to β-lactam **28**. Finally, the C-2′ hydroxy group in **57** was deprotected with TBAF, which afforded **58** in good yield.



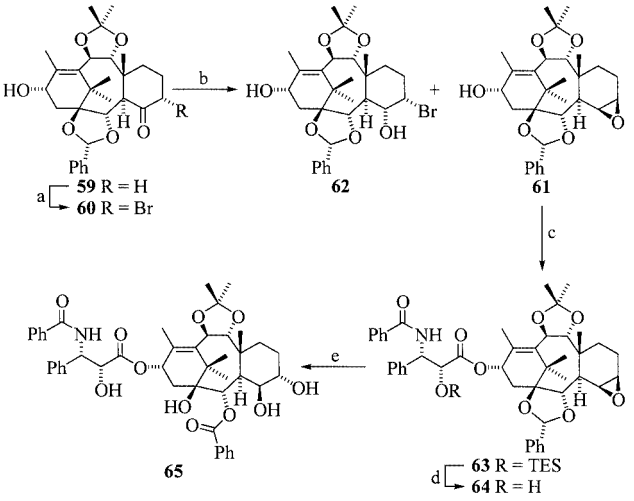
Scheme 10. Conversion of **49** into paclitaxel derivative **58**; reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 1 h, 77%; (b) NaH, MeI, THF, 3 h, 69%; (c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 30 min, 73%; (d) TESCl, imidazole, DMF, 2 h, 97%; (e) *t*BuOOH, $Pd(OAc)_2$, toluene, 70 °C, 20 h, 35%; (f) TBAF, THF, 15 min, 85%; (g) **28**, NaHMDS, THF, −78 °C, 1 h, 49%; (h) TBAF, THF, 5 min, 81%

The preparation of a paclitaxel derivative with an epoxide D-ring protruding from the convex face of the molecule was considered valuable, as comparison of its biological activity with that of **10** could provide information about the importance of the oxetane ring oxygen atom for cytotoxic activity, while comparison of its biological activity with that of **58** could provide information about the effect of a differently exerted rigidity on cytotoxic activity.

It was envisaged that the approach towards such a paclitaxel derivative would involve intermediate **59**, which was prepared from **14** by a reaction sequence similar to that depicted in Scheme 3.[9] Construction of a β-oriented epoxide ring would be feasible through the introduction of an α-oriented leaving group at C-5, reduction of the C-4 carbonyl group, and subsequent ring-closure by intramolecular substitution.

Conversion of **59** to **60** was accomplished by treatment of a THF solution of **59** with phenyltrimethylammonium tribromide (Scheme 11). Reduction of **60** with sodium borohydride gave compounds **61** and **62** in an approximate 6:5 ratio. Ring-closure on the epimer of **62** occurred under the reaction conditions involved, affording **61**. NOE correlations of 4-H with 5-H, 3-H, and 14α-H clearly denoted a β orientation of the epoxide oxygen atom.

Coupling of the C-13 hydroxy group in **61** to β-lactam **28** afforded **63**. Unfortunately, palladium(II)-catalyzed oxidative opening of the acetal moiety in **63** with *tert*-butyl hydroperoxide failed to give the desired product, and so desilylation was carried out first. Oxidative opening of the acetal moiety in **64** gave several products, from which we were only able to obtain the main product pure. NMR spectroscopy and mass spectrometry showed the compound to be taxane **65**, which contains the desired C-2 benzoyloxy group, but also a vicinal diol moiety at C-4/C-5. Apparently, opening of the epoxide by water occurred under the reaction conditions involved. NOE correlations of 4-H with



Scheme 11. Conversion of **59** into paclitaxel derivative **65**; reagents and conditions: (a) PTAB, THF, −15 °C → 10 °C, 3 h, 77%; (b) $NaBH_4$, THF/MeOH, 0 °C, 2 h, **61**: 36%, **62**: 31%; (c) **28**, NaHMDS, THF, −78 °C, 1 h, 74%; (d) TBAF, THF, 5 min, 96%; (e) *t*BuOOH, $Pd(OAc)_2$, toluene, 70 °C, 40 h, 17%

both 3-H and 14α-H and correlations of 5-H with 6α-H are supportive of nucleophilic attack at C-5.

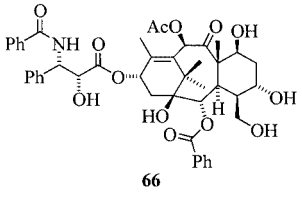
Taxanes **30**, **31**, **40**, **46**, **58**, and **65** were evaluated for their in vitro cytotoxicities against seven well-characterized human tumor cell lines (MCF7, EVSA-T, WIDR, IGROV, M19 MEL, A498, and H226) by a previously reported procedure.[32] The ID_{50} values, which reflect the concentrations at which cell proliferation is inhibited by 50%, are listed in Table 1.

The ID_{50} values listed in Table 1 clearly show that compounds **30**, **31**, **40**, **46**, **58**, and **65** all exhibit strongly reduced cytotoxicities with respect to paclitaxel ($ID_{50}/ID_{50,paclitaxel} > 550$). Comparison of the biological activity of **30** with that of **31** reveals that the presence of the isopropylidene protecting group in **30** hardly affects cytotoxicity. This is in full agreement with previously obtained results that have demonstrated that modifications at C-9 and C-10 generally affect cytotoxicity only marginally.[18,22]

The low biological activities exhibited by **30**, **31**, and **40**, which have AM1 energy-minimized polar conformations similar to the polar conformation of paclitaxel,[33] may be attributable to the absence of a suitable substitute for paclitaxel's 4α-acetoxy group, which has been shown to be an important group for retention of cytotoxic activity.[22,24] Although **40** bears a C-4 methyl group intended as a substitute for the acetoxy group, this group may well be too small to be a good replacement. On the other hand, 4-deacetoxypaclitaxel shows considerably higher cytotoxicity than **30**, **31**, and **40**[24], which may point to an important contribution of the oxetane ring oxygen atom in 4-deacetoxypaclitaxel to its cytotoxicity.

At first glance, the low cytotoxicity exhibited by **46** and **58** may be ascribed to a preferred conformation different from that preferably adopted by paclitaxel. Comparison of the AM1 energy-minimized polar conformations of paclitaxel, **46**, and **58** shows that the C-rings in **46** and **58** preferably adopt boat conformations. A change to a flattened chair conformation, as adopted by the C-ring in paclitaxel, however, is accompanied by only a small increase in energy and should therefore be attainable for **46** and **58**. It is more likely that the cyclopropane methylene group in **46** and the epoxide oxygen atom in **58** are unsuitable replacements for the C-4 acetoxy group in paclitaxel. Furthermore, models show that the 4β-methoxymethyl group in **58** requires more space than the oxetane ring in paclitaxel, which may cause steric congestion upon binding of **58** to the receptor on β-tubulin. Although this cannot be true for **46**, the oxygen atom of the 4β-hydroxy group may be so far displaced from the spatial position occupied by the oxetane ring oxygen in paclitaxel that an energy-lowering interaction with the receptor is no longer achievable.

Comparison of **65** with **66**[24] (Figure 2), which exhibits a cytotoxic activity against human CA46 Burkitt lymphoma ten times lower than that of paclitaxel and is even somewhat more active than 4-deacetoxypaclitaxel, supports the idea that the presence of a hydrogen bond acceptor in the proper position in space significantly contributes to cytotoxic activity.



66

Figure 2. Paclitaxel derivative **66**

In conclusion, paclitaxel analogues **30**, **31**, **40**, **46**, **58**, and **65** were prepared from taxine in 13−16 steps. All paclitaxel derivatives exhibited strongly reduced cytotoxicities against

Table 1. ID_{50} values [μM] of paclitaxel, **30**, **31**, **40**, **46**, **58**, and **65** against 7 human tumor cell lines (MCF7: breast cancer; EVSA-T: breast cancer; WIDR: colon cancer; IGROV: ovarian cancer; M19 MEL: melanoma; A498: renal cancer; H226: non-small cell lung cancer)

Compound	MCF7	EVSA-T	WIDR	IGROV	M19 MEL	A498	H226
Paclitaxel	< 0.0037	< 0.0037	< 0.0037	< 0.0037	< 0.0037	< 0.0037	< 0.0037
30	3.3	2.2	3.6	4.6	4.0	4.5	3.8
31	5.2	5.4	11	12	10	10	10
40	2.3	2.0	3.4	4.6	3.4	4.6	4.5
46	13	14	15	16	15	15	8.9
58	6.0	5.4	12	19	9.1	13	8.2
65	9.1	10	10	18	10	14	14

a range of seven well-defined human tumor cell lines. Although no definite conclusion can be drawn from these biological data with respect to the way in which the oxetane ring contributes to the cytotoxicity of paclitaxel, it seems plausible that at least the interaction of the oxetane ring oxygen atom in paclitaxel with the receptor on β-tubulin significantly contributes to the cytotoxicity profile exhibited by paclitaxel.

Experimental Section

General Remarks: When necessary, solvents were dried and distilled by standard procedures prior to use. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Bruker AC 300 spectrometer in $CDCl_3$ with TMS as the internal standard, unless otherwise stated. 2D NMR experiments (NOESY) were performed in $CDCl_3$ with a Bruker AM 400 spectrometer, unless otherwise stated. Chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). Mass spectra were recorded with a Finnigan MAT900S double-focusing mass spectrometer coupled to an ICIS data system in FAB and EI modes. High-resolution FAB spectra were recorded with a JEOL JMS SX/SX102A four-sector mass spectrometer coupled to an MS-MP 21D/UPD data system. Elemental analyses were carried out with a Carlo Erba Instruments CHNSO EA 1108 element analyzer. Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F-254 plates (thickness: 0.25 mm). All reactions were monitored by TLC. Compounds were viewed by UV or by dipping the TLC plate into a 6.2% aqueous sulfuric acid solution containing ammonium molybdate (42 g/L) and ceric ammonium sulfate (3.6 g/L) followed by charring. Column chromatography was carried out with Baker silica gel (63−200 mesh). Generally, products were freeze-dried after chromatographic purification. Experimental procedures for the isolation of taxine and the preparation of **12**, **13**, **14**, **47**, and **59** are described in refs.[9,21]

Conversion of a Mixture of 12 and 13 into 15 and 16: A solution of a mixture of **12** and **13** (5.05 g, 9.41 mmol) and carbonyldiimidazole (6.10 g, 37.6 mmol) in butanone (140 mL) was stirred at reflux temperature for 3 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (150 mL), and extracted with water (200 mL). The aqueous fraction was extracted with ethyl acetate (75 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:5) afforded **15** (4.54 g, 8.07 mmol, 86%) as a white solid and **16** (514 mg, 0.836 mmol, 9%) as an off-white solid. **15:** ^{1}H NMR: δ = 1.16 (s, 3 H, 19-H), 1.43 (s, 3 H, 17-H), 1.45 (s, 3 H, acetonide), 1.50 (s, 3 H, acetonide), 1.68 (s, 3 H, 16-H), 2.17 (s, 3 H, 18-H), 2.96 (s, 2 H, 2 × 14-H), 3.22 (d, J_{3-2} = 5.7 Hz, 1 H, 3-H), 4.13 (d, 1 H, J_{9-10} = 9.1 Hz, 9-H), 4.88 (d, J_{10-9} = 9.1 Hz, 1 H, 10-H), 4.93 (d, J_{2-3} = 5.7 Hz, 1 H, 2-H), 5.35 (br. s, 1 H, 5-H), 5.37 (br. s, 1 H, 20-H), 5.52 (br. s, 1 H, 20-H), 6.27 [d, *J* = 15.9 Hz, 1 H, C(O)C*H*CHPh], 7.44 (m, 3 H, Ph), 7.64 [d, *J* = 15.9 Hz, 1 H, C(O)CHC*H*Ph], 7.71 (m, 2 H, Ph) ppm. FAB-MS: *m*/*z* = 563 [M + H]$^+$. $C_{33}H_{38}O_8$·0.5H_2O (571.7): calcd. C 69.33, H 6.88; found C 69.37, H 6.72. **16:** ^{1}H NMR: δ = 1.12 (s, 3 H, 19-H), 1.29 (s, 3 H, 17-H), 1.46 (s, 3 H, acetonide), 1.54 (s, 3 H, acetonide), 1.81 (s, 3 H, 16-H), 2.19 (s, 3 H, 18-H), 2.46 (dd, J_{1-2} = 1.9, J_{1-14} = 7.1 Hz, 1 H, 1-H), 2.46 (d, J_{gem} = 19.9 Hz, 1 H, 14-H), 2.94 (d, J_{gem} = 19.9 Hz, 1 H, J_{14-1} = 7.1 Hz, 14-H), 3.42 (d, J_{3-2} = 6.5 Hz, 1 H, 3-H), 4.31 (d, J_{9-10} = 9.1 Hz, 1 H, 9-H), 4.67 (br. s, 1 H, 20-H), 4.95 (d, J_{10-9} = 9.1 Hz, 1 H, 10-H), 5.36 (br. s, 1 H, 20-H), 5.38 (m, 1 H, 5-H), 5.73 (dd, J_{2-1} = 1.9, J_{2-3} = 6.5 Hz, 1 H, 2-H), 6.44 [d, *J* = 15.9 Hz, 1 H, C(O)C*H*CHPh], 7.08 (m, 1 H, imidazole), 7.37−7.48 (m, 4 H, Ph + imidazole), 7.68 [d, *J* = 15.9 Hz, 1 H, C(O)CHC*H*Ph], 7.77 (m, 2 H, Ph), 8.13 (br. s, 1 H, imidazole) ppm. FAB-MS: *m*/*z* = 615 [M + H]$^+$, 637 [M + Na]$^+$, 1230 [2 M + H]$^+$, 1252 [2 M + Na]$^+$. $C_{36}H_{42}O_7N_2$ (614.7): calcd. C 70.34, H 6.89; found C 70.22, H 6.94.

Conversion of 15 into 17: Triphenylphosphane (161 mg, 0.615 mmol) was added at room temperature to a stirred solution of bis(dibenzylideneacetone)palladium(0) (70.7 mg, 0.123 mmol) in THF (40 mL). The yellow solution was cooled to 0 °C, and triethylamine (1.71 mL, 12.3 mmol), formic acid (0.470 mL, 12.3 mmol), and **15** (3.46 g, 6.15 mmol) were added successively. The solution was stirred at reflux temperature for 2 d. The solution was cooled down to room temperature, diluted with ethyl acetate (60 mL), washed with a saturated aqueous NH_4Cl solution, water, a saturated aqueous $NaHCO_3$ solution, and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:7) afforded **17** (2.49 g, 5.98 mmol, 97%) as a white solid. ^{1}H NMR: δ = 1.11 (s, 3 H, 19-H), 1.40 (s, 3 H, 17-H), 1.44 (s, 3 H, acetonide), 1.48 (s, 3 H, acetonide), 1.67 (s, 3 H, 16-H), 2.05 (s, 3 H, 18-H), 2.47 (d, J_{3-2} = 5.8 Hz, 1 H, 3-H), 2.90 (s, 2 H, 2 × 14-H), 4.12 (d, J_{9-10} = 9.2 Hz, 1 H, 9-H), 4.82 (d, J_{10-9} = 9.2 Hz, 1 H, 10-H), 4.88 (d, J_{2-3} = 5.8 Hz, 1 H, 2-H), 5.05 (br. s, 1 H, 20-H), 5.33 (br. s, 1 H, 20-H) ppm. FAB-MS: *m*/*z* = 417 [M + H]$^+$, 439 [M + Na]$^+$, 856 [2 M + Na]$^+$. $C_{24}H_{32}O_6$ (416.5): calcd. C 69.21, H 7.74; found C 69.61, H 7.77.

Conversion of 17 into 18: Osmium tetroxide (4.0 wt% solution in water, 6.68 mL, 1.1 mmol) and 4-methylmorpholine *N*-oxide (2.51 g, 18.6 mmol) were added at room temperature to a stirred solution of **17** (4.55 g, 10.9 mmol) in THF (85 mL). The solution was stirred at room temperature for 5 d, water (2 mL) being added to the reaction mixture every day. The reaction was quenched by addition of $Na_2S_2O_4$ (585 mg, 3.36 mmol) and Florisil® (4.5 g). After 20 min of additional stirring, the reaction mixture was filtered through Celite®. The filter agent was rinsed with ethyl acetate (90 mL). The aqueous layer of the filtrate was separated from the organic layer and extracted with ethyl acetate (25 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:1) yielded **18** (4.46 g, 9.90 mmol, 91%) as a white solid. ^{1}H NMR: δ = 1.09 (s, 3 H, 19-H), 1.39 (s, 3 H, 17-H), 1.42 (s, 3 H, acetonide), 1.46 (s, 3 H, acetonide), 1.63 (s, 3 H, 16-H), 2.01 (s, 3 H, 18-H), 2.13 (d, J_{3-2} = 4.7 Hz, 1 H, 3-H), 2.80 (d, J_{gem} = 19.2 Hz, 1 H, 14-H), 3.66 (br. dd, J_{gem} = 10.5, J_{20-OH} = 5.3 Hz, 1 H, 20-H), 3.97 (br. d, J_{gem} = 10.5 Hz, 1 H, 20-H), 4.02 (d, J_{gem} = 19.2 Hz, 1 H, 14-H), 4.09 (d, J_{9-10} = 8.8 Hz, 1 H, 9-H), 4.72 (d, J_{10-9} = 8.8 Hz, 1 H, 10-H), 4.80 (d, J_{2-3} = 4.7 Hz, 1 H, 2-H). FAB-MS: *m*/*z* = 451 [M + H]$^+$, 473 [M + Na]$^+$. $C_{24}H_{34}O_8$·0.5H_2O (459.5): calcd. C 62.73, H 7.68; found C 62.77, H 7.71.

Conversion of 18 into a Mixture of 19a and 19b: Cerium(III) chloride heptahydrate (8.87 g, 23.8 mmol) was added at 0 °C to a stirred solution of **18** (2.68 g, 5.95 mmol) in methanol (200 mL). After 5 min, sodium borohydride (900 mg, 23.8 mmol) was added in small portions. The reaction mixture was stirred at 0 °C for 30 min. Subsequently, the reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (50 mL). Ethyl acetate (300 mL) and a 10% aqueous citric acid solution (200 mL) were added to the resulting suspension. The aqueous layer was separated from the organic layer and extracted twice with ethyl acetate (2 × 200 mL).

The combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude mixture of **19a** and **19b** (2.57 g, max. 5.68 mmol), which was used as such in the next reaction step. **19a:** ^{1}H NMR: δ = 1.05 (s, 3 H, 19-H), 1.19 (s, 3 H, 17-H), 1.40 (s, 3 H, acetonide), 1.43 (s, 3 H, acetonide), 1.55 (s, 3 H, 16-H), 2.02 (s, 3 H, 18-H), 2.56 (d, J_{3-2} = 4.4 Hz, 1 H, 3-H), 2.67 (dd, J_{gem} = 15.8, J_{14-13} = 9.7 Hz, 1 H, 14-H), 2.79 (dd, J_{gem} = 15.8, J_{14-13} = 2.6 Hz, 1 H, 14-H), 3.42 (br. d, J_{OH-13} = 8.8 Hz, 1 H, 13-OH), 3.64 (d, J_{gem} = 10.5 Hz, 1 H, 20-H), 3.74 (s, 1 H, 4-OH), 3.92 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.07 (br. d, J_{gem} = 10.5 Hz, 1 H, 20-H), 4.53 (m, 1 H, 13-H), 4.64 (d, J_{2-3} = 4.4 Hz, 1 H, 2-H), 4.69 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H) ppm. FAB-MS = *m*/*z*: 453 $[M + H]^+$, 475 $[M + Na]^+$ [after purification by column chromatography (EtOAc/heptanes, 1:1)].

Conversion of a Mixture of 19a and 19b into 20a and 20b: $NaIO_4$ (4.86 g, 22.7 mmol) was added at room temperature to a clear solution of a crude mixture of **19a** and **19b** (2.57 g, max. 5.68 mmol) in THF/water (150 mL, 3:2, v/v). The reaction mixture, which became cloudy within a few minutes, was stirred at room temperature for 3 h, diluted with ethyl acetate (200 mL), and washed with water (100 mL). The aqueous fraction was extracted with ethyl acetate (100 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:1) afforded **20a** [1.22 g, 2.90 mmol, 49% (2 steps)] and **20b** [290 mg, 0.690 mmol, 12% (2 steps)], both as white solids. **20a:** ^{1}H NMR: δ = 1.09 (s, 3 H, 19-H), 1.21 (s, 3 H, 17-H), 1.44 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.55 (s, 3 H, 16-H), 1.59 (m, 1 H, 6-H/7-H), 1.85−2.05 (m, 3 H, 3 × 6-H/7-H), 2.10 (s, 3 H, 18-H), 2.18 (dd, J_{gem} = 15.7, J_{14-13} = 3.5 Hz, 1 H, 14-H), 2.27−2.40 (m, 3 H, 2 × 5-H + 13-OH), 2.64 (dd, J_{gem} = 15.7, J_{14-13} = 9.5 Hz, 1 H, 14-H), 3.33 (d, J_{3-2} = 6.1 Hz, 1 H, 3-H), 3.90 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.61 (d, J_{2-3} = 6.1 Hz, 1 H, 2-H), 4.82 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 4.82 (m, 1 H, 13-H) ppm. FAB-MS: *m*/*z* = 443 $[M + Na]^+$, 863 $[2 M + Na]^+$. $C_{23}H_{32}O_7$ (420.5): calcd. C 65.70, H 7.67; found C 65.65, H 7.66. **20b:** ^{1}H NMR: δ = 1.07 (s, 3 H, 19-H), 1.42 (s, 3 H, acetonide), 1.44 (s, 3 H, acetonide), 1.48 (m, 1 H, 7-H), 1.49 (s, 3 H, 17-H), 1.53 (s, 3 H, 16-H), 1.82−2.07 (m, 3 H, 2 × 6-H + 7-H), 2.07 (s, 3 H, 18-H), 2.15−2.37 (m, 3 H, 2 × 5-H + 14-H), 2.56 (dd, J_{gem} = 15.3, J_{14-13} = 9.5 Hz, 1 H, 14-H), 2.64 (d, J_{3-2} = 6.2 Hz, 1 H, 3-H), 3.92 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.10 (m, 1 H, 13-H), 4.63 (d, J_{2-3} = 6.2 Hz, 1 H, 2-H), 4.74 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H) ppm. FAB-MS: *m*/*z* = 443 $[M + Na]^+$, 863 $[2 M + Na]^+$. $C_{23}H_{32}O_7$ (420.5): calcd. C 65.70, H 7.67; found C 65.36, H 7.37.

Conversion of 20a into 21: Chlorotriethylsilane (2.13 mL, 12.7 mmol) was added at room temperature to a solution of imidazole (2.25 g, 33.1 mmol) in DMF (30 mL). After 20 min, **20a** (1.07 g, 2.54 mmol) in DMF (20 mL) was added. The reaction mixture was then stirred for 4 h, diluted with ethyl acetate (200 mL), and washed with water (100 mL). The aqueous fraction was extracted with ethyl acetate (100 mL), and the combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:7) afforded **21** (1.17 g, 2.19 mmol, 86%) as a white solid. ^{1}H NMR: δ = 0.63 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.96 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.08 (s, 3 H, 19-H), 1.20 (s, 3 H, 17-H), 1.43 (s, 3 H, acetonide), 1.44 (s, 3 H, acetonide), 1.53 (s, 3 H, 16-H), 2.02 (s, 3 H, 18-H), 2.09 (dd, J_{gem} = 15.6, J_{14-13} = 3.5 Hz, 1 H, 14-H), 2.60 (dd, J_{gem} = 15.6, J_{14-13} = 9.4 Hz, 1 H, 14-H), 3.31 (d, J_{3-2} = 6.0 Hz, 1 H, 3-H), 3.88 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.59 (d, J_{2-3} = 6.0 Hz, 1 H, 2-H), 4.61 (m, 1 H, 13-H), 4.81 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H) ppm. FAB-MS: *m*/*z* = 557 $[M + Na]^+$, 1092 $[2 M + Na]^+$. $C_{29}H_{46}O_7Si$ (534.8): calcd. C 65.13, H 8.67; found C 65.18, H 8.63.

Conversion of 21 into 22: Sodium borohydride (58.0 mg, 1.53 mmol) was slowly added at 0 °C to a stirred solution of **21** (745 mg, 1.39 mmol) in methanol (40 mL). The reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (25 mL). The resultant mixture was extracted twice with ethyl acetate (2 × 75 mL). The combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution, water, and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This gave **22** (808 mg, max. 1.39 mmol), which was used as such in the next reaction step. ^{1}H NMR: δ = 0.64 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.98 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.14 (m, 1 H, 7-H), 1.21 (s, 3 H, 17-H), 1.35 (m, 1 H, 5-H), 1.38 (s, 3 H, 19-H), 1.40 (s, 3 H, acetonide), 1.42 (s, 3 H, acetonide), 1.53 (m, 1 H, 6-H), 1.55 (s, 3 H, 16-H), 1.85−1.92 (m, 3 H, 5-H + 6-H + 7-H), 1.91 (s, 3 H, 18-H), 2.10 (m, 1 H, 3-H), 2.14 (dd, J_{gem} = 15.3, J_{14-13} = 3.8 Hz, 1 H, 14-H), 2.15 (br. s, 1 H, 4-OH), 2.60 (dd, J_{gem} = 15.3, J_{14-13} = 9.3 Hz, 1 H, 14-H), 3.89 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.20 (br. s, 1 H, 4-H), 4.64 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 4.70 (d, J_{2-3} = 5.0 Hz, 1 H, 2-H), 4.75 (m, 1 H, 13-H) ppm. ^{13}C NMR: δ = 4.8, 6.8, 16.5, 18.0, 20.2, 20.2, 26.8, 26.9, 28.6, 30.7, 32.4, 37.8, 38.1, 40.3, 44.0, 68.3, 68.8, 75.0, 81.0, 82.3, 91.5, 106.8, 132.9, 147.8, 153.6 ppm. FAB-MS: *m*/*z* = 536 $[M]^+$, 559 $[M + Na]^+$. $C_{29}H_{48}O_7Si$ (536.8): calcd. C 64.89, H 9.01; found C 65.06, H 8.64 [after purification by column chromatography (EtOAc/heptanes, 1:3)].

Dehydration of 22 with Trifluoromethanesulfonyl Chloride, Giving a Mixture of 23 and 24, 25a, and 25b: Trifluoromethanesulfonyl chloride (0.296 mL, 2.78 mmol) was added to a stirred solution of crude **22** (808 mg, max. 1.39 mmol) and 4-(dimethylamino)pyridine (5.09 g, 41.7 mmol) in dichloromethane (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 d, additional amounts of trifluoromethanesulfonyl chloride (2 × 0.296 mL, 2 × 2.78 mmol) being added at 0 °C after 24 and 30 h. The reaction mixture was diluted with ethyl acetate (75 mL), washed with water and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:9) gave a 9:1 mixture of **23** and **24** [220 mg, 0.424 mmol, 31% (2 steps)], **25a** or **25b** (higher R_f value) [154 mg, 0.236 mmol, 17% (2 steps)], and **25b** or **25a** (lower R_f value) [32.3 mg, 49.4 μmol, 4% (2 steps)], all as white solids, together with recovered **22** (225 mg, 0.419 mmol). **23:** ^{1}H NMR: δ = 0.62 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.96 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.08 (s, 3 H, 19-H), 1.22 (s, 3 H, 17-H), 1.41 (s, 3 H, acetonide), 1.44 (s, 3 H, acetonide), 1.57 (s, 3 H, 16-H), 1.87 (s, 3 H, 18-H), 2.07−2.16 (m, 3 H, 2 × 6-H/7-H + 14-H), 2.54 (dd, J_{gem} = 15.2, J_{14-13} = 9.1 Hz, 1 H, 14-H), 2.88 (m, 1 H, 3-H), 4.02 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.58 (d, 1 H, 2-H), 4.60 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.77 (m, 1 H, 13-H), 5.57−5.66 (m, 2 H, 4-H + 5-H) ppm. FAB-MS: *m*/*z* = 519 $[M + H]^+$, 541 $[M + Na]^+$, 1038 $[2 M + H]^+$, 1060 $[2 M + Na]^+$, 1578 $[3 M + Na]^+$. $C_{29}H_{46}O_6Si$ (518.8): calcd. C 67.14, H 8.94; found C 67.27, H 9.04. **25a or 25b** (higher R_f value): ^{1}H NMR: δ = 0.66 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.99 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.20 (s, 3 H, 17-H), 1.29 (s, 3 H, 19-H), 1.40 (s, 3 H, acetonide), 1.42 (s, 3 H, acetonide), 1.55 (s, 3 H, 16-H), 1.92 (s, 3 H, 18-H), 2.04 (dd, J_{gem} = 15.5, J_{14-13} = 3.6 Hz, 1 H, 14-H), 2.35 (dd, J_{3-2} = 5.0, J_{3-4} = 2.3 Hz, 1 H, 3-H), 2.64 (dd, J_{gem} = 15.5, J_{14-13} = 9.3 Hz, 1 H, 14-H), 3.90 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.61 (d, J_{2-3} = 5.0 Hz, 1 H, 2-H), 4.65

(d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 4.70 (m, 1 H, 4-H), 4.72 (m, 1 H, 13-H) ppm. FAB-MS: *m*/*z* = 653 [M + H]$^+$, 675 [M + Na]$^+$, 1328 [2 M + Na]$^+$. $C_{30}H_{47}F_3O_8SSi{\cdot}2H_2O$ (688.9): calcd. C 52.31, H 7.46; found C 52.40, H 6.97. **25b or 25a** (lower R_f value): ^{1}H NMR: δ = 0.65 [q, *J* = 7.9 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$], 0.98 [t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$], 1.20 (s, 3 H, 17-H), 1.32 (s, 3 H, 19-H), 1.40 (s, 3 H, acetonide), 1.42 (s, 3 H, acetonide), 1.54 (s, 3 H, 16-H), 1.92 (s, 3 H, 18-H), 2.05 (dd, J_{gem} = 15.5 Hz, 1 H, 14-H), 2.37 (dd, 1 H, 3-H), 2.65 (dd, J_{gem} = 15.5, J_{14-13} = 9.1 Hz, 1 H, 14-H), 3.91 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.65 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 4.68 (d, 1 H, 2-H), 4.72 (m, 1 H, 13-H), 4.79 (m, 1 H, 4-H) ppm. FAB-MS: *m*/*z* = 653 [M + H]$^+$, 675 [M + Na]$^+$.

Dehydration of 22 with Trifluoromethanesulfonic Anhydride, Giving a Mixture of 23 and 24, 25a, and 25b: Trifluoromethanesulfonic anhydride (15.7 μL, 93.1 μmol) was added at −30 °C to a solution of **22** (25.0 mg, 46.6 μmol) and pyridine (113 μL, 1.40 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 2 d, additional trifluoromethanesulfonic anhydride (15.7 μL, 93.1 μmol) being added at −30 °C after 1 d. The reaction mixture was diluted with ethyl acetate (20 mL), washed with water and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:9) afforded a 1:10 mixture of **23** and **24** (8.1 mg, 16 μmol, 34%), **25a** or **25b** (higher R_f value, 5.0 mg, 7.7 μmol, 16%), and **25b** or **25a** (lower R_f value, 1.3 mg, 2.0 μmol, 4%), all as white solids, together with recovered **22** (7.2 mg, 13 μmol). **24:** ^{1}H NMR: δ = 0.63 [q, *J* = 7.9 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$], 0.98 [t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$], 1.19 (s, 3 H, 19-H), 1.24 (s, 3 H, 17-H), 1.42 (s, 3 H, acetonide), 1.46 (s, 3 H, acetonide), 1.58 (s, 3 H, 16-H), 1.85 (s, 3 H, 18-H), 2.40−2.51 (m, 2 H, 2 × 14-H), 4.10 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.67 (m, 1 H, 13-H), 4.76 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 4.96 (s, 1 H, 2-H), 5.92 (m, 1 H, 4-H) ppm. FAB-MS: *m*/*z* = 519 [M + H]$^+$, 541 [M + Na]$^+$, 1038 [2 M + H]$^+$, 1060 [2 M + Na]$^+$. $C_{29}H_{46}O_6Si$ (518.8): calcd. C 67.14, H 8.94; found C 67.17, H 9.07.

Conversion of 23 into 26: Phenyllithium (1.8 M solution in cyclohexane/diethyl ether, 0.535 mL, 0.96 mmol) was added at −78 °C to a stirred solution of **23** (200 mg, 0.386 mmol) in THF (4 mL). The reaction mixture was stirred at −78 °C for 30 min, after which the reaction was quenched by slow addition of a 10% aqueous citric acid solution (10 mL). The mixture was allowed to warm to room temperature and extracted twice with ethyl acetate (2 × 15 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:4) afforded **26** (230 mg, 0.386 mmol, 100%) as a white solid. ^{1}H NMR: δ = 0.66 [q, *J* = 7.9 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$], 1.01 [t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$], 1.12 (s, 3 H, 19-H), 1.18 (s, 3 H, 17-H), 1.44 (s, 3 H, acetonide), 1.51 (s, 3 H, acetonide), 1.65 (s, 3 H, 16-H), 1.88 (s, 3 H, 18-H), 2.24 (dd, J_{gem} = 14.9, J_{14-13} = 4.9 Hz, 1 H, 14-H), 2.39 (dd, J_{gem} = 14.9, J_{14-13} = 9.2 Hz, 1 H, 14-H), 3.29 (m, 1 H, 3-H), 4.39 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.70 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.81 (m, 1 H, 13-H), 5.44−5.51 (m, 2 H, 2-H + 4-H/5-H), 5.73 (m, 1 H, 4-H/5-H), 7.46 (m, 2 H, Ph), 7.58 (m, 1 H, Ph), 8.05 (m, 2 H, Ph) ppm. FAB-MS: *m*/*z* = 597 [M + H]$^+$, 619 [M + Na]$^+$, 1216 [2 M + Na]$^+$. $C_{35}H_{52}O_6Si$ (596.9): calcd. C 70.43, H 8.78; found C 70.37, H 8.84.

Conversion of 26 into 27: Tetrabutylammonium fluoride (1.0 M solution in THF, 0.771 mL, 0.77 mmol) was added at room temperature to a solution of **26** (230 mg, 0.385 mmol) in THF (15 mL). After 5 min, the solution was diluted with ethyl acetate (75 mL), washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:3) gave **27** (176 mg, 0.365 mmol, 95%) as a white solid. ^{1}H NMR: δ = 1.13 (s, 3 H, 19-H), 1.19 (s, 3 H, 17-H), 1.45 (s, 3 H, acetonide), 1.52 (s, 3 H, acetonide), 1.66 (s, 3 H, 16-H), 1.97 (s, 3 H, 18-H), 2.23 (dd, J_{gem} = 15.3, J_{14-13} = 4.9 Hz, 1 H, 14-H), 2.53 (dd, J_{gem} = 15.3, J_{14-13} = 9.7 Hz, 1 H, 14-H), 3.26 (br. s, 1 H, 3-H), 4.41 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.70 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.85 (m, 1 H, 13-H), 5.52 (m, 2 H, 2-H + 4-H/5-H), 5.77 (m, 1 H, 4-H/5-H), 7.47 (m, 2 H, Ph), 7.58 (m, 1 H, Ph), 8.07 (m, 2 H, Ph) ppm. FAB-MS: *m*/*z* = 505 [M + Na]$^+$. $C_{29}H_{38}O_6{\cdot}2H_2O$ (518.6): calcd. C 67.16, H 8.16; found C 67.18, H 7.83.

Coupling of 27 to β-Lactam 28, Affording 29: Sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 0.389 mL, 0.39 mmol) was added at −78 °C to a stirred solution of **27** (75.0 mg, 0.155 mmol) and β-lactam **28** (94.9 mmol, 0.249 mmol) in THF (3 mL). The reaction mixture was stirred at −78 °C for 20 min. Subsequently, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL). The mixture was allowed to warm to room temperature, ethyl acetate (20 mL) and brine (20 mL) were added, and the two layers were separated. The organic fraction was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:3) yielded **29** (113 mg, 0.131 mmol, 84%) as a white solid. ^{1}H NMR: δ = 0.45 [m, 6 H, Si(C*H*$_2$CH$_3$)$_3$], 0.82 [t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$], 1.17 and 1.19 (2 × s, 6 H, 17-H + 19-H), 1.46 (s, 3 H, acetonide), 1.53 (s, 3 H, acetonide), 1.66 (s, 3 H, 16-H), 1.78 (s, 3 H, 18-H), 2.30 (dd, J_{gem} = 15.7, J_{14-13} = 4.0 Hz, 1 H, 14-H), 2.47 (dd, J_{gem} = 15.7, J_{14-13} = 9.9 Hz, 1 H, 14-H), 3.36 (br. s, 1 H, 3-H), 4.45 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.53 (d, $J_{2'-3'}$ = 1.5 Hz, 1 H, 2′-H), 4.70 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 5.57−5.64 (m, 2 H, 2-H + 4-H/5-H), 5.73 (dd, $J_{3'-NH}$ = 8.8, $J_{3'-2'}$ = 1.5 Hz, 1 H, 3′-H), 5.97 (m, 1 H, 13-H), 6.14 (m, 1 H, 4-H/5-H), 7.24−7.55 (m, 12 H, Ph + NH), 7.85 (m, 2 H, Ph), 8.26 (m, 2 H, Ph) ppm. FAB-MS: *m*/*z* = 864 [M + H]$^+$, 886 [M + Na]$^+$. $C_{51}H_{65}NO_9Si$ (864.2): calcd. C 70.89, H 7.58, N 1.62; found C 71.01, H 7.81, N 1.57.

Conversion of 29 into 30: Tetrabutylammonium fluoride (1.0 M solution in THF, 0.167 mL, 0.17 mmol) was added at room temperature to a stirred solution of **29** (103 mg, 0.119 mmol) in THF (8 mL). After 5 min, the reaction mixture was poured into water (20 mL). The mixture was extracted twice with ethyl acetate (2 × 20 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:3) afforded **30** (82.2 mg, 0.110 mmol, 92%) as a white solid. ^{1}H NMR: δ = 1.17 and 1.20 (2 × s, 6 H, 17-H + 19-H), 1.46 (s, 3 H, acetonide), 1.53 (s, 3 H, acetonide), 1.67 (s, 3 H, 16-H), 1.79 (s, 3 H, 18-H), 2.44 (dd, J_{gem} = 15.9, J_{14-13} = 9.5 Hz, 1 H, 14-H), 2.56 (dd, J_{gem} = 15.9, J_{14-13} = 3.8 Hz, 1 H, 14-H), 3.38 (br. s, 1 H, 3-H), 4.44 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.63 (d, $J_{2'-3'}$ = 1.6 Hz, 1 H, 2′-H), 4.68 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 5.60 (m, 2 H, 2-H + 4-H/5-H), 5.84 (dd, $J_{3'-NH}$ = 9.4, $J_{3'-2'}$ = 1.6 Hz, 1 H, 3′-H), 6.06 (m, 1 H, 13-H), 6.18 (m, 1 H, 4-H/5-H), 6.94 (d, $J_{NH-3'}$ = 9.4 Hz, 1 H, NH), 7.28−7.55 (m, 11 H, Ph), 7.80 (m, 2 H, Ph), 8.31 (m, 2 H, Ph) ppm. FAB-MS: *m*/*z* = 750 [M + H]$^+$, 772 [M + Na]$^+$, 1500 [2 M + H], 1522 [2 M + Na]. $C_{45}H_{51}NO_9{\cdot}0.5H_2O$ (758.9): calcd. C 71.22, H 6.91, N 1.84; found C 70.97, H 6.99, N 1.93.

Conversion of 30 into 31: *p*-Toluenesulfonic acid monohydrate (12.7 mg, 66.7 μmol) was added at room temperature to a stirred solution of **30** (50.0 mg, 66.7 μmol) in methanol (4 mL). After 3 h, the reaction mixture was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous $NaHCO_3$ solution. The aqueous

fraction was extracted with ethyl acetate (30 mL), and the combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 5:1) afforded **31** (37.4 mg, 53.3 μmol, 80%) as a white solid. ^{1}H NMR: δ = 1.12 and 1.15 (2 × s, 6 H, 17-H + 19-H), 1.32 (s, 3 H, 16-H), 1.77 (s, 3 H, 18-H), 2.16 (dd, J_{gem} = 14.5, J_{14-13} = 7.5 Hz, 1 H, 14-H), 2.39 (dd, J_{gem} = 14.5, J_{14-13} = 7.0 Hz, 1 H, 14-H), 2.73 (m, 1 H, 3-H), 4.22 (br. d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.36 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 4.74 (d, $J_{2'-3'}$ = 2.7 Hz, 1 H, 2′-H), 5.35 (m, 1 H, 4-H/5-H), 5.52 (m, 1 H, 4-H/5-H), 5.69 (d, J_{2-3} = 8.2 Hz, 1 H, 2-H), 5.75−5.80 (m, 2 H, 3′-H + 13-H), 7.01 (d, $J_{NH-3'}$ = 9.1 Hz, 1 H, NH), 7.27−7.57 (m, 11 H, Ph), 7.79 (m, 2 H, Ph), 8.06 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 710 $[M + H]^+$, 732 $[M + Na]^+$. $C_{42}H_{47}NO_9 \cdot 1.5H_2O$ (736.9): calcd. C 68.46, H 6.84, N 1.90; found C 68.58, H 6.84, N 1.96.

Conversion of 21 into 32 and 33: Methyllithium (1.6 M solution in diethyl ether, 0.617 mL, 0.99 mmol) was slowly added at −78 °C to a solution of **21** (440 mg, 0.823 mmol) in THF (18 mL). After the addition of methyllithium had been completed, the reaction mixture was stirred at −78 °C for 15 min. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was allowed to warm to room temperature, ethyl acetate (75 mL) and water (75 mL) were added, and the resultant two layers were separated. The aqueous fraction was extracted with ethyl acetate (50 mL), and the combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:7) yielded **32** (371 mg, 0.674 mmol, 82%) and **33** (19.6 mg, 34.6 μmol, 4%), both as a white solids. **32:** ^{1}H NMR: δ = 0.64 [q, J = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.97 [t, J = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.04 (m, 1 H, 7-H), 1.20 (m, 1 H, 5-H), 1.22 (s, 3 H, 17-H), 1.38 (s, 3 H, 19-H), 1.39 (s, 3 H, acetonide), 1.42 (s, 3 H, acetonide), 1.46 (s, 3 H, 20-H), 1.47 (m, 1 H, 6-H), 1.57 (s, 3 H, 16-H), 1.72−1.93 (m, 3 H, 5-H + 6-H + 7-H), 1.88 (s, 3 H, 18-H), 1.92 (d, J_{3-2} = 4.5 Hz, 1 H, 3-H), 2.49 (dd, J_{gem} = 15.4, J_{14-13} = 4.1 Hz, 1 H, 14-H), 2.58 (dd, J_{gem} = 15.4, J_{14-13} = 8.9 Hz, 1 H, 14-H), 3.97 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.60 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.75 (m, 1 H, 13-H), 4.76 (d, J_{2-3} = 4.5 Hz, 1 H, 2-H) ppm. FAB-MS: *m/z* = 550 $[M]^+$, 573 $[M + Na]^+$, 1102 $[2 M + H]^+$, 1124 $[2 M + Na]^+$. $C_{30}H_{50}O_7Si$ (550.8): calcd. C 65.42, H 9.15; found C 65.83, H 9.17. **33:** ^{1}H NMR: δ = 0.64 [q, 6 H, J = 7.9 Hz, $Si(CH_2CH_3)_3$], 0.98 [t, 9 H, J = 7.9 Hz, $Si(CH_2CH_3)_3$], 1.11 (s, 3 H, 19-H), 1.28 (s, 3 H, 17-H), 1.39 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.57 (s, 3 H, 20-H), 1.59 (s, 3 H, 16-H), 1.85 (s, 3 H, 18-H), 2.10 (d, J_{3-2} = 3.9 Hz, 1 H, 3-H), 2.16 [s, 3 H, $C(O)CH_3$], 2.27 (dd, J_{gem} = 15.3, J_{14-13} = 9.9 Hz, 1 H, 14-H), 2.44 (dd, J_{gem} = 15.3, J_{14-13} = 3.9 Hz, 1 H, 14-H), 4.21 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.67 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.75 (m, 1 H, 13-H), 5.48 (d, J_{2-3} = 3.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR: δ = 4.8, 6.9, 17.1, 17.4, 19.8, 20.6, 21.7, 26.9, 27.3, 28.9, 30.9, 33.7, 39.3, 39.9, 43.1, 43.8, 49.4, 69.5, 74.0, 74.6, 76.2, 78.2, 82.1, 106.7, 134.2, 144.7, 171.8 ppm. FAB-MS: *m/z* = 549 $[M - OH]^+$, 566 $[M]^+$, 589 $[M + H]^+$, 1156 $[2 M + Na]^+$. $C_{31}H_{54}O_7Si$ (566.8): calcd. C 65.69, H 9.60; found C 66.11, H 9.65.

Dehydration of 32 with Trifluoromethanesulfonyl Chloride, Giving a Mixture of 34 and 35, 36a, and 36b: The same procedure as used for the preparation of **23** and **24** from **22** was followed, except that 20, 10, and 0 equivalents of trifluoromethanesulfonyl chloride were added at the beginning of the reaction, after 24 h, and after 30 h, respectively. In this way, 470 mg of **32** (0.853 mmol) afforded 85.0 mg of a 10:1 mixture of **34** and **35** (0.160 mmol, 19%), 180 mg of **36a** or **36b** (higher R_f value, 0.270 mmol, 32%), and 167 mg of **36b** or **36a** (lower R_f value, 0.250 mmol, 29%). **34:** ^{1}H NMR: δ = 0.64 [q, J = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.97 [t, J = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.14 (s, 3 H, 19-H), 1.23 (s, 3 H, 17-H), 1.42 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.59 (s, 3 H, 16-H), 1.86 (s, 3 H, 18-H), 1.91 (s, 3 H, 20-H), 2.40 (dd, J_{gem} = 15.3, J_{14-13} = 3.6 Hz, 1 H, 14-H), 2.63 (dd, J_{gem} = 15.3, J_{14-13} = 9.4 Hz, 1 H, 14-H), 2.99 (br. s, 1 H, 3-H), 4.06 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.60 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.76 (m, 1 H, 13-H), 4.77 (d, J_{2-3} = 4.3 Hz, 1 H, 2-H), 5.37 (br. s, 1 H, 5-H) ppm. FAB-MS: *m/z* = 532 $[M]^+$, 555 $[M + Na]^+$, 647 $[M + TES]^+$, 1088 $[2 M + Na]^+$. $C_{30}H_{48}O_6Si \cdot H_2O$ (550.8): calcd. C 65.42, H 9.15; found C 65.52, H 8.72. **35:** ^{1}H NMR: δ = 0.62 [q, J = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.96 [t, J = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.07 (s, 3 H, 19-H), 1.21 (s, 3 H, 17-H), 1.41 (s, 3 H, acetonide), 1.44 (s, 3 H, acetonide), 1.56 (s, 3 H, 16-H), 1.98 (s, 3 H, 18-H), 2.16 (dd, J_{gem} = 15.3, J_{14-13} = 4.0 Hz, 1 H, 14-H), 2.54 (dd, J_{gem} = 15.3, J_{14-13} = 9.4 Hz, 1 H, 14-H), 2.81 (d, J_{3-2} = 5.5 Hz, 1 H, 3-H), 3.94 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.70−4.79 (d + d + m, 3 H, 2-H + 9-H + 13-H), 5.00 (br. s, 1 H, 20-H), 5.29 (br. s, 1 H, 20-H). **36a or 36b** (higher R_f value): ^{1}H NMR: δ = 0.66 [q, J = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.98 [t, J = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.21 (s, 3 H, 17-H), 1.33 (s, 3 H, 19-H), 1.39 (s, 3 H, acetonide), 1.43 (s, 3 H, acetonide), 1.58 (s, 3 H, 16-H), 1.88 (s, 3 H, 18-H), 1.90 (s, 3 H, 20-H), 2.09 (d, J_{3-2} = 4.3 Hz, 1 H, 3-H), 2.38 (dd, J_{gem} = 15.6, J_{14-13} = 3.1 Hz, 1 H, 14-H), 2.62 (dd,, J_{gem} = 15.6, J_{14-13} = 9.6 Hz 1 H, 14-H), 3.98 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.62 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.68 (d, J_{2-3} = 4.3 Hz, 1 H, 2-H), 4.73 (m, 1 H, 13-H) ppm. FAB-MS: *m/z* = 666 $[M]^+$, 781 $[M + TES]^+$, 1356 $[2 M + Na]^+$. $C_{31}H_{49}O_8SF_3Si$ (666.9): calcd. C 55.83, H 7.41; found C 55.63, H 7.28. **36b or 36a** (lower R_f value): ^{1}H NMR: δ = 0.65 [q, J = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.98 [t, J = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.21 (s, 3 H, 17-H), 1.30 (s, 3 H, 19-H), 1.39 (s, 3 H, acetonide), 1.43 (s, 3 H, acetonide), 1.57 (s, 3 H, 16-H), 1.89 (s, 3 H, 18-H), 1.90 (s, 3 H, 20-H), 2.12 (d, J_{3-2} = 4.4 Hz, 1 H, 3-H), 2.40 (dd, J_{gem} = 15.6, J_{14-13} = 3.1 Hz, 1 H, 14-H), 2.63 (dd, J_{gem} = 15.6, J_{14-13} = 9.6 Hz, 1 H, 14-H), 3.99 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.62 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.73 (d, J_{2-3} = 4.4 Hz, 1 H, 2-H), 4.73 (m, 1 H, 13-H) ppm. FAB-MS: *m/z* = 666 $[M]^+$, 689 $[M + Na]^+$, 781 $[M + TES]^+$, 1356 $[2 M + Na]^+$. $C_{31}H_{49}O_8SF_3Si$ (666.9): calcd. C 55.83, H 7.41; found C 55.47, H 7.31.

Conversion of 34 into 37: The same procedure as used for the preparation of **26** was applied. In this way, 85.0 mg of **34** (0.160 mmol) afforded 78.2 mg of **37** (0.128 mmol, 80%) as a white solid. ^{1}H NMR: δ = 0.67 [q, J = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 1.00 [t, J = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.11 and 1.16 (2 × s, 6 H, 17-H + 19-H), 1.44 (s, 3 H, acetonide), 1.51 (s, 3 H, acetonide), 1.70 (s, 3 H, 16-H), 1.86 (s, 3 H, 18-H), 2.15 (s, 3 H, 20-H), 2.39 (dd, J_{gem} = 15.2, J_{14-13} = 9.7 Hz, 1 H, 14-H), 2.56 (dd, J_{gem} = 15.2, J_{14-13} = 4.0 Hz, 1 H, 14-H), 3.30 (br. s, 1 H, 3-H), 4.42 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.67 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.81 (m, 1 H, 13-H), 5.37 (br. s, 1 H, 5-H), 5.82 (d, J_{2-3} = 2.9 Hz, 1 H, 2-H), 7.45 (m, 2 H, Ph), 7.57 (m, 1 H, Ph), 8.01 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 611 $[M + H]^+$, 633 $[M + Na]^+$, 725 $[M + TES]^+$, 1244 $[2 M + Na]^+$. $C_{36}H_{54}O_6Si$ (610.9): calcd. C 70.78, H 8.91; found C 70.85, H 8.66.

Conversion of 37 into 38: The same procedure as used for the preparation of **27** was applied. In this way, 68.0 mg of **37** (0.111 mmol) gave 46.2 mg of **38** (93.0 μmol, 84%) as a white solid. ^{1}H NMR: δ = 1.13 and 1.15 (2 × s, 6 H, 17-H + 19-H), 1.44 (s, 3 H, acetonide), 1.52 (s, 3 H, acetonide), 1.70 (s, 3 H, 16-H), 1.94 (s, 3 H, 18-H), 2.17 (s, 3 H, 20-H), 2.48 (dd, J_{gem} = 15.4, J_{14-13} = 9.5 Hz, 1

H, 14-H), 2.58 (dd, J_{gem} = 15.4, J_{14-13} = 4.2 Hz, 1 H, 14-H), 3.30 (br. s, 1 H, 3-H), 4.44 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.66 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.83 (m, 1 H, 13-H), 5.38 (br. s, 1 H, 5-H), 5.84 (d, J_{2-3} = 3.1 Hz, 1 H, 2-H), 7.44 (m, 2 H, Ph), 7.57 (m, 1 H, Ph), 8.01 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 519 $[M + Na]^+$. $C_{30}H_{40}O_6 \cdot 0.5H_2O$ (505.7): calcd. C 71.26, H 8.17; found C 71.04, H 8.05.

Coupling of 38 to β-Lactam 28, Affording 39: The same procedure as used for the preparation of **29** was applied. In this way, 39.8 mg of **38** (80.1 μmol) gave 46.4 mg of **39** (52.8 mmol, 66%) after column chromatography (EtOAc/heptanes, 1:4). ^{1}H NMR: δ = 0.44 [m, 6 H, $Si(CH_2CH_3)_3$], 0.82 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.20 (s, 6 H, 17-H + 19-H), 1.45 (s, 3 H, acetonide), 1.53 (s, 3 H, acetonide), 1.71 (s, 3 H, 16-H), 1.77 (s, 3 H, 18-H), 2.33 (s, 3 H, 20-H), 2.42 (dd, J_{gem} = 15.7, J_{14-13} = 10.3 Hz, 1 H, 14-H), 2.66 (dd, J_{gem} = 15.7, J_{14-13} = 4.2 Hz, 1 H, 14-H), 3.29 (br. s, 1 H, 3-H), 4.51 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.58 (d, $J_{2'-3'}$ = 1.6 Hz, 1 H, 2′-H), 4.65 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 5.48 (br. s, 1 H, 5-H), 5.70 (dd, $J_{3'-NH}$ = 8.8, $J_{3'-2'}$ = 1.6 Hz, 1 H, 3′-H), 5.88 (d, J_{2-3} = 3.3 Hz, 1 H, 2-H), 6.16 (m, 1 H, 13-H), 7.24 (d, $J_{NH-3'}$ = 8.8 Hz, 1 H, NH), 7.26−7.57 (m, 11 H, Ph), 7.84 (m, 2 H, Ph), 8.11 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 877 $[M]^+$, 900 $[M + Na]^+$, 993 $[M + TES]^+$. $C_{52}H_{67}NO_9Si$ (878.2): calcd. C 71.12, H 7.69, N 1.59; found C 70.80, H 7.70, N 1.46.

Conversion of 39 into 40: The same procedure as used for the preparation of **30** was applied. In this way, 32.6 mg of **39** (37.1 μmol) gave 22.4 mg of **40** (29.3 μmol, 79%) as a white solid. ^{1}H NMR: δ = 1.18 and 1.20 (2 × s, 6 H, 17-H + 19-H), 1.44 (s, 3 H, acetonide), 1.52 (s, 3 H, acetonide), 1.71 (s, 6 H, 16-H + 18-H), 2.27 (s, 3 H, 20-H), 2.47 (dd, J_{gem} = 15.9, J_{14-13} = 10.5 Hz, 1 H, 14-H), 2.74 (dd, J_{gem} = 15.9, J_{14-13} = 3.9 Hz, 1 H, 14-H), 3.27 (br. s, 1 H, 3-H), 3.32 (br. s, 1 H, 2′-OH), 4.49 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.63 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.69 (br. s, 1 H, 2′-H), 5.43 (br. s, 1 H, 5-H), 5.79 (dd, $J_{3'-NH}$ = 9.0, $J_{3'-2'}$ = 2.1 Hz, 1 H, 3′-H), 5.87 (d, J_{2-3} = 3.3 Hz, 1 H, 2-H), 6.16 (m, 1 H, 13-H), 6.98 (d, $J_{NH-3'}$ = 9.0 Hz, 1 H, NH), 7.31−7.57 (m, 11 H, Ph), 7.80 (m, 2 H, Ph), 8.10 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 786 $[M + Na]^+$. $C_{46}H_{53}NO_9 \cdot 2H_2O$ (800.0): calcd. C 69.07, H 7.18, N 1.75; found C 69.12, H 6.79, N 1.44.

Conversion of 21 into 41: A solution of lithium diisopropylamide, prepared from diisopropylamine (57.0 μL, 0.407 mmol) and butyllithium (1.6 M solution in hexane, 0.236 mL, 0.38 mmol) in THF (0.234 mL) at 0 °C, was added at −78 °C to a solution of **21** (101 mg, 0.189 mmol) in THF (2 mL). After 10 min, trimethylsilyl chloride (0.240 mL, 1.89 mmol) was added. The reaction mixture was stirred for 1 h, the reaction temperature gradually being raised to −20 °C, and then diluted with diethyl ether (10 mL). The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was separated from the organic layer and extracted with diethyl ether (10 mL). The combined organic fractions were washed with water and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes/triethylamine, 15:75:1) yielded **41** (106 mg, 0.175 mmol, 92%) as a white solid. ^{1}H NMR: δ = 0.19 [s, 9 H, $Si(CH_3)_3$], 0.64 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.98 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.18 and 1.24 (2 × s, 6 H, 17-H + 19-H), 1.41 (s, 3 H, acetonide), 1.44 (s, 3 H, acetonide), 1.55 (s, 3 H, 16-H), 1.88 (s, 3 H, 18-H), 2.47 (dd, J_{gem} = 15.1, J_{14-13} = 9.3 Hz, 1 H, 14-H), 2.72 (dd, J_{gem} = 15.1, J_{14-13} = 4.7 Hz, 1 H, 14-H), 3.14 (br. s, 1 H, 3-H), 4.02 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.60 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 4.66 (m, 2 H, 2-H + 5-H), 4.83 (m, 1 H, 13-H) ppm. FAB-MS: *m/z* = 606 $[M]^+$, 629 $[M + Na]^+$, 679 $[M + TMS]^+$, 721 $[M + TES]^+$. $C_{32}H_{54}O_7Si_2$ (606.9): calcd. C 63.33, H 8.97; found C 62.93, H 8.67.

Conversion of 41 into 42: Diiodomethane (20.0 μL, 0.248 mmol) and **41** (755 mg, 1.24 mmol) were added successively to a stirred suspension of activated zinc[34] (244 mg, 3.73 mmol) in diethyl ether/1,2-dimethoxyethane (1.5 mL, 4:1, v/v). The suspension was warmed to 50 °C, after which diiodomethane (0.301 mL, 3.73 mmol) was added. The reaction mixture was stirred at 50 °C for 60 h, additional activated zinc (122 mg, 1.87 mmol) and diiodomethane (0.150 mL, 1.87 mmol) being added after 40 h. The reaction mixture was cooled down to room temperature, diluted with ethyl acetate (50 mL), and filtered through Celite®. The filter agent was thoroughly rinsed with ethyl acetate (50 mL). The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, water, and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:10) afforded **42** (447 mg, 0.720 mmol, 58%) as a white solid. ^{1}H NMR: δ = 0.09 [s, 9 H, $Si(CH_3)_3$], 0.20 (dd, 1 H, 20-H), 0.61 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.96 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 0.96 (m, 1 H, 5-H), 1.05 (d, J_{3-2} = 8.7 Hz, 1 H, 3-H), 1.26 (dd, 1 H, 20-H), 1.34 and 1.36 and 1.37 and 1.41 (4 × s, 12 H, 17-H + 19-H + 2 × acetonide), 1.63 (s, 3 H, 16-H), 1.64 (dd, 1 H, 14-H), 1.80 (s, 3 H, 18-H), 2.38 (dd, J_{gem} = 13.4, J_{14-13} = 5.9 Hz, 1 H, 14-H), 3.73 (d, *J* = 10.1 Hz, 1 H, 9-H/10-H), 4.17 (d, *J* = 10.1 Hz, 1 H, 9-H/10-H), 4.70 (m, 1 H, 13-H), 4.80 (d, J_{2-3} = 8.7 Hz, 1 H, 2-H) ppm. FAB-MS: *m/z* = 621 $[M + H]^+$, 643 $[M + Na]^+$, 693 $[M + TMS]^+$, 735 $[M + TES]^+$, 1242 $[2 M + H]^+$, 1264 $[2 M + Na]^+$. $C_{33}H_{56}O_7Si_2$ (621.0): calcd. C 63.83, H 9.10; found C 63.87, H 9.10.

Conversion of 42 into 43: Phenyllithium (1.8 M solution in cyclohexane/diethyl ether, 2.00 mL, 3.6 mmol) was added at −78 °C to a stirred solution of **42** (447 mg, 0.720 mmol) in THF (20 mL). The reaction mixture was stirred at −78 °C for 2.5 h. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (25 mL). The mixture was allowed to warm to room temperature and extracted twice with ethyl acetate (2 × 50 mL). The combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:10) yielded **43** (432 mg, 0.618 mmol, 86%) as a white solid. ^{1}H NMR: δ = −0.32 [s, 9 H, $Si(CH_3)_3$], 0.26 (dd, 1 H, 20-H), 0.65 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.65 (m, 1 H, 6-H), 0.87 (dd, J_{gem} = 5.8, J_{20-5} = 9.3 Hz, 1 H, 20-H), 1.02 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.09 (s, 3 H, 17-H), 1.21 (s, 3 H, 16-H), 1.22 (m, 1 H, 5-H), 1.26 (d, J_{3-2} = 8.4 Hz, 1 H, 3-H), 1.36 (m, 1 H, 7-H), 1.42 (s, 3 H, acetonide), 1.42 (s, 3 H, 19-H), 1.45 (s, 3 H, acetonide), 1.81 (s, 3 H, 18-H), 1.85 (m, 1 H, 7-H), 2.07 (m, 1 H, 6-H), 2.15 (dd, J_{gem} = 14.0, J_{14-13} = 7.0 Hz, 1 H, 14-H), 2.24 (dd, J_{gem} = 14.0, J_{14-13} = 6.5 Hz, 1 H, 14-H), 4.17 (d, J_{10-9} = 9.9 Hz, 1 H, 10-H), 4.31 (d, J_{9-10} = 9.9 Hz, 1 H, 9-H), 4.58 (m, 1 H, 13-H), 6.02 (d, J_{2-3} = 8.4 Hz, 1 H, 2-H), 7.40 (m, 2 H, Ph), 7.52 (m, 1 H, Ph), 8.04 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 698 $[M]^+$, 721 $[M + Na]^+$, 771 $[M + TMS]^+$, 1420 $[2 M + Na]^+$. $C_{39}H_{62}O_7Si_2$ (699.1): calcd. C 67.01, H 8.94; found C 66.95, H 8.84.

Conversion of 43 into 44: Tetrabutylammonium fluoride (1.0 M solution in THF, 1.80 mL, 1.8 mmol) was added at room temperature to a stirred solution of **43** (420 mg, 0.601 mmol) in THF (20 mL). After 30 min, the reaction mixture was poured into water (100 mL). The resultant mixture was extracted twice with ethyl acetate (2 × 100 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 3:2)

gave **44** (178 mg, 0.347 mmol, 58%) as a white solid. ^{1}H NMR: δ = 0.23 (m, 1 H, 20-H), 0.75−0.95 (m, 2 H, 5-H + 20-H), 1.09 (s, 3 H, 17-H), 1.22 (s, 3 H, 16-H), 1.39 (d, J_{3-2} = 8.7 Hz, 1 H, 3-H), 1.44 and 1.46 and 1.48 (3 × s, 9 H, 19-H + 2 × acetonide), 1.90 (s, 3 H, 18-H), 2.14 (dd, J_{gem} = 14.1, J_{14-13} = 7.3 Hz, 1 H, 14-H), 2.43 (dd, J_{gem} = 14.1, J_{14-13} = 6.7 Hz, 1 H, 14-H), 4.23 (d, J = 9.8 Hz, 1 H, 9-H/10-H), 4.41 (d, J = 9.8 Hz, 1 H, 9-H/10-H), 4.69 (m, 1 H, 13-H), 6.11 (d, J_{2-3} = 8.7 Hz, 1 H, 2-H), 7.42 (m, 2 H, Ph), 7.52 (m, 1 H, Ph), 8.03 (m, 2 H, Ph) ppm. FAB-MS: *m*/*z* = 513 [M + H]$^+$, 535 [M + Na]$^+$, 1026 [2 M + H]$^+$, 1048 [2 M + Na]$^+$. $C_{30}H_{40}O_7$ (512.6): calcd. C 70.29, H 7.86; found C 70.21, H 7.92.

Coupling of 44 to β-Lactam 28, Affording 45: Sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 0.488 mL, 0.49 mmol) was added at −78 °C to a stirred solution of **44** (100 mg, 0.195 mmol) and β-lactam **28** (149 mg, 0.390 mmol) in THF (5 mL). The reaction mixture was stirred at −78 °C for 45 min. Subsequently, the reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (5 mL). The mixture was allowed to warm to room temperature. Water (20 mL) and ethyl acetate (20 mL) were added. The aqueous layer was separated from the organic layer and extracted with ethyl acetate (20 mL). The combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution, water, and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:5) yielded **45** (79.2 mg, 88.6 μmol, 45%) as a white solid. ^{1}H NMR: δ = 0.30 (m, 1 H, 20-H), 0.50 [m, 6 H, Si(C*H*$_2$CH$_3$)$_3$], 0.87 [t, J = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$], 0.95 (m, 2 H, 5-H + 20-H), 1.12 (s, 3 H, 17-H), 1.20 (s, 3 H, 16-H), 1.39 (d, J_{3-2} = 8.6 Hz, 1 H, 3-H), 1.43 and 1.43 and 1.48 (3 × s, 9 H, 19-H + 2 × acetonide), 1.64 (s, 3 H, 18-H), 2.32 (dd, J_{gem} = 14.2, J_{14-13} = 7.4 Hz, 1 H, 14-H), 2.45 (dd, J_{gem} = 14.2, J_{14-13} = 6.9 Hz, 1 H, 14-H), 4.16 (d, J = 9.8 Hz, 1 H, 9-H/10-H), 4.43 (d, J = 9.8 Hz, 1 H, 9-H/10-H), 4.64 (d, $J_{2'-3'}$ = 1.9 Hz, 1 H, 2′-H), 5.65 (dd, $J_{3'-NH}$ = 8.7, $J_{3'-2'}$ = 1.9 Hz, 1 H, 3′-H), 5.70 (m, 1 H, 13-H), 6.12 (d, J_{2-3} = 8.6 Hz, 1 H, 2-H), 7.26−7.56 (m, 12 H, Ph + NH), 7.83 (m, 2 H, Ph), 7.98 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 4.4, 6.6, 11.5, 19.7, 22.1, 23.7, 24.0, 24.4, 26.6, 26.9, 27.9, 28.9, 35.3, 38.2, 49.0, 55.5, 56.0, 69.6, 69.9, 72.0, 75.5, 76.5, 81.0, 81.9, 108.6, 126.6, 127.0, 127.7, 128.4, 128.4, 128.7, 129.4, 131.1, 131.7, 132.6, 134.3, 136.2, 138.9, 147.3, 166.2, 166.4, 171.6 ppm. FAB-MS: *m*/*z* = 894 [M + H]$^+$, 916 [M + Na]$^+$, 1788 [2 M + H]$^+$, 1810 [2 M + Na]$^+$. $C_{52}H_{67}NO_{10}Si{\cdot}0.5H_2O$ (903.2): calcd. C 69.15, H 7.59, N 1.55; found C 69.25, H 7.55, N 1.42.

Conversion of 45 into 46: Tetrabutylammonium fluoride (1.0 M solution in THF, 0.116 mL, 0.12 mmol) was added at room temperature to a stirred solution of **45** (69.3 mg, 77.5 μmol) in THF (3 mL). After 5 min, the reaction mixture was poured into water (20 mL). The mixture was extracted twice with ethyl acetate (2 × 15 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:1) gave **46** (46.1 mg, 59.1 μmol, 76%) as a white solid. ^{1}H NMR: δ = 0.35 (br. s, 1 H, 20-H), 0.81−1.02 (m, 2 H, 5-H + 20-H), 1.13 (s, 3 H, 17-H), 1.21 (s, 3 H, 16-H), 1.41 (d, J_{3-2} = 8.6 Hz, 1 H, 3-H), 1.44 and 1.46 and 1.49 (3 × s, 9 H, 19-H + 2 × acetonide), 1.77 (s, 3 H, 18-H), 2.40 (dd, J_{gem} = 14.5, J_{14-13} = 7.2 Hz, 1 H, 14-H), 2.48 (dd, J_{gem} = 14.5, J_{14-13} = 6.9 Hz, 1 H, 14-H), 4.23 (d, J = 9.8 Hz, 1 H, 9-H/10-H), 4.43 (d, J = 9.8 Hz, 1 H, 9-H/10-H), 4.72 (d, $J_{2'-3'}$ = 2.2 Hz, 1 H, 2′-H), 5.76−5.82 (m, 2 H, 3′-H + 13-H), 6.14 (d, J_{2-3} = 8.6 Hz, 1 H, 2-H), 7.00 (d, $J_{NH-3'}$ = 9.1 Hz, 1 H, NH), 7.23−7.54 (m, 11 H, Ph), 7.78 (m, 2 H, Ph), 8.03 (m, 2 H, Ph) ppm. FAB-MS: *m*/*z* = 780 [M + H]$^+$, 802 [M + Na]$^+$, 1560 [M + H]$^+$, 1582 [M + Na]$^+$. $C_{46}H_{53}NO_{10}{\cdot}0.5H_2O$ (788.9): calcd. C 70.03, H 6.90, N 1.78; found C 69.91, H 7.03, N 2.22.

Conversion of 47 into 48, 49, and 50: Pyridinium chlorochromate (3.63 g, 16.9 mmol) in dichloromethane (100 mL) was added at room temperature to a stirred solution of **47** (2.78 g, 5.62 mmol) in dichloromethane (30 mL). After 3.5 h, the reaction mixture was diluted with diethyl ether (100 mL) and filtered through Celite®. The filter agent was rinsed with diethyl ether (50 mL). The filtrate was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:5) gave **48** (141 mg, 0.286 mmol, 5%), **49** (1.23 g, 2.42 mmol, 43%), and **50** (57.3 mg, 0.112 mmol, 2%), all as white solids. **48:** ^{1}H NMR: δ = 1.21 (s, 3 H, 19-H), 1.40 (s, 3 H, 17-H), 1.48 (s, 3 H, acetonide), 1.54 (s, 3 H, acetonide), 1.72 (s, 3 H, 16-H), 1.95 (s, 3 H, 18-H), 2.84 (d, J_{gem} = 19.7 Hz, 1 H, 14-H), 3.01 (m, 1 H, 3-H), 3.94 (d, J_{gem} = 19.7 Hz, 1 H, 14-H), 4.35 (d, J_{2-3} = 4.1 Hz, 1 H, 2-H), 4.48 (d, J_{9-10} = 9.6 Hz, 1 H, 9-H), 4.70 (d, J_{10-9} = 9.6 Hz, 1 H, 10-H), 5.76 (s, 1 H, PhCH), 6.55 (m, 1 H, 5-H), 7.35−7.47 (m, 5 H, Ph), 9.49 (s, 1 H, CHO) ppm. FAB-MS: *m*/*z* = 492 [M]$^+$, 515 [M + Na]$^+$, 986 [2 M + H]$^+$, 1008 [2 M + Na]$^+$. $C_{30}H_{36}O_6$ (492.6): calcd. C 73.15, H 7.37; found C 72.99, H 7.39. **49:** ^{1}H NMR: δ = 1.30 and 1.35 (2 × s, 3 H, 17-H + 19-H), 1.45 (s, 3 H, acetonide), 1.52 (s, 3 H, acetonide), 1.68 (s, 3 H, 16-H), 1.93 (s, 3 H, 18-H), 2.05 (d, J_{3-2} = 6.7 Hz, 1 H, 3-H), 2.63 (d, J_{gem} = 19.7 Hz, 1 H, 14-H), 2.72 (d, J_{gem} = 19.7 Hz, 1 H, 14-H), 3.05 (d, J_{5-6} = 3.6 Hz, 1 H, 5-H), 4.33 (d, J_{9-10} = 9.3 Hz, 1 H, 9-H), 4.39 (d, J_{2-3} = 6.7 Hz, 1 H, 2-H), 4.70 (d, 1 H, J_{10-9} = 9.3 Hz, 10-H), 5.96 (s, 1 H, PhCH), 7.35 (m, 5 H, Ph), 9.57 (s, 1 H, CHO) ppm. ^{13}C NMR: δ = 14.4, 18.6, 19.7, 20.2, 25.6, 26.7, 27.1, 33.5, 36.2, 41.6, 45.7, 47.5, 57.7, 63.6, 75.7, 77.2, 81.3, 84.7, 102.4, 108.3, 126.0, 128.5, 129.2, 137.1, 141.4, 151.4, 193.5, 198.6 ppm. FAB-MS: *m*/*z* = 509 [M + H]$^+$, 531 [M + Na]$^+$, 1039 [2 M + Na]$^+$. $C_{30}H_{36}O_7{\cdot}0.25H_2O$ (513.1): calcd. C 70.22, H 7.17; found C 69.95, H 6.85. **50:** ^{1}H NMR: δ = 1.19 (s, 3 H, 19-H), 1.39 (s, 3 H, 17-H), 1.45 (s, 3 H, acetonide), 1.51 (s, 3 H, acetonide), 1.68 (s, 3 H, 16-H), 1.96 (s, 3 H, 18-H), 2.32 (d, J_{3-2} = 4.6 Hz, 1 H, 3-H), 2.90 (d, J_{gem} = 19.5 Hz, 1 H, 14-H), 2.97 (d, J_{gem} = 19.5 Hz, 1 H, 14-H), 3.14 (br. s, 1 H, 5-H), 3.22 (br. d, J_{gem} = 12.6 Hz, 1 H, 20-H), 4.07 (br. d, J_{gem} = 12.6 Hz, 1 H, 20-H), 4.30 (d, J_{9-10} = 9.3 Hz, 1 H, 9-H), 4.42 (d, J_{2-3} = 4.6 Hz, 1 H, 2-H), 4.68 (d, J_{10-9} = 9.3 Hz, 1 H, 10-H), 5.84 (s, 1 H, PhCH), 7.44 (m, 5 H, Ph) ppm. FAB-MS: *m*/*z* = 511 [M + H]$^+$, 533 [M + Na]$^+$, 1021 [2 M + H]$^+$, 1043 [2 M + Na]$^+$. $C_{30}H_{38}O_7{\cdot}0.5H_2O$ (519.6): calcd. C 69.34, H 7.56; found C 69.27, H 7.68.

Conversion of 47 into 51: A solution of dimethyl sulfoxide (0.241 mL, 3.40 mmol) in dichloromethane (0.5 mL) was added at −50 °C to a stirred solution of oxalyl chloride (0.141 mL, 1.62 mmol) in dichloromethane (2 mL). After 10 min, the reaction mixture was allowed to warm to −10 °C, and **47** (100 mg, 0.202 mmol) in dichloromethane (0.8 mL) was added slowly. The resultant mixture was stirred at −10 °C for 20 min, treated with triethylamine (0.564 mL, 4.04 mmol), stirred at −10 °C for 20 min, allowed to warm to room temperature, and stirred for another 20 min. The reaction mixture was diluted with dichloromethane (10 mL), washed with water and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:6) gave **51** (21.8 mg, 42.5 μmol, 21%) as a white solid. ^{1}H NMR: δ = 1.20 (s, 3 H, 19-H), 1.40 (s, 3 H, 17-H), 1.48 (s, 3 H, acetonide), 1.54 (s, 3 H, acetonide), 1.72 (s, 3 H, 16-H), 1.97 (s, 3 H, 18-H), 2.90 (d, J_{gem} = 19.6 Hz, 1 H, 14-H), 2.99 (m, 1 H, 3-H), 3.55 (d, J_{gem} = 19.6 Hz, 1 H, 14-H),

4.04 (d, J_{gem} = 11.0 Hz, 1 H, 20-H), 4.43 (d, J_{2-3} = 4.0 Hz, 1 H, 2-H), 4.46 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.72 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 4.92 (d, J_{gem} = 11.0 Hz, 1 H, 20-H), 5.75 (s, 1 H, PhCH), 5.92 (m, 1 H, 5-H), 7.39−7.50 (m, 5 H, Ph) ppm. ^{13}C NMR: δ = 14.1, 18.1, 20.3, 23.0, 26.6, 26.8, 27.2, 34.0, 38.4, 40.6, 43.0, 45.8, 50.7, 75.7, 80.8, 82.1, 85.1, 103.4, 108.2, 127.0, 128.6, 129.7, 132.9, 135.1, 137.0, 141.5, 152.8, 199.8 ppm. FAB-MS: *m/z* = 513 $[M + H]^+$. $C_{30}H_{37}ClO_5$ (513.1): calcd. C 70.23, H 7.27; found C 70.24, H 7.32.

Conversion of 49 into 50: Sodium borohydride (36.6 mg, 0.967 mmol) was added at 0 °C in small portions to a stirred solution of **49** (1.23 g, 2.42 mmol) in methanol (100 mL). The reaction mixture was stirred at 0 °C for 1 h, additional sodium borohydride (36.6 mg, 0.967 mmol) being added after 30 min. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (50 mL). The resultant mixture was concentrated to 75 mL under reduced pressure and then extracted three times with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:2) afforded **50** (950 mg, 1.86 mmol, 77%) as a white solid.

Conversion of 50 into 52: Sodium hydride (179 mg, 7.44 mmol) and methyl iodide (1.16 mL, 18.6 mmol) were added successively at 0 °C to a stirred solution of **50** (950 mg, 1.86 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (30 mL). The resultant mixture was extracted twice with ethyl acetate (2 × 40 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:5) gave **52** (677 mg, 1.29 mmol, 69%) as a white solid. ^{1}H NMR: δ = 1.17−1.27 (m, 2 H, 6-H + 7-H), 1.19 (s, 3 H, 19-H), 1.36 (s, 3 H, 17-H), 1.45 (s, 3 H, acetonide), 1.50 (s, 3 H, acetonide), 1.66 (s, 3 H, 16-H), 1.76 (m, 1 H, 7-H), 1.93 (m, 1 H, 6-H), 1.94 (s, 3 H, 18-H), 2.12 (d, J_{3-2} = 5.3 Hz, 1 H, 3-H), 2.83 (d, J_{gem} = 19.5 Hz, 1 H, 14-H), 3.00 (d, J_{gem} = 19.5 Hz, 1 H, 14-H), 3.10 (s, 3 H, OCH_3), 3.36 (m, 1 H, 5-H), 3.59 (d, J_{gem} = 11.7 Hz, 1 H, 20-H), 3.75 (d, J_{gem} = 11.7 Hz, 1 H, 20-H), 4.29 (d, J_{9-10} = 9.3 Hz, 1 H, 9-H), 4.31 (d, J_{2-3} = 5.3 Hz, 1 H, 2-H), 4.68 (d, J_{10-9} = 9.3 Hz, 1 H, 10-H), 5.80 (s, 1 H, PhCH), 7.41 (m, 3 H, Ph), 7.48 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 524 $[M]^+$, 547 $[M + Na]^+$, 1072 $[2 M + Na]^+$. $C_{31}H_{40}O_7 \cdot 1.25H_2O$ (547.2): calcd. C 68.05, H 7.83; found C 67.87, H 7.36.

Conversion of 52 into 53: Sodium borohydride (111 mg, 2.94 mmol) was added at 0 °C to a stirred solution of **52** (386 mg, 0.736 mmol) and cerium(III) chloride heptahydrate (1.10 g, 2.94 mmol) in methanol (50 mL). The reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by slow addition of a 10% aqueous citric acid solution (25 mL). The resultant mixture was concentrated to 35 mL under reduced pressure, diluted with water (15 mL), and then extracted three times with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:2) yielded **53** (283 mg, 0.537 mmol, 73%) as a white solid. ^{1}H NMR: δ = 1.16 and 1.18 (2 × s, 6 H, 17-H + 19-H), 1.43 (s, 3 H, acetonide), 1.47 (s, 3 H, acetonide), 1.57 (s, 3 H, 16-H), 1.98 (s, 3 H, 18-H), 2.15 (dd, J_{gem} = 16.0, J_{14-13} = 4.2 Hz, 1 H, 14-H), 2.37 (d, J_{3-2} = 4.6 Hz, 1 H, 3-H), 2.74 (dd, J_{gem} = 16.0, J_{14-13} = 10.1 Hz, 1 H, 14-H), 3.13 (s, 3 H, OCH_3), 3.51 (m, 1 H, 5-H), 3.73 (d, J_{gem} = 12.1 Hz, 1 H, 20-H), 3.81 (d, J_{gem} = 12.1 Hz, 1 H, 20-H), 4.12 (d, J_{9-10} = 9.3 Hz, 1 H, 9-H), 4.19 (d, J_{2-3} = 4.6 Hz, 1 H, 2-H), 4.61 (m, 1 H, 13-H), 4.64 (d, J_{10-9} = 9.3 Hz, 1 H, 10-H), 5.72 (s, 1 H, PhCH), 7.39 (m, 3 H, Ph), 7.50 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 549 $[M + Na]^+$, 1076 $[2 M + Na]^+$. $C_{31}H_{42}O_7 \cdot 0.25H_2O$ (531.2): calcd. C 70.10, H 8.06; found C 69.77, H 8.03.

Conversion of 53 into 54: Chlorotriethylsilane (0.161 mL, 0.959 mmol) was added at room temperature to a stirred solution of imidazole (170 mg, 2.49 mmol) in DMF (4 mL). After 20 min, **53** (101 mg, 0.192 mmol) in DMF (3 mL) was added. After 2 h, the reaction mixture was diluted with water (25 mL) and extracted twice with ethyl acetate (2 × 30 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes/dichloromethane, 1:2:2) gave **54** (119 mg, 0.186 mmol, 97%) as a white solid. ^{1}H NMR: δ = 0.63 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.99 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.16 and 1.21 (2 × s, 6 H, 17-H + 19-H), 1.42 (s, 3 H, acetonide), 1.46 (s, 3 H, acetonide), 1.59 (s, 3 H, 16-H), 1.89 (s, 3 H, 18-H), 2.11 (dd, J_{gem} = 15.2, J_{14-13} = 5.1 Hz, 1 H, 14-H), 2.29 (d, J_{3-2} = 5.4 Hz, 1 H, 3-H), 2.42 (dd, J_{gem} = 15.2, J_{14-13} = 9.2 Hz, 1 H, 14-H), 3.14 (s, 3 H, OCH_3), 3.41 (m, 1 H, 5-H), 3.63 (d, J_{gem} = 12.0 Hz, 1 H, 20-H), 3.88 (d, J_{gem} = 12.0 Hz, 1 H, 20-H), 4.13 (d, 1 H, J_{9-10} = 9.5 Hz, 9-H), 4.13 (d, J_{2-3} = 5.4 Hz, 1 H, 2-H), 4.65 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 4.76 (m, 1 H, 13-H), 5.73 (s, 1 H, PhCH), 7.40 (m, 3 H, Ph), 7.51 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 641 $[M + H]^+$, 663 $[M + Na]^+$. $C_{37}H_{56}O_7Si$ (640.9): calcd. C 69.34, H 8.81; found C 69.12, H 8.75.

Conversion of 54 into 55: *tert*-Butyl hydroperoxide (5.0−6.0 M solution in decane, 0.161 mL, min. 0.81 mmol) was added at room temperature to a solution of **54** (51.7 mg, 80.7 μmol) and palladium(II) acetate (3.6 mg, 16 μmol) in toluene (1 mL). The reaction mixture was stirred at 70 °C for 20 h, additional *tert*-butyl hydroperoxide (5.0−6.0 M solution in decane, 0.161 mL, min. 0.81 mmol) being added after 12 h. The reaction mixture was cooled down to room temperature, and water (5 mL) and ethyl acetate (5 mL) were added. The aqueous layer was separated from the organic layer and extracted with ethyl acetate (5 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:8) afforded **55** (18.6 mg, 28.3 μmol, 35%) as a white solid. ^{1}H NMR: δ = 0.70 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 1.05 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.15 and 1.20 (2 × s, 6 H, 17-H + 19-H), 1.44 (s, 3 H, acetonide), 1.50 (s, 3 H, acetonide), 1.63 (s, 3 H, 16-H), 1.90 (s, 3 H, 18-H), 2.34 (dd, J_{gem} = 15.2, J_{14-13} = 9.3 Hz, 1 H, 14-H), 2.54 (m, 2 H, 3-H + 14-H), 2.96 (s, 3 H, OCH_3), 3.36 (m, 1 H, 5-H), 3.41 (d, J_{gem} = 11.2 Hz, 1 H, 20-H), 3.48 (d, J_{gem} = 11.2 Hz, 1 H, 20-H), 4.25 (d, 1 H, J_{9-10} = 9.4 Hz, 9-H), 4.66 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 4.79 (m, 1 H, 13-H), 5.70 (d, J_{2-3} = 6.1 Hz, 1 H, 2-H), 7.47 (m, 2 H, Ph), 7.58 (m, 1 H, Ph), 8.10 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 657 $[M + H]^+$, 679 $[M + Na]^+$.

Conversion of 55 into 56: Tetrabutylammonium fluoride (1.0 M solution in THF, 82.2 μL, 82 μmol) was added at room temperature to a stirred solution of **55** (36.0 mg, 54.8 μmol) in THF (3 mL). After 15 min, the reaction mixture was poured into water (20 mL). The mixture was extracted three times with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:1) afforded **56** (25.3 mg, 46.6 μmol, 85%) as a white solid. ^{1}H NMR: δ = 1.10 (s, 3 H, 19-H), 1.19 (s, 3 H, 17-H), 1.45 (s, 3 H, acetonide), 1.51 (s, 3 H, acetonide), 1.60 (s, 3 H, 16-H), 2.00 (s, 3 H, 18-H), 2.50 (dd,

J_{gem} = 15.9, J_{14-13} = 3.8 Hz, 1 H, 14-H), 2.65 (dd, J_{gem} = 15.9, J_{14-13} = 9.7 Hz, 1 H, 14-H), 2.75 (d, J_{3-2} = 4.8 Hz, 1 H, 3-H), 3.00 (s, 3 H, OCH_3), 3.42 (d, J_{gem} = 11.4 Hz, 1 H, 20-H), 3.51 (m, 1 H, 5-H), 3.64 (d, J_{gem} = 11.4 Hz, 1 H, 20-H), 4.25 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.61 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 4.61 (m, 1 H, 13-H), 5.78 (d, J_{2-3} = 4.8 Hz, 1 H, 2-H), 7.49 (m, 2 H, Ph), 7.61 (m, 1 H, Ph), 8.10 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 565 $[M + Na]^+$. $C_{31}H_{42}O_8$ (542.7): calcd. C 68.61, H 7.80; found C 68.50, H 7.79.

Coupling of 56 to β-Lactam 28, Giving 57: Sodium bis(trimethylsilyl)-amide (1.0 M solution in THF, 78.3 μL, 78 μmol) was added at −78 °C to a stirred solution of **56** (17.0 mg, 31.3 μmol) and β-lactam **28** (19.1 mg, 50.1 μmol) in THF (2 mL). The reaction mixture was stirred at −78 °C for 1 h, additional sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 78.3 μL, 78 μmol) and β-lactam **28** (19.1 mg, 50.1 μmol) being added after 30 min. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (2 mL). The mixture was allowed to warm to room temperature. Brine (15 mL) and ethyl acetate (15 mL) were added next. The aqueous layer was separated from the organic layer and extracted with ethyl acetate (15 mL). The combined organic fractions were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:5) yielded **57** (14.1 mg, 15.3 μmol, 49%) together with recovered **56** (3.8 mg, 7.0 μmol). ^{1}H NMR: δ = 0.44 [m, 6 H, $Si(CH_2CH_3)_3$], 0.80 [t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$], 1.15 (s, 3 H, 19-H), 1.22 (s, 3 H, 17-H), 1.44 (s, 3 H, acetonide), 1.52 (s, 3 H, acetonide), 1.62 (s, 3 H, 16-H), 1.85 (s, 3 H, 18-H), 2.39 (dd, J_{gem} = 15.6, J_{14-13} = 10.1 Hz, 1 H, 14-H), 2.59 (dd, J_{gem} = 15.6, J_{14-13} = 3.7 Hz, 1 H, 14-H), 2.74 (s, 3 H, OCH_3), 2.91 (d, J_{3-2} = 4.8 Hz, 1 H, 3-H), 3.33 (m, 1 H, 5-H), 3.46 (d, J_{gem} = 10.8 Hz, 1 H, 20-H), 4.09 (d, J_{gem} = 10.8 Hz, 1 H, 20-H), 4.38 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.67 (d, $J_{2'-3'}$ = 1.6 Hz, 1 H, 2′-H), 4.69 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 5.79 (d, J_{2-3} = 4.8 Hz, 1 H, 2-H), 5.91 (br. d, $J_{3'-NH}$ = 9.3 Hz, 1 H, 3′-H), 6.06 (m, 1 H, 13-H), 7.22−7.55 (m, 12 H, Ph + NH), 7.89 (m, 2 H, Ph), 8.30 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 946 $[M + Na]^+$. $C_{53}H_{69}NO_{11}Si$ (924.2): calcd. C 68.88, H 7.52; found C 68.97, H 7.35.

Conversion of 57 into 58: Tetrabutylammonium fluoride (1.0 M solution in THF, 20.6 μL, 21 μmol) was added at room temperature to a solution of **57** (13.6 mg, 14.7 μmol) in THF (2 mL). After 5 min, the reaction mixture was poured into water (20 mL). The mixture was extracted three times with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:3) afforded **58** (9.7 mg, 12 μmol, 81%) as a white solid. ^{1}H NMR: δ = 1.12 and 1.15 (2 × s, 6 H, 17-H + 19-H), 1.41 (s, 3 H, acetonide), 1.49 (s, 3 H, acetonide), 1.59 (s, 3 H, 16-H), 1.60 (s, 3 H, 18-H), 2.56 (dd, J_{gem} = 15.8, J_{14-13} = 9.8 Hz, 1 H, 14-H), 2.72 (dd, J_{gem} = 15.8, J_{14-13} = 2.7 Hz, 1 H, 14-H), 2.87 (d, J_{3-2} = 4.6 Hz, 1 H, 3-H), 3.00 (s, 3 H, OCH_3), 3.30 (m, 1 H, 5-H), 3.34 (d, J_{gem} = 10.7 Hz, 1 H, 20-H), 3.64 (d, J_{gem} = 10.7 Hz, 1 H, 20-H), 4.29 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.57 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 4.59 (br. s, 1 H, 2′-OH), 4.77 (br. s, 1 H, 2′-H), 5.77 (m, 2 H, 2-H + 13-H), 5.86 (dd, $J_{3'-NH}$ = 9.1, $J_{3'-2'}$ = 2.2 Hz, 1 H, 3′-H), 7.27−7.58 (m, 12 H, Ph + NH), 7.87 (m, 2 H, Ph), 8.09 (m, 2 H, Ph) ppm. FAB-MS: *m/z* = 810 $[M + H]^+$, 832 $[M + Na]^+$. HRFAB-MS for $C_{47}H_{55}NNaO_{11}$ $[M + Na]^+$: calcd. 832.3673; found 832.3679 ± 0.0166.

Conversion of 59 into 60: Phenyltrimethylammonium tribromide (418 mg, 1.11 mmol) in THF (5 mL) was slowly added at −15 °C to a stirred solution of **59** (510 mg, 1.06 mmol) in THF (10 mL). The reaction mixture was stirred for 3 h. During this period, the reaction temperature was slowly raised from −15 °C to 10 °C. The reaction mixture was poured into a mixture of a saturated aqueous solution of $NaHCO_3$ (20 mL) and a 0.2 M $Na_2S_2O_3$ solution (20 mL). The resultant mixture was extracted twice with ethyl acetate (2 × 30 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 2:5) gave **60** (454 mg, 0.809 mmol, 77%) as a white solid. ^{1}H NMR: δ = 1.11 (s, 3 H, 19-H), 1.26 (s, 3 H, 17-H), 1.45 (s, 3 H, acetonide), 1.48 (s, 3 H, acetonide), 1.61 (s, 3 H, 16-H), 1.83 (dd, J_{gem} = 15.9, J_{14-13} = 6.2 Hz, 1 H, 14-H), 1.98 (m, 2 H, 2 × 7-H), 2.21 (s, 3 H, 18-H), 2.24 (m, 1 H, 6-H), 2.50 (m, 1 H, 6-H), 2.50 (dd, J_{gem} = 15.9, J_{14-13} = 9.6 Hz, 1 H, 14-H), 4.06 (d, J_{3-2} = 5.7 Hz, 1 H, 3-H), 4.12 (d, J_{2-3} = 5.7 Hz, 1 H, 2-H), 4.13 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.36 (m, 1 H, 5-H), 4.79 (m, 1 H, 13-H), 4.92 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 5.85 (s, 1 H, PhCH), 7.35 (m, 3 H, Ph), 7.48 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 16.8, 18.8, 21.0, 25.7, 26.8, 27.2, 28.4, 31.3, 41.0, 43.6, 45.0, 49.1, 54.6, 69.1, 75.0, 78.1, 81.0, 86.0, 102.4, 107.4, 126.6, 128.2, 128.9, 133.4, 138.3, 146.2, 199.0 ppm. EI-MS: *m/z* = 481 $[M - Br]^+$, 560/562 $[M]^+$. $C_{29}H_{37}BrO_6 \cdot 0.5H_2O$ (570.5): calcd. C 61.05, H 6.71; found C 61.28, H 6.88.

Conversion of 60 into 61 and 62: Sodium borohydride (15.5 mg, 0.463 mmol) was added at 0 °C to a stirred solution of **60** (200 mg, 0.356 mmol) in THF/methanol (12 mL, 1:5 v/v). The reaction mixture was stirred at 0 °C for 2 h, additional sodium borohydride (15.5 mg, 0.463 mmol) being added after 1 h. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (10 mL). The resultant mixture was extracted three times with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:2) afforded **61** (62.7 mg, 0.130 mmol, 36%) and **62** (63.0 mg, 0.112 mmol, 31%), both as white solids. **61:** ^{1}H NMR: δ = 1.18 (m, 1 H, 7-H), 1.24 (s, 3 H, 17-H), 1.33 (s, 3 H, 19-H), 1.41 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.61 (s, 3 H, 16-H), 1.84 (dd, J_{gem} = 13.4, J_{7-6} = 6.5 Hz, 1 H, 7-H), 1.96 (s, 3 H, 18-H), 1.96−2.05 (m, 2 H, 6-H + 14-H), 2.12 (m, 1 H, 6-H), 2.50 (m, 2 H, 3-H + 14-H), 3.11 (m, 1 H, 5-H), 3.44 (dd, J_{4-3} = 1.4, J_{4-5} = 4.2 Hz, 1 H, 4-H), 4.10 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.19 (d, J_{2-3} = 4.3 Hz, 1 H, 2-H), 4.59 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 4.83 (m, 1 H, 13-H), 5.88 (s, 1 H, PhCH), 7.36 (m, 3 H, Ph), 7.53 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 16.8, 19.4, 20.5, 20.6, 26.9, 27.0, 29.1, 37.6, 40.4, 41.3, 41.9, 50.1, 54.1, 68.8, 75.2, 78.7, 82.4, 84.8, 102.2, 106.5, 126.8, 128.1, 128.9, 135.1, 138.5, 145.3, 208.4 ppm. FAB-MS: *m/z* = 483 $[M + H]^+$, 505 $[M + Na]^+$, 988 $[2 M + Na]^+$. $C_{29}H_{38}O_6 \cdot 0.75H_2O$ (496.1): calcd. C 70.21, H 8.02; found C 70.16, H 8.12. **62:** ^{1}H NMR: δ = 1.18 (s, 3 H, 19-H), 1.25 (s, 3 H, 17-H), 1.44 (s, 3 H, acetonide), 1.47 (s, 3 H, acetonide), 1.60 (s, 3 H, 16-H), 2.19 (s, 3 H, 18-H), 2.35 (dd, J_{gem} = 15.7, J_{14-13} = 5.0 Hz, 1 H, 14-H), 2.49 (dd, J_{3-2} = 4.6, J_{3-4} = 10.5 Hz, 1 H, 3-H), 2.74 (dd, J_{gem} = 15.7, J_{14-13} = 9.8 Hz, 1 H, 14-H), 3.87 (m, 1 H, 4-H), 4.08 (br. s, 1 H, 4-OH), 4.12 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.26 (d, J_{2-3} = 4.6 Hz, 1 H, 2-H), 4.75 (m, 2 H, 5-H + 13-H), 4.80 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 5.78 (s, 1 H, PhCH), 7.37−7.47 (m, 5 H, Ph) ppm. FAB-MS: *m/z* = 563/565 $[M + H]^+$, 585/587 $[M + Na]^+$. $C_{29}H_{39}BrO_6 \cdot 0.5H_2O$ (572.5): calcd. C 60.84, H 7.04; found C 60.81, H 6.96.

Coupling of 61 to β-Lactam 28, Furnishing 63: Sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 0.606 mL, 0.61 mmol) was added at −78 °C to a stirred solution of **61** (117 mg,

0.242 mmol) and β-lactam **28** (148 mg, 0.388 mmol) in THF (4 mL). The reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (4 mL) and the reaction mixture was allowed to warm to room temperature. Water (10 mL) and ethyl acetate (20 mL) were added, and the two resultant layers were separated. The aqueous fraction was extracted with ethyl acetate (20 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:2) afforded **63** (155 mg, 0.179 mmol, 74%) as a white solid. ^{1}H NMR: δ = 0.48 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.84 [t, J = 7.9 Hz, 9 H, Si(CH$_2$CH_3)$_3$], 1.27 (s, 3 H, 17-H), 1.34 (s, 3 H, 19-H), 1.40 (s, 3 H, acetonide), 1.44 (s, 3 H, acetonide), 1.61 (s, 3 H, 16-H), 1.67 (s, 3 H, 18-H), 1.86 (dd, J_{gem} = 13.4, J_{7-6} = 6.5 Hz, 1 H, 7-H), 1.95−2.23 (m, 3 H, 2 × 6-H + 14-H), 2.46 (m, 1 H, 3-H), 2.51 (dd, J_{gem} = 15.9, J_{14-13} = 9.7 Hz, 1 H, 14-H), 3.15 (m, 1 H, 5-H), 3.62 (m, 1 H, 4-H), 4.12 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.19 (d, J_{2-3} = 4.2 Hz, 1 H, 2-H), 4.53 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 4.61 (d, $J_{2'-3'}$ = 2.0 Hz, 1 H, 2′-H), 5.64 (dd, $J_{3'-NH}$ = 8.9, $J_{3'-2'}$ = 2.0 Hz, 1 H, 3′-H), 5.81 (s, 1 H, PhCH), 5.98 (m, 1 H, 13-H), 7.17−7.55 (m, 14 H, Ph + NH), 7.78 (m, 2 H, Ph) ppm. FAB-MS: m/z = 864 [M + H]$^+$, 886 [M + Na]$^+$, 1750 [2 M + Na]$^+$. $C_{51}H_{65}NO_9Si{\cdot}0.5H_2O$ (873.2): calcd. C 70.15, H 7.62, N 1.60; found C 70.38, H 7.55, N 1.76.

Conversion of 63 into 64: Tetrabutylammonium fluoride (1.0 M solution in THF, 62.3 μL, 62 μmol) was added at room temperature to a stirred solution of **63** (35.9 mg, 41.5 μmol) in THF (2 mL). After 5 min, the reaction mixture was poured into water (10 mL). The mixture was extracted three times with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes, 1:1) yielded **64** (29.8 mg, 39.7 μmol, 96%) as a white solid. ^{1}H NMR: δ = 1.27 (s, 3 H, 17-H), 1.34 (s, 3 H, 19-H), 1.41 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.62 (s, 3 H, 16-H), 1.79 (s, 3 H, 18-H), 1.86 (dd, J_{gem} = 12.8, J_{7-6} = 6.5 Hz, 1 H, 7-H), 1.95−2.21 (m, 2 H, 2 × 6-H), 2.22 (dd, J_{gem} = 16.1, J_{14-13} = 4.8 Hz, 1 H, 14-H), 2.47 (m, 1 H, 3-H), 2.52 (dd, J_{gem} = 16.1, J_{14-13} = 9.6 Hz, 1 H, 14-H), 3.15 (m, 1 H, 5-H), 3.44 (d, $J_{OH-2'}$ = 4.3 Hz, 1 H, 2′-OH), 3.69 (br. d, J_{4-5} = 4.1 Hz, 1 H, 4-H), 4.13 (d, J_{9-10} = 9.5 Hz, 1 H, 9-H), 4.21 (d, J_{2-3} = 4.2 Hz, 1 H, 2-H), 4.56 (d, J_{10-9} = 9.5 Hz, 1 H, 10-H), 4.68 (m, 1 H, 2′-H), 5.73 (dd, $J_{3'-NH}$ = 9.0, $J_{3'-2'}$ = 2.5 Hz, 1 H, 3′-H), 5.81 (s, 1 H, PhCH), 6.03 (m, 1 H, 13-H), 6.85 (d, $J_{NH-3'}$ = 9.0 Hz, 1 H, NH), 7.17−7.52 (m, 13 H, Ph), 7.71 (m, 2 H, Ph) ppm. FAB-MS: m/z = 750 [M + H]$^+$, 772 [M + Na]$^+$, 1500 [2 M + H]$^+$, 1522 [2 M + Na]$^+$. $C_{45}H_{51}NO_9$ (749.9): calcd. C 72.08, H 6.85, N 1.87; found C 72.38, H 6.99, N 1.82.

Conversion of 64 into 65: *tert*-Butyl hydroperoxide (5.0−6.0 M solution in decane, 10.7 μL, min. 0.53 mmol) was added at room temperature to a solution of **64** (40.0 mg, 53.3 μmol) and palladium(II) acetate (3.0 mg, 13 μmol) in toluene (1 mL). The reaction mixture was stirred at 70 °C for 40 h and allowed to cool to room temperature, and water (5 mL) and ethyl acetate (5 mL) were added. The aqueous layer was separated from the organic layer and extracted with ethyl acetate (5 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (EtOAc/heptanes/dichloromethane, 1:2:2) afforded **65** (7.1 mg, 9.27 μmol, 17%) as a white solid. ^{1}H NMR: δ = 1.23 (s, 3 H, 17-H), 1.36 (s, 3 H, 19-H), 1.44 (s, 3 H, acetonide), 1.50 (s, 3 H, acetonide), 1.68 (s, 3 H, 16-H), 2.00 (s, 3 H, 18-H), 2.16 (dd, J_{gem} = 15.3, J_{14-13} = 5.4 Hz, 1 H, 14-H), 2.56 (dd, J_{gem} = 15.3, J_{14-13} = 9.6 Hz, 1 H, 14-H), 2.83 (dd, J_{3-2} = 5.0, J_{3-4} = 2.5 Hz, 1 H, 3-H), 3.97 (m, 1 H, 5-H), 4.27 (br. s, 1 H, 4-H), 4.29 (d, J_{9-10} = 9.4 Hz, 1 H, 9-H), 4.66 (d, $J_{2'-3'}$ = 3.7 Hz, 1 H, 2′-H), 4.83 (d, J_{10-9} = 9.4 Hz, 1 H, 10-H), 5.70 (d, J_{2-3} = 5.0 Hz, 1 H, 2-H), 5.75 (dd, $J_{3'-NH}$ = 9.6, $J_{3'-2'}$ = 3.7 Hz, 1 H, 3′-H), 5.95 (m, 1 H, 13-H), 7.07 (d, $J_{NH-3'}$ = 9.6 Hz, 1 H, NH), 7.25−7.60 (m, 11 H, Ph), 7.80 (m, 2 H, Ph), 7.90 (m, 2 H, Ph) ppm. FAB-MS: m/z = 784 [M + H]$^+$, 806 [M + Na]$^+$. $C_{45}H_{53}NO_{11}{\cdot}4H_2O$ (856.0): calcd. C 63.14, H 7.18, N 1.63; found C 62.76, H 6.77, N 1.20.

Acknowledgments

The authors gratefully acknowledge financial support from the European Commission (FAIR CT96-1781) and Pharmachemie BV, Haarlem, The Netherlands.

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Received August 5, 2002
[O02455]