Synthesis and Conformational Analysis of 2,9-Disubstituted 1-Oxaquinolizidines

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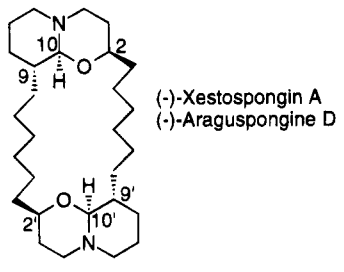
The synthesis of (2*S*,9*R*,10*S*)-9-(5-((*tert*-butyldiphenylsilyl)oxy)pentyl)-2-(hydroxymethyl)-1-oxaquinolizidine (**29a**) from (*S*)-malic acid, 1,5-pentanediol, and trifluoroacetamide is reported. Conformational analysis using molecular mechanics calculations and NMR spectroscopy of **29** together with X-ray crystallographic analysis of (2*S*,10*S*)-2-(hydroxymethyl)-1-oxaquinolizidine (**30**) are used to determine the structure and conformational preferences of these 1-oxaquinolizidine derivatives.

Introduction

The vasodilative alkaloids Xestospongins A–D/Araguspongines A–H and J have been isolated from the marine sponges *Xestospongia exigua* and *Xestospongia* sp.[1,2] Some of these alkaloids have a stronger vasodilative effect than papaverin.[3] The mechanism for this effect is not known, but one may speculate that the heteroatoms play an important role through complexation of an ionic species in a manner similar to that of crown and azacrown ethers.

These compounds have very similar structures; each has the same basic pentacyclic ring system, with differences occurring in the stereochemistry of the two 1-oxaquinolizidine skeletons. In the preferred conformation of (−)-Xestospongin A[4] (**1**), the lone pair on the nitrogen and the hydrogen bound to C10 are situated *trans* to each other, giving the oxaquinolizidine a *trans*-decalin-like structure. The alkyl chains attached to C2 and C9 adopt



(-)-Xestospongin A
(-)-Araguspongine D

1

equatorial positions and are therefore also *trans* to each other, giving the thermodynamically most stable conformation, in good agreement with recently reported conformational studies.[5] A *cis*-decalin-like structure would give extra stabilization through an extra anomeric effect; however, this appears to be outweighed by steric interactions present in such structures. The stereogenic centers in both of the oxaquinolizidines in **1** have the same configuration, giving the compound a C_2 symmetry axis.

A number of preliminary studies related to xestospongin synthesis have been presented,[6–10] and the total synthesis of (+)-Xestospongin A has recently been reported.[11]

The aim of our studies is to develop a synthetic strategy for (−)-Xestospongin A that makes use of simple building blocks and is well-suited for the preparation of xestospongin analogues, differing either through ring size or by the introduction of heteroatoms onto the large ring connecting the oxaquinolizidines.

Retrosynthetic analysis of **1** shows that it can be fragmented into two units, a four-carbon fragment with functionalizations at positions 1, 2, and 4 that can be derived from (*S*)-malic acid and a ten-carbon fragment that can be further split into two five-carbon fragments derived from 1,5-pentanediol, and a nitrogen atom, which can be introduced from several different sources. We have chosen trifluoroacetamide. A synthesis of (−)-Xestospongin A can therefore be designed using these simple starting materials. Rings A and A′ are derived from malic acid, while rings B, B′, and C, the alkyl chains connecting the oxaquinolizidines, are derived from 1,5-pentanediol (Figure 1). The absolute configuration of the molecule is dictated by the choice of (*S*)-malic acid as chiral starting material.

Xestospongin A has eight stereogenic centers and five rings. The C_2 symmetry of **1** reduces the stereochemical complexity of the molecule and allows the synthetic work to be concentrated on synthesis of half of the molecule, followed by dimerization. We chose to first make the 1-oxaquinolizidine skeleton and to subsequently form the 20-membered ring. This route gives us good control over the stereochemistry of **1**.

The oxaquinolizidine is at equilibrium with its open

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(4) Xestospongin A is identical to Araguspongine D. In this article, we have chosen to use the name Xestospongin A.
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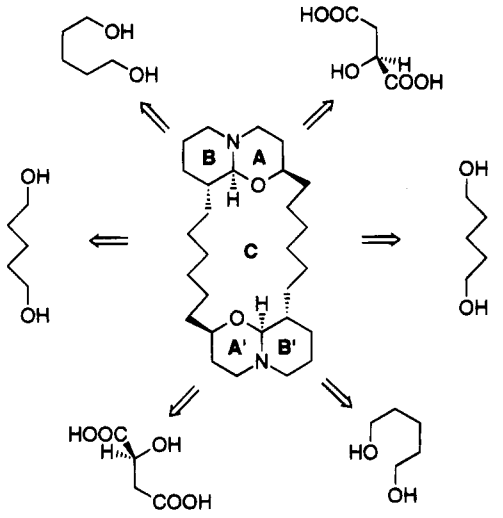


Figure 1. Retrosynthetic analysis of (−)-Xestospongin A.

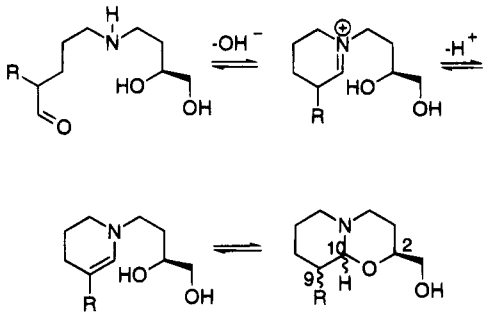


Figure 2. Oxaquinolizidine formation and equilibration.

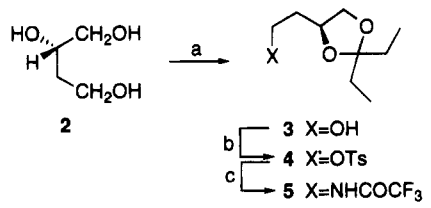
forms,[6] and the ring closure gives isomer distribution in accordance with the thermodynamic stability of individual isomers (Figure 2). The configuration at C2 directs the configuration of C9, C10, and the nitrogen, through a preference for a *trans*-decalin-like structure with equatorial substituents. This allows for the use of prochiral and racemic starting materials since the configurations of the stereogenic centers are determined in the ring closure. The only stereogenic center that must have a defined stereochemistry from the start is thus the carbon destined to be C2 in the oxaquinolizidine. Use of (*S*)-malic acid confers the *R*-configuration at C2, which is the configuration of (−)-Xestospongin A. This in turn induces *R*-, *R*-, and *S*-configurations at N5, C9, and C10, respectively.[12]

In this route, we create three new stereogenic centers, with desired configuration from one. The synthesis of 2-(hydroxymethyl)-1-oxaquinolizidine, giving the required stereoisomer, with this synthetic strategy has been reported by us before.[7] The sole product in this case was found to have a *trans*-decalin-like structure.

Results and Discussion

Synthesis. With (*S*)-1,2,4-butanetriol (**2**) as starting material,[13] the 1,3-dioxolane (**3**)[14−16] was prepared using a slightly modified procedure and was used as the starting material for the synthesis.

Scheme 1



[a] Key: (a) 3-pentanone, TsOH, THF, 71%; (b) TsCl, NEt_3, DMAP, CH_2Cl_2, 87%; (c) CF_3CONH_2, NaH, THF, 68%.

Introduction of the nitrogen was achieved in a two-step process. First, the primary alcohol was converted to the tosyl ester **4** with tosyl chloride and triethylamine. The tosylate **4** was a good substrate for reaction with sodium trifluoroacetamide, generated *in situ* from trifluoroacetamide and sodium hydride, giving good yields of the secondary trifluoroacetamide **5** (Scheme 1).[17−19]

The fragment required for the formation of ring B and to act as the long chain in the macrocycle is a 1,9-nonanediol protected with complementary groups on both alcohol groups and further functionalized with an aldehyde attached to the fourth carbon. For the synthesis shown here, the aldehyde was protected as the 1,3-dioxolane with ethylene glycol. This fragment containing 10 carbon atoms was prepared from 1,5-pentanediol (**6**). The crucial reaction involved monoalkylation of the position α to the aldehyde. Several substrates for this alkylation were tested, including the alkyl bromide, iodide, and tosylate. The alkylation reaction was performed on the aldehyde indirectly by first converting it to the imine. Alkylation of the carboxylic acid and its ester were also examined.

The aldehyde (**8**),[20] the carboxylic acid (**9**),[21] and the ester (**10**) were prepared from 1,5-pentanediol by a procedure whereby one alcohol group was selectively protected as the benzyl ether (**7**)[21] (Scheme 2). A large excess (4−5 equiv) of the diol was required for this reaction. Oxidation of the remaining unprotected alcohol using the method of Swern[22] furnished aldehyde **8**. The subsequent reactions were performed as soon as possible, owing to the tendency of the aldehyde to trimerize to the 2,4,6-trisubstituted 1,3,5-trioxane. Oxidation of the alcohol function of **7** using Jones' reagent[23] gave the acid (**9**), which in turn was esterified with thionyl chloride and methanol to give the methyl ester (**10**).

The alkylating reagents used were prepared from 1,5-pentanediol in a similar manner. A large excess of the diol was treated with *tert*-butyldiphenylsilyl chloride and

(12) (*S*)-Malic acid confers *S*-configuration at C2 in 2-(hydroxymethyl)-1-oxaquinolizidine derivatives.

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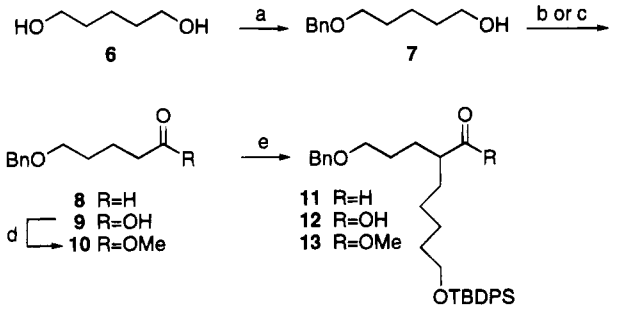
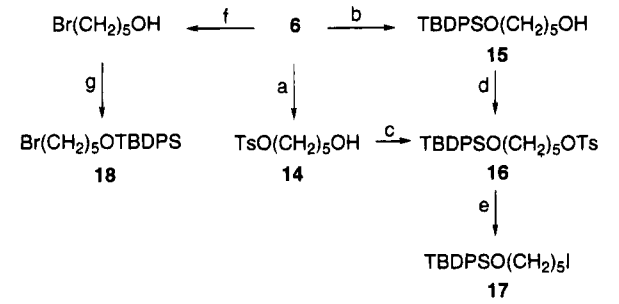
Scheme 2



[a] Key: (a) BnBr, NaH, THF, 87%; (b) **7**, Swern oxidation, 78%; (c) **7**, Jones' reagent, 86%; (d) **9**, $SOCl_2$, MeOH, 95%; (e) reagents shown in Table 1.

Scheme 3

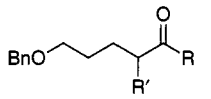


[a] Key: (a) TsCl, NEt_3, DMAP, CH_2Cl_2, 87%; (b) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 74%; (c) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 85%; (d) TsCl, NEt_3, DMAP, CH_2Cl_2, 83%; (e) NaI, THF, 92%; (f) HBr, benzene (not isolated); (g) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 48%.

triethylamine with a catalytic amount of DMAP,[24] giving the monosilyl ether **15** (Scheme 3).[21,25] Treatment of this compound with tosyl chloride gave the tosyl ester (**16**) which was used for alkylation. The two steps in this reaction scheme, silylation and tosylation, could be performed in the opposite order,[26] giving the same product in comparable yield. The iodide (**17**) was readily prepared by treatment of the tosyl ester with sodium iodide in THF. The corresponding alkyl bromide, **18**, was obtained by treatment of 1,5-pentanediol with hydrogen bromide, forming 5-bromopentanol,[27,28] which was treated directly with the silylating reagent, giving the product (**18**) in reasonable yield.

The alkylation reactions were performed by generating the lithiated derivatives of the substrates.[29-31] For the aldehyde (**8**), the imine was prepared *in situ*[32] and was treated with 1 equiv of LDA. The acid (**9**) and the ester (**10**) were used directly; 2 equiv of LDA was required for the acid and 1 equiv for the ester. The alkylating reagents were added, and, after suitable workup, the products, **11**, **12**, and **13**, were isolated. The results of this study are presented in Table 1. We found that the

Table 1. α-Alkylations of Carbonyl Compounds[a]



	yields of isolated products (%)		
leaving group	R = H (**8**)	R = OH (**9**)	R = OMe (**10**)
OTs (**16**)	9	2	*b*
Br (**18**)	48	26	10
I (**17**)	71	40	22

[a] R' = $(CH_2)_5$OTBDPS. [b] No product detected.

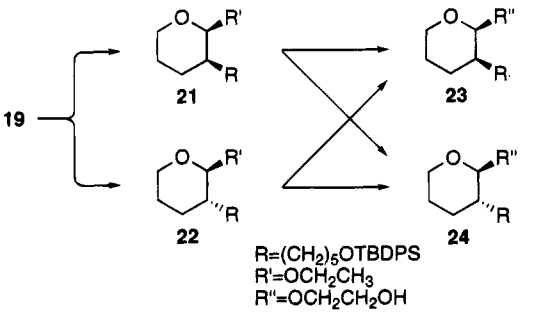


Figure 3. Byproducts formed during the cleavage of the benzyl group from **19**.

alkylation reaction proceeded best when the alkyl iodide was used to alkylate the imine. For further studies, this particular method has been chosen.

The alkylated product (**11**) containing two alcohols protected by benzyl and *tert*-butyldiphenylsilyl groups was further protected by reaction of the aldehyde with ethylene glycol in the presence of a small amount of toluenesulfonic acid.[33] Conditions generally used for debenzylation require hydrogenation either at atmospheric pressure or at moderate pressure with palladium on charcoal as catalyst. Performing this reaction with our substrate (**19**) in ethanol gave rise to the formation of two products. These products were isolated and fully characterized and shown to be the racemic tetrahydropyranyl acetals **21** and **22** (Figure 3). The assignment of **21** and **22** as *cis*- and *trans*-3-(5-((*tert*-butyldiphenylsilyl)oxy)pentyl)-2-ethoxy-2*H*-tetrahydropyran is based on ^1H and ^{13}C NMR data and further supported by electron-impact mass spectroscopy and mass determination through vapor pressure osmometry. The ^1H NMR spectra of both compounds showed doublets corresponding to protons bound to an acetal carbon. For compound **21**, this signal was observed at δ 4.58 with a coupling constant J = 2.7 Hz, while for compound **22**, the signal appeared at δ 4.13 with a coupling constant J = 6.1 Hz. These signals at δ 4.58 and 4.13 were shown by HETCOR spectra to be coupled to ^{13}C signals at δ 99.1 and 104.2, respectively, consistent with the presence of an acetal and in full agreement with the assignment of similar compounds.[34] Both compounds **21** and **22** showed ^1H NMR signals for the ethyl group consisting of a triplet at δ 1.35 and 1.21, respectively, assigned to the terminal methyl group and a pair of octets (dq) for the methylene protons, in the range δ 3.50–3.95, showing the magnetic inequivalence of these protons[35] and indicating their prox-

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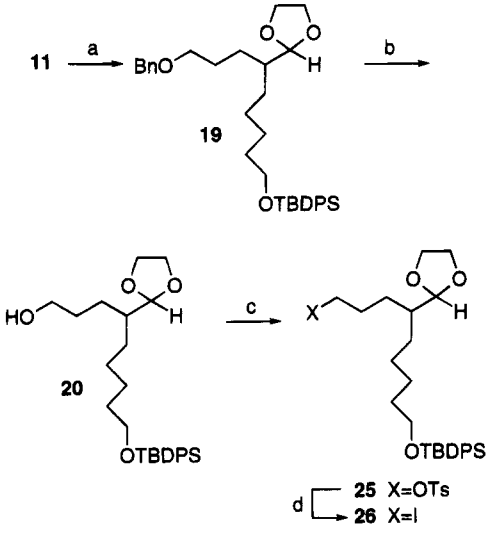
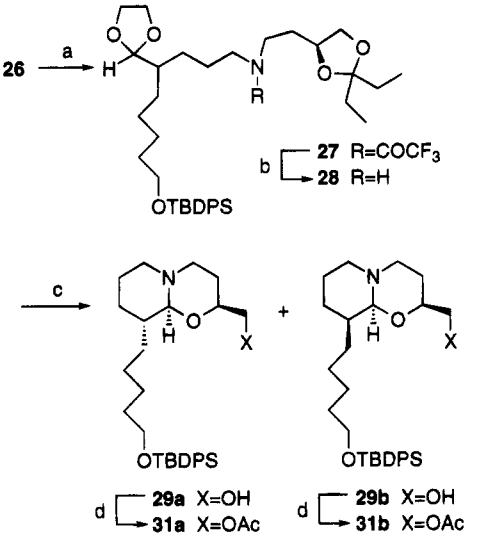
Scheme 4



[a] Key: (a) ethylene glycol, TsOH, benzene, 96%; (b) $Pd(OH)_2$, cyclohexene, EtOH, 72%; (c) TsCl, NEt_3, DMAP, CH_2Cl_2, 94%; (d) NaI, THF, 89%.

Scheme 5



[a] Key: (a) NaH, **5**, THF, 41%; (b) KOH, MeOH, THF, 93%; (c) (i) TsOH; (ii) $NaHCO_3$, 68%; (d) $(Ac)_2O$, NEt_3, DMAP, CH_2Cl_2, 58%.

imity to an asymmetric center. The electron impact mass spectra of these compounds showed fragmentation patterns typical for 2-alkoxytetrahydropyrans.[36] It appears that, during the deprotection reaction, equilibration has occurred between the dioxolane present in the desired product and the tetrahydropyran in the isolated products. We conclude, therefore, that the pyrannyl form is thermodynamically favored over the dioxolane. Treatment of compounds **21** and **22** with ethylene glycol and a catalytic amount of acid in an attempt to reform the dioxolane resulted in the isolation of the 2-(2-hydroxyethoxy)-3-alkyl-2*H*-tetrahydropyrans **23** and **24**. It should be noted that, when performing the reaction with either pure racemic **21** or **22**, the same *cis/trans* mixture of **23** and **24** was obtained.

We turned our attention to finding an alternative debenzylation procedure that does not promote the *trans* acetalation reaction. It has been reported that palladium hydroxide on charcoal catalyzes transfer hydrogenation with cyclohexene as hydrogen donor, causing debenzylation in good yields.[37] When this reaction was used for the debenzylation of **19** in refluxing ethanol, the desired product (**20**) was formed. However, the byproducts (**21** and **22**) were also formed in amounts which increased with increasing reaction time. Reducing the reaction temperature to 60 °C limited formation of the byproducts, allowing **20** to be isolated in high yield. The undesired reaction could also be prevented by addition of a very small quantity of triethylamine. If too much triethylamine is used, the yield of the reaction is reduced considerably. The alcohol generated by the debenzylation was converted to the tosyl ester (**25**) by treatment with tosyl chloride and subsequently to the iodide (**26**) by treatment with sodium iodide (Scheme 4). This gave a substrate which could be coupled with the trifluoroacetamide (**5**).

Coupling of the two molecules **5** and **26** was achieved by first generating the amide salt through treatment with sodium hydride (Scheme 5). Introduction of **26** caused formation of the fully protected tertiary amide (**27**). This compound exists as a mixture of *cis* and *trans* amide rotamers as shown by the duplicity of signals in the NMR spectra. After treatment with potassium hydroxide in aqueous methanol and removal of the trifluoroacetyl group, the secondary amine (**28**) was isolated and fully characterized.

The final deprotection of the acid labile protecting groups on the aldehyde and vicinal diol was achieved by treating a wet dichloromethane solution of **28** with a slight excess of toluenesulfonic acid. The cyclization reaction forming the oxaquinolizidine is thought not to occur until the amine function is deprotonated.[6] A basic workup procedure is therefore used. Prolonged shaking with a saturated sodium bicarbonate solution and extraction with dichloromethane gave a mixture of products shown to be the (2*S*,9*R*,10*S*)- and (2*S*,9*S*,10*S*)-9-(5-((*tert*-butyldiphenylsilyl)oxy)pentyl)-2-(hydroxymethyl)-1-oxaquinolizidines (**29a** and **29b**, respectively). These diastereomers were present in a ratio of approximately 7:1 to 10:1, determined by integration of the corresponding peaks in the ^1H NMR spectrum.

Compounds **29a** and **29b** differ in the relationship between the substituents at positions 2 and 9 and in the stereochemistry of ring fusion, giving the two compounds structures resembling *trans*- and *cis*-decalin. These differences are clearly seen in the ^1H and ^{13}C NMR spectra. For compound **29a**, the aminal proton, H10, assigned through its coupling to the ^{13}C signal at δ 96.8 gives a ^1H NMR signal at δ 3.08 with a coupling constant $J = 8.3$ Hz for the coupling to H9. This coupling constant indicates that both protons lie in positions axial to the ring, showing that the alkyl substituent attached to C9 and the oxygen atom are in positions equatorial to the same ring. Furthermore, the observation of a NOE effect between H10 and H2 showing their close proximity leads to the conclusion that the oxaquinolizidine adopts a *trans*-decalin conformation with the 2-hydroxymethyl residue in an equatorial position. Thus, the structure of this isomer is established.

For compound **29b**, the signals corresponding to H10 appear as a broad doublet at δ 4.10 in the ^1H NMR

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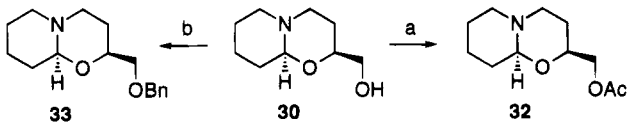
Scheme 6



[a] Key: (a) $(Ac)_2O$, NEt_3, DMAP, CH_2Cl_2, 36%; (b) BnBr, NaH, THF, 44%.

spectrum, and the signal for C10 appears at δ 89.2 in the ^{13}C NMR spectrum. The downfield shift of the proton signal and upfield shift of the ^{13}C signal are due to the change to a *cis*-fused ring system, in agreement with recently reported results for similar compounds.[5] Even in the *cis* isomer, both substituents are able to adopt equatorial positions.

Isomers **29a** and **29b** could not be separated as the free bases; however, precipitation from ethereal hydrogen chloride solution followed by recrystallization from ethanol and diethyl ether furnished the hydrochloride salt of **29a**.

Results recently presented by Hoye *et al.* clearly demonstrate that a *trans* relationship between the substituents at positions 2 and 9 causes formation of a *trans*-fused oxaquinolizidine, whereas a *cis* relationship between these substituents leads to the formation of a *cis*-fused oxaquinolizidine.[5] We have found that our results and the assignments of structures **29a** and **29b** are in complete agreement with this observation.

Synthesis of (−)-Xestospongin A and analogous compounds from **29a** and **29b** requires derivatization of the alcohol function that is left unprotected after cyclization. We studied several reactions on compounds **29a** and **29b** and also on the previously described compound **30** which lacks the substituent at position 9.[7] It was observed that all attempts at the conversion of the alcohol to a leaving group resulted in breakdown of the reactant into unidentified compounds which lack the characteristic ^1H NMR signals associated with 1-oxaquinolizidines. The conditions used included basic tosylation with tosyl chloride in the presence of triethylamine, neutral conditions such as treatment with triphenylphosphine and carbon tetrachloride, and even acidic conditions such as phosphorus trichloride. Although we have not been able to isolate the breakdown products from these reactions, we suspect that introduction of the leaving group is accompanied by either base-catalyzed elimination followed by vinyl ether cleavage, giving a ketone which can react further, or an alkyl or hydride shift, giving an aldehyde or ketone, each of which would also be capable of further reaction.

Functionalization of the alcohol in compounds **29a,b** and **30** to the acetate esters or the benzyl ether was possible as demonstrated by the formation of esters **31a,b** and **32** by treatment with acetic anhydride and triethylamine. Compound **30** was also converted to the benzyl ether (**33**) by treatment first with sodium hydride, followed by introduction of benzyl bromide (Scheme 6). Formation of an ether at this position shows that synthesis of analogues of Xestospongin A with an extra oxygen should be possible.

The possibility that the undesired breakdown of the oxaquinolizidines was caused directly by the basic and acidic reaction conditions employed was ruled out by treatment of the model substrate (**30**) with either acid (acetic acid, 2 equiv for 2 weeks) or base (DABCO, 2 equiv for 2 weeks). In both cases, the substrate remained unaffected. The pK_a of the hydrochloride salt of **30** was determined to be 7.69 ± 0.02, which suggests that the compound is largely protonated under the acidic conditions used and largely deprotonated under the basic conditions. The chemical shifts of protons 2, 4, 6, and 10 varied slightly with the acidity of the medium, but the coupling patterns showed that the oxaquinolizidine ring system remained unaltered.

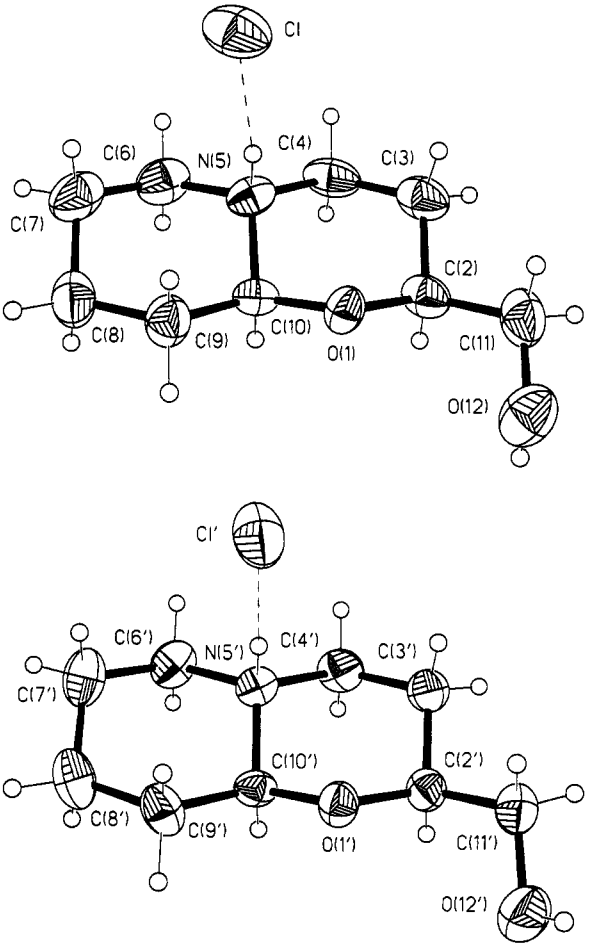
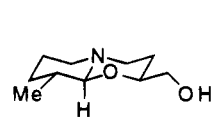
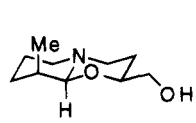
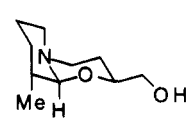
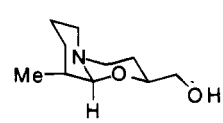
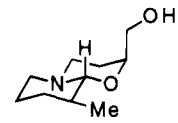


Figure 4. Perspective views of the two solid state conformers of the hydrochloride salt of (2*S*,5*R*,10*S*)-**30** with crystallographic numbering of the atoms. Solid and dashed lines represent covalent and hydrogen bonds, respectively.

Crystallography. The stereochemistry of the 1-oxaquinolizidine skeleton was determined by X-ray diffraction analysis using a single crystal of the hydrochloride salt of **30** and was found to be as postulated.[7,38] The absolute configurations of the chiral centers at C10 and N5 proved to be *S* and *R*, respectively. These configurations could be deduced directly from the molecular geometry, since **30** has one asymmetry center, at C2, with known configuration (*S*). The crystal contains two crystallographically independent molecules (**30a** and **30b**, unprimed and primed, respectively) with very similar conformations (Figure 4). The oxaquinolizidine adopts a *trans*-decalin-like structure with the hydroxymethyl substitutent in an equatorial position in both cases [the C10−O1−C2−C11 torsion angles have the values −177.1(3) and 179.8(3)° in **30a** and **30b**, respectively]. The only significant difference between the two conformers is in the orientation of the O12−H group [the C2−C11−O12−H12 torsion angle is 61° in **30a** and −157° in

(38) **29a** gave no crystals that were suitable for X-ray analysis.

Table 2. Calculated Boltzmann Distribution at 25 °C

	Conformations, stereochemistry and Boltzmann distribution %[a,b,c]				
					
Force field	2*S*,5*R*,9*R*,10*S*	2*S*,5*R*,9*S*,10*S*	2*S*,5*S*,9*S*,10*S*	2*S*,5*S*,9*R*,10*S*	2*S*,5*S*,9*S*,10*R*
MM2(91)	11.8	0.8	80.7	6.7	[d]
MMX	90.0	5.4	4.0	[d]	0.4
MM2* ($CHCl_3$)	75.9	6.3	17.1	0.7	[d]
MM2* (H_2O)	92.2	5.2	2.1	[d]	0.4
MM2* (Vacuum)	87.5	5.1	7.0	[d]	[d]

[a] Several rotamers were found for each isomer; the figures shown represent the sum of all rotamers. [b] Energy values and population are presented in the supplementary material. [c] All conformers with steric energy in excess of 3 kcal/mol are ignored. [d] No isomers below cutoff value.

30b]. The crystal structure consists of endless hydrogen-bonded chains, in which the protonated oxaquinolizidine cations are hydrogen-bonded *via* the chloride anions, involving the N–H and O–H functions of both molecules.

Molecular Mechanics Calculations. Molecular mechanics calculations have been performed to determine the relative steric energy of all relevant conformational forms of 2-(hydroxymethyl)-9-methyl-1-oxaquinolizidine, as a help in determining the conformation and stereochemistry of products **29a** and **29b** and compound **30**. The stereochemistry of **30** has previously been determined by NMR analysis and is confirmed by the X-ray data presented herein. The good correlation of the molecular mechanics-calculated results for compound **30** with those obtained experimentally allow us to use the calculation results for compounds **29a** and **29b** with a high level of confidence. Unrestricted molecular mechanics calculations were performed using MM2(91) (modified with O–C–N parameters according to Senderowitz *et al.*[39]), MMX, and MM2* force fields. For the last case, calculations were performed for the compounds in vacuum as well as in water and chloroform matrices.

In all, 144 starting geometries were used for **29,** which after minimization were reduced to between 6 and 13 conformations with steric energies below the cutoff level of 3 kcal/mol. These conformers were found to be different rotamers of five stereoisomers. The total population for each of the stereoisomers is presented in Table 2.[40] It can be clearly seen that the modified MM2(91) calculations predict that the major isomer formed should be the *cis* isomer with stereochemistry 2*S*,9*S*,10*S*; all of the other calculations predict that the *trans* isomer with stereochemistry 2*S*,9*R*,10*S* should dominate the product distribution. X-ray analysis has shown that both the naturally occurring Xestospongin A and the synthetic 2-(hydroxymethyl)-1-oxaquinolizidine (**30**) adopt a *trans* conformation. It is therefore concluded that, for the modified MM2(91) force field, the weighting in favor of anomeric stabilization in O–C–N bound systems is overrepresented.

The vicinal NMR coupling constants, $^3J_{H-H}$, were calculated for H10 in the two major conformers, using the Karplus equation as modified by Altona.[41,42] The values obtained were compared with the values obtained for the synthetic compounds **29a** and **29b**. Compound **29a** shows a signal at δ 3.08 with a coupling constant of 8.3 Hz. This compares well with the calculated value, 7.9 Hz. Compound **29b** shows a broad doublet with a small coupling constant at δ 4.10. The predicted value for the coupling constant is 2.3 Hz, so good correlation between the experimental and theoretical values is found. Measurement of the coupling constant for **29b** was not improved by observation at higher magnetic field. The broadening of the H10 NMR signals for **29b** could be a consequence of w-coupling to H8, consistent with other observations.[5]

Conclusions

By using this synthetic strategy, we are able to synthesize 2,9-disubstituted 1-oxaquinolizidines with the desired stereochemistry from inexpensive and simple starting materials. We cannot make (−)-Xestospongin A because of the breakdown of one of the intermediates after the introduction of a leaving group. What we should be able to achieve is the synthesis of analogues to **1** with ether functions in the large ring which should enhance the crown and aza-crown ether-like properties of these compounds. The flexibility in this strategy also allows for the inherent possibility of synthesizing analogues altered in the oxaquinolizidine part of **1**. By changing the order of events in the strategy, *e.g.* ring closure of the large ring before the formation of the oxaquinolizidine, we should be able to overcome the problems in the synthesis of **1**. Work in this direction is continuing in our laboratory.

Experimental Section

General Comments. ^1H and ^{13}C NMR spectra were recorded on a JEOL-EX270 spectrometer at 270.05 and 67.8 MHz, respectively. Chloroform δ = 7.26 and δ = 77.0 were used as internal references, respectively. ^{19}F NMR spectra were recorded on a JEOL FX90Q spectrometer at 84.2 MHz, using trifluoroacetic acid, δ = −76.5 as internal reference. All spectra were recorded in $CDCl_3$ solutions unless otherwise

(39) Senderowitz, H.; Aped, P.; Fuchs, B. *J. Comput. Chem.* **1993**, *14*, 944–960.

(40) See supplementary material for torsional angles and relative energies for the conformers with $\Delta E \leq 3$ kcal/mol.

(41) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.

(42) Huggins, M. L. *J. Am. Chem. Soc.* **1953**, *75*, 4123–4126.

noted. Assignments were made using $^1H-^1H$ and $^1H-^{13}C$ correlation experiments. Low-resolution electron-impact mass spectra were recorded on a Hewlett-Packard mass spectrometer HP5971A MSD, connected with a gas chromatograph, HP GC5890 Series 2. Infrared spectra were recorded on a Perkin-Elmer 1605 FTIR spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at ambient temperature. Thin-layer chromatography (TLC) was performed by using aluminum sheets precoated with silica gel 60 (F_{254}, Merck) or neutral aluminum oxide 60 (F_{254}, type E, Merck), and the spots were detected with UV light, H_2SO_4, or ninhydrin. Column chromatography was performed on silica gel using Kieselgel 60 (0.040–0.063 mm, Merck) or aluminum oxide 90 (0.063–0.200 mm, Merck). The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden. Molecular weight determination was performed by Galbraith Laboratories Inc., Knoxville, TN. Melting points were determined in open capillary tubes on an Electrothermal melting point apparatus and are uncorrected. Sodium hydride was used as an 80% oil suspension. THF was dried and distilled from sodium and benzophenone. Trifluoroacetamide was recrystallized from $CHCl_3$. Cyclohexylamine and diisopropylamine were distilled and stored over NaOH. All other commercial chemicals were used without further purification.

(*S*)-1,2-*O*-3-Pentylidene-1,2,4-butanetriol (3).[14-16] (*S*)-1,2,4-Butanetriol (**2**) (2.06 g, 19.4 mmol) and 3-pentanone (40 mL, 377 mmol) were dissolved in THF (40 mL). A catalytic amount of *p*-toluenesulfonic acid (TsOH) was added, and the reaction mixture was refluxed for 14 h and partitioned between saturated aqueous $NaHCO_3$ solution and diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, ethyl acetate (EtOAc)), giving a light yellowish oil, 2.41 g, 71%: TLC $R_f = 0.6$ (EtOAc); $[\alpha]_D$ +1.5° (c = 1.0, CH_2Cl_2); ^1H NMR δ 4.21 (m, 1H, H-2), 4.07 (dd, J = 7.9, 6.1 Hz, 1H, H-1), 3.77 (brq, J = 5.4 Hz, 2H, H-4), 3.50 (t, J = 7.9, 1H, H-1), 2.61 (brt, J = 5 Hz, 1H, OH), 2.10–1.75 (m, 2H, H-3), 1.62 (q, J = 7.5 Hz, 2H, CH_2), 1.59 (q, J = 7.5 Hz, 2H, CH_2), 0.87 (t, J = 7.5 Hz, 3H, CH_3), 0.86 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR δ 112.9 (*O*CO), 75.27 (C-2), 70.01 (C-1), 60.47 (C-4), 35.38 (C-3), 29.79 (CH_2), 29.52 (CH_2), 8.13 (CH_3), 7.88 (CH_3); IR (neat) 3429 cm^{-1}.

(*S*)-4-(Tosyloxy)-1,2-*O*-3-pentylidene-1,2-butanediol (4). Compound **3** (10.32 g, 59.2 mmol), triethylamine (NEt_3) (25 mL, 177.6 mmol), and 4-(dimethylamino)pyridine (DMAP) (catalytic amount) were dissolved in CH_2Cl_2 (100 mL). TsCl (16.9 g, 88.8 mmol) dissolved in CH_2Cl_2 (250 mL) was added dropwise. This mixture was stirred at rt for 19 h and extracted successively with saturated aqueous $NaHCO_3$ and citric acid solutions. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethanol, 0–8%), giving a light yellowish oil, 16.97 g, 87%: TLC $R_f = 0.25$ (CH_2Cl_2); $[\alpha]_D$ −15.4° (c = 1.0, CH_2Cl_2); ^1H NMR δ 7.89 (d, J = 8.2 Hz, 2H, Ph), 7.45 (d, J = 8.2 Hz, 2H, Ph), 4.33–4.09 (m, 4H, H-1, H-2, H-4), 3.56 (dd, J = 7.6, 7.3 Hz, 1H, H-1), 2.55 (s, 3H, PhCH_3), 2.09–1.96 (m, 2H, H-3), 1.66 (q, J = 7.6 Hz, 2H, CH_2), 1.65 (q, J = 7.6 Hz, 2H, CH_2), 0.93 (t, J = 7.6 Hz, 3H, CH_3), 0.92 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR δ 144.76, 132.78, 129.78, 127.78 (aromatic C's), 112.79 (*O*CO), 72.36 (C-2), 69.56 (C-1), 67.4 (C-4), 32.85 (C-3), 29.63 (CH_2), 29.40 (CH_2), 21.51 (PhCH_3), 8.07 (CH_3), 7.78 (CH_3); IR (neat) 1361, 1179 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_5S$: C, 58.6; H, 7.4. Found: C, 58.7; H, 6.9.

(*S*)-4-(Trifluoroacetamido)-1,2-*O*-3-pentylidene-1,2-butanediol (5). Trifluoroacetamide (1.80 g, 15.9 mmol) was dissolved in dry THF (30 mL) under a nitrogen atmosphere. Sodium hydride (NaH) (0.57 g, 19.1 mmol) was added in one portion. This slurry was stirred at rt for 1 h. Compound **4** (3.49 g, 10.6 mmol) was dissolved in dry THF (15 mL) and the solution added dropwise to the slurry. After it was refluxed for 15 h and stirred for 4 h at rt, the reaction mixture was partitioned between saturated aqueous NH_4Cl solution and diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether (P-ether)/EtOAc, 0–40%), giving a light yellowish oil, 1.94 g, 68%: TLC $R_f = 0.5$ (25% EtOAc in P-ether); $[\alpha]_D$ +18.1° (c = 1.0, CH_2Cl_2); ^1H NMR δ 7.38 (brs, 1H, NH), 4.19–4.10 (m, 1H, H-2), 4.06 (dd, J = 7.6, 6.3 Hz, 1H, H-1), 3.77–3.66 (m, 1H, H-4), 3.47 (dd, J = 7.9, 7.6 Hz, 1H, H-1), 3.32–3.17 (m, 1H, H-4), 1.89–1.80 (m, 1H, H-3), 1.78–1.52 (m, 5H), 0.84 (t, J = 7.4 Hz, 3H, CH_3), 0.83 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR δ 156.93 (q, J_{CF} = 36 Hz, C=O), 115.85 (q, J_{CF} = 288 Hz, CF_3), 113.73 (*O*CO), 76.28 (C-2), 69.72 (C-1), 38.34 (C-4), 31.27 (C-3), 29.61 (CH_2), 29.27 (CH_2), 8.12 (CH_3), 7.86 (CH_3); ^{19}F NMR δ −78.10 (s); IR (neat) 3321, 1714 cm^{-1}. Anal. Calcd for $C_{11}H_{18}F_3NO_3$: C, 49.1; H, 6.7; N, 5.2. Found: C, 49.3; H, 6.9; N, 5.3.

5-(Benzyloxy)-1-pentanol (7). 1,5-Pentanediol (**6**) (40.4 g, 388 mmol) was dissolved in THF (600 mL). NaH (12.0 g, 400 mmol) was added in portions. This slurry was stirred at rt for 10 min. Benzyl bromide (18 mL, 152 mmol) was dissolved in THF (100 mL) and the solution added dropwise. The reaction mixture was refluxed for 28 h, quenched by adding water dropwise, and partitioned between brine and diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, P-ether/EtOAc, 0–100%), giving a yellowish oil, 25.63 g, 87% yield: TLC $R_f = 0.8$ (EtOAc); ^1H NMR δ 7.35–7.27 (m, 5H, Ph), 4.50 (s, 2H, PhCH_2), 3.64 (m, 2H, H-1), 3.48 (t, J = 6 Hz, 2H, H-5), 1.68–1.37 (m, 7H); ^{13}C NMR δ 138.5, 128.3, 127.6, 127.5 (aromatic C's), 72.9 (Ph*C*H_2), 70.2 (C-5), 62.8 (C-1), 32.5 (CH_2), 29.4 (CH_2), 22.4 (CH_2); IR (neat) 3384 cm^{-1}.

5-(Benzyloxy)pentanal (8). Oxalyl chloride (1.7 mL, 19.6 mmol) was dissolved in CH_2Cl_2 (50 mL) under a nitrogen atmosphere and the solution cooled to −78 °C. DMSO (2.8 mL, 39.3 mmol) was dissolved in CH_2Cl_2 (20 mL), and the mixture was added to the cold solution over a 15 min period. Compound **7** (3.47 g, 17.9 mmol) was dissolved in CH_2Cl_2 (35 mL) and the solution added dropwise over a 25 min period. This mixture was stirred for 1 h at −78 °C, quenched by adding diisopropylethylamine (15.5 mL, 89.3 mmol), heated to rt, and washed with water and 10% citric acid solution. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2), giving a yellowish oil, 2.64 g, 78%: TLC $R_f = 0.5$ (CH_2Cl_2); ^1H NMR δ 9.76 (t, J = 2 Hz, 1H, H-1), 7.38–7.28 (m, 5H, Ph), 4.50 (s, 2H, PhCH_2), 3.49 (t, J = 6 Hz, 2H, H-5), 2.46 (dt, J = 2, 7 Hz, 2H, H-2), 1.78–1.60 (m, 4H); ^{13}C NMR δ 202.5 (C-1), 138.4, 128.4, 127.6, 127.5 (aromatic C's), 72.9 (Ph*C*H_2), 69.7 (C-5), 43.6 (C-2), 29.1 (CH_2), 18.9 (CH_2); IR (neat) 1723 cm^{-1}.

5-(Benzyloxy)pentanoic Acid (9). Compound **7** (11.0 g, 56.6 mmol) was dissolved in acetone (400 mL) and the solution cooled to 0 °C. Jones' reagent (210 mL, 141.5 mmol, 0.67 M) was added dropwise over a 20 min period. This solution was stirred at 0 °C for 1 h. Workup by acid/base extractions gave a colorless oil, 10.18 g, 86%: ^1H NMR δ 7.45–7.36 (m, 5H, Ph), 4.61 (s, 2H, PhCH_2), 3.60 (t, J = 5.7 Hz, 2H, H-5), 2.49 (t, J = 6.9 Hz, 2H, H-2), 1.87–1.79 (m, 4H); ^{13}C NMR δ 179.71 (C-1), 138.33, 128.36, 127.62, 127.55 (aromatic C's), 72.88 (Ph*C*H_2), 69.69 (C-5), 33.69 (C-2), 28.97 (CH_2), 21.46 (CH_2); IR (neat) 3030, 1707 cm^{-1}.

Methyl 5-(Benzyloxy)pentanoate (10). Compound **9** (7.0 g, 33.6 mmol) was dissolved in methanol (300 mL) and the solution cooled to 0 °C. Thionyl chloride (2.7 mL, 37.0 mmol) was added slowly. This solution was stirred at rt for 15 h, saturated aqueous $NaHCO_3$ solution was added, and the methanol was evaporated. The residue was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated, giving a colorless oil, 7.11 g, 95%: GC–MS retention time 14.96 min; GC–MS m/z (relative intensity) 222 (M^+, 2), 131 (6), 116 (18), 107 (23), 91 (100); ^1H NMR δ 7.58–7.27 (m, 5H, Ph), 4.46 (s, 2H, PhCH_2), 3.59 (s, 3H, CH_3), 3.42 (t, J = 6.1 Hz, 2H, H-5), 2.27 (t, J = 7.2 Hz, 2H, H-2), 1.69–1.53 (m, 4H); ^{13}C NMR δ 174.23 (C-1), 138.69, 128.55, 127.80, 127.71 (aromatic C's), 73.08 (Ph*C*H_2), 69.99 (C-5), 51.68 (CH_3), 33.98 (C-2), 29.35 (CH_2), 21.94 (CH_2); IR (neat) 1738 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2. Found: C, 70.2; H, 8.5.

(2*R*,*S*)-2-(3-(Benzyloxy)propyl)-7-((*tert*-butyldiphenylsilyl)oxy)heptanal (11). Compound **8** (9.61 g, 50.0 mmol) and cyclohexylamine (5.7 mL, 50.0 mmol) were refluxed in benzene (150 mL) with a catalytic amount of TsOH, using a Dean–Stark apparatus, for 1.5 h. The benzene was removed

by evaporation, giving the crude imine.[43] Diisopropylamine (8.4 mL, 60.0 mmol) was dissolved in dry THF (20 mL) under a nitrogen atmosphere and the solution cooled to −78 °C. *n*-Butyllithium (*n*-BuLi) (37.5 mL, 60.0 mmol, 1.6 M in hexanes) was added. This solution was stirred at −78 °C for about 20 min. The crude imine was dissolved in dry THF (40 mL) and the solution added dropwise to the cold solution. After the cold solution was stirred for 2.5 h, compound **17** (22.6 g, 50.0 mmol) dissolved in dry THF (40 mL) was added dropwise. The reaction mixture was allowed to slowly reach rt over a 14 h period, and 0.5 M HCl was added until the pH was 2−3. This mixture was extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2), giving a colorless oil, 18.42 g, 71%, TLC $R_f = 0.6$ (CH_2Cl_2). Using the same experimental conditions, compound **11** was obtained from **16** and **18** in 9% and 48% yield, respectively: ^{1}H NMR δ 9.54 (d, J = 3.0 Hz, 1H, H-1), 7.68−7.64 (m, 3H, Ph), 7.45−7.27 (m, 12H, Ph), 4.49 (s, 2H, PhCH_2), 3.64 (t, J = 6.4 Hz, 2H, H-7), 3.46 (t, J = 6.0 Hz, 2H, H-3′), 2.24−2.23 (m, 1H, H-2), 1.73−1.25 (m, 12H) 1.04 (s, 9H, (CH_3)$_3$C); ^{13}C NMR δ 205.24 (C-1), 138.39, 135.52, 134.01, 129.49, 128.35, 127.60, 127.56 (aromatic C's), 72.87 (PhCH_2), 69.87 (C-3′), 63.71 (C-7), 51.58 (C-2), 32.28 (CH_2), 28.85 (CH_2), 27.20 (CH_2), 26.83 ((CH_3)$_3$C), 26.75 (CH_2), 25.88 (CH_2), 25.41 (CH_2), 19.17 ((CH_3)$_3$C); IR (neat) 1724 cm^{-1}. Anal. Calcd for $C_{33}H_{44}O_3Si$: C, 76.7; H, 8.6. Found: C, 76.0; H, 8.7.

(2*R*,*S*)-2-(3-(Benzyloxy)propyl)-7-((*tert*-butyldiphenylsilyl)oxy)heptanoic Acid (12). Diisopropylamine (0.64 g, 6.3 mmol) was dissolved in dry THF (3 mL) under a nitrogen atmosphere and the solution cooled to −78 °C. *n*-BuLi (2.5 mL, 6.3 mmol, 2.5 M in hexanes) was added. After the solution was stirred for 15 min, compound **9** (0.62 g, 3.0 mmol), dissolved in dry THF (2 mL), was added dropwise. This solution was stirred at −78 °C for 1.5 h. Compound **17** (1.5 g, 3.3 mmol) was dissolved in dry THF (3 mL) and the solution added dropwise to the cold solution, which was allowed to slowly reach rt over a 14 h period. The reaction mixture was partitioned between 1 M HCl and diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, P-ether/EtOAc, 0−40%), giving a yellowish oil, 0.64 g, 40%, TLC $R_f = 0.25$ (25% EtOAc in P-ether). Using the same experimental conditions, compound **12** was obtained from **16** and **18** in 3% and 26% yield, respectively: ^{1}H NMR δ 7.69−7.66 (m, 4H, Ph), 7.45−7.28 (m, 11H, Ph), 4.51 (s, 2H, PhCH_2), 3.66 (t, J = 6.2 Hz, 2H, H-7), 3.49 (brt, 2H, H-3′), 2.37−2.34 (m, 1H, H-2), 1.74−1.21 (m, 12H), 1.06 (s, 9H, (CH_3)$_3$C); ^{13}C NMR δ 182.25 (C-1), 138.35, 135.52, 134.03, 129.47, 128.35, 127.64, 127.56 (aromatic C's), 72.87 (PhCH_2), 69.94 (C-3′), 63.79 (C-7), 45.13 (C-2), 32.31, 32.13, 28.72, 27.45, 27.07 (CH_2's), 26.84 ((CH_3)$_3$C), 25.73 (CH_2), 19.17 ((CH_3)$_3$C); IR (neat) 3069, 3030, 1734, 1704 cm^{-1}. Anal. Calcd for $C_{33}H_{44}O_4Si$: C, 74.4; H, 8.3. Found: C, 74.3; H, 8.3.

(2*R*,*S*)-Methyl 2-(3-(Benzyloxy)propyl)-7-((*tert*-butyldiphenylsilyl)oxy)heptanoate (13). Diisopropylamine (0.45 g, 4.5 mmol) was dissolved in dry THF (3 mL) under a nitrogen atmosphere and the solution cooled to −78 °C. *n*-BuLi (1.8 mL, 4.5 mmol, 2.5 M in hexanes) was added. After the solution was stirred for 15 min, compound **10** (0.67 g, 3.0 mmol) dissolved in dry THF (2 mL) was added dropwise. This solution was stirred at −78 °C for 2.5 h. Compound **17** (2.0 g, 4.5 mmol) dissolved in dry THF (2 mL) was added dropwise. The reaction mixture was slowly allowed to reach rt during a 14 h period and extracted between saturated aqueous NH_4Cl solution and diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2), giving a colorless oil, 0.36 g, 22%, TLC $R_f = 0.5$ (CH_2Cl_2). Using the same experimental conditions, compound **13** was obtained from **18** in 10% yield. Reaction with compound **16** gave no detectable product: ^{1}H NMR δ 7.79−7.74 (m, 3H, Ph), 7.55−7.36 (m, 12H, Ph), 4.59 (s, 2H, PhCH_2), 3.75 (s, 3H, CH_3), 3.73 (t, J = 6.4 Hz, 2H, H-7), 3.55 (t, J = 5.9 Hz, 2H, H-3′), 2.48−2.42 (m, 1H, H-2), 1.77−1.31 (m, 12H), 1.14 (s, 9H, (CH_3)$_3$C); ^{13}C NMR δ 176.75 (C-1), 138.47, 135.52, 134.07, 129.47, 128.34, 127.58, 127.54, 127.49 (aromatic C's), 72.85 (PhCH_2), 69.97 (C-3′), 63.81 (C-7), 51.34 (CH_3), 45.34 (C-2), 32.45, 32.36, 28.99, 27.66, 27.17 (CH_2's), 26.83 ((CH_3)$_3$C), 25.72 (CH_2), 19.19 ((CH_3)$_3$C). IR (neat) 1740 cm^{-1}. Anal. Calcd for $C_{34}H_{46}O_4Si$: C, 74.7; H, 8.5. Found: C, 74.6; H, 8.5.

5-((*tert*-Butyldiphenylsilyl)oxy)pentanol (15). Compound **6** (30.5 g, 293 mmol), NEt_3 (20 mL, 146 mmol), and DMAP (0.60 g, 5 mmol) were dissolved in CH_2Cl_2 (600 mL). *tert*-Butyldiphenylsilyl chloride (TBDPSCl) (26.85 g, 97.7 mmol) was dissolved in CH_2Cl_2 (200 mL) and the solution added dropwise over a 2 h period to the reaction mixture which was then stirred at rt for 16 h. The reaction mixture was concentrated to 400 mL and extracted successively with saturated aqueous $NaHCO_3$ and citric acid solutions. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethanol, 0−10%), giving a colorless oil, 24.6 g, 74%: TLC R_f = 0.25 (2% ethanol in CH_2Cl_2); ^{1}H NMR δ 7.80−7.75 (m, 4H, Ph), 7.56−7.46 (m, 6H, Ph), 3.92−3.70 (m, 5H, H-5, H-1, OH), 1.75−1.46 (m, 6H), 1.15 (s, 9H, (CH_3)$_3$C); ^{13}C NMR δ 135.55, 134.02, 129.52, 127.57 (aromatic C's), 63.75, 62.97 (C-1, C-5), 32.45 (CH_2), 32.24 (CH_2), 26.85 ((CH_3)$_3$C), 21.94 (CH_2), 19.19 ((CH_3)$_3$C); IR (neat) 3340 cm^{-1}.

1-((*tert*-Butyldiphenylsilyl)oxy)-5-(tosyloxy)pentane (16). Compound **14**[26] (11.0 g, 42.6 mmol), NEt_3 (17.7 mL, 127.7 mmol), and DMAP (0.05 g, 0.4 mmol) were dissolved in CH_2Cl_2 (300 mL). TBDPSCl (23.4 g, 85.16 mmol) was dissolved in CH_2Cl_2 (100 mL) and the solution added dropwise. This reaction mixture was stirred at rt for 16 h and extracted succesively with saturated aqueous $NaHCO_3$ and citric acid solutions. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2), giving a light yellowish oil, which crystallized upon storage at 4 °C. Recrystallization (hexane) gave the product as white crystals, 17.95 g, 85%: mp 43−44 °C; TLC $R_f = 0.9$ (CH_2Cl_2); ^{1}H NMR δ 7.94 (d, J = 8.2 Hz, 2H, Ph), 7.81−7.78 (m, 4H, Ph), 7.59−7.42 (m, 8H, Ph), 4.16 (t, J = 6.5 Hz, 2H, H-5), 3.76 (t, J = 6.1 Hz, 2H, H-1), 2.59 (s, 3H, CH_3), 1.89−1.43 (m, 6H), 1.19 (s, 9H, (CH_3)$_3$C); ^{13}C NMR δ 144.60, 135.50, 133.87, 133.15, 129.77, 129.55, 127.84, 127.60 (aromatic C's), 70.52 (C-5), 63.39 (C-1), 31.73 (CH_2), 28.51 (CH_2), 26.82 ((CH_3)$_3$C), 21.74 (CH_2), 21.61 (PhCH_3), 19.17 ((CH_3)$_3$C); IR (neat) 1176, 1368 cm^{-1}. Anal. Calcd for $C_{28}H_{36}O_4SSi$: C, 67.7; H, 7.3. Found: C, 68.0; H, 7.2.

Compound **16** could also be prepared from **15**. Compound **15** (1.40 g, 4.08 mmol), NEt_3 (1.70 mL, 12.26 mmol), and a catalytic amount of DMAP were dissolved in CH_2Cl_2 (35 mL). TsCl (1.17 g, 6.13 mmol) was dissolved in CH_2Cl_2 (15 mL) and the solution added dropwise. The reaction mixture was stirred at rt for 16 h. The same workup procedure as described above was used, giving **16** in 83% yield.

1-((*tert*-Butyldiphenylsilyl)oxy)-5-iodopentane (17). Compound **16** (11.59 g, 23.3 mmol) was dissolved in THF (150 mL). Sodium iodide (5.2 g, 35.0 mmol) was added. This two-phase system was stirred at rt for 48 h and partitioned between brine and diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, P-ether/EtOAc, 10%), giving a yellow oil, 9.68 g, 92%: TLC $R_f = 0.8$ (10% EtOAc in P-ether); GC−MS retention time 26.15 min; GC−MS m/z (relative intensity) 395 (66), 309 (100), 199 (45); ^{1}H NMR δ 7.69−7.65 (m, 4H, Ph), 7.46−7.35 (m, 6H, Ph), 3.66 (t, J = 6.1 Hz, 2H, H-1), 3.17 (t, J = 7.0 Hz, 2H, H-5), 1.81 (q, J = 7.2 Hz, H-4), 1.59 (m, 4H), 1.05 (s, 9H, (CH_3)$_3$C); ^{13}C NMR δ 135.54, 133.94, 129.54, 127.60 (aromatic C's), 63.50 (C-1), 33.21 (C-4), 31.37 (2C, C-2, C-3), 26.85 ((CH_3)$_3$C), 19.18 ((CH_3)$_3$C), 7.08 (C-5). Anal. Calcd for $C_{21}H_{29}IOSi$: C, 55.7; H, 6.5. Found: C, 55.9; H, 6.5.

5-Bromo-1-((*tert*-butyldiphenylsilyl)oxy)pentane (18). Compound **6** (5.2 g, 50 mmol) was dissolved in benzene (100 mL), and aqueous HBr (6.25 mL, 56.0 mmol) was added. This mixture was refluxed with a Dean−Stark apparatus for 18 h, cooled to rt, and extracted with 6 M NaOH, 10% HCl, and brine, using diethyl ether as the organic phase. The organic phase was dried ($MgSO_4$) and evaporated to dryness, giving a

(43) The presence of the imine was confirmed by the observation of a strong absorption at 1665 cm^{-1} in the infrared spectrum.

light yellowish oil, 6.72 g, 40 mmol. This oil, consisting primarily of 5-bromo-1-pentanol, was dissolved in CH_2Cl_2 (150 mL) without further purification. NEt_3 (16.7 mL, 120 mmol) and DMAP (catalytic amount) were added. TBDPSCl (12.1 g, 44.2 mmol) was dissolved in CH_2Cl_2 (75 mL) and the solution added dropwise. This solution was stirred at rt for 16 h and extracted with saturated aqueous $NaHCO_3$ and citric acid solutions. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, P-ether/EtOAc, 0–10%) giving a colorless oil, 9.72 g, 48% yield from **7**: TLC R_f = 0.9 (5% EtOAc in P-ether); ^{1}H NMR δ 7.69–7.66 (m, 4H, Ph), 7.44–7.37 (m, 6H, Ph), 3.67 (t, J = 6.0 Hz, 2H, H-1), 3.39 (t, J = 6.8 Hz, 2H, H-5), 1.85 (qn, J = 6.9 Hz, 2H, H-4), 1.61–1.51 (m, 4H), 1.06 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 135.55, 133.94, 129.55, 127.60 (aromatic C's), 63.51 (C-1), 33.85 (C-5), 32.49 (CH_2), 31.59 (CH_2), 26.85 ($(CH_3)_3C$), 24.50 (CH_2), 19.19 ($(CH_3)_3C$). Anal. Calcd for $C_{21}H_{29}BrOSi$: C, 62.2; H, 7.2. Found: C, 64.5; H, 7.3.

(2*R*,*S*)-2-(3-(Benzyloxy)propyl)-7-((*tert*-butyldiphenylsilyl)oxy)heptanal Ethylene Acetal (19). Ethylene glycol (5.0 g, 80.4 mmol) and TsOH (catalytic amount) were refluxed in benzene (500 mL) with a Dean–Stark apparatus for 1.5 h. Compound **11** (31.95 g, 61.8 mmol) was dissolved in benzene (20 mL), and the solution was added to the reaction mixture and refluxed for 3 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2), giving a light yellowish oil, 32.54 g, 96%: TLC R_f = 0.2 (CH_2Cl_2); FAB-MS (3-nitrobenzyl chloride matrix) m/z (relative intensity) 559 (27), 409 (9), 199 (100), 135 (100), 91 (100), 57 (100); FAB-MS m/z (relative intensity) 559 (10), 199 (100), 134 (100), 90 (100); EI-MS m/z (relative intensity) 560 (8), 199 (100), 135 (100), 91 (100); ^{1}H NMR δ 7.69–7.66 (m, 4H, Ph), 7.43–7.29 (m, 11H, Ph), 4.77 (d, J = 4.0 Hz, 1H, H-1), 4.51 (s, 2H, $PhCH_2$), 3.95–3.83 (m, 4H, OCH_2CH_2O), 3.66 (t, J = 6.4 Hz, 2H, H-7), 3.47 (t, J = 6.5 Hz, 2H, H-3′), 1.69–1.34 (m, 13H), 1.06 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 138.62, 135.53, 134.11, 129.44, 128.30, 127.59, 127.54, 127.43 (aromatic C's), 106.59 (C-1), 72.83 ($PhCH_2$), 70.76, (C-3′), 64.84 (2C, OCH_2CH_2O), 63.93 (C-7), 41.26 (C-2), 32.53, 29.15, 27.34, 26.95 (CH_2's), 26.85 ($(CH_3)_3C$), 26.27 (CH_2), 25.44 (CH_2), 19.19 ($(CH_3)_3C$). Anal. Calcd for $C_{35}H_{48}O_4Si$: C, 75.0; H, 8.6. Found: C, 74.8; H, 8.9.

(2*R*,*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-2-(3-hydroxypropyl)heptanal Ethylene Acetal (20). Compound **19** (1.0 g, 1.82 mmol) was dissolved in ethanol (14 mL). $Pd(OH)_2$ (1.0 g, 20% on activated charcoal) and cyclohexene (7 mL) were added. This slurry was heated at 60 °C for 14 h and filtered through Celite. The solvent was evaporated and the residue purified by flash chromatography (SiO_2, P-ether/EtOAc, 0–40%), giving a colorless oil, 0.71 g, 83%: TLC R_f = 0.2 (25% EtOAc in P-ether); FAB-MS glycerol m/z (relative intensity) 469 (11), 409 (13), 199 (100), 73 (100); EI-MS m/z (relative intensity) 470 (M^+, 2), 413 (8), 199 (100), 73 (80); ^{1}H NMR δ 7.68–7.65 (m, 4H, Ph), 7.42–7.35 (m, 6H, Ph), 4.76 (d, J = 4.1 Hz, 1H, H-1), 3.98–3.81 (m, 4H, OCH_2CH_2O), 3.65 (t, J = 6.1 Hz, 2H, H-7), 3.63 (t, J = 6.0 Hz, 2H, H-3′), 1.63–1.22 (m, 13H), 1.04 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 135.53, 134.11, 129.45, 127.54 (aromatic C's), 106.64 (C-1), 64.84 (2C, OCH_2CH_2O), 63.92 (C-7), 63.08 (C-3′), 41.03 (C-2), 32.49, 30.35, 29.53, 26.87 (CH_2's), 26.84 ($(CH_3)_3C$), 26.24 (CH_2), 24.84 (CH_2), 19.19 ($(CH_3)_3C$); IR (neat) 3423 cm^{-1}. Anal. Calcd for $C_{28}H_{42}O_4Si$: C, 71.4; H, 9.0. Found: C, 71.5; H, 9.1.

Catalytic Hydrogenation of 19. Compound **19** (0.55 g, 1.0 mmol) was dissolved in ethanol (5 mL), and palladium (0.03 g, 10% on activated charcoal) was added. The mixture was agitated under a hydrogen atmosphere at either 1 or 4 atm for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated and purified by chromatography (SiO_2, P-ether/EtOAc, 0–60%). Compound **21** was eluted, followed by compound **22**.

(2*R,3*S**)-2-Ethoxy-3-(5-((*tert*-butyldiphenylsilyl)oxy)pentyl)-3,4,5,6-tetrahydro-2*H*-pyran (21):** TLC R_f = 0.4 (CH_2Cl_2); molecular weight 424; GC–MS retention time 28.60 min; GC–MS m/z (relative intensity) 397 (3), 351 (100), 199 (100); FAB-MS m/z (relative intensity) 453 (M − 1, 28), 351 (100), 199 (100); EI-MS m/z (relative intensity) 453 (M − 1, 1), 397 (15), 351 (73), 199 (100); ^{1}H NMR δ 7.89–7.81 (m, 4H, Ph), 7.60–7.40 (m, 6H, Ph), 4.58 (d, J = 2.7 Hz, 1H, H-2), 3.92–3.84 (m, 2H, H-6, CH_2O), 3.81 (t, 2H, J = 6.5 Hz, $SiOCH_2$), 3.70–3.51 (m, 2H, H-6, CH_2O), 1.86–1.22 (m, 15H), 1.35 (t, J = 6.9 Hz, 3H, CH_3), 1.20 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 135.5, 134.1, 129.4, 127.5 (aromatic C's), 99.1 (C-2), 63.9 ($SiOCH_2$), 62.5 (CH_3CH_2O), 59.5 (C-6), 39.8 (C-3), 32.5 (CH_2), 31.6 (CH_2), 26.8 ($(CH_3)_3C$), 26.4, 26.0, 25.7, 24.3 (CH_2's), 19.2 ($(CH_3)_3C$), 15.1 (CH_3). Anal. Calcd for $C_{28}H_{42}O_3Si$: C, 74.0; H, 9.3. Found: C, 73.9; H, 9.3.

(2*R,3*R**)-2-Ethoxy-3-(5-((*tert*-butyldiphenylsilyl)oxy)pentyl)-3,4,5,6-tetrahydro-2*H*-pyran (22):** TLC R_f = 0.2 (CH_2Cl_2); molecular weight 439; GC–MS retention time 28.59 min; GC–MS m/z (relative intensity) 454 (M^+, 1), 351 (100), 199 (71); EI-MS m/z (relative intensity) 453 (M − 1, 1), 409 (2), 397 (5), 351 (43), 199 (68); FAB-MS m/z (relative intensity) 453 (M − 1, 36), 351 (100); ^{1}H NMR δ 7.68–7.65 (m, 4H, Ph), 7.42–7.34 (m, 6H, Ph), 4.13 (d, J = 6.1 Hz, 1H, H-2), 3.93–3.81 (m, 2H, H-6, CH_2O), 3.64 (t, J = 6.4 Hz, 2H, $SiOCH_2$), 3.50–3.39 (m, 2H, H-6, CH_2O), 1.90–1.83 (m, 1H), 1.61–1.10 (m, 14H), 1.21 (t, J = 7.1 Hz, 3H, CH_3), 1.04 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 135.5, 134.1, 129.4, 127.5 (aromatic C's), 104.2 (C-2), 64.1 (CH_2O), 63.9 (CH_2O), 63.6 (CH_2O), 39.6 (C-3), 32.5 (CH_2), 30.7 (CH_2), 26.8 ($(CH_3)3C$), 26.5, 26.3, 26.0, 24.0 (CH_2's), 19.2 ($(CH_3)_3C$), 15.2 (CH_3). Anal. Calcd for $C_{28}H_{42}O_3Si$: C, 74.0; H, 9.3. Found: C, 74.1; H, 9.0.

(2*R*,*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-2-(3-(tosyloxy)propyl)heptanal Ethylene Acetal (25). Compound **20** (3.99 g, 8.46 mmol), NEt_3 (3.5 mL, 25.4 mmol), and DMAP (catalytic amount) were dissolved in CH_2Cl_2 (50 mL). TsCl (2.42 g, 12.69 mmol) was dissolved in CH_2Cl_2 (50 mL) and the solution added dropwise. The reaction mixture was stirred at rt for 14 h and extracted successively with saturated aqueous $NaHCO_3$ and citric acid solutions. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, P-ether/EtOAc, 0–50%), giving a colorless oil, 4.96 g, 94%: TLC R_f = 0.8 (25% EtOAc in P-ether); ^{1}H NMR δ 7.79 (d, J = 8.2 Hz, 2H, Ph), 7.68–7.65 (m, 4H, Ph), 7.42–7.31 (m, 8H, Ph), 4.69 (d, J = 3.8 Hz, 1H, H-1), 4.00 (t, J = 6.5 Hz, 2H, H-3′), 3.93–3.80 (m, 4H, OCH_2CH_2O), 3.64 (t, J = 6.3 Hz, 2H, H-7), 2.43 (s, 3H, CH_3), 1.73–1.19 (m, 13H), 1.04 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 144.57, 135.52, 134.08, 133.18, 129.76, 129.47, 127.87, 127.55 (aromatic C's), 106.30 (C-1), 70.79 (C-3′), 64.84, 64.77 (OCH_2CH_2O), 63.9 (C-7), 40.90 (C-2), 32.46 (CH_2), 29.31 (CH_2), 26.84 ($(CH_3)_3C$), 26.67 (CH_2), 26.20 (CH_2), 24.71 (CH_2), 21.61 ($PhCH_3$), 19.18 ($(CH_3)_3C$); IR (neat): 1180, 1105 cm^{-1}. Anal. Calcd for $C_{35}H_{48}O_6SSi$: C, 67.3; H, 7.7. Found: C, 68.2; H, 7.7.

(2*R*,*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-2-(3-iodopropyl)heptanal Ethylene Acetal (26). Compound **25** (2.59 g, 4.14 mmol) was dissolved in THF (50 mL), and sodium iodide (0.93 g, 6.21 mmol) was added. This two-phase system was stirred at rt for 48 h and partitioned between diethyl ether and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, P-ether/EtOAc 10%) giving a yellow oil, 2.13 g, 89%: TLC R_f = 0.7 (10% EtOAc in P-ether); ^{1}H NMR δ 7.71–7.76 (m, 4H, Ph), 7.46–7.30 (m, 6H, Ph), 4.74 (d, J = 4.0 Hz, 1H, H-1), 4.00–3.78 (m, 4H, OCH_2CH_2O), 3.65 (t, J = 6.5 Hz, 2H, H-7), 3.17 (t, J = 6.9 Hz, 2H, H-3′), 1.94–1.81 (m, 2H, H-2′), 1.66–1.26 (m, 11H), 1.04 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 135.34, 134.09, 129.45, 127.55 (aromatic C's), 106.47 (C-1), 64.89, 64.84 (OCH_2CH_2O), 63.90 (C-7), 40.72 (C-2), 32.47, 31.38, 29.96, 29.36 (CH_2's), 26.85 ($(CH_3)_3C$), 26.18 (CH_2), 19.19 ($(CH_3)_3C$), 7.37 (C-3′). Anal. Calcd for $C_{28}H_{41}IO_3Si$: C, 57.9; H, 7.1. Found: C, 57.9; H, 6.8.

(2*R*,9*S*)- and (2*S*,9*S*)-6-Aza-2-(5-((*tert*-butyldiphenylsilyl)oxy)pentyl)-9,10-dihydroxy-9,10-*O*-3-pentylidene-6-(trifluoroacetyl)decanal Ethylene Acetal (27). Compound **5** (0.76 g, 2.84 mmol) was dissolved in dry THF (5 mL) under a nitrogen atmosphere. NaH (102 mg, 3.40 mmol) was added in one portion. This slurry was stirred at rt for 30 min. Compound **26** (1.65 g, 2.84 mmol) was dissolved in dry THF (5 mL) and the solution added dropwise. This mixture was

refluxed for 22 h and partitioned between saturated aqueous NH_4Cl solution and diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, hexane/diethyl ether, 1:1), giving a colorless oil, 0.85 g, 41%: TLC R_f = 0.7 (hexane/diethyl ether, 1:2); $[\alpha]_D$ −1.1° (c = 1.0, CH_2Cl_2); ^{1}H NMR δ 7.69−7.65 (m, 4H, Ph), 7.45−7.34 (m, 6H, Ph), 4.77−4.72 (m, 1H, H-1), 4.10−4.04 (m, 2H), 3.97−3.81 (m, 4H), 3.67−3.33 (m, 7H), 1.68−1.26 (m, 19H), 1.03 (s, 9H, $(CH_3)_3C$), 0.93−0.85 (m, 6H, CH_3); ^{19}F NMR δ −62.31 (s), 62.42 (s); IR (neat) 1692 cm^{-1}. Anal. Calcd for $C_{39}H_{58}F_3NO_6Si$: C, 64.9; H, 8.1; N, 1.9. Found: C, 64.8; H, 8.0; N, 2.2.

(2*R*,9*S*)- and (2*S*,9*S*)-6-Aza-2-(5-((*tert*-butyldiphenylsilyl)oxy)pentyl)-9,10-dihydroxy-9,10-*O*-3-pentylidenedecanal Ethylene Acetal (28). Compound **27** (0.84 g, 1.16 mmol) was dissolved in THF (7.5 mL). Aqueous KOH (6%, 2.5 mL) and methanol (7.5 mL) were mixed and poured into the reaction mixture. This solution was stirred at rt for 22 h and partitioned between brine and diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated, giving a colorless oil, 0.68 g, 93%: $[\alpha]_D$ +1.2° (c = 1.0, CH_2Cl_2); ^{1}H NMR δ 7.96−7.65 (m, 4H, Ph), 7.62−7.29 (m, 6H, Ph), 4.75 (d, J = 4.3 Hz, 1H, H-1), 4.17−4.03 (m, 2H, H-9, H-10), 3.99−3.79 (m, 4H, OCH_2CH_2), 3.64 (t, J = 6.4 Hz, 2H, H-5′), 3.48 (t, J = 7.6, 1H, H-10) 2.75−2.56 (m, 4H, H-5, H-7), 1.85−1.32 (m, 19H), 1.24 (s, 9H, $(CH_3)_3C$), 0.90 (t, J = 7.4 Hz, 3H, CH_3), 0.88 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR δ 135.5, 134.0, 129.40, 127.50 (aromatic C's), 112.60 (OCO), 106.50 (C-1), 75.11 (C-9), 70.13 (C-10), 64.79 (2C, OCH_2CH_2O), 63.93 (C-5′), 50.20 (C-5), 46.86 (C-7), 41.29 (C-2), 33.69, 32.50, 29.88, 29.68, 29.14, 27.56, 26.90 (7 × CH_2), 26.81 ($(CH_3)_3C$), 26.56 (CH_2), 26.25 (CH_2), 19.15 ($(CH_3)_3C$), 8.23 (CH_3), 7.92 (CH_3). Anal. Calcd for $C_{37}H_{59}NO_5Si$: C, 71.0; H, 9.5; N, 2.2. Found: C, 70.4; H, 9.6; N, 2.2.

(2*S*,9*R*,10*S*)-9-(5-((*tert*-Butyldiphenylsilyl)oxy)pentyl)-2-(hydroxymethyl)-1-oxaquinolizidine, Hydrochloride Salt (29a). Compound **28** (0.66 g, 1.10 mmol) and $TsOH·H_2O$ (0.23 g, 1.21 mmol) were dissolved in CH_2Cl_2 (25 mL), and 25 drops of water was added. This mixture was stirred vigorously at rt for 36 h. Saturated aqueous $NaHCO_3$ (25 mL) was added, and stirring was continued for 45 min. This mixture was washed repeatedly with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethanol, 0−15%), giving a yellowish oil as the *cis*/*trans* mixture, 0.37 g, 68%, TLC R_f = 0.1 (10% ethanol in CH_2Cl_2). The oxaquinolizidine was converted to the hydrochloride salt in ethereal HCl, giving the pure *trans* form, and recrystallized from ethanol/diethyl ether: mp 143−146 °C; $[\alpha]_D$ (HCl salt) −35.8° (c = 1.0, CH_2Cl_2); $[\alpha]_D$ (free base) −18.5° (c = 1.0, CH_2Cl_2); ^{1}H NMR (HCl salt) (CD_3OD) δ 7.69−7.61 (m, 4H, Ph), 7.47−7.36 (m, 6H, Ph), 4.27 (d, J = 9.6 Hz, 1H, H-10), 3.91−3.83 (m, 1H, H-2), 3.69−3.53 (m, 5H, CH_2OH, CH_2OSi, CH_2N), 3.38−3.21 (m, 2H, CH_2N), 2.98 (dt, J = 12.8, 3.2 Hz, 1H, CH_2N), 2.05−1.20 (m, 15H), 1.03 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (HCl-salt) (CD_3OD) δ 136.69, 135.02, 130.85, 128.79 (aromatic C's), 96.85 (C-10), 79.62 (C-2), 64.90 (CH_2O), 64.69 (CH_2O), 53.69 (CH_2N), 53.15 (CH_2N), 41.41, 33.49, 31.52, 28.07, 27.39 ($(CH_3)_3C$), 27.06, 26.83, 26.38, 23.50, 20.05 ($(CH_3)_3C$); IR[44] (free base, neat) 3390 (br), 2752 cm^{-1}. Anal. Calcd for $C_{30}H_{45}NO_3Si$: C, 72.7; H, 9.1; N, 2.8. Found: C, 72.5; H, 9.3; N, 2.8.

(2*S*,9*R*,10*S*)- and (2*S*,9*S*,10*S*)-9-(5-((*tert*-Butyldiphenylsilyloxy)pentyl)-2-(acetoxymethyl)-1-oxaquinolizidine (31a and 31b). Compound **29** (52 mg, 0.10 mmol), NEt_3 (29 μL, 0.21 mmol), and a catalytic amount of DMAP were dissolved in CH_2Cl_2 (1 mL). Acetic anhydride (15 μL, 0.16 mmol) was added. The reaction mixture was stirred at rt for 3 h and extracted with brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethanol, 0−15%), giving a colorless oil, 32.4 mg, 58%, of the *cis*/*trans* mixture. The *trans* form could be enriched by repeated flash chromatography: TLC R_f = 0.7 (15% ethanol in CH_2Cl_2); $[\alpha]_D$ −17.0° (c = 1.0, CH_2Cl_2); ^{1}H NMR δ 7.68−7.65 (m, 4H, Ph), 7.44−7.34 (m, 6H, Ph), 4.13−4.04 (m, 2H, CH_2O), 3.66−3.60 (m, 3H, H-2, CH_2OSi), 3.04 (d, J = 8.3 Hz, 1H, H-10), 3.00−2.94 (m, 1H, H-4$_{eq}$), 2.80−2.75 (m, 1H, H-6$_{eq}$), 2.31−2.21 (m, 1H, H-4$_{ax}$), 2.04 (s, 3H, CH_3), 2.10−2.00 (m, 1H, H-6$_{ax}$), 1.88−1.08 (m, 15H), 1.04 (s, 9H, $(CH_3)_3C$); ^{13}C NMR δ 170.94 (C=O), 135.52, 134.14, 129.43, 127.53 (aromatic C's), 97.05 (C-10), 74.70 (C-2), 66.78 (CH_2O), 63.97 (CH_2O), 53.37 (CH_2N), 53.31 (CH_2N), 40.56 (CH_3), 32.56, 31.41, 28.79, 27.28, 26.85 ($(CH_3)_3C$), 26.47, 26.20, 24.35, 20.85, 19.19 ($(CH_3)_3C$); IR (neat) 2803, 2751, 1742 cm^{-1}. The presence of the *cis* isomer was concluded from the observation of the characteristic ^{13}C NMR signal at δ 90.5 ppm (C-10).

(2*S*,10*S*)-2-(Acetoxymethyl)-1-oxaquinolizidine (32). Compound **30**[7] (25 mg, 0.15 mmol), NEt_3 (40 μL, 0.30 mmol), and DMAP (catalytic amount) were dissolved in CH_2Cl_2 (1 mL). Acetic anhydride (21 μL, 0.22 mmol) was added in one portion. The solution was stirred at rt for 1 h and extracted with brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (Al_2O_3, CH_2Cl_2), giving a yellowish oil, 11 mg, 36%: TLC R_f = 0.6 (CH_2Cl_2 on Al_2O_3); $[\alpha]_D$ +5.3° (c = 1.0, CH_2Cl_2); ^{1}H NMR δ 4.16−4.01 (m, 2H, CH_2O), 3.72−3.66 (m, 1H, H-2), 3.46 (dd, J = 8.7, 3.0 Hz, 1H, H-10), 2.96 (ddd, J = 11.6, 4.4, 2.2 Hz, 1H, H-4$_{eq}$), 2.82 (ddt, J = 11.4, 3.7, 1.3, 1H, H-6$_{eq}$), 2.34 (dt, J = 3.2, 12.1 Hz, 1H, H-4$_{ax}$), 2.08 (s, 3H, CH_3), 2.13−2.04 (m, 1H, H-6$_{ax}$), 1.85−1.24 (m, 8H); ^{13}C NMR δ 171.07 (C=O), 92.44 (C-10), 74.70 (C-2), 66.89 (CH_2O), 53.00 (C-6), 52.74 (C-4), 31.41 (C-3), 26.72 (CH_2), 25.04 (CH_2), 22.58 (CH_2), 20.96 (CH_2).

(2S,10S)-2-((Benzyloxy)methyl)-1-oxaquinolizidine (33). Compound **30** (43 mg, 0.25 mmol) was dissolved in dry THF (1 mL) under a nitrogen atmosphere. NaH (15 mg, 0.50 mmol) was added, and the slurry was stirred at rt for 1 h. Benzyl bromide (35 μL, 0.30 mmol) was dissolved in dry THF (1 mL) and the solution added dropwise. The reaction mixture was stirred at rt for 20 h and partitioned between brine and CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethanol, 0−6%), giving a colorless oil, 29 mg, 44%: TLC R_f = 0.8 (10% ethanol in CH_2Cl_2); ^{1}H NMR δ 7.35−7.28 (m, 5H, Ph), 4.62 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.52 (d, J = 12.3 Hz, 1H, $PhCH_2$), 3.71−3.65 (m, 1H, H-2), 3.55 (dd, J = 9.8, 6.4 Hz, 1H, CH_2O), 3.46 (dd, J = 8.9, 2.7 Hz, 1H, H-10), 3.40 (dd, J = 9.9, 4.4 Hz, 1H, CH_2O), 2.92 (ddd, J = 12.0, 4.5, 2.0 Hz, 1H, H-4$_{eq}$), 2.83−2.79 (m, 1H, H-6$_{eq}$), 2.33 (dt, J = 12.0, 3.0 Hz, 1H, H-4$_{ax}$), 2.11−2.01 (m, 1H, H-6$_{ax}$), 1.80−1.17 (m, 8H); ^{13}C NMR δ 138.18, 128.27, 127.71, 127.51 (aromatic C's), 92.35 (C-10), 76.07 (C-2), 73.30 ($PhCH_2$), 73.06 (CH_2O), 53.13 (C-6), 52.75 (C-4), 31.43 (C-3), 27.36 (CH_2), 25.03 (CH_2), 22.60 (CH_2).

Ionization Constant Determination.[45] The pK_a for the hydrochloride salt of **30** was determined by using a calibrated (buffers pH 7 and 10, Titrisol, Merck) glass electrode with an internal reference electrode (Mettler DG 111-SC) by potentiometric titration using an automatic titrator (Mettler DL25). The hydrochloride salt (32.51 mg) was dissolved in 50 mL of 0.1 M NaCl in carbonate-free water, giving a concentration of 3.13 mM. The titration was performed with 0.1 N NaOH (Titrisol, Merck) by constant volume addition of 0.10 mL at 25 °C, giving a pK_a = 7.69 ± 0.02.

X-ray Diffraction Analysis. Compound **30** was crystallized as a hydrochloride salt. Crystals with suitable size for X-ray study were grown from an ethanol/diethyl ether mixture (mp 146−148 °C). Crystal data: 30 × HCl, $C_9H_{18}NO_2Cl$, M = 207.70, monoclinic ($P2_1$), a = 7.345(1) Å, b = 13.855(1) Å, c = 10.735(1) Å, β = 97.06(1)°, V_c = 1086.0(2) Å^3, Z = 4, F(000) = 448, D_c = 1.2703(2) g cm^{-3}, μ = 0.323 mm^{-1}. Setting angles of 36 reflections with 16° < 2θ > 24° were used in the refinement of the unit cell parameters. Intensity data were collected from a colorless single crystal with the approximate dimensions 0.41 × 0.41 × 0.11 mm. A total of 3290 reflections were collected at room temperature (291(2) K) with Mo Kα radiation (λ = 0.710 69 Å, θ_{max} = 30°), using the ω−2θ scan

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technique. Data reduction included corrections for Lorentz and polarization effects.

The structure was solved by application of direct methods (SHELXS-90)[46] and refined by full-matrix least-squares calculations (SHELXL-93)[47] based on F^2 for all reflections. A difference electron density map showed the presence of all hydrogen atoms, except H12′, at reasonable positions. The non-hydrogen atoms were treated anisotropically, whereas isotropic vibrational parameters were refined for the H atom positions, which were calculated using geometric evidence (SHELXL-93). Thus, the refinement procedure of 271 variables yielded $R = 0.041$ for 1515 observations with $F > 4\sigma(F)$, $R_w = 0.0916$ for 3278 F^2 values, and S (= goodness of fit for all reflections) = 0.916. Twelve reflections were excluded from the final refinement calculation due to potential errors. The weights of the reflections were assumed as $w = 1/[\sigma^2(F_o^2) + (0.0400P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$.[47] Material for publication was prepared using the software of SHELXL-93 and PARST.[48] The illustrations were drawn with the molecular graphics program XP of the SHELXTL PC system.

Molecular Mechanics Calculations. Unrestricted molecular mechanics calculations were performed using the MM2(91) force field as included in the MacMimic[49] program, the MMX force field as included in the PcModel[50,51] program (Version PI 3.1), and the MM2* force field included in the MacroModel[52] program (Version V3.5X). The calculations using the MM2* force field were performed in vacuum, H_2O, and $CHCl_3$ matrices.[53-55] The H-BND was activated during the minimizations to take into account potential hydrogen bonds. The starting geometries were built from *trans*- and *cis*-decalin in chair and boat forms. Nitrogen and oxygen were added, and the structures were minimized. Stepwise addition of the substituents on C9 and C2, keeping the *S*-configuration on C2, gave 144 starting geometries for **29**, the alkyl group at C9 being simplified to a methyl group. The MM2(91) force field does not contain parameters for the hemiaminal system, N−C−O. The parameters reported by Senderowtitz *et al.* were used.[39]

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Supplementary Material Available: Torsional angles and relative energies for all conformers from molecular mechanics calculations for **29** and **30** within the cutoff value (Tables I−VII) (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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