Synthesis of the C_2-Symmetric, Macrocyclic Alkaloid, (+)-Xestospongin A and Its C(9)-Epimer, (−)-Xestospongin C: Impact of Substrate Rigidity and Reaction Conditions on the Efficiency of the Macrocyclic Dimerization Reaction

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Abstract: Xestospongin A [also known as araguspongine D (**1**)], a C_2-symmetric macrocyclic alkaloid isolated from the sponge *Xestospongia exigua* (*Xestospongia* sp.), and its C(9) epimer xestospongin C [also known as araguspongine E (**2**)] have been synthesized. The route capitalizes on the facile condensation between 5-halovaleraldehydes and 1,3-aminoalcohols to produce an oxaquinolizidine ring system in which all proper relative stereochemical relationships are controlled by equilibration. A linchpin synthesis was used to construct one key monomeric precursor—a 2,5-disubstituted thiophene derivative **26** [N≡CCH_2CH(OH)-2-Th-5-$CH_2CH_2CH(CH(OMe)_2)CH_2CH_2CH_2Cl$]. A second precursor lacking the thiophene ring **38** [N≡$CCH_2CH(OH)(CH_2)_6CH(CH(OMe)_2)CH_2CH_2CH_2Cl$] was assembled in a similar fashion. The carbinol center in each of these precursors was efficiently resolved enzymatically; lipase (PS-30) hydrolysis of the racemic acetate derivative of the thiophenemethanol derivative **26** and SP-435-catalyzed esterification of the β-hydroxynitrile **38** proved effective. The initial macrocyclization strategy involved (i) hydrolysis of a portion of monomer **(+)-26** to the corresponding aldehyde, (ii) reduction of the nitrile to a 1,3-aminoalcohol derivative with a second portion of the monomer, (iii) condensation of these two, end-differentiated monomers to give the "half-cyclized" oxaquinolizidine **30** that bears pendant nitrile and acetal groups, (iv) sequential reduction and acid-catalyzed hydrolysis to give the corresponding aldehyde ammonium ion **31**, and v) dilution and elevation of pH leading to the macrocyclic bis-thiophene **(−)-32**. Final reductive removal of both thiophenes with Raney nickel proceeded smoothly to give (+)-xestospongin A/(+)-araguspongine D (**1**). The impact of pH-control, concentration effects, and monomer rigidity on the macrocyclic dimerization event are discussed. A more direct strategy involved sequential nitrile reduction and acetal hydrolysis within **(+)-26** and direct, two-stage macrocyclic dimerization to **(−)-32**. Control of pH is important to the success of this cyclization. In an analogous fashion the non-thiophene monomer **(−)-38** was converted to the ammonium ion/aldehyde ***S*-41**. This could be used to probe the effect of substrate rigidity on the efficiency of macrocycle formation. Substrate ***S*-41** spontaneously dimerized to produce a mixture of xestospongin A (**1**) and xestospongin C (**2**) with similar efficiency to the thiophene-containing **33**.

Introduction

Xestospongins[1] A (**1**) and C (**2**) were isolated from the Australian sponge *Xestospongia exigua* by Nakagawa and Endo in 1984.[2] Kitagawa later isolated a related set of alkaloids, araguspongines A−H, from the Okinawan sponge *Xestospongia* sp. and demonstrated that araguspongine D was identical with xestospongin A (**1**).[3] Various xestospongin/araguspongine alkaloids possess vasodilative[4] and cytotoxic[5] properties.

We recently showed that araguspongine E is identical with xestospongin C (**2**).[6] Isomers **1** and **2** are C(9) epimers of one another and each contains a pair of bis-oxaquinolizidine (hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine) moieties. As is clear from analysis of the single crystal X-ray structure of **2**,[2] the parent oxaquinolizidine ring system can access both *trans*-decalin-like and *cis*-decalin-like conformations by bridgehead nitrogen atom inversion. In addition, the two attachment sites of the hexamethylene chains on any single oxaquinolizidine ring [C(2) and C(9)] can have a *trans*-dialkylated (2,9-*like*) or a *cis*-dialkylated (2,9-*unlike*) orientation. We have reported detailed analyses and discussion of the conformational and configurational intricacies within the natural products as well as a series of 2-mono-, 9-mono-, and 2,9-dialkylated model 1-oxaquinolizidine systems.[6,7] All of our (principally NMR-based) observations are consistent with the notions that (i) *trans*-dialkylated rings coincidentally reside to a large extent in the *trans*-decalin-like conformation (cf. both of the identical oxaquinolizidine rings in **1** as well as the "bottom" ring in **2**) and (ii) *cis*-dialkylated rings reside to a large extent in the *cis*-decalin-like conformation (cf. the "top" ring in **2**). The absolute configuration of the araguspongines, including araguspongine D (xestospongin A, **1**), was assigned by Kitagawa *et. al.* on the basis of applications of Hudson's rule and the Horeau method.[3] Several strategies for synthesis of the xestospongins have been

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(2) Nakagawa, M.; Endo, M.; Tanaka, N.; Lee, G. *Tetrahedron Lett.* **1984**, *25*, 3227.

(3) Kobayashi, M.; Kawazoe, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 1676.

(4) (a) Kitagawa, I.; Kobayashi, M. *Gazz. Chim. Ital.* **1993**, *123*, 321. (b) Vassas, A.; Bourdy, G.; Paillard, J. J.; Lavayre, J.; Pais, M.; Quirion, J. C.; Debitus, C. *Planta Med.* **1996**, *62*, 28.

(5) (a) Stingl, J.; Andersen, R. J.; Emerman, J. T. *Cancer Chemother. Pharmacol.* **1992**, *30*, 401. (b) Quirion, J-C.; Sevenet, T.; Husson, H-P.; Weniger, B.; Debitus, C. *J. Nat. Prod.* **1992**, *55*, 1505.

(6) Hoye, T. R.; North, J. T.; Yao, L. J. *J. Org. Chem.* **1994**, *59*, 6904.

(7) Hoye, T. R.; North, J. T. *Tetrahedron Lett.* **1990**, *31*, 4281.

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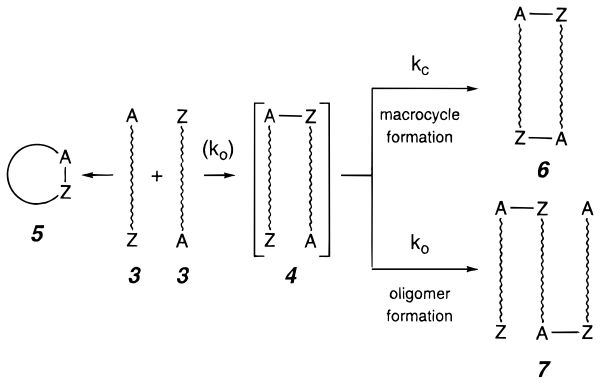
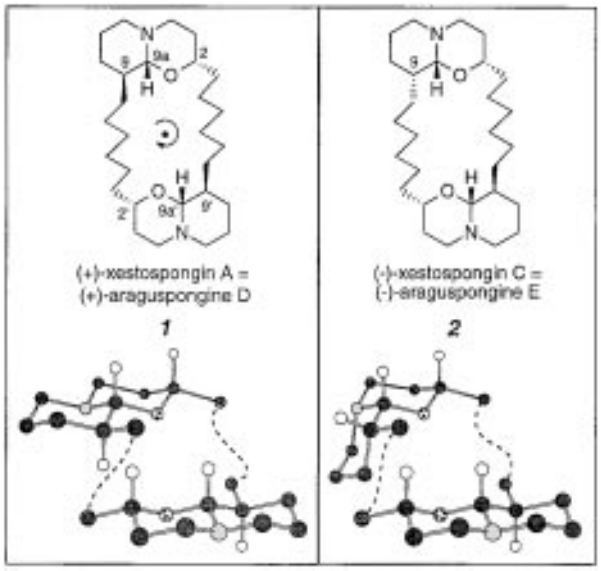
Scheme 1



reported,[7,8] and we communicated the first synthesis of xestospongin A in 1994.[8c]

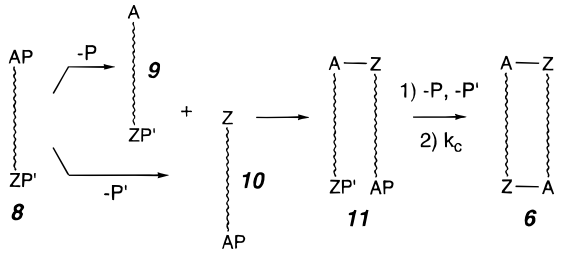


Given the C_2-symmetry of xestospongin A (**1**), we initially envisioned the construction of this macrocycle via the dimerization of two, bifunctional, monomeric units **3** in which the A and Z groups are cross-reactive[9] (strategy A, Scheme 1). The constraints on the coupling reactions of A with Z are as follows: (i) two molecules of **3** must react intermolecularly to generate **4** faster than the intramolecular reaction to generate monocyclic product **5** and (ii) the observed rate of macrocyclization of **4** (i.e., k_c[**4**]) must be faster than a second (and subsequent) intermolecular event (i.e., k_o [**3**][**4**]) to generate a trimer (and higher oligomers). It is reasonable to assume that the oligomerization rate constant, k_o, will be essentially the same as that for the initial coupling of two molecules of **3**. Clearly the overall concentration of **3** will significantly impact the product ratio—**6** can only be formed by initial bimolecular and subsequent unimolecular events. Likewise, the degree of rigidity within the tether connecting A with Z in **4** will influence its rate of cyclization (k_c)—fewer degrees of freedom in **4** would be expected to bias the branching ratio for **4** favorably toward formation of **6** by increasing k_c.

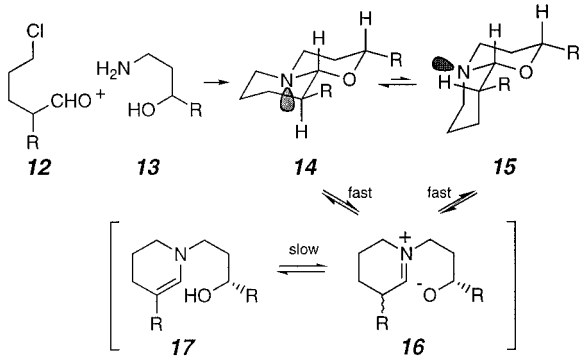
(8) (a) Ahn, K. H.; Lee, S. J. *Tetrahedron Lett.* **1992**, *33*, 507. (b) Börjesson, L.; Welch, C. J. *Tetrahedron* **1992**, *48*, 6325. (c) Hoye, T. R.; North, J. T.; Yao, L. *J. Am. Chem. Soc.* **1994**, *116*, 2617. (d) Börjesson, L.; Csoeregh, I.; Welch, C. J. *J. Org. Chem.* **1995**, *60*, 2989.

(9) (a) Ercolani, G.; Mandolini, L.; Mencarelli, P. *Macromolecules* **1988**, *21*, 1241. (b) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901.

Scheme 2



Scheme 3



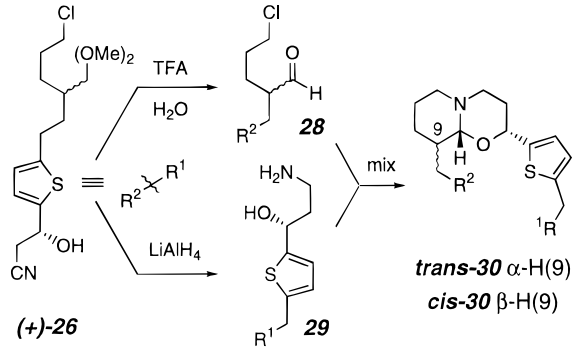
We initially chose to investigate a more conservative, stepwise route (strategy B, Scheme 2). In this scenario, the functional groups A and Z are differentially protected by P and P′, respectively. The first pair of deprotections within individual samples of **8** is followed by the first A to Z coupling event between **9** and **10**. The remaining P and P′ protecting groups are removed from **11**, and the formation of the macrocyclic dimer **6** is achieved. There is no possibility for oligomerization during the initial cross-reaction, and, if necessary, the macrocyclization can benefit from the traditional use of high-dilution conditions. We successfully implemented strategy B in our initial synthesis of xestospongin A (**1**);[8c] we also describe here our more recent successes using strategy A to prepare both xestospongins A (**1**) and C (**2**). Important features of this study include (i) the use of protons as amine protecting groups (i.e., pH control of amine concentration) and (ii) the effect of substrate rigidity on the macrocyclization reactions.

Discussion

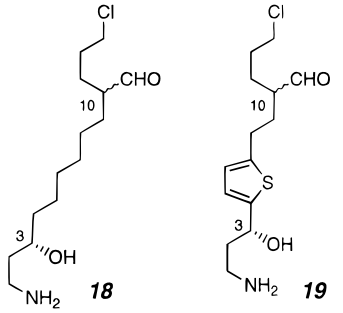
Each of strategies A and B required the development of a facile reaction for coupling of the two halves (i.e., A + Z to A−Z). The simple condensation of a 5-halovaleraldehyde like **12** with a 1,3-aminoalcohol like **13** proved to be ideal (Scheme 3).[7] Studies of the dialkylated oxaquinolizidines **14** and **15** (R = Me or Bu) established the clear thermodynamic preference for the *trans*-dialkylated (or xestospongin A-like) orientation of the alkyl groups (i.e., **14** is more stable than its C(9)-epimer **15**) as well as the fact that these diastereomers could be efficiently interconverted. This was explained by a rapidly reversible opening of **14** or **15** to the iminium ion **16** and a slower, reversible proton transfer in **16** to generate the enamine **17**.[7] These experiments clearly implied that the configuration of the carbinol center in **13** would control all relative configurations within the newly formed oxaquinolizidines **14** and **15**. Thus, eventual dimerization of a monomer containing a C(3) carbinol center of a single configuration would control all relative and absolute stereochemical features within C_2-symmetric **1**.

Bifunctional monomer **18** (and protected versions thereof) was identified as the key intermediate for the ultimate xesto-

Scheme 4



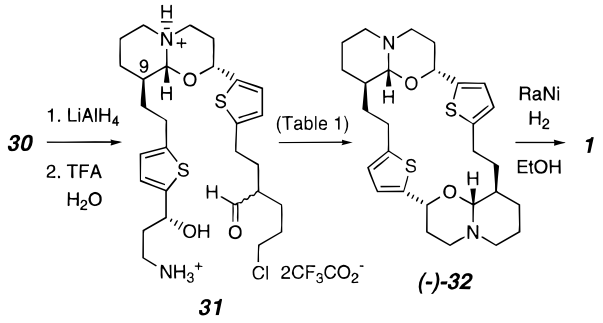
spongin synthesis. It contains the naturally configured *S*-carbinol center and a (tolerable) mixture of epimers at the formyl substituted center. For expediency in construction of a synthetic equivalent of **18** bearing a single carbinol configuration, we initially targeted the corresponding thiophene **19**. The thiophene was envisioned as a linchpin for introduction of the remaining atoms of the monomer carbon skeleton, as an aromatic moiety for keying an anticipated enzyme-mediated carbinol resolution, and as a rigidifying unit to ensure lack of monocyclization (cf. **3** to **5**) and for promotion of the ultimate macrocyclization reaction (i.e., a more favorable k_c/k_o ratio).



β-Hydroxynitrile **(+)-26**, a protected version of monomer **19**, was synthesized in nine steps from 5-chlorovaleronitrile.[10] Implementation of strategy B involved hydrolysis of the acetal in a portion of the orthogonally protected monomer **(+)-26** (Scheme 4) to give the aldehyde **28** (99%); a second portion of **(+)-26** was reduced with lithium aluminum hydride to the aminoalcohol **29** (92%). When this 1,3-aminoalcohol and 5-chlorovaleraldehyde were combined at room temperature in methylene chloride, they spontaneously condensed[7] to afford a separable mixture of the oxaquinolizidine isomers ***trans*-30** and ***cis*-30** in 42% and 29% isolated yield, respectively. The *cis* isomer could be equilibrated[3,6,7] with the *trans* ($K_{eq(trans/cis)}$ ~2) in the presence of triethylamine at 80 °C ($CDCl_3$ solution, ~3 h). This equilibration presumably occurred by the pathway outlined in Scheme 3.

The termini in the "half-cyclized" ***trans*-30** were prepared for macrocyclization by stepwise revelation of the amine and aldehyde functional groups (Scheme 5). Lithium aluminum hydride reduction of the nitrile proceeded smoothly (78%) and, fortunately, was not complicated by competitive reduction of the aminal center. The resultant aminoalcohol was subjected to acid-catalyzed hydrolysis to generate the bis-ammonium ion **31**. This ion was characterized by ^{1}H NMR spectroscopy. In fact, the original conditions for effecting this hydrolysis were identified by reactions performed in DMSO-d_6/D_2O with TFA-*d* at 80 °C. The resultant bis-ammonium ion **31** was stable for at least 2 weeks at room temperature (NMR analysis). Under these same conditions ***cis*-30** gave the same, *trans*-substituted bis-ammonium ion **31**. In other words, isomerization of the oxaquinolizidine diastereomers occurs during the acid-catalyzed hydrolysis, and the equilibrium of the protonated oxaquinolizidine ring system is strongly shifted in favor of the *trans*-fused (or xestospongin A-like) stereochemistry. The epimerization at C(9) of the oxaquinolizidine was accompanied by deuterium incorporation at that site, again consistent with protonation of the enamine **17** in Scheme 3. The stability of **31** in solutions of low pH demonstrated that the proton on the primary ammonium ion served as an effective protecting group that prevented condensation with the aldehyde. This made it possible to dilute the concentration of solutions of **31** and then raise the pH to increase the concentration of free amine. Specifically, when excess 5% aqueous sodium hydroxide was added to the upper layer of a two-phase mixture of **31** in dichloromethane (8 μM) and water until the pH reached ~12, the C_2-symmetric macrocyclic bis-thiophene **(-)32** was isolated in ~70% yield following purification (90:10:0.01 MeOH:H_2O:Et_3N on C_{18}-silica). Both thiophene rings in macrocycle **(−)-32** were then cleanly removed by Raney nickel reduction (1 atm H_2, 95% EtOH, room temperature, 1 h, 72%) to give the first synthetically derived sample of xestospongin A.[8c]

Scheme 5



The extremely high-dilution (run 1 in Table 1) necessary for this initial macrocyclization reaction prompted us to study in some detail the role of concentration and pH on the efficiency of this cyclization. That such high dilution was critical when the cyclization was performed in a two-phase mixture using a high pH was supported by the experiment reported in run 2; the yield fell to 25% when the bulk concentration of amine was 600 μM. We recognized that the concentration of free amine would be directly related to the effective pH of the cyclization medium. When a DMSO solution of the bis-ammonium ion **31** was added to a 10% aqueous methanol solution containing 0.05 M acetate or phosphate buffer, a homogeneous solution resulted. The rates of disappearance of starting material could be monitored directly by reverse-phase HPLC. Starting with a bulk concentration of 1.5 mM of **31** at pHs ranging from 6.0−8.0, the conversion rates at room temperature were convenient to follow. As the pH of the buffer was gradually decreased, the reaction rates slowed, and the yields of macrocycle **(−)-32** increased slightly. In general, the yields were quite good under any of these conditions, consistent with the notion that the buffer

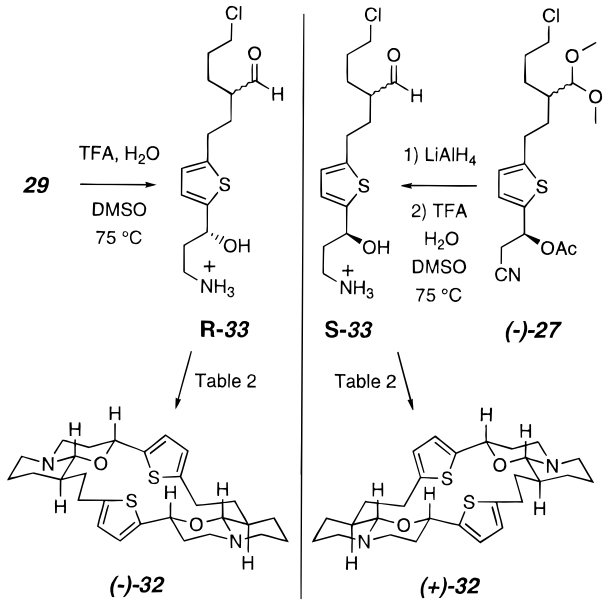
(10) Intermediates **(+)-26** (Scheme 4) and **(−)-27** (Scheme 6) were prepared from (±)-5-chloro-2-(2-hydroxyethyl)pentanenitrile (**20**). Thus, the primary alcohol was converted to bromide **21**, the nitrile was reduced to aldehyde **22**, the aldehyde was protected as its dimethyl acetal **23**, the primary bromide was chemoselectively displaced with 2-lithiothiophene to give **24**, the 5-position of this thiophene was lithiated and formylated to give aldehyde **25**, lithioacetonitrile was added to provide a racemic *β*-hydroxynitrile **(±)-26**, and the secondary alcohol was acetylated to the racemic acetates **(±)-27**. Enzymatic kinetic resolution with Amano PS-30 in a two-phase water/ether system gave **(+)-26** and **(−)-27**. This is the same sequence reported in our original communication.[8c] However, the procedures for preparing **20**−**27** are included as Supporting Information for this paper since improvements in yield accompanied scale-up in work done subsequent to the preliminary report.

Table 1. Effect of pH on the Macrocyclization of Bis-Thiophene ***trans*-31**

run no.	conc (mM)[a]	pH[b]	time (h)	solvents	yield (%) of **(−)-32**[c]
1	0.008	>12	20	1:1 CH_2Cl_2:H_2O[d]	70[e]
2	0.6	>12	20	1:1 CH_2Cl_2:H_2O[d]	25[f]
3	1.5	8.0	3[g]	9:1 MeOH:buffer[h]	76
4	1.5	7.5	7[g]	9:1 MeOH:buffer[h]	79
5	1.5	7.0	12[g]	9:1 MeOH:buffer[i]	81
6	1.5	6.5	24[g]	9:1 MeOH:buffer[i]	84
7	1.5	6.0	120[g]	9:1 MeOH:buffer[i]	85
8[j]	2.0	7.0	12[g]	9:1 MeOH:buffer[i]	58[k]

[a] Concentration of the starting ammonium ion *trans*-31. [b] The measured pH of the methanol/water buffer solution. [c] Yields are for isolated material for runs 1, 2, and 8 and were determined by HPLC [9:1 MeOH:buffer (pH 5.0) on C_{18}-silica] integration vs an internal standard (4,4′-bis-*tert*-butylbiphenyl) for the other runs. [d] Two phase reaction mixture. [e] Reaction performed on a 3 mg scale. [f] Reaction performed on a 10−80 mg scale. [g] Time at which initial quantity of thiophene had diminished to <1%. [h] KH_2PO_4/K_2HPO_4 buffer (0.05 M), pH = 7.0−8.0. [i] AcOH/NaOAc buffer (0.05 M), pH = 6.0−7.0. [j] Starting dimethyl acetal for hydrolysis was ***cis*-30**. [k] Reaction performed on a ∼25 mg scale.

Scheme 6



is reducing the concentration of free amine by 2−4 orders of magnitude below the bulk concentration of starting ammonium ion. For preparative runs we settled on the pH = 6.5 buffer; under these conditions a 76% yield of **(−)-32** was isolated. A small amount (1−2%) of a byproduct was occasionally observed during this reaction, but we were unable to determine its structure. Thus, at most, only a few percent of a macrocycle containing the cis-disubstituted oxaquinolizidine ring stereochemistry characteristic of xestospongin C (**2**) was formed from the bis-thiophene precursor ***trans*-31**.

Armed with this encouraging information we next studied the implementation of strategy A (direct macrocyclic dimerization from monomers) for the case of the thiophene linked monomer **19**. Thus, the nonracemic amino acetal **29** was hydrolyzed in aqueous, acidic DMSO to once again give the solution stable (at least 3 months at ∼−20 °C in DMSO/D_2O/TFA) ammonium ion ***R*-33** (Scheme 6). Likewise, ***S*-33** could be prepared from acetoxynitrile **(−)-27** by direct reduction with lithium aluminum hydride and subsequent acetal hydrolysis. We were delighted to observe reasonably efficient macrocyclic dimerization of ***R*-33** to generate the macrocyclic bis-thiophene **(−)-32**. The enantiomer ***S*-33** was independently cyclized to **(+)-32**, which was desulfurized to produce *ent*-xestospongin A **(−)-1**.[11] The results of performing this cyclization at various concentrations are summarized in Table 2. The optimal concentration appears to be near 1−2 mM at pH = 7 (51% isolated yield of **32**).

Table 2. [a] Effect of Concentration on the Yield of Macrocyclic Dimerization of Thiophene Monomers ***R*-33** and ***S*-33** at pH = 7.0[b]

run no.	concn (mM)[c]	solvent	yield (%) of **32**[d]
1	4	CH_2Cl_2/H_2O/NaOH[e]	8
2	4	100% buffer	31
3	1	9:1 MeOH:buffer	51
4	2	9:1 MeOH:buffer	60
5	10	9:1 MeOH:buffer	53
6	20	9:1 MeOH:buffer	49
7	50	9:1 MeOH:buffer	37

[a] All reactions were allowed to proceed for 24 h; HPLC analysis indicated that all starting material had been consumed in each case; it was assumed that oligomers comprised the remaining products. [b] The measured pH of the methanol/water buffer solution [AcOH/NaOAc buffer (0.05 M)]. [c] Concentration of the starting ammonium ion **33**. [d] Yields were for isolated material for runs 1−3 and were determined by HPLC [9:1 MeOH:buffer (pH 5.0) on C_{18}-silica] integration vs an internal standard (4,4′-bis-*tert*-butylbiphenyl) for runs 4−7. [e] pH > 12.

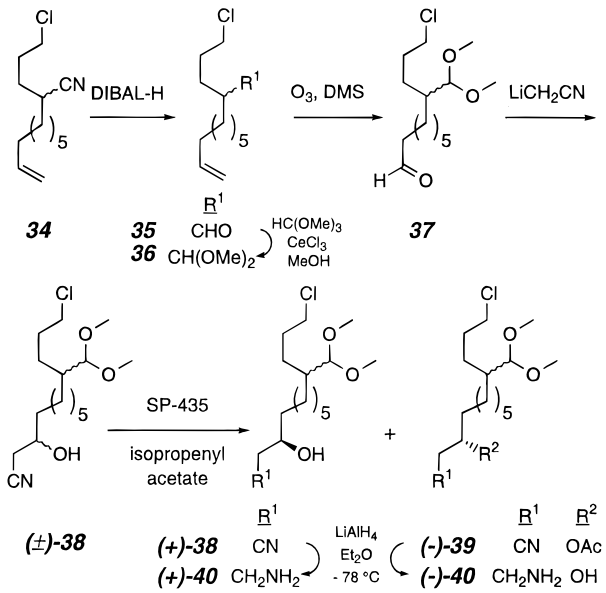
Attention was next turned to the question of whether the rigid thiophenes were necessary for favorable partitioning between cyclization and oligomerization (k_c/k_o ratio, Scheme 1). Thus, monomer **18**, containing four methylenes in lieu of the thiophene ring, was needed for cyclization. We initially attempted to prepare **38**, a protected version of monomer **18**, by Raney nickel reduction of the thiophene ring in acetate **26**, alcohol **29**, or the corresponding TBS ether. These reactions were only marginally successful. Competitive hydrogenolysis of the "thiophenylic" C−O bond and/or of the terminal C−Cl bond and nitrile reduction were often observed. Although on two occasions we obtained over 50% yield of the desired tetramethylene compound, the reactions were not easily reproducible, presumably because of irregularities in catalyst preparation that made overreduction difficult to control.

Nitrile acetal **38** was instead synthesized by the sequence summarized in Scheme 7. Alkylation of 5-chlorovaleronitrile with 8-bromo-1-octene (LDA, −78 °C) gave **34** (89%), which was reduced to aldehyde **35** (86%) and protected as the dimethyl acetal **36** (97%). Ozonolysis exposed a terminal aldehyde to which was added lithioacetonitrile to give the racemic β-hydroxynitrile **(±)-38** (78%). The carbinol center could be efficiently resolved by transesterification with vinyl acetate using SP-435 as the catalyst.[12] the immobilized lipase from Novo Nordisk, into alcohol **(+)-38** [49% yield, 91% "ee" by MTPA analysis; this material was resubjected to the same conditions and **(+)-38** (≥98% "ee") was recovered in 44% overall yield] and the acetate **(−)-39** [42%, ≥98% "ee" by MTPA analysis of the alcohol **(−)-38** arising from MeLi treatment of **(−)-39**]. Lithium aluminum hydride reduction of the nitrile group in **(+)-38** or in **(−)-39** gave the aminoalcohol **(+)-40** (87%) or **(−)-40** (79%), respectively, differing in configuration at the carbinol center. The acetal in **(−)-40** was hydrolyzed to the aldehyde ***S*-41** (Scheme 8). Cyclization of ***S*-41** under the same conditions used for the thiophene-containing monomers **33** [pH = 7.0 acetate buffer in 10% aqueous MeOH (2.0 mM)] proceeded

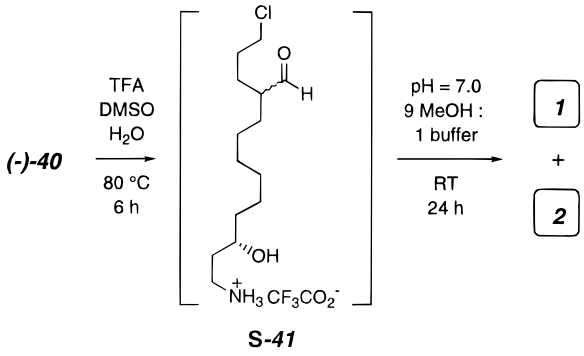
(11) *ent*-Xestospongin A **(−)-1** was also prepared by the stepwise route proceeding from **(−)-27** via ***ent*-28-Ac**, ***ent*-29**, ***ent-trans*-30-Ac**, ***ent-cis*-30-Ac**, ***ent*-31**, and **(+)-32** [where −Ac designates the acetate ester of the enantiomers of the corresponding alcohols **28**, ***trans*-30**, and ***cis*-30** (Scheme 5)].

(12) (a) β-Hydroxynitriles: Itoh, T.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1991**, *56*, 1521. (b) SP-435: Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287.

Scheme 7



Scheme 8



remarkably smoothly to give, following basic workup, xestospongins A (**1**) and C (**2**) in ~50% yield and in a ratio of ~2.1−2.5:1. We cannot distinguish whether the formation of xestospongin C (**2**) under these conditions directly reflects the initial formation of *cis*- vs *trans* 1-oxaquinolizidines at stage one of the condensation (cf. formation of ***trans*-30** and ***cis*-30**) or a subsequent kinetic partitioning of half-cyclized intermediates to the macrocyclic natural products. A control experiment starting with pure **1** indicated that **1** and **2** do not equilibrate under the reaction conditions. The carbinol epimer ***R*-41** behaved similarly to produce *ent*-xestospongins A [**(−)-1**] and C [**(+)-2**] in ~40% yield. These syntheses serve to confirm the absolute configurations of xestospongins A and C as correctly deduced by Kitagawa.[3] Namely, the specific rotations of synthetic **1** and **2** derived from alcohol **(−)-40** [+8.9 ± 0.2° and −1.2 ± 0.6°, respectively], which has the *S*-configuration at the carbinol center, match those of (+)-xestospongin A (**1**, +10°) and (−)-xestospongin C (**2**, −2°) that were assigned the 2*S*-configuration.

Finally, we have studied the equilibration of xestospongins A (**1**) and C (**2**) under both acidic and basic conditions that were more forcing than those of the cyclization reaction medium (*vide supra*). Isomerization at 80 °C in $CDCl_3$ solutions of either isomer in the presence of excess trifluoroacetic acid or excess triethylamine can be conveniently monitored by ^{1}H NMR spectroscopy. The equilibrium values are different for the free base vs bis-ammonium ion forms of the molecules. It is interesting that the observed equilibrium value of the free base forms of xestospongins A and C (i.e., [**1**]/[**2**] ≈ 2.5) is very similar to that predicted from simple monocyclic 1-oxaquinolizidines previously studied.[3,7,8a] It appears that the two hexamethylene linking chains in these macrocyclic dimers are sufficiently flexible to render the individual 1-oxaquinolizidines energetically independent. This is also true of their contributions to the NMR spectroscopic and optical rotation properties of the intact natural products. In contrast, when the equilibration of the bis-thiophene-containing macrocycle **(−)-32** was carried out under identical base- or acid-catalyzed[13a] conditions, there was no evidence for isomerization to the bis-thiophene corresponding to xestospongin C (**2**).[13b] Although negative, this evidence is most consistent with the interpretation that the rigidity imposed upon the macrocycle by the thiophenes in **32** does influence the relative stability of the *cis*- and *trans*-1-oxaquinolizidine on the opposite side of the molecule. This is supported by a spectroscopic observation as well. Namely, proton H(2) in **32** appears as a doublet of doublets with J = 7.2 and 6.6 Hz [consistent with dihedral angles of ~150° and 30° to the vicinal pair at C(3)], whereas in all thiophene-containing but noncyclized precursors like **30** as well as in the less rigid macrocycle in xestospongin itself (**1**), $J_{H(2)/H(3ax)}$ was large (~10 Hz) while $J_{H(2)/H(3eq)}$ was small (~3 Hz). Thus, the rigidity imposed by the thiophenes expresses itself, in part, by distorting the geometry of each oxaquinolizidine ring.

In summary, the condensation of 5-haloaldehydes with 1,3-amino alcohols constitutes a straightforward, spontaneous synthesis of 1-oxaquinolizidine rings. The single stereogenic carbinol center in thiophene **26** or the analogous tetramethylene analog **41** controls the relative configuration of the remaining stereogenic centers required to establish the xestospongin macrocycle through equilibration. The thiophene ring serves as a convenient four-carbon linchpin for the preparation of **26**. However, its rigidifying effect on the macrocyclization of half-cyclized **31** or monomer **33** is not a critical requirement, since direct macrocyclic dimerization of the analogous monomer **41** is also an efficient process. Regulation of pH conveniently and effectively modulates the proton protecting group in ammonium ions **31**, **33**, and **41**. We continue to study stereochemical and spectroscopic features of these fascinating and important natural products.

Experimental Section

Preparation of [*R*-(*R,*R**)]- and [*R*-(*R**,*S**)]-5-(6-Chloro-3-formylhexyl)-*β*-hydroxy-2-thiophenepropionitrile (28).** DMSO (4.3 mL), H_2O (280 μL), TFA (1.16 mmol, 133 mg), and the acetal **(+)-26** (431 μmol, 149 mg) were placed in a culture tube. The solution was heated to 65 °C for 2.5 h and then cooled to room temperature. H_2O (~20 mL) was added, and the reaction mixture was extracted with CH_2Cl_2. The organic layers were combined, washed (5% aqueous NaOH and saturated aqueous NaCl), dried (Na_2SO_4 anhydrous), and concentrated to give the aldehyde **28** (129 mg, 99% yield). The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (d, 1H, J = 2.4 Hz, 6.88 (d, 1H, J = 3.4 Hz), 6.68 (d, 1H, J = 3.4 Hz), 5.20 (dd, 1H, J = 6.2 and 6.2 Hz), 3.54 (dd, 2H, J = 6.0 and 6.0 Hz), 2.88−2.81 (m, 4H), 2.37 (ddddd, 1H, J ≅ 7, 7, 7, 7, and 2.4 Hz), 2.05 (dddd, 1H, J = 14.4, 8.0, 6.7, and 6.7 Hz), and 1.90−1.54 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.0, 143.9, 143.4, 124.5, 124.2, 117.4, 65.9, 50.2, 44.7, 30.4, 29.7, 28.3, 27.5, and 25.7. IR (neat, thin layer): 3270, 3012, 2249, and 1719 cm^{-1}. HRMS (EI) *m/e* 299.0760 ($C_{14}H_{18}ClNO_2S^+$ requires 299.0746).

Preparation of [*R*-(*R,*R**)]- and [*R*-(*R**,*S**)]-α-(2-Aminoethyl)-5-[6-chloro-3-(dimethoxymethyl)hexyl]-2-thiophenemethanol (29).**

(13) (a) Under acidic conditions, **(−)-32** decomposed slowly (2 days) at room temperature and extensively at 80 °C (1 day). (b) We judge that as little as 5% of the stereoisomer would have been detectable given the open spectral windows in the chemical shift ranges where we could confidently anticipate resonances for the diastereomer to appear.

A solution of the nitrile **(+)-26** (451 μmol, 156 mg) in Et_2O (15 mL) was cooled to 0 °C. LAH (900 μmol, 900 μL of a 1 M solution in THF) was added, and the reaction mixture was warmed to room temperature and stirred for 1 h. Addition of $Na_2SO_4 \cdot 10H_2O$ until no gas evolved from the reaction flask was followed by dropwise addition of a saturated aqueous Na_2SO_4 solution until all solid in the flask was white in appearance. The solids were removed by filtration and washed several times with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4 anhydrous), and concentrated to give the aminol **29** (144 mg, 92% yield). The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (d, 1H, J = 3.4 Hz), 6.62 (d, 1H, J = 3.4 Hz), 5.11 (dd, 1H, J = 8.3 and 3.4 Hz), 4.16 (d, 1H, J = 5.5 Hz), 3.50 (dd, 2H, J = 6.6 and 6.6 Hz), 3.35 (s, 3H), 3.34 (s, 3H), 3.13 (ddd, 1H, J = 12.5, 5.8, and 4.2 Hz), 2.94 (ddd, 1H, J = 12.5, 9.0, and 4.0 Hz), 2.81 (dd, 2H, J = 7.3 and 7.3 Hz), 1.94−1.58 (m, 8H), and 1.44 (dddd, 1H, J = 14.1, 8.0, 6.7, and 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.9, 144.0, 123.5, 122.3, 107.8, 71.5, 54.7, 54.6, 45.4, 40.3, 39.9, 39.6, 31.2, 30.1, 27.6, and 26.3. IR (neat, thin layer): 3357, 3275, 3173, and 3072 cm^{-1}. HRMS (EI) *m/e* 317.1211 [($C_{16}H_{28}ClNO_3S$ − MeOH)$^+$ requires 317.1216].

Preparation of (+)-[2*R*-[2α(*R),9*β*(*R**),9a*β*]]- and (+)-[2*R*-[2α-(*S**),9*β*(*R**),9a*β*]]-5-[2-[2-[5-[6-Chloro-3-(dimethoxymethyl)hexyl]-2-thienyl]hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazin-9-yl]ethyl]-*β*-hydroxy-2-thiophenepropanenitrile (*trans*-30) and (+)-[2*R*-[2α(*R**),9α(*R**),9a*β*]]- and (+)-[2*R*-[2α(*S**),9α(*R**),9a*β*]]-5-[2-[2-[5-[6-Chloro-3-(dimethoxymethyl)hexyl]-2-thienyl]hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazin-9-yl]ethyl]-*β*-hydroxy-2-thiophenepropanenitrile (*cis*-30).** A flask containing the aldehyde **28** (722 μmol, 216 mg) in CH_2Cl_2 (4.2 mL) was charged with a solution of the aminol **29** (698 μmol, 244 mg) in CH_2Cl_2 (3.9 mL). The reaction mixture was stirred overnight (∼15 h) and then diluted with CH_2Cl_2 (20 mL). The organic layer was washed (5% aqueous NaOH and saturated aqueous NaCl), dried (Na_2SO_4 anhydrous), and concentrated to give a mixture of the oxaquinolizidines ***trans*-30** and ***cis*-30**. The mixture was separated by MPLC (1:2::Hex:EtOAc containing 3% triethylamine) to give the oxaquinolizidines ***trans*-30** (176 mg, 42% yield) and ***cis*-30** (122 mg, 29% yield). ***trans*-30**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (d, 1H, J = 3.7 Hz), 6.76 (d, 1H, J = 3.7 Hz), 6.66 (d, 1H, J = 3.7 Hz), 6.64 (d, 1H, J = 3.7 Hz), 5.19 (dd, 1H, J = 6.4 and 6.4 Hz), 4.56 (dd, 1H, J = 11.5 and 2.5 Hz), 4.17 (d, 1H, J = 5 Hz) 3.50 (dd, 2H, J = 6.8 and 6.8 Hz), 3.32 (s, 3H) 3.31 (s, 3H), 3.20 (d, 1H, J = 8.3 Hz), 3.03 (ddd, 1H, J = 11.8, 4, and 2 Hz), 2.91−2.73 (m, 7H), 2.38 (ddd, 1H, J = 11.8, 11.8, and 3 Hz), 2.20−2.00 (m, 3H), and 1.97−1.02 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.5, 144.7, 142.7, 142.0, 124.3, 123.8, 123.4, 123.0, 117.2, 107.7, 97.5, 75.3, 66.2, 54.7, 54.4, 53.7, 53.3, 45.4, 39.9, 39.2, 33.7, 32.5, 31.0, 30.0, 29.1, 28.1, 27.7, 27.5, 26.3, and 24.2. IR (neat, thin layer): 3380, 3070, 2755, 2675, 2250, and 1642 cm^{-1}. HRMS (CI, CH_4) *m/e* 595.2410 ($C_{30}H_{44}ClN_2O_4S_2$ + H^+ requires 595.2431). $[\alpha]_D^{RT}$ = + 21.7 (c = 0.67, $CHCl_3$). ***cis*-30**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (d, 1H, J = 3.4 Hz), 6.73 (d, 1H, J = 3.4 Hz), 6.66 (d, 1H, J = 3.4 Hz), 6.64 (d, 1H, J = 3.4 Hz), 5.14 (dd, 1H, J = 6.3 and 6.3 Hz), 4.68 (brd, 1H, J = 11.1 Hz), 4.23 (brs, 1H), 4.17 (d, 1H, J = 5.5 Hz), 3.51 (dd, 2H, J = 6.5 and 6.5 Hz), 3.35 (s, 3H), 3.34 (s, 3H), 3.15−2.95 (m, 2H), 2.95−2.80 (m, 6H), 2.38−2.25 (m, 1H), 2.23−1.99 (m, 2H), and 1.98−1.02 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.8, 144.4, 143.6, 142.6, 124.0, 123.7, 123.2, 122.2, 117.3, 107.5, 89.6, 75.6, 65.8, 54.6, 54.4, 51.9, 45.2, 39.1, 38.9, 32.8, 30.9, 29.9, 28.1, 27.4$^+$, 27.4$^-$, 26.2, 24.6, and 24.4. IR (neat, thin layer): 3382, 3069, 2250, and 1650 cm^{-1}. HRMS (CI, CH_4) *m/e* 595.2418 ($C_{30}H_{44}ClN_2O_4S_2$ + H^+ requires 595.2431).

Preparation of (+)-[2*R*-[2α(*R),9*β*(*R**),9a*β*]]- and (+)-[2*R*-[2α-(*S**),9*β*(*R**),9a*β*]]-α-(2-Aminoethyl)-5-[2-[2-[5-[6-chloro-3-(dimethoxymethyl)hexyl]-2-thienyl]hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazin-9-yl]ethyl]-2-thiophenemethanol (*trans*-30a).** A solution of the nitrile ***trans*-30** (313 μmol, 186 mg) in Et_2O (60 mL) was cooled to 0 °C. Lithium aluminum hydride (630 μmol, 630 μL of a 1.0 M solution in THF) was added. The solution was warmed to room temperature and stirred for 1 h. Addition of $Na_2SO_4 \cdot 10H_2O$ until no gas evolved from the reaction flask was followed by dropwise addition of a saturated aqueous Na_2SO_4 solution until all of the solid in the flask was white in appearance. The solids were removed by filtration and washed several times with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4 anhydrous), and concentrated to give the aminol ***trans*-30a** (145 mg, 78% yield). The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, 1H, J = 3.3 Hz) 6.72 (d, 1H, J = 3.3 Hz) 6.68−6.60 (m, 2H), 5.10 (dd, 1H, J = 7.8 and 3.9 Hz), 4.56 (brd, 1H, J = 11 Hz), 4.17 (d, 1H, J = 5.4 Hz), 3.51 (dd, 2H, J = 6.6 and 6.6 Hz), 3.35 (s, 3H), 3.34 (s, 3H), 3.29 (d, 1H, J = 8.2 Hz), 3.19−2.68 (m, 8H), 2.40 (ddd, 1H, J = 11.8, 11.8, and 2.4 Hz), 2.21−2.01 (m, 2H), 2.12 (ddd, 1H, J = 11, 11, and 3.0 Hz), and 2.01−1.02 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.52, 144.48, 144.41, 142.79, 123.33, 123.04, 122.37, 107.71, 97.46, 75.31, 71.29, 54.68, 54.56, 53.78, 53.25, 45.36, 40.14, 40.08, 39.50, 39.24, 33.76, 32.62, 31.05, 30.09, 28.98, 27.73, 27.55, 26.30, and 24.26. IR (neat, thin layer): 3351, 3299, 3223, 3072, 2754, 2671, and 1585 cm^{-1}. HRMS (CI, CH_4) *m/e* 599.2751 ($C_{30}H_{48}ClN_2O_4S_2$ + H^+ requires 599.2744). $[\alpha]_D^{RT}$ = + 32.4 (c = 1.89, $CHCl_3$).

Macrocyclization of [2*R*-[2α(*R),9*β*(*R**),9a*β*]]- and [2*R*-[2α-(*S**),9*β*(*R**),9a*β*]]-5-[9-[2-[5-(3-Ammonio-1-hydroxypropyl)-2-thienyl]ethyl]hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazin-2-yl]-α-(3-chloropropyl)-2-thiophenebutanal bis-(trifluoroacetate) (salt) (31) to give [4a*R*-(4a*R**,11*R**,12a*R**,16a*R**,23*R**,24a*R**)]-3,4,4a,6,11,-12a,15,16,16a,18,23,24a-Dodecahydro-5*H*,17*H*-7,10:19,22-diepithio-1,23:11,13-diethano-2*H*,14*H*-[1,11]dioxacycloeicosino[2,3-b:12,13-b′]dipyridine [(−)-32].** A solution of salt **31** was generated *in situ* by heating a mixture of the aminol ***trans*-30a** (8 μmol, 5 mg), DMSO (300 μL), H_2O (30 μL), and TFA (3 μL) to 80 °C for 1 h. The solution of **31** was then diluted with CH_2Cl_2 (1 L) and H_2O (1 L) and made strongly basic (pH ≥ 11) with a 5% aqueous NaOH (∼20 mL) solution. The reaction mixture was stirred at room temperature overnight (∼12 h). The layers were separated, and the aqueous layer was extracted several times with CH_2Cl_2. The organic layers were combined, washed (H_2O and saturated aqueous NaCl), dried (Na_2SO_4 anhydrousrous), and concentrated. The residue was purified by reverse phase HPLC (C_{18}-silica, 9:1::MeOH:H_2O containing 0.01% triethylamine) to give the thiophene macrocycle **(−)-32** (3 mg, 72% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.53 (d, 2H, J = 3.3 Hz), 6.51 (dd, 2H, J = 3.3 and 0.9 Hz), 4.53 (dd, 2H, J = 7.2 and 6.6 Hz), 3.14 (d, 2H, J = 8.7 Hz), 2.97 (ddd, 2H, J = 11.0, 6.3, and 3.0 Hz), 2.95 (ddd, 2H, J = 12.6, 8.7, and 4.5 Hz), 2.84−2.72 (m, 4H), 2.49 (ddd, 2H, J = 12.6, 12.6, and 3.9 Hz), 2.31 (ddd, 2H, J = 11, 9.3, and 6.6 Hz), 2.17−1.95 (m, 8H), 1.64−1.52 (m, 4H), 1.51−1.12 (m, 4H), and 1.00−0.90 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 144.8, 123.4, 119.7, 96.1, 74.7, 53.5, 53.4, 38.6, 32.9, 31.0, 28.9, 26.9, and 24.5. IR ($CDCl_3$ solution): 2755 and 2638 cm^{-1}. HRMS (CI, NH_3 gas) *m/e* 499.2448 ($C_{28}H_{38}N_2O_2S_2$ + H^+ requires 499.2453). $[\alpha]_D^{RT}$ = −17 (c = 1.5, $CHCl_3$).

Macrocyclization of 31 in Buffer Solutions to Give [(−)-32]. A solution of salt **31** was generated *in situ* by heating a mixture of the amino ***trans*-30a** (147 μmol, 87.8 mg), DMSO (4.4 mL), H_2O (32.7 mmol, 588 mg), and trifluoroacetic acid (573 μmol, 65.3 mg) to 80 °C for 1 h. The solution was added to 50 mL of 9:1 MeOH:buffer (AcOH/NaOAc, 0.50 M, pH = 6.5). The reaction mixture was stirred at room temperature for 24 h, and methylene chloride (50 mL) was added. The layers were separated, and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were washed (H_2O and saturated aqueous NaCl), dried (Na_2SO_4 anhydrous), and concentrated to give a yellow solid. The crude products were separated partially by MPLC (1:2::Hex:EtOAc containing 3% triethylamine) and further purified by reversed phase HPLC (C_{18}-silica, 9:1::MeOH:H_2O containing 0.01% triethylamine) to give the thiophene macrocycle **(−)-32** (55.3 mg, 76% yield) as a white solid.

Dimerization of [*R*-(*R,*R**)]- and [*R*-(*R**,*S**)]-α-(2-Aminoethyl)-5-(6-chloro-3-formylhexyl)-2-thiophenemethanol trifluoroacetate (*R*-33) in Buffer Solutions to Give Macrocycle (−)-32.** A solution of salt ***R*-33** was generated *in situ* by heating a mixture of the aminol **29** (78.9 μmol, 27.6 mg), DMSO (1.0 mL), H_2O (6.28 mmol, 125 mg), and trifluoroacetic acid (147 μmol, 16.8 mg) at 75 °C for 5 h. The resulting mixture was added to 20 mL of 9:1::MeOH:buffer (AcOH/NaOAc, 0.50 M, pH = 7.0). The reaction mixture was stirred at room temperature for 20 h before methylene chloride (20 mL) was added. The layers were separated, and the aqueous layer was extracted several

times with CH_2Cl_2. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried (Na_2SO_4 anhydrous), and concentrated to give a yellow solid. The crude products were separated partially by MPLC (1:2::hexane:EtOAc containing 3% triethylamine) and further purifed by reverse phase HPLC (C_{18}-silica, 9:1::MeOH:H_2O containing 0.01% triethylamine) to give the bis-thiophene macrocycle **(−)-32** (9.9 mg, 51% yield) as a white solid. The bis-thiophene macrocycle **(+)-32** was also prepared by the above procedures from ***ent*-31** (37% yield, pH > 11, CH_2Cl_2/aq NaOH, c = 0.03 mM) or ***S*-33** (42% yield, pH = 7.0, MeOH, NaOAc/AcOH). **(+)-32:** $[\alpha]_D^{RT}$ = + 15 (c = 1.7, $CHCl_3$).

Reduction of (−)-32 to [4a*S*-(4a*R,11*R**,12a*S**,16a*R**,23*R**,-24a*S**)]-Eicosahydro-5*H*,17*H*-1,23:11,13-diethano-2*H*,14*H*-[1,11]dioxacycloeicosino[2,3-*b*:12,13-*b*′]dipyridine, (+)-Xestospongin A [(+)-Araguspongine D] (1).** Raney nickel (∼0.5 mL, 50% w/w in H_2O, as obtained from Aldrich Chemical Co.) was washed with H_2O (∼5 times) and absolute ethanol (∼5 times). The ethanolic slurry of nickel catalyst was added to a solution of the macrocycle **(−)-32** (78.5 μmol, 39.1 mg) in 95% ethanol (5 mL) at room temperature. The reaction mixture was flushed with hydrogen and stirred vigorously at room temperature for 1 h under an atmosphere of hydrogen. The organic layer was decanted, and the Raney nickel was washed sequentially with absolute ethanol (∼100 mL in small increments), EtOAc (∼100 mL), and CH_2Cl_2 (∼25 mL). The organic layers were combined, filtered through Celite, and concentrated to give a yellow solid, which was purified by HPLC (1:2::hex:EtOAc containing 3% diisopropylamine, freshly mixed) to give **1** (25.2 mg, 72%) as a white solid. *ent*-Xestospongin A **(−)-1** was also prepared by the same procedure from **(+)-32**. **(+)-1:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.35 (brdd, 2H, J = 10.7 and 10.7 Hz), 3.06 (d, 2H, J = 8.5 Hz), 2.93 (ddd, 2H, J = 11.3, 4.2, and 2.1 Hz), 2.76 (brd, 2H, J = 11.6 Hz), 2.18 (ddd, 2H, J = 12.2, 11.8, and 3.1 Hz), 1.98 (ddd, 2H, J = 11.6, 11.6, and 3.0 Hz), and 1.66−1.07 (m, 38H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 95.8, 75.2, 54.3, 54.1, 40.5, 35.4, 32.2, 31.6, 31.2, 28.9, 28.8, 25.3, 25.2, and 24.9. IR ($CDCl_3$ solution): 2806 and 2751 cm^{-1}. HRMS (CI, isobutane gas) *m/e* 447.3943 ($C_{28}H_{50}N_2O_2$ + H^+ requires 447.3950) and 446.3874 ($C_{28}H_{50}N_2O_2^+$ requires 446.3872). $[\alpha]_D^{RT}$ = + 8.9 (c = 1.23, $CHCl_3$); **(−)-1**: $[\alpha]_D^{RT}$ = −9.2 (c = 0.76, $CHCl_3$).

Preparation of (±)-2-(3-Chloropropyl)-9-decenenitrile (34). A solution of diisopropylamine (8.39 mmol, 849 mg) in THF (10 mL) was cooled to 0 °C. *n*-BuLi (8.25 mmol, 3.30 mL of a 2.5 M solution in hexane) was added. The reaction mixture was stirred for 15 min and cooled to −78 °C. After addition of 5-chlorovaleronitrile (8.89 mmol, 1.05 g), the reaction mixture was stirred for 20 min. 8-Bromo-1-octene (5.49 mmol, 1.05 g) was added. The mixture was stirred at −78 °C, and reaction progress was monitored by TLC. When the reaction was judged complete, the solution was warmed to room temperature, quenched (saturated aqueous NH_4Cl), and extracted with diethyl ether (3 × 20 mL). The organic layers were combined, washed (saturated aqueous NH_4Cl and saturated aqueous NaCl), dried (Na_2SO_4 anhydrous), and concentrated. The crude product was purified by MPLC (19:1::Hex:EtOAc) to give the nitrile **34** as a clear, colorless liquid (1.11 g, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (dddd, 1H, J = 17.1, 10.4, 6.4 and 6.4 Hz), 4.97 (dddd, 1H, J = 17.1, 1.5, 1.5 and 1.5 Hz), 4.91 (dddd, 1H, J = 10.4, 1.5, 0.6 and 0.6 Hz), 3.56 (dd, 2H, J = 6.1 and 6.1 Hz), 2.53 (dddd, 1H, J = 9.4, 9.4, 5.2 and 5.2 Hz), and 2.06−1.26 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.82, 121.72, 114.27, 44.01, 33.59, 32.16, 31.02, 29.84, 29.46, 28.83, 28.75, 28.69 and 26.99. IR (neat, thin layer): 3076, 2238, 1713, and 1640 cm^{-1}. HRMS (EI) *m/e* 227.1437 ($C_{13}H_{22}ClN^+$ requires 227.1441).

Preparation of (±)-2-(3-Chloropropyl)-9-decenal (35). A solution of the nitrile **34** (24.1 mmol, 5.50 g) in CH_2Cl_2 (150 mL) was cooled to −78 °C. DIBAL-H (30.9 mmol, 5.50 mL of a 0.5 M solution in hexane) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h, slowly quenched at −78 °C with 1 N HCl (200 mL, over 30 min), warmed to room temperature over 30 min, and stirred for an additional 20 min. The reaction mixture was extracted with ether, and the organic layers were combined, washed (1 N HCl and saturated aqueous NaCl), dried (Na_2SO_4 anhydrous), and concentrated. The residue was purified by MPLC (19:1::Hex:EtOAc) to give the aldehyde **35** (4.76 g, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (d, 1H, J = 2.8 Hz), 5.79 (dddd, 1H, J = 17.1, 10.4, 6.4, and 6.4 Hz), 4.98 (dddd, 1H, J = 17.1, 1.5, 1.5, and 1.5 Hz), 4.93 (dddd, 1H, J = 10.4, 1.5, 0.6, and 0.6 Hz), 3.53 (dd, 2H, J = 6.1 and 6.1 Hz), 2.28 (dddd, 1H, J ≅ 8.3, 8.3, 8.3, and 8.3 Hz), 2.04 (ddd, 2H, J = 6.4, 6.4, and 6.4 Hz), and 1.83−1.18 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.64, 138.87, 114.18, 51.11, 44.65, 33.63, 29.88, 29.41, 28.78, 28.70, 26.82 and 25.80. IR (neat, thin layer): 1720 cm^{-1}. HRMS (EI) *m/e* 230.1443 ($C_{13}H_{23}ClO^+$ requires 230.1437).

Preparation of (±)-12-Chloro-9-(dimethoxymethyl)-1-dodecene (36). The aldehyde **35** (19.8 mmol, 4.58 g) was dissolved in a methanolic solution of $CeCl_3$ (0.04 M, 1.51 g of $CeCl_3$ in 50 mL of MeOH) and trimethyl orthoformate (37.3 mmol, 3.98 g). The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether. The combined organic layers were washed (saturated aqueous NaCl), dried ($MgSO_4$ anhydrous), and concentrated. The residue was purified by MPLC (19:1::Hex:EtOAc) to give the acetal **36** (5.30 g, 97% yield) as a clear, colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (dddd, 1H, J = 17.1, 10.4, 6.4, and 6.4 Hz), 4.99 (dddd, 1H, J = 17.1, 1.5, 1.5, and 1.5 Hz), 4.93 (dddd, 1H, J = 10.4, 1.5, 0.6, and 0.6 Hz), 4.14 (d, 1H, J = 5.8 Hz), 3.52 (dd, 2H, J = 6.7 and 6.7 Hz), 3.36 (s, 3H), 3.35 (s, 3H), 2.04 (ddd, 2H, J = 6.4, 6.4, and 6.4 Hz), 1.79 (m, 1H), and 1.68−1.24 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.14, 114.12, 107.76, 54.69, 54.28, 45.46, 39.99, 33.76, 30.27, 29.88, 29.03, 29.00, 28.88, 26.73 and 26.29. IR (neat, thin layer): 3076, 1726, and 1640 cm^{-1}. HRMS (EI) *m/e* 276.1855 ($C_{15}H_{30}ClO_2^+$ requires 276.1856).

Preparation of (±)-11-Chloro-8-(dimethoxymethyl)undecanal (37). The olefin **36** (18.6 mmol, 5.15 g) in methylene chloride (50 mL) and methanol (25 mL) was cooled to −78 °C, and ozone was bubbled into the solution through a glass tube until the solution turned blue. The reaction mixture was purged with nitrigen for 30 min, and then dimethyl sulfide was added. The mixture was allowed to warm to room temperature and stirred overnight. After washing with water and brine, the solution was dried ($MgSO_4$ anhydrous) and concentrated. The crude product was purified by MPLC (6:1::hex:EtOAc) to give the aldehyde **37** as a colorless oil (4.11 g, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (br s, 1H), 4.14 (d, 1H, J = 5.8 Hz), 3.52 (dd, 2H, J = 6.7 and 6.7 Hz), 3.36 (s, 3H), 3.35 (s, 3H), 2.42 (dd, 2H, J = 7.0 and 7.0 Hz), 1.79 (m, 1H), and 1.68−1.24 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.99, 107.23, 54.13, 53.79, 44.96, 43.36, 39.47, 29.79, 29.32, 28.59, 28.50, 26.12, 25.86, and 21.56. IR (neat, thin layer): 1721 cm^{-1}. HRMS (EI) *m/e* 246.1386 [$(C_{14}H_{27}ClO_3 - MeOH)^+$ requires 246.1384].

Preparation of (±)-13-Chloro-10-(dimethoxymethyl)-3-hydroxytridecanenitrile (38). A flask containing THF (25 mL) was cooled to −78 °C. *n*-BuLi (5.75 mmol, 2.30 mL of a 2.5 M solution in hexane) was added. Acetonitrile (6.70 mmol, 275 mg) was added. The solution was stirred for 30 min. The aldehyde **37** (3.50 mmol, 975 mg) in THF (20 mL) was added, and the reaction mixture was stirred for 1 h. The reaction mixture was quenched (saturated aqueous NH_4Cl) at −78 °C, warmed to room temperature, and extracted with ether. The organic layers were combined, washed (saturated aqueous NH_4Cl and saturated aqueous NaCl), dried (Na_2SO_4 anhydrous), and concentrated. The residue was purified by flash chromatography (2:1::hex:EtOAc) to give the alcohol **38** (1.10 g, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.14 (d, 1H, J = 6.1 Hz), 3.93 (br ddd, 1H, J = 6.1, 5.2, and 5.2 Hz), 3.53 (dd, 2H, J = 6.7 and 6.7 Hz), 3.37 (s, 3H), 3.35 (s, 3H), 2.57 (dd, 1H, J = 16.5 and 4.5 Hz), 2.49 (dd, 1H, J = 16.5 and 6.5 Hz), 2.41 (brs, 1H), 1.79 (m, 1H), and 1.68−1.24 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 117.69, 107.70, 107.68, 67.62, 54.67, 54.31, 54.23, 45.45, 39.92, 39.91, 36.45, 30.17, 29.77, 29.10, 28.83, 26.56, 26.52, 26.26, 26.05 and 25.24. IR (neat, thin layer): 3459 and 2253 cm^{-1}. HRMS (EI) *m/e* 287.1647 [$(C_{16}H_{30}ClNO_3 - MeOH)^+$ requires 287.1652].

Preparation of (+)-[*R*-(*R,*R**)]- and (+)-[*R*-(*R**,*S**)]-13-Chloro-10-(dimethoxymethyl)-3-hydroxytridecanenitrile [(+)-38] and (−)-[*S*-(*R**,*R**)]- and (−)-[*S*-(*R**,*S**)]-3-(Acetoxy)-13-chloro-10-(dimethoxymethyl)tridecanenitrile [(−)-39].** Into a flask were placed (±)-38 (2.03 mmol, 650 mg), hexane (25 mL), isopropenyl acetate (10 mL), and lipase SP-435. The reaction mixture was stirred at 65 °C for 2 days, while being monitored closely by TLC (1:1::hex:EtOAc) and ^{1}H NMR analysis. The reaction mixture was filtered, and the solid was washed with hexane (2 × 10 mL). The combined organics were

concentrated, and the residue was separated by MPLC (2:1::Hex:EtOAc) to give the optically enriched *S*-alcohol **(+)-38** [319 mg, 49% yield, 91%ee as determined by Mosher ester analysis; this material was resubjected to the same conditions and **(+)-38**, which had an optical purity of ≥98%, was recovered in 44% overall yield (286 mg)] and the *R*-acetate **(−)-39** [309 mg, 42% yield, ≥98%ee by Mosher ester analysis of **(−)-38** arising from MeLi treatment of **(−)-39**]. The spectral data of **(+)-38** corresponded to those previously reported for the racemic samples. **(+)-38:** $[\alpha]_D^{RT} = +2.52$ ($c = 1.11$, $CHCl_3$); **(−)-39:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.95 (dddd, 1H, $J = 7.9$, 5.5, 5.2, and 5.2 Hz), 4.14 (d, 1H, $J = 5.8$ Hz), 3.52 (dd, 2H, $J = 6.7$ and 6.7 Hz), 3.37 (s, 3H), 3.35 (s, 3H), 2.72 (dd, 1H, $J = 17.1$ and 5.2 Hz), 2.49 (dd, 1H, $J = 17.1$ and 4.9 Hz), 2.10 (s, 3H), 1.79 (m, 1H), 1.68−1.24 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 116.25, 107.66, 68.61, 54.63, 54.30, 45.41, 39.91, 33.06, 30.17, 29.70, 28.99, 28.86, 26.58, 26.25, 24.96, 22.81, and 20.87. IR (neat, thin layer): 2252 and 1743 cm^{-1}. HRMS (EI) *m/e* 329.1770 [$(C_{18}H_{32}ClNO_4 - MeOH)^+$ requires 329.1758]. $[\alpha]_D^{RT} = -20.8$ ($c = 1.31$, $CHCl_3$).

Preparation of (−)-[*R*-(*R,*R**)]- and (−)-[*R*-(*R**,*S**)]-1-Amino-13-chloro-10-(dimethoxymethyl)tridecan-3-ol [(−)-40].** A solution of the nitrile **(−)-39** (503 μmol, 182 mg) in Et_2O (15 mL) was cooled to 0 °C. Lithium aluminum hydride (3.0 mmol, 3.0 mL of a 1 M solution in THF) was added, and the reaction mixture was warmed to room temperature and stirred for 1.5 h. Addition of $Na_2SO_4 \cdot 10H_2O$ until no gas evolved from the reaction flask was followed by dropwise addition of a saturated aqueous Na_2SO_4 solution until all solid in the flask was white in appearance. The solids were removed by filtration and washed several times with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4 anhydrous), and concentrated to give the aminol **(−)-40** (141 mg, 87% yield). The product was used without further purification. **(+)-40** was also prepared by the same precedure from **(+)-38** (81% yield). **(−)-40:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.14 (d, 1H, $J = 5.8$ Hz), 3.79 (br ddd, 1H, $J = 5.5$, 5.2, and 5.2 Hz), 3.52 (dd, 2H, $J = 6.7$ and 6.7 Hz), 3.37 (s, 3H), 3.35 (s, 3H) 3.12 (ddd, 1H, $J = 12.2$, 4.9, and 4.9 Hz), 2.84 (ddd, 1H, $J = 12.2$, 9.8, and 4.2 Hz), 2.56 (brs, 1H), 1.79 (m, 1H), and 1.68−1.24 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 107.67, 72.93, 62.30, 54.63, 54.22, 45.40, 40.70, 39.91, 37.81, 37.60, 30.20, 30.01, 29.97, 29.58, 28.93, 26.66, 26.19, and 25.46. IR (neat, thin layer): 3357, 3275, 3173, and 3072 cm^{-1}. HRMS (EI) *m/e* 291.1957 [$(C_{16}H_{34}ClNO_3 - MeOH)^+$ requires 291.1965]. $[\alpha]_D^{RT} = -5.6$ ($c = 0.98$, $CHCl_3$); **(+)-40:** $[\alpha]_D^{RT} = +5.5$ ($c = 1.04$, $CHCl_3$).

Preparation of [*S*-(*R,*R**)]- and [*S*-(*R**,*S**)]-11-Amino-2-(3-chloropropyl)-9-hydroxyundecanal Trifluoroacetate (41).** The aminol **(−)-40** (176 μmol, 57.0 mg), DMSO (500 μL), H_2O (5.55 mmol, 100 μL, 100 mg), and trifluoroacetic acid (454 μmol, 51.8 mg) were placed in a culture tube and heated to 80 °C overnight. No attempt was made to isolate the product **41**. These reaction conditions were optimized by using deuterated solvents (DMSO-d_6 and D_2O) and monitoring by ^{1}H NMR spectroscopy. A solution of **41** prepared in this way gave the following spectral data: ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.47 (brs, 1H), 3.54 (dd, 2H, $J = 6.3$ and 6.3 Hz), 3.47 (br ddd, 1H, $J = 5.5$, 5.2, and 5.2 Hz), 2.83 (m, 2H), and 1.70−1.10 (m, 19H). ^{13}C NMR (75 MHz, DMSO$_{d6}$): δ 207.07, 79.69, 68.71, 61.60, 49.36, 46.08, 37.81, 37.43, 34.63, 30.29, 29.90, 29.71, 29.64, 28.69, 27.08, 25.89, and 25.76.

Dimerization of 41 in Buffer Solutions to Give Xestospongin A [(+)-1] and C [(−)-2]: The solution of aldehyde **41** generated in the above experiment was added to 15 mL of 9:1::MeOH:buffer (AcOH/NaOAc, 0.50 M, pH = 7.0). The reaction mixture was stirred at room temperature for 24 h before methylene chloride (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried (Na_2SO_4 anhydrous), and concentrated to give a yellow solid. The crude products were separated partially by MPLC (1:2 hexane:EtOAc contained 3% of triethylamine) and further purifed by reverse phase HPLC (C_{18}-silica, 9:1::MeOH:H_2O containing 0.01% triethylamine) to give **(+)-1** (12.2 mg, 31% yield) and **(−)-2** (5.5 mg, 14% yield) as white solids. *ent*-Xestospongin A **[(−)-1]** (28% yield) and C **[(+)-2]** (11% yield) were also prepared by the same procedure from ***ent*-41**. **(−)-2 [4a*S*-(4a*R**,11*R**,12a*S**,16a*S**,23*R**,24a*S**)]-Eicosahydro-5*H*,17*H*-1,23:11,13-diethano-2*H*,14*H*-[1,11]dioxacycloeicosino[2,3-*b*:12,13-*b*′]dipyridine, (−)-xestospongin C [(−)-araguspongine E]:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.30 (brd, 1H, $J = 2.4$ Hz), 3.54 (brdd, 1H, $J = 10.7$ and 10.7 Hz), 3.35 (brdd, 1H, $J = 10.4$ and 10.4 Hz), 3.18 (brdd, 1H, $J = 12.2$ and 12.2 Hz), 3.06 (m, 2H), 2.90 (m, 2H), 2.76 (brd, 1H, $J = 11.5$ Hz), 2.39 (brd,1H, $J = 10.0$ Hz), 2.12 (ddd, 1H, $J = 12.0$, 12.0), 2.00 (ddd, 1H, $J = 11.5$, 11.5, and 3.4 Hz), and 1.79−1.02 (m, 38H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 95.8, 87.4, 75.8, 75.3, 54.3, 54.1, 52.7, 45.2, 40.5, 40.2, 36.0, 35.6, 35.4, 32.3, 31.6$^+$, 31.6$^-$, 31.1, 29.2, 28.9, 28.8$^+$, 28.9$^-$, 27.1, 26.5, 26.2, 25.3, 25.1, 24.9, and 24.7. IR ($CDCl_3$ solution): 2772 and 2679 cm^{-1}. HRMS (EI) *m/e* 446.3869 ($C_{28}H_{50}N_2O_2^+$ requires 446.3872). $[\alpha]_D^{RT} = -1.2$ ($c = 0.47$, $CHCl_3$); **(+)-2**: $[\alpha]_D^{RT} = +0.9$ ($c = 0.32$, $CHCl_3$).

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Supporting Information Available: A description of experimental details and spectral data for preparation of intermediates **20**−**27** [including the resolution of racemic **27** to **(+)-26** and **(−)-27**] and acetates **28-Ac**, ***trans*-30-Ac**, and ***cis*-30-Ac** (8 pages). See any current masthead page for ordering and Internet access instructions.

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