A Total Synthesis of (+)-Xestospongin A/(+)-Araguspongine D

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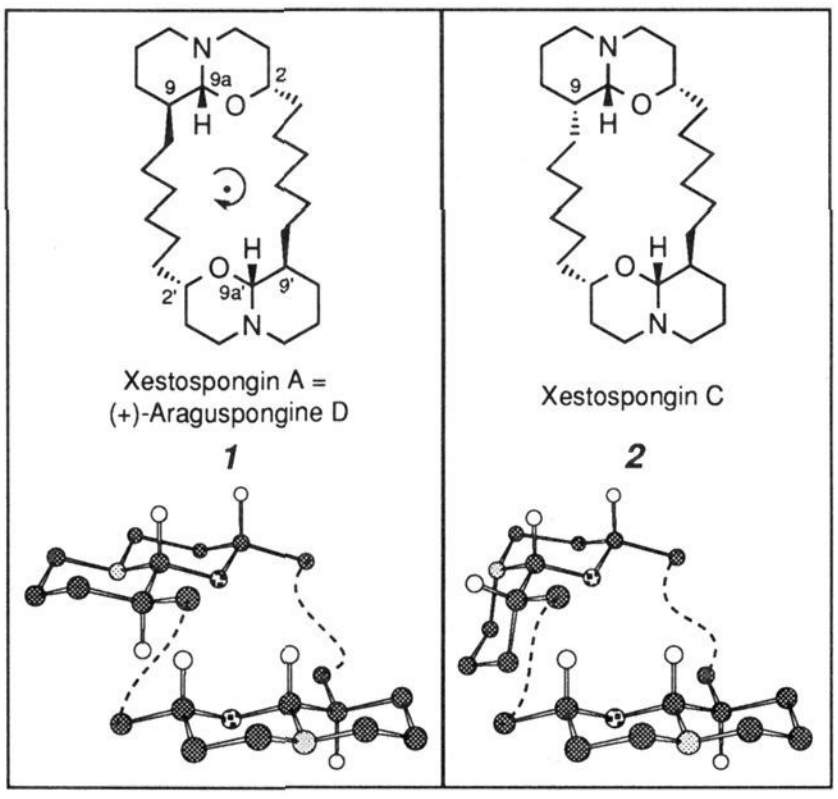
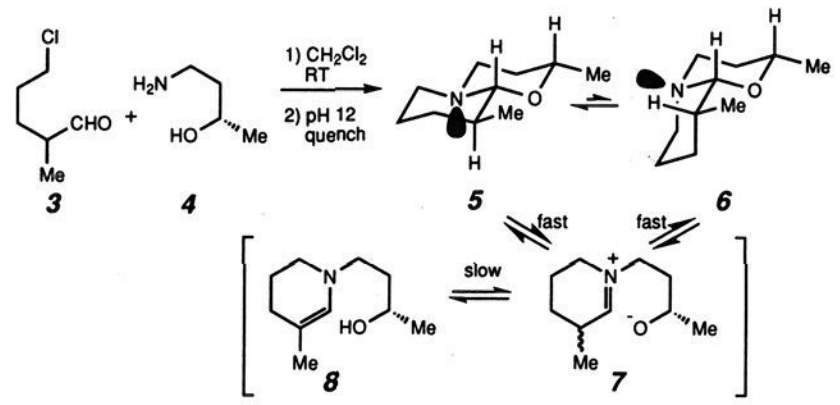
Xestospongins A (**1**) and C (**2**) were isolated from the Australian sponge *Xestospongia exigua* by Nakagawa and Endo in 1984.[2] These vasodilative alkaloids are C(9) epimers of one another, and each contains a pair of oxaquinolizidine (hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine) moieties. As is clear from analysis of the single-crystal X-ray structure of **2**, 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. 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**).



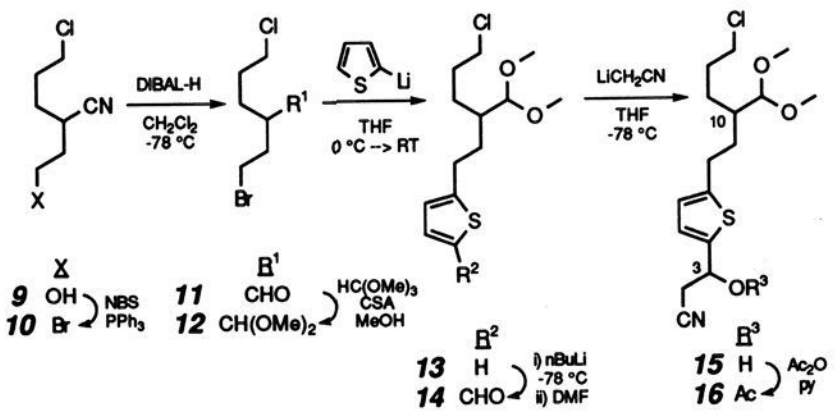
The absolute configuration of xestospongin A (**1**) was assigned in 1989 by Kitagawa *et al.*, who isolated araguspongine D from *Xestospongia* sp.[3] as an ~70:30 mixture of enantiomers, the minor component of which was identical to xestospongin A (**1**). We describe here the first synthesis[4] of (+)-xestospongin A/(+)-araguspongine D (**1**).

Our synthetic strategy capitalized on the C_2 symmetry of the target **1**. The macrocycle was to be constructed by stepwise dimerization of two monomers. This strategy required the development of a facile reaction for eventual coupling of the two halves. The simple condensation of a 5-halovaleraldehyde like **3** with a 1,3-amino alcohol like **4** proved to be ideal (Scheme 1).[4a] Studies of the dimethylated oxaquinolizidines **5** and **6** established the clear thermodynamic preference for the trans-dialkylated, or xestospongin A-like, orientation of the methyl groups (i.e., **5** more stable than **6**). This was explained by a rapidly reversible opening of **5**/**6** to the iminium ion **7** and a slower, reversible proton transfer in **7** to generate the enamine **8**.[4a] These experiments clearly implied that the configuration of the carbinol center would control all relative configurations within the newly formed oxaquinolizidine. 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**. The doubly "protected" monomer **15** was identified as a key intermediate. It contains nitrile and acetal groups as precursors to the required amine and aldehyde functionalities and a thiophene unit to permit use of a linchpin strategy for its synthesis.

Scheme 1



Scheme 2



Racemic carbinol **15** was synthesized (Scheme 2) in seven steps by way of the alcohol **9** (81%, ethylene oxide alkylation of 2-lithio-5-chlorovaleronitrile), bromide **10** (77%), aldehyde **11** (92%), dimethyl acetal **12** (69%), monosubstituted thiophene **13** (70%), thiophenecarbaldehyde **14** (57%), and addition of lithioacetonitrile (87%). Kinetic "resolution" of the diastereomeric mixture of racemic acetate esters **16** (Amano P-30 from *Pseudomonas fluorescens*) gave (–)-**16** (45%) and (+)-**15** (38%),[5a–c] the pivotal intermediate bearing a single configuration at C(3). A portion of the monomer (+)-**15** (Scheme 3) was hydrolyzed to the aldehyde **17** (99%); a second portion was reduced to the amino alcohol **18** (92%). These were smoothly condensed to afford a separable mixture of the oxaquinolizidine isomers *trans*-**19** and *cis*-**19** (~2.3:1 trans:cis by ^{1}H NMR integration,

(1) National Science Foundation Graduate Fellow (1989–1992); DuPont Fellow (1993–1994).

(2) Nakagawa, M.; Endo, M.; Tanaka, N.; Gen-Pei, L. *Tetrahedron Lett.* **1984**, *25*, 3227.

(3) Kobayashi, M.; Kawazoe, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 1676. (By the Horeau method and Hudson's rule.)

(4) For previous preliminary studies related to xestospongin synthesis, see: (a) Hoye, T. R.; North, J. T. *Tetrahedron Lett.* **1990**, *31*, 4281. (b) Ahn, K. H.; Lee, S. J. *Tetrahedron Lett.* **1992**, *33*, 507. (c) Börjesson, L.; Welch, C. J. *Tetrahedron* **1992**, *48*, 6325.

(5) (a) Alcohol (+)-**15** represents a pair of diastereomers epimeric at the center α to the acetal [C(10)] but of a single configuration at C(3). The "stereogenic purity" of the carbinol center was found to be ≥95% "ee" by ^{1}H and ^{19}F NMR analysis of the corresponding Mosher ester derivatives, and the configuration was determined to be *R*. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *93*, 512. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

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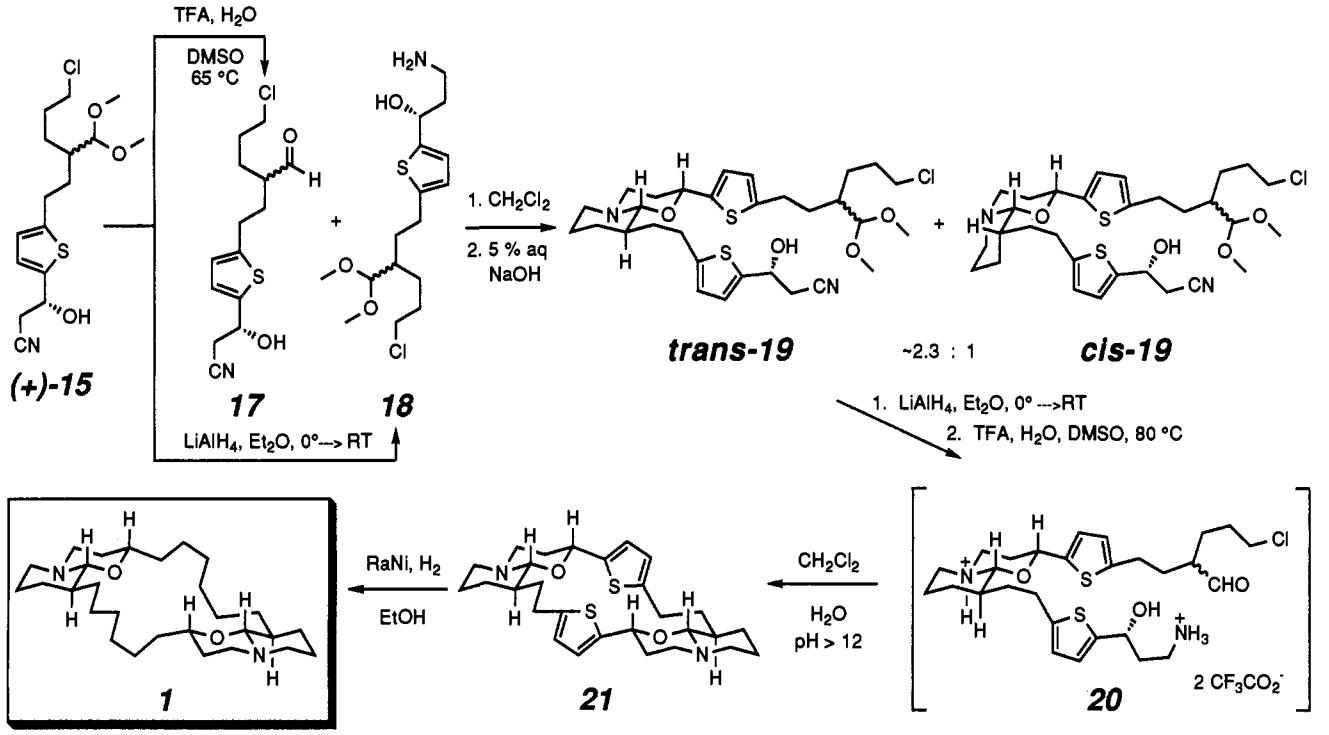
Scheme 3



42% and 29% isolated yields). The cis isomer could be equilibrated with the trans ($K_{eq(trans/cis)} \sim 2$) in the presence of triethylamine ($CDCl_3$ solution, 80 °C, ~3 h, cf. Scheme 1).

The termini in *trans*-**19** were prepared for macrocyclization by stepwise removal of each protecting group [(1) LAH, 78%; (2) TFA, DMSO, H_2O, 80 °C; not isolated]. On one occasion the final hydrolysis was performed in d_6-DMSO/D_2O, and the solution of the deuterated version of the ammonium ion **20** was observed by ^1H NMR analysis to be stable for at least 2 weeks at room temperature. Thus, the proton on the primary ammonium ion in **20** served as an effective protecting group that prevented oligomerization until subsequent dilution and elevation of the pH, which provided the free amine. Specifically, an ~0.02 M solution of **20** in DMSO was diluted to 0.02 mM with a 1:1 mixture of dichloromethane and water, and the pH was subsequently raised to 12 by addition of excess 5% aqueous sodium hydroxide. The C_2-symmetric macrocyclic bis-thiophene **21** was isolated in ~70% yield following purification (9000:1000:1 MeOH/H_2O/Et_3N on C_{18} silica). Both thiophene rings in macrocycle **21** were cleanly removed by Raney nickel reduction (1 atm of H_2, EtOH, room temperature, 3 h, 69%) to give xestospongin A. The positive specific rotation observed for **1**[6] coupled with the absolute configuration of (+)-**15**, assigned by MTPA ester analysis, is consistent with the original assignment of absolute configuration[3] of the natural product.

There are a number of important aspects to this synthesis. Condensation of 5-haloaldehydes with 1,3-amino alcohols constitutes a straightforward, spontaneous synthesis of the oxaquinolizidine rings; the single stereogenic carbinol center in (+)-**15** controls all the remaining relative configurations through equilibration; the thiophene ring serves as a four-carbon linchpin in the preparation of **15** as well as a rigidifier for the macrocyclization of **20**; regulation of pH conveniently and effectively modulates the proton protecting group in ammonium ion **20**; and bis-thiophene **21** represents one of the more complex substrates ever subjected to reductive desulfurization.

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Supplementary Material Available: Detailed experimental procedures and spectroscopic data of key intermediates (27 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(6) Given the relatively low specific rotation of the natural sample of **1**[3] ($[\alpha]^n_D = +10°$) and the small quantities of synthetic **1** available, the magnitudes of our measured specific rotations of various samples ($[\alpha]^n_D = +6$ to $+17°$) differed from the literature value but, importantly, were of the same sign.