Biomimetic Synthesis of (−)-Xestospongin A, (+)-Xestospongin C, (+)-Araguspongine B and the Correction of Their Absolute Configurations

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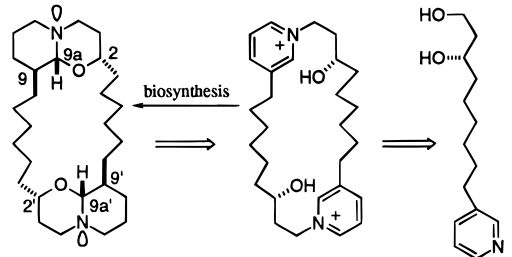
(+)-Xestospongin A (**1**) is one of the four bis-oxaquinolizidine alkaloids first isolated from the Australian sponge *Xestospongia exigua* by Nakagawa et al.[1] in 1984. Subsequently in 1989, Kitagawa et al.[2] reported the isolation of nine bis-oxaquinolizidine alkaloids (Araguspongines A−J) from a marine sponge *Xestospongia sp*. found in the Okinawa region. Interestingly, it was found that Araguspongine D is a 3:7 mixture of (+)- and (−)-Xestospongin A. In all previous publications,[2−5] the absolute configuration of (+)-Xestospongin A is depicted as (2*S*,9*S*,-9a*R*,2′*S*,9′*S*,9a′*R*). Throughout this paper we shall refer to Kitagawa's proposed structure of (+)-Xestospongin A as **1**.



The intriguing structure of (+)-Xestospongin A and its vasodilatory properties have encouraged a number of studies directed toward its synthesis.[3] To date only one total synthesis of (+)-Xestospongin A and its enantiomer has been reported.[4,5] Herein we disclose the synthesis of **1** and other related alkaloids based on a biosynthetic hypothesis along with the surprising results which lead to the correction of their absolute configurations. Biosynthetically, **1** and other related alkaloids [including Araguspongine B (**13**)[2,15,16] and Xestospongin C (**14**)[1]] can be derived from bis-hydroxypyridinium dimer **2**. The occurrence of macrocyclic and polymeric 3-alkylpyridinium compounds among marine sponges[6] supports this proposal. In fact the hypothesis suggesting bis-3-alkyldihydropyridine dimers as biosynthetic precursors for marine alkaloids has been previously proposed by Baldwin.[7] The proposed dimeric biosynthetic intermediate **2** could be prepared from monomer **8** which is the cornerstone and the initial target of our synthesis.

Thus Weiler alkylation of ethyl acetoacetate with 1-bromo-4-chlorobutane[8,9] gave ethyl 8-chloro-3-oxooctanoate (**3**, 78%). Noyori hydrogenation of **3** with [Ru(II)-*S*-BINAP][10] provided hydroxy ester **4** (96% yield, ee 96% as determined by ^{19}F NMR analysis of its Mosher ester[11]). Reduction of **4** by lithium borohydride afforded diol **5** (84%) which was converted into its acetonide derivative **6** (94%) by pyridinium tosylate/2,2-dimethoxypropane/acetone. Reaction of **6** with sodium iodide in refluxing acetone gave iodide **7** (98%). Treatment of **7** with lithiated 3-picoline,[12] generated from 3-picoline and LDA, provided pyridine **8** (72%). Diol **9** was obtained (94%) by removal of acetonide with dilute hydrochloric acid in ethanol. Selective tosylation of **9** afforded monotosylate **10** (88%). Slow addition of a solution of **10** in butan-2-one to a refluxing solution of sodium iodide in the same solvent gave a mixture of products, containing dimer **2**. Reduction of this mixture with lithium borohydride gave the tetrahydropyridine dimer **11** (34%) after chromatographic separation. The ^{1}H NMR of **11** revealed a small amount of its Δ-4,5 double bond isomer (ca. 5%) was present. Reaction of **11** with diethyl azodicarboxylate (DEAD)[13] gave dehydro-bis-oxaquinolizidine **12** (53%), presumably via an iminium ion intermediate. X-ray diffraction studies revealed the trans-ring junctions in crystalline **12**.[14] Hydrogenation of **12** with Raney nickel in methanol surprisingly delivered Araguspongine B (**13**)[2,15,16] as the major product (77%) and a small amount of Xestospongin C (**14**)[1] (7%). Hydrogenation of **12** with rhodium on alumina in methanol followed by refluxing the reaction mixture with a small amount of alumina[16] gave Xestospongin A (**1**, 23%), Xestospongin C (**14**, 17%), and Araguspongine B (**13**, 9.5%) after HPLC separation (Scheme 1).

The identities of the synthetic **13**, **1**, and **14** were established by comparison with the published ^{1}H and ^{13}C NMR data[2,5,16] and confirmed by doping experiments with the authentic samples. Surprisingly **13**, which was described by Kitagawa[2] and Kobayashi[16] as (−)-Araguspongine B, possessed a specific rotation value of $[\alpha]^{23}_D$ +10.7. Interestingly, the observed specific rotation value of our synthetic **1** is $[\alpha]^{23}_D$ −9.5 {lit. value[5] of (+)-Xestospongin A $[\alpha]^{RT}_D$ +8.9} and that of synthetic **14** is $[\alpha]_D^{23}$ +1.6 {lit. value[5] of (−)-Xestospongin C $[\alpha]_D^{RT}$ −1.2}, i.e., the specific rotations of both **1** and **14** are *opposite* to their expected values. These results differ significantly from those of Hoye[4,5] and Kitagawa.[2,17] We are certain about the stereochemistries of **13**, **1**, and **14** because their precursors **9** and **10** were also

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(14) Crystal structure data for **12**: $C_{28}H_{46}O_2N_2$, monoclinic, $P2_1$, a = 8.62(1) Å, b = 9.88(1) Å, c = 15.31(1) Å, β = 96.33(1)°, Z = 2, R = 0.0311, GOF = 1.0308.
(15) (a) Hoye, T. R.; North, J. T.; Yao, L. J.; *J. Org. Chem.* **1994**, *59*, 6904−6910. (b) Hoye, T. R.; North, J. T.; Yao, L. J. *J. Org. Chem.* **1995**, *60*, 4958.
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(17) The absolute stereochemistry of (−)-Araguspongine D [enantiomer of (+)-Xestospongin A] was assigned by chemical correlation with a C_2 symmetrical diol obtained from the degradation of (−)-Araguspongine J. However, the complication arising from the desymmetrization of the diol was not addressed, see ref 2 for details.
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(19) The authors concluded that the absolute configurations of Araguspongine F, G, H, and J were similar to that of (−)-Araguspongine D, see ref 2 for details.

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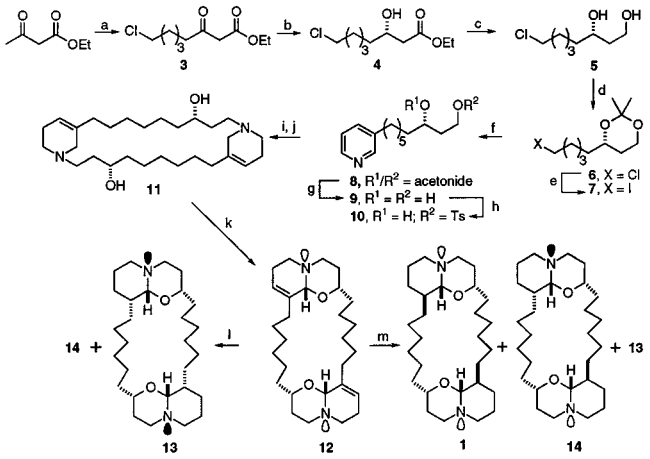
Scheme 1[a]

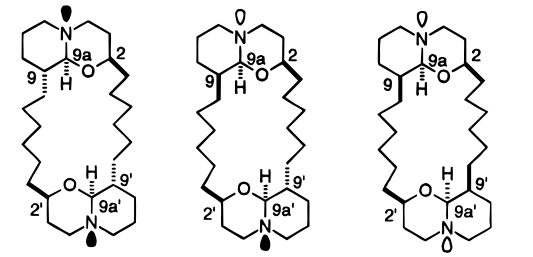


[a] Key: (a) i. NaH, THF; ii. ^{n}BuLi; iii. $Br(CH_2)_4Cl$, 78%; (b) Ru(II)-*S*-BINAP, H_2, EtOH, 96%; (c) $LiBH_4$, Et_2O, 84%; (d) PPTS, 2,2-dimethoxypropane, acetone, 94%; (e) NaI, acetone, reflux, 98%; (f) 3-picoline, LDA, THF, 72%; (g) HCl(aq), EtOH, 94%; (h) TsCl, Et_3N, CH_2Cl_2, 88%; (i) NaI, butan-2-one, reflux; (j) $LiBH_4$, MeOH, ^{i}PrOH, 34%, over 2 steps; (k) DEAD, CH_2Cl_2, 53%; (l) Raney Ni, H_2, MeOH, 77% for **13** and 7% for **14**; (m) Rh on alumina, MeOH, H_2, then add alumina, reflux and HPLC, 23% for **1**, 17% for **14**, 9.5% for **13**.

previously prepared from (*S*)-aspartic acid.[18] It is beyond doubt that synthetic **13**, **1**, and **14** are (+)-Araguspongine B, (−)-Xestospongin A, and (+)-Xestospongin C, respectively.

In conclusion we have demonstrated the validity of our proposed biosynthetic theory. In addition our results unambiguously establish the correct absolute configurations of (+)-Xestospongin A as (2*R*,9*R*,9a*S*,2′*R*,9′*R*,9a′*S*), of (−)-Xestospongin C as (2*R*,9*S*,9a*S*,2′*R*,9′*R*,9a′*S*), and of (−)-Araguspongine B as (2*R*,9*S*,9a*S*,2′*R*,9′*S*,9a′*S*) (Chart 1). Furthermore, our results also

Chart 1. Revised Structures of (+)-Xestospongin A, (−)-Xestospongin C, and (−)-Araguspongine B



imply that the absolute stereochemistries of other Araguspongine alkaloids (Araguspongines F, G, H, and J)[2,19] may need to be reexamined and, finally, it is likely that the intermediate **12** is an as yet undiscovered sponge alkaloid.

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Supporting Information Available: Detailed experimental procedures for the preparation of all new compounds, X-ray structural information on **12**, and the schematic summary of the alternative synthesis of **9** and **10** from (*S*)-aspartic acid (15 pages, print/PDF). An X-ray crystallographic file, in CIF format, is available via the Web only. See any current masthead page for ordering information and Web access instructions.

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