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[16] Triphenylene and the substituted derivatives gave correct analytical and spectroscopic data. **3**: M.p. 194 °C (literature value[6a] 198 °C). **7**: ^{1}H NMR ([D$_8$]THF) $\delta = 8.42$ (t, $J = 10.3$ Hz, 6H); MS: *m*/*z* (%): 336 (100), 168 (16); HR-MS: calcd for $C_{18}H_6F_6$: 336.0374, found: 336.0364. **11**: M.p. 188 °C; ^{1}H NMR ($CDCl_3$) $\delta = 9.04$ (dd, $J = 8.5$, 0.8 Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.48 (m, 3H), 4.04 (s, 3H), 3.97 (s, 6H); ^{13}C NMR ($CDCl_3$) $\delta = 158.2$, 157.9, 157.0, 133.0, 132.6, 131.9, 127.3, 127.0, 126.8, 121.1, 118.8, 118.4, 118.1, 115.9, 115.0, 110.4, 108.7, 108.5, 56.1, 55.8, 55.7; MS: *m*/*z* (%): 318 (100), 303 (25), 288 (15); HR-MS: calcd for $C_{21}H_{18}O_3$: 318.1256, found: 318.1268. **12**: ^{1}H NMR ($CDCl_3$) $\delta = 9.00$ (dd, $J = 8.5$, 1.2 Hz, 3H), 7.48 (t, $J = 8.2$ Hz, 3H), 7.14 (dd, $J = 8.1$, 1.0 Hz, 3H), 4.02 (s, 9H); MS: *m*/*z* (%): 318 (100), 303 (22), 288 (30).

Investigations into the Manzamine Alkaloid Biosynthetic Hypothesis**

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Over the past decade there has been an upsurge in the discovery of biologically active natural products from marine sponges.[1] In comparison to terrestrial plant and microbial systems, little is known about the biosynthesis of sponge metabolites.[2] One class of cytotoxic sponge metabolites which have recently fascinated organic chemists are the manzamine alkaloids. The first member of this class, manzamine A (**1**, Figure 1), was isolated in 1986 by Higa et al.[3]

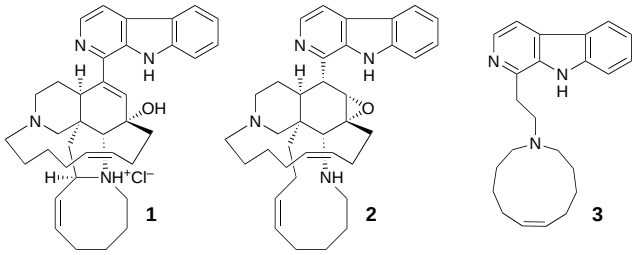

Figure 1. Manzamine A (**1**), B (**2**), and C (**3**).

and recently synthesized.[12] The unprecedented structure led the authors to the conclusion that "no obvious biogenetic path" could be envisaged leading to **1**. Manzamines B (**2**) and C (**3**) were subsequently isolated from the same sponge.[4]

In 1992, we put forward a biogenetic hypothesis for the formation of the manzamines.[5] We proposed that each structure could be reduced into four building blocks: ammonia, a C_{10} unit (a symmetrical dialdehyde), tryptophan, and a C_3 unit (an acrolein equivalent), shown in Scheme 1 for manzamine B (**2**). The key step in the proposal is the intramolecular *endo* Diels – Alder cycloaddition of the bis-dihydropyridine **4**.[6] To date it is not known whether a "Diels – Alderase" exists.[7]

Since the publication of the hypothesis a large number of manzamine and related alkaloids have been isolated from various species of sponge worldwide.[8] Despite the lack of experimental evidence, the proposal has been applied repeatedly to explain the biogenetic origin of the manzamine and related alkaloids. One related alkaloid is keramaphidin B (**5**, Scheme 1), which was isolated independently by both the Kobayashi and Andersen groups.[9] Structurally **5** is simply the reduced form of the proposed cycloadduct **6** (Scheme 1). Herein, we report the biomimetic synthesis of **5**, the first in vitro chemical evidence for this proposal.

The synthesis of **7** was first communicated in 1996,[6e] but we found the route unsatisfactory because of moderate yields (7% overall) and the instability of one intermediate. Since then we have modified the synthesis (Scheme 2) with significant improvements (37% overall yield). Hydroxyphosphonium salt **8** was masked as its tetrahydropyranyl (THP) derivative **9** (93%). Olefin **10** was obtained from the ylide generated from **9** and 3-(3-pyridyl)propanal in 83% yield. Acid-mediated deprotection gave the alcohol **11** (94%), which was treated with *p*-toluenesulfonyl chloride to give **12** (95%). A one-pot Finkelstein reaction, dimerization and macrocyclization was effected by the slow addition of **12** into a mixture of NaI in 2-butanone under reflux. The crude product was reduced to give bis-tetrahydropyridine **13** in 56% yield over the two steps. Oxidation of **13** with 3-chloroperbenzoic acid (*m*CPBA) furnished diastereomeric N-oxides (98%), which could be treated with trifluoroacetic anhydride to give bis-dihydropyridine **7** (100%).

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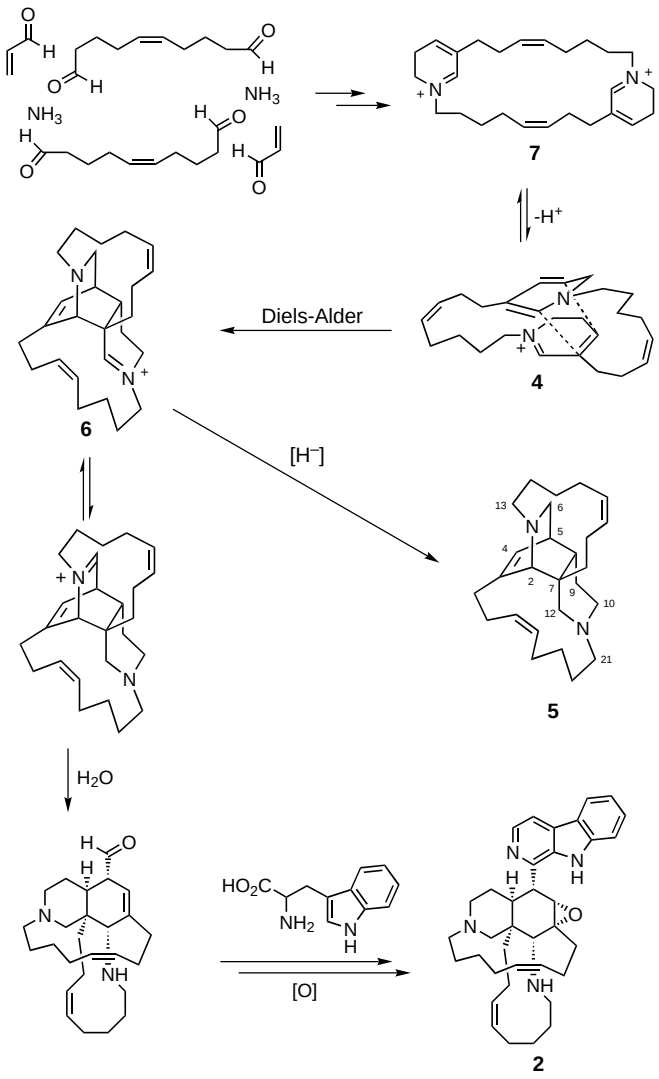
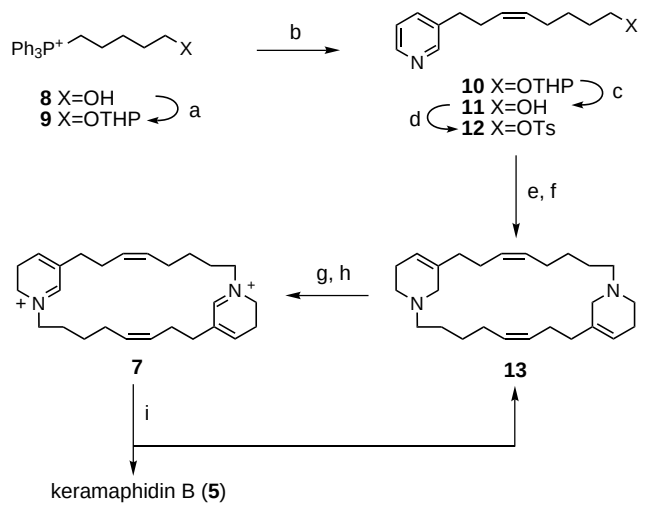


Scheme 1. A hypothesis for the biosynthesis of the manzamine alkaloids.[5]



Scheme 2. Synthesis of bis-dihydropyridine **7**. Reagents and conditions: a) 1.5 equiv 3,4-dihydro-2*H*-pyran, 0.01 equiv pyridinium *p*-toluenesulfonate, CH_2Cl_2, 15 h, 93%; b) 1.2 equiv potassium hexamethyldisilazide, THF, −78°C to RT, 1 h, then 3-(3-pyridyl)propanal, −78°C to RT, 2 h, 83% (Z:$E \approx 99$:1); c) 3M HCl, MeOH, 3 h, 94%; d) 1.5 equiv *p*-toluenesulfonyl chloride, 2 equiv Et_3N, CH_2Cl_2, 0°C, 3 h, 95%; e) 1.2 equiv NaI, 2-butanone, △, 192 h; f) 3 equiv $NaBH_4$, MeOH, −78°C to RT, 0.5 h, 56% over 2 steps; g) 2 equiv *m*CPBA, CH_2Cl_2, 0°C, 98%; h) 4 equiv trifluoroacetic anhydride, CH_2Cl_2, 100%; i) MeOH/1M aqueous TRIS buffer (1/1; pH 7.3; TRIS = tris(hydroxymethyl)aminomethane), 1 h; then 3 equiv $NaBH_4$, MeOH, −78°C to RT, 0.5 h, 0.2–0.3%.

It was eventually discovered that dissolution of **7** in an aqueous methanol buffer, followed by reduction, yielded a small but detectable amount of keramaphidin B (**5**) within a complex mixture of products. After extensive chromatographic purification of this mixture, **5** was isolated in 0.2–0.3% yield.[10] The synthetic material was identified by NMR spectroscopy, LC-MS, and by doping the synthetic sample with authentic material (Figure 2). The major product (60–85%) was the recyclable bis-tetrahydropyridine **13**. This compound originated from disproportionation of **4** giving a mixture of tetrahydropyridine and the pyridinium salt, which was subsequently reduced to afford **13**.[11]

In conclusion, we have demonstrated the chemical feasibility of our theoretical proposal for the biosynthesis of the manzamine alkaloids. The low yield of keramaphidin B (**5**) reflects the preference of **4** to disproportionate and the difficulty of purification. A "Diels–Alderase" that limited the conformational mobility of the substrate would not only decrease the change in entropy towards the transition state, but could also exclude the disproportionation.

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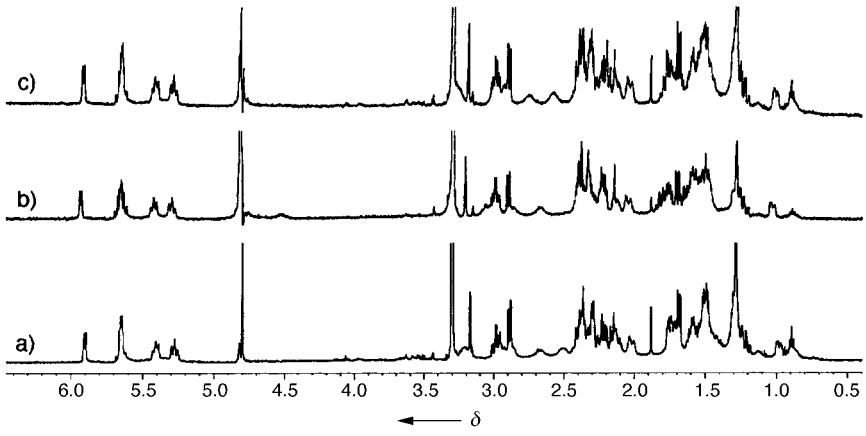

Figure 2. ^1H NMR doping experiment of **5** (500 MHz, CD_3OD): a) synthetic material; b) authentic material of similar concentration; c) 1:1 mixture of (a) and (b).

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[10] ^{1}H NMR (750 MHz, CD_3OD, 50 °C): $\delta = 0.93$ (1H, ddd, $J = 12$, 4.5, 1.5 Hz; C(8)H), 1.21 (1H, qd, $J = 14$, 4 Hz; C(9)H), 1.36 – 1.40 (1H, m; C(14)H), 1.42 – 1.63 (8H, m; C(14)H′, C(15)H_2, C(16)H, C(22)H, C(23)H_2, and C(9)H′), 1.67 (1H, dd, $J = 9$, 2.5 Hz; C(6)H), 1.69 – 1.76 (4H, m; C(20)H_2, C(19)H, and C(22)H′), 1.99 (1H, br d, $J = 13$ Hz; C(24)H), 2.08 (1H, d, $J = 11.5$ Hz; C(12)H), 2.09 – 2.12 (1H, m; C(27)H), 2.20 (1H, ddd, $J = 12.5$, 5.5, 1.5 Hz; C(13)H), 2.20 – 2.28 (2H, m; C(5)H and C(24)H′), 2.30 – 2.42 (7H, m; C(28)H_2, C(27)H′, C(19)H′, C(16)H′, C(21)H, and C(12)H′), 2.69 – 2.71 (1H, m; C(10)H), 2.78 (1H, br t, $J = 13$ Hz, C(10)H′), 2.87 (1H, dd, $J = 9$, 2 Hz; C(6)H′), 2.95 (1H, td, $J = 12.5$, 5 Hz; C(13)H′), 3.03 – 3.06 (1H, m; C(21)H′), 3.11 (1H, s; C(2)H), 5.25 (1H, pseudo t, $J = 10.5$ Hz; C(25)H), 5.38 (1H, pseudo t, $J = 10$ Hz, C(26)H), 5.60 – 5.66 (2H, m; C(17)H and C(18)H), 5.86 (1H, d, $J = 6$ Hz; C(4)H); diastereotopic protons are assigned as X and X′, where the ′ indicates the lower field proton; ^{13}C NMR (188.7 MHz, CD_3OD) $\delta = 21.32$ (C22), 21.68 (C19), 23.80 (C16), 26.10 (C24), 26.53 (C27), 27.12 (C9), 27.50 (C14, C15 and C23), 37.81 (C28), 38.99 (C5), 42.10 (C20), 44.62 (C8), 48.77 (C10), 50.94 (C12), 54.48 (C6), 55.15 (C13), 57.04 (C21), 65.04 (C2), 124.52 (C4), 131.27 (C18), 132.59 (C25), 132.60 (C17), 133.33 (C26), 142.94 (C3); only signals which can be clearly observed above the noise or which can be traced back through HMQC experiments are reported; *m*/*z* (APCI) 381 (MH^+, 100%); HRMS found: 381.3270; calcd for $C_{26}H_{41}N_2$ (MH^+): 381.3270.

[11] The reaction of **7** in buffer was monitored by ^{1}H NMR spectroscopy. By the time the reaction was quenched with $NaBH_4$, all the signals arising from **7** had virtually disappeared. Therefore, the majority of **13** was not derived from the reduction of **7**.

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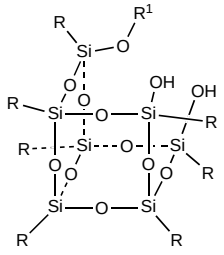
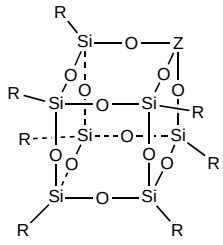
A New Route to Heterosilsesquioxane Frameworks**

Frank J. Feher,* Daravong Soulivong, Frank Nguyen, and Joseph W. Ziller

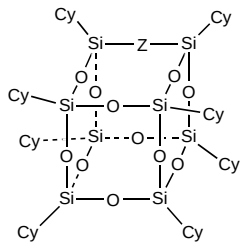
Incompletely condensed silsesquioxanes such as **1** and **2**[1, 2] are versatile precursors to a diverse range of Si/O and Si/O/M frameworks, and a wide variety of heterosilsesquioxanes can be prepared by reactions that transform Si – OH groups into new siloxane (i.e., Si-O-Si) or heterosiloxane (i.e., Si-O-M) linkages.[3–11] In virtually all cases, the resulting products are formally derived from the substitution of heteroatoms for Si atoms in a silsesquioxane framework (e.g., **3**). In this paper we report a new method for preparing discrete heterosilsesquioxane frameworks. This method introduces heteroatoms and heteroatom-containing groups by nucleophilic substitution reactions at framework Si atoms and affords products derived from the formal replacement of a framework oxygen atom in **4** by a heteroatom or other divalent bridging group (e.g., **5**).



1, R^1 = H
2, R^1 = $SiMe_3$



3, Z = heteroatom and any ligands



4, Z = O; Cy = *c*-C_6H_{11}
5, Z = heteroatom or other bridging group

The key to our approach is ditriflate **6**, which can be prepared in high yield by the reaction of $Cy_8Si_8O_{12}$ (**4**) with triflic acid (TfOH) in noncoordinating solvents such as CH_2Cl_2 or C_6H_6.[12] The triflate groups from **6** are rapidly displaced by many nucleophiles with complete stereochemical inversion at both Si centers. With difunctional nucleophiles (e.g., H_2O), there are two possible products: difunctional derivatives resulting from two sequential bimolecular displacement reactions (e.g., **7**) or "edge-capped" products resulting from intramolecular cyclization of the monosubstituted (e.g., **4**).[12] Cyclization is usually favored when reactions are performed in dilute solutions with stoichiometric quantities of reagents.

The reaction of **6** with aniline produces **8** and/or **9** in high yield. When the reaction is performed in toluene/Et_3N with an excess of aniline (> 4 equiv), **8** is obtained in > 95% NMR yield. The structure of **8**, which was assigned on the basis of

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