Reactions of Aminopentadienal Derivatives with 5,6-Dihydropyridinium Salts as an Approach to Manzamine Alkaloids Based upon Biogenetic Considerations

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Recent results from our laboratory have prompted us to introduce a modification of the original Baldwin proposal for the biosynthesis of manzamine alkaloids. In this new model, aminopentadienal derivatives of general structures **2** or **3** can not only cyclize to give pyridinium salts such as cyclostellettamines but also react with 5,6-dihydropyridinium salts **1** leading to species such as **6** or **7**, which would be key intermediates in the syntheses of manzamine A and halicyclamine B. On the basis of the chemistry depicted in Scheme 2, model reactions of dienes **9**, **10**, **12**, and **13** with salts **1** have been investigated. Diene **9** gave an interesting rearrangement product **15a**, while dienes **10** and **12** gave halicyclamine- and manzamine-type adducts **19** and **23**, respectively. In addition, glutaconaldehyde derivative **13** gave adduct **32** possessing some characteristic features of sarain A.

Introduction

Manzamine A (Figure 1), isolated[1] from a sponge (*Haliclona sp.)* collected off Manzamo, Okinawa, has been the subject of much synthetic effort during the past few years.[2] Interest in this field not only arose from the challenging structure and biological activity of manzamine A itself but also from the recent discovery of a large number of related natural alkaloids isolated from sponges in the same order (*Haplosclerida*),[3] some representative members of which are depicted in Figure 1.

That these apparently different structures are biogenetically closely related was postulated by Baldwin and Whitehead,[4,5] who suggested that manzamine A and keramaphidin B can arise from the intramolecular cyclization of a macrocyclic dihydropyridine intermediate. Central to this hypothesis is the chemistry of dihydropyridinium salts **1**, which could result from the condensation of an aldehyde and a primary amine with acrolein (Scheme 1).

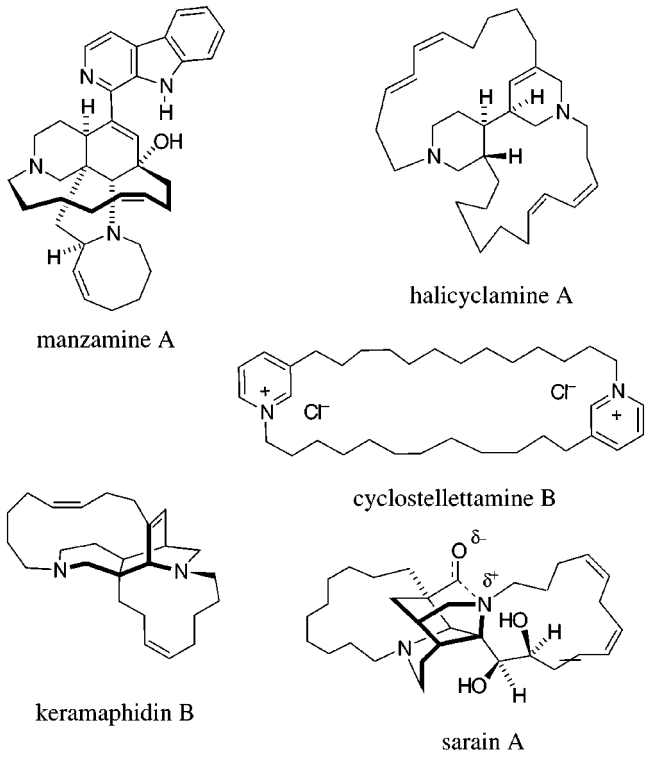

Figure 1. Representative members of manzamine alkaloids.

Recent results from our laboratory prompted us to introduce a modification of the original Baldwin proposal.[6] In our new model, condensation of malonaldehyde with an aldehyde and a primary amine would produce key aminopentadienal derivatives (two possible regioisomers **2** and **3**) that are very likely to cyclize in an acidic

(1) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404−6405.

(2) For a recent review on synthetic approaches to manzamines, see: Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201−6258. Total synthesis of manzamine A: (a) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425−6426. (b) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866−867.

(3) For comprehensive reviews, see: (a) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proc. Int.* **1998**, *30*, 3−51. (b) Andersen, R. J.; Van Soest, R. W. M.; Kong, F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: Elsevier Science 1996; Vol. 10, pp 301−355. (c) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765−794. (d) Crews, P.; Cheng, X.-C.; Adamczeski, M.; Rodriguez, J.; Jaspar, M.; Schmitz, F. J.; Traeger, S. C.; Pordesimo, E. O. *Tetrahedron* **1994**, *50*, 13567−13574.

(4) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059−2062.

(5) For model reactions leading to keramaphidin B and halicyclamine A skeletons, see: (a) Baldwin, J. E.; Bischoff, L.; Claridge, T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. *Tetrahedron* **1997**, *53*, 2271−2290 and references therein. (b) Gil, L.; Baucherel, X.; Martin, M.-T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 6231−6234.

(6) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 0, 8026−8034.

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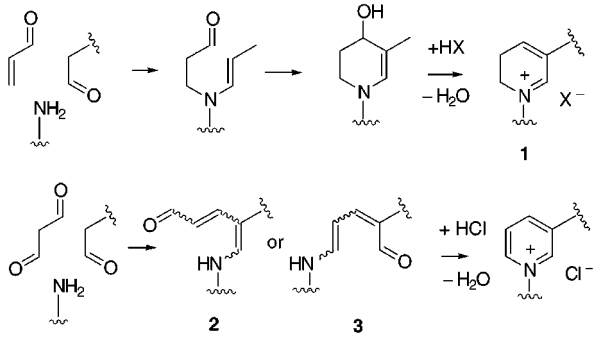
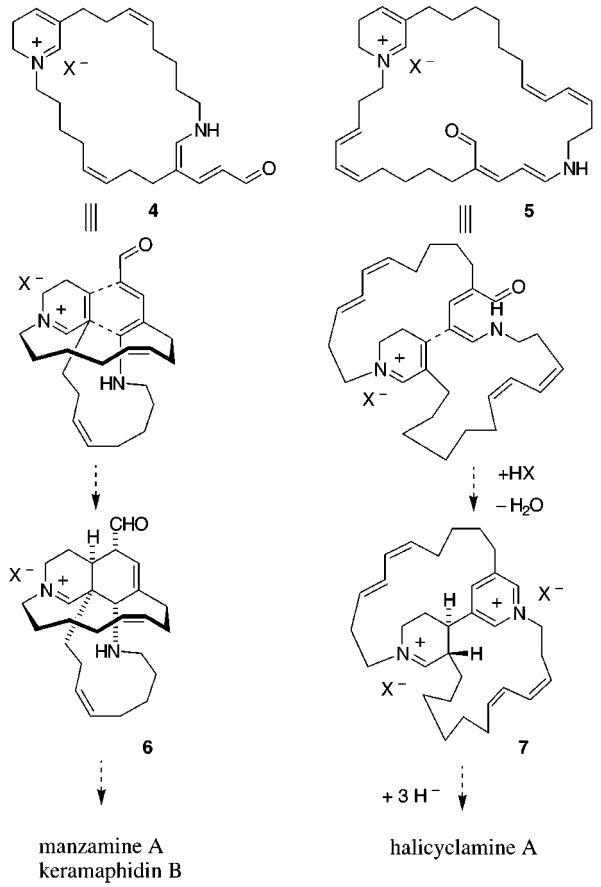
Scheme 1. Two Possible Biogenetic Pathways to Six-membered Nitrogen Heterocycles Starting from Acrolein[4] or Malondialdehyde[6]

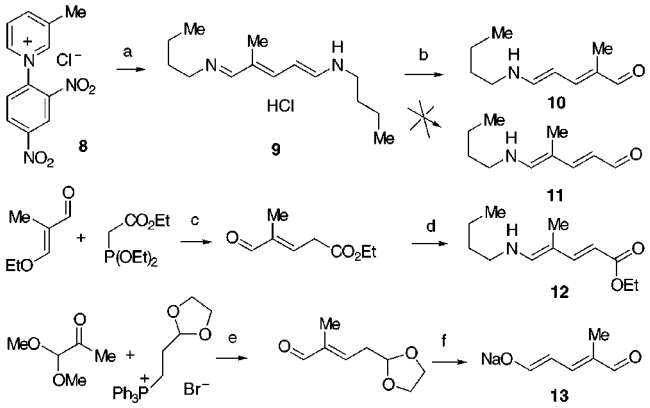


Scheme 2. Proposed Biogenetic Pathways to Manzamine A and Halicylamine A



medium to give natural 3-alkylpyridinium salt derivatives such as cyclostellettamines and pyridinium macrocyclic oligomers. These aminopentadienal derivatives can not only produce pyridinium salts but also could alternatively condense with salts **1**, this chemistry being at the origin of our modified model[6] for the construction of manzamine A and halicyclamine B. This proposal is summarized in Scheme 2. In this model, macrocycles such as **4** and **5**,[7] both possessing dihydropyridinium and aminopentadienal species, can react in two different ways to give polycycles **6** and **7**, respectively. These polycycles could then be considered as advanced intermediates in the syntheses of manzamine A and halicyclamine B, while reductive cyclization of **6** would give keramaphidin B.

Scheme 3. Synthesis of Aminopentadienal Derivatives or Their Equivalents[a]



[a] Key: (a) *n*-$BuNH_2$ (2 equiv); (b) NaOH, H_2O; (c) (i) NaH, THF; (ii) HCO_2H, Et_2O; (d) *n*-$BuNH_2$, CH_2Cl_2, Al_2O_3; (e) (i) *n*-BuLi, THF, −20 °C; (ii) H^+ (pH 3); (f) (i) Dowex 50WX8; (ii) NaOH.

In this paper, we report details of a series of model reactions intended to test the chemistry summarized in Scheme 2.

Results and Discussion

A. Synthesis of Aminopentadienal Derivatives or Their Equivalents. Since dihydropyridinium salts **1** are readily available,[8] the first problem to be addressed was the regioselective synthesis of substituted aminopentadienal derivatives corresponding to species **2** or **3**.[9] Ring opening of Zincke salt **8** (Scheme 3) with 2 equiv of *n*-butylamine gave the crystalline salt **9** in good yield. It was anticipated that the hydrolysis of this intermediate in the presence of sodium hydroxide would give a separable mixture of the two aminopentadienal derivatives **10** and **11**. In fact, the immediate recording of the ^{1}H NMR spectrum of the crude reaction mixture after hydrolysis showed the initial formation of the two desired isomers **10** and **11** in an 85:15 ratio. However, it was not possible to isolate the minor isomer **11** since it readily rearranged when chromatographed, or left in solution, to give thermodynamically more stable isomer **10**, which was thus obtained as a single product in good yield. Since the synthesis of **11** was not feasible by this approach, we targeted the corresponding ester **12**, the synthesis of which was readily accomplished from commercial products via a Wittig−Horner reaction. We additionally synthesized the sodium salt of 2-methylglutaconaldehyde **13**[10] also from commercially available precursors using a Wittig reaction.

Nucleophilic additions of these new derivatives **9**, **10**, **12**, and **13** to dihydropyridinium salts **1a** were next investigated.

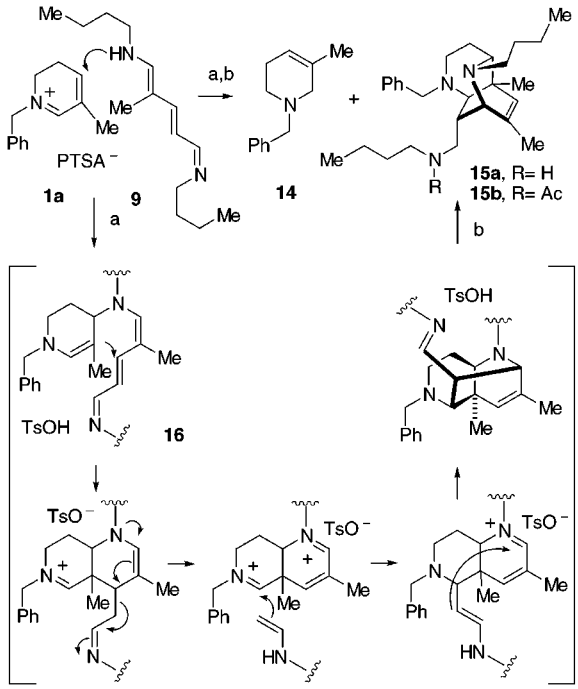
(7) Note that an aminopentadienal regioisomer of type **2** is required for construction of the manzamine A skeleton, while both isomers of type **2** and **3** can lead to the halicyclamine A skeleton (only the regioisomer of type **3** is shown in Scheme 2).

(8) (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064−1082. (b) For a review, see: Grierson, D. S. *Org. React.* **1990**, *39*, 85−295.

(9) For a review on the synthesis and reactions of glutaconaldehyde and the corresponding amino derivatives (aminopentadienals), see: Becher, I. *Synthesis* **1980**, 589−612.

(10) For previous synthesis of glutaconaldehyde and derivatives, see ref 8. For 2-alkyl derivatives, see also: Yanovskaya, L. A.; Kucherov, V. F. *Izv. Akad. Nauk. SSSR* **1960**, 2184; *C. A.* ***1961***, *55*, 14452. Free glutacondialdehyde derivatives are very unstable intermediates (glutaconaldehyde is stable for only ∼30 min at ∼−70 °C).[9]

Scheme 4[a]

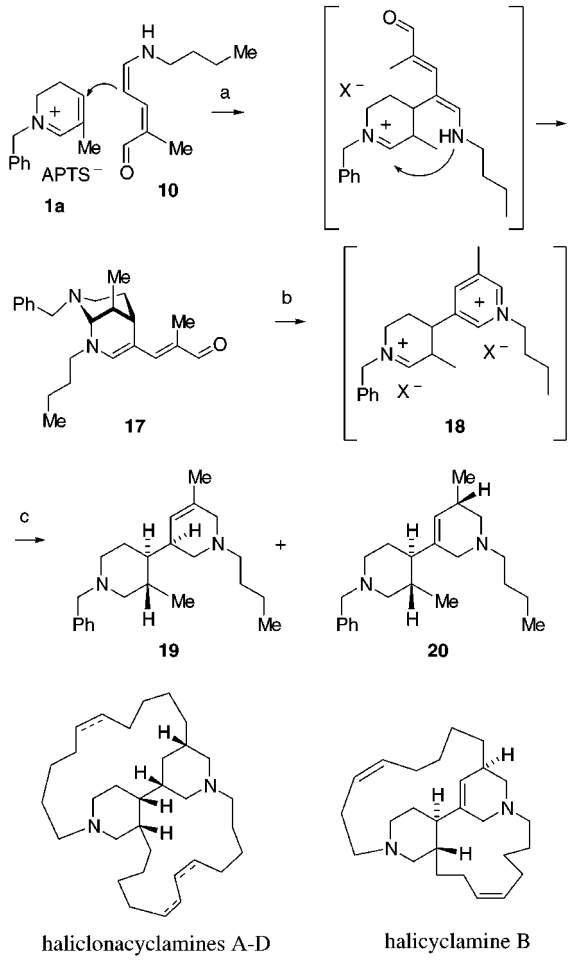


[a] Key: (a) CH_2Cl_2, 64 h, 20 °C; (b) $NaBH_4$, 2-propanol, 15% yield for **15a**.

B. Addition of Diene 9 to Salt 1a.[11] The results of the reaction of salt **1a**[12] with diamino derivative **9** (free base) are summarized in Scheme 4. The reaction was monitored by GC−MS analysis of aliquots after reduction with $NaBH_4$. The major compounds detected were tetrahydropyridine **14** and a reduction product of **9** (structure not determined), which were accompanied by products seemingly corresponding to those arising from the dimerization of salt **1a** in the presence of a base.[5] After 60 h, these products disappeared and a new adduct (**15a**) was formed, which was recovered in 15% yield after chromatography, along with major tetrahydropyridine **14** (37%). The structure of the adduct was established as **15a** by an NMR study of the corresponding acetate **15b**.[13a] A plausible mechanism for the formation of **15a** is shown in Scheme 4. Noteworthy is the fact that this mechanism necessarily implies formation of the initial adduct **16** resulting from the attack of one nitrogen of **9** on salt **1a**. No product corresponding to the attack of a nucleophilic carbon of **9**, as required in our tentative routes (Scheme 2), was detected. Albeit disappointing, this result revealed some new interesting features of the chemistry of reactants such as **1a** and **9**.

C. Halicyclamine Model.[11] Addition of aminopentadienal **10** to salt **1a** (Scheme 5) was more encouraging since it proceeded smoothly in methylene chloride to form a carbon−carbon bond, providing aminal **17**[13b] that was isolated in 55% yield. Treatment of this adduct with methanesulfonic acid in water presumably gave the

Scheme 5[a]



[a] Key: (a) CH_2Cl_2, 12 h; (b) $MeSO_3H$, H_2O, MeOH, 50 °C; (c) $NaBH_4$, MeOH (**19**/**20**: 3/1 ratio, 23% yield from **1a**).

pyridinium salt **18**, which was not isolated, but was directly treated with an excess of $NaBH_4$. GC−MS analysis of the crude reaction mixture revealed the formation of mainly two adducts **19** and **20** in a 3:1 ratio along with traces of other minor diastereoisomers. These two adducts were recovered in 23% overall yield, and pure samples of each isomer were obtained by HPLC, allowing structure resolution by NMR spectroscopy.[13a] The structure **19** of the major isomer was confirmed unambiguously by comparison with a related halicyclamine-type analogue resulting from previous model reactions.[5b] This sequence thus represents an encouraging result in favor of our proposed route to halicyclamine A. The yields of **19** are consistently superior to those obtained from our previous procedure,[2b] an added advantage being the differentiation of the two nitrogen substituents. In addition, the minor adduct **20** can be considered as a halicyclamine B[14a] model, albeit the relative stereochemistry of the asymmetric center of the tetrahydropyridine ring is inverted. We believe that this epi structure is not of much significance since the macrocyclic structure leading to the natural alkaloid can

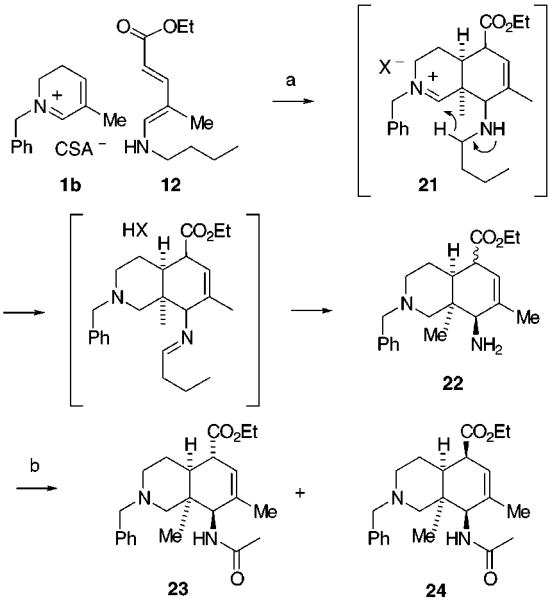
(11) Jakubowicz, K. Ph.D. Thesis in preparation.

(12) Pure salts **1a**,**b** were obtained from the corresponding methoxy adduct according to our reported procedure: Gil, L.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 707−710.

(13) (a) All complex structures were resolved by intensive NMR spectroscopy studies including 1D and 2D NMR experiments (COSY 90, NOESY, HMQC, HMBC; see the Supporting Information). (b) Structure **17** was confirmed by an X-ray analysis that will be reported separately.

(14) (a) Harrisson, B.; Talapatra, S.; Lobkovsky, E.; Clardy, J.; Crews, P. *Tetrahedron Lett.* **1996**, *51*, 9151−9154. (b) Charan, R. D.; Garson, M. J.; Brereton, I. M.; Willis, A. C.; Hooper, J. N. A. *Tetrahedron* **1996**, *52*, 9111−9120. (c) Clark, R. J.; Field, K. L.; Charan, R. D.; Garson, M. J.; Brereton, I. M.; Willis, A. C. *Tetrahedron* **1998**, *54*, 8811−9126.

Scheme 6. Manzamine Model[a]



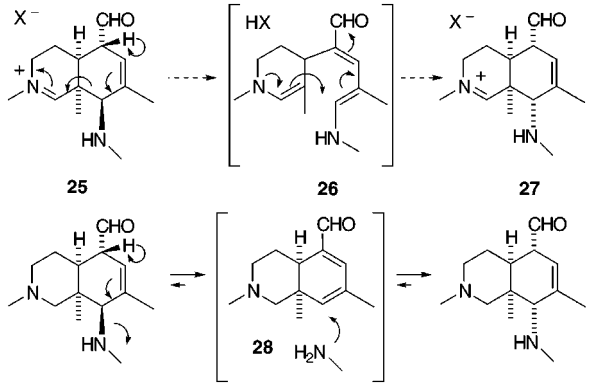
[a] Key: (a) CH_2Cl_2, 0−4 °C, 15 h; (b) Ac_2O, pyridine (43% overall for **23**, 7% for **24**).

significantly influence the stereochemistry of such reduction process. Pyridinium salts related to **18** are also likely to be precursors of haliclonacyclamines A−C core skeletons.[14b,c]

D. Manzamine Model.[15] The cycloaddition reaction of salt **1a** with diene **12** (Scheme 6) proceeded smoothly at 0−4 °C.[16,17] The iminium adduct **21** was likely formed first, but an unexpected intramolecular hydride transfer occurred[18] and the products of the reaction were esters **22** (resulting from the hydrolysis of the intermediate imine), which were isolated as their acetyl derivatives **23** and **24**. These two bicyclic adducts were isolated after chromatography in 43% and 7% yield, respectively, and their structure was elucidated by NMR spectroscopy.[13a] No other adducts that could result from the reaction of salt **1a** with diene **12** were detected in significant amounts as determined by GC−MS analysis of the crude reaction mixture. The ease of this cycloaddition process supports the model proposed in Scheme 2. In addition, among the rather numerous Diels−Alder strategies[2] for the construction of manzamine A central AB rings, this approach is certainly one of the most efficient since it brings together all the important functionalities in a single step.

Separate treatment of the esters **23** and **24** with *t*-BuOK resulted in each case in the recovery of a mixture of these two esters in approximately a 1:1 ratio. This result suggests that the stereochemistry of the ester function in the major product **23** was not the result of

Scheme 7



an equilibration process. Accordingly, the product **23** is likely to be derived from the major primary adduct of the cycloaddition reaction. This proposal is reinforced by the fact that the intramolecular reduction of the very unstable iminium function[19] probably takes place immediately after the cycloaddition, thus preventing any further equilibration. The inverted stereochemistry of the exocyclic amino group in our experimental model (see **23**) when compared to the proposed intermediate **6** can be explained by the same considerations. Thus, if the intramolecular reduction process has "trapped" the stereochemistry of the primary cycloadduct, further thermodynamic equilibration of this center was not possible. The intramolecular reduction might be avoided, for example, by the temporary addition of a nucleophile to stabilize the iminium function.[19] If this is the case, it is conceivable that the expected cycloadduct **25** (Scheme 7) could rearrange to give the open intermediate **26**, which would then cyclize to give the thermodynamically more stable iminium ion **27**. Another isomerization mechanism would be an elimination-addition process through diene **28**. Further work in this direction is now in progress.

E. An Approach to the Sarain A Skeleton.[20] A further series of results is depicted in Scheme 8. Methyl-substituted glutaconaldehyde salt **13** adds to salt **1a** in a two-phase system (H_2O/CH_2Cl_2), giving intermediate **29** that readily cyclized, affording a mixture of isomers **30** and **31** (approximately 5:95 ratio) in practically quantitative yield. Filtration of this mixture through silica gel using CH_2Cl_2 as eluent resulted in its complete isomerization to give a 2:1 mixture of dialdehydes **32** and **33**,[13a] which were isolated in 33% yield. This isomerization also takes place on alumina with CH_2Cl_2 as eluent but is slower. The relatively modest yield of the dialdehydes is probably due to competitive polymerization processes. When the reaction of **1a** with **13** was performed in MeOH, formation of dialdehyde adducts **32** and **33** was also observed, but these products were isolated in very low yield, again due to competing polymerization processes. All data suggest that these relatively unstable dialdehydes are in thermodynamic equilibrium and were thus inseparable. Reduction of this mixture, followed by acetylation of the resulting diols, gave two adducts that were separated and characterized by NMR as **34** and **35** (1:2 ratio).[13a] The structures of the adducts **32** and **33** retain salient features of the sarain A core skeleton. Adducts **32** and **33** thus possess the correct junction of

(15) Herdemann, M. Ph.D. Thesis in preparation.

(16) For the related cycloaddition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene to aminonitrile derivatives of **1**, see: Baldwin, J. E.; Spring, D. R., Whitehead, R. C. *Tetrahedron Lett.* **1998**, *39*, 5417−5420.

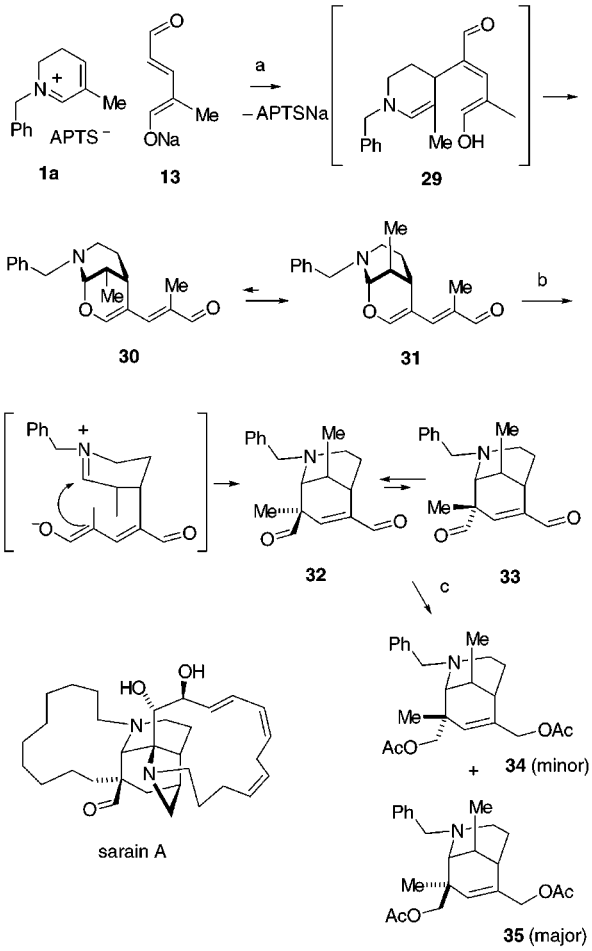
(17) Examples of push−pull dienes cycloadditions to classical dienophiles under high pressure: Branchadell, V.; Sodupe, M.; Ortuno, R. M.; Oliva, A.; Gomez-Pardo, D.; Guinguant, A.; d'Angelo, J. *J. Org. Chem.* **1991**, *56*, 4135−4141.

(18) For a discussion of analogous intramolecular reductions, see: Cohen, T.; Onopchenko, A. *J. Org. Chem.* **1983**, *48*, 4531−4537. Note that treatment of the reaction mixture with $NaBH_4$ in MeOH prior to acetylation gave the same results and is therefore unnecessary.

(19) Mitch, C. H. *Tetrahedron Lett.* **1988**, *29*, 6831−6834.

(20) Ben Abdeljelil, K. Ph.D. Thesis in preparation.

Scheme 8. An Approach to Sarain A Skeleton[a]



[a] Key: (a) CH_2Cl_2, 20 °C, (**30**/**31**: 5/95 ratio, 95% yield); (b) Al_2O_3, CH_2Cl_2 (**32**/**33**: 3/2 ratio, 33% yield); (c) (i) $NaBH_4$, MeOH; (ii) Ac_2O, pyridine.

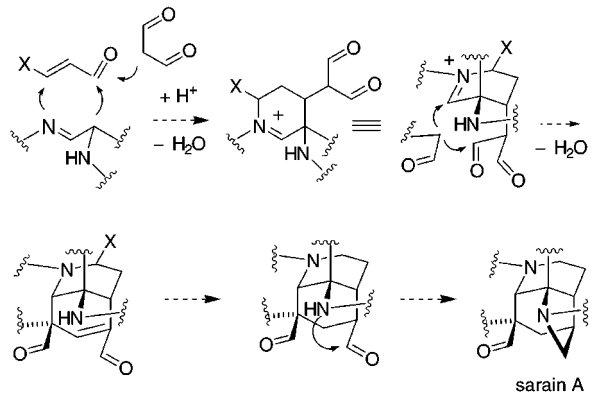
the two six-membered rings, the quaternary carbon center, and carbons for the construction of the five-membered nitrogen heterocycle.

Albeit incomplete, this model represents the first experimental evidence supporting the well-accepted idea that the biosyntheses of sarain A and manzamines are closely related.[3] In this context, one of the possible biogenetic scenarios leading to sarain A from malonaldehyde chemistry (cf Scheme 1)[6] is depicted in Scheme 9. Such chemistry would avoid the intermediacy of dihydropyridinium and dihydropyridine species (our previous proposal),[12] whose chemistry is difficult to control (vide infra).

Experimental Section

Addition of Diene 9 to Salt 1a. To a solution of dihydropyridinium salt **1a** (1.92 g, 5.4 mmol, prepared from 1-benzyl-4-methoxy-3-methyl-1,4,5,6-tetrahydropyridine and *p*-toluenesulfonic acid)[12] in dry CH_2Cl_2 (20 mL) was added derivative **9** (free base, 1.2 g, 5.4 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 64 h and then cooled to −78 °C. 2-Propanol (30 mL) and $NaBH_4$ (611 mg, 16 mmol) were added. After the mixture was stirred for 4 h at room temperature, an aqueous solution of 2 N HCl was added dropwise under vigorous stirring. The resulting mixture was basified with 2 N NaOH and the product extracted with CH_2Cl_2. Removal of solvent under reduced pressure left a crude product, which was purified by chromatography over alumina

Scheme 9. Malonaldehyde Biogenetic Scenario to Sarain A



(AcOEt/heptane, gradient from 10:90 to 50:50) to afford pure product **15a** (325 mg, 15% yield) as a pale yellow oil. An analytical sample of **15a** was treated with pyridine and Ac_2O to give the corresponding acetate ***N*-(6-benzyl-2-butyl-8,10-dimethyl-2,6-diaza-tricyclo[5.3.1.0^{3,8}]undec-9-en-11-ylmethyl)-*N*-butylacetamide (15b)**: IR (film) 3024, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.2 Hz, 3 H), 0.97 (t, J = 7.4 Hz, 3 H), 1.24−1.38 (m, 7 H), 1.34 (s, 3 H), 1.55 (m, 2 H), 1.76 (d, J = 11.5 Hz, 1 H), 1.82 (s, 3 H), 1.85 (m, 1 H), 2.04 (d, J = 10.2 Hz, 1 H), 2.09 (s, 3 H), 2.18 (m, 1 H), 2.37 (m, 1 H), 2.44 (m, 1 H), 2.46 (m, 1 H), 2.66 (dt, J = 3.5, 12.0 Hz, 1 H), 2.86 (dd, J = 4.7, 13.7 Hz, 1 H), 3.07 (s, 1 H), 3.14 (dd, J = 9.6, 13.7 Hz, 1 H), 3.30 (m, 1 H), 3.36 (m, 1 H), 3.40 (d, J = 13.0 Hz, 1 H), 3.63 (d, J = 13.0 Hz, 1 H), 5.57 (s, 1 H), 7.19−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 14.2, 20.3, 20.7, 21.5, 21.8, 22.3, 26.8, 30.7, 31.2, 35.6, 38.6, 42.4, 48.3, 48.9, 57.8, 59.8, 60.7, 61.2, 61.8, 126.7, 128.2 (2 C), 128.6, 129.7 (2 C), 139.9, 140.3, 170.5; MS (EI) *m*/*z* (rel intensity) 451 (M$^{\bullet+}$, 13), 360 (10), 164 (100), 91 (92); HRMS (CI) calcd for $C_{29}H_{46}N_3O$ *m*/*z* 452.3641, found *m*/*z* 452.3631.

Halicyclamine Model. 3-(8-Benzyl-2-butyl-9-methyl-2,8-diazabicyclo[3.3.1]non-3-en-4-yl)-2-methylpropenal (17). 5,6-Dihydropyridinium salt **1a** (2.68 g, 7.5 mmol) was slowly added to aminopentadienal **10** (1.03 g, 6.2 mmol) in dry CH_2Cl_2 (30 mL). After the mixture was stirred for 12 h at room temperature, the solvent was removed under reduced pressure. The crude reaction mixture was chromatographed on a short column of alumina using AcOEt/heptane (1:1) as eluent. Aminal **17** (1.2 g, 55% yield) was obtained as a yellow oil. Pure crystals of **17** were obtained from CH_2Cl_2/heptane: mp 135 °C; IR ($CHCl_3$) 2964, 2871, 2818, 2705, 1649, 1563, 1197, 1144, 1084 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 14 Hz, 3 H), 1.26 (m, 2 H), 1.34 (m, 1 H), 1.36 (d, J = 7 Hz, 3 H), 1.46 (dt, J = 6, 7 Hz, 3 H), 1.85 (m, 1 H), 1.93 (s, 3 H), 2.15 (ddt, J = 4.5, 13, 13 Hz, 1 H), 2.33 (ddd, J = 3.5, 12.5, 12.5 Hz, 3 H), 2.56 (dd, J = 3.5, 11 Hz, 1 H), 2.91 (m, 1 H), 3.23 (m, 2 H), 3.56 (d, J = 13.5 Hz, 1 H), 3.73 (d, J = 13.5 Hz, 1 H), 3.85 (bs, 1 H), 6.55 (s, 1 H), 6.98 (s, 1 H), 7.21−7.37 (m, 5 H), 9.15 (s, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 10.1, 13.8, 15.7, 19.9, 25.3, 32.1, 32.4, 33.7, 43.7, 55.7, 59.6, 74.5, 112.3, 124.1, 127.2, 128.4 (2C), 128.5 (2C), 138.8, 149.1, 153.8, 194.0. MS (EI) *m*/*z* (rel intensity) 352 (M$^{\bullet+}$, 100), 91 (48). Anal. Calcd for $C_{23}H_{31}N_2O$: C, 77.59; H, 8.77; N, 7.86. Found: C, 77.72; H, 8.97; N, 7.83.

1′-Benzyl-1-butyl-5,3′-dimethyl-1,2,3,6,1′,2′,3′,4′,5′,6′-decahydro[3,4′]biperidinyl (19). Methanesulfonic acid (0.5 mL, 7.7 mmol) was added dropwise to a stirred suspension of aminal **17** (1.2 g, 3.4 mmol) in a mixture of H_2O (40 mL) and MeOH (4 mL) at 50 °C. The reaction mixture was warmed to 50 °C and maintained for 3 h at this temperature. The heating bath was then removed, and the crude mixture was slowly added to a solution of $NaBH_4$ (10 equiv) in MeOH at 0 °C and then stirred for 16 h at room temperature. The reaction mixture was quenched with a solution of 2 N aqueous HCl, basified with 5% aqueous NaOH, and then extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over

alumina using AcOEt/heptane (5:95) as eluent to give a mixture of adducts **19** and **20** (261 mg, 23% yield) in a 3:1 ratio as calculated by GC analysis. Pure samples of each adduct were obtained after HPLC on silica gel using a mixture CH_2Cl_2/MeOH/Et_3N (99:1:0.2) as eluent. Major adduct **19**: IR (film) 2956, 2932, 2874, 2801, 2755, 2357, 1660, 1455, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6 Hz, 3 H), 0.92 (t, J = 7 Hz, 3 H), 1.04 (m, 1 H), 1.24−1.41 (m, 3 H), 1.42−1.54 (m, 3 H), 1.54−1.61 (m, 2 H), 1.64 (bs, 3 H), 1.85 (ddd, J = 2.5, 11, 11 Hz, 1 H), 1.96 (dd, J = 9, 9 Hz, 1 H), 2.37 (dt, J = 2, 8 Hz, 2 H), 2.53 (bd, J = 15 Hz, 1 H), 2.72 (m, 2 H), 2.80 (dd, J = 1.5, 8 Hz, 1 H), 2.89 (m, 1 H), 3.00 (bd, J = 15 Hz, 1 H), 3.46 (dd, J = 12, 12 Hz, 2 H), 5.14 (bs, 1 H), 7.18−7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 17.0, 20.9, 21.1, 26.3, 29.3, 32.8, 35.8, 46.2, 50.7, 54.7, 57.2, 58.6, 62.4, 63.4, 124.8, 126.9, 128.2 (2 C), 129.2 (2 C), 132.5, 138.6; MS (EI) m/z (rel intensity) 340 ($M^{+\cdot}$, 59), 249 (50), 186 (58), 91 (100); HRMS (CI) calcd for $C_{23}H_{37}N_2$ (MH^+) 341.2958, found 341.2956. Minor adduct **20**: IR (film) 2956, 2932, 2874, 2801, 2756, 1652, 1455, 1377 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.80 (d, J = 6.6 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 1.40 (m, 2 H), 1.47 (m, 1 H), 1.50 (m, 1 H), 1.56 (m, 2 H), 1.58 (m, 1 H), 1.80 (m, 1 H), 1.82 (m, 1 H), 1.87 (m, 1 H), 1.96 (dd, J = 7.7, 10.8 Hz, 1 H), 2.40 (m, 2 H), 2.48 (m, 1 H), 2.70 (dd, J = 5.6, 10.8 Hz, 1 H), 2.73 (bd, J = 15.0 Hz, 1 H), 2.91 (bd, 2 H), 3.01 (bd, J = 15.0 Hz, 1 H), 3.44 (s, 2 H), 5.40 (bs, 1 H), 7.19−7.46 (m, 5 H); ^{13}C NMR (75 MHz, C_6D_6) δ 14.3, 17.5, 19.6, 21.0, 29.7, 31.2, 32.6, 34.2, 50.7, 54.3, 54.7, 58.5, 58.8, 62.3, 63.7, 126.7, 127.20−129.22 (5 C), 139.6, 140.0; HRMS (CI) calcd for $C_{23}H_{37}N_2$ (MH^+) 341.2962, found 341.2959.

Manzamine Model. 8-Acetylamino-2-benzyl-7,8a-dimethyl-1,2,3,4,4a,5,8,8a-octahydroisoquinoline-5-carboxylic Acid Ethyl Ester (23). To dihydropyridinum salt **1b** [2.4 mmol, prepared from 1-benzyl-4-methoxy-3-methyl-1,4,5,6-tetrahydropyridine (651 mg) and camphorsulfonic acid (697 mg)],[12] dissolved in anhydrous CH_2Cl_2 (20 mL), was added at 0 °C diene **12** (661 mg, 1.25 mmol) in CH_2Cl_2 (20 mL). After 10 min at 0 °C, the solution was stirred for 15 h at 4 °C. The reaction mixture was then poured into a mixture of saturated $NaHCO_3$ and H_2O. The CH_2Cl_2 phase was collected, and the H_2O layer was extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (60 mL), and to this solution were added pyridine (1.21 mL) and Ac_2O (0.71 mL, 7.5 mmol). After the mixture was stirred during 1.5 h at ambient temperature, crushed ice and saturated $NaHCO_3$ were added. The resulting mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue (1.49 g) was chromatographed over silica gel (150 g) using a heptane/AcOEt/CH_3OH/Et_3N mixture (gradient from 90:10:0:0.1 to 79:20:1:0.1). The major adduct **23** was isolated as a pale yellow oil (360 mg, 43% yield): IR ($CHCl_3$) 3444, 3007, 2945, 2811, 1721, 1661 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.31 (m, 5 H), 5.49 (bs, 1 H), 4.42 (bs, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 3.52 (d, J = 13.4 Hz, 1 H), 3.47 (d, J = 13.4 Hz, 1 H), 3.26 (m, 1 H), 2.56 (m, 1H), 2.37 (m, 1 H), 2.34 (bd, J = 11.8 Hz, 1 H), 2.17 (bd, J = 11.8 Hz, 1 H), 2.08 (m, 1 H), 1.99 (m, 1 H), 1.94 (s, 3 H), 1.62 (bs, 3 H), 1.40 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.17 (s, 3 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.5, 20.7, 22.6, 25.0, 26.9, 38.7, 39.6, 44.7, 50.0, 56.7, 56.8, 62.0, 64.3, 120.7, 128.0, 129.2, 129.9, 135.7, 139.7, 173.6, 175.7; MS (IE) m/z 384 (M^+), 326 ($M^+ - NHCOCH_3$), 310 ($C_3H_6O_2$), 186, 146 ($C_{10}H_{12}N$), 91 (C_7H_7); HRMS (CI) calcd. for $C_{23}H_{33}N_2O_3$ (MH^+) 385.2490, found 385.2466. Minor isomer **24** (60 mg, 7% yield): IR ($CHCl_3$) 3254, 3016, 2826, 1721, 1661 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.24 (m, 5 H), 5.65 (bs, 1 H), 4.15 (q, J = 7.1 Hz, 3 H), 3.60 (d, J = 13.1 Hz, 1 H), 3.40 (m, 1 H), 3.30 (d, J = 13.1 Hz, 1 H), 2.96 (bd, J = 11.0 Hz, 1 H), 2.88 (d, J = 11.8 Hz, 1 H), 1.95 (s, 3 H), 1.92 (d, J = 11.8 Hz, 1 H), 1.84 (m, 1 H), 1.74 (m, 1 H), 1.69 (bs, 3 H), 1.50 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.14 (m, 1 H), 1.02 (s, 3 H); ^{13}C NMR (CD_3OD, 75 MHz) δ 14.6. 21.5, 23.4, 25.2, 28.1, 36.9, 42.6, 43.3, 53.8, 55.3, 61.8, 64.1, 65.2, 120.1, 128.3, 129.3, 130.5, 135.4, 138.5, 173.1, 175.3; MS (IE) m/z 384 ($M^{+\cdot}$), 326 ($M^{+\cdot} - NHCOCH_3$), 310 ($C_3H_6O_2$), 186, 146 ($C_{10}H_{12}N$), 91 (C_7H_7).

An Approach to the Sarain A Skeleton. 3-(8-Benzyl-9-methyl-2-oxa-8-azabicyclo[3.3.1]non-3-en-4-yl)-2-methylpropenal (31). 5,6-Dihydropyridinium salt **1a** (1.2 g, 3.92 mmol), in CH_2Cl_2 (15 mL), was added dropwise to a solution of salt **13** (432 mg, 3.24 mmol) in H_2O (25 mL). After vigorous stirring of the resulting biphasic mixture for 2 h at room temperature, the organic phase was decanted and collected. The remaining H_2O phase was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give an unseparable mixture of adducts **30** and **31** (900 mg, 94% yield) in a 5:95 ratio (determined by ^1H NMR spectroscopy): MS (IC) m/z 298 (MH^+). Major adduct **27**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, J = 6.9 Hz, 3 H), 1.41 (m, 1 H), 1.92 (s, 3 H), 2.1 (m, 1 H), 2.19 (m, 1 H), 2.55 (dd, J = 12.1, 4.1 Hz, 1 H), 2.68 (m, 1.H), 2.82 (m, 1H), 3.65 (d, J = 13.7 Hz, 1 H), 3.92 (d, J = 10.3 Hz, 1 H), 4.75 (d, J = 2.5 Hz, 1 H), 6.50 (s, 1 H), 7.30 (s, 1 H), 7.32 (m, 5 H), 9.29 (s, 1 H);^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.3, 15.6, 23.4, 31.4, 32.1, 43.1, 58.9, 91.9, 117.4, 127.4, 128.5, 128.8, 130.8, 138.5, 150.5, 156.6, 195.2.

2-Benzyl-8,9-dimethyl-2-azabicyclo[3.3.1]non-6-ene-6,8-dicarbaldehydes 32 and 33. Adduct **31** (60 mg) was dissolved in a solution of CH_2Cl_2/MeOH (99:1, 8 mL). Silica gel (1.2 g) was added, and the resulting heterogeneous mixture was vigorously stirred during 4 h at room temperature. After filtration and removal of solvent under reduced pressure, an inseparable mixture of dialdehydes **32** and **33** was obtained as a pale yellow oil (20 mg, 33% yield) in a 2:1 ratio: MS (IC) m/z 298 (MH^+). Major isomer **32**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (m, 1 H), 1.25 (s, 3 H), 1.39 (d, J = 7.12 Hz, 3 H), 1.84 (m, 1 H), 2.2 (m, 1 H), 2.37 (dd, J = 14, 4.8 Hz, 1 H), 2.60 (dt, J = 14.6, 3.2 Hz, 1 H), 2.82 (s, 1 H), 3.85 (s, 1 H), 3.85 (d, J = 14.1 Hz, 1 H), 3.95 (d, J = 14.1 Hz, 1 H), 6.95 (s, 1 H), 7.27 (m, 5 H), 9.49 (s, 1 H), 9.65 (s, 1 H);^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 18.6, 21.9, 30.9, 30.9, 41.0, 56.0, 62.0, 65.3, 127.1, 128.0, 128.4, 140.0, 144.5, 151.9, 192.5, 199.9. Minor isomer **33** (characteristic signals): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (m, 1 H), 1.34 (1.34 (d, J = 6.8 Hz, 3H), 1.47 (s, 3 H), 1.67 (m, 1 H), 2.79 (d, J = 3 Hz, 1 H), 3.10 (s, 1 H), 3.92 (d, J = 2.1 Hz, 1 H), 4.02 (d, J = 2.1 Hz, 1 H), 6.68 (d, J = 1.3 Hz, 1 H), 9.44 (s, 1 H), 9.47 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.1, 19.0, 21.0, 30.4, 31.0, 41.4, 55.7, 62.0, 65.3, 127.0, 128.0, 128.4, 141.0, 146.0, 151.3, 192.2, 199.9.

Acetic Acid 6-Acetoxymethyl-2-benzyl-8,9 dimethyl-2-azabicyclo[3.3.1]non-6-en-8-ylmethyl Esters 34 and 35. The above mixture of dialdehydes **32** and **33** was reduced with an excess of $NaBH_4$ in MeOH at ambient temperature during 3 h. After usual extraction, the crude diol mixture was treated with an excess of Ac_2O in pyridine. After removal of pyridine and excess Ac_2O under reduced pressure, the crude mixture was purified by chromatography over alumina using EtOAc/heptane (3:1) as eluent. A fraction containing a mixture of **34** and **35** (1:2 ratio) and a fraction of practically pure **35** was thus obtained, allowing detailed NMR analysis. Minor isomer **34**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (m, 1 H), 1.07 (s, 3 H), 1.35 (d, J = 6.8 Hz, 3 H), 1.79 (m, 1 H), 2.07 (s, 3 H), 2.09 (s, 3 H), 2.13 (d, J = 3.4 Hz, 1 H), 2.15 (m, 1 H) 2.39 (dd, J = 12.4 Hz, J = 4.9 Hz, 1 H), 2.60 (s, 1 H), 2.7 (m, 1 H), 3.75 (d, J = 14.3 Hz, 1 H), 3.96 (d, J = 14.3 Hz, 1 H), 4.08 (d, J = 10.4 Hz, 1 H), 4.13 (d, J = 10.7 Hz, 1 H), 4.41 (d, J = 12.9 Hz, 1 H), 4,53 (d, J = 12.9 Hz, 1 H), 5.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.9, 20.5, 21.2, 25.1, 31.8, 35.5, 41.1, 44.2, 61.8, 65.7, 66.7, 70.0 126.8, 128.1, 128.26, 128.3, 131.6, 142.0, 172.0; HRMS (EI) calcd for $C_{23}H_{31}NO_4$ 385.2253, found 385.2253. Major isomer **35**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (m, 1 H), 1.05 (s, 3 H), 1.25 (d, J = 6.7 Hz, 3 H), 1.90 (m, 1 H), 2.05 (s, 3 H), 2.08 (s, 3 H), 2.45 (dd, J = 12.2, 5 Hz, 1 H), 2.60 (s, 1 H), 2.85 (m, 1 H), 3.75 (d, J = 11 Hz, 1 H), 3.85 (d, J = 11 Hz, 1 H), 3.88 (d, J = 5 Hz, 1 H), 3.92 (d, J = 5 Hz, 1 H), 4.4 (d, J = 12.9 Hz, 1 H), 4.55 (d, J = 12.9 Hz, 1 H), 5.50 (s, 1 H), 7.25 (m, 5 H), 7.30 (m, 1 H), 7.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6, 21.0, 21.5, 22.0, 32.4, 35.2, 41.9, 44.4, 61.7, 62.2, 66.6, 70.8, 126.7, 128.2, 131.9, 137.7, 170.9, 171.2.

Conclusion

The above results gave some experimental support in favor of our recently proposed[6] modification of the Baldwin and Whitehead hypothesis concerning the biogenesis of manzamine alkaloids.[4] This model cannot be ruled out, but, as it stands, it suffers from competitive reactions, in particular oxidoreductive reactions between dihydropyridine intermediates, a process that is difficult to control (or requires an enzymatic process).[21] Aminopentadienal derivatives are not prone to oxidation and thus do not present the disavantages inherent to dihydropyridine reactivity. The chemistry of aminopentadienal derivatives offers further opportunities for undertaking experiments toward "biomimetic synthesis"[22,23] of natural products depicted in Figure 1. Another interesting feature of this chemistry is the generation of very different and fairly complex polycyclic molecules such as **15a**, **19**, **23**, and **32** using in all cases the same dihydropyridinium species **1** as well as simple and very closely related dienes such as **9**, **10**, **12**, and **13**.

Supporting Information Available: Experimental procedures for preparation of dienes **9**, **10**, **12**, and **13** and procedures used for NMR determination of complex structures. Copies of ^{1}H and ^{13}C NMR spectra of dienes **9**, **10**, **12**, **13**, adducts **15b**, **17**, **19**, **20**, **23**, **24**, **31**, **32**−**33** (mixture at equilibrium), **34**, and **35** with attribution of signals and schemes showing observed NOEs for compounds **23** and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This model has recently received additional support by a short synthesis of keramaphidin B, albeit in low yield: Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2661−2663.

(22) A pertinent definition has been formulated by C. H. Heathcock: "A particularly powerful strategy is "biomimetic synthesis", in which we try to guess how Nature might assemble a particular molecule and then try to mimic this hypothetical route in the laboratory".

(23) For examples of particularly efficient biomimetic syntheses of natural alkaloids, see, inter alia: Robinson, R. *J. Chem. Soc.* **1917**, 762. Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665−681. François, D.; Lallemand, M.-C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H.-P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 104−105. For a review with more examples, see: Tietze, L.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−312.