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Total Synthesis of Dimeric Pyrrole−Imidazole Alkaloids: Sceptrin, Ageliferin, Nagelamide E, Oxysceptrin, Nakamuric Acid, and the Axinellamine Carbon Skeleton

Daniel P. O'Malley, Ke Li, Michael Maue, Alexandros L. Zografos, and Phil S. Baran*

Contribution from the Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received December 17, 2006; E-mail: pbaran@scripps.edu

Abstract: The dimeric pyrrole imidazole natural products are a growing class of alkaloids with exotic connectivity, unique topologies, high nitrogen content, and exciting bioactivities. This full account traces the evolution of a strategy that culminated in the first total syntheses of several members of this family, including sceptrin, ageliferin, nagelamide E, nakamuric acid (and its methyl ester), and oxysceptrin. Details on the fascinating conversion of sceptrin to ageliferin, which has been used to produce gram quantities of this sensitive natural product, are provided. In addition, the first enantioselective total synthesis of sceptrin and ageliferin are reported by programming the fragmentation of an oxaquadricyclane. A hallmark of our approach to this family of alkaloids is the minimal use of protecting groups despite the presence of 10 nitrogen atoms in the target compounds. Thus, the fundamental chemistry of the 2-aminoimidazole heterocycle was explored without masking its innate reactivity. Insights gained during these explorations led to total syntheses of oxysceptrin and nakamuric acid and a successful construction of the carbon skeleton of axinellamine.

Introduction

The mysteries of natural product biosynthesis can often be solved like jigsaw puzzles if enough "pieces", or members of a related family, can be found. Contemplating the relationship between members of a family of related natural products can often guide chemists to a reasonable retrosynthesis.[1] Even when these presumed "biosynthetic" relationships do not reflect the true metabolic pathway followed in the source organism, they can provide a useful heuristic for synthetic analysis, as was the case with Woodward's hypothesis for the biosynthesis of strychnine.[2] This synthetic program toward the dimeric pyrrole−imidazole alkaloids (Figure 1) has been inspired by the unique hypothesis that sceptrin (**1**) could serve as a precursor to other related alkaloids.

The isolation of sceptrin (**1**) in 1981 by Faulkner and Clardy[3a] was the first report of a pyrrole−imidazole alkaloid containing two hymenidin (**2**) subunits. The family of dimeric pyrrole−imidazole alkaloids has since grown to include the ageliferins (**3**),[4] axinellamines (**4**−**7**),[5] palau'amines,[6] nagelamides,[7] massadine (**8**),[8] and the noncyclized mauritiamine.[9] The recent isolation of the "tetrameric" stylissadine A (**9**) and tetrabromostyloguanidine (**10**) by Köck[10a,b] and Quinn[10c] holds the promise of even more exciting discoveries to come.

In addition to their ornate structures, these molecules also possess a diverse range of potentially useful biological properties. Sceptrin is a potent antibacterial as well as an antiviral, antihistiminic, and antimuscarinic agent.[3,6b] Ageliferin also

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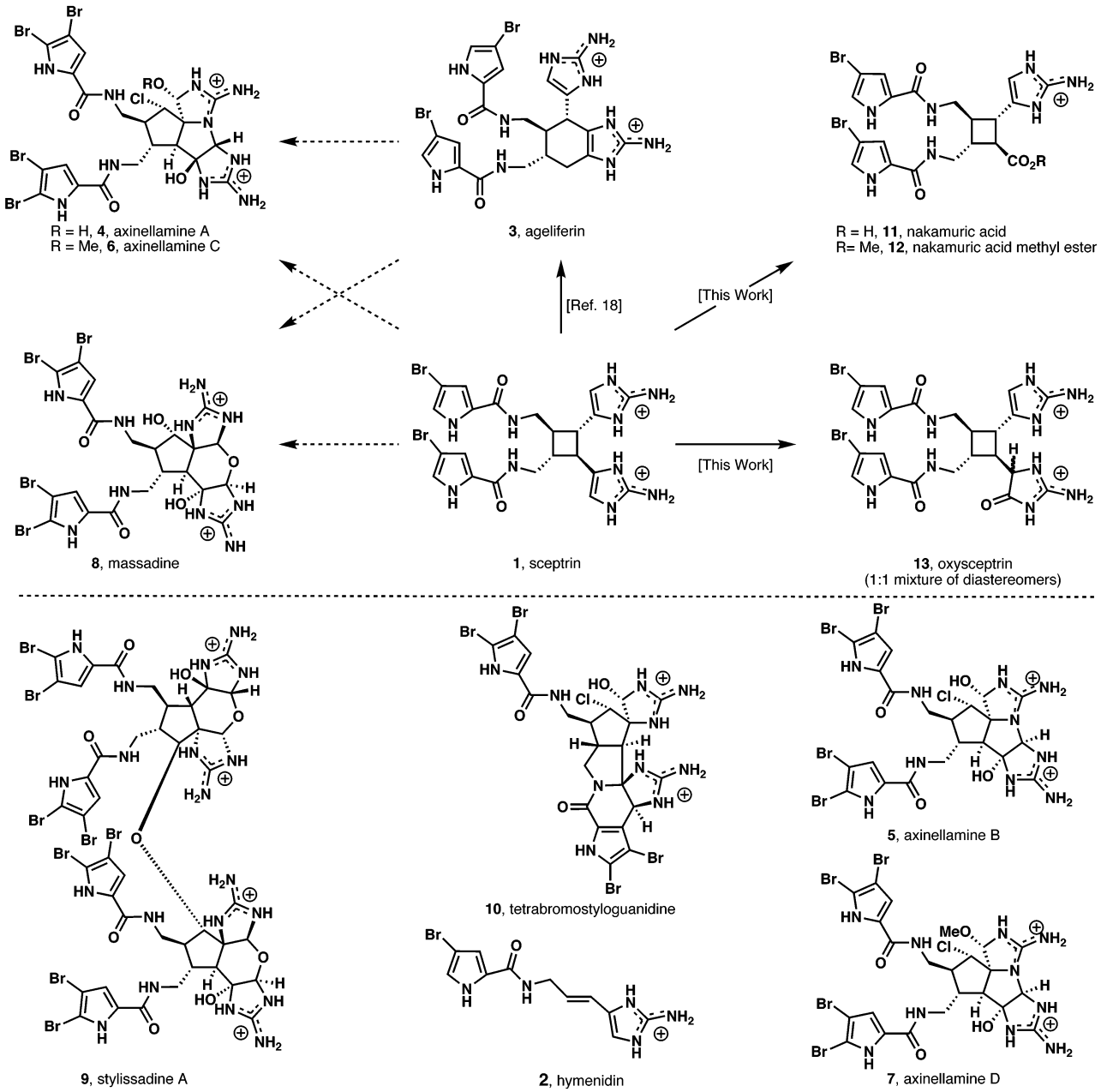

Figure 1. Pyrrole−imidazole alkaloids and proposed synthetic relationships.

possesses antibiotic and antiviral activity and is a useful agent for the study of actin−myosin contractile systems.[4] The nagelamides have also been identified as possessing antibacterial activity, and nagelamide G is also an inhibitor of protein phosphatase 2A.[7] Nakamuric acid (**11**) and its methyl ester (**12**) both exhibit antibiotic activity against *Bacillus subtilis*,[11] while oxysceptrin (**13**) exhibits both antibacterial and antiviral activity.[12] Some biological activity has been observed for the pyrrole−imidazole alkaloids possessing cyclopentane cores, but full investigation has been hampered by a lack of sufficient material.

Despite a flurry of synthetic activity in this area,[13] there have been relatively few successful syntheses of members of this family. Horne and co-workers completed mauritiamine,[14] and Ohta et al. prepared a non-natural methylated derivative of ageliferin.[15] Recently, we[16] and Birman[17] reported racemic syntheses of sceptrin. We have also reported the conversion of sceptrin to ageliferin[18] and nagelamide E[19] and an enantioselective synthesis of sceptrin and ageliferin.[20]

A hallmark of our final approach to this family of alkaloids is the minimal use of protecting group manipulations[21] despite the presence of 10 nitrogen atoms in the target compounds. Thus, the fundamental chemistry of the 2-aminoimidazole heterocycle was explored without masking its innate reactivity. In some cases, this required the development of unconventional strategies since most reactions needed to be performed in water.

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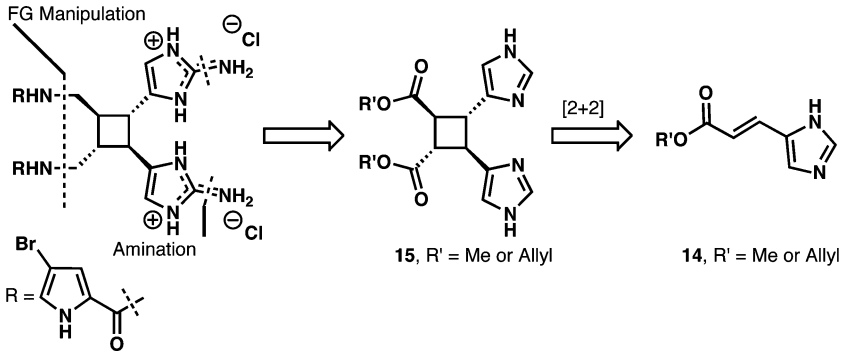
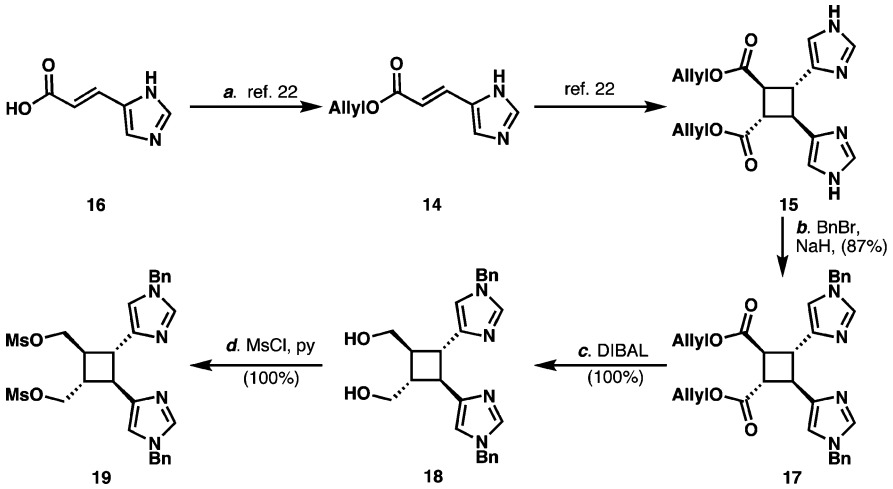


Figure 2. First generation retrosynthesis of sceptrin.

Scheme 1. Synthesis of Mesylate **19**[a]



[a] Reagents and conditions: (a) see ref 22; (b) NaH (4.0 equiv), DME; then BnBr (2.0 equiv), 20 °C, 32 h, 87%; (c) DIBAL (6.5 equiv), CH_2Cl_2, 0 → 20 °C, 24 h, quantitative; (d) MsCl (28 equiv), py, 0 °C, 3 h, quantitative. DME = 1,2-dimethoxyethane, DIBAL = diisobutylaluminum hydride, py = pyridine.

The insights gained during these explorations led to total syntheses of oxysceptrin, nakamuric acid (and its methyl ester), and a successful construction of the carbon skeleton of axinellamine. This full account details our studies in this area setting the stage for the construction of the most complex members of this intriguing alkaloid family.

First Generation Approach to Sceptrin

Having identified sceptrin (**1**) as the keystone to a synthetic program toward the other dimeric pyrrole−imidazole alkaloids, a synthesis capable of providing sceptrin in large quantities was required. The initial retrosynthesis, shown in Figure 2, was based upon the known dimerization of allyl urocanate (**14**, R′ = allyl) to form all-*trans* cyclobutane **15**.[22] From **15**, simple functional group manipulations could install the required pyrrole amide sidechains, leaving only amination of the imidazoles to complete the natural product.

As expected, esterification of commericially available uracanic acid (**16**, Scheme 1) followed by benzophenone-sensitized photodimerization[22] proceeded in good yield to give all-*trans* cyclobutane **15**. Interestingly, attempts at photodimerization of the methyl ester analogue of **14** under similar conditions gave a mixture of stereoisomers. Benzyl protection of the imidazoles and DIBAL reduction of the esters gave diol **18** in high yield.

Although formation of bis-mesylate **19** proceeded in excellent yield, **19** proved unexpectedly resistant to nucleophilic attack

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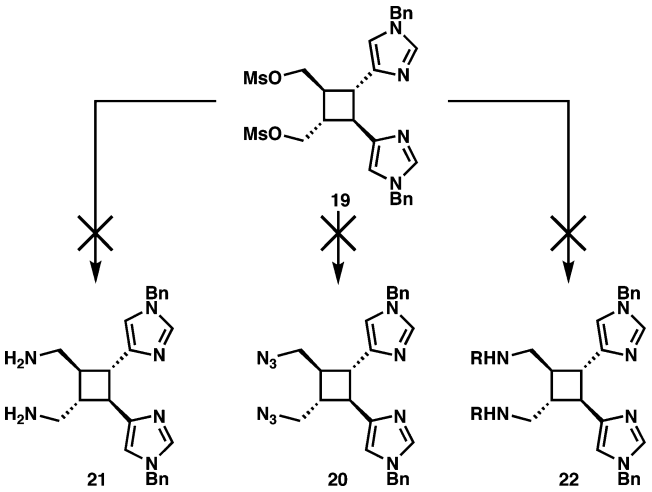
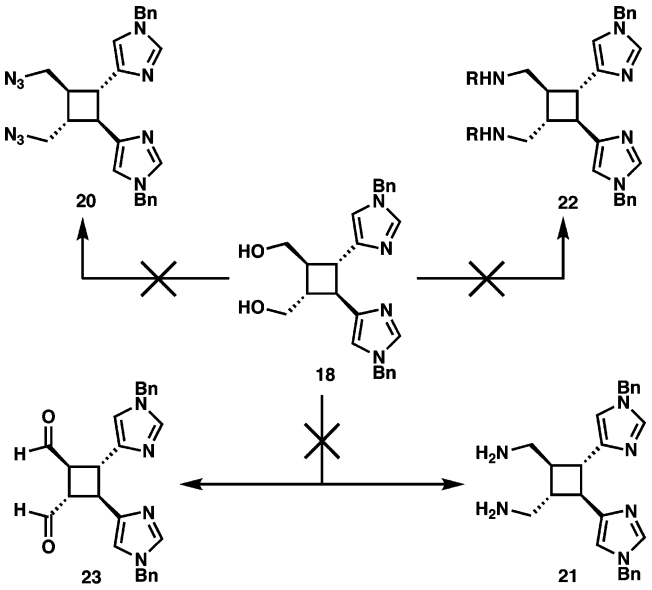
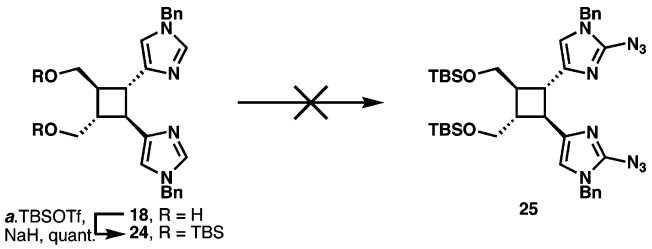
Scheme 2. Failed Attempts To Elaborate Mesylate **19**



Scheme 3. Failed Attempts To Elaborate Alcohol **18**



Scheme 4. Failure To Aminate Imidazole **24**[a]

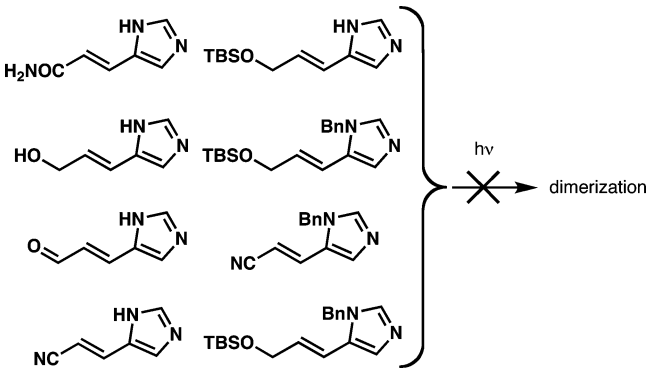


[a] Reagents and conditions: (a) NaH (12 equiv), TBSOTf (6.0 equiv), DMF, 20 °C, quantitative. DMF = *N*,*N*-dimethylformamide.

(Scheme 2). Reaction with sodium azide failed to form **20**, as did attempts to form amine **21** or amide **22** directly.

Alcohol **18** also proved remarkably intransigent (Scheme 3); attempts to form azide **20** or amide **22** via Mitsonobu displacement proved fruitless. Although triflation of **18** appeared to proceed via thin layer chromatography, attempts to form **20**, **22**, or amine **21** by direct displacement of this putative triflate were unsuccessful, as were attempts to isolate the triflate and confirm its structure. Finally, the oxidation of **18** to aldehyde

Scheme 5. Failed Dimerization Attempts



23, as a prelude to preparing amine **21** via reductive amination, also proved unexpectedly difficult.

The imidazole subunits were similarly resistant to functionalization; although **18** could readily be protected as its bis silyl ether **24** (Scheme 4), attempts to deprotonate the imidazole at C-2 and quench with an electrophilic azide source[23] failed to give **25**. After a screen for alternative dimerization partners carrying functionality that might prove more amenable to modification (Scheme 5) failed to provide any promising leads, it became apparent that a completely new strategy was required.

Second Generation Approach to Sceptrin

A new strategy was devised with the cyclobutane ketoazide **26** as a key intermediate (Figure 3). From this intermediate, three logical pathways could lead to sceptrin. In pathway A, the 2-aminoimidazole would be elaborated first from bromoketone **27**, followed by reduction of the azides of intermediate **28** and attachment of the bromopyrrole amides. In pathway B, the azides would be reduced and acylated first to give **29** and then the 2-aminoimidazole would be installed on intermediate **30**. Pathway C represented a hybrid of these routes in which a protected amine would be installed on the methyl group of the ketone as a placeholder for the 2-aminioimidazole, as in **31**, before reduction and acylation of the azide to yield **32**. Key intermediate **26** could be obtained by simple functional group manipulations from ketoester **34** via diol **33**.

Ketoester **34** was a known compound, obtained via fragmentation of oxaquadricyclane **35**,[24] formed from the union of 2,5-dimethylfuran and dimethyl acetylenedicarboxylate. In addition to promising rapid, diastereoselective access to the cyclobutane core of sceptrin, this route would facilitate the exploration of oxaquadricyclane chemistry. Although there had been some interest in these unusual, highly strained species from a physical organic perspective,[24] the initial research had lain dormant for over 30 years without application in synthetic chemistry. Enlisting this reaction in the synthesis of sceptrin would represent an interesting alternative to the traditional methods of cyclobutane synthesis: intermolecular [2 + 2] dimerization and linking two alkenes with a disposable tether prior to intramolecular [2 + 2] cyclization.

Although the synthesis of oxaquadricyclane **35** had already been reported,[24] extensive effort was spent developing stream-

(23) Spagnolo, P.; Zanirato, P. *J. Org. Chem.* **1978**, *43*, 3539−3541.
(24) (a) Laing, J.; McCulloch, A. W.; Smith, D. G.; McInnes, A. G. *Can. J. Chem.* **1971**, *49*, 574−582. (b) Nelson, S. F.; Calabrese, J. C. *J. Am. Chem. Soc.* **1973**, *95*, 8385−8388. (c) For a review of oxaquadricyclane chemistry, see: Tochterman, W.; Olsson, G. *Chem. Rev.* **1989**, *89*, 1203−1214.

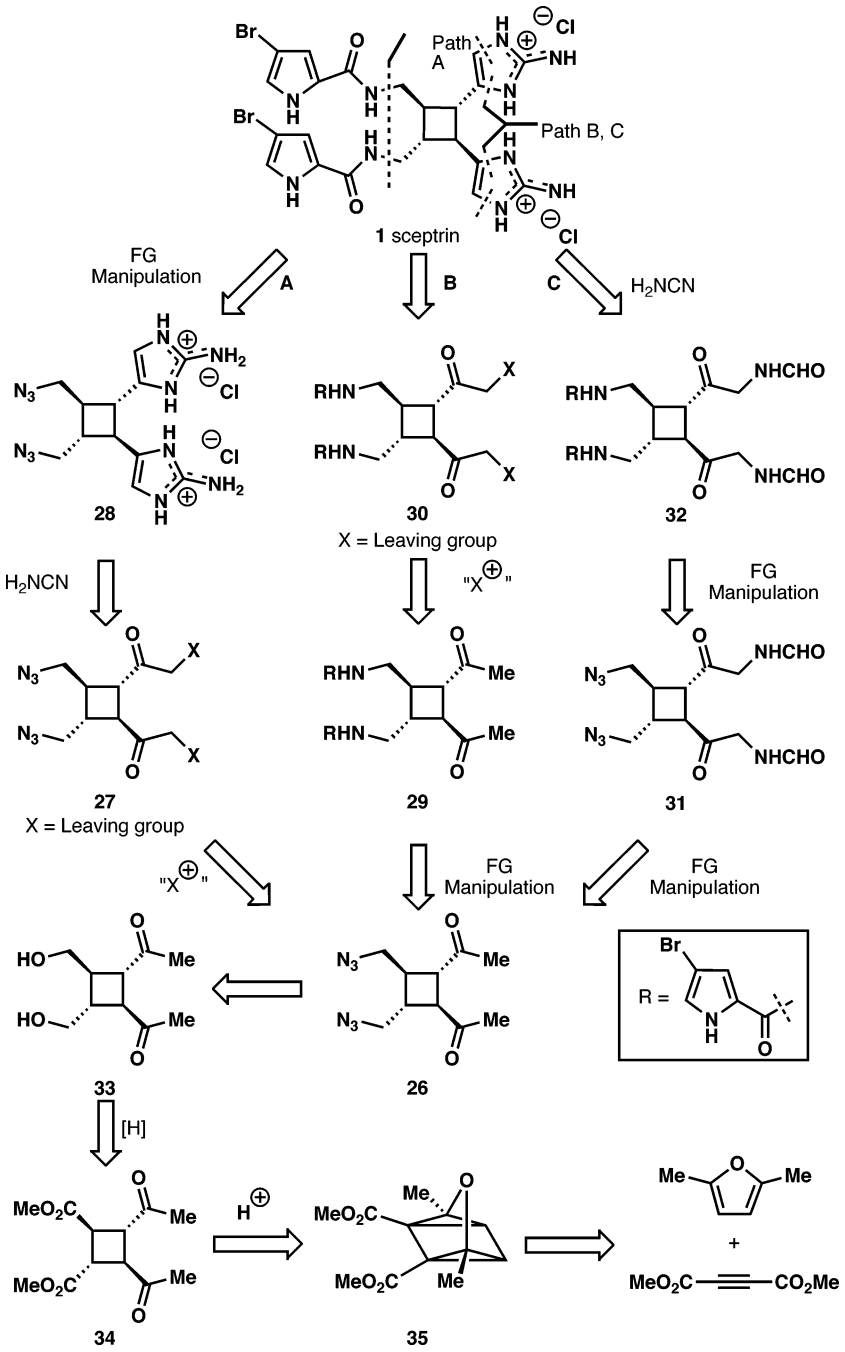
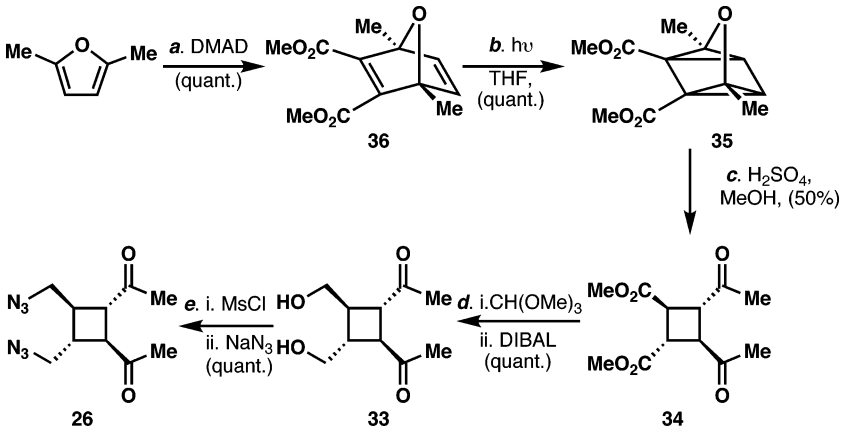


Figure 3. Second generation retrosynthesis of sceptrin.

lined conditions to facilitate large-scale synthesis (Scheme 6). By using a slight excess of 2,5-dimethylfuran in the Diels–Alder reaction, oxabicycle **36** could be obtained in quantitative yield. In the [2 + 2] cyclization to form oxaquadricyclane **35**, it was found that switching the solvent from diethyl ether to THF not only accelerated the reaction but also avoided potential complications due to the low boiling point of ether. The highly unstable **35** was taken on in crude form to the fragmentation step. The known procedure for the fragmentation of oxaquadricylane **35** gave only low yield and required repeated preparative thin layer chromatography to obtain cyclobutane **34** cleanly. As this was clearly not a viable option to support extensive synthetic efforts, a more expedient procedure was needed. It was found that the addition of diethyl ether after evaporation of methanol would cause the precipitation of cyclobutane **34** in ca. 50% yield, allowing expedient access to multigram quantities of **34**.

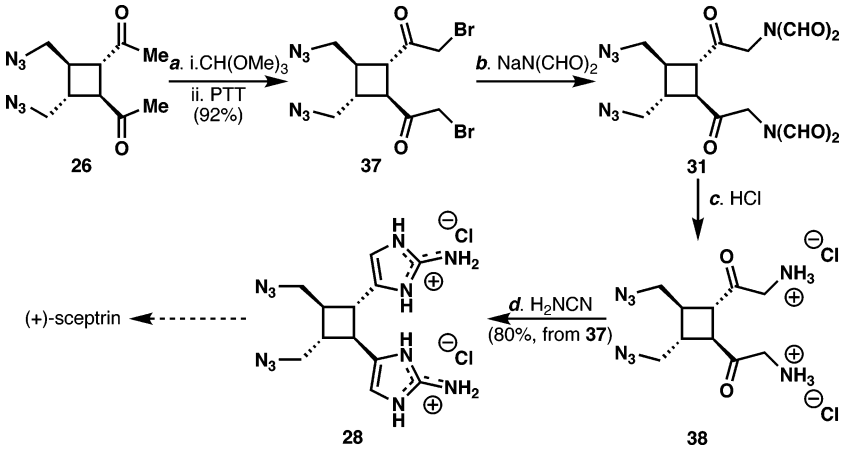
With the all-*trans* cyclobutane framework in place, **26** proved easily obtainable. Protection of the ketone moieties of **34** as the corresponding methyl ketals and DIBAL reduction furnished diol **33** in quantitative yield. Although the reduction initially appeared to generate many products by TLC analysis, it was discovered that this was caused by the newly formed alcohol cyclizing into the ketal during the quenching of excess DIBAL. A simple workup in 70% aqueous acetic acid provided diol **33** without recourse to chromatographic purification. Mesylation of the diol and displacement with sodium azide gave the key azide **26** in sufficient purity to be used without purification.

Scheme 6. Synthesis of Key Intermediate **26**[a]



[a] Reagents and conditions: (a) DMAD (1.0 equiv), 2,5-dimethylfuran (1.2 equiv), 1,4-dioxane, 100 °C, 12 h, quantitative; (b) 450 W Hanovia lamp, THF, 24 h, quantitative; (c) H_2SO_4, MeOH, 24 h, 50%; (d) (i) MeOH, $CH(OMe)_3$ (14 equiv), TsOH (0.15 equiv), 50 °C, 24 h; (ii) DIBAL (6.0 equiv), CH_2Cl_2, −78 °C, 1.5 h, then AcOH, H_2O, 10 min, quantitative; (e) (i) MsCl (4.4 equiv), py 0→20 °C, 1 h; (ii) NaN_3 (6.0 equiv), DMF, 50 °C, 24 h, quantitative. DMAD = dimethyl acetylenedicarboxylate, THF = tetrahydrofuran, DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide.

Scheme 7. Attempt To Synthesize Sceptrin via Intermediate **28**[a]



[a] Reagents and conditions: (a) (i) MeOH, $CH(OMe)_3$ (14 equiv), TsOH (0.15 equiv), 50 °C, 24 h; (ii) PTT (2.1 equiv), THF/MeOH/$CH(OMe)_3$ 2:1:0.1, 20 °C, 2 h; AcOH(aq), 50 °C, 12 h, 92%; (b) $NaN(CHO)_2$ (6 equiv), MeCN, 18 h, 20 °C; (c) MeOH, HCl (1% v/v), 16 h; (d) H_2NCN (80 equiv), H_2O, 140 °C μwave, 3 min, 80% from **37**. PTT = phenyltrimethylammonium tribromide, THF = tetrahydrofuran.

Given the unexpected difficulties in performing functional group modifications on the superficially similar cyclobutane **18**, it was decided that all three routes from **26** to sceptrin outlined in Figure 3 should be pursued simultaneously, in the event similar roadblocks were encountered. The first steps of pathway A (initial construction of the 2-aminoimidazole) proceeded quite smoothly. Ketalization of **26** under standard conditions (Scheme 7), followed by bromination of the crude ketal with phenyltrimethyl ammonium tribromide,[25] gave bromoketone **37** in 92% yield. Displacement with sodium diformamide[26] gave **31**, which was hydrolyzed with aqueous HCl to give **38** and reacted with cyanamide[27] to form **28** in 80% yield over three steps, thereby completing installation of the 2-aminoimidazole, along with 5−10% of an oxazole byproduct. Attempts to reduce the azide and install the necessary bromopyrrole amide resulted in complex mixtures from which only trace quantities of product could be obtained. Reduction of intermediate **31** (pathway C) appeared successful, but no acylated products could be obtained. Further attempts at resolving these issues were obviated by the success of an alternative pathway. It should be noted here, however, that the subsequently reported synthesis of sceptrin by Birman[17] proceeded from **37** via a Boc protected analogue of **28**.

As early attempts to handle 2-aminoimidazole containing compounds revealed their intractable nature, deferring the installation of this ring until the final stages of the synthesis seemed advantageous. Accordingly, initial attachment of the bromopyrrole was pursued as outlined in Scheme 8. Protection of the ketone as the ketal, followed by reduction with Lindlar catalyst[28] and acylation with **39**,[29] gave **40** in 70% yield. Compound **40** fortuitously precipitated from acetonitrile in pure form during the course of the acylation, eliminating the need for chromatography. Attempts to functionalize the methyl group of **40** or its ketone analogue ran afoul of selectivity issues. Competitive halogenation at the α-methine position and the pyrrole as well as polybromination of the methyl groups thwarted most attempts at halogenation. This was further complicated by the dimeric nature of **40**, which meant that the

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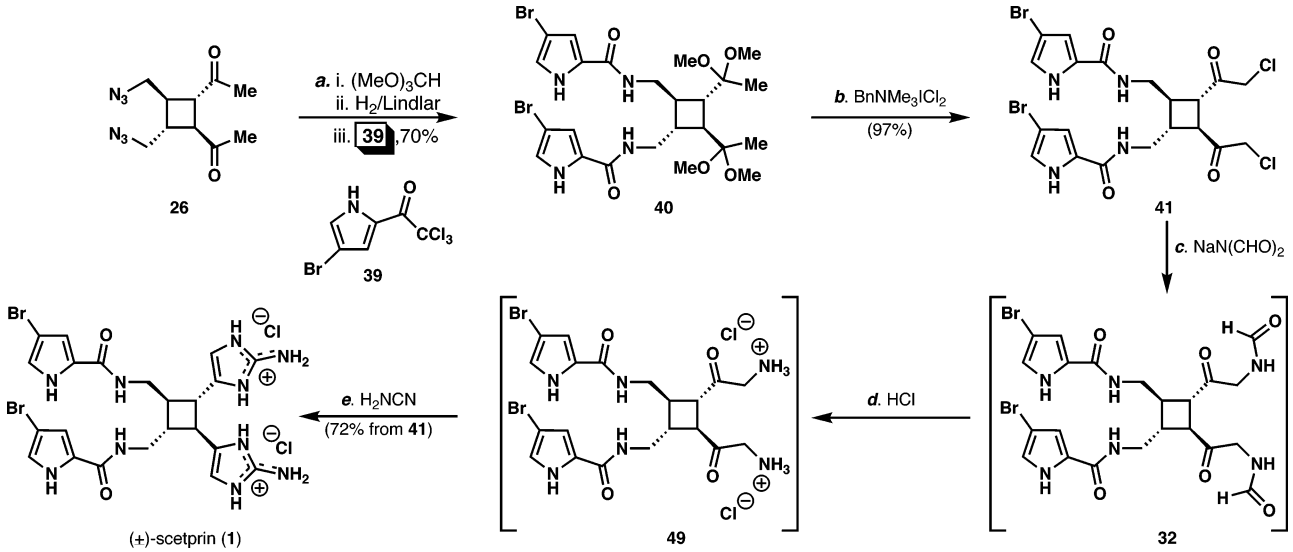
(26) Han, Y.; Hu, H. *Synthesis* **1990**, 122−124.
(27) Lancini, G. C.; Lazzari, E.; Arioli, V.; Bellani, P. *J. Med. Chem.* **1969**, *12*, 775−780.
(28) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590−591.
(29) Kitamura, C.; Yamashita, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1443−1447.

Scheme 8. Completion of Sceptrin[a]



[a] Reagents and conditions: (a) (i) MeOH, $CH(OMe)_3$ (14 equiv), TsOH (0.15 equiv), 50 °C, 24 h; (ii) H_2 (1 atm), Lindlar catalyst, MeOH, 12 h; (iii) **39** (2.2 equiv), MeCN, 4 h, 70% from **26**; (b) $BnNMe_3ICl_2$ (3.3 equiv), THF, 60 °C, 1.75 h, 97%; (c) $NaN(CHO)_2$ (5.5 equiv), 35 °C, 40 h; (d) HCl, MeOH, 20 °C, 16 h; (e) H_2NCN, H_2O, 95 °C, 4 h, 72% from **41**. THF = tetrahydrofuran.

desired functionalization would have to occur twice on the same molecule to obtain the desired product. Attempts to purify the complex mixtures resulting from standard α-functionalization protocols or to selectively react the desired product directly from the mixture met with little or no success. After much experimentation, a solution involving benzyl trimethylammonium dichloriodate was devised. Although this reagent was known to slowly chlorinate ketones,[30] it had not previously been employed on ketals. When carefully monitored and quenched, heating ketal **40** with this reagent in tetrahydrofuran (THF) at 60 °C gave desired chloroketone **41** in nearly quantitative yield. Interestingly, if methanol and trimethyl orthoformate were included in the solvent mixture, the dimethyl ketal of **41** was obtained directly. This reaction presumably takes place via chlorination of the methyl enol ether derived from the ketal. The previously applied protocol for aminoimidazole formation was now used: reaction with sodium diformamide gave **32**, which was hydrolyzed with methanolic HCl to give **49**. Finally, reaction with cyanamide completed the first total synthesis of sceptrin in 72% from chloroketone **41**. Thus a total synthesis of sceptrin which proceeds rapidly and in high yield from dimethyl acetylenedicarboxylate and 2,5-dimethylfuran has been developed.

Conversion of Sceptrin to Ageliferin

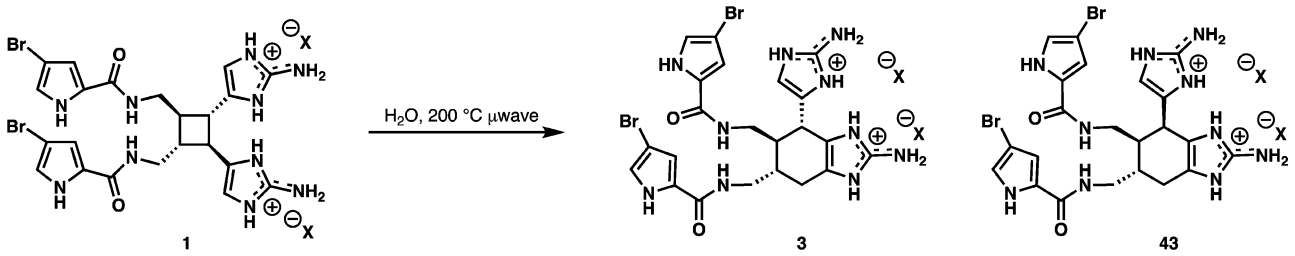
With a route to sceptrin in hand, ageliferin was selected as the next target. The reigning biosynthetic hypothesis at this point was that ageliferin arose from enzyme-catalyzed Diels−Alder dimerization of hymenidin (**2**).[4,31] However, cursory examination of oroidin indicated that the electronic nature of its alkene moiety would be poorly suited to function as a dienophile in a Diels−Alder reaction. This has been recently confirmed by Lindel et al.,[32] who found that bromooroidin (hymenidin) undergoes Diels−Alder reactions in moderate yield with active dienophiles such as maleimide but does not dimerize under thermal conditions. Close examination of isolation literature[33] indicated that crude sponge extracts typically contained far more sceptrin than any other dimeric oroidin derivative, which led to the hypothesis that sceptrin could function as a biosynthetic precursor to ageliferin.

Sceptrin and ageliferin are related by a formal [1,3] sigmatropic rearrangement followed by a double bond isomerization. Orbital symmetry considerations indicate that a concerted transformation of this nature would have to occur under photochemical conditions, so initial experiments centered on UV irradiation of sceptrin. Extended irradiation with a 5.5 W UV lamp (pyrex filter) had no observable effect, while use of a 450 W Hanovia lamp caused rapid decomposition. Attempts at effecting a stepwise transformation with conventional heating were likewise fruitless. Attempts to increase the reactivity of sceptrin by forming the free base simply accelerated decomposition. Ultimately, microwave irradiation proved to be the key to transforming sceptrin into ageliferin. Initial small-scale (≤5 mg) experiments using sceptrin bis-hydrochloride led to a mixture of sceptrin (**1**) and ageliferin (**3**)[18] (Scheme 9) upon heating to 200 °C for 2 min. HPLC separation of the mixture gave ageliferin in 40% yield, along with ca. 50% recovered sceptrin.

Attempts to scale up this reaction gave inconsistent results. It was discovered that a third compound was formed in the reaction, albeit in low yield (in an approximately 1:20 ratio to ageliferin). Qualitatively, the amount of this compound present appeared to increase with extended heating. Inspection of the ^1H NMR spectrum revealed that it was remarkably similar to ageliferin, although the shifts of several protons were slightly different. The compound was tentatively assigned as an epimer of ageliferin. Based on mechanistic considerations, the attachment of the pendent 2-aminoimidazole was believed to be the epimeric position, although initially the matter was not studied in detail. Subsequently, Kobayashi et al. reported the isolation

(30) Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Fujisaki, S.; Maeno, K.; Okamoto, T. *Synthesis* **1988**, 545−546.
(31) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243.
(32) Pöverlein, C.; Breckle, G.; Lindel, T. *Org. Lett.* **2006**, *8*, 819−821.
(33) Assmann, M.; Köck, M. *Z. Naturforsch. C* **2002**, *57*, 157−160; Assmann, M.; Lichte, E.; Köck, M. *Proceedings of the 6th International Sponge Symposium* **2004**, 187−193.

Scheme 9. Synthesis of Ageliferin and Nagelamide E[a]



[a] Reagents and conditions: (a) H_2O, 200 °C μwave; see text for details.

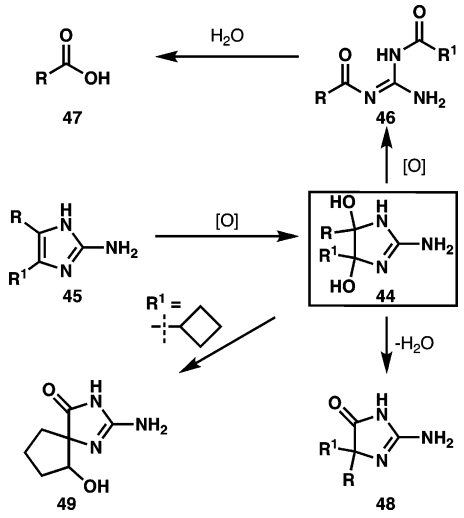


Figure 4. Dihydroxylated 2-aminoimidazoles as synthetic intermediates.

of the nagelamides,[7] a series of dimeric pyrrole−imidazole alkaloids. Surprisingly, nagelamide E (**43**, Scheme 9), isolated in a 1:24 ratio to ageliferin, possessed the same structure as the "epi-ageliferin" isolated from the conversion of sceptrin to ageliferin.[19] It was subsequently discovered that resubjection of purified ageliferin or nagelamide to the reaction conditions resulted in a mixture of the two, which stabilized at a ratio of approximately 2:1 in favor of ageliferin after 7 min of heating.

Further examination of the reaction conditions led to the discovery of an unexpected counterion dependence in the conversion of sceptrin to ageliferin. The acetate and formate salts of sceptrin proved far superior to the trifluoroacetate and initially used hydrochloride salts in terms of speed and conversion. The use of sceptrin bis-acetate provided far more consistent results upon scale-up as well, giving a 50% yield of ageliferin, along with 28% of nagelamide E and 12% recovered sceptrin.

The thermal rearrangement of vinyl cyclobutanes has been reported previously, although all prior instances of this reaction involved simple hydrocarbon substrates and thermolysis at temperatures in excess of 300 °C. It has been determined that these reactions proceed through diradical intermediates.[34] Given the highly functionalized nature of **1** and the significantly lower temperature at which its rearrangement occurs, there was a possibility that the rearrangement of sceptrin progresses through an alternative pathway. However, computational studies[19] indicate that the rearrangement of **1** likely proceeds via radical scission of the cyclobutane bond, followed by 6-endo-*trig* recombination and olefin isomerization to rearomatize the 2-aminoimidazole. The formation of nagelamide E can be accounted for either by inversion of the radical center prior to recombination or by epimerization of ageliferin under the reaction conditions.

The completion of ageliferin and nagelamide E represents the first synthesis of these molecules as well as the first use of the vinylcyclobutane rearrangement in natural products synthesis. This procedure has proven to be both robust and scalable; *it has allowed the synthesis of ageliferin and dibromoageliferin in gram quantities.*

Synthesis of Oxysceptrin, Nakamuric Acid, and Nakamuric Acid Methyl Ester

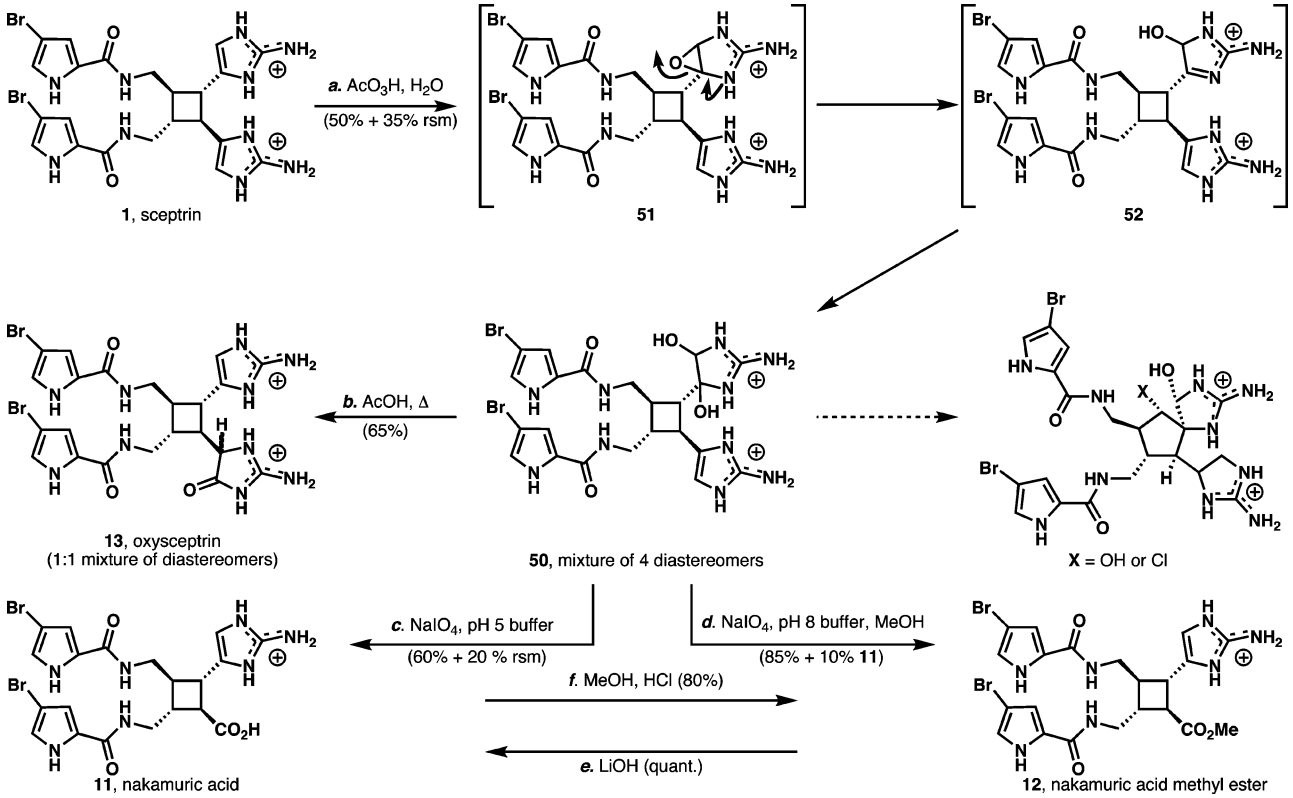
Having synthesized ageliferin and nagelamide E, which possess the same level of oxidation as sceptrin, questions remained as to the viability of sceptrin as a synthetic precursor for more highly oxidized members of the pyrrole−imidazole family, such as oxysceptrin (**13**), nakamuric acid (**11**), massadine (**8**), and the axinellamines (**4**−**7**). Although the structural homology of sceptrin to oxysceptrin and nakamuric acid is readily apparent, its relationship to massadine and the axinellamines is less obvious. Furthermore, although the relationship of oxysceptrin and nakamuric acid to sceptrin appeared to be quite simple, there was no guarantee that an attempt to synthesize them from sceptrin would prove nearly as simple or even possible.

Examining this family of natural products, it is apparent that a dihydroxylated 2-aminoimidazole of type **44** (Figure 4), formed by oxidation of the parent aminoimidazole **45**, could serve as a precursor to all the various guanidine rings identified thus far. Oxidative cleavage of the diol would lead to bis-acylated guanidine **46**, which could in turn be hydrolyzed to the carboxylic acid **47**, analogous to that found in nakamuric acid (**11**). Alternatively, expulsion of H_2O from **44** would set the stage for a hydroxyl group assisted [1,2] shift to form **48**. If R = H, this would form the aminoimidazolinone present in oxysceptrin (**13**). Oxysceptrin could also be formed by elimination of H_2O followed by tautomerization of the resulting hydroxyaminoimidazole. Alternatively, if R = R^1 = cyclohexyl, the same [1,2] shift would initiate a ring contraction to a spiro [5.5] system **48** (R = R^1 = $-C_4H_8-$), reminiscent of the axinellamines (**4**−**7**) and massadine (**8**).[13c,j,n] Similarly, if R was a strained ring such as a cyclobutane, expulsion of H_2O could initiate a Demjanov-like ring expansion.[35] Stereoselective

(34) Leber, P. A.; Baldwin, J. E. *Acc. Chem. Res.* **2002**, *35*, 279−287; see also references cited in ref 19.

(35) (a) Corey, E. J.; Liu, K. *Tetrahedron Lett.* **1997**, *38*, 7491−7494. (b) Fitjer, L.; Majewski, M.; Kanshik, A.; Egert, E.; Sheldrick, G. M. *Tetrahedron Lett.* **1986**, *27*, 3603−3606. (c) Fadel, A.; Salaün, J. *Tetrahedron* **1985**, *41*, 413−420. (d) Jahangir; Fisher, L. E.; Clark, R. D.; Muchowski, J. M. *J. Org. Chem.* **1989**, *54*, 2992−2996. (e) Feline, T. C.; Mellows, G. *J. Chem. Soc., Chem. Commun.* **1974**, 63−64. (f) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2795−2796.

Scheme 10. Synthesis of Oxysceptrin, Nakamuric Acid, and Nakamuric Acid Methyl Ester[a]



[a] Reagents and conditions: (a) see text; (b) aq. AcOH, 140 °C, 30 min, 65%; (c) 1.2 equiv of $NaIO_4$, pH 5 buffer (AcOH/NaOAc), 60%; (d) 1.2 equiv of $NaIO_4$, pH 8 buffer (0.1 M phosphate buffer), 85%; (e) LiOH, THF/H_2O = 1:1, quantitative; (f) MeOH/HCl, 80 °C, 1 h, 80%.

quenching of the resulting cyclopentyl cation would form **49**, the massadine ring system.

Although this plan would allow rapid access to this family of highly complex alkaloids, significant questions remained about its feasibility. Natural products containing guanidines or 2-aminoimidazoles have historically been approached either by deferring their installation until the final stages of the synthesis or by completely masking their reactivity through protection.[13] Since Nature apparently manipulates these species with ease, our goal was to learn about their innate reactivity and avoid any kind of protection.[21] This decision added a new level of practical difficulty since all reactions would have to be performed in protic solvents and chromatography would be quite challenging. Although 2-aminoimidazoles had previously been oxidized to bis-alkoxy imidazoles and thence converted to aminoimidazolinones,[36] it was unclear if the precedent set on these relatively simple molecules could be translated to sceptrin. The presence of the pyrrole subunits raised the issue of chemoselectivity, and the dimeric nature of sceptrin required the site-selective oxidation of only one of the two 2-aminoimidazoles.

Gratifyingly, exposure of sceptrin (**1**) to a variety of oxidizing agents provided the corresponding dihydroxy compound **50** as an inconsequential mixture of four diastereomers (Scheme 10). Operationally, it was found that aqueous peracetic acid was the optimum oxidant, giving 50% yield of **50**, along with 35% recovered starting material. Although this reaction could be induced to proceed further, attempts to do so resulted in increased amounts of tetrahydroxylated byproducts resulting from oxidation of the second aminoimidazole. This reaction likely occurs by epoxidation of the aminoimidazole to form intermediate **51**, followed by ring opening of the epoxide to iminium **52**. Attack of H_2O then affords diol **50**.

With key intermediate **50** in hand, the next step was to effect dehydration to oxysceptrin (**13**). The diol mixture **50** proved to be labile when evaporated to dryness. In fact, the ^1H NMR of **50** (after purification by prep HPLC) indicated the presence of a significant quantity (ca. 20−30%) of oxysceptrin (**13**). In order to drive the reaction to completion, microwave irradiation of **50** at 140 °C in aqueous acetic acid induced the required [1,2]-hydride shift (or simple dehydration/tautomerization) to complete the synthesis of oxysceptrin in 65% yield. We were able to confirm the isolation chemists' observation[12] that oxysceptrin exists as a 1:1 mixture of epimers at the imidazolinone stereocenter.

Initial attempts to elicit oxidative cleavage of diol **50** to nakamuric acid (**11**) were stymied by the instability of the substrate under oxidizing conditions. After considerable exploration, periodate-based oxidation protocols on diol **50** were developed to controllably direct cleavage to **11** or **12**. Thus, by running the reaction in pH 5 buffer (AcOH/NaOAc), nakamuric acid (**11**) could be obtained in 60% yield, along with 20% recovered **50**. Nakamuric acid methyl ester (**12**) could be obtained by instead using pH 8 buffer (0.1 M phosphate) and methanol in order to dissolve **50** (85% yield, along with 10% **11**). Under oxidizing conditions, a pH window of 4.5−8.0 results in diol cleavage while reactions outside of this range lead to extensive decomposition. Based on LC/MS data, these reactions

(36) Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1998**, *63*, 1248−1253.

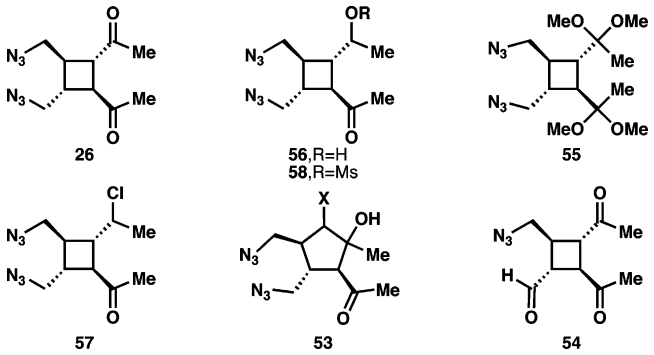


Figure 5. Attempts at ring expansion of model system **26**.

proceed via a bis-acylated guanidine species (see **46**, Figure 4). Nakamuric acid (**11**) and its methyl ester (**12**) are readily interconvertible; hydrolysis of **12** with LiOH provided **11** in quantitative yield, while careful esterification of **11** with HCl in methanol furnished **12** in 80% yield (diazomethane is not chemoselective for the carboxylic acid).

Although the ^{1}H NMR spectroscopic data of both nakamuric acid (**11**) and its methyl ester (**12**) matched nicely with that published by Proksch and co-workers,[11] there were some minor discrepancies with the assignments of the ^{13}C NMR data. Using HMQC (^{1}H−^{13}C correlation, see Supporting Information) it was determined that three carbon atoms were incorrectly assigned including one carbon atom which was actually underneath the solvent peak (DMSO-d_6).

Synthesis of the Axinellamine Carbon Skeleton

Attempts to induce ring expansion of sceptrin (**1**) to compounds of type **44** were less successful. The facility of dehydration to generate oxysceptrin (**13**) prevented the formation of the requisite cyclopentyl carbocation. Seeking to determine if the failure of **50** to undergo ring expansion was due solely to the facility of the hydride shift to form oxysceptrin, or if the cyclobutane was intrinsically resistant to ring expansion, a series of model studies on ketoazide **26** was undertaken (Figure 5). Most attempts at Lewis or Brønsted acid initiated ring expansion to cyclopentane **53** yielded only recovered starting material or nonspecific decomposition. One notable exception was the reaction of **26** with $SbCl_5$, which formed aldehyde **54** in 20% yield. Although the conversion of azides to aldehydes under strong Brønsted acid conditions is known,[37] to the best of our knowledge, this is the first report of such a transformation initiated by a Lewis acid. Attempts to use ketal **55** to induce a ring expansion were likewise unsuccessful; most conditions simply resulted in deketalization to **26**. Reduction of **26** with $NaBH_4$ gave alcohol **56** as a mixture of diastereomers. However, reactions of **56** proved no more fruitful; exposure to HCl resulted in conversion to chloride **57** rather than ring expansion. The derived mesylate **58** changed from a 3:1 mixture of diasteromers to a 1:1 mixture upon heating in toluene. As this epimerization must have occurred via cation formation and recombination, it was clear that the cyclobutane was reluctant to undergo ring expansion, even in the presence of a cation on an adjacent carbon. In light of these results, it was clear that ring expansion of sceptrin would be unlikely without significant structural modifications, so a new strategy was devised.

It was reasoned that the same driving force that had stymied efforts to induce ring expansion of sceptrin by promoting hydride shift would be beneficial in the ring *contraction* of systems of type **59** (Scheme 11) to type **60**. This approach is reminiscent of the proposal of Scheuer et al. for the biosynthesis of palau'amine;[6b] Romo[13c,j,n] and Lovely[13e,g,l,o] have also reported approaches to palau'amine and axinellamine based on contraction of a cyclohexene. Thus, dihydroxylation of ageliferin (**3**) was attempted. Although our ability to dihydroxylate sceptrin was encouraging, the unsymmetrical nature of ageliferin complicated matters, as the dialkylated 2-aminoimidazole would have to be oxidized in preference to the monoalkylated ring.

A screening of various oxidants found that magnesium monoperoxyphthalate (MMPP) in H_2O oxidized ageliferin most cleanly, providing the somewhat unstable diol **59** as a single, unassigned diastereomer in 32% isolated yield after preparative HPLC. Inducing rearrangement of diol **59** proved to be a greater challenge. Many conditions resulted in fragmentation to presumed diketone **61** as the major product. Basic reaction media were found to suppress this fragmentation; microwave irradiation of diol **59** in 5% aqueous $NaHCO_3$ provided spirocycle **60** in 31% yield. Operationally, it was found that telescoping these two operations into one step greatly improved yields; addition of saturated aqueous $NaHCO_3$ to crude diol **59** and subjecting the resulting suspension to microwave irradiation directly provided spirocycle **60** in 36% overall yield from ageliferin. The connectivity and stereochemistry of compound **60** were confirmed by HMQC and ROESY analysis in rigorously dried DMSO-d_6. Unfortunately, the stereochemistry of **60** is epimeric to massadine and the axinellamines at the spriro ring juncture.

Asymmetric Synthesis of Sceptrin and Ageliferin

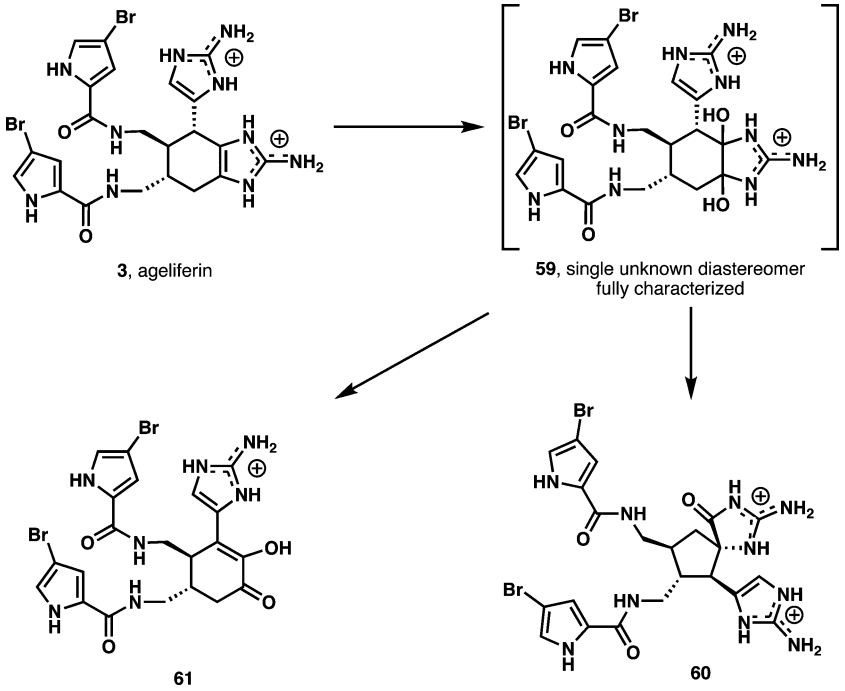
Although the previously discussed syntheses of sceptrin and ageliferin allowed rapid and efficient access to these alkaloids in racemic form, prospects for the development of an asymmetric synthesis were uncertain. There is a general scarcity of methods for the synthesis of enantiopure cyclobutanes,[38] and most of the existing procedures depend on the attachment of a stoichiometric chiral auxiliary prior to [2 + 2] dimerization. This is undesirable from the perspectives of both atom and step economy as well as potentially costly if the auxiliary is expensive and/or not amenable to recycling. The use of an oxaquadracyclane fragmentation to generate the all-*trans* cyclobutane core of sceptrin posed an exciting challenge; despite a number of elegant studies,[23] the mechanism of this physical organic oddity remained ill-defined. Without a definitive understanding of this reaction, it was unclear how, or even if, stereochemical information in an oxaquadracyclane could be transferred to the product cyclobutane. The task was further complicated by the fact that the absolute configuration of ageliferin was unknown.

The cascade rearrangement of oxaquadricyclanes to cyclobutanes was initially discovered by McInnes and co-workers,[23a] who proposed a mechanism involving the initial fragmentation of the oxo bridge with water. The cascade was later studied by Nelsen,[23b] who posited an alternative mechanism initiated by fragmentation of a cyclopropyl ring to form an oxocarbonium ion. After the work of Nelsen, little notice was taken of this reaction until it was adapted for use in the synthesis of sceptrin.

(37) Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5009−5011.

(38) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449−1483.

Scheme 11. Synthesis of the Axinellamine Carbon Skeleton[a]



[a] Reagents and conditions: see text.

In addition to allowing enantioselective access to sceptrin and ageliferin, developing a variant of this reaction for the synthesis of enantiomerically pure cyclobutanes would shed light on the mechanism of this intriguing transformation.

In an attempt to ascertain what modifications to oxaquadricyclane **35** ought to be made to effect an enantioselective fragmentation, the potential mechanisms of the reaction were analyzed. McInnes et al. proposed a mechanism which was initiated by attack of water to rupture the oxo bridge, forming intermediate **62** (path A in Figure 6).[23a] Fragmentation of the cyclopropane rings was proposed to occur with retention of stereochemistry at one ester bearing cyclobutane carbon and inversion at the other. It was suggested that this was the result of intramolecular protonation at one carbon and intermolecular protonation at the other. The resulting *cis*-acetyl compound **63** would then isomerize under the reaction conditions to give the product all-*trans* cyclobutane **34**. An alternative mechanism (path B in Figure 6), similar to the one suggested by Nelsen,[23b] is initiated by the opening of a cyclopropane ring to form an ester enol intermediate such as **64**. Capture of this intermediate by water and tautomerization of the ester enol to a position *trans* to the other ester forms **65**, which then fragments to the *cis*-acetyl cyclobutane **63** and epimerizes to **34**.

Careful analysis of the McInnes mechanism reveals that the stereochemistry of the product cyclobutane is governed by the carbon which is protonated in an intramolecular sense. In intermediate **62**, only the alcohol resulting from the oxo bridge is properly situated to effect intramolecular protonation, so the final stereochemistry of the product is determined by which face of the oxaquadracyclane is attacked by water to initiate the fragmentation. Although the initiation step in this proposal seemed somewhat improbable, it was of some concern, as inducing facial selectivity by modification of the carbonyl units would be a difficult proposition indeed. In the alternative mechanism, however, the configuration of the final product is

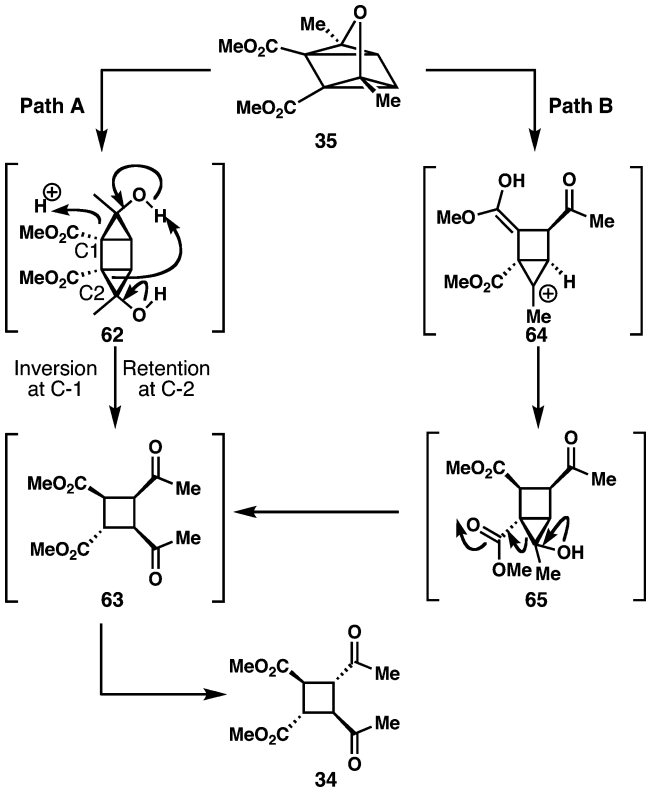
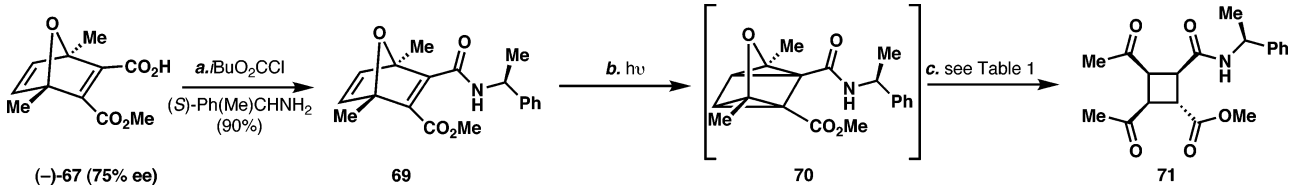


Figure 6. Mechanistic proposals for the transformation of oxaquadricyclane **35** to cyclobutane **34**.

controlled by the order of carbonyl enolization in the fragmentation (see Scheme 13). Synthesizing a derivative of **35** possessing two types of carbonyls with distinct enolization energies would therefore be the key to obtaining a diastereoselective fragmentation. Although there is presently a paucity of experimental data concerning the relative stabilities of ester and amide enols, theoretical predictions indicate that enols of amides are more

Scheme 12. Screening of Conditions for Diastereoselective Oxaquadricyclane Fragmentation[a]



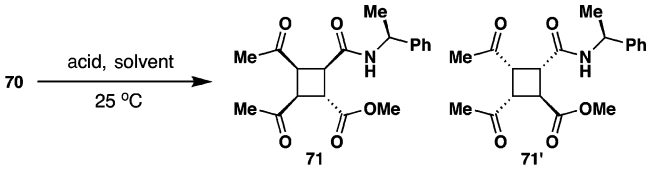
[a] Reagents and conditions: (a) isobutyl chloroformate, Et_3N, CH_2Cl_2, 0 °C then (*S*)-α-methylbenzylamine, 90%; (b) *hν*, THF; (c) Table 1.

stable than those of carboxylic acids or esters. Heinrich and co-workers calculated that the energy difference between the keto and enol forms of acetic acid was 35.6 kcal/mol, while that of acetamide was 33.3 kcal/mol.[39a] More recently, Rosenberg calculated that the ΔH of enolization was 16.0 kcal/mol for methyl acetate, while that of acetamide was calculated to be 14.1 kcal/mol.[39b] As the highly unstable oxaquadricyclane **35** was clearly not amenable to modification, Diels–Alder product **36** was identified as the optimal stage for installing the necessary functionality. An amide of type **66** (Scheme 13) was therefore targeted.

Inspired by encouraging literature precedent for the enzymatic desymmetrization of similar meso intermediates,[40] pig liver esterase (0.1 M pH 8 phosphate buffer, acetone, 20 °C) was used to furnish the monoester **67** (Scheme 13) in quantitative yield and 75% ee as determined by ^{1}H NMR of the (*S*)-α-methylbenzylamine-derived amide. The absolute configuration was determined by X-ray analysis of the salt **68** formed by the same amine and carboxylic acid **67**. Having succeeded in enantioselectively differentiating the carbonyl units of **36**, the next major task was finding conditions for the enantiospecific fragmentation of the derived oxaquadricyclane. Would the chirality of the oxiquadricyclane translate into the fragmented product? In order to answer this question, the chiral amide **69** was prepared as depicted in Scheme 12. After photolysis (to form **70**) and rearrangement to cyclobutanes **71** and **71′**, the resulting dr can be rapidly ascertained by ^{1}H NMR. As shown in Table 1, the use of H_2SO_4 emerged as the optimum acid in terms of overall yield and diastereoselectivity.

Having determined conditions for diastereospecific fragmentation of oxaquadricyclanes, the enantioselective synthesis proceeded as outlined in Scheme 13. Acid **67** was converted to benzyl amide **66** with DMT-MM in 92% yield. UV irradiation gave oxaquadricyclane **72**, which was immediately subjected to fragmentation. Cyclobutane **73** was obtained in 50% overall yield and 75% ee, which represents complete retention of chiral information from **72**. This fragmentation presumably proceeds via initial enolization of the amide to form **74**, followed by quenching of the resulting carbocation to form **75**. Fragmentation of the remaining cyclopropane then gives **73**. Before continuing, amide **73** was recrystalized to upgrade the ee to >95%. Conversion to key ketoester **34** now required only epimerization of one ketone side chain and methanolysis of the benzyl amide. These transformations could be accomplished in one pot by heating **73** with toluenesulfonic acid and methanol to 105 °C

Table 1. Optimization of Fragmentation Conditions on Substrate **70**



entry	acid	solvent	dr (**71**:**71′**)	yield[a] (%)
1	H_2SO_4	THF/MeOH 1:1	7:1	57
2	H_2SO_4	THF/H_2O 1:1	4:1	66
3	H_2SO_4	H_2O/MeOH 1:1	5:1	57
4	H_2SO_4	MeOH	4.7:1	58
5	HCl	THF/MeOH 1:1	4.7:1	35
6[b]	$Yb(OTf)_3$	THF/MeOH 1:1	5.2:1	62
7	$Sc(OTf)_3$	THF/MeOH 1:1	n.d.	0
8[c]	none	THF/MeOH 1:1	n.d.	0

[a] Isolated yield. [b] Reaction run at 60 °C. [c] Reaction run at 100 °C.

in toluene.[41] The methanolysis of the amide under these unusually mild conditions can be explained by invoking intramolecular assistance from the methyl ketone in epimerized cyclobutane **76**, as illustrated in intermediate **77**. The configuration of ketoester (−)-**34** was assigned by conversion to sceptrin by the method described previously. Comparison to a natural sample of sceptrin bishydrochloride revealed that *ent*-sceptrin had been synthesized ($[\alpha]_D = +16.0$ (MeOH, $c = 0.25$, HCl salt), lit.[3] $[\alpha]_D = -7.4$ (MeOH, $c = 1.2$, HCl salt)). As the optical rotation of sceptrin was found to vary with the nature of its counterion (vide infra), this assignment was confirmed by circular dichroism analysis (see Supporting Information). The *ent*-sceptrin thus obtained was then subjected to the previously developed conditions for conversion to ageliferin (vide supra), yielding (+)-*ent*-ageliferin ($[\alpha]_D = +8.0$ (MeOH, $c = 0.05$, TFA salt), natural product $[\alpha]_D = -10.0$ (MeOH, $c = 0.1$, TFA salt)). This allowed the determination of the absolute configuration of ageliferin as depicted in Scheme 13 and the correlation of the absolute configurations of sceptrin and ageliferin.

The transformation of oxaquadricyclane **72** into cyclobutane **73** supports the mechanistic pathway shown in Scheme 13 and pathway B of Figure 6; initial enolization of the amide in accordance with theoretical predictions accounts for the stereochemisty observed in product **73**. As the stereospecifity of this reaction is difficult to rationalize using the mechanism illustrated in pathway A, these results strongly support the initiation of the reaction by the enolization of a carbonyl moiety.

With this conclusion in mind, the logical way to obtain *nat*-sceptrin was to switch the location of the amide and ester groups in oxaquadricyclane **72**. This was accomplished by esterification

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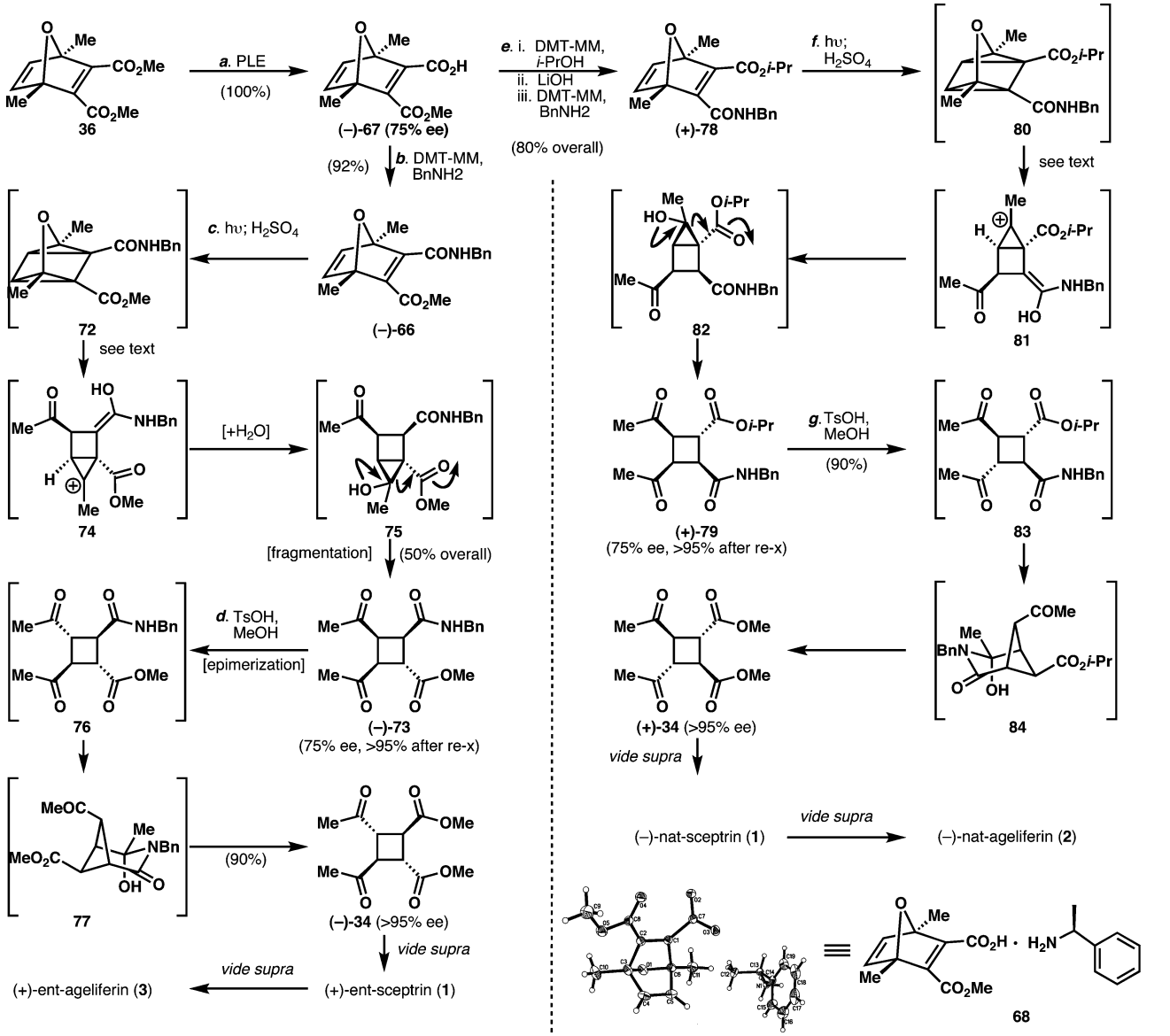
Scheme 13. Enantioselective Synthesis of (+)- and (−)- Sceptrin and Ageliferin[a]



[a] Reagents and conditions: (a) PLE (50 unit/mmol), acetone/phosphate buffer (pH 8), 23 °C, 1 week, 100%, 75% ee; (b) $BnNH_2$ (1.05 equiv), DMT-MM (1.05 equiv), THF, 3 h, 92%; (c) *hυ*, THF, 72 h, then H_2SO_4, THF/MeOH (1:1), 3 h, 45 − 50%; (d) recrystallization from hexanes/EtOAc (1:1), then TsOH (4.0 equiv), MeOH (20 equiv), toluene, 105 °C, sealed tube, 12 h, 50%; (e) $BnNH_2$ (1.05 equiv), DMT-MM (1.05 equiv), THF, 3 h, 92%; (f) h*υ*, THF, 72 h, then H_2SO_4, THF/MeOH (1:1), 3 h, 45 − 50%; (g) recrystallization from hexanes/EtOAc (1:1), then TsOH (4.0 equiv), MeOH (20 equiv), toluene, 105 °C, sealed tube, 12 h, 50%. PLE = pig liver esterase, THF = tetrahydrofuran; TsOH = toluenesulfonic acid, DMT-MM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride.

of enzyme product **67** with 2-propanol, selective hydrolysis of the methyl ester, and benzyl amide formation to give **78** in 80% yield. Using the previously applied cyclization and fragmentation conditions gave cyclobutane **79** in 50% yield and 75% ee, presumably through the intermediacy of **80**−**82**. Crystallization of **79** then increased the ee to >95%. Heating with toluenesulfonic acid and methanol under the conditions used for **73** proceeded analogously through **83** and **84** with simultaneous transesterification of the isopropyl ester to give (+)-**34**. As expected, (+)-**34** was elaborated to (−)-*nat*-sceptrin ($[\alpha]_D$ = −11.7 (MeOH, c = 0.12, HCl salt)) and (−)-*nat*-ageliferin ($[\alpha]_D$ = −10.0 (MeOH, c = 0.03, TFA salt)).

The determination of the absolute configuration of these compounds was not without complication, however. When the optical rotation of *ent*-sceptrin bistrifluoroacetate synthesized from (−)-**34** (obtained directly from HPLC purification) was measured, it was found to an optical rotation that was both larger and of the opposite direction than expected based on data reported for the hydrochloride salt ($[\alpha]_D$ = −23.5 (MeOH, c = 0.75, TFA salt)). Although not completely unprecedented,[42] the dependence of the sign of optical rotation upon the identity of the counterion was entirely unexpected.

Conclusion

This full account has traced the development of a successful strategy for the total synthesis of sceptrin from the initial failure of an allyl urocanate dimerization route to an ultimately successful oxaquadricyclane fragmentation strategy. Along the

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way, a new method for the α-chlorination of ketals was developed to confront unexpected chemo- and regioselectivity issues. This synthesis also contained a unique application of the oxaquadricyclane fragmentation cascade to total synthesis. Following our biosynthetic hypothesis, sceptrin was then converted into the related natural products ageliferin (**3**) and nagelamide E (**43**) via the first example of a vinyl cyclobutane rearrangement in natural products synthesis. Computational studies[19] support a stepwise radical mechanism for this interesting transformation.

Extension of this biosynthetic hypothesis coupled with a desire to avoid protecting groups led to the examination of the chemistry of hydroxylated aminoimidazoles.[21] Following proposed biogenetic relationships and using the empirical intelligence gathered led to the first syntheses of oxysceptrin, nakamuric acid, and nakamuric acid methyl ester. These syntheses proceed from sceptrin quickly and without masking the reactivity of the 2-aminoimidazole with protecting groups. The axinellamine carbon skeleton was likewise obtained from ageliferin by harnessing the innate reactivity of 2-aminoimidazoles.

Finally, mechanistic consideration of the oxaquadricyclane fragmentation allowed the enantioselective synthesis of both enantiomers of sceptrin and ageliferin. This study represented the first enantioselective synthesis of any dimeric pyrrole−imidazole alkaloid and allowed the assignment of ageliferin's absolute configuration. The fact that the absolute configurations of sceptrin and ageliferin match lends further credence to the hypothesis that sceptrin is the biosynthetic precursor of ageliferin. The enantioselective synthesis of sceptrin via enzymatic desymmetrization and an oxaquadricyclane fragmentation represents an interesting alternative to traditional templated [2 + 2] cyclization approaches to enantioselective cyclobutane synthesis. Efforts to synthesize the remaining members of this class of thought-provoking marine alkaloids are currently underway.

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Supporting Information Available: Full characterization, including copies of ^{1}H and ^{13}C NMR spectra, and experimental procedures for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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