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(54) METHOD FOR THE SYNTHESIS OF 4- AND/OR 5-(DI)SUBSTITUTED 2-AMINOIMIDAZOLES FROM 2-AMINOIMIDAZOLES AND ALDEHYDES

VERFAHREN ZUR SYNTHESE VON 4-UND/ODER 5-(DI) SUBSTITUIERTEN 2-AMINOIMIDAZOLEN AUS 2-AMINOIMIDAZOLEN UND ALDEHYDEN

PROCEDE DE SYNTHESE DE 2-AMINOIMIDAZOLES (BI)SUBSTITUES EN POSITION 4 et/ou 5 A PARTIR DE 2-AMINOIMIDAZOLES ET D'ALDEHYDES

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- **TETRAHEDRON LETT. (1994), 35(3), 351-4 CODEN: TELEAY;ISSN: 0040-4039, 1994, XP002035214 XU, YINGZI ET AL: "A synthesis of (.+-.)-hymenin"**

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(Cont. next page)

- **CHEMICAL ABSTRACTS, vol. 108, no. 15, 11 April 1988 Columbus, Ohio, US; abstract no. 124371, KOBAYASHI, J. ET AL: ".alpha.-Adrenoceptor blocking action of hymenin, a novel marine alkaloid" XP002035215 & EXPERIENTIA (1988), 44(1), 86-7 CODEN: EXPEAM;ISSN: 0014-4754, 1988,**

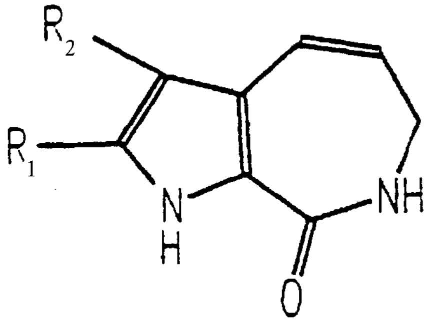
Description

[0001] Throughout this application various patents and publications are referenced and cited in parentheses.

[0002] The chemistry of 2-aminoimidazoles is virtually undetermined. Many marine natural products contain this heterocyclic moiety. Some representative members of this alkaloid class with known biological activities are discussed here. There are, however, many natural derivatives which appear to be biogenetically related having diverged from a common, yet unidentified, intermediate. Further discussion involving biogenic hypotheses of these metabolites is described later. Since the majority of these marine products have been isolated from depths ranging from 30 to 800 meters below sea level, metabolite availability has been a problem for both chemical and biochemical investigations. Very often, minute amounts contained within the marine source make it impractical to obtain suitable quantities of material necessary for further study. Versatile and efficient syntheses of these metabolites would not only remedy this situation, but would also provide access to structurally modified or specifically labeled substrates for biomedical research.

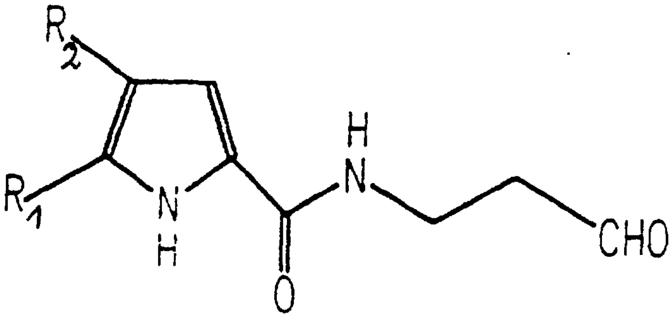
[0003] Hymenin, a marine alkaloid, was shown to have competitive antagonist activity of α-adrenoceptors in vascular smooth muscles of rabbit (ref. 71). New compounds with antitumor activity have been isolated from marine sponges. These compounds differ from a hymenin compound in that the lactam ring is unsaturated (ref. 72).

[0004] The subject invention provides a bicyclic pyrrole compound having the structure



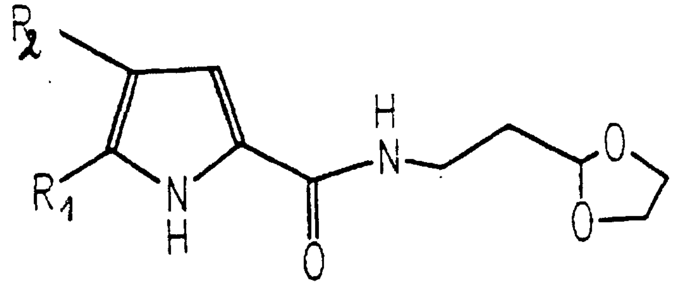
wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl group, which alkyl groups are substituted or unsubstituted; or halogen.

[0005] The subject invention provides an aldehyde aminoimidazole compound having the structure



wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl group, which alkyl group is substituted or unsubstituted; or halogen.

[0006] The subject invention provides a ketal aminoimidazole compound having the structure



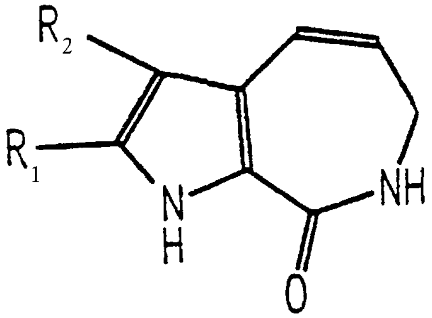
wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl group, which alkyl group is substituted or unsubstituted; or halogen.

[0007] Figure 1A depicts the synthesis of the α-adrenoceptor antagonist (±)-hymenin (16), involving an acid-promoted intramolecular cyclization and dehydration of pyrrole aldehyde (14) to give the cyclic olefin (15), and the coupling of olefin (15) with 2-aminoimidazole (AI) under acidic conditions to give (±)-hymenin.

[0008] Figure 1B depicts the the synthesis of the α-adrenoceptor antagonist (±)-hymenin (16), showing that the two steps in Figure 2A can be combined into one operation in which the combination of aldehyde (14) and AI produces (±)-hymenin (16) in a 'single pot'.

[0009] Figure 2 depicts the process for preparing the bicyclic pyrrole compound of the subject invention.

[0010] The subject invention provides a bicyclic pyrrole compound having the structure

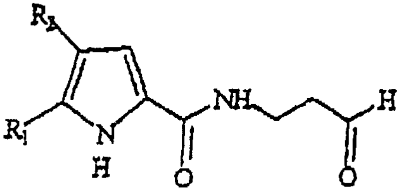


wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl group, which alkyl group is substituted or unsubstituted; or halogen.

[0011] Regarding bicyclic pyrrole compound, the subject invention provides that the alkyl group may be substituted with halogen, alcohol, alkoxy, dialkyl amine, alkyl aryl amine, diaryl amine, thiol, or sulfide groups.

[0012] The subject invention provides the process for preparing the bicyclic pyrrole compound of the subject invention,
wherein R_1 and R_2, are the same as defined above, which process comprises:

reacting a pyrrole having the structure



in a solvent, wherein the solvent is methane sulfonic acid, trifluroacetic acid, or trifluromethane sulfonic acid, to form the bicyclic pyrrole compound.

[0013] Regarding the process for preparing the bicyclic pyrrole compound, the subject invention provides that the process may be performed at a temperature of 0 °C to 100 °C.

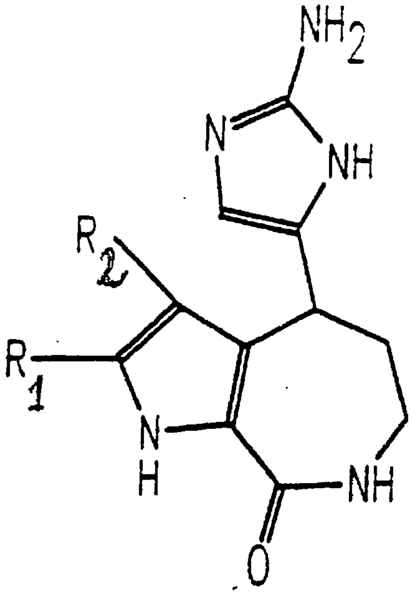
[0014] Regarding the process for preparing the bicyclic pyrrole compound, the subject invention provides that the process may be performed at a temperature of 25 °C to 100 °C.

[0015] Regarding the process for preparing the bicyclic pyrrole compound, the subject invention provides that the process may be perf ormed at a temperature of 25°C to 50 °C.

[0016] Regarding the process for preparing the bicyclic pyrrole compound, the subject invention provides that the process may be performed for a reaction time of from 3 days to 5 days. In general, the reaction time is solvent dependent; wherein when the solvent is methane sulfonic acid then the reaction time is about 3 days; when the solvent is trifluroacetic acid then the reaction time is about 5 days.

[0017] Regarding the process for preparing the bicyclic pyrrole compound, the subject invention provides that the solvent may be saturated with an inert gas. An example of an appropriate inert gas is argon. The inert gas is used to avoid oxidation of the pyrrole compound.

[0018] The subject invention provides a process for preparing a hymenin compound having the structure

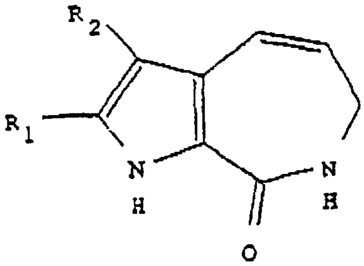


wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl group, which alkyl is substituted or unsubstituted; or halogen.

[0019] Regarding the hymenin compound the subject invention provides that the alkyl groups may be substituted with halogen, alcohol, alkoxy, dialkyl amine, alkyl aryl amine, diaryl amine, thiol, or sulfide groups.

[0020] The subject invention provides the process for preparing the hymenin compound, wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl or branched alkyl, which alkyl may be substituted or unsubstituted; or halogen; which process comprises:

reacting one molecular equivalent of a compound having the structure



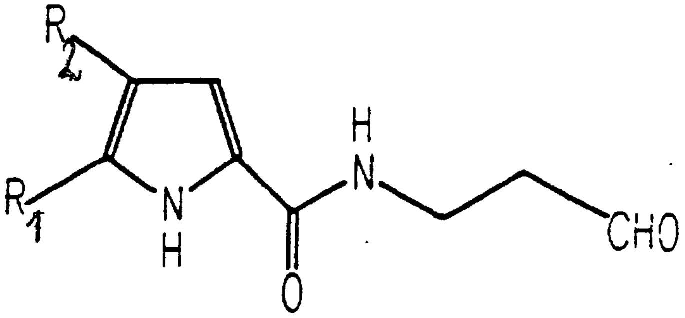
with one molecular equivalent of 2-aminoimidazole or a salt of 2-aminoimidazole; in a solvent wherein the solvent is methane sulfonic acid, trifluroacetic acid, or trifluromethane sulfonic acid; to form the hymenin compound.

[0021] Regarding the process for preparing the hymenin compound, the subject invention provides that the process may be performed at a temperature of 0 °C to 100 °C. Regarding the process for preparing the hymenin compound, the subject invention provides that the process may be performed at a temperature of 25 °C to 50 °C. Regarding the process for preparing the hymenin compound, the subject invention provides that the process may be performed at a temperature of about 30 °C.

[0022] Regarding the process for preparing the hymenin compound, the subject invention provides that the process may be performed for a reaction time of from 3 days to 5 days.

[0023] Regarding the process for preparing the hymenin compound, the subject invention provides that the solvent may be saturated with an inert gas. An example of an appropriate inert gas is argon. The inert gas is used to avoid oxidation of the compounds that could be oxidized by air that might be in the solution.

[0024] The subject invention provides an aldehyde aminoimidazole compound having the structure

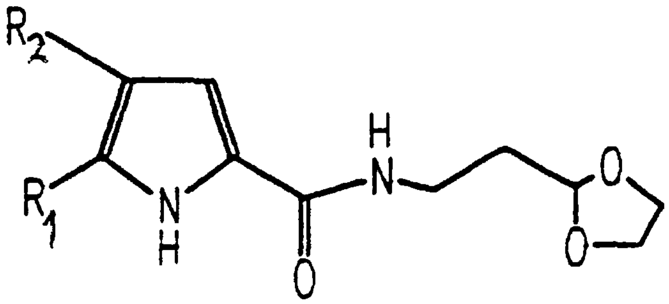


wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl group, which alkyl group is substituted or unsubstituted; or halogen.

[0025] Regarding the aldehyde aminoimidazole compound of the subject invention, the subject invention provides that the alkyl groups may be substituted with halogen, alcohol, alkoxy, dialkyl amine, alkyl aryl amine, diaryl amine, thiol, or sulfide groups.

[0026] The subject invention provides the process for preparing the aldehyde aminoimidazole compound of the subject invention, wherein R_5 and R_6 are the same as defined for the aldehyde aminoimidazole compound; which process comprises:

reacting one molecular equivalent of a ketal having the structure



with 0.5 molecular equivalent of p-toluene sulfonic acid monohydrate, at a temperature of 0 °C to 100 °C;

in a solvent, wherein the solvent is a mixture of water and a polar nonhydroxylic organic solvent, and the volume ratio of the water and the polar nonhydroxylic organic solvent is from 1/10 to 10/1;

to form the aldehyde aminoimidazole compound.

[0027] Regarding the process for preparing the aldehyde aminoimidazole compound, the subject invention provides that the polar nonhydroxylic organic solvent may be N,N-dimethylformamide; dioxane; tetrahydrofuran; dimethyl sulfoxide; or acetonitrile.

[0028] Regarding the process for preparing the aldehyde aminoimidazole compound, and further regarding the volume ratio of the water and the polar nonhydroxylic organic solvent, the subject invention provides that the volume ratio of the water and the polar nonhydroxylic organic solvent may be from 40/60 to 60/40.

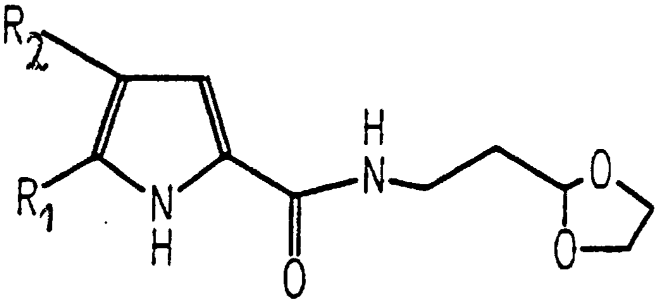
[0029] Regarding the process for preparing the aldehyde aminoimidazole compound, the subject invention provides that the solvent may be a mixture of water and acetone in a volume ratio of from 40/60 to 60/40.

[0030] Regarding the process for preparing the aldehyde aminoimidazole compound, the subject invention provides that the temperature may be 80 °C to 100 °C.

[0031] Regarding the process for preparing the aldehyde amino imidazole compound, the subject invention provides that the process may be performed for a reaction time of from 3 hours to 24 hours.

[0032] Regarding the process for preparing the aldehyde aminoimidazole compound, the subject invention provides that the process may be performed for a reaction time of from 6 hours to 10 hours.

[0033] The subject invention provides a ketal aminoimidazole compound having the structure

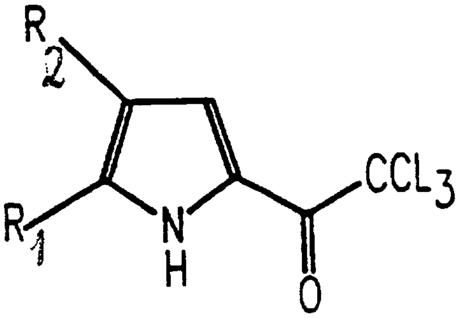


wherein R_1 and R_2 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl group, which alkyl group is substituted or unsubstituted; or halogen.

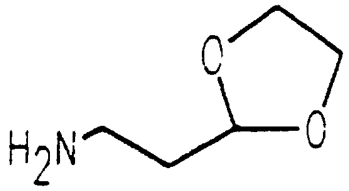
[0034] Regarding the ketal aminoimidazole compound of the subject invention, the subject invention provides that the alkyl group may be substituted with halogen, alcohol, alkoxy, dialkyl amine, alkyl aryl amine, diaryl amine, thiol, or sulfide groups.

[0035] The subject invention provides the process for preparing the ketal aminoimidazole compound of the subject invention, wherein R_5 and R_6 are the same as defined for the ketal aminoimidazole compound; which process comprises:

reacting one molecular equivalent of a trichloroacetylpyrrole having the structure



with one molecular equivalent of an aminoketal having the structure



in a polar nonhydroxylic solvent, to form the ketal aminoimidazole compound.

[0036] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the polar nonhydroxylic solvent may be N,N-dimethylformamide; dioxane; tetrahydrofuran; dimethyl sulfoxide; or acetonitrile.

[0037] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the polar nonhydroxylic solvent is acetonitrile.

[0038] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the process may be performed at a temperature of 25 °C to 70 °C.

[0039] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the process may be performed at a temperature of 25 °C to 50 °C.

[0040] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the process may be performed for a reaction time of from 5 hours to 48 hours.

[0041] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the process may be performed for a reaction time of from 16 hours to 48 hours.

[0042] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the polar nonhydroxylic solvent may be saturated with an inert gas. The inert gas is used to avoid oxidation of the compounds that could be oxidized by air that might be in the solution. An example of an appropriate inert gas is argon.

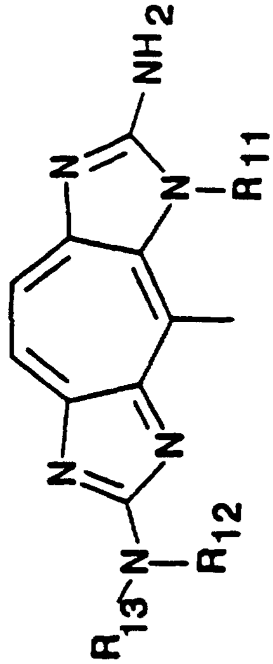
[0043] Regarding the process for preparing the ketal aminoimidazole compound, the subject invention provides that the polar nonhydroxylic solvent may additionally contain one equivalent of triethylamine. The triethylamine is used to neutralize acid that is formed in the process.

Experimental Details

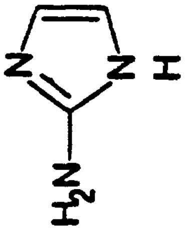
[0044] Chemical reagents are obtained at various chemical supply companies, such as Fisher, Pittsburgh, Pennsylvania; Aldrich Chemical Company, Milwaukee, Wisconsin; and Spectrum Chemical Company, New Brunswick, New Jersey.

Experiment One

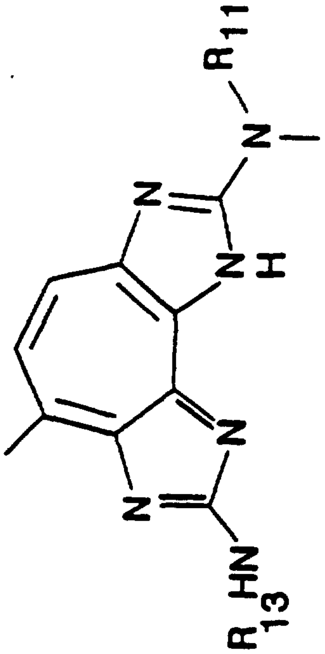
[0045] A common structural unit encountered in biologically active marine alkaloids is the 2-aminoimidazole nucleus. (For reviews of marine alkaloids, see ref. 1, 2, 3, 4; for recent reports of biologically active aminoimidazole derivatives, see ref. 5, 6, 7, 8, 9, 10, 11, 12). This weakly basic heterocycle is also an integral component of the highly fluorescent marine pigments known collectively as zoanthoxanthins (ref. 13, 14, 15, 16, 17, 18, 19, 20, 21, 22). The structurally related linear zoanthoxanthins (1) and angular pseudozoanthoxanthins (2) are representative of the zoanthoxanthin family in which over twenty N-methylated variations exist. The ring system of these pigments is based on either a 1,3,5,7-tetrazacyclopent[f]azulene (1) or a 1,3,7,9-tetrazacyclopent[e]azulene (2) skeleton. The latter occurs in two types depending on the N-methylation pattern. Several of these metabolites have been assayed for biological activity. They include the DNA intercalators zoanthoxanthin (1B) and 3-norzoanthoxanthin (1C) both of which inhibit the activity of rat liver DNA polymerase in vitro (ref. 23, 24), while paragracine (2B) possesses papaverine-like and antihistamine properties as well as having sodium channel blocking effects (ref. 21, 22). The biosynthesis of zoanthoxanthins has not been determined and awaits experimental verification. A longstanding hypothesis by Prota (ref. 15), however, involves the dimerization of two C_5N_3 monomers thought to be derived from arginine. Although the exact nature of the C_5N_3 monomer remains unknown, it is unclear how this moiety would result from arginine metabolism. In this report, we describe the conversions of an arginine derived C_3N_3 heterocycle, namely 2-aminoimidazole (AI), into both parazoanthoxanthin A (1A) and pseudozoanthoxanthin A (2A) thus implicating the intermediacy of 2-aminoimidazole as an in vivo progenitor of zoanthoxanthins.



(1)



AI

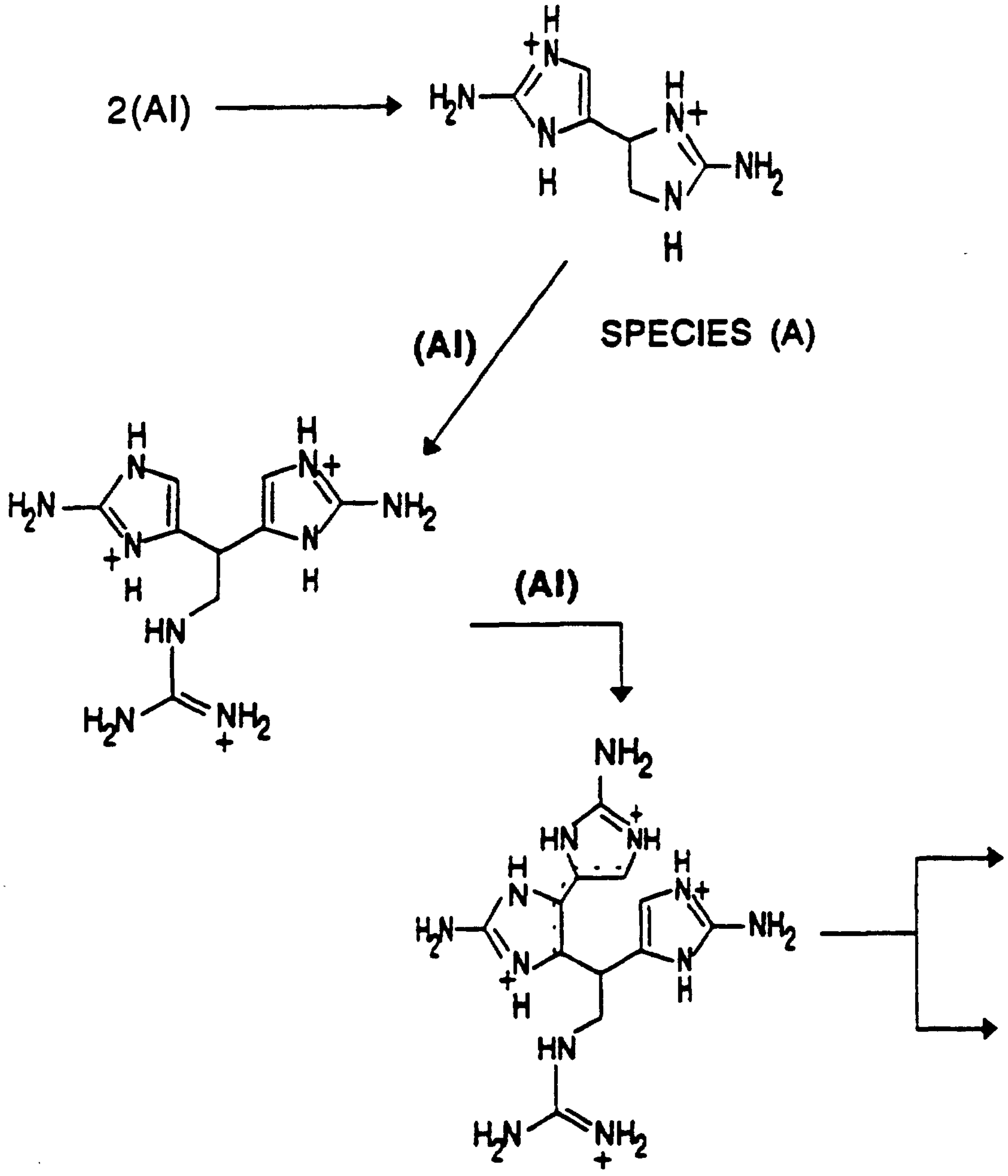


(2)

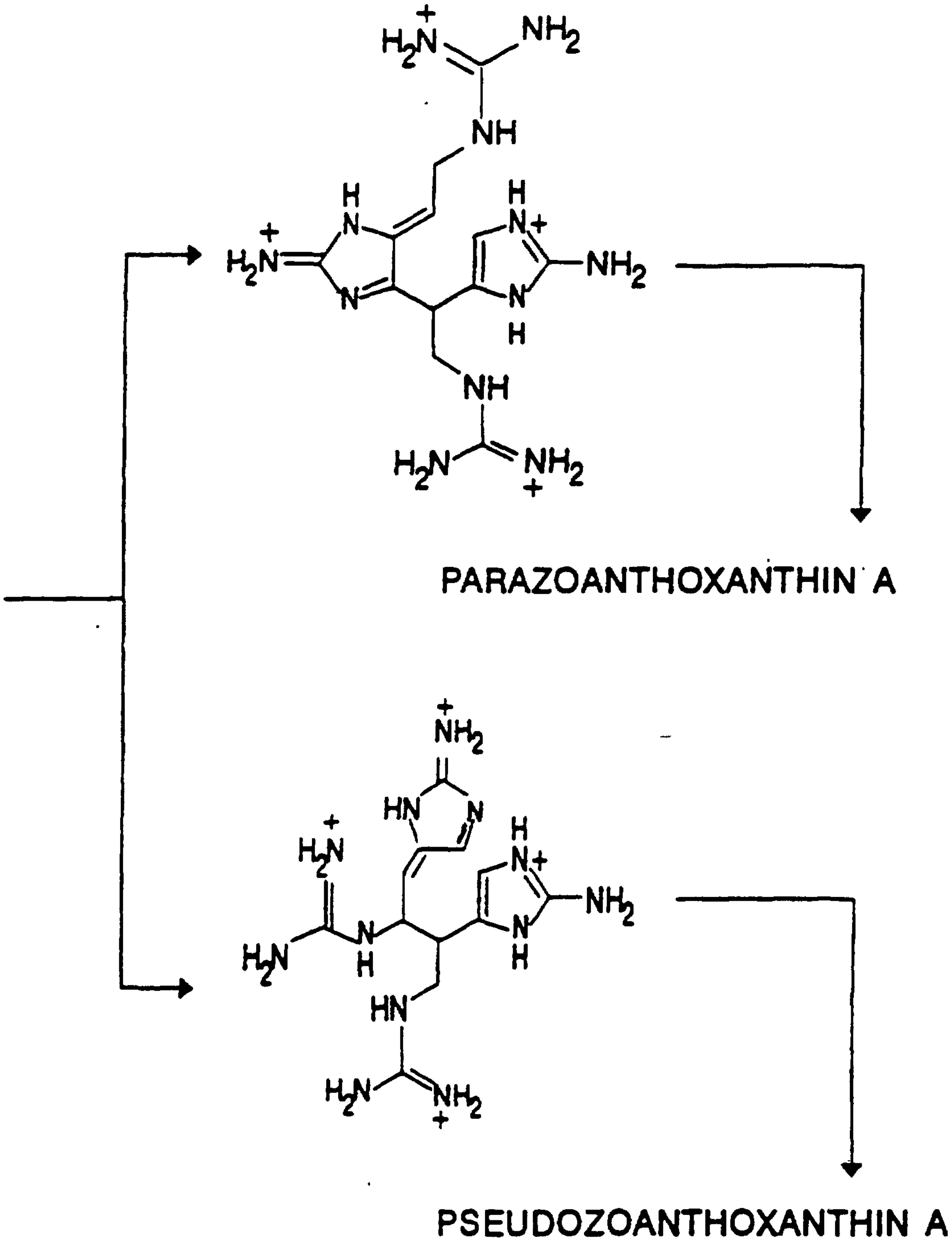
a: $R_{11}=R_{12}=R_{13}=H$
b: $R_{11}=R_{12}=R_{13}=CH_3$
c: $R_{11}=H, R_{12}=R_{13}=CH_3$

[0046] The notion that zoanthoxanthins (1) and (2) could possibly be derived from 2-aminoimidazole (AI) is based on the identification of (AI) as a marine metabolite of the sponge Reneira cratera (ref. 25). Combination of four molecules of the C_3N_3 heterocycle with loss of two molecules of guanidine would give the desired $C_{10}N_6$ pigments. (For acid promoted dimerizations and trimerizations of indoles and pyrroles, see ref. 26, 27). When 2-aminoimidazole sulfate was exposed to methanesulfonic acid at 23 °C, no reaction occurred. Upon heating, however, between 140-150 °C for 20 hours, small amounts of parazoanthoxanthin A (1A) and pseudozoanthoxanthin A (2A) were obtained (10 % yield) in a 4:1 ratio, respectfully. ^{1}H NMR, UV, IR, and MS data are in agreement with previously reported values (ref. 15, 28, 29). Although no intermediates of the reaction have been confirmed, a possible mechanism for the formation of (1A) and (2A) is shown in Scheme (1) and is based on related chemistry observed for indoles and pyrroles. (For acid promoted dimerizations and trimerizations of indoles and pyrroles, see ref. 26, 27). Using sulfuric acid in place of methanesulfonic acid no zoanthoxanthins could be detected. The major product of the reaction is glycocyamidine (11) (ref. 30) which results from sulfonation of the starting material followed by hydrolysis. These results indicate that while involvement of (AI) in the biogenesis of zoanthoxanthins remains a curious possibility, its sole participation is unlikely.

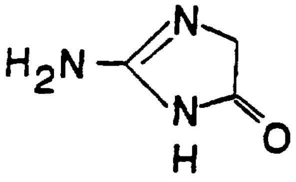
SCHEME(1)



Scheme (1)



Nature's utilization of a potential counterpart in the formation of zoanthoxanthins forms a basis of our biogenic hypothesis and involves the introduction of a two-carbon unit (or equivalent) to the C_3N_3 heterocycle as the penultimate step prior to dimerization. Incorporation of this hypothetical two-carbon entity could be accomplished by a hitherto unknown hydroxyalkylation of 2-aminoimidazole with a suitably functionalized two-carbon aldehyde or pyruvic acid. To test this hypothesis, 2-aminoimidazole sulfate was heated at 95-100 °C with chloroacetaldehyde in concentrated hydrochloric acid for 24 hours. After basification to pH 12 and chromatography, parazoanthoxanthin A (1A) (41 % yield) and pseudozoanthoxanthin A (2A) (7 % yield) were obtained. Most importantly, moderate amounts of (1A) and (2A) were produced at room temperature after 7 days. Under acidic conditions, the proton serves as a natural protecting group for nitrogen as well as catalyst for hydroxyalkylation and subsequent dimerization. Similar results were seen with pyruvic acid and the more highly reduced two-carbon unit, acetaldehyde, but with less efficiency. Reactions involving pyruvic acid and acetaldehyde were carried out in 37 % HCl between 95-100 °C for 24 hours. Acetaldehyde gave a 25 % yield of parazoanthoxanthin A and pseudozoanthoxanthin A in a 3:1 ratio, respectively, whereas pyruvic acid produced a 15 % yield of parazoanthoxanthin A and trace amounts of pseudozoanthoxanthin A. with these reactants, decarboxylation and / or final oxidation to the ten-electron azulene ring system is necessary (the oxidation is probably assisted by sulfuric acid derived from the commercial starting material, 2-aminoimidazole sulfate) and most likely accounts for the lower overall yields. At 23 °C, the reaction between (AI) and acetaldehyde afforded products (12) (ref. 29); and (14) [Compound 5·2HCl, colorless solid, mp 240 °C (dec); ^{1}H NMR (DMSO-D_6, 300 MHz) δ ppm: 1.51 (d, 7.2 Hz, 3H), 3.97 (q, 7.2 Hz, 1H), 6.65 (s, 2H), 7.37 (s, 4H, exchanged with D_2O), 11.85 (s, 2H, exchanged with D_2O), 12.37 (s, 2H, exchanged with D_2O); ^{13}C NMR (free-base, DMSO-D_6, 75.1 MHz) δ ppm: 20.0 (q), 30.4 (d), 111.0 (d), 135.8 (s), 148.9 (s); IR (nujol) u cm^{-1}: 3240, 3126, 1667; MS (CI, NH_3) m/z 193 (MH^+)] (10-40 % yields); in addition to small amounts of zoanthoxanthins. Formation of (14) [Dimer (14), when heated at 95-100 °C with 1 eq. of acetaldehyde produced parazoanthoxanthin A], a precursor to parazoanthoxanthin A (1A), can be explained by dehydration of (12) to intermediate (B) followed by C-attack of the imidazole to the exocyclic double bond. Intermediate (14) could next undergo hydroxyalkylation with acetaldehyde followed by dehydration, cyclization, and oxidation to give (1A). A similar process in which initial addition to the endocyclic double bond of species (B) would account for the formation of pseudozoanthoxanthin A (2A), although no intermediates have been isolated. Whether the actual biosynthetic pathway proceeds via a sequential series of hydroxyalkylation - dimerization - hydroxyalkylation events involving 2-aminoimidazole or by direct dimerization of two C_5N_3 monomers (ref. 28, 29) remains to be determined. Our results in combination with the known metabolic conversion of arginine to (AI) (ref. 31) suggest that the key biosynthetic intermediate is not a direct product of arginine metabolism but evolves from hydroxyalkylation of arginine derived (AI). One additional consideration is formation of the methylated metabolites of zoanthoxanthins since they comprise the majority of pigments isolated. The parent compounds (1A) and (2A) could serve as potential precursors in a late methylation scheme, or contrastly, an early, predimeric methylation process would yield N-methylated 2-aminoimidazoles as biogenic forerunners.



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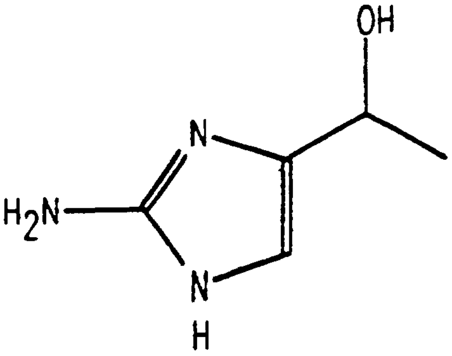

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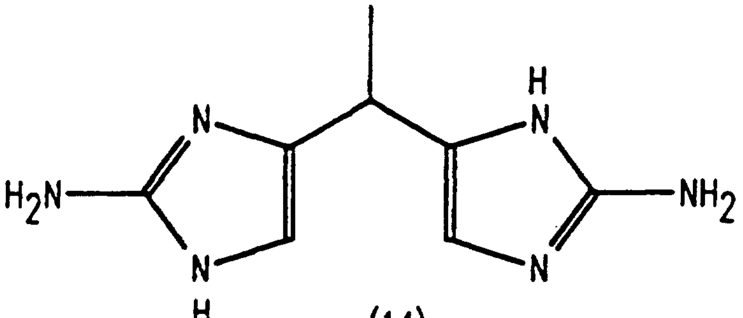

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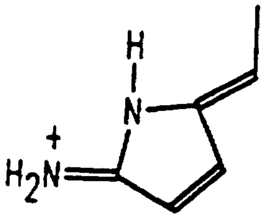


(B)

[0047] The generality and simplicity of hydroxyalkylation should find useful applications in the synthesis of aminoimidazole heterocycles. In our initial demonstration, we have shown that zoanthoxanthins can be prepared in (essentially) a single step from commercially available 2-aminoimidazole sulfate and acetaldehydes. The mild reaction conditions under which pigments (1A) and (2A) are produced suggests that the series of events leading to their formation parallel those operating in nature. Due to the difficulties encountered in culturing marine organisms, biosynthetic studies in the area of marine alkaloids are rare. The biogenic chemistry developed here, points to 2-aminoimidazole as a potential precursor to zoanthoxanthins.

[0048] Other references of interest are ref. 68, 69, 70.

Experiment Two

A. Specific Aims

[0049] The development of new synthetic methodologies and strategies for the construction of guanidine-based marine natural products possessing important biological functions is considered. The generality of this approach is demonstrated by the synthesis of zoanthoxanthins (1) and (2), hymenin (3), hymenialdisines (4), sceptrin (5), oxysceptrin (6), ageliferins (7), girolline (8), as well as saxitoxin (9). Collectively, these and other structurally related compounds possess potent biological activities. They include antiviral, antileukemic, antineoplastic, antiserotonergic as well as α-adrenoceptor and ion-channel blocking properties. In addition, a rare example of ATPase stimulating activities of myosin and actomyosin has recently been observed. Although many of these marine metabolites are structurally unique, they appear, however, to diverge from a common biogenetically related intermediate. Possible biosynthetic pathways for the in vivo formation of these marine metabolites are considered. The development of methods for transforming 2-aminoimidazole (AI) into key intermediates for the synthesis of the naturally occurring compounds is considered.

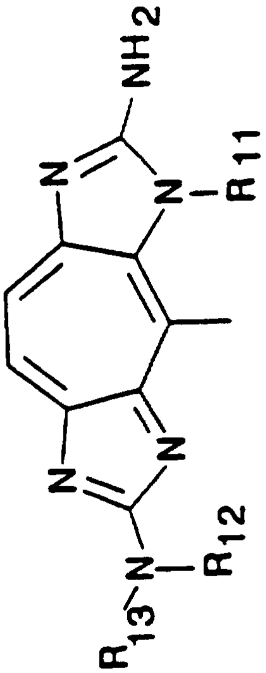
B. Background And Significance

[0050] Nitrogen-containing marine natural products (ref. 1, 2, 3, 32) are often unique to marine organisms having structural features that are not encountered in terrestrial flora or fauna. Many of these metabolites are non-traditional guanidine-based alkaloids that possess powerful biological activities. A common structural unit contained in many of these alkaloids is the 2-aminoimidazole (AI) moiety. This weakly basic heterocycle and its functionalized derivatives are present in over fifty marine alkaloids isolated to date. In fact, 2-aminoimidazole (AI) itself is a marine metabolite that has been obtained from the sponge Reneira crotera (ref. 25). It has also been shown to result from arginine metabolism in streptomyces eurocidius (ref . 31). The following representative examples, together with a brief description of their biological activities, serve to illustrate the ubiquitous nature of the 2-aminoimidazole moiety contained in marine alkaloids.

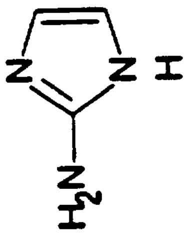
Zoanthoxanthins (1) And (2)

[0051] One family of colonial anthozoans of the order Zoanthidea yields a variety of yellow, highly fluorescent pigments known collectively as zoanthoxanthins (ref. 13, 14, 15, 16, 17, 18, 19, 20, 21, 22). These pigments are responsible for the bright yellow pigmentation of numerous zoanthids of the genus Parazoanthus. Structurally, zoanthoxanthins can be grouped into two distinct classes, linear zoanthoxanthins (1,3,5,7-tetrazacyclopent[f]azulenes) (1) and angular pseudozoanthoxanthins (1, 3, 7, 9-tetrazacyclopent[e]azulenes) (2). Within these two groups over twenty variations of these metabolites are known and can be distinguished mainly by their N-methylation patterns. The synthesis of parazoanthoxanthin A (1) (R_{11}=R_{12}=R_{13}=H), and pseudozoanthoxanthin (2) (R_{11}=R_{12}=R_{13}=H), has been achieved from 2-amino-4-α or β-hydroxyethylimidazoles prepared in several steps (ref. 28, 29).

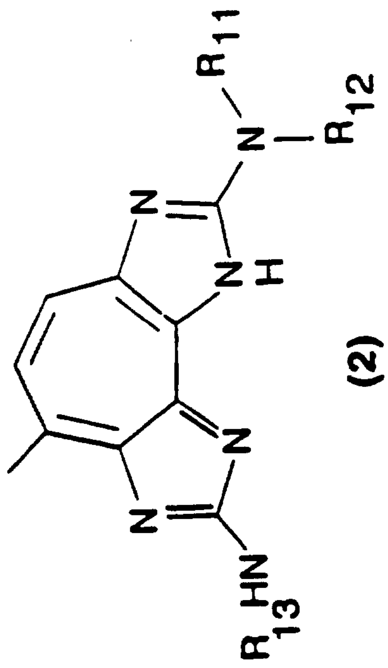
[0052] The biological significance and pharmacological properties of these metabolites remain virtually unknown. Of the few known biological activities of zoanthoxanthins, paragracine (2) (R_{11}=R_{12}=R_{13}=CH_3), has been shown to have papaverine-like and antihistamine properties (ref. 21, 22) while zoanthoxanthin (1) (R_{11}=R_{12}=R_{13}=CH_3), and 3-norzoanthoxanthin (1) (R_{11}=H, R_{12}=R_{13}=CH_3), have been shown to inhibit rat liver DNA polymerase in vitro. The role of inhibition is presumably through intercalative-type binding to duplex DNA (ref. 23, 24).



(1)



AI



(2)

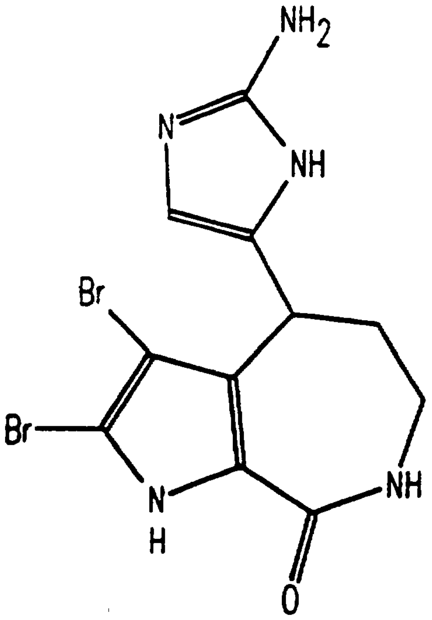
a: $R_{11}=R_{12}=R_{13}=H$

b: $R_{11}=R_{12}=R_{13}=CH_3$

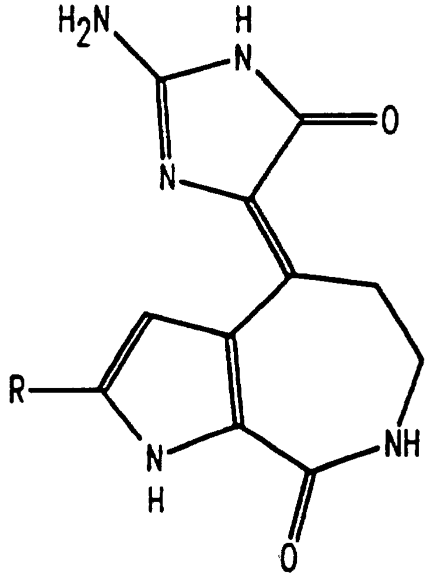
c: $R_{11}=H, R_{12}=R_{13}=CH_3$

Hymenin (3) And Hymenialdisines (4)

[0053] Hymenin (3) (ref. 6, 33) has been identified as the active constituent of the sponge Hymenacidon sp. possessing potent α-adrenoceptor blocking activity. At 5 mg/kg, hymenin produced a 15 ± 1 mm Hg reduction in arterial blood pressure in rats and its hypotensive effects lasted at least thirty minutes. In addition, hymen in at micromolar concentrations in isolated rabbit aorta caused a parallel rightward shift of the dose-response curve for norepinephrine (NE) without affecting responses for histamine or KCl. These results suggest specific competitive antagonism of NE binding to its receptor. Hymenin represents one member of fused pyrrole-seven-membered ring lactams containing a 2-aminoimidazole appendage. The structurally related metabolite, yellow compound (debromohymenialdisine) (4) (R=H) and hymenialdisine (4) (R=Br) have also been isolated from marine sources (ref. 34, 35, 36, 37). Hymenialdisines exhibited cytostatic and antineoplastic activities against murine P388 lymphocytic leukemic (ED_{50} 2.5 mg/ml and T/C 143 @ 3.6 mg/kg) (ref. 8).



(3)HYMENIN

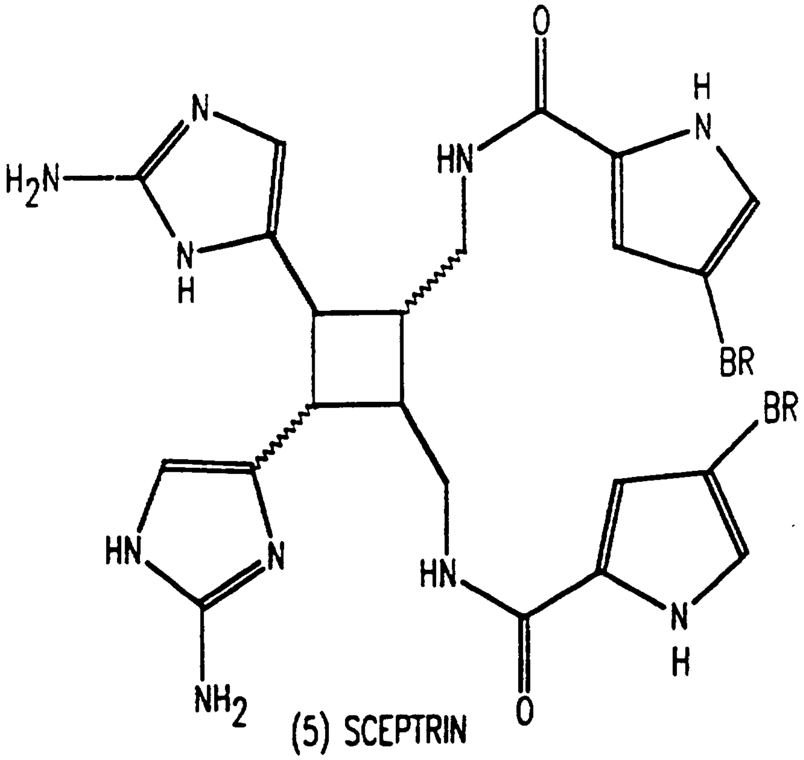


(4) R=H OR Br
HYMENIALDISINES

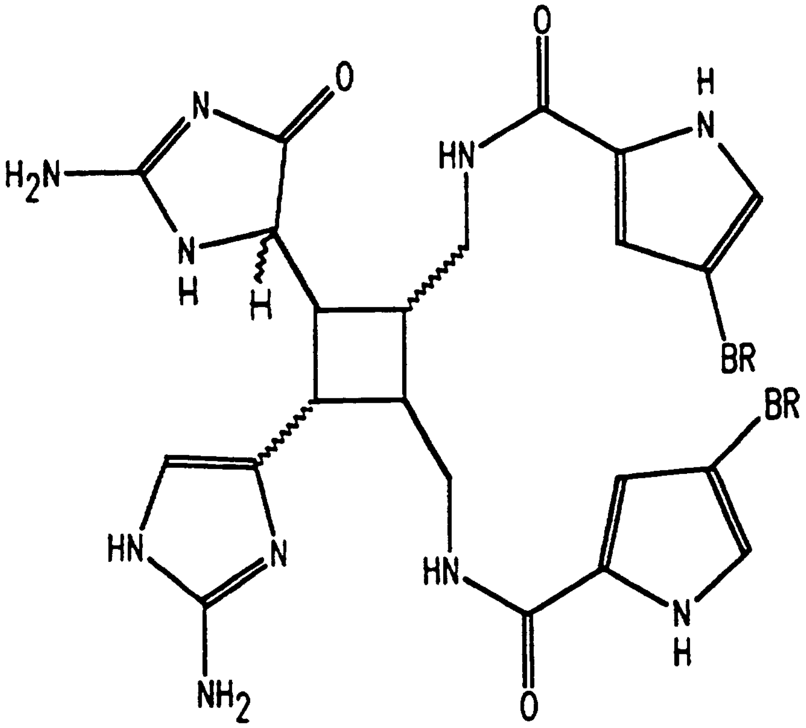
DEBROMOHYMENIALDISINE (R=H)
HYMENIALDISINE (R=Br)

Sceptrin (5), Oxysceptrin (6), And Ageliferins (7)

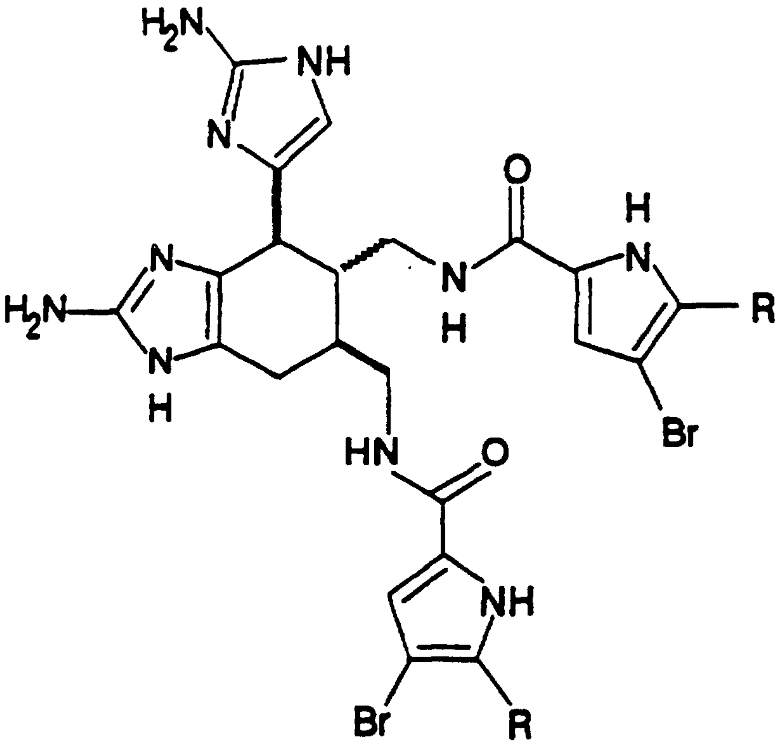
[0054] Sceptrin (5) has been isolated from the marine sponge Agelas sp. (ref. 38). More recently, the isolation and structural determination of the closely related oxysceptrin (6) (ref. 39, 10) and ageliferins (7) (ref. 40, 9) have been reported. The unique structural feature of sceptrins is the cyclobutane ring system which is only sparsely seen in natural products. Both sceptrins and ageliferins are potent actomyosin ATPase activators (ref. 10, 9). The ATPase activity of myofibrils from rabbit skeletal muscle was elevated 150 % of the control value at 10^{-5} M concentrations of these alkaloids. Since substances that moderate ATPase activities of myosin and actomyosin are rare, these alkaloids are invaluable chemical tools for investigating the mechanism of actin-myosin contractile systems.



(5) SCEPTRIN



(6) OXYSCEPTRIN

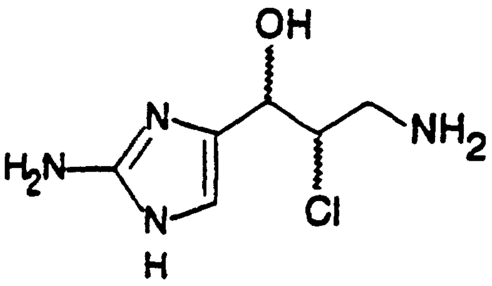


(7) AGELIFERINS

R=H OR Br

Girolline (8)

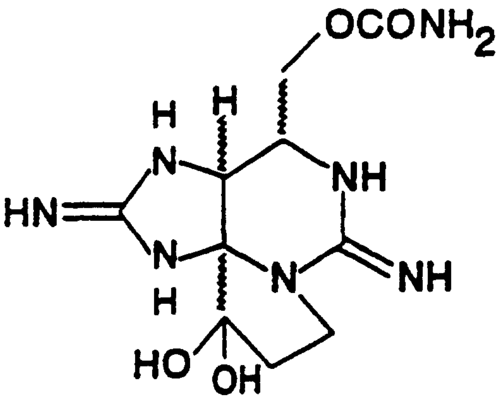
[0055] Girolline (8) (ref. 41) is a new antitumor agent isolated from the New Caledonian sponge Pseudaxinissa cantharella. This compound exhibited potent antitumor activities against P388 leukemic cells at concentrations as low as 1 ng/ml in vitro and at 1 mg/kg in vivo when administered intraperitoneally. This base has been recently prepared from imidazole carboxaldehyde in which the 2-amino group was introduced in the final step of the synthesis (ref. 42, 43, 11).



(8) GIROLLINE

Saxitoxin (9)

[0056] One of the most notable of marine toxins is saxitoxin (9) (ref. 44, 45, 46). This modified purine alkaloid has been responsible for numerous deaths resulting from paralytic shellfish poisoning. Saxitoxin is present in dinoflagellates and accumulates in shellfish or other sea fish via the food chain. The biological mode of action of saxitoxin is specific blockage of the sodium channel thus preventing passage of sodium ions across the cell membrane. Since its discovery, saxitoxin has proved to be an invaluable neurobiological tool for the study of ion channels. The lack of useful synthetic procedures (ref. 47, 48) for the synthesis of saxitoxin and suitably labeled analogues have prevented further advances in understanding structure and conformation as it relates to function.



(9) SAXITOXIN

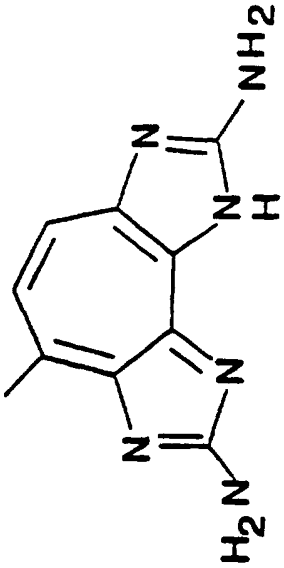
[0057] The chemistry of 2-aminoimidazoles is virtually undetermined. Many marine natural products contain this heterocyclic moiety. Some representative members of this alkaloid class with known biological activities are discussed here. There are, however, many natural derivatives which appear to be biogenetically related having diverged from a common, yet unidentified, intermediate. Further discussion involving biogenic hypotheses of these metabolites is described later. Since the majority of these marine products have been isolated from depths ranging from 30 to 800 meters below sea level, metabolite availability has been a problem for both chemical and biochemical investigations. Very often, minute amounts contained within the marine source make it impractical to obtain suitable quantities of material necessary for further study.

C. Preliminary Studies

[0058] Preliminary investigations dealing with the chemistry of 2-aminoimidazole indicate we have made a breakthrough discovery which is outlined below.

Biogenic Implication Of 2-Aminoimidazole From The Synthesis Of Zoanthoxanthins

[0059] One step in the biogenesis of zoanthoxanthins has been postulated to involve dimerization of two C_5N_3 units derived from arginine (ref. 15). Although the exact nature of the C_5N_3 unit remains unknown, it is unlikely that this unit is a direct product of arginine metabolism. Since 2-aminoimidazole has been identified as a marine metabolite (ref. 25), our initial investigations entertained the possibility that zoanthoxanthins could be derived from four molecules of a C_3N_3 heterocycle with loss of two molecules of guanidine. The synthetic strategy is based on the acid promoted dimerization of pyrroles and indoles (ref. 26, 27). Treatment of tryptophan methylester with methanesulfonic acid at room temperature produces good yields of the hemisaturated C-2 dimer (10). Under similar conditions 2-aminoimidazole was virtually unreactive. However, when 2-aminoimidazole was heated in methanesulfonic acid between 140-150 °C for 20 hours, small amounts of parazoanthoxanthin A (1) and pseudozoanthoxanthin (2) were obtained in a 5:1 ratio, respectively. ^1H NMR, UV, IR, and MS data were in agreement with previously reported values (ref. 15, 28, 29). The majority of the material recovered from the reaction was unreacted starting material. Although no intermediates of the reaction have yet been confirmed, a likely mechanism would involve an acid promoted dimerization of 2-aminoimidazole to Species (A) of Scheme (1) as the initial step. Scheme (1) shows the proposed mechanism for the formation of parazoanthoxanthin A and pseudozoanthoxanthin from 2-aminoimidazole (AI). When sulfuric acid was used in place of methanesulfonic acid, no zoanthoxanthins could be detected. The major product of the reaction is glycocyamidine (11) (ref. 30) which results from sulfonation of the starting material followed by hydrolysis.



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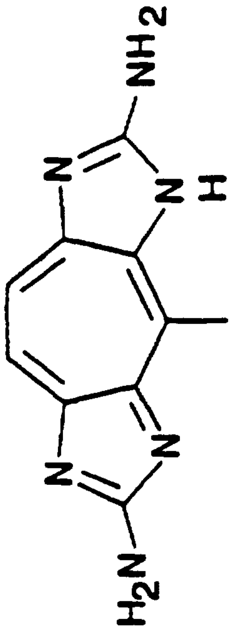

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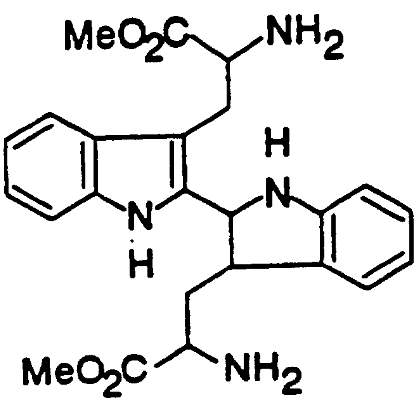

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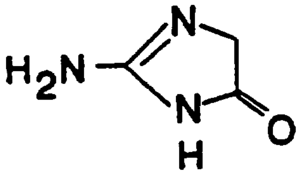

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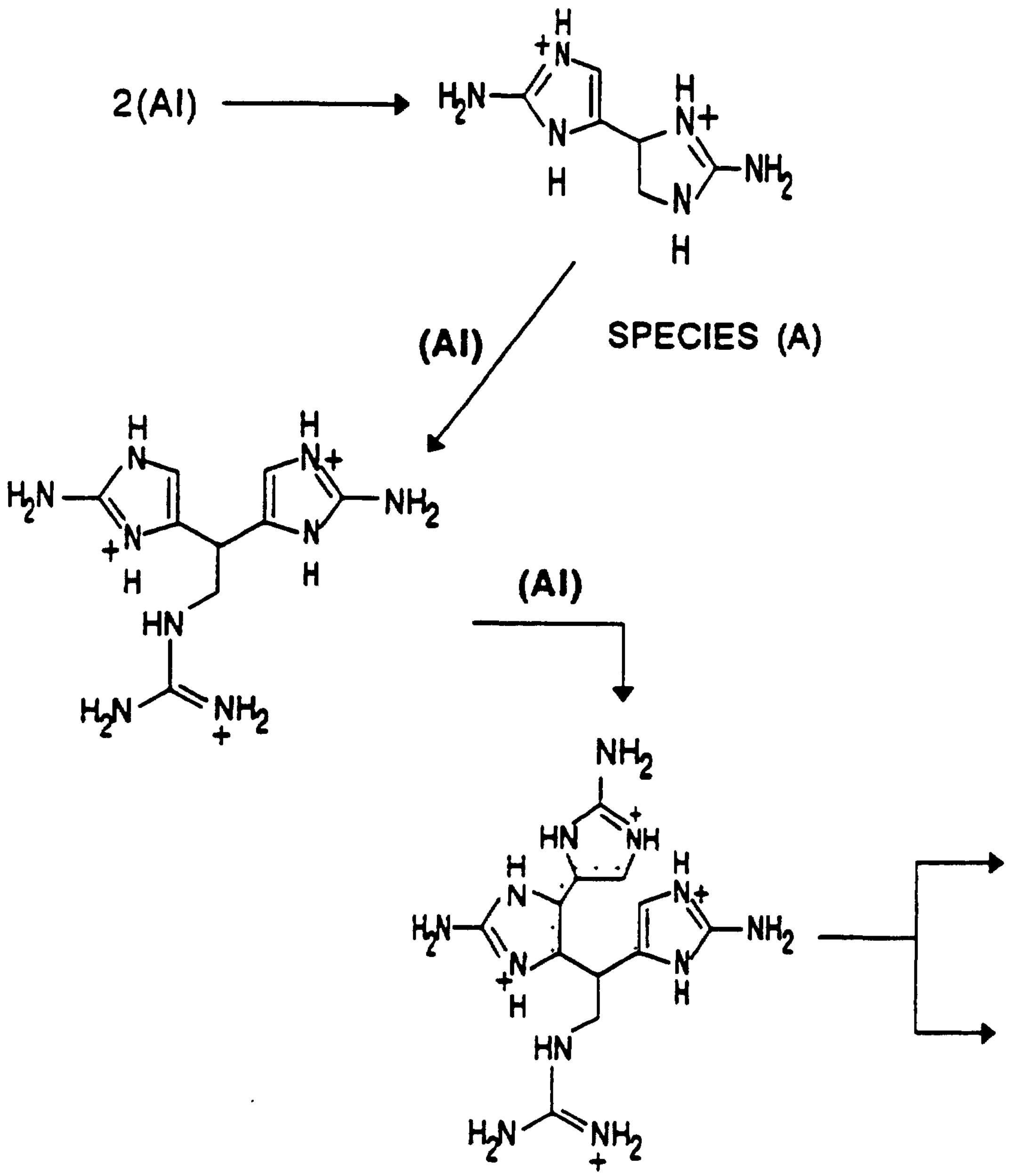
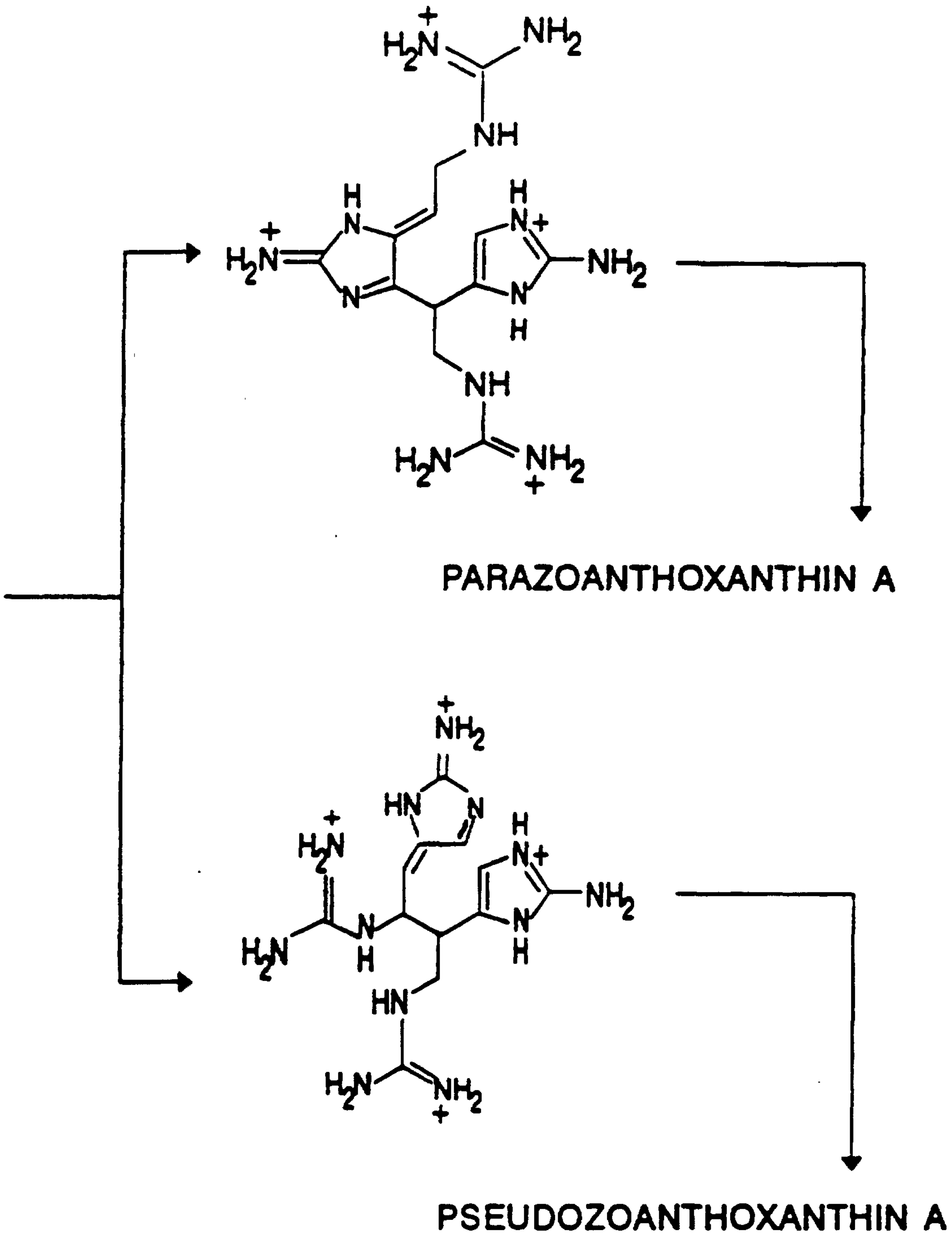
SCHEME(1)



Scheme (1)

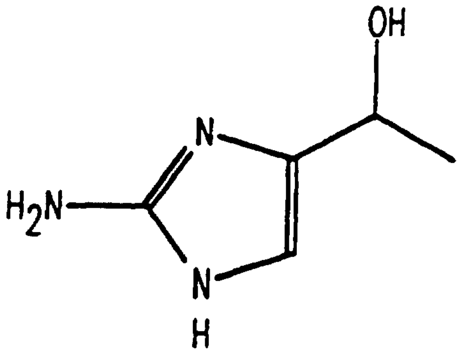


These initial results indicate that while involvement of 2-aminoimidazole in the biogenesis of zoanthoxanthins remains an intriguing possibility, its sole participation is unlikely. One other consideration involves the introduction of a two-carbon unit to the C_3N_3 moiety as the penultimate biogenetic step prior to dimerization. Indeed, when 2-aminoimidazole was heated with chloroacetaldehyde in concentrated hydrochloric acid a 50 % yield of zoanthoxanthins was obtained.

The major product of the reaction is parazoanthoxanthin A (1). Similar results were seen with acetaldehyde but with lower overall yields. In this case, postdimeric oxidation to the ten electron azulene ring system is needed and is probably assisted by sulfuric acid derived from the commercial starting material, 2-aminoimidazole sulfate.

[0060] When acetaldehyde and 2-aminoimidazole were mixed under acidic aqueous conditions at 23 °C, the following products (12), (13), (14), and (15), in addition to the aforementioned zoanthoxanthins, were obtained. These products can be explained by hydroxyalkylation of 2-aminoimidazole with acetaldehyde to give the C_5N_3 hydroxyethyl derivative (s). These results can be compared to that of imidazole in which no reaction is observed under analogous conditions. Dehydration of (12) to the diazafulvene intermediate (B), followed by N-attach or C-attack would produce the dimers (14) and (15). Under acidic conditions N-C dimer (15) undergoes conversion to the C-C dimer (14). While the possibility that zoanthoxanthins result from a concerted [4+6] cycloaddition involving intermediates (B) and (C) cannot be excluded (ref. 28, 29), the presence of dimer (14) strongly suggests a stepwise mechanism, Scheme (2). Scheme (2) shows the proposed mechanism for formation of parazoanthoxanthin A and pseudozoanthoxanthin from 2-aminoimidazole and acetaldehyde. In one of our most significant findings, small amounts of zoanthoxanthins were produced from 2-aminoimidazole and acetaldehyde at room temperature after 24 hours.

[0061] This result suggests that the biogenesis of zoanthoxanthins might involve the following series of events: (i) metabolism of arginine to 2-aminoimidazole (ref. 31); (ii) introduction of a two carbon unit by hydroxyalkylation; (iii) acid promoted dimerization, and, if necessary; (iv) oxidation to the azulene skeleton. The latter would depend upon the oxidation state of the two-carbon unit incorporated.



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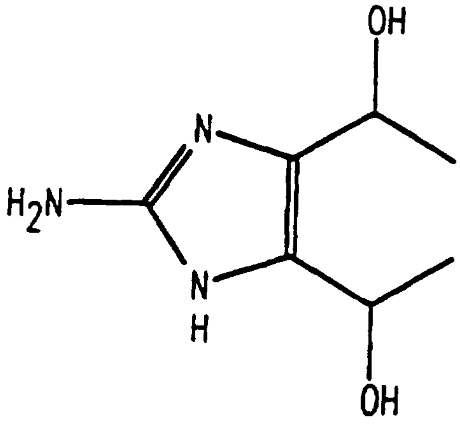

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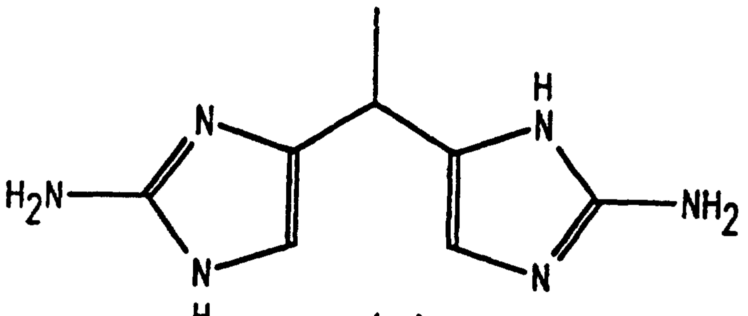

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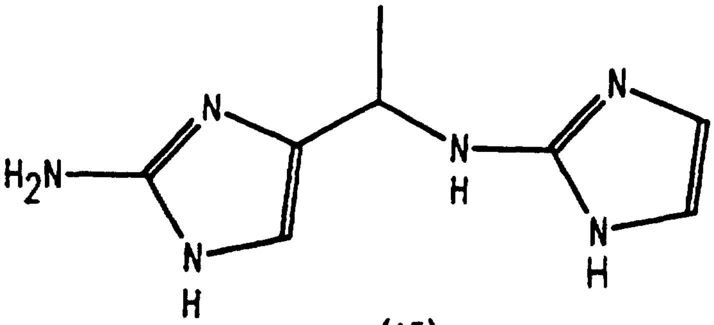

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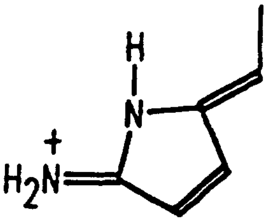
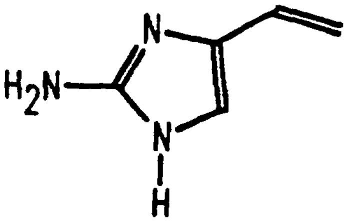
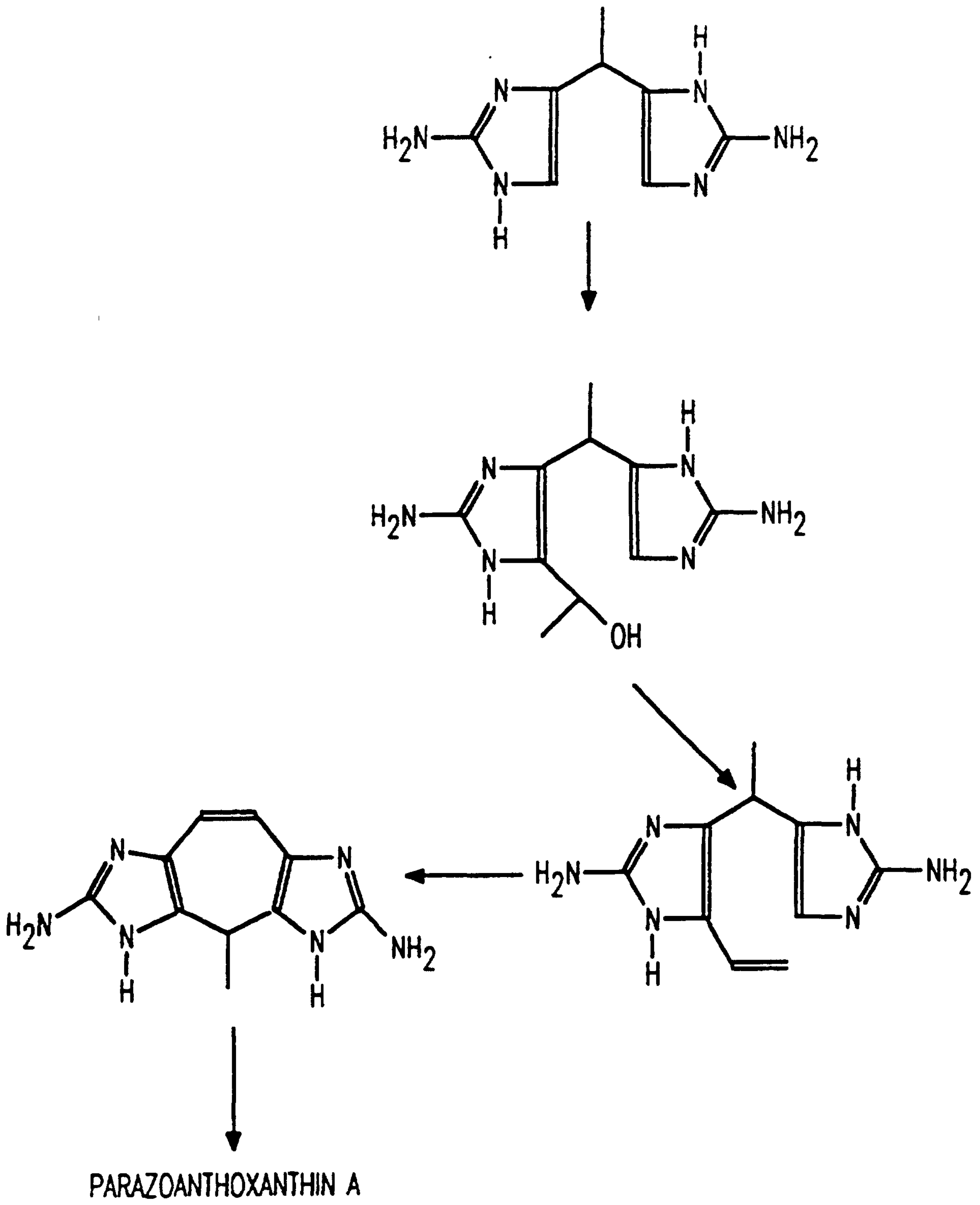


(B)



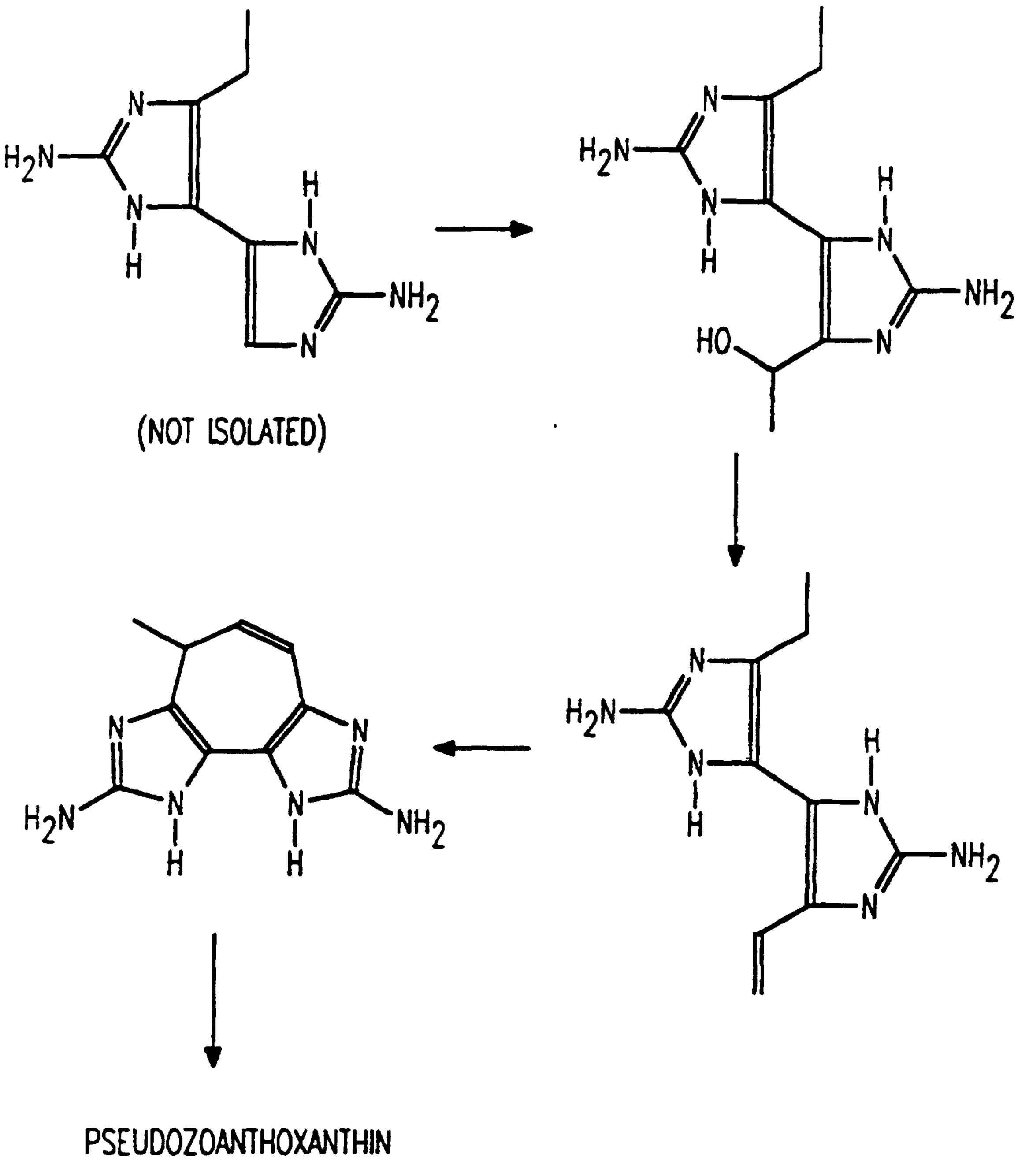
(C)

SCHEME (2)



PARAZOANTHOXANTHIN A

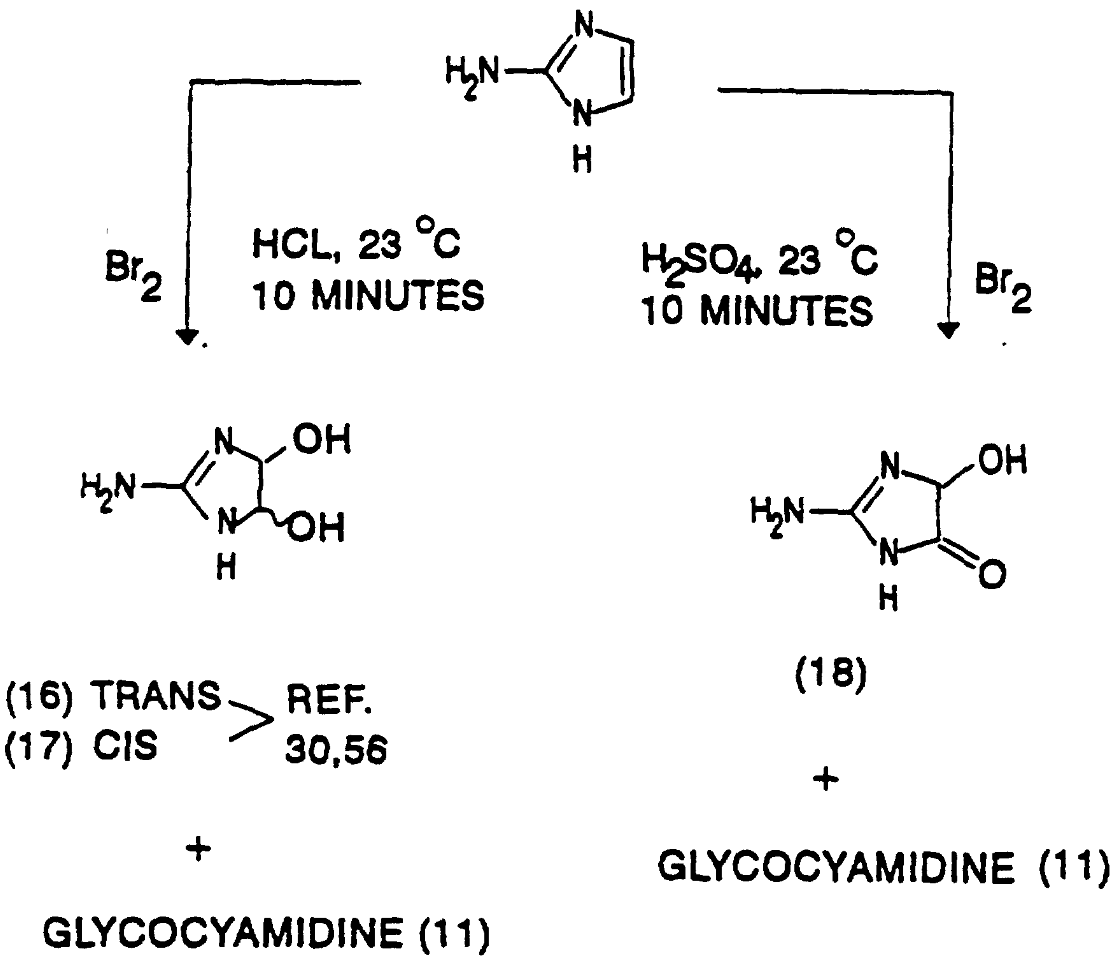
SCHEME (2)



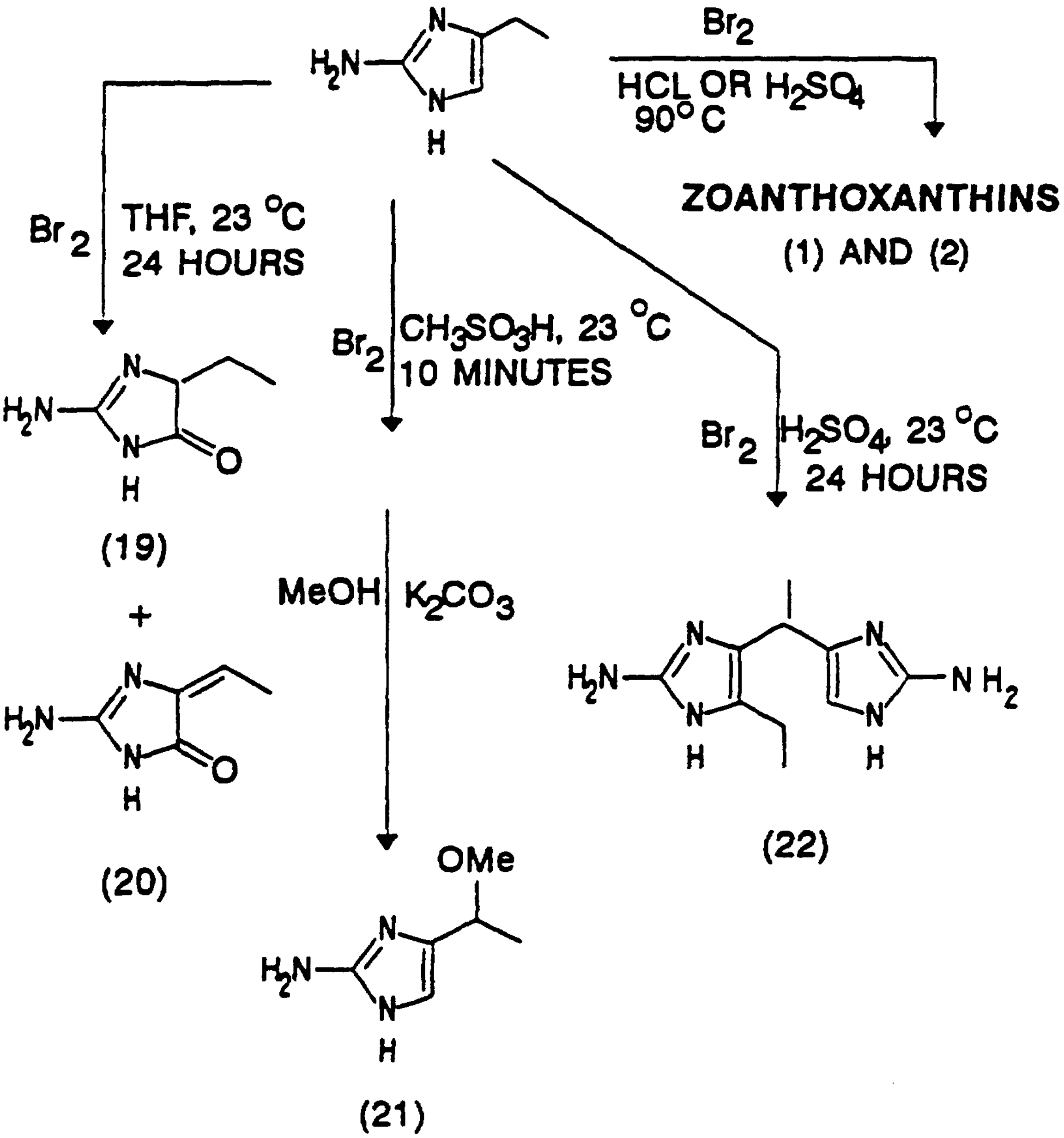
[0062] A common feature unique to marine natural products is the frequent occurrence of halogenated and particularly brominated metabolites (ref. 49). Biosynthetically, introduction of bromine is believed to proceed via an active bromonium ion species generated from bromide and catalyzed bromoperoxidases (ref. 50). The interaction between bromonium ion and 2-aminoimidazoles is likely to be important. Many of the metabolites outlined here either contain bromine or may result from bromonium ion assisted oxidations / transformations. In order to delineate the bromination chemistry of 2-aminoimidazoles, the following transformations have been accomplished, Scheme (3). Scheme (3) shows the reactions of 2-aminoimidazoles with bromine. In contrast to the bromination of imidazoles (ref. 51, 52, 53), which does not occur under acidic conditions, the 2-amino analogue readily reacts with bromine in concentrated HCl or H_2SO_4. Under these conditions, incorporation of bromine was not observed in the final product. Moreover, oxidation of 4-ethylaminoimidazole [ref. 54 (preparation for 2-amino-4-ethylimidazole); 55] with bromine produced parazoanthoxanthin A (1) and pseudozoanthoxanthin (2) in moderate yield. When the reaction was carried out in sulfuric acid at 23 °C, a 30 % yield of the dimer (22) was obtained. These results further manifest a stepwise process for the formation of zoanthoxanthins.

[0063] By developing the chemistry of 2-aminoimidazole, several important findings have been made. In general, we have discovered a method that allows introduction of alkyl sidechains to the 4,(5)-carbon of 2-aminoimidazole. The reaction appears general and involves a simple hydroxyalkylation of 2-aminoimidazole with the requisite aldehyde. This results in the formation of a new carbon-carbon bond. In particular, we have initially applied this methodology by demonstrating that zoanthoxanthins can be synthesized in a single step from commercially available 2-aminoimidazole sulfate and acetaldehydes. The mild reaction conditions under which these natural metabolites are formed suggest that the series of steps leading to these products parallel those found in nature. Due to the difficulties involved in culturing marine organisms, biosynthetic studies in the area of marine alkaloids are extremely rare. The biogenic chemistry developed here points to 2-aminoimidazole as a natural precursor to zoanthoxanthins.

SCHEME(3)

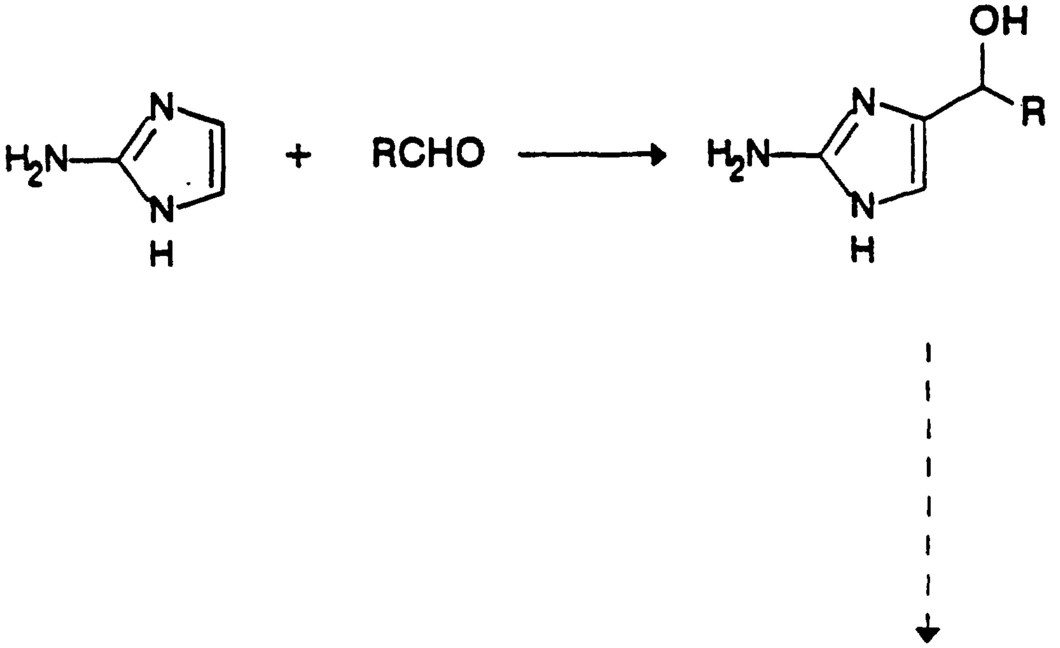

Br$_2$
HCL, 23 °C
10 MINUTES
H$_2$SO$_4$, 23 °C
10 MINUTES
Br$_2$
(16) TRANS
(17) CIS
REF. 30,56
+
GLYCOCYAMIDINE (11)
(18)
+
GLYCOCYAMIDINE (11)

SCHEME(3)



D. Methods

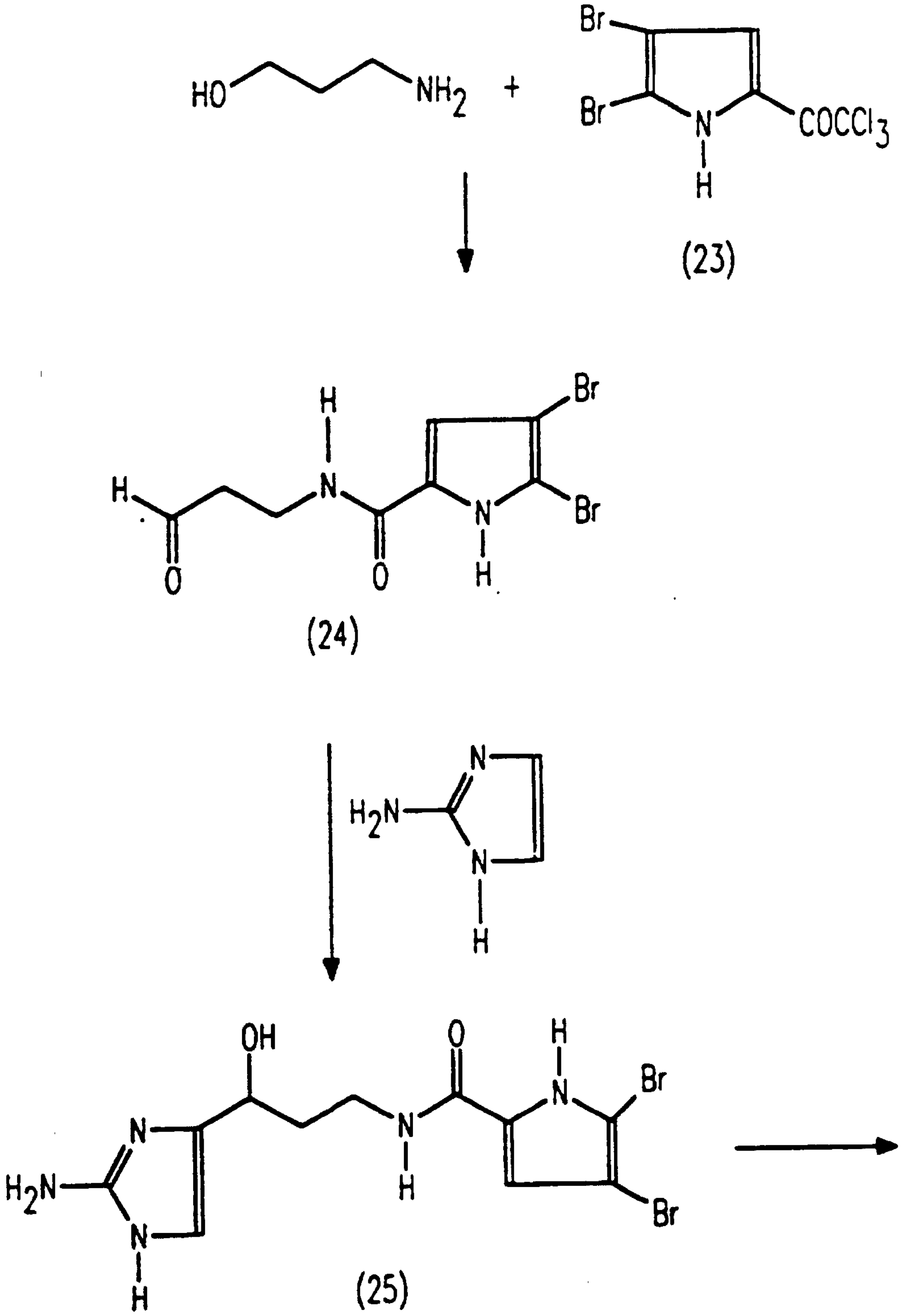
[0064] The basic elements entail coupling of 2-aminoimidazole with the requisite aldehyde and its ensuing transformation to the natural product. The hydroxyalkyl aminoimidazole constitutes a versatile intermediate, since it can be potentially converted to a vide variety of different marine alkaloid ring systems. This approach is likely biomimetic, and necessarily convergent for efficiency while potentially divergent for versatility. The general outline of this strategy is depicted below.



AMINOIMIDAZOLE MARINE NATURAL PRODUCTS

[0065] The constitution of the novel fused seven-membered ring lactams of the hymenin family is designed to test a likely biosynthetic pathway. The reactions are simple to carry out and are based on the aminoimidazole chemistry described in Section C. Formation of 2-amino-α-hydroxyalkyl imidazoles from 2-aminoimidazole and the corresponding aldehydes proceeds efficiently at 23 °C in neutral or acidic media. The resulting α-hydroxyalkyl aminoimidazole can be activated by acid or base catalysis to form, presumably, a reactive diazafulvene intermediate. In presence of nucleophiles, addition can occur at the α-position of the alkyl side chain. In the present case, R would be derived from a 3-carbon aldehyde linked to an amide pyrrole, Scheme (4). Scheme (4) shows the synthesis of hymen in (3), phakellin (27) and (28), and oroidin (29) marine alkaloids. This 3-carbon unit should be easily prepared from 3-aminopropanol and the trichloroacetylpyrrole (ref. 57, 58, 59). Condensation and oxidation of the resulting alcohol would give the desired aldehyde (24) of Scheme (4). By analogy with the hydroxyalkylation chemistry for the synthesis of zoanthoxanthins, aldehyde (24) would undergo facile transformation with 2-aminoimidazole giving the hydroxyalkyl derivative (25), Scheme (4). Dehydration of alcohol (25) under acidic conditions generates the active resonance stabilized intermediate (D), Scheme (4). In contrast to the intermolecular dimerization of intermediates seen in the zoanthoxanthin synthesis, the intermediate (D) possesses several nucleophilic groups that could intramolecularly add to the α-carbon. Attack at this position by the pyrrole carbon would give (±)-hymenin (3). Although the possible nucleophilic participation of the amide oxygen is anticipated, the resulting isoxazoline species (E), Scheme (4), would most likely be in equilibrium with species (D) in acidic media. This equilibration should facilitate formation of the 7-membered lactam ring system of (±)-hymenin (3).

SCHEME (4)

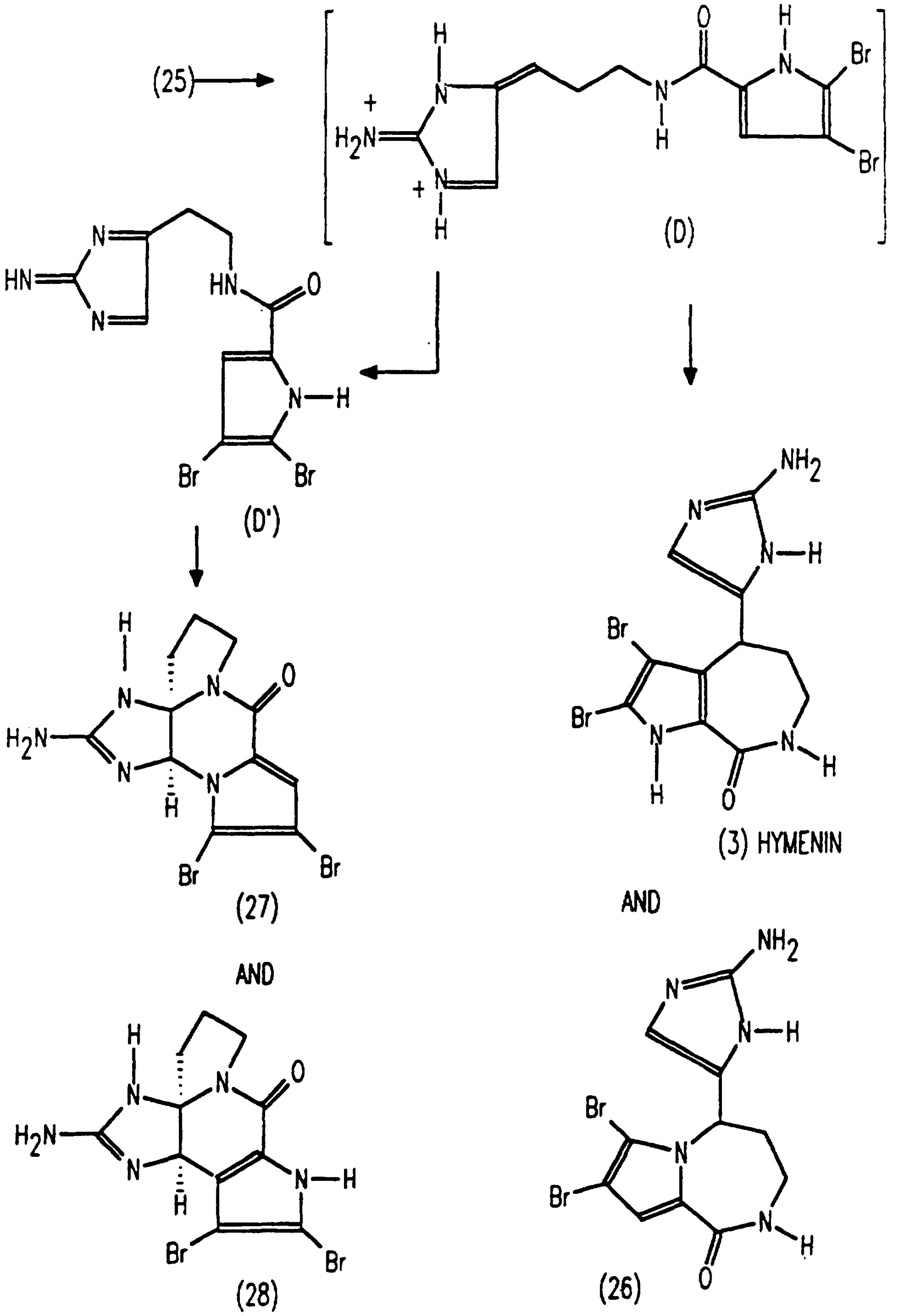


(23)

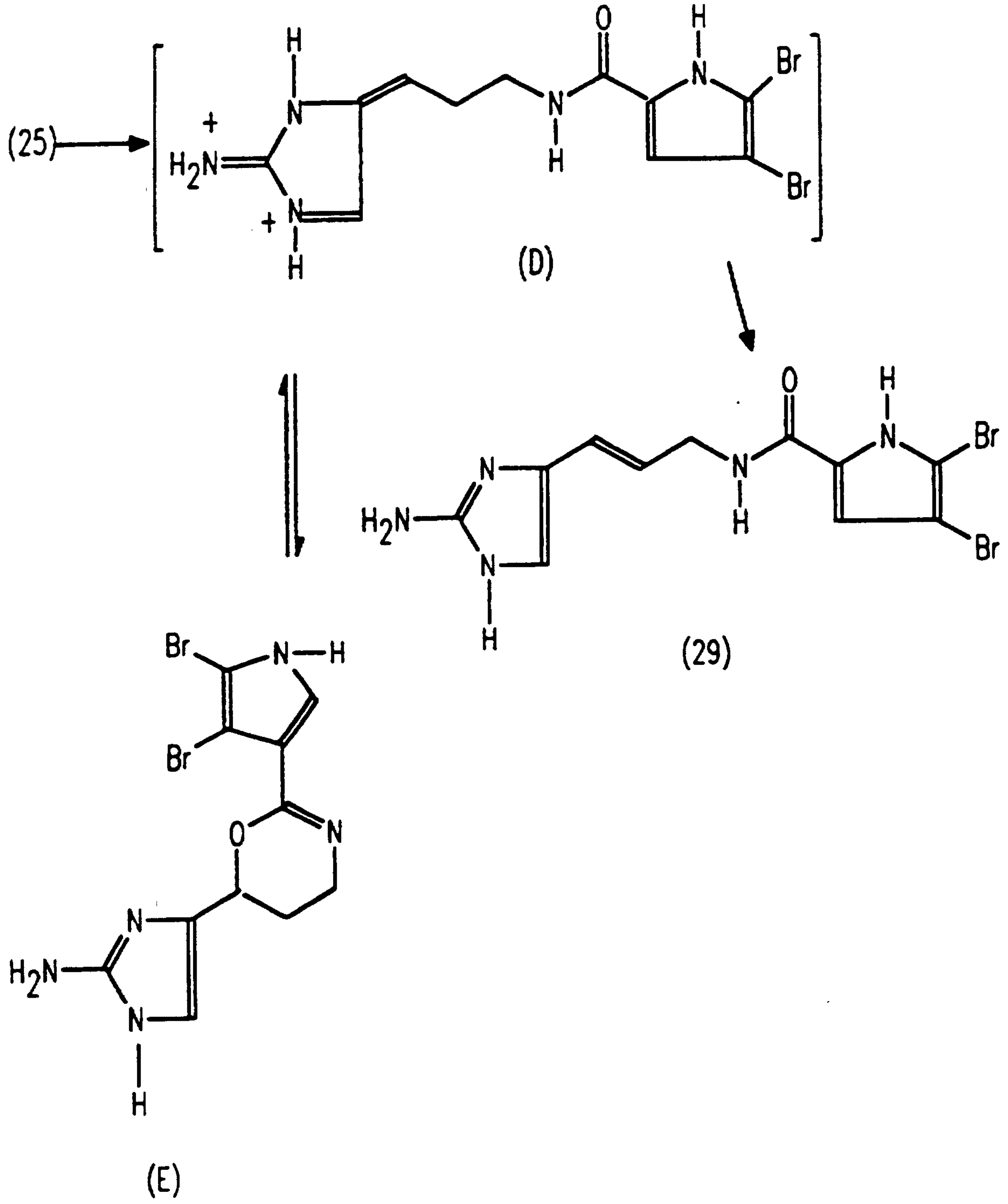
(24)

(25)

SCHEME (4)



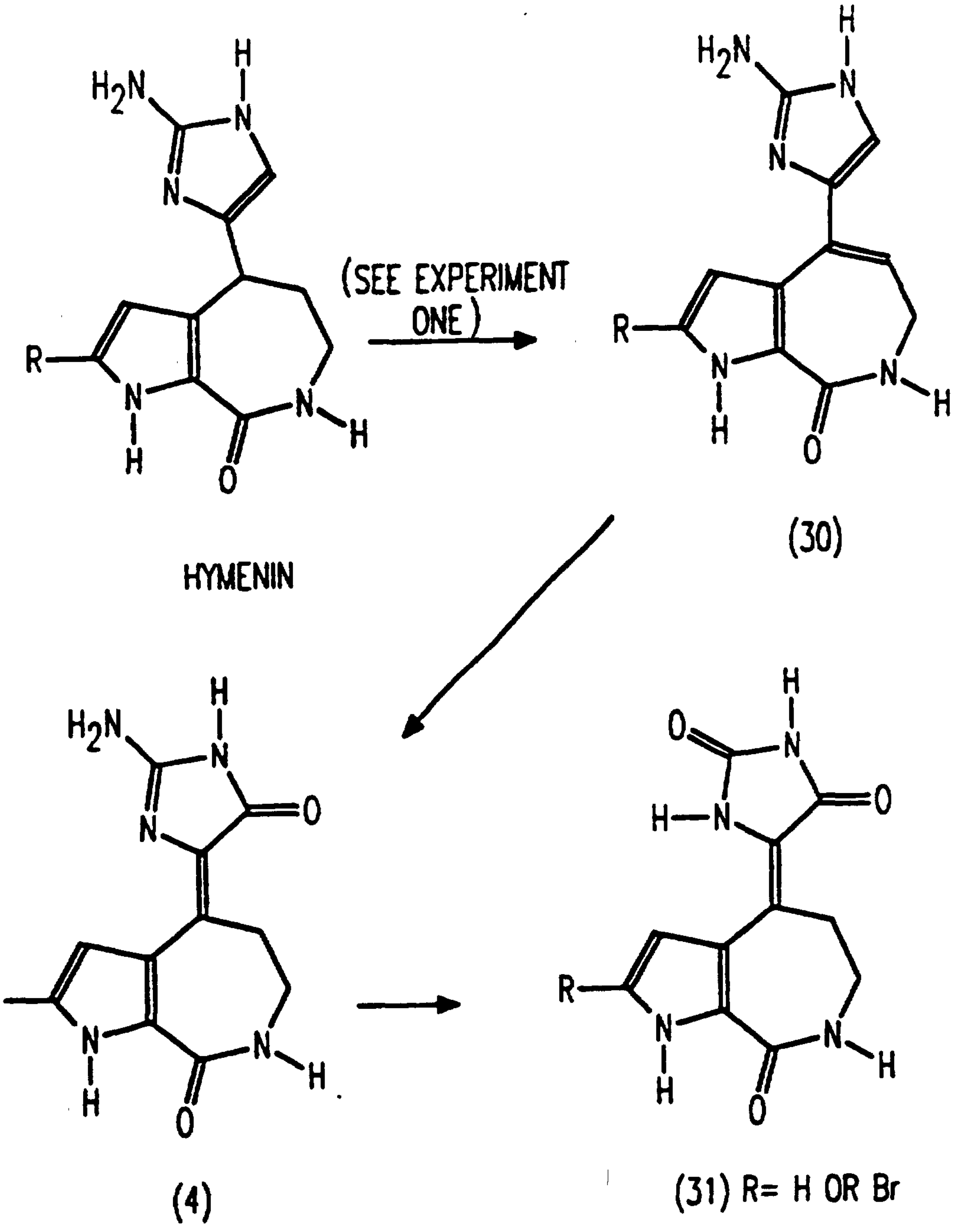
SCHEME (4)



[0066] At this point, we cannot rule out the possible attack by the pyrrole nitrogen leading to the lactam (26), Scheme (4), but the N-regioselection or the C-regioselection might be controlled by altering reaction conditions. Moreover, in the absence of strong acids, species (D) could tautomerize to species (D'), Scheme (4), from which the tetracyclic alkaloids (±)-dibromophakellin (27), Scheme (4), (ref. 37, 60, 61) and (±)-dibromocantheralline (28), Scheme (4), (ref. 37) (also known as dibromoisophakellin (ref. 62)) can be derived. The relative stereochemistry of ring closures should afford the more stable cis-fused A-B ring system of the natural product. In addition, preparation of oroidine (29), Scheme (4), (ref. 37, 63, 64) could proceed by elimination of alcohol (25), Scheme (4), under basic, non-nucleophilic conditions.

The generality of this strategy would be further demonstrated by synthesis of the related hymen in lactam natural products hymenialdisine (4) (R=Br), Scheme (5); debromohymenialdisine (R=H), Scheme (5) ; debromostevensine or monobromostevensine (30), Scheme (5), (ref. 37, 65) (also known as odiline); and axinohydantoin (31), Scheme (5), (R=Br), (ref. 8), Scheme (5). Scheme (5) shows the synthesis of hymenialdisines. The oxidation chemistry developed in Section C would be entirely applicable for transforming the forerunner hymenins (3) to its oxidative homologues (4), (30), and (31), Scheme (5).

SCHEME (5)



HYMENIN

(30)

(4)

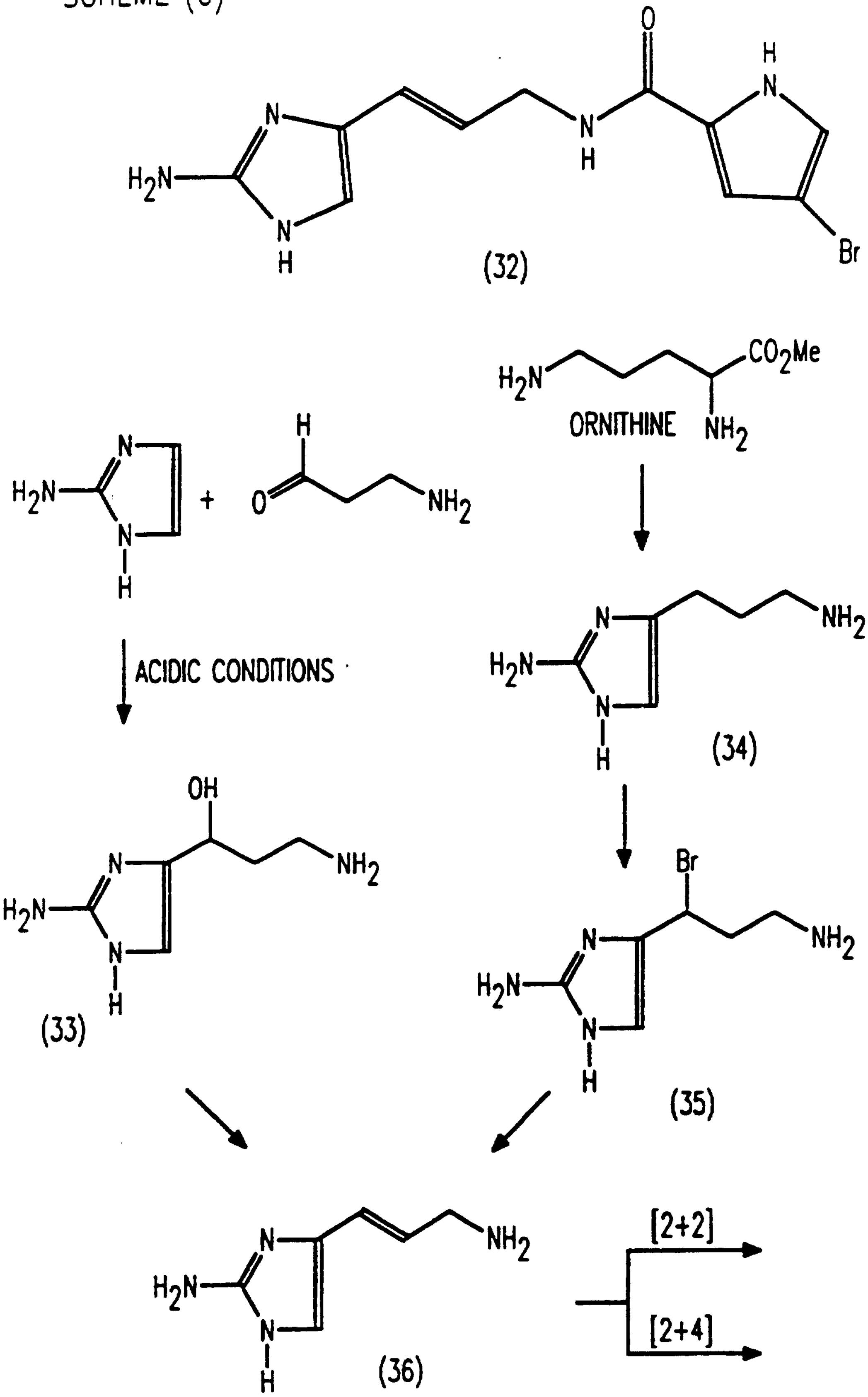
(31) R= H OR Br

Sceptrin (5), oxysceptrin (6), and ageliferins (7) could result from either a [2+2] or [2+4] head to head dimerization of hymenidin (32). The only previously reported attempt to initiate [2+2] photodimerizations of (29) was unsuccessful (ref. 38). Very few experimental details were given although the investigators concluded that the biosynthesis of sceptrin (5) is unlikely to involve such photodimerizations. Based on the chemistry described in the Preliminary Results Section (Section C), as well as in this section, one possible explanation for the hymenidin photocyclization failure is the intramolecular participation of the pyrrole moiety with the photoactivated alkene. Based on this rationale, aminoimidazole (36) which lacks the pyrrole unit, would be an excellent candidate for both thermal and photodimerizations to the 6-membered and 4-membered ring systems of ageliferins and sceptrins, respectively. The preparation of the intermediate (36) should be straightforward and follows completely analogous chemistry for hydroxyalkylation of 2-aminoimidazoles. An alternative route to aminoimidazole (36) begins with the methylester of ornithine. The patented procedure [ref. 55; see also ref. 54 (preparation for 2-amino-4-ethylimidazole)] for the synthesis of 4-substituted 2-aminoimidzoles from α-aminoesters should work well for the preparation of (34). By analogy with the radical bromination chemistry of 4-substituted 2-thioimidazoles (ref. 66), aminoimidazole (34) would undergo facile bromination at the α-carbon when exposed to N-bromosuccinimide (1-bromo-2,5-pyrrolidinedione; NBS) and benzoyl peroxide. Dehydrohalogenation of the resulting α-bromo derivative (35) under basic conditions would produce the desired E-olefin (36), Scheme (6). Scheme (6) shows the synthesis of sceptrin (5), oxysceptrin (6) and ageliferins (7).

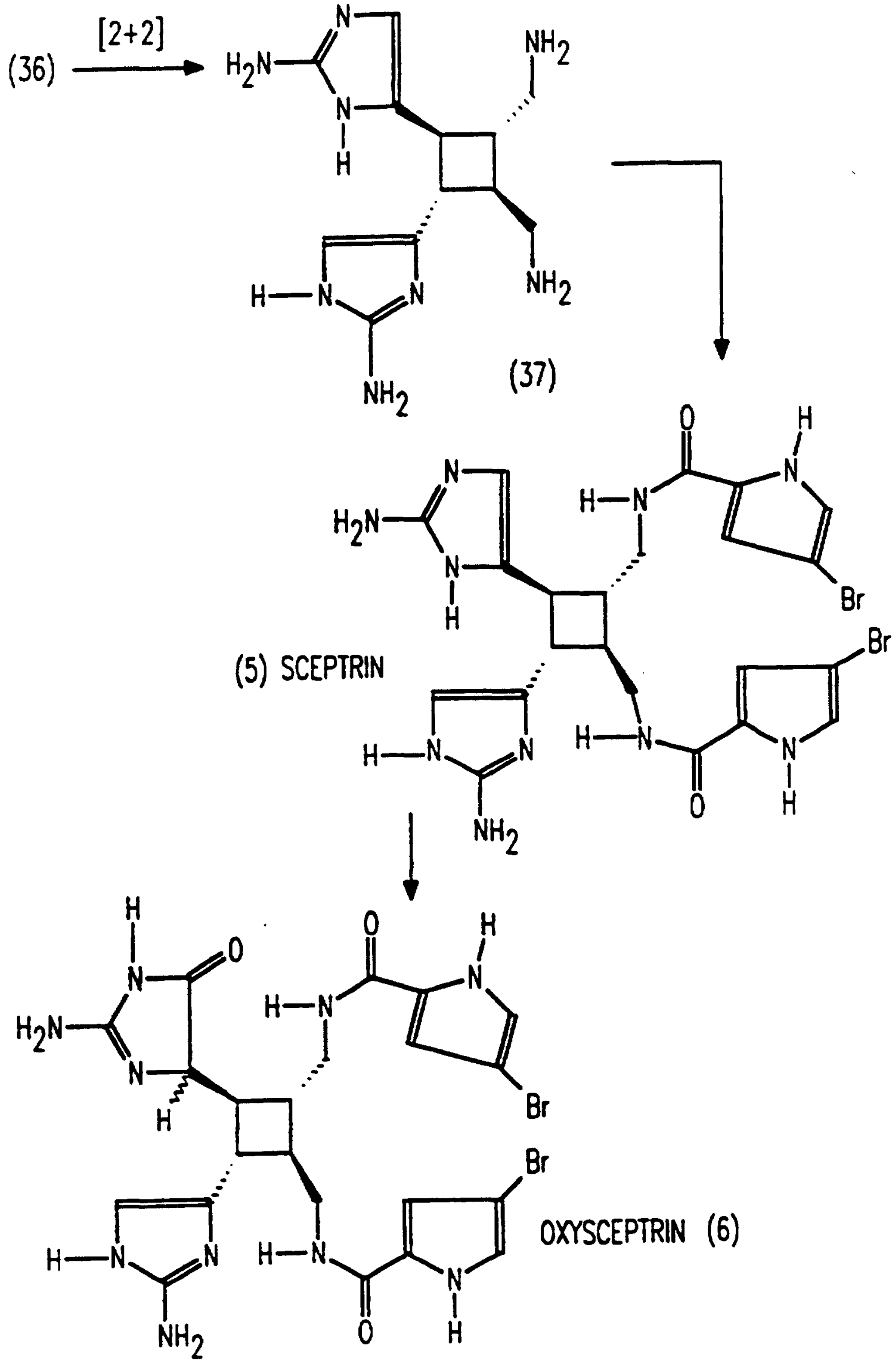
[0067] Imidazole (36) represents a versatile intermediate applicable to the synthesis of oroidin (29), hymenin (3), phakellins (27) and (28), sceptrin (5), and ageliferins (7). The recently isolated antitumor agent girolline (8) also appears to be progeny of (36) . Treatment of (36) with hypochlorite would give both the syn and anti chlorohydrins of girolline (6), Scheme (7). Scheme (7) shows the synthesis of girolline (8). An alternative route to (8) would involve hydroxyalkylation of chloroaldehyde (39) derived from alkylamine. Neither of these synthetic approaches appear to be diastereoselective.

[0068] For the construction of (±)-saxitoxin (9), a completely analogous sequence of hydroxyalkylations is envisaged and is outlined in Scheme 8. Starting from 2-aminoimidazoles, condensation of aldehyde (40) followed by oxidation of the resulting alcohol would give ketone (42), Scheme (9). Scheme (9) shows the synthesis of saxitoxin (9). At this point, we cannot predict with certainty whether formation of this ketone will deactivate the imidazole ring toward a second, necessary hydroxyalkylation. Results from our studies (see Section C) with acetaldehyde and 2-aminoimidazole indicate that introduction of two alkyl appendages to the 4-position and 5-position of the imidazole ring can proceed by bis-hydroxyalkylation of a non-deactivated aminoimidazole. Masking the ketone as its corresponding ketal should overcome any problems associated with diminished reactivity of the imidazole moiety in (42). The addition of glycoaldehyde (or equivalent) would give intermediate (43). Activated of this intermediate to species (F), Scheme (8), followed by a double intramolecular cyclization, as in the proposed synthesis of phakellins, would afford the more stable, cis-fused (tetrahydropurine) tricyclic ring system of (±)-saxitoxin. Scheme (8) shows the retrosynthetic strategy for the construction of saxitoxin (9). Final incorporation of the carbamate moiety has previously been described (ref. 47, 48).

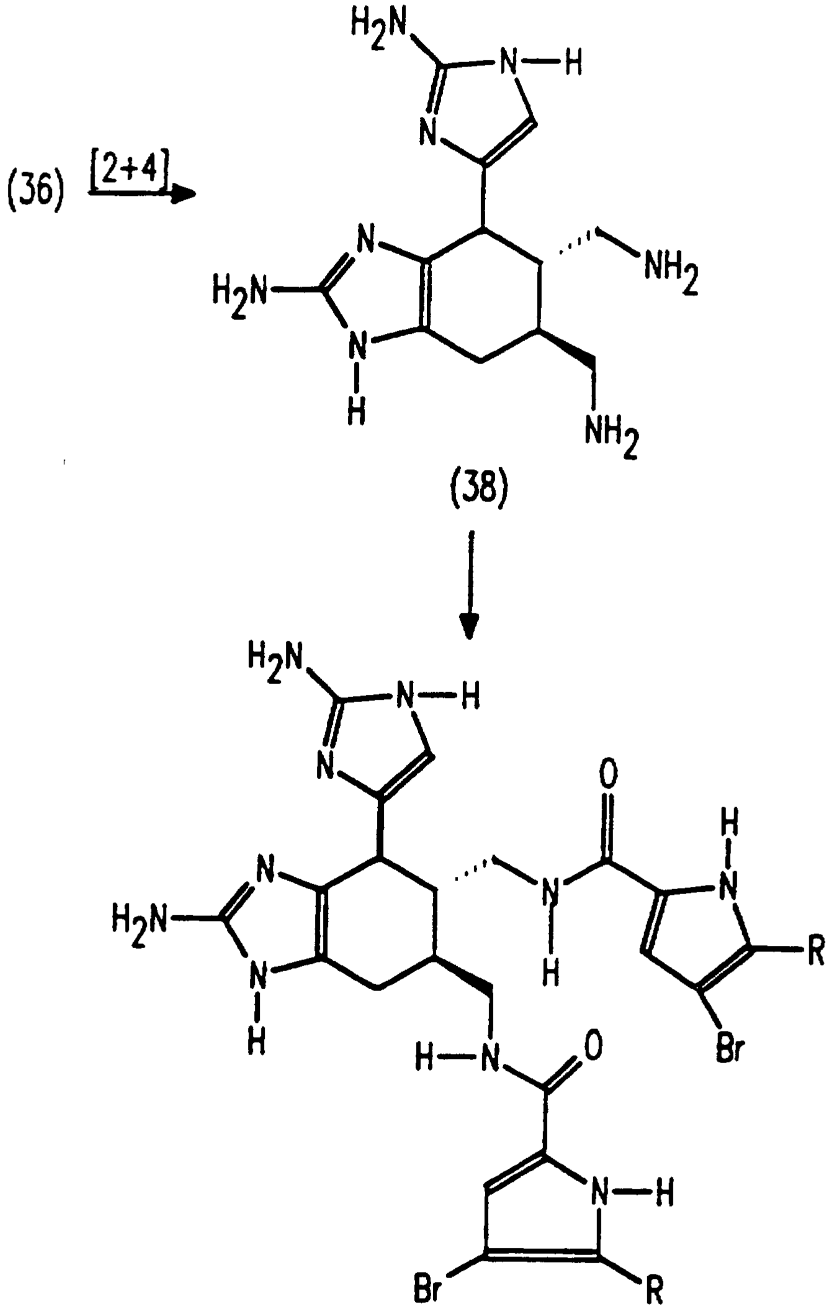
SCHEME (6)


O
H
N
H
H₂N
N
N
H
(32)
Br
H₂N
CO₂Me
ORNITHINE
NH₂
H
H₂N
N
N
H
+
O
NH₂
ACIDIC CONDITIONS
NH₂
(34)
OH
NH₂
(33)
Br
NH₂
(35)
NH₂
(36)
[2+2]
[2+4]

SCHEME (6)



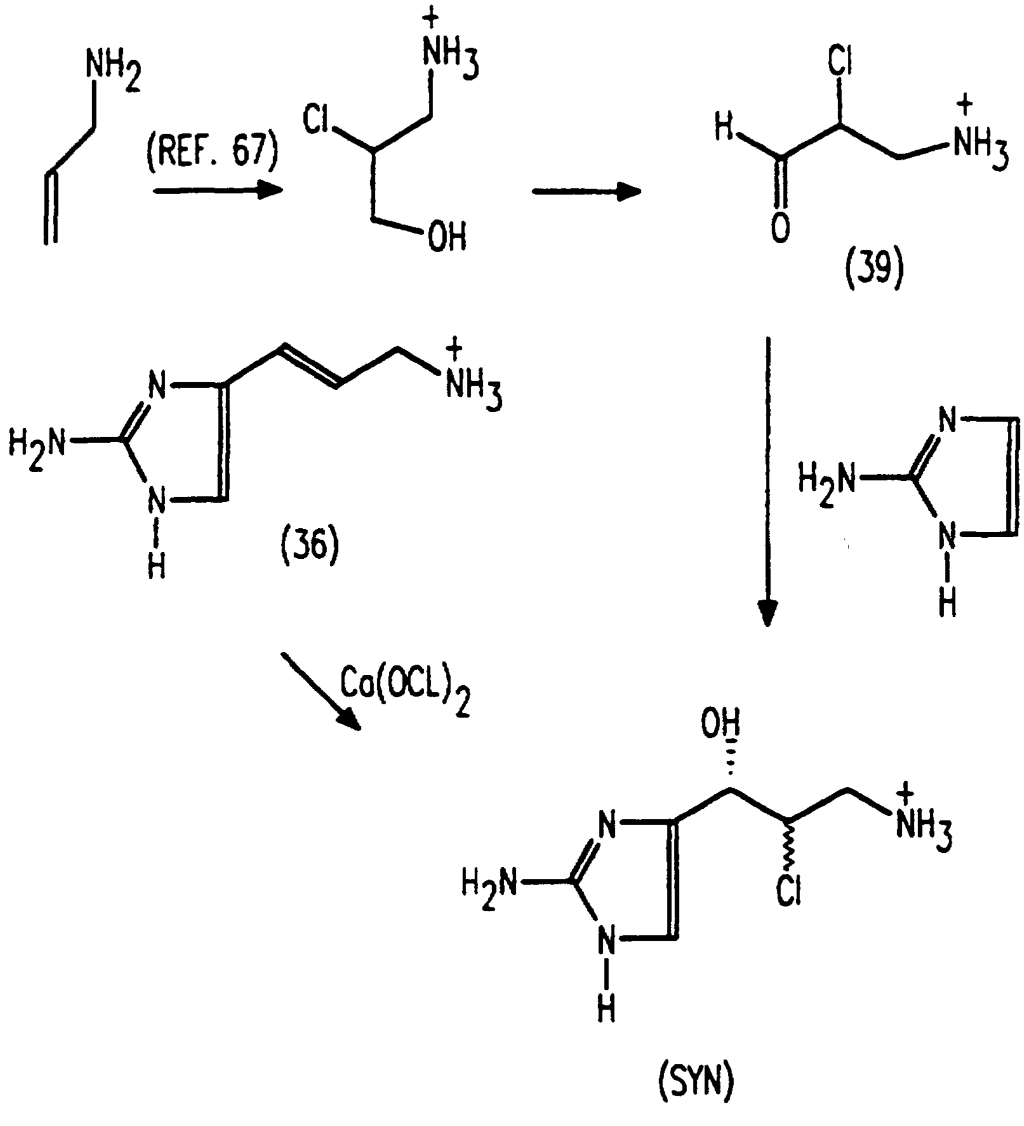
SCHEME (6)



R=H OR Br

AGELIFERINS

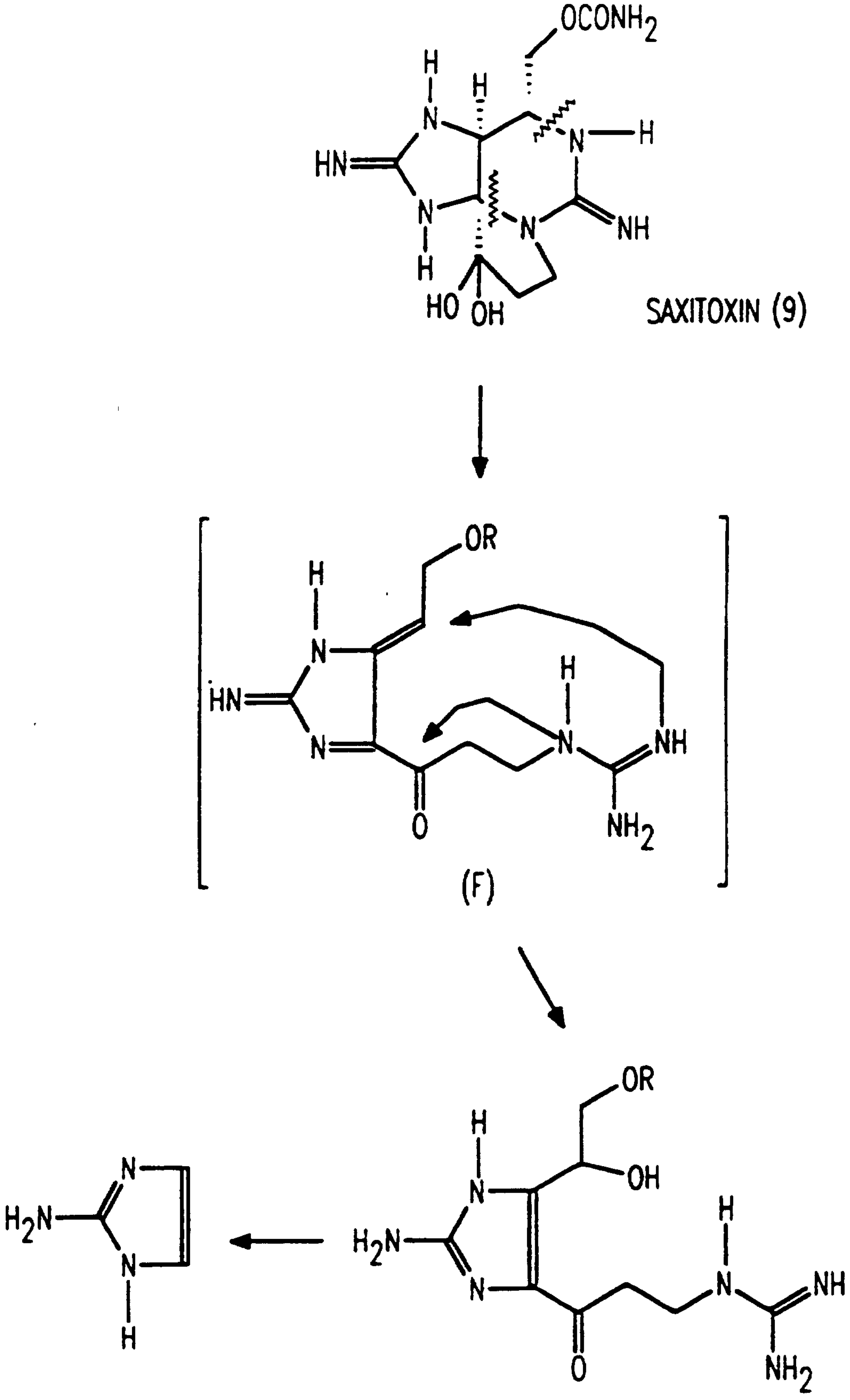
SCHEME (7)



(SYN)

(8) GIROLLINE

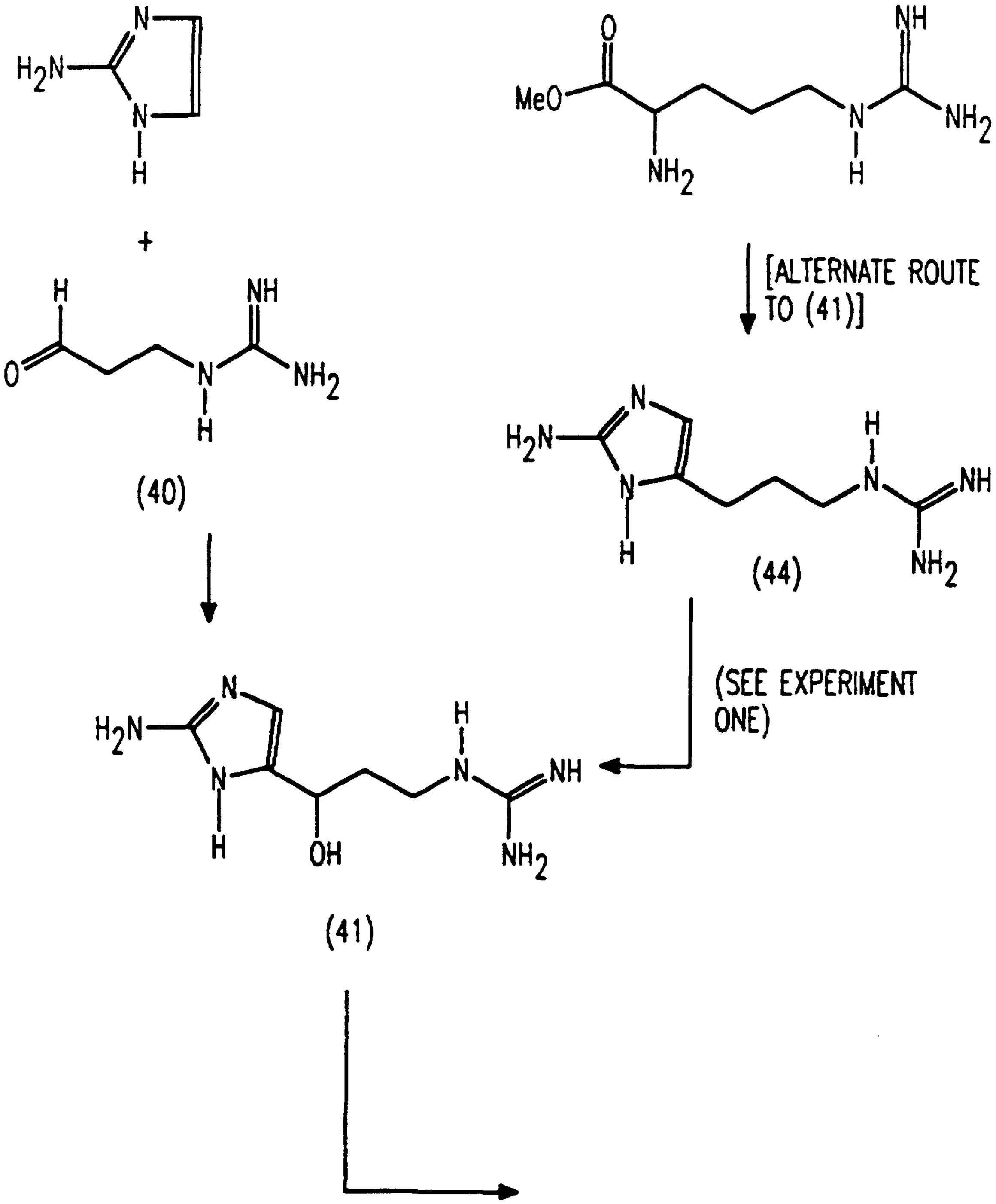
SCHEME (8)



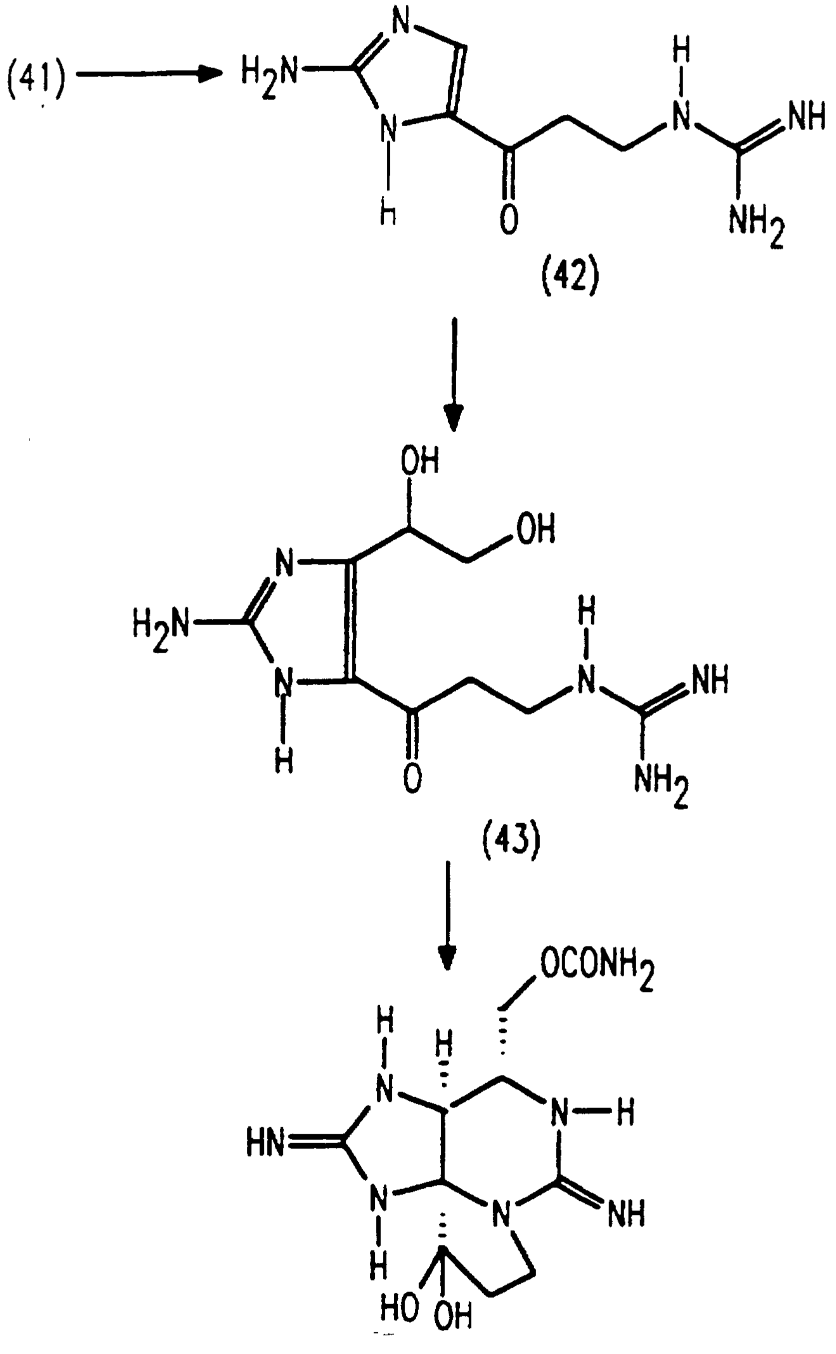
SAXITOXIN (9)

(F)

SCHEME (9)



SCHEME (9)



SAXITOXIN (9)

[0069] Figure 1 depicts the synthesis of the α-adrenoceptor antagonist (±)-hymenin (16), a 2-aminoimidazole marine natural product with antihypertension activity. There are two important reactions in this synthetic scheme, neither of which has been previously described. The first is an acid-promoted intramolecular cyclization and dehydration of pyrrole aldehyde (14) to give the cyclic olefin (15). As in the imidazoazepine series, this reaction can also be generalized to include a wide variety of substituted pyrroles differing in R_A and R_B as well as in the size of the newly formed ring (Figure 3). The second equally important step in this synthesis involves the coupling of olefin (15) with 2-aminoimidazole (AI) under acidic conditions to give (±)-hymenin (16). This reaction is yet another example that illustrates the utility of using 2-aminoimidazole (AI) in combination with active electophiles as starting materials for the synthesis of 2-aminoimidazole derived natural products. Moreover, these two steps can be combined into one operation in which the combination of aldehyde (14) and AI produces (±)-hymenin (16) in a 'single pot' (eq. VI). This eliminates the need for isolation of potential intermediate (15). Figure 1 depicts the synthesis of compounds made and described below.

[0070] As discussed earlier, a large number of 2-aminoimidazole alkaloids have been isolated from marine sources. Most importantly, these metabolites have been shown to possess a myriad of biological activities.

[0071] Figure 2 depicts the process for preparing the bicyclic pyrrole compound of the subject invention, wherein, n is an integer from 1 to about 6;
wherein R_5 and R_6 are the same or different, and are H; a C_1 to about C_{10} straight chain alkyl group or branched alkyl groups, which alkyl groups are substituted or unsubstituted; or halogen.

[0072] Regarding bicyclic pyrrole compound, the subject invention provides that the alkyl groups may be substituted with halogen, alcohol, alkoxy, dialkyl amine, alkyl aryl amine, diaryl amine, thiol, or sulfide groups.

Ketal (13 of Figure 1)

[0073] A 25 ml acetonitrile solution of trichloroacetylpyrrole (11) (11 mmol) [prepared from (ref. 57: Bailey, D.M., et al., Journal Of Medicinal Chemistry, (1973), vol. 16, pages 1300-1302], aminoketal (12) (10 mmol) [commercial], and triethylamine (30 mmol) was stirred at 25 °C for 24 h under argon. The mixture was partitioned between 150 ml of methylene chloride and 100 ml of 5 % (aq.) citric acid. The organic layer was washed with sat. $NaHCO_3$ and dried ($MgSO_4$). Concentration afforded a solid which was recrystallized from acetone/methylene chloride to give (13) (80 % yield) as a colorless solid, mp 155-157 °C. ^1H NMR (300 MHz, CD_3OD) δ 2.73 (td, J=4.7 Hz, 7.1Hz, 2H) , 3.42 (t, J-7.1 Hz, 2H), 3.83 (m, 2H), 3.95 (m, 2H), 4.90 (t, J=4.7 Hz, 1H), 6.76 (s, 1H).
IR (Nujol) cm^{-1} 3358, 3110, 1646, 1569, 1530, 1433, 1412, 1372, 1328, 1244, 1136, 905, 837.
MS (DCI, CH4) m/z 369 (M^++3, 100), 367 (M^++1, 48), 289 (13).

Aldehyde (14 of Figure 1)

[0074] A 70 ml acetone/water (1/1) solution of ketal (13) (10 mmol) and p-toluene sulfonic acid monohydrate (5 mmol) was refluxed for 8 h. The solution was poured into 350 ml of methylene chloride, washed with 100 ml of sat. $NaHCO_3$, and dried over $MgSO_4$. Concentration afforded a solid which was recrystallized from ethyl acetate / methylene chloride to give (14) (85 % yield) as a colorless solid, mp 160-163 °C.
^1H NMR (300 MHz, Acetone-D_6) δ 2.73 (td, J=6.5 Hz, 1.5 Hz, 2H), 3. 63 (q, J-6.5 Hz, 2H), 6.85 (d, J=2.9 Hz, 1H), 7.63 (br, 1H), 9.75 (t, J=1.5 Hz, 1H), 11.73 (br, 1H). ^{13}C NMR (300 MHz, Acetone-D_6) δ 33.9, 44.3, 99.5, 105.6, 113.3, 128.8, 160.3, 201.6.

Bromopyrrole (15 of Figure 1) (R_1 = R_2 = Br)

[0075] A solution of aldehyde (14) (10 mmol) in 5 ml of methane sulfonic acid was stirred at 25 °C under argon for 3 days. The reaction mixture neutralized with sat. $NaHCO_3$ and extracted with 200 ml of methylene chloride. The organic layer was dried over $MgSO_4$ and concentrated to afford a solid. Silica gel chromatography of the solid with CH_2Cl_2 / $MeOH(NH_3)$, 9/1, as the eluent gave (15) a colorless solid in 82 % yield.
mp 172-175 °C (dec).
^1H NHR (300 MHz, CD_3OD) δ 3.57 (d, J=6.4 Hz, 2H), 6.01 (dt, J=10.1 Hz, 6.4 Hz, 1H), 6.65 (d, J=10.1 Hz, 1H).
^{13}C NMR (300 MHz, CD_3OD) δ 39.6, 100.2, 108.4, 126.4, 126.7, 126.8, 127.0, 164.6.
IR (Nujol) cm^{-1} 3270, 3184, 3020, 1639, 1603, 1541, 1477, 1419, 1265, 1146, 921.
MS (DCI, CH4) m/z 307 (M^++3, 100), 305 (M^++1, 55), 278 (20) , 264 (22).

(±)-Hymenin (16 of Figure 1) (From Pyrrole (15 of Figure 1))

[0076] A solution of aldehyde (14) ((14) is also called a pyrrole) (10 mmol) and 2-aminoimidazole sulfate (12 mmol) in 5 ml of methane sulfonic acid was stirred at 25 °C under argon for 5 days. The reaction was neutralized with sat. $NaHCO_3$ and concentrated to afford a solid. The solid was taken up in 75 ml of ethanol, filtered and the filtrate was concentrated. Silica gel chromatography of the resulting residue with CH_2Cl_2 / $MeOH(NH_3)$, 8/2, afforded a 76 % yield

of (±)-hymenin (16) as a solid, mp 86-90 °C (dec),
^1H NMR (300 MHz, CD_3OD) δ 1.92 (m,1H), 2.25 (m, 1H), 3.06 (dd, J-14.0 Hz, 7.3 Hz, 1H), 3.16 (dd, J=14.0 Hz, 9.8 Hz, 1H), 4.12 (t, J=3.5 Hz, 1H), 5.88 (s, 1H)
^{13}C NMR (300 MHz, CD_3OD) 32.7, 37.9, 38.4, 102.8, 107.7, 113.0, 125.3, 128.5, 136.8, 150.6, 164.2.
IR (Nujol) cm^{-1} 3360, 3270, 3150, 1676, 1625, 1566, 1481, 1425, 1327, 1216, 1095, 949.
MS (DCI, CH_4) m/z 390 (M^++3, 50), 388 (M^++1, 35), 312 (22), 112 (100).

(±)-Hymenin (16 of Figure 1) (From Aldehyde 14 of Figure 1)

[0077] The process described here for (±)-Hymenin (16) (From Aldehyde (14)) represents the most preferable process. A solution of aldehyde (14) (10 mmol) and 2-aminoimidazole sulfate (12 mmol) in 5 ml of methane sulfonic acid was stirred at 25 °C under argon for 5 days. The reaction was neutralized with sat. $NaHCO_3$ and concentrated to afford a solid. The solid was taken up in 75 ml of ethanol, filtered and the filtrate was concentrated. Silica gel chromatography of the resulting residue with CH_2Cl_2 / MeOH(NH_3), 8/2, afforded a 63 % yield of (±)-hymenin (16) as a solid, mp 86-90 °C (dec), ^1H NMR (300 MHz, CD_3OD) δ 1.92 (m, 1H), 2.25 (m, 1H), 3.06 (dd, J=14.0 Hz, 7.3 Hz, 1H), 3.16 (dd, J=14.0 Hz, 9.8 Hz, 1H), 4.12 (t, J=3.5 Hz, 1H), 5.88 (s, 1H)
^{13}C MMR (300 MHz, CD_3OD) 32.7, 37.9, 38.4, 102.8, 107.7, 113.0, 125.3, 128.5, 136.8, 150.6, 164.2.
IR (Nujol) cm^{-1} 3360, 3270, 3150, 1676, 1625, 1566, 1481, 1425, 1327, 1216, 1095, 949.
MS (DCI, CH_4) m/z 390 (M^++3, 50), 388 (M^++1, 35), 312 (22), 112 (100) .

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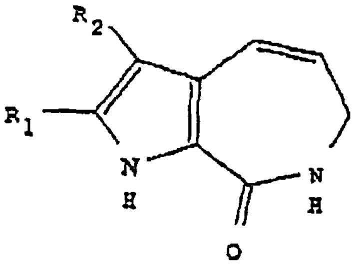
72. WO 87/07274

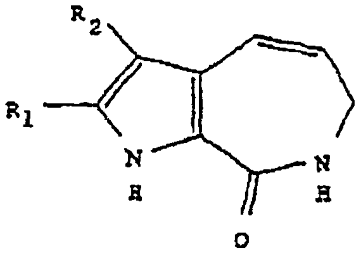
Claims

1. A compound having the structure:



wherein R_1 and R_2 are the same or different, and are H, a substituted or unsubstituted C_1 to C_{10} straight chain alkyl group or branched alkyl group, or halogen.

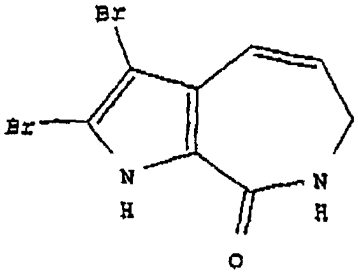
2. A compound according to claim 1 having the structure :



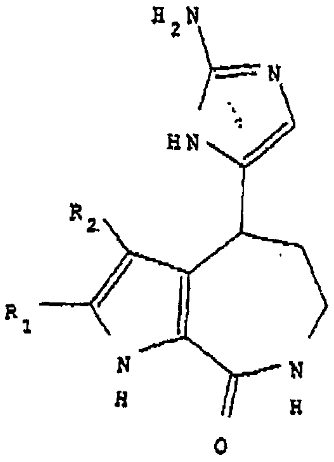
wherein R_1 is H, a substituted or unsubstituted C_1 to C_{10} straight chain alkyl group or branched alkyl group, or halogen, and
wherein R_2 is a substituted or unsubstituted C_1 to C_{10} straight chain alkyl group or branched alkyl group, or halogen.

3. The compound of claim 1, wherein the alkyl groups are substituted with halogen, hydroxy, alkoxy, dialkyl amino, alkyl aryl amino, diaryl amino, mercapto, or alkylmercapto groups.

4. The compound of claim 1 having the structure:



5. A method of using the compound of claim 1 to prepare a hymenin compound having the structure:



comprising reacting one molecular equivalent of the compound of claim 2 or claim 4 with one molecular equivalent of 2-aminoimidazole or a salt of 2-aminoimidazole in a solvent wherein the solvent is methane sulfonic acid, trifluoroacetic acid, or trifluoromethane sulfonic acid, to form the hymenin compound.

6. The method of claim 5 wherein the process is performed at a temperature from 0°C to 100°C.

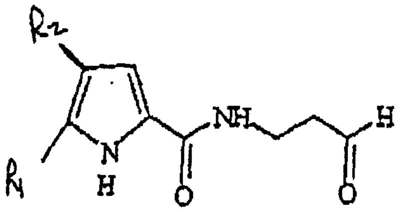
7. The method of claim 5 wherein the process is performed for a reaction time of 3-5 days.

8. The method of claim 5 wherein the solvent is saturated with inert gas.

9. The method of claim 5 wherein R_1 and R_2 are Br.

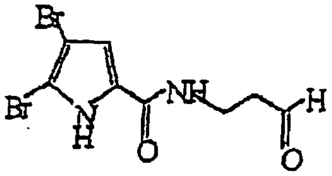
10. The method of claim 5 wherein R_1 and R_2 are H.

11. A compound having the structure :



wherein R_1 and R_2 are the same or different, and are H, a substituted or unsubstituted C_1 to C_{10} straight chain alkyl group or branched alkyl group, or halogen.

12. The compound of claim 11 having the structure:

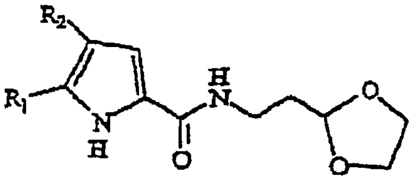


13. The compound of claim 11, wherein the alkyl groups are substituted with halogen, hydroxy, alkoxy, dialkyl amino,

alkyl aryl amino, diaryl amino, mercapto, or alkylmercapto groups.

14. The process for preparing the compound of claim 11, wherein R_1 and R_2 are the same as defined for the compound; which process comprises:

reacting one molecular equivalent of a ketal having the structure



with 0.5 molecular equivalent of p-toluene sulfonic acid monohydrate, at a temperature of about 0°C to about 100°C,

in a solvent, wherein the solvent is a mixture of water and a polar nonhydroxylic organic solvent, and the volume ratio of the water and the polar nonhydroxylic organic solvent is from about 1/10 to about 10/1,

to form the compound.

15. The process of claim 14, wherein the polar nonhydroxylic organic solvent is N,N-dimethylformamide; dioxane; tetrahydrofuran; dimethylsulfoxide; or acetonitrile.

16. The process of claim 14, wherein the volume ratio of the water and the polar nonhydroxylic organic solvent is from about 40/60 to about 60/40.

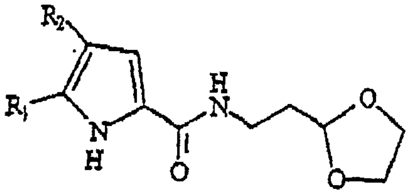
17. The process of claim 14, wherein the solvent is a mixture of water and acetone in a volume ratio of from about 40/60 to about 60/40.

18. The process of claim 14 , therein the temperature is about 80°C to about 100°C.

19. The process of claim 14, wherein the process is performed for a reaction time of from about 3 hours to about 24 hours.

20. The process of claim 14 , wherein the process is performed for a reaction time of from about 6 hours to about 10 hours.

21. A ketal compound having the structure:

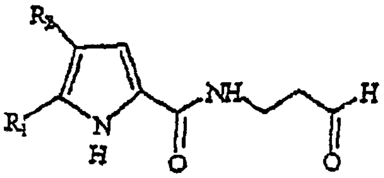


wherein R_1 and R_2 are the same or different, and are H, a substituted or unsubstituted C_1 to C_{10} straight chain alkyl group or branched alkyl group, or halogen.

22. The compound of claim 21, wherein the alkyl groups are substituted with halogen, hydroxy, alkoxy, dialkyl amino, alkyl aryl amino, diaryl amino, mercapto, of alkylmercapto groups.

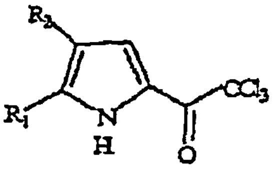
23. A process for preparing the bicyclic pyrrole compound of any one of claims 1 to 4, wherein R_1 and R_2 are the same as defined in claim 2, which process comprises:

reacting a pyrrole having the structure

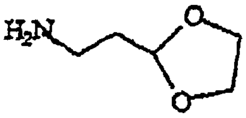


in a solvent, wherein the solvent is methanesulfonic a cid, trifluoroacetic acid, or trifluoromethanesulfonic acid, to form the bicyclic pyrrole compound.

24. A process for preparing the ketal of claim 21 or 22 , wherein R_1 and R_2 are the same as defined for the ketal; which process comprises: reacting one molecular equivalent of a trichloroacetylpyrrole having the structure

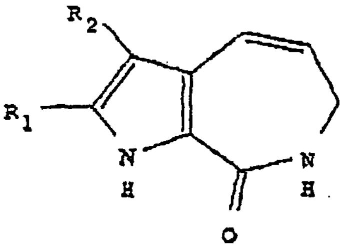


with one molecular equivalent of an aminoketal having the structure



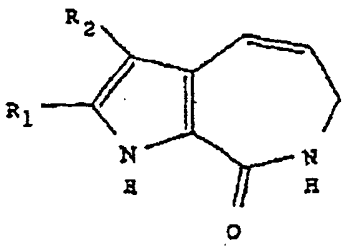
Patentansprüche

1. Verbindung der Struktur:



wobei R_1 und R_2 gleich oder verschieden sind und ein Wasserstoffatom, ein substituierter oder nicht substituierter, unverzweigter oder verzweigter C_{1-10}-Alkylrest oder ein Halogenatom sind.

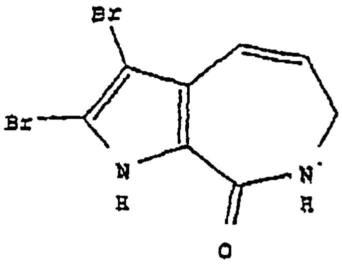
2. Verbindung gemäß Anspruch 1 der Struktur:



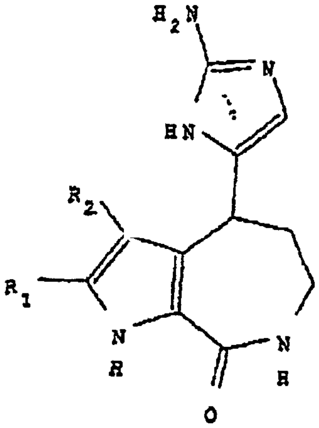
wobei R_1 ein Wasserstoffatom, ein substituierter oder nicht substituierter, unverzweigter oder verzweigter $C_{1\text{-}10}$-Alkylrest oder ein Halogenatom ist, und
wobei R_2 ein substituierter oder nicht substituierter, unverzweigter oder verzweigter $C_{1\text{-}10}$-Alkylrest oder ein Halogenatom ist.

3. Verbindung gemäß Anspruch 1, wobei die Alkylreste mit Halogen-, Hydroxy-, Alkoxy-, Dialkylamino-, Alkylarylamino-, Diarylamino-, Mercapto- oder Alkylmercaptoresten substituiert sind.

4. Verbindung gemäß Anspruch 1 der Struktur:



5. Verfahren zur Verwendung der Verbindung gemäß Anspruch 1 zur Herstellung einer Hymeninverbindung der Struktur:



umfassend das Umsetzen eines Moläquivalents der Verbindung gemäß Anspruch 2 oder 4 mit einem Moläquivalent 2-Aminoimidazol oder einem Salz von 2-Aminoimidazol in einem Lösungsmittel, wobei das Lösungsmittel Methansulfonsäure, Trifluoressigsäure oder Trifluormethansulfonsäure ist, um die Hymeninverbindung zu erzeugen.

6. Verfahren gemäß Anspruch 5, wobei das Verfahren bei einer Temperatur von 0 °C bis 100 °C durchgeführt wird.

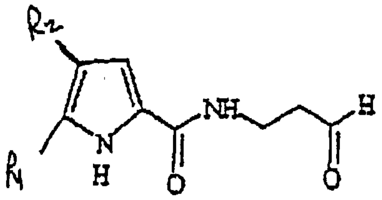
7. Verfahren gemäß Anspruch 5, wobei das Verfahren für eine Reaktionszeit von 3 bis 5 Tagen durchgeführt wird.

8. Verfahren gemäß Anspruch 5, wobei das Lösungsmittel mit einem inerten Gas gesättigt ist.

9. Verfahren gemäß Anspruch 5, wobei R_1 und R_2 Bromatome sind.

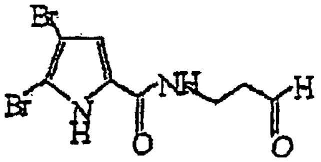
10. Verfahren gemäß Anspruch 5, wobei R_1 und R_2 Wasserstoffatome sind.

11. Verbindung der Struktur:



wobei R_1 und R_2 gleich oder verschieden sind und ein Wasserstoffatom, ein substituierter oder nicht substituierter, unverzweigter oder verzweigter C_{1-10}-Alkylrest oder ein Halogenatom sind.

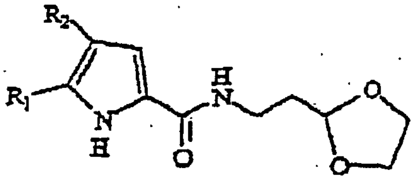
12. Verbindung gemäß Anspruch 11 der Struktur:



13. Verbindung gemäß Anspruch 11, wobei die Alkylreste mit Halogen-, Hydroxy-, Alkoxy-, Dialkylamino-, Alkylarylamino-, Diarylamino-, Mercapto- oder Alkylmercaptoresten substituiert sind.

14. Verfahren zur Herstellung der Verbindung gemäß Anspruch 11, wobei R_1 und R_2 die gleichen Reste sind, wie für die Verbindung definiert; wobei das Verfahren umfasst:

Umsetzen eines Moläquivalents eines Ketals der Struktur



mit 0,5 Moläquivalent p-Toluolsulfonsäuremonohydrat bei einer Temperatur von etwa 0 °C bis etwa 100 °C in einem Lösungsmittel, wobei das Lösungsmittel ein Gemisch aus Wasser und einem polaren, nicht-hydroxylischen organischen Lösungsmittel ist und das Volumenverhältnis von Wasser und dem polaren, nicht-hydroxylischen organischen Lösungsmittel etwa 1/10 bis etwa 10/1 ist; um die Verbindung zu erzeugen.

15. Verfahren gemäß Anspruch 14, wobei das polare, nicht-hydroxylische organische Lösungsmittel N,N-Dimethylformamid; Dioxan; Tetrahydrofuran; Dimethylsulfoxid oder Acetonitril ist.

16. Verfahren gemäß Anspruch 14, wobei das Volumenverhältnis von Wasser und dem polaren, nicht-hydroxylischen

organischen Lösungsmittel etwa 40/60 bis etwa 60/40 ist.

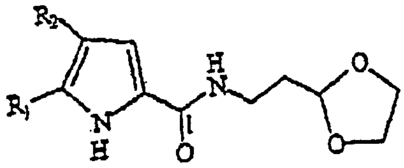
17. Verfahren gemäß Anspruch 14, wobei das Lösungsmittel ein Gemisch aus Wasser und Aceton in einem Volumenverhältnis von etwa 40/60 bis etwa 60/40 ist.

18. Verfahren gemäß Anspruch 14, wobei die Temperatur bei etwa 80 °C bis etwa 100 °C liegt.

19. Verfahren gemäß Anspruch 14, wobei das Verfahren für eine Reaktionszeit von etwa 3 Stunden bis etwa 24 Stunden durchgeführt wird.

20. Verfahren gemäß Anspruch 14, wobei das Verfahren für eine Reaktionszeit von etwa 6 Stunden bis etwa 10 Stunden durchgeführt wird.

21. Ketal Verbindung der Struktur:

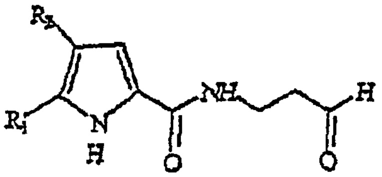


wobei R_1 und R_2 gleich oder verschieden sind und ein Wasserstoffatom, ein substituierter oder nicht substituierter, unverzweigter oder verzweigter C_{1-10}-Alkylrest oder ein Halogenatom sind.

22. Verbindung gemäß Anspruch 21, wobei die Alkylreste mit Halogen-, Hydroxy-, Alkoxy-, Dialkylamino-, Alkylarylamino-, Diarylamino-, Mercapto- oder Alkylmercaptoresten substituiert sind.

23. Verfahren zur Herstellung der bicyclischen Pyrrolverbindung gemäß einem der Ansprüche 1 bis 4, wobei R_1 und R_2 die gleiche wie in Anspruch 2 definierte Bedeutung haben, wobei das Verfahren umfasst:

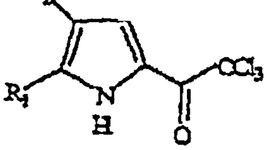
Umsetzen eines Pyrrols der Struktur



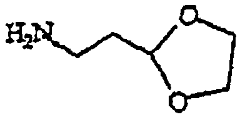
in einem Lösungsmittel, wobei das Lösungsmittel Methansulfonsäure, Trifluoressigsäure oder Trifluormethansulfonsäure ist, um die bicyclische Pyrrolverbindung zu erzeugen.

24. Verfahren zur Herstellung des Ketals gemäß Anspruch 21 oder 22, wobei R_1 und R_2 die gleichen Reste sind, wie für das Ketal definiert; wobei das Verfahren umfasst:

Umsetzen eines Moläquivalents eines Trichloracetylpyrrols der Struktur

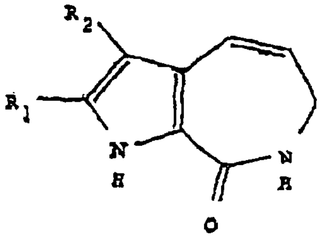


mit einem Moläquivalent eines Aminoketals der Struktur



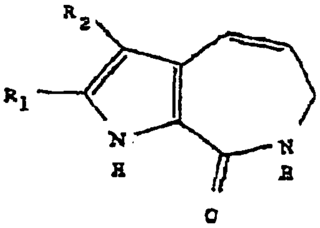
Revendications

1. Composé ayant la structure :



dans laquelle R_1 et R_2 sont identiques ou différents et représentent H, un groupe alkyle linéaire ou ramifié en C_1 à C_{10}, substitué ou non substitué, ou un halogène.

2. Composé selon la revendication 1 ayant la structure :

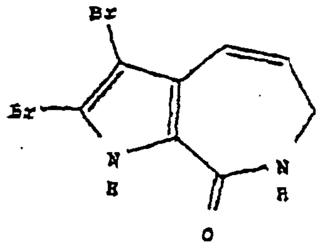


dans laquelle R_1 est H, un groupe alkyle linéaire ou ramifié en C_1 à C_{10}, substitué ou non substitué, ou un halogène, et

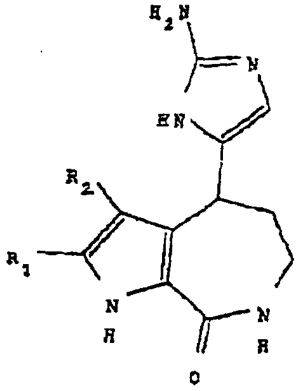
dans laquelle R_2 est un groupe alkyle linéaire ou ramifié en Ci à C_{10}, substitué ou non substitué, ou un halogène.

3. Composé de la revendication 1 dans lequel les groupes alkyle sont substitués par des groupes halogène, hydroxy, alkoxy, dialkylamino, alkylarylamino, diarylamino, mercapto, ou alkylmercapto.

4. Composé de la revendication 1 ayant la structure :



5. Procédé d'utilisation du composé de la revendication 1 pour la préparation d'un composé du type hyménine ayant la structure :



comportant la réaction d'un équivalent moléculaire du composé de la revendication 2 ou la revendication 4 avec un équivalent moléculaire de 2-aminoimidazole ou d'un sel de 2-aminoimidazole dans un solvant, le solvant étant l'acide méthane-sulfonique, l'acide trifluoroacétique, ou l'acide trifluorométhane-sulfonique, pour former le composé du type hyménine.

6. Procédé de la revendication 5 dans lequel le procédé est réalisé à une température allant de 0° C à 100° C.

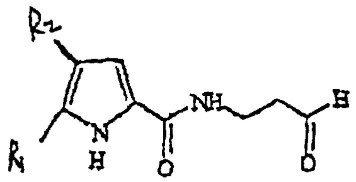
7. Procédé de la revendication 5 dans lequel le procédé est réalisé durant un temps de réaction de 3 à 5 jours.

8. Procédé de la revendication 5 dans lequel le solvant est saturé en gaz inerte.

9. Procédé de la revendication 5 dans lequel R_1 et R_2 sont B r.

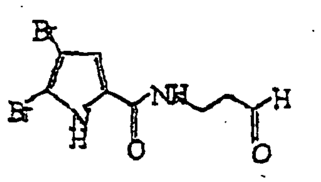
10. Procédé de la revendication 5 dans lequel R_1 et R_2 sont H.

11. Composé ayant la structure :



dans laquelle R_1 et R_2 sont identiques ou différents et sont H, un groupe alkyle linéaire ou ramifié en C_1 à $C_{10,}$ substitué ou non substitué, ou un halogène.

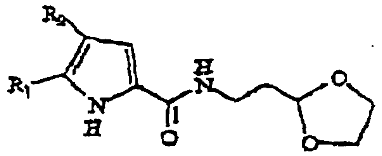
12. Composé de la revendication 11 ayant la structure :



13. Composé de la revendication 11 dans lequel les groupes alkyle sont substitués par des groupes halogène, hydroxy, alkoxy, dialkylamino, alkylarylamino, diarylamino, mercapto, ou alkylmercapto.

14. Procédé de préparation d'un composé de la revendication 11, dans lequel R_1 et R_2 sont définis de la même façon que pour le composé, ledit procédé comportant :

    la réaction d'un équivalent moléculaire d'un cétal ayant la structure :

    avec 0,5 équivalent moléculaire de monohydrate d'acide p-toluène-sulfonique à une température d'environ 0° C à environ 100° C ;
    dans un solvant, le solvant étant un mélange d'eau et d'un solvant organique non hydroxylique polaire, et le rapport volumique de l'eau au solvant organique non hydroxylique polaire allant d'environ 1/10 à environ 10/1 ;
    pour former le composé.

15. Procédé de la revendication 14, dans lequel le solvant organique non hydroxylique polaire est la N, N-diméthylformamide, le dioxanne, le tétrahydrofuranne, le diméthylsulfoxide, ou l'acétonitrile.

16. Procédé de la revendication 14, dans lequel le rapport volumique de l'eau au solvant organique non hydroxylique polaire va d'environ 40/60 à environ 60/40.

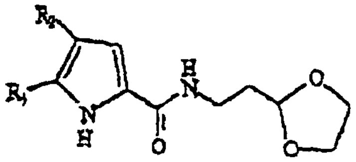
17. Procédé de la revendication 14, dans lequel le solvant est un mélange d'eau et d'acétone dans un rapport volumique allant d'environ 40/60 à environ 60/40.

18. Procédé de la revendication 14, dans lequel la température va d'environ 80° C à environ 100° C.

19. Procédé de la revendication 14, dans lequel le procédé est mis en oeuvre pendant un temps de réaction allant d'environ 3 heures à environ 24 heures.

20. Procédé de la revendication 14, dans lequel le procédé est mis en oeuvre pour un temps de réaction allant d'environ 6 heures à environ 10 heures.

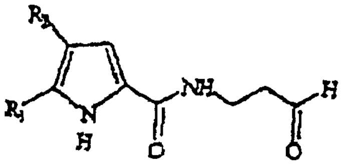
21. Composé du type cétal ayant la structure



dans laquelle R_1 et R_2 sont identiques ou différents et représentent H, un groupe alkyle linéaire ou ramifié en C_1 à C_{10}, substitué ou non substitué, ou un halogène.

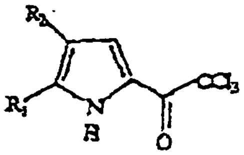
22. Composé de la revendication 21, dans lequel les groupes alkyle sont substitués par des groupes halogène, hydroxy, alkoxy, dialkylamino, alkylarylamino, diarylamino, mercapto, ou alkylmercapto.

23. Procédé de préparation d'un composé du type pyrrole bicyclique d'une quelconque des revendications 1 à 4, dans laquelle R_1 et R_2 sont définis de la même façon que dans la revendication 2, ledit procédé comportant : la réaction d'un pyrrole ayant la structure



dans un solvant, le solvant étant l'acide méthane-sulfonique, l'acide trifluoroacétique, ou l'acide trifluorométhane-sulfonique, pour former le composé du type pyrrole bicyclique.

24. Procédé de préparation du cétal des revendications 21 ou 22 dans lequel R_1 et R_2 sont définis de la même façon que pour le cétal, ledit procédé comportant la réaction d'un équivalent moléculaire d'un trichloroacétylpyrrole ayant la structure



avec un équivalent moléculaire d'un aminoacétal ayant la structure

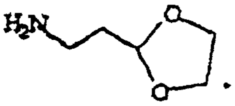


FIGURE 1 A

V.

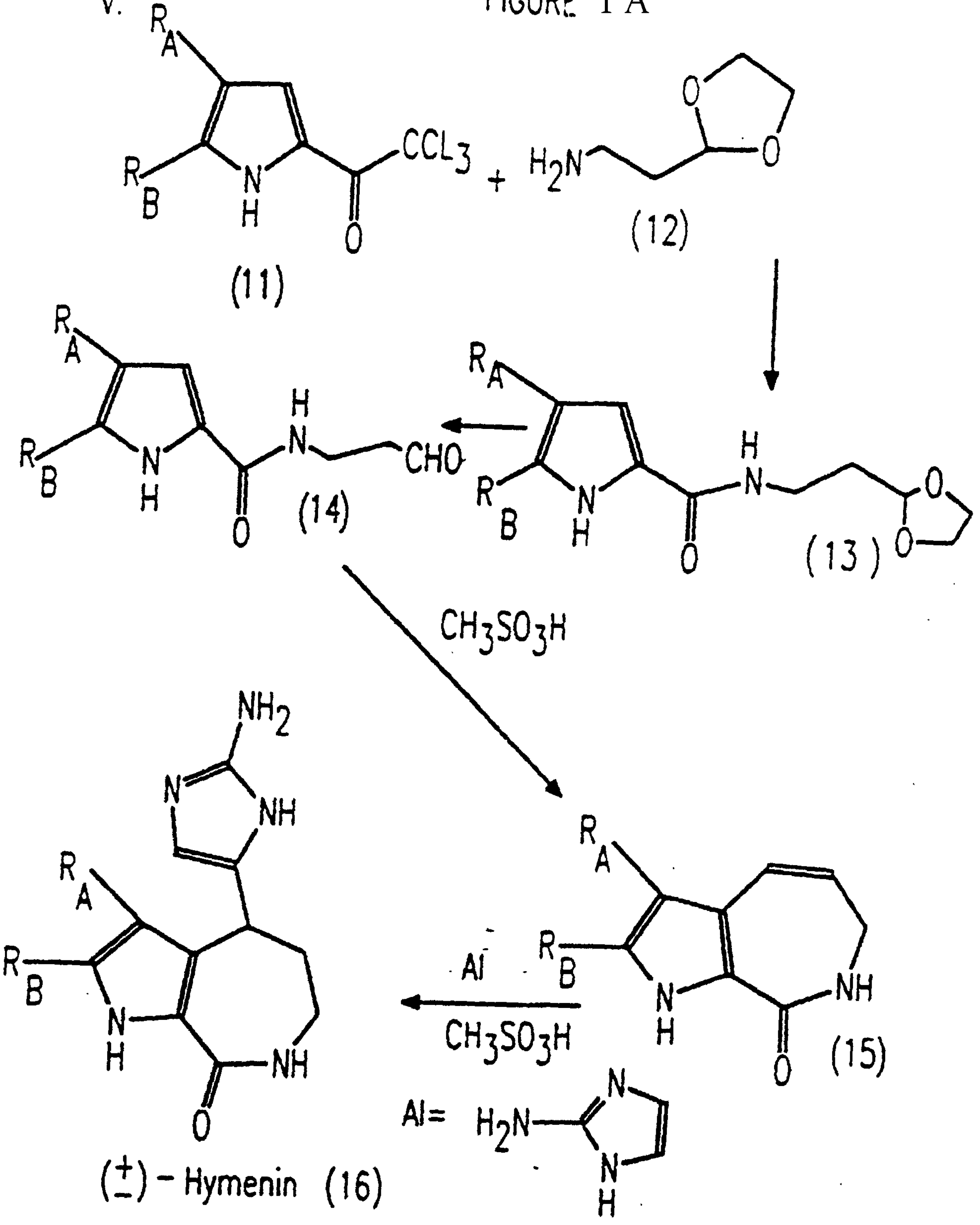
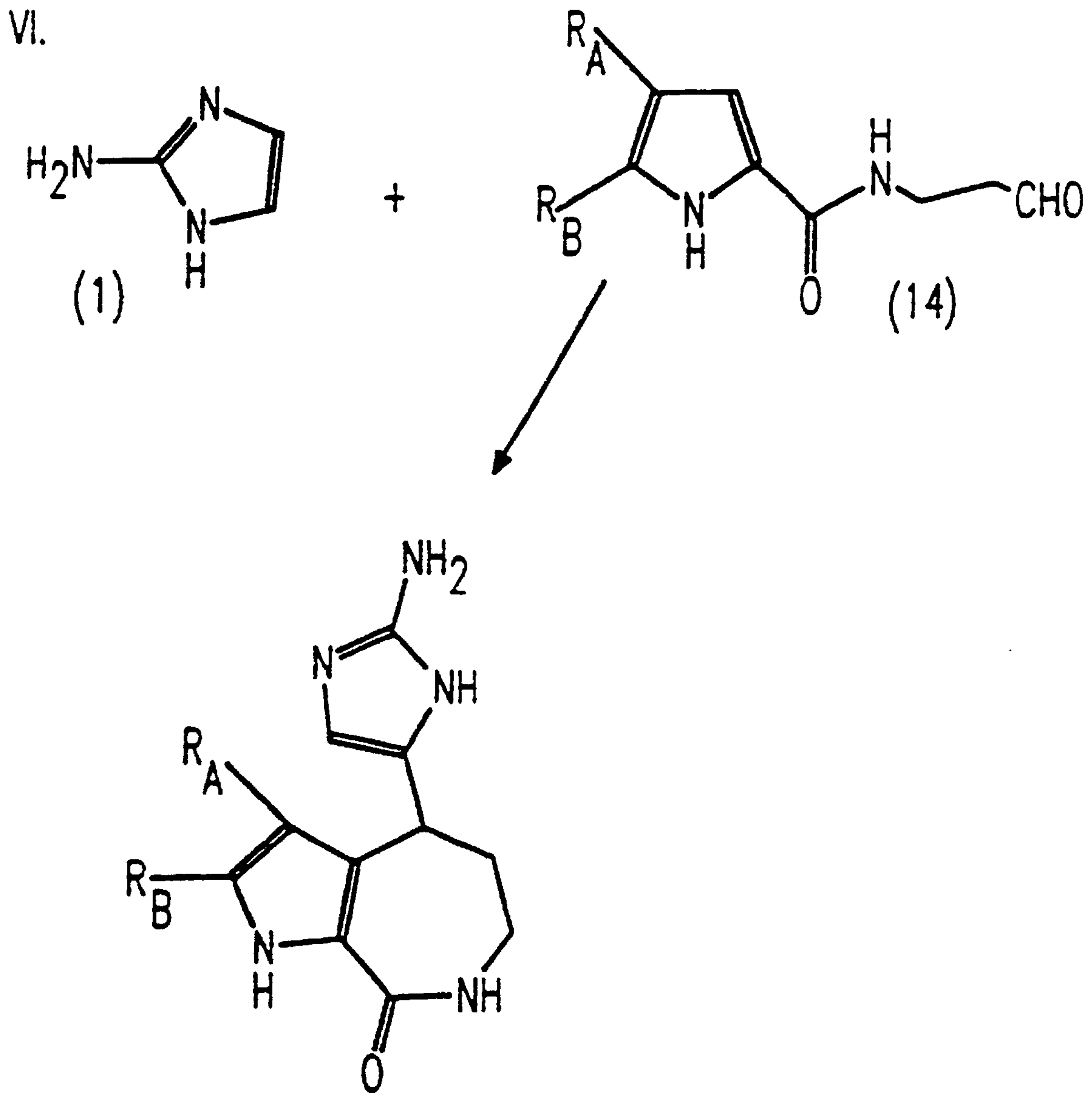
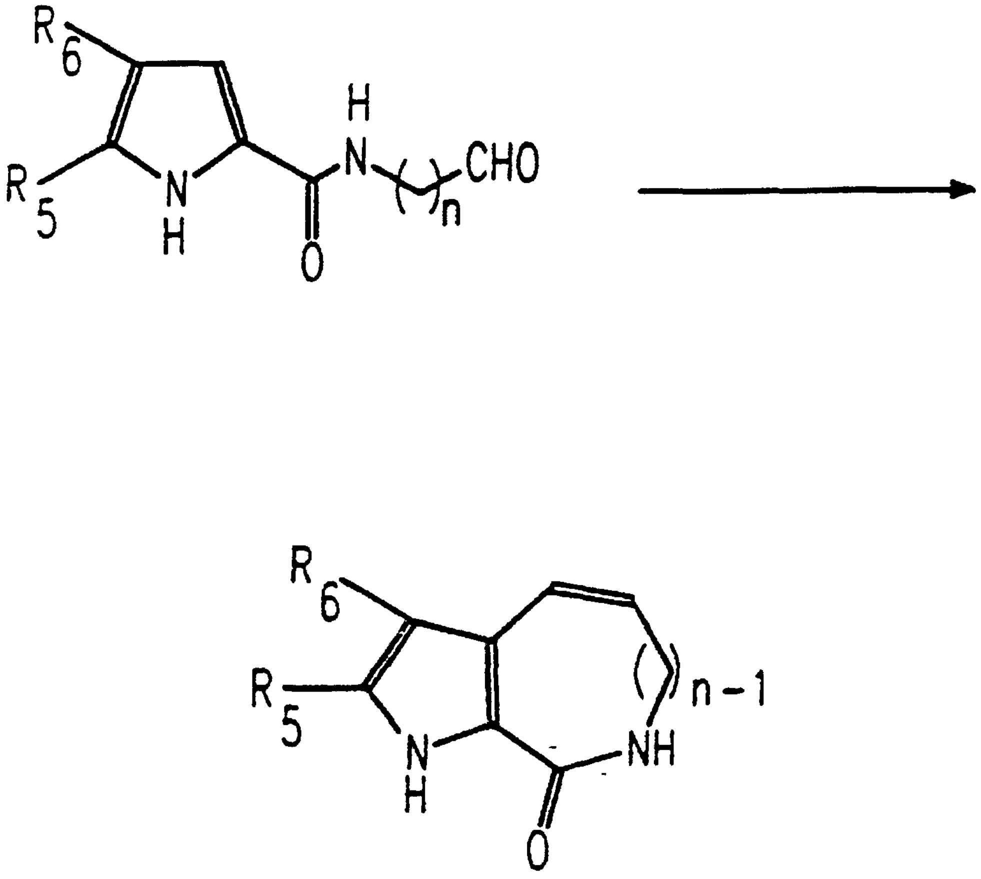

R_A
R_B
CCL3
+
H2N
(11)
(12)
(13)
(14)
CHO
CH3SO3H
(15)
Al⁻
CH3SO3H
Al= H2N
(±) - Hymenin (16)
NH2

FIGURE 1 B



(±) - Hymenin (16)

FIGURE 2



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