Synthesis of Aza Macrocycles from Polycyclic 5-Aminoisoxazoline Precursors[1]

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A series of novel isoxazolo analogues 11 of the dibenzazonine alkaloid protostephanine (1) has been prepared. A new regiospecific and potentially general aza macrocyclic ring forming process was developed where the first step was the 1,3-dipolar cycloaddition of benzonitrile oxide to the readily available enamine 6. The product, isoxazoline 9a, under solvolytic conditions that normally convert monocyclic 5-aminoisoxazolines to isoxazoles failed to give the desired aza macrocycle 14. Alternate sequences involving quaternization of 9a with methyl iodide followed by either solvolysis in polar solvents or base-induced elimination were successful and gave the target structure 11a in excellent overall yield. X-ray crystallographic analysis of the quaternized intermediate 10a corroborated the assignment of structure and defined the crystal-state conformation.

As part of a drug discovery effort to identify new antihypertensive agents, we prepared a novel series of isoxazolo[4,5-*f*][3]benzazonine and isoxazolo[4,5-*g*][3]-benzazecine derivatives 11 that are analogues of the hypotensive dibenzazonine alkaloid protostephanine (1).[2] We felt the advantages of the isoxazolo fusion would be 2-fold. First, it could act as a potential benzene isostere. Second, the latent functionality (e.g., vinylogous amide, β-diketone) preserved in these versatile heterocycles would enable us to convert the isoxazole ring to a wide variety of cyclic and acyclic derivatives.[3]

Our synthetic strategy (see retrosynthetic analysis in Scheme I) utilized a known method for making isoxazoles.[4] The first step of the general procedure involves the regiospecific 1,3-dipolar cycloaddition of a nitrile oxide to an enamine. Subjecting the 5-aminoisoxazoline intermediate to acid under solvolytic conditions generates the heteroaromatic isoxazole via elimination of a secondary amine.

Since the carbon-nitrogen trigonal bond (noted by the arrow in Scheme I) of the requisite starting enamine is the *bridge* of a polycyclic ring system, the secondary amine formed upon aromatization would be retained within the molecule, thus providing the two key structural components (isoxazole and aza macrocycle) of our targets. Enamines having these structural characteristics are known[5,6] and, in general, are much more stable than their ring-opened amino ketone counterparts (i.e., 2). Reference to their use as 1,3-dipolarophiles in the reaction with nitrile oxides, however, could not be found. There are numerous examples of nitrile oxide cycloadditions to cyclic enamines where the N-C trigonal bond was simply part of a ring but not a bridge.[7] In several of these examples, the 5-aminoisoxazoline intermediates gave isoxazoles with an alkylamino group tethered to the 4-position.[7a,d,h-j] We now wish to report our results indicating that aza macrocycle formation using this new methodology is a facile and potentially general procedure.

Results and Discussion

The known polycyclic enamine 6 needed for our study was prepared in large scale (0.5 mol) using a highly efficient literature procedure.[8] Bischler-Napieralski cyclodehydration of the crude product from the condensation of 3,4-dimethoxyphenethylamine and butyrolactone gave a good yield (65% for the two steps) of 6 isolated and stored as the HBr salt 3.

The reaction of 6 with benzonitrile oxide[9] (8; R = C_6H_5) (both generated in situ from 3 and benzenecarbohydroximoyl chloride 5 (R = C_6H_5), respectively, with Et_3N in $CHCl_3$) gave an excellent yield (82%) of the desired cycloadduct 9a (see Scheme II). The indicated regio- and stereochemistry is based on well-documented studies concerning the concerted nature of the reaction and the normal electronic demands of the reacting functional groups.[4] X-ray crystallographic analysis of a methiodide derivative of 9a (to be described in a later section) corroborated the structural assignment. With use of identical conditions, the reaction of 6 with the nitrile oxides derived from 4-chloro- and 4-methoxybenzenecarbohydroximoyl chlorides[9] worked equally as well to give 9b and 9c in 81 and 91% yields, respectively.

Exposure of 9a-c to a variety of acids under solvolytic conditions gave none of the desired aza macrocycles 11 (R_1 = H, n = 1). For example, when 9b was treated with 5 N HCl at 100 °C (conventional conditions for isoxazole formation[4a]) it was cleanly converted to the vinylogous amide derivative 12. Compound 9a remained unchanged in re-

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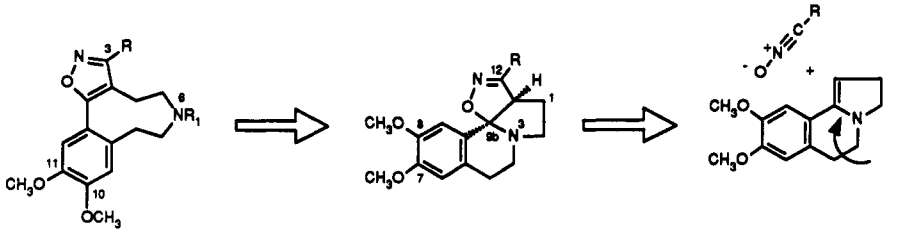
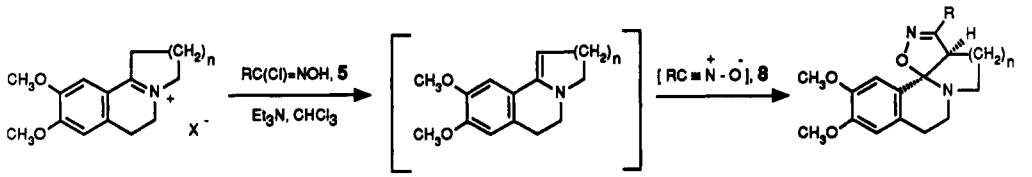
Scheme I



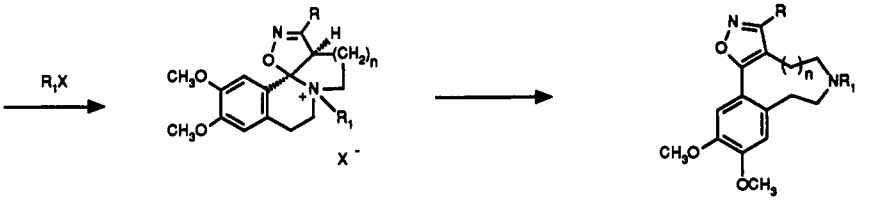
Scheme II



3; X = Br, n = 1
4; X = Cl, n = 2

6; n = 1
7; n = 2

9a; R = C_6H_5, n = 1
9b; R = 4-ClC_6H_4, n = 1
9c; R = 4-$CH_3OC_6H_4$, n = 1
9f; R = C_6H_5, n = 2



10a; R = C_6H_5, R_1 = CH_3, X = I, n = 1
10b; R = 4-ClC_6H_4, R_1 = CH_3, X = I, n = 1
10c; R = 4-$CH_3OC_6H_4$, R_1 = CH_3, X = I, n = 1
10d; R = C_6H_5, R_1 = $CH_2C_6H_5$, X = Br, n = 1
10e; R = 4-ClC_6H_4, R_1 = $CH_2CH{=}CH_2$, X = Br, n = 1
10f; R = C_6H_5, R_1 = $CH_2CH_2CH_3$, X = I, n = 2

11a; R = C_6H_5, R_1 = CH_3, n = 1
11b; R = 4-ClC_6H_4, R_1 = CH_3, n = 1
11c; R = 4-$CH_3OC_6H_4$, R_1 = CH_3, n = 1
11d; R = C_6H_5, R_1 = $CH_2C_6H_5$, n = 1
11e; R = 4-ClC_6H_4, R_1 = $CH_2CH{=}CH_2$, n = 1
11f; R = C_6H_5, R_1 = $CH_2CH_2CH_3$, n = 2

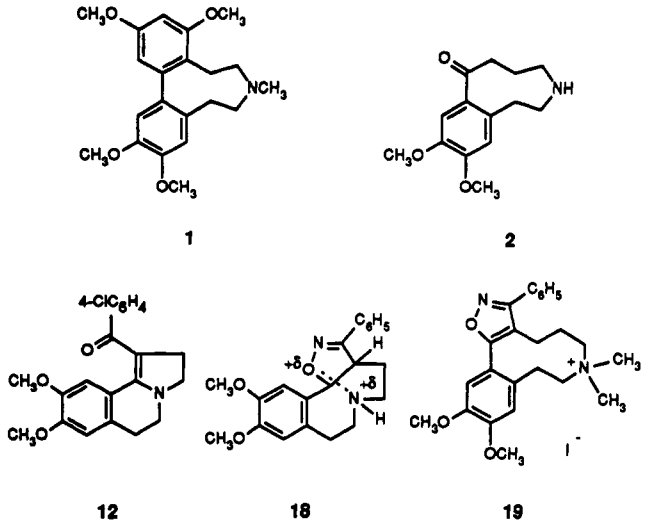
fluxing ethanolic HCl but when heated in boiling glacial acetic acid under an N_2 atmosphere, a time-dependent (over 18 h) decomposition to uncharacterizable, base-line (by TLC) materials was noted. Neither the desired product **14** nor its acetylated counterpart **15** was observed by TLC.

As an alternative to the acid-catalyzed approach, we quaternized **9a–c** with neat excess methyl iodide at reflux. This gave excellent yields of methiodide salts **10a–c**. Analyses of the ^1H NMR spectra of the recrystallized methiodides **10a–c** indicated that one diastereomer was isolated, although a small amount (ca. 4%) of an isomeric compound (epimeric about the newly formed quaternary nitrogen position) was evident for **10b**. X-ray crystallographic analysis (see Experimental Section, supplementary material, and Figure 1) of compound **10a** not only corroborated the stereo- and regiochemical assignments originally made for the isoxazoline ring fusion in **9a**, it additionally defined the configuration of the *N*-methyl group in **10a** as trans to the dimethoxyphenyl and bridgehead hydrogen groups. We assume that the diastereomer perferentially formed in the quaternization of **9b** or **9c** has the same relative configuration as **10a**.

When compound **10a** was heated to reflux in water (9 d) or glacial acetic acid (5 h), aza macrocycle **11a** was formed. Under both sets of conditions, little or no byproducts were detected by TLC. In contrast to the formation of methiodides **10a–c**, the only product isolated (in 77% yield) from the reaction of **9a** with benzyl bromide at 100 °C (2 h) was the HBr salt of aza macrocycle **11d**. The putative intermediate, quaternary **10d**, undergoes ring opening at the higher temperature of the reaction medium. When **9b** was heated at reflux (71 °C, 4 h) in allyl bromide, a nearly equal mixture of **10e** and the HBr salt of **11e** was obtained.

A more convenient procedure to effect the desired transformation involved treating quaternaries **10a–c** with excess $NaOCH_3$ in methanol at 25 °C. These reactions gave excellent yields (72–93%) of recrystallized products **11a–c** and were complete in less than 1 h. A similar procedure (methylation followed by base-induced elimination) has been reported using a cycloadduct derived from benzonitrile oxide and a 3-pyrazoline derivative.[7h] Similarly, subjecting **10e** (mixture with **11e**·HBr) to these basic conditions gave **11e**. We also treated compound **9a**, the nonquaternized cycloadduct, with $NaOCH_3/CH_3OH$ to see if ring opening would occur under the base conditions; no reaction was evident. When CH_3OD was used in place of CH_3OH and dry THF added to solubilize the reactants, deuterium incorporation (ca. 60%) at position 12a of **9a** and no aza macrocycle formation to **14** was observed as measured by ^1H NMR and TLC. These data show that the substrate for the base must be a quaternary salt in that a neutral amine leaving group (vs an amide anion) is necessary for the elimination to occur.

Since the secondary amine aza macrocycle **14** could not be made directly from **9a** by the methodology described thus far, an alternate route was used. Debenzylation of **11d** using catalytic hydrogenation conditions was precluded due to the likelihood of hydrogenolysis of the isoxazole ring. However, another standard dealkylation sequence as shown in Scheme III was successful. The reaction of **11d** with phenyl chloroformate in refluxing toluene gave urethane **13** that was hydrolyzed to provide



1 2

12 18 19

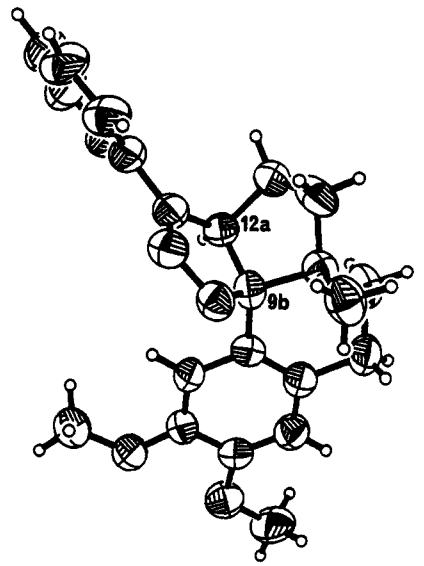
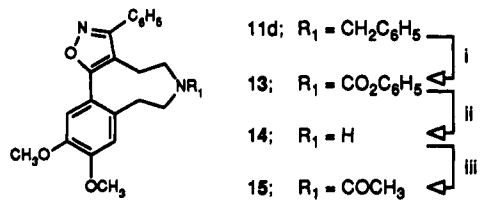


Figure 1. ORTEP drawing of **10a**.

Scheme III[a]



[a] **Reagents:** (i) C_6H_5OCOCl, $PhCH_3$, 110 °C; (ii) NaOH, H_2O, EtOH, 78 °C; (iii) CH_3CO_2H, 116 °C.

14 in 65% yield for the two steps. Compound **14** remained unchanged in refluxing ethanolic HCl but when heated in acetic acid it was cleanly converted to the acetylated derivative **15** (Scheme III). At no time during the reaction could **9a** be detected by TLC.

For **9a**, the difference in reactivity noted between the acid-catalyzed and quaternization approaches to aza macrocycle formation may be rationalized using the series of bond-making/bond-breaking steps illustrated in Scheme IV. For those reactions done in less stringent acidic medium (e.g., glacial acetic acid or EtOH/HCl), the lack of desired reactivity may be attributed to having too low a concentration of protonated amine **16** in solution. This would result in a very slow breakage of the C–N bond (step b in Scheme IV). While strongly acidic aqueous conditions would increase the concentration of **16**, the data for the related analogue **9b** indicate the rate of isoxazole/aza macrocycle formation is slow compared to acid-catalyzed hydrolysis of the oxime functionality.

An alternate explanation to account for the lack of desired reactivity of **9a** in acid could be that equilibrium b lies far to the side of **16**. One would expect this tetracyclic intermediate to be quite stable on the basis of the geometries defined in the X-ray structure of the related compound **10a**. The highly ordered conformation for the oxonium species as depicted by **17b** is likely to be stabilized by a transannular effect[10] (i.e., **18**) and thus has overcome the entropy requirements involved in orienting the reacting groups to give back **16**. A series of energetically unfavorable single bond rotations would have to occur for **17b** to adopt another conformation (i.e., one where there was little or no transannular stabilization) that would allow the forward reaction (to **14**) to occur.

Another possible, and perhaps unlikely, explanation of these limited data could be that an equilibrium exists between **9a** and **14** and the inherent thermodynamic stability of starting material **9a** is high compared to that of the heteroaromatized product **14**. Since **14** is not converted to **9a** in acid, we assume that such an equilibrium, should it exist, lies far to the side of **14**. Alternatively, the kinetic barrier to convert **14** to **17b** or **16** is much higher than that for acetylation to **15**. It is interesting to note that compound **15** could conceptually be made directly from **9a** by treatment of the latter with acetic anhydride or an equivalent reagent. Using a variety of reagents and conditions to accomplish this conversion, we were unable to detect **15**.

In contrast to the acid-catalyzed system, quaternized intermediate **10a** is undoubtedly not in equilibrium with **9a**, increasing the likelihood of the forward reaction to **17a** and **11a**. It is also possible that there is a greater release of strain energy in step b when R_1 is methyl (or benzyl) compared to the corresponding R_1 = H system.

The syntheses of 10-membered ring aza macrocycles (**11**, n = 2) were also investigated. The known iminium salt **4**[11] was converted to the cycloaddition product **9f** in the usual manner (Scheme II). The reaction of **9f** with methyl iodide, however, gave equivocal results, and in one instance **19** was isolated in 9% yield when the crude product was treated with base. We do not know if **19** was formed during methyl iodide treatment or upon exposure to base, nor did we design/conduct any additional experiments to address how this minor product was formed.

In contrast to the methylation experiments, the reaction of **9f** with 1-propyl iodide at reflux (101 °C) gave a crude product containing the desired benzazecine derivative **11f** as the primary component. In this reaction a similar observation, namely aza macrocycle formation during alkylation at high temperature, was made relative to two previously discussed examples (**9a**/benzyl bromide and **9b**/allyl bromide). This crude reaction product was treated with NaOMe/MeOH to convert a small amount of **10f** present to **11f**. A 47% overall yield of **11f** was realized. On the basis of this and other (e.g., the successful methylations of **9a–c**) results, we have no explanation as to the lack of desired reactivity of **9f** with methyl iodide.

In conclusion, we have demonstrated that isoxazolo-fused aza macrocycles can be efficiently made via a new variation of a known general method for making isoxazoles. We have also shown that the polycyclic nature of the novel 5-aminoisoxazoline cycloadducts plays an important role in determining their reactivity toward a variety of chemical

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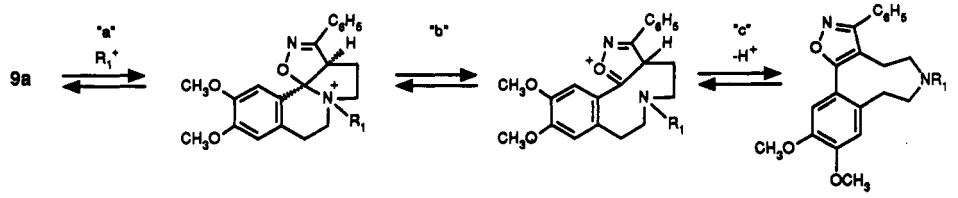
Scheme IV



10a; $R_1 = CH_3$
16; $R_1 = H$

17a; $R_1 = CH_3$
17b; $R_1 = H$

11a; $R_1 = CH_3$
14; $R_1 = H$

reagents. For example, acid-catalyzed isoxazole formation is slow compared to competing reactions. If, however, the 5-amino group of the 5-aminoisoxazoline is quaternized, solvolytic or basic conditions readily provides the isoxazolo-fused aza macrocycle. With regard to biological activity, representative examples of 11 were evaluated in the spontaneously hypertensive rat model where little or no lowering of blood pressure was observed.

Experimental Section

General Methods. High-field proton NMR, chemical ionization mass spectra, and infrared spectra were obtained for all new compounds reported and were consistent with the assigned structures. ^{13}C NMR data were collected for representative compounds. Carbon, hydrogen, and nitrogen elemental analyses data were obtained for all new compounds and were within ±0.4% of theoretical values. Reactions were generally performed under a N_2 atmosphere. The TLC analyses where indicated used 97:3 $CHCl_3$/2-propylamine as eluent on silica gel.

(9b*RS*,12a*RS*)-1,4,5,12a-Tetrahydro-7,8-dimethoxy-12-phenyl-2*H*-isoxazolo[5′,4′:2,3]pyrrolo[2,1-*a*]isoquinoline (9a). To a cold (0 °C) solution of iminium salt **3**[8] (69 g, 0.22 mol) in 700 mL of $CHCl_3$ were added sequentially 44 g (0.44 mol) of triethylamine (by pipet) and 34 g (0.22 mol) of benzenecarbohydroximoyl chloride[9] in 70 mL of $CHCl_3$ (dropwise over 10 min). After being stirred in an ice bath 0.5 h and at 25 °C for 1 h, the solution was washed with 1 N NaOH and was dried over $MgSO_4$. Concentration of the resulting solution gave a crude crystalline product that was recrystallized from CH_3CN to give 63 g (82%) of **9a**: mp 173–175 °C; IR (KBr) 1608 cm^{-1}; MS *m/z* 351 (MH^+); ^1H NMR ($CDCl_3$) δ 1.95–2.08 (m, 1 H), 2.26–2.45 (m, 1 H), 2.61–2.74 (m, 1 H), 2.96–3.21 (m, 4 H), 3.35–3.51 (m, 1 H), 3.76 (s, 3 H), 3.87 (s, 3 H), 4.04 (dd, *J* = 3.5, 9.7 Hz, 1 H), 6.63 (s, 2 H), 7.40–7.47 (m, 3 H), 7.71–7.78 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.69, 29.58, 42.19, 49.22, 54.40, 55.82, 56.10, 107.05, 108.55, 110.92, 126.63, 127.10, 127.53, 128.73, 129.55, 129.62, 147.89, 149.20, 158.32. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 72.18; H, 6.28; N, 7.96.

(9b*RS*,12a*RS*)-12-(4-Chlorophenyl)-1,4,5,12a-tetrahydro-7,8-dimethoxy-2*H*-isoxazolo[5′,4′:2,3]pyrrolo[2,1-*a*]isoquinoline (9b). By use of a procedure similar to that used for making **9a**, 4-chlorobenzenecarbohydroximoyl chloride,[9] Et_3N, and **3** (20.0 g, 0.064 mol) were converted to **9b** (81% after recrystallization from EtOH): mp 153–154 °C; IR (KBr) 1610 cm^{-1}; MS *m/z* 385 (MH^+); ^1H NMR ($CDCl_3$) δ 1.90–2.05 (m, 1 H), 2.26–2.42 (m, 1 H), 2.59–2.73 (m, 1 H), 2.96–3.22 (m, 4 H), 3.35–3.51 (m, 1 H), 3.76 (s, 3 H), 3.87 (s, 3 H), 3.99 (dd, *J* = 3.4, 9.8 Hz, 1 H), 6.60 (s, 1 H), 6.64 (s, 1 H), 7.41, 7.68 (A_2B_2, 4 H). Anal. Calcd for $C_{21}H_{21}ClN_2O_3$: C, 65.54; H, 5.50; N, 7.28. Found: C, 65.34; H, 5.39; N, 7.06.

(9b*RS*,12a*RS*)-1,4,5,12a-Tetrahydro-7,8-dimethoxy-12-(4-methoxyphenyl)-2*H*-isoxazolo[5′,4′:2,3]pyrrolo[2,1-*a*]isoquinoline (9c). By use of a procedure similar to that used for making **9a**, 4-methoxybenzenecarbohydroximoyl chloride,[9] Et_3N, and **3** (11.4 g, 0.062 mol) were converted to **9c** (91% after recrystallization from EtOH): mp 167–169 °C; IR (KBr) 1608 cm^{-1}; MS *m/z* 381 (MH^+); ^1H NMR ($CDCl_3$) δ 1.93–2.08 (m, 1 H), 2.26–2.43 (m, 1 H), 2.60–2.72 (m, 1 H), 2.97–3.21 (m, 4 H), 3.36–3.52 (m, 1 H), 3.76 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.01 (dd, *J* = 3.5, 9.8 Hz, 1 H), 6.63 (s, 1 H), 6.64 (s, 1 H), 6.96, 7.69 (A_2B_2, 4 H). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.18; H, 6.35; N, 7.35.

(10b*RS*,13a*RS*)-1,2,3,5,6,13a-Hexahydro-8,9-dimethoxy-13-phenylisoxazolo[6′,5′:3,4]pyrido[2,1-*a*]isoquinoline (9f). By use of a procedure similar to that used for making **9a**, benzenecarbohydroximoyl chloride, Et_3N, and **4**[11] (34.6 g, 0.11 mol) were converted to **9f** (82% after recrystallization from cyclohexane): mp 122–123 °C; IR (KBr) 1611 cm^{-1}; MS *m/z* 365 (MH^+); ^1H NMR ($CDCl_3$) δ 1.41–1.57 (m, 1 H), 1.68–1.87 (m, 2 H), 1.91–2.09 (m, 1 H), 2.55–3.33 (m, 6 H), 3.71 (s, 3 H), 3.87 (s, 3 H), 3.92–4.00 (m, 1 H), 6.58 (s, 1 H), 6.71 (s, 1 H), 7.40–7.48 (m, 3 H), 7.69–7.78 (m, 2 H). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.59; H, 6.69; N, 7.65.

(3*RS*,9b*RS*,12a*RS*)-1,4,5,12a-Tetrahydro-7,8-dimethoxy-3-methyl-12-phenyl-2*H*-isoxazolo[5′,4′:2,3]pyrrolo[2,1-*a*]isoquinolinium Iodide (10a). A mixture of 5.0 g (0.143 mol) of **9a** and 70 mL of CH_3I was stirred at reflux for 8 h and cooled. The solid that separated was collected and recrystallized from EtOH to 6.6 g (94%) of product suitable for use in subsequent steps. A portion (2.4 g) of this material was recrystallized (EtOH) to give 1.7 g of crystals of **10a** of suitable quality for X-ray crystallographic analysis (see supplementary material): mp 188–191 °C; IR (KBr) 1608 cm^{-1}; MS *m/z* 365 (MH^+ for loss of HI), 351 (MH^+ for loss of CH_3I); ^1H NMR (CF_3CO_2D) δ 2.54 (dd, *J* = 6.4, 14.6 Hz, 1 H), 3.22–3.61 (m, 3 H), 3.43 (s, 3 H), 3.82–4.44 (m, 4 H), 3.89 (s, 3 H), 4.00 (s, 3 H), 5.00 (d, *J* = 9.0 Hz, 1 H), 6.91 (s, 2 H), 7.51–7.70 (m, 3 H), 7.79–7.88 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 22.09, 26.93, 43.47, 55.73, 55.77, 57.11, 58.42, 61.50, 109.40, 110.57, 110.68, 120.45, 123.99, 126.09, 127.50, 129.13, 131.36, 148.58, 150.29, 160.82. Anal. Calcd for $C_{22}H_{25}IN_2O_3$: C, 53.67; H, 5.12; N, 5.69. Found: C, 53.71; H, 5.24; N, 5.50.

(3*RS*,9b*RS*,12a*RS*)-12-(4-Chlorophenyl)-1,4,5,12a-tetrahydro-7,8-dimethoxy-3-methyl-2*H*-isoxazolo[5′,4′:2,3]pyrrolo[2,1-*a*]isoquinolinium Iodide (10b). By use of a procedure similar to that used for making **10a**, **9b** (5.0 g, 0.013 mol) was converted to 6.6 g (96%) of **10b** suitable for use in subsequent steps. Analytically pure material (from CH_3OH) had mp 203–210 °C dec: IR (KBr) 1615 cm^{-1}; MS *m/z* 399 (MH^+ for loss of HI), 385 (MH^+ for loss of CH_3I); ^1H NMR (CF_3CO_2D) δ 2.51 (dd, *J* = 6.2, 14.7 Hz, 1 H), 3.22–3.59 (m, 3 H), 3.43 (s, 3 H), 3.83–4.44 (m, 4 H), 3.89 (s, 3 H), 4.00 (s, 3 H), 5.00 (d, *J* = 4.1 Hz, 1 H), 6.88 (s, 1 H), 6.92 (s, 1 H), 7.55 (d, *J* = 8.6 Hz, 2 H), 7.77 (d, *J* = 8.6 Hz, 2 H). We assume that a pair of singlets at δ 7.00 and 7.07 (H's at C-6 and C-9) indicate the presence of a minor component (ca. 4%) that is epimeric with **10b** about the quaternary nitrogen. Anal. Calcd for $C_{22}H_{24}ClIN_2O_3$: C, 50.16; H, 4.59; N, 5.32. Found: C, 50.34; H, 4.80; N, 5.19.

(3*RS*,9b*RS*,12a*RS*)-1,4,5,12a-Tetrahydro-7,8-dimethoxy-12-(4-methoxyphenyl)-3-methyl-2*H*-isoxazolo[5′,4′:2,3]pyrrolo[2,1-*a*]isoquinolinium Iodide (10c). By use of a procedure similar to that used for making **10a**, **9c** (1.4 g, 0.0036 mol) was converted to 1.9 g (98%) of **10c** suitable for use in subsequent steps. Analytically pure material (from EtOH) had mp 192–203 °C: IR (KBr) 1605 cm^{-1}; MS *m/z* 395 (MH^+ for loss of HI), 381 (MH^+ for loss of CH_3I); ^1H NMR (CF_3CO_2D) δ 2.54 (dd, *J* = 6.1 14.7 Hz, 1 H), 3.25–3.54 (m, 3 H), 3.42 (s, 3 H), 3.77–4.45 (m, 4 H), 3.89 (s, 3 H), 4.00 (s, 6 H), 5.00 (d, *J* = 9.1 Hz, 1 H), 6.91 (s, 2 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 7.79 (d, *J* = 8.8 Hz, 2 H). Anal. Calcd for $C_{23}H_{27}IN_2O_4$: C, 52.88; H, 5.21; N, 5.36. Found: C, 52.79; H, 5.30; N, 5.39.

5,6,7,8-Tetrahydro-10,11-dimethoxy-6-methyl-3-phenyl-4*H*-isoxazolo[4,5-*f*][3]benzazonine (11a). Method A. Sodium methoxide (7.0 g, 0.13 mol) was added to a solution of 28.0 g (0.057

mol) of **10a** in 250 mL of CH_3OH at 25 °C. The resulting solution was stirred at 25 °C for 2 h and concentrated. The residue was partitioned between $CHCl_3$ and H_2O, and the organic layer was dried ($MgSO_4$) and concentrated. After the residue was dissolved in EtOH, crystallization commenced and compound **11a** (15.0 g, 72%) was collected, mp 140–142 °C: IR (KBr) 1624, 1602 cm^{-1}; MS m/z 365 (MH^+); ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.54–2.79 (m, 8 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 6.77 (s, 1 H), 6.94 (s, 1 H), 7.41–7.60 (m, 5 H); ^{13}C NMR ($CHCl_3$) δ 24.82, 34.28, 47.04, 55.28, 55.88, 55.92, 59.08, 111.41, 112.12, 115.12, 121.50, 128.62, 128.81, 129.22, 129.70, 134.46, 146.93, 150.47, 163.65, 167.27. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.69; H, 6.44; N, 7.51. **Method B (Solvolysis).** An alternate method for this conversion involved heating 0.20 g (0.000 41 mol) of **10a** at reflux in either 6 mL of H_2O for 9 d or 6 mL of HOAc for 5 h. In the former case, the aqueous solution was basified with K_2CO_3 and, following an extractive workup, a crude oil was obtained. TLC analysis showed this to be homogeneous and identical with **11a**. Crystalline material (0.070 g, 47%, from EtOH) was identical in every respect with **11a** made by method A. Following concentration of the HOAc in the second alternate method, a similar procedure to that just described was used and 0.080 g (54%) of recrystallized **11a** was obtained.

3-(4-Chlorophenyl)-5,6,7,8-tetrahydro-10,11-dimethoxy-6-methyl-4*H*-isoxazolo[4,5-*f*][3]benzazonine (11b). By use of a procedure similar to method A for making **11a**, 24.4 g (0.046 mol) of **10b** was converted to **11b** (92% after recrystallization from CH_3CN): mp 138.5–140 °C; IR (KBr) 1622, 1600 cm^{-1}; MS m/z 399 (MH^+); ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.52–2.80 (m, 8 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 6.77 (s, 1 H), 6.92 (s, 1 H), 7.47, 7.54 (A_2B_2, 4 H). Anal. Calcd for $C_{22}H_{23}ClN_2O_3$: C, 66.24; H, 5.81; N, 7.02. Found: C, 66.46; H, 5.92; N, 7.11.

5,6,7,8-Tetrahydro-10,11-dimethoxy-3-(4-methoxyphenyl)-6-methyl-4*H*-isoxazolo[4,5-*f*][3]benzazonine (11c). By use of a procedure similar to method A for making **11a**, 21.0 g (0.040 mol) of **10c** was converted to **11c** (93% after recrystallization from CH_3CN): mp 145–147 °C; IR (KBr) 1611 cm^{-1}; MS m/z 395 (MH^+); ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.51–2.79 (m, 8 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 6.77 (s, 1 H), 6.93 (s, 1 H), 7.02, 7.52 (A_2B_2, 4 H). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.02; H, 6.64; N, 7.10. Found: C, 70.06; H, 6.62; N, 7.12.

5,6,7,8-Tetrahydro-10,11-dimethoxy-3-phenyl-6-(phenylmethyl)-4*H*-isoxazolo[4,5-*f*][3]benzazonine (11d). A mixture of 20.0 g (0.051 mol) of **9a** and 28.8 g (0.171 mol) of benzyl bromide was heated at 100 °C for 2 h. The solid that separated was collected and recrystallized (CH_3OH) to give 23.0 g (77%) of the HBr salt of **11d**: mp 266–270 °C dec. Anal. Calcd for $C_{28}H_{28}N_2O_3$·HBr: C, 64.49; H, 5.61; N, 5.37. Found: C, 64.56; H, 5.76; N, 5.37. The HBr salt was converted to **11d** with aqueous K_2CO_3: mp 134–136 °C (after recrystallization from EtOH); IR (KBr) 1628, 1600 cm^{-1}; MS m/z 441 (MH^+); ^1H NMR ($CDCl_3$) δ 2.56–2.82 (m, 8 H), 3.54 (s, 2 H), 3.71 (s, 3 H), 3.96 (s, 3 H), 6.38 (s, 1 H), 6.73–6.82 (m, 2 H), 7.04 (s, 1 H), 7.08–7.11 (m, 3 H), 7.46–7.58 (m, 5 H). Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.33; H, 6.55; N, 6.20.

3-(4-Chlorophenyl)-5,6,7,8-tetrahydro-10,11-dimethoxy-6-(2-propenyl)-4*H*-isoxazolo[4,5-*f*][3]benzazonine (11e). A mixture of 8.0 g (0.021 mol) of **9b** and 28.0 g (0.23 mol) of allyl bromide was heated at reflux for 4 h. The solid that separated (8.2 g) was collected and recrystallized from EtOH to give 3.6 g (34%) of a nearly equal mixture (by TLC and ^1H NMR) of **10e** and **11e**·HBr: mp 162–225 °C dec. Anal. Calcd for $C_{24}H_{25}ClN_2O_3$·HBr: C, 56.99; H, 5.18; N, 5.54. Found: C, 57.34; H, 5.30; N, 5.41. A portion (3.3 g, 0.0056 mol) of this mixture was treated with NaOMe/MeOH as described in method A for making **11a**. The crude product (nearly quantitative mass balance recovery of an oil homogeneous by TLC) was converted to an HCl salt that was recrystallized from acetone/H_2O to give 0.8 g (24%) of **11e**·HCl: mp 216–218 °C; IR (KBr) 1637, 1600 cm^{-1}; MS m/z 425 (MH^+); ^1H NMR (CF_3CO_2D) δ 3.13–3.39 (br m, 3 H), 3.40–3.97 (m, 7 H), 4.03 (s, 3 H), 4.06 (s, 3 H), 5.62–5.80 (m, 2 H), 5.81–6.02 (m, 1 H), 7.13 (s, 1 H), 7.18 (s, 1 H), 7.59 (br s, 4 H). Anal. Calcd for $C_{24}H_{25}ClN_2O_3$·HCl: C, 62.48; H, 5.68; N, 6.07. Found: C, 62.21; H, 5.64; N, 5.78.

4,5,6,7,8,9-Hexahydro-11,12-dimethoxy-3-phenyl-7-(1-propyl)-4*H*-isoxazolo[4,5-*g*][3]benzazecine (11f). A mixture of 4.0 g (0.011 mol) of **9f** and 25 mL of 1-propyl iodide was stirred at reflux under an N_2 atmostphere for 40 h. The amorphous solid that separated upon cooling was collected and washed with ether. TLC showed this to be mainly **11f** along with a small amount of base-line material assumed to be **10f**. The crude solid was dissolved in 50 mL of CH_3OH containing 2.0 g (0.037 mol) of CH_3ONa. After the mixture was stirred at 25 °C for 2 h, a solid separated and 2.1 g (47%) of **11f** was collected. Recrystallization (EtOH) of a small portion gave analytically pure material: mp 188–190 °C: IR (KBr) 1629, 1600 cm^{-1}; MS m/z 407 (MH^+); ^1H NMR ($CDCl_3$) δ 0.45 (t, J = 7.3 Hz, 3 H), 0.96–1.01 (br m, 2 H), 1.39–1.68 (br m, 2 H), 1.89–2.77 (br m, 10 H), 3.87 (s, 3 H), 3.93 (s, 3 H), 6.74 (s, 1 H), 6.80 (s, 1 H), 7.42–7.51 (m, 3 H), 7.73–7.81 (m, 2 H). Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.87; H, 7.38; N, 6.85.

(4-Chlorophenyl)(2,3,5,6-tetrahydro-8,9-dimethoxy-1*H*-pyrrolo[2,1-*a*]isoquinolin-1-yl)methanone (12). A mixture of 5.0 g (0.013 mol) of **9b** and 50 mL of 5 N HCl was heated at 100 °C for 3 h. The dark solution was washed with ether, treated with activated charcoal, filtered, and basified with 1 N NaOH. The organic material was extracted into $CHCl_3$, and the resulting solution was dried and concentrated. The residual solid (3.0 g) was recrystallized from cyclohexane/EtOAc to provide 1.8 g (37%) of **12**: mp 156–158 °C; IR (KBr) 1610, 1580 cm^{-1}; MS m/z 370 (MH^+); ^1H NMR ($CDCl_3$) δ 2.92 (t, J = 6.4 Hz, 2 H), 3.03 (t, J = 9.8 Hz, 2 H), 3.31 (t, J = 6.4 Hz, 2 H), 3.52 (s, 3 H), 3.62 (t, J = 9.8 Hz, 2 H), 3.89 (s, 3 H), 6.65 (s, 1 H), 7.20, 7.47 (A_2B_2, 4 H), 7.45 (s, 1 H). Anal. Calcd for $C_{21}H_{20}ClNO_3$: C, 68.20; H, 5.45; N, 3.79. Found: C, 68.23; H, 5.47; N, 3.74.

5,6,7,8-Tetrahydro-10,11-dimethoxy-3-phenyl-4*H*-isoxazolo[4,5-*f*][3]benzazonine (14). A solution containing 9.7 g (0.022 mol) of **11d**, 3.8 g (0.0242 mol) of phenyl chloroformate, and 100 mL of toluene was stirred at reflux for 20 h, and the resulting solution was concentrated in vacuo. The residue was dissolved in a mixture of 60 mL of EtOH and 20 mL of 35% NaOH and was heated at reflux for 4 d. After concentration of the solution, the residue was partitioned between $CHCl_3$ and H_2O. The basic organic material was extracted into 6% HCl from the $CHCl_3$ layer. The aqueous acid portion was made strongly basic with NaOH, and organic material was extracted into ether. The ether extracts were dried ($MgSO_4$) and concentrated, giving a crystalline residue that was recrystallized from EtOH to give 5.0 g (65%) of **14**: mp 125–127 °C; IR (KBr) 3344, 1630, 1600 cm^{-1}, MS m/z 351 (MH^+); ^1H NMR ($CDCl_3$) δ 1.48 (br s, 1 H), 2.52–2.70 (m, 4 H), 2.94–3.07 (m, 4 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 6.77 (s, 1 H), 7.00 (s, 1 H), 7.49–7.61 (m, 5 H). An HCl salt of **14** recrystallized from CH_3CN had mp 158–161 °C. Anal. Calcd for $C_{21}H_{22}N_2O_3$·HCl·CH_3CN: C, 64.55; H, 6.12; N, 9.82. Found: C, 64.79; H, 6.00; N, 9.61.

6-Acetyl-5,6,7,8-tetrahydro-10,11-dimethoxy-3-phenyl-4*H*-isoxazolo[4,5-*f*][3]benzazonine (15). A solution of 0.164 g (0.000 47 mol) of **14** and 5 mL of HOAc was stirred at reflux for 18 h. At no time during the reaction was the presence of **9a** detectable by TLC. The solution was concentrated and the residue partitioned between CH_2Cl_2 and aqueous K_2CO_3. The organic portion was dried ($MgSO_4$) and concentrated, giving 0.18 g of **15**. Recrystallization from EtOAc gave analytically pure material (0.080 g, 44%): mp 173–174 °C; IR (KBr) 1628, 1601 cm^{-1}; MS m/z 393 (MH^+); ^1H NMR ($CDCl_3$) δ 1.64 and 1.88 (pair of s due to rotomers, 3 H), 2.68–2.80 (m, 4 H), 3.45–3.54 (m, 2 H), 3.63–3.74 (m, 2 H), 3.89 and 3.90 (pair of s due to rotomers, 3 H), 3.94 and 3.95 (pair of s due to rotomers, 3 H), 6.86–6.89 (m, 2 H), 7.49–7.63 (m, 5 H). Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.01; H, 6.20; N, 6.95.

4,5,6,7,8,9-Hexahydro-11,12-dimethoxy-3-phenyl-7,7-dimethyl-4*H*-isoxazolo[4,5-*g*][3]benzazecinium Iodide (19). A mixture of 10.0 g (0.0274 mol) of **9f** and 50 mL of CH_3I was stirred at reflux for 4 d. The excess solvent was decanted and the residue triturated with ether. A solid was collected and washed with more ether and was slurried in 200 mL of MeOH containing NaOMe (1.0 g, 0.02 mol). The slurry was heated on a steam bath for 15 min and the resulting solution stirred at 25 °C for 2 h. After the solution was concentrated, the residue was dissolved in H_2O and after a short time a solid separated and was recrystallized from EtOH to give 1.3 g (9%) of **19**: mp 248–249 °C; IR (KBr) 1626, 1600 cm^{-1}; MS m/z 379 (MH^+ for loss of CH_3I); ^1H NMR

(DMSO-d_6, 60 °C) δ 1.86 (br s, 2 H), 2.77 (br t, J = 6.7 Hz, 2 H), 2.92 (br t, J = 6.7 Hz, 2 H), 3.08 (s, 6 H), 3.32–3.40 (br m, 2 H), 3.63–3.72 (br m, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 7.10 (s, 2 H), 7.59–7.63 (m, 3 H), 7.73–7.77 (m, 2 H); ^{13}C NMR δ 19.80, 20.51, 24.94, 51.74, 55.66, 55.74, 56.97, 61.60, 112.72, 113.16, 113.26, 118.09, 127.65, 128.91, 129.23, 129.32, 129.63, 147.72, 150.50, 161.45, 167.17. Anal. Calcd for $C_{24}H_{29}IN_2O_3$: C, 55.39; H, 5.62; N, 5.38; I, 24.39. Found: C, 55.32; H, 5.86; N, 5.32; I, 24.39.

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Registry No. **3**, 123420-50-8; **4**, 104751-08-8; **5**(R = C_6H_5), 698-16-8; **5** (R = 4-ClC_6H_5), 28123-63-9; **5**(R = 4-$CH_3OC_6H_4$), 38435-51-7; (±)-**9a**, 133964-05-3; (±)-**9b**, 133964-02-0; (±)-**9c**, 133964-07-5; (±)-**9f**, 133910-69-7; (±)-**10a**, 133964-06-4; (±)-**10b**, 133964-03-1; (±)-*N-epi*-**10b**, 133964-08-6; (±)-**10c**, 133964-04-2; **11a**, 123420-59-7; **11b**, 123420-57-5; **11c**, 123420-58-6; **11d**, 133910-73-3; **11d**·HBr, 133910-75-5; **11e**, 123420-60-0; **11e**·HCl, 133910-76-6; **11f**, 133910-74-4; **12**, 133910-70-0; **14**, 133910-71-1; **15**, 133910-72-2; **19**, 133930-03-7.

Supplementary Material Available: Details of the X-ray crystallographic analysis of **10a** (10 pages). Ordering information is given on any current masthead page.

Synthesis of a Tetramethyl Analogue of Teleocidin

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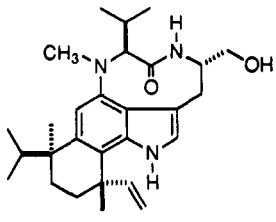
A simplified tetramethyl analogue **3** of Teleocidin B-4 (**1**) has been synthesized from dinitrotoluene **6** via indole **4**. The valine moiety of analogue **3** was provided by the coupling of (*N*-methylamino)indole **16** derived from **4** with the triflate of (*R*)-2-hydroxyvaleric acid benzyl ester, and the tryptophanyl portion was constructed by alkylation of the resulting (*S*)-*N*-valylindole **17** with ethyl (3-bromo-2-oximido)propionate to give the oxime **18**. After reduction to the diastereomeric amines **20** and **21**, closure to the 9-membered lactam–esters **24** and **23** (respectively) was accomplished using BOP. Separation and reduction of the esters led to teleocidin analogue **3** and its epimeric alcohol **25**, respectively.

The teleocidins are a family of indolactam-based alkaloids known for their tumor promoting activity.[1-3] As represented by Teleocidin B-4 (**1**), they possess the core nine-membered ring lactam present in (−)-indolactam-V (IL-V, **2**), as well as a monoterpenoid ring attached to the indole. In addition to potent tumor promotion, they are also known to activate protein kinase C (PKC),[4,5] with activities similar to that displayed by the phorbol esters.[6] Since PKC plays a major role in mediating signal transduction and cell differentiation in many cell types,[4,5] the ability to modulate PKC activity might allow the development of strategies for therapeutic intervention in many disease pathologies.



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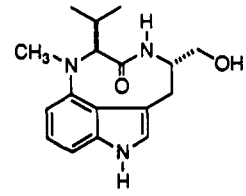

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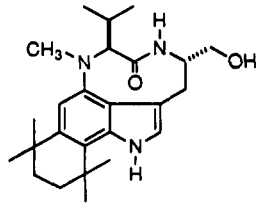

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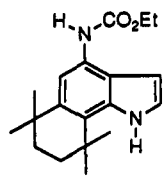

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Toward this end, we sought to obtain a more potent and synthetically accessible IL-V analogue for biochemical studies. Analogue **3** seemed a reasonable target of this effort, wherein methyl groups would replace the isopropyl and vinyl groups of the monoterpenoid ring of teleocidin B-4 (**1**), yet the saturated six-membered ring would be retained. This would obviate the need for the synthesis of a chiral monoterpene ring appendage but would hopefully retain the level of activity exhibited by the teleocidins. Although much synthetic effort has been directed at IL-V and various 7-substituted derivatives,[7a-g] little activity regarding the synthesis of analogues of teleocidin B-4 (**1**) has been recorded.[8] We report herein the first synthesis of a teleocidin analogue retaining the saturated six-mem-

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