Total Synthesis of the Clavicipitic Acids by an Intramolecular Azide Cycloaddition Strategy

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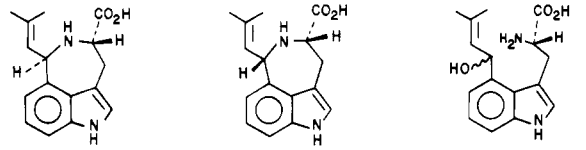
A straightforward total synthesis approach to the structurally unique ergot derailment products, the clavicipitic acids **1** and **2**, is described. The synthetic strategy is based on the formation of the seven-membered nitrogen-containing ring of **1** and **2** through an intramolecular azide cycloaddition process. The cycloaddition strategy, which produces solely the imine product **24**, does in some sense mimic the proposed biosynthetic pathway to these acids.

The structurally unique ergot derailment products, the clavicipitic acids,[1] can be assembled in the laboratory through a strategy related conceptually to our intramolecular nitrile oxide cycloaddition (INOC) approach to the ergot alkaloids themselves.[2] Herein we document the full details of this effort. Our synthesis, which is the first to be reported, underscores the versatility of a biomimetic-like approach to the indole alkaloids and provides further structural information for these compounds.

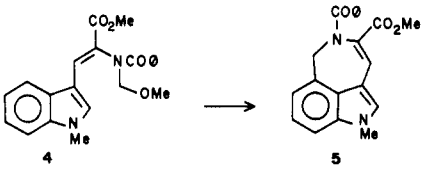
The clavicipitic acids are produced in nature as a mixture of diastereomers (one major and one minor) by *Claviceps* strain SD 58[1a] and as an approximately 1:1 mixture of diastereomers by *Claviceps fusiformis* 1392/2/1G.[1b,c] While the structures of the clavicipitic acids were initially assigned incorrectly by Floss,[3] the structures were later reassigned (correctly) by King and Waight.[1c] Subsequently, Floss carried out an X-ray analysis on his major isomer and found it to possess the structure embodied by structure **1**.[1a] The substituents at C_5 and C_{10} in the



clavicipitic acid (major, 1) clavicipitic acid (minor, 2) 10-hydroxy-DMAT (3)

"major" acid assume a trans disposition about the seven-membered ring. The minor isomer is assumed to possess the 5*S*,10*S* configuration as shown in **2**. From isotopic labeling studies, Floss has concluded that the clavicipitic acids represent derailment products in ergot biosynthesis between the first step, the isoprenylation of tryptophan, and the second, the N-methylation of 4-(γ,γ-dimethylallyl)tryptophan (DMAT).[1a] DMAT oxidase apparently catalyzes the 10-hydroxylation of DMAT, and the product **3** then undergoes internal displacement to produce the clavicipitic acids. Alternatively, a direct oxidative cyclization mechanism may be involved.

During the course of our work in this area, the only report to appear concerning a synthetic approach to the clavicipitic acids was that of Nakatsuka et al.[4] The dehydrotryptophan derivative **4** (*E*,*Z* mixture) was cyclized to the 4-substituted indole **5**. No specific plans for appending the isobutenyl side chain at C-10 were, however, disclosed.



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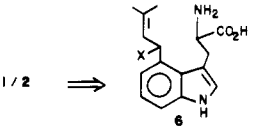
Results and Discussion

The proposed biosynthetic pathway to the clavicipitic acids does, in fact, suggest a logical sequence for assembling these compounds in the laboratory. One would only need to build a DMAT derivative containing some potential leaving group in the γ,γ-dimethylallyl appendage. With this notion in mind, we thus set out to prepare a 3,4-disubstituted indole such as **6**. The *N*-tosyl derivative of



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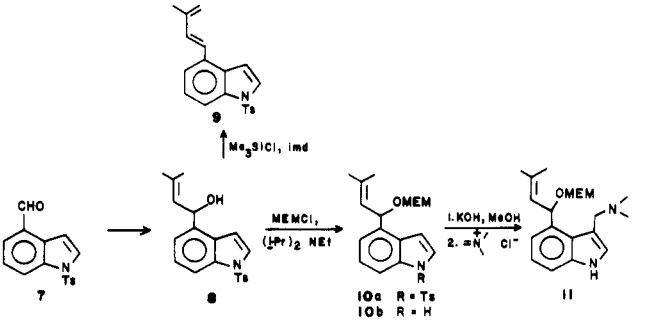
indole-4-carboxaldehyde (**7**) underwent smooth addition of 2-methyl-1-propenylmagnesium bromide to afford the alcohol **8**. Protection of the hydroxyl of **8** was now deemed necessary prior to introduction of the requisite amino acid residue at C_3.

While attempted trimethylsilylation led primarily to dehydration with formation of the diene **9**,[5] the hydroxyl group of **8** could be protected as its methoxyethoxymethyl (MEM) ether.[6] N-Detosylation of **10a** with methanolic potassium hydroxide then rendered the indole 3-position active toward electrophilic substitution. Our plan called for converting **10b** to its tryptophan derivative by way of a gramine intermediate. Unfortunately, reaction of **10b** with dimethylmethyleneammonium chloride resulted in only a 5% isolated yield of the desired amine **11**.[7]



7 8 10a R = Ts 10b R = H 11

(1) (a) Robbers, J. E.; Otsuka, H.; Floss, H. G.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1117. (b) King, G. S.; Mantle, P. G.; Szczyrbak, C. A.; Waight, E. S. *Tetrahedron Lett.* **1973**, 215. (c) King, G. S.; Waight, E. S.; Mantle, P. G.; Szczyrbak, C. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2099. (d) Kozikowski, A. P.; Greco, M. N. *Heterocycles* **1982**, *19*, 2269.

(2) Kozikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265. Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. Kozikowski, A. P.; Greco, M. N. *J. Am. Chem. Soc.* **1982**, *104*, 7622.

(3) Robbers, J. E.; Floss, H. G. *Tetrahedron Lett.* **1969**, 1857.

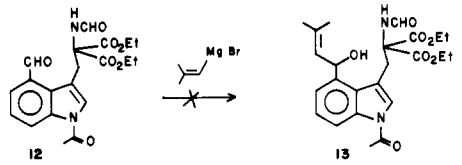
(4) Nakatsuka, S.; Miyazaki, H.; Goto T. *Chem. Lett.* **1981**, 407.

(5) Chaudry, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

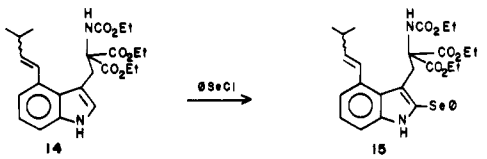
(6) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

0022-3263/84/1949-2310$01.50/0

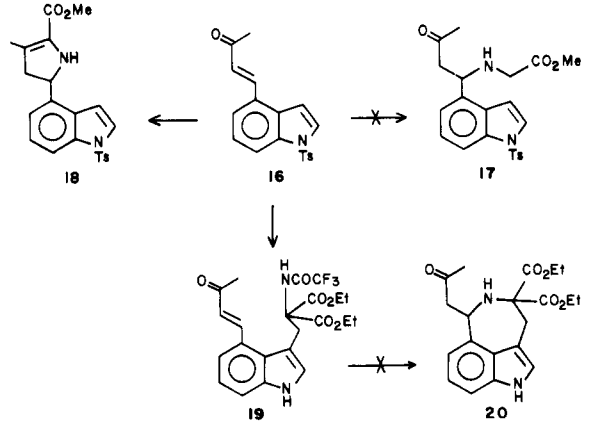
An attempt was therefore made to elaborate the 3-position of indole-4-carboxaldehyde first and then to introduce the isobutenyl unit by way of the Grignard reagent. While **12** could be prepared readily and in high yield, its coupling reaction with 2-methyl-1-propenylmagnesium bromide led to intractable products rather than the desired allylic alcohol **13**.



A tryptophan derivative (**14**) related to **6** but in a lower oxidation level (X = H) was constructed next with the intention of keying a direct oxidative cyclization reaction, a process which might also mimic the actual biosynthetic pathway. Yet again success eluded us, for neither aminoselenation[8] nor aminometalation procedures brought about the desired ring closure.[9,10] Phenylselenenyl chloride appeared to give the 2-substituted (phenylseleno)indole **15** in poor yield.



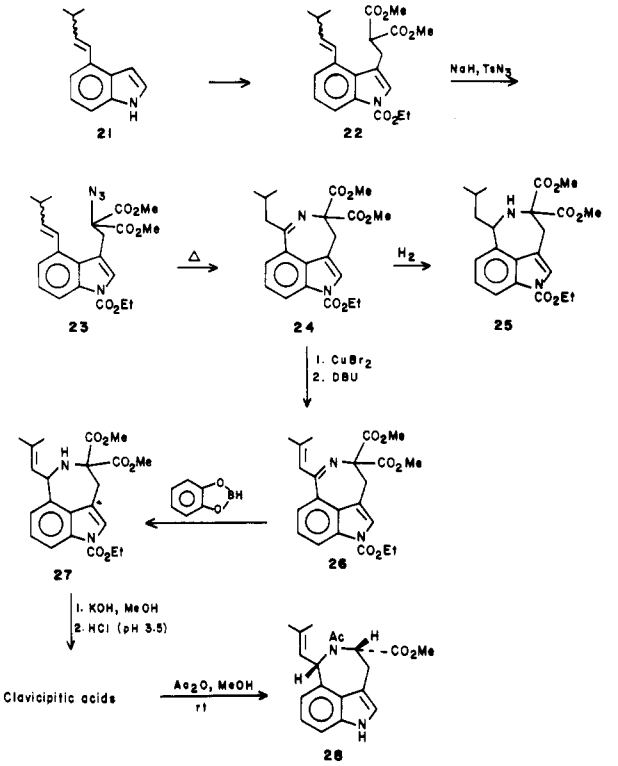
Before finally finding a productive synthetic pathway to the clavicipitic acids, we had examined additionally both the intermolecular Michael reaction of the butenone **16**



with methyl glycinate and a possible intramolecular Michael route as well. The obtention of **17** would have allowed us to subsequently formylate the indole 3-position in order to key an internal Knoevenagel condensation. The Michael reaction succeeded, but a second intramolecular condensation with the ketone carbonyl group intervened to produce the dihydropyrrole **18**. The intermediate **19** required for use in the intramolecular Michael approach was easily assembled, but attempts to cleave its *N*-trifluoroacetyl group resulted in the generation of polar, uncharacterizable products.

Faced with the foregoing difficulties of generating the C_{10}–N_6 bond by a "polar, stepwise" process, we eventually

Scheme I



decided to investigate the concerted intramolecular addition of an azide to the neighboring double bond of the indole C_4 appendage. Dipolar additions of azides to olefins are well precedented, and the intermediate triazolines generated in the initial [3 + 2] reaction have been shown to lose nitrogen with formation of aziridines and/or imines. Important mechanistic details on the decompositions of 1,2,3-triazolines have been provided by Scheiner.[11,12]

The olefin **21**, prepared from the Wittig reaction between indole-4-carboxaldehyde and isobutylidenetriphenylphosphorane as a 3:1 *Z*/*E* mixture, was thus converted to its gramine derivative via a conventional Mannich procedure. Reaction of this gramine derivative in turn with dimethyl malonate using tri-*n*-butylphosphine as catalyst followed by protection of the indole nitrogen with ethyl chloroformate gave **22**.

The anion of **22**, generated by sodium hydride treatment, was treated with tosyl azide to furnish the required intermediate **23**.[13] On heating **23** in *o*-dichlorobenzene at 190–195 °C for 8 h, a single imine was formed in good yield (Scheme I). While the ^{1}H NMR of this product displayed relatively broad peaks, upon hydrogenation an amine was generated which gave an ^{1}H NMR spectrum possessing sharp and easily interpretable signals. Decoupling experiments confirmed the structure of this amine as **25** and thus further secured the structure of the imine **24**. That none of the aziridine was produced in the azide cycloaddition reaction can be attributed perhaps to both the strain associated with generating such a three-membered ring fused to a fairly constrained seven-membered ring and a hydrogen migration made favorable by benzylic stabilization.[14] The regiochemistry of the [3 + 2] cycloaddition

(7) Kozikowski, A. P.; Ishida, H. *Heterocycles* **1980**, *14*, 55.
(8) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120.
(9) Hegedus, L. F.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.
(10) Hegedus, L. F.; Korte, D. E.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.
(11) Padwa, A. In "Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; Wiley: New York, 1984; Chapter 12, Vol. 2. Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123.
(12) (a) Scheiner, P. *J. Am. Chem. Soc.* **1968**, *90*, 988. (b) Scheiner, P. *Tetrahedron* **1968**, *24*, 2757. (c) Scheiner, P. In "Selective Organic Transformations"; Wiley Interscience: New York, 1970; Vol. 1, p 327.
(13) Wasserman, H.; Lipshutz, B.; Tremper, A.; Wu, J. *J. Org. Chem.* **1981**, *46*, 2999.

reaction is guided primarily by the geometric and steric constraints imposed on the reaction as a consequence of its intramolecularity.[15]

The fact that the reaction proceeded readily in the more polar solvent *o*-dichlorobenzene, but poorly in toluene (sealed tube, 190 °C), provides indirect evidence for the formation of a polar intermediate (i.e., the zwitterion formed on loss of nitrogen from the triazoline) during the course of the seven-membered ring formation.[14] Such a solvent effect would not be anticipated if a nitrene mechanism was operative. The absence of other products in this reaction (e.g., the amine formed via proton abstraction from the solvent or the pyrroline formed by nitrene insertion into the indole C_2–H bond)[16] also provide good support for the formation of **24** by way of an initial [3 + 2] cycloaddition reaction.

To complete the synthesis, the imine was simply brominated with cupric bromide in $CHCl_3$/EtOAc,[17] and the resulting α-bromo imine dehydrohalogenated with DBU in toluene. The enimine product **26** was then selectively reduced with catecholborane to provide the olefin **27**.[18] Hydrolysis and decarboxylation of **27** with 2 N KOH/MeOH yielded clavicipitic acid as a mixture of both isomers in a ratio of ~1:1. The R_f values of these isomeric acids were identical with those of the natural products.[19] Additionally, the mass and UV spectral data obtained for the synthetic acids were identical with those obtained for the natural acids. Since we found it difficult to obtain an NMR of these acids for reasons of their insolubility, both the synthetic and natural acids were derivatized by treatment with acetic anhydride/methanol[20] to yield in each instance a chromatographically homogeneous product, an *N*-acetyl methyl ester, possessing identical R_f, IR, and 300-MHz ^{1}H NMR characteristics. Interestingly, we made the observation that under these derivatization conditions only a single product was formed (HPLC analysis).[21] Apparently, one of the isomers of clavicipitic acid had undergone epimerization so that only a single *N*-acetyl methyl ester resulted. Epimerization of amino acids by way of their azalactone intermediates is, of course, a well-documented event. A related epimerization mechanism could operate here even though the seven-membered ring nitrogen is secondary. The only question that remained then is which isomer is being converted into the other? Such an epimerization reaction does, of course, possess the virtue of turning a stereorandom synthesis scheme into a stereoselective one. During the course of pursuing an answer to this question, we received a reprint of a paper from Professor Natsume of the Itsuu Laboratory in which he had examined this precise point. He and his co-workers had separated the individual clavicipitic acids and examined their behavior in acetic anhydride/methanol. That isomer possessing a trans relationship between the carboxyl group and the isobutenyl appendage isomerized to the more stable cis compound **28**.[22] In the cis compound, the various nonbonded (transannular) interactions associated with placing substituents about a fairly constrained seven-membered ring are apparently minimized.

In conclusion, we believe that the azide cycloaddition chemistry provides a remarkably efficient route to the clavicipitic acids. The chemistry underscores the importance of considering concerted, cycloaddition based approaches to C–N bond formation in cases where alternative nonconcerted, polar processes fail. The seven-membered nitrogen ring forming strategy should find application in the construction of the pharmacologically important agents, the 2-benzazepines.[23,24]

Experimental Section

^{1}H NMR spectra were recorded on a Varian T-60, Varian EM-360, Varian EM-390, or Bruker WH-300 spectrometer by using tetramethylsilane as the internal standard. Infrared spectra were recorded on either a Perkin-Elmer 247 or 700 infrared spectrophotometer with the polystyrene absorption at 1602 cm^{-1} as the reference. Low-resolution mass spectra were determined on a LKB-9000 instrument. High-resolution mass spectra were determined on a Varian MAT CH-5DF instrument by peak matching.

Gravity column chromatography and flash column chromatography were carried out on E. Merck 0.063–0.200-mm and 0.040–0.063-mm silica gel, respectively. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F-254 on plastic or aluminum supported plates. Alumina column chromatography was carried out on Woelm basic alumina, while analytical thin-layer chromatography was performed on E. M. Merck aluminum oxide F-254 neutral Type T 0.20-mm aluminum supported plates. Distilled reagent-grade solvents were used for all chromatographic separations. High-pressure liquid chromatography was carried out on a Waters Associates instrument on a μ-Porasil column.

Benzene, toluene, and hexamethylphosphoramide were distilled from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

4-(3-Methyl-1-butenyl)indole (21). To a slurry of 317 mg (0.826 mmol) of (2-methylpropyl)triphenylphosphonium bromide (prepared from commercially available 1-bromo-2-methylpropane) and 4 mL of dry THF was added dropwise 0.52 mL (0.826 mmol) of *n*-butyllithium at 0 °C under a nitrogen atmosphere. The dark red solution was warmed to room temperature over 45 min after which time a 1 M THF solution of indole-4-carboxaldehyde (57 mg, 0.39 mmol) was added dropwise at room temperature. After 1.5 h at room temperature, the reaction mixture was poured into saturated ammonium chloride and extracted repeatedly with ethyl acetate. The organic extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using 3:1 ethyl acetate–hexanes yielded 55 mg (77%) of **21** as a pale yellow oil which was a 3:1 cis/trans mixture: IR ($CHCl_3$) 3509, 3448, 1626, 1600, 1370, 1351 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.96 (d, 6 H, J = 7 Hz, cis), 1.08 (d, 6 H, J = 7 Hz, trans), 2.68–3.08 (m, 1 H, cis), 2.08–2.65 (m, 1 H, trans), 5.53 (dd, 1 H, J = 12, 9 Hz, cis), 6.16 (dd, 1 H, J = 15, 7.5 Hz, trans), 6.38–7.31 (m, 7 H), 8.01–8.42 (br s, 1 H); exact mass calcd for $C_{13}H_{15}N$ 185.1204, found 185.1204.

4-(3-Methyl-1-butenyl)-3-[(dimethylamino)methyl]indole. A stock solution of the Mannich reagent was prepared according to Plieninger et al.[24] To 72 mg (0.39 mmol) of **21** was added 0.13 mL of the Mannich reagent at 0 °C. The reaction was stirred

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(15) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403. Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. The addition of phenyl azide to *cis*- or *trans*-β-methylstyrene has been shown to provide a single triazoline possessing a 1,5-disposition of phenyl groups in each instance. Scheiner, P. *J. Am. Chem. Soc.* **1968**, *90*, 988.

(16) A recent study demonstrates that indoles are formed from (*o*-azidophenyl)alkenes by a mechanism involving attack of a nitrene directly on the β-carbon atom and not by insertion: Smith, P. A. S.; Rowe, C. D.; Hansen, O. W. *Tetrahedron Lett.* **1983**, *24*, 5169.

(17) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.

(18) Kabalka, G. W.; Baker, J. D.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512.

(19) We thank Professor Heinz Floss of The Ohio State University for providing us with a sample of the natural acids.

(20) Morris, H. R.; Williams, D. H.; Ambler, R. P. *Biochem. J.* **1971**, *125*, 189.

(21) See footnote 10 of ref 1d.

(22) Muratake, H.; Takahashi, T.; Natsume, M. *Heterocycles* **1983**, *20*, 1963.

(23) Kasparek, S. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J. Eds.; Academic Press: New York, 1974; Vol. 17.

(24) Plieninger, H.; Wagner, C.; Immel, H. *Liebigs Ann. Chem.* **1971**, *743*, 95.

for 0.5 h at 0 °C and 3 h at room temperature. The products were acidified with 0.2 mL of 2 N HCl and extracted repeatedly with ethyl acetate. The ethyl acetate phase was extracted repeatedly with dilute HCl and then discarded. The aqueous phases were combined and adjusted to pH 10 with ice-cold 40% sodium hydroxide. The product which separated as an oil was extracted with ethyl acetate, and the extract was washed with water, dried over $MgSO_4$, concentrated, and chromatographed on activity grade III basic alumina to yield 76 mg (81%) of the title compound as a white solid. Analytical samples of the cis (mp 124–126 °C) and trans (mp 85–87 °C) compounds were prepared by recrystallization from hexanes: IR ($CHCl_3$) cis 3416, 1616, 1355, 1337 cm^{-1}; trans 3481, 1455, 1260, 1240, cm^{-1}; ^1H NMR ($CDCl_3$) cis δ 1.00 (d, 6 H, J = 7 Hz), 2.30 (s, 6 H), 2.67–3.07 (m, 1 H), 3.61 (s, 2 H), 5.55 (dd, 1 H, J = 12, 11 Hz), 6.90–7.30 (m, 5 H), 8.01–8.23 (br s, 1 H); ^1H NMR ($CDCl_3$) δ trans 1.08 (d, 6 H, J = 7 Hz), 2.31 (s, 6 H), 2.33–2.59 (m, 1 H), 3.61 (s, 2 H), 5.97 (dd, 1 H, J = 15, 7.5 Hz), 6.68–7.50 (m, 5 H), 8.01–8.22 (br s, 1 H); exact mass calcd for $C_{16}H_{22}N_2$ 242.1778, found 242.1778.

Methyl 2-Carbomethoxy-3-[4-(3-methyl-1-butenyl)-3-indolyl]propionate. To a solution of 50 mg (0.21 mmol) of the preceding gramine derivative, 0.03 mL (0.25 mmol) of dimethyl malonate, and 2 mL of acetonitrile was added at room temperature under a nitrogen atmosphere 12.8 mg (0.06 mmol) of tri-*n*-butylphosphine in 0.15 mL of acetonitrile. The reaction was refluxed for 7 h, cooled to room temperature, and acidified with 0.5 N HCl (red litmus). The aqueous layer was extracted twice with ethyl acetate, and the extracts were dried ($MgSO_4$) and concentrated. Chromatography on silica gel using 3.5:6.5 ethyl acetate–hexanes yielded 51 mg (74%, 3:1 cis/trans) of the title compound as a clear, viscous oil: IR ($CHCl_3$) 3546, 1748, 1616, 1337, 1278; cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 6 H, J = 6.67 Hz, cis), 1.13 (d, 6 H, J = 6.87 Hz, trans), 2.47–2.60 (m, 1 H, trans), 2.73–2.81 (m, 1 H, cis), 3.46 (d, 2 H, J = 7.68 Hz, cis), 3.52 (d, 3 H, J = 7.68 Hz, trans), 3.69 (s, 6 H, cis), 3.70 (s, 6 H, trans) 3.83–3.88 (overlapping m, 1 H), 5.62 (dd, 1 H, J = 11.32, 10.30 Hz, cis), 6.14 (dd, 1 H, J = 15.56, 6.87 Hz, trans), 6.82–7.25 (m, 5 H), 8.05 (br s, 1 H); exact mass clacd for $C_{19}H_{23}NO_4$ 329.1627; found 329.1627.

Methyl 2-Carbomethoxy-3-[4-(3-methyl-1-butenyl)-1-carbethoxy-3-indolyl]propionate (22). To a solution of 200 mg (0.61 mmol) of the preceding propionate, 69 mg (0.67 mmol) of triethylamine, and 1 mL of dry acetonitrile was added dropwise with stirring at 0 °C 73 mg (0.67 mmol) of ethyl chloroformate. After 3 h at 0 °C, 1 mmol of triethylamine was added followed by 1 mmol of ethyl chloroformate. The reaction mixture was stirred for 29 h at 4 °C and then quenched with ice and extracted 3 times with ethyl acetate. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Chromatography on silica gel using 3:1 hexanes–ethyl acetate as eluent provided 215 mg (88%) of the desired *N*-carbethoxylated compound as a clear viscous oil (3:1 cis/trans mixture): IR ($CHCl_3$) 1730, 1340, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 6 H, J = 6.5 Hz, cis), 1.12 (d, 6 H, J = 6.7 Hz, trans), 1.44 (t, 3 H, J = 7.05 Hz), 2.49–2.61 (m, 1 H, trans), 2.63–2.71 (m, 1 H, cis), 3.40 (d, 2 H, J = 7.50 Hz, cis), 3.45 (d, 2 H, J = 7.87 Hz, trans), 3.72 (s, 3 H), 3.81–3.87 (overlapping m, 1 H, cis and trans), 4.45 (q, 2 H, J = 7.05 Hz), 5.65 (dd, 1 H, J = 11.11, 10.51 Hz, cis), 6.13 (dd, 1 H, J = 15.56, 6.67 Hz, trans), 6.74–7.40 (m, 5 H), 8.10–8.13 (m, 1 H); exact mass calcd for $C_{22}H_{27}NO_6$: 401.1838, found 401.1838. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.80; H, 6.80; N, 3.49. Found: C, 65.55; H, 6.96; N, 3.48.

Methyl 2-Azido-2-carbomethoxy-3-[4-(3-methyl-1-butenyl)-1-carbethoxy-3-indolyl]propionate (23). To 5.2 mL of THF, 0.62 mL of HMPA, and 42 mg (1.72 mmol) of NaH (degreased with benzene) was added all at once at room temperature under nitrogen 625 mg (1.56 mmol) of **22** dissolved in 1.5 mL of THF. After 2 h, 341 mg (1.72 mmol) of tosyl azide was added dropwise at room temperature, and the reaction was refluxed for 2 h. After cooling to room temperature, the products were poured into saturated $NaHCO_3$ and extracted 3 times with ethyl acetate. The organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography with 1:9 ethyl acetate–hexanes provided 426 mg (62%) of the azido olefin **23** as a 3:1 cis/trans mixture. An analytical sample of *cis*-**23** was prepared from the pure cis-gramine derivative: mp 83–84 °C (hexanes); IR ($CHCl_3$) 2050, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 6 H, J = 6.5 Hz), 1.47 (t, 3 H, J = 7.2 Hz), 2.49–2.59 (m, 1 H), 3.60 (s, 2 H), 3.83 (s, 6 H), 4.48 (q, 2 H, J = 7.2 Hz), 5.64 (dd, 1 H, J = 11.4, 10.0 Hz), 6.82–7.53 (m, 4 H), 8.12 (br d, 1 H, J = 8.4 Hz); exact mass calcd for $C_{22}H_{26}N_4O_6$ 442.1852, found 442.1852. Anal. Calcd for $C_{22}H_{26}N_4O_6$: C, 59.70; H, 5.93; N, 12.67. Found: C, 59.68; H, 5.87; N, 12.46.

Dimethyl 1-Carbethoxy-3,4-dihydro-6-(2-methylpropyl)-azepino[5,4,3-*cd*]indole-4,4-dicarboxylate (24). A solution containing 0.6 mL of *o*-dichlorobenzene and 25 mg of **23** was refluxed for 3.75 h (nitrogen evolution could be monitored by using a bubbler). After being cooled to room temperature, the solution was chromatographed on silica gel with 4:1 ethyl acetate–hexanes to yield 15 mg (62%) of the desired imine **24** as a light yellow semisolid: IR 1740, 1619 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 6 H, J = 7 Hz), 1.46 (t, 3 H, J = 7 Hz), 1.90–2.33 (m, 1 H), 2.88 (br d, 2 H, J = 6 Hz), 3.60 (br s, 8 H), 4.51 (q, 2 H, J = 7 Hz, 7.33–7.70 (m, 3 H), 8.26–8.35 (m, 1 H); mass spectrum (15 eV), m/z 414 (M^+), 385, 372. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.67; H, 6.31; N, 6.62.

Dimethyl 1-Carbethoxy-3,4-dihydro-6-(1-bromo-2-methylpropyl)azepino[5,4,3-*cd*]indole-4,4-dicarboxylate. To a suspension of 328 mg (1.5 mmol) of finely ground cuprous bromide in 2.0 mL of dry ethyl acetate was added dropwise with stirring at room temperature 363 mg (0.88 mmol) of imine **24** in 1.0 mL of dry chloroform. After stirring for 3 days at room temperature, the crude products were filtered through Celite, concentrated in vacuo, and chromatographed on silica gel by using 5:1 ethyl acetate–hexanes as eluent to yield 334 mg (77%) of the title compound: mp 131 °C dec (hexanes); IR ($CHCl_3$) 1748, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (br s, 3 H), 1.36 (br s, 3 H), 1.47 (t, 3 H, J = 7.00 Hz), 1.64–1.78 (br m, 1 H), 3.18–3.37 (overlapping m, 5 H, BrC*H* and $H_3COC(O)CCH$), 3.69 (br d, 1 H, J = 15.00 Hz), 3.88 (br s, 3 H), 4.49 (q, 2 H, J = 7.00 Hz), 7.36–8.59 (m, 4 H); exact mass calcd for $C_{22}H_{24}N_2O_6Br$ 491.0818, found 491.0811.

Dimethyl 1-Carbethoxy-3,4-dihydro-6-(2-methyl-1-propenyl)azepino[5,4,3-*cd*]indole-4,4-dicarboxylate (26). A solution of the preceding bromide (10 mg, 0.02 mmol), DBU (9 μL, 0.06 mmol), and 0.5 mL of dry toluene were stirred under a nitrogen atmosphere at 80 °C for 6 h. After being cooled to room temperature, the reaction mixture was poured into water and extracted 3 times with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was taken up in ethyl acetate and passed through a silica gel plug. The crude enimine was further purified by HPLC on a μ-Porasil column using 1:3 hexanes–ethyl acetate as the eluent. The enimine **26** was isolated in 33% yield (55% based on recovered starting material) as a light yellow oil: IR ($CHCl_3$) 1737, 1651, 1611, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (t, 3 H, J = 7 Hz), 1.97 (s, 6 H), 3.63 (br s, 8 H), 4.5 (q, 2 H, J = 7 Hz), 6.20–6.40 (m, 1 H) 7.23–7.57 (m, 3 H), 8.14–8.33 (m, 1 H); exact mass calcd for $C_{22}H_{24}N_2O_6$ 412.1634, found 412.1635.

Dimethyl 1-Carbethoxy-3,4,5,6-tetrahydro-6-(2-methyl-1-propenyl)azepino[5,4,3-*cd*]indole-4,4-dicarboxylate (27). To a solution of the enimine **26** (58 mg, 0.14 mmol) in 0.2 mL of chloroform was added 3.4 mg (0.28 mmol) of catecholborane dropwise at 0 °C under a nitrogen atmosphere. After 0.5 h, the reaction was warmed to room temperature and quenched with excess concentrated ammonium chloride. The mixture was then poured into ethyl acetate and extracted 3 times with additional ethyl acetate. The combined ethyl acetate layers were washed repeatedly with 0.1 N Na_2CO_3. The organic layer was washed with water, dried, and concentrated. Chromatography on SilicAR CC-7 using 4:1 ethyl acetate–hexanes as eluent provided 51 mg (87%) of the desired amine **27** as a crystalline solid: mp 124–125 °C (CH_2Cl_2–hexanes); IR ($CHCl_3$) 3388, 1724, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.00 Hz), 1.72 (s, 3 H), 1.87 (s, 3 H), 3.01 (br s, 1 H), 3.48 (d, 1 H, J = 16.03 Hz) 3.72 (s, 3 H), 3.77 (d, 1 H, J = 16.03 Hz), 3.78 (s, 3 H), 4.43 (q, 2 H, J = 7.00 Hz), 5.21 (d, 1 H, J = 8.04 Hz), 5.39 (d, 1 H, J = 8.04 Hz), 6.78–7.38 (m, 3 H), 7.86–7.98 (m, 1 H); exact mass calcd for $C_{22}H_{26}N_2O_6$ 414.1791, found 414.1788.

Clavicipitic Acids [3,4,5,6-Tetrahydro-6-(2-methyl-1-propenyl)-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylic Acids] (1 and 2). To 0.3 mL of 2 N methanolic potassium hydroxide was added 25 mg (0.06 mmol) of **27** at room temperature. The reaction was stirred for 4 h at room temperature and then adjusted to pH 3.5 at 0 °C with 2.0 N HCl. The precipitate was filtered,

washed thoroughly with water, and then pumped to dryness. Recrystallization from ethanol produced 5.6 mg (36%) of the clavicipitic acids as a 1:1 mixture of isomers: R_f 0.27 and 0.24 (silica gel, 75:25:1 $CHCl_3$/MeOH/concentrated NH_4OH); mp 239–244 °C dec; UV (EtOH) λ_{max} 221, 288 nm; IR (KBr) 3300, 1580, 1410 cm^{-1}; mass spectrum (15 eV), m/z 270, 269, 255, 225, 215, 196, 183, 182, 169, 167, 154.

Derivitization of the Clavicipitic Acids. The acids were treated with 1 mL of dry methanol containing 0.25 mL of acetic anhydride, and the resulting solution was stirred under a nitrogen atmosphere for 9 h at room temperature. The reaction mixture was concentrated and chromatographed on SilicAR CC-7 to yield the *N*-acetyl methyl ester derivative **28** of clavicipitic acid: mp 117–119 °C (CCl_4–hexanes); UV ($CHCl_3$) λ_{max} 285 nm; IR ($CHCl_3$) 3485, 1736, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (s, 3 H), 1.91 (s, 3 H), 2.17 (s, 3 H), 3.37, 3.93 (AB portion of ABX, 2 H, J_{AB} = 16.0 Hz, J_{AX} = 6.05 Hz, J_{BX} = 4.03 Hz), 3.72 (s, 3 H), 4.44 (dd, 1 H, J = 6.05, 4.03 Hz), 5.23 (d, 1 H, J = 7 Hz), 5.86 (d, 1 H, J = 7 Hz), 6.85–7.29 (m, 4 H), 8.31 (br s, 1 H); mass spectrum (15 eV), m/z 326, 311, 283.

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Registry No. 1 (isomer 1), 33062-26-9; 1 (isomer 2), 72690-85-8; **7**, 79681-04-2; **8**, 90150-60-0; **9**, 90150-61-1; **10a**, 90150-69-9; **10b**, 90150-62-2; **11**, 90150-63-3; **12**, 90150-64-4; **14**, 90150-65-5; **15**, 90150-66-6; **16**, 88246-05-3; **18**, 90150-67-7; **19**, 90150-68-8; (*E*)-**21**, 82958-16-5; (*Z*)-**21**, 82958-15-4; (*Z*)-**22**, 82958-20-1; (*E*)-**22**, 82958-19-8; (*Z*)-**23**, 82958-22-3; (*E*)-**23**, 82958-21-2; **24**, 84935-69-3; **26**, 84935-70-6; **27**, 90150-59-7; **28**, 90242-26-5; *cis*-4-(3-methyl-1-butenyl)-3-[(dimethylamino)methyl]indole, 82958-18-7; *trans*-4-(3-methyl-1-butenyl)-3-[(dimethylamino)methyl]indole, 82958-17-6; methyl *cis*-2-carbomethoxy-3-[4-(3-methyl-1-butenyl)-3-indolyl]propionate, 90150-57-5; methyl *trans*-2-carbomethoxy-3-[4-(3-methyl-1-butenyl)-3-indolyl]propionate, 90150-58-6; dimethyl 1-carbethoxy-3,4-dihydro-6-(1-bromo-2-methylpropyl)azepino[5,4,3-*cd*]indole-4,4-dicarboxylate, 84935-71-7; indole-4-carboxaldehyde, 1074-86-8; (2-methylpropyl)triphenylphosphonium bromide, 22884-29-3; dimethyl malonate, 108-59-8; ethyl chloroformate, 541-41-3; 2-methyl-1-propenyl bromide, 3017-69-4; phenylselenyl chloride, 5707-04-0; methyl glycinate, 616-34-2.

Synthesis of *P*-Thioadenylyl-(2′–5′)-adenosine and *P*-Thioadenylyl-(2′–5′)-*P*-thioadenylyl-(2′–5′)-adenosine[1]

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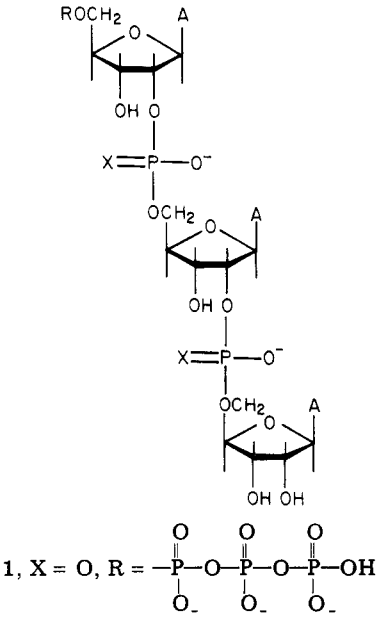
Dimer and trimer adenylates with 2′–5′ phosphorothioate linkages were synthesized via the phosphite triester approach in conjunction with sulfur oxidation. Both stability of the 2′–5′ phosphorothioate internucleotide bond and absolute configuration of the A2′p(s)5′A diastereomers (**6**) were investigated by snake venom phosphodiesterase degradation.

In recent years, analogues of the antiviral and antitumor agent pppA2′p5′A2′p5′A (**1**, commonly known as 2–5A) and its core (**2**) have been the subject of numerous syntheses.[2]



Only a few syntheses have involved the alteration of the internucleotide phosphodiester linkage, all of which removed the electrostatic charge of the phosphodiester resulting in nonionic derivatives.[2c,f] An analogue of 2–5A core, such as phosphorothioate **3**, which possesses a modified phosphodiester with retention of ionic character, would be a most interesting species. Along with the potential antiviral value of **3**, the added chirality of the two phosphorothioate groups, which results in four stereoisomers, may prove beneficial as mechanistic probes for the action of 2–5A.[3]

Since 2–5A is rapidly digested by a 2′-phosphodiesterase which shortens its duration of action, stability toward this enzyme is an essential element in the design of any 2–5A analogue.[4] It has been previously demonstrated that the

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