Intermolecular Si-H insertion competes effectively with intramolecular processes. For example, intramolecular C-H insertion reactions[19] of 1-diazo-2-nonanone, 3-diazobicyclo[2.2.1]heptan-2-one, and 2-diazo-4-*tert*-butylcyclohexanone are not observed in the presence of organosilanes. However, electrophilic substitution from catalytic decomposition of 1-diazo-3-phenyl-2-propanone resulting in the formation of 2-indanone[20] is not completely supressed with the use of 2.0 molar equiv of triethylsilane. As an alternative, copper(II) acetylacetonate, which is not as active as $Rh_2(OAc)_4$ for electrophilic substitution reactions, promotes only C-silylation in the decomposition of 1-diazo-3-phenyl-2-propanone (91% yield with Et_3SiH, 2.5 molar equiv).

The use of $Cu(acac)_2$ as an alternative to $Rh_2(OAc)_4$ was examined. With α-diazoacetophenone, $Cu(acac)_2$ promoted Si-H insertion with triethylsilane to give the corresponding α-(triethylsilyl)acetophenone cleanly in 95% yield when this reaction was performed in refluxing dichloromethane.[21] However, the product mixture from the reaction between α-diazopropiophenone and triethylsilane was complex relative to that from reactions performed with $Rh_2(OAc)_4$, the yield of silylated ketone was low (<60%), and the relative amount of O-silylation (12%) was comparable to that obtained with $Rh_2(OAc)_4$. Thus $Cu(acac)_2$ in refluxing dichloromethane appears to be comparable to $Rh_2(OAc)_4$ in its effectiveness for Si-H insertion except with α-alkyl-substituted diazo ketones. Investigations of this and related insertion reactions are currently under way.

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(19) Burke, S. D.; Grieco, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361.
(20) Nakatani, K. *Tetrahedron Lett.* **1987**, *28*, 165.
(21) In contrast, $Cu(OTf)_2$ gave complex mixture of products even when this reaction was performed at 0 °C.

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A Concise Route to the Penitrem Series of Tremorgenic Mycotoxins: Preparation of an Oxocane-Fused Indole

Summary: In this paper we record an efficient synthesis of tricyclic aniline **4**, an advanced intermediate which embodies the B-C-D rings of penitrem D (**1**). In addition, a diminutive version of the natural product, hexacycle **10**, was prepared.

Sir: In an elegant series of papers published in 1981-1983, Steyn et al. announced the structures of the penitrems (A-F), a small family of tremorgenic mycotoxins produced by the ergot fungus *Penicillium crustosum*.[1,2] The connectivity and relative stereochemistry of these complex metabolites were deduced primarily by means of high-field NMR experiments; the "partial resolution" method of Horeau served to establish their absolute configuration.[3] At that time, several studies had already implicated the penitrems in livestock syndromes characterized by acute neurologic dysfunction.[2a,4] Intrigued by their novel architecture, we recently mounted an investigation with a

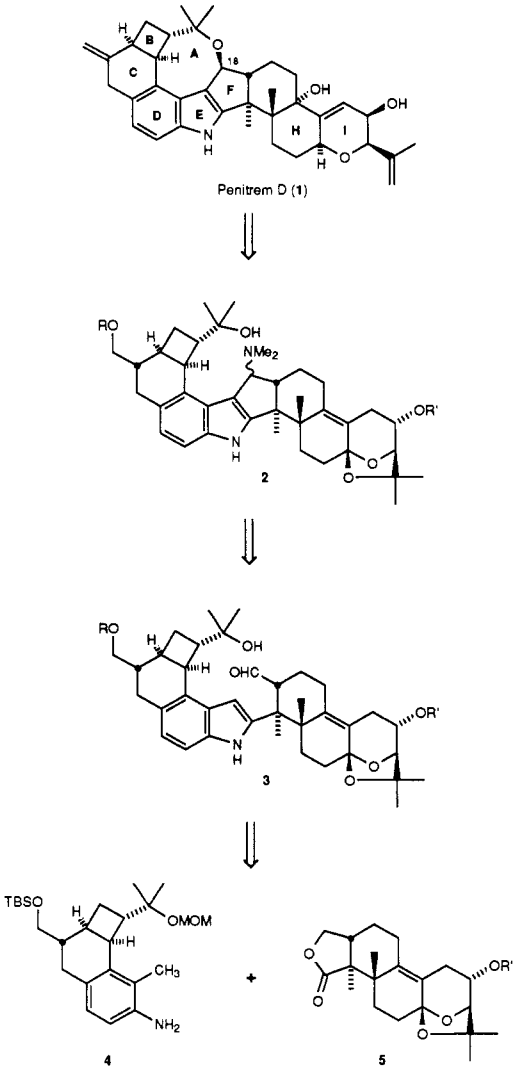

Figure 1.

(1) (a) De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289-291. (b) De Jesus, A. E.; Hull, W. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1982**, 837-838. (c) De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1847-1861. (d) De Jesus, A. E. Gorst-Allman, C. P.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans 1* **1983**, 1863-1868.

(2) Isolation studies, see: (a) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77-78. (b) Ciegler, A. *Appl. Microbiol.* **1969**, *18*, 128-129. (c) Ciegler, A.; Pitt, J. I. *Mycopathol. Mycol. Appl.* **1970**, *42*, 119-124. (d) Hou, C. T.; Ciegler, A.; Hesseltine, C. W. *Can. J. Microbiol.* **1971**, *17*, 599-603. (e) Pitt, J. I. *Mycologia* **1979**, *71*, 1166-1177. (f) Wagener, R. E.; Davis, N. D.; Diener, U. L. *Appl. Environ. Microbiol.* **1980**, *39*, 882-887. (g) Vesonder, R. F.; Tjarks, L.; Rohwedder, W.; Kieswetter, D. O. *Experentia* **1980**, *36*, 1308. (h) Kyriakidis, N.; Waight, E. S.; Day, J. B.; Mantle, P. G. *Appl. Environ. Microbiol.* **1981**, *42*, 61-62.

(3) (a) Horeau, A. *Tetrahedron Lett.* **1961**, 506-512. (b) Horeau, A.; Sutherland, J. K.; *J. Chem. Soc. C* **1966**, 247-248. (c) Herz, W.; Kagan, H. B. *J. Org. Chem.* **1967**, *32*, 216-218.

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view toward total synthesis, as well as further insight into their mode of biological action.[5] In this paper we record an efficient approach to tricyclic aniline **4**, an advanced synthetic intermediate that embodies the B–C–D rings of penitrem D (**1**), structurally the simplest member of the family. In addition, we demonstrate the viability of a general synthetic tactic for sequential generation of the E, F, and A rings of this class of tremorgens.

Our approach to penitrem D is contingent to a significant extent upon two operations. The first strategic transformation was envisioned to unite **4** with a functionalized lactone (**5**) representing rings F–I of the penitrem skeleton, thereby taking full advantage of a convergent approach. We have previously related a protocol, developed in part for this purpose, for the construction of 2-substituted indoles.[5b,c] The second strategy-level reaction would then involve formation of the oxocane ring fused to the indole nucleus. Analysis of the local connectivity in **1** led us to conjecture that the F and A rings might be conveniently installed via a tandem Mannich cyclization–gramine fragmentation;[6,7] refunctionalization of the H and I rings would then complete the synthesis of penitrem D (i.e., **3** → **2** → **1**). Importantly, it was anticipated that the ultimate cation, generated in the gramine fragmentation, would be captured stereoselectively by the proximal tertiary hydroxy group, thereby providing the necessary β-ether linkage at C(18).[8] The appeal of this scenario derived in part from the possibility that both the Mannich and gramine reactions could proceed in a single step (vide infra). Furthermore, generic versions of both reactions are known to occur under mild conditions.[6]

The synthesis of **4** begins with the preparation of enone **6**.[9a] This material was obtained in 77% yield from 3-ethoxy-2-cyclohexenone via the method of Stork and Danheiser.[10] Irradiation of **6** in the presence of excess

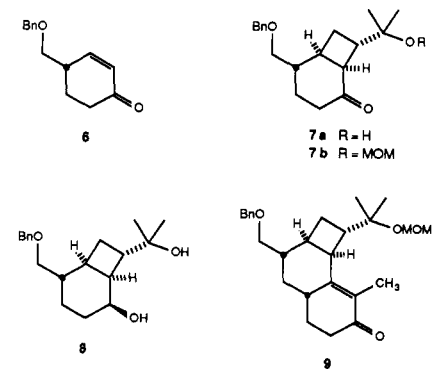


Figure 2.

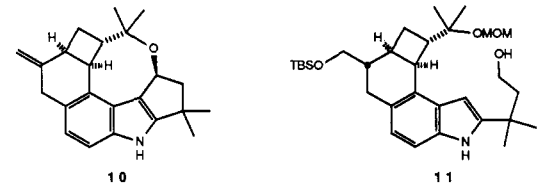


Figure 3.

methyl acrylate (CH_2Cl_2, uranium filter, 4 °C) produced a complex mixture of photoproducts, which, without purification, was subjected to the sequence: ketalization [$(MeO)_3CH$, Amberlyst-15, 0 °C], Grignard reaction (2.5 equiv of MeMgBr, benzene, room temperature), and deketalization (PPTS, acetone, room temperature); flash column chromatography then afforded keto alcohol **7a**[9] in 49% yield from **6**. Protection as the MOM ether[11] (MOMCl, *i*-Pr_2NEt, CH_2Cl_2) gave **7b**[9] in 82% yield. That the requisite relative stereochemistry had been obtained in the photocycloaddition was demonstrated by single-crystal X-ray analysis of **8**,[9,12] the major hydrogenation product of **7a** (10% Pt/C, MeOH, 42%, mp 112.5–115 °C).[13] Robinson annelation of **7b** [(a) NaH, EtOCHO, THF; (b) EVK, Et_3N; (c) KOH, $MeOH/H_2O$, Δ, 86%][14] next appended ring D to afford enone **9**.[9] The corresponding oxime was then formed (NH_2OH·HCl, NaOAc, MeOH, Δ, 87%) and subjected to a Semmler–Wolff reaction (Bz_2O, xylenes, Δ, 60%)[15] to effect aromatization. Hydrolysis of the derived benzamide (NaOH, $EtOH/H_2O$, Δ, 90%) and conversion of the benzyl ether to the TBS ether[16] [(1) H_2, $Pd(OH)_2/C$, CSA, EtOAc; (2) TBSCl, Et_3N, DMAP, CH_2Cl_2; 84%] completed construction of **4**,[9] the projected precursor of the B–C–D rings of penitrem D. The overall yield for the 15-step sequence was 10.5%.

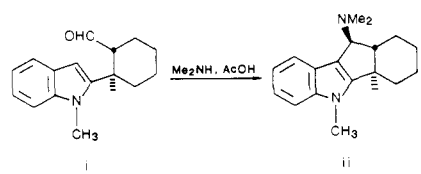
At this point, we elected to assess the feasibility of the previously mentioned strategic transformations by preparation of a diminutive version of the natural product, specifically hexacycle **10**. This model system subsumes the

(4) (a) Peterson, D. W.; Penny, R. H. C.; Day, J. B.; Mantle, P. G. *Res. Vet. Sci.* **1977**, *33*, 183. (b) Hayes, A. W.; Hood, R. D. *Toxicon* **1978**, *16*, 92. (c) Hayes, A. W.; Presley, D. B.; Neville, J. A. *Toxicol. Appl. Pharmacol.* **1976**, *35*, 311–320. (d) Hayes, A. W.; Phillips, R. D.; Wallace, L. C. *Toxicon* **1977**, *15*, 293. (e) Sobotka, T. J.; Brodie, R. E.; Spaid, S. L. *Pharmacology* **1978**, *16*, 287–294. (f) Mantle, P. G.; Mortimer, P. H.; White, E. P. *Res. Vet. Sci.* **1977**, *24*, 49–56.

(5) The work described herein is part of a larger program in our laboratory concerned with the synthesis of tremorgenic indole alkaloids. For preceding papers, see: (a) Smith, A. B., III; Mewshaw, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 1769–1771. (b) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757–3760. (c) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957–2969. (d) Smith, A. B., III; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2787–2790. (e) Smith, A. B., III; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2791–2792.

(6) For examples of similar Mannich cyclizations, see: (a) Scopes, D. I. C.; Allen, M. S.; Hignett, G. J.; Wilson, N. D. V.; Harris, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans 1*, **1977**, 2376–2385. (b) Baldwin, J. E.; Forrest, A. K.; Monaco, S.; Young, R. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1586–1587. For earlier examples of the Mannich reaction with indoles, see: (c) Kuhn, H.; Stein, O. *Chem. Ber.* **1937**, *70*, 567–569. (d) Snyder, H. R.; Eliel, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 1703–1705. For examples of gramine-type fragmentation, see: (e) Brewster, J. H.; Eliel, E. L. *Org. React.* **1953**, *7*, 106ff.

(7) Precedent for the Mannich cyclization derives from the model system (i → ii):[5c]



(8) Molecular mechanics calculations suggested an approximately 14 kcal/mol difference in the relative enthalpies of the two possible diastereomers which could derive from the oxocane formation.

(9) (a) The structure assigned to each new compound is in accord with its infrared and high-field (250 or 500 MHz) ^1H NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this new compound, obtained by recrystallization or liquid chromatography, gave satisfactory C and H combustion analysis with 0.4%.

(10) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776 and references therein.

(11) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275–1276.

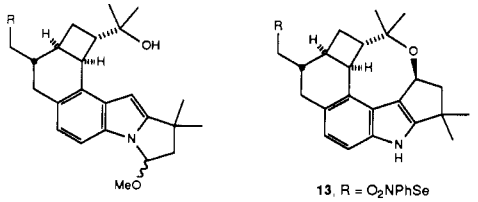
(12) Unpublished results of Dr. P. Carroll, University of Pennsylvania X-Ray Crystallographic Facility.

(13) For examples of similar regioselectivity and facial selectivity in [2 + 2]-photocycloadditions, see, respectively]: (a) Corey, E. J.; Bass, J. D.; Le Mahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570–5583. (b) Cargill, R. L.; Morton, G. H.; Bordner, J. *J. Org. Chem.* **1980**, *45*, 3929–3930.

(14) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.

(15) (a) Semmler, W. *Chem. Ber.* **1892**, *25*, 3352–3354. (b) Wolff, L. *Annalen* **1902**, *322*, 351–391. (c) For a review of the transformation, see: Conley, R. T.; Ghosh, S. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1971; Vol. 4, pp 251–308. Our conditions represent a modification of standard procedures, which typically afford the aniline as the acetamide.

(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.



12a, R = HO
12b, R = O_2NPhSe

13, R = O_2NPhSe

Figure 4.

A–E–F ring system, whose successful establishment would validate our basic strategy for the penitrems. Notably, aniline **4** was the most complex substrate to which we had applied our indole protocol.[5b,c] With this proviso in mind, **4** was silylated in situ (*n*-BuLi, TMSCl, Et_2O, −78 °C → room temperature) and then exposed to *s*-BuLi (2 equiv, room temperature, 0.75 h) to generate the presumed dianion.[17] Addition of dimethylbutyrolactone[18] at −78 °C resulted in a 20–30% yield of the desired indole (**11**),[9] in addition to 40–50% of recovered aniline **4**; attempts to improve upon this conversion were unsuccessful. Fortunately, indole **11** could be obtained in high yield from **4** by acylation with dimethylbutyrolactone (2.5 equiv of LDA, THF, −78 °C → room temperature, 88%) and subsequent subjection to the modified Madelung conditions of Fuhrer and Gschwend (4 equiv of *n*-BuLi, THF, 0 °C → room temperature, 80%).[19]

Turning next to oxocane formation,[20] the primary hydroxyl group of **11** was oxidized to the corresponding aldehyde under Moffatt conditions;[21] camphorsulfonic acid in methanol then served to deprotect the remaining hydroxyl groups to afford anomeric mixture **12a**,[9a] which was selenated ($O_2NPhSeCN$, Bu_3P, THF, room temperature)[22] to give **12b**[9a] (46% from **11**). At this juncture, we intended to exploit the previously developed Mannich cyclization for construction of the F ring;[7] oxocane formation would then follow via gramine fragmentation and carbocation capture.[6] *To our delight, however, simple exposure of* ***12b*** *to camphorsulfonic acid (benzene, room temperature) resulted in direct tandem cyclization to oxocane* ***13***[9] *in 58–64% yield*! That the relative configuration at the new stereocenter in **13** had been correctly established was deduced initially from NOE experiments and then confirmed by single-crystal X-ray diffraction.[12] Oxidative elimination of the seleno group (*m*-CPBA, collidine, CH_2Cl_2)[23] completed construction of **10**.[9] The colorless crystalline solid (mp 187 °C dec, 69%) so obtained was fully characterized. Importantly, the derived spectroscopic data (MS, UV, ^1H and ^{13}C NMR) were found to correlate well in all pertinent respects with the data obtained by Steyn for penitrem D,[1c] thereby providing additional support for the structures assigned to the penitrems.

In summary, we have completed an economic (i.e., short) synthesis of an advanced tricyclic aniline that embodies the B–C–D rings of penitrem D. In addition, we demonstrated the viability of two strategic transformations by successfully completing construction of an A–B–C–D–E–F hexacyclic analogue of the natural product. These achievements affirm the potential of the proposed penitrem synthetic strategy. Further progress in this area will be reported in due course.

Acknowledgment. Support of this research was provided by the National Institutes of Health (Institute of Neurology, Communicative Disorders and Stroke) through Grant 18254 and by the American Cancer Society through a fellowship to M.V. We also thank Drs. G. Furst, J. Dykins, and P. Carroll, Directors of the University of Pennsylvania Spectroscopic Facilities, for aid in obtaining respectively the high-field NMR, high-resolution mass spectral, and X-ray crystallographic data.

Supplementary Material Available: Full spectral and analytical data for compounds **7a**, **8**, **9**, **4**, **11**, and **10** (3 pages). Ordering information is given on any current masthead page.

(17) The use of *sec*-butyllithium in ether at ambient temperature for the formation of such dianions represents an improvement in the previously reported method,[5b,c] wherein a solution of an *N*-TMS-*o*-toluidine in hexane was treated with *n*-butyllithium (2 equiv) and then heated at reflux for 6 h under an inert atmosphere.

(18) Baas, J. L.; Davies-Fidder, A.; Huisman, H. O. *Tetrahedron* **1966**, *22*, 285–291.

(19) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133–1136. See also: Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511–4515.

(20) For examples of cationic formation of medium-ring cyclic ethers, see: Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516–3517 and references cited therein.

(21) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661–5678.

(22) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(23) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947–949.

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Additions and Corrections

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Peter M. Gannett,* Donald L. Nagel, Pam J. Reilly, Terence Lawson, Jody Sharpe, and Bela Toth. The Capsaicinoids: Their Separation, Synthesis, and Mutagenicity.

Page 1064. The following reference was inadvertently omitted: Suzuki, T.; Iwai, K. In *The Alkaloids*; Brossi, A., Ed.; Academic Press; New York, 1984; Vol. 23, pp 227–229. We thank Drs. J. Jurenitsch and H. Viernstein for bringing this to our attention.

Jurenitsch and co-workers (Jurenitsch, J.; David, M.; Heresch, F.; Kubelka, W. *Plant Med.* **1979**, *36*, 61) have concluded from degradation studies of homocapsaicin (**2c**) that the double bond is in the 6-position of the side chain and not the 7-position as we claimed.

Page 1065, column 1, line 13. Replace "norcapsaicin (**2a**)" with "norcapsaicin (**1a**)".

Page 1067, Table III. Footnotes *c*, *d*, and *f* should read as follows: [c] ***1b*/2b** control 18 ± 1, 2-aminoanthracene (AA) 2498 ± 147, red pepper extract (RPE) 32 ± 2, AA 1989 + 105. [d] ***1b*/2b** control 32 ± 3, AA 2656 ± 69, RPE 18 ± 2, AA 2566 ± 149. [f] ***1b*/2b** control 19 ± 2, AA 252 ± 39, RPE 14 ± 2, AA 224 ± 39.

Page 1067, column 2, line 49. Replace "**2a** (t_R 10.2 min), **1a** (t_R 14.8 min)" with "**1a** t_R 10.2 min), **2a** (t_R 14.8 min)".

Page 1070, column 2, line 53. Replace "procedures.[24]" with "procedures.[6,24]"

Page 1070, column 2, line 55. Replace "Bhide.[6]" with "Bhide.[7]"

The page number for ref 20a should be 3463.