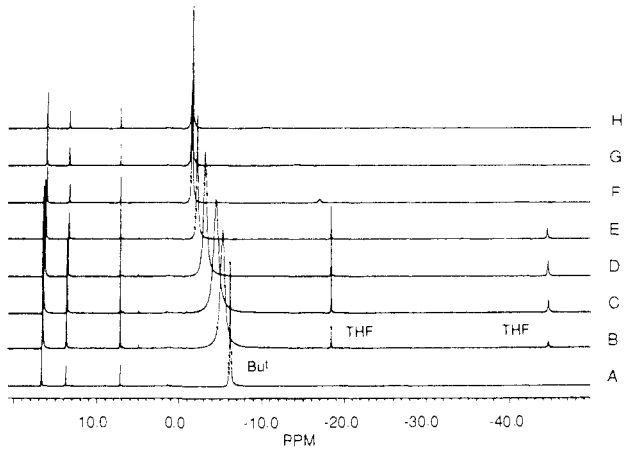

Figure 2. A series of ^{1}H NMR spectra (300 MHz, 22 °C) in which (A) 0 equiv; (B) 0.208 equiv; (C) 0.417 equiv; (D) 0.625 equiv; (E) 0.833 equiv; (F) 1.04 equiv; (G) 1.25 equiv; (H) 1.77 equiv of THF were added to 50.0 mg of U(O-2,6-$Bu^t_2C_6H_3)_3$ in ca. 2 mL of benzene-d_6. The ^{1}H impurity signal of the benzene-d_6 solvent is indicated with an asterisk.

bridges rather than phenoxide oxygens. If we assume that it does so for steric reasons, then replacement of the diisopropylphenoxide with less bulky aryloxides or alkoxides may well lead to other interesting geometries. We are currently investigating this possibility. The phenoxide π-arene-uranium(III) interaction in [U(O-2,6-$Pr^i_2C_6H_3)_3]_2$ is weak, and the dimer is cleaved in benzene-d_6. Only one broad isopropyl methyl resonance is observed in the proton NMR spectrum, consistent with either mononuclear U(O-2,6-$Pr^i_2C_6H_3)_3$ or (C_6D_6)U(O-2,6-$Pr^i_2C_6H_3)_3$.

Thus far, we have not been able to grow X-ray quality crystals of **1**, but a comparison of the Nujol mull infrared spectra of **1** and **2** indicates that they have different solid-state structures. Most important is the observation of two aromatic C=C stretching vibrations at 1588 cm^{-1} (terminal OAr) and 1553 cm^{-1} (bridging OAr) in the IR spectrum of **2** and only one, at 1583 cm^{-1}, in the IR spectrum of **1**. We propose, therefore, that **1** is monomeric in the solid state. It is reasonable to suggest that intermolecular aryloxide ring coordination does not occur in **1** because of the increased steric requirements of the *tert*-butyl groups.

Unlike U[$N(SiMe_3)_2]_3$, which has a very limited coordination chemistry,[10] the uranium(III) tris-aryloxides readily coordinate a number of Lewis bases (e.g., THF, EtCN, and $OPPh_3$) in solution *and* form isolable, presumably pseudotetrahedral, adducts.[16] For example, recrystallization of **1** from THF provides a brown crystalline complex, which by elemental analysis and proton NMR[17] is (THF)U(O-2,6-$Bu^t_2C_6H_3)_3$, **3** (eq 2). Adduct

$$\underset{\mathbf{1}}{U(O\text{-}2,6\text{-}Bu^t_2C_6H_3)_3} + THF \rightarrow \underset{\mathbf{3}}{(THF)U(O\text{-}2,6\text{-}Bu^t_2C_6H_3)_3} \quad (2)$$

3 is stable at room temperature and does not lose THF under dynamic vacuum (10^{-6} Torr). We have monitored the course of reaction 2 by ^{1}H NMR spectroscopy at ambient temperature, and the results are shown in Figure 2. At THF:**1** ratios less than 1.0, the NMR resonances of THF (at δ -18.4 and δ -44.6) correspond to those for coordinated THF, and the *tert*-butyl resonance is the weighted average of the *tert*-butyl resonances of U(O-2,6-$Bu^t_2C_6H_3)_3$ and (THF)U(O-2,6-$Bu^t_2C_6H_3)_3$. At THF:**1** ratios greater than 1.0, chemical exchange of free and coordinated THF begins. The broad THF resonances (now barely visible in spectra F→H) are the weighted average of free and coordinated THF, and the *tert*-butyl resonance corresponds to (THF)U(O-2,6-$Bu^t_2C_6H_3)_3$.

(16) Van Der Sluys, W. G.; Burns, C. J.; Sattelberger, A. P., work in progress.

(17) ^{1}H NMR (25 °C, benzene-d_6, 300 MHz) (THF)U[O-2,6-$(Me_3C)_2C_6H_3]_3$ δ 16.0 (br s, meta), δ 13.4 (br s, para), δ -1.5 (br s, Me_3C), δ -18.4 (s, THF-β), δ -44.6 (br s, THF-α). Anal. Calcd (Found) for $UO_4C_{46}H_{71}$: C, 59.59 (59.57); H, 7.73 (7.58).

Further studies of the reactivity, electronic structure, and magnetic properties of the U$(OAr)_3$ molecules described herein are in progress.

Acknowledgment. We thank Drs. James R. Brainard and Kimberly A. Kubat-Martin for technical assistance and Professor Bruce E. Bursten and Dr. David L. Clark for helpful discussions. This work was performed under the auspices of the U.S. Dept. of Energy and, in part, under the auspices of the Division of Chemical Energy Sciences, Office of Basic Energy Sciences, U.S. Dept. of Energy.

Supplementary Material Available: Tables of atomic positional and isotropic equivalent thermal parameters (S1), anisotropic thermal parameters (S2), and selected bond distances and angles (S3) for **2** (6 pages). Ordering information is given on any current masthead page.

A Concise Strategy for the Syntheses of Indole Alkaloids of the Heteroyohimboid and Corynantheioid Families. Total Syntheses of (±)-Tetrahydroalstonine, (±)-Cathenamine, and (±)-Geissoschizine

Stephen F. Martin,*[1] Brigitte Benage, and James E. Hunter

Department of Chemistry, The University of Texas Austin, Texas 78712

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For a number of years, we have been engaged in the design of general strategies for the total syntheses of structurally complex alkaloids of the indole family.[2] Within this context we have recently developed an effective approach to the yohimboid[3] and heteroyohimboid classes[4] utilizing a strategy that features an intramolecular Diels-Alder reaction as a key step for the construction of the D/E ring subunit. In order to expand further the scope of these initial results in the indole alkaloid arena, we focused upon some of the unresolved challenges posed by the syntheses of tetrahydroalstonine (**1**)[5] and its biogenetic precursor cathenamine (**2**),[6] which are members of the heteroyohimboid group,

(1) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980-1985.

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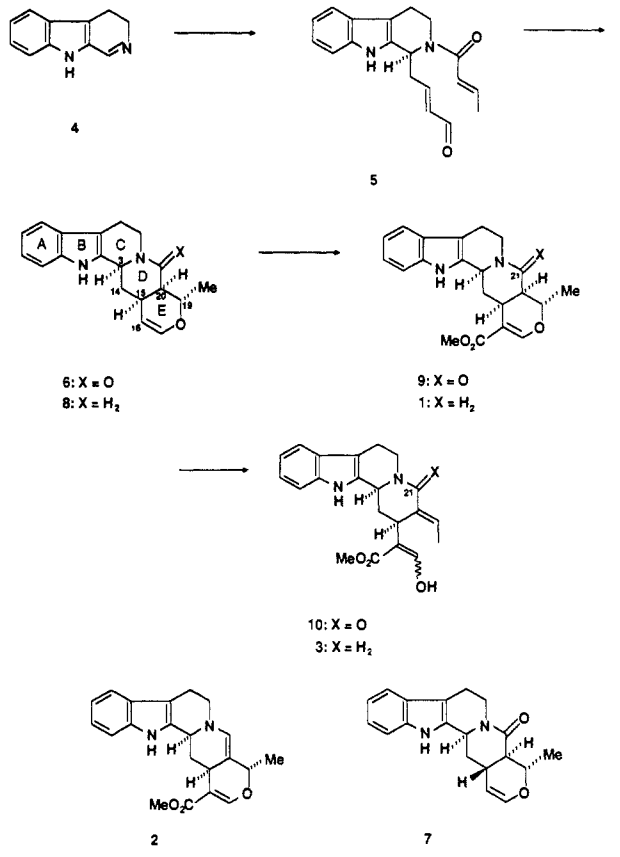
and geissoschizine (**3**),[7] a representative of the corynantheioid group.

There are several regiochemical and stereochemical problems[8] inherent in most of those approaches to the heteroyohimboid alkaloids (e.g., **1**) that rely upon tactics for the formation of the C ring via cyclization of an ABDE ring precursor as the final step of skeletal construction. One strategic device that would allow circumvention of these difficulties requires an alternative sequence in which the ABC ring subunit is secured prior to the elaboration of the D and E rings. On another front, the formulation of a satisfactory entry to the corynantheioid alkaloid geissoschizine (**3**) necessitates the attainment of a high level of control over the relative stereochemistry between the stereogenic centers at C(3) and C(15), a task that has historically proven problematic.[7] In order to resolve the deficiencies in the prevailing state of the art, we devised an improved approach to the heteroyohimboid and corynantheioid alkaloids that has culminated in extraordinarily concise routes to the title alkaloids **1–3**. Central to the success of this venture was the formulation and execution of a highly effective plan for the rapid assemblage of the pentacyclic intermediate **6** via the novel intramolecular hetero Diels–Alder reaction[9-11] of the readily accessible triene **5**.

The opening move of this endeavor required the preparation of the heterotriene **5**, and, although a variety of routes to this crucial intermediate might be envisioned, one eventuated that met the demanding criteria of brevity and efficiency. The known β-dihydrocarboline (**4**),[12] which was prepared from commercially available tryptamine in two steps [(a) EtOCHO; Δ; 12 h. (b) $POCl_3$ (10 equiv); CH_2Cl_2; 0 °C → room temperature; 5 h; 85–90% overall], was allowed to react with crotonyl chloride in the presence of 1-[(trimethylsilyl)oxy]butadiene[13] (CH_2Cl_2; −78 °C → room temperature; 1.5 h) to deliver the desired triene **5** (78%) in a *single step* (Scheme I).[14] This interesting process presumably proceeded via the nucleophilic addition of the electron rich dienyl ether to the intermediate acyl iminium salt formed by the N-acylation of **4**. Subsequent thermolysis of **5** in mesitylene (reflux, 40 h) produced a readily separable mixture (ca. 9:1) of the two pentacyclic cycloadducts **6** and **7** in 89% total yield; there was no evidence for the formation of either of the other two possible cycloadducts.[15] Although the structures of **6** and **7** were initially assigned on the basis of their ^1H NMR spectra and the relevant coupling constants,[16] the subsequent transformations of **6** and **7** into known natural products (vide infra)[18] verified these structural assignments. The carbomethoxy moiety present at

Scheme I



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(8) For example, one of the principal deficiencies in those approaches to the yohimboid and heteroyohimboid alkaloids that relies upon the oxidative cyclizations of seco-derivatives is that the initial oxidation of the tertiary amino function of the D ring rarely proceeds with a high degree of regioselectivity. Namely, in addition to the desired pentacyclic substance, significant amounts of the corresponding "inside" derivatives are invariably formed. Furthermore, the stereoselective reduction of the $\Delta^{3,4}$-dehydro derivatives of the natural bases, which may be produced either by oxidation of a pentacyclic precursor or by Bischler–Napieralski cyclization of an ABDE ring starting material, is sometimes problematic with mixtures of products epimeric at C(3) being obtained in certain instances. For a recent discussion of some of these issues, see ref 2 and 3a.

(9) For a review of the hetero Diels–Alder reaction, see: Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.

(10) For other examples of intramolecular [4 + 2] cycloadditions involving simple α,β-unsaturated aldehydes as the 4π components, see: (a) Snider, B. B.; Dunčia, J. V. *J. Org. Chem.* **1980**, *45*, 3461. (b) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274. (c) Denmark, S. E.; Sternberg, J. A. *Ibid.* **1986**, *108*, 8277. (d) See ref 4.

(11) For further examples of intramolecular hetero Diels–Alder reactions involving unsaturated carbonyl compounds as the dienic partners, see: (a) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696. (b) Hug, R.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1675. (c) Begley, M. J.; Crombie, L.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2402. (d) Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023. (e) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981**, *22*, 4437. (f) Tietze, L. F.; Stegelmeier, H.; Harms, K.; Brumby, T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 863. (g) Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671. (h) Takano, S.; Satoh, S.; Ogasawara, K. *Heterocycles* **1985**, *23*, 41. (i) Tietze, L. F.; Brand, S.; Pfeiffer, T.; Antel, J.; Harms, K.; Sheldrick, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 921. (j) Tietze, L. F.; Bratz, M.; Machinek, R.; v. Kiedrowski, G. *J. Org. Chem.* **1987**, *52*, 1638.

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(14) The structure assigned to each compound was in full accord with its spectral (^1H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by recrystallization or preparative HPLC and gave satisfactory data for elemental composition via combustion analysis (C, H, N) and/or high-resolution mass spectrometry. All yields are based on isolated purified material judged >95% pure by ^1H NMR spectroscopy.

(15) Cycloadducts **6** and **7** were presumably produced via a boat/boat transition state wherein amide overlap may be largely retained, whereas in the alternative half-chair/boat transition states that would lead to the other two isomeric cycloadducts, a significant degree of amide overlap is lost. The relative energies of the possible transition states that may be surmised from the observed ratio of products from the thermal cyclization of **5** are consistent with calculations that were performed with a combination of semiempirical (AM1) and molecular (MM2) mechanics. The details and results of these calculations will be reported elsewhere.

(16) For **6**: $J_{3,14ax} = J_{14ax,15} = 11.7$ Hz; $J_{3,14eq} = 4.5$ Hz; $J_{14eq,15} = 2.1$ Hz; $J_{19,20} = 8.9$ Hz. Because of overlap of the signals for protons at C(15) and C(20) with other signals in the NMR spectrum of **6**, it was necessary to establish the stereochemistry of the cis ring fusion of **6** from the derived tertiary amine **8**[17] ($J_{15,20} = 5.0$ Hz). For **7**: $J_{3,14ax} = 7.1$ Hz; $J_{3,14eq} = J_{14eq,15} = 3.0$ Hz; $J_{14ax,15} = 12.0$ Hz; $J_{15,20} = 11.5$ Hz; $J_{19,20} = 9.7$ Hz.

(17) Compound **8** was prepared from **6** by reduction with alane (2 equiv; THF; −78 °C → room temperature; 10 min; 92%).

(18) The cycloadduct **7** was converted into (±)-3-*iso*-19-*epi*-ajmalicine, which gave spectral data identical with those reported,[19] by the same sequence of reactions as described for the transformation of **6** into **1**.

C(16) of the target alkaloids was then conveniently installed to provide **9** in 66% overall yield by exploiting a useful two-step process that had been previously utilized in our laboratories[4,20] [(a) Cl_3CCOCl (8.4 equiv); 2,6-di-*tert*-butyl-4-methylpyridine (4 equiv); CH_2Cl_2; room temperature; 60 h. (b) MeOH; Et_3N; 50 °C; 6 h].

At this juncture, the pathways to the heteroyohimboid and corynantheioid alkaloids diverge. Two reductive tactics were developed for the transformation of **9** into (±)-tetrahydroalstonine (**1**) and (±)-cathenamine (**2**). Thus, treatment of **9** with alane (2 equiv; THF; −52 °C; 1 h) followed by the sequential addition of 2% AcOH/MeOH and excess sodium cyanoborohydride (room temperature; 2 h) delivered (±)-tetrahydroalstonine (**1**) in 90% overall yield. The total synthesis of (±)-cathenamine (**2**) was completed by the selective delivery of 1 equiv of hydride to the amide function of **9** by the action of lithium diethoxyaluminum hydride (8 equiv; THF; −45 °C; 2 h; 70% yield). The racemic tetrahydroalstonine and cathenamine thus obtained had spectral properties identical with those reported in the literature,[6b,f,19] and the synthetic sample of racemic **1** was spectroscopically identical with an authentic sample.[21]

Access to the manifold of the corynantheioid alkaloids now mandated the cleavage of the E ring of **9** by scission of the carbon oxygen bond via base-induced β-elimination to give **10**, and it was imperative that this process ensue with a high level of stereoselectivity to provide the *E*-α,β-unsaturated lactam.[22] Previous results from several laboratories[4,7e] augured well for the successful realization of this objective. Consistent with those observations, treatment of **9** with excess sodium amide (12 equiv; THF; room temperature; 2 h) provided **10** in 95% yield; none of the isomeric *Z* exocyclic olefin was isolated. Only the superficially simple, chemoselective 1,2-reduction of the α,β-unsaturated lactam moiety of **10** remained to complete a total synthesis of (±)-geissoschizine (**3**). Nevertheless, this seemingly straightforward transformation proved to be surprisingly difficult to achieve in practice. It was ultimately discovered that **10** could be reproducibly converted into **3** according to a strictly defined protocol. Namely, sequential treatment of **10** with $LiN(SiMe_3)_2$ (2 equiv; THF; −78 °C; 30 min) followed by transmetalation with $AlEt_3$ (2 equiv; −78 °C; 15 min) and hydride reduction with DIBAL (3 equiv; −78 °C → 10 °C; 3 h) provided in 35% yield (50% based on recovered starting material) (±)-geissoschizine (**3**), which was spectroscopically identical with an authentic sample.[21]

Thus, racemic tetrahydroalstonine (**1**), cathenamine (**2**), and geissoschizine (**3**) have been prepared from commercially available tryptamine in a highly concise fashion involving a linear sequence of merely seven or eight chemical operations. This novel approach features the rapid assemblage of the triene **5** that then undergoes an efficient intramolecular hetero Diels–Alder reaction to establish *in a single transformation* the pentacyclic ring system possessing the correct relative stereochemistry at each of the stereocenters of the target alkaloids **1–3**. Application and further extensions of this methodology toward the syntheses of other alkaloids will be described in due course.

Acknowledgment. We thank the National Institutes of Health (GM 25439) and the Robert A. Welch Foundation for generous support of this research. Brigitte Benage also gratefully acknowledges the Eastman Kodak Company for financial support as a Kodak Fellow.

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Facial Selectivity of the Intramolecular S_N2' Cyclization: Stereocontrolled Total Synthesis of Brevianamide B

Robert M. Williams,*,† Tomasz Glinka, and Ewa Kwast

Department of Chemistry, Colorado State University Fort Collins, Colorado 80523

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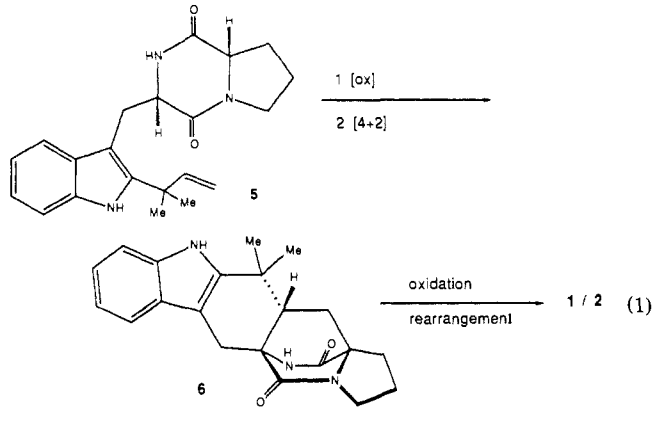
The culture extracts of *Penicillium brevicompactum* were observed by Birch and Wright[1] to produce in low yield several highly colored, neutral toxic metabolites named brevianamides A–D. The structure of brevianamide A (**1**, the major metabolite) was proposed by Birch[1] on the basis of spectroscopic evidence, chemical degradation, and biogenetic considerations; this was later confirmed[2] by single-crystal X-ray analysis. Brevianamide B (**2**), the least abundant metabolite, was thought[1] to be epimeric to **1** at the spiro indoxyl center based on the successful conversion of **1** → **2** via a redox pathway. These complex alkaloids are part of a unique, small class of natural products that have recently been joined by the mycotoxins marcfortine (**3**)[3] and paraherquamide (**4**).[4] The biogenesis of these compounds has prompted considerable speculation. A shunt metabolite, deoxy brevianamide E,[5] was proposed[1,6] to be an important biosynthetic precursor leading to the hypothetical hexacyclic indole **6** via oxidative [4 + 2] intramolecular cycloaddition of the prenyl moiety across the piperazinedione nucleus. Further oxidation of **6** to epimeric 3-hydroxyindolenines and ring-contractive rearrangement would furnish **1** and **2**. Total synthesis of **1**/**2** and experimental support for any segment of the proposed biogenesis of these complex alkaloids has not yet been recorded.



(1)

Herein is described the first total synthesis[7] of brevianamide B that features the construction of a hexacyclic indole corresponding to **6** via a stereocontrolled intramolecular S_N2' cyclization.

The known optically active allylated proline derivative **7** was prepared according to Seebach.[8] Conversion of this compound to the piperazinedione **9** was achieved by aminolysis with *p*-methoxybenzylamine followed by condensation with bromoacetyl bromide and ring closure. Ozonolysis of **9** afforded aldehyde **10**,

† Fellow of the Alfred P. Sloan Foundation 1986–88. NIH Research Career Development Awardee 1984–89. Eli Lilly Grantee 1986–88.

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