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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(20) See, also: (a) Effenberger, F.; Maier, R.; Schönwälder, K.-H.; Ziegler, T. *Chem. Ber.* **1982**, *115*, 2766. (b) Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6755; **1986**, *108*, 4974.

(21) We thank Professor E. Wenkert (University of California, San Diego) and Dr. M. R. Uskokovič (Hoffmann-LaRoche) for providing authentic samples of natural tetrahydroalstonine (**1**) and Professor H. Rapoport (University of California, Berkeley) for an authentic sample of natural geissoschizine (**3**).

(22) For an excellent review of methods for elaboration of the ethylidene substituent in indole alkaloids, see: Bosch, J.; Bennasar, M. L. *Heterocycles* **1983**, *20*, 2471.

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

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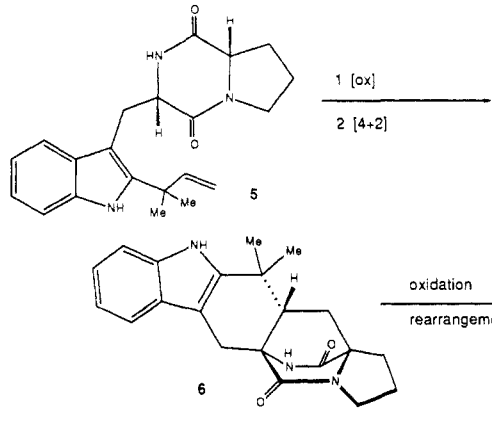
Received April 18, 1988

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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(2) Coetzer, J. *Acta. Crystallogr.* **1974**, *B30*, 2254.

(3) Polonsky, J.; Merrien, M.-A.; Prange, T.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1980**, 601.

(4) Yamazaki, M.; Okuyama, E. *Tetrahedron Lett.* **1981**, *22*, 135.

(5) Steyn, P. S. *Tetrahedron Lett.* **1971**, 3331.

(6) Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1970**, 1103.

(7) For a model study, see: Williams, R. M.; Glinka, T. *Tetrahedron Lett.* **1986**, *27*, 3581.

(8) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. F. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

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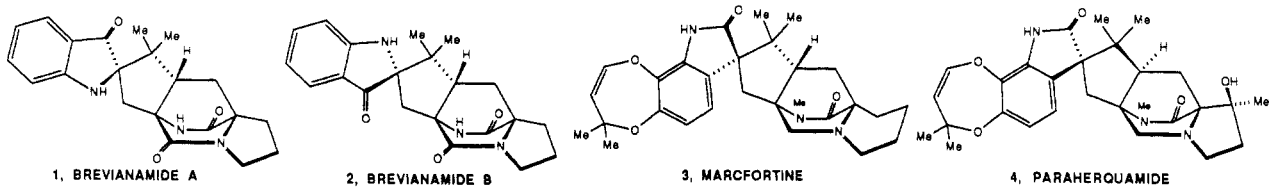
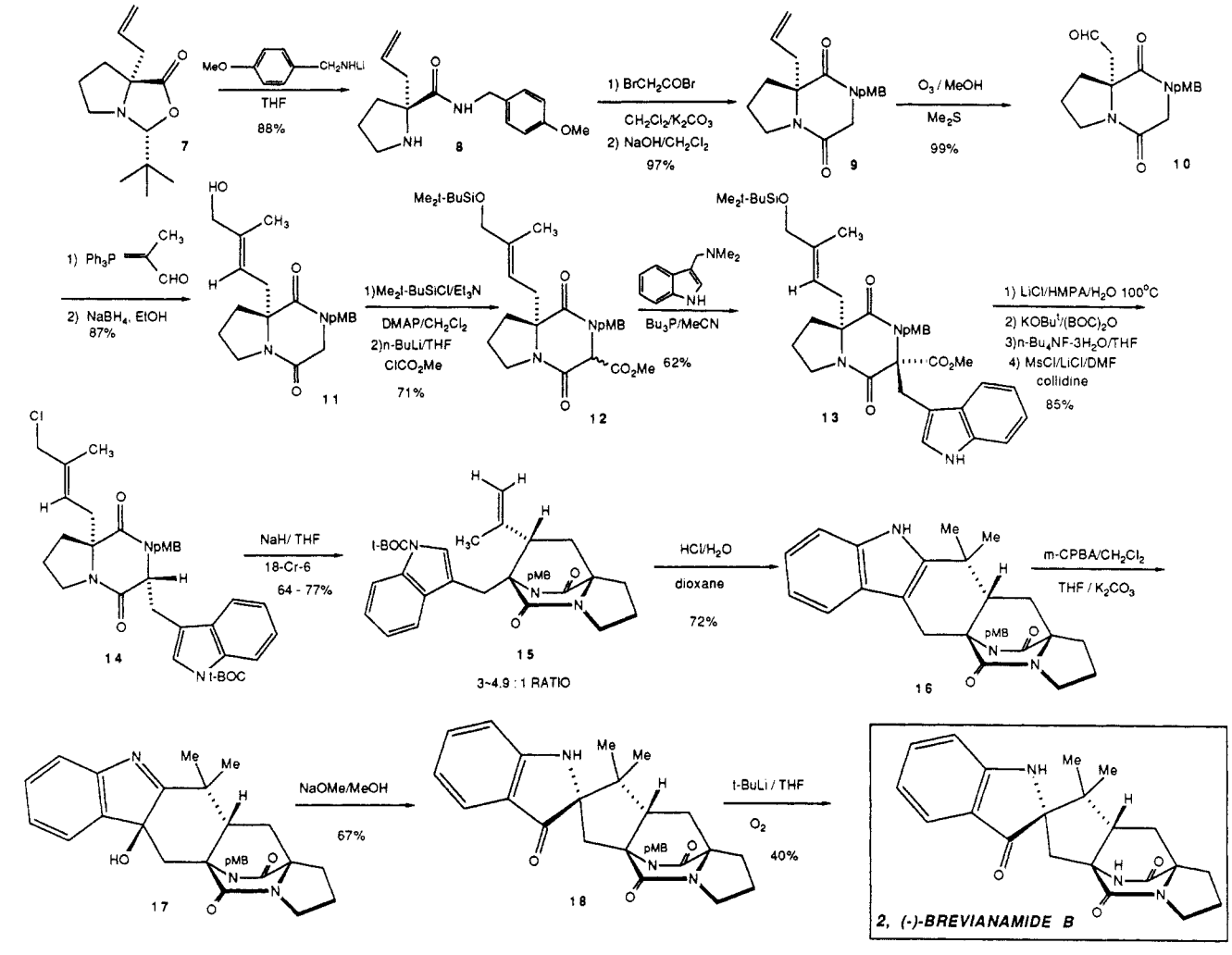
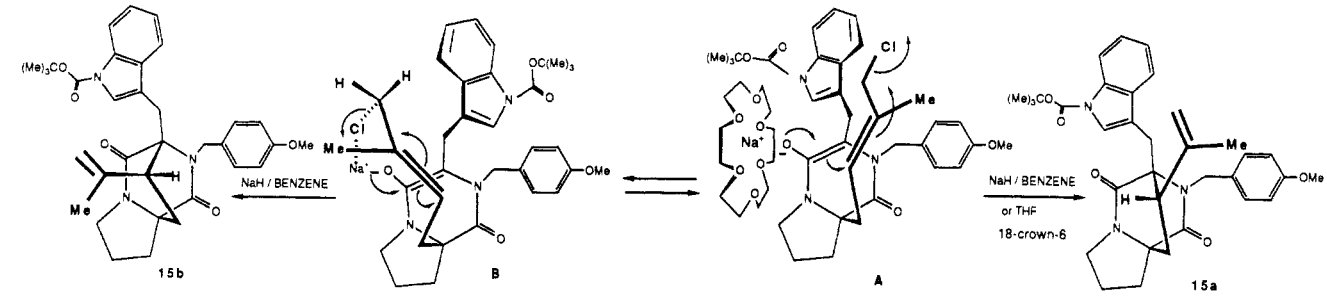
Chart I



Scheme I



Scheme II



which was homologated to the *E*-allylic alcohol **11** by Wittig reaction and $NaBH_4$ reduction. Silylation of **11** followed by carbomethoxylation afforded **12** as a 4:1 mixture that was used (as the mixture) for the subsequent Kametani[9] condensation. Treatment of **12** with gramine and tri-*n*-butylphosphine furnished a single diastereomeric indole (**13**) in 32% overall yield from **7**.

Conversion of **13** to the allylic chloride **14** was achieved in four straightforward steps (Scheme I). The subsequent key intramolecular S_N2' cyclization sets the remaining crucial stereogenic center at C-10 and required extensive investigation. Using the conditions employed in a model study[7] (NaH, DMF, 25 °C) provided the desired cyclic material **15a** along with the epimer **15b** (2:1 ratio, 62% combined). We were quite surprised to discover that simply changing the solvent to hot benzene and using NaH as the base resulted in a highly stereoselective reaction

(9) (a) Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 3974. (b) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941.

producing **15b** to the virtual *exclusion* of **15a** (97:3 ratio, 82% combined). When **14** was subjected to cyclization under the same conditions (NaH, hot benzene) except in the presence of 18-crown-6, the stereoselectivity *reversed* and **15a**/**15b** was obtained in a 3.85:1 ratio (56% combined). The change in stereoselectivity can be rationalized by considering the environments of the two possible conformers (**A** and **B**) of the putative enolate generated from **14**. In the absence of good metal cation complexing or ligating agents, such as the reaction in benzene without crown ether, the allylic group is expected to fold over the enolate (**B**) to bring the chloride ion and sodium cation proximal in the transition state. Steric interaction between the *p*-methoxybenzyl group and the allylic halide in the alternative conformer **A** would accentuate the preponderance of **B**. However, in a good cation-complexing system such as the reaction in DMF or that in the presence of 18-crown-6,[10] the solvent shell surrounding the sodium would be expected to create a significant sterically compressed environment for the allylic chloride moiety in the folded conformer **B**. In this situation, conformer **A** would be expected to predominate and the more polar environment could facilitate solvation of the NaCl produced in the transition state. In a slightly improved procedure, reaction of **14** with NaH (10 equiv) in warm THF (5 equiv 18-crown-6) gives **15a**:**15b** in a 3-4.9:1 ratio in 64-77% combined yield.

Completion of the synthesis involved treatment of **15a** with concentrated HCl in dioxane to effect removal of the N-*t*-BOC group and olefin/cation cyclization[11] furnishing the crystalline hexacyclic indole **16** in 72% yield. Oxidation of **16** with *m*-CPBA in CH_2Cl_2/THF occurred stereospecifically, giving a single hydroxy indolenine (**17**) that was directly treated with NaOMe in MeOH furnishing the crystalline, yellow indoxyl[12] **18** in 67% overall yield from **16**. The structure of **18** was rigorously confirmed by single-crystal X-ray analysis.[13] Removal of the *p*-methoxybenzyl group proved quite difficult and was recalcitrant to the standard[14] oxidative conditions. After examining a host of reductive, oxidative, and hydrolytic conditions, it was found that treatment of **18** with excess *t*-butyllithium in THF deprotonated the benzylic position; quenching the incipient benzylic anion with oxygen effected removal of the *p*-methoxybenzyl group, affording brevianamide B (40%) that was identical by ^1H NMR, IR, TLC, and UV with an authentic sample of brevianamide B.[15] It is significant that the oxidation of **16** does not produce any of the corresponding epimeric hydroxyindolenine that would produce brevianamide A. Since brevianamide A is the major metabolite produced in nature, this raises the question whether the hypothetical biogenetic precursor **6** is oxidized enzymatically or by air autoxidation. For *both* **6** and **16**, the sterically most accessible face of the indole to autoxidation is the "brevianamide B" face.

In summary, the synthesis of brevianamide B has been achieved in 17 chemical steps and provides unambiguous evidence for the structure (**2**) tentatively proposed by Birch. The discovery of means to control the facial selectivity of the intramolecular S_N2' cyclization promises to embrace both the brevianamide/marcfortine relative stereochemistry as well as the relative stereochemistry of paraherquamide. The fundamental significance of this reaction for other applications in synthesis as well as efforts to construct **3** and **4** are in progress.

Acknowledgment. We thank the National Institutes of Health (CA43969) and the Colorado State University Agricultural Experiment Station (part of USDA SAES Western Project W-122) for financial support of this work. We also thank Professor James E. Robbers and Professor Constance M. Harris for providing samples of natural brevianamide A. The X-ray crystal structure of **18** was performed by Professor Oren Anderson, Joe Reibenspies, and Susie Miller (Colorado State University NSF-funded X-ray crystal facility). Hazel Coffman is acknowledged for growing cultures of *Penicillium brevicompactum* and providing natural samples of brevianamides A and B. James Stille is acknowledged for providing valuable technical assistance.

Supplementary Material Available: Complete spectroscopic and analytical data for all new compounds and an ORTEP stereostructure for compound **18** (7 pages). Ordering information is given on any current masthead page.

(10) It is curious that 15-crown-5 with NaH and 18-crown-6 with KH give essentially a 1:1 ratio of **15a**:**15b**.

(11) For a related example, see: Darbre, T.; Nussbaumer, C.; Borschberg, H.-J. *Helv. Chim. Acta* **1984**, *67*, 1040.

(12) In addition to the precedent cited for the conversion of **1** → **2** via a similar oxidation/rearrangement in ref 1, see: (a) Hutchinson, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6787. (b) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188.

(13) Details of the structure determination to be published elsewhere.

(14) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

(15) Authentic samples of brevianamide B were obtained both from brevianamide A as described by Birch (ref 1) and from cultures of *Pencillium brevicompactum* grown in our own laboratories. The natural and synthetic materials proved to be of *opposite* absolute configuration as evidenced by the opposite signs of the respective specific rotations: natural $[\alpha]^{25}_D$ +124° (*c* 0.77, CH_2Cl_2/2.5% HCO_2H); synthetic $[\alpha]^{25}_D$ −124° (*c* 0.77, CH_2Cl_2/2.5% HCO_2H). The absolute configuration of the synthetic material is that depicted in the manuscript.

First EPR Spectroscopic Detection of Photochemically Generated Carbonyloxyl Radicals in Solution under Steady-State Conditions[1]

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The direct detection of carbonyloxyl radicals, $XCO_2^\bullet$, in solution has proven to be extremely difficult. There is only one report of their detection in solution by EPR spectroscopy:[3,4] Yamauchi et al.[3] used a modified spectrometer with a very fast response to obtain time-resolved EPR spectra in the absorption mode (rather than the normal, first derivative spectra) for three aroyloxyl radicals, $ArCO_2^\bullet$, that had been generated by 308 nm laser flash photolysis (LFP) of the corresponding diaroyl peroxides in CCl_4. We have studied the kinetic behavior of numerous aroyloxyl[7] and alkoxycarbonyloxyl,[8] $ROCO_2^\bullet$, radicals produced by LFP of suitable precursors in solution by monitoring absorptions that these radicals possess in the visible region of the spectrum.[9] These kinetic studies led us to hypothesize that $XCO_2^\bullet$ radicals which would yield destabilized $X^\bullet$ radicals and hence might be expected to have relatively strong $X\text{-}CO_2^\bullet$ bonds ought to be observable

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(3) Yamauchi, S.; Hirota, N.; Takahara, S.; Sakuragi, H.; Tokumaru, K. *J. Am. Chem. Soc.* **1985**, *107*, 5021-5022.

(4) $HO_2CCH{=}CHCO_2^\bullet$,[5a-d] $HO_2CC{\equiv}CCO_2^\bullet$,[5e] and $C_6H_5CO_2^\bullet$[6] radicals have been detected by EPR in crystals at temperatures of 77 K and lower.

(5) (a) Iwasaki, M.; Eda, B.; Toriyama, K. *J. Am. Chem. Soc.* **1970**, *92*, 3211-3212. (b) Toriyama, K.; Iwasaki, M.; Noda, S.; Eda, B. *Ibid.* **1971**, *93*, 6415-6421. (c) Eda, B.; Iwasaki, M. *J. Chem. Phys.* **1971**, *55*, 3442-3449. (d) Minakata, K.; Iwasaki, M. *Ibid.* **1972**, *57*, 4758-4763. (e) Muto, H.; Toriyama, K.; Iwasaki, M. *Ibid.* **1972**, *57*, 3016-3017.

(6) (a) Karch, N. J.; Koh, E. T.; Whitsel, B. L.; McBride, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 6729-6743. (b) McBride, J. M.; Merrill, R. A. *Ibid.* **1980**, *102*, 1723-1725.

(7) (a) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1987**, *109*, 897-899; (b) **1988**, *110*, 2877-2885; (c) **1988**, **110**, 2886-2893.

(8) Chateauneuf, J.; Lusztyk, J.; Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.*, in press.

(9) As first indicated by the photodecarboxylation of vinylcarbonyloxyl[5] and benzoyloxyl[6a] radicals by visible light.

0002-7863/88/1510-5929$01.50/0 Published 1988 by the American Chemical Society