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PROMISING CYCLIZATION REACTIONS TO CONSTRUCT THE RING SYSTEMS OF BREVIANAMIDES A,B

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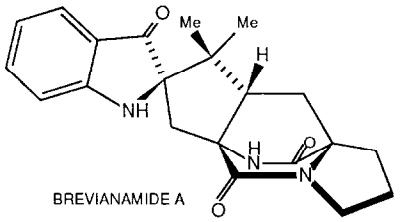
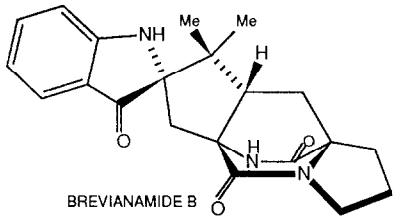
Summary: An effective intramolecular Michael cyclization and intramolecular SN_2' cyclization is described for constructing the tricyclic framework of the natural mycotoxins brevianamides A,B.

Brevianamides A,B (1) have been isolated[1] from several species of Penicillium associated with corn, rice and other stored grains subject to growth of molds and fungi. Birch[1a] and his associates first isolated these toxic metabolites from cultures of Penicillium brevi-compactum and proposed the structures 1 based on spectroscopic and chemical degradative evidence.



BREVIANAMIDE A



BREVIANAMIDE B

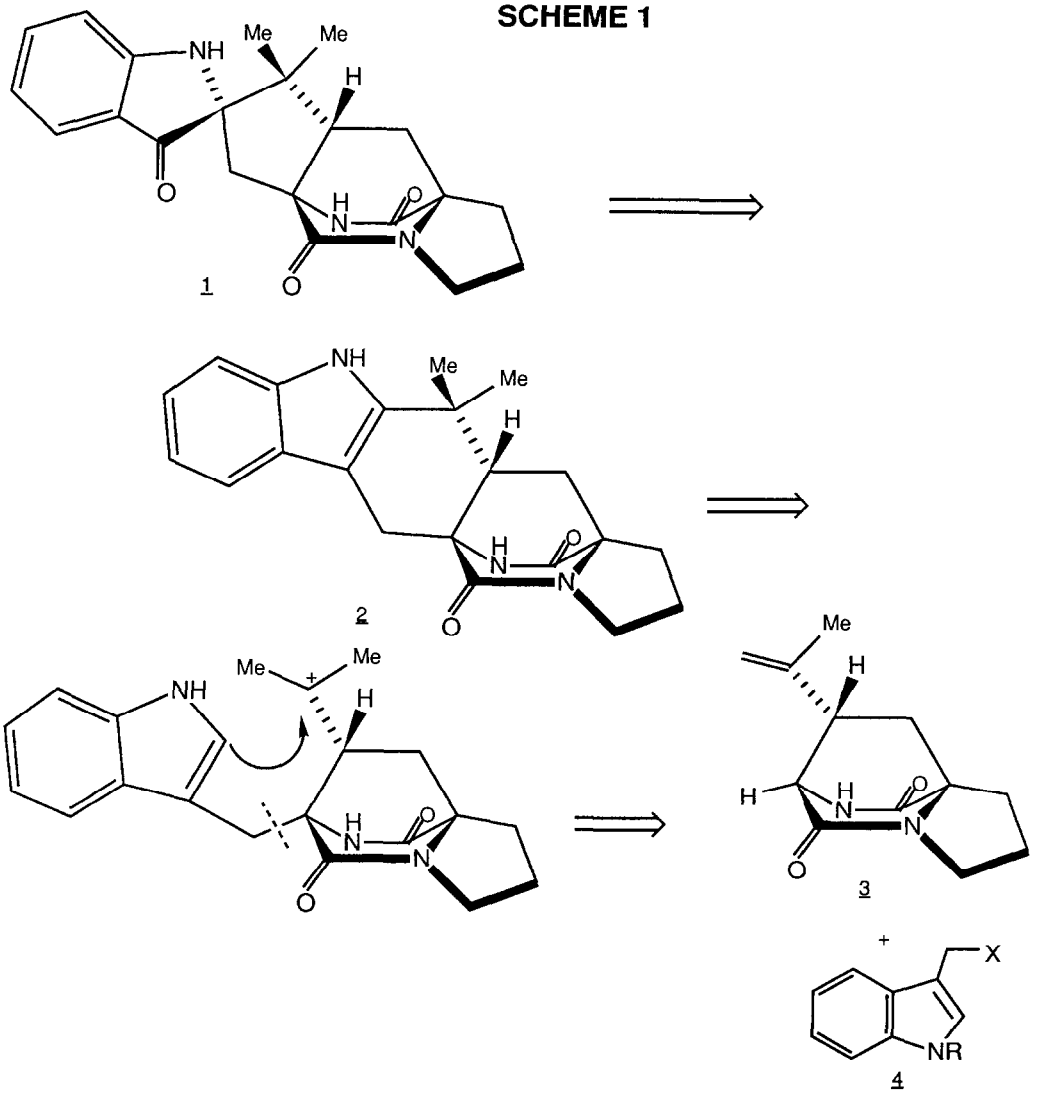
The relative and absolute stereochemistries of these compounds have been firmly established through x-ray crystallography;[2] brevianamide A is thought to be epimeric to brevianamide B at the spiro indoxyl juncture based on their reported interconversion via a redox pathway.[1c] An effective synthesis of the tricyclic nucleus of these complex alkaloids has been developed and is described herein. Our approach, outlined in Scheme I, called for the preparation of the tricyclic olefin 3 which was approached via two routes.

(±)-N-Carbobenzoxy homoserine (5) is silylated (Me_2Bu^+SiCl, DMF, Et_3N, 0°C) and condensed with N-para-methoxybenzylglycine ethyl ester (DCC, THF, 25°C). The crude 7 was directly subjected to hydrogenolysis (10% Pd/C, EtOH, H_2 1 atm) to afford the piperazinedione 8 (mp 98-100°C, EtOAc) in 40% overall yield from 5. Alkylation with 1,3-dibromo propane (DMF, $KOBu^+$, 0°C) affords 9 which is directly treated with NaH in DMF (25°C) to furnish the proline derivative 10 (28% overall from 8). Desilylation of 10 (HF·pyridine, THF, 25°C, 93%) furnishes the alcohol 11 which is oxidized to the stable aldehyde 12 (ClCOCOCl, DMSO, CH_2Cl_2, Et_3N) in 82% isolated yield. Homologation of 12 with $(EtO)_2POCH(CH_3)CO_2Et$ (NaH, DMF, 0°C)

provided the unsaturated esters 13 which directly suffered intramolecular Michael cyclization in situ to provide the tricyclic compounds 17a, b and 18a, b (79%) in a 2:1:1:1 ratio. The structure of the major isomer (17a) was unambiguously established by single crystal x-ray analysis[5] (Figure 1) and was found to possess the unnatural relative stereochemistry.

In an alternative approach, the aldehyde 12 was homologated with $Ph_3P{=}C(CH_3)CHO$[6] (o-dichlorobenzene, 115°, 3h) to furnish the E olefin 14 in 96% yield. Reduction to the alcohol 15 (5 eq $NaBH_4$, EtOH, 40°C, 20 min, 91% yield) followed by conversion to the allylic chloride (MsCl, collidine, LiCl, DMF, 87%) and cyclization (NaH, DMF, 25°C, 5h) furnished the desired tricyclic olefins 19a,b in a 10:1 ratio (60%), respectively.

SCHEME 1



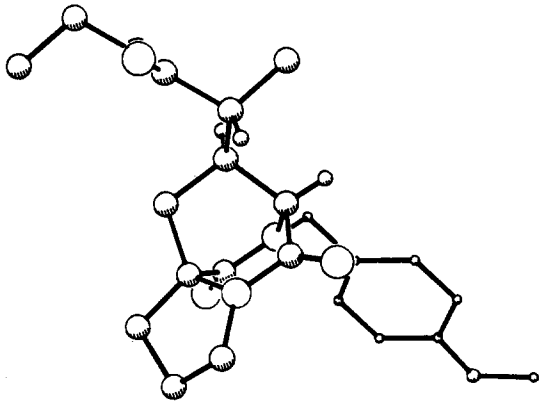
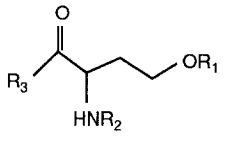
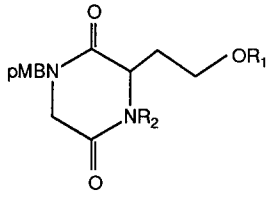


FIGURE 1. Molecular structure of compound 17a. Atoms are shown as spheres of fixed, arbitrary radius. (The para-methoxybenzyl group has been diminished for clarity)

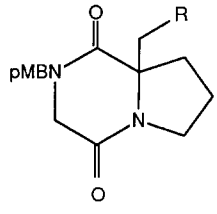


5, R_1=H; R_2=CO_2CH_2Ph; R_3=OH
6, R_1=$SiMe_2Bu^+$; R_2=CO_2CH_2Ph; R_3=OH
7, R_1=$SiMe_2Bu^+$; R_2=CO_2CH_2Ph; R_3=NH(pMB)CH_2CO_2Et

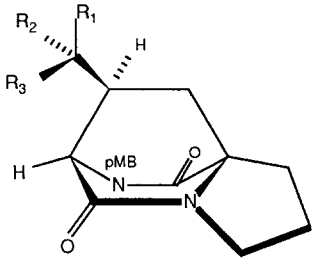
pMB= para- methoxybenzyl



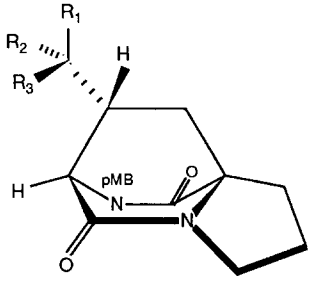
8, R_1=$SiMe_2Bu^+$; R_2=H
9, R_1=$SiMe_2Bu^+$; R_2=$(CH_2)_3Br$



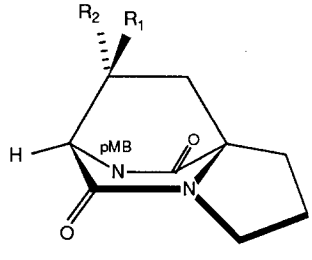
10, R = $CH_2OSiMe_2Bu^+$
11, R = CH_2OH
12, R = CHO
13, R = CH=C(Me)CO_2Et
14, R = CH=C(Me)CHO
15, R = CH=C(Me)CH_2OH
16, R = CH=C(Me)CH_2Cl



17a, R_1= CO_2Et, R_2=Me, R_3=H
17b, R_1=CO_2Et, R_2=H, R_3=Me



18a, R_1=CO_2Et, R_2=Me, R_3=H
18b, R_1=CO_2Et, R_2=H, R_3=Me



19a, R_1=H, R_2= 
19b R_1=  , R_2=H

The relative stereochemistry of the major diastereomer (19a, mp 128.5-129.5°C) was unambiguously determined to be opposite that of the major diastereomer (17a) obtained from the intramolecular Michael cyclization by a combination of spectroscopic and chemical correlations. Specifically, the bridgehead methine protons of the minor diastereomers 18a,b appeared as a doublet at δ3.83 (J<1Hz) and a singlet at 3.88 ppm, respectively; whereas the methine protons of 17a,b appeared as doublets (δ3.89, J=2.5Hz and δ3.92, J=3.0Hz). The major diastereomer 19a exhibited a bridgehead methine resonance at δ3.9 as a doublet (J<1Hz) whereas the bridgehead methine of minor isomer 19b resonated at δ4.18 as a doublet (J=3.0Hz). Firm stereochemical evidence was provided by the three step conversion of 19a into one of the minor diastereomers 18. Hydroboration/oxidation with $(Sia)_2BH$ in THF at 25°C for 8h (then $NaOH/H_2O_2$) followed by Jones oxidation of the resulting major diastereomeric primary alcohol and esterification (0.5 N HCl in EtOH) furnished a single diastereomer of 18 that was identical to that obtained from 13.

The application of these strategies to total syntheses of the brevianamides and related alkaloids of this class paraherquamide[7a] and marcfortine[7b] are under active investigation in these laboratories.

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REFERENCES AND FOOTNOTES

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3. All new compounds gave satisfactory spectroscopic and analytical data.

4. Diastereomer 17a when treated with 0.5 N NaOEt in EtOH formed a 2:1 equilibrium mixture of 17a:17b with no detectable traces of 18a,b.

5. The details of this x-ray structure determination shall be reported separately.

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