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Concise Total Synthesis of (+)-Luteoalbusins A and B

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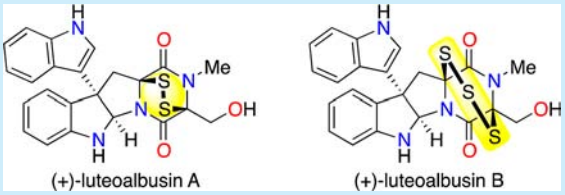
Supporting Information

ABSTRACT: The first total synthesis of (+)-luteoalbusins A and B is described. Highly regio- and diastereoselective chemical transformations in our syntheses include a Friedel–Crafts C3-indole addition to a cyclotryptophan-derived diketopiperazine, a late-stage diketopiperazine dihydroxylation, and a C11-sulfidation sequence, in addition to congener-specific polysulfane synthesis and cyclization to the corresponding epipolythiodiketopiperazine. We also report the cytoxicity of both alkaloids, and closely related derivatives, against A549, HeLa, HCT116, and MCF7 human cancer cell lines.



Epipolythiodiketopiperazine alkaloids represent a structurally complex and biologically active class of secondary fungal metabolites.[1,2] Many members of this family of natural products share a *cyclo*-tryptophan core and an eponymous epipolythiodiketopiperazine (ETP) substructure (Figure 1).

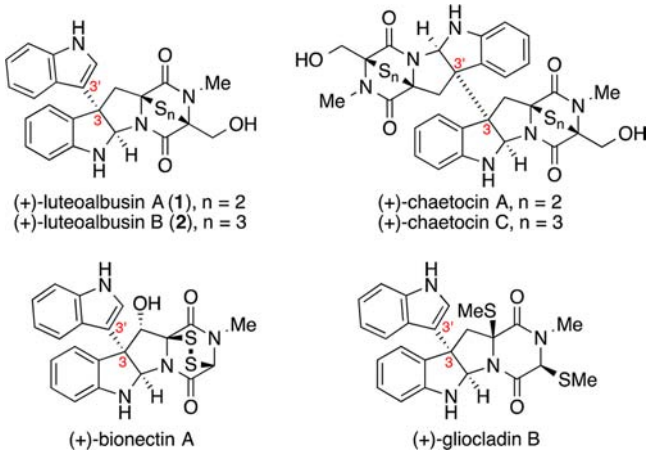


Figure 1. Representative ETP alkaloids.

Notwithstanding these similarities, individual ETP alkaloids offer an array of structural variations including the nature of the substituent at the C3 quaternary carbon,[3−5] the degree of oxidation of the core structure,[4l,n] and the dipeptide constituting the diketopiperazine substructure, in addition to the nature and degree of sulfuration of the ETP structure.[3n,4i,6] Access to complex ETPs via total synthesis requires efficient strategies and chemical transformations adaptable to this repertoire of structural diversity along with the respective challenges offered by each distinct combination. As part of our program focused on accessing structurally unique ETP alkaloids, we became interested in (+)-luteoalbusin A (**1**) and (+)-luteoalbusin B (**2**), recently discovered ETPs isolated from the marine fungi *Acrostalagmus luteoalbus* SCSIO F457 by Wang and co-workers.[7] These natural products contain a C3-(3′-indolyl) substituent and an ETP substructure, possessing a di- or trisulfide bridge with a diketopiperazine composed of tryptophan and serine. These structural features of (+)-luteoalbusins A (**1**) and B (**2**) are shared in part with the related ETP alkaloids (+)-gliocladin B and (+)-chaetocins A and C (Figure 1) that were the subject of our prior investigations.[3n,4i] Herein, we report the first total syntheses of (+)-luteoalbusins A (**1**) and B (**2**) using a concise and unified approach as well as their cytotoxic activity against four human cancer cell lines.

Our retrosynthetic analysis of these natural alkaloids is illustrated in Scheme 1. We envisioned having efficient access to both alkaloids from a versatile C11-thiolated diketopiperazine **3** via the application of our polysulfane cyclization chemistry to accurately introduce the disulfane and trisulfane substructures in the final stage of the synthesis.[3n,6o] The regio- and diastereoselective C11-sulfidation of the key dihydroxylated diketopiperazine (+)-**4** was planned on the basis of the faster expected rate of iminium ion formation at C11 vs C15 due to the inductive electron-withdrawing influence of the C17 acetate. Rapid access to the key intermediate (+)-**4** was expected through introduction of the C3-indolyl substituent by Friedel–Crafts arylation[4d] followed by application of our diketopiperazine dihydroxylation chemistry.[3l] Tetracyclic diketopiperazine bromide (+)-**5** is readily available on a multigram scale as outlined in our synthesis of (+)-chaetocins A and C.[3n]

Our unified synthesis of alkaloids (+)-**1** and (+)-**2** began with the silver-mediated Friedel–Crafts arylation of diketopiperazine (+)-**5** (Scheme 2).[8] Based on our earlier studies concerning the

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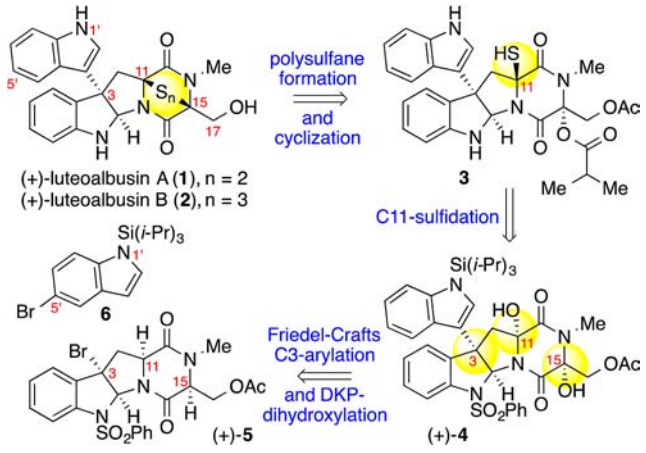
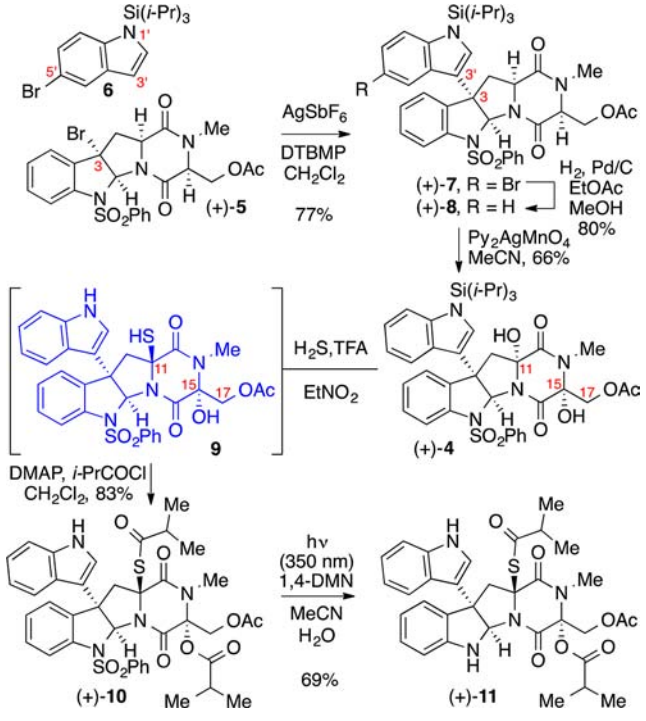
Scheme 1. Retrosynthetic Analysis



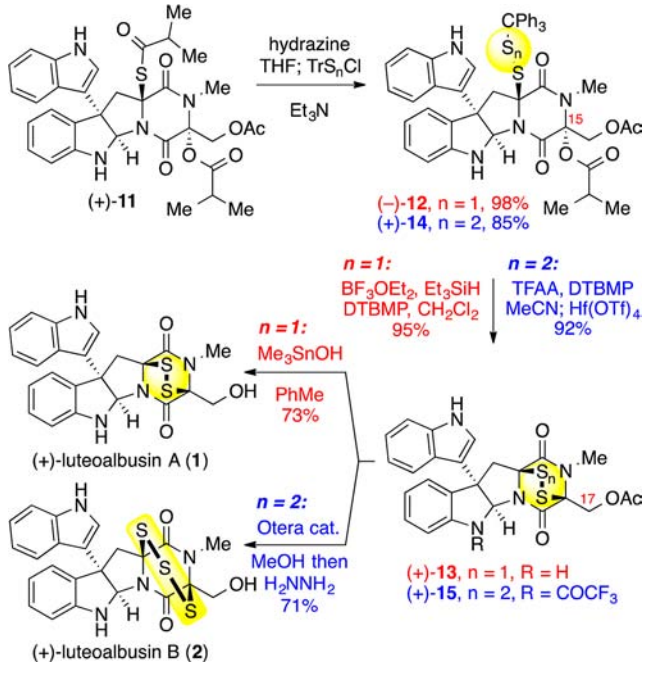
Scheme 2. Preparation of Key Intermediate (+)-11



regioselective introduction of the C3-indolyl substructure, we employed the readily available 1-(triisopropylsilyl)-1*H*-indole (**6**) to provide the C3−C3′ linkage exclusively.[4i] Treatment of a solution of C3-bromo diketopiperazine (+)-**5** in dichloromethane with indole derivative **6** and silver(I) hexafluoroantimonate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at 23 °C afforded the desired C3-indolylhexacycle (+)-**7** in 77% yield. Exposure of C3-bromoindolyl diketopiperazine (+)-**7** and palladium on carbon to an atmosphere of dihydrogen in ethyl acetate−methanol (2:3) at 23 °C gave C3-indolyl diketopiperazine (+)-**8** in 80% yield. Consistent with our biogenetically inspired strategy for synthesis of ETP alkaloids,[2f,3l] further functionalization of the diketopiperazine substructure was addressed after construction of the hexacyclic core. Treatment of diketopiperazine (+)-**8** in acetonitrile with bis(pyridine)silver(I) permanganate (Py_2AgMnO_4) provided the desired dihydroxylated diketopiperazine (+)-**4** as a single diastereomer in 66% yield.[3l,9] This oxidation reaction likely proceeds via a stereoretentive radical rebound mechanism with initial hydrogen atom abstraction, followed by trapping of the generated carbon-centered radical.[10] For the subsequent sulfidation of the C11 position, we have previously observed in related systems that non-nucleophilic solvents are necessary for the selective ionization of the C11 alcohol and trapping with an alkyl mercaptan.[4n] Furthermore, because of the inductive effect of the neighboring heteroatom at C17, the rate of ionization at the C15 position was anticipated to decrease.[3n] Thus, exposure of diol (+)-**4** to trifluoroacetic acid (TFA) in hydrogen sulfide saturated nitroethane at 0 °C produced monothiol **9** with concomitant loss of the triisopropylsilyl group at the N1′ position. After concentration of the reaction mixture, the residue was treated with 4-(dimethylamino)pyridine (DMAP) and isobutyryl chloride in dichloromethane at 0 °C to generate the desired isobutyryl thioester (+)-**10** in 83% yield over two steps. The isobutyrate groups at C11 and C15 served two purposes: First, activation of the tertiary alcohol at C15 through esterification with isobutyryl chloride is required for the polysulfane cyclization step. Second, acylation of the C11 thiol was necessary to enhance the stability of the molecule for the photoinduced removal of the N1-benzenesulfonyl group.[11] Thus, irradiation of benzenesulfonyl (+)-**10** with light (350 nm) in the presence of 1,4-dimethoxynapthalene (1,4-DMN) in buffered aqueous ascorbic acid−acetonitrile solution afforded the desired key indoline (+)-**11** in 69% yield.

The final stages of our synthesis of (+)-luteoalbusin A (**1**) relied on selective hydrazinolysis of the thioisobutyryl group at C11 over the C15 isobutyrate by treatment with 1 equiv of hydrazine in THF at 0 °C (Scheme 3). Subsequent exposure of the hemithioaminal **3** to triphenylmethanesulfenyl chloride (TrSCl) and triethylamine provided the desired mixed disulfide (−)-**12** in 98% yield.[3n] Activation of the C15 isobutyrate group and subsequent cyclization of the disulfide with concomitant loss of the triphenylmethyl cation was accomplished through the treatment of disulfide (−)-**12** with boron trifluoride diethyl

Scheme 3. Synthesis of (+)-Luteoalbusin A (1) and B (2)



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etherate in dichloromethane at 23 °C to furnish (+)-luteoalbusin A acetate (**13**) in 95% yield. Unveiling of the C17 alcohol from acetate (+)-**13** was achieved by utilizing trimethyltin hydroxide[12] in toluene at 90 °C to afford (+)-luteoalbusin A (**1**) in 73% yield. All spectroscopic data for our synthetic sample of (+)-luteoalbusin A (**1**) are consistent with those reported by Wang.[7,8]

The total synthesis of (+)-luteoalbusin B (**2**) also utilized the key intermediate thioisobutyrate (+)-**11**. Sequential treatment of thioisobutyrate (+)-**11** with hydrazine, followed by the addition of chloro(triphenylmethyl)disulfane (TrSSCl)[8] under basic conditions as described above produced the corresponding mixed trisulfide (+)-**14** in 85% yield (Scheme 3).[3n] Notably, exposure of trisulfide (+)-**14** to boron trifluoride diethyl etherate in dichloromethane resulted in decomposition of the substrate, an outcome likely caused by competing pathways involving the indoline nitrogen due to a decrease in the rate of cyclization relative to disulfide (−)-**12**.[3n] Based on this observation, we reasoned that protection of the N1 indoline nitrogen of trisulfide (+)-**14** as well as employing a solvent with higher dielectric constant might increase the cyclization efficiency. Thus, *in situ* acylation of the N1 indoline nitrogen of trisulfide (+)-**14** with trifluoroacetic anhydride and DTBMP in acetonitrile, followed by the addition of boron trifluoride diethyl etherate at 23 °C, afforded the desired epitrithiodiketopiperazine (+)-**15** in 43% yield.

Importantly, replacing boron trifluoride diethyl etherate with hafnium trifluoromethanesulfonate as the Lewis acid additive further enhanced the cyclization of the trisulfide to provide epitrithiodiketopiperazine (+)-**15** in 92% yield as a 1.6:1 mixture of epitrisulfide conformers (Scheme 3). Sequential C17-deacylation of luteoalbusin B derivative (+)-**15** by mild methanolysis using Otera's catalyst[13] followed by N1-deacylation by hydrazinolysis[3n] afforded the first synthetic sample of (+)-luteoalbusin B (**2**) in 71% yield as a 4:1 mixture of epitrisulfide conformers. All spectroscopic data for our synthetic sample of (+)-luteoalbusin B (**2**) are consistent with those reported by Wang.[7,8]

Epipolythiodiketopiperazine alkaloids are known to possess an impressive array of potent biological activities including anticancer,[6o,q] antiviral, and antibacterial properties.[14] Previous studies have linked the unique biological activity of these natural products to their polysulfide structures.[14h,i] Recently, we disclosed a comprehensive SAR study of a large collection of natural and synthetic ETP derivatives for cytotoxic activity against multiple human cancer cell lines.[6o] As part of our ongoing interest to evaluate the translational potential of ETPs, we examined synthetic (+)-luteoalbusins A (**1**) and B (**2**) as well as all novel synthetic intermediates described above prepared en route to both natural products for cytotoxic activity against human lung carcinoma (A549), cervical carcinoma (HeLa), colorectal carcinoma (HCT116), and breast carcinoma (MCF7) cell lines.[8] Among all compounds tested, natural products (+)-**1** and (+)-**2** and acetylated derivatives (+)-**13** and (+)-**15**, also possessing a bridged polysulfide, were found to exhibit significant anticancer activity (Table 1). Both natural alkaloids (+)-**1** and (+)-**2** displayed consistently high cytotoxicity across all cell lines tested. However, the C17 acetylated derivatives ETP (+)-**13** and ETP (+)-**15** were found to be less potent relative to the (+)-luteoalbusins A (**1**) and B (**2**), respectively. The IC_{50} values for ETPs (+)-**1**, (+)-**2**, (+)-**13**, and (+)-**15** across the four human cancer cell lines tested are listed in Table 1. Our results complement those reported by Wang.[15]

Table 1. Cytotoxicity (IC_{50}, μM) of (+)-Luteoalbusin A and B and Related Derivatives against A549, HeLa, HCT116, and MCF7 Cancer Cell Lines[8]

compd	A549	HeLa	HCT116	MCF7
(+)-**13**	11.31 ± 2.54	5.50 ± 2.81	4.73 ± 4.34	5.17 ± 0.20
(+)-**15**	11.02 ± 0.23	5.19 ± 2.05	5.11 ± 3.37	6.53 ± 0.84
(+)-**1**	2.33 ± 0.59	1.00 ± 0.24	1.22 ± 1.02	0.86 ± 0.13
(+)-**2**	0.91 ± 0.29	0.52 ± 0.15	0.58 ± 0.38	0.51 ± 0.14

We report the first total synthesis of (+)-luteoalbusins A (**1**) and B (**2**). This unified synthetic strategy was based on our versatile and biogenetically inspired[2f] late-stage functionalization of a complex diketopiperazine via an oxidation followed by sulfidation sequence to access the desired epidi- and epitrithiodiketopiperazines (+)-**1** and (+)-**2**, respectively. Our synthesis relied on highly regio- and diastereoselective chemical transformations including a Friedel−Crafts C3-indole addition to the readily available diketopiperazine (+)-**5**, dihydroxylation, and C11-sulfidation of C3-(3′-indoyl)diketopiperazine (+)-**8** and the use of a versatile thioisobutyrate (+)-**11** as a substrate for congener-specific polysulfane synthesis and cyclization to access both (+)-luteoalbusins A (**1**) and B (**2**). We also report the cytoxicity of both alkaloids (+)-**1** and **2** along with closely related ETPs (+)-**13** and (+)-**15** against A549, HeLa, HCT116, and MCF7 human cancer cell lines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02059.

Experimental procedures and spectral data for all new compounds (PDF)

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Author Contributions

§T.C.A. and J.N.P. contributed equally to this manuscript.

Notes

The authors declare no competing financial interest.

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