

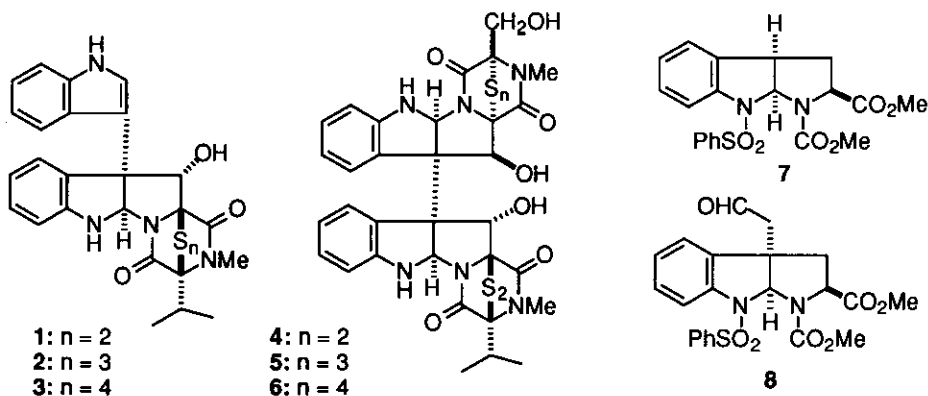
## SYNTHESIS OF THE 3a-(3-INDOLYL)-1,2,3,3a,8,8a-HEXAHYDROPYRROLO[2,3-*b*]INDOLE CORE OF LEPTOSINS D-F

David Crich,\* Ewa Fredette, and William J. Flosi

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607-7061, USA

**Abstract-** The Fischer indole reaction of aldehyde and phenyl hydrazine in the presence of zinc chloride smoothly provides the core structure of the leptosins D-F in good to excellent yield.

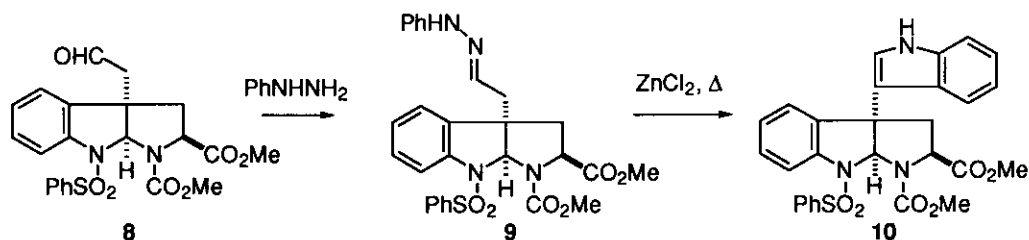
Leptosins D-F (**1-3**) were isolated in 1994 from the culture of a strain of *Leptoshacteria* sp. which itself was isolated from the marine alga *Sargassum tortile*.<sup>1</sup> These compounds which may arise from leptosins A-C (**4-6**),<sup>1,2</sup> isolated from the same broth, by Grob type fragmentation, were found to possess cytotoxic activity against the P-388 lymphocytic leukemia cell line comparable to that of mitomycin C.<sup>1</sup> This activity, and the unusual 3a-(3-indolyl)-hexahydropyrrolo[2,3-*b*]indole skeleton of **1-3**, prompted us to investigate the potential for their asymmetric synthesis using chemistry previously developed in this laboratory for the construction of the related alkaloids debromoflustramine B and pseudophrynaminol.<sup>3,4</sup>



Thus, *N,N'*-dimethoxycarbonyl-L-tryptophan was converted to the optically and diastereomerically pure, crystalline hexahydropyrroloindole (**7**) in two steps and excellent yield.<sup>5</sup> This substance was converted in three steps to the known aldehyde (**8**) in good overall yield.<sup>3</sup>

The Fischer indole reaction of **8** with phenylhydrazine was then investigated. Initially, we were concerned that the aminal function in hydrazone (**9**) would be incompatible with the acidic conditions required for the Fischer indole reaction<sup>6</sup> and so sought out the mildest conditions possible. To this end we investigated various protocols, especially catalysis by pyridinium hydrochloride,<sup>7</sup> but met with little

success. Eventually, we turned to more forcing conditions involving the use of zinc chloride. Thus, aldehyde (**8**) was condensed with phenylhydrazine hydrochloride in pyridine to give the somewhat unstable hydrazone (**9**) in around 87% yield. This substance was then heated briefly to 170 °C, essentially according to an Organic Synthesis protocol,<sup>8</sup> with anhydrous zinc chloride. Remarkably, chromatographic isolation yielded the desired indole (**10**) in yields ranging from 47-82% (Scheme 1).



Scheme 1

The structure of **10** was confirmed by MS spectroscopic measurements, with the presence of the anticipated molecular ion, and <sup>1</sup>H- and <sup>13</sup>C-NMR spectroscopy. In particular, the continued presence of the hexahydropyrroloindole skeleton was indicated by the presence of the 8a-H (aminal-H) at δ 6.57 and the corresponding 8a-C at δ 84.5. The presence of the indole function is signaled by the presence of the NH proton at δ 7.73, minimally coupled to the indole 2-H at δ 6.02. This latter proton resonates very significantly upfield of typical indole H-2's and indeed of the corresponding protons in **1-3**. This must be a consequence of its shielding by the sulfonamide positioned<sup>5</sup> on the *exo*-face of the hexahydropyrroloindole. It is also noteworthy that the Lewis acidic reaction conditions did not promote epimerization at C-2 of the hexahydropyrroloindole framework as evident from the typical, upfield chemical shift of the ester methyl group (δ 3.22) in the <sup>1</sup>H-NMR spectrum.<sup>5,9</sup>

To our knowledge, this represents the first preparation of the title skeleton, other than by fragmentation of substances related to **4-6**.<sup>1,2</sup> Together with chemistry developed previously in this laboratory for functionalization at C-3 of the hexahydropyrroloindole skeleton<sup>10</sup> and known routes<sup>11</sup> to the epidithiodiketopiperazine function, as applied in the synthesis of the related sporidesmins,<sup>12,13</sup> this straightforward synthesis of **12** points the way toward the total asymmetric synthesis of **1**.

## EXPERIMENTAL

**2(S),3a(R),8a(S)-3a-(3-Indolyl)-1,2-bis(methoxycarbonyl)-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (10).** Aldehyde (**8**) (200 mg, 0.44 mmol) and phenylhydrazine hydrochloride (72 mg, 0.5 mmol) were heated to reflux in pyridine (2 mL) under Ar for 5.5 h when TLC indicated completion. After cooling the solvent was removed under vacuum and toluene (2 mL) added and removed under vacuum to give a brown gum, which was taken up in a minimum of THF and crude **9** (231 mg, 87%) precipitated with Et<sub>2</sub>O. Crude **9** (220 mg, 0.4 mmol) was powdered and mixed with fused ZnCl<sub>2</sub> (0.39 g, 2.89 mmol) then heated under Ar to 170 °C with occasional stirring with a copper wire. After removal from the heating bath, sand (0.2 g) was added to the hot reaction

mixture to prevent solidification. After cooling the reaction mixture was stirred with dilute (10%) HCl (4 mL) for 5 h then filtered on a sinter. The mixture of organic products and sand was boiled in 95% ethanol (5 mL) and filtered on a sinter. The sand was further rinsed with several portions of hot ethanol and the combined ethanol solutions concentrated to dryness to give a green brown solid. Chromatography on silica gel (eluent: hexane/ethyl acetate 7/2) gave **10** as a white solid (0.21 g, 82%). mp 125-127 °C;  $[\alpha]_D^{20}$  -19.6° (c = 1.1, CHCl<sub>3</sub>); <sup>1</sup>H NMR δ (CDCl<sub>3</sub>, 300 MHz): 2.82 (1H, d, *J* = 13.2 Hz, 3-*endo*-H), 3.19 (1H, dd, *J* = 13.2 and 9.0 Hz, 3-*exo*-H), 3.22 (3H, s, ester CO<sub>2</sub>CH<sub>3</sub>), 3.75 (3H, s, carbamate CO<sub>2</sub>CH<sub>3</sub>), 4.86 (1H, d, *J* = 9.0 Hz, 2-H), 6.02 (1H, d, *J* = 2.3 Hz, indole N-CH=), 6.57 (1H, s, 8a-H), 6.98 (2H, t, *J* = 7.5 Hz, Ar-H), 7.1 - 7.45 (9H, m, Ar-H), 7.47 (1H, d, *J* = 7.8 Hz, Ar-H), 7.67 (1H, d, *J* = 8.0 Hz, Ar-H), 7.73 (1H, br s, N-H); <sup>13</sup>C NMR δ (CDCl<sub>3</sub>, 75 MHz): 39.6, 52.4, 53.2, 57.0, 60.1, 84.5, 112.0, 115.6, 118.9, 119.0, 120.5, 122.8, 123.6, 124.3, 125.2, 125.3, 126.7, 128.2, 129.7, 132.5, 135.4, 137.2, 139.1, 142.3, 155.3, 171.6; UV λ<sub>max</sub> (EtOH): 300 (log ε = 3.32), 266 (log ε = 3.26), 238 (log ε = 3.19) nm; MS *m/z*: 531 (100%, M<sup>+</sup>), 390 (61%, M-PhSO<sub>2</sub>), 315 (90%), 256 (56%), 245 (96%); HRMS: 531.14648 (M<sup>+</sup>, Calcd for C<sub>28</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>S: 531.14641).

## ACKNOWLEDGMENTS

E. F. was the recipient of a B. M. Goldwater Scholarship and acknowledges additional support from the Fanny and John Hertz Foundation and Phi Kappa Phi UIC Chapter.

## REFERENCES

1. C. Takahashi, A. Numata, Y. Ito, E. Matsumura, H. Iwaki, and K. Kushida, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1859.
2. H. Minato, M. Matsumoto, and T. Katayama, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1819.
3. M. Bruncko, D. Crich, and R. Samy, *J. Org. Chem.*, 1994, **59**, 5543.
4. D. Crich, A. B. Pavlovic, and R. Samy, *Tetrahedron*, 1995, **51**, 6379.
5. D. Crich, M. Bruncko, S. Natarajan, B. K. Teo, and D. A. Tocher, *Tetrahedron*, 1995, **51**, 2215; M. Taniguchi and T. Hino, *Tetrahedron*, 1981, **37**, 1487.
6. B. Robinson, 'The Fischer Indole Synthesis', Wiley, 1982.
7. W. M. Welch, *Synthesis*, 1977, 645.
8. R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Synth., Coll. Vol.*, 1955, **III**, 725.
9. G. T. Bourne, D. Crich, J. W. Davies, and D. C. Horwell, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1693.
10. M. Bruncko and D. Crich, *J. Org. Chem.*, 1994, **59**, 4239.
11. Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.*, 1973, **95**, 6490.
12. Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *J. Am. Chem. Soc.*, 1973, **95**, 6493.
13. S. Nakatsuka, T. Fukuyama, and Y. Kishi, *Tetrahedron Lett.*, 1974, 1549.