Total Synthesis of Petrosin

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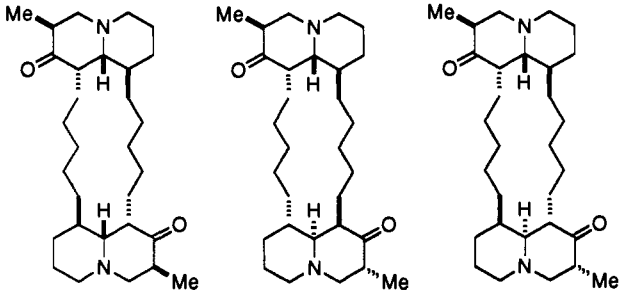
Received July 18, 1994

Braekman and co-workers have reported the isolation and structural determination of three ichthyotoxic bis-quinolizidone alkaloids from the sponge *Petrosia seriata*, collected near Papua, New Guinea.[2] The three diastereomers are petrosin (**1**), petrosin A (**2**), and petrosin B (**3**). These natural products present a fascinating stereochemical and biosynthetic puzzle. In spite of the fact that it contains eight stereocenters, petrosin (**1**) is racemic as isolated. Petrosin A (**A**) is also devoid of optical activity because it is an achiral meso compound. Each of the quinolizidone units in petrosin and petrosin A has the same relative configuration. Petrosin B (**3**), on the other hand, is optically active ($[\alpha]_{579}$ = −12). In this isomer, one of the quinolizidone units has the same relative configuration as that found in petrosin and petrosin A, but the other quinolizidone has a different relative configuration. Petrosin and petrosin A have also been isolated from the sponge *Xestospongia* sp.[3]

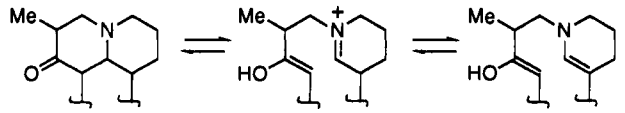


Since it is uncommon for natural products to be biosynthesized in racemic form, we think that petrosin and petrosin A might be products of some post-biosynthetic equilibration. Additonally, we think that petrosin might be the most abundant isomer simply due to its thermodynamic stability relative to the other possible isomers, and this hypothesis is supported by extensive global minimization studies.[4]

It is clear that the stereocenters α to the carbonyl could be epimerized by simple enolization. As shown in Scheme 1, epimerization of the more remote stereocenters might occur by retro–Mannich–Mannich and immonium ion–enamine equilibria. This hypothsis led us to undertake the synthesis of petrosin without regard to stereochemistry, with the hope that the desired relative configuration could be established in a final acid–catalyzed equilibration step.

Ozonolysis of methyl oleate provided the known compound methyl azelaldehyde (**4**) (Scheme 2). Aldehyde **4** was cyanoethylated by way of its pyrrolidine enamine to obtain **5**.[5] The aldehyde was then reduced, and the resulting primary alcohol (**6**) was protected as the *tert*-butyldimethylsilyl ether (**7**). The ester function was reduced with diisobutylaluminum hydride (DIBAL-H) at −95 °C.[6] Treatment of aldehyde **8** with the dianion of propionic acid gave, after acidic workup, acid **9** as a 1:1 mixture of *syn* and *anti* diastereomers.[7] At this point the material was partitioned as this precursor is used for both halves of the molecule. One portion was treated with diazomethane to form the methyl ester (**10**), which was hydrogenated to convert the cyano group to primary amine **11**. This provides us with two differentially functionalized building blocks to proceed with the sequential amide bond formations, as one segment has a free carboxylic acid and a latent amine (nitrile), whereas the other contains a protected carboxyic acid (ester) and free amine.

Scheme 1



Acid **9** and amine **11** were coupled with DCC and hydroxybenzotriazole (HOBT) to obtain amide **12**.[8] The cyano group of **12** was reduced (in the presence of HCl) to the amine hydrochloride while simultaneously both TBS protecting groups were removed. The crude amine hydrochloride was neutralized with $NaHCO_3$ and the amine protected as the BOC derivative to give **14**.

Macrolactamization was accomplished by a four-step procedure that was optimized on the basis of several literature precedents.[9] The methyl ester of **14** was saponified and the resulting carboxylic acid converted to the pentafluorophenyl (pfp) ester by treatment with DCC and pentafluorophenol. The crude active ester was treated with anhydrous HCl in dioxane to remove the BOC group and simultaneously protect the amine as the hydrochloride salt. A solution of this hydrochloride salt in dioxane–THF was slowly added with a syringe pump to a hot 5:1 dioxane–pyridine solution, providing the desired 28-membered macrolactam **18** in 78% overall yield for the four steps.

The amide linkages were reduced with $LiAlH_4$ and the resulting secondary amines protected as BOC derivatives (**20**). This protection step not only facilitated purification of the diamine tetraol but also was found to be necessary to avoid side reactions in the tetraoxidation step to follow. The hydroxy groups were oxidized with Dess–Martin periodinane,[10] which performs the tetraoxidation quickly (<30 min) and efficiently. The BOC groups were removed with HCl in aqueous ethanol, and the intramolecular Mannich condensation was achieved by treatment of the crude deprotection product with 0.2 M acetic acid in refluxing ethanol.

The foregoing protocol provided the desired skeleton, as a mixture of diastereomers, in 62% yield for the three-step procedure. Petrosin (**1**) directly crystallized from this mixture in 23% yield. The synthetic material was identical with an authentic sample by ^1H and ^{13}C NMR spectroscopy and by mp (215–216 °C). Chromatographic purification of the mother

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(2) (a) Braekman, J. C.; Daloze, D.; Macedo de Abreu, P.; Piccini-Leopardi, C.; Germain, G.; Van Meerssche, M. *Tetrahedron Lett.* **1982**, *23*, 4277. (b) Braekman, J. C.; Daloze , D.; Defay, N.; Zimmerman, D. *Bull. Soc. Chim. Belg.* **1984**, *93*, 941. (c) Braekman, J. C.; Daloze, D.; Cimino, G.; Trivellone, E. *Bull Soc. Chim Belg.* **1988**, *97*, 519.

(3) Kobayashi, M.; Kawazoe, K.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 4149.

(4) These studies were carried out in collaboration with Professor J. M. Coxon using PCMODEL and Macromodel. Details will be reported in the full account of this work.

(5) Stork, G. A.; Brizzolara, H.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(6) Reaction at −78 °C proceeded with 10–15% overrduction to the alcohol.

(7) Moersch, G. W.; Burkett, A. R. *J. Org. Chem.* **1971**, *36*, 1149.

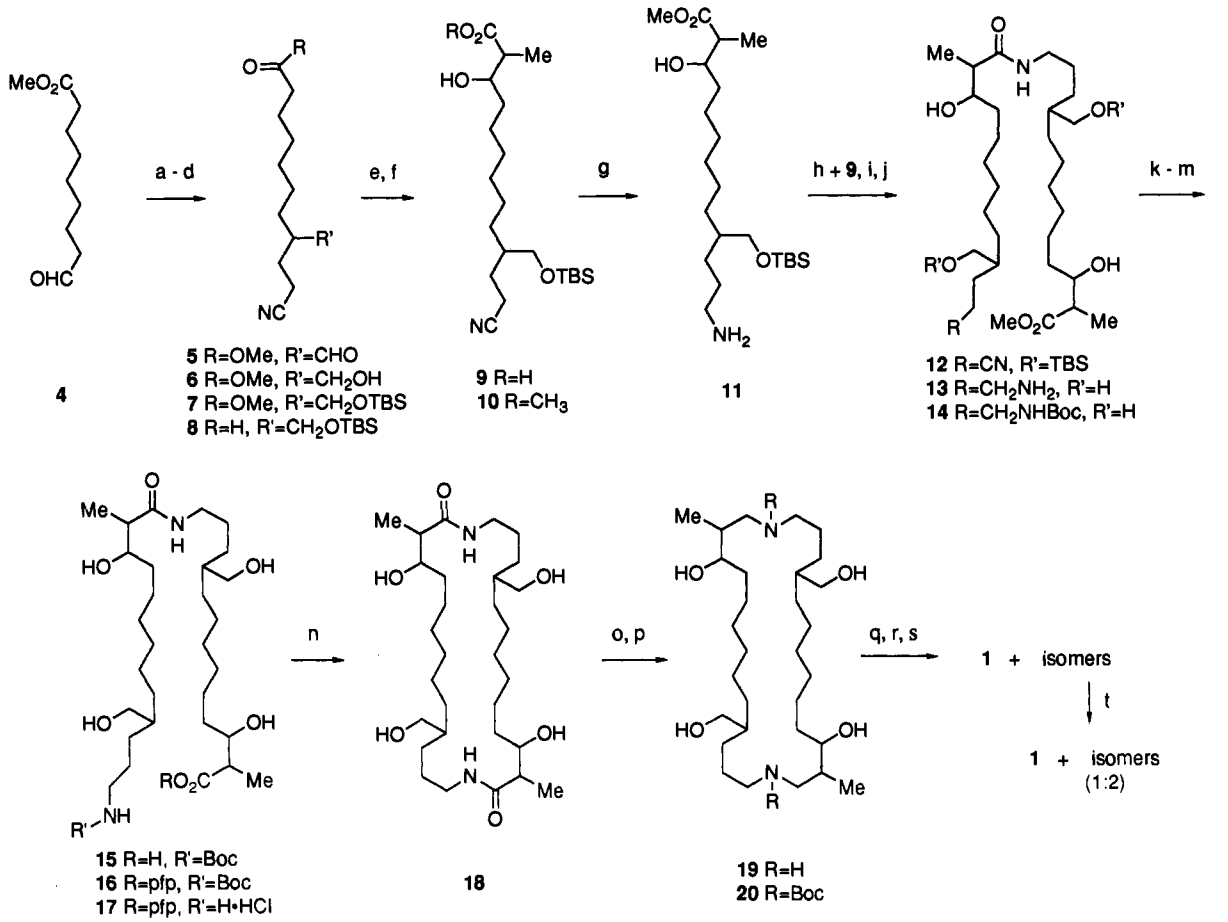
(8) Windridge, G. C.; Jorgensen, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 6318.

(9) (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. (b) Schmidt, U.; Meyer, R.; Leitenberger, V.; Griesser, H.; Lieberknecht, A. *Synthesis* **1982**, *1025*. (c) Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248. (d) Schmidt, U.; Griesser, H. *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 280. (e) Schmidt, U.; Kroner, M.; Griesser, H. *Synthesis* **1991**, 294. (f) Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 236.

(10) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

0002-7863/94/1516-8853$04.50/0

Scheme 2[a]



[a] (a) (i) pyrrolidine, K_2CO_3, (ii) CH_2=CHCN, CH_3CN, (iii) H_2O, 73%; (b) $NaBH_4$, MeOH, 100%; (c) TBS-Cl, imid., DMF, 95%; (d) DIBAL-H, CH_2Cl_2, -95 °C, 80%; (e) dianion of propionic acid (from LDA), THF, 77%; (f) CH_2N_2, Et_2O, 100%; (g) H_2, PtO_2, EtOAc, HOAc, 97%; (h) DCC, HOBT, THF, 70%; (i) H_2, PtO_2, HCl, EtOH; (j) $(Boc)_2O$, dioxane, H_2O, 73% (two steps); (k) NaOH, MeOH, THF; (l) DCC, C_6F_5OH, THF; (m) 6 N HCl, dioxane; (n) high dilution into dioxane/pyridine, 90 °C, 78% (four steps); (o) LAH, THF; (p) $(Boc)_2O$, dioxane, H_2O, 90% (two steps); (q) Dess-Martin periodinane, CH_2Cl_2; (r) 1 M HCl, EtOH, H_2O; (s) 0.2 M HOAc, EtOH, 62% (three steps); (t) (i) butylamine, 3 Å molecular sieves, (ii) propylammonium acetate, $Cl(CH_2)_2Cl$, (iii) H_2O, 80%.

liquors from this crystallization afforded a 38% yield of petrosin isomers. This mixture included the known alkaloids petrosin A (**2**), and (±)-petrosin B (**3**), which were identified by comparison of their ^{13}C NMR spectra with published data. Attempted proton- or Lewis acid-mediated equilibration of the isomeric material to produce additional petrosin has, so far, been unsuccessful. However, conversion of the ketones to the imines provided a substrate which undergoes the desired equilibration. Under these conditions, petrosin was produced as the major isomer, qualitatively supporting our equilibration hypothesis of biogenesis. Although the equilibration conditions led to some decomposition, by employing one equilibration cycle the yield of crystalline petrosin for the final sequence was increased to 33% from **20**, while the combined yield of petrosin isomers (mostly petrosin A and petrosin B) was reduced to 20%.

In summary, (±)-petrosin has been synthesized in 20 steps from methyl oleate. Although the yield in the final intramolecular Mannich reaction is only modest, the overall yield of crystalline petrosin that can be obtained by this synthesis is approximately 4.6%, based on methyl oleate. The discovery that we can enrich the mixture of petrosin diastereomers by equilibration of the imine derivatives provides qualitative support for the hypothesis that the stereostructure of naturally-derived petrosin might result from post-biosynthetic equilibrations. Further equilibration studies are underway to further probe the possible biosynthetic origin of these alkaloids.

Acknowledgment. We thank the National Institutes of Health (GM 46057) for support of this research. R.W.S. thanks the National Science Foundation for a graduate fellowship. We also thank Professor J. C. Braekman for a comparison sample of natural petrosin.

Supplementary Material Available: Detailed experimental procedures and full characterization of all compounds (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.