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The First Total Synthesis of Roquefortine D

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Abstract: The synthesis of roquefortine D (**1**), an alkaloid isolated from the cultures of *Penicillium roqueforti*, is described. The absolute stereochemistry of the natural product was determined by comparison of its optical rotation with that of the synthetic product. A photo-cleavable *o*-nitrobenzyl group was utilized for histidine side chain protection, and the cyclization to the diketopiperazine was carried out under mild conditions. © 1998 Elsevier Science Ltd. All rights reserved.

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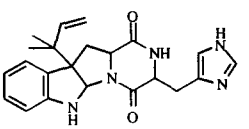
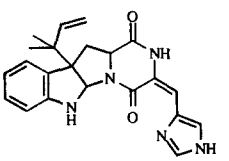
Roquefortine D (**1**) was first isolated by Ohmomo et al.[1] from a culture of *Penicillium roqueforti*. Roquefortine D was found as a minor alkaloid extracted from the culture along with roquefortine C and other metabolites. (50 mg roquefortine D: 600 mg roquefortine C). Roquefortine C (**2**) is the didehydro derivative of **1**. Roquefortine D (**1**) was presumed to be the biosynthetic precursor of **2**.[2]



roquefortine D (1)



roquefortine C (2)

The absolute stereochemistry of roquefortine D has not been directly examined yet. A report by Yamaguchi in 1991[3] established the absolute configuration of roquefortine C (**2**) by chemical degradation and spectrometric methods. The tryptophan moiety was found to be the of the *L*-configuration and the reverse-prenyl was in the *alpha*-orientation as was the hydrogen between the two nitrogens. Ohmomo found that reduction of **2** with zinc in acetic acid afforded **1** and another isomer.[1] Therefore the left portion of **1** should

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possess the same configuration as that of **2**.

Investigations of the biosyntheses of roquefortines C and D by Ohmomo,[2] suggested that histidine, tryptophan and mevalonic acid were the precursors of **1**, which was further converted to roquefortine C. They used *L*-histidine-2-^{14}C as the labeled precursor. However, since the *alpha* proton of tryptophan was lost during the biosynthesis, the final compound might not have inherited the chirality of the *L*-histidine precursor. Thus, a synthetic approach was needed to establish the stereochemistry of this compound.

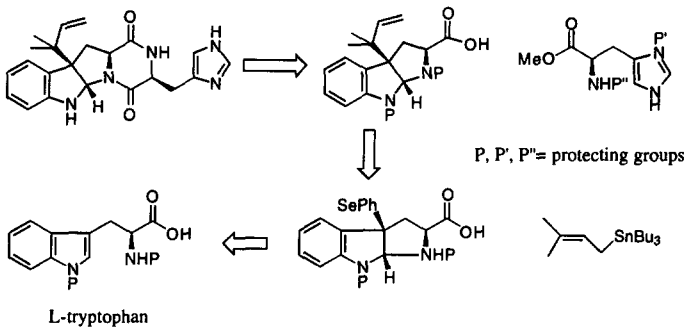
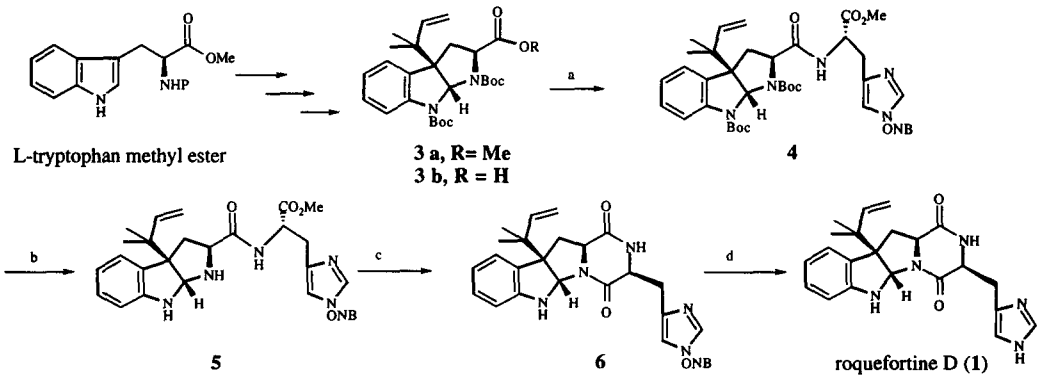


Figure 1. Retrosynthesis of roquefortine D (**1**).

The retrosynthesis of **1** is shown in Fig.1. The diketopiperazine was disconnected to a reverse-prenylated pyrrolo[2,3-*b*]indole moiety and the assumed *L*-configurated histidine. Although in peptide synthesis the imidazole nitrogen of the histidine often does not need protection, a better yield and avoidance of epimerization was observed with protected cases.[4] In addition, we found that protection also simplified the purification process. The protecting group of choice should be orthogonal to other protecting groups and reaction conditions. We chose the *o*-nitrobenzyl (ONB) group, which could be cleaved by photolysis.[5] The *o*-nitrobenzyl group has been used to block amino and carboxyl groups and is stable under most of the conditions of peptide synthesis, both acidic or basic. It is very slowly cleaved by catalytic hydrogenation.

The total synthesis of **1** is shown on Scheme 1.

Scheme 1



Scheme 1: (a) ONBHis-OMe, DCC, HOBt, DIEA, CH_2Cl_2, 77%; (b) TMSI (4 eq.), 0 °C, 1h, 76%; (c) 10% NH_4OH/MeOH, 81%; (d) Hg vapor lamp, Pyrex filter, 1h, 82%.

The synthesis began with the protection of the amino groups of *L*-tryptophan methyl ester using Boc anhydride under basic conditions and a phase transfer catalyst. The reverse-prenyl group was introduced by a selenide-mediated cyclization-prenylation developed by Danishefsky's group.[6] In our case, the N-phenylselenophthalimide reaction afforded two diastereomeric selenide esters in ratios varying from 20:1 to 10:1. Prenylation of the major diastereomer gave the prenylated compound **3a**. X-ray analysis of **3a** showed that this product had the reverse prenyl group in the *alpha* configuration. This finding agreed with the absolute stereochemistry of roquefortine C (**2**) as determined by NMR difference nOe experiments.[3] The X-ray structure of **3a** is shown in Fig. 2.

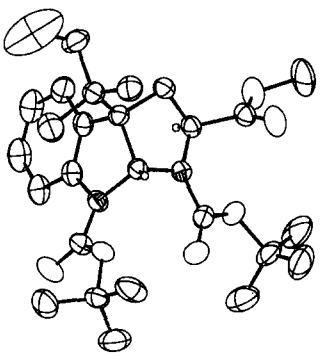


Figure 2. ORTEP Diagram of compound **3a.**

The histidine portion with side chain protection was synthesized by literature procedures[7] from Boc-*L*-histidine, which was first esterified to its methyl ester with thionyl chloride and methanol at reflux (44% yield). The histidine ester was converted to its silver salt with silver nitrate and sodium hydroxide in ethanol (67% yield). The silver salt was heated in refluxing benzene with *o*-nitrobenzyl bromide to afford the protected histidine (70% yield), and the Boc group was removed with TFA in CH_2Cl_2.

The prenylated tryptophan acid (**3b**) was coupled with the protected histidine ester to afford **4** in 77% yield. Deprotection of the two Boc groups by TFA to give **5** led to complex mixtures. The best deprotecting reagent was TMSI (76% yield). Although TMSCl and NaI[8] also worked, they required longer reaction times and afforded lower yields (50%). The cyclization to the diketopiperazine (**6**) was attempted under various conditions (neutral, acidic, basic). The classical cyclization by saturated ammonia in methanol was known to cause epimerization and was not considered. Instead, reaction with 10% NH_4OH in methanol at room temperature for 3 days accomplished the cyclization in good yield (81%) and under mild conditions. Attempts to heat the reaction promoted epimerization and decreasing the basicity lowered the reaction rate (up to 7 days for completion). The final step was the cleavage of the ONB group with a mercury vapor lamp, with a Pyrex filter in a quartz immersion well, under nitrogen. A solution of the substrate in 1,4-dioxane was irradiated for 1h and one single product was obtained.[9]

In conclusion, we have accomplished the first total synthesis of roquefortine D (**1**) and established its absolute stereochemistry.

Acknowledgments. We wish to thank Professor Danishefsky and Dr. K. Depew for their help with the reverse prenylation reaction. We are indebted to Professor Ohmomo for his generous gift of roquefortine C. We acknowledge the support of the University of Pennsylvania analytical facilities and Dr. P. J. Carroll, Dr. G. Furst, Dr. R. Kohli and Mr. John Dykins for their expert technical assistance.

References and Notes

1. Ohmomo, S.; Oguma, K.; Ohashi, T.; Abe, M. *Agric. Biol. Chem.* **1978**, *42*, 2387-2389.
2. Ohmomo, S.; Ohashi, T.; Abe, M. *Agric. Biol. Chem.* **1979**, *43*, 2035-2038.
3. Yamaguchi, T.; Nozawa, K.; Nakajima, S.; Kawai, K.-I.; Udagawa, S.-I. *Proc. Jpn. Assoc. Mycotoxicol.* **1991**, *34*, 29-32.
4. Wagener, R. E.; Davis, N. D.; Diener, U. L. *Appl. Environ. Microbiol.* **1980**, *39*, 882-887.
5. Franck, B. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 493-505.
6. Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143-11144.
7. Kalbag, S. M.; Roeske, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 440-441 and references cited therein.
8. Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247-1251.
9. Roquefortine D: m.p. 152-153°C; R_f 0.2 (1:10:99:NH_4OH:MeOH:CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.67 (s, 1H), 7.18 (d, J=7.4 Hz, 1H), 7.13 (m, 1H), 6.97 (s, 1H), 6.79 (m, 1H), 6.60 (d, J=7.8 Hz, 1H), 5.99 (dd, J=10.9, 17.4 Hz, 1H), 5.56 (s, 1H), 5.15 (d, J=10.9 Hz, 1H), 5.10 (d, J=17.4 Hz, 1H), 5.02 (s, 1H, broad), 4.19 (d, J=7.9 Hz, 1H), 3.94 (dd, J=10.4, 6.3 Hz, 1H), 3.44 (d, J=14.1 Hz, 1H), 3.00 (dd, J=7.9, 14.1 Hz, 2H), 2.57 (dd, J=12.5, 6.3 Hz, 1H), 2.47 (dd, J=12.5, 10.4 Hz, 1H), 1.14 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 165.9, 149.9, 143.4, 135.2, 134.8, 129.0, 128.9, 125.1, 118.9, 115.7, 114.4, 109.2, 77.7, 61.5, 58.8, 55.7, 40.8, 36.1, 27.8, 22.8, 22.4; IR (neat) 3298, 2968, 2930, 1667, 1651, 1606, 1482, 1462, 1445, 1315, 1214, 1081, 910 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{26}N_5O_2$ $(M+H)^+$: 392.2087, found 392.2097. The optical rotation was close to that of the natural product, $[\alpha]^{25}_D$ -359 (c 0.23, pyr); lit[1] $[\alpha]^{15}_D$ -370 (c 0.23, pyr).