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FIRST SYNTHESIS OF LYCOPERDIC ACID

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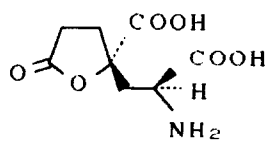
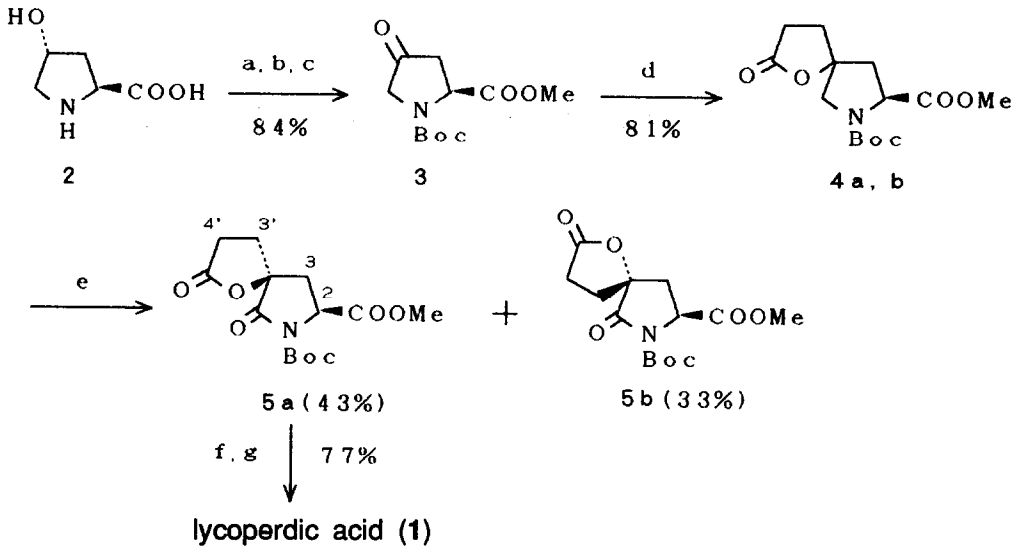
Abstract: Lycoperdic acid, (2S,2'S)-2-amino-3-(2'-carboxy-5'-oxo-2'-tetrahydrofuranyl)propanoic acid, was synthesized from *trans*-4-hydroxy-L-proline.

Lycoperdic acid (**1**) is a non-proteinogenic α-amino acid isolated from the mushroom *Lycoperdon perlatum* by R-Banga, *et al.* in 1978.[1] The structural elucidation of it was done based on spectroscopic and X-ray crystallographic studies.[2] This compound is a novel analogue of L-glutamic acid, a major neuroexcitatory amino acid in the mammalian central nervous system. We describe here the first synthesis of lycoperdic acid. Our synthetic approach to **1** is based on SmI_2 mediated formation of the spirolactone at C4 position of *trans*-4-hydroxy-L-proline and RuO_4 oxidation of the pyrrolidine ring to the pyroglutamic acid derivative.



lycoperdic acid (**1**)

Commercially available *trans*-4-hydroxy-L-proline (**2**) was converted to the *N,C*-protected 4-keto-L-proline (**3**, 84%).[3] Reductive cross coupling[4] of **3** with methyl acrylate in the presence of SmI_2 afforded a mixture of two diastereomeric spirolactones (**4a,b**, 81%). The RuO_4 oxidation of the mixture (**4a,b**) was achieved using our previously established method[5] to produce the corresponding pyroglutamic acid derivatives (**5a,b**) which could be easily separated by chromatography on silica-gel (**5a**, 43% and **5b**, 33%). The (2S,4S)- and (2S,4R)-configurations of the two isomers were determined by ^{1}H-NMR experiments including difference NOE. Irradiation of C3-α-H of (2S,4S)-**5a** resulted in enhancements of C3'-H_2 (lactone ring protons) and C2-H resonances. While, the NOE in (2S,4R)-**5b** was observed between C3-β-H and C3'-H_2.



(a) $SOCl_2$, MeOH; (b) Boc_2O, Et_3N, CH_2Cl_2; (c) $RuO_2 \cdot xH_2O$, $NaIO_4$, CCl_4-$CHCl_3$-H_2O (3:2:7.5 v/v) (d) CH_2=$CHCOOCH_3$, SmI_2, THF-MeOH-HMPA, 0°C, 1hr; (e) i. $RuO_2 \cdot xH_2O$, $NaIO_4$, CH_3NO_2-H_2O (1:3 v/v), r.t., 2days; ii. silica-gel chromatography (hexane-AcOEt, 1:1 v/v); (f) 6N HCl, reflux, 12hr; (g) Dowex 1x8 (2N AcOH).

Hydrolysis of **5a** in refluxing 6N hydrochloric acid followed by ion-exchange chromatography (Dowex 1x8, eluted with 2N AcOH) gave the crude amino acid (77%) in solid state,[6] which was recrystallized from H_2O to afford lycoperdic acid (**1**), mp 200−201°C,[7] $[\alpha]_D^{21}$ +14.2° (c 0.47, H_2O) and $[\alpha]_D^{22}$ +37.2° (c 1.37, 1N HCl)[8] (lit.[2] $[\alpha]_D^{20}$ +14.9° (c 0.47, H_2O) and $[\alpha]_D^{20}$ +36.5° (c 1.37, 1N HCl)). The spectral data (MS, IR, ^{1}H- and ^{13}C-NMR, CD) of the synthetic material were essentially in accord with the reported values for natural lycoperdic acid.

Our work is now under way in an effort to improve the low stereoselectivity in the SmI_2 mediated spirolactonization.

References and Notes

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6. The crude product was found to exist in the form of the lactone (**1**) and it did not change to the corresponding hydroxy acid in D_2O within 6hr (NMR analysis).
7. Melting point of natural lycoperdic acid has not been reported.
8. The $[\alpha]_D$ of **1** in 1N HCl must be measured immediately after dissolving because it was gradually hydrolyzed to give an equilibrium mixture of **1** and the corresponding hydroxy acid.

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