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Catalytic Enantioselective Total Synthesis of (+)-Lycoperdic Acid

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Supporting Information Placeholder

ABSTRACT: A concise enantio- and stereocontrolled synthesis of (+)-lycoperdic acid is presented. The stereochemical control is based on iminium-catalyzed Mukaiyama–Michael reaction and enamine-catalyzed organocatalytic α -chlorination steps. The amino group was then introduced by azide displacement, affording the final stereochemistry of (+)-lycoperdic acid. Penultimate hydrogenation and saponification afforded pure (+)-lycoperdic acid in seven steps from a known silyloxyfuran.

(+)-Lycoperdic acid (**1**) was isolated from a mushroom *Lycoperdon perlatum* by Rhugenda-Banga *et al.*¹ It is an amino acid that shares structural similarities with both L-glutamic acid (**2**) and dysiherbaines (**3a**, **3b**, Figure 1).^{2,3} The dysiherbaines are well-known ionotropic glutamate receptor binders^{3,4}, a fact which has raised questions about the biological activity of (+)-**1** over the years.^{5–7}

Figure 1. Glutamate-Related Amino Acids

To date, there are seven total syntheses and one formal synthesis for (+)-**1**.^{5–14} Most of them rely on either chiral pool or chiral auxiliaries to set the stereochemistry at C2 and C4 (Figure 2). Very recently, the Oikawa group disclosed an approach where catalytic enantioselective hydrogenation was used to control the stereochemistry at C2 of (+)-**1**, but the construction of C4 was not stereoselective.⁷

Herein, a total synthesis for (+)-**1** is presented where the stereochemistry is fully controlled by organocatalytic reactions. Retrosynthetically, the C2 stereocenter was envisioned to be set via α -amination reaction (Scheme 1).^{15,16} The challenging C4 tertiary stereogenic center would be accessed *via* a Mukaiyama–Michael reaction between a silyloxyfuran **4** and acrolein (**6**).¹⁷

Synthesis	control of C4	control of C2
Yoshifuji 1992/1995	no stereocontrol	chiral pool
Hatakeyama 2000	Sharpless asym. epoxidation	chiral pool
Hamada 2002	stereoselective hydroxylation	chiral pool
Tamura 2005	chiral auxiliary	chiral auxiliary
Chamberlin 2007	stereoselective bromination	chiral pool
Reiser 2013	stereoselective radical cyclisation	chiral pool
Lopp 2015	asym. oxidation	chiral pool
Oikawa 2019	no stereocontrol	enantioselective hydrogenation
This work	enantioselective conjugate addit.	stereoselective amination

Figure 2. Sources of stereochemistry in the published routes

Our first challenge was to find the conditions for the desired Mukaiyama–Michael reaction with silyloxyfuran esters such as **4**. The closest precedent was set by Pansare group who demonstrated that MacMillan's trimethyl imidazolidinone **5** would catalyse reactions between acrolein and silyloxyfurans with good enantioselectivities but with poor yields (Scheme 1).¹⁸ Our own previous experience with enantioselective Mukaiyama–Michael reactions with acrolein involving diphenylpyrrolidine (**9**)¹⁹ and pyroglutamic-acid-derived pyrrolidine²⁰ catalysts suggested that systematic optimization of the catalyst might offer better results.

In contrast with the Pansare precedent, we wanted to avoid the use of any bulky ester groups, or even benzyl esters in the

nucleophilic component to prevent any conflict with later operations along the route (Scheme 1). For example, benzyl esters were deemed unsuitable as they might require special precautions in the projected hydrogenation of the butenolide C=C bond. We thus selected the methyl ester **4** as the starting point for catalyst development.

Scheme 1. Background of the study

The work commenced by screening studies with typical iminium catalysts **9** and **13–15** (Scheme 2). These catalysts, unfortunately, gave only poor to moderate enantiomeric ratios. Nevertheless, comparison of differently substituted catalysts revealed potentially useful trends. Thus, catalysts with electron withdrawing substituents enhanced the enantioselectivities: with *para*-substituted diarylpyrrolidine catalysts, there was a rising trend from F (*er* 80:20, **16**) via NO₂ (*er* 18:82, **17**) to CF₃ (*er* 85:15, **18**). In contrast, electron-donating groups (*t*-Bu) had a detrimental effect on *er* (catalyst **15**, 29:71 *er*, see the Supporting Information, Scheme S1). Interestingly, catalysts **18** and **19**, bearing either *p*-CF₃ (**18**) or two *m*-CF₃ groups (**19**) afforded similar enantioselectivities. Finally, diarylpyrrolidine **20** with four CF₃-substituents provided a reaction with excellent level of enantioselectivity.

Studies to further enhance the *er* of the reaction were also carried out. For further optimization, it was clear that the diarylpyrrolidine core of catalysts **16–20** was lacking the needed modularity. Thus, we also screened with pyrrolidine catalysts and the above trend was also observed with these catalysts (Scheme 2). Catalyst **21** gave almost a racemic product, along with a group of catalysts with electron

donating substituents (see Supporting information, Scheme S1) but addition of electron-withdrawing CF₃-groups improved the *er* of the reaction from 68:32 to 89:11 (catalysts **22** and **23**). Unfortunately, the change of the phenyl-substituent of **23** to a 3,5-bis-CF₃-phenyl (catalyst **24**) or a pentafluorophenyl-substituent (catalyst **25**) failed to elicit higher enantioselectivities. With these results, we decided to proceed with the total synthesis with our most selective catalyst **20**.

Scheme 2. Screening the catalysts for the Mukaiyama-Michael reaction^a

a) Enantiomeric ratios determined by chiral GC from the reaction mixture.

Further optimization of the reaction conditions (Table S1, entry 7, Supporting Information) revealed that TFA was the optimal counteracid. Lowering the temperature to −30 °C had no effect on *er* but the conversion fell dramatically. Interestingly, when water was excluded from the reaction, *er* of 95:5 was achieved (Table S1, entries 10 and 11, Supporting information). Unfortunately, the reaction never reached completion, thus making these conditions unpractical.²¹

With these conditions at hand, we continued with the total synthesis. The entire route is shown in Scheme 3 starting from

the known silyloxyfuran **4** (see also the Supporting Information).^{22,23} In gram-scale, the enantioselective Mukaiyama–Michael reaction afforded the aldehyde (+)-**7** in 47% yield and *er* 94:6. (+)-**7** was then reduced to **27** with an 86% yield after chromatographic purification. In both of these transformations, the sensitivity of acrolein, (+)-**7** or **27** to polymerization were found to hamper the yields.

In our initial route, aldehyde **27** was first α -aminated with DBAD (**28**) using List's protocol¹⁶, and the resulting amino aldehyde **29** was oxidised to the corresponding carboxylic acid **30**. Unfortunately, this relatively straightforward route to (+)-lycoperdic acid had to be abandoned since the subsequent N–N-bond cleavage could not be reliably achieved (Scheme 3).²⁴

In the alternative, ultimately successful route (Scheme 3), aldehyde **27** was subjected to an organocatalytic α -chlorination reaction, using perchlorinated quinone **31** as the Cl^+ -source and the MacMillan imidazolidinone TFA-salt **14** as the catalyst.^{25,26} Instead of **31**, *N*-chlorosuccinimide was also tested in this reaction, but it afforded lower conversions than quinone **31**.²⁷ The intermediate α -chloroaldehyde was directly oxidised in the same pot to the corresponding carboxylic acid **32**.²⁸ The crude acid was then methylated with MeI under basic conditions, yielding the diester **33** in 71% yield over two steps. It was noteworthy that this two-step sequence could not be carried out with unsaturated aldehyde (+)-**7**; a complex mixture of compounds was obtained under the same reaction conditions. The diester **33** was then converted into the corresponding azide *via* $\text{S}_{\text{N}}2$ -reaction with NaN_3 , yielding the azide **34** in 84% yield. The azide group was then converted to the Boc-protected amino group *via* hydrogenolysis in the presence of Boc_2O . To our delight, the diastereomers were separable chromatographically at this stage, giving the desired full-protected natural product **35** in 74% yield, alongside with 4-*epi*-**35** (9%, 86:14 diastereomeric purity).

With diastereomerically pure **35**, the final stages were then explored. Saponification under basic conditions led to epimerization of the labile C2 stereocenter. In contrast, refluxing the compound **35** in 6 M HCl smoothly removed the Boc- and ester protecting groups, and after neutralization of the hydrochloride salt by an ion exchange column, crude (+)-**1** was in our hands. In order to get analytically pure samples and to remove the hydroxy acid **36**, the crude product was recrystallized twice from water giving us pure (+)-**1** in 28% yield. It was noteworthy that **36** could not be transformed to the lactone by dehydration (e.g. benzene, reflux) since these conditions resulted in the formation of several side products.

Scheme 3. The total synthesis route.

In summary, we have developed an enantioselective organocatalytic total synthesis route for (+)-lycoperdic acid without using a chiral pool approach. As the key transformation, iminium-catalysed Mukaiyama–Michael reaction between silyloxyfuran **4** and acrolein (**6**) using a specifically optimized catalyst **20** successfully installed the key C4 tertiary stereogenic center. Efforts to synthesise derivatives of (+)-**1** as well as wider studies of the developed Mukaiyama–Michael reaction are on their way.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterisation data and copies of ^1H and ^{13}C NMR spectra (PDF) are available free of charge on the ACS Publications website. Crystallographic data was deposited with the accession number 1972521, and can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/structures.

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Notes

The authors declare no competing financial interest.

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