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# Catalytic Enantioselective Total Synthesis of (+)–Lycoperdic Acid

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**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  $\alpha$ -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.*<sup>1</sup> It is an amino acid that shares structural similarities with both L-glutamic acid (2) and dysiherbaines (**3a**, **3b**, Figure 1).<sup>2,3</sup> The dysiherbaines are well-known ionotropic glutamate receptor binders<sup>3,4</sup>, a fact which has raised questions about the biological activity of (+)-1 over the years.<sup>5–7</sup>



Figure 1. Glutamate-Related Amino Acids

To date, there are seven total syntheses and one formal synthesis for (+)-1.<sup>5–14</sup> 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.<sup>7</sup>

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*  $\alpha$ -amination reaction (Scheme 1).<sup>15,16</sup> The challenging C4 tertiary stereogenic center would be accessed *via* a Mukai-yama–Michael reaction between a silyloxyfuran **4** and acrolein (**6**).<sup>17</sup>



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).<sup>18</sup> Our own previous experience with enantioselective Mukaiyama-Michael reactions with acrolein involving diphenylpyrrolidine (**9**)<sup>19</sup> and pyroglutamic-acid-derived pyrrolidine<sup>20</sup> 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



Precedents:

Problems with vield and selectivity (Pansare and co-workers, 2010)



• The starting material is not functionalized (Pihko and co-workers, 2012)



Hypothesis: optimized catalyst should give better yield/selectivity towards 7



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* NO<sub>2</sub> (*er* 18:82, **17**) to CF<sub>3</sub> (*er* 85:15, **18**). In contrast, electron-donating groups (*t*-Bu) had a detrimental effect on *er* (catalyst **S37**, 57:43 *er*, see the Supporting Information, Scheme S1). Interestingly, catalysts **18** and **19**, bearing either *p*-CF<sub>3</sub> (**18**) or two *m*-CF<sub>3</sub> groups (**19**) afforded similar enantioselectivities. Finally, diarylpyrrolidine **20** with four CF<sub>3</sub>-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 pyroglutamic-acid-derived 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 CF<sub>3</sub>-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-CF<sub>3</sub>-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<sup>a</sup>



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.<sup>21</sup>

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).<sup>22,23</sup> 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  $\alpha$ -aminated with DBAD (**28**) using List's protocol<sup>16</sup>, 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).<sup>24</sup>

In the alternative, ultimately successful route (Scheme 3), aldehyde 27 was subjected to an organocatalytic  $\alpha$ -chlorination reaction, using perchlorinated quinone 31 as the Cl<sup>+</sup>-source and the MacMillan imidazolidinone TFA-salt 14 as the catalyst.<sup>25,26</sup> Instead of 31, N-chlorosuccinimide was also tested in this reaction, but it afforded lower conversions than quinone **31**.<sup>27</sup> The intermediate a-chloroaldehyde was directly oxidised in the same pot to the corresponding carboxylic acid 32.<sup>28</sup> 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 S<sub>N</sub>2reaction with NaN<sub>3</sub>, 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<sub>2</sub>O. 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 <sup>1</sup>H and <sup>13</sup>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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