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Kenji Morokuma, Raku Irie, Masato Oikawa

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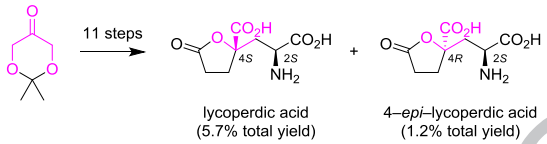

lycoperdic acid
(5.7% total yield)

4–*epi*–lycoperdic acid
(1.2% total yield)

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Total synthesis of lycoperdic acid and its C4–epimer

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Yokohama City University, Seto 22–2, Kanazawa–ku, Yokohama, 236–0027, Japan

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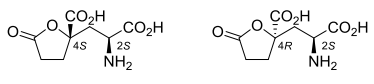
ABSTRACT

Efficient stereodivergent syntheses of (+)–lycoperdic acid (LPA) and 4–*epi*–LPA have been achieved based on asymmetric hydrogenation (H_2, Rh/(*R*,*S*)–MeBoPhoz) of racemic enamide as a key step.

Introduction

Ionotropic glutamate receptors (iGluRs) mediate the majority of the fast excitatory neurotransmission in the mammalian central nervous system to play a pivotal role in the higher brain functions such as learning, memory, and nociception [1,2]. Many of the naturally occurring ligands for iGluR typically contain glutamic acid motif fused to five-membered heterocycle such as tetrahydrofuran [3,4] and pyrrolidine [5–8].

Herein, we report enantioselective synthesis of mushroom-derived lycoperdic acid (LPA, **1**, Fig. 1) [9] and the 4–*epi*–congener **2**, as a part of our ongoing project to develop artificial glutamate analogs as a novel ligand for iGluR [10–17]. Whilst LPA (**1**) also bears glutamic acid motif on the γ–butyrolactone core structurally, the neuronal activity has not yet been reported. From our successful demonstration of synthesis-based development of iGluR antagonist selective to AMPA-type receptor [18,19], however, we anticipate structural modification of LPA (**1**) would enable to develop analogs with diverse neuroactivity profiles.



lycoperdic acid (LPA, **1**) 4–*epi*–LPA (**2**)

Figure 1. Mushroom-derived natural glutamate **1** and the congener **2** in this study.

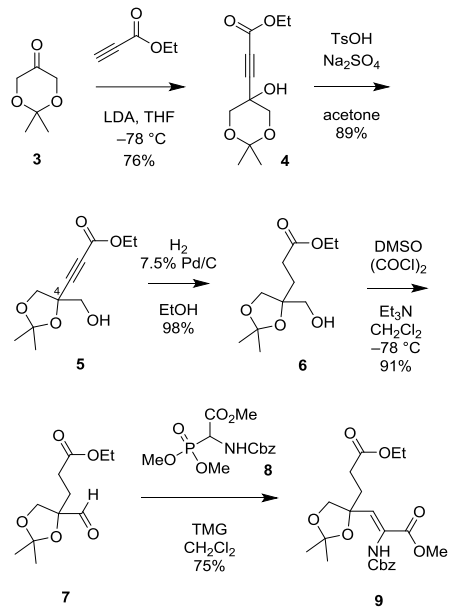
LPA (**1**) contains two stereogenic centers at the C2 and C4 positions. We planned to divergently synthesize natural-type LPA (**1**) with (2*S*,4*S*)–configuration, and the 4–*epi*–congener **2** (see Fig. 1), by 1) enantioselective introduction of the (2*S*) stereochemistry to a substrate racemic at the C4 position, followed by 2) chromatographic separation of the thereby generating (2*S*,4*S*)– and (2*S*,4*R*)–diastereomers, as follows.

Results and discussion

Synthesis of racemic enamide ester *rac*–**9** as a substrate for the enantioselective reaction is shown in Scheme 1. Here, we decided to employ commercially available 2,2–dimethyl–1,3–dioxan–5–one (**3**) [20] as a starting material, and the coupling with ethyl propiolate (LDA, THF, –78 °C) provided propargylic alcohol **4** in 76% yield. Treatment of 1,3–diol acetonide **4** with TsOH under anhydrous conditions [21] resulted in clean migration of the acetal toward 1,2–diol acetonide **5** which is racemic at the C4 position (LPA numbering), in 89% yield.

Alkyne **5** was then subjected to heterogeneous hydrogenation (H_2, 7.5% Pd/C, EtOH) to give rise to **6** in high yield. Swern oxidation [22] of primary alcohol **6** delivered aldehyde **7**, which, without purification, was subjected to Horner–Wadsworth–Emmons olefination with *N*–Cbz–(α–phosphono)glycine trimethyl ester (**8**) [23] and 1,1,3,3–tetramethylguanidine (TMG) to afford (*Z*)–enamide *rac*–**9** in 75% yield accompanied by the (*E*)–isomer (3.5%).

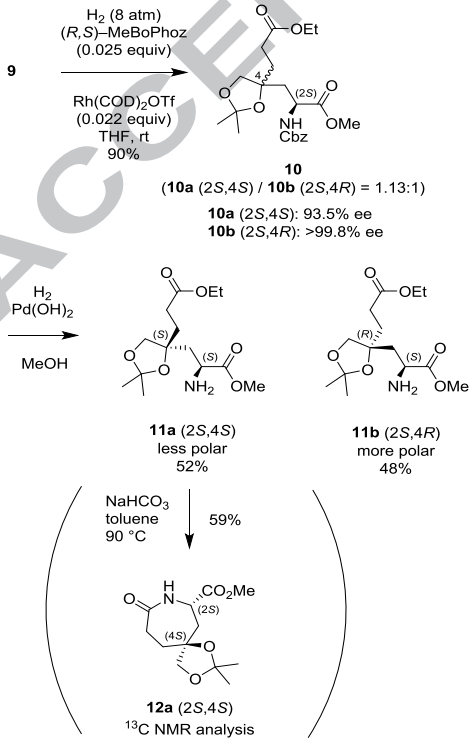
* Corresponding author. Tel.: +81–45–787–2403; fax: +81–45–787–2403; e-mail: moikawa@yokohama-cu.ac.jp



Scheme 1. Synthesis of enamide ester *rac*–**9**.

With enamide *rac*–**9** in hand, asymmetric hydrogenation (H_2, Rh/(*R*,*S*)–MeBoPhoz) [24] was then conducted to provide an inseparable mixture of (2*S*,4*S*)–**10a** with natural configuration (93.5% ee) and unnatural (2*S*,4*R*)–**10b** (>99.8% ee) (**10a**/**10b** = 1.13:1, Scheme 2). The structures were determined in the next two steps in Scheme 2 (see below), and the enantiomeric purities were determined here by chiral HPLC analysis (DAICEL CHIRALPAK IF–3 column, 150 × 4.6 mm) of the mixture (see the Supplementary data).

Fortunately, deprotection of the Cbz group allowed a facile separation of the diastereomers by silica gel column chromatography to give amines (2*S*,4*S*)–**11a** (less polar on TLC) and (2*S*,4*R*)–**11b** (more polar on TLC) in 52% and 48% yields, respectively.



Scheme 2. Asymmetric hydrogenation and separation toward amino esters **11a** and **11b**.

After isolation, amino ester **11a** was found to be unstable even at rt and gradually converted to lactam **12a**. Actually, 24% of **11a** was converted into **12a** under these conditions after 10 days (data not shown). For preparative purpose, the transformation could be realized by heating a solution of **11a** in toluene to 90 °C in the presence of $NaHCO_3$ (59% yield). While the reaction was not optimized, addition of $NaHCO_3$ may accelerate the reaction. At the time, the relative configuration of lactam **12a** was determined to be (2*S**,4*S**), but not (2*S**,4*R**), by comparison of the ^{13}C NMR chemical shifts with those expected by density functional theory (DFT) calculation, as follows [25,26]. Thus, theoretical ^{13}C chemical shift values for (2*S*,4*S*)–**12A** generated with ωB97X–V/6–311+G(2df,2p)[6–311+G*]//ωB97X–D/6–31G* model (Fig. 2) (Spartan '18 software; Wavefunction, Irvine, CA, U.S.A.) was found to agree well with the experimental data for **12a** (root mean square deviation (RMS) 0.73 ppm), whereas RMS value for the (2*S*,4*R*)–isomer **12B** was higher (1.73 ppm) (for detailed discussions, see the Supplementary data). In addition, analysis using DP4 probability statistics [25,27] of the calculated shifts with the experimental data of **12a** showed that the probability ratio for (2*S*,4*S*)–isomer/(2*S*,4*R*)–isomer was 99.5%:0.5%. These results are consistent with the NOESY cross peaks observed and depicted also in Fig. 2.

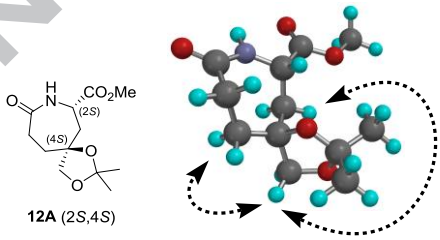
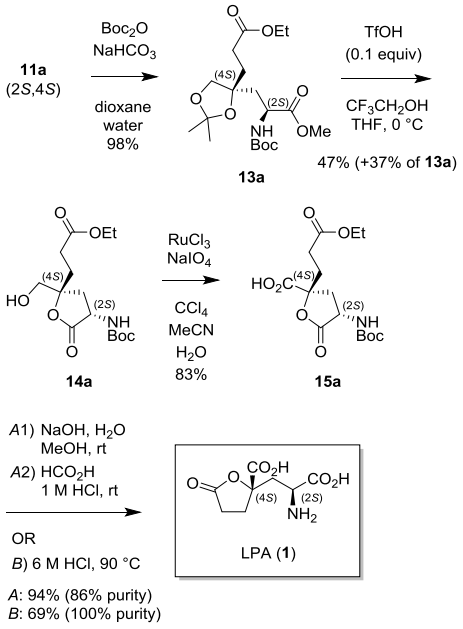


Figure 2. The most stable conformer (population: 77%) in top three conformers (total population: 100%) for **12A** (2*S*,4*S*), which were generated by DFT calculation with ωB97X–D/6–31G* model. Dashed arrows indicate NOESY correlations observed for **12a**.

Assuming that asymmetric hydrogenation has generated (2*S*)–configuration according to the empirical rule [24], **12a** bears configuration identical with natural LPA. The assignment was finally confirmed by syntheses of known alcohol **14a** and LPA (**1**), from **11a** (see below).



Scheme 3. Final elaboration toward LPA (**1**).

For the synthesis of natural (2*S*,4*S*)–LPA (**1**), amine **11a** was reprotected with Boc group (Boc_2O, $NaHCO_3$) to give rise to **13a** (Scheme 3). Next we tried chemoselective removal of isopropylidene group of **13a** over the *N*–Boc group. While attempts using standard procedure (80% AcOH or Amberlyst–15 (EtOH, water)) [28] met with failure, we found that Inoue's procedure (TfOH, CF_3CH_2OH, THF) [29,30] effected selective deprotection of the isopropylidene group and concomitant lactonization without affecting the acid-labile *N*–Boc group to afford γ–butyrolactone (2*S*,4*S*)–**14a** in 47% yield, whose spectroscopic data were in good accord with those reported [14].

The primary hydroxy group of **14a** was then oxidized with RuO_4 to furnish carboxylic acid **15a** in 83% yield. To complete the synthesis, protective group manipulation and lactone construction at the correct position were first attempted according to the reported two-step procedure [14] (*procedure A*) as follows. Thus, exposure of carboxylic acid **15a** to NaOH in MeOH and water at rt induced translactonization smoothly in 1 h. Then removal of the Boc group was carried out with HCO_2H and 1 M HCl, to afford LPA (**1**) in 94% yield (86% purity) [31] for 2 steps (32% after recrystallization from water). Spectroscopic data of the synthetic LPA (**1**) were in good accord with those reported [11,14]. For these transformations, however, we found that a simple one-step procedure (*B*, 1 M HCl, 90 °C) is also effective to furnish LPA (**1**) in 69% yield (25% yield after recrystallization). By the latter *one-step procedure B*, no epimerization at the C2 position took place, which we observed in the former *two-step procedure A* in approximately 13% (see above) [31]. 4–*epi*–LPA (**2**) was also synthesized from (2*S*,4*R*)–**11b** (see Scheme 2) after the same sequence of reaction in 6.2% yield (see the Supplementary data). The total yields for LPA (**1**) and 4–*epi*–LPA (**2**) were 5.7% and 1.2%, respectively, for 11 steps each from ketone **3**.

In conclusion, we have achieved enantiospecific syntheses of mushroom-derived lycoperdic acid (**1**) and the 4–*epi*–congener **2** for development of glutamate analogs with diverse neuroactivities. The key reaction was enantioselective hydrogenation of enamide ester *rac*–**9** mediated by (*R*,*S*)–MeBoPhoz. From the enantioselectivity profile shown in Scheme 2, (4*S*)–**9** and (*R*,*S*)–MeBoPhoz are stereochemically rather mismatched, and hydrogenation of (4*R*)–**9** with (*R*,*S*)–MeBoPhoz is a matched double asymmetric reaction [32,33]. The synthetic route reported herein is reasonably expected to provide other isomers of LPA. Works on the synthesis and evaluation are currently underway, and the results will be reported in due course.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.########.

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Lycoperdic acid and the 4–*epi*–congener have been enantiospecifically synthesized.

Asymmetric hydrogenation by (*R*,*S*)–MeBoPhoz ligand was employed for the amino acid.

Configuration was analyzed by experimental and calculated ^{13}C NMR data.