Pergamon

Tetrahedron 58 (2002) 9737–9740

TETRAHEDRON

Stereoselective synthesis of (*S*)-(+)-lycoperdic acid through an *endo* selective hydroxylation of the chiral bicyclic lactam enolate with MoOPH

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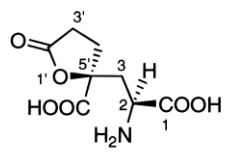
Received 4 September 2002; accepted 30 September 2002

Abstract—Efficient synthesis of (*S*)-(+)-lycoperdic acid has been achieved by use of the stereoselective hydroxylation of the enolate derived from the bicyclic lactam **3** with the molybdenum oxidizing reagent, MoOPH (MoO_5·Py·HMPA, oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)), as a key step.

1. Introduction

(*S*)-(+)-Lycoperdic acid (**1**), was isolated as an unusual α-amino acid from the mushroom *Lycoperdon perlatum* by R-Banga et al. in 1978.[1] From the structural similarity of this compound with (*S*)-glutamic acid, (*S*)-(+)-lycoperdic acid is expected to have antagonistic or agonistic activity for glutamate receptor in the mammalian central nervous system. In our continuous efforts[2] directed towards the development of stereocontrolled transformations of the chiral bicyclic lactam **2**, we have disclosed a highly stereoselective hydroxylation reaction of the chiral bicyclic lactam enolate with *endo* selectivity using MoOPH (MoO_5·Py·HMPA) and MoOPD (MoO_5·Py·DMPU).[2c] The synthesis of **1** has been already reported by Yoshifuji's[3a,b] and Hatakeyama's[3c] groups independently. As an application of our developed method, we wish to report here an efficient synthesis of (*S*)-(+)-lycoperdic acid featuring stereoselective construction of the quaternary carbon by this *endo* selective hydroxylation as a key step (Fig. 1).



(+)-lycoperdic acid (**1**)

Figure 1.

2. Results and discussion

The synthesis of (*S*)-(+)-lycoperdic acid (Scheme 1) commenced with the allylation of the chiral bicyclic lactam **2**,[4] a versatile synthon in the synthesis of a variety of natural products,[5] to afford a 1:1 mixture of diastereomeric isomers **3** in 95% yield. This mixture **3** was directly treated with 2 equiv. of LDA at −78°C for 2 h followed by addition of 2 equiv. of freshly prepared MoOPH[6] to give the α-hydroxylated lactam **4** as a single diastereomer in 77% yield (95% conversion yield). Alternatively, the use of molecular oxygen[7] as an oxidizing reagent showed low diastereoselectivity (*endo*/*exo*=2.8:1) in 65% yield. The stereostructure of the *endo* product **4** was unambiguously confirmed by NOE experiment of **4** and X-ray crystallographic analysis of the latent **6**. Catalyzed hydroboration of **4** using catecholborane in the presence of a catalytic amount of *N*,*N*-dimethylacetamide[8] or $Rh(PPh_3)_3Cl$[9] gave no product and the starting material was recovered. The use of a borane–dimethylsulfide complex afforded the desired alcohol in moderate yield (55%). The treatment of **4** with a borane–tetrahydrofuran complex followed by alkaline hydrogen peroxide work-up, however, provided the desired alcohol **5** in 85% yield along with small amounts of the regioisomer (5%). Oxidation of the alcohol **5** with Jones reagent directly afforded the γ-lactone **6** in 67% yield. The crystalline **6** was subjected to X-ray crystallographic analysis of which the oxygen in the lactone ring at the *endo* position clearly supports the NOE-assigned stereostructure of **4** as shown in Fig. 2. In subsequent conversion of **6** to **1**, we encountered unexpected epimerization during Jones oxidation. Thus, after removal of the *N*,*O*-benzylidene acetal with trifluoroacetic acid, the lactam alcohol was

Keywords: (*S*)-(+)-lycoperdic acid; hydroxylation; MoOPH; bicyclic lactam; *endo* selectivity.

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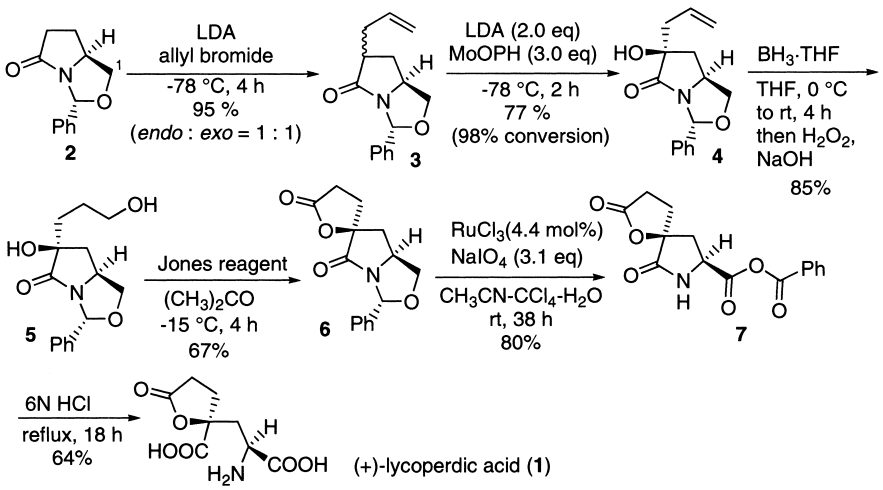
0040–4020/02/$ - see front matter
PII: S0040-4020(02)01254-1



Scheme 1.

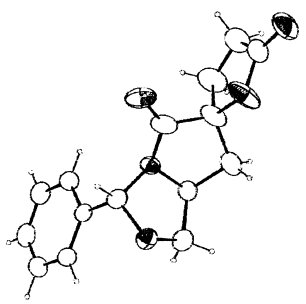


Figure 2. X-Ray crystallographic structure of **6**.

subjected to the Jones oxidation and the resulting carboxylic acid was hydrolyzed with 6N hydrochloric acid to afford the lycoperdic acid. The obtained lycoperdic acid, however, showed minus value in specific rotation different from plus one of the natural product, which seemed to suggest the extensive epimerization at C2. After some experiments, we found novel two-step conversion without epimerization. Direct oxidation of **6** using sodium periodate and ruthenium trichloride[10] in acetonitrile–carbon tetrachloride–water at room temperature for 38 h furnished the unexpected anhydride **7** in 80% yield, which was derived from the oxidation at C1 and *N*,*O*-acetal benzylic position. Finally, hydrolysis of **7** in hydrochloric acid under refluxing conditions for 18 h followed by purification using ion-exchange chromatography (Dowex 1x8, eluted 2N acetic acid) gave the crude product, which was recrystallized from water to furnish (*S*)-(+)-lycoperdic acid in 64% yield in pure form, mp 200–202°C, $[\alpha]_D^{25}$=+14.4 (*c* 0.48, H_2O) (lit. $[\alpha]_D^{20}$=+14.9 (*c* 0.47, H_2O),[1] $[\alpha]_D^{21}$=+14.2 (*c* 0.47, H_2O),[3a,b] $[\alpha]_D^{28}$=+12.7 (*c* 0.21, H_2O)[3c]). The synthetic material was found to be identical with natural lycoperdic acid through spectral comparisons (^1H and ^{13}C NMR).

In conclusion, we have achieved the synthesis of (*S*)-(+)-lycoperdic acid in six steps from the chiral bicyclic lactam **2** with an overall yield of 21% based on the highly *endo* selective hydroxylation using MoOPH as a key step.

3. Experimental

3.1. General

Melting points are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-230 spectrometer. Optical rotations were determined on a JASCO DIP-140 polarimeter. NMR spectra were recorded on JEOL JNM GSX 400A, JNM GSX500A and JNM ECP400 spectrometers. Mass spectra were obtained on a JEOL HX-110A (LRFAB, LREI) spectrometer. Column chromatography was performed with silica gel BW-820MH (Fuji silysia).

3.2. Experimental procedures

3.2.1. (2*R*,5*S*,7*S*) and (2*R*,5*S*,7*R*)-7-Allyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one (3). To a stirred solution of lithium diisopropylamide in THF at −78°C, prepared from diisopropylamine (15.8 mL, 11.7 mmol) and *n*-BuLi (1.57 M in *n*-hexane, 65.5 mL, 103 mmol) in THF (150 mL) at 0°C for 0.5 h, was added dropwise a solution of bicyclic lactam **2** (20.8 g, 103 mmol) in THF (70 mL) under an argon atmosphere. After stirring the mixture for 1 h, allylbromide (17.7 mL, 205 mmol) was added dropwise at −78°C and the resulting mixture was stirred at the same temperature for 4 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (200 g, ethyl acetate/*n*-hexane=1:4) to afford **3** (23.7 g, 97.4 mmol, 95%) as a yellow oil (*endo*-isomer/*exo*-isomer=1:1). Analytical samples of *endo*-**3** and *exo*-**3** were obtained through separation using silica gel column chromatography.

endo-**3**: $[\alpha]_D^{24}$=+219 (*c* 1.11, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (ddd, *J*=7.0, 10.9, 12.9 Hz, 1H), 2.20 (ddd, *J*=7.4, 8.8, 14.6 Hz, 1H), 2.50 (ddd, *J*=7.1, 8.8, 12.9 Hz, 1H), 2.62–2.67 (m, 1H), 2.98–3.01 (m, 1H), 3.49 (t, *J*=8.0 Hz, 1H), 4.06 (quintet, *J*=7.1 Hz, 1H), 4.22 (dd, *J*=6.3, 8.1 Hz, 1H), 5.07–5.14 (m, 2H), 5.74–5.83 (m, 1H), 6.33 (s, 1H), 7.32–7.46 (m, 5H); ^{13}C NMR (400 MHz,

$CDCl_3$) δ 29.6, 31.2, 34.7, 44.5, 56.5, 72.3, 86.7, 117.1, 125.9, 128.4, 135.2, 138.6, 177.7; IR (neat) 2924, 1705, 1452, 1377, 1169, 918 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{18}NO_2$: 244.1338 ($M+H^+$). Found 244.1352.

exo-**3**: $[\alpha]_D^{24}=+145$ (*c* 1.15, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 2.08–2.12 (m, 2H), 2.36–2.41 (m, 1H), 2.57–2.63 (m, 1H), 2.77–2.80 (m, 1H), 3.40 (dd, *J*=8.1, 8.8 Hz, 1H), 4.04–4.07 (m, 1H), 4.21 (dd, *J*=6.2, 8.1 Hz, 1H), 5.10–5.16 (m, 2H), 5.77–5.84 (m, 1H), 6.33 (s, 1H), 7.30–7.46 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 27.0, 36.1, 44.2, 57.1, 71.1, 87.1, 117.5, 125.7, 128.3, 134.5, 138.8, 180.0; IR (neat) 2945, 1705, 1379, 1354, 1159, 1026, 918 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{18}NO_2$: 244.1338 ($M+H^+$). Found 244.1319.

3.2.2. (2*R*,5*S*,7*S*)-7-Allyl-7-hydroxy-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one (4). To a stirred solution of lithium diisopropylamide in THF at −78°C, prepared from diisopropylamine (6.3 mL, 45.2 mmol) and *n*-BuLi (1.57 M in *n*-hexane, 26.2 mL, 41.1 mmol) in THF (10 mL) at 0°C for 1.5 h, was added dropwise a solution of bicyclic lactams **3** (5.00 g, 20.6 mmol) in THF (20 mL) under an argon atmosphere. After stirring the mixture for 1.5 h, freshly prepared MoOPH (17.8 g, 41.1 mmol) was added portionwise at −78°C and the resulting mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous sodium sulfite (150 mL) and extracted three times with ethyl acetate. The combined organic extracts were washed with 5% aqueous ammonium chloride and saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (200 g, ethyl acetate/*n*-hexane=1:2) to afford **4** (4.13 g, 15.9 mmol, 77%) as a colorless oil along with the starting material **3** (1.05 g, 4.3 mmol, 21%) as a yellow oil.

$[\alpha]_D^{25}=+125$ (*c* 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (dd, *J*=7.1, 13.0 Hz, 1H), 2.47 (dd, *J*=7.9, 13.8 Hz), 2.55–2.62 (m, 2H), 2.92 (brs, 1H), 3.56 (t, *J*=8.2 Hz, 1H), 3.95 (m, 1H), 4.29 (dd, *J*=6.1, 8.3 Hz, 1H), 5.19–5.24 (m, 2H), 5.82–5.92 (m, 1H), 6.31 (s, 1H), 7.34–7.44 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 38.1, 43.0, 54.5, 72.4, 80.4, 86.7, 119.8, 125.9, 128.4, 128.7, 131.5, 138.0, 177.7; IR (neat) 3380, 2920, 1700, 1450, 1360, 1280, 1220, 1170, 1070, 1020, 920 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{18}NO_3$ 260.1287 ($M+H^+$). Found 260.1295.

3.2.3. (2*R*,5*S*,7*S*)-7-Hydroxy-7-(1-ol-propyl)-2-phenyl-1-aza-3-oxabicyclo[3.3.0] octan-8-one (5). To a stirred solution of **4** (130 mg, 0.500 mmol) in THF (2.0 mL) at 0°C was added dropwise borane–tetrahydrofuran complex (1.0 M in THF, 1.0 mL, 1.0 mmol) under an argon atmosphere. After the mixture was warmed to room temperature over 4 h, the reaction was quenched with sodium hydroxide (3N in water, 2 mL) and 30% aqueous hydrogen peroxide (2 mL) at 0°C. After the resulting mixture was extracted with chloroform, the organic layer was washed with saturated aqueous sodium thiosulfate, saturated aqueous ammonium chloride and saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (2 g, ethyl acetate/*n*-hexane=2:1) to afford the desired diol **5** (119 mg, 0.429 mmol, 86%) and its regioisomer (7.4 mg, 0.029 mmol, 5%) as a colorless oil. $[\alpha]_D^{24}=+121$ (*c* 1.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.73–1.76 (m, 2H), 1.84–1.88 (m, 1H), 1.97–2.09 (m, 2H), 2.51 (dd, *J*=6.6, 12.9 Hz, 1H), 3.58–3.64 (m, 2H), 3.72–3.76 (m, 1H), 3.41 (quint, *J*=6.8 Hz, 1H), 4.29 (dd, *J*=6.2, 8.2 Hz, 1H), 6.29 (s, 1H), 7.33–7.43 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 27.0, 35.9, 39.6, 54.7, 62.5, 72.6, 80.6, 86.8, 126.0, 128.8, 138.1, 178.3; IR (neat) 3421, 2924, 1699, 1405, 1043 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{20}NO_4$ 278.1392 ($M+H^+$). Found 278.1374.

3.2.4. (2*R*,5*S*,7*S*)-7-(2′-Tetrahydrofuranyl-5′-oxo)-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one (6). To a stirred solution of diol **5** (97.0 mg, 0.350 mmol) in acetone (1.4 mL) at −15°C was added dropwise Jones reagent (7.8 M in water, 180 μL, 1.40 mmol). After the mixture was stirred at −15°C to 0°C for 4 h, the reaction was quenched with isopropanol (1 mL) and saturated aqueous sodium hydrogen carbonate (1 mL). After the resulting mixture was extracted with chloroform, the organic extracts were washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by recrystallization from ethyl acetate to afford the lactone **6** (63.7 mg, 0.233 mmol, 67%) as white solids. Mp 171°C; $[\alpha]_D^{27}=+122$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (dt, *J*=10.1, 13.4 Hz, 1H), 2.45 (dd, *J*=5.9, 13.9 Hz, 1H), 2.56–2.64 (m, 3H), 2.89–2.98 (m, 1H), 3.58 (t, *J*=8.4 Hz, 1H), 4.02–4.09 (m, 1H), 4.37 (dd, *J*=8.3, 5.9 Hz, 1H), 6.31 (s, 1H), 7.34–7.47 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 28.1, 32.0, 36.4, 53.9, 71.9, 87.1, 87.7, 125.9, 128.5, 128.9, 137.7, 173.4, 175.3; IR (KBr) 1788, 1726, 1398, 1340, 1221, 1174, 1011, 918 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{16}NO_4$ ($M+H^+$) 274.1079. Found 274.1084.

3.2.5. Benzoic (5*S*,8*S*)-2,6-dioxo-1-oxa-7-aza-spiro[4.4]-nonane-8-carboxylic anhydride (7). To a stirred solution of **6** (20.0 mg, 0.0732 mmol) in CH_3CN (1.2 mL) and CCl_4 (0.8 mL) at 0°C was added a solution of sodium periodate (62.5 mg, 0.292 mmol) in water (1.2 mL) and ruthenium trichloride (1.5 mg, 0.00723 mmol). After stirring the mixture for 72 h at rt, the reaction was quenched with isopropanol (0.1 mL). The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (10 g, chloroform/methanol=9:1) to afford **7** (17.8 mg, 0.0587 mmol, 80%) as a colorless oil. $[\alpha]_D^{27}=-126$ (*c* 0.41, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 2.18–2.26 (m, 2H), 2.54–2.72 (m, 4H), 2.79–2.95 (m, 2H), 5.8 (dd, *J*=4.8, 8.8 Hz), 7.46–7.73 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 28.1, 29.6, 34.1, 54.5, 85.1, 128.1, 129.3, 133.2, 170.0, 170.3, 172.7, 175.1; IR (neat) 3016, 1792, 1752, 1734, 1693, 1601, 1453, 1285, 1162 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{14}NO_6$ ($M+H^+$) 304.0821. Found 304.0848. Anal. calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.07; H, 5.59; N, 5.12.

3.2.6. (+)-Lycoperdic acid (1). A suspension of **7** (80.2 mg, 0.265 mmol) in hydrochloric acid (6N, 5.0 mL) was heated under reflux for 24 h. After the resulting mixture was concentrated in vacuo, the residue was applied to a column of Dowex 1×8 (200–400 mesh, acetate form), and eluted with aqueous acetic acid (2N). Concentration of the

eluate to dryness afforded the crude product as a white solid, which was recrystallized from water to furnish (+)-lycoperdic acid **1** (33.1 mg, 0.153 mmol, 64%) as colorless solids. Mp 200–202°C (lit 200–201°C,[3a,b] 200–202°C[3c]); $[\alpha]_D^{24}$=+14.4 (*c* 0.48, H_2O) (lit $[\alpha]_D^{20}$=+14.9 (*c* 0.47, H_2O),[1] $[\alpha]_D^{21}$=+14.2 (*c* 0.47, H_2O)[3a,b], $[\alpha]_D^{28}$=+12.7 (*c* 0.21, H_2O)[3c]); ^{1}H NMR (400 MHz, D_2O) δ 2.14–2.25 (m, 2H), 2.44–2.50 (m, 1H), 2.55–2.60 (m, 2H), 2.74 (dd, *J*=2.8, 15.2 Hz, 1H), 3.80 (dd, *J*=3.2, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 27.8, 32.3, 37.9, 52.0, 88.3, 172.5, 175.9, 179.9; IR (KBr) 3446, 3235, 2954, 2919, 2849, 2594, 1777, 1734, 1653, 1560, 1206, 1101 cm^{-1}; HRMS (FAB) calcd for $C_8H_{11}NO_6$ ($M+H^+$) 218.0665. Found 218.0660.

Acknowledgements

This work was partially supported by the Sasakawa Scientific Research Grant from the Japan Science Society (to K. M.).

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