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# Diastereoselective Synthesis of Glutamate-Appended Oxolane Rings: Synthesis of (*S*)-(+)-Lycoperdic Acid

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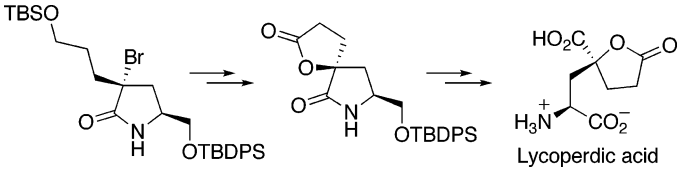


The stereocontrolled synthesis of the glutamate-containing natural product (*S*)-(+)-lycoperdic acid is described. The key transformation in the synthetic route was an efficient diastereoselective annulation of an oxolane ring onto a pyroglutamate scaffold to construct either a $\gamma,\gamma$-disubstituted glutamate-appended tetrahydrofuran or a $\gamma$-lactone. The reaction sequence also featured an improved method for the halogenation of pyroglutamate derivatives in high yield with enhanced stereoselection.

## Introduction

Glutamate-containing natural products have attracted attention in the chemical and biological communities due to their unique structures and biological profiles.[1] Members of the class of glutamate-containing natural products include dysiherbaine[2] (**1**), neodysiherbaine[3] (**2**), and lycoperdic acid[4] (**3**), each of which contains a $\gamma,\gamma$-disubstituted glutamic acid moiety that is appended to the α-position of an oxolane (tetrahydrofuran) ring (Figure 1). Our interest in this family of structurally similar $\gamma,\gamma$-disubstituted glutamates was motivated by the agonist activity of dysiherbaine and neodysiherbaine at the ionotropic glutamate receptors (iGluRs) in the mammalian central nervous system (CNS).[2,3,5] The iGluRs are ligand-gated ion channels that mediate neurotransmission and neuronal development, and

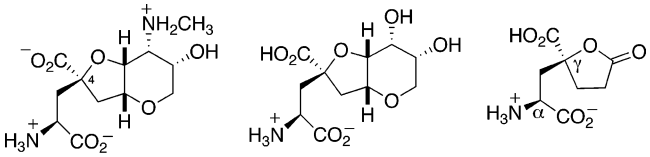


**FIGURE 1.** Glutamate-containing natural products.

characterizing the iGluRs is a current priority not only due to their function in normal CNS processes such as memory and learning but also due to their role in causing damage in a variety of neurodegenerative disorders, including stroke, epilepsy, and Alzheimer's disease.[6] As potent and selective iGluR ligands, glutamate-containing natural products have thus emerged as valuable pharmacological tools for investigating neurotransmission in the CNS.[5,7]

The impressive biological properties, low natural abundance, and the distinctive architectures of dysiherbaine (**1**), neodysi-

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(1) For a representative example, see: (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, *24*, 5127−5143. (b) Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 4569−4577.

(2) Sakai, R.; Kamiyla, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112−4116.

(3) Sakai, R.; Koike, T.; Sasaki, M.; Shimamoto, K.; Oiwa, C.; Yano, A.; Suzuki, K.; Tachibana, K.; Kamiya, H. *Org. Lett.* **2001**, *3*, 1479−1482.

(4) (a) Banga, N. R.; Welter, A.; Jadot, J.; Casimir, J. *Phytochemistry* **1979**, *18*, 482−484. (b) Lamotte, J.; Oleksyn, B.; Dupont, L.; Didberg, O.; Campsteyn, H.; Vermeire, M. *Acta Crystallogr.* **1978**, *B34*, 3635−3638.

(5) (a) Sanders, J.; Ito, K.; Settimo, L.; Pentikainen, O.; Shoji, M.; Sasaki, M.; Johnson, M.; Sakai, R.; Swanson, G. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1068−1078. (b) Sakai, R.; Swanson, G.; Shimamoto, K.; Green, T.; Contractor, A.; Ghetti, A.; Tamura-Horikawa, Y.; Owia, C.; Kamiya, H. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 650−665. (c) Swanson, G. T.; Green, T.; Sakai, R.; Contractor, A.; Che, W.; Kamiya, H.; Heinemann, S. *Neuron* **2002**, *34*, 589−598.

(6) (a) *The Ionotropic Glutamate Receptors*; Monaghan, D. T., Wenthold, R. J., Eds.; Humana Press: Totowa, NJ, 1997. (b) Dingledine, R.; Borges, K.; Bowie, D.; Traynelis, S. *Pharmacol. Rev.* **1999**, *51*, 7−61. (c) Michaelis, E. *Prog. Neurobiol.* **1998**, *54*, 369−415. (d) Madden, D. R. *Nat. Rev. Neurosci.* **2002**, *3*, 91−101. (e) Bleakman, D.; Lodge, D. *Neuropharmacology* **1998**, *37*, 1187−1204. (f) Doble, A. *Pharmacol. Ther.* **1999**, *81*, 163−221. (g) Loscher, W. *Prog. Neurobiol.* **1998**, *54*, 721−741. (h) Trist, D. G. *Pharmaceut. Acta Helv.* **2000**, *74*, 221−229.

(7) (a) Sanders, J. M.; Pentikainen, O. T.; Settimo, L.; Pentikainen, U.; Shoji, M.; Sasaki, M.; Sakai, R.; Johnson, M. S.; Swanson, G. T. *Mol. Pharmacol.* **2006**, *69*, 1849−1860. (b) Sakai, R.; Swanson, G. T.; Sasaki, M.; Shimamoto, K.; Kamiya, H. *Cent. Nerv. Syst. Agents Med. Chem.* **2006**, *6* (2), 83−108.

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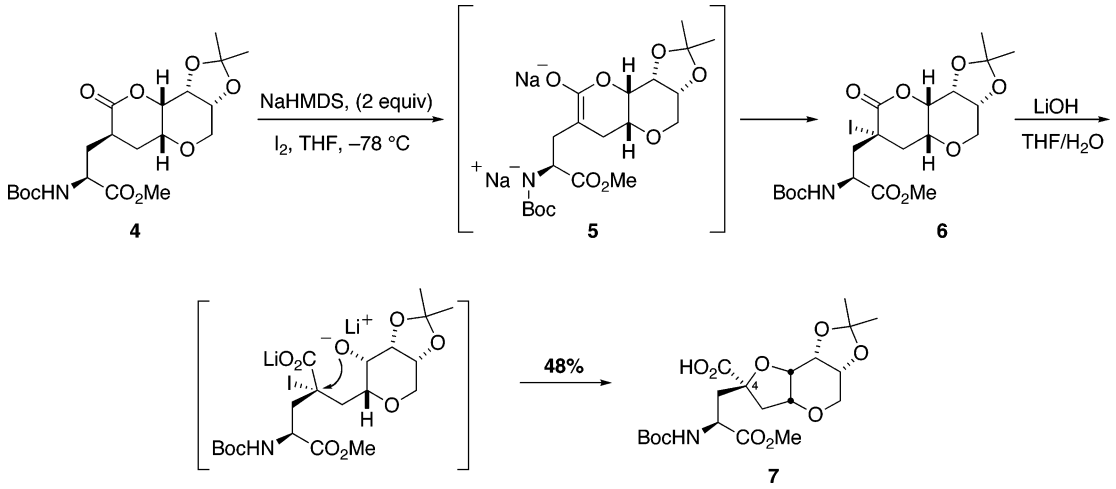
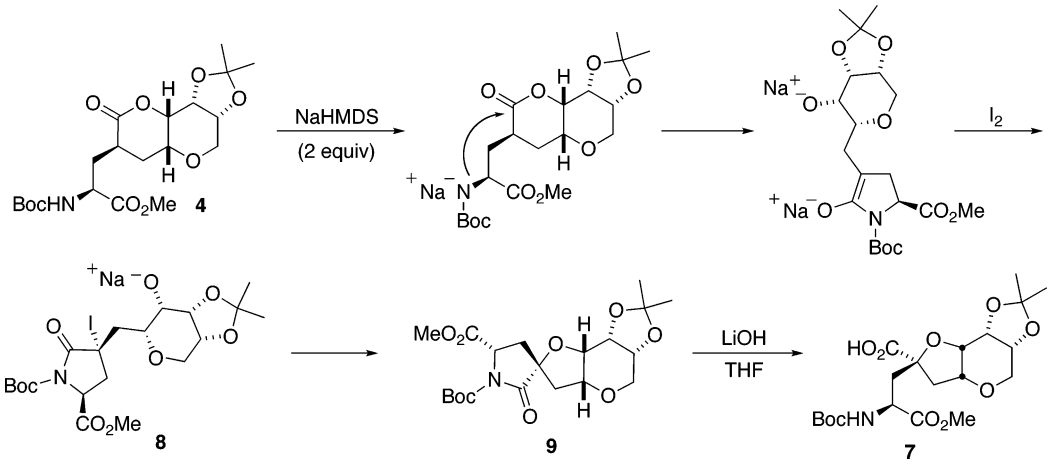
**SCHEME 1. Formation of Glutamate-Appended Oxolane Ring of 1 via Fleet Ring Expansion**




**SCHEME 2. Alternative Pathway for Ring Contraction of Lactone 4**




herbaine (**2**), and lycoperdic acid (**3**) make these natural products compelling targets for total synthesis.[8−10] From a structural perspective, assembling the glutamate-appended oxolane ring of **1**, **2**, and **3** and controlling the stereochemistry at the tetrasubstituted $\gamma$-carbon (C-4) poses a significant synthetic challenge, and several research groups, including our own, have documented strategies to address the synthetically demanding C-4 stereocenter in the context of total synthesis.[8−10] The key strategic element in the synthesis of dysiherbaine completed by our research group was a ring contraction of the $\delta$-lactone **4**, which simultaneously provided the glutamate-appended oxolane ring of dysiherbaine (**1**) and established the stereochemistry at the tetrasubstituted C-4 stereocenter[7a] via a diastereoselective halogenation of the lactone enolate, as shown, followed by a Fleet ring contraction[11] of α-iodo lactone **6** (Scheme 1).

Analysis of the crude reaction mixture, however, suggested that the ring contraction of lactone **4** to construct the glutamate-appended oxolane ring of **7** might not have proceeded by the pathway illustrated in Scheme 1. Rather, the isolation of the tetracyclic imide **9** from the reaction mixture suggested the possibility of an alternative pathway for the formation of the glutamate-appended oxolane ring of **7** that proceeds instead through several pyroglutamate intermediates (Scheme 2). Entry into this alternative reaction manifold would be initiated by the deprotonation of the amino group in **4**. Interception of the resulting anion by the lactone carbonyl group would give the

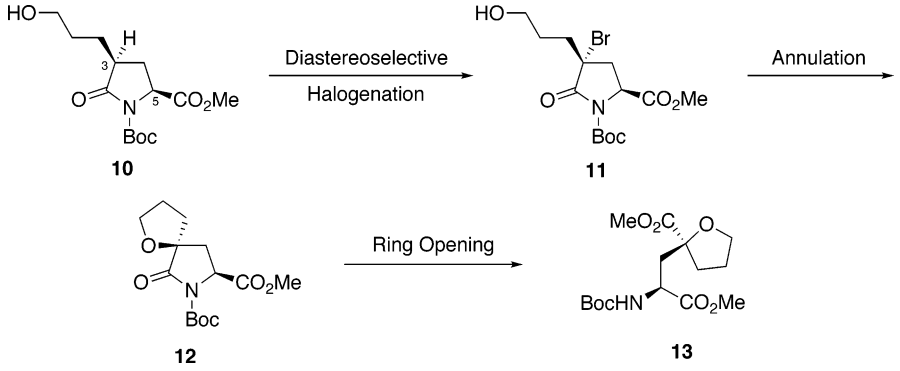
(8) Total syntheses of dysiherbaine: (a) Phillips, D. P.; Chamberlin, A. R. *J. Org. Chem.* **2002**, *67*, 3194−3201. (b) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635−638. (c) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216−5217. (d) Sasaki, M.; Koike, T.; Sakia, R.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 3923−3926. Dysiherbaine synthetic studies: (e) Kang, S.; Lee, Y. *Synlett* **2003**, *7*, 993−994. (f) Miyata, O.; Iba, R.; Hashimoto, J.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 772−774. (g) Xu, K.; Loh, T. *Synthesis* **2003**, *5*, 755−764. (h) Naito, T.; Nair, S.; Nishiki, A.; Yamashita, K.; Kiguchi, T. *Heterocycles* **2000**, *53*, 2611−2615.

(9) Total syntheses of neodysiherbaine: (a) Sakai, R.; Koike, T.; Sasaki, M.; Shimamoto, K.; Oiwa, C.; Yano, A.; Suzuki, K.; Tachibana, K.; Kamiya, H. *Org. Lett.* **2001**, *3*, 1479−1482. (b) Lygo, B.; Slack, D.; Wilson, C. *Tetrahedron Lett.* **2005**, *46*, 6629−6632. (c) Shoji, M.; Akiyama, N.; Tsubone, K.; Lash, L. L.; Sanders, J. M.; Swanson, G. T.; Sakai, R.; Shimamoto, K.; Oikawa, M.; Sasaki, M. *J. Org. Chem.* **2006**, *71*, 5208−5220. (d) Takahashi, K.; Matsumura, T.; Corbin, G. R. M.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2006**, *71*, 4227−4231. Synthesis of *epi*-C8,C9-neodysiherbaine: Shoji, M.; Shiohara, K.; Oikawa, M.; Sakai, R.; Sasaki, M. *Tetrahedron Lett.* **2005**, *46*, 5559−5562.

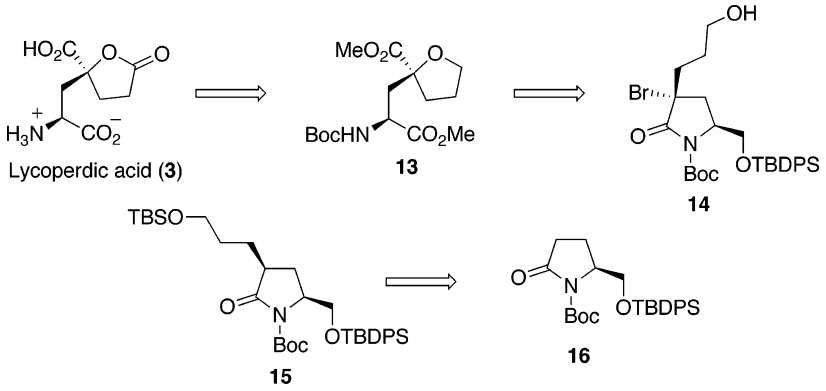
(10) Total syntheses of lycoperdic acid: (a) Yoshifuji, S.; Kaname, M. *Chem. Pharm. Bull.* **1995**, *43*, 1617−1620. (b) Kaname, M.; Yoshifuji, S. *Tetrahedron Lett.* **1992**, *33*, 8103−8104. (c) Masaki, H.; Mizozoe, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Tetrahedron Lett.* **2000**, *41*, 4801−4804. (d) Makino, K.; Shintani, K.; Yamatake, T.; Hara, O.; Hatano, K.; Hamada, Y. *Tetrahedron* **2002**, *58*, 9737−9740. (e) Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 4569−4577.

(11) (a) Estevez, J. C.; Fairbanks, A. J.; Fleet, G. W. J. *Tetrahedron* **1998**, *54*, 13591−13620. (b) Bichard, C. J. F.; Brandstetter, T. W.; Estevez, J. C.; Fleet, G. W. J.; Hughes, D. J.; Wheatley, J. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2151−2156. (c) Son, J. C.; Fleet, G. W. J.; Saunders, J.; Brown, D. *J. Chem. Soc., Chem. Commun.* **1992**, 1605−1607.

**SCHEME 3. Pyroglutmate Ring Annulation Strategy**




**SCHEME 4. Retrosynthetic Analysis for (*S*)-(+)-Lycoperdic Acid (3)**




enolate of an α-substituted pyroglutamate derivative, which might in turn undergo halogenation to give α-iodo lactam **8**. Ring closure would then produce **9**, which delivers the target glutamate-appended oxolane **7** upon ring opening of the lactam in the presence of base.

The intermediacy of α-iodo lactam **8** was unsubstantiated, but this possibility, although speculative, inspired our exploration of an alternative strategy for constructing glutamate appended oxolane rings (such as **7**) by means of sequential pyroglutamate manipulations. We therefore investigated the cyclization reactions of α-halogenated pyroglutamate derivatives as the key step in the diastereoselective annulation of oxolane rings onto the γ-position of glutamic acid (Scheme 3). In this paper, we describe the development of an efficient pyroglutamate halogenation and spiroannulation reaction sequence for the stereocontrolled synthesis of (*S*)-(+)-lycoperdic acid.

## Results and Discussion

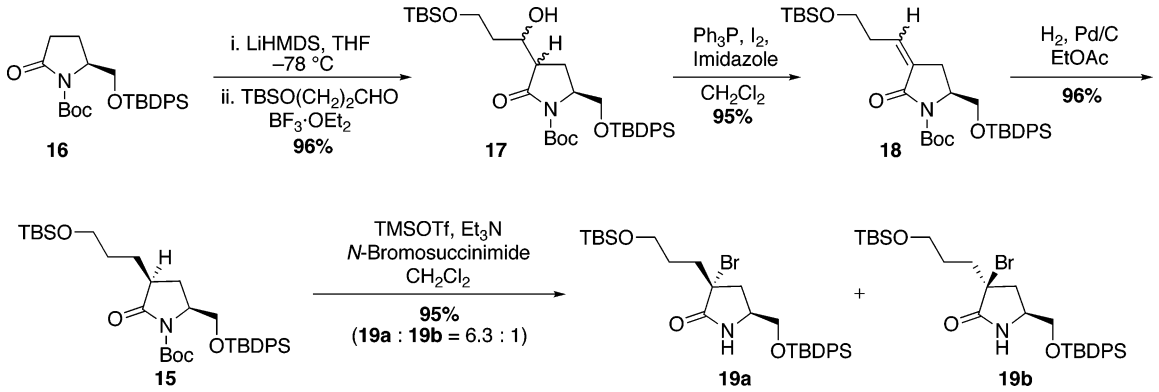
The alternative pyroglutamate ring annulation pathway (Scheme 2) suggests a revised approach not only to the synthesis of **1** but also to the structurally related glutamate-containing natural product (*S*)-(+)-lycoperdic acid (**3**). Since the carbon skeleton of lycoperdic acid corresponds to the glutamate-appended oxolane ring substructure of dysiherbaine, a synthesis of lycoperdic acid employing the pyroglutamate ring annulation as the key bond construction would provide important precedent for a modified synthesis of dysiherbaine as well as validate the pyroglutamate ring annulation reaction sequence itself. Furthermore, while the structural resemblance between dysiherbaine and lycoperdic acid is evident, it is currently unknown if the biological properties of lycoperdic acid and dysiherbaine are comparable. Since its isolation in 1978 and five ensuing total syntheses, the pharmacological properties of lycoperdic acid have not been described.[17] Thus, a synthesis plan for lycoperdic acid was envisioned that would facilitate the production of ample quantities of **3** for biological evaluation.

Analogous to the synthetic challenges faced in the total synthesis of dysiherbaine (**2**), the major issue in the preparation of lycoperdic acid (**3**) is establishing the stereochemistry at the tetrasubstituted carbon center of the glutamate-appended oxolane ring. For the synthesis of lycoperdic acid, we originally envisioned the simplest embodiment of the proposed pyroglutamate ring annulation strategy, an $S_N2$ cyclization of the brominated pyrrolidinone **14** with an unadorned *n*-propanol appendage as the precursor of the glutamate-appended oxolane ring in **13** (Scheme 4). The annulation precursor, the 3,5-disubstituted pyrrolidinone **15**, would be derived from the lactam **16**, which is turn is readily prepared in four steps from commercially available and enantiomerically pure (*S*)-pyroglutamic acid.[12] The protected pyroglutaminol derivative **16** emerged as a viable synthetic intermediate that would minimize the propensity for α-epimerization, maximize compatibility with the anticipated reaction conditions, and introduce a bulky substituent as a potential stereochemical directing group.

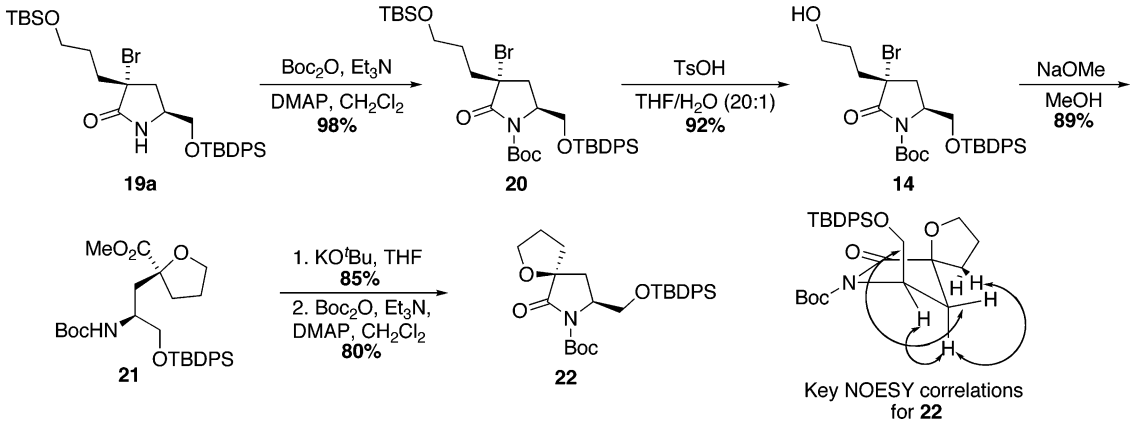
The synthesis of lycoperdic acid commenced with the preparation of the 3,5-disubstituted pyrrolidinone **15**. Direction alkylation of the lithium enolate derived from lactam **16** with

(12) Synthesis of pyroglutamate derivative **16** adapted from procedures in: (a) Otsuka, M.; Masuda, T.; Haupt, A.; Ohno, M.; Shiaki, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838−845. (b) Evans, D.; Lundy, K. *J. Am. Chem. Soc.* **1992**, *114*, 1495−1496. (c) Pickering, L.; Malhi, B.; Coe, P.; Walker, R. *Nucleosides Nucleotides* **1994**, *13*, 1493−1506. Shin, C.; Nakamura, Y.; Yamada, Y.; Yonezawa, Y.; Umemura, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3151−3160. Barrett, A.; Head, J.; Smith, M.; Stock, N.; White, A.; Williams, D. *J. Org. Chem.* **1999**, *64*, 6005−6018.

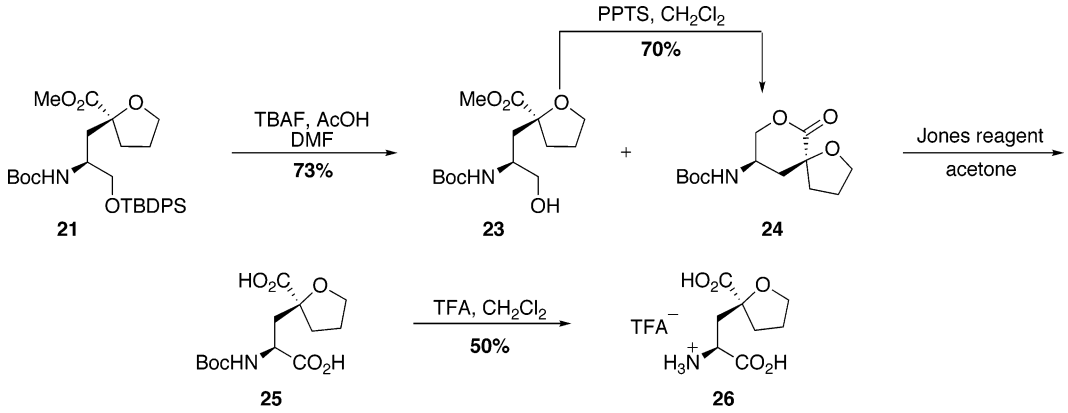
**SCHEME 5. Synthesis and Bromination of 3,5-Disubstituted Pyrrolidinone 15**




**SCHEME 6. Ring Annulation to Construct Glutamate-Appended Oxolane 21**




**SCHEME 7. Synthesis of Glutamate-Appended Oxolane Ring 26**



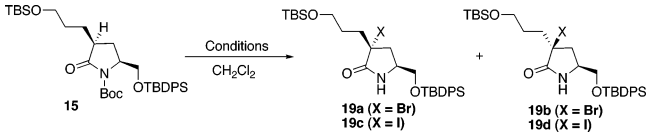

1-Iodo-3-[(*tert*-butyldimethylsilyl)oxy]propane[13] failed to provide the C-3 alkylated product. To circumvent this problem, we implemented a more circuitous strategy for the synthesis of **15** that involved a three-step aldol reaction, dehydration, and hydrogenation sequence (Scheme 5).[14a] The $BF_3$·$OEt_2$-mediated aldol reaction of the lithium enolate derived from lactam **16** with 3-(*tert*-butyldimethylsilyloxy)propanal proceeded smoothly to afford a diastereomeric mixture of aldol adducts **17** in 96% yield. Chromatographic separation of the aldol products was difficult, and in practice, no attempts were made to separate the diastereomeric mixture of aldol adducts since both newly formed chiral centers would become $sp^2$ hybridized in the following step.

Dehydration of the aldol product mixture **17** proved to be problematic and required an exhaustive screening of reagents to optimize the reaction parameters. Treatment of alcohol **17** with MsCl (1.05 equiv) and excess $Et_3N$ (5.0 equiv) in $CH_2Cl_2$ gave the corresponding mesylate, which failed to eliminate under the reaction conditions to deliver the desired olefin **18**, even at elevated temperatures. The addition of DBU (6.0 equiv) to a solution of the preformed mesylate facilitated the elimination to furnish **18** as a separable 1.5:1.0 mixture of *E*/*Z* alkene isomers in yields ranging from 18 to 75%. Unfortunately, these reaction parameters (MsCl, $Et_3N$, then DBU) gave irreproducible

(13) (a) Hu, T.; Schaus, J. V.; Lam, K.; Palfreyman, M. G.; Wuonola, M.; Gustafson, G.; Panek, J. S. *J. Org. Chem.* **1998**, *63*, 2401−2406. (b) Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037−8041.

(14) (a) Ezquerra, J.; Pedregal, C.; Yryretagoyena, B.; Rubio, A. *J. Org. Chem.* **1995**, *60*, 2925−2930. (b) Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, *23*, 3519−3530. (c) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1994**, *35*, 7277−7280.

**TABLE 1. Halogenation of Pyrrolidinone 15**

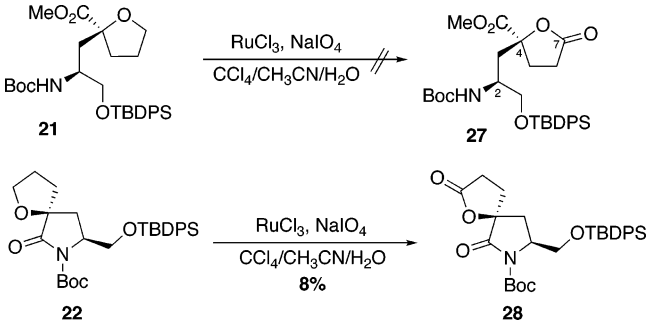



| entry | reagents | electrophile | *T* (°C) | X | yield (%) | **19a:19b** (X = Br) **19c:19d** (X = I) |
|---|---|---|---|---|---|---|
| 1 | TMSOTf $Et_3N$ | NBS | 0 to rt | Br | 95 | 6.3:1 |
| 2 | TMSOTf $Et_3N$ | bromonium *sym*-collidine | 0 to rt | Br | 72 | 5.1:1 |
| 3 | TMSOTf $Et_3N$ | NBS | −78 °C | recovered SM | | |
| 4 | TMSOTf $Et_3N$ | NBS | add TMSOTf at 0 °C; add NBS at −78 °C | Br | 43 | 12.5:1 |
| 5 | TMSOTf $Et_3N$ | NIS | 0 to rt | I | 55 | 7.0:1 |
| 6 | TMSCl $Et_3N$ | NBS | 0 to rt | recovered SM | | |

yields and inconsistent results, which necessitated further screening of elimination conditions. The use of TFAA/$Et_3N$[26] *p*-nitrobenzenesulfonyl chloride/$Et_3N$, Martin's sulfurane,[27] or Furukawa's reagent[28] (MsCl, DMAP, $CH_2Cl_2/H_2O$) was uniformly unsatisfactory as dehydrating reagents. Ultimately, it was found that dehydration of the aldol mixture could be consistently achieved in >90% yield using $Ph_3P$, $I_2$, and imidazole in $CH_2Cl_2$ to give **18** as a 5:1 mixture of (*E*)- to (*Z*)-alkene isomers. The alkene geometry was assigned based on the $^1$H NMR downfield shift of the (*E*)-isomer ($\delta$ 6.7) relative to the chemical shift of the (*Z*)-isomer ($\delta$ 6.2), in agreement with studies conducted on similar systems.[14a] Finally, Pd/C-catalyzed hydrogenation of the alkyldiene isomers **18** furnished a single diastereomer of the 3,5-disubstituted pyrrolidinone **15** in 96% yield; the stereochemistry of **15** is immaterial because this center is enolized in the following step, but it is likely the syn-product based on previous reports of similar reductions.[14a−c]

The key step in the lycoperdic acid (**3**) synthesis plan is the diastereoselective annulation of an oxolane ring onto a pyroglutamic acid scaffold by intramolecular $S_N2$ displacement of a bromide by an alkoxide nucelophile (Scheme 4). Since the stereochemical information in bromide **14** would be translated stereospecifically into the C-4 stereocenter of the oxolane ring **13**, the diastereoselective halogenation of pyroglutamate derivative **15** is paramount to the success of this approach.[15] Direct trapping of the lithium enolate of lactam **15** with $Br_2$ or $CBr_4$ gave unsatisfactory results, affording bromides **19a** and **19b** as a 2:1 mixture of diastereomers in 28% yield. After considerable experimentation to improve the yield and diastereoselectivity of this critical transformation, we found that the C-3 brominated intermediates could be prepared in high yield with good diastereoselectivity via halogenation of the lactam silyl enol ether.[16] Thus, sequential treatment of **15** with $Et_3N$, TMSOTf, and NBS afforded a separable mixture of diastereomeric bromides in 95% yield (Scheme 5). These products, **19a** and **19b**, were formed in a diastereomeric ratio of 6.3:1 as determined by $^1$H NMR analysis of the crude reaction mixture. The assignment of the anti isomer, **19a**, as the major product is consistent with considerable literature precedent in similar $\gamma$-lactam and $\gamma$-lactone systems that a bulky protecting group on the primary alcohol dictates facial selectivity by directing electrophiles to the opposite face of the nearly planar ring system.[17] This assignment is also supported by subsequent conversion of the major isomer into a bicyclic intermediate (**22**) in which more definitive NOE data could be obtained (see below).

**SCHEME 8. Unsuccessful C−H Oxidation to $\gamma$-Lactone**




The success of this pyroglutamate halogenation procedure prompted us to further explore the scope, reactivity, and diastereoselectivity of this transformation (Table 1). Comparison of entries 1 and 2 demonstrates that variations in the electrophile had little effect on the diastereoselectivity or yield, as indicated by the replacement of NBS with bromonium di-*sym*-collidine perchlorate.[31] Variations in reaction temperature had adverse effects on yield and favorable effects on stereoselection (entries 3 and 4). For example, when the lactam halogenation is performed and quenched at −78 °C, only starting material is recovered, suggesting that the silyl enol ether did not form. However, treatment of lactam **15** with TMSOTf and $Et_3N$ at 0 °C and subsequent cooling of the preformed silyl enol ether to −78 °C before addition of NBS afforded brominated products **19a** and **19b** in a decreased yield of 43% with an improved

(15) Examples of C-3 brominations of pyroglutamate derivatives: (a) Konas, D.; Coward, J. *J. Org. Chem.* **2001**, *66*, 8831−8842. (b) Avent, A.; Bowler, A.; Doyle, P.; Marchand, C.; Yound, D. *Tetrahedron Lett.* **1992**, *33*, 1509−1512. (c) Anwar, M.; Bailey, J.; Dickinson, L.; Edwards, H.; Goswami, R.; Moloney, M. *Org. Biomol. Chem.* **2003**, *1*, 2364−2376. (d) Beard, M.; Bailey, J.; Cherry, D.; Moloney, M.; Shim, S.; Statham, K. *Tetrahedron* **1996**, *52*, 3719−3740−2073.

(16) Lactam halogenation via silyl enol ether: (a) King, A. O.; Anderson, R. K.; Shuman, R. F.; Karady, S.; Abramson, N. L.; Douglas, A. W. *J. Org. Chem.* **1993**, *58*, 3384−3386. (b) Chung, J. Y. L.; Hughes, D. L.; Zhao, D.; Song, Z.; Mathre, D. J.; Ho, G. J.; McNamara, J. M.; Douglas, A. W.; Reamer, R. A.; Tsay, F. R.; Varsolona, R.; McCauley, J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 215−222. (c) For a synthesis of α-bromo esters and α-bromo lactones using TMSOTf and NBS, see: Shimona, F.; Kusaka, H.; Azami, H.; Wada, K.; Suzuki, T.; Hagiwara, H.; Ando, M. *J. Org. Chem.* **1998**, *63*, 3758−3763.

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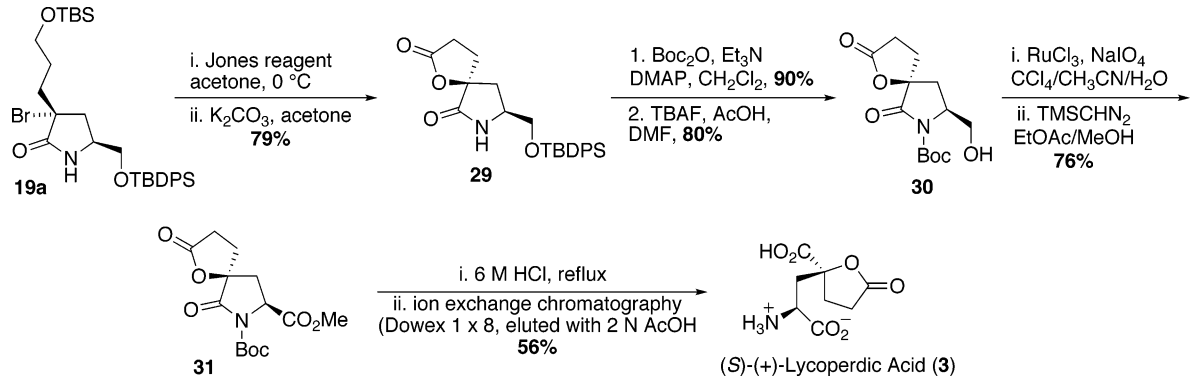
**SCHEME 9. Completion of the Synthesis of (*S*)-(+)-Lycoperdic Acid (3)**




diastereomeric ratio of 12.5:1, respectively. Entry 6 indicates that TMSCl is not a reasonable surrogate for TMSOTf in this reaction. In a related observation, efficient bromination of **15** required the use of 2.1 equiv of TMSOTf, in which one equivalent sequestered the *N*-Boc carbamate to afford the *N*-H brominated lactams after workup. Finally, entry 5 indicates that this lactam halogenation procedure can also be applied to the synthesis of α-iodo lactams. The iodinated lactams were found to be extremely sensitive to light and moisture and would rapidly degrade at room temperature. Furthermore, attempts to advance the α-iodo lactam through the reaction sequence resulted in degradation of the starting material, which precluded the use of the iodinated lactam as a synthetic intermediate. By contrast, the corresponding α-bromo lactam **19** proved to be a stable and viable synthetic intermediate that could be further elaborated. In practice, the lactam bromination of **15** was performed at 0 °C to afford 6:1 mixture of diastereomeric bromides **19a** and **19b** in 95% yield (Table 1, entry 1). The bromide diastereomers were separable by silica gel chromatography, and the major diastereomer, **19a**, was advanced through the reaction sequence.

Following the successful preparation of brominated lactam **20**, the key ring annulation to construct the glutamate-appended oxolane ring of lycoperdic acid was investigated. Conversion of brominated lactam **20** into the key ring annulation substrate required the selective deprotection of the TBS silyl ether, which was accomplished using TsOH in THF/$H_2O$ (20:1) to furnish the ring annulation substrate **14** in 90% yield (Scheme 6). Treatment of **14** with DBU in $CH_2Cl_2$ or KO$^t$Bu in THF failed to deliver the desired annulation product **21**. Under these reaction conditions, complex mixtures were obtained and none of the desired product was detected. Gratifyingly, exposure of **14** to 1.1 equiv of NaOMe in MeOH triggered cyclization and lactam ring opening (although not necessarily in that order) to furnish the glutamate-appended oxolane ring **21** and, thus, the complete carbon skeleton of lycoperdic acid, in 89% yield (Scheme 6). The stereochemistry at the tetrasubstituted carbon center was assigned by NOESY correlations performed on the cyclized derivative **22**, indicating that the $S_N2$ displacement of the bromide proceeded stereospecifically, as expected, with inversion.[18] Removal of the TBDPS group of **21** was accomplished using TBAF to produce a mixture of alcohol **23** and lactone **24**. Alcohol **23** slowly cyclized to form lactone **24**, and this propensity toward lactonization was facilitated in the presence of acid (PPTS) to give lactone **24** in 51% yield over two steps from **21**. Sequential Jones oxidation and *N*-Boc deprotection transformed lactone **24** into the glutamate appended THF ring **26**, demonstrating an efficient synthesis of the glutamate-appended oxolane substructure of dysiherbaine, neodysiherbaine, and lycoperdic acid, and the first synthesis of deoxylycoperdic acid **26** in enantiopure form (Scheme 7).[19]

According to the retrosynthetic analysis outlined in Scheme 4, we planned to prepare lycoperdic acid (**3**) from deoxylycoperdic acid derivative **13** using a C−H oxidation to convert the cyclic ether into the corresponding γ-lactone. Following the precedent established in Hatakeyama's synthesis of lycoperdic acid, the $RuO_4$ mediated C−H oxidation of the protected deoxylycoperdic acid derivative **21** was investigated (Scheme 8).[10c] Despite an exhaustive screening of reaction conditions varying precatalyst loading ($RuCl_3$, $RuO_2$) and solvent (EtOAc, $CCl_4$, $CH_3CN$, or $CH_3NO_2$ with $H_2O$ or pH = 7 phosphate buffer), all attempts to prepare lactone **27** from ether **21** met with failure. Similarly, exposure of **22** to $RuO_4$ under numerous conditions yielded only 8% of the desired γ-lactone **28** after 36 h. These results indicated that deoxylycoperdic acid derivatives **21** and **22** were poor substrates for the C−H oxidation reaction, and the failure to improve the yield of this key transformation necessitated a revision of our synthetic strategy to prepare lycoperdic acid.

Since the metal-mediated C−H oxidation of **21** failed to give satisfactory yields of lactone **27**, an alternative strategy was formulated for the synthesis of lycoperdic acid in order to introduce the requisite C-7 oxidation at an earlier stage in the synthesis. We reasoned that the γ-lactone of lycoperdic acid could be directly introduced during the ring annulation event if the cyclization substrate (**14**) was modified to contain a carboxylate nucleophile in place of the alkoxide. To investigate the feasibility of this tandem oxidation−annulation reaction, the brominated lactam **19a** was treated with Jones reagent at 0 °C followed by a $K_2CO_3$ workup (Scheme 9). Satisfyingly, this experiment reproducibly delivered spirolactone **29** in 79% yield. With spirolactone **29** successfully prepared, the remainder of the synthesis of lycoperdic acid was addressed (Scheme 9). Sequential Boc protection and TBAF desilylation afforded pyroglutaminol **30** in 72% yield over two steps. Completion of the synthesis required oxidation of **30** to the corresponding carboxylic acid, which was accomplished using $RuO_4$. Initial difficulties in the isolation and purification of this acid were

(18) Subjecting the minor bromination diastereomer **19b** to the identical four-step reaction sequence used to convert **19a** into **22** produced a diastereomer of **22** based on preliminary MS, chromatographic, and NMR spectral comparisons, supporting the expected stereospecific $S_N2$ bromide displacement for the cyclization reaction, but there was insufficient material for full characterization.

(19) For a racemic synthesis of **23**, see: Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635−638.

circumvented by exposure of the crude reaction mixture to $TMSCHN_2$, affording methyl ester **31** in 76% yield over two steps. Acidic hydrolysis of **31** and purification of crude **3** by ion exchange chromatrography were accomplished following the method of Yoshifuji and Kaname to furnish lycoperdic acid as a white solid.[10a] Recrystallization of solid **3** from water provided thin crystals that were suitable to obtain a single-crystal X-ray structure of synthetic **3**.[20] The spectral data of synthetic **3** ($^1$H NMR, $^{13}$C NMR, $[\alpha]_D$, HRMS) were in accord with the reported values for natural lycoperdic acid.[10]

## Conclusion

The successful stereocontrolled total syntheses of lycoperdic acid (**3**) and deoxylycoperdic acid (**26**) demonstrate that the pyroglutamate ring annulation sequence is an efficient method for the stereocontrolled annulation of an oxolane ring onto the $\gamma$-position of glutamic acid. The key transformation in the synthetic route was a high yielding diastereoselective annulation of an oxolane ring onto a pyroglutamate scaffold to construct the carbon framework of **3** and **26**. The reaction sequence also featured an improved method for the halogenation of pyroglutamate derivatives in high yield with enhanced stereoselection. Furthermore, the syntheses of lycoperdic acid and deoxylycoperdic acid reported herein provided ample material for biological evaluation, and preliminary testing for iGluR activity is currently underway.

## Experimental Section

**Bromide (19).** A cooled (0 °C) solution of **15**[21] (3.14 g, 5.02 mmol) in $CH_2Cl_2$ (25 mL) was treated with $Et_3N$ (2.20 mL, 16.1 mmol) followed by TMSOTf (2.01 mL, 11.0 mmol). The clear, colorless solution was stirred at 0 °C for 1 h. A solution of *N*-bromosuccinimide (1.07 g, 6.02 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise via cannula over 10 min. The resultant brown solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL), and the mixture was further diluted with water (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were washed with 1.0 M HCl (20 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a crude orange oil. $^1$H NMR analysis of the crude reaction mixture revealed that two diastereomeric bromides (**19a/19b**) were formed in a ratio of 6.3:1, respectively. Purification of the crude orange oil by flash chromatography (10:90 EtOAc/Hex−15:85 EtOAc/hexanes) afforded bromides **19a** (2.46 g) and **19b** (0.418 g) as white foams (2.88 g, 95%).

**19a:** $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.66−7.64 (m, 4H), 7.47−7.39 (m, 6H), 6.67 (s, 1H), 3.92 (m, 1H), 3.74 (dd, $J$ = 10.5, 3.7, 1H), 3.66 (m, 2H), 3.56 (dd, $J$ = 10.5, 7.2, 1H), 2.44 (dd, $J$ = 14.2, 5.4 1H), 2.25 (m, 1H), 1.92−1.78 (m, 3H), 1.08 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 174.8, 136.0, 135.9, 133.3, 133.1, 130.5, 130.4, 128.4, 128.3, 66.1, 65.4, 62.9, 53.6, 40.5, 36.1, 29.6, 27.2, 26.4, 19.6, 18.7, −4.9; IR (thin film) 3194, 3071, 2948, 2860, 1714, 1476, 1425, 1384, 1249, 1106 cm$^{-1}$; HRMS (CI/methanol) *m*/*z* calcd for $C_{30}H_{46}BrNO_3Si_2$ $(M + Na)^+$ 626.2097, found 626.2076; $[\alpha]^{24}_D$ +18.4 (*c* 1.37, $CHCl_3$).

**19b:** $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.67−7.64 (m, 4H), 7.46−7.38 (m, 6H), 6.64 (s, 1H), 3.90 (dd, $J$ = 9.7, 8.4, 1H), 3.82−3.77 (m, 1H), 3.72 (dd, $J$ = 9.8, 5.2, 1H), 3.69−3.63 (m, 2H), 2.58 (dd, $J$ = 15.1, 8.2, 1H), 2.42 (dd, $J$ = 15.1, 2.8, 1H), 2.19 (td, $J$ = 13.6, 4.0, 1H), 1.90 (td, $J$ = 13.7, 4.0, 1H), 1.86−1.77 (m, 1H), 1.64−1.56 (m, 1H), 1.06 (s, 9H), 0.88 (s, 9H), 0.05 (d, $J$ = 1.2, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 175.4, 136.0, 135.9, 135.4, 133.4, 133.3, 130.3, 128.3, 128.3, 65.9, 62.9, 62.1, 53.7, 39.2, 37.6, 29.5, 27.3, 26.4, 19.7, 18.7, −4.9; IR (thin film) 3215, 3071, 2948, 1714, 1466, 1255, 1102 cm$^{-1}$; HRMS (CI/methanol) *m*/*z* calcd for $C_{30}H_{46}BrNO_3Si_2$ $(M + Na)^+$ 626.2097, found 626.2125; $[\alpha]^{24}_D$ +26.7 (*c* 0.28, $CHCl_3$).

**Glutamate Appended Oxolane (21).** To a cooled (0 °C) solution of **14**[21] (0.055 g, 0.088 mmol) in anhydrous MeOH (6 mL) was added NaOMe (0.006 g, 0.106 mmol). The slightly cloudy reaction mixture was slowly warmed to room temperature. After 22 h, saturated aqueous $NH_4Cl$ (1.5 mL) was added, and the cloudy white reaction mixture was diluted with EtOAc (4 mL) and $H_2O$ (4 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (8 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude oil by flash chromatography (25:75 EtOAc/hexanes) furnished the title compound as a clear oil (0.043 g, 89%): $^1$H NMR (500 MHz, DMSO-$d_6$, 368 K) $\delta$ 7.66−7.62 (m, 4H), 7.45−7.39 (m, 6H), 5.95 (br s, 1H), 3.82 (dd, $J$ = 15.1, 6.2, 1H), 3.79−3.71 (m, 2H), 3.61 (s, 3H), 3.59−3.55 (m, 2H), 2.23−2.18 (m, 1H), 2.06 (dd, $J$ = 14.4, 4.5, 1H), 1.94−1.78 (m, 4H), 1.38 (s, 9H), 1.04 (s, 9H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 175.0, 155.8, 136.0, 135.9, 133.9, 133.6, 130.6, 130.2, 128.7, 128.6, 85.4, 78.3, 69.0, 66.9, 52.6, 49.5, 38.8, 34.7, 29.1, 27.4, 25.8, 19.7; IR (thin film) 3406, 2941, 2866, 1717, 1500, 1361, 1068 cm$^{-1}$; HRMS (CI/methanol) *m*/*z* calcd for $C_{30}H_{43}NO_6Si$ $(M + Na)^+$ 564.2758, found 564.2758; $[\alpha]^{24}_D$ −17.9 (*c* 0.33, $CHCl_3$).

**Spirolactone (29).** To a cooled (0 °C) solution of bromide **19a** (0.997 g, 1.65 mmol) in acetone (15 mL) was added Jones reagent (1.3 mL, 3.63 mmol, 2.7 M $CrO_3$ in 4 M $H_2SO_4$). The clear red solution was slowly warmed to room temperature over 1 h, and a brown precipitate formed. After being stirred for 2 h at room temperature, the brown reaction mixture was cooled to 0 °C and 2-propanol (2 mL) was added. The resulting green reaction mixture was warmed to room temperature and stirred for 30 min. The mixture was filtered through Celite, the Celite pad was washed with EtOAc (3 × 10 mL), and the filtrate was concentrated in vacuo to a green residue. The crude residue was dissolved in acetone (10 mL), and $K_2CO_3$ (1.14 g, 8.25 mmol) was added. The green suspension was stirred vigorously for 40 min at room temperature. The reaction mixture was diluted with EtOAc (12 mL) and $H_2O$ (8 mL), and 1 M HCl was added until the solution was acidic. The aqueous layer was removed and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to give a white foam. The crude foam was purified by flash chromatography (50:50 EtOAc/hexanes−60:40 EtOAc/hexanes) to afford the title compound as a white foam (0.552 g, 79%): mp = 45−49 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.65−7.60 (m, 4H), 7.46−7.38 (m, 6H), 6.78 (s, 1H), 3.76−3.71 (m, 1H), 3.69−3.65 (dd, $J$ = 10.3, 4.5, 1H), 3.65−3.59 (dd, $J$ = 10.2, 8.1, 1H), 2.97−2.89 (m, 1H), 2.56−2.49 (m, 2H), 2.26 (dd, $J$ = 14.1, 7.3, 1H), 2.20 (dd, $J$ = 14.1, 5.1, 1H), 2.16−2.08 (m, 1H), 1.06 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 176.2, 174.2, 136.0, 135.9, 133.3, 133.1, 130.5, 130.4, 128.4, 128.3, 84.7, 67.4, 52.6, 35.7, 31.4, 29.0, 27.2, 19.6; IR (KBr) 2955, 2853, 1785, 1714, 1425, 1109 cm$^{-1}$; HRMS (CI/methanol) *m*/*z* calcd for $C_{24}H_{29}NO_4Si$ $(M + Na)^+$ 446.1764, found 446.1752; $[\alpha]^{24}_D$ −20.9 (*c* 0.31, $CHCl_3$).

**(*S*)-(+)-Lycoperdic Acid (3).** A suspension of methyl ester **31**[21] (0.064 g, 0.206 mmol) in 6 M HCl (4 mL) was heated at reflux for 9 h. The resulting clear, colorless solution was cooled to room temperature and concentrated in vacuo to give a white residue. The residue was applied to an ion-exchange column (AG 1 × 8, 200−400 mesh, acetate form) and eluded with 2 N AcOH (150 mL). The collected fractions were lyophilized to furnish the title

(20) Crystallographic data (excluding structure factors) for structure **3** in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 299403 and are presented in the Supporting Information.

(21) The experimental procedure is provided in the Supporting Information.

compound[10] as white solid (0.017 g, 43%): $^1$H NMR (400 MHz, $D_2O$) $\delta$ 3.96 (dd, $J$ = 10.2, 3.2, 1H), 2.88 (dd, $J$ = 15.6, 3.3, 1H), 2.70−2.65 (m, 2H), 2.62−2.54 (m, 1H), 2.36−2.25 (m, 2H); $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 179.7, 175.4, 171.9, 87.7, 51.5, 37.6, 32.2, 27.6; HRMS (CI/methanol) $m/z$ calcd for $C_8H_{11}NO_6$ (M + Na)$^+$ 218.0665, found 218.0658; $[\alpha]^{24}_D$ +14.4 ($c$ 0.47, $H_2O$).

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**Supporting Information Available:** Experimental procedures, compound characterization, $^1$H NMR and $^{13}$C NMR spectra for all new compounds, and X-ray crystallographic data for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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