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Stereoselective Syntheses of 4-Hydroxy 4-Substituted Glutamic Acids

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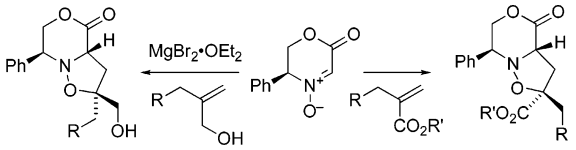

The 4-hydroxy 4-substituted glutamic acid moiety is a common substructure of biologically important natural products such as monatin [(2*S*,4*S*)-**2**], lycoperdic acid (**3**), and dysiherbaine (**4**). To develop methodology for syntheses of these natural products, cycloadditions of nitrone **5** with 2-substituted 2-propen-1-ols **6** and 2-substituted acrylates **8** were investigated. Reactions of nitrone **5** with alcohols **6** in the presence of $MgBr_2OEt_2$ gave cycloadducts **7** in a highly stereoselective manner, whereas noncatalyzed reactions of **5** with acrylates **8** afforded adducts **9**. Using the former reaction, syntheses of monatin [(2*S*,4*S*)-**2**], monatin derivative **18**, and lycoperdic acid (**3**) were accomplished. The C4-epimer of monatin [(2*S*,4*R*)-**2**)] was also synthesized by employing the latter cycloaddition.

Introduction

Since α-amino acids are fundamental materials for life, stereoselective synthesis of α-amino acids has been one of the main topics in organic chemistry during the last two decades.[1] The 4-hydroxy 4-substituted glutamic acid moiety is the common substructure (structure **1**) of biologically important, naturally occurring, unusual amino acids such as monatin [(2*S*,4*S*)-**2**][2] (high-intensity sweetener) and lycoperdic acid (**3**)[3] as well as dysiherbaine (**4**)[4] (agonist of non-NMDA-type glutamate receptor) (Figure 1). Although there have been intensive studies on syntheses of these natural products[5−7] because of their significant biological activities, stereogenic centers at the 2- and 4-positions were constructed independently in all previous studies. Therefore, it appears valuable to explore a methodology for construction of both stereochemistries in a single operation. Recently, we reported[8] a concise synthesis of monatin [(2*S*,4*S*)-**2**] (natural) based on 1,3-dipolar cycloaddition of nitrone **5**[9] with allyl alcohol **6b** in the presence of $MgBr_2{\cdot}OEt_2$ that enables construction of the requisite stereochemistries in one step. We have extended this methodology to several other allyl alcohols **6** and **23**, and cycloadducts **7c** and **24** were used for the syntheses of monatin congener **18** and lycoperdic acid (**3**), respectively. We have also found that cycloaddition of nitrone **5** with 2-substituted acrylate **8** proceeded in a highly stereoselective manner to give cycloadducts **9**

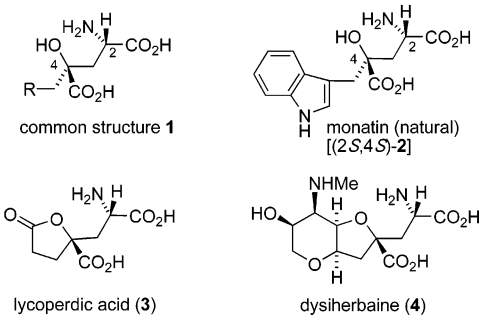

FIGURE 1. Structures of 4-hydroxy 4-substituted glutamic acid derivatives.

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(1) For reviews on syntheses of α-amino acids, see: (a) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon: Oxford, 1989. (b) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

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

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having opposite C4 stereochemistries. The C4 stereoisomer of monatin (2*S*,4*R*)-**2** was synthesized by using this reaction. We now describe the details of this area.

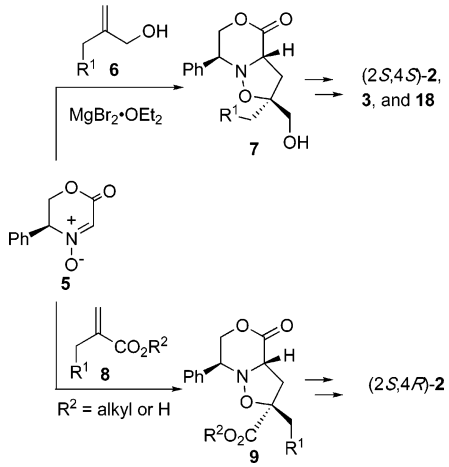
Results and Discussion

Cycloaddition of Nitrone 5 with Allyl Alcohols 6 in the Presence of $MgBr_2$·OEt_2. The requisite alcohols **6** and esters **8** were prepared as outlined in Scheme 2. Treatment of bromide **10**[10] with metalated reagents gave α,β-unsaturated esters **8**, which were reduced by DIBAL-H to afford allyl alcohols **6** (see Supporting Information).

Cycloadditions of nitrone **5** with allyl alcohols **6a**−**f** in the presence of $MgBr_2$·OEt_2 were examined (Table 1). When nitrone **5** was treated with allyl alcohol **6a** (1.5 equiv) and $MgBr_2$·OEt_2 (1.5 equiv) in CH_2Cl_2 at room temperature for 10 h, cycloadduct **7a** was obtained in 88% yield as the sole product (entry 1). In a similar manner, nitrone **5** underwent highly stereoselective cycloaddition with alcohol **6b**, having a 3-indolylmethyl group, in the presence of $MgBr_2$·OEt_2 to give **7b** in 98% yield (entry 2). Reactions of nitrone **5** with other arylmethyl-substituted allyl alcohols **6c**−**e** also gave cycloadducts **7c**−**e** in excellent yields with high stereoselectivities (entries 3−5). Allyl alcohol **6f** also reacted with nitrone **5** in the presence of $MgBr_2$·OEt_2 to afford adduct **7f** in a highly stereoselective manner (entry 6). The stereochemistry of cycloadduct **7b** was established by elaboration of **7b** into natural monatin [(2*S*,4*S*)-**2**] (vide infra), and the stereochemistries of other cycloadducts **7a** and **7c**−**f** were tentatively assigned as depicted.

In contrast to entry 1 in Table 1, reaction of nitrone **5** with alcohol **6a** in the absence of $MgBr_2$·OEt_2 took a very long time to afford a 13:87 mixture of cycloadducts **7a**

SCHEME 1



SCHEME 2

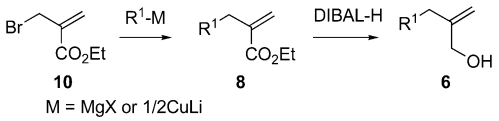
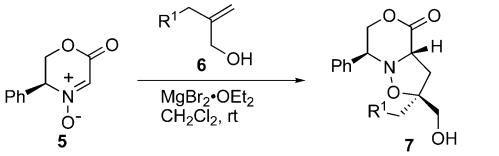
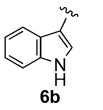
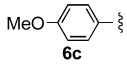
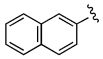


TABLE 1. Cycloaddition of Nitrone 5 with Alcohols 6a−f



Entry	R^1 Alchol	Time	Yield (%)	Ratio[a] (**7**:other isomer)
1	H **6a**	10 h	88	> 98:2>
2	 **6b**	3.5 days	98	> 98:2>
3	 **6c**	20 h	98	> 98:2>
4	 **6d**	3.5 days	97	> 98:2>
5	 **6e**	4 days	98	96:4
6	^{i}Pr **6f**	18 h	quant.	95:5

[a] Ratios were based on 500 MHz ^{1}H NMR spectra of the cycloadducts.

(5) For syntheses of racemic monatin, see: (a) Holzapfel, C. W.; Bischofberger, K.; Olivier, J. *Synth. Commun*. **1994**, *24*, 3197. (b) Abushanab, E.; Arumugam, S. U.S. Patent 5994559, 1999. (c) Amino, Y.; Kawahara, S.; Funakoshi, T.; Sugiyama, M. Jpn. Kokai Tokkyo Koho JP-171365, 2003. (d) Sugiyama, M.; Watanabe, K.; Funakoshi, N.; Amino, Y.; Kawahara, S.; Takemoto, T. PCT Int. Appl. WO 056026, 2003. For syntheses of optically active monatin, see: (e) Kitahara, T.; Watanabe, H. Jpn. Kokai Tokkyo Koho JP-060382, 2000. (f) Nakamura, K.; Baker, T. J.; Goodman, M. *Org. Lett*. **2000**, *2*, 2967. (g) Oliveira, D. D. J.; Coelho, F. *Tetrahedron Lett*. **2001**, *42*, 6793. Recent patents for monatin, see: (h) Amino, Y.; Yuzawa, K.; Mori, K.; Takemoto, T. WO 2003045914. (i) Amino, Y.; Kawahara, S.; Funakoshi, T.; Sugiyama, M. JP 2003171365. (j) Sugiyama, M.; Watanabe, K.; Funakoshi, N.; Amino, Y.; Kawahara, S.; Takemoto, T. WO 2003056026. (k) Kawahara, S.; Amino, Y.; Mori, K.; Funakoshi, N.; Takemoto, T. WO 2003059865. (l) Amino, Y.; Kawahara, S. EP 1350791. (m) Abraham, T. W.; Cameron, D. C.; Dalluge, J.; Hicks, P. M.; Hobson, R. J.; McFarlan, S. C.; Millis, J.; Rosazza, J. WO 2003091396. (n) Sugiyama, M.; Watanabe, K. WO 2004018672. (o) Sugiyama, M.; Watanabe, K.; Kashiwagi, T.; Suzuki, E. WO 2004053125. (p) Sugiyama, M.; Amino, Y.; Mori, K. JP 2004222657. (q) Amino, Y. WO 2004067494.

(6) For syntheses of lycoperdic acid, see: (a) Kaname, M.; Yoshifuji, S. *Tetrahedron Lett*. **1992**, *33*, 8103. (b) Yoshifuji, S.; Kaname, M. *Chem. Pharm. Bull*. **1995**, *43*, 1617. (c) Masaki, H.; Mizozoe, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Tetrahedron Lett*. **2000**, *41*, 4801. (d) Makino, K.; Shintani, K.; Yamatake, T.; Hara, O.; Hatano, K.; Hamada, Y. *Tetrahedron* **2002**, *58*, 9737.

(7) For syntheses of dysiherbaine, see: (a) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc*. **2000**, *122*, 5216. (b) Snider, B. B.; Hawryluk, N. A. *Org. Lett*. **2000**, *2*, 635. (c) Sasaki, M.; Koike, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett*. **2000**, *41*, 3923. (d) Phillips, D.; Chamberlin, R. *J. Org. Chem*. **2002**, *67*, 3194. See also: (e) Kang, S. H.; Lee, Y. M. *Synlett* **2003**, 993. (f) Miyata, O.; Iba, R.; Hashimoto, J.; Naito, T. *Org. Biomol. Chem*. **2003**, *1*, 772.

(8) Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Commun*. **2003**, 2678.

(9) (a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun*. **1996**, 1861. (b) Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett*. **1999**, *40*, 895. (c) Tamura, O.; Yoshida, S.; Sugita, H.; Mita, N.; Uyama, Y.; Morita, N.; Ishiguro, M.; Kawasaki, T.; Ishibashi, H.; Sakamoto, M. *Synlett* **2000**, 1553. (d) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem*. **2000**, *65*, 8544. See also: (e) Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett*. **1998**, *39*, 6819. (f) Long, A.; Baldwin, S. W. *Tetrahedron Lett*. **2001**, *42*, 5343. For a related nitrone, see: (g) Baldwin, S. W.; Long, A. *Org. Lett*. **2004**, *6*, 1653 and references therein.

(10) Drewes, S. E.; Loizou, G.; Roos, G. H. P. *Synth. Commun*. **1987**, *17*, 291.

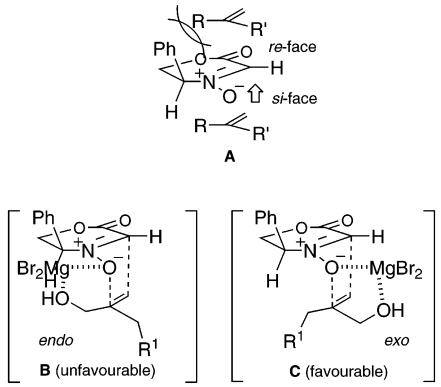
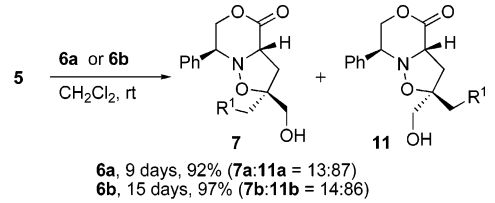


FIGURE 2. Transition states models **A**−**C**.

SCHEME 3



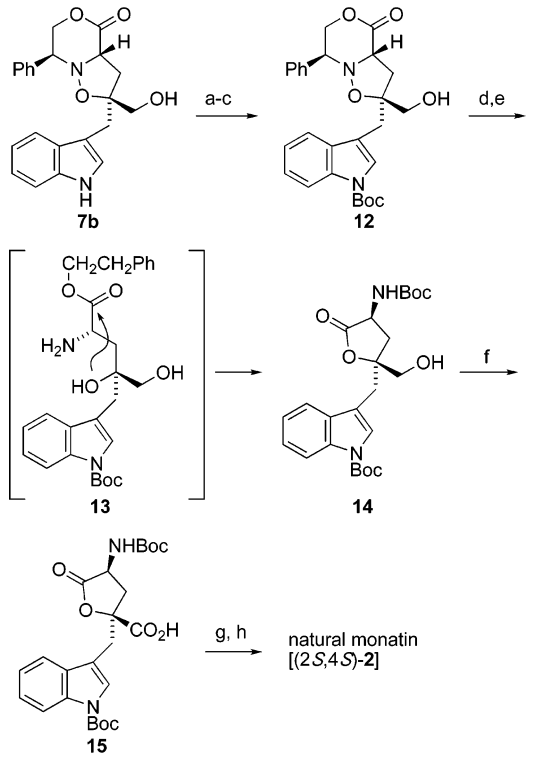
and **11a** (Scheme 3). Reaction of nitrone **5** with alcohol **6b** also afforded a 14:86 mixture of cycloadducts **7b** and **11b**.

The stereoselectivities of the reactions of nitrone **5** with alcohols **6** can be explained by considering their transition states **A**−**C** (Figure 2). The *re*-face of nitrone **5** is effectively shielded by the phenyl group, and hence the nitrone **5** reacts with alcohol **6** from the *si*-face (see formula **A**).[9d] Taking into account the fact that $MgBr_2 \cdot OEt_2$ accelerates the cycloaddtion, chelated transition-state models **B** and **C** may be involved in the reaction of **5** and **6**.[11] Since model **B** has severe steric interaction between $MgBr_2$ and the phenyl group, it is reasonable to assume that the cycloaddition proceeds via model **C** to give cycloadduct **7** with high stereoselectivity. The model **C** might explain the prolonged reaction time for the cycloaddition of **6b**, **6d**, and **6e** because relatively bulky R^1 groups occupy the sterically demanding endo position in **C**.

Syntheses of Monatin, Monatin Congener, and Lycoperdic Acid. In 1992, monatin [(2*S*,4*S*)-**2**], a 4-hydroxy 4-substituted glutamic acid, was isolated from the bark of the roots of *Schlerochiton ilicifolius* and reported

(11) For $MgBr_2$-promoted cycloaddition of nitrones with allyl alcohols, see: (a) Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87. (b) Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49. (c) Hanselmann, R.; Zhou, J.; Ma, P.; Confalone, P. N. *J. Org. Chem.* **2003**, *68*, 8739. (d) Dugovic, B.; Fisera, L.; Hametner, C.; Pronayava, N. *Arkivoc* **2003**, 162. For $Zn(OTf)_2$-promoted cycloaddition of nitrones with allyl alcohols, see: (e) Zhao, Q.; Han, F.; Romero, D. L. *J. Org. Chem.* **2002**, *67*, 3317. For a review on chiral zinc-complex-mediated cycloaddition of nitrones with allyl alcohols, see: (f) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075. For chelation-promoted cycloaddition of nitrile oxides with allyl alcohols, see: (g) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324. (h) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082. (i) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611. Harwood and co-workers reported that the azomethine ylid prepared from (5*R*)-5-phenylmorpholin-2-one and formaldehyde in the presence of $MgBr_2 \cdot OEt_2$ underwent cycloaddition with dipolarophiles to give cycloadducts. However, the diastereo- and regioselectivities were inverted with respect to those of the corresponding uncatalyzed reaction; see: (j) Harwood, L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D. J.; Williams, C. E. *Synlett* **1993**, 777.

SCHEME 4[a]



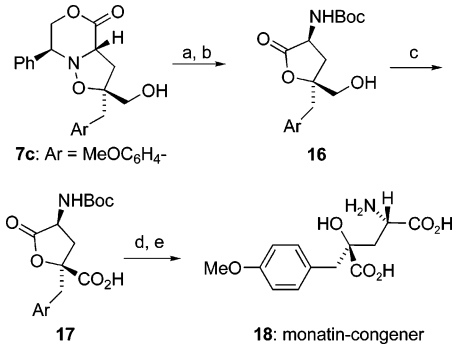
[a] Reagent and conditions: (a) TBSCl, imidazole, DMF, 97%. (b) Boc_2O, DMAP, CH_3CN, 97%. (c) HF·pyridine, THF, 100%. (d) H_2, $Pd(OH)_2$/C, MeOH. (e) Boc_2O, CH_3CN, 81% (two steps). (f) PDC, DMF, 69%. (g) HCl, HCO_2H. (h) NaOH, MeOH then Amberlite IR-120-H^+ form, aq NH_3, 92% (two steps).

to be 1000−1400-times sweeter than sucrose.[2] However, the natural supply of (2*S*,4*S*)-**2** from dried bark is insufficient for further studies of (2*S*,4*S*)-**2** as a sweetener. Moreover, despite the structural simplicity of (2*S*,4*S*)-**2**, stereoselective synthesis of **2** is not easy because of the presence of an asymmetric quarternary carbon at the 4-position.[5]

With cycloadduct **7b** in hand, we turned our attention to synthesis of (2*S*,4*S*)-**2** (Scheme 4). Hydrogenolysis of **7b** with Pearlman's catalyst in methanol exhibited poor reproducibility (15−68%), and the indolyl NH group of **7b** was thereby protected to afford **12** in 94% yield. In contrast to **7b**, reductive cleavage of the N−O bond and *N*-benzylic position of **12** by hydrogenolysis proceeded cleanly to afford lactone **14**, probably via amino alcohol **13**, in 81% yield after protection of the primary amino group. Oxidation of the primary hydroxyl group of **14** with PDC gave carboxylic acid **15** in 69% yield. Finally, removal of two Boc groups followed by alkaline hydrolysis gave monatin [(2*S*,4*S*)-**2**] in 92% yield.

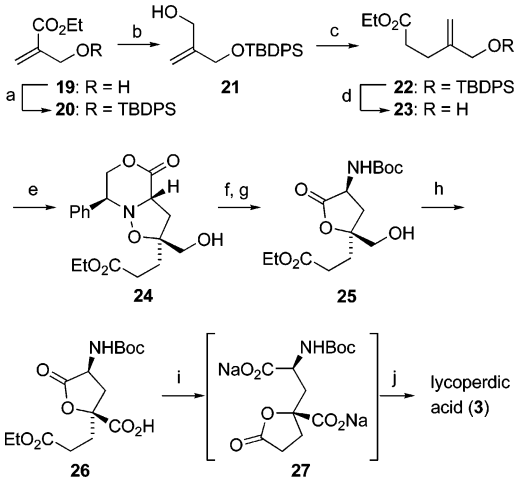
Establishment of a method for preparation of monatin congeners would be required for conducting the structure−activity relationship of monatin [(2*S*,4*S*)-**2**]. Thus, monatin congener **18** was synthesized from cycloadduct **7c** (Scheme 5). Hydrogenolysis of **7c** followed by protection of the resulting primary amino group with a Boc group gave lactone **16**, whose primary hydroxyl group was oxidized by PDC to afford carboxylic acid **17**. Finally, removal of the Boc group and hydrolysis of the lactone ring gave monatin congener **18** in 49% overall yield from cycloadduct **7c**.

SCHEME 5[a]



[a] Reagent and conditions: (a) H_2, $Pd(OH)_2$/C, MeOH. (b) Boc_2O, CH_3CN, 74% (two steps). (c) PDC, DMF, 72%. (d) HCl, HCO_2H. (e) NaOH, MeOH then Amberlite H^+ form, aq NH_3, 93% (two steps).

SCHEME 6[a]

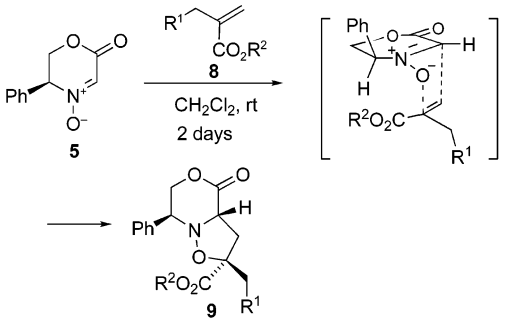


[a] Reagent and conditions: (a) TBDPSCl, imidazole, DMF, 91%. (b) DIBAL-H, CH_2Cl_2, 93%. (c) $CH_3C(OEt)_3$, cat. $C_2H_5CO_2H$, 145 °C, 65%. (d) TBAF, THF, 65%. (e) nitrone **5**, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, rt, 94%, 91:9 selectivity. (f) H_2, $Pd(OH)_2$/C, MeOH. (g) Boc_2O, CH_3CN, aq $NaHCO_3$, 72%, two steps. (h) PDC, DMF, 82%. (i) NaOH, MeOH−H_2O. (j) HCl−HCO_2H, 87%, two steps.

Next, synthesis of lycoperdic acid (**3**) was examined as an application of the present method. Lycoperdic acid (**3**), a glutamic acid derivative, was isolated from the mushroom *Lycoperdon perlatum* in 1978[3] and has been a synthetic target for several groups.[6] Our synthesis of **3** using cycloaddition of nitrone **5** is outlined in Scheme 6. Reduction of acrylate **20** prepared from alcohol **19**[12] by DIBAL-H gave allyl alcohol **21** (91%), which, on heating with ethyl orthoformate in the presence of propionic acid, underwent Johnson−Claisen rearrangement to give γ,δ-unsaturated ester **22** in 65% yield. The silyl ether of ester **22** was deprotected with TBAF to afford allyl alcohol **23** in 65% yield. With allyl alcohol **23** in hand, cycloaddition with nitrone **5** was next conducted. When nitrone **5** was treated with alcohol **23** in the presence of $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 3 days, clean cycloaddition occurred to give a 91:9 mixture of cycloadduct **24** and its diastereomer in 94% yield. After separation, hydrogenolysis of adduct **24** with Perlman's catalyst

(12) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.

TABLE 2. Cycloaddition of Nitrone 5 with Acrylates 8



Entry	8	R^1	R^2	Product[a] (% yield, **9**:other isomer)
1	**8a**	H	Me	**9a** (98, > 98:2>)
2	**8b**		Me	**9b** (99, > 98:2>)
3	**8c**		Et	**9c** (89, > 98:2>)
4	**8d**		Bn	**9d** (89, 95:5)
5	**8e**		H	**9e** (83, > 98:2>)
6	**8f**	EtO_2C-CH_2- 	Et	**9f** (87, 96:4)

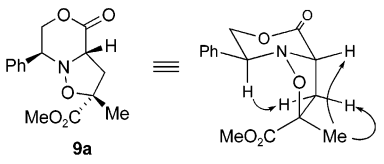
[a] Ratios were based on 500 MHz ^{1}H NMR spectra of the cycloadducts.

followed by protection of the primary amino group with a Boc group afforded lactone **25** in 72% yield from adduct **24**. Oxidation of the primary hydroxyl group of **25** to carboxylic acid with PDC proceeded without any problem to give acid **26** in 82% yield. When acid **26** was exposed to NaOH in MeOH−H_2O at room temperature for 30 min, hydrolysis of the lactone ring and translactonization occurred to generate acid salt **27**. Without purification, the mixture was acidified with HCO_2H−1 N HCl to remove the Boc group and treated with Dowex G-10 to afford lycoperdic acid (**3**) in 87% from acid **26**.

Cycloaddition of Nitrone 5 with 2-Substituted Acrylates: Synthesis of (2*S*,4*R*)-Monatin. We have described methodology for syntheses of (2*S*,4*S*)-4-hydroxy-4-substituted glutamic acids using cycloaddition of cyclic nitrone **5** with 2-substituted allyl alcohols. Since biologically active compounds having stereogenic centers often exhibit activities different from those of their stereoisomers, we examined cycloaddition of nitrone **5** with 2-substituted acrylates to explore the method for synthsis of the (2*S*,4*R*)-isomer.[13]

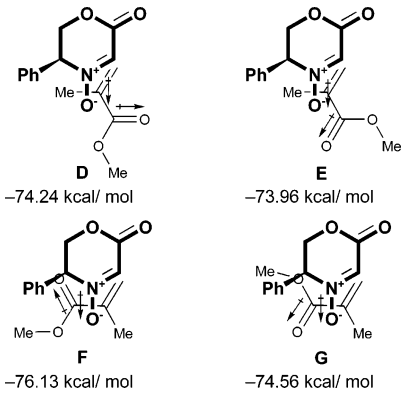
Results of cycloaddition of nitrone **5** with 2-substituted acrylates **8** are summarized in Table 2. Surprisingly and

(13) Recently, four stereoisomers of monatin were found to exhibit different extents of sweet taste. See ref 5h.



9a

FIGURE 3. Selected NOEs of cycloadduct **9a**.



D –74.24 kcal/ mol

E –73.96 kcal/ mol

F –76.13 kcal/ mol

G –74.56 kcal/ mol

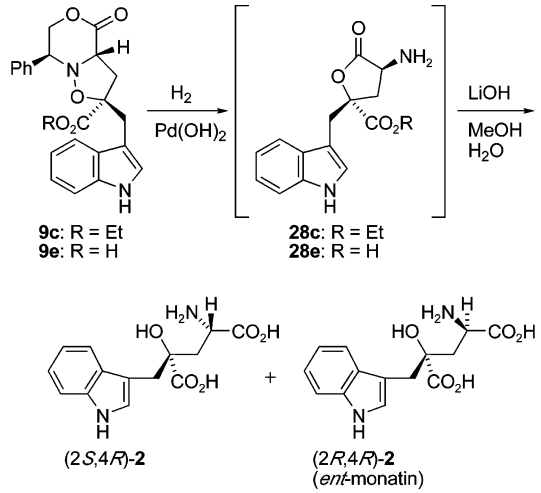
FIGURE 4. Heats of formations of possible TSs **D**−**G**.

delightfully, all reactions proceeded at room temperature and were completed within 2 days to give cycloadducts **9** with the opposite C4 stereochemistries in highly stereoselective manners. For example, reaction of methyl methacrylate (**8a**) exclusively gave cycloadduct **9a** in 98% yield via an ester-endo transition state (entry 1). The stereoselectivity was independent of R^2 groups of the esters (or carboxyl group). The reactions of alkenes **8b**−**e** gave **9b**−**e**, respectively, with high selectivities in high yields (entries 2−5). Diester **8f** also stereoselectively afforded **9f** in 87% yield (entry 6). The stereostructure of **9a** was assigned by means of NOEs as depicted in Figure 3. The structures of cycloadducts **9c** and **9e** were established by leading them to (2*S*,4*R*)-monatin.

To understand the stereoselectivity of the cycloaddition, calculations (PM3 level) of transition states (TSs) **D**−**G** of cycloaddition of nitrone **5** with methyl methacrylate (**8a**) were conducted, and the calculations revealed that TS **F** may be most stable among the four TSs (Figure 4). Although the exact origin of the stability is obscure at the moment, one possibility may involve dipole−dipole interaction.[14] Dipole−dipole interaction in TS **F** would be minimized because the dipoles of N^+-O^- of nitrone **5** and C=O of methacrylate may be oppositely directed.

To demonstrate the synthetic application of the cycloaddition of nitrone **5** with alkene **8**, synthesis of the C4-isomer of monatin (2*S*,4*R*)-**2** from cycloadduct **9c** was examined (Scheme 7). Adduct **9c** was hydrogenolyzed by using Perlman's catalyst to give lactone **28c**, which, without purification, was exposed to LiOH in MeOH−H_2O. Hydrolysis of **28c** to (2*S*,4*R*)-**2**, however, did not proceed at room temperature. The mixture was then heated at reflux for 3 h to give a 5:1 mixture of (2*S*,4*R*)-**2**

SCHEME 7



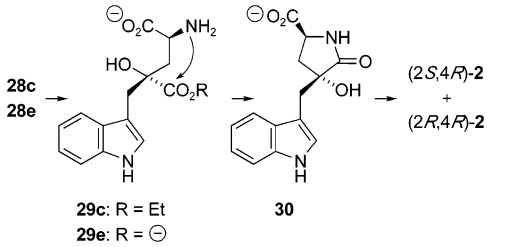
9c: R = Et
9e: R = H

28c: R = Et
28e: R = H

(2*S*,4*R*)-**2**

(2*R*,4*R*)-**2** (*ent*-monatin)

SCHEME 8



28c
28e

29c: R = Et
29e: R = ⊖

30

(2*S*,4*R*)-**2** + (2*R*,4*R*)-**2**

[diastereomer of natural (2*S*,4*S*)-monatin] and (2*R*,4*R*)-**2** (*ent*-monatin) in 79% yield from cycloadduct **9c**.[15]

The partial epimerization may involve formation of lactam **30** (Scheme 8). Hydrolysis of the lactone ring of **28c** occurs first, and then the primary amino group attacks the ester group to afford lactam **30**. For hydrolysis of the lactam ring of **30**, forcing reaction conditions are required to induce partial epimerization leading to *ent*-monatin (2*R*,4*R*)-**2**. To avoid lactam formation, cycloadduct **9e** was selected for the starting material because the amino group of **29e** generated from lactone **28e** should not attack at the carboxylate anion. Hydrogenolysis of **9e** under conditions similar to those for **9c** gave lactone **28e**, which, on treatment with LiOH in MeOH−H_2O at room temperature, underwent hydrolysis to give (2*S*,4*R*)-**2** without isomerization in 33% yield.[16]

In conclusion, we have developed methods for syntheses of (2*S*,4*S*)- and (2*S*,4*R*)-4-hydroxy 4-substituted glutamic acids using cycloaddition of nitrone **5**. Since the enantiomer of nitrone **5** is readily available,[9d] we have now obtained methods for syntheses of all four stereoisomers of 4-hydroxy 4-substituted glutamic acids.

Experimental Section

(2*S*,5*S*,8a*S*)-2-(Hydroxymethyl)-2-[(indol-3-yl)methyl]-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizin-8-one (7b) (Table 1, Entry 2): General Procedure for Table 1. To a stirred mixture of nitrone **5** (231 mg, 1.2 mmol) and $MgBr_2 \cdot OEt_2$ (465 mg, 1.8 mmol) in CH_2Cl_2 (15 mL) was added a

(14) For dipole−dipole interaction in nitrone cycloaddition, see: Annunziata, R.; Benaglia, M.; Clinquini, M.; Cozzi, F.; Raimondi, L. *Eur. J. Org. Chem.* **1998**, 1823.

(15) Similar epimerization was observed for hydrolysis of the *N*,*N*′-Cbz-benzyl ester derivative of lactone **28c**. See ref 5e.

(16) Low yield of (2*S*,4*R*)-**2** is probably due to the instability of the starting material **9e**. In fact, heating **9e** or chromatography of **9e** gave a complex mixture.

solution of **6b** (337 mg, 1.8 mmol) in CH_2Cl_2 (2 mL) at room temperature, and the mixture was further stirred at the same temperature for 3.5 days. Water was added to the mixture, and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 5:1) to give **7b** (438 mg, 98%) as a syrup: $[\alpha]^{25}_D$ +49.1 (*c* 0.480, $CHCl_3$); IR ($CHCl_3$) 3605, 3480, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.42 (1H, br s), 2.61 (1H, dd, J = 12.7, 8.8 Hz), 2.80 (1H, dd, J = 12.7, 6.3 Hz), 3.08 (2H, s), 3.59 (2H, br s), 4.17−4.32 (4H, m), 6.87 (1H, d, J = 1.8 Hz), 7.01−7.45 (8H, m), 7.53 (1H, d, J = 7.3 Hz), 8.12 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.8, 38.5, 61.8, 63.3, 67.3, 68.9, 85.9, 110.0, 111.1, 119.0, 119.6, 122.0, 123.8, 127.5, 128.0, 128.5, 128.9, 135.6, 135.9, 169.8. Anal. Calcd for $C_{22}H_{22}N_2O_4 \cdot 1/2H_2O$: C, 68.42; H, 6.00; N, 7.25. Found: C, 68.60; H, 6.10; N, 7.02.

Reaction of 5 and 6a in the Absence of $MgBr_2 \cdot OEt_2$: 7a and Its (2*R*,5*S*,8a*S*)-Isomer (11a). A solution of **5** (50 mg, 0.26 mmol) and **6a** (28 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) was stirred for 9 days, and the mixture was concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 5:1) to give an inseparable 13:87 mixture of **7a** and **11a** (63 mg, 92%) as a syrup: ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H × 87/100, s), 1.31 (3H × 13/100, s), 1.83 (13/100H, br s), 2.05 (87/100H, br s), 2.38 (87/100H, dd, J = 12.7, 7.3 Hz), 2.62 (13/100H, dd, J = 13.2, 6.8 Hz), 2.75 (13/100H, dd, J = 13.2, 8.8 Hz), 2.85 (87/100H, dd, J = 12.7, 10.3 Hz), 3.45−3.52 (2H, m), 4.19−4.41 (2H + 13/100H, m), 4.49 (87/100H, dd, J = 10.3, 7.3 Hz), 7.32−7.45 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6 (minor), 23.4 (major), 39.3 (major), 39.9 (minor), 62.2 (minor), 62.5 (major), 62.9 (major), 63.9 (minor), 68.8 (minor), 70.1 (major), 82.9 (minor), 84.0 (major), 127.5, 128.5, 128.7, 128.9, 129.0, 135.6, 169.2 (major), 169.8 (minor); HRMS calcd for for $C_{14}H_{17}NO_4$ 263.1159, found 263.1156.

Reaction of 5 and 6b in the Absence of $MgBr_2 \cdot OEt_2$: 7b and Its (2*R*,5*S*,8a*S*)-Isomer (11b). A solution of **5** (19 mg, 0.10 mmol) and **6b** (28 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was stirred for 15 days, and the mixture was concentrated under reduced pressure. The crude product was chromatographed ($CHCl_3$−AcOEt, 10:1) to give an inseparable 14:86 mixture of **7b** and **11b** (37 mg, 97%) as a syrup: ^1H NMR (500 MHz, $CDCl_3$) δ 1.82 (86/100H, br s), 2.45 (14/100H, br s), 2.61 (14/100H, dd, J = 12.7, 8.8 Hz), 2.64 (86/100H, dd J = 12.7, 7.8 Hz), 2.70 (86/100H, dd J = 12.7, 9.3 Hz), 2.81 (14/100H, dd, J = 12.7, 6.3 Hz), 2.98 (86/100H, d, J = 14.7 Hz), 3.05 (86/100H, d, J = 14.7 Hz), 3.06 (2H × 14/100, s), 3.47−3.60 (2H, m), 4.15−4.30 (4H, m), 6.83 (14/100H, s), 6.99 (86/100H, s), 7.08 (1H, br t, J = 7.3 Hz), 7.17 (1H, br t, J = 7.3 Hz), 7.31 (1H, br t, J = 7.3 Hz), 7.34−7.41 (5H, m), 7.46 (1H, br d, J = 6.8 Hz), 7.62 (1H, br d, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9 (minor), 31.8 (major), 37.8 (major), 38.5 (minor), 61.8 (minor), 62.6 (major), 63.3 (major), 65.4 (major), 67.3 (minor), 68.9 (minor), 70.0 (major), 85.9 (minor), 86.7 (major), 110.3, 111.1, 119.2, 119.6, 121.9, 123.7, 127.4, 127.5, 127.7, 128.6, 128.9, 129.0, 135.7, 135.9, 169.5. HRMS calcd for for $C_{22}H_{22}N_2O_4$ 378.1580, found 378.1583.

(2*S*,5*S*,8a*S*)-2-[(1-*tert*-Butyloxycarbonylindol-3-yl)methyl]-2-(hydroxymethyl)-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizin-8-one (12). To a stirred solution of **7b** (900 mg, 2.4 mmol) in DMF (6 mL) were added imidazole (654 mg, 9.6 mmol) and *tert*-butyldimethylsilyl chloride (434 mg, 2.9 mmol) at 0 °C, and the mixture was further stirred at room temperature for 3 h. Water was added to the mixture, and the whole was extracted with Et_2O. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 4:1) to give (2*S*,5*S*,8a*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-2-[(indol-3-yl)methyl]-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizin-8-one (*O*-TBDMS derivative of **7b**) (1.14 g, 97%) as a syrup: IR ($CHCl_3$) 3480, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.05 (3H, s), 0.93 (9H, s), 2.57 (1H, br dd, J = 12.7, 8.8 Hz), 2.71 (1H, dd, J = 12.7, 8.0 Hz), 3.04 (2H, s), 3.50 (2H, s), 4.07 (1H, dd, J = 9.8, 3.4 Hz), 4.19 (1H, br t, J = 10.8 Hz), 4.29 (1H, dd, J = 11.7, 3.4 Hz), 4.36 (1H, br t, J = 8.1 Hz), 7.03 (1H, t, J = 7.3 Hz), 7.23−7.44 (9 H, m), 8.11 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 25.9, 30.7, 38.6, 61.8, 62.9, 66.1, 69.5, 86.0, 171.5, 110.8, 119.3, 119.5, 121.9, 124.0, 127.7, 128.2, 128.3, 128.7, 135.9, 171.5. This material was used for the next step without further purification.

To a stirred solution of the *O*-TBDMS derivative of **7b** (110 mg, 0.22 mmol) in MeCN (4 mL) were added Boc_2O (210 mg, 0.88 mmol) and DMAP (3.0 mg, 0.022 mmol) at room temperature, and the mixture was further stirred at the same temperature for 1 h. Water was added to the mixture, and the whole was extracted with AcOEt. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 6:1) to give (2*S*,5*S*,8a*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-2-[(1-*tert*-butyloxycarbonylindol-3-yl)methyl]-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizin-8-one (*O*-TBDMS-*N*-Boc derivative of **7b**) (126 mg, 97%) as a syrup: IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.05 (3H, s), 0.92 (9H, s), 1.66 (9H, s), 2.56 (1H, dd, J = 12.9, 8.9 Hz), 2.72 (1H, dd, J = 12.9, 7.9 Hz), 3.04 (2H, s), 3.50 (2H, *s*), 4.06 (1H, dd, J = 9.2, 3.6 Hz), 4.19 (1H, dd, J = 11.5, 9.2 Hz), 4.30 (1H, dd, J = 11.5, 3.6 Hz), 4.38 (1H, br t, J = 8.2 Hz), 7.03 (1H, br t, J = 7.6 Hz), 7.20−7.45 (8H, m), 8.11 (1H, d, J = 8.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.3, 19.7, 25.9, 28.2, 30.6, 38.7, 61.6, 63.4, 65.5, 69.5, 83.5, 85.5, 115.0, 115.3, 119.7, 122.5, 124.2, 125.2, 125.8, 127.6, 128.4, 128.8, 131.1, 135.8, 149.6, 169.7. This material was immediately used for the next step. To a stirred solution of *O*-TBDMS-*N*-Boc derivative of **7b** (120 mg, 0.20 mmol) in THF (2.4 mL) was added 70% HF·pyrdine (1 mL) at 0 °C, and the mixture was further stirred at the same temperature for 1 h. A saturated aqueous solution of $NaHCO_3$ was added to the mixture, and the whole was extracted with AcOEt. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 2:1) to give **12** (103 mg, 100%) as a syrup: $[\alpha]^{25}_D$ +44.8 (*c* 0.400, $CHCl_3$); IR ($CHCl_3$) 3570, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (9H, s), 2.63 (1H, dd, J = 12.7, 8.8 Hz), 2.80 (1H, dd, J = 12.7, 7.3 Hz), 3.01 (1H, d, J = 14.6 Hz), 3.06 (1H, d, J = 14.6 Hz), 3.59 (1H, d, J = 11.7 Hz), 3.63 (1H, d, J = 11.7 Hz), 4.19 (1H, dd, J = 9.3, 3.4 Hz), 4.24 (1H, dd, J = 11.2, 9.3 Hz), 4.34 (1H, dd, J = 11.2, 3.4 Hz), 4.36 (1H, br t, J = 7.8 Hz), 7.28 (1H, br t, J = 7.3 Hz), 7.29 (1H, br t, J = 7.3 Hz), 7.32−7.41 (6H, m), 7.46 (1H, d, J = 7.8 Hz), 8.11 (1H, br d, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 28.2, 30.4, 38.4, 61.8, 63.7, 67.1, 69.0, 85.2, 114.8, 115.1, 119.4, 122.6, 124.4, 124.9, 126.0, 128.5, 129.0, 129.5, 130.9, 135.6, 150.0, 170.0. Anal. Calcd for $C_{27}H_{30}N_2O_6$: C, 67.40; H, 6.47; N, 5.65. Found: C, 67.70; H, 6.32; N, 5.85.

(2*S*,4*S*)-4-*tert*-Butyloxycarbonylamino-2-[(1-*tert*-butyloxycarbonylindol-3-yl)methyl]-2-(hydroxymethyl)oxolan-5-one (14). A mixture of **12** (20 mg, 0.042 mmol) and 20% $Pd(OH)_2$ on charcoal (20 mg) in MeOH (0.5 mL) was stirred at room temperature under an atmosphere of hydrogen for 5 h. The mixture was passed through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of MeCN (0.5 mL) and a saturated aqueous solution of $NaHCO_3$ (one drop). To the stirred mixture was added Boc_2O (46 mg, 0.21 mmol) at room temperature, and the mixture was further stirred at the same temperature for 24 h. Water was added to the mixture, and the whole was extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 2:1) to give **14** (15.6 mg, 81%) as a syrup: $[\alpha]^{25}_D$ −3.26 (*c* 0.854, $CHCl_3$); IR ($CHCl_3$) 3435, 1780, 1720 cm^{-1}; ^1H NMR

(270 MHz, $CDCl_3$) δ 1.39 (9H, s), 1.67 (9H, s), 2.23 (1H, br t, J = 10.9 Hz), 2.40 (1H, dd, J = 13.2, 10.6 Hz), 2.72 (1H, br t, J = 5.9 Hz), 2.99 (1H, d, J = 14.8 Hz), 3.11 (1H, d, J = 14.8 Hz), 3.66 (1H, dd, J = 12.2, 6.3 Hz), 3.87 (1H, dd, J = 12.2, 5.3 Hz), 3.93 (1H, m), 5.15 (1H, br s), 7.23−7.35 (2H, m), 7.50 (1H, s), 7.57 (1H, br t, J = 6.9 Hz), 8.13 (1H, d, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 28.2, 31.3, 31.6, 50.9, 67.4, 84.1, 86.4, 113.6, 115.3, 119.2, 123.0, 124.8, 125.5, 130.5, 135.3, 149.5, 174.8; HRMS calcd for $C_{24}H_{32}O_7N_2$ 460.2210, found 460.2214.

(2*S*,4*S*)-4-*tert*-Butyloxycarbonylamino-2-[(1-*tert*-butyloxycarbonylindol-3-yl)methyl]-5-oxooxolane-2-carboxylic Acid (15). To a stirred suspension of PDC (1.62 g, 4.30 mmol) in DMF (1 mL) was added a solution of **14** (200 mg, 0.430 mmol) in DMF (2 mL) at room temperature, and the mixture was further stirred at the same temperature for 24 h. A 10% solution of citric acid was added to the mixture, and the mixture was further stirred for 30 min. The whole was extracted with Et_2O, and the organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed ($CHCl_3$−AcOEt−AcOH, 50:10:1) to give **15** (124 mg, 69%) as a syrup: $[\alpha]^{25}_D$ −22.9 (*c* 0.328, MeOH); IR ($CHCl_3$) 3030, 1780, 1710 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.43 (9H, s), 1.70 (9H, s), 2.51 (1H, br d, J = 11.5 Hz), 2.80 (1H, br d, J = 10.8 Hz), 3.46 (2H, br s), 4.04 (1H, t, J = 9.3 Hz), 7.28 (1H, br d, J = 7.3 Hz), 7.33 (1H, br t, J = 7.5 Hz), 7.61 (1H, s), 7.67 (1H, d, J = 7.8 Hz), 8.14 (1H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 14.2, 19.3, 28.3, 28.6, 38.6, 30.7, 33.3, 51.5, 80.9, 84.8, 116.6, 117.6, 120.7, 123.9, 125.3, 126.4, 132.4, 1 36.6, 175.1, 176.8; HRMS (FAB) calcd for $C_{24}H_{30}N_2O_8$-Na (MNa^+) 497.1900, found 497.1905.

Monatin [(2*S*,4*S*)-2]. To the stirred solution of **15** (96 mg, 0.2 mmol) in HCO_2H (3 mL) was added 1 N HCl (6 mL) at room temperature, and the mixture was further stirred at the same temperature for 4 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in MeOH (3 mL). To the mixture was added a 1 N aqueous NaOH (6 mL) at room temperature, and the mixture was further stirred at the same temperature for 6 h. The mixture was concentrated under reduced pressure, and the pH value of the mixture was adjusted to ca. pH 3 by adding 1 N HCl. The mixture was dissolved in distilled water (6 mL). To the mixture was added Amberlite IR-120 H^+-form (2 g), and then the mixture was stirred gently for 6 h. The resins were collected by filtration and washed thoroughly with distilled water. The resins were placed in 6 N aq NH_3 (5 mL) and stirred gently for 1 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give monatin [(2*S*,4*S*)-**2**] (54 mg, 92%): $[\alpha]^{25}_D$ −10.95 (*c* 1.00, 1 N HCl) [lit.[2] $[\alpha]^{20}_D$ −7.6 (*c* 1.0, 1 N HCl)]; ^{1}H NMR (500 MHz, D_2O) δ 2.04 (1H, dd, J = 15.1, 11.7 Hz), 2.66 (1H, br d, J = 15.1 Hz), 3.12 (1H, d, J = 14.6 Hz), 3.32 (1H, d, J = 14.6 Hz), 3.62 (1H, br d, J = 11.2 Hz), 7.19 (1H, br t, J = 7.3 Hz), 7.26 (1H, br d, J = 7.3 Hz), 7.28 (1H, s), 7.53 (1H, d, J = 8.3 Hz), 7.77 (1H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, D_2O) δ 38.1, 41.7, 56.6, 83.1, 111.9, 114.4, 121.8, 122.0, 124.3, 127.6, 130.7, 138.6, 179.0, 181.8. The spectral data shown above were identical to those reported.[2]

(2*S*,4*S*)-4-*tert*-Butyloxycarbonylamino-2-[(4-methoxyphenyl)methyl]-2-(hydroxymethyl)oxolan-5-one (16). According to the procedure for the preparation of **14**, compound **7c** (40 mg, 0.11 mmol) was hydrogenolyzed with 20% $Pd(OH)_2$ on charcoal (300 mg) in MeOH (6 mL) for 3 h. After workup, the crude amine was treated with Boc_2O (118 mg, 0.55 mmol) and a saturated aqueous solution of $NaHCO_3$ (one drop) in MeCN (1 mL) for 24 h. Workup and chromatography (hexane−AcOEt, 1:1) gave **16** (136 mg, 54%) as a syrup: $[\alpha]^{24}_D$ +11.5 (*c* 0.740, $CHCl_3$); IR ($CHCl_3$) 3430, 1780, 1710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (9H, s), 2.24 (3H, br t, J = 8.3 Hz), 2.48 (3H, br t, J = 10.3 Hz), 2.67 (1H, br s), 2.74 (1H, d, J = 14.2 Hz), 2.99 (1H, d, J = 14.2 Hz), 3.52 (1H, br s), 3.60 (1H, dd, J = 12.2, 6.3 Hz), 3.73 (1H, m), 3.78 (3H, s), 5.10 (1H, br s), 6.86 (2H, d, J = 8.8 Hz), 7.15 (2H, d, J = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 33.5, 50.8, 55.2, 67.4, 80.5, 86.6, 114.3, 126.2, 131.4, 155.2, 158.9, 175.0; HRMS (FAB) calcd for $C_{18}H_{26}$-NO_6 (MH^+) 352.1760, found 352.1762.

(2*S*,4*S*)-4-(*tert*-Butyloxycarbonylamino)-2-[(4-methoxyphenyl)methyl]-5-oxooxolane-2-carboxylic Acid (17). According to the procedure for the preparation of **15**, compound **16** (20 mg, 0.057 mmol) was treated with PDC (215 mg, 0.57 mmol) in DMF (0.8 mL) for 24 h. After workup, the crude product was chromatographed ($CHCl_3$−AcOEt−AcOH, 50:10:1) to give **17** (15 mg, 72%) as a syrup: $[\alpha]^{25}_D$ −16.6 (*c* 0.140, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 1.38 (9H, s), 2.31 (1H, br s), 2.68 (1H, br s), 3.10 (1H, br s), 3.17 (1H, br s), 3.45 (1H, br s), 4.83 (1H, br s), 6.87 (2H, br d, J = 6.4 Hz), 7.20 (2H, br s); ^{13}C NMR (125 MHz, CD_3OD) δ 29.4, 38.0, 44.1, 52.3, 56.4, 81.5, 115.9, 129.1, 133.4, 158.1, 161.3, 177.8. This material was immediately used for the next step.

(2*S*,4*S*)-4-Hydroxy-4-[(4-methoxyphenyl)methyl]glutamic Acid (18) (Monatin Congener). According to the procedure for the preparation of (2*S*,4*S*)-**2**, compound **17** (10 mg, 0.027 mmol) was treated with HCO_2H−1 N HCl (1:3, 4 mL) for 3 h. After concentration, the residue was treated with 1 N NaOH (3.1 mL, 3.1 mmol) in MeOH (1 mL) for 3 h. Workup using Amberlite IR-120 (1 g) gave **18** (10.3 mg, 93%): $[\alpha]^{26}_D$ +4.5 (*c* 0.12, 1 N HCl); ^{1}H NMR (500 MHz, D_2O) δ 1.88 (1H, br d J = 13.7 Hz), 2.50 (1H, br d, J = 14.2 Hz), 2.84 (1H, d, J = 13.4 Hz), 3.09 (1H, d, J = 13.4 Hz), 3.49 (1H, br d J = 8.3 Hz), 3.85 (3H, s), 6.96 (2H, br s), 7.23 (2H, br s); ^{13}C NMR (125 MHz, D_2O) δ 41.1, 45.4, 54.9, 56.2, 81.1, 114.6, 130.1, 132.3, 158.4, 164.2, 180.8; HRMS (FAB) calcd for $C_{13}H_{18}NO_6$ (MH^+) 284.1134, found 284.1129.

2-[(*tert*-Butyldiphenylsilyloxy)methyl]acrylic Acid Ethyl Ester (20). To a stirred solution of **19** (390 mg, 3.0 mmol) in DMF (3 mL) was added imidazole (612 mg, 9.0 mmol) and TBDPSCl (117 mL, 4.5 mmol) at 0 °C, and the mixture was further stirred at room temperature for 1 h. Water was added to the mixture, and the whole was extracted with Et_2O. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 30:1) to give **20** (1.0 g, 91%) as a colorless oil: IR ($CHCl_3$) 1710, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.24 (3H, t, J = 7.1 Hz), 4.16 (2H, q, J = 7.1 Hz), 4.44 (2H, s), 6.09 (1H, s), 6.32 (1H, s), 7.36−7.43 (6H, m), 7.67−7.48 (4H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.1, 19.3, 26.8, 60.4, 62.2, 123.7, 127.7, 129.7, 133.3, 135.6, 139.6, 165.8. Anal. Calcd for $C_{22}H_{28}O_3Si$: C, 71.70; H, 7.66. Found: C, 71.74; H, 7.83.

2-[(*tert*-Butyldiphenylsilyloxy)methyl]prop-2-en-1-ol (21). To a solution of **20** (737 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added a 0.95 M solution of DIBAL in hexane (5.3 mL, 5.0 mmol) at −78 °C, and the mixture was allowed to warm to room temperature. After being stirred for 30 min, the mixture was cooled to −78 °C. MeOH (2.5 mL) and water (0.5 mL) were added to the mixture, and the mixture was allowed to warm to room temperature. Celite and Et_2O were added to the mixture, and the resulting mixture was passed though a pad of Celite. The filtrate was concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 8:1) to give **21** (607 mg, 93%) as a colorless oil: IR ($CHCl_3$) 3610, 1590 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (9H, s), 4.15 (2H, s), 4.25 (2H, s), 5.10 (1H, s), 5.15 (1H, s), 7.36−7.43 (6H, m), 7.67−7.69 (4H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.2, 26.8, 64.3, 65.4, 110.9, 127.9, 129.7, 133.2, 135.7, 147.1. The ^{1}H NMR spectral data were identical to those reported.[17]

2-[(*tert*-Butyldiphenylsilyloxy)methyl]pent-4-enoic Acid Ethyl Ester (22). A solution of **21** (500 mg, 1.53 mmol) and propionic acid (6.8 μL, 0.092 mmol) in $HC(OEt)_3$ (2.50 g, 15.3 mmol) was heated at 145 °C for 40 min. After the solution was

(17) Weigand, S.; Brückner, R. *Synthesis* **1996**, 475.

cooled, water and a saturated aqueous solution of $NaHCO_3$ (0.5 mL) were added to the mixture, and the whole was extracted with AcOEt. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed ($CHCl_3$−hexane, 1:1) to give **22** (392 mg, 65%) as a colorless oil: IR ($CHCl_3$) 1730, 1660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.23 (3H, t, J = 7.1 Hz), 2.34 (2H, br t, J = 7.6 Hz), 2.42−2.45 (2H, m), 4.09−4.13 (4H, m), 4.87 (1H, s), 5.17 (1H, s), 7.36−7.44 (6H, m), 7.66−7.68 (4H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.2, 19.3, 26.8, 27.8, 32.7, 60.3, 66.4, 109.3, 127.7, 129.7, 133.6, 135.5, 146.6, 173.1. Anal. Calcd for $C_{24}H_{32}O_3Si$: C, 72.68; H, 8.13. Found: C, 71.74; H, 8.23.

4-(Hydroxymethyl)pent-4-enoic Acid Ethyl Ester (23). To a stirred solution of **22** (1.14 g, 2.87 mmol) in THF (50 mL) was added a 1 M solution of TBAF (3.20 mL, 3.20 mmol) at 0 °C, and the mixture was further stirred at the same temperature for 3.5 h. Water was added to the mixture, and the whole was extracted with AcOEt. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (hexane−AcOEt, 3:1) to give **23** (290 mg, 64%) as a colorless oil: IR ($CHCl_3$) 1730, 1660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.3 Hz), 1.82 (1H, br s), 2.41 (2H, br t, J = 7.6 Hz), 2.50−2.53 (2H, m), 4.09 (2H, s), 4.14 (2H, q, J = 7.3 Hz), 4.89 (1H, s), 5.07 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 27.7, 32.7, 60.5, 65.9, 110.3, 147.4, 173.3. Since **23** was not stable, it was immediately used for the next step.

(2*S*,5*S*,8a*S*)-2-(Hydroxymethyl)-2-[(ethoxycarbonyl)-ethyl]-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizin-8-one (24). To a stirred mixture of nitrone **5** (10 mg, 0.052 mmol) and $MgBr_2{\cdot}OEt_2$ (21 mg, 0.078 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of **23** (10 mg, 0.063 mmol) in CH_2Cl_2 (1.5 mL) at room temperature, and the mixture was further stirred at the same temperature for 3 days. After workup, the crude product was chromatographed ($CHCl_3$−AcOEt, 9:1) to give a 91:9 mixture of **24** and its isomer (17 mg, 94%). Pure **24** was obtained by column chromatography (hexane−acetone, 7:1): $[\alpha]^{26}_D$ +73.6 (*c* 0.400, $CHCl_3$); IR ($CHCl_3$) 3040, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.3 Hz), 1.94 (1H, dt, J = 14.7, 7.8 Hz), 2.07 (1H, dt, J = 14.7, 7.8 Hz), 2.32 (2H, t, J = 7.8 Hz), 2.60 (1H, br t, J = 6.4 Hz), 2.65 (1H, dd, J = 13.2, 6.4 Hz), 2.69 (1H, dd, J = 13.2, 8.8 Hz), 3.51−3.59 (2H, m), 4.11 (2H, q, J = 7.3 Hz), 4.23−4.34 (3H, m), 4.43 (1H, dd, J = 11.2, 2.9 Hz), 7.34−7.42 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 29.0, 30.1, 38.1, 60.7, 61.7, 64.0, 67.1, 69.0, 84.3, 127.3, 128.7, 128.8, 135.7, 169.7, 173.2; HRMS calcd for (M^+) $C_{18}H_{23}NO_6$ 349.1525, found 349.1524.

(2*S*,4*S*)-4-*tert*-Butyloxycarbonylamino-2-[(ethoxycarbonyl)ethyl]-2-(hydroxymethyl)oxolan-5-one (25). According to the procedure for the preparation of **14**, compound **24** (295 mg, 0.845 mmol) was hydrogenolized with 20% $Pd(OH)_2$ on charcoal (300 mg) in MeOH (6 mL) for 3 h. After workup, the crude amine was treated with Boc_2O (922 mg, 4.23 mmol) and a saturated aqueous solution of $NaHCO_3$ (one drop) in MeCN (5 mL) for 18 h. After workup, the crude product was chromatographed (hexane−AcOEt, 1:1) to give **25** (202 mg, 72%) as a syrup: $[\alpha]^{25}_D$ −11.3 (*c* 0.560, $CHCl_3$); IR ($CHCl_3$) 1780, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.3 Hz), 1.45 (9H, s), 2.04 (2H, br t, J = 7.3 Hz), 2.24−2.30 (1H, m), 2.41−2.47 (3H, m), 3.08 (1H, br s), 3.52 (1H, dd, J = 11.7, 6.3 Hz), 3.76 (1H, dd, J = 11.7, 4.9 Hz), 4.14 (2H, q, J = 7.3 Hz), 4.57 (1H, br d, J = 8.3 Hz), 5.41 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 28.2, 28.4, 30.7, 34.8, 50.5, 60.9, 66.1, 80.5, 85.6, 155.5, 172.8, 174.9; HRMS (FAB) calcd for $C_{15}H_{26}NO_7$ (MH^+) 332.1709, found 332.1703.

Lycoperdic Acid (3). According to the procedure for the preparation of **15**, compound **25** (88 mg, 0.27 mmol) was treated with PDC (215 mg, 0.57 mmol) in DMF (0.8 mL) for 24 h. After workup, the crude product was dissolved in Et_2O and the solution was passed through a glass filter (11 G). The filtrate was concentrated under reduced pressure to give (2*S*,4*S*)-4-[(*tert*-butyloxycarbonyl)amino]-2-[(ethoxycarbonyl)-ethyl]-5-oxooxolane-2-carboxylic acid (**26**) (75 mg, 82%) as a syrup: $[\alpha]^{26}_D$ −18.6 (*c* 0.240, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 1.17 (3H, t, J = 7.1 Hz), 1.44 (9H, s), 2.27−2.46 (5H, m), 2.64 (1H, dd, J = 12.7, 9.8 Hz), 4.11 (2H, q, J = 7.1 Hz), 4.53 (1H, br s); ^{13}C NMR (125 MHz, CD_3OD) δ 15.2, 29.4, 30.8, 34.3, 38.6, 51.7, 62.7, 81.9, 158.5, 174.9, 176.3. This material was immediately used for the next step.

To a stirred solution of **26** (20 mg, 0.058 mmol) in MeOH (0.5 mL) was added a 1 N aqueous solution of NaOH (0.15 mL, 0.15 mmol) at room temperature, and the mixture was further stirred for 30 min. The mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of HCO_2H (2 mL) and 1 N HCl (0.26 mL, 0.26 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. The residue was chromatographed on Dowex G-10 (2 N AcOH) to give lycoperdic acid (**3**) (11 mg, 87%): $[\alpha]^{26}_D$ +14.24 (*c* 0.144, H_2O) [lit.[6b] $[\alpha]^{21}_D$ +14.2 (*c* 0.46, H_2O)]; ^1H NMR (500 MHz, D_2O) δ 2.30−2.36 (2H, m), 2.58 (1H, m), 2.67−2.70 (2H, m), 2.91 (1H, dd, J = 15.6, 3.9 Hz), 4.11 (2H, dd, J = 9.3, 3.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 33.1, 38.0, 51.5, 87.2, 172.0, 175.0, 180.3. The spectral data shown above were identical to those reported.[6b]

(2*R*,5*S*,8a*S*)-2-Methyl-8-oxo-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizine-2-carboxylic Acid Methyl Ester (9a) (Table 2, Entry 1). A solution of nitrone **5** (30 mg, 0.16 mmol) and **8a** (23.3 mg, 0.23 mmol) in CH_2Cl_2 (2.5 mL) was stirred at room temperature for 2 days. After concentration, the crude product was chromatographed (hexane−AcOEt, 3:1) to give **9a** (45.3 mg, 98%) as colorless crystals, mp 113−114 °C (hexane−AcOEt): $[\alpha]^{25}_D$ +66.7 (*c* 0.400, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.51 (3H, s), 2.68 (1H, dd, J = 13.2, 7.8 Hz), 3.28 (1H, dd, J = 13.2, 9.8 Hz), 3.69 (3H, s), 4.22 (1H, br t, J = 11.2 Hz), 4.29 (1H, dd, J = 11.7, 3.9 Hz), 4.41 (1H, dd, J = 10.3, 3.9 Hz), 4.48 (1H, br t, J = 8.8 Hz), 7.33−7.43 (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 24.0, 43.0, 52.7, 62.0, 62.9, 70.1, 82.9, 127.7, 127.8, 128.6, 128.8, 129.0, 135.2, 168.2, 173.4. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.70; H, 5.89; N, 4.63.

(2*R*,5*S*,8a*S*)-2-[(Indol-3-yl)methyl]-8-oxo-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizine-2-carboxylic Acid Methyl Ester (9b) (Table 2, Entry 2). A solution of nitrone **5** (12 mg, 0.062 mmol) and **8b** (20 mg, 0.093 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 2 days. After concentration, the crude product was chromatographed (hexane−AcOEt, 1:1) to give **9b** (25 mg, 99%) as a syrup: $[\alpha]^{25}_D$ +36.3 (*c* 0.400, $CHCl_3$); IR ($CHCl_3$) 3480, 1750 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.89 (1H, dd, J = 13.2, 8.6 Hz), 3.25 (1H, dd, J = 13.2, 9.6 Hz), 3.31 (2H, s), 3.67 (3H, s), 4.02 (1H, br t, J = 8.9 Hz), 4.16 (1H, dd, J = 11.2, 9.9 Hz), 4.24−4.34 (2H, m), 7.08 (1H, br d, J = 2.3 Hz), 7.11−7.23 (2H, m), 7.34−7.45 (6H, m), 7.65 (1H, br d, J = 7.9 Hz), 8.13 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.2, 40.1, 52.7, 62.1, 63.3, 70.2, 86.2, 108.9, 111.1, 119.2, 119.6, 119.8, 122.2, 123.9, 127.7, 127.9, 128.7, 128.8, 135.2, 135.9, 168.4, 173.5; HRMS (FAB) calcd for $C_{23}H_{22}N_2O_5$ (MH^+) 407.1607, found 407.1610.

(2*R*,5*S*,8a*S*)-2-(Indol-3-ylmethyl)-8-oxo-5-phenyl-1,5,6,8a-tetrahydro-3,7-dioxaindolizine-2-carboxylic Acid (9e) (Table 2, Entry 5). A solution of nitrone **5** (23 mg, 0.12 mmol) and **8e** (30 mg, 0.15 mmol) in CH_2Cl_2 (0.4 mL) was stirred at room temperature for 15 h. The precipitated crystals **9e** (39 mg, 83%) were collected by filtration, mp 125−127 °C (dec., hexanes−EtOH): $[\alpha]^{26}_D$ +57.9 (c 0.400, THF); ^1H NMR (500 MHz, acetone-d_6) δ 2.86 (1H, dd, J = 13.2, 8.8 Hz), 3.23 (1H, J = 13.2, 8.3 Hz), 3.29 (1H, d, J = 15.1 Hz), 3.33 (1H, d, J = 15.1 Hz), 4.20 (1H, t, J = 8.8 Hz), 4.22 (1H, t, J = 11.7 Hz), 4.29 (1H, J = 11.7, 3.4 Hz), 4.46 (1H, dd, J = 10.7, 3.4 Hz), 6.96 (1H, t, J = 6.8 Hz), 7.07 (1H, t, J = 6.8 Hz), 7.20 (1H, d, J = 2.0 Hz), 7.37 (4H, m), 7.53 (2H, d, J = 6.8 Hz), 7.64 (1H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 30.1, 41.0,

63.4, 70.4, 86.7, 109.7, 112.0, 119.7, 120.0, 122.1, 125.5, 128.8, 128.9, 129.18, 129.24, 137.3, 137.6, 169.2, 174.2; HRMS (FAB) calcd for $C_{22}H_{20}N_2O_5$ (MH^+) 393.1450, found 393.1443. Anal. Calcd for $C_{22}H_{20}N_2O_5 \cdot 1/4H_2O$: C, 66.57; H, 5.20; N, 7.05. Found: C, 66.55; H, 5.14; N, 6.94.

(2*S*,4*R*)-4-Hydroxy-4-[(indol-3-yl)methyl]glutamic Acid [(2*S*,4*R*)-2]. A mixture of **9e** (50 mg, 0.13 mmol) and 20% $Pd(OH)_2$ on charcoal (75 mg) in MeOH (4 mL) was stirred at room temperature under an atmosphere of hydrogen for 3 h. The mixture was passed through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF−water (1:1, 2 mL) and a 1 N aqueous solution of LiOH (0.32 mL, 0.32 mmol). After being stirred for 10 min, the mixture was concentrated under reduced pressure. The residue was acidified to pH 3 by adding 1 N HCl. The mixture was concentrated to give a residue, which was dissolved in distilled water. According to the procedure for the preparation of monatin [(2*S*,4*S*)-**2**], the solution was treated with Amberlite IR-120 (500 mg) to give crude **11**, which was further purified by column chromatography on Sephadex G-10 (distilled water) to afford (2*S*,4*R*)-**2** (12.2 mg, 33%): $[\alpha]^{26}_D$ −22.6 (*c* 0.16, D_2O) [lit.[5e] $[\alpha]^{25.0}_D$ −25.7 (*c* 1.00, D_2O)]; ^{1}H NMR (500 MHz, D_2O) δ 2.16 (1H, dd, J = 15.1, 10.3 Hz), 2.41 (1H, dd, J = 15.1, 2.4 Hz), 3.15 (1H, d, J = 14.7 Hz), 3.19 (1H, J = 14.7 Hz), 3.90 (1H, dd, J = 10.3, 2.4 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.19 (1H, s), 7.44 (1H, d, J = 7.8 Hz), 7.69 (1H, d, J = 7.8 Hz); ^{13}C NHR (67.5 MHz, D2O) δ 35.1, 41.8, 53.2, 79.1, 110.3, 112.4, 119.8, 120.1, 122.4, 125.5, 128.7, 136.6, 163.2, 182.2. The spectral data shown above are identical to those reported.[5e]

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Note Added after ASAP Publication. Due to a production error, the graphic for Figure 2 was incorrect in the version published ASAP May 10, 2005; the corrected version was published May 26, 2005.

Supporting Information Available: Experimental methods for compounds **6**, **8**, **7a**, **7c**−**f**, **9a**−**d**, and **9f**; computation of TS **D**−**G**; ^{1}H NMR spectra for compounds **7a** and **7f**, a mixture of **7a** and **11a**, a mixture of **7b** and **11b**, and **14**, **15**, (2*S*,4*S*)-**2**, **16**−**18**, **21**, **23**, **25**, **3**, **9b**, **9d**, **9f**, (2*S*,4*R*)-**2**, **8g**−**i**, and **6c**−**e**; and the ^{13}C NMR spectrum of compound **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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