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Total Synthesis of Monatin

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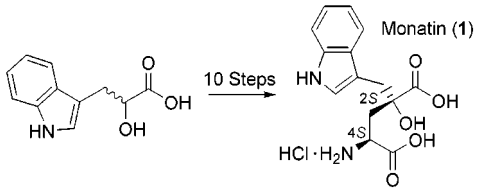
ABSTRACT

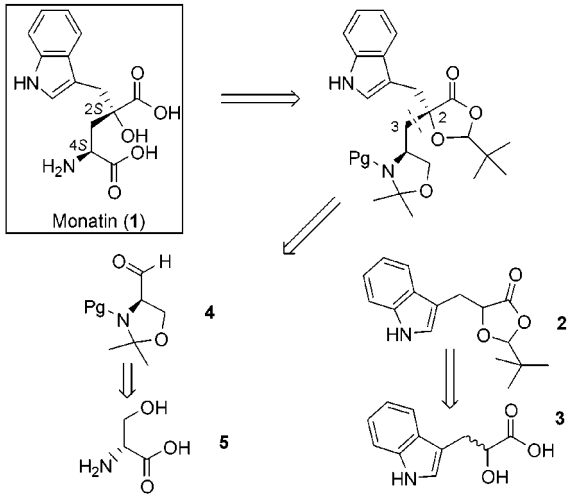


The naturally occurring sweetener Monatin, a diastereomer of Monatin, and a phenyl analogue of Monatin have been prepared and isolated in their enantiomerically pure forms.

The sweet, naturally occurring, unusual amino acid Monatin [**1**, (2*S*,4*S*)-4-hydroxy-4-(indol-3-ylmethyl)glutamic acid] was isolated in South Africa from *Schlerochiton ilicifolius*.[1] This small molecule exhibits a potent sweet taste, i.e., about 1000 times sweeter than sucrose on a weight basis[1] and is an attractive target to synthesize as a molecule exhibiting a sweet taste. The syntheses of racemates and an analogue of Monatin have been reported.[2] In this Letter, we report the synthesis of optically pure Monatin (**1**). For this undertaking, we utilized the strategy outlined in Scheme 1. In the retrosynthetic analysis shown, a bond is formed between a derivative of indolelactic acid (**2**) and an optically active protected oxazolidine **4**. These reactants are readily formed from commercially available racemic indolelactic acid (**3**) and L-serine (**5**), respectively.

Monatin contains two asymmetric centers at C2 and C4. The C4 center has an α-proton which is easily epimerized under basic conditions. Therefore, we employed the highly reactive Garner aldehyde (**4**) to react with the enolate of compound **2**, thus avoiding epimerization of aldehyde **4**. With one asymmetric center fixed and the removal of the hydroxyl at C3, we obtained two diastereomers in our synthesis. The separation of the final intermediate **19a** from its diastereomer **19b** was readily accomplished.

Scheme 1. Strategy for the Synthesis of Monatin (**1**)[a]



[a] Pg = protecting group.

Before we undertook the synthesis of Monatin (**1**), we applied the strategy to the preparation of the phenyl analogue **13** in which a phenyl ring replaces the indole group. This enantioselective route began with commercially available D-phenyllactic acid (**6**, Scheme 2). In 1984, Seebach reported the enantiospecific alkylations of several 1,3-dioxolanones

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(1) Vleggaar, R.; Ackerman, L. G. J.; Steyn, P. S. *J. Chem. Soc., Perkin. Trans. 1* **1992**, *22*, 3095−3098.

(2) (a) Holzapfel, C. W.; Bischofberger, K.; Olivier, J. *Synth. Commun.* **1994**, *24*(22), 3197−3211. (b) Abushanab, E.; Arumugam, S. U.S. Patent 5,994,559, November 30, 1999. (c) Holzapfel, C. W.; Olivier, J. *Synth. Commun.* **1993**, *23*(18), 2511−2526.

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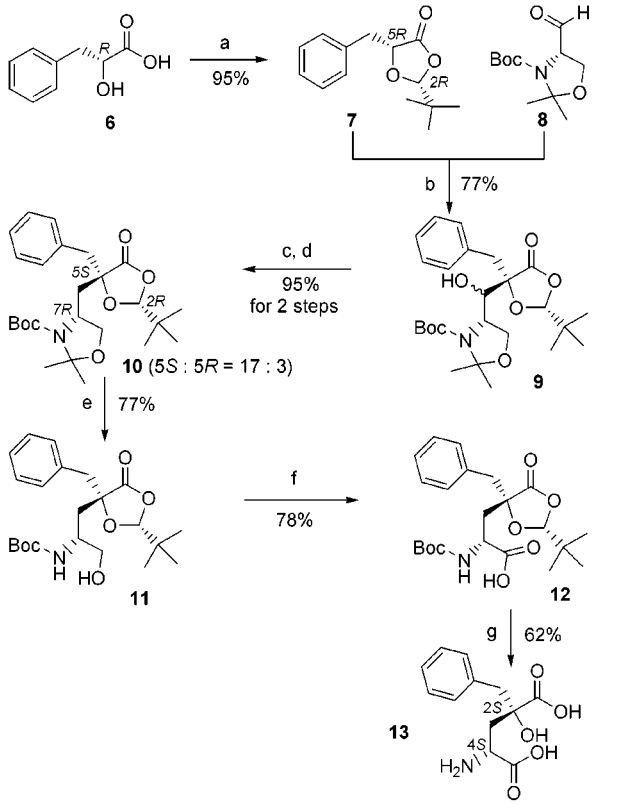
Scheme 2. Synthesis of a Phenyl Analogue of Monatin (**13**)



[a] (a) $(CH_3)_3CCHO$ (1.2 equiv), $BF_3{\cdot}Et_2O$ (1.2 equiv), Et_2O, −20 °C, 2 h; (b) **7** (1.0 equiv), **8** (1.1 equiv), LDA (1.2 equiv), THF, −78 °C, 2 h; (c) NaH (3.0 equiv), THF, −15 °C → rt, 40 min, CS_2 (3.0 equiv), 0 °C, 20 min, MeI (3.0 equiv), rt, 30 min; (d) *n*-Bu_3SnH (6.0 equiv), AIBN (3.0 equiv), Ph-CH_3, Δ, 2 h, Ar; (e) PPTS (1.0 equiv × 3), EtOH/H_2O (95:5), Δ, 6 h; (f) PDC (6.0 equiv), DMF, rt, 24 h; (g) 0.1 N HCl/HCO_2H, Δ, 3 h. LDA = lithium diisopropylamide, AIBN = 2,2′-azobis(isobutyronitrile), PPTS = pyridinium *p*-toluenesulfonate, PDC = pyridinium dichromate, DMF = *N*,*N*′-dimethylformamide.

prepared from α-hydroxycarboxylic acids and pivalaldehyde through the Li-enolate.[3] This reaction has been applied to many total syntheses.[4] We used this method as a key step in the synthesis of a phenyl analogue of Monatin (**13**). The optically pure *cis*-dioxolanone **7** was obtained in 95% yield.[5] Alkylation at the α-carbon of compound **7** was unsuccessful using iodoalanine derivatives. We believe that the sterically hindered enolate of compound **7** cannot react with the bulky iodoalanine derivatives in a displacement reaction.[6] The Garner aldehyde (**8**)[7] derived from L-serine did react with the enolate of compound **7** generated with LDA at −78 °C to produce condensation product **9**. This molecule possesses a β-hydroxyl group which was removed by Barton deoxygenation[6,8] to provide the deoxygenated product **10** with excellent diastereoselectivity (17:3) as determined by ^{1}H NMR spectroscopy. Selective deprotection with PPTS in refluxing ethanol[9] afforded the Boc-protected β-amino alcohol **11** in good yield. The primary alcohol **11** was oxidized to carboxylic acid **12** with PDC without epimerization at the C4 position.[9] Compound **12** and the small amount of diastereomer were separable, and optically pure product **12** was obtained. We established by NMR spectroscopy that the major product **12** possessed the (2*S*,4*R*) configuration.[4,5] Final deprotection of the Boc and pivalidene protections of compound **12** was afforded by allowing the reaction to reflux in 0.1 N HCl/HCO_2H for 3 h. Subsequent purification provided the (2*S*,4*R*) phenyl analogue of Monatin (**13**) which did not possess a sweet taste.

Since separation of the diastereomers of the phenyl analogue **12** was successful, we applied this strategy to the preparation of Monatin (**1**, Scheme 3). This synthesis commences with commercially available racemic indolelactic acid (**3**). The pivalidene derivatives **2** were obtained in good yield by following the same procedure as that reported above for the preparation of compound **7**. Reaction of the appropriate enantiomer of the Garner aldehyde (**14**) with the enolates of intermediates **2** produced compounds **15**. In this reaction, dimerization of intermediates **2** can readily occur. To avoid this side reaction, it was necessary to maintain the reaction temperature below −76 °C. Deoxygenation of isomers **15** produced the diastereomeric pair **16**.[10] Deprotection of the pivalidene group gave the hydroxymethylene molecules **17a** and **17b**[11] which were readily oxidized to the carboxylic acid structures **18a** and **18b**[12] using PDC. These reactions were successfully carried out using reaction conditions similar to those described above for the preparation of a phenyl analogue of Monatin, compound **13**.

The final deprotection steps used for the phenyl analogue could not be applied to Monatin (**1**) because decomposition of the indole group occurs under the acidic conditions employed. Compounds **18a** and **18b** were successfully converted to the diastereomeric mixture of lactams **19a** and

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(4) (a) Hiwa, H.; Ogawa, T.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3707−3709. (b) Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682−9684. (c) Bojack, G.; Bornowski, H. *Tetrahedron* **1991**, *47*(44), 9179−9186. (d) McPherson, D. W.; Knapp, F. F., Jr. *J. Org. Chem.* **1996**, *61*, 8335−8337. (e) Visser, T. J.; Waarde, A. V.; Jansen, T. J. H.; Visser, G. M.; Mark, T. W. V. D.; Kraan, J.; Ensing, K.; Vaalburg, W. *J. Med. Chem.* **1997**, *40*, 117−124.

(5) (a) Farines, M.; Soulier, J. *Bull. Soc. Chim. Fr.* **1970**, 332. (b) Hoye, T. R.; Peterson, B. H.; Miller, J. D. *J. Org. Chem.* **1987**, *52*, 1351. (c) Pearson, W. H.; Cheng, M. J. *J. Org. Chem.* **1987**, *52*, 1353. (d) Ortholand, J. Y.; Greiner, A. *J. Bull. Soc. Chim. Fr.* **1993**, *130*, 133. (e) Nicos, A. P.; Shao-Po, L. *J. Am. Chem. Soc.* **1995**, *117*, 6394−6395.

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(7) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18.

(8) Barton, D. H. R.; McCombie,S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

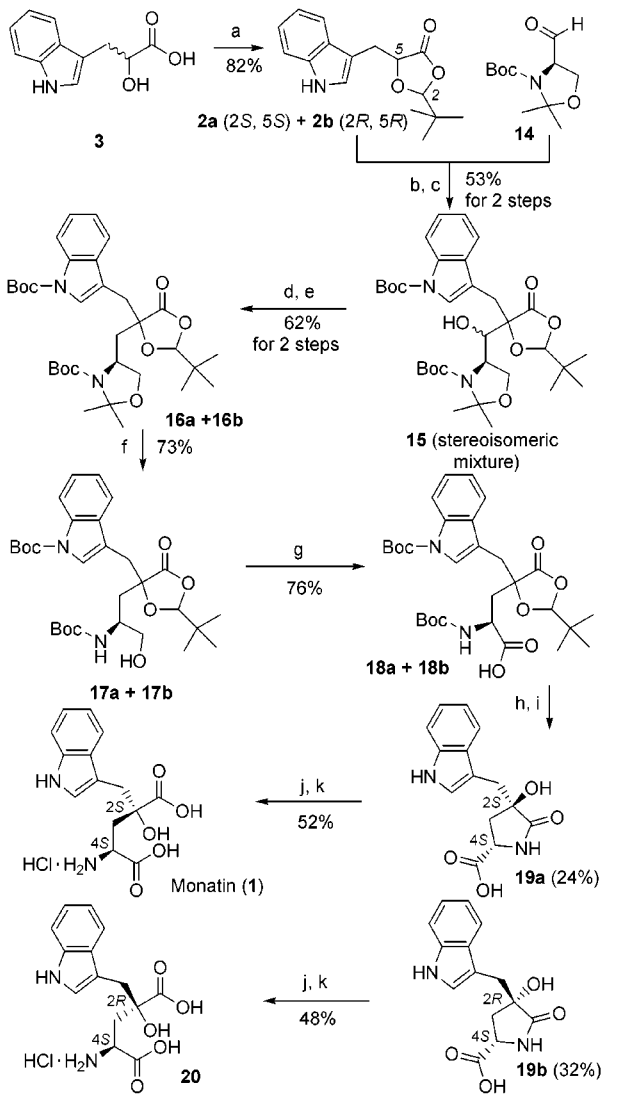
(9) (a) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C.-G.; Boulanger, T.; Norberg, B.; Evard, G.; Durand, F. *J. Org. Chem.* **1991**, *56*, 5729. (b) Muller, M.; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1993**, *34*, 3289. (c) D'Aniello, F.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.* **1994**, *42*, 7775. (d) D'Aniello, F.; Falorni, M.; Mann, A.; Taddei, M. *Tetrahedron: Asymmetry* **1996**, *7*(4), 1217−1226.

(10) The diastereomeric ratio was not established.

(11) The ratio of diastereomers was approximately 3:2 as determined by ^{1}H NMR spectroscopy.

(12) The ratio of diastereomers was approximately 4:3 as determined by HPLC.

Scheme 3. Synthesis of Monatin (**1**)[a]



[a] (a) $(CH_3)_3CCHO$ (1.2 equiv), $BF_3{\cdot}Et_2O$ (1.2 equiv), Et_2O, −20 °C, 2 h; (b) **2** (1.2 equiv) **14** (1.0 equiv), LDA (1.3 equiv), THF, −78 °C, 2 h; (c) $(Boc)_2O$ (1.1 equiv), DMAP (0.1 equiv), CH_3CN, rt; (d) NaH (5.0 equiv), THF, −15 °C → rt, 40 min, CS_2 (5.0 equiv), 0 °C, 20 min; (e) *n*-Bu_3SnH (10.0 equiv), AIBN (5.0 equiv), Ph-CH_3, Δ, 2 h, Ar; (f) PPTS (0.8 equiv × 4), EtOH/H_2O (95:5), Δ, 6 h; (g) PDC (6.0 equiv), DMF, rt, 24 h; (h) 0.1 N HCl/HCO_2H, rt, 3 h; (i) 3 N KOH (10 equiv), 0 °C, 1 min; (j) 3 N NaOH (5 equiv), EtOH, Δ, 3 h; (k) HCl. DMAP = 4-(dimethylamino)pyridine.

19b[13] by treatment with 0.1 N HCl/HCO_2H at room temperature for 3 h followed by 3 N KOH at 0 °C for 1 min. In this reaction, only lactam formation was observed with no ring-opened products detected.

Diastereomers **19a** and **19b** were easily separated by RP-HPLC using a C18 column. Optically pure lactam **19a** which possessed the same asymmetric configuration as Monatin (**1**)-was refluxed in the presence of 3 N NaOH in ethanol. No

(13) The ratio of diastereomers was approximately 4:3 as determined by product yields.

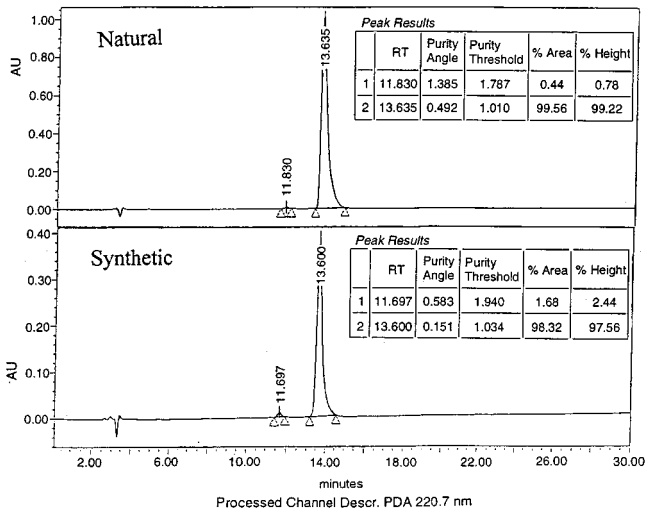


Figure 1. HPLC charts of natural and synthetic Monatin (**1**). The original scans are shown.

epimerization at C4 was detected by HPLC. The ring opening of lactam **19a** after acidification led directly to synthetic Monatin (**1**) which chromatographed identically with natural Monatin (Figure 1). In addition, the ^1H NMR spectrum of naturally isolated Monatin is identical to the spectrum of synthetic Monatin (**1**, Figure 2), and HRMALDI established that the synthetic product possesses the same formula as natural Monatin. Last, the optical rotation ($[\alpha]^{25}_D$) of synthetic Monatin is consistent with that reported for natural Monatin [− 7.6 (lit.) vs − 8.8 (experimentally determined under the same conditions)]. Indeed, synthetic Monatin (**1**) exhibits a sweet potency equal to that of the natural product.[11] The diastereomer of Monatin, compound **20**, obtained in this synthesis exhibits a slightly sweet taste which may be due to the presence of a trace amount of Monatin (**1**). Were

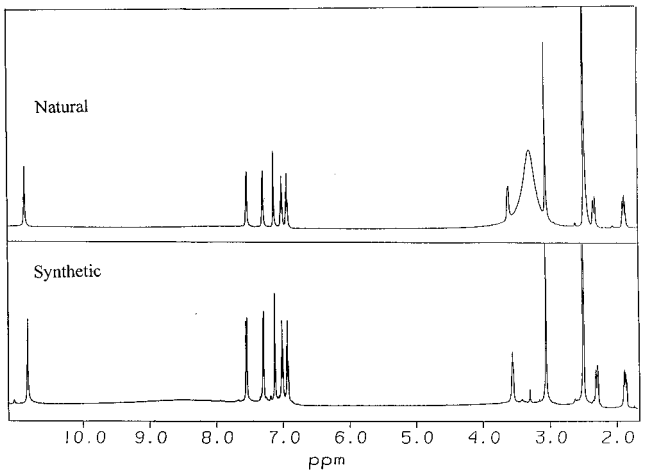


Figure 2. 500 MHz ^1H NMR spectra of natural and synthetic Monatin (**1**).

optically pure D-indolelactic acid available, only pure synthetic Monatin (**1**) would have been produced.

In conclusion, we have reported the total synthesis of Monatin (**1**), the diastereomer of Monatin (**20**) and a phenyl analogue of Monatin (**13**). The syntheses of these target molecules will prove to be most useful in our studies of the molecular basis of the sweet taste.

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Supporting Information Available: Experimental procedures with spectroscopic data for compounds **1**, **15**, **19a**, and **19b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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