Concise Synthesis of (2R,4R)-Monatin

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Monatin, 4-hydroxy-4-(3-indolylmethyl)-glutamic acid, is a naturally occurring sweet amino acid. The (2R,4R)-isomer has been found to be the sweetest among its four stereoisomers. A concise and efficient synthesis of (2R,4R)-monatin was accomplished by the alkylation of (4R)-N-tert-butoxycarbonyl (tBoc)-4-tert-butyldimethylsilyloxy-n-pyroglutamic acid methyl ester with tert-butyl 3-(bromomethyl)-1H-indole-1-carboxylate to give (4R)-N-tBoc-4-tert-butyldimethylsilyloxy-4-(N-tBoc-3-indolylmethyl)-n-pyroglutamic acid methyl ester, i.e., the lactam form of (2R,4R)-monatin with protecting groups. This was followed by the hydrolysis of the lactam ring and deprotection. The 4-hydroxyl n-pyroglutamic acid derivative was demonstrated to be a suitable precursor for the efficient preparation of (2R,4R)-monatin in high optical purity because the alkylation proceeded in regioselective and stereoselective manners at C4 to form appropriate asymmetric tetra-substituted carbon center; the resulting alkylated pyroglutamic acid derivative was then easily converted into the linear form of monatin.

Key words monatin; sweet amino acid; pyroglutamic acid; alkylation; tetra-substituted carbon center

Monatin is a naturally occurring amino acid derivative isolated from the bark of Schlerochiton ilicifolius roots, a plant native to northwestern Transvaal in South Africa. Monatin has four stereoisomers because of its two asymmetric centers at C2 and C4. Vleggar et al. reported the structure of natural monatin as (2S,4S)-4-hydroxy-4-(3-indolylmethyl)-glutamic acid and its sweetness as 1200–1400-fold more intense than sucrose.1) We previously reported that all isomers exhibit a sweet taste; however, (2S,4S)-monatin was found to be the least sweet isomer, whereas the other three isomers, especially (2R,4R)-monatin, were found to be intensely sweet (1700 times at 10% sucrose equivalent).2,3)

A major problem in the synthesis of (2R,4R)-monatin is the highly diastereoselective formation of a tetra-substituted carbon center at C4. Various chemical synthetic methods have been reported for the formation of the (2S,4S)-isomer, some of which produce a mixture of stereoisomers,4–7) whereas others describe stereoselective syntheses.8–13) In addition, some procedures require several steps after the construction of asymmetric tetra-substituted carbon center to complete the total synthesis.

A few groups have reported the chemoenzymatic synthesis of stereoisomers of monatin, in which the stereogenic center at C4 was introduced by an enantiospecific enzymatic hydrolysis of the chemically synthesized racemic ester derivatives using a protease.3,14) Since the racemization at C4 of these ester derivatives is impossible, these methods are not efficient for obtaining a single stereoisomer of monatin.

The lactam form of monatin, i.e., the pyroglutamic acid derivative, is an active intermediate in the retrosynthetic analysis of monatin. Indeed, Nakamura et al. and Tamura et al. observed the formation of the lactam form of monatin during their total synthesis.8,13) A concise method to obtain 4-substituted glutamic acid is the alkylation of the lithium enolate derived from N-protected pyroglutamic acid esters, followed by the cleavage of the lactam ring. Ezquerra et al. reported that lithium enolates of N-tert-butoxycarbonyl (Boc)-protected pyroglutamic acid alkyl ester stereospecifically reacted with benzyl bromides, exclusively yielding the trans isomer.15) Bassoli et al. also reported the same stereoselectivity in the synthesis of a monatin derivative that lacked the 4-hydroxyl group.16)

Oliveira and Coelho12) examined a similar stereospecific synthesis of (2S,4S)-monatin via the oxidation and alkylation of an enolate originating from (S)-pyroglutaminol derivative. The alkylation of their derivative proceeded in a regioselective manner because it has a single active hydrogen atom at C4. In addition, the alkylation of their derivative at C4 asymmetric center was proceeded from the less hindered face of the lactam ring opposite from the bulky tert-butyldimethylsilyloxy-methyl substituent at C2. However, the transformation of the hydroxymethyl group to a carboxylic acid was required in the final stage of their total synthesis.12)

Merino et al. reported the synthesis of (4R)-N-tBoc-4-tert-butyldimethylsilyloxy-n-pyroglutamic acid methyl ester (6), a possible precursor for the synthesis of the lactam form of (2R,4R)-monatin.17) Zhang et al. also reported the synthesis of (4S)-N-tBoc-4-tert-butyldimethylsilyloxy-3-methylglutamates, an antipode of (6).18) However, the alkylation of the lithium enolate of these compounds has not been examined. As such, we examined the utilization of (6) for the synthesis of (2R,4R)-monatin.19)

Results and Discussion

The synthetic sequence using commercially available cis-4-hydroxy-D-proline (2) as a starting material was performed following Zhang et al.18) (Chart 1). The conversion of 2 to (4R)-N-tBoc-cis-4-hydroxy-D-proline methyl ester (4) (81% yield, two steps) was followed by the protection of the alcohol moiety with tert-butyldimethylsilyl (TBDSMS) group to give (4R)-N-tBoc-cis-4-(tert-butyldimethylsilyloxy)-D-proline methyl ester (5) in 94% yield.20,21) The oxidation of 5 using ruthenium oxide and periodate (NaIO₄) gave 6 in 86% yield.22) A modification of Christiansen et al. was followed to generate tert-buty1 3-(bromomethyl)-1H-indole-1-carboxylate (10) starting from indole-3-carbaldehyde (7)19) (Chart 2). The usual
Boc protection method ((tBoc)₂O, CH₃CN) was applied to 7 to obtain tert-butyl 3-formyl-1H-indole-1-carboxylate (8), followed by the reduction of 8 with NaBH₄ to give tert-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (9) in 96% total yield.  

The synthesis of 10 required careful purification at the final stage because of its instability. Thus, the bromination of 9 was performed using carbon tetrabromide (CBr₄) and triphenylphosphine (PPh₃) to generate phosphorus tribromide in situ in CH₂Cl₂ at −20°C, followed by the removal of triphenylphosphine oxide by continuous crystallization to give 10 in 88% yield, which was stored in a refrigerator and used as soon as possible.

Next, regioselectivity and stereoselectivity in the alkylation of the lithium enolate of 6 were examined. Reaction sites for the alkylation of 6, i.e., C₂ or C₄, as well as the stereoselectivity in the alkylation of the enolate of 6 were of particular interest. Eventually, compound 6 was selectively enolized at C₄ using 1.2 eq of lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran (THF) at −78°C, and the enolate form was then reacted with 1.0 eq of 10 to furnish (4R)-N-tBoc-4-tert-butyl(dimethyl)silyloxy-4-(N-tBoc-3-indolylmethyl)-d-pyroglutamic acid methyl ester (11) in 72% yield after purification (Chart 3). There was slight improvement in the yield with the use of N,N'-dimethylpropyleneurea as a co-solvent. As expected from the reaction of the analogue lacking the 4-protected hydroxyl group, 15,16) the alkylation of 6 by 10 proceeded in a stereoselective manner. The stereochemistry at C₄ of 11 was confirmed after the transformation of 11 to the linear form of monatin. The relative trans configuration at the ring junctions (C₂, C₄) of 11 obtained by this alkylation coincided with the relative configuration of C₂ and C₄ of (2R,4R)-monatin. Therefore, the alkylation at C₄ of 6 proceeded in a stereoselective manner from the less hindered face of the pyroglutamic acid ring opposite from the methoxycarbonyl group at C₂. 12)

As the electrophile of this reaction, tert-butyl 3-(chloromethyl)-1H-indole-1-carboxylate, 25) easily obtainable from gramine in two steps without purification, was used instead of 10; however, no coupling product was obtained, probably because of its low reactivity. N-tBoc-gramine methiodide was prepared immediately before use from N-tBoc-gramine and methyl iodide following the preparation of N-trisopro-
The reaction of this compound gave a complex mixture; however, the desired product was obtained in about 10% yield after careful purification by silica gel chromatography.

To cleave the lactam ring, compound 11 was treated with LiOH in a mixture of isopropyl alcohol (iPrOH), THF, and H2O to give possible intermediate 12, the exact structure of which was not confirmed, but a part of the tBoc group on the indole ring appeared to be deprotected under basic conditions. To remove the TBDMS group and remaining tBoc group, 12, without purification, was treated with a mixture of 4N HCl–dioxane and formic acid to give (2R,4R)-monatin (1·HCl); however, HPLC analysis indicated the existence of a significant amount of its lactone (13·HCl) and a small amount (5 to 10%) of lactam (14). The distinctive structure of monatin is considered to be a cause of the facile formation of five-membered ring compounds under acidic conditions. Indeed, during our previous study on the stability of monatin, we found that monatin and its lactone were in equilibrium in strongly acidic aqueous solutions, which gradually converted to lactam. Therefore, it is suggested that a part of 14 originated from unreacted 11 in the ring-opening step and remaining 14 might be regenerated during deprotection under acidic conditions after ring cleavage by LiOH.

Nakamura et al. reported that the lactam form of monatin underwent ring opening to return to the linear form of monatin by hydrolysis with NaOH in refluxing aqueous ethanol for 3 h. Accordingly, a mixture of 1·HCl, 13·HCl, and 14 was treated with excess NaOH at 95°C in aqueous ethanol for 3 h to convert to the linear form of (2R,4R)-monatin sodium salt (1 sodium salt). The resulting solution was neutralized and desalted, and then, 1 sodium salt was recovered by precipitation
in aqueous ethanol in a 49% yield. In chiral HPLC analysis, (2R,4R)- and (2R,4S)-monatin were observed in a ratio of 98.2:2 accompanied by a small amount of lactam (14) (Figs. 1a, b). Therefore, product 1 was shown to be of high diastereoisomeric purity at the newly created asymmetric center.

When the order of the original conversion route was reversed, i.e., deprotection under acidic conditions followed by heating at reflux in ethanol with aqueous NaOH for 18h, the desired linear form of monatin was still obtained; however, compared with the original method, a larger number of impurities were detected by HPLC analysis.

Using a similar procedure, unsubstituted or substituted phenyl analogs of (2R,4R)-monatin (17–19) were prepared (Chart 4). Phenyl analog (17) was obtained using benzyl bromide as an electrophile in a modest total yield (31% total yield) and good stereoselectivity (>99%, Figs. 1c, d). Because of the low electrophilicity of 4-methoxybenzyl chloride and 3,5-dimethoxybenzyl chloride, the yields of analogs 18 and 19 were unsatisfactory, although excess LHMDS and electrophiles were used. Phenyl analogues 17–19 were accordingly faintly sweet because the indole moiety is considered to be indispensable to elicit the strong sweet taste in this series of compounds.

**Conclusion**

(2R,4R)-Monatin (1) was successfully synthesized with high optical purity, employing the regioselective and stereoselective alkylation of (4R)-N-Boc-4-tert-butyldimethylsilyloxy-3-(bromomethyl)-1H-indole-1-carboxylate (6) with tert-butyl 3-(bromomethyl)-1H-indole-1-carboxylate (10) to give (4R)-N-Boc-4-tert-butyldimethylsilyloxy-3-(N-Boc-3-indolylmethyl)-o-prolylglutamic acid methyl ester (11). This was followed by the hydrolysis of the lactam ring and deprotection.

**Experimental**

$^1$H-NMR spectra were obtained using Brucker Avance 400 (400MHz) and electrospray ionization (ESI)-MS spectra were obtained using Thermo Quest TSQ 700.

Analytical conditions for the determination of the optical purity of monatin stereoisomers: Column: Crownpack CR(+), 4x150 mm. Detection: UV 210 nm. Eluent: 1-aqueous perchloric acid (pH 1.9–12% methanol; 17–aqueous perchloric acid (pH 1.5). Flow rate: 1.2 mL/min. Temperature: 20°C.

(4R)-N-Boc-4-tert-Butyldimethylsilyloxy-o-prolylglutamic acid methyl ester (6) was obtained as a colorless oily substance in a total yield of 66% from cis-4-hydroxy-o-proline (2) in accordance with the method described in the literatures.18,19,22 tert-Butyl 3-(bromomethyl)-1H-indole-1-carboxylate (10) was obtained as a white solid in a total yield of 85% from indole-3-carbalddehyde (7) in accordance with the method described in the literatures.23,24

(4R)-N-Boc-4-tert-Butyldimethylsilyloxy-o-prolylglutamic Acid Methyl Ester (6)

$^1$H-NMR (CDCl₃) δ: 0.11 (3H, s), 0.16 (3H, s), 0.89 (9H, s), 1.50 (9H, s), 1.99 (1H, dt, J=7.0, 13.0 Hz), 2.57 (1H, dt, J=7.7, 13.0 Hz), 3.76 (3H, s), 4.28 (1H, t, J=7.4 Hz), 4.46 (1H, t, J=7.4 Hz). ESI-MS m/z: 374.61 (M+H)+, 396.59 (M+Na)+.

tert-Butyl 3-(Bromomethyl)-1H-indole-1-carboxylate (10)

$^1$H-NMR (CDCl₃) δ: 1.66 (9H, s), 4.69 (2H, s), 7.29–7.38 (2H, m), 7.44–7.50 (1H, m), 7.64–7.69 (2H, m), 8.13 (1H, d, J=7.8 Hz).

(4R)-N-Boc-4-tert-Butyldimethylsilyloxy-4-(N-Boc-3-indolylmethyl)-o-prolylglutamic Acid Methyl Ester (11)

LHMS was added (1.7 mol/L in THF, 29.10 mL, 50.34 mmol) to a stirred solution of compound 6 (15.67 g, 41.95 mmol) in anhydrous THF (60 mL) under an argon atmosphere at −78°C. The resulting solution was stirred at −78°C for 1h. A solution of compound 10 (13.01 g, 41.95 mmol) in anhydrous THF (20 mL) was added portionwise into the reaction solution; the solution was stirred at −78°C for 25 min and then warmed to room temperature (r.t.) and allowed to stir for 2h. The reaction was quenched with aqueous NH₄Cl (50 mL) and extracted with AcOEt (100 mL, thrice). Combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel 300g, n-hexane–AcOEt=20:1–4:1) to give 11 as a pale yellow foam (18.20 g, 30.19 mmol). The $^1$H-NMR spectrum showed a peak marked by a very small amount (several percent) of impurity beside the isomers of the compound.

3H-NMR (CDCl₃) δ: 0.14 (3H, s), 0.30 (3H, s), 0.87 (9H, s), 1.45 (9H, s), 1.66 (9H), 2.09 (1H, dd, J=4.5, 13.6 Hz), 2.42 (1H, d, dd, J=9.2, 13.6 Hz), 3.02 (1H, d, J=14.6 Hz), 3.19 (1H, d, J=14.6 Hz), 3.71 (3H, s), 4.16 (1H, dd, J=4.5, 9.2 Hz), 7.22–7.25 (1H, m), 7.31 (1H, t, J=7.1 Hz), 7.49–7.52 (2H, m), 8.17 (1H, brd, J=7.9 Hz). ESI-MS m/z: 626.07 (M+Na)+.

(2R,4R)-Monatin (1) Sodium Salt LiOH·H₂O (20.14 g, 480 mmol) was added to a solution of 11 (18.0 g, 29.86 mmol) in a mixed solvent of isopropyl alcohol (50 mL), THF (50 mL), and water (100 mL) cooled to 0°C. The solution was stirred at 0°C for 10 min, warmed to r.t., and stirred for 16 h. The solvent was evaporated in vacuo, and the residue was suspended in water (50 mL). The pH of the solution was then adjusted to approximately 3 with aqueous HCl (2n). The aqueous phase was extracted with AcOEt (80 mL, thrice). Combined organic layers were washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated to give a colorless foam (12, 15.3 g).

A solution of HCl (4n in dioxane, 40 mL) was added portionwise to a solution of the abovementioned residue in formic acid (40 mL) cooled to 0°C. The mixture was stirred at 0°C for 5 min, warmed to r.t., and stirred for 30 min. The mixture was concentrated in vacuo, and the residue was triturated and washed by Et₂O (30 mL) and then with AcOEt (30 mL) to give a yellow powder (1·HCl, 13·HCl, 14, 13.22 g).

A solution of the abovementioned residue in a mixed solvent of EtOH (160 mL) and aqueous NaOH (2 g, 40 mL) was heated at 95°C for 3 h, and the insoluble material was removed by filtration after cooling to r.t. The filtrate was concentrated in vacuo. The residue was dissolved in water (100 mL), and the solution was successively washed with AcOEt (50 mL) and Et₂O (50 mL). The solution was neutralized by the addition of Amberlite IR 120B AG (1+), filtered, and concentrated in vacuo. The residue was suspended in EtOH (50 mL), and the insoluble material (NaCl) was removed by filtration. The filtrate was concentrated in vacuo, and the residue was crystallized with aqueous EtOH (95%) at r.t. to give 1 sodium salt as a white crystal (4.64 g, 14.71 mmol). Analysis was conducted by HPLC using a chiral column and revealed the (2R,4R) and (2R,4S) forms of isomers having an integrated peak ratio of 98.2.

$^1$H-NMR (D₂O) δ: (sodium salt of (2R,4R)-monatin) 2.06 (1H, dd, J=11.6, 15.2 Hz), 2.68 (1H, dd, J=2.0, 15.2 Hz), 3.02 (1H, t, J=7.4 Hz), 7.22–7.25 (1H, m), 7.31 (1H, t, J=7.1 Hz), 7.49–7.52 (2H, m), 8.17 (1H, brd, J=7.9 Hz).
1H-NMR (D2O) δ: 2.38 (1H, dd, J = 10.7, 13.6 Hz), 2.92 (1H, dd, J = 9.8, 13.6 Hz), 3.17 (1H, dd, J = 9.8, 10.7 Hz), 3.37 (1H, dd, J = 2.6 Hz), 7.16 (1H, t, J = 6.9 Hz), 7.18 (1H, t, J = 8.2 Hz), 7.27 (1H, s), 7.46 (1H, d, J = 8.0 Hz), 7.68 (1H, d, J = 8.0 Hz). ESI-MS m/z: 275.51 (M+H)+.

(2R,4R)-2-Amino-2,3-dideoxy-4-C-(1H-indol-3-ymethyl)pyranylpentaric Acid 1,4-Lactone (13, Monatin Lactone) was obtained in an overall yield of 13.5% as a white solid. Analysis was conducted by HPLC using a chiral column and revealed only the (R) form of isomers having an integrated peak ratio of 99 : 1 or higher.

1H-NMR (D2O): (sodium salt of (2R,4R)-4-hydroxy-4-benzylglutamic acid) 1.95 (1H, dd, J = 11.7, 15.3 Hz), 2.56 (1H, d, J = 15.3 Hz), 2.81 (1H, d, J = 13.5 Hz), 3.07 (1H, d, J = 13.5 Hz), 3.55 (1H, d, J = 11.7 Hz), 7.19–7.31 (m, 5H). ESI-MS: 315.0937 (M+Na)+, 315.0957 (M+Na)+. 

(2R,4R)-4-Hydroxy-4-(1H-indol-3-ymethyl)-5-oxo-proline (14, Monatin Lactam) 1H-NMR (DMSO-d6) δ: 1.80 (1H, dd, J = 6.8, 13.0 Hz), 2.41 (1H, dd, J = 8.0, 13.0 Hz), 2.89 (1H, d, J = 14.1 Hz), 2.97 (1H, d, J = 14.1 Hz), 3.45 (1H, dd, J = 6.8, 8.0 Hz), 5.45 (1H, br s), 6.93–6.98 (1H, m), 7.04 (1H, t, J = 7.0 Hz), 7.16 (1H, d, J = 2.3 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.62 (1H, d, J = 8.0 Hz), 7.97 (1H, s), 10.88 (1H, brs). ESI-MS m/z: 275.06 (M+H)+.

N-terminal Butyldimethylsilyloxy-4-benzyl-D-pyroglutamic Acid Methyl Ester (15) To a stirred solution of 6 (1.09 g, 3.0 mmol) in anhydrous THF (10 mL) under an argon atmosphere at ~78°C was added LHMDS (1.7 mol/L in THF, 2.1 mL, 3.6 mmol). The resulting solution was stirred at ~78°C for 1h. Benzyl bromide (0.38 mL, 3.15 mmol) was added dropwise into the reaction solution, the solution was stirred at ~78°C for 25 min then warmed to r.t. and allowed to stir for 1.5h. The reaction was quenched with aqueous NH4Cl (10 mL) and extracted with AcOEt (20 mL). The aqueous layer was neutralized with aqueous NaOH (2 N) and Amberlite IR 120B AG (H+1) then filtered. The filtrate was concentrated in vacuo to about one fifth of volume and 20 mL of ethanol was added. The resulting crystals were collected by filtration and dried under reduced pressure to give 130 mg (0.47 mmol) of 17 sodium salt. Analysis was conducted by HPLC using a chiral column and revealed only the (2R,4R) and (2R,4S) forms of isomers having an integrated peak ratio of 99 : 1 or higher. 

1H-NMR (D2O): (sodium salt of (2R,4R)-4-hydroxy-4-benzylglutamic acid) 1.95 (1H, dd, J = 11.7, 15.3 Hz), 2.56 (1H, d, J = 15.3 Hz), 2.81 (1H, d, J = 13.5 Hz), 3.07 (1H, d, J = 13.5 Hz), 3.55 (1H, d, J = 11.7 Hz), 7.19–7.31 (m, 5H). ESI-MS: 315.0937 (M+Na)+, 315.0957 (M+Na)+. 

(2R,4R)-4-Hydroxy-4-(4-methoxybenzyl)glutamic Acid (18) Sodium Salt The same operation described for 17 was performed using 4-methoxy benzyl chloride, and 18 was obtained in an overall yield of 13.5% as a white solid.

1H-NMR (D2O): δ: 1.53 (1H, dd, J = 10.6, 14.3 Hz), 2.18 (1H, dd, J = 2.5, 14.3 Hz), 2.66 (1H, d, J = 13.8 Hz), 2.90 (1H, d, J = 13.8 Hz), 3.14 (1H, dd, J = 2.5, 10.6 Hz), 3.68 (3H, s), 6.79 (2H, m), 7.06 (2H, m). ESI-MS: 305.9 (M+Na)+, 281.8 (M–H)+.

(2R,4R)-4-Hydroxy-4-(3,5-dimethoxybenzyl)glutamic Acid (19) Sodium Salt The same operation described for 17 was performed using 3,5-dimethoxy benzyl chloride and 19 was obtained in an overall yield of 18.5% as a white solid.

1H-NMR (D2O): δ: 1.59 (1H, dd, J = 10.7, 14.3 Hz), 2.23 (1H, dd, J = 2.4, 14.3 Hz), 2.72 (1H, d, J = 13.5 Hz), 2.98 (1H, d, J = 13.5 Hz), 3.21 (1H, dd, J = 2.4, 10.7 Hz), 3.72 (6H, s), 6.38 (1H, m), 6.43 (2H, m). ESI-MS: 336.2 (M+Na)+, 318.1 (M–H)+.

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Conflict of Interest The author is an employee of Ajinomoto Co., Inc. and has no further conflicts of interest to declare.

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