Preparation of 7-Halo-indoles by Thallation of N-Formylindoline and Their Attempted Use for Synthesis of the Right-Hand Segment of Chloropeptin

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7-Substituted (Cl, Br, I) indoles were synthesized by using thallation of N-formylindoline as a key reaction. Two precursor tripeptides for the right-hand segment of chloropeptin were synthesized by using (R)-7′-iodo and 7′-bromotryptophans derived from each 7-substituted indole (I, Br) obtained by the above procedure.

Key words 7-substituted indole; thallation; formyl group; tripeptide

In 1994, chloropeptin (1) was isolated by Matsuzaki et al. from Streptomyces sp. WK-3490 together with complestatin (2) both as inhibitors of gp120-CD4 receptor (concentration causing 50% inhibition (IC_{50}) values of 2.0 and 3.3 mM for 1 and 2, respectively). The absolute stereostructure of chloropeptin was determined in 1996 by combination of acid hydrolysis, molecular dynamics and NMR spectroscopy. It is a bismacrocyclic heptapeptide having a biaryl ether and biphenyl moiety. Because of its unique structure together with interesting biological activity, 1, 2 and related compounds are an attractive target for synthesis. In 2003, Hoveyda et al. first reported an elegant total synthesis of 1.

We have been interested in the synthesis of 1 and 2 and already reported a synthesis of the left-hand segment of 1 and 2 and also synthesis of linear tripeptides which are key intermediates for the right-hand segment of 2. Now, we are working to develop a route for the right-hand segment of 1. We planned the synthesis of 3 as the right-hand segment of 1. Compound 3 is a 16-membered macrocyclic lactam consisting of (R)-4′-hydroxy-3′,5′-dichlorophenylglycine (E-ring), (R)-tryptophan (F-ring), (R)-4′-hydroxyphenylglycine (D-ring), and the D, E-rings and E, F-rings are each connected by a peptide bond whereas, the D, F rings are connected by a biaryl bond (Fig. 1).

The success of the synthesis of 3 depends upon how to get the (R)-7′-substituted tryptophan and how to connect the D, F rings by biaryl coupling. In this paper, at first, an effective route for the 7-substituted indoles by using thallation of N-formylindoline as a key reaction and also their conversion to the (R)-7′-substituted tryptophan using our method already reported are described. Next, an effective synthesis of two precursor tripeptides for 3 is described by using the obtained (R)-7′-bromo and 7′-iodotryptophan.

Results and Discussion

At first, effective synthesis of 7-substituted indoles was performed. The direct introduction of halogen into a tryptophan at the position of 2′ and 5′-C was already reported; however, selective halogenation directly at the position of 7′-C in tryptophan has not been reported. We planned the procedure for (R)-7′-substituted tryptophan using 7-substituted indole. Connection of a serine with it should give racemic N-acetyl-7′-substituted tryptophan, which should be followed by enzymatic resolution by D-aminoacylase to afford (R)-7′-substituted tryptophan.

The synthetic procedure of the 7-substituted indoles is as follows. 7-Substituted indoles were already synthesized by Somei et al. using N-acetyl indoline as a starting material and carrying out the thallation of it as a key reaction, followed by substitution reaction with halogen, removal of the acetyl group, dehydrogenation to afford halogeno indoles. Our procedure for 7-substituted indoles is a modification of the Somei method using N-formylindoline.

Considerable synthetic utility of thallium trifluoroacetate (TTFA) in organic chemistry has been reported up to date. Among them, there is an attractive report, in which Taylor et al. found that high ortho thallation occurred in substituted aromatic compounds such as benzoic acid, methyl benzoate. Also, they reported their use of the resulting arythallium ditrifluoroacetates with aqueous KI giving selectively ortho substituted aryl iodide (Fig. 2). Somei et al. also reported a regioselective synthetic method for 7-halogenoindoles by thallation at the 7-C position with TTFA chelating to an N-acetyl carbonyl group (Fig. 2). However, when the carbonyl...
group of N-acetyl is used for thallation, strong reaction condition is required for removal of the acetyl group, such as a strong base (40% NaOH). The selection of the functional group is important for effective use of this thallation method as a key reaction. Various functional groups such as COOH, COOMe, CH₂OH were used for regioselective thallation of substituted benzenes in the literature. However, the formyl group, which is expected more easily to be removed, has not been used as a functional group for thallation up to date, so we examined use of the N-formyl group to perform selective thallation at 7’-C in indoline to obtain 7-substituted indolines (Chart 1).

Three halogens (I, Br, Cl) and a hydroxyl group were examined to obtain 7-substituted indoles by thallation of N-formylindoline and successive synthesis of 7-iodo, bromo, chloro indoles was achieved as shown in Chart 1.

7-Bromoindole (8b) was obtained as follows. Indoline (3) was treated with HCOOH and EDCI (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide) in pyridine to give N-formyl derivative 4 in 94% yield. Thallation was performed by adding TTFA to the solution of 4 in TFA (trifluoroacetic acid) to afford thallium complex 5, which was treated with CuBr₂ in DMF at 135 °C to give the bromide 6b in 73% yield from 4. Alkaline hydrolysis of 6b by 20% NaOH at 80 °C for 30 min afforded indoline 7b in 94% yield. Dehydrogenation of 7b was carried out under a stream of oxygen gas in the presence of salcomine as a catalyst to give 7-bromoindole (8b) in 79% yield (total yield from 4: 54%). 7-Chloroindole (8a) was obtained from 4 in a similar manner except for using CuCl₂ at the step of the substitution reaction in 46% total yield from 4. 7-Iodoindole (8c) was also prepared in a similar manner as the above procedure. In this case, KI was used at the step of the substitution reaction using H₂O as a solvent and 10% NaOH was used at the step of the removal of the formyl group with ease. Thus the formyl group was removed more easily than an acetyl group (40% NaOH) and it will be removed with much more mild conditions using a weak base such as NaHCO₃ according to the literature.

Using the formyl group on thallation will serve to enlarge the utility of its method in compounds having an alkaline-sensitive functional group other than indolines.

Next, synthesis of 7-hydroxyindole was examined according to the procedure in a literature. Thallated complex 5 obtained from 4 in a similar way was treated by CuSO₄·5H₂O in DMF–H₂O to afford 6d in low yield (25%), which resulted in stopping further examination. Thus, three 7-halogenoindoles were obtained using a formyl group as a functional group for thallation.

Next, preparation of the (R)-7’-halogenotryptophan from 7-halogenoindole was carried out. The synthesis of (R)-7’-bromotryptophan ((R)-10b) and its Cbz derivative ((R)-11b) was already reported by us by using enzymatic resolution by l-aminoacylase and its procedure is shown in Chart 2. In this paper, (R)-7’-iodotryptophan was prepared according to our procedure. Addition of l-serine to 8c in the presence of Ac₂O in AcOH gave racemic N-acetyl tryptophan ((RS)-9c) in 84% yield. This was treated with D-aminoacylase in a similar way to D-aminoacylase afforded (S)-9c in 45% yield, which was converted to Cbz derivative (S)-12c.

The amino group of (R)-10c was protected by treatment with carbobenzyloxy chloride (Cbz-Cl) and 10% Na₂CO₃ in aqueous ether solution to afford (R)-11c in 88% yield (Chart 2).

Optical purity of (R)-10c was determined according to our recent report procedure same as (R)-7’-bromotryptophan and (R)-6’-iodotryptophan (Chart 3). Compound (R)-11c was condensed with (R)-(+)-phenylethylamine using DECI and hydroxy-benzotriazole (HOBt) to afford amide (R)-12c as a single product in 65% yield and none of its diastereomer (S)-12c was obtained. Compound (S)-12c was synthesized as follows. Enzymatic optical resolution of (RS)-9c using l-aminoacylase in a similar way to l-aminoacylase afforded (S)-10c in 45% yield, which was converted to Cbz derivative
(S)-11c in 86% yield, then this was transformed into phenylethylamide (S)-12c in 59% yield. These results proved enzymatic resolution proceeded enantiomerically to give optically pure amino acid (R)-10c, which is the same case as that of 6'-iodotryptophan5), 6'-bromo and 7'-bromotryptophan.6) Thus a new amino acid (R)-10c was obtained effectively.

Next, synthesis of two precursors (16), (22) for the right-hand segment of cholopeptin by using the amino acid (R)-11b and (R)-11c was examined. The synthesis of 16 from (R)-11b was performed as shown in Chart 4. The precursor 16 should be utilized for 3 by biaryl coupling using organic metals as a catalyst. Dipeptide 15 was already obtained by us using compound 13 and 14.5) The synthetic method and detailed experimental procedure of compounds 13, 14 and 15 were already described in our preliminary paper.5) The Boc group of dipeptide 15 was removed by TFA, followed by neutralization with NMM (N-methylmorpholine) to afford a dipeptideamine as an intermediate, which was condensed with (R)-11b by treatment with EDCI and HOBT (hydroxy benzotriazole) to give tripeptide 16 in 76% total yield from 15. Intramolecular carbon–carbon couplings between biaryl halide by using an organometallic catalyst of Ni such as (Ph3P)2NiCl2 were successively achieved for the synthesis of Vancomycin14) and a model compound in Kistamycin.15) Intramolecular cyclization of a precursor 16 using (Ph3P)2NiCl2 as a catalyst, Zn as an additive and Ph3P as a ligand was performed according to the procedure5) however, cyclic product 3 could not be obtained in spite of alternation of the amount of the catalyst (0.04—1.8 equivalent), solvent (DMF, THF, HMPA), regrettably. More reactive condition should be needed to achieve carbon–carbon coupling between biaryl halide of 16, because fairly strong steric interaction between the tryptophan moiety and phenylglycine is considered. Next, another precursor 22 for 3 was planned as shown in Chart 5. The precursor 22 should be utilized for macrocyclic lactamization at the last step to provide 3. The precursor 22 was prepared by using (R)-11c. The reason for using 7'-iodotryptophan is that aryl iodide is a more strong coupling reagent than aryl bromide in Stille coupling. The synthesis of 3',5'-dichlorophenylglycine tert-butyl ester (17) was already reported by us.5) Connection of 17 to (R)-11c by using FDPP in the presence of iPr2NET provided dipeptide 18 in 56% yield. The phenol was protected to afford methyl ether 19 by TM-SCHN2 in 94% yield. The synthesis of tributylstann derivative 20, which is a key compound for Stille coupling, was also already described in our paper.5) Coupling reaction between 20 and 19 was carried out at the condition of Stille coupling using Pd(0)(dba)3·CHCl35,16,17) as a catalyst, Cul, as an additive, Ph3As as a ligand, iPr2NET as a base to give biarylic tripeptide 21 in 39% yield, successively. The Boc group of 21 was removed by TFA–CHCl3 solution (1:1) to provide a precursor 22 for 3 quantitatively. Detailed examination of the reaction condition should be needed for macrolac-
tization, which is a subject for future study.

In conclusion, 7-substituted (Cl, Br, I) indoles were synthesized using thallation of N-formylindoline as a key reaction according to a modified procedure in the literature. In this paper, the formyl group was newly proved to be a useful functional group for thallation. In addition, two precursor tripeptides for the right-hand segment of chloropeptin were synthesized by using 7-ido and 7'-bromotryptophans derived from each 7'-substituted indole (I, Br) which were obtained by the above procedure.

Experimental

General Procedures Melting points were taken on a Yanagimoto hot stage and are uncorrected. Optical rotations were measured on a JASCO (art. 1.09385, Merck). 2M Solution in CHCl3 (Merck). Flash column chromatography was done using Silica gel 60 (100 ml). IR (KBr) max cm⁻¹: 550, 670, 1500, 1600 (arom), 3400 (NH). 1H-NMR (400 MHz) /H11005: 6.59 (1H, dd, J=8.5 Hz, 2-H), 6.56 (1H, d, J=9.5 Hz, 5-H), 7.01 (1H, d, J=7.5, 10-H, 4.0 Hz), 7.15 (1H, dd, J=1.0, 7.5 Hz, 6-H), 7.40 (1H, s, 1-H). IR (KBr) νmax cm⁻¹: 530 (Ar-Br), 1505, 1610 (arom), 3450 (NH). 1H-NMR (300 MHz) δH: 3.14 (2H, t, J=8.5 Hz, 3-H), 3.61 (2H, t, J=8.5 Hz, 2-H), 6.56 (1H, d, J=9.5 Hz, 5-H), 7.02 (1H, d, J=7.5, 5-H), 7.25 (1H, dd, J=1.0, 7.5 Hz, 6-H), 7.40 (1H, s, 1-H). 13C-NMR (100 MHz) δC: 135.80 (s, 3a-C), 137.75 (s, 7a-C). HR-EI-MS m/z: 196.9840 [M]+, Calcd for C9H8ONBr79: 196.9842 [M]+.

7-Br-Indole (6b) To a solution of 7b (1.24 g, 6.30 mmol) in MeOH (250 ml) was added sodium (205 mg, 0.630 mmol). After the mixture was stirred in a stream of oxygen gas for 3 h at room temperature, the reaction mixture was concentrated in vacuo to afford a black oil (1.2 g, 94%) as light brown oil. The residue was purified by flash column chromatography (hexane/AcOEt = 2: 1) to give 6b (1.69 g, 73%) as light purple crystals. 

IR (KBr): 550 (Ar-Br), 1500, 1600 (arom), 3400 (NH). 1H-NMR (400 MHz) /H11005: 6.59 (1H, dd, J=8.5 Hz, 2-H), 6.56 (1H, d, J=9.5 Hz, 5-H), 7.01 (1H, d, J=7.5, 10-H, 4.0 Hz), 7.15 (1H, dd, J=1.0, 15-H, 5-H), 7.25 (1H, t, J=7.5, 6-H), 7.40 (1H, s, 1-H). IR (KBr) νmax cm⁻¹: 530 (Ar-Br), 1505, 1610 (arom), 3450 (NH). 1H-NMR (300 MHz) δH: 3.14 (2H, t, J=8.5 Hz, 3-H), 3.61 (2H, t, J=8.5 Hz, 2-H), 6.56 (1H, d, J=9.5 Hz, 5-H), 7.02 (1H, d, J=7.5, 5-H), 7.25 (1H, dd, J=1.0, 7.5 Hz, 6-H), 7.40 (1H, s, 1-H). 13C-NMR (100 MHz) δC: 135.80 (s, 3a-C), 137.75 (s, 7a-C). HR-EI-MS m/z: 196.9840 [M]+, Calcd for C9H8ONBr79: 196.9842 [M]+.
HR-EL-MS m/z: 151.0196 [M]+, Calcd for C7H7NO2; 151.0189 [M]+.

**N-Formyl-7-iodoindoline (6c)** A mixture of 4 (1.00 g, 6.60 mmol) and TFTA (7.3 g, 13.6 mmol) in TFA (28 ml) was stirred for 24 h under argon at room temperature. The reaction mixture was concentrated in vacuo by azotropic distillation with benzene (10 ml×5) to provide 5 as tarry oil. The residue was dissolved in a solution of CH2Cl2/Methanol (3:2:1). mp: 119.68 (d, 4.5 Hz, 2-H), 7.53 (1H, d, J=7.5 Hz, 6-H), 7.68 (1H, d, J=7.5 Hz, 4'-H). 1H-NMR (75 MHz, acetone-d6) δ: 22.6 (q, J=4.5, 9.0 Hz, 2-d), 6.85 (1H, d, J=7.5 Hz, 5-H), 7.29 (1H, s, 2-H), 7.51 (1H, d, J=7.5 Hz, 6-H), 7.73 (1H, d, J=7.5 Hz, 4'-H).

**4-Carbobenzyloxy-7-iodoindoline (10c)** To a solution of (9S)-9c (1.8 g, 4.84 mmol) and n-aminoacylase (576 g) in phosphate buffer (227 ml, pH 7.4) and 10% aqueous Na2CO3 (4.0 ml) was added CoCl2·6H2O (3 mg). After the solution was shaken for 24 h at 37 °C, the reaction mixture was adjusted at pH 5 with 1 N HCl, then filtered and dried to provide 10c (258.6 mg, 88%) as white crystals. The water layer was purified by column chromatography (SEPAPrep SP207, H2O: 300 ml) to provide (R)-10c (717 mg, 45%) as white powder.


**N-Formyl-7-hydroxyindoline (6d)** To a solution of 6d (502 mg, 3.00 mmol) in TFA (15 ml) was added a solution of TFTA (3.7 g, 6.80 mmol) in TFA (8 ml) (0.8 ml×4). After the mixture was stirred for 24 h at room temperature, the reaction mixture was concentrated in vacuo by azotropic distillation with a solution of benzene (20 ml×3) to provide 5 as a black tarry oil. The residue was dissolved in a mixture of DMF/H2O (1:1, 15 ml) and CuSO4·5H2O (3.40 g, 13.6 mmol) was added to the mixture. After the mixture was stirred for 5 h at 120 °C, then stirred for 5 d at room temperature under argon. The reaction mixture was concentrated in vacuo and the residue was dissolved in a mixture of CHCl3/Methanol=95:5 (15 ml) and saturated NaCl (20 ml). The mixture was filtered off through celite pad. The filtrate was concentrated in vacuo to afford (R)‑11c (285.6 mg, 88%) as white crystals. The water layer was purified by column chromatography (SEPAPrep SP207, H2O: 300 mlMeOH: 600 ml) to provide (S)-11c (120 mg, 45%) as white powder. HR-FAB-MS m/z: 464.0211 [M]+, Calcd for C24H19NO4: 464.0206 [M]+.

**S-7-Iodotryptophan (10c)** To a solution of (S)-9c (1.8 g, 4.84 mmol) and n-aminoacylase (576 g) in phosphate buffer (227 ml, pH 7.4) was added CoCl2·6H2O (3 mg). After the solution was shaken for 24 h at 37 °C, the reaction mixture was adjusted at pH 5 with 1 N HCl, then filtered and dried to provide 10c (258.6 mg, 88%) as white crystals. The water layer was purified by column chromatography (SEPAPrep SP207, H2O: 300 mlMeOH: 600 ml) to provide (S)-11c (120 mg, 45%) as white powder. HR-FAB-MS m/z: 464.0211 [M]+, Calcd for C24H19NO4: 464.0206 [M]+. 

**S-4-Carbobenzyloxy-7-iodoindoline (10c)** To a solution of (S)-9c (1.8 g, 4.84 mmol) and n-aminoacylase (576 g) in phosphate buffer (227 ml, pH 7.4) was added CoCl2·6H2O (3 mg). After the mixture was stirred for 24 h at 115 °C, it was acidified with 10% HCl (pH 3). Resulting precipitates were filtered off, washed with water (2 ml×2) and dried to provide (R)-11c (285.6 mg, 88%) as white crystals. The water layer was purified by column chromatography (SEPAPrep SP207, H2O: 300 mlMeOH: 600 ml) to provide (S)-11c (120 mg, 45%) as white powder. HR-FAB-MS m/z: 464.0211 [M]+, Calcd for C24H19NO4: 464.0206 [M]+.
vacuo. Resorbed residue was purified by preparative TLC (CHCl3:MeOH=5:1). mp: 193–195°C. \[\text{RF}^{0.84} (\text{CHCl3}:\text{MeOH}=5:1). \text{mp: 193–195°C.} \]

**(S)-N-Carboxybzyloxy-7'-iodothyptphan (R=)-Phenylalanilamide (5z-12c)** To a solution of 5z-11c (20 mg, 0.043 mmol) in THF (1 ml) were added (R=)-phenylalanine (5.2 mg, 0.043 mmol), EDCI (8.3 mg, 0.043 mmol), and HOBT (5.8 mg, 0.043 mmol). The mixture was stirred for 2h at room temperature under argon, the reaction mixture was washed with 10% citric acid (5 ml), and the solution was extracted with 10% KF (20 ml) and 10% Na2SO4, concentrated in vacuo. The residue was purified by column chromatography (silica gel, CHCl3:MeOH=50:1) to afford 5z-12c (14 mg, 59%) as white brown powder.

**Acetic Acid tert-Butyl Ester (21)** To a solution of 20 (65 mg, 0.092 mmol), 19 (138 mg, 0.183 mmol) in DMF (6.5 ml) were added Pd2(dba)3CHCl3 (19 mg, 0.024 mmol) in TFA (0.6 ml) was stirred for 7h (at 5°C under argon). After the reaction mixture was stirred for 2h at room temperature under argon, the reaction mixture was diluted with ether (100 ml), then the solution was washed with saturated NH4Cl (20 ml × 2), 10% HF (20 ml × 3), dried over Na2SO4, concentrated in vacuo. The residue was purified by preparative TLC (CHCl3) to give 21 (36.7 mg, 39%) as light brown powder. 

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\[\text{RF}^{0.24} (c=0.5, \text{CHCl3}). \text{H-NMR (400 MHz)} \text{d}_{2.2} 1.35 (9H, s, Bu), 1.44 (9H, s, Boc), 3.22 (1H, dd, J=7.5, 15.0 Hz, Trp 3-Ha), 3.27, 3.29 (total 3H, s, CH2), 3.79 (3H, s, CH2), 5.11, 5.15 (total 2H, each d, J=14.0 Hz, benzylic-CH), 5.13 (1H, hidden, CHPG 2-H), 5.38 (1H, d, J=7.5 Hz, Trp NHCO), 6.07 (1H, br, Trp 2-H), 6.83 (1H, t, J=7.7 Hz, Trp 5'-H), 6.90 (1H, br, CHPG NHCO), 7.00 (1H, d, J=2.0 Hz, Trp 2'-H), 7.10 (2H, s, CHPG 2', 6'-H), 7.34 (5H, m, benzylic-arnom SH), 7.54 (1H, d, J=7.5 Hz, Trp 4'-H), 7.55 (1H, d, J=7.5 Hz, Trp 6'-H), 8.18 (1H, s, Trp 1'-H). 

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3.4 h at 0 °C under argon. The reaction mixture was concentrated in vacuo to remove TFA by azeotropic distillation with benzene to afford 22 quantitatively.

Rf: 0.30 (CHCl$_3$: MeOH=5:1). $^1$H-NMR (400 MHz, CD$_3$OD) δ$_H$: 3.13 (1H, dd, J/H$_1$ 8.0, 14.5 Hz, Trp 3-Ha), 3.31 (1H, dd, J/H$_1$ 6.0, 14.5 Hz, Trp 3-Ha), 3.23 (3H, s, IHPG OMe), 3.83 (3H, COOMe), 3.86 (3H, s, OMe), 4.56 (1H, dd, J/H$_1$ 6.5, 7.7 Hz, Trp 2-H), 5.04 (2H, s, benzyl CH$_2$), 5.23 (1H, s, IHPG 2-H), 5.34 (1H, br s, CHPG 2-H), 7.14 (1H, d, J/H$_1$ 3.0 Hz, Trp 2-H), 7.14 (1H, hidden Trp 5-H), 7.29 (5H, benzyl arom-H), 7.44 (2H, br s, CHPG 2-), 6.6 (J/H$_1$ 2.5 Hz, IHPG 6-H), 7.70 (2H, m, Trp 4-H), 7.99 (1H, d, J=2.0 Hz, IHPG 2-H). $^{13}$C-NMR (100 MHz, CD$_3$OD) δ$_C$: 54.20 (q, COOMe), 56.25 (d, IHPG 2-C), 57.00 (d, CHPG 2-C), 57.18 (d, Trp 2-C), 60.89 (t, Trp 3-C), 61.22 (q, IHPG OMe), 61.22 (q, CHPG OMe), 67.71 (t, benzyl CH$_2$), 94.50 (s, IHPG 5-C), 111.32 (s, Trp 3'-C, Trp 3a'-C), 120.25 (d, Trp 5'-C), 120.25 (d, Trp 6', 4'-C), 122.25 (s, Trp 7'-C), 123.62 (d, Trp 5'-C), 125.61 (d, Trp 2'-C), 128.77, 128.85, 129.27, 129.32, 129.39 (each d, benzyl-arom-C), 129.45, 129.54 (each d, CHPG 2-, 6'-C), 130.01, 130.41 (each s, CHPG 3', 5'-C), 130.72 (s, IHPG 3-C), 133.44 (d, IHPG 6'-C), 135.13 (s, Trp 7a'-C), 135.20 (s, IHPG 1-C), 136.60 (d, IHPG 4'-C), 153.33 (CHPG 4'-C), 158.33 (s, NHCOO), 160.16 (s, IHPG 4'-C), 169.80 (s, COOMe), 172.31 (s, COOH), 173.95 (s, Trp 1-C). HR-FAB-MS m/z: 889.0934 [M+H]+, Calcd for C$_{38}$H$_{56}$O$_9$N$_4$Cl$_3$52I: 889.0904 [M+H]+.

References