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AN IMPROVED SYNTHESIS OF OPTICALLY PURE (*R*)-4-BROMO-*N*-METHYL-1-TOSYLTRYPTOPHAN DERIVATIVE, A KEY INTERMEDIATE IN THE SYNTHESIS OF ERGOT ALKALOIDS

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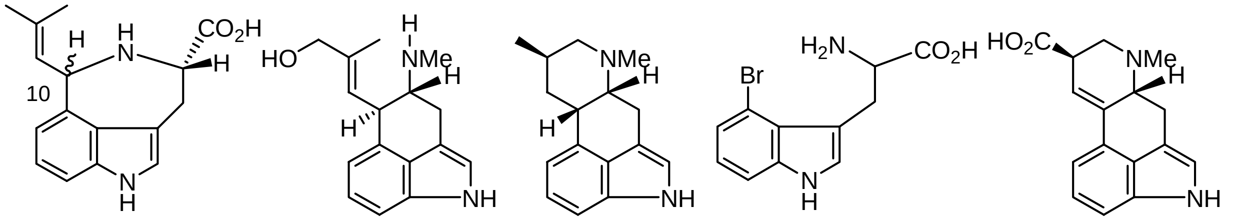
Abstract – Optically pure (*R*)-*N*-Boc- or (*R*)-Cbz-4-bromo-*N*-methyl-1-tosyltryptophan methyl ester (**11a** or **b**) was synthesized in 2 steps from (*R*)-*N*-acetyl-4-bromo-1-tosyltryptophan methyl ester (**7**) by simultaneous *N*-methylation and deacetylation using methyl trifluoromethanesulfonate (TfOMe) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).

INTRODUCTION

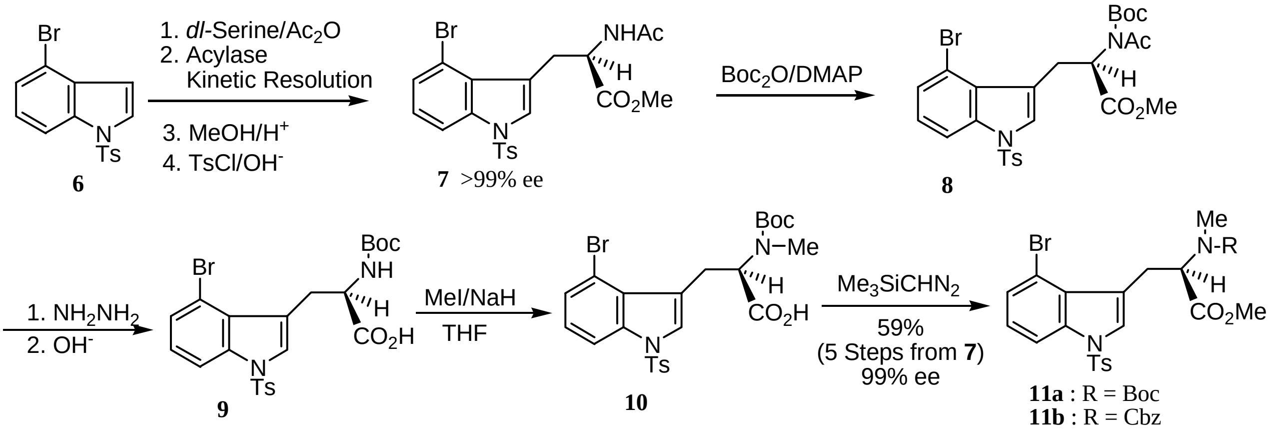
During the investigation of total synthesis of optically active ergot alkaloids such as clavicipitic acids (**1**),[1] chanoclavine-I (**2**)[2] and costaclavine (**3**)[3] through 4-bromotryptophan (**4**), a large quantity of (*R*)-*N*-Boc-4-bromo- *N*-methyl-1-tosyltryptophan methyl ester (**11a**) was needed as an important intermediate, and we developed[4] a synthetic method of **11a** through optically pure *N*-acetyl-4-bromo-1-tosyltryptophan methyl ester (**7**), which was prepared from 4-bromoindole (**6**) with *dl*-serine by 4 steps (Scheme 1). However, this route is rather lengthy involving the hydrolysis and esterification steps of carboxylic acid during the *N*-methylation of **9** for suppressing the racemization, and the yield was only moderate (56% from **7**). Furthermore, Cbz-protected *N*-methyl derivative (**11b**), which was also required for our

Figure 1



Clavicipitic Acid (**1**) Chanoclavine-I (**2**) Costaclavine (**3**) 4-Bromotryptophan (**4**) Lysergic Acid (**5**)

Scheme 1 Synthetic Route for *N*-Boc-4-bromo-*N*-methyl-1-tosyl-D-tryptophan methyl ester (**11**)



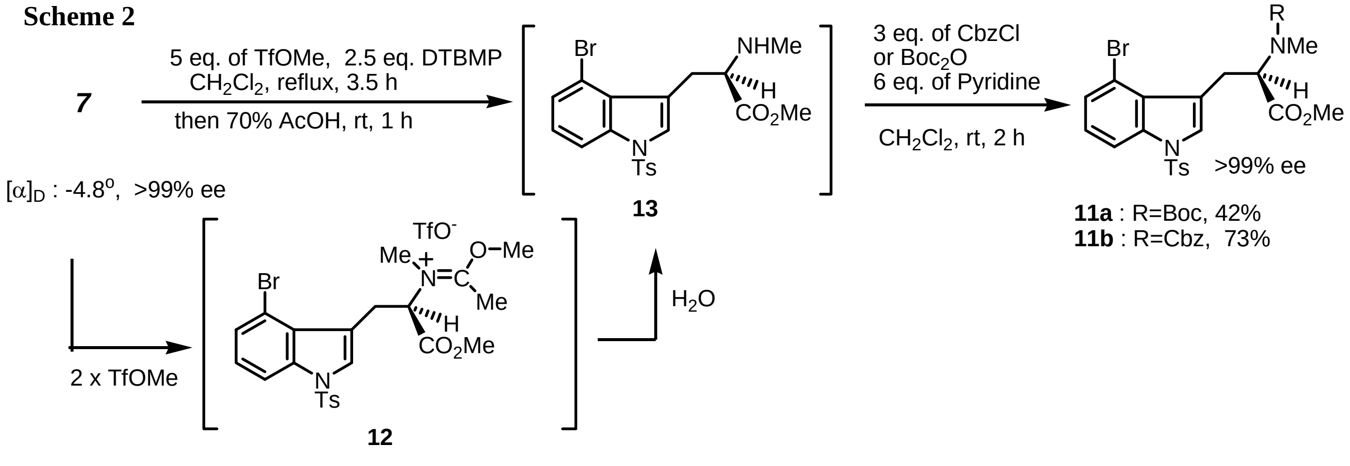
investigation of the total synthesis of lysergic acid (**5**), could not be obtained by this route, because the reaction of **7** with Cbz-Cl or Cbz_2O did not proceed. In the present paper, we report an improved practical synthesis of optically pure **11a** and **b** from **7**.

RESULTS AND DISCUSSION

Arnarp reported[5] the simultaneous methylation and deacetylation of *N*-acetylglucosamine using methyl trifluoromethanesulfonate (TfOMe) as a methylating reagent in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), and Sakamoto applied[6] this method to obtain the racemic *N*-Boc-*N*-methypeptide from an *N*-acetyl protected peptide.

(*R*)-*N*-Acetyl-4-bromo-1-tosyltryptophan methyl ester (**7**) was treated with TfOMe in CH_2Cl_2 according to Sakamoto's report. Although large excess of expensive DTBMP (20 eq.) was used in the literature, we found that 2.5 eq. of DTBMP was enough to promote simultaneous methylation and deacetylation. At first, *N*,*O*-dimethylation should occurre to form imminium salt (**12**), which was unstable and easily hydrolyzed by the addition of 70% aq. AcOH to give *N*-methylamine (**13**). The formation of **13** was

Scheme 2



confirmed by NMR spectrum after isolation by repeated silica gel column chromatography. The crude **13,** which was contaminated[7] with TfOH and DTBMP after work-up, was reacted with Boc_2O or CbzCl to give the desired product (**11a** or **11b**). Although the reaction with CbzCl gave **11b** in 73% yield from **7**, the reaction with Boc_2O gave **11a** in much lower yield (42%). It was noteworthy that this reaction was racemization-free, as optical purity of the products was >99% ee. The reason for the lower yield of **11a** was considered to be the acidic condition during the reaction of **13** with Boc_2O, because contaminated TfOH in crude amine (**13**) could not be neutralized with pyridine that was used during the second step.[8] Therefore, instead of pyridine, DTBMP was used as a base in the second step. Although the yield of **11a** was increased to 65%, considerable racemization occurred (82% ee) for stronger basicity of DTBMP. The present method is not only a two-step reaction giving better yield than the 5-step route (Scheme 1), but also can give Cbz-derivative (**11b**) in optically pure form. We are now studying the total synthesis of optically active lysergic acid (**5**) from Cbz-protected derivative (**11b**) as the starting material.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Optical rotations were recorded on a JASCO DIP-1000 instrument. IR spectra were performed with a JASCO FT/IR-230 spectrophotometer. ^{1}H-NMR spectra were taken with a JEOL EX-400 spectrometer in chloroform-d_3 ($CDCl_3$). Chemical shifts of protons are referenced to tetramethylsilane as an internal standard, or the residual chloroform (7.26 ppm) was used as the internal reference when measured in $CDCl_3$. MS spectra were measured on a JEOL JMS-AM II 50. TLC was performed on Merck 25 DC-Platten 20×20 cm Kieselgel 60 F_{254} (Art 5715). In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise indicated.

Isolation of (dl)-4-Bromo-N-methyl-1-tosyltryptophan Methyl Ester (13)

A mixture of *dl*-*N*-acetyl-4-bromo-1-tosyltryptophan methyl ester (**7**, 101 mg, 0.24 mmol), 2,6-di-(*tert*-butyl)-4-methylpyridine (DTBMP, 857 mg, 4.18 mmol) and CH_2Cl_2 (4.7 mL) in a two-necked flask was stirred under Ar atmosphere at rt. After addition of methyl trifluoromethanesulfonate (TfOMe, 120 μL, 1.03 mmol), the reaction mixture was refluxed for 3.5 h, then 70% aq. AcOH (4.7 mL) was added to the mixture at rt, and stirred for 1 h. After addition of conc. HCl, the aqueous layer was extracted with AcOEt for 3 times. The combined organic layer was washed with sat. NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resulted pale brown residue (294 mg) was subjected silica gel column chromatography with (*n*-Hexane:AcOEt=1:1) repeatedly to give crude amine (**13**) (59.5 mg) as pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.37 (3H, s), 3.20 (1H, dd, J = 10.8, 8.0 Hz), 3.30 (1H, dd, J = 8.0, 6.8 Hz), 3.62 (3H, s), 3.64 (1H, t), 6.90 (1H, br s), 7.12 (1H, t, *J* = 8.0 Hz), 7.22 (1H, *J* = 8.4 Hz), 7.36 (2H, d, *J* = 5.2 Hz), 7.46 (1H, s), 7.72 (2H, d, *J* = 8.4 Hz), 7.96 (1H, d, *J* = 8.4 Hz).

Synthesis of (R)-4-Bromo-N-tert-butoxycarbonyl-N-methyl-1-tosyltryptophan Methyl Ester (R-11a)

A mixture of (*R*)-*N*-acetyl-4-bromo-1-tosyltryptophan methyl ester [(*R*)-**7**, 100 mg, 0.20 mmol], DTBMP (104 mg, 0.51 mmol) and CH_2Cl_2 (5.0 mL) in two-necked flask was stirred under Ar atmosphere at rt. TfOMe (115 μL, 1.0 mmol) was added to this mixture and the reaction mixture was refluxed for 3.5 h. After cooling to rt, 70% aq. AcOH (5.0 mL) was added and the whole was stirred for 1 h. Then, work-up was done as above-mentioned to give the crude amine (**13**) as a brown oil (174 mg), which was divided into two portions (109 mg and 64 mg).

i) DTBMT as a Base

To the crude amine (**13,** 109 mg) in CH_2Cl_2 (2.5 mL) were added DTBMP (197 mg, 0.96 mmol) and Boc_2O (295 μL, 1.28 mmol). Then, the reaction mixture was stirred for 14 h at rt. After evaporation of the solvent, the residue was directly subjected to silica gel chromatography (benzene : AcOEt = 80 : 1) to give the desired product [(*R*)-**11a**] as a colorless viscous oil (47 mg, 65% from **7**), of which optical purity was 82% ee based on HPLC using chiral column (Daicel Chiralcel OD-H, *n*-hexane : *i*-PrOH = 50 : 1). All spectral data were identical with those of reported ones. [3]

ii) Pyridine as a Base

To the crude amine (**13,** 64 mg) in CH_2Cl_2 (1.8 mL) were added pyridine (125 μL, 1.5 mmol) and Boc_2O (175 μL, 0.75 mmol). Then, the reaction mixture was stirred for 14 h at rt. After evaporation of the solvent, the residue was directly subjected to silica gel chromatography (benzene : AcOEt = 80 : 1) to give the desired product [(*R*)-**11a**] as colorless viscous oil (18.9 mg, 46% from **7**), of which optical purity was more than 95% ee based on HPLC using chiral column (Daicel Chiralcel OD-H, *n*-hexane : *i*-PrOH = 50 : 1). $[\alpha]^{23}_D$ +34.2° (*c*= 0.64, $CHCl_3$) [lit.,[3] $[\alpha]^{23}_D$ +35° (*c*= 2.14, $CHCl_3$)]. All spectral data were identical with those of reported ones. [3]

Synthesis of (R)-4-Bromo-N-carbobenzyloxy-N-methyl-1-tosyltryptophan Methyl Ester (R-11b)

A mixture of (*R*)-N-acetyl-4-bromo-1-tosyltryptophan methyl ester [(*R*)-**7**, 50 mg, 0.10 mmol], DTBMP (52 mg, 0.25 mmol) and CH_2Cl_2 (2.5 mL) in a two-necked flask was stirred under Ar atmosphere at rt. TfOMe (57 μL, 0.51 mmol) was added to this mixture and the reaction mixture was refluxed for 3.5 h. After cooling to rt, 70% aq. AcOH (2.5 mL) was added and the whole was stirred for 1 h. Then, work-up was done as above-mentioned to give the crude amine (**13**) as a brown oil (83 mg), which was dissolved in CH_2Cl_2 (2.5 mL) and pyridine (50 μL, 0.61 mmol). Then, CbzCl (46 μL, 3.0 mmol) was added to the mixture, which was stirred for 2 h at rt. Then, 10% HCl (1 mL) and H_2O (20 mL) were added and the mixture was extracted with CH_2Cl_2 3 times. The combined organic layer was washed with sat. aq. NaCl and dried over $MgSO_4$. After evaporation of the solvent, the obtained crude oil was subjected to silica gel chromatography (benzene : AcOEt = 40 : 1) to give the desired product [(*R*)-**11b**] as a colorless viscous oil (44 mg, 73%), of which optical purity was 99% ee based on HPLC using chiral column (Daicel Chiralcel OD-H, *n*-hexane : *i*-PrOH = 50 : 1). $[\alpha]^{23}_{D}$ +34° (*c*= 0.21, $CHCl_3$). IR (neat) cm^{-1}: 1740, 1703. ^{1}H-NMR (DMSO-d_6, 100 ^{o}C) δ: 2.28 (3H, s), 2.77 (3H, s), 3.31 (1H, dd, *J* = 15.2, 11.5 Hz), 3.63 (1H, dd, *J* = 15.2, 4.8 Hz), 3.65 (3H, s), 4.7 - 4.9 (2H, m), 5.05 (1H, dd, *J* = 4.8, 10.8 Hz), 7.10 (1H, br s), 7.20 (1H, t, *J* = 8.0 Hz), 7.22 (1H, br s), 7.30 (2H, d, *J* = 8.0 Hz), 7.41 (1H, d, *J* = 7.2 Hz), 7.61 (1H, s), 7.70 (2H, d, *J* = 8.0 Hz), 7.92 (1H, d, *J* = 8.0 Hz). ^{13}C-NMR (DMSO-d_6, 100^{o}C) δ: 20.5, 24.5, 31.4, 51.7, 59.1, 66.1, 112.4, 113.1, 117.6, 124.8, 125.5, 126.1, 126.6, 127.2, 127.5, 127.6, 127.7, 127.8, 128.4, 129.8, 133.7, 135.5, 145.2, 170.0. EI–MS *m/z*: (%) 598 (M^+, 45), 596 (M^+-2, 40), 57 (100),. HRMS (EI-MS) Calcd for $C_{28}H_{27}N_2O_6BrS$: 598.0772 (M^+), 600.0753 (M^++2), Found: 598.0742 (M^+), 600.0753 (M^++2).

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7 The amine could not be extracted to an acidic aqueous solution during the work up, because the salt of amine (**13** or DTBMP) with trifluoromethansulfonic acid might be extremely soluble in an organic solvent.

8 Since the molar ratio of TfOMe and DTBMP in the first step is 7 : 2, excess TfOH would acidify the reaction mixture.