Synthesis of (-)-trachelanthamidine using a single electron transfer reaction in 1,4-dimethylpiperazine

Synthesis of (–)-trachelanthamidine using a single electron transfer reaction in 1,4-dimethylpiperazine

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Abstract

Synthesis of (–)-trachelanthamidine, one of pyrrolizidine alkaloids, has been achieved by using a single electron transfer reaction of 2-(2-acetoxyethenyl)-*N*-(trichloroacetyl)pyrrolidine in boiling 1,4-dimethylpiperazine as the key step.

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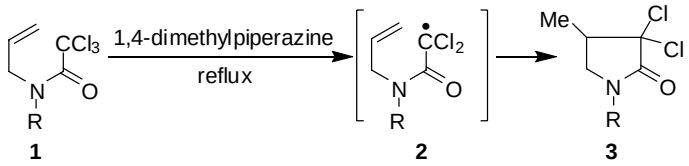
1. Introduction

We previously reported that *N*-allylic trichloroacetamides **1** underwent radical cyclization in boiling 1,4-dimethylpiperazine to give 5-membered lactams **3** in good yields.[1] This cyclization can be explained as proceeding via a single electron transfer (SET) reaction from the nitrogen atom of 1,4-dimethylpiperazine used as a solvent to the substrates **1** followed by an elimination of chloride anion to give radical **2**. This method is highly promising for the following reasons: 1) the reaction is completed in a very short time (usually within 15 min), 2) 1,4-dimethylpiperazine used as a solvent can be easily removed by an evaporator, and 3) a combination of a radical initiator such as azobis(isobutyronitrile) (AIBN) and a hydrogen atom source such as Bu_3SnH is not required for this radical cyclization.



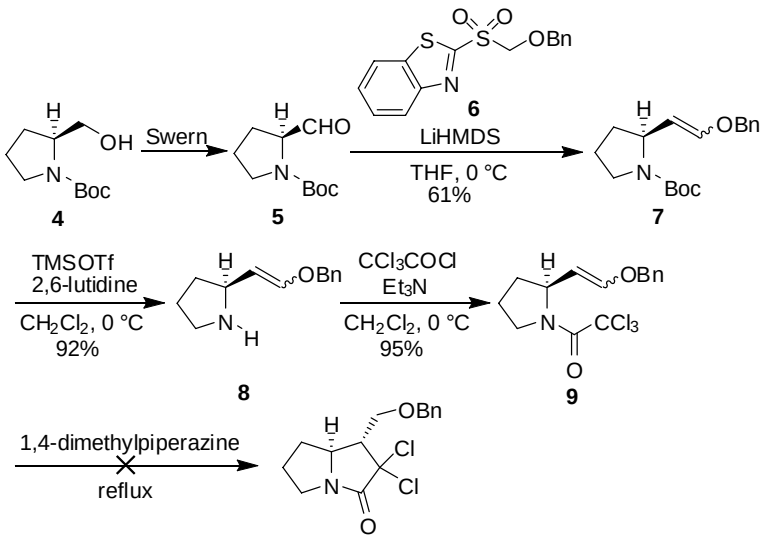
Scheme 1. Radacal cyclization of **1** in 1,4-dimethylpiperazine to give **3**.

We applied this method to the synthesis of (–)-trachelanthamidine (**14**),[2] one of the pyrrolizidine alkaloids,[3] from L-prolinol [(*S*)-(+)-2-pyrrolidinemethanol]. We report herein the results of work in this area.

2. Results and discussion

2.1. Attempt to cyclize *N*-trichloroacetyl derivative 9 in boiling 1,4-dimethylpiperazine

We initiated our investigation by examining the cyclization of trichloroacetamide **9**. Synthesis of **9** was begun by Julia olefination between aldehyde **5**, prepared by Swern oxidation of **4**, and α-benzyloxy sulfone **6**[4] to give alkene **7**. *N*-Deprotection of compound **7** followed by *N*-trichloroacetylation of the resultant **8** gave **9**. ^{1}H NMR spectra of **9** showed it to be a mixture of *E* and *Z* isomers in a ratio of ca. 1:2.



Scheme 2. Preparation and attempted radical cyclization of **9**.

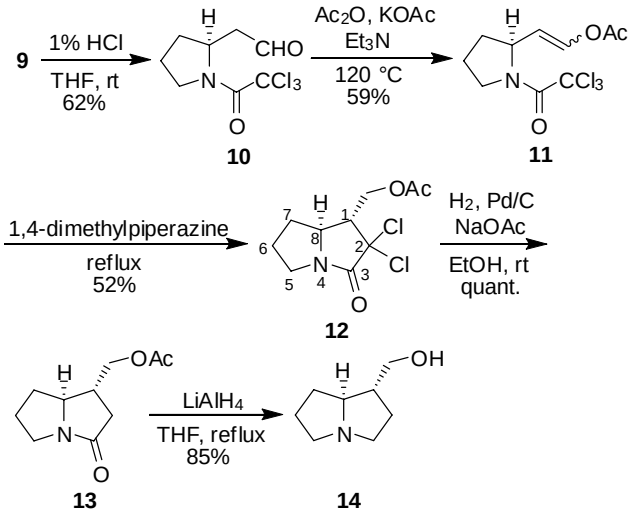
Heating of compound **9** in boiling 1,4-dimethylpiperazine, however, gave no cyclization product after 72 h of heating. This result is particularly surprising in view of the previous result that compound **1** gave cyclization product **3** in good yield. We then turned our attention to

compound **11**.

2.2. Synthesis of (–)-trachelanthamidine using a single electron transfer reaction of *N*-trichloroacetyl derivative 11 in boiling 1,4-dimethylpiperazine

Compound **11** having an acetoxy alkene was easily prepared by acid hydrolysis of compound **9** followed by treatment of the resulting aldehyde **10** with acetic anhydride.[5] ^{1}H NMR spectra of **11** showed it to be a mixture of *E* and *Z* isomers in a ratio of ca. 1:1.

We were delighted to find that compound **11** gave the desired cyclization product **12** in 52% yield by heating in 1,4-dimethylpiperazine for 15 min. ^{1}H NMR spectra of **12** showed it to be a single stereoisomer.



Scheme 3. Synthesis of (–)-trachelanthamidine (**14**) using radical cyclization of **11**.

Dichlorine atoms of compound **12** were removed by catalytic hydrogenolysis, quantitatively.

Finally, reduction of both the acetoxy group and the carbonyl group of lactam **13** by $LiAlH_4$ furnished (–)-trachelanthamidine (**14**) in 86% yield: $[\alpha]_D$ -13.2 (*c* 0.72, EtOH),[6] lit.[7] $[\alpha]_D$ -13.8 (*c* 1.28, EtOH), lit.[8] $[\alpha]_D$ -13.5 (*c* 2.0, EtOH).

3. Conclusion

We have achieved a short synthesis of (–)-trachelanthamidine (**14**) from L-prolinol by using single electron transfer (SET) reaction of compound **11** in boiling 1,4-dimethylpiperazine. It is still obscure why no radical cyclization product can be obtained by reaction of trichloroacetyl derivative **9** in boiling 1,4-dimethylpiperazine. The benzyloxy group in **9** is apparently more electron-rich than is an acetoxy group in **11**. It can therefore be presumed that the electron density of the alkenic bond plays an important role in effecting the single electron transfer (SET) reaction in 1,4-dimethylpiperazine. Elucidation of the mechanism of this SET reaction must await further experiments.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were measured on a JEOL EX 500 (500 MHz) or a JEOL JNM-EX 270 (270 MHz) spectrometer. Chemical shifts (δ) quoted are

relative to tetramethylsilane. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX-102A mass spectrometer. Column chromatography was carried out on silica gel 60N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm) or on alumina 90 (Merck, neutral, 63-200 μm) under pressure.

4.2. 2-(2-Benzyloxyethenyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine (7)

To a mixture of **5** (966 mg, 5.00 mmol), prepared by Swern oxidation of **4**,[9] and α-benzyloxy sulfone **6** (1.74 g, 5.46 mmol) in THF (50 mL) was added a 1.05 M solution of LiHMDS in THF (10.4 mL, 10.9 mmol) at 0 °C over a period of 5 min, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 19:1) to give **7** (918 mg, 61%, *E*:*Z* = 1:2) as a pale yellow oil. $[\alpha]_D^{24}$ +17.2 (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) ν 1660, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ1.43 (9H, s). 1.66-2.13 (4H, m), 3.37 (2H, br s), 4.19, 4.44 (total 1H, both br s), 4.70-4.85 (1H, m), 4.72, 4.77 (total 2H, both s), 5.99, 6.45 (total 1H, both br s), 7.30-7.38 (5H. m); ^{13}C NMR (125 MHz, $CDCl_3$) δ28.51, 28.52, 52.6, 71.2, 73.8, 78.8, 78.9, 127.3, 127.5, 127.8, 127.9, 128.4, 128.5, 137.0, 147.7; HRMS calcd for $C_{18}H_{25}NO_3$: 303.1835. Found: 303.1823

4.3. 2-(2-Benzyloxyethenyl)pyrrolidine (8)

To a solution of **7** (300 mg, 0.989 mmol) and 2,6-lutidine (318 mg, 2.97 mmol) in CH_2Cl_2

(10 mL) was added trimethylsilyl trifluoromethanesulfonate (242 mg, 1.09 mmol) at 0 °C, and the mixture was stirred at the same temperature for 10 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel ($CHCl_3$/MeOH/Et_3N, 20:1:1) to give **8** (184 mg, 92%, *E*:*Z* = 1:2) as a pale yellow oil. $[\alpha]_D^{25}$ –7.4 (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) ν 1655, 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32-1.46, 1.70-1.85, 1.87-1.98 (total 5H, all m), 2.82-2.88 (1H, m), 3.00-3.06 (1H, m), 3.44 (1/3H, q, *J* = 7.9 Hz), 4.00 (2/3H, d, *J* = 7.9 Hz), 4.74 (2/3H, dd, *J* = 7.9, 6.7 Hz), 4.72 (1/3 × 2H, s), 4.79 (2/3 × 2H, s), 4.91 (1/3H, dd, *J* = 12.2, 7.9 Hz), 6.04 (2/3H, d, *J* = 6.7 Hz), 6.50 (1/3H, d, 12.2 Hz), 7.28 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 25.3, 32.6, 33.1, 46.2, 53.3, 57.6, 71.1, 73.8, 107.6, 110.8, 127.3, 127.6, 127.9, 128.4, 136.9, 137.4, 145.3, 146.9 ; HRMS calcd for $C_{13}H_{17}NO$: 203.1310. Found: 203.1308.

4.4. 2-(2-Benzyloxyethenyl)-*N*-(trichloroacetyl)pyrrolidine (9)

To a solution of **8** (1.34 g, 6.59 mmol) and triethylamine (1.00 g, 9.89 mmol) in CH_2Cl_2 (65 mL) was added trichloroacetyl chloride (1.44 g, 7.91 mmol) at 0 °C, and the mixture was stirred at the same temperature for 10 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 13:1) to give **9** (2.19 mg, 95%) as a pale yellow oil. $[\alpha]_D^{25}$ +2.7 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71-2.20 (4H, m), 3.78-3.83 (1H, m), 3.98-4.03 (1H, m), 4.44 (2/3H, t, *J* = 7.3 Hz),

4.64 (1/3H, br s), 4.74 (1/3H × 2H, s), 4.76-4.78 (1/3H, m), 4.84 (2/3 × 2H, AB q, J = 12.2 Hz), 5.00 (2/3H, dd, J = 13.4, 7.3 Hz), 6.10 (2/3H, d, J = 6.7 Hz), 6.67 (1/3H, d, J = 12.8 Hz), 7.30-7.38 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 25.7, 31.2, 31.4, 49.0, 49.5, 56.8, 59.6, 71.5, 74.1, 94.0, 102.9, 107.1, 127.3, 127.6, 127.85, 127.90, 128.4, 136.7, 137.3, 145.7, 149.9, 158.2, 158.3; HRMS calcd for $C_{15}H_{16}Cl_3NO_2$: 347.0247. Found: 347.0241.

4.5. 2-*N*-(Trichloroacetyl)pyrrolidineacetaldehyde (10)

To a solution of **9** (450 mg, 1.29 mmol) in THF (26 mL) was added 1% HCl (30 mL) at 0 °C, and the mixture was stirred at room temperature for 36 h. The mixture was basified by adding a saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **10** (321 mg, 96%) as a pale yellow oil. $[\alpha]_D^{25}$ –31.5 (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) ν 1665, 1725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67-1.74 (1H, m), 1.90-2.08 (2H, m), 2.21-2.28 (1H, m), 2.64 (1H, ddd, J = 17.1, 7.9, 1.2 Hz), 3.08 (1H, ddd, J = 17.1, 4.3, 1.8), 3.78-3.82 (1H, m), 4.06-4.10 (1H, m), 4.51-4.56 (1H, m), 9.79 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 30.1, 47.0, 49.8, 56.3, 93.4, 159.1, 199.5; HRMS calcd for $C_8H_{10}Cl_3NO_2$: 256.9778. Found: 256.9772.

4.6. 2-(2-Acetoxyethenyl)-*N*-(trichloroacetyl)pyrrolidine (11)

A mixture of **10** (40.0 mg, 0.155 mmol), triethylamine (31.0 mg, 0.309 mmol), potassium

acetate (1.5 mg, 0.0155 mmol) and acetic anhydride (324 mg, 3.17 mmol) was heated at 120 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 8:1) to give **11** (27.6 mg, 59%) as a colorless oil. IR ($CHCl_3$) ν 1660, 1755 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.72-1.83 (1H, m), 1.95-2.23 (3H, m), 2.11, 2.19 (total 3H, both s), 3.81-3.90 (1H, m), 3.99-4.09 (1H, m), 4.69-4.73(1/2H, m), 4.82 (1/2H, dd, *J* =7.9, 6.7), 5.03-5.07 (1/2H, m), 5.38 (1/2H, dd, *J* = 12.2, 7.3 Hz), 7.15 (1/2H, d, *J* = 6.7 Hz), 7.35 (1/2H, d, *J* = 12.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 20.7, 25.1, 25.7, 30.5, 31.1, 49.4, 49.6, 56.3, 58.6, 93.7, 112.5, 112.9, 134.9, 138.1, 158.6, 167.4, 167.7; HRMS calcd for $C_{10}H_{12}Cl_3NO_3$: 298.9883. Found: 298.9884.

4.7. (1*R*,8*S*)-1-Acetoxymethyl-2,2-dichloropyrrolizidin-3-one（12)

A solution of **11** (42.5 mg, 0.14 mmol) in *N*,*N*'-dimethylpiperazine (2 mL) was heated at reflux for 15 min. After cooling to room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **12** (19.5 mg, 52%) as a pale yellow oil. $[\alpha]_D^{25}$ –34.6 (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) ν 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50-1.58 (1H, m), 2.10-2.25 (3H, m), 2.11 (3H, s), 2.77 (1H, dd, *J* = 13.7, 7.8 Hz), 3.26-3.30 (1H, m), 3.55-3.61 (1H, m), 3.67 (1H, m, *J* = 14.6, 8.9 Hz), 4.49-4.57 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 26.5, 30.4, 41.9, 58.1, 61.41, 61.45,

86.8, 164.5, 170.5; HRMS calcd for $C_{10}H_{13}Cl_2NO_3$: 265.0273. Found: 265.0256.

4.8. (1*R*,8*S*)-1-(Acetoxymethyl)pyrrolizidin-3-one（13)

A solution of **12** (17.0 mg, 0.064 mmol) in EtOH (2 mL) was vigorously stirred under H_2 atmosphere at room temperature in the presence of 10% Pd/C (2 mg) and NaOAc (13 mg, 0.16 mmol) for 4 d. The reaction mixture was filtered through celite and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:3) to give **13** (12.6 mg, 100%) as a colorless oil. $[\alpha]_D^{25}$ –27.3 (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) ν 1680, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39-1.50 (1H, m), 2.02-2.19 (3H, m), 2.08 (3H, s), 2.41-2.51 (1H, m), 2,54-2.58 (2H, m), 3.06 (1H, ddd, *J* = 12.2, 9.1, 3.7 Hz), 3.56 (1H, dt, *J* = 10.6, 7.9 Hz), 3.66-3.70 (1H, m), 4.11 (1H, dd, *J* = 11.0, 7.3 Hz), 4.20 (1H, dd, *J* = 11.0, 5.5 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.8, 26.8, 31.4, 38.3, 41.1, 41.2, 65.0, 65.3, 170.7, 173.0; HRMS calcd for $C_{10}H_{15}NO_3$: 197.1052. Found: 197.1049.

4.9. (1*R*,8*S*)-1-Pyrrolizidinemethanol (Trachelanthamidine) (14)

To a solution of **13** (90.0 mg, 0.46 mmol) in THF (5 mL) was added lithium aluminum hydride (70 mg, 1.83 mmol) at 0 °C, and the mixture was heated at reflux for 3 h. After cooling to room temperature, water (0.07 mL), 10% NaOH (0.1 mL) and water (0.21 mL) were added successively, and the mixture was further stirred for 30 min. The mixture was filtered through celite and the filtrate was concentrated. The residue was chromatographed on alumina

(CH_2Cl_2/MeOH, 5:1) to give **14** (55.0 mg, 86%) as a pale yellow oil. $[\alpha]_D^{25}$ –13.2 (*c* 0.72, $CHCl_3$), lit.[7] $[\alpha]_D$ -13.8 (*c* 1.28, EtOH), lit.[8] $[\alpha]_D$ -13.5 (*c* 2.0, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.50-2.05 (7H, m), 2.48-2.64 (2H, m), 2.95 (1H, dt, *J* = 10.5, 6.3 Hz), 3.13 (1H, ddd, *J* = 10.1, 7.1, 3.5 Hz), 3.22 (1H, dd, *J* =13.2, 6.3 Hz), 3.59 (2H, d, 6.3 Hz), 4.05-4.25 (1H, br); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.6, 29.9, 31.9, 48.3, 54.4, 54.7, 64.9. 67.6; HRMS calcd for $C_8H_{15}NO$: 141.1154. Found: 141.1154.

Acknowledgements

This work was supported by a Grant–in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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