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FORMAL SYNTHESIS OF (±)-TRACHELANTHAMIDINE

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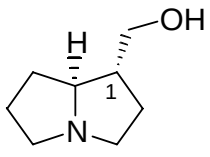
Abstract — Base-induced coupling-cyclization stepwise [3+2] annulation of α-sulfonylacetamide with (*Z*)-2-bromoacrylate yielded the polysubstituted pyroglutamate with three contiguous chiral centers with *trans-trans* orientation in a one-pot synthesis. The pyrrolizidine skeleton was obtained *via* the ring-closing metathesis (RCM) method. This facile strategy was used to synthesize (±)-trachelanthamidine.

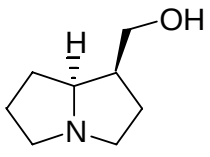
INTRODUCTION

Pyrrolizidine alkaloids have long attracted synthetic interest due to their relatively structural features and wide range of pharmacological activity.[1] Diverse and elegant synthetic approaches have been developed for construction of this core structure, such as 1-hydroxymethylpyrrolizidines.[2] In Figure 1, trachelanthamidine (**1**, also called laburnine) and isoretronecanol (**2**) have a common framework and their only difference is the C1-configuration. Basically, the adopted strategies can be summarized in Lewis acid promoted tandem [4+2]/[3+2][2h] cycloaddition, intramolecular palladium,[2a,2i] tungsten[2c] or titanium[2f] catalyzed ring closure, intermolecular conjugation of cyclic tertiary amines *via* organocuprate mediated[2b] or photochemically radical initiated[2e] and chiral material such as glucosamine.[2j] Here we report a formal synthesis of (±)-trachelanthamidine (**1**)[2-4] *via* the stepwise [3+2] annulation[5] and ring-closing metathesis.[6-7]

Figure 1.



trachelanthamidine (**1**)

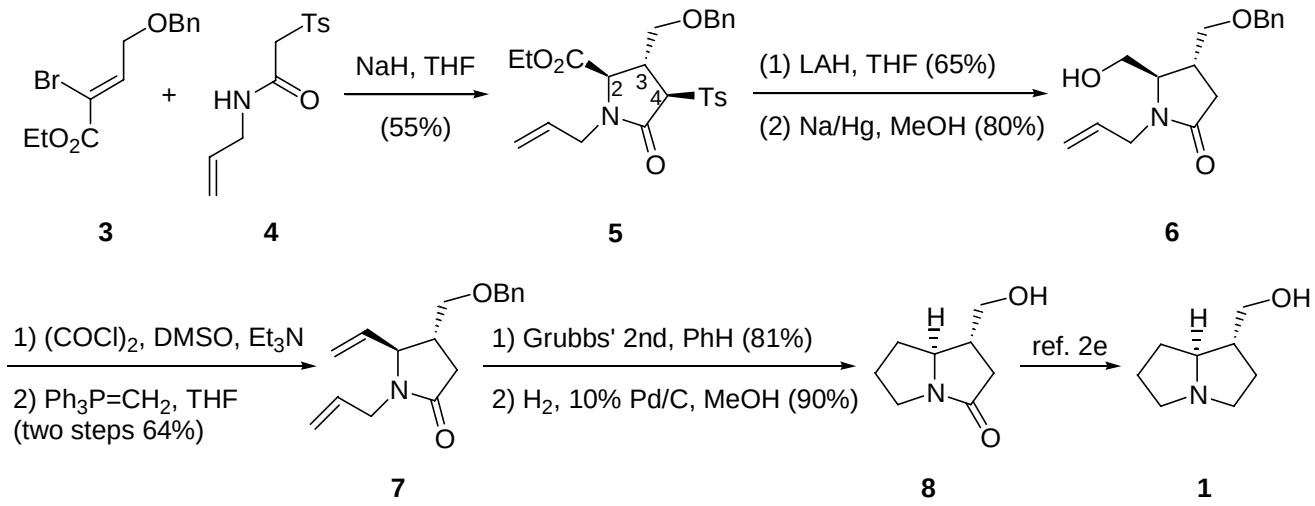


isoretronecanol (**2**)

RESULTS AND DISCUSSION

For the synthesis of pyroglutamate (**5**) *via* a stepwise [3+2] annulation reaction,[5] (*Z*)-2-bromoacrylate (**3**) and α-sulfonylacetamide (**4**) were chosen as the starting materials. (*Z*)-2-Bromoacrylate (**3**) was given by ozonolysis of allyl benzyl ether and Wittig olefination of the resulting aldehyde with $Ph_3P{=}C(Br)CO_2Et$ in 86% yield. Allylamine was treated with chloroacetyl chloride and triethylamine to produce α-chloroacetamide, which was then treated with sodium *p*-toluenesulfinate salt to give α-sulfonylacetamide (**4**) in 85% yield from the two-steps reaction. The one-pot synthesis began with the reaction of (*Z*)-2-bromoacrylate (**3**) with α-sulfonylacetamide (**4**) (NaH/THF) and proceeded through stereo- and regioselective annulation with the appropriate carbonyl substrate in a [3+2] mode, resulting in the overall formation of single pyroglutamate isomer (**5**) in which the substitutents at C_2 and C_3 and C_3 and C_4 are *trans* to each other.

Scheme 1. Formal synthesis of (±)-trachelanthamidine (**1**).



3 **4** **5** **6** **7** **8** **1**

As shown in Scheme 1, compound (**6**) was accomplished by reduction of pyroglutamate (**5**) with lithium aluminum hydride followed by desulfonation of the resulting alcohol with sodium amalgam. Preparation of diene (**7**) was achieved by Swern oxidation of alcohol (**6**) in dichloromethane followed by Wittig olefination of the resulting aldehyde with methyltriphenylphosphonium bromide and *n*-butyllithium in tetrahydrofuran. To build up the pyrrolizidine skeleton, diene (**7**) was subjected to ring-closing metathesis (RCM) reaction employing second generation Grubbs catalyst.[6-7] In order to achieve the formal synthesis of (±)-trachelanthamidine (**1**), hydrogenation was accomplished by treatment of the resulting compound with hydrogen on 10% palladium-activated carbon to afford known lactam (**8**).[2e,3i]

CONCLUSION

We explored a new synthetic strategy of (±)-trachelanthamidine (**1**) by an intermolecular stepwise [3+2] annulation and an intramolecular ring-closing metathesis as the key reactions.

EXPERIMENTAL

General. Tetrahydrofuran was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents were obtained from commercial sources and used without further purification. Reaction was routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude product was purified using column chromatography on silica gel.

Ethyl 1-allyl-3-benzyloxymethyl-4-(4-methylphenylsulfonyl)pyroglutamate (5).

A solution of compound (**4**) (253 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was carefully added to a rapidly stirred suspension of sodium hydride (132 mg, 3.3 mmol, 60%) in tetrahydrofuran (30 mL). After the reaction mixture was stirred at rt for 15 min, a solution of compound (**3**) (300 mg, 1.01 mmol) in tetrahydrofuran (30 mL) was added. The reaction mixture was further refluxed for 1 h. The reaction was quenched with 15% ammonium chloride solution (1 mL) in an ice bath, and concentrated under reduced pressure. Water (20 mL) was added to the crude product, and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 4/1) afforded product (**5**) (260 mg, 55%) as a viscous oil: HRMS (ESI, M^++1) calcd for $C_{25}H_{30}NO_6S$ 472.1794, found 472.1797; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.36-7.25 (m, 7H), 5.60-5.52 (m, 1H), 5.14-5.11 (m, 2H), 4.55 (s, 2H), 4.43 (dd, *J* = 4.5, 15.5 Hz, 1H), 4.30-4.17 (m, 2H), 4.09 (d, *J* = 4.0 Hz, 1H), 3.99 (d, *J* = 4.0 Hz, 1H), 3.72 (d, *J* = 4.0 Hz, 2H), 3.65 (dd, *J* = 8.0, 15.5 Hz, 1H), 3.35-3.32 (m, 1H), 2.45 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.85, 164.99, 145.29, 137.23, 134.30, 130.82, 129.55 (2C), 129.43 (2C), 128.43 (2C), 127.91, 127.68 (2C), 119.03, 73.14, 69.85, 67.08, 61.05, 59.05, 45.03, 37.66, 21.69, 14.07; Anal. Calcd for $C_{25}H_{29}NO_6S$ C, 63.67; H, 6.20; N, 2.97; Found C, 63.90; H, 6.34; N, 2.89.

1-Allyl-4-benzyloxymethyl-5-hydroxymethylpyrrolidin-2-one (6).

Lithium aluminum hydride (38 mg, 1.0 mmol) was added to a stirred solution of compound (**5**) (118 mg, 0.25 mmol) in tetrahydrofuran (10 mL) at ice bath. The mixture was further stirred for 2 h at rt. The reaction was quenched with 15% ammonium chloride solution (1 mL) and the mixture was concentrated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 2/1) afforded pure alcohol (70 mg, 65%) as a viscous oil: IR ($CHCl_3$) 3447, 1925, 1690 cm^{-1}; FAB-MS: $C_{23}H_{28}NO_5S$ m/z (%) = 91 (100), 136 (87), 154 (93), 430 (M^++1, 9); HRMS (ESI, M^++1) calcd for $C_{23}H_{28}NO_5S$ 430.1688, found 430.1685;^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.32-7.22 (m, 7H), 5.66-5.58 (m, 1H), 5.16-5.09 (m, 2H), 4.48 (s, 2H), 4.11 (dd, *J* = 5.0, 16.0 Hz, 1H), 3.99 (d, *J* = 5.5 Hz, 1H), 3.71-3.66 (m, 3H), 3.58 (d, *J* = 4.5 Hz, 2H), 3.54 (dd, *J* = 4.0, 9.0 Hz, 1H), 3.07-3.03 (m, 1H), 2.85 (br s, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 165.10, 145.15, 137.29, 134.41, 131.47, 129.45 (2C), 129.26 (2C), 128.29 (2C), 127.71, 127.52 (2C), 117.90, 72.99, 70.08, 67.29, 61.89, 59.78, 44.13, 35.86, 21.56. 6% Sodium amalgam (Na/Hg, 500 mg) and sodium phosphate (71 mg, 0.5 mmol) were added to a stirred solution of alcohol compound (90 mg, 0.21 mmol) in methanol (5 mL). The mixture was vigorously stirred for 2 h at rt. The residue was filtered and washed with methanol (2 x 10 mL). The combined organic layers were concentrated under the reduced pressure to afford the residue. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 1/1) produced compound (**6**) (46 mg, 80%) as a viscous oil: FAB-MS: $C_{16}H_{22}NO_3$ m/z (%) = 91 (51), 107 (37), 137 (100), 154 (100), 219 (10), 276 (M^++1, 14); HRMS (ESI, M^++1) calcd for $C_{16}H_{22}NO_3$ 276.1600, found 276.1602; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.73-5.65 (m, 1H), 5.22-5.15 (m, 2H), 4.52 (dd, *J* = 11.5, 19.5 Hz, 2H), 4.20 (dd, *J* = 5.0, 15.5 Hz, 1H), 3.74 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.64 (d, *J* = 4.0, 12.0 Hz, 1H), 3.59 (d, *J* = 7.0 Hz, 1H), 3.51 (dd, *J* = 3.5, 7.0 Hz, 1H), 3.46 (dd, *J* = 5.5, 9.5 Hz, 1H), 3.38 (t, *J* = 8.5 Hz, 1H), 2.63 (dd, *J* = 9.5, 17.0 Hz, 1H), 2.58-2.52 (m, 1H), 2.45 (br s, 1H), 2.13 (dd, *J* = 5.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.49, 137.60, 132.62, 128.47 (2C), 127.86, 127.70 (2C), 118.07, 73.24, 71.89, 62.63, 62.33, 43.52, 34.87, 33.70; Anal. Calcd for $C_{16}H_{21}NO_3$ C, 69.79; H, 7.69; N, 5.09; Found C, 69.83; H, 7.54; N, 4.89.

1-Allyl-4-benzyloxymethyl-5-vinylpyrrolidin-2-one (7).

A solution of oxalyl chloride (200 mg, 1.58 mmol) in dichloromethane (10 mL) was mixed with dimethyl sulfoxide (200 mg, 2.56 mmol) at –78 ^{o}C carefully. The solution was warmed to –40 ^{o}C for 5 min and recooled to –78 ^{o}C, and then a solution of alcohol (**6**) (140 mg, 0.51 mmol) in dichloromethane (5 mL) was added dropwise for 40 min followed by excess triethylamine (800 mg, 7.91 mmol) for 30 min. The reaction mixture was warmed to rt and poured into 15% ammonium chloride solution (2 mL), and concentrated under the reduced pressure. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine and water, dried, filtered and evaporated to give the crude aldehyde. To a stirred solution of methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) in tetrahydrofuran (30 mL) was added *n*-butyllithium (1.0 mL, 1.6 M, 1.6 mmol) at –78 ^{o}C. The orange red colored mixture was stirred at –78 ^{o}C for 1 h. The crude aldehyde in dry tetrahydrofuran (5 mL) was added to the reaction mixture at –78 ^{o}C *via* a syringe and further stirred at –78 ^{o}C for 2 h. The reaction was quenched with 15% ammonium chloride solution (1 mL) and the mixture was concentrated. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 2/1) produced compound (**7**) (88 mg, two steps 64%) as a viscous oil: IR ($CHCl_3$) 2924, 1684, 1456 cm^{-1}; FAB-MS: $C_{17}H_{22}NO_2$ m/z (%) = 81 (100),

91 (78), 133 (78), 219 (36), 272 (M^++1, 21); HRMS (ESI, M^++1) calcd for $C_{17}H_{22}NO_2$ 272.1650, found 272.1648; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.69-5.61 (m, 2H), 5.24-5.10 (m, 4H), 4.52 (s, 2H), 4.28 (ddt, *J* = 1.5, 5.0, 15.5 Hz, 1H), 3.89 (dd, *J* = 4.5, 8.5 Hz, 1H), 3.47 (dd, *J* = 5.5, 9.0 Hz, 1H), 3.42 (dd, *J* = 5.5, 9.0 Hz, 1H), 3.39 (dd, *J* = 7.5, 15.5 Hz, 1H), 2.61-2.55 (m, 1H), 2.54-2.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.72, 137.94, 136.91, 132.22, 128.42 (2C), 127.75, 127.63 (2C), 118.48, 117.80, 73.14, 70.39, 63.21, 43.05, 38.56, 33.31.

1-Hydroxymethylhexahydropyrrolizin-3-one (8).[2e,3i]

Grubbs' 2nd catalyst (6 mg, 0.007 mmol) was added to a stirred solution of compound (**7**) (35 mg, 0.13 mmol) in benzene (30 mL). The reaction mixture was reflux for 36 h. The mixture was concentrated and the residue was purified by flash column chromatography (hexane/ethyl acetate = 1/1) to yield bicyclic lactam (25 mg, 81%) as a viscous oil: IR ($CHCl_3$) 2923, 1699, 1457 cm^{-1}; FAB-MS: $C_{15}H_{18}NO_2$ m/z (%) = 91 (100), 133 (11), 154 (5), 244 (M^++1, 13); HRMS (ESI, M^++1) calcd for $C_{15}H_{18}NO_2$ 244.1337, found 244.1339; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 5.96 (dd, *J* = 1.5, 6.5 Hz, 1H), 5.86 (dd, *J* = 1.5, 6.5 Hz, 1H), 4.58 (d, *J* = 12.5 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 4.44-4.38 (m, 2H), 3.68-3.63 (m, 2H), 3.56-3.53 (m, 1H), 2.57-2.50 (m, 2H), 2.41-2.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.84, 137.99, 130.57, 128.45 (2C), 128.04, 127.74, 127.47 (2C), 73.21, 71.47, 71.42, 49.87, 44.46, 36.91. 10% Palladium on activated carbon (10 mg) was added to a stirred solution of bicyclic lactam (24 mg, 0.10 mmol) in methanol (5 mL). Hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir for 3 h at rt under hydrogen atmosphere. The catalyst was filtered through a short plug of Celite and washing with methanol (2 x 10 mL). The combined organic layers were evaporated to afford crude products. Purification on silica gel (dichloromethane/methanol = 10/1) produced known lactam (**8**) (14 mg, 90%) as a viscous oil: HRMS (ESI, M^++1) calcd for $C_8H_{14}NO_2$ 156.1025, found 156.1026; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74-3.63 (m, 3H), 3.53-3.48 (m, 1H), 3.05-3.00(m, 2H), 2.58-2.45 (m, 2H), 2.36-2.30 (m, 1H), 2.13-1.97 (m, 3H), 1.44-1.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.99, 65.14, 63.91, 44.02, 41.02, 38.11, 31.55, 26.85. Compound (**8**) was treated with lithium aluminum hydride in tetrahydrofuran to yield (±)-trachelanthamidine (**1**). The procedure was shown in references 2e and 3i.

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