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A General Approach to the Quinolizidine Alkaloids via an Intramolecular Aza-[3 + 3] Annulation. Synthesis of (±)-2-Deoxy-Lasubine II

Yu Zhang, Aleksey I. Gerasyuto, Quincy A. Long, and Richard P. Hsung*

Division of Pharmaceutical Sciences and Department of Chemistry, 777 Highland Avenue, Rennebohm Hall University of Wisconsin, Madison, WI 53705

Abstract

The first success in constructing a member of quinolizidine family of alkaloids employing an intramolecular *aza*-[3 + 3] annulation strategy is described here. The key feature is the usage of vinylogous urethane tethered to a vinyl iminium intermediate with trifluoroacetate serving as the counter anion. The proof-of-concept is illustrated with the synthesis of 2-deoxy-lasubine II.

Keywords

Intramolecular *aza*-[3 + 3] annulation; lasubine I and II; quinolizidines; piperidinium trifluoroacetate salt; Barton's decarboxylation

In the last ten years, we have been developing an *aza*-[3 + 3] annulation reaction^{1,2} as a general strategy toward alkaloid synthesis.^{3,4} The intramolecular variant of this annulation has been particularly useful in natural product synthesis. Specifically, reactions of vinylogous amides **1** [Scheme 1] tethered to a vinyl iminium motif through a tandem sequence of *N*-1,4-addition and *C*-1,2-addition³ can lead to a diverse array of nitrogen heterocycles **2a–e**, which have been applied to a number of total syntheses of alkaloids.^{5–8} Despite such success, our annulation strategy has not been useful in approaching simple quinolizidine and indolizidine structural motifs **3** and **4**, which could be accessed only in low yields. Consequently, this limitation precluded us from synthesizing any quinolizidine and indolizidine alkaloids, and limited us to the construction of nitrogen heterocycles **2a–e** with quinolizidine and indolizidine motifs embedded therein.

It was not until recently did we learn that the counter anion [X[⊖]] in these iminium salts plays a significant role in the annulation.⁹ In particular, for the synthesis of **2e**,^{8b} while iminium salts with acetate as the counter anion was completely ineffective, generating the more reactive trifluoroacetate iminium salt⁹ proved to be the solution, rendering a vinylogous urethane deployable for the first time in the *aza*-[3 + 3] annulation.⁸ We had long recognized a distinct advantage of employing vinylogous urethanes in our *aza*-[3 + 3] annulation being that the resulting methoxy carbonyl group in **2e** represents an excellent functional handle for further transformations or removal.⁸ Therefore, we investigated annulation reactions of vinylogous urethanes **5** tethered to a trifluoroacetate iminium salt with the intent to develop a general approach toward the quinolizidine family of alkaloids [Scheme 2]. We report here our preliminary success in the synthesis of (±)-2-deoxy-lasubine II.^{10–15}

Our efforts commenced with alkyl bromide **7** prepared from propargyl alcohol in three steps [TBDPS-silylation, alkylation with 1,4-dibromopropane, and Lindlar hydrogenation] with an overall yield of 57% [Scheme 3]. Displacement of the bromide in **7** with NaN_3 gave azide **8**, and azide reduction using Staudinger's protocol followed by vinylogous urethane formation using alkynoate **10**¹⁶ led to vinylogous urethane **11**¹⁷ in 76% overall yield. Stereochemistry of vinylogous urethane **11** is exclusively *Z* [see NOE] likely due to the favorable internal hydrogen bonding [proton shift of the hydrogen bonded NH : δ 8.48 ppm (t, 1H, $J = 5.9$ Hz);].^{4a,7,8} Desilylation and Parikh-Doering oxidation¹⁸ gave annulation precursor **13** with a *Z/E* ratio of 3.3:1 for the enal.

With the vinylogous urethane **13** tethered to the enal in hand, 50 mol% of piperidinium trifluoroacetate salt was used to promote the formation of vinyl iminium intermediate **14**, and an *in situ* hydrogenation allowed successful isolation of the annulation product **16** in good yield over two operations. Although the initial annulation product **15** could be isolated, it is not as stable as **16**. It is note-worthy that this work represents the first time our *aza*-[3 + 3] annulation method has succeeded in constructing a simple quinolizidine structural motif such as **16** in a synthetically reliable manner.

Having established the feasibility of this intramolecular *aza*-[3 + 3] annulation, we were able to complete a facile synthesis of 2-deoxy-lasubine II **19** employing **16**. As shown in Scheme 5, hydrogenation of the vinylogous urethane in **16** using Adam's catalyst gave ester **17** as a single diastereomer. The assignment of relative stereo-chemistry in **17** was accomplished using NOE experiments. LiI promoted demethylation of **17** followed by Barton's standard protocol for decarboxylation gave **19** in 39% overall yield for the sequence.

We have described here our first success in constructing a member of quinolizidine family of alkaloids employing the intramolecular *aza*-[3 + 3] annulation strategy. The key feature is the usage of vinylogous urethane tethered to a vinyl iminium ion with trifluoroacetate serving as the counter anion, and the proof-of-concept is shown with the synthesis of 2-deoxy-lasubine II. Efforts in achieving syntheses of other quinolizidine family members are ongoing.

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17. **Selected Experimental Procedures and Characterizations. Synthesis of Azide 8.** To a solution of bromide **7** (9.31 g, 21.7 mmol) in DMSO (50 mL) was added NaN₃ (2.11 g, 32.5 mmol). The suspension was stirred at rt for 18 h. The reaction was quenched with H₂O (200 mL), and the mixture was extracted with methyl *t*-butyl ether (4 × 60 mL). The combined organic layers were washed with

H₂O (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified using silica gel flash column chromatography [Isocratic eluent: 1:40 EtOAc/hexanes] to give the desired azide **8** (8.43 g, 21.4 mmol) in 99% yield as colorless oil. **8**: *R*_f = 0.21 (1:40 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 1.06 (s, 9H), 1.33–1.38 (m, 2H), 1.47–1.55 (m, 2H), 1.89 (td, 2H, *J* = 6.8 Hz, 7.4 Hz), 3.19 (t, 2H, *J* = 6.8 Hz), 4.26 (d, 2H, *J* = 6.2 Hz), 5.38–5.41 (m, 1H), 5.63–5.66 (m, 1H), 7.36–7.46 (m, 6H), 7.69–7.72 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 19.1, 26.5, 26.8, 26.9, 28.3, 51.2, 60.2, 127.6, 129.6, 129.7, 130.1, 133.8, 135.6; IR (neat) cm⁻¹ 2931s, 2857s, 2093s, 1472s, 1109s, 700s; mass spectrum (APCI): 394 (75) (M+H)⁺. **Synthesis of Amine 9**. To a solution of azide **8** (8.23 g, 21.0 mmol) in H₂O (10 mL) and THF (100 mL) was added PPh₃ (11.0 g, 42.0 mmol) in once at rt. The resulting suspension was stirred at rt for 4 h. The crude reaction mixture was then concentrated *in vacuo*, and benzene (100 mL) was added. The resulting solution was concentrated again *in vacuo* before additional benzene (100 mL) was added followed by another azeotropic concentration *in vacuo* to remove excess amount of H₂O. The crude reaction mixture was purified by silica gel flash column chromatography buffered Et₃N [Gradient eluent: 100% CH₂Cl₂ to 70:5 CH₂Cl₂/MeOH to 70:6:1 CH₂Cl₂/MeOH/30% aq NH₄OH] to give amine **9** (6.75 g, 18.4 mmol) in 88% yield as slightly yellow oil. **9**: *R*_f = 0.28 (70:6:1 CH₂Cl₂/MeOH/30% aq NH₄OH); ¹H NMR (400 MHz, CDCl₃) δ 1.04 (s, 9H), 1.25–1.32 (m, 2H), 1.34–1.41 (m, 2H), 1.87 (q, 2H, *J* = 7.2 Hz), 1.93 (s, 2H), 2.62 (t, 2H, *J* = 6.8 Hz), 4.24 (dd, 2H, *J* = 0.8, 6.2 Hz), 5.37–5.43 (m, 1H), 5.58–5.64 (m, 1H), 7.35–7.44 (m, 6H), 7.65–7.70 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 19.1, 26.7, 26.8, 27.3, 32.8, 41.7, 60.2, 127.6, 129.3, 129.5, 130.7, 133.9, 135.6; IR (neat) cm⁻¹ 2930s, 2856s, 1427s, 1108s, 700s; mass spectrum (APCI): *m/e* (relative intensity) 368 (100) (M+H)⁺. **Synthesis of Vinylogous Urethane 11**. To a solution of alkyne **10** (2.20 g, 10.0 mmol) in MeOH (90 mL) was added amine **9** (4.32 g, 10.6 mmol). This solution was purged with nitrogen for 30 min before being sealed under nitrogen and heated in an oil bath at 100–110 °C for 24 h. After which, it was cooled down to rt and concentrated *in vacuo*. Purification of the crude by silica gel flash column chromatography, [Isocratic eluent: 1:5 EtOAc/hexanes] to give the desired product **11** (5.07 g, 8.6 mmol) in 86% yield as colorless oil. **11**: *R*_f = 0.26 (1:5 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 1.03 (s, 9H), 1.24–1.30 (m, 2H), 1.36–1.40 (m, 2H), 1.81 (q, 2H, *J* = 7.2 Hz), 3.03 (q, 2H, *J* = 6.6 Hz), 3.67 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.21 (dd, 2H, *J* = 1.4, 6.2 Hz), 4.59 (s, 1H), 5.32–5.37 (m, 1H), 5.56–5.61 (m, 1H), 6.83–6.91 (m, 3H), 7.35–7.43 (m, 6H), 7.65–7.69 (m, 4H), 8.48 (t, 1H, *J* = 5.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 19.1, 26.5, 26.8, 27.1, 30.6, 44.6, 50.2, 55.8, 55.9, 60.2, 84.3, 110.7, 111.0, 120.5, 127.6, 128.7, 129.6, 130.3, 133.8, 135.5, 148.7, 149.8, 165.0, 170.7 (one sp² carbon not located); IR (neat) cm⁻¹ 3227brs, 2909s, 1606s, 1132s; mass spectrum (APCI): *m/e* (relative intensity) 588 (100) (M+H)⁺. **Synthesis of Annulation Precursor Enal 13**. To a vigorously stirring heterogeneous suspension of pyridine-SO₃ complex (1.56 g, 9.81 mmol) in pyridine (0.838 g, 10.61 mmol) and DMSO (1.53 g, 19.65 mmol) was added anhyd CH₂Cl₂ (12 mL) at rt. The resulting suspension was cooled to 0 °C, and to this suspension was added a chilled solution of alcohol **12** (1.37 g, 3.93 mmol), DIPEA (2.03 g, 15.72 mmol), and DMSO (1.53 g, 19.65 mmol) in anhyd CH₂Cl₂ (23 mL) via syringe dropwise over 10 min. After stirring at 0 °C, the reaction was quenched with H₂O (20 mL). The organic layer was collected and washed with an additional H₂O (20 mL). The combined aqueous layers were washed with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed with 15% aq HCl (40 mL and then 20 mL), 20 mL sat aq NaHCO₃, sat aq NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by a short (3 × 8 cm) silica gel column buffered with Et₃N [Isocratic eluent: 1:2 EtOAc/hexanes] to afford enal **13** (1.23 g, 3.54 mmol) in 90% yield as slightly yellow oil and as inseparable mixture of 3.3:1 *Z/E* isomers. **13**: *R*_f = 0.27 (1:2 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) (major *Z*-isomer) δ 1.51–1.55 (m, 4H), 2.54–2.60 (m, 2H), 3.10–3.17 (m, 2H), 3.68 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.63 (s, 1H), 5.93–5.98 (m, 1H), 6.55 (td, 1H, *J* = 8.0 Hz, 11.1 Hz), 6.86–6.94 (m, 3H), 8.53 (t, 1H, *J* = 5.5 Hz), 10.0 (d, 1H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) (major *Z*-isomer) δ 26.1, 27.5, 30.4, 44.2, 50.2, 55.8, 55.9, 84.8, 110.8, 110.8, 120.5, 128.5, 130.3, 148.7, 149.9, 152.2, 164.9, 170.7, 190.6; IR (neat) cm⁻¹ 2941m, 1678s, 1648s, 1608s, 1134s, 1025s, 724s; mass spectrum (APCI): *m/e* (relative intensity) 348 (100) (M+H)⁺. **Aza-[3 + 3] Annulation**. To a stirring heterogeneous suspension of enal **13** (2.81 g, 8.09 mmol) and grounded Na₂SO₄ (flame-dried, 9.00 g) in freshly distilled anhyd EtOAc (180 mL) was added piperidinium trifluoroacetate salt (796.0 mg, 4.00 mmol) at 0 °C. The resulting suspension was allowed to warm up to rt slowly. After 16 h, NMR showed complete consumption of the aldehyde. To this reaction mixture was added Pd/C (869.0 mg, 0.81 mmol), and the flask was filled with H₂ gas by five evacuate-back-fill cycles. After which,

the mixture was stirred under H₂ at rt for 6 h. The mixture was then filtered through Celite™ to remove the solid, and the solution was concentrated *in vacuo* to give a reddish oil. The crude product was purified by silica gel flash column chromatography buffered with Et₃N [Isocratic eluent: 1:2 EtOAc/hexanes] to give the desired annulation product **16** (1.65 g, 4.98 mmol) in 62% yield as yellow solid. **16**: *R_f* = 0.32 (1:2 EtOAc/hexanes); mp 114–117 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.21–1.25 (m, 1H), 1.36–1.42 (m, 3H), 1.66–1.75 (m, 2H), 1.78 (d, 1H, *J* = 6.4 Hz), 1.95 (dd, 1H, *J* = 6.5, 13.1 Hz), 2.37–2.54 (m, 3H), 3.11–3.14 (m, 2H), 3.36 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 6.63 (s, 1H), 6.67 (d, 1H, *J* = 8.2 Hz), 6.82 (d, 1H, *J* = 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.4, 24.5, 26.5, 29.0, 32.7, 49.5, 50.3, 55.6, 55.8, 57.0, 95.9, 109.7, 110.6, 120.8, 130.9, 148.2, 148.6, 156.1, 168.9; IR (neat) cm^{−1} 2940s, 1643s, 1562s, 1511s, 1122s; mass spectrum (APCI): *m/e* (relative intensity) 332 (100) (M+H)⁺; *m/e* calcd for C₁₉H₂₅NO₄Na 354.1676, found 354.1679. **Hydrogenation**. To a flame-dried 100-mL RB-flask was added PtO₂ (102.0 mg, 0.45 mmol) and MeOH (10 mL). The flask was filled with H₂ by three evacuate-back-fill cycles and the resulting suspension was stirred at rt for 20 min, and the original brown powder of PtO₂ turned into black sponge. To this heterogeneous mixture was added via syringe a solution of the freshly purified annulation product **16** (296.0 mg, 0.89 mmol) in MeOH (30 mL). The resulting mixture was stirred at rt for 16 h and TLC showed complete conversion of the starting material. The solution was filtered through Celite™ and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography buffered with Et₃N [Isocratic eluent: 1:4 EtOAc/hexanes] to give ester **17** (258.0 mg, 0.77 mmol) in 87% yield as colorless oil. **17**: *R_f* = 0.26 (1:4 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 1.23 (tq, 1H, *J* = 4.3, 12.5 Hz), 1.35–1.44 (m, 3H), 1.46–1.58 (m, 3H), 1.61–1.70 (m, 2H), 1.87 (1H, t, *J* = 4.5, 13.0 Hz), 1.87–1.91 (m, 1H), 2.11 (1H, dq, *J* = 3.6, 13.0 Hz), 2.70 (t, 1H, *J* = 4.5 Hz), 2.78–2.81 (m, 1H), 3.09 (d, 1H, *J* = 4.4 Hz), 3.30 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 6.71–6.76 (m, 2H), 6.86 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 24.9, 26.0, 26.7, 28.7, 33.6, 47.3, 50.7, 53.9, 55.7, 55.8, 63.3, 69.9, 110.3, 110.5, 119.7, 134.9, 147.7, 148.6, 173.6; IR (neat) cm^{−1} 2929s, 1735s, 1591s, 1259s, 1152s; mass spectrum (APCI): *m/e* (relative intensity) 334 (100) (M+H)⁺; *m/e* calcd for C₁₉H₂₇NO₄Na 356.1832, found 356.1848. **Demethylation of 17**. To a solution of ester **17** (112 mg, 0.336 mmol) in freshly distilled EtOAc (7 mL) was added LiI (270 mg, 2.02 mmol). The resulting solution was deoxygenated via purging with Argon gas for 15 min, and then the reaction vessel was sealed under Argon, wrapped with aluminum foil, and heated in a 105 °C oil bath. After heating for 36 h, the solution was cooled down to rt and filtered. The light brown solid filter cake was washed with EtOAc (3 mL) and Et₂O (2 mL), and dried *in vacuo* to give a brown solid. The solid salt was then dissolved in H₂O (10 mL), and acidified via dropwise addition of 1.0 *N* aq HCl solution until the pH value of the aqueous solution reached 3–4. The aqueous solution was then saturated with solid NaCl, and extracted with CHCl₃ (6 × 8 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give product acid **18** (91.0 mg, 0.29 mmol) in 85% yield as a light brown solid. Acid **18** was used immediately for decarboxylation. **Barton's Decarboxylation**. To a solution of acid **18** (130.0 mg, 0.41 mmol) in anhyd CH₂Cl₂ (10 mL) was added one drop of DMF. The solution was stirred at 0 °C for 2 min before oxalyl chloride (104.0 mg, 0.82 mmol) was added via syringe. The resulting solution was allowed to warm up to rt over 30 min, and was stirred at rt for an additional 1 h. After which, a high vacuum (0.5–1.0 mmHg) was slowly applied to remove solvent and volatile materials. The residual material was then further dried under high vacuum for 30 min, before it was dissolved in anhyd CH₂Cl₂ (8 mL) and transferred via syringe to a chilled solution of 2-mercaptopyridine-1-oxide sodium salt (122.0 mg, 0.82 mmol) and DMAP (10 mg, 0.08 mmol) anhyd CH₂Cl₂ (8 mL). The resulting suspension was stirred at 0 °C with the flask shielded from light using Al-foil. It was then slowly warmed up to rt and stirred at rt for 1.5 h. After which, *t*-BuSH (587.0 mg, 6.50 mmol) was added via syringe all at once and the yellowish suspension was then irradiated with 300 Watt W-lamp for 3 h with the solution cooled by a water bath. Solvent and excess of *t*-BuSH was then removed *in vacuo*, and 5% aq NaHCO₃ (30 mL) solution was added. The aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel flash column chromatography buffered with NEt₃ [Isocratic eluent: 1:4 EtOAc/hexanes] to give product (±)-2-deoxylasubine II **19** (44.0 mg, 0.16 mmol) in 39% yield as colorless oil, which solidified upon standing. **19**: *R_f* = 0.29 (1:4 EtOAc/hexanes); mp 68–70 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.25 (t, 1H, *J* = 4.3, 11.5 Hz), 1.33–1.47 (m, 5H), 1.54–1.61 (m, 4H), 1.63–1.75 (m, 3H), 1.87–1.92 (t, 1H, *J* = 10.5 Hz), 2.66 (d, 1H, *J* = 9.3 Hz), 2.82 (dd, 1H, *J* = 2.9, 10.9 Hz), 3.85 (s, 3H), 3.88 (s, 3H), 6.76–6.89 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) α 24.8,

24.9, 26.2, 33.7, 33.8, 36.5, 53.5, 55.7, 55.9, 63.4, 70.2, 110.3, 110.7, 119.5, 138.2, 147.6, 148.9; IR (neat) cm^{-1} 2926s, 1502s, 1147s; mass spectrum (APCI): m/e (relative intensity) 276 (100) (M+H)⁺; m/e calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_2$ 276.1958, found 276.1958.

18. See: Parikh JR, von Doering WE. J. Am. Chem. Soc 1967;89:5505. This is the only oxidation in which the Z-geometry of the vinylogous urethane does not scramble.

Scheme 1.
A Deficiency in the Aza-[3 + 3] Annulation.

Scheme 2.
Establishing a General Approach to Quinolizidines.

Scheme 3.
Synthesis of the Vinylogous Urethane Precursor **13**.

Scheme 4.
Sequential Aza-[3 + 3] Annulation-Hydrogenation.

Scheme 5.
Synthesis of (±)-2-Deoxy-Lasubine II.