Synthesis of (±)-*trans*-Indolizidine-8-carboxylic Acid

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Abstract: A facile synthesis of a novel amino acid, *trans*-indolizidine-8-carboxylic acid, is described.

Key words: amino acids, bicyclic compounds, heterocycles, hydroformylation, tandem reactions

Indolizidines are very important compounds because of their presence in many natural alkaloids, pharmaceuticals, and synthetic useful intermediates. In addition, rigidified amino acids, linking its nitrogen to its carbon backbone, are proven to be a useful concept in rational design of peptidomimetics.[1,2] In the course of our interest in this field, a rapid and convenient synthesis of indolizidine-8-carboxylic acid is required. However, to the best of our knowledge, there is no reported method to synthesize this amino acid. Herein we describe a facile synthesis of this compound using our recently developed tandem Rh-catalyzed hydroformylation–double cyclization reactions.[3]

Our syntheses commenced with hydroformylation on *N*-allylamides of 4-alkynoic acid **1** (Scheme 1), readily available from the corresponding acid and allylamine.[4] The key reaction was carried out using a low loading of Rh-BIPHEPHOS[5,6] (0.5 mol%) at 60 °C under 4 atm of CO and H_2 (1:1) in acetic acid, providing a single product in 83% isolated yield. After hydroformylation of **1** was complete, spontaneous intramolecular addition of the amide moiety on the resulting aldehyde led the formation of hemiamidal. In the presence of acid, dehydration to *N*-acyliminium followed by intramolecular addition of the 4-methoxyphenyl-acetylene moiety furnished the indolizidine moiety. Subsequent addition with a solvent molecule afforded enol acetate **2** as the product.[7] The configuration of enol acetate **2** was clearly identified by ROESY spectroscopy, showing clearly a strong correlation between the phenyl protons δ = 7.28 (H-2′) ppm and the bridgehead proton δ = 4.18 (H-8a) ppm. The distance of these two protons calculated by DFT was 3.017 Å, which also supported the experimental observation (Figure 1).

Exposure of enol acetate **2** in a basic methanol solution at room temperature produced aryl ketone **3** in 81% yield. A ^{1}H-^{1}H coupling constant of 10.8 Hz was observed in both peaks of δ = 3.30 and 3.83 ppm, which assigned as H-8 and H-8a, respectively. The larger coupling constant indicated a *trans* arrangement between H-8 and H-8a.[8] In fact, ketone **3** was able to be achieved by direct treatment of the crude product in a basic methanol solution, affording 71% combined yield over two steps.

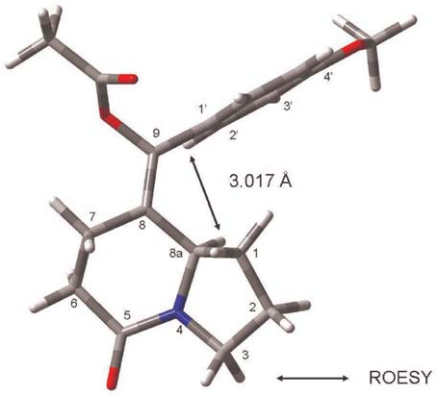

Figure 1 The ROESY correlation and calculated geometry of (*E*)-enol acetate **2**, calculated by DFT at the level of B3LYP/6-31G* and verified by vibrational analysis (see the Supporting Information)

In order to functionalize the arylketone substituent at C-8 of the indolizidinone moiety, the ketone group needed to be oxidized to an ester group for the subsequent transformations. Various Baeyer–Villiger oxidation[9] conditions of ketone **3** were investigated, including MCPBA in a chlorinated solvent or in buffer solutions, UHP (urea-hydrogen peroxide)–TFAA in buffer solutions, and $(TMSO)_2$ with different Lewis acids. Unfortunately, formation of the desired ester was not observed even under forcing conditions. Gratifying, Uneyama's protocol,[10] using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a cosolvent in dichloromethane and a phosphate buffer solution, brought about the formation of desired ester **4**, confirmed by appearance of a new δ = 171.5 ppm peak and disappearance of the ketone peak. Moreover, a large shift of a doublet peak from δ = 7.93 to 6.97 ppm in the ^{1}H NMR spectra implied that the oxygen atom has been inserted at the aromatic side, rather than at the alkyl side.

Direct treatment of lactam **4** in basic conditions led to a messy mixture, implying the indolizidinone was vulnerable in the basic conditions. Thus, selective reduction of lactam was carried out with $BH_3{\cdot}SMe_2$, affording amine **5** in 72% yield. Transesterification to methyl ester **6** was carried out in basic methanol solution, yielding a yellowish product in 82% yield. Acidic hydrolysis of methyl ester **6** followed by treatment with propylene oxide to neutralize excess hydrogen chloride gave *trans*-indolizidine-8-carboxylic acid (**7**) in 99% yield.

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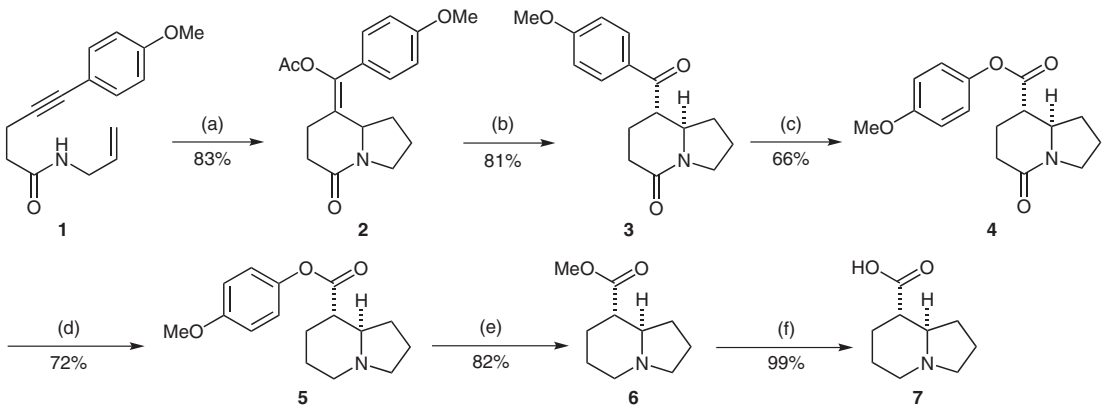

Scheme 1 Synthesis of *trans*-indolizidine-8-carboxylic acid. *Reagents and conditions*: (a) $Rh(acac)(CO)_2$ (0.5 mol%), BIPHEPHOS (1.0 mol%), CO (2 atm), H_2 (2 atm), PTSA (10 mol%), AcOH, 60 °C 18 h; (b) K_2CO_3 (25 mol%), MeOH, r.t., overnight; (c) MCPBA (3.0 equiv), HFIP/phosphate buffer, 40 °C, overnight; (d) $BH_3{\cdot}SMe_2$ (4 equiv), 0 °C to r.t., 2 h; (e) K_2CO_3 (1.1 equiv), MeOH, r.t., overnight; (f) aq HCl, reflux, 2 h; propylene oxide, EtOH, reflux.

In conclusion, we utilize a novel domino reaction, alkyne-mediated Rh-catalyzed hydroformylation tandem double cyclization reaction, to synthesize to a novel amino acid, *trans*-indolizidine-8-carboxylic acid (**7**) in 26% overall yield. Application of the amino acid in the research of peptidomimetics and extension of this methodology toward other natural products of interest are currently under way and will be reported in the future.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) **(*E*)-8-(α-acetyloxy-4′-methoxybenzylidenyl)-5-oxoindolizidine (2)**
$Rh(acac)(CO)_2$ (3.9 mg, 15.0 μmol, 0.5 mol%) and BIPHEPHOS (23.4 mg, 30 μmol, 1.0 mol%) were dissolved in AcOH (1 mL) under nitrogen. The resulting catalyst solution was degassed by a freeze–thaw procedure at least three times. Amide **1**[4] (730 mg, 3.0 mmol, 1.00 equiv) and PTSA (57 mg, 0.3 mmol, 10 mol%) were placed in a 100 mL flask. The catalyst solution was transferred to the reaction flask containing the substrate by a pipette, and the total volume was adjusted to 60 mL with AcOH. The reaction flask was placed in a 300 mL stainless steel autoclave and then was pressurized with CO (2 atm) followed by H_2 (2 atm). The reaction mixture was stirred at 60 °C for 16–20 h. Upon completion of the reaction, the gas was carefully released in a good ventilated hood, and the reaction mixture was concentrated under reduced pressure to give a crude residue. The residue was partitioned with CH_2Cl_2 (20 mL) and aq $NaHCO_3$ (10 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhyd Na_2SO_4, and then concentrated under reduced pressure to give the crude product. The crude product was purified by flash chromatography on silica gel using MeOH–CH_2Cl_2 as the eluant to give the product in 83% yield as a light yellow oil. R_f = 0.45 (MeOH–CH_2Cl_2 = 1:9). ^{1}H NMR (600 MHz, 25 °C, $CDCl_3$): δ = 1.35 (dq, *J* = 5.4, 10.8 Hz, 1 H, H-1), 1.57–1.63 (m, 1 H, H-2), 1.63–1.69 (m, 1 H, H-1), 1.76–1.84 (m, 1 H, H-2), 2.13 (s, 3 H, $OCCH_3$), 2.24 (ddd, *J* = 3.6, 15.0, 15.0 Hz, 1 H, H-7), 2.36 (ddd, *J* = 4.2, 15.6, 15.6 Hz, 1 H, H-6), 2.52 (ddd, *J* = 3.6, 3.6, 15.6 Hz, 1 H, H-6), 2.65 (ddd, *J* = 3.0, 4.2, 14.4 Hz, 1 H, H-7), 3.30 (dd, *J* = 3.6, 11.4 Hz, 1 H, H-3), 3.64 (ddd, *J* = 8.4, 8.4, 12.0 Hz, 1 H, H-3), 3.82 (s, 3 H, OCH_3), 4.18 (dd, *J* = 5.4, 10.8 Hz, 1 H, H-8a), 6.88 (d, *J* = 8.4 Hz, 2 H, H-3′), 7.28 (d, *J* = 8.4 Hz, 2 H, H-2′). ^{13}C NMR (150 MHz, 25 °C, $CDCl_3$): δ = 20.7 (q, CH_3CO), 22.1 (t, C-2), 22.6 (t, C-7), 32.2 (t, C-6), 32.4 (t, C-1), 43.6 (t, C-3), 55.1 (q, CH_3O), 58.0 (d, C-8a), 113.7 (d, C-3′), 124.8 (s, C-8), 127.3 (s, C-1′), 130.4 (d, C-2′), 142.2 (s, C-9), 159.8 (s, C-4′), 168.7 (s, CH_3CO), 170.0 (s, C-5), HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}NO_4^+$: 316.1549; found: 316.1541 (Δ = 2.5 ppm).
(8) The results of DFT calculations for ketone *trans*-**3** and *cis*-**3** at the level of B3LYP/6-31G* showed *trans*-**3** is more stable than *cis*-**3** by 2.1 kcal/mol.
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