Supporting Information

Palladium-Catalyzed Aerobic Oxidative Cyclization of Aliphatic Alkenyl Amides for the Construction of Pyrrolizidine and Indolizidine Derivatives

Kai-Yip Lo, Liu Ye, Dan Yang*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

yangdan@hku.hk

Table of Contents

General Methods S2
Preparation of Substrates S3
Characterization Data of Substrates S14
Representative Procedure of Pd-Catalyzed Intramolecular Cyclization S20
Characterization Data of Products S20
References S26
NMR Spectra of New Compounds S27
General Information:

All reactions were performed in oven-dried flasks. Palladium(II) trifluoroacetate and palladium(II) acetate were purchased from Aldrich and Precious Metals, respectively, and were used as received. All other commercially available chemicals were used as received. Reactions were monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 pre-coated glass plates with 0.25 mm thickness. Components were visualized by illumination with short-wavelength ultra-violet light, iodine and/or staining in phosphomolybdic acid (PMA) solution followed by heating. Flash column chromatography were performed on E. Merck silica gel 60 (230–400 mesh ASTM) using ethyl acetate/n-hexane as eluting solvents.

$^1$H and $^{13}$C NMR spectra were recorded in deuteriochloroform (CDCl$_3$) with tetramethylsilane (TMS) as internal standard at ambient temperature unless otherwise indicated on a Bruker Avance DPX 300 Fourier Transform Spectrometer operating at 300 MHz for $^1$H and 75 MHz for $^{13}$C, a Bruker Avance DPX 400 Fourier Transform Spectrometer operating at 400 MHz for $^1$H and 100 MHz for $^{13}$C, or a Bruker Avance DPX 500 Fourier Transform Spectrometer operating at 500 MHz for $^1$H and 125 MHz for $^{13}$C. Infrared absorption spectra were recorded as a solution in CH$_2$Cl$_2$ with a Bio-Rad FTS 165 Fourier Transform spectrophotometer. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low resolution and high resolution mass spectra. Melting points were determined by Axiolab ZEISS microscope apparatus and were uncorrected.
General procedure for preparation of unsaturated amides 2.4a–b

Reagents and conditions: (a) (i) oxalyl chloride, DMF, CH₂Cl₂, r.t., 8 h; (ii) aqueous ammonia, r.t., 22 h.

Typical procedure for the preparation of unsaturated amides 2.4a–b

To a solution of 4-pentenoic acid (6.17 g, 61.5 mmol) in dry CH₂Cl₂ (80 mL) with dry tube packed with anhydrous calcium chloride was added oxalyl chloride (6.2 mL, 73.9 mmol) dropwise at room temperature, followed by the addition of 2 drops of DMF. After 8 h, the resulting mixture was concentrated in vacuo and the residue was taken up with CH₂Cl₂ (40 mL). The mixture was added aqueous ammonia solution (28%, 100 mL) dropwise through a funnel in an iced-water bath. After 22 h, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo.

The pale yellow residue (4.41 g, 72% yield) was pure enough for the next step.

2.4a: 72% yield; pale yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 5.90–5.80 (m, 2H), 5.58 (brs, 1H), 5.09 (dd, J = 17.1, 1.6 Hz, 1H), 5.03 (dd, J = 10.2, 1.3 Hz, 1H), 2.43–2.37 (m, 2H), 2.35–2.31 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 174.9 (C), 136.8 (CH), 115.7 (CH₂), 35.0 (CH₂), 29.3 (CH₂). The spectral data is consistent with the reported data.¹

2.4b: 79% yield; orange solid; ¹H NMR (400 MHz, CDCl₃) δ 6.10 (brs, 1H), 5.79 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.68 (brs, 1H), 5.06–4.97 (m, 2H), 2.23 (t, J = 7.6 Hz, 2H),
2.11 (q, $J = 7.1$ Hz, 2H), 1.74 (quintet, $J = 7.5$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.7 (C), 137.7 (CH), 115.3 (CH$_2$), 34.9 (CH$_2$), 32.9 (CH$_2$), 24.4 (CH$_2$). The spectral data is consistent with the reported data.$^2$

**General procedure for the preparation of unsaturated nitriles 2.4c–d**

```
R-CN \[ \rightarrow \] \[ \rightarrow \]
```

Reagents and conditions: (a) For 2.3c, (i) LDA, THF, $-40$ °C, 45 min; for 2.3d, (i) NaH, DMF, 0 °C to r.t., 1 h; (ii) for 2.3c–d, allyl bromide, 0 °C to r.t., 18 h.

**Procedure for the preparation of unsaturated nitriles 2.4c**

In an oven-dried round-bottomed flask, a solution of freshly distilled diisopropylamine (8.5 mL, 60.5 mmol) in dry THF (140 mL) was cooled to $-40$ °C for 10 min under an Ar atmosphere. n-BuLi solution (1.5 M, 40.3 mL, 60.1 mmol) was added slowly and the mixture was warmed to room temperature for 30 min. The solution was cooled to $-40$ °C, and isobutyronitrile (4.9 mL, 55.0 mmol) in dry THF (20 mL) was added slowly. After stirring for 45 min, allyl bromide (9.6 mL, 110.0 mmol) was added, and the mixture was warmed to room temperature for 18 h. CH$_2$Cl$_2$ (25 mL) was added and the solution was washed with water (100 mL × 3) followed by brine, dried over anhydrous Na$_2$SO$_4$, filtered with a short pad of silica gel, eluted with ethyl acetate, and concentrated in vacuo. Crude nitrile 2.4c was used in the next step directly.

**Procedure for the preparation of unsaturated nitrile 2.4d**

To a suspension of NaH (60 % dispersion in oil, 2.68 g, 67.1 mmol) in dry DMF (65 mL) in an oven-dried round-bottomed flask under an Ar atmosphere was added diphenylacetonitrile (10.1 g, 52.3 mmol) portionwise at 0 °C, and the mixture was warmed to room temperature. After 1 h, the reaction mixture was cooled to 0 °C and allyl bromide (5.0 mL, 57.5 mmol) was slowly added. The resulting mixture was warmed to
room temperature. After 12 h, the mixture was quenched with water (150 mL) and extracted with CH₂Cl₂ (50 mL × 3). The combined organic layers were washed with water (100 mL × 3) followed by brine, dried over anhydrous Na₂SO₄, filtered with a short pad of silica gel, eluted with ethyl acetate and concentrated in vacuo. Crude nitrile 2.4d was used in the next step directly.

**General procedure for the preparation of unsaturated amide 2.4e**

![Diagram](image)

Reagents and conditions: (a) (i) oxalyl chloride, DMF, CH₂Cl₂, r.t., 7 h, (ii) MeOH, r.t., 19 h; (b) (i) LDA, THF, −78 °C, 30 min, (ii) allyl bromide, −78 °C to r.t., 22 h; (c) potassium hydroxide, 1:1 ethanol/water solution, reflux, 24 h; (d) (i) oxalyl chloride, DMF, CH₂Cl₂, r.t., 8 h, (ii) aqueous ammonia, r.t., 22 h.

**Procedure for the preparation of ester 2.8e**

To a solution of cyclopentanecarboxylic acid (9.5 mL, 87.6 mmol) in dry CH₂Cl₂ (100 mL) in an oven-dried flask equipped with an anhydrous CaCl₂ tube was added oxalyl chloride (8.8 mL, 105.1 mmol) dropwise, followed by 2 drops of DMF. After 7 h, the resulting mixture was concentrated in vacuo and the residue was taken up with MeOH (25 mL). After 19 h, the mixture was concentrated in vacuo and the residue was dissolved in CH₂Cl₂ (100 mL), then washed with saturated NaHCO₃ and brine. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by simple distillation to afford 2.8e (9.5 g, 74.3 mmol, 85 % yield) as a colourless oil.

![Diagram](image)

**2.8e**: 85 % yield; colourless oil; ¹H NMR (300 MHz, CDCl₃) δ 3.67 (s, 3H), 2.73 (quintet,
$J = 7.8$ Hz, 1H), 1.91–1.55 (m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.2 (C), 51.5 (CH$_3$), 43.6 (CH), 29.9 (CH$_2$), 25.7 (CH$_2$). The spectral data is consistent with the reported data.\textsuperscript{3}

**Procedure for the preparation of acid 2.10e**

To an oven-dried round bottom flask was added a solution of freshly distilled diisopropylamine (1.6 mL, 11.3 mmol) in dry THF (10 mL), together with n-BuLi solution (1.5 M, 5.7 mL, 8.58 mmol) at 0 °C. After 30 min, the resulting mixture was cooled to −78 °C and ester 2.8e (1.00 g, 7.80 mmol) was added. After 30 min, allyl bromide (0.75 mL, 8.58 mmol) was added to the mixture and it was stirred for 10 min. The mixture was warmed to room temperature. After 22 h, the solution was quenched with water (20 mL) and extracted with Et$_2$O (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, filtered and concentrated \textit{in vacuo} to afford crude ester 2.9e.

To a solution of crude ester 2.9e in ethanol (15 mL) was added KOH solution (2 M, 15 mL) and the reaction mixture was heated under reflux for 24 h. The solvent was evaporated and water (10 mL) was added. The mixture was washed with Et$_2$O (15 mL × 3), then acidified to pH 1 and extracted with Et$_2$O (15 mL × 3). The organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated \textit{in vacuo} to obtain crude acid 2.10e.

Amide 2.4e was prepared from crude carboxylic acid 2.10e by following the procedure for the preparation of amides 2.4a–b from carboxylic acids 2.3a–b, and the crude amide was pure enough to be used in the next reaction directly.

![amidestructure](image)

\textbf{2.4e:} Yield 85\% (3 steps from 2.8e); orange solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.79 (ddt, $J = 16.6$, 10.6, 7.3 Hz, 1H), 5.60 (brs, 2H), 5.12–5.06 (m, 2H), 2.34 (dd, $J = 7.2$, 1.1 Hz, 2H), 2.03–1.97 (m, 2H), 1.71–1.64 (m, 4H), 1.63–1.56 (m, 2H); $^{13}$C NMR (100 MHz,
CDCl₃) δ 179.9 (C), 134.7 (CH), 117.8 (CH₂), 53.9 (C), 43.2 (CH₂), 35.5 (CH₂), 24.5 (CH₂); HRMS (EI) for C₉H₁₅NO (M⁺): calcd 153.1154, found 153.1149.

**General procedure for the preparation of unsaturated amine 2.5f**

![Chemical structure](image)

Reagents and conditions: (a) benzylamine, p-toluenesulfonic acid monohydrate, toluene, reflux, 19 h; (b) KtOBu, THF, reflux, 2 h; (c) (i) oxalic acid, H₂O, CH₂Cl₂, reflux, 2 h, (ii) sodium hydroxide solution.

**General procedure for the preparation of unsaturated amine 2.5f**

To a solution of 2-allylcyclohexanone 2.11f (1.1 mL, 7.2 mmol) in toluene (40 mL) were added benzylamine (7.9 mL, 72.4 mmol) and p-toluenesulfonic acid monohydrate (0.34 g, 1.8 mmol) slowly. The mixture was heated under reflux with a Dean-stark apparatus for 19 h. Saturated NaHCO₃ solution (30 mL) was added to the resulting mixture and it was extracted with CH₂Cl₂ (30 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford crude imine 2.12f.

To the solution of crude imine residue 2.12f in dry THF (30 mL) was added KtOBu (4.06 g, 36.2 mmol), and the reaction mixture was heated under reflux for 2 h. Water (100 mL) was added and the mixture was extracted with Et₂O (100 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to obtain crude imine 2.13f.

To a solution of crude imine 2.13f in CH₂Cl₂ (10 mL) and H₂O (10 mL) was added oxalic acid (0.91 g, 7.24 mmol), and the resulting mixture was heated under reflux with vigorous stirring for 2 h. The reaction mixture was concentrated and water (10 mL) was added. The aqueous layer was washed with Et₂O (20 mL × 3), basified to pH 14, extracted with Et₂O (20 mL × 4). The combined organic payers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude amine was used in the next step without purification to afford amine 2.5f.
General procedure for the preparation of unsaturated amide 2.1h

Reagents and conditions: (a) p-toluenesulfonyl chloride, CH₂Cl₂, 0 °C, 4 h; (b) acrylic acid, N-methylmorpholine, isobutyl chloroformate, CH₂Cl₂, 20 °C; (c) allyl bromide, K₂CO₃, CH₃CN, reflux, 1.5 h, 91 % yield (3 steps).

General procedure for the preparation of unsaturated amide 2.1h

To a solution of ethylenediamine (30.0 g, 498.3 mmol) in dry CH₂Cl₂ (125 mL) was added slowly p-toluenesulfonyl chloride (9.5 g, 49.8 mmol) in dry CH₂Cl₂ (125 mL) at 0 °C. The reaction mixture was stirred for 4 h. The resulting solution was concentrated and washed with water (50 mL × 2), dried over anhydrous Na₂SO₄ and KOH pellets, filtered and evaporated in vacuo to obtain crude amine 2.5h.

To a solution of acrylic acid (2.5 mL, 36.4 mmol) in dry CH₂Cl₂ (300 mL) was added N-methylmorpholine (5.6 mL, 50.9 mmol) slowly under an argon atmosphere, then the solution was cooled to –20 °C for 15 min. Isobutyl chloroformate (5.0 mL, 38.5 mmol) was added dropwise and the mixture was stirred for 1 h. Amine 2.5h was added to the solution and the resulting mixture was stirred for 15 min, then warmed to room temperature and stirred for 18 h. The reaction mixture was sequentially washed with 1M K₂HPO₄ solution (200 mL), water (50 ml) and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford amide 2.22h.

To a mixture of amide 2.22h and K₂CO₃ (5.52 g, 40.0 mmol) in CH₃CN (200 mL) was added allyl bromide (3.4 mL, 40.0 mmol). The resulting mixture was heated under reflux for 1.5 h. The solution was concentrated and filtered through a short pad of silica gel with ethyl acetate as the eluent, then the filtrate was concentrated in vacuo to afford a pale yellow solid 2.1h (10.22 g, 91 % yield).
General procedure for the preparation of unsaturated amide 2.4i

\[ \text{Ph} = \text{C} = \text{CH-CHO} \xrightarrow{a} \xrightarrow{b} \text{COOH} \xrightarrow{b} \text{NH}_{2} \]

Reagents and conditions: (a) Meldrum’s acid, triethylammonium formate solution, Et$_{3}$N, DMF, 90 °C, 2 h; (b) (i) oxalyl chloride, DMF, CH$_{2}$Cl$_{2}$, r.t., 8 h, (ii) aqueous ammonia, r.t., 22 h.

Procedure for the preparation of acid 2.3i

To a solution of trans-cinnamaldehyde (3.6 mL, 28.9 mmol) and Meldrum’s acid (4.58 g, 31.8 mmol) in DMF (10 mL) was added triethylammonium formate solution, which was prepared from triethylamine (4.86 mL, 34.9 mmol) and formic acid (3.28 mL, 86.9 mmol). The reaction mixture was heated to 90 °C. After 2 h, iced water (20 mL) was added to the cooled reaction mixture, and then 15% NaOH solution (10 mL) was added. The aqueous solution was washed with Et$_{2}$O (30 mL x 3), then acidified to pH 1 with 6M HCl solution and extracted with Et$_{2}$O (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous MgSO$_{4}$, filtered and concentrated in vacuo to obtain crude carboxylic acid 2.3i.

Amine 2.4i was prepared from crude carboxylic acid 2.3i by following the procedure for the preparation of 2.4a–b from corresponding carboxylic acids 2.3a–b.

General procedure for the preparation of unsaturated amine 2.5j

\[ \text{Ph} = \xrightarrow{a} \xrightarrow{b} \xrightarrow{c} \xrightarrow{d} \xrightarrow{e} \]

59
Reagents and conditions: (a) Pd(PPh₃)₄, CuI, PhI, Et₃N, THF, r.t., 24 h; (b) 5 % w/w Lindlar catalyst, quinoline, MeOH, H₂, r.t., 15 h; (c) MsCl, Et₃N, CH₂Cl₂, 0 °C, 4 h; (d) NaN₃, DMF, 55 °C, 6 h; (e) LiAlH₄, Et₂O, 0 °C, 22 h.

Procedure for the preparation of unsaturated amine 2.5j
To a dry and argon-flushed 100-mL round-bottomed flask was added Et₃N (9.7 mL, 69.9 mmol) in THF (4 mL). To this solution were added iodobenzene (1.9 mL, 17.3 mmol) and 4-pentyn-1-ol (0.8 mL, 8.6 mmol). The mixture solution was degassed with argon for 30 min before Pd(PPh₃)₄ (100 mg, 0.086 mmol) and copper(I) iodide (33 mg, 0.17 mmol) were added to the mixture. The reaction mixture was stirred in the dark at room temperature. After 24 h, the mixture was filtered and concentrated in vacuo to obtain the crude alkynol 2.16j.

To a solution of the crude alkynol 2.16j and quinoline (0.64 mL, 5.4 mmol) in MeOH (20 mL) was added 5 % w/w Lindlar’s catalyst (1.38 g, 0.65 mmol). The mixture solution was stirred under a hydrogen atmosphere at room temperature for 15 h, then the solution was filtered and concentrated in vacuo to afford the crude alkenyl alcohol 2.17j.

To a solution of the crude alkenyl alcohol 2.17j and Et₃N (2.4 mL, 17.3 mmol) in dry CH₂Cl₂ (40 mL) was added methanesulfonyl chloride (0.87 mL, 11.2 mmol) dropwise at 0 °C under an argon atmosphere. After 4 h, the mixture solution was washed with 2 M HCl (40 mL), and extracted with CH₂Cl₂ (40 mL × 3). The combined organic layers were washed with saturated NaHCO₃ solution and brine. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to obtain the crude mesylate 2.18j.

To a solution of the crude mesylate 2.18j in DMF (30 mL) was added sodium azide (1.12 g, 17.3 mmol), and the resulting solution was heated to 55 °C. After 6 h, the solution was added with water (60 mL) and extracted with Et₂O (30 × 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to obtain the crude azide 2.19j.
To an oven-dried round-bottomed flask charged with a solution of LiAlH₄ (0.49 g, 13.0 mmol) in dry Et₂O (50 mL) was added crude azide 2.19j dropwise at 0 °C. The reaction mixture was warmed to room temperature. After 22 h, the reaction mixture was cooled to 0 °C and was quenched with water (1.0 mL) and 15 % NaOH solution (1.0 mL). The reaction mixture was stirred for 15 min and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to afford the crude amine 2.5j.

**General procedure for the preparation of unsaturated nitrile 2.4k**

![Diagram](image)

Reagents and conditions: (a) (i) n-BuLi, THF, –80 °C, 1 h, (ii) 3-bromocyclohexene, –70 °C to r.t., 8 h.

**Procedure for the preparation of unsaturated nitrile 2.4k**

A solution of freshly distilled acetonitrile (2.5 mL, 46.6 mmol) in dry THF (120 mL) in an oven-dried round-bottomed flask was cooled to –80 °C for 10 min in an argon atmosphere. n-BuLi solution (2.4 M, 22.0 mL, 52.8 mmol) was added slowly and the solution was warmed to room temperature for 1 h. The solution was cooled to –70 °C and 3-bromocyclohexene (3.6 mL, 31.1 mmol) was added. The solution was stirred at –70 °C for 1 h, then warmed to room temperature gradually for 4 h. The mixture was quenched with aqueous ammonium chloride solution and extracted with Et₂O (100 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered with a short pad of silica gel to obtain crude nitrile 2.4k which was used in the next step directly.

**General procedure for the preparation of unsaturated nitrile 2.4l**

511
Reagents and conditions: (a) (i) pyrrolidine, toluene, reflux, 4 h, (ii) acrylonitrile, dioxane, r.t. to reflux, 19 h; (b) PPh₃CH₃Br, KO'Bu, toluene, 0 °C to r.t., 24 h.

Procedure for the preparation of unsaturated nitrile 2.21l
To a solution of cyclohexanone (2.84 mL, 27.4 mmol) in toluene (20 mL) was added pyrrolidine (2.5 mL, 30.1 mmol), and the solution was heated under reflux with Dean-Stark trap apparatus until no more water evolved. The solution was then evaporated to remove any toluene and excess pyrrolidine. To a solution of the residue in dry dioxane (20 mL) was added acrylonitrile (2.3 mL, 35.6 mmol), and the solution was heated under reflux for 21 h. The solution was cooled to room temperature, and water (20 mL) was added into the solution. After reflux for 19 h, the reaction mixture was cooled and extracted with Et₂O (20 mL × 3). The combined organic layers were washed with 2 M HCl solution and brine, then dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to obtain the crude nitrile 2.21l.

Procedure for the preparation of unsaturated nitrile 2.4l
To a solution of methyltriphenylphosphonium bromide (19.1 g, 53.4 mmol) in dry toluene (200 mL) was added potassium tert-butoxide (3.0 g, 53.4 mmol) at 0 °C, and the yellow solution was stirred for 1.5 h. Ketone 2.21l (4.04 g, 26.7 mmol) was added into the reaction mixture and it was stirred at room temperature for 18 h. The orange solution was quenched with aqueous ammonium chloride solution and extracted with Et₂O (150 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to obtain the crude nitrile 2.4l.

Typical procedure for the preparation of unsaturated amines 2.5a–b, 2.5e and 2.5i
To a dry diethyl ether solution (100 mL) of LiAlH$_4$ (2.53 g, 66.7 mmol) at 0 °C was added amide 2.4a (4.41 g, 44.5 mmol) portionwise. The reaction mixture was warmed to room temperature. After 18 h, the reaction mixture was cooled to 0 °C, and water (2.5 mL) was added dropwise, followed by addition of 15 \% NaOH solution (2.5 mL). The reaction mixture was stirred for 15 min until white precipitation was formed. The reaction mixture was filtered and the filtrate was dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo to obtain crude amine 2.5a.

**Typical procedure for the preparation of unsaturated amines 2.5c–d, 2.5k, and 2.5l**

![Chemical reaction diagram]

To a dry diethyl ether (Et$_2$O) solution of LiAlH$_4$ (1.21 g, 31.9 mmol) at 0 °C was added crude nitrile 2.4c dropwise. The reaction mixture was warmed to room temperature. After 16 h, the reaction mixture was cooled to 0 °C and was quenched with water (1.5 mL) and 15 \% NaOH solution (1.5 mL). The reaction mixture was stirred for 15 min until white precipitation was formed. The reaction mixture was filtered and the filtrate was dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo to obtain crude amine 2.5c.

**General procedure for the preparation of 2.5c–d, 2.5k and 2.5l**

To an oven-dried round-bottomed flask charged with a solution of LiAlH$_4$ (1.21 g, 31.9 mmol) in dry Et$_2$O (50 mL) was added crude nitrile 2.4e dropwise at 0 °C. The reaction mixture was warmed to room temperature. After 16 h, the reaction mixture was cooled to 0 °C and was quenched with water (1.5 mL) and 15 \% NaOH solution (1.5 mL). The reaction mixture was stirred for 15 min until white precipitation was formed. The reaction mixture was filtered and the filtrate was dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo to obtain crude amine 2.5c.

**Typical procedure for the preparation of unsaturated amides 1a–l**

![Chemical reaction diagram]
To a solution of crude amine \(2.5a\) and Et\(\text{N}\) (7.0 mL, 49.3 mmol) in dry CH\(_2\)Cl\(_2\) (70 mL) at 0 °C was added a CH\(_2\)Cl\(_2\) (70 mL) solution of acryloyl chloride (4.0 mL, 49.3 mmol) via a funnel during a period of 15 min. The reaction mixture was warmed to room temperature and stirred for 22 h. The solution was washed with 2 M HCl (70 mL), saturated NaHCO\(_3\) solution (70 mL) and brine. The combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The residue was purified by flash column chromatography to afford \(1a\) (3.40 g, 24.4 mmol, 59 % yield) as a yellow oil.

\[
\text{1a: Yield 59 % (2 steps from 2.4a); yellow oil; analytical TLC (silica gel 60), 70% EtOAc in n-hexane, } R_f = 0.61; \text{ }^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 6.79 \text{ (brs, 1H), 6.26 (dd, } J = 17.0, 2.6 \text{ Hz, 1H), 6.19 (dd, } J = 17.0, 9.3 \text{ Hz, 1H), 5.79 (ddt, } J = 16.9, 10.2, 6.6 \text{ Hz, 1H), 5.60 (dd, } J = 9.3, 2.6 \text{ Hz, 1H), 5.03 (dd, } J = 17.1, 3.4, 1.6 \text{ Hz, 1H), 4.97 (dd, } J = 10.2, 3.0, 1.2 \text{ Hz, 1H), 3.33 (td, } J = 7.1 \text{ Hz, 2H), 2.17–2.02 (m, 2H), 1.65 (quintet, } J = 7.5 \text{ Hz, 2H); } ^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 165.8 \text{ (C), 137.6 (CH), 131.0 (CH), 125.7 (CH}_2\text{), 115.0 (CH}_2\text{), 39.0 (CH}_2\text{), 30.9 (CH}_2\text{), 28.4 (CH}_2\text{); IR (CH}_2\text{Cl}_2\text{) 3447, 1833, 1684, 1216, 1153, 1064, 803 cm}^{-1}; \text{ HRMS (EI) for C}_8\text{H}_{13}\text{NO (M}^+\text{): calcd 139.0997, found 130.0995.}
\]

\[
\text{1b: Yield 75 % (2 steps from 2.4b); yellow oil; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, } R_f = 0.45; \text{ }^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 6.93 \text{ (brs, 1H), 6.28–6.18 (m, 2H), 5.77 (ddt, } J = 16.9, 10.2, 6.7 \text{ Hz, 1H), 5.60 (dd, } J = 8.3, 3.7 \text{ Hz, 1H), 5.02-4.92 (m, 2H), 3.31 (d, } J = 7.1 \text{ Hz, 2H), 2.06 (q, } J = 7.1 \text{ Hz, 2H), 1.60–1.52 (m, 2H), 1.47–1.39 (m, 2H); } ^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 165.8 \text{ (C), 138.2 (CH), 131.0 (CH), 125.6 (CH}_2\text{), 114.5 (CH}_2\text{), 39.3 (CH}_2\text{), 33.1 (CH}_2\text{), 28.7 (CH}_2\text{), 26.0 (CH}_2\text{); IR (CH}_2\text{Cl}_2\text{) 3447, 3308, 2859, 1833, 1684, 1216, 1153, 1064, 802 cm}^{-1}; \text{ HRMS (EI) for C}_9\text{H}_{15}\text{NO (M}^+\text{): calcd 153.1154, found 153.1139.}
\]
1c: 21 % yield (3 steps from 2.3c); orange oil; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, Rf = 0.32; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 6.38 (brs, 1H), 6.25 (d, J = 3.6 Hz, 1H), 6.24 (d, J = 8.3 Hz, 1H), 5.90–5.76 (m, 1H), 5.62 (dd, J = 8.3, 3.6 Hz, 1H), 5.07–5.00 (m, 2H), 3.18 (d, J = 6.5 Hz, 2H), 2.01 (d, J = 7.5 Hz, 2H), 0.90 (s, 6H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) δ 165.8 (C), 134.7 (CH), 131.1 (CH), 125.9 (CH\(_2\)), 117.4 (CH\(_2\)), 49.0 (CH\(_2\)), 44.4 (CH\(_2\)), 34.7 (C), 24.8 (CH\(_3\)); IR (CH\(_2\)Cl\(_2\)) 3445, 3337, 3047, 2873, 1686, 1639, 1214, 1115, 1063 cm\(^{-1}\); HRMS (EI) for C\(_{10}\)H\(_{17}\)NO (M\(^+\)): calcd 167.1310, found 167.1322.

1d: 73 % yield (3 steps from 2.3d); white solid; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, Rf = 0.29; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.34–7.30 (m, 4H), 7.26–7.19 (m, 6H), 6.15 (dd, J = 17.0, 1.2 Hz, 1H), 5.89 (dd, J = 17.0, 10.3 Hz, 1H), 5.56 (dd, J = 10.3, 1.2 Hz, 1H), 5.48–5.39 (m, 1H), 5.08 (brs, 1H), 4.97 (d, J = 13.7 Hz, 2H), 4.05 (d, J = 5.9 Hz, 2H), 2.86 (d, J = 7.1 Hz, 2H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) δ 165.3 (C), 145.1 (C), 133.6 (CH), 130.9 (CH), 128.3 (CH), 128.0 (CH), 126.6 (CH), 126.3 (CH\(_2\)), 118.8 (CH\(_2\)), 50.3 (C), 45.9 (CH\(_2\)), 42.0 (CH\(_2\)); IR (CH\(_2\)Cl\(_2\)) 3428, 3049, 2987, 2832, 1970, 1678, 1515, 1444, 1247, 1157 cm\(^{-1}\); HRMS (EI) for C\(_{20}\)H\(_{21}\)NO (M\(^+\)): calcd 291.1623, found 291.1617.

1e: 60% yield (2 steps from 2.4e); orange oil; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, Rf = 0.62; \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 6.29–6.12 (m, 3H), 5.90–5.78 (m, 1H), 5.62 (dd, J = 9.6, 2.2 Hz, 1H), 5.07 (d, J = 17.0 Hz, 1H), 5.06 (d, J = 9.6 Hz, 1H),
3.27 (d, $J = 6.2$ Hz, 2H), 2.11 (d, $J = 7.4$ Hz, 2H), 1.72–1.57 (m, 4H), 1.49–1.42 (m, 4H); 
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.8 (C), 135.6 (CH), 131.0 (CH), 126.0 (CH$_2$), 117.2 (CH$_2$), 46.3 (CH$_2$), 46.1 (C), 42.5 (CH$_2$), 35.0 (CH$_2$), 24.7 (CH$_2$); IR (CH$_2$Cl$_2$) 3445, 3328, 3047, 2865, 1685, 1638, 1506, 1214, 1155 cm$^{-1}$; HRMS (EI) for C$_{12}$H$_{19}$NO (M$^+$): calcd 193.1467, found 193.1466.

![Image](image.png)

1f: 32 % yield (4 steps from 2.11f); white solid; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f$ = 0.50; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.27 (dd, $J = 16.9$, 1.9 Hz, 1H), 6.19 (dd, $J = 17.0$, 9.8 Hz, 1H), 6.05 (d, $J = 7.4$ Hz, 1H), 5.62 (dd, $J = 9.8$, 1.9 Hz, 1H), 5.00 (d, $J = 15.9$ Hz, 1H), 4.99 (d, $J = 11.2$ Hz, 2H), 4.32–4.24 (m, 1H), 2.15–2.09 (m, 1H), 1.95–1.89 (m, 1H), 1.78–1.70 (m, 2H), 1.70–1.58 (m, 2H), 1.55–1.48 (m, 2H), 1.47–1.40 (m, 1H), 1.30–1.19 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.9 (C), 136.9 (CH), 131.2 (CH), 125.9 (CH$_2$), 115.9 (CH$_2$), 48.2 (CH), 39.1 (CH), 35.9 (CH$_2$), 30.2 (CH$_2$), 27.3 (CH$_2$), 24.0 (CH$_2$), 21.8 (CH$_2$); IR (CH$_2$Cl$_2$) 3440, 3047, 2859, 2686, 1679 cm$^{-1}$; HRMS (EI) for C$_{12}$H$_{19}$NO (M$^+$): calcd 193.1467, found 193.1466.

![Image](image.png)

1g: 21 % yield (4 steps from 2.11f); white solid; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f$ = 0.39; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.27 (dd, $J = 16.9$, 1.5 Hz, 1H), 6.09 (dd, $J = 16.9$, 10.2 Hz, 1H), 5.78–5.70 (m, 1H), 5.63 (dd, $J = 10.2$, 1.5 Hz, 1H), 5.50 (d, $J = 7.7$ Hz, 1H), 4.98 (d, $J = 10.8$ Hz, 2H), 3.70 (ddd, $J = 20.5$, 10.7, 4.0 Hz, 1H), 2.35–2.26 (m, 1H), 2.05–1.68 (m, 5H), 1.36–1.05 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.9 (C), 136.7 (CH), 131.2 (CH), 126.1 (CH$_2$), 116.2 (CH$_2$), 52.32 (CH), 43.1 (CH), 37.3 (CH$_2$), 33.8 (CH$_2$), 30.9 (CH$_2$), 25.5 (CH$_2$), 25.2 (CH$_2$); IR (CH$_2$Cl$_2$) 3425, 3049, 2934, 1674 cm$^{-1}$; HRMS (EI) for C$_{12}$H$_{19}$NO (M$^+$): calcd 193.1467, found 193.1477.
**1h:** 91 % yield (3 steps from 2.14 h); pale yellow solid; analytical TLC (silica gel 60), 75% EtOAc in n-hexane, R$_f$ = 0.37; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.76 (bs, 1H), 6.27 (dd, J = 17.1, 1.7 Hz, 1H), 6.16 (dd, J = 17.1, 10.1 Hz, 1H), 5.68– 5.58 (m, 2H), 5.19 (dd, J = 17.2, 1.4 Hz, 1H), 5.15 (dd, J = 10.1, 1.2 Hz, 1H), 3.83 (d, J = 6.5 Hz, 2H), 3.48 (q, J = 5.8 Hz, 2H), 3.27 (t, J = 6.0 Hz, 2H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.8 (C), 143.5 (C), 135.9 (C), 132.4 (CH), 130.8 (CH), 129.7 (CH), 126.9 (CH), 126.0 (CH$_2$), 119.5 (CH$_2$), 51.6 (CH$_2$), 46.2 (CH$_2$), 38.2 (CH$_2$), 21.3 (CH$_3$); IR (CH$_2$Cl$_2$) 3442, 3392, 3048, 2985, 1679, 1520, 1421, 1249, 1157, 1091, 989 cm$^{-1}$; HRMS (EI) for C$_{11}$H$_{14}$NO$_2$S (M$^+$ - C$_4$H$_6$NO): calcd 224.0745, found 224.0749.

**1i:** 36 % yield (4 steps from trans-cinnamaldehyde); colourless liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R$_f$ = 0.55; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.34– 7.29 (m, 2H), 7.27–7.19 (m, 3H), 6.45 (d, J = 11.6 Hz, 1H), 6.19 (dd, J = 17.0, 1.6 Hz, 1H), 6.17 (bs, 1H), 6.02 (dd, J = 17.0, 10.2 Hz, 1H), 5.62 (dt, J = 11.7, 7.3 Hz, 1H), 5.55 (dd, J = 10.1, 1.6 Hz, 1H), 3.29 (q, J = 6.9 Hz, 2H), 2.36 (qd, J = 7.5, 1.6 Hz, 2H), 1.66 (quintet, 7.4 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 165.6 (C), 137.3 (C), 131.4 (CH), 130.8 (CH), 129.6 (CH), 128.6 (CH), 128.1 (CH), 126.5 (CH), 125.8 (CH$_2$), 38.8 (CH$_2$), 29.3 (CH$_2$), 25.5 (CH$_2$); IR (CH$_2$Cl$_2$) 3441, 3049, 2987, 1678 cm$^{-1}$; HRMS (EI) for C$_{14}$H$_{17}$NO (M$^+$): calcd 215.1310, found 215.1289.
1j: 29 % yield (6 steps from 4-pentyn-1-ol); colourless liquid; analytical TLC (silica gel 60); 50% EtOAc in n-hexane, Rf = 0.24; 1H NMR (400 MHz, CDCl3) δ 7.34–7.27 (m, 4H), 7.22–7.18 (m, 1H), 6.41(d, J = 15.8 Hz, 1H), 6.27 (dd, J = 17.0, 1.4 Hz, 1H), 6.20 (dt, J = 15.8, 6.9 Hz, 1H), 6.08 (dd, J = 17.0, 10.3 Hz, 1H), 5.71 (brs, 1H), 5.63 (dd, J = 10.3, 1.4 Hz, 1H), 3.40 (q, J = 10.1, 1.6 Hz, 2H), 3.27 (q, J = 7.9 Hz, 2H), 1.74 (quintet, J = 7.2 Hz, 2H); 13C NMR (100 MHz, CDCl3) δ 165.5 (C), 137.4 (C), 130.8 (CH), 130.6 (CH), 129.5 (CH), 128.5 (CH), 127.0 (CH), 126.3 (CH2), 125.9 (CH), 39.2 (CH2), 30.4 (CH2), 29.2 (CH2); IR (CH2Cl2) 3441, 3051, 2988, 1676 cm⁻¹; HRMS (EI) for C14H17NO (M⁺): calcd 215.1305, found 215.1291.

1k: 53 % yield (3 steps from 3-bromocyclohexene); colourless liquid; analytical TLC (silica gel 60); 50% EtOAc in n-hexane, Rf = 0.39; 1H NMR (400 MHz, CDCl3) δ 7.37 (brs, 1H), 6.32–6.21 (m, 2H), 5.68–5.65 (m, 1H), 5.60–5.53 (m, 2H), 3.37 (dd, J = 13.6, 7.0 Hz, 2H), 2.14 (brs, 1H), 1.96 (brs, 2H), 1.83–1.76 (m, 1H), 1.74–1.66 (m, 1H), 1.64–1.45 (m, 3H), 1.28–1.19 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 158.8 (C), 131.0 (CH), 130.7 (CH), 127.1 (CH), 125.3 (CH2), 37.1 (CH2), 35.5 (CH2), 32.5 (CH), 28.5 (CH2), 24.9 (CH2), 21.0 (CH2); IR (CH2Cl2) 3443, 3052, 2986, 1679 cm⁻¹; HRMS (EI) for C11H17NO (M⁺): calcd 179.1310, found 179.1306.
II: 34 % yield (4 steps from cyclohexanone); colourless liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, Rf = 0.56; ¹H NMR (300 MHz, CDCl₃) δ 7.26 (brs, 1H), 6.26–6.20 (m, 2H), 5.58 (dd, J = 7.0, 5.0 Hz, 1H), 4.63 (s, 1H), 4.54 (s, 1H), 3.30 (dd, J = 13.0, 6.7 Hz, 2H), 2.23–2.15 (m, 1H), 2.04–1.95 (m, 2H), 1.77–1.20 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 165.7 (C), 152.0 (C), 131.1 (CH), 125.3 (CH₂), 105.5 (CH₂), 42.6 (CH), 39.6 (CH₂), 34.3 (CH₂), 33.5 (CH₂), 29.1 (CH₂), 28.4 (CH₂), 27.2 (CH₂), 23.8 (CH₂); IR (CH₂Cl₂) 3440, 3052, 2989, 1677 cm⁻¹; HRMS (EI) for C₁₃H₂₁NO (M⁺): calcd 207.1623, found 207.1615.
Representative Procedure of Pd-Catalyzed Intramolecular Cyclization

Condition A for amide 1a:

To a well-stirred solution of Pd(TFA)$_2$ (33.2 mg, 0.1 mmol) in toluene (5 mL) were added pyridine (32.3 μl, 0.4 mmol) and DABCO (44.9 mg, 0.4 mmol), and the mixture was stirred continuously until the solid dissolved. The reaction solution was oxygenated for 15 min, then amide 1a (139.2 mg, 1.0 mmol) and toluene (5 mL) were added. The resulting solution was stirred under an O$_2$ atmosphere for 15 min, then heated at 95 °C with an air condenser under an O$_2$ atmosphere for 21 h. The reaction mixture was filtered through a short pad of celite and then concentrated in vacuo. The residue was purified by flash column chromatography to afford 2a (101.5 mg, 0.74 mmol, 74 % yield) as a yellow oil.

![Structure of 2a](image.png)

2a: Yield 74 %; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, $R_f$ = 0.18; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.93 (t, $J$ = 2.7 Hz, 1H), 5.28 (t, $J$ = 2.2 Hz, 1H), 3.77 (tt, $J$ = 7.2, 4.9 Hz, 1H), 3.67 (dt, $J$ = 12.0 Hz, 8.1 Hz, 1H), 3.21 (ddd, $J$ = 12.3, 9.6, 3.0 Hz, 1H), 3.00 (ddt, $J$ = 17.0 Hz, 7.4 Hz, 2.1 Hz, 1H), 2.50 (dd, $J$ = 17.0 Hz, 7.4 Hz, 3.1 Hz, 1H), 2.26–1.93 (m, 3H), 1.30–1.21 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.3 (C), 143.0 (C), 115.2 (CH$_2$), 58.5 (CH), 41.4 (CH$_2$), 31.9 (CH$_2$), 31.4 (CH$_2$), 25.9 (CH$_2$); IR (CH$_2$Cl$_2$) 3048, 2981, 2888, 1692, 1659 cm$^{-1}$; HRMS (EI) for C$_8$H$_{11}$NO (M$^+$): calcd 137.0841, found 137.0843.

![Structure of 2c](image.png)

2c: Yield 63 %; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, $R_f$ = 0.38; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.92 (t, $J$ = 2.6 Hz, 1H), 5.28 (t, $J$ = 2.1 Hz, 1H), 4.00 (ddd, $J$ = 12.7, 10.8, 5.6 Hz, 1H), 3.45 (d, $J$ = 11.9 Hz, 1H), 3.00 (ddt, $J$ = 11.9, 7.3, 2.0 Hz, 1H), 2.96 (d, $J$ = 11.9 Hz, 1H), 2.52–2.42 (m, 1H), 1.85 (dd, $J$ = 12.0, 5.8 Hz, 1H), 1.29–1.21 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.4
(C), 142.8 (C), 115.2 (CH₂), 57.5 (CH), 55.8 (CH₂), 47.3 (CH₂), 41.4 (C), 32.5 (CH₂), 28.7 (CH₃), 28.2 (CH₃); IR (CH₂Cl₂) 3049, 2985, 2884, 1693, 1655, 1441, 1247, 1205, 1159 cm⁻¹; HRMS (EI) for C₁₀H₁₅NO (M⁺): calcd 165.1154, found 165.1154.

**2d:** Yield 66%; white solid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, Rf = 0.51; ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.25 (m, 4H), 7.21–7.17 (m, 6H), 5.94 (s, 1H), 5.27 (s, 1H), 4.30 (d, J = 12.4 Hz, 1H), 3.94 (d, J = 12.4 Hz, 1H), 3.92–3.88 (m, 1H), 2.94 (dd, J = 16.8, 7.2 Hz, 1H), 2.59–2.51 (m, 2H), 2.13 (t, J = 11.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 169.1 (C), 146.1 (C), 146.1 (C), 142.6 (C), 128.3 (CH), 128.3 (CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 126.4 (CH), 115.5 (CH₂), 57.0 (C), 56.7 (CH), 53.9 (CH₂), 44.7 (CH₂), 32.0 (CH₂); IR (CH₂Cl₂) 3056, 2983, 2893, 1692, 1400 cm⁻¹; HRMS (EI) for C₂₀H₁₉NO (M⁺): calcd 289.1467, found 289.1465.

**2e:** Yield 64%; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, Rf = 0.40; ¹H NMR (400 MHz, CDCl₃) δ 5.92 (t, J = 2.6 Hz, 1H), 5.27 (t, J = 2.3 Hz, 1H), 3.94 (ddt, J = 10.5, 7.1, 5.4 Hz, 1H), 3.55 (d, J = 11.9 Hz, 1H), 3.07 (d, J = 11.9 Hz, 1H), 2.99 (ddt, J = 16.9, 7.3, 2.1 Hz, 1H), 2.47 (ddt, J = 16.9, 5.2, 3.1 Hz, 1H), 1.94 (dd, J = 11.9, 5.6 Hz, 1H), 1.74–1.56 (m, 8H), 1.33 (dd, J = 11.9, 10.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 168.4 (C), 142.9 (C), 115.1 (CH₂), 57.9 (CH), 54.4 (CH₂), 52.5(C), 45.1 (CH₂), 39.0 (CH₂), 38.6 (CH₂), 32.3 (CH₂), 24.2 (2CH₂); IR (CH₂Cl₂) 3051, 1699, 1404 cm⁻¹; HRMS (EI) for C₁₂H₁₇NO (M⁺): calcd 191.1310, found 191.1310.

**2f (major diastereomer):** Yield 35%; yellow liquid; analytical TLC (silica gel 60), 50%
EtOAc in n-hexane, R$_f$ = 0.29; $^1$H NMR (500 MHz, CDCl$_3$) δ 5.84 (d, J = 2.4 Hz, 1H), 5.22 (d, J = 2.2 Hz, 1H), 3.88 (td, J = 13.4, 6.2 Hz, 1H), 3.72 (dd, J = 15.0, 7.2 Hz, 1H), 2.94 (dd, J = 15.6, 6.3 Hz, 1H), 2.64–2.59 (m, 1H), 2.56–2.42 (m, 2H), 1.86 (dt, J = 11.2, 5.5 Hz, 1H), 1.72–1.48 (m, 5H), 1.39–1.14 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.7 (C), 145.5 (C), 113.9 (CH$_2$), 59.7 (CH), 53.8 (CH), 40.4 (CH), 35.0 (CH$_2$), 34.3 (CH$_2$), 27.5 (CH$_2$), 26.8 (CH$_2$), 23.0 (CH$_2$), 21.6 (CH$_2$); IR (CH$_2$Cl$_2$) 3054, 1702, 1413 cm$^{-1}$; HRMS (EI) for C$_{12}$H$_{17}$NO (M$^+$): calcd 191.1310, found 191.1312.

**2f** (minor diastereomer): Yield 14 %; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R$_f$ = 0.50; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.88 (dd, J = 2.6, 1.9 Hz, 1H), 5.26 (dd, J = 2.5, 1.1 Hz, 1H), 4.07 (quintet, J = 7.0 Hz, 1H), 4.00 (dd, J = 13.9, 6.2 Hz, 1H), 3.03 (dd, J = 16.3, 7.2 Hz, 1H), 2.42 (ddt, J = 16.3, 6.4, 3.2 Hz, 1H), 2.37–2.28 (m, 1H), 1.97–1.91 (m, 1H), 1.86–1.63 (m, 3H), 1.57–1.31 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.2 (C), 143.7 (C), 114.6 (CH$_2$), 56.0 (CH), 55.1 (CH), 38.6 (CH), 36.1 (CH$_2$), 34.5 (CH$_2$), 26.9 (CH$_2$), 26.8 (CH$_2$), 22.1 (CH$_2$), 21.4 (CH$_2$); IR (CH$_2$Cl$_2$) 2988, 1685 cm$^{-1}$; HRMS (EI) for C$_{12}$H$_{17}$NO (M$^+$): calcd 191.1310, found 191.1311.

**2g** (major diastereomer): Yield 38 %; white solid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R$_f$ = 0.48; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.85 (s, 1H), 5.24 (s, 1H), 3.93–3.86 (m, 1H), 3.00 (ddt, J = 15.6, 7.0, 1.4 Hz, 1H), 2.81–2.76 (m, 1H), 2.71–2.65 (m, 1H), 2.34 (ddt, J = 15.5, 8.0, 3.3 Hz, 1H), 1.93–1.88 (m, 2H), 1.83–1.73 (m, 3H), 1.64 (q, J = 11.3 Hz, 1H), 1.52–1.43 (m, 1H), 1.28–1.18 (m, 2H), 1.17–1.13 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.1 (C), 144.3 (C), 114.0 (CH$_2$), 64.0 (CH), 56.7 (CH), 47.2 (CH), 36.0 (CH$_2$), 35.2 (CH$_2$), 30.0 (CH$_2$), 28.5 (CH$_2$), 26.0 (CH$_2$), 25.2 (CH$_2$); IR (CH$_2$Cl$_2$) 3052, 2988, 1685, 1656 cm$^{-1}$; HRMS (EI) for C$_{12}$H$_{17}$NO (M$^+$): calcd 191.1310,
found 191.1305.

2g’ (minor diastereomer): Yield 4%; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, Rf = 0.54; 1H NMR (500 MHz, CDCl₃) δ 5.88–5.87 (m, 1H), 5.26–5.25 (m, 1H), 4.07 (quintet, J = 7.0 Hz, 1H), 4.00 (dd, J = 13.9, 6.2 Hz, 1H), 3.03 (tdd, J = 16.3, 7.4, 1.6 Hz, 1H), 2.42 (tdd, J = 16.3, 6.4, 3.2 Hz, 1H), 2.37–2.28 (m, 1H), 1.97–1.91 (m, 1H), 1.86–1.63 (m, 3H), 1.57–1.31 (m, 6H); 13C NMR (125 MHz, CDCl₃) δ 171.0 (C), 144.2 (C), 114.8 (CH₂), 63.0 (CH), 59.8 (CH), 49.1 (CH), 38.3 (CH₂), 33.4 (CH₂), 31.9 (CH₂), 29.7 (CH₂), 26.1 (CH₂), 24.9 (CH₂); IR (CH₂Cl₂) 3054, 1686 cm⁻¹; HRMS (EI) for C₁₂H₁₇NO (M⁺): calcd 191.1310, found 191.1312.

2h: Yield 58%; white solid; analytical TLC (silica gel 60), 75% EtOAc in n-hexane, Rf = 0.27; 1H NMR (500 MHz, CDCl₃) δ 7.60 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.96 (t, J = 2.8 Hz, 1H), 5.32 (t, J = 2.3 Hz, 1H), 4.17 (ddd, J = 13.2, 3.5, 1.2 Hz, 1H), 3.89 (ddd, J = 11.3, 3.8, 1.6 Hz, 1H), 3.79–3.72 (m, 2H), 3.06 (ddd, J = 13.1, 12.2, 4.0 Hz, 1H), 2.92 (ddt, J = 17.4, 8.0, 2.5 Hz, 1H), 2.42 (s, 3H), 2.28 (ddt, J = 17.4, 4.3, 2.7 Hz, 1H), 2.22 (td, J = 11.9, 3.6 Hz, 1H), 1.92 (t, J = 11.1 Hz, 1H); 13C NMR (125 MHz, CDCl₃) δ 166.1 (C), 144.2 (C), 137.5 (C), 132.7 (C), 129.9 (CH), 127.5 (CH), 116.9 (CH₂), 52.3 (CH), 51.7 (CH₂), 45.1 (CH₂), 39.5 (CH₂), 28.1 (CH₂), 21.5 (CH₃); IR (CH₂Cl₂) 3048, 2986, 1677, 1421 cm⁻¹; HRMS (EI) for C₁₅H₁₈N₂O₃S (M⁺): calcd 306.1038, found 306.1044.
2i: Yield 60%; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, \( R_f \) = 0.43; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.39–7.24 (m, 5H), 6.02 (d, \( J = 3.1 \) Hz, 1H), 5.02 (d, \( J = 2.3 \) Hz, 1H), 3.82–3.69 (m, 3H), 3.33–3.24 (m, 1H), 2.24–1.95 (m, 3H), 1.46 (dq, \( J = 19.0, 9.5 \) Hz, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 167.5 (C), 148.7 (C), 141.0 (C), 128.9 (CH), 128.3 (CH), 127.3 (CH), 116.7 (CH\(_2\)), 67.7 (CH), 52.1 (CH), 41.7 (CH\(_2\)), 31.4 (CH\(_2\)), 26.1 (CH\(_2\)); IR (CH\(_2\)Cl\(_2\)) 3052, 2981, 1684, 1440 cm\(^{-1}\); HRMS (EI) for C\(_{14}\)H\(_{15}\)NO (M\(^+\)): calcd 213.1154, found 213.1159.

\[
\begin{align*}
\text{2i} & : \text{Yield 60\%; yellow liquid; analytical TLC (silica gel 60), 50\% EtOAc in n-hexane, R}_f \ = \ 0.43; \ ^1\text{H NMR (500 MHz, CDCl}_3\text{) } \delta \ 7.39–7.24 \ (m, 5H), 6.02 \ (d, J = 3.1 \ Hz, 1H), 5.02 \ (d, J = 2.3 \ Hz, 1H), 3.82–3.69 \ (m, 3H), 3.33–3.24 \ (m, 1H), 2.24–1.95 \ (m, 3H), 1.46 \ (dq, J = 19.0, 9.5 \ Hz, 1H); ^{13}\text{C NMR (125 MHz, CDCl}_3\text{) } \delta \ 167.5 \ (C), 148.7 \ (C), 141.0 \ (C), 128.9 \ (CH), 128.3 \ (CH), 127.3 \ (CH), 116.7 \ (CH}_2\text{), 67.7 \ (CH), 52.1 \ (CH), 41.7 \ (CH}_2\text{), 31.4 \ (CH}_2\text{), 26.1 \ (CH}_2\text{); IR (CH}_2\text{Cl}_2\text{) 3052, 2981, 1684, 1440 cm}^{-1}; \text{HRMS (EI) for C}_{14}\text{H}_{15}\text{NO (M}^+\text{): calcd 213.1154, found 213.1159.}
\end{align*}
\]

2j: Yield 38%; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, \( R_f \) = 0.43; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.34–7.30 (m, 2H), 7.27–7.23 (m, 1H), 7.13–7.11 (m, 2H), 6.23 (d, \( J = 2.6 \) Hz, 1H), 5.30 (d, \( J = 2.1 \) Hz, 1H), 4.40 (dt, \( J = 8.0, 2.3 \) Hz, 1H), 4.09 (ddd, \( J = 10.8, 8.0, 5.5 \) Hz, 1H), 3.70 (dt, \( J = 12.0, 8.3 \) Hz, 1H), 3.28–3.22 (m, 1H), 1.98–1.87 (m, 2H), 1.37 (td, \( J = 12.2, 2.0 \) Hz, 1H), 0.87 (quintet, \( J = 11.0 \) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 168.5 (C), 145.8 (C), 139.8 (C), 128.7 (CH), 128.5 (CH), 127.0 (CH), 118.9 (CH\(_2\)), 63.6 (CH), 45.5 (CH), 42.1 (CH\(_2\)), 27.6 (CH\(_2\)), 25.4 (CH\(_2\)); IR (CH\(_2\)Cl\(_2\)) 3058, 2985, 1688, 1653, 1420 cm\(^{-1}\); HRMS (EI) for C\(_{14}\)H\(_{15}\)NO (M\(^+\)): calcd 213.1154, found 213.1150.

\[
\begin{align*}
\text{2j} & : \text{Yield 38\%; yellow liquid; analytical TLC (silica gel 60), 50\% EtOAc in n-hexane, R}_f \ = \ 0.43; \ ^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \ 7.34–7.30 \ (m, 2H), 7.27–7.23 \ (m, 1H), 7.13–7.11 \ (m, 2H), 6.23 \ (d, J = 2.6 \ Hz, 1H), 5.30 \ (d, J = 2.1 \ Hz, 1H), 4.40 \ (dt, J = 8.0, 2.3 \ Hz, 1H), 4.09 \ (ddd, J = 10.8, 8.0, 5.5 \ Hz, 1H), 3.70 \ (dt, J = 12.0, 8.3 \ Hz, 1H), 3.28–3.22 \ (m, 1H), 1.98–1.87 \ (m, 2H), 1.37 \ (td, J = 12.2, 2.0 \ Hz, 1H), 0.87 \ (quintet, J = 11.0 \ Hz, 1H); ^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta \ 168.5 \ (C), 145.8 \ (C), 139.8 \ (C), 128.7 \ (CH), 128.5 \ (CH), 127.0 \ (CH), 118.9 \ (CH}_2\text{), 63.6 \ (CH), 45.5 \ (CH), 42.1 \ (CH}_2\text{), 27.6 \ (CH}_2\text{), 25.4 \ (CH}_2\text{); IR (CH}_2\text{Cl}_2\text{) 3058, 2985, 1688, 1653, 1420 cm}^{-1}; \text{HRMS (EI) for C}_{14}\text{H}_{15}\text{NO (M}^+\text{): calcd 213.1154, found 213.1150.}
\end{align*}
\]

2k: Yield 22%; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, \( R_f \) = 0.28; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.80 (d, \( J = 1.0 \) Hz, 1H), 5.18 (s, 1H), 3.84 (t, \( J = 5.9 \) Hz, 1H), 3.54–3.48 (m, 1H), 3.33–3.28 (m, 1H), 2.96 (dd, \( J = 15.4, 7.7 \) Hz, 1H), 2.25 (ddd, \( J = 13.1, 9.8, 6.6 \) Hz, 1H), 2.09 (qd, \( J = 12.4, 6.2 \) Hz, 1H), 1.90–1.80 (m, 2H), 1.66–1.56 (m, 2H), 1.23–1.08 (m, 2H), 0.89–0.80 (m, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 166.9 (C), 150.9 (C), 113.2 (CH\(_2\)), 60.5 (CH), 39.2 (CH\(_2\)), 37.5 (CH), 34.2 (CH), 32.8
(CH₂), 28.9 (CH₂), 26.2 (CH₂), 21.5 (CH₂); IR (CH₂Cl₂) 3060, 2968, 1676, 1443 cm⁻¹; HRMS (EI) for C₁₁H₁₅NO (M⁺): calcd 177.1154, found 177.1152.

2l: Yield 24 %; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, Rf = 0.50; ¹H NMR (400 MHz, CDCl₃) δ 5.94 (d, J = 3.2 Hz, 1H), 5.34 (d, J = 2.9 Hz, 1H), 4.01 (dd, J = 13.7, 8.6 Hz, 1H), 2.94 (ddd, J = 13.7, 10.9, 7.1 Hz, 1H), 2.64 (d, J = 15.6 Hz, 1H), 2.54 (td, J = 15.6, 2.5 Hz, 1H), 1.90–1.59 (m, 5H), 1.58–1.48 (m, 4H), 1.43–1.31 (m, 2H), 1.28–1.12 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.9 (C), 141.0 (C), 114.8 (CH₂), 62.3 (C), 41.9 (CH), 35.9 (CH₂), 34.0 (CH₂), 32.7 (CH₂), 27.6 (CH₂), 26.1 (CH₂), 23.4 (CH₂), 23.1 (CH₂), 21.6 (CH₂); IR (CH₂Cl₂) 3058, 2980, 1687, 1435 cm⁻¹; HRMS (EI) for C₁₃H₁₉NO (M⁺): calcd 205.1467, found 205.1472.

Condition B for amide 1b:
To a well-stirred solution of Pd(OAc)₂ (22.5 mg, 0.1 mmol) in toluene (5 mL) were added pyridine (32.3 μl, 0.4 mmol) and K₂HPO₄ (348.4 mg, 2.0 mmol), and the mixture was stirred continuously until the solid dissolved. The reaction solution was oxygenated for 15 min, then amide 1b (153.2 mg, 1.0 mmol) and toluene (5 mL) were added, the resulting solution was stirred under an O₂ atmosphere for 15 min, then heated at 95 °C with an air condenser under an O₂ atmosphere for 28 h. The reaction mixture was filtered through a short pad of celite and then concentrated in vacuo. The residue was purified by flash column chromatography to afford 2b (110.4 mg, 0.73 mmol, 73 % yield) as a yellow oil.

2b: Yield 73 %; yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in n-hexane, Rf = 0.28; ¹H NMR (400 MHz, CDCl₃) δ 5.97 (t, J = 2.8 Hz, 1H), 5.30 (t, J = 2.4 Hz, 1H),
4.24 (dd, J = 13.2, 4.6 Hz, 1H), 3.44 (tdd, J = 7.9, 4.5, 3.4 Hz, 1H), 2.92 (ddt, J = 17.1, 7.7, 2.4 Hz, 1H), 2.73 (td, J = 12.8, 3.5 Hz, 1H), 2.33 (ddt, J = 17.1, 4.8, 2.8 Hz, 1H), 1.93–1.87 (m, 2H), 1.74–1.69 (m, 1H), 1.54–1.33 (m, 2H), 1.22–1.12 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 166.4 (C), 139.4 (C), 115.0 (CH2), 54.4 (CH), 40.6 (CH2), 33.6 (CH2), 31.7 (CH2), 24.5 (CH2), 23.8 (CH2); IR (CH2Cl2) 3050, 2988, 1685, 1439 cm⁻¹; HRMS (EI) for C9H13NO (M⁺): calcd 151.0997, found 151.0993.

References:

NMR Spectra of Products

**2a**

**2a**