HETEROCYCLES, Vol. 101, No. 2, 2020, pp. 717 - 725. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 16th July, 2019, Accepted, 9th September, 2019, Published online, 10th October, 2019
DOI: 10.3987/COM-19-S(F)50

LEWIS ACID MEDIATED SYNTHESIS OF INDOLIZIDINE DERIVATIVES †

Sambasivarao Kotha* and Sunil Pulletikurti

Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai-400 076, India. Fax: +91(22)-2572 7152; E-mail: srk@chem.iitb.ac.in

† This article is dedicated to Prof. Kaoru Fuji on the occasion of his 80th birth anniversary.

Abstract – Here, we have reported a short and efficient $BF_3{\cdot}Et_2O$ catalyzed synthesis of indolizidine derivatives. Morever, we have expanded this strategy to synthesize oxa-aza-cyclic derivatives. The stereochemistry of the indolizidine derivative **16** was confirmed by X-ray studies.

Nitrogen-containing hetereocycles are present in many natural products and biological active compounds. Among these, indolizidine unit **1** is a key structural motif, found in a variety of alkaloids.[1] Indolizidines are heterocyclic compounds that are fused piperidines and it is a core unit of alkaloids such as swainsonine **2**, castenospermine **3**, (-)-antifone **4** and (-)-tylophorine **5**. In addition, schizogaline **6**, schizogamine **7**, isoschizogaline **8**, isoschizogamine **9** and (-)-leuconolam **10** are other class of indolizidine alkaloids that has lactam ring (Figure 1).[2] Schizogaline and schizogamine are indole based systems with six membered lactam ring moiety whereas isoschizogaline and isoschizogamine are quinoline based systems with five membered lactam ring moiety. Polyhydroxylated derivatives of indolizidines exhibit anti-HIV, anticancer, anti-inflammatory activites and inhibit glycosidase and glycosyl transfer enzymes.[3] In view of structural and biological importance, synthesis of indolizidines has drawn the attention of synthetic chemists. Recently, attempts towards the synthesis of indolizidines have been reported by palladium catalyzed cyclization.[4] Here, we have developed a simple Lewis acid mediated one-step synthesis of indolizidine derivatives.

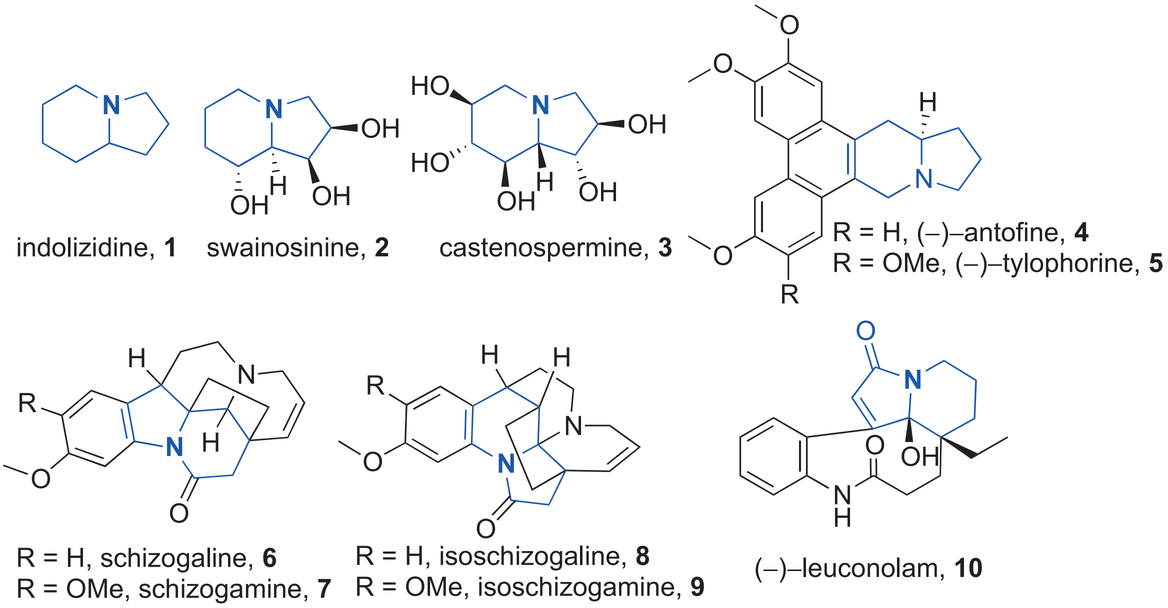
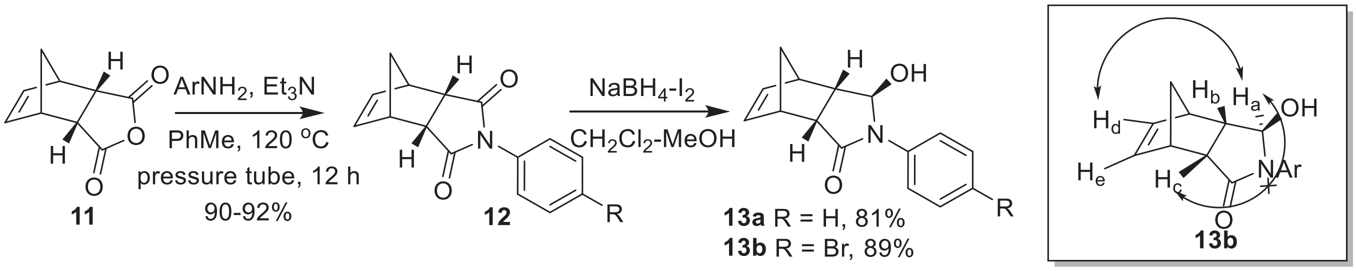


Figure 1. Indolizidine alkaloids

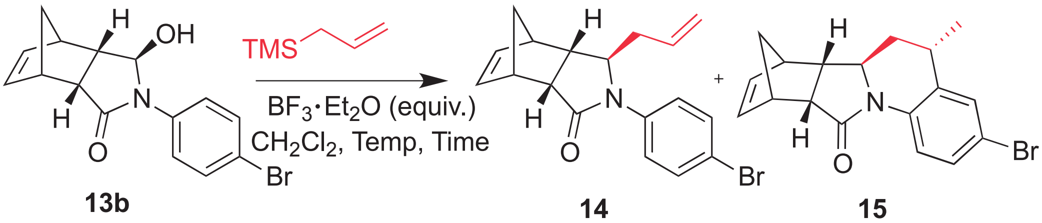
We begin our synthesis with the preparation of Diels-Alder (DA) adduct **12**,[5] which on reduction with $NaBH_4$-I_2 delivered the hydroxyl compound **13** (**13a**, 81%; **13b**, 89% yields).[6] The stereochemistry of the hydroxyl group of compound **13** was assigned as β by NOE study (Scheme 1). H_a proton is having NOE correlation with bridged olefin proton H_d indicating that the hydroxyl group of compound **13** is in β-orientation.



Scheme 1. Diasteroselective reduction of imide **12**

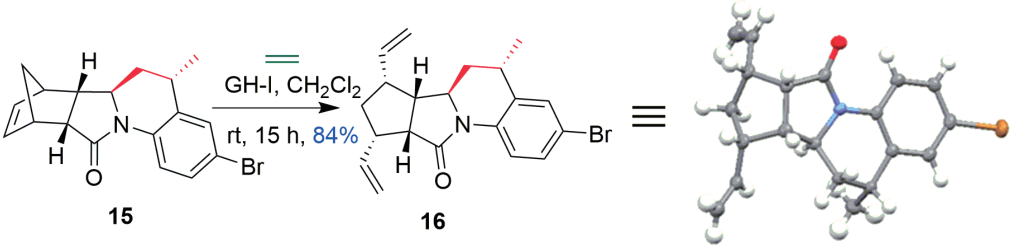
Later, the hydroxyl compound **13** was treated with allyltrimethylsilane in the presence of Lewis acid such as BF_3•Et_2O to give the allyl derivative **14** along with indolizidine derivative **15** (Scheme 2).[7] We have optimized the reaction conditions by varying the concentration of BF_3•Et_2O and temperature (Table 1). By using excess amount of Lewis acid BF_3•Et_2O at room temperature for longer time results better yield of indolizidine derivative **15** (Table 1, Entry 7).

Table 1. Synthesis and optimization for indolizidine derivative **15**



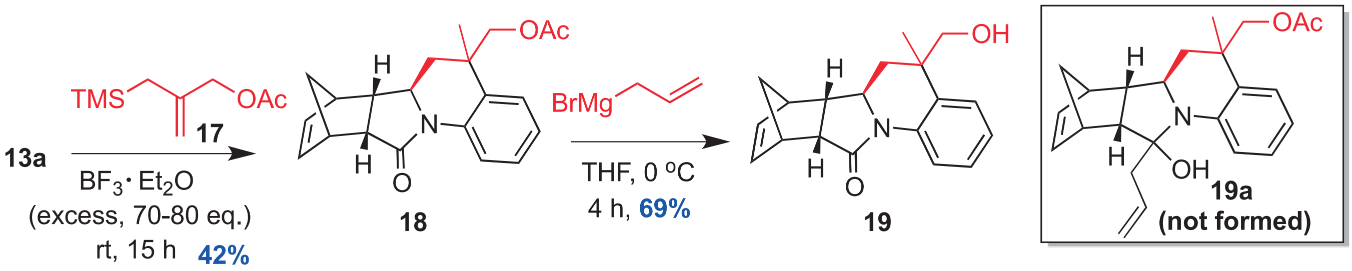
Entry	Equiv. of 50% of BF_3•Et_2O	Temp (°C)	Time (hrs)	Yield[a] **14**	Yield[a] **15**
1	5	-40	8	85	15
2	5	-20	8	80	20
3	5	0	8	55	45
4	10	0	8	40	60
5	10	rt	12	40	60
6	10	rt	16	35	65
7	excess (70-80)	rt	16	20	80

[a] Yields are based on ^1H NMR data and not isolated yields



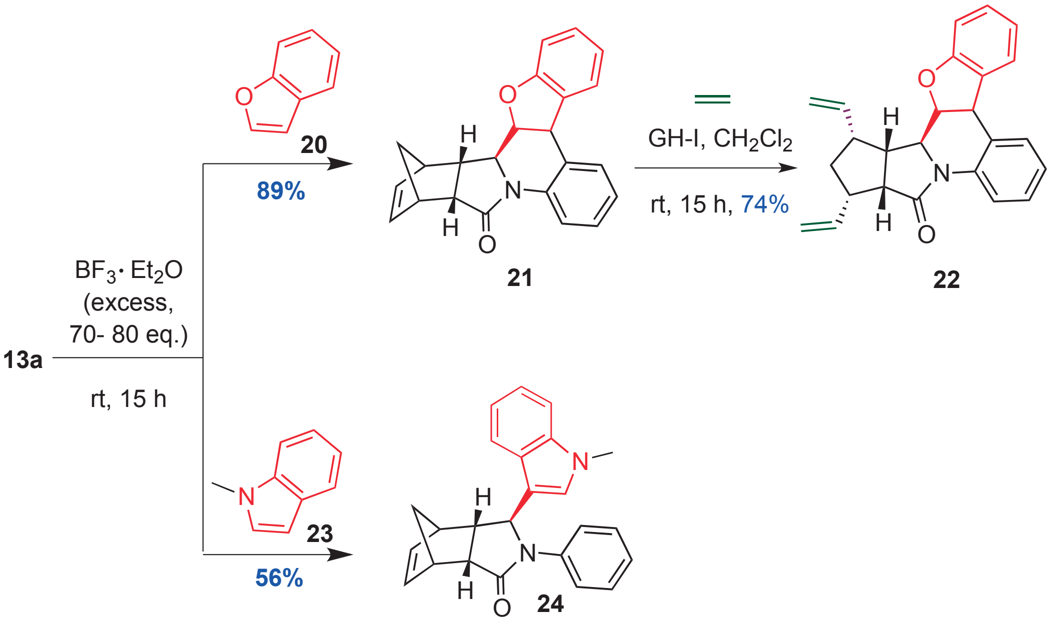
Scheme 2. ROM of the indolizidine derivative **15**

Later, the indolizidine derivative **15** was subjected to ring-opening metathesis (ROM) using Grubbs-Hoveyda 1st generation catalyst (GH-I) at room temperature under ethylene to deliver the divinyl derivative **16** in 84% yield.[8] The stereochemistry of **16** was confirmed by single crystal XRD data (CCDC no. 1887404).[9] Similarly, the hydroxyl derivative **13a** was treated with allyltrimethylsilyl acetate **17** in the presence of BF_3•Et_2O at room temperature to give the acetyl indolizidine derivative **18** in 42% yields. Further, compound **18** has undergone hydrolysis by reaction with allyl Grignard reagent to deliver the hydroxyl indolizidine derivative **19** in 69% yields. However, we did not observe the expected allyl derivative **19a** (Scheme 3).[10]



Scheme 3. Synthesis of indolizidine derivatives **18** and **19**

Along the similar lines, the hydroxyl derivative **13a** was treated with benzofuran **20**, and *N*-methylindole **23** moieties. To our surprise, only benzofuran **20** delivered the furan derivative **21** diastereoselectively in 89% yields. This was further subjected to ROM to obtain the oxa-aza-hexacyclic derivative **22** in 74% yield. Whereas, *N*-methylindole **23** afford the 3-substituted derivative **24** in 56% yield. This is because of reactivity of benzofuran **20**, and *N*-methylindole **23** are different. Electrophilic substitution of benzofuran **20** is more feasible at 2nd position whereas *N*-methylindole **23** is feasible at 3rd position (Scheme 4).



Scheme 4. Synthesis of oxa-, aza- indolizidine derivatives

In conclusion, we have successfully developed a simple synthetic strategy to synthesis indolizidine derivatives using Lewis acid like $BF_3 \cdot Et_2O$ diastereoselectively. We have synthesized oxa-aza-hexacyclic derivative using benzofuran as a starting material. However, *N*-methylindole behaves differently with acyl iminium ion compared to benzofuran system.

EXPERIMENTAL

All commercially available reagents were used without further purification and the reactions involving air-sensitive catalysts or reagents were performed in degassed solvents. Grubbs-Hoveyda (GH-I) catalyst, allyl grignard reagent were purchased from Aldrich chemical company. All metathesis reactions were carried out under ethylene atmosphere. The ^{1}H NMR (400 & 500 MHz) chemical shifts were reported in parts per million (δ) relative to internal standard TMS (7.26 ppm) and the coupling constants J are reported in hertz (Hz). The ^{13}C NMR (100 & 125 MHz) chemical shifts were referenced to the internal solvent signals (central peak is 77.16 ppm in $CDCl_3$). The high-resolution mass spectrometric (HRMS) measurements were carried out using a Bruker (Maxis Impact) or Micromass Q-ToF spectrometer. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT-IR spectrometer and absorption bands are given in wavenumbers (cm^{-1}).

Compound 12 White solid R_f = 0.38 (20% EtOAc/hexane) ^{1}H and ^{13}C NMR of compound **9c** were matched with the reported literature.

Synthesis of hydroxylamide compound 13

Amide **12** (250 mg, 0.788 mmol, 1 equiv.) was dissolved in CH_2Cl_2-MeOH (1:1, 20 mL) and I_2 (catalytic amount) was added at room temperature (rt) under N_2 atmosphere. Later, the resultant solution was stirred for 15 min at rt, $NaBH_4$ (150 mg, 3.94 mmol, 5 equiv.) was added and the mixture was allowed to stir for 8 h-12 h at rt. After completion of the reaction, solvents were removed under reduced pressure. The residue was diluted with CH_2Cl_2, washed with H_2O (2 × 30 mL) and concentrated to obtain the desired compound as a pure diastereomer.

Compound 13a Pale yellow liquid (200 mg, 81%); R_f = 0.32 (30% EtOAc/hexane); IR (neat): νmax 2946, 2931, 1687, 1551, 1392, 822, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.45–7.33 (m, 2H), 7.26–7.19 (m, 1H), 6.25 (dd, 1H, *J* = 5.40 Hz, 2.60 Hz), 6.16 (dd, 1H, *J* = 5.45 Hz, 2.55 Hz), 4.97 (d, 1H, *J* = 7.20 Hz), 3.38–3.31 (m, 2H), 3.26 (brs, 1H), 2.88 (d, 1H, *J* = 7.35 Hz), 2.75 (dd, 1H, *J* = 8.25 Hz, 4.25 Hz), 1.62 (dd, 1H, *J* = 8.55 Hz, 1.30 Hz), 1.44 (dd, 1H, *J* = 8.50 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 175.2 (C), 137.1 (C), 136.7 (CH), 133.4 (CH), 129.3 (CH), 126.8 (CH), 124.6 (CH), 87.1 (CH), 51.4 (CH_2), 49.6 (CH), 46.5 (CH), 45.9 (CH), 45.30 (CH); HRMS (ESI, Q-ToF) *m/z*: [M+Na]$^+$ calcd for $C_{15}H_{15}NO_2$, 264.0996; found, 264.0993.

Compound 13b White solid Mp 186.1–188.3 °C; (223 mg, 89%) R_f = 0.29 (30% EtOAc/hexane). IR (neat): νmax 2922, 1689, 1516, 1429, 989, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43 (dt, 2H, *J* = 8.84 Hz, 2.04 Hz), 7.30 (dt, 2H, *J* = 8.88 Hz, 2.04 Hz), 6.17 (dd, 1H, *J* = 5.64 Hz, 2.96 Hz), 6.09 (dd, 1H, *J* = 5.56 Hz, 2.88 Hz), 4.85 (d, 1H, *J* = 6.32 Hz), 3.61 (d, 1H, *J* = 8.08 Hz), 3.31 (brt, 1H, *J* = 1.26 Hz), 3.27–3.20 (m, 2H), 2.70 (ddd, 1H, *J* = 8.52 Hz, 4.24 Hz, 0.76 Hz), 1.60 (dt, 1H, *J* = 8.55 Hz, 1.52 Hz), 1.38 (d, 1H, *J* = 8.52 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.7 (C), 136.4 (CH), 133.5 (CH), 132.1 (CH), 125.4 (CH), 119.7 (C), 87.2 (CH), 51.4 (CH_2), 49.6 (CH), 46.6 (CH), 46.1 (CH), 45.3 (CH). HRMS (ESI, Q-ToF) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{21}NO_3$, 334.1413; found, 334.1414.

General procedure for the synthesis of indolizidine derivatives

$BF_3{\cdot}Et_2O$ [(6 mL for 0.6 mmol of **13** (70-80 eq.)] was added to the solution of compound **13** in dry CH_2Cl_2 (18 mL) and stirred for 20 min at rt under N_2 atmosphere. At which, allyltrimethylsilane (or **17** or **20** or **23**) (2 eq.) was added at room temperature and allowed to stir for 15 h. After completion of reaction, the reaction mixture was washed with H_2O (2 × 10 mL), the organic layer was dried over Na_2SO_4 and concentrated to obtain crude compound. The crude compound was purified by silica column chromatography to furnish the desired compound.

Compound 15 The compound **15** was isolated as inseparable mixture with the compound **14** (20:80 = **14**:**15**). Thus the mixture was subjected to ring-opening metathesis to get the ROM derivative **16**.

Compound 18 Colourless liquid (59 mg from 100 mg of **13a**, 42%), R_f (0.55, 20% EtOAc/hexane). IR (neat): νmax 2959, 2935, 1739, 1686, 1393, 1376, 1237, 1036 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.12 (dd, 1H, J = 8.22 Hz, 1.05 Hz), 7.28 (dd, 1H, J = 7.91 Hz, 1.30 Hz), 7.21 (dt, 1H, J = 8.40 Hz, 1.37 Hz), 7.07 (dt, 1H, J = 7.69 Hz, 1.15 Hz), 6.31 (dd, 1H, J = 5.70 Hz, 2.92 Hz), 6.17 (dd, 1H, J = 5.66 Hz, 2.93 Hz), 4.08 (ABq, 2H, J = 37.62 Hz, J = 11.25 Hz), 3.36 (brs, 1H), 3.34 (dt, 1H, J = 13.30 Hz, J = 2.55 Hz), 3.22 (dd, 1H, J = 9.62 Hz, J = 4.50 Hz), 3.15 (brs, 1H), 2.53 (dt, 1H, J = 9.58 Hz, 3.64 Hz), 2.12 (dd, 1H, J = 13.57 Hz, 2.31 Hz), 2.09 (s, 3H), 1.65–1.57 (m, 2H), 1.42 (d, 1H, J = 8.43 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.1 (C), 171.0 (C), 136.6, 135.5, 134.8, 130.9, 127.4, 127.3, 124.5, 121.5, 71.1, 56.0, 51.3, 50.8, 46.0, 45.8, 42.3, 40.9, 37.3, 26.4, 21.0. HRMS (ESI, Q-ToF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{21}NO_3$, 360.1576; found, 360.1585.

Compound 21 Pale yellow liquid (50 mg from 40 mg of **13a**, 89%), R_f (0.55, 20% EtOAc/hexane). IR (neat): νmax 2969, 2936, 2871, 1686, 1600, 1493, 1478, 1400, 1229 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.82 (d, 1H, J = 7.84 Hz), 7.38 (d, 1H, J = 7.40 Hz), 7.23 – 7.15 (m, 2H), 7.12 (t, 1H, J = 7.12 Hz), 7.08 (t, 1H, J = 7.60 Hz), 6.78 (t, 1H, J = 7.42 Hz), 6.72 (d, 1H, J = 8.00 Hz), 6.37 (dd, 1H, J = 5.40 Hz, 2.24 Hz), 6.15 (dd, 1H, J = 5.28 Hz, 2.52 Hz), 5.27 (dd, 1H, J = 8.56 Hz, 2.00 Hz), 4.60 (d, 1H, J = 8.76 Hz), 3.45–3.33 (m, 2H), 3.23 (dd, 1H, J = 8.68 Hz, 2.96 Hz), 3.18 (brs, 1H), 1.68 (d, 1H, J = 8.44 Hz), 1.53 (d, 1H, J = 8.36 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ =173.7 (C), 158.7, 137.1, 135.3, 133.9, 130.1, 129.8, 128.9, 127.4, 127.2, 125.4, 124.9, 121.8, 121.1, 110.0, 84.7, 77.36, 61.2, 51.2 (CH_2), 50.8, 45.8, 45.5, 43.8, 38.1. HRMS (ESI, Q-ToF) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{21}NO_2$, 318.1470; found, 318.1471.

Compound 24 Yellow liquid (32 mg from 40 mg of **13a**, 56%), R_f (0.48, 20% EtOAc/hexane). IR (neat): νmax 2925, 2852, 1690, 1491, 1478, 1227 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, 1H, J = 7.88 Hz), 7.31–7.26 (m, 4H), 7.18 (t, 3H, J = 7.76 Hz), 6.78 (s, 1H), 6.41 (s, 2H), 4.8 (d, 1H, J = 2.48 Hz), 3.64 (s, 3H), 3.54 (dd, 1H, J = 9.13 Hz, 4.59 Hz), 3.48 (brs, 1H), 3.31 (brs, 1H), 2.97–2.91 (m, 1H), 1.66 (d, 1H, J = 8.55 Hz), 1.42 (d, 1H, J = 8.44 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.0, 138.4, 137.7, 137.5, 133.5, 128.6, 126.7, 125.5, 125.3, 123.8, 122.1, 119.5, 119.0, 116.5, 109.7, 60.8, 51.0, 50.8, 46.6, 46.0, 45.0, 32.7. HRMS (ESI, Q-ToF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{22}N_2O$, 377.1630; found, 377.1627.

General procedure for ROM

The compound was dissolved in dry solvent (7 mM, CH_2Cl_2) and degassed with nitrogen followed by ethylene for about 20 min. To this, Grubbs catalyst (5 moL%) was added and stirred at rt for 12-15 h under ethylene atmosphere. Solvents were removed and purified by column chromatography to obtain the desired product.

Compound 16 White solid in 84% yield. R_f = 0.60 (20% EtOAc/hexane); Mp 121.6–125.2 °C; IR (neat): νmax 2945, 1686, 1482, 1390, 1371, 915, 822, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 8.42 (d, *J* = 8.55 Hz, 1H), 7.27 (s, 2H), 6.03–5.87 (m, 2H), 5.20–5.06 (m, 4H), 3.68–3.59 (m, 1H), 3.14 (t, *J* = 9.72 Hz, 1H), 3.04–2.92 (m, 2H), 2.84 (t, *J* = 5.75 Hz, 1H), 2.56 (q, *J* = 6.80 Hz, 1H), 1.99–1.89 (m, 1H), 1.82–1.64 (m, 3H), 1.60 (q, *J* = 12.45 Hz, 1H), 1.26 (d, *J* = 7.0.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 172.8 (C), 137.8 (CH), 136.5 (CH), 134.6 (C), 134.0 (C), 132.0 (CH), 130.2 (C), 129.6 (CH), 121.8 (CH), 116.8 (CH_2), 116.6 (C), 115.2 (CH_2), 53.0 (CH), 51.0 (CH), 46.6 (CH), 46.2 (CH), 46.1 (CH), 36.5 (CH_2), 34.8 (CH_2), 31.3 (CH), 24.6 (CH); HRMS (ESI, Q-ToF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{22}BrNO$, 394.0777; found, 394.0777.

Compound 22 Colourless liquid (16 mg from **20** mg of **21**, 74%), R_f (0.60, 20% EtOAc/hexane). IR (neat): νmax 2955, 2918, 2850, 1694, 1493, 1395, 1224, 1025 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.00 (d, 1H, *J* = 4.05 Hz), 7.41 (d, 1H, *J* = 7.45 Hz), 7.25 (d, 1H, *J* = 7.35 Hz), 7.20 (td, 1H, *J* = 8.40 Hz, 1.20 Hz), 7.13 (td, 1H, *J* = 7.60 Hz, 1.15 Hz), 7.06 (t, 1H, *J* = 5.13 Hz), 6.79 (t, 1H, *J* = 4.76 Hz), 6.70 (d, 1H, *J* = 8.00 Hz), 6.16–6.07 (m, 1H), 6.02–5.93 (m, 1H), 5.21–5.11 (m, 4H), 5.06 (dd, 1H, *J* = 8.55 Hz, 2.15 Hz), 4.59 (d, 1H, *J* = 8.55 Hz), 3.83 (dd, 1H, *J* = 4.90 Hz, 2.10 Hz), 3.44–3.37 (m, 1H), 3.28 (t, 1H, *J* = 9.45 Hz), 3.06–2.97 (m, 1H), 2.97–2.85 (m, 1H), 1.99–1.91 (m, 1H), 1.55 (d, 1H, *J* = 12.54 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.8 (C), 158.5, 137.8, 136.8, 135.3, 130.4, 129.1, 129.0, 127.3, 125.4, 124.8, 121.7, 121.2, 117.3 (CH_2), 114.9 (CH_2), 110.2, 84.5, 58.6, 51.0, 47.1, 46.1, 43.5, 40.8, 34.5 (CH_2). HRMS (ESI, Q-ToF) *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{23}NO_2$, 392.1626; found, 392.1621.

Synthesis of compound 19 Allyl Grignard (1M in THF, 0.2 mL, 1.6 eq) was added dropwise to the solution of compound **18** (35 mg, 0.10 mmol) in dry THF (6.0 mL) at 0 °C under N_2 atmosphere and slowly warm to rt. The reaction mixture was stirred for 4 h at rt and quenched with sat. aqueous NH_4Cl after being completion of reaction. The compound was extracted with EtOAc (3 × 15 mL) and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to obtain crude compound which was further purified by column chromatography to get the compound **19** (21 mg, 69%) as a colourless liquid, R_f (0.35, 30% EtOAc/hexane). IR (neat): νmax 3388, 2965, 2865, 1688, 1388, 1222, 1045 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.14 (dd, 1H, *J* = 9.44 Hz, 1.20 Hz), 7.26–7.18 (m, 2H), 7.11 (td, 1H, *J* = 7.80 Hz, 1.52 Hz), 6.32 (dd, 1H, *J* = 5.68 Hz, 2.96 Hz), 6.16 (dd, 1H, *J* = 6.00 Hz, 2.92 Hz), 3.80 (d, 1H, *J* = 11.08 Hz), 3.53 (dd, 1H, *J* = 11.08 Hz), 3.38 (brs, 1H), 3.32–3.21 (m, 2H), 3.16 (brs, 1H), 2.59 (dt, 1H, *J* = 9.52 Hz, 3.60 Hz), 2.15 (t, 1H, *J* = 12.88 Hz), 1.76 (dd, 1H, *J* = 13.12 Hz, 2.40 Hz), 1.63 (dt, 1H, 1.56 (brs, 2H), 1.45 (d, 1H, *J* = 8.44). ^{13}C NMR ($CDCl_3$, 125MHz): δ = 173.1 (C), 123.1, 136.7, 134.7, 131.8, 127.2, 126.4, 124.8, 121.8, 71.4 (CH_2), 56.2, 51.3 (CH_2), 51.0, 46.0, 45.8, 42.4, 40.9, 39.8 (CH_2), 27.8. HRMS (ESI, Q-ToF) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{21}NO_2$, 318.1470; found, 318.1471.

ACKNOWLEDGEMENTS

We are thankful to the Department of Science and Technology (EMR/2015/002053), New Delhi and CSIR (02(0272)/16/EMR-II), New Delhi for financial support. SP thanks UGC, New Delhi for financial support and the awarding of a SRF. SK thanks the DST for the awarding J. C. Bose fellowship (SR/S2/JCB-33/2010). We are also thankful to Praj industries for Pramod Chaudhari Chair Professor (Green Chemistry).

REFERENCES AND NOTES

1. (a) J. P. Michael, *Nat. Prod. Rev.*, 2008, **25**, 139; (b) D. S. Seigler, Pyrrolizidine, Quinolizidine, and Indolizidine Alkaloids. In: Plant Secondary Metabolism. Springer, Boston, MA, 1998; (c) E. Gellert, *J. Nat. Prod.*, 1982, **45**, 50.
2. (a) D. Kalaitzakis, M. Traintafyllakis, M. Sofiadis, D. Noutsias, and G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, 2016, **55**, 4605; (b) D. Koley, Y. Krishna, A. A. Khan, and R. Kant, *Angew. Chem. Int. Ed.*, 2014, **53**, 13196; (c) X. Wang, M. Li, Y. Yang, M. Guo, X. Tang, and G. Wang *Adv. Synth. Catal.*, 2018, **360**, 2151.
3. (a) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669; (b) A. Lagana, J. G. Goetz, P. Cheung, A. Raz, J. W. Dennis, and R. Nabi, *Mol. Cell. Biol.*, 2006, **26**, 3181; (c) N. Asano, R. J. Nash, R. J. Molyneux, and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645.
4. (a) S. Nicolai, C. Piemontesi, and J. Waser, *Angew. Chem. Int. Ed.*, 2011, **50**, 4680; (b) P. G. Andersson and J.-E. Bäckvall, *J. Am. Chem. Soc.*, 1992, **114**, 8696; (c) K. Srinivas, N. Singh, D. Das, and D. Koley, *Org. Lett.*, 2017, **19**, 274.
5. (a) S. Kotha and V. R. Aswar, *Org. Lett.*, 2016, **18**, 1808; (b) S. Kotha and S. Pulletikurti, *RSC Adv.*, 2018, **8**, 14906.
6. (a) M. Periasamy and M. Thirumalaikumar, *Organomet. Chem.*, 2000, **609**, 137; (b) P. Haldar and J. K. Ray, *Tetrahedron Lett.*, 2003, **44**, 8229.
7. (a) A. Yazici, U. Wille, and S. G. Pyne, *J. Org. Chem.*, 2016, **81**, 1434; (b) K. L. Burgess, N. J. Lajkiewicz, A. Sanyal, W. Yan, and J. K. Snyder, *Org. Lett.*, 2005, **7**, 31; (c) X. Liu and J. K. Snyder, *J. Org. Chem.*, 2008, **73**, 2935.

8. (a) S. Kotha, S. Pulletikurti, and Y. Dommaraju *Heterocycles*, 2019, **98**, 79; (b) S. Kotha, N. N. Rao, O. Ravikumar, and G. Sreevani, *Tetrahedron Lett.*, 2017, **58**, 1283; (c) K. Grela, *Beilstein J. Org. Chem.*, 2015, **11**, 1639; (d) S. Kotha, A. K. Chinnam, and M. E. Shirbhate, *J. Org. Chem.*, 2015, **80**, 9141; (e) S. Kotha, E. Manivannan, T. Ganesh, N. Sreenivasachary, and A. Deb, *Synlett*, 1999, 1618; (f) R. K. Acharyya, R. K. Rej, and S. Nanda, *J. Org. Chem.*, 2018, **83**, 2087; (g) S. Bose, M. Ghosh, and S. Ghosh, *J. Org. Chem.*, 2012, **77**, 6345; (h) S. Kotha and N. Sreenivasachary, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 257; (i) S. Kotha and G. T. Waghule, *J. Org. Chem.*, 2012, **77**, 6314.
9. CCDC number of compound **21** is 1887404 contain the supplementary crystallographic data for this paper. The data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
10. (a) S. Kotha and O. Ravikumar, *Eur. J. Org. Chem.*, 2016, 3900; (b) S. Kotha, A. K. Chinnam, and M. Shirabate, *Beilstein J. Org. Chem.*, 2015, **11**, 1514; (c) S. Kotha and R. Ali, *J. Indian Chem. Soc.*, 2015, **92**, 277.