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PAPER

Efficient synthesis of esermethole and its analogues†

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In this work, a general and flexible synthetic route towards the synthesis of pyrroloindoline alkaloids was developed. This new strategy features with a palladium mediated sequential arylation–allylation of *o*-bromoanilides and leads to the construction of oxindoles bearing a full carbon quaternary center. The cheap triphenylphosphine was proved to be a highly effective ligand for this one pot transformation. On the basis of this new method, esermethole and its analogues were synthesized.

Introduction

The hexahydropyrrolo[2,3-*b*]indole ring system is presented in a wide selection of natural alkaloids[1] and a number of marketed drugs and drug candidates.[2] Representative alkaloids of the hexahydropyrrolo[2,3-*b*]indole skeleton are shown in Fig. 1. Those pyrrolidinoindoline containing compounds, exemplified by physostigmine which was isolated from the African Calabar bean seeds,[3] display a broad range of biological activities.[4] Numerous synthetic efforts have been made towards the synthesis of the hexahydropyrrolo[2,3-*b*]indole alkaloids,[5] with the anticholinergic agent physostigmine being a subject of intensive interests.[6] As indicated in Fig. 1, hexahydropyrrolo[2,3-*b*]indole alkaloids are characterized by a sterically congested all carbon quaternary center at its C-3a position. Construction of the full carbon quaternary center imposes certain synthetic challenges.

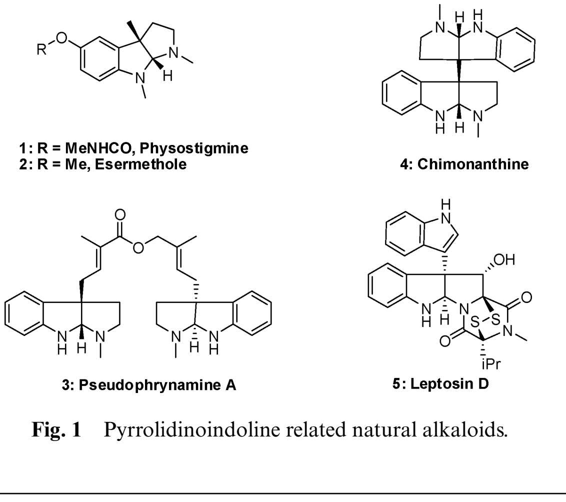
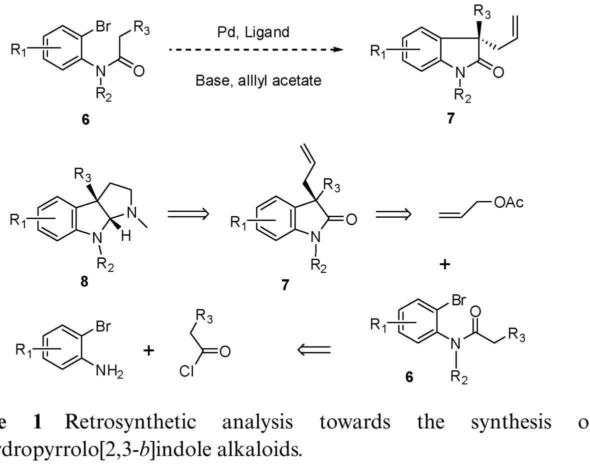


Fig. 1 Pyrrolidinoindoline related natural alkaloids.

Recently, we have established an intermolecular sequential procedure for palladium-BINAP catalyzed arylation and allylic alkylation of highly functional ketones.[7] We envisaged that this protocol would be a flexible and economic way for the construction of oxindoles bearing a full carbon quaternary center at its C-3a position. As indicated in Scheme 1, an intramolecular arylation of amide **6** followed by an allylation, namely an "one-pot" palladium mediated reaction (Scheme 1), would furnish the quaternary carbon center with necessary functionality required for the synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids. Herein we report our results for the sequential arylation–allylation of *o*-bromoanilides and the synthesis of esermethole and its analogues from simple and inexpensive starting materials.



Scheme 1 Retrosynthetic analysis towards the synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids.

In the literature, numerous procedures dealing with palladium catalyzed arylation of amides have been reported.[8] Elegant work on the formation of oxindoles bearing a quaternary carbon center has also been documented.[9] To the best of our knowledge, however, no flexible and economic "one-pot" arylation–allylation of *o*-haloanilides has been conducted. It was therefore our goal to evaluate the efficacy of some common ligands such as BINAP and triphenylphosphine in the sequential arylation–allylation of *o*-bromoanilides.

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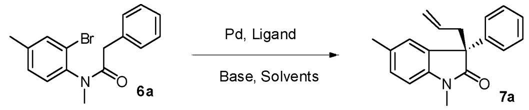
Table 1 Evaluation of ligands and reaction conditions for arylation–allylation of bromoanilide[a]

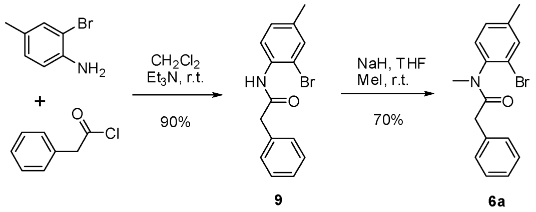


Entry	Pd/ligand lactams	Base lactams	Solvents	Yield
1	$Pd_2(dba)_3$, BINAP	Cs_2CO_3	toluene	—
2	$Pd_2(dba)_3$, BINAP	NaO^{t}Bu	1,4-dioxane	—
3	$Pd_2(dba)_3$, BINAP	$KN(SiMe_3)_2$	THF	trace
4	$Pd_2(dba)_3$, BINAP	$NaN(SiMe_3)_2$	THF	5%
5	$Pd_2(dba)_3$, BINAP	$LiN(SiMe_3)_2$	THF	51%
6	$Pd_2(dba)_3$, BINAP	$LiN(SiMe_3)_2$	1,4-dioxane	50%
7	$Pd_2(dba)_3$, Ph_3P	$LiN(SiMe_3)_2$	THF	92%[b]
8	$Pd_2(dba)_3$, Ph_3P	$LiN(SiMe_3)_2$	THF	87%[c]
9	$Pd_2(dba)_3$, Ph_3P	$LiN(SiMe_3)_2$	THF	73%[d]

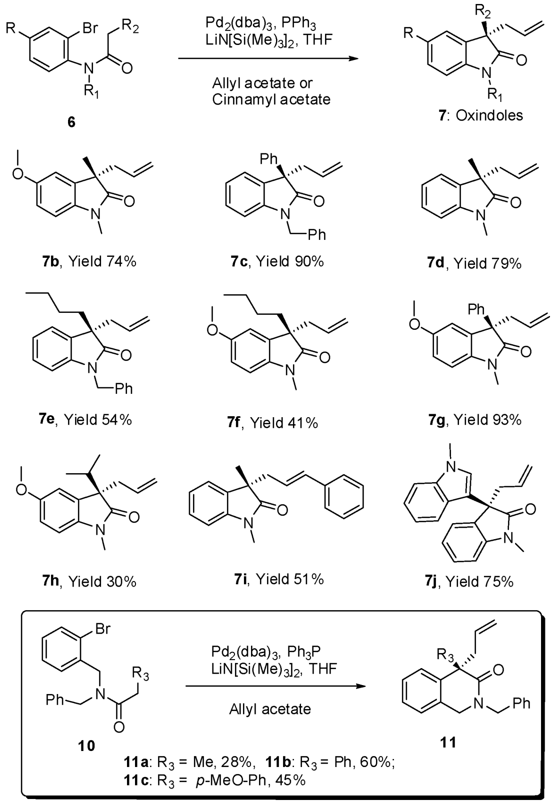
[a] All reactions were conducted with 1 mmol of *o*-bromoanilide. Reaction procedures: see experimental section. Reaction was conducted with $Pd_2(dba)_3$ (0.03 mmol) and BINAP (0.036 mmol) in corresponding solvents at 75 °C oil bath. [b] Reaction was conducted with $Pd_2(dba)_3$ (0.03 mmol) and Ph_3P (0.06 mmol) in THF at 75 °C oil bath. [c] Reaction was conducted with $Pd_2(dba)_3$ (0.03 mmol) and Ph_3P (0.09 mmol) in THF at 75 °C oil bath. [d] Reaction was conducted with $Pd_2(dba)_3$ (0.03 mmol) and Ph_3P (0.12 mmol) in THF at 75 °C oil bath.

Results and Discussion

2-Bromoanilide **6a** was synthesized by treatment of 2-bromo-4-methylaniline with 2-phenylacetyl chloride in dichloromethane in the presence of triethylamine (Scheme 2). With amide **6a** in hand, we then initiated the research towards palladium-mediated arylation–allylation of bromoanilides. After several fruitless attempts (see Table 1), we finally found that the desired transformation could be effected with a Pd-ligand complex in the presence of lithium bistrimethylsilylamide as a base in THF (75 °C oil bath). To our surprise, monodentated triphenylphosphine was a better ligand than bidentated BINAP for this transformation (Table 1, entries 5,6 and 7). In general, a better yield was obtained using less triphenylphosphine (Pd : Ph_3P = 1 : 1, Table 1, entry 7).[10] It is also noteworthy and of interests that only lithium bistrimethylsilylamide (the counter ion Li^+ with a small ionic radius) provided good yields in this transformation.



Scheme 2 Synthesis of amide **6a**.



Yields represent isolated yields (average of two runs)

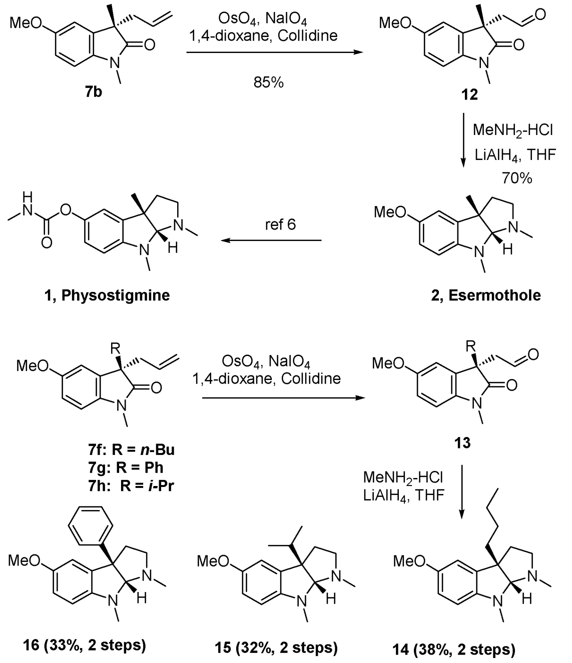
Scheme 3 Arylation–allylation of *o*-bromoanilides.

To get further examples of the sequential arylation–allylation of 2-bromoanilides, a number of 2-bromoanilides were synthesized and utilized as substrates in this typical transformation under optimized conditions. The results are shown in Scheme 3. This palladium-mediated sequential arylation–allylation procedure is practical and provides useful oxindole building blocks bearing a full carbon quaternary center at its C3 position. Our reaction conditions could also be extended to the synthesis of isoquinolinones as indicated in Scheme 3. To the best of our knowledge, there are no reported cases of palladium-mediated arylation of *o*-bromoanilides that leads to the synthesis of isoquinolinones with a full quaternary carbon center.[11]

Having successfully established a new method to oxindoles bearing a full carbon quaternary center at its C3 position, we then pursued our next goal, the synthesis of esermethole and its analogues. Starting from compound **7b**, after oxidative cleavage of the double bond and reductive aminocyclization, the (±)-esermethole was obtained over two steps (60%, Scheme 4). Following the well established procedure, three other analogues were also synthesized (see Scheme 4).

Conclusions

In conclusion, we have developed an alternative and efficient method for the preparation of oxindoles bearing an all carbon quaternary center at its C3 position. The functionalized oxindole building blocks are of use for the synthesis of both natural alkaloids and natural product-like compounds. The results obtained in this research indicate that the inexpensive triphenylphosphine is the ligand of choice for sequential arylation–allylation of *o*-bromoanilides. Based on this methodology, a practical and flexible procedure was established for the synthesis of esermethole and its analogues.



Scheme 4 Synthesis of esermethole and its analogues.

Experimental Section

General

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) was recorded on a Bruker Avance 300 spectrometer at 75 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. Low-resolution Mass spectra were recorded on a VG Auto Spec-3000 magnetic sector MS spectrometer. High Resolution Mass spectra were taken on an AB QSTAR Pulsar mass spectrometer. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Fluka and were used without purification, unless otherwise indicated. THF and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane were distilled over P_2O_5. Silica gel (Qingdao, 300–400 mesh) was used for column chromatography.

General procedure for palladium catalyzed arylation–allylation of bromoanilides

A mixture of tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$, FW 915.72, 13.7 mg, 0.015 mmol, 0.03 eq.] and triphenylphosphine (FW 262.29, 7.9 mg, 0.03 mmol, 0.06 eq.) in anhydrous tetrahydrofuran (5 mL) was degassed and purged with nitrogen (3 times). A solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.75 mL, 0.75 mmol, 1.5 eq.) was added followed by addition of a solution of bromoanilides (0.5 mmol) in anhydrous tetrahydrofuran (5 mL). The resulting mixture was then stirred at 75 °C (oil bath) under nitrogen for 4–6 h. The reaction was monitored by thin layer chromatography (TLC). After cooling to room temperature, a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.75 mL, 0.75 mmol, 1.5 eq.) was added followed by allyl acetate (150 mg, 1.5 mmol, 3.0 eq.). The reaction was then stirred at room temperature for 6–10 h. Water (0.1 mL) was added. The solvent was removed under reduced pressure and the residue was diluted with water (25 mL) and extracted with ethyl acetate (3 × 15 mL). The organic phases were combined and washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was chromatographed on silica gel to afford the products.

Compound 7a. Yield 92%, White crystal, mp: 67–68 °C, R_f 0.55 (Petroleum ether/EtOAc = 5 : 1). **IR** (ν_{max} cm^{-1}): 3401 (w), 3060 (w), 3007 (w), 2970 (w), 2926 (w), 2355 (w), 1708 (s), 1608 (m), 1495 (s), 1445 (m), 1350 (s), 1256 (w), 1144 (w), 1082 (m), 999 (w), 917 (m), 807 (m). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.40–7.20 (5H, m), 7.10 (1H, d, J = 7.9 Hz), 7.05 (1H, s), 6.76 (1H, d, J = 7.9 Hz), 5.42–5.26 (1H, m), 5.03 (1H, dd, J = 1.8, 15.2 Hz), 4.90 (1H, dt, J = 0.9, 10.1 Hz), 3.17 (3H, s), 3.01 (2H, d, J = 7.8 Hz), 2.34 (3H, s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 178.07 (s), 141.63 (s), 139.92 (s), 132.66 (s), 132.09 (s), 131.98 (d), 128.63 (d), 127.38 (d), 127.17 (d), 125.96 (d), 119.14 (t), 108.00 (d), 56.63 (s), 41.95 (t), 26.47 (q), 21.35 (q). **EIMS** *m/z* (%):278 (M^++1, 62%), 277 (M^+, 89%), 261 (4), 248 (19), 236 (100), 221 (78), 208 (75), 206 (72), 193 (75), 178 (68), 165 (96), 152 (64), 139 (39), 130 (51), 115 (62), 103 (53), 91 (47), 77 (53). **HRMS** *m/z* Found: 277.1469, Calcd. for $C_{19}H_{19}NO$ $(M)^+$: 277.1467.

Compound 7b. Yield 74%, Pale yellow oil, R_f 0.58 (Petroleum ether/EtOAc = 3 : 1). **IR** (ν_{max} cm^{-1}): 3447 (w), 2965 (w), 2925 (w), 2357 (w), 1706 (s), 1641 (w), 1605 (w), 1497 (m), 1463 (w), 1366 (w), 1288 (w), 1236 (w), 1213 (w), 1040 (m), 920 (w), 873 (w), 806 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 6.80 (1H, d, J = 2.3 Hz), 6.77 (1H, dd, J = 2.3, 8.3 Hz), 6.71 (1H, d, J = 8.3 Hz), 5.52–5.32 (1H, m), 4.98 (1H, dd, J = 1.4, 17.0 Hz), 4.91 (1H, d, J = 10.1 Hz), 3.79 (3H, s), 3.16 (3H, s), 2.56–2.40 (2H, m), 1.35 (3H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 179.95 (s), 156.06 (s), 136.86 (s), 135.17 (s), 132.65 (d), 118.75 (t), 111.76 (d), 110.86 (d), 108.18 (d), 55.93 (q), 48.78 (s), 42.54 (t), 26.29 (q), 22.88 (q). **EIMS** *m/z* (%):232 (M^++1, 60%), 231 (M^+, 50%), 216 (32), 204 (30), 191 (73), 189 (82), 175 (71), 161 (73), 145 (75), 132 (88), 117 (91), 104 (100), 91 (95), 78 (72), 63 (56). **HRMS** *m/z* Found: 231.1263, Calcd. for $C_{14}H_{17}NO_2$ $(M)^+$: 231.1259.

Compound 7c. Yield 90%, Pale yellow plate, m.p.: 90–91 °C, R_f 0.53 (Petroleum ether/EtOAc = 15 : 1). **IR** (ν_{max} cm^{-1}): 3394 (w), 3073 (w), 3023 (w), 2918 (w), 1959 (w), 1704 (s), 1603 (m), 1483 (m), 1439 (w), 1356 (m), 1302 (w), 1183 (m), 1079 (w), 1025 (w), 995 (w), 921 (m), 884 (w), 811 (w), 751 (m), 699 (m), 651 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.39 (2H, dd, J = 1.7, 7.0 Hz), 7.31–7.18 (9H, m), 7.17 (1H, d, J = 7.7 Hz), 7.05 (1H, t, J = 7.5 Hz), 6.74 (1H, d, J = 7.7 Hz), 5.51–5.32 (1H, m), 5.07 (1H, d, J = 17.0 Hz), 4.95 (1H, d, J = 15.7 Hz), 4.93 (1H, d, J = 10.0 Hz), 4.82 (1H, d, J = 15.7 Hz), 3.20–3.02 (2H, m). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 178.16 (s), 143.10 (s), 139.86 (s), 136.00 (s), 132.59 (d), 131.88 (s), 128.76 (d), 128.72 (d), 128.23 (d), 127.64 (d), 127.46 (d), 127.14 (d), 125.25 (d), 122.61 (d), 119.51 (t), 109.43 (d), 56.52 (s), 44.03 (t), 42.06 (t). **EIMS** *m/z* (%):340 (M^++1, 52%), 339 (M^+, 76%), 310 (11), 299 (86), 298 (98), 280 (13), 270 (54), 268 (26), 254 (8), 248 (13), 233 (12), 230 (13), 220 (28), 208 (46), 193 (37), 179 (67), 165 (70), 152 (48), 139 (21), 128 (33), 115 (43), 103 (20), 91

(100), 77 (43), 65 (72). **HRMS** *m/z* Found: 339.1626, Calcd. for $C_{24}H_{21}NO$ $(M)^+$: 339.1623.

Compound 7d. Yield 79%, Yellow oil, R_f 0.60 (Petroleum ether/EtOAc = 5 : 1). **IR** (ν_{max} cm^{-1}): 3425 (w), 3065 (w), 2968 (w), 2927 (w), 1712 (s), 1610 (m), 1480 (m), 1463 (m), 1364 (m), 1313 (w), 1252 (w), 1124 (w), 1090 (w), 1025 (w), 921 (m), 751 (m), 698 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.26 (1H, t, J = 7.6 Hz), 7.19 (1H, d, J = 7.5 Hz), 7.05 (1H, t, J = 7.5 Hz), 6.83 (1H, d, J = 7.6 Hz), 5.52–5.34 (1H, m), 4.98 (1H, d, J = 17.0 Hz), 4.91 (1H, d, J = 10.1 Hz), 3.20 (3H, s), 2.60–2.42 (2H, m), 1.37 (3H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 180.22 (s), 143.24 (s), 133.67 (s), 132.65 (d), 127.82 (d), 122.93 (d), 122.40 (d), 118.66 (t), 107.96 (d), 48.29 (s), 42.52 (t), 26.15 (q), 22.79 (q). **EIMS** *m/z* (%):202 (M^++1, 5%), 201 (M^+, 8%), 169 (17), 160 (27), 156 (100), 155 (36), 145 (10), 128 (27), 115 (17), 91 (26), 83 (23), 77 (21). **HRMS** *m/z* Found: 201.1156, Calcd. for $C_{13}H_{15}NO$ $(M)^+$: 201.1154.

Compound 7e. Yield 54%, Pale yellow syrup, R_f 0.58 (Petroleum ether/EtOAc = 20 : 1). **IR** (ν_{max} cm^{-1}): 3444 (w), 3065 (w), 2926 (m), 2862 (w), 1712 (s), 1609 (m), 1479 (m), 1355 (m), 1174 (w), 1084 (w), 996 (w), 920 (w), 745 (m), 699 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.38–7.20 (5H, m), 7.17 (1H, d, J = 7.1 Hz), 7.12 (1H, dd, J = 1.2, 7.6 Hz), 7.02 (1H, t, J = 7.1 Hz), 6.69 (1H, d, J = 7.6 Hz), 5.50–5.31 (1H, m), 5.01 (1H, d, J = 14.9 Hz), 4.90 (1H, d, J = 14.9 Hz), 4.89 (1H, d, J = 11.3 Hz), 4.85 (1H, d, J = 15.6 Hz), 2.62–2.49 (2H, m), 1.97 (1H, ddd, J = 4.6, 13.0, 13.1 Hz), 1.80 (1H, ddd, J = 4.2, 13.0, 13.1 Hz), 1.30–1.12 (2H, m), 1.12–0.75 (2H, m), 0.77 (3H, t, J = 7.2 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 179.72 (s), 143.19 (s), 136.24 (s), 132.71 (d), 132.12 (s), 128.72 (d), 127.70 (d), 127.58 (d), 127.52 (d), 123.15 (d), 122.40 (d), 118.76 (t), 108.97 (d), 53.02 (s), 43.77 (t), 42.49 (t), 37.34 (t), 26.57 (t), 22.97 (t), 13.92 (q). **EIMS** *m/z* (%):320 (M^++1, 55%), 319 (M^+, 89%), 279 (71), 278 (99), 263 (53), 250 (16), 236 (36), 222 (42), 206 (19), 186 (12), 172 (22), 158 (29), 145 (19), 132 (34), 130 (38), 115 (32), 103 (16), 91 (100), 77 (33). **HRMS** *m/z* Found: 319.1937, Calcd. for $C_{22}H_{25}NO$ $(M)^+$: 319.1936.

Compound 7f. Yield 41%, Colorless oil, R_f 0.59 (Petroleum ether/EtOAc = 4 : 1). **IR** (ν_{max} cm^{-1}): 3437 (m), 2927 (m), 2858 (w), 2353 (w), 1708 (s), 1606 (m), 1494 (m), 1462 (m), 1364 (w), 1285 (w), 1227 (w), 1116 (w), 1035 (m), 917 (w), 802 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 6.80–6.72 (2H, m), 6.70 (1H, d, J = 8.3 Hz), 5.48–5.30 (1H, m), 4.96 (1H, d, J = 17.0 Hz), 4.87 (1H, dt, J = 1.0, 10.1 Hz), 3.79 (3H, s), 3.16 (3H, s), 2.58–2.40 (2H, m), 1.88 (1H, ddd, J = 4.7, 12.5, 12.6 Hz), 1.71 (1H, ddd, J = 4.5, 12.5, 12.6 Hz), 1.23–1.08 (2H, m), 0.99–0.76 (2H, m), 0.75 (3H, t, J = 7.3 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 179.32 (s), 155.98 (s), 137.65 (s), 133.63 (s), 132.55 (d), 118.59 (t), 111.49 (d), 110.97 (d), 107.96 (d), 55.88 (q), 53.45 (s), 42.30 (t), 37.06 (t), 26.39 (t), 26.17 (q), 22.94 (t), 13.91 (q). **EIMS** *m/z* (%):274 (M^++1, 48%), 273 (M^+, 90%), 256 (5), 242 (23), 232 (100), 217 (23), 204 (40), 190 (83), 176 (82), 174 (68), 162 (16), 160 (15), 146 (17), 131 (12), 115 (17), 99 (13), 91 (16), 85 (30), 71 (40). **HRMS** *m/z* Found: 273.1732, Calcd. for $C_{17}H_{23}NO_2$ $(M)^+$: 273.1729.

Compound 7g. Yield 93%, Pale yellow syrup, R_f 0.60 (Petroleum ether/EtOAc = 3 : 1). **IR** (ν_{max} cm^{-1}): 3470 (w), 3068 (w), 2941 (w), 2835 (w), 1708 (s), 1601 (m), 1495 (s), 1462 (m), 1356 (m), 1285 (m), 1231 (w), 1151 (w), 1034 (m), 992 (w), 921 (w), 872 (w), 806 (w), 731 (w), 690 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.41–7.20 (5H, m), 6.87 (1H, s), 6.85 (1H, dd, J = 2.4, 7.8 Hz), 6.79 (1H, d, J = 7.8 Hz), 5.47–5.30 (1H, m), 5.04 (1H, d, J = 17.0 Hz), 4.92 (1H, dd, J = 0.76, 10.1 Hz), 3.78 (3H, s), 3.17 (3H, s), 3.01 (2H, d, J = 7.1 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ (ppm): 177.75 (s), 155.99 (s), 139.59 (s), 137.54 (s), 133.17 (s), 132.51 (d), 128.64 (d), 127.43 (d), 127.12 (d), 119.28 (t), 112.76 (d), 112.47 (d), 108.51 (d), 56.91 (s), 55.90 (q), 41.94 (t), 26.51 (q). **EIMS** *m/z* (%):294 (M^++1, 52%), 293 (M^+, 100%), 277 (13), 264 (22), 253 (89), 252 (78), 234 (34), 223 (36), 208 (78), 193 (61), 178 (62), 167 (76), 154 (83), 140 (90), 128 (72), 115 (100), 103 (50), 91 (89), 77 (85), 66 (84). **HRMS** *m/z* Found: 293.1420, Calcd. for $C_{19}H_{19}NO_2$ $(M)^+$: 293.1416.

Compound 7h. Yield 30%, Colorless oil, R_f 0.52 (Petroleum ether/EtOAc = 5 : 1). **IR** (ν_{max} cm^{-1}): 3444 (w), 2961 (m), 2354 (w), 1706 (s), 1601 (w), 1495 (s), 1465 (s), 1364 (m), 1285 (m), 1233 (w), 1169 (w), 1124 (w), 1035 (m), 992 (w), 919 (w), 869 (w), 806 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 6.80 (1H, d, J = 2.3 Hz), 6.76 (1H, dd, J = 2.3, 8.3 Hz), 6.68 (1H, d, J = 8.3 Hz), 5.38–5.20 (1H, m), 4.92 (1H, d, J = 17.0 Hz), 4.79 (1H, d, J = 10.1 Hz), 3.78 (3H, s), 3.13 (3H, s), 2.57 (2H, d, J = 7.2 Hz), 2.16 (1H, sep, J = 6.9 Hz), 0.94 (3H, d, J = 6.9 Hz), 0.72 (3H, d, J = 6.9 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 179.05 (s), 155.68 (s), 137.99 (s), 132.96 (d), 132.43 (s), 118.29 (t), 111.86 (d), 111.36 (d), 107.70 (d), 56.73 (s), 55.84 (q), 39.68 (t), 34.83 (d), 25.94 (q), 17.45 (q), 17.25 (q). **EIMS** *m/z* (%):260 (M^+, 63%), 259 (48), 219 (47), 216 (73), 203 (48), 202 (40), 190 (46), 188 (52), 174 (46), 160 (38), 144 (55), 131 (58), 130 (56), 117 (82), 115 (100), 103 (79), 91 (88), 77 (74). **HRMS** *m/z* Found: 259.1576, Calcd. for $C_{16}H_{21}NO_2$ $(M)^+$: 259.1572.

Compound 7i. Yield 51%, Pale yellow syrup, R_f 0.51 (Petroleum ether/EtOAc = 5 : 1). **IR** (ν_{max} cm^{-1}): 3028 (w), 2966 (w), 2921 (w), 2356 (w), 1712 (s), 1609 (m), 1481 (m), 1461 (m), 1367 (m), 1343 (m), 1250 (w), 1111 (w), 1023 (w), 969 (w), 927 (w), 748 (m), 695 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.30–7.11 (7H, m), 7.06 (1H, t, J = 7.5 Hz), 6.81 (1H, d, J = 7.7 Hz), 6.34 (1H, d, J = 15.7 Hz), 5.88 (1H, dt, J = 7.6, 15.7 Hz), 3.17 (3H, s), 2.64 (2H, d, J = 7.6 Hz), 1.41 (3H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 180.27 (s), 143.24 (s), 137.36 (s), 133.79 (d), 133.68 (s), 128.50 (d), 127.94 (d), 127.28 (d), 126.25 (d), 124.31 (d), 123.04 (d), 122.48 (d), 108.08 (d), 48.71 (s), 41.75 (t), 26.24 (q), 22.64 (q). **EIMS** *m/z* (%):278 (M^++1, 59%), 277 (M^+, 92%), 262 (6), 232 (7), 217 (11), 202 (12), 189 (7), 174 (10), 161 (80), 160 (96), 145 (48), 132 (70), 130 (83), 118 (93), 117 (98), 115 (100), 103 (50), 91 (100), 89 (50), 77 (79), 65 (50). **HRMS** *m/z* Found: 277.1469, Calcd. for $C_{19}H_{19}NO$ $(M)^+$: 277.1467.

Compound 7j. Yield 75%, Yellow plate, mp: 139–140 °C, R_f 0.58 (Petroleum ether/EtOAc = 3 : 1). **IR** (ν_{max} cm^{-1}): 3401 (w), 3049 (w), 3002 (w), 2926 (w), 2884 (w), 2354 (w), 1708 (s), 1607 (m), 1539 (w), 1476 (m), 1424 (w), 1342 (m), 1252 (m), 1204 (w), 1132 (w), 1084 (m), 1008 (m), 927 (m), 886 (w), 809 (w), 751 (s), 675 (m). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.30 (1H, t, J = 7.5 Hz), 7.22–6.86 (8H, m), 5.55–5.38 (1H, m), 5.04 (1H, d, J = 17.0 Hz), 4.91 (1H, dt, J = 1.2, 10.1 Hz), 3.65 (3H, s), 3.21 (3H, s), 3.20–3.04 (2H, m). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 178.29 (s), 143.82 (s), 137.61 (s), 132.46 (d), 132.45 (s), 128.16 (d), 127.54 (d), 125.98 (s), 124.56 (d), 122.51 (d), 121.74 (d), 120.56 (d), 119.23

(d), 119.01 (t), 113.41 (s), 109.38 (d), 108.00 (d), 52.52 (s), 40.87 (t), 32.78 (q), 26.33 (q). **EIMS** *m/z* (%):317 (M^++1, 40%), 316 (M^+, 73%), 305 (47), 290 (19), 275 (100), 259 (31), 247 (53), 245 (45), 232 (68), 218 (50), 204 (55), 190 (46), 176 (30), 165 (22), 158 (33), 144 (27), 137 (97), 131 (68), 130 (62), 123 (43), 115 (47), 109 (35), 102 (46), 91 (30). **HRMS** *m/z* Found: 316.1579, Calcd. for $C_{21}H_{20}N_2O$ $(M)^+$: 316.1576.

Compound 11a. Yield 28%, Pale yellow syrup, R_f 0.48 (Petroleum ether/EtOAc = 5 : 1). **IR** (ν_{max} cm^{-1}): 3446 (w), 3069 (w), 3027 (w), 2974 (w), 2925 (w), 1712 (w), 1644 (s), 1489 (m), 1442 (m), 1352 (m), 1305 (w), 1214 (w), 1163 (w), 1082 (w), 996 (w), 920 (w), 758 (m), 706 (m). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.40–7.22 (7H, m), 7.18 (1H, td, J = 1.6, 7.6 Hz), 7.02 (1H, d, J = 7.6 Hz), 5.53–5.32 (1H, m), 4.95 (1H, d, J = 16.5 Hz), 4.91 (1H, d, J = 10.2 Hz), 4.90 (1H, d, J = 14.6 Hz), 4.63 (1H, d, J = 14.6 Hz), 4.45 (1H, d, J = 16.1 Hz), 4.30 (1H, d, J = 16.1 Hz), 2.81 (1H, dd, J = 7.2, 13.6 Hz), 2.47 (1H, dd, J = 7.2, 13.6 Hz), 1.61 (3H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 173.01 (s), 139.27 (s), 137.02 (s), 133.82 (d), 130.38 (s), 128.75 (d), 128.25 (d), 127.60 (d), 126.42 (d), 126.12 (d), 125.35 (d), 118.32 (t), 50.76 (t), 49.64 (t), 46.07 (t), 45.08 (s), 25.21 (q). **EIMS** *m/z* (%):292 (M^++1, 80%), 291 (M^+, 96%), 276 (68), 264 (27), 250 (94), 236 (40), 222 (96), 206 (12), 200 (41), 186 (44), 172 (58), 158 (90), 143 (85), 130 (86), 115 (92), 103 (78), 91 (99), 77 (84), 65 (100). **HRMS** *m/z* Found: 291.1624, Calcd. for $C_{20}H_{21}NO$ $(M)^+$: 291.1623.

Compound 11b. Yield 60%, Colorless oil, R_f 0.52 (Petroleum ether/EtOAc = 6 : 1). **IR** (ν_{max} cm^{-1}): 3444 (w), 3066 (w), 3019 (w), 2921 (w), 2847 (w), 2354 (w), 1649 (s), 1486 (m), 1439 (m), 1349 (w), 1272 (m), 1202 (w), 1077 (w), 995 (w), 917 (w), 754 (m), 704 (m). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.35–7.11 (11H, m), 7.10–7.02 (3H, m), 5.73–5.56 (1H, m), 5.13 (1H, d, J = 17.2 Hz), 4.99 (1H, d, J = 10.2 Hz), 4.77 (1H, d, J = 15.9 Hz), 4.72 (1H, d, J = 15.9 Hz), 4.14 (2H, s), 3.64 (1H, dd, J = 6.1, 14.4 Hz), 2.98 (1H, dd, J = 6.5, 14.4 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 171.30 (s), 143.14 (s), 137.78 (s), 136.85 (s), 135.22 (d), 132.78 (s), 128.65 (d), 128.55 (d), 128.40 (d), 128.09 (d), 127.51 (d), 127.24 (d), 126.98 (d), 126.78 (d), 125.36 (d), 117.93 (t), 55.13 (s), 50.85 (t), 49.49 (t), 42.61 (t). **EIMS** *m/z* (%):354 (M^++1, 34%), 353 (M^+, 51%), 337 (7), 326 (12), 312 (30), 297 (10), 284 (52), 262 (36), 249 (21), 234 (30), 217 (26), 205 (36), 192 (39), 179 (42), 165 (35), 152(56), 142 (40), 127 (46), 117 (48), 105 (93), 104 (84), 92 (74), 77 (100), 65 (97). **HRMS** *m/z* Found: 353.1783, Calcd. for $C_{25}H_{23}NO$ $(M)^+$: 353.1780.

Compound 11c. Yield 45%, Pale yellow syrup, R_f 0.59 (Petroleum ether/EtOAc = 8 : 1). **IR** (ν_{max} cm^{-1}): 3471 (w), 3068 (w), 3019 (w), 2926 (w), 2843 (w), 1648 (s), 1504 (m), 1442 (m), 1352 (w), 1250 (m), 1183 (m), 1118 (w), 1033 (m), 917 (w), 827 (w), 751 (m), 705 (m). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.38–7.13 (8H, m), 7.06 (1H, d, J = 7.2 Hz), 6.98 (2H, d, J = 7.8 Hz), 6.74 (2H, d, J = 7.8 Hz), 5.73–5.52 (1H, m), 5.12 (1H, d, J = 17.2 Hz), 4.97 (1H, d, J = 10.2 Hz), 4.74 (2H, s), 4.15 (2H, s), 3.74 (3H, s), 3.61 (1H, dd, J = 6.1, 14.4 Hz), 2.94 (1H, dd, J = 7.1, 14.4 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 171.50 (s), 158.48 (s), 137.98 (s), 136.90 (s), 135.30 (d), 132.72 (s), 128.66 (d), 128.65 (s), 128.47 (d), 128.37 (d), 128.09 (d), 127.49 (d), 126.72 (d), 125.33 (d), 117.86 (t), 113.72 (d), 55.30 (q), 54.42 (s), 50.84 (t), 49.48 (t), 42.73 (t). **EIMS** *m/z* (%):384 (M^++1, 19%), 383 (M^+, 23%), 342 (31), 315 (29), 275 (49), 250 (51), 235 (53), 179 (85), 165 (88), 152 (63), 135 (42), 121 (87), 104 (45), 92 (84), 77 (56), 65 (100). **HRMS** *m/z* Found: 383.1890, Calcd. for $C_{26}H_{25}NO_2$ $(M)^+$: 383.1885.

General procedure for oxidative cleavage of double bond[12]

To a mixture of olefin **7b** or **7f–7h** (0.52 mmol) in 1,4-dioxane-H_2O (8 mL, 3 : 1) was added osmium tetroxide (5.3 mg, 0.021 mmol, 0.04 eq.), 2,6-lutidine (0.12 mL, 1.04 mmol, 2.0 eq.) and sodium periodate ($NaIO_4$, 556 mg, 2.60 mmol, 5.0 eq.). The resulting mixture was stirred at room temperature. The reaction progress was monitored by thin layer chromatography. Aqueous saturated sodium sulfite (5 mL) was added. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 15 mL). The organic phases were combined and washed with brine (10 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel (Petroleum ether 60–90 °C/ethyl acetate = 4 : 1–2 : 1) to afford the products.

Compound 12. Yield 85%, White plate, mp: 96–97 °C, R_f 0.45 (Petroleum ether/EtOAc = 2 : 1). **IR** (ν_{max} cm^{-1}): 3416 (w), 2963 (m), 2933 (m), 2872 (m), 2757 (w), 1707 (s), 1604 (m), 1498 (s), 1383 (m), 1335 (w), 1291 (s), 1226 (s), 1184 (w), 1125 (m), 1033 (m), 909 (w), 867 (w), 804 (s), 747 (w), 703 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 9.50 (1H, d, J = 1.1 Hz), 6.81–6.75 (3H, m), 3.77 (3H, s), 3.22 (3H, s), 2.98 (1H, d, J = 17.3 Hz), 2.90 (1H, d, J = 17.3 Hz), 1.39 (3H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 198.82 (d), 179.26 (s), 156.26 (s), 136.82 (s), 134.27 (s), 112.29 (d), 110.49 (d), 108.75 (d), 55.91 (q), 50.67 (t), 45.51 (s), 26.60 (q), 24.09 (q). **EIMS** *m/z* (%):234 (M^++1, 32%), 233 (M^+, 95%), 218 (11), 205 (55), 204 (100), 190 (94), 175 (40), 174 (29), 162 (23), 147 (34), 146 (18), 132 (16), 118 (27), 103 (9), 91 (16). **HRMS** *m/z* Found: 233.1056, Calcd. for $C_{13}H_{15}NO_3$ $(M)^+$: 233.1052.

Compound 13a (R = *n*-Butyl). Yield 75%, Pale yellow oil, R_f 0.41 (Petroleum ether/EtOAc = 4 : 1). **IR** (ν_{max} cm^{-1}): 2944 (w), 2864 (w), 2733 (w), 2356 (w), 1708 (s), 1601 (w), 1494 (m), 1462 (m), 1366 (w), 1287 (m), 1232 (w), 1168 (w), 1121 (w), 1035 (m), 918 (w), 882 (w), 808 (m), 755 (w), 698 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 9.43 (1H, d, J = 1.3 Hz), 6.82–6.70 (3H, m), 3.75 (3H, s), 3.21 (3H, s), 2.95 (1H, d, J = 17.3 Hz), 2.87 (1H, d, J = 17.3 Hz), 1.94–1.68 (2H, m), 1.20–1.08 (2H, m), 1.08–0.70 (2H, m), 0.74 (3H, t, J = 7.2 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 198.90 (d), 178.67 (s), 156.13 (s), 137.54 (s), 132.59 (s), 112.01 (d), 110.64 (d), 108.48 (d), 55.80 (q), 50.42 (t), 49.65 (s), 37.70 (t), 26.43 (q), 25.55 (t), 22.71 (t), 13.82 (q). **EIMS** *m/z* (%):276 (M^++1, 8%), 275 (M^+, 33%), 246 (67), 233 (20), 218 (9), 204 (44), 190 (100), 174 (27), 147 (8), 118 (6), 91 (7). **HRMS** *m/z* Found: 275.1518, Calcd. for $C_{16}H_{21}NO_3$ $(M)^+$: 275.1521.

Compound 13b (R = *i*-Propyl). Yield 78%, Colorless oil, R_f 0.38 (Petroleum ether/EtOAc = 4 : 1). **IR** (ν_{max} cm^{-1}): 3440 (s), 2956 (m), 2913 (m), 2839 (w), 2729 (w), 1705 (s), 1607 (m), 1495 (m), 1459 (m), 1373 (m), 1287 (m), 1124 (w), 1036 (m), 919 (w), 803 (w), 739 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 9.39 (1H, d, J = 1.4 Hz), 6.86–6.68 (3H, m), 3.76 (3H, s), 3.20 (3H, m), 2.99 (2H, s), 2.20–2.02 (1H, m), 0.94 (3H, d, J = 6.9 Hz), 0.69 (3H, d, J = 6.7 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 199.12 (d), 178.65 (s), 155.84 (s), 137.99 (s), 131.20 (s), 111.95 (d), 111.65 (d), 108.26 (d), 55.81 (q), 52.75 (s), 48.61 (t), 35.28 (d), 26.29 (q), 16.98 (q), 16.81 (q). **EIMS** *m/z* (%):262 (M^++1, 99%), 261 (M^+, 78%), 246

(16), 233 (62), 232 (95), 218 (93), 204 (36), 191 (100), 190 (62), 174 (95), 160 (40), 159 (38), 147 (41), 146 (37), 131 (26), 130 (26), 118 (39), 117 (43), 103 (26), 102 (19), 91 (43). **HRMS** *m/z* Found: 261.1373, Calcd. for $C_{15}H_{19}NO_3$ $(M)^+$: 261.1365.

Compound 13c (R = Phenyl). Yield 83%, Colorless oil, R_f 0.32 (Petroleum ether/EtOAc = 3 : 1). **IR** (ν_{max} cm^{-1}): 3429 (w), 2926 (w), 2835 (w), 2729 (w), 1712 (s), 1601 (w), 1496 (m), 1458 (w), 1358 (w), 1285 (w), 1231 (w), 1165 (w), 1111 (w), 1035 (m), 927 (w), 808 (w), 730 (w), 700 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 9.52 (1H, s), 7.40–7.20 (5H, m), 6.91–6.75 (3H, m), 3.77 (3H, s), 3.43 (1H, d, J = 17.3 Hz), 3.34 (1H, d, J = 17.3 Hz), 3.23 (3H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 198.57 (d), 177.40 (s), 156.22 (s), 138.76 (s), 137.52 (s), 132.49 (s), 128.93 (d), 127.82 (d), 126.62 (d), 112.87 (d), 112.32 (d), 109.07 (d), 55.86 (q), 53.13 (s), 50.55 (t), 26.85 (q). **EIMS** *m/z* (%):296 (M^++1, 15%), 295 (M^+, 73%), 267 (24), 266 (100), 252 (51), 237 (8), 209 (14), 190 (13), 180 (8), 165 (3), 153 (2), 126 (1), 115 (1), 91 (2). **HRMS** *m/z* Found: 295.1203, Calcd. for $C_{18}H_{17}NO_3$ $(M)^+$: 295.1208.

General procedure for reductive aminocyclization

To a solution of aldehyde **12** or **13** (0.43 mmol), triethylamine (435 mg, 4.3 mmol, 10 eq.) and $MeNH_2$–HCl (291 mg, 4.3 mmol, 10 eq.) in anhydrous THF (10 ml) was added a powder of $MgSO_4$ (361 mg, 3.0 mmol). The resulting mixture was stirred at room temperature for 12–15 h. A powder of lithium aluminum hydride (163 mg, 4.3 mmol, 10 eq.) was added and the resulting mixture was stirred at reflux for 2–3 h. After cooling to room temperature, ethyl acetate (20 mL) was added followed by saturated aqueous sodium bicarbonate (20 mL). The mixture was then extracted with ethyl acetate (3 × 10 mL). The organic phases were combined and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the residue was chromatographed on silica gel (dichloromethane/methanol = 40 : 1–10 : 1) to afford the products.

Esermethole. Yield 70%, Pale yellow plate, mp: 51–52 °C, R_f 0.51 (CH_2Cl_2/CH_3OH = 20 : 1). **IR** (ν_{max} cm^{-1}): 3444 (m), 2945 (m), 2862 (w), 2786 (w), 2354 (w), 2320 (w), 1677 (m), 1494 (s), 1454 (m), 1382 (w), 1286 (m), 1213 (s), 1173 (w), 1119 (m), 1031 (s), 959 (w), 866 (w), 804 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 6.63 (1H, dd, J = 2.4, 8.0 Hz), 6.64 (1H, d, J = 2.4 Hz), 6.34 (1H, d, J = 8.0 Hz), 4.06 (1H, s), 3.72 (3H, s), 2.87 (3H, s), 2.80–2.54 (2H, m), 2.52 (3H, s), 1.98–1.90 (2H, m), 1.42 (3H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 153.97 (s), 146.43 (s), 138.12 (s), 112.16 (d), 109.70 (d), 107.50 (d), 98.20 (d), 55.90 (q), 53.12 (t), 52.73 (s), 40.72 (t), 38.00 (q), 38.00 (d), 27.37 (q). **EIMS** *m/z* (%):232 (M^+, 78%), 218 (81), 203 (43), 190 (55), 188 (85), 174 (100), 160 (76), 146 (33), 131 (30), 117 (21), 96 (21), 77 (15). **HRMS** *m/z* Found: 232.1575, Calcd. for $C_{14}H_{20}N_2O$ $(M)^+$: 232.1576.

Compound 14. Yield 50%, Yellow syrups, R_f 0.45 (CH_2Cl/CH_3OH = 40 : 1). **IR** (ν_{max} cm^{-1}): 3471 (w), 2928 (m), 2861 (w), 1715 (w), 1677 (w), 1601 (w), 1496 (s), 1459 (m), 1380 (w), 1343 (w), 1279 (m), 1218 (m), 1168 (w), 1119 (m), 1074 (w), 1032 (m), 951 (w), 884 (w), 804 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 6.65 (1H, dd, J = 2.5, 8.4 Hz), 6.59 (1H, d, J = 2.5 Hz), 6.36 (1H, d, J = 8.4 Hz), 4.22 (1H, s), 3.74 (3H, s), 2.89 (3H, s), 2.80–2.70 (1H, m), 2.61–2.45 (1H, m), 2.52 (3H, s), 2.12–1.86 (2H, m), 1.84–1.60 (2H, m), 1.35–0.98 (4H, m), 0.83 (3H, t, J = 7.1 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 153.31 (s), 147.28 (s), 136.53 (s), 112.36 (d), 110.36 (d), 107.73 (d), 95.07 (d), 57.49 (s), 56.15 (q), 52.58 (t), 39.87 (t), 39.74 (t), 38.06 (q), 37.31 (q), 28.12 (t), 23.23 (t), 14.08 (q). **EIMS** *m/z* (%):275 (M^++1, 66%), 274 (M^+, 85%), 259 (51), 245 (43), 230 (78), 217 (67), 203 (58), 188 (70), 174 (100), 159 (69), 145 (43), 144 (52), 131 (68), 130 (46), 115 (55), 101 (43), 96 (34), 85 (77). **HRMS** *m/z* Found: 274.2050, Calcd. for $C_{17}H_{26}N_2O$ $(M)^+$: 274.2045.

Compound 15. Yield 41%, pale yellow plate, mp: 55–56 °C, R_f 0.35 (CH_2Cl_2/CH_3OH = 15 : 1). **IR** (ν_{max} cm^{-1}): 3439 (s), 2923 (m), 2855 (w), 2351 (w), 1634 (m), 1491 (m), 1450 (m), 1379 (m), 1286 (w), 1216 (w), 1090 (m), 1037 (m), 915 (w). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 6.75 (1H, dd, J = 2.5, 8.5 Hz), 6.67 (1H, d, J = 2.5 Hz), 6.49 (1H, d, J = 8.5 Hz), 4.79 (1H, brs), 3.76 (3H, s), 3.38–3.30 (1H, m), 3.01 (3H, s), 2.67 (3H, s), 2.61–2.38 (2H, m), 2.23–2.03 (2H, m), 0.97 (3H, d, J = 6.9 Hz), 0.72 (3H, d, J = 6.7 Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 152.02 (s), 143.64 (s), 130.04 (s), 111.21 (d), 108.98 (d), 106.56 (d), 91.76 (d), 59.93 (s), 53.81 (q), 50.91 (t), 35.32 (q), 33.92 (t), 33.41 (d), 32.40 (q), 16.36 (q), 15.93 (q). **EIMS** *m/z* (%):261 (M^++1, 24%), 260 (M^+, 100%), 245 (13), 231 (5), 217 (60), 216 (23), 202 (38), 188 (32), 187 (15), 174 (68), 160 (15), 144 (9), 131 (15), 115 (6), 102 (4). **HRMS** *m/z* Found: 260.1890, Calcd. for $C_{16}H_{24}N_2O$ $(M)^+$: 260.1889.

Compound 16. Yield 40%, Brown syrups, R_f 0.48 (CH_2Cl_2/CH_3OH = 40 : 1). **IR** (ν_{max} cm^{-1}): 3427 (w), 2928 (m), 2859 (w), 2355 (w), 1663 (m), 1499 (s), 1454 (m), 1280 (m), 1219 (m), 1149 (w), 1106 (w), 1034 (m), 923 (w), 860 (w), 806 (w), 765 (w), 704 (m). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.35–7.12 (5H, m), 6.69 (1H, dd, J = 2.5, 8.5 Hz), 6.54 (1H, d, J = 2.5 Hz), 6.43 (1H, d, J = 8.5 Hz), 4.46 (1H, s), 3.70 (3H, s), 2.95 (3H, s), 2.98–2.70 (3H, m), 2.53 (3H, s), 2.35–2.25 (1H, m). **^{13}C-NMR** (75 MHz, $CDCl_3$), δ (ppm): 153.17 (s), 147.05 (s), 146.63 (s), 136.64 (s), 128.52 (d), 126.70 (d), 126.34 (d), 113.07 (d), 111.78 (d), 107.80 (d), 99.19 (d), 61.71 (s), 56.14 (q), 53.49 (t), 39.86 (t), 38.29 (q), 37.42 (q). **EIMS** *m/z* (%):295 (M^++1, 52%), 294 (M^+, 100%), 279 (33), 264 (20), 250 (92), 237 (50), 236 (54), 222 (65), 207 (37), 194 (31), 191 (21), 174 (42), 165 (18), 147 (19), 139 (19), 131 (12), 115 (13), 105 (12), 91 (17), 77 (16). **HRMS** *m/z* Found: 294.1725, Calcd. for $C_{19}H_{22}N_2O$ $(M)^+$: 294.1732.

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