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ARTICLE

Collective Synthesis of Basic Carbazole Alkaloids

Shivaji B. Markad and Narshinha P. Argade✉

ABSTRACT

Starting from *N*-boc-protected 3-formylindole, practical synthesis of carbazole alkaloids clausine E, mukonine, koenoline, murrayafoline A and murrayanine has been accomplished in overall seven steps. The application of dimethyl maleate to construct the suitably substituted aromatic ring and selective transformation of mukonine to murrayafoline A are the important features.

KEYWORDS

3-Formylindole, Wittig reaction, Intramolecular cyclization, Selective reductions, Carbazole alkaloids.

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Author affiliations:

Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune-411 008, India

✉To whom correspondence to be addressed:

E-mail: np.argade@ncl.res.in

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INTRODUCTION

A large number of natural and unnatural bioactive carbazoles are known and important due to a range of biological activities' point of view and their electrical and thermal properties [1-3]. Several efficient syntheses of these essential compounds are also reported in literature [1-3]. The carbazole alkaloids clausine E, mukonine, koenoline, murrayafoline A and murrayanine have been isolated from the genus Murraya and exhibited antibiotic, antifungal, cytotoxic and antimalarial properties [4]. A few general synthetic protocols have been known to design above-specified basic carbazoles [5-11].

Recently, we synthesized dimethyl (*E*)-2-((1-(*t*-butoxycarbonyl)-1*H*-indol-3-yl)methylene)succinate from the readily available N-boc-protected 3-formylindole and dimethyl maleate by using Bu_3P-induced-efficient Wittig reaction. The formed product was rationally used as a potential building block to accomplish collective total synthesis of range of structurally interesting and biologically important carbazole alkaloids [12-14]. In continuation with our above-mentioned studies, we herein report concise and efficient synthesis of target compounds (Fig. 1).

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz) and 500 NMR (125 MHz) spectrometers. Mass spectra were taken on MS-TOF mass spectrometer. The IR spectra were recorded on an FT-IR spectrometer. Column chromato-

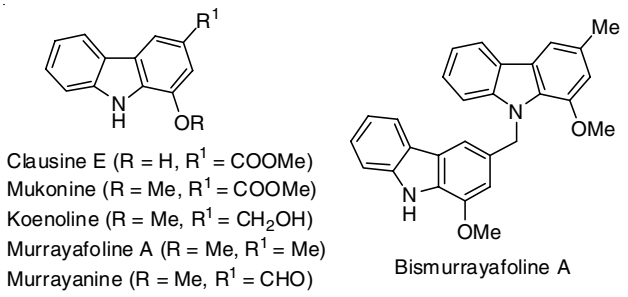


Fig. 1. Basic carbazole alkaloids and the dimer of murrayafoline A

graphic separations were carried out on silica gel (60-120 mesh). Commercially available 3-formylindole, tributylphosphine, dimethyl maleate, trifluoroacetic anhydride, dimethyl sulphate, lithium aluminium hydride and pyridinium chlorochromate (PCC) were used as received.

(*E*)-4-(1*H*-Indol-3-yl)-3-(methoxycarbonyl)but-3-enoic acid (4): To a solution of compound **3** (4.00 g, 10.72 mmol) in MeOH:H_2O (3:1, 20 mL) was added KOH (1.20 g, 21.44 mmol) at 25 ºC and the reaction mixture was stirred for 20 h at same temperature. The reaction mixture was concentrated *in vacuo* and the obtained residue was acidified by 2 N HCl (15 mL) and extracted with ethyl acetate (40 mL × 3). The combined extract was washed with water and brine, and finally dried over Na_2SO_4. The organic layer was concentrated *in vacuo* and the obtained residue was purified by silica gel (60-120 mesh) column chromatography using ethyl acetate:petroleum ether (1:1) as an eluent to yield acid **4** as a solid (Yield: 2.44 g, 88 %). m.p.:178-180 ºC; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.59 (s, 2H), 3.77 (s, 3H), 7.00-7.30 (m, 2H), 7.49 (d, *J* = 8 Hz, 1H), 7.60-7.80 (m, 2H), 8.05 (s, 1H), 11.84 (brs, 1H), 12.43 (brs, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 34.4, 51.8, 110.1, 112.1, 117.9, 119.4, 120.4, 122.4, 127.2, 127.3, 132.4, 135.8, 167.9 and 172.1; ESI-MS (*m/z*): 282 $[M+Na]^+$; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3335, 1708, 1687, 1614. Anal. calcd. (found) (%) for $C_{14}H_{13}NO_4$: C, 64.86 (64.97); H, 5.05 (5.21); N, 5.40 (5.33).

Methyl-1-hydroxy-9*H*-carbazole-3-carboxylate (Clausine E, 5): To a solution of compound **4** (2.00 g, 7.72 mmol) in dichloromethane (15 mL) was added trifluoroacetic anhydride (4.86 g, 3.28 mL, 23.16 mmol) and the reaction mixture was refluxed for 24 h. The reaction mixture was allowed to reach room temperature and concentrated *in vacuo*. The obtained residue was dissolved in ethyl acetate (60 mL) and washed with saturated aqueous sodium bicarbonate solution and brine, and dried over Na_2SO_4. The concentration of organic layer *in vacuo* followed silica gel (60-120 mesh) column chromatographic purification using ethyl acetate:petroleum ether (2:8) as an eluent to provide product **5** as a solid (Yield: 1.32 g, 71 %). m.p. 218-220 ºC; ^{1}H NMR (acetone-d_6, 500 MHz): δ 3.89 (s, 3H), 7.24 (t, *J* = 10 Hz, 1H), 7.44 (t, *J* = 10 Hz, 1H), 7.59 (s, 1H), 7.62 (d, *J* = 10 Hz, 1H), 8.19 (d, *J* = 10 Hz, 1H), 8.39 (s, 1H), 9.13 (brs, 1H), 10.66 (brs, 1H); ^{13}C NMR (acetone-d_6,125 MHz): δ 52.1, 111.5, 112.6, 115.5, 120.6, 121.4, 122.6, 124.5, 125.1, 127.1, 133.8, 141.5, 143.5 and 168.1; ESI-MS (*m/z*): 264 $[M+Na]^+$; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3351, 3020, 1702. Anal. calcd. (found) (%) for $C_{14}H_{11}NO_3$: C, 69.70 (69.94); H, 4.60 (4.41); N, 5.81 (6.03).

Methyl-1-methoxy-9*H*-carbazole-3-carboxylate (Mukonine, 6): To a stirred solution of compound **5** (1.00 g, 3.92 mmol) in dry acetone (15 mL) was added K_2CO_3 (540 mg, 3.92 mmol) and dimethyl sulphate (334 µL, 3.52 mmol) at 25 ºC and the reaction mixture was refluxed for 8 h. The reaction mixture was allowed to reach room temperature and concentrated *in vacuo*. The obtained residue was dissolved in ethyl acetate (50 mL) and the organic layer was washed with water and brine, and then dried over Na_2SO_4. The organic layer was concentrated *in vacuo* and the obtained residue was purified by silica gel (60-120 mesh) column chromatography using ethyl acetate:petroleum ether (2:8) as an eluent to yield pure product **6** as a solid (Yield: 0.97 g, 92 %). m.p.: 194-196 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.97 (s, 3H), 4.03 (s, 3H), 7.20-7.55 (m, 3H), 7.58 (s, 1H), 8.09 (d, *J* = 8 Hz, 1H), 8.47 (s, 1H), 8.52 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.0, 55.7, 106.6, 111.2, 116.2, 120.2, 120.7, 121.8, 123.5, 123.7, 126.3, 132.9, 139.5, 145.0 and 168.0; ESI-MS (*m/z*): 256 $[M+H]^+$; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3468, 1692. Anal. calcd. (found) (%) for $C_{15}H_{13}NO_3$: C, 70.58 (70.33); H, 5.13 (5.36); N, 5.49 (5.28).

(1-Methoxy-9*H*-carbazol-3-yl)methanol (Koenoline, 7): To the slurry of lithium aluminium hydride (44 mg, 1.17 mmol) in THF (5 mL) was added compound **6** (300 mg, 1.17 mmol) in THF (10 mL) under argon atmosphere at -10 ºC. The reaction mixture was stirred for 2 h at -10 to 0 ºC in ice-salt-bath and the reaction was quenched with saturated aqueous sodium sulphate (10 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (40 mL). The organic phase was washed with water and brine and then dried over Na_2SO_4. The concentration of organic layer *in vacuo* followed by silica gel (60-120 mesh) column chromatographic purification of resulting residue using ethyl acetate:petroleum ether (3:7) as an eluent furnished pure product **7** as a solid (Yield: 237 mg, 89 %). m.p.138-140 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.92 (s, 3H), 4.74 (s, 2H), 6.85 (s, 1H), 7.05-7.22 (m, 1H), 7.25-7.40 (m, 2H), 7.56 (s, 1H), 7.94 (d, *J* = 8 Hz, 1H), 8.19 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.5, 66.5, 105.6, 111.1, 111.7, 119.5, 120.5, 123.5, 124.0, 125.8, 129.4, 132.8, 139.4 and 145.7; ESI-MS (*m/z*): 228 $[M+H]^+$; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3447, 3238, 1612. Anal. calcd. (found) (%) for $C_{14}H_{13}NO_2$: C, 73.99 (74.24); H, 5.77 (5.87); N, 6.16 (6.02)

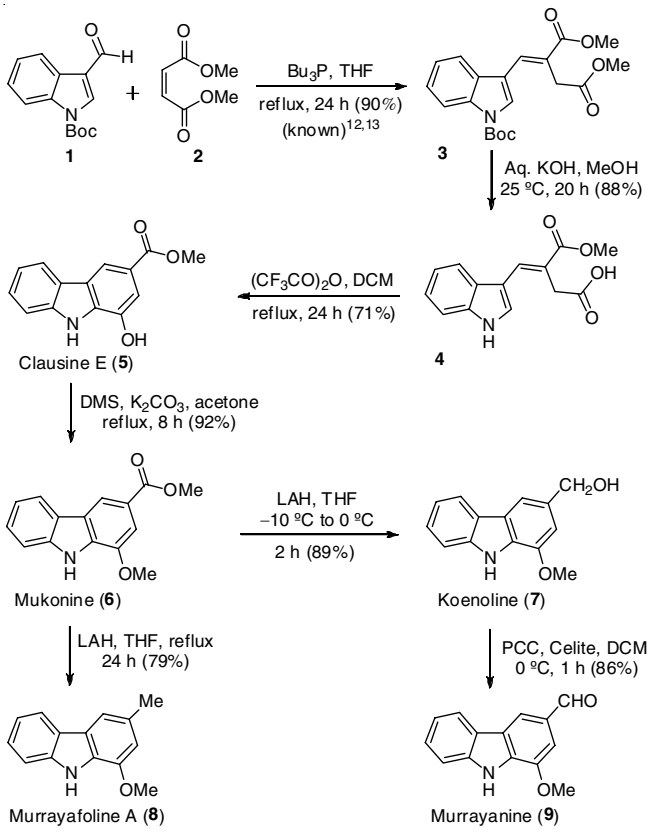
1-Methoxy-3-methyl-9*H*-carbazole (Murrayafoline A, 8): To the refluxing slurry of lithium aluminium hydride (44 mg, 1.17 mmol) in THF (15 mL) was added compound **6** (300 mg, 1.17 mmol) in THF (5 mL) under argon atmosphere and refluxed for 24 h. The reaction mixture was allowed to reach room temperature, and the reaction was quenched with saturated aqueous sodium sulphate (10 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (100 mL). The organic phase was washed with water and brine, and then dried over Na_2SO_4. The concentration of organic layer *in vacuo* followed by silica gel (60-120 mesh) column chromatographic purification of the resulting residue using ethyl acetate:petroleum ether (1:9) as an eluent furnished pure product **8** as colourless oil (Yield: 196 mg, 79 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.60 (s, 3H), 4.03 (s, 3H), 6.79 (s, 1H), 7.27 (dt, *J* = 10 and 5 Hz, 1H), 7.42-7.48 (m, 2H), 7.55 (s, 1H), 8.09 (d, *J* = 10 Hz, 1H), 8.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125

MHz): δ 21.9, 55.4, 107.6, 110.9, 112.5, 119.1, 120.4, 123.5, 124.2, 125.4, 127.9, 129.4, 139.4 and 145.2; ESI-MS (*m/z*): 212 $[M+H]^+$; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3462, 1620. Anal. calcd. (found) (%) for $C_{14}H_{13}NO$: C, 79.59 (79.44); H, 6.20 (6.11); N, 6.63 (6.49).

1-Methoxy-9*H*-carbazole-3-carbaldehyde (Murrayanine, 9): To a mixture of compound **7** (100 mg, 0.44 mmol) and celite (100 mg) in dichloromethane (8 mL) was added pyridinium chlorochromate (94 mg, 0.44 mmol) at 0 ºC under argon atmosphere and the reaction mixture was stirred at same temperature for 1 h. The reaction mixture was filtered and concentrated *in vacuo*. The silica gel (60-120 mesh) column chromatographic purification of the resulting residue using ethyl acetate:petroleum ether (2:8) as an eluent furnished aldehyde **9** as a solid (Yield: 85 mg, 86 %). m.p.168-170 ºC; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 7.32 (t, *J* = 8 Hz, 1H), 7.45 (s, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8 Hz, 1H), 8.10 (d, *J* = 8 Hz, 1H), 8.17 (s, 1H), 8.74 (brs, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.7, 103.5, 111.5, 120.4, 120.6, 123.55, 123.60 (2C), 126.6, 130.1, 134.1, 139.4, 146.0 and 191.9; ESI-MS (*m/z*): 226 $[M+H]^+$; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3461, 3019, 1676, 1608. Anal. calcd. (found) (%) for $C_{14}H_{11}NO_2$: C, 74.65 (74.83); H, 4.92 (5.00); N, 6.22 (6.06).

RESULTS AND DISCUSSION

The Wittig adduct dimethyl (*E*)-2-((1-(*t*-butoxycarbonyl)-1*H*-indol-3-yl)methylene)succinate (**3**) on selective base-induced hydrolysis of more reactive saturated ester moiety exclusively provided the desired monocarboxylic acid **4** in 88 % yield (**Scheme-I**). The N-boc deprotection and regioselective ester hydrolysis took place in one pot due to the conjugation of nitrogen lone pair with an electron-withdrawing ester moiety. Carboxylic acid **4** on trifluoroacetic anhydride-induced intramolecular acylation directly furnished the first natural product clausine E (**5**) in 71 % yield *via* keto-phenol tautomerism. Clausine E (**5**) on treatment with dimethyl sulphate chemoselectively delivered O-methylated second natural product mukonine (**6**) in 92 % yield. Mukonine (**6**) under kinetically controlled lithium aluminium hydride-reduction conditions (-10 to 0 ºC, 2 h) exclusively provided third natural product koenoline (**7**) in 89 % yield. As expected, the reduction of ester moiety stopped with the formation of corresponding benzyl alcohol under the above-specified reaction conditions.



Scheme-I: Facile approach to bioactive carbazole alkaloids

Mukonine (**6**) under thermodynamically controlled lithium aluminium hydride-reduction conditions is known to produce mixture of products in varying proportions [15]. Mukonine (**6**) on thermodynamically controlled lithium aluminium hydride-reduction in THF (25 ºC, 3 h and then reflux for 21 h) provided the mixture of natural product murrayafoline A (**8**) in 59 % yield and its dimeric natural product bismurrayafoline A (Fig. 1) in 21% yield [14]. Remarkably, the addition of solution of mukonine (**6**) in THF to the refluxing slurry of lithium aluminium hydride in THF exclusively provided fourth natural product murrayafoline A (**8**) in 79 % yield. Mechanistically, transformation of mukonine (**6**) to murrayafoline A (**8**) takes place *via* intermediates aldehyde, alcohol, alcohol-aluminium complex formation and exocyclic product formation *via* elimination of aluminium oxide through anchimeric assistance of indole nitrogen lone pair and addition of hydride to exocyclic double bond takes place to deliver the final product. Finally, koenoline (**7**) on pyridinium chlorochromate oxidation furnished fifth natural product murrayanine (**9**) in 86 % yield. The obtained analytical and spectral data for all the target compounds **5** to **9** were in complete agreement for the assigned structures.

Conclusion

In conclusion, a simple and efficient collective total synthesis of five carbazole alkaloids has been reported, which also completes the formal synthesis of several other related carbazole alkaloids. Selective direct transformation of carbomethoxy group in clausine E to methyl group to form murrayafoline A is noteworthy from basic chemistry point of view. These carbazoles would also be useful as appropriate precursors to design several structurally complex carbazole alkaloids and their hybrids for structure-activity relationship studies.

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