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Divergent Syntheses of Carbazole Alkaloids Clausenapin, Indizoline, Claulansine M, and Clausenaline D

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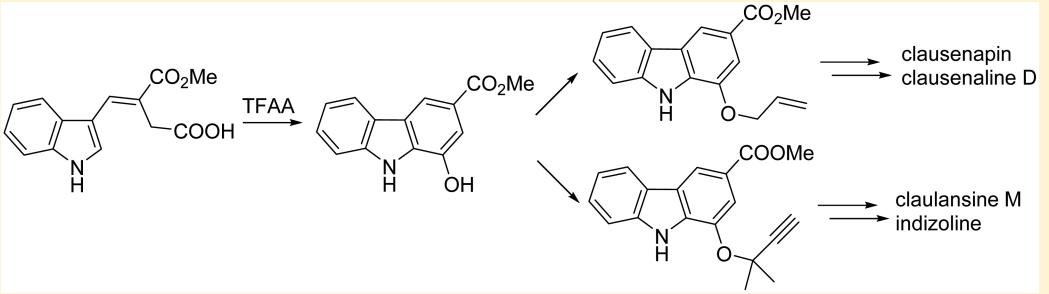
Supporting Information



ABSTRACT: We described the first total syntheses of clausenapin, indizoline, claulansine M, and a novel synthetic route to clausenaline D via divergent method. Key steps involved TFAA-mediated intramolecular acylation to construct the carbazole core and subsequent Claisen rearrangement to generate key intermediates for further elaboration to target molecules.

INTRODUCTION

The carbazole alkaloids are mainly isolated from plants.[1] For example, clausenapin (**1**)[2] and indizoline (**2**)[3] were isolated from *Clausena heptaphylla* and *Clausena indica*, respectively, while claulansine I (**3**),[4] clausenaline D (**4**), claulamine E (**7**),[5] claulansine M (**5**),[6] claulamine A (**6**),[7] and mafaicheenaine A (**8**)[8] were isolated from *Clausena lansium* (Figure 1). Furthermore, microbes[9] and algae[10] are also reported to be sources of natural cabazoles. Because of their promising biological activities, numerous methods have been developed for the synthesis of carbazole alkaloids. These methods could be further divided into two categories based on the way to construct the carbazole core. One way is to form the pyrrolyl ring, including Fischer-Borsche synthesis,[11] Graebe-Ullmann synthesis,[12] palladium-catalyzed cyclization,[13] iron-mediated synthesis,[14] etc. The other way starts from an indole derivative to construct the benzene ring, such as electrocyclic reaction,[15] cycloaddition reaction,[16] and so on. Herein, we report the first total syntheses of clausenapin, indizoline, and claulansine M, and a facile synthetic route to clausenaline D via divergent method.

RESULTS AND DISSCUTION

Our synthesis commenced with Stobbe condensation of indole-3-carbaldehyde **9** with dimethyl succinate in the presence of sodium hydride, which produced succinic monoester **10** in 97% isolated yield (Scheme 1). It should be indicated that compound **10** could be obtained only in low yield if methoxide was used as the base.[17] TFAA-mediated intramolecular acylation[18] of **10** provided carbazole **11**, allylation of which followed by Claisen rearrangement and methylation gave the key intermediate **13** in good combined yield over the three steps. Dihydroxylation of **13** followed by sodium periodate oxidation furnished aldehyde **14** in 70% yield. Treatment of **14** with boron tribromide resulted in the formation of furocarbazole **15** in 51% isolated yield via demethylation and concomitant furan ring formation. Transformation of the methyl ester functional group of **15** into aldehyde by lithium aluminum hydride reduction and Dess-Martin oxidation gave clausenaline D[19,20] (**4**) in 40% isolated yield over the two steps. On the other hand, treatment of **13** with lithium aluminum hydride in refluxing 1,4-dioxane[21] afforded **16** in 94% isolated yield. Olefin metathesis of **16** with 2,3-dimethyl-2-butene **17** gave access to clausenapin (**1**) in excellent yield.

The successful synthesis of clausenapin (**1**) inspired us to tackle our next target, indizoline (**2**). Thus, ester **13** was first converted into aldehyde **18** in 81% isolated yield following a two-step procedure (Scheme 2). The olefin metathesis reaction of **18** with 2,3-dimethyl-2-butene **17** was then carried out in the hope to obtain the desired indizoline (**2**). Unfortunately, compound **19** resulting from self-metathesis of **18** was actually obtained as it readily precipitated out of the reaction media. We then attempted the olefin metathesis of **13** with **17**. However, the reaction was difficult to be driven to completion under a variety of conditions. At best, the desired product **20** was isolated in 44% yield together with substantial amount of the unreacted starting material **13** recovered.

Since there is low conversion rate of **13** to **20** and it is hard to separate the two, we next explored an alternative strategy to introduce the requisite prenyl group of indizoline (**2**). As shown in Scheme 3, propargylation of **11** with 1,1-

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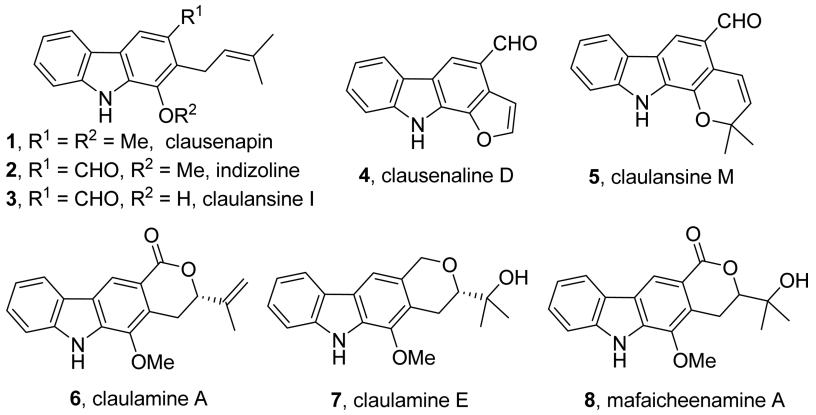
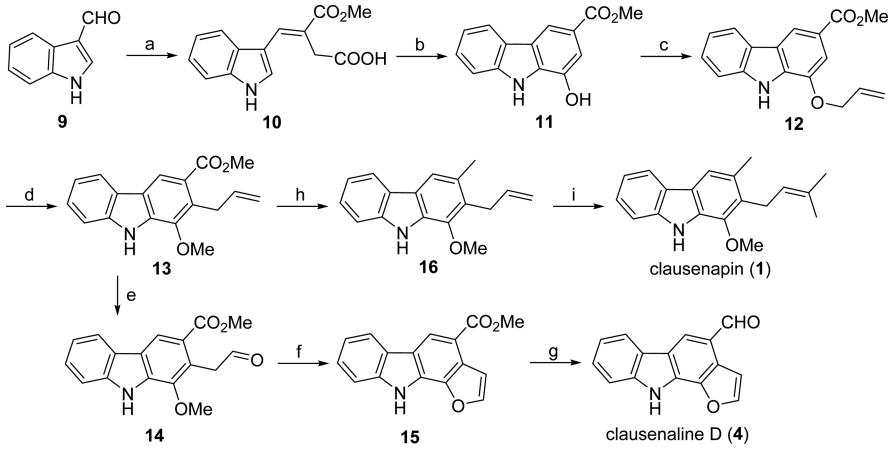


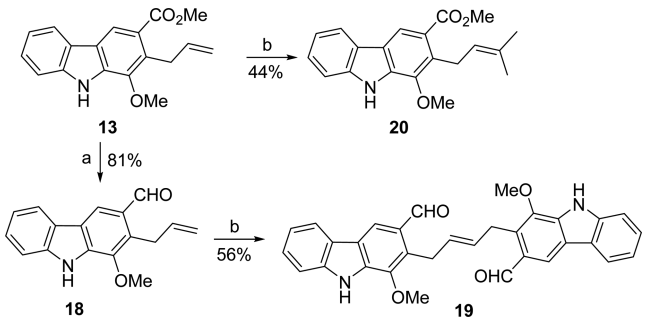
Figure 1. Representative carbazole alkaloids.

Scheme 1[a]



[a]Reagents and conditions: (a) dimethyl succinate, NaH, THF, reflux, 97%; (b) TFAA, DCM, reflux, 70%; (c) allyl bromide, K_2CO_3, acetone, 77%; (d) (i) DMF, reflux; (ii) K_2CO_3, MeI, 71% over the two steps; (e) OsO_4, $NaIO_4$, THF-H_2O, 70%; (f) BBr_3, DCM, 51%; (g) (i) $LiAlH_4$, THF, 0 °C; (ii) DMP, DCM, 40% over the two steps; (h) $LiAlH_4$, 1,4-dioxane, reflux, 94%; (i) 2,3-dimethyl-2-butene (**17**), Grubbs 2nd generation catalyst, DCM, reflux, 84%.

Scheme 2[a]



[a]Reagents and conditions: (a) (i) $LiAlH_4$, THF, 0 °C; (ii) DMP, DCM; (b) **17**, Grubbs 2nd generation catalyst, DCM, reflux.

dimethylpropargyl trifluoroacetate provided **21** in 60% isolated yield.[22] Hydrogenation of the triple bond in **21** in the presence of Lindlar's catalyst followed by Claisen rearrangement of the resulting allyl ether provided **22** in 71% isolated yield over the two steps. Methylation of phenol **22** gave **20**, ester group manipulation of which as described for the synthesis of clausenaline D (**4**) furnished indizoline (**2**) in good yield. On the other hand, [3,3]-sigmatropic rearrangement of propargyl ether **21** followed by rearomatization and cyclization gave pyranocarbazole **23** in almost quantitative yield. Finally, two-step transformation of the ester group into aldehyde completed the total synthesis of claulansine M (**5**).

CONCLUSION

In summary, we have accomplished the first total syntheses of clausenapin, indizoline, and claulansine M, as well as the synthesis of clausenaline D via divergent method. Studies toward the total synthesis of other carbazole alkaloids using the valuable precursor **20** are currently underway in our laboratory.

EXPERIMENTAL SECTION

Melting points were determined on a hot-stage apparatus and were uncorrected. Infrared spectra were obtained using an FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer. High-resolution mass spectra were recorded on a Q-TOF mass spectrometer. Flash column chromatography was performed over silica gel 200−300 mesh.

***(E)*-4-(1′*H*-Indol-3′-yl)-3-(methoxycarbonyl)but-3-enoic Acid (10).** Sodium hydride (60% dispersion in mineral oil, 6.4 g, 160 mmol) was added slowly at 0 °C to a solution of indole-3-carbaldehyde **9** (5.8 g, 40 mmol) and dimethyl succinate (11.7 g, 10 mL, 80 mmol) in dry THF (200 mL). The resulting mixture was heated at reflux under nitrogen atmosphere for 20 h. The mixture was cooled to −20 °C, and water (100 mL) was added to quench the reaction. The mixture was acidified with concentrated HCl until a pH of 1 was reached, and then

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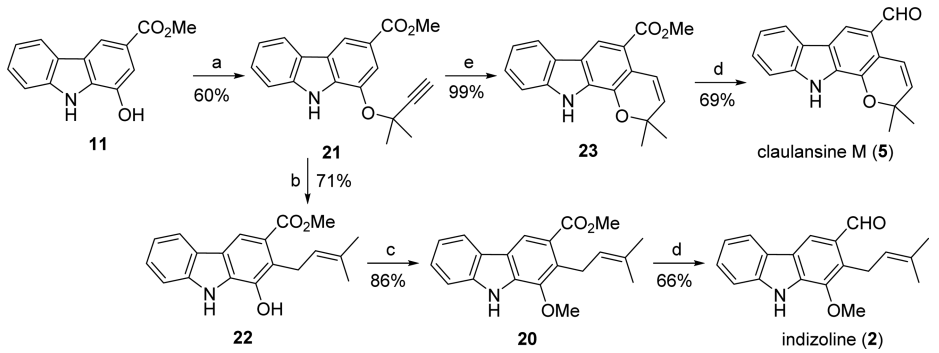
Scheme 3[a]



[a]Reagents and conditions: (a) 1,1-dimethylpropargyl trifluoroacetate, $CuCl_2$, DBU, MeCN, 0 °C; (b) (i) Lindlar's catalyst, quinoline, H_2, EtOAc; (ii) silica gel, EtOAc, 50 °C; (c) MeI, K_2CO_3, acetone; (d) (i) $LiAlH_4$, THF, 0 °C; (ii) DMP, DCM; (e) *p*-xylene, reflux.

extracted with ethyl acetate (100 mL × 4). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (13% ethyl acetate in petroleum ether, then ethyl acetate) to give acid **10** (10.1 g, 97%) as a pale-yellow solid: mp 180−183 °C [lit.[17b] mp 166−168 °C]. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.44 (s, 1H), 11.83 (s, 1H), 8.07 (s, 1H), 7.73 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 3.77 (s, 3H), 3.60 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 172.3, 168.0, 135.8, 132.5, 127.4, 127.3, 122.5, 120.5, 119.4, 118.0, 112.1, 110.2, 51.8, 34.4 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{14}H_{13}NO_4Na$ 282.0737; found 282.0737.

Methyl 1-Hydroxy-9*H*-carbazole-3-carboxylate (11). To a solution of acid **10** (10.1 g, 39 mmol) in DCM (150 mL) was added trifluoroacetic anhydride (24.6 g, 16.5 mL, 117 mmol). The mixture was stirred under reflux for 5 h before being cooled to −20 °C and neutralized with saturated aqueous sodium bicarbonate. The separated aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (30% ethyl acetate in petroleum ether) to provide carbazolecarboxylate **11** (6.6 g, 70%) as a colorless solid: mp 121−123 °C, [lit.[17a] mp 203−205 °C]. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.57 (s, 1H), 10.23 (s, 1H), 8.33 (d, J = 3.6 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.55−7.49 (m, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 3.88 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 167.1, 142.9, 140.2, 132.7, 126.0, 123.4, 123.0, 120.6, 120.5, 119.3, 114.1, 111.7, 110.1, 51.7 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{14}H_{11}NO_3$ Na 264.0631; found 264.0633.

Methyl 1-Allyloxy-9*H*-carbazole-3-carboxylate (12). Potassium carbonate (5.7 g, 41 mmol) and allyl bromide (5.0 g, 3.5 mL, 41 mmol) were added to a solution of **11** (4.0 g, 16 mmol) in acetone (20 mL). The mixture was stirred at ambient temperature for 15 h and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (6% then 12% ethyl acetate in petroleum ether) to give **12** (3.4 g, 73%) as a pale-yellow solid: mp 179−180 °C. IR (KBr, cm^{-1}): ν_{max} 3368, 1686, 1248, 1215. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.54 (s, 1H), 8.47 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.49−7.42 (m, 2H), 7.28 (t, J = 7.2 Hz, 1H), 6.15 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H), 5.49 (d, J = 17.2 Hz, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.77 (d, J = 5.2 Hz, 2H), 3.97 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.1, 144.1, 139.6, 133.2, 133.0, 126.5, 123.9, 122.0, 120.9, 120.4, 118.5, 116.5, 111.4, 108.0, 69.5, 52.2 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{15}NO_3Na$ 304.0944; found 304.0956.

Methyl 2-Allyl-1-methoxy-9*H*-carbazole-3-carboxylate (13). Ester **12** (3.1 g, 11 mmol) was dissolved in DMF (15 mL) and the solution was heated to reflux for 5 h. The mixture was cooled to ambient temperature. Potassium carbonate (1.5 g, 11 mmol) and iodomethane (1.6 g, 0.7 mL, 11 mmol) were added, and the mixture was stirred at ambient temperature for 15 h. The mixture was diluted with 30 mL of ethyl acetate and washed with brine (20 mL × 2). The separated aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were dried over sodium sulfate. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to give **13** (2.3 g, 71%) as a colorless solid: mp 112−115 °C. IR (KBr, cm^{-1}): ν_{max} 3345, 1684, 1607, 1346, 1262. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.51 (s, 1H), 8.42 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.47−7.41 (m, 2H), 7.26 (t, J = 6.4 Hz, 1H), 6.11 (ddt, J = 16.8, 10.0, 5.6 Hz, 1H), 5.02−4.93 (m, 2H), 4.03 (dt, J = 5.6, 1.6 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H) ppm. ^{13}C NMR($CDCl_3$, 100 MHz): δ = 168.5, 143.5, 140.0, 138.4, 135.6, 131.3, 126.6, 124.0, 123.0, 122.4, 120.7, 120.5, 120.4, 114.7, 111.3, 61.5, 52.0, 30.8 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{17}NO_3Na$ 318.1101; found 318.1095.

Methyl 1-Methoxy-2-(2′-oxoethyl)-9*H*-carbazole-3-carboxylate (14). Sodium periodate (1.3 g, 6 mmol) and osmium tetroxide (40 mg/mL in *t*-BuOH, 1.6 mL, 0.25 mmol) were added to a solution of ester **13** (0.3 g, 1 mmol) in THF-H_2O (3:1, 20 mL). The mixture was stirred at ambient temperature for 13 h before being quenched with 2 M sodium dithionite solution (15 mL). The mixture was stirred for 0.5 h, and then filtered through a pad of Celite. The filter cake was washed with ethyl acetate (10 mL × 3). The filtrate was separated. The aqueous layer was extracted with ethyl acetate (20 mL × 4). The combined organic extracts were dried over sodium sulfate. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (30% ethyl acetate in petroleum ether) to provide **14** (0.2 g, 70%) as a colorless solid: mp 171−174 °C. IR (KBr, cm^{-1}): ν_{max} 3336, 1703, 1240, 1058, 756. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.81 (s, 1H), 9.80 (s, 1H), 8.64 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.48 (m, 1H), 7.24 (m, 1H), 4.25 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 200.1, 167.2, 144.0, 140.5, 135.2, 126.5, 124.5, 122.9, 122.8, 120.6, 120.0, 119.8, 111.7, 61.1, 51.8, 41.3 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{15}NO_4Na$ 320.0893; found 320.0893.

Methyl 10*H*-Furo[2,3-*a*]carbazole-4-carboxylate (15).[19] Boron tribromide (1 M solution in DCM, 2 mL, 2.0 mmol) was added to a solution of **14** (144 mg, 0.5 mmol) in dry DCM (5 mL) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 10 min before being allowed to warm to ambient temperature and stirred for a further 3 h. The reaction was quenched by the addition of methanol (1 mL) and the mixture was stirred for 1 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (13% ethyl acetate in petroleum ether) to provide **15** (67 mg, 51%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.75 (s, 1H), 8.70 (s, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 4.04 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.8, 145.2, 140.6, 139.5, 127.9, 126.2, 126.1, 124.2, 121.0, 120.8, 120.5, 119.9, 114.7, 111.4, 109.4, 52.0 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{11}NO_3Na$ 288.0637; Found 288.0631.

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Clausenaline D (4).[19] Lithium aluminum hydride (14 mg, 0.4 mmol) was added to a solution of **15** (50 mg, 0.2 mmol) in dry THF (5 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 15 h before being quenched with saturated aqueous ammonium chloride (10 mL). The mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (10 mL × 3). The filtrate was separated. The aqueous phase was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over sodium sulfate. The bulk of solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (13% ethyl acetate in petroleum ether) to provide **(10*H*-furo[2,3-*a*]carbazol-4-yl)-methanol** (27 mg, 61%) as a colorless oil. ^{1}H NMR (CD_3OD, 400 MHz): δ = 8.04 (d, J = 7.6 Hz, 1H), 7.89 (s, 1H), 7.82 (m, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.12 (m, 1H), 4.96 (s, 2H) ppm. ^{13}C NMR (CD_3COCD_3, 100 MHz): δ = 145.1, 141.9, 140.8, 126.1, 125.9, 125.8, 124.8, 123.6, 121.5, 120.6, 120.3, 116.3, 112.3, 107.9, 71.3 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{11}NO_2Na$ 260.0687; found 260.0688.

Dess-Martin periodinane (48 mg, 0.1 mmol) was added to a solution of (10*H*-furo[2,3-*a*]carbazol-4-yl)methanol (27 mg, 0.1 mmol) in DCM (2 mL). The resulting mixture was stirred for 3 h at ambient temperature and filtered. The filter cake was washed with ethyl acetate (10 mL × 3). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to give clausenaline D **4** (18 mg, 65%) as a colorless solid. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ = 11.46 (s, 1H), 10.26 (s, 1H), 8.65 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H) ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_9NO_2Na$ 258.0531; Found 258.0525.

2-Allyl-1-methoxy-3-methyl-9*H*-carbazole (16). Lithium aluminum hydride (190 mg, 5.0 mmol) was added to a solution of **13** (738 mg, 2.5 mmol) in dry 1,4-dioxane (15 mL). The mixture was heated at reflux under nitrogen for 4 h before being cooled to 0 °C and quenched with saturated aqueous ammonium chloride (20 mL). The mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (15 mL × 3). The filtrate was separated. The aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over sodium sulfate. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (3% ethyl acetate in petroleum ether) to provide carbazole **16** (590 mg, 94%) as a colorless solid: mp 92−95 °C. IR (KBr, cm^{-1}): ν_{max} 3350, 1310, 1276. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.08 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (m, 1H), 7.23 (m, 1H), 6.06 (ddt, J = 17.2, 10.0, 5.2 Hz, 1H), 5.06 (dq, J = 10.0, 1.0 Hz, 1H), 4.95 (dq, J = 17.2, 1.8 Hz, 1H), 3.97 (s, 3H), 3.64 (dt, J = 5.2, 1.8 Hz, 2H), 2.47 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.4, 139.8, 136.9, 131.6, 129.6, 128.0, 125.7, 124.0, 123.7, 120.3, 119.5, 117.2, 115.1, 110.9, 61.4, 30.9, 19.9 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{17}NONa$ 274.1202; found 274.1188.

Clausenapin (1).[2] Under nitrogen atmosphere, Grubbs second generation catalyst (13 mg, 0.015 mmol) and 2,3-dimethyl-2-butene **17** (498 mg, 0.7 mL, 6.0 mmol) were added to a solution of carbazole **16** (77 mg, 0.3 mmol) in dry DCM (10 mL). The resulting mixture was heated at reflux for 24 h and cooled. The mixture was filtered through a pad of silica gel. The filter cake was washed with DCM (10 mL × 3). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (3% ethyl acetate in petroleum ether) to give clausenapin **1** (72 mg, 84%) as a pale-yellow solid: mp 81−83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.10 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 5.16 (m, 1H), 3.96 (s, 3H), 3.56 (d, J = 6.4 Hz, 2H), 2.47 (s, 3H), 1.85 (s, 3H), 1.73 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.1, 139.7, 131.8, 131.7, 130.4, 129.3, 125.5, 124.0, 123.3, 123.2, 120.3, 119.4, 117.2, 110.9, 61.2, 26.0, 25.9, 20.1, 18.2 ppm. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{22}NO$ 280.1696; found 280.1689.

2-Allyl-1-methoxy-9*H*-carbazole-3-carbaldehyde (18). At 0 °C, lithium aluminum hydride (58 mg, 1.5 mmol) was added to a solution of ester **13** (90 mg, 0.3 mmol) in dry THF (10 mL). After addition, the mixture was stirred at 0 °C for 15 h before being quenched with saturated aqueous ammonium chloride (10 mL). The mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (10 mL × 3). The separated aqueous layer of the filtrate was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over sodium sulfate, and then filtered. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (13% ethyl acetate in petroleum ether) to give **(2-allyl-1-methoxy-9*H*-carbazol-3-yl)-methanol** (73 mg, 86%) as a pale-yellow solid: mp 137−140 °C. IR (KBr, cm^{-1}): ν_{max} 3425, 1450, 1348, 1117. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.15 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.88 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.23 (m, 1H), 6.13 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H), 5.06 (dq, J = 10.4, 1.6 Hz, 1H), 4.93 (dq, J = 17.2, 1.6 Hz, 1H), 4.83 (s, 2H), 3.96 (s, 3H), 3.73 (dt, J = 5.2, 1.6 Hz, 2H), 1.69 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.6, 139.8, 138.4, 132.9, 132.1, 127.6, 126.0, 124.0, 123.8, 120.5, 119.9, 116.9, 115.3, 111.1, 64.3, 61.4, 30.1 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{17}NO_2Na$ 290.1151; Found 290.1155.

Dess-Martin periodinane (68 mg, 0.2 mmol) was added to a solution of (2-allyl-1-methoxy-9*H*-carbazol-3-yl)methanol (43 mg, 0.2 mmol) in DCM (5 mL). The resulting mixture was stirred for 10 h at ambient temperature, and then filtered. The filter cake was washed with ethyl acetate (10 mL × 3). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (13% ethyl acetate in petroleum ether) to give aldehyde **18** (39 mg, 94%) as an orange oil. IR (KBr, cm^{-1}): ν_{max} 3279, 1662, 1595, 1232, 1106. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.26 (s, 1H), 8.63 (s, 1H), 8.44 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.47 (td, J = 8.0, 0.8 Hz, 1H), 7.30 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 6.16 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.08 (dq, J = 10.4, 1.6 Hz, 1H), 4.93 (dq, J = 17.2, 1.6 Hz, 1H), 4.04 (dt, J = 5.6, 1.6 Hz, 2H), 3.98 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 192.0, 143.3, 140.0, 138.0, 137.0, 131.3, 127.8, 126.9, 124.0, 123.7, 121.9, 120.9, 120.8, 115.8, 111.5, 61.7, 29.0 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{15}NO_2Na$ 288.0995; found 288.1001.

2,2′-(But-2″-ene-1″,4″-diyl)bis(1-methoxy-9*H*-carbazole-3-carbaldehyde) (19). Under nitrogen atmosphere, Grubbs second generation catalyst (18 mg, 0.02 mmol) and 2,3-dimethyl-2-butene **17** (698 mg, 1.0 mL, 8.3 mmol) were added to a solution of carbazole **18** (110 mg, 0.4 mmol) in dry DCM (20 mL). The resulting mixture was heated at reflux for 12 h and cooled. The formed precipitate was filtered and washed with DCM (5 mL × 3) to provide **19** (58 mg, 56%) as a colorless solid: mp 271 °C, decomposition. IR (KBr, cm^{-1}): ν_{max} 3266, 1665, 1595, 1232. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.81 (s, 2H), 10.13 (s, 2H), 8.45 (s, 2H), 8.18 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.46 (m, 2H), 7.24 (t, J = 7.6 Hz, 2H), 5.64 (t, J = 2.0 Hz, 2H), 3.91 (d, J = 2.0 Hz, 4H), 3.85 (s, 6H) ppm. ^{13}C NMR (DMSO-d_6, 400 MHz): δ = 191.7, 142.9, 140.5, 136.4, 130.9, 130.4, 126.6, 126.5, 123.0, 122.6, 121.8, 120.6, 120.0, 111.8, 61.0, 27.2 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{32}H_{26}N_2O_4Na$ 525.1785; found 525.1782.

Methyl 1-[(2′-Methylbut-3′-yn-2′-yl)oxy]-9*H*-carbazole-3-carboxylate (21). At 0 °C, DBU (1.1 g, 1.1 mL, 8 mmol) was added to a solution of 2-methyl-3-butyn-2-ol (0.5 g, 0.6 mL, 6 mmol) in acetonitrile (10 mL). TFAA (1.1 g, 0.7 mL, 5 mmol) was then added dropwise. The solution was stirred at 0 °C for 0.5 h before being poured into a mixture of ester **11** (1.2 g, 5 mmol), DBU (1.1 g, 1.1 mL, 8 mmol) and $CuCl_2$ (1 mg, 0.005 mmol) in acetonitrile (30 mL). The resulting mixture was stirred at 0 °C for 4 h. The solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (30 mL) and washed successively with 2 M hydrochloric acid (30 mL), 2 M sodium hydroxide (30 mL), saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL). The organic layer was dried over sodium sulfate, and then filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to provide **21** (1.4 g, 60%) as a yellow solid: mp 120−123 °C. IR (KBr, cm^{-1}): ν_{max} 3319, 1687, 1343, 1261, 1218. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.60 (s, 1H), 8.56 (s, 1H), 8.15 (d, J =

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1.2 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.48−7.42 (m, 2H), 7.27 (ddd, J = 8.0, 6.8, 1.6 Hz, 1H), 3.97 (s, 3H), 2.61 (s, 1H), 1.79 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.0, 140.4, 139.7, 136.4, 126.6, 124.5, 123.9, 121.7, 120.9, 120.4, 118.0, 117.4, 111.2, 85.9, 74.6, 73.8, 52.2, 29.8 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{17}NO_3Na$ 330.1101; found 330.1104.

Methyl 1-Hydroxy-2-(3′-methylbut-2′-en-1′-yl)-9*H*-carbazole-3-carboxylate (22). Palladium (5% on calcium carbonate, poisoned with lead, 149 mg, 0.07 mmol) and quinoline (3.9 g, 3.6 mL, 30.5 mmol) were added to a solution of acetylene **21** (1.1 g, 3.5 mmol) in ethyl acetate (20 mL). The resulting mixture was hydrogenated (3 atm) for 4 h. Silica gel (200−300 mesh, 1.0 g) was added. The mixture was heated at 50 °C for 12 h, and then cooled. The mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (20 mL × 3). The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on aluminum oxide (13% ethyl acetate in petroleum ether) to provide alkene **22** (0.8 g, 71%) as a yellow solid: mp 146−149 °C. IR (KBr, cm^{-1}): ν_{max} 3427, 1656, 1429, 1301. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.42 (s, 1H), 8.29 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.43−7.38 (m, 2H), 7.24 (m, 1H), 5.84 (s, 1H), 5.35 (t, J = 6.8 Hz, 1H), 3.96−3.94 (m, 5H), 1.88 (s, 3H), 1.77 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.3, 140.8, 139.9, 135.2, 132.2, 126.3, 123.9, 123.8, 122.6, 122.4, 122.0, 120.7, 120.2, 116.9, 111.2, 52.2, 26.8, 25.9, 18.1 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{19}NO_3Na$ 332.1257; found 332.1254.

Methyl 1-Methoxy-2-(3′-methylbut-2′-en-1′-yl)-9*H*-carbazole-3-carboxylate (20). Potassium carbonate (191 mg, 1.4 mmol) and methyl iodide (196 mg, 1.4 mmol) were added to a solution of phenol **22** (285 mg, 0.9 mmol) in acetone (5 mL). The resulting mixture was stirred at ambient temperature for 15 h. The solvent was evaporated *in vacuo*. The residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The separated aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over sodium sulfate, and then filtered. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to provide ether **20** (256 mg, 86%) as a colorless solid: mp 139−142 °C. IR (KBr, cm^{-1}): ν_{max} 3341, 1687, 1608, 1260. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (s, 1H), 8.34 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.48−7.41 (m, 2H), 7.27 (ddd, J = 8.0, 6.8, 1.6 Hz, 1H), 5.25 (m, 1H), 3.95 (s, 3H), 3.94−3.92 (m, 5H), 1.83 (s, 3H), 1.70 (d, J = 0.8 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.8, 143.3, 140.0, 135.6, 133.4, 131.5, 126.4, 124.3, 124.1, 122.8, 122.6, 120.6, 120.4, 120.3, 111.2, 61.3, 52.1, 26.1, 25.9, 18.2 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{21}NO_3Na$ 346.1414; found 346.1414.

Indizoline (2). Lithium aluminum hydride (80 mg, 2.1 mmol) was added to a solution of ester **20** (226 mg, 0.7 mmol) in dry THF (10 mL) 0 °C. The reaction was stirred at 0 °C for 15 h before being quenched with saturated aqueous ammonium chloride (15 mL). The mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (15 mL × 3). The separated aqueous layer of the filtrate was extracted with ethyl acetate (15 mL × 3). The combined organic extracts were dried over sodium sulfate, and then filtered. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (13% ethyl acetate in petroleum ether) to provide **[1-methoxy-2-(3′-methylbut-2′-en-1′-yl)-9*H*-carbazol-3-yl]-methanol** (148 mg, 72%) as a colorless solid: mp 141−144 °C. IR (KBr, cm^{-1}): ν_{max} 3417, 3239, 1451, 1341, 1250. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.17 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.39 (t, J = 8.6 Hz, 1H), 7.22 (t, J = 8.6 Hz, 1H), 5.20 (t, J = 6.4 Hz, 1H), 4.81 (s, 2H), 3.95 (s, 3H), 3.65 (d, J = 6.4 Hz, 2H), 1.85 (s, 3H), 1.78 (s, 1H), 1.71 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.4, 139.8, 132.9, 132.3, 132.1, 130.1, 125.9, 124.2, 124.1, 123.5, 120.4, 119.8, 116.9, 111.0, 64.4, 61.3, 25.9, 25.2, 18.2 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{21}NO_2Na$ 318.1465; found 318.1448.

Dess-Martin periodinane (212 mg, 0.5 mmol) was added to a solution of [1-methoxy-2-(3′-methylbut-2′-en-1′-yl)-9*H*-carbazol-3-yl]methanol (148 mg, 0.5 mmol) in DCM (15 mL). The resulting mixture was stirred for 5 h at ambient temperature, and then filtered through a pad of Celite. The filter cake was washed with ethyl acetate (15 mL × 3). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to provide indizoline **2** (135 mg, 92%) as a colorless solid: mp 168−171 °C [lit[23] mp =169−170 °C]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.29 (s, 1H), 8.64 (s, 1H), 8.44 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.45 (td, J = 8.0, 1.2 Hz, 1H), 7.28 (ddd, J = 8.0, 6.8, 1.6 Hz, 1H), 5.24 (m, 1H), 3.96−3.94 (m, 5H), 1.84 (s, 3H), 1.69 (d, J = 0.8 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 192.1, 142.9, 140.0, 137.1, 134.1, 132.2, 127.9, 126.8, 124.2, 124.0, 123.4, 121.3, 120.9, 120.8, 111.4, 61.6, 25.8, 24.2, 18.3. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{19}NO_2Na$ 316.1308; found 316.1299.

Methyl 2,2-Dimethyl-2,11-dihydropyrano[2,3-*a*]carbazole-5-carboxylate (23). A solution of acetylene **21** (98 mg, 0.3 mmol) in *p*-xylene was refluxed for 1 h and cooled. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to provide **23** (97 mg, 99%) as a colorless solid: mp 152−155 °C. IR (KBr, cm^{-1}): ν_{max} 3378, 1689, 1340, 1248, 1049. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (s, 1H), 8.35 (s, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.51 (d, J = 10.0 Hz, 1H), 7.44−7.39 (m, 2H), 7.23 (ddd, J = 8.0, 6.4, 2.0 Hz, 1H), 5.73 (d, J = 10.0 Hz, 1H), 3.95 (s, 3H), 1.51 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.3, 140.2, 138.6, 132.0, 130.1, 126.6, 124.0, 123.3, 121.6, 120.7, 120.3, 118.2, 118.1, 116.8, 111.2, 76.1, 52.0, 27.8 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{17}NO_3Na$ 330.1101; found 330.1107.

Claulansine M (5).[6] Lithium aluminum hydride (61 mg, 1.6 mmol) was add to a solution of **23** (97 mg, 0.3 mmol) in dry THF (10 mL) at 0 °C. The reaction was stirred at 0 °C for 15 h before being quenched with saturated aqueous ammonium chloride (15 mL). The mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (15 mL × 3). The separated aqueous layer of the filtrate was extracted with ethyl acetate (15 mL × 3). The combined organic extracts were dried over sodium sulfate, and then filtered. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (13% ethyl acetate in petroleum ether) to provide **(2,2-dimethyl-2,11-dihydropyrano[2,3-*a*]carbazol-5-yl)methanol** (82 mg, 93%) as a yellow solid: mp 142−145 °C. IR (KBr, cm^{-1}): ν_{max} 3246, 1250, 1128. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.33 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.39−7.34 (m, 2H), 7.18 (ddd, J = 8.0, 6.4, 2.4 Hz, 1H), 6.78 (d, J = 10.0 Hz, 1H), 5.64 (d, J = 10.0 Hz, 1H), 4.81 (s, 2H), 1.83 (s, 1H), 1.49 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.0, 138.6, 129.4, 129.2, 128.1, 126.0, 124.1, 123.8, 120.4, 119.9, 119.6, 116.1, 112.8, 111.1, 76.4, 64.0, 28.0 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{17}NO_2Na$ 302.1151; found 302.1149.

Dess-Martin periodinane (127 mg, 0.3 mmol) was added to a solution of (2,2-dimethyl-2,11-dihydropyrano[2,3-*a*]carbazol-5-yl)-methanol (82 mg, 0.3 mmol) in DCM (5 mL). The resulting mixture was stirred for 5 h at ambient temperature, and then filtered through a pad of Celite. The filter cake was washed with ethyl acetate (10 mL × 3). The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to provide claulansine M **5** (60 mg, 74%) as a pale yellow solid: mp 124−127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.18 (s, 1H), 8.54 (s, 1H), 8.07−8.05 (m, 2H), 7.64 (d, J = 10.0 Hz, 1H), 7.49−7.43 (m, 2H), 7.29 (ddd, J = 8.0, 6.8, 2.0 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 1.53 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.0, 140.1, 138.7, 132.7, 131.1, 126.9, 124.6, 123.9, 123.7, 121.8, 120.8, 120.7, 120.0, 117.2, 111.5, 76.6, 27.9 ppm. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{15}NO_2Na$ 300.0995; found 300.1006.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00729.

^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **5**, **10**−**16**, and **18**−**23**. ^{1}H NMR spectra for compound **4** (PDF)

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Notes

The authors declare no competing financial interest.

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