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A Concise Synthesis of 1-Oxygenated Carbazole Alkaloids, Clausine E and Clausine F

Durga P. Kamat, Sonia B. Parsekar, Vijayendra P. Kamat, Santosh G. Tilve*

Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 206, India
E-mail: stilve@unigoa.ac.in

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Abstract: A rapid entry into naturally occurring and biologically important 1-oxygenated carbazole clausine E was established through Wittig reaction and annulation. Further O-prenylation of clausine E by Mitsunobu reaction followed by *p*-Claisen rearrangement delivered clausine F.

Key words: alkaloids, Wittig reaction, annulation, Mitsunobu reaction, *p*-Claisen rearrangement

1-Oxygenated tricyclic carbazole alkaloids are of plant origin and most, including the 1-hydroxycarbazoles, have promising biological activities (Figure 1).[1] Clausine E[2] (**1**) and clausine F[3] (**7**) were isolated from the stem bark of *Clausena excavata*, with the former showing inhibition of rabbit platelet aggregation and vasocontraction.[2b] Recently, its growth inhibitory activity against several cancer cell lines by inhibiting PKC$^{\delta}$ phosphorylation as well as decreasing F-actin staining RhoA activity has been reported.[4] Clausine F also showed inhibition of platelet aggregation[3] and possesses antitumor properties.[5] Clausena plant extracts are known to exhibit antifungal,[6] antimicrobial,[7] antiplasmodial,[8] and anti-HIV activities.[9]

The synthetic methods employed for the construction of carbazole frameworks have been periodically reviewed.[1,10–12] Fischer indolization with appropriate phenyl hydrazones,[13] intramolecular cyclization of indole,[14–17] and allene-mediated electrocyclic reaction involving the indole 2,3-bond[18] are well known. Recently, [2+2+2] cycloaddition,[19] Diels–Alder reaction between an imine quinone and cyclic diene,[20] Suzuki–Miyaura coupling,[21] Lewis acid promoted intramolecular amination and oxylation of biaryl triazenes,[22] ring-closing metathesis,[23] benzannulation,[24] and transition-metal-catalyzed C–C or C–N bond-forming reactions[25] have also been examined. Knölker et al. have reported numerous iron-mediated syntheses[26] of carbazole alkaloids over the past two decades.

There are five reported procedures for the synthesis of clausine E. The first was described in 1998 by Bringmann et al.,[16] starting from indole-3-carbaldehyde using Horner–Emmons reaction as the key step. In the same year, Brenna et al.[15] synthesized clausine E by carrying out Stobbe condensation on indole-3-carbaldehyde followed by annulation. In 2006, Bergman and Johnson[17] reported the synthesis of clausine E by utilizing a Michael addition type reaction between itaconic anhydride and indole in the presence of Lewis acid catalyst. Recent reports include an allene-mediated electrocyclization route described by Hibino and co-workers[18] in 2009, and a benzannulation approach developed by Jana et al.[24a] in 2012.

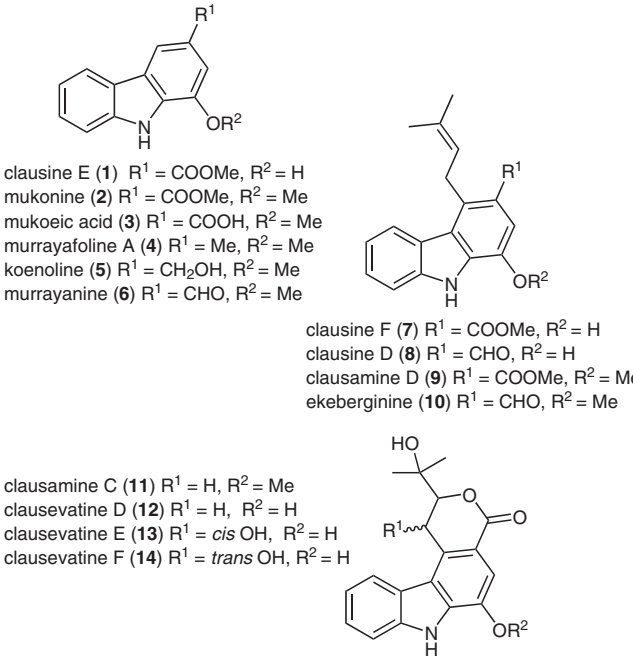

Figure 1 Structures of some naturally occurring 1-oxygenated tricyclic carbazole alkaloids

Prenyl carbazoles have developed synthetic significance owing to their wide range of biological activities.[3,5,27] In 2010, the group of Mal[24b] reported an efficient first total synthesis of clausine F by carrying out benzannulation of furoindolone with a suitable Michael acceptor followed by incorporation of the prenyl group, ester driven *p*-Claisen rearrangement, selective decarboxylation, and esterification. In 2012, the same group reported that *N*-benzyl protected prenylated furoindolone, on benzannulation and selective decarboxylation, gave *N*-benzyl protected clausine F.[24a] However, the requisite N-deprotection step failed to provide clausine F. The first total synthesis of ekeberginine **10** was achieved by Thomas and Knölker using a palladium-catalyzed oxidative cyclization and a regioselective nickel-mediated prenylation as the key steps.[28]

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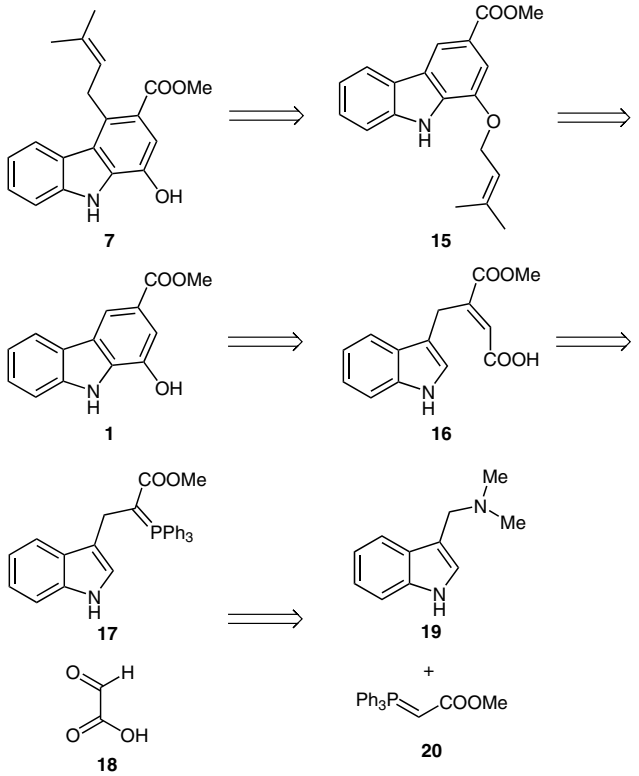
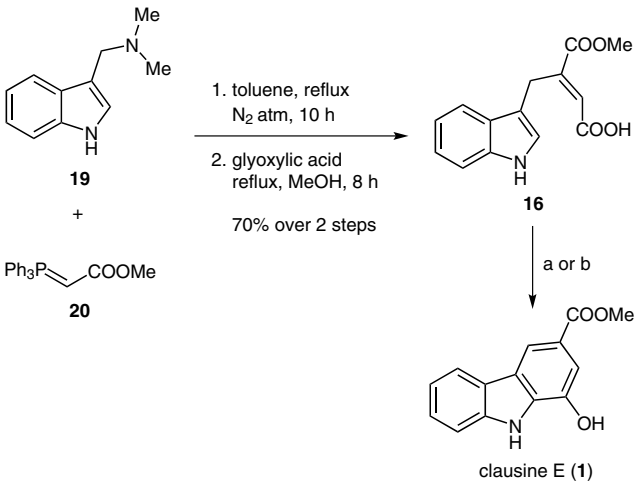
Our profound interest in the application of the Wittig reaction in myriad synthetic strategies[29] prompted us to investigate the use of phosphorane chemistry towards the synthesis of 1-oxygenated carbazole alkaloids. Our retrosynthetic analysis of clausine E and clausine F is shown in Scheme 1. We envisaged that clausine F (**7**) could be synthesized directly from clausine E (**1**) through *p*-Claisen rearrangement[29c] of its *O*-prenyl ether **15**. The [3,3]-sigmatropic rearrangement of an allyl aryl ether to an *o*-allyl phenol is termed the Claisen rearrangement; however, when the product obtained is *p*-allyl phenol, it is called a *p*-Claisen rearrangement, which involves a tandem Claisen and Cope rearrangement. Synthesis of clausine E could be achieved from annulation of acid **16**, which, in turn, could be obtained from a Wittig reaction between phosphorane **17** and glyoxylic acid (**18**). The required phosphorane **17** could be prepared from alkylation of stable phosphorane **20** by gramine (**19**). The crucial steps of our synthetic approach towards the synthesis of clausine E were the Wittig reaction and annulation, and for the synthesis of clausine F was the *p*-Claisen rearrangement without the need for any directing group or N-protection.



Scheme 1 Retrosynthetic approach

The synthesis began with alkylation of the phosphorane [methyl (triphenylphosphoranylidene)acetate] (**20**) with Mannich base **19** in refluxing toluene,[30] followed by sequential Wittig reaction of this product with glyoxylic acid, which gave the expected product **16** (Scheme 2). The *E*-geometry of the double bond was confirmed by the ^{1}H NMR chemical shift at the vinylic proton, which was observed at $\delta = 6.74$ ppm (s, 1 H). The downfield shift of this proton indicated it to be *cis* to the methyl ester.[32]



Scheme 2 Synthesis of clausine E (see Table 1 for conditions a and b)

The next step was annulation of **16**, which was first attempted by heating with polyphosphoric acid in the absence of solvent. Very little product (clausine E) formation was observed at 80 °C, with much of the starting remaining intact. When the reaction temperature was increased to 100–110 °C, clausine E was obtained in 20% yield in three hours (Table 1, conditions a). Extending the reaction time resulted in a decrease in the yield due to decomposition of the reaction mass. The same results were observed when the temperature was increased beyond 110 °C. We then attempted the intramolecular cyclization of **16** by the action of sodium acetate in acetic anhydride,[16] which, to our delight, gave a mixture of cyclized carbazole derivatives, methyl 1-acetoxy-9-acetyl-carbazole-3-carboxylate (**22**) and methyl 1-acetoxy-carbazole-3-carboxylate (**21**) (Figure 2). This mixture was directly subjected to deprotection with potassium carbonate in methanol to give clausine E in 55% yield over the two steps (Table 1, conditions b).

Table 1 Reaction Conditions for Annulation of **16** To Give Clausine E

Conditions	Reaction conditions	Time	Yield (%)
a	Polyphosphoric acid, 100–110 °C	3 h	20
b	i. NaOAc, Ac_2O, 140 °C ii. K_2CO_3, MeOH, reflux	9 h 40 min	55 (two steps)

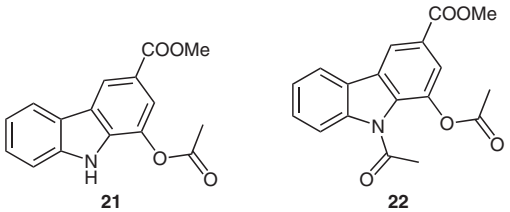
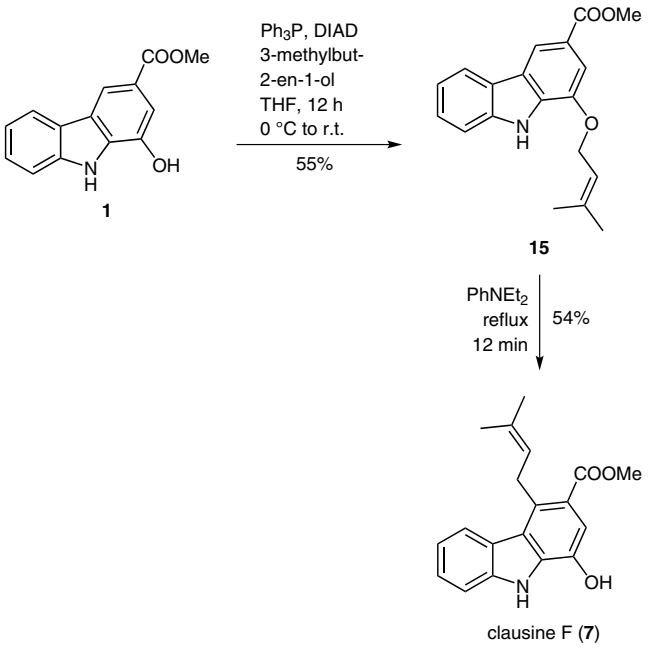


Figure 2 Products of annulation of **16** using sodium acetate and acetic anhydride

For the synthesis of clausine F, O-prenylation of clausine E was required. Accordingly, O-prenylation of clausine E was attempted by heating with prenyl bromide in the presence of potassium carbonate in acetone, however no product formation was observed. Hence, we carried out O-prenylation of clausine E through a Mitsunobu reaction,[31] which provided the O-prenylated ether of clausine E **15** in good yield. Further heating of product **15** to reflux in diethylaniline gave clausine F through *p*-Claisen rearrangement with 54% yield in just 12 minutes (Scheme 3). The highlights of our approach are that protection of the indole nitrogen is not required and that *para* selectivity was observed in the Claisen rearrangement.



Scheme 3 Synthesis of clausine F

In conclusion, we have developed an efficient total synthesis of clausine E involving Wittig reaction and annulation as the key steps. The synthesis constitutes a formal synthesis of naturally occurring mukonine[24a] (**2**) and related naturally occurring carbazoles such as murrayafoline A, koenoline, mukoeic acid, and murrayanine.[16] In addition, the synthesis of clausine F was successfully implemented through a *p*-Claisen rearrangement of O-prenylated clausine E, which also completes the formal synthesis of naturally occurring carbazole alkaloids clausevatine D (**12**), clausamine C (**11**), and clausamine D (**9**).[24b]

Commercial reagents were purchased from Sigma–Aldrich or Spectrochem and used without further purification. Solvents were distilled prior to use. Reactions were monitored by thin-layer chromatography with TLC Silica Gel 60 F254 purchased from Merck. Column chromatography was performed on silica gel (60–120 mesh). Melting points were recorded in open capillary tubes with Thiele's apparatus and are uncorrected. The IR spectra were recorded with a Shimadzu FTIR spectrophotometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded with a Bruker AVANCE 400 instrument using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts δ are expressed relative to TMS, the coupling constant *J* is given in Hz. The multiplicities of the carbon signals were obtained from DEPT-135 experiments. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet. HRMS were recorded with a Micro-Mass ES-QTOF.

(2*E*)-4-Methoxy-3-(1*H*-indol-3-ylmethyl)-4-oxobut-2-enoic Acid (16)

Gramine (**19**; 2500 mg, 14.34 mmol) was added to a solution of phosphorane (**20**; 4790 mg, 14.32 mmol) in toluene (30 mL) and heated to reflux for 10 h under a nitrogen atmosphere to give phosphorane **17**, as white solid after filtration, which, without further purification was directly subjected to Wittig reaction with glyoxylic acid (50% in water, 2.242 g, 15.15 mmol) in MeOH (30 mL) heated to reflux for 8 h. MeOH was then evaporated and the residue was dissolved in EtOAc (30 mL). The organic layer was extracted with saturated $NaHCO_3$ (3 × 30 mL) and the combined aqueous layer was cooled, acidified with aq HCl, and extracted with EtOAc (3 × 30 mL). The crude product was further purified by column chromatography (hexanes–EtOAc, 4:1) to give **16**.

Yield: 2.597 g (70%); brown gummy mass.

IR (neat): 1273, 1454, 1643, 1710, 2600, 3057, 3408 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H), 4.28 (s, 2 H), 6.74 (s, 1 H), 6.96 (s, 1 H), 7.02–7.12 (m, 2 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 7.6 Hz, 1 H), 7.93 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.32 (CH_2), 52.70 (CH_3), 111.07 (CH), 112.00 (Cq), 119.19 (CH), 119.51 (CH), 122.01 (CH), 122.98 (CH), 125.02 (CH), 127.26 (Cq), 136.02 (Cq), 148.53 (Cq), 167.32 (Cq), 170.29 (Cq).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{13}NO_4Na$: 282.0742; found: 282.0746.

Methyl Carbazole-3-carboxylates 21 and 22

Compound **16** (600 mg, 2.316 mmol) was heated at reflux in acetic anhydride (6 mL) with freshly fused sodium acetate (380 mg, 4.632 mmol) for 9 h. The acetic anhydride was removed by vacuum distillation and the remaining residue was purified by column chromatography (hexanes–EtOAc, 4:1) to give a mixture of acetylated carbazoles **21** and **22**.

Methyl 1-Acetoxy-carbazole-3-carboxylate (21)

Brown gummy mass.

IR (neat): 1433, 1610, 1710, 1766, 2924, 2953, 3334 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.90 (s, 3 H), 7.21 (m, 1 H), 7.40 (m, 2 H), 7.86 (s, 1 H), 8.04 (d, *J* = 7.60 Hz, 1 H), 8.24 (br s, 1 H), 8.62 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.11 (CH_3), 52.15 (CH_3), 111.30 (CH), 119.41 (CH), 120.46 (CH), 120.80 (2 × CH), 121.86 (Cq), 123.49 (Cq), 125.80 (Cq), 127.06 (CH), 134.51 (Cq), 135.03 (Cq), 139.97 (Cq), 167.15 (Cq), 168.84 (Cq).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{13}NO_4Na$: 306.0742; found: 306.0744.

Methyl 1-Acetoxy-9-acetyl-carbazole-3-carboxylate (22)

White solid; mp 108 °C (Lit.[33] 110 °C).

IR (KBr): 1485, 1581, 1714, 1722, 1770, 2398, 2439, 2924, 3498, 3520, 3558 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 2.72 (s, 3 H), 3.91 (s, 3 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.83 (m, 2 H), 8.01 (d, *J* = 7.6 Hz, 1 H), 8.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.88 (CH_3), 25.94 (CH_3), 51.39 (CH_3), 113.21 (CH), 118.21 (CH), 119.61 (CH), 122.06 (CH), 122.81 (CH), 124.28 (Cq), 125.31 (Cq), 127.22 (CH), 128.34 (Cq),

132.17 (Cq), 136.74 (Cq), 138.33 (Cq), 165.24 (Cq), 167.21 (Cq), 169.06 (Cq).

Methyl 1-Hydroxy-9*H*-carbazole-3-carboxylate (Clausine E; 1)
The mixture containing acetylated products was heated at reflux with K_2CO_3 (250 mg) in MeOH (30 mL) for 40 min. MeOH was evaporated under reduced pressure and the residue was dissolved in EtOAc (30 mL) and washed with 10% aq HCl (3 × 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated. The crude product was then purified by column chromatography (hexanes–EtOAc, 3:1) to give **1**. Recrystallization of the obtained solid from toluene provided white crystals.

Yield: 305 mg (55%); white solid; mp 214–215 °C (Lit.[17] 215–216.5 °C).

IR (KBr): 1367, 1496, 1600, 1651, 1655, 2848, 2951, 3051, 3360 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.86 (s, 3 H), 7.16–7.20 (t, *J* = 7.6 Hz, 1 H), 7.39–7.46 (m, 2 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 8.30 (s, 1 H), 10.28 (br s, 1 H), 11.57 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 51.74 (CH_3), 110.00 (CH), 111.66 (CH), 113.99 (CH), 119.36 (CH), 120.46 (CH), 120.51 (Cq), 122.83 (Cq), 123.31 (Cq), 126.04 (CH), 132.66 (Cq), 140.07 (Cq), 142.80 (Cq), 167.12 (Cq).

Methyl 1-(3-Methyl-2-butenyloxy)-9*H*-carbazole-3-carboxylate (15)
A solution of diisopropyl azodicarboxylate (0.7 mL, 3.566 mmol) was added dropwise to a well-stirred suspension of **1** (430 mg, 1.784 mmol), Ph_3P (701 mg, 2.676 mmol), and 3-methyl-2-buten-1-ol (230 mg, 2.676 mmol) in anhydrous THF (20 mL) at 0 °C under a nitrogen atmosphere. The suspension was stirred at 0 °C for 1 h, then stirred at ambient temperature for 11 h. After removal of the solvent under reduced pressure, the reaction mixture was purified by column chromatography on silica gel (hexanes–EtOAc, 9:1) to give **15**. Recrystallization of the obtained solid from hexane–EtOAc (9:1) provided white crystals.

Yield: 305 mg (55%); white solid; mp 166–168 °C.

IR (KBr): 1240, 1350, 1377, 1431, 1440, 1583, 1629, 1687, 2918, 2956, 3358 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.74 (s, 3 H), 1.77 (s, 3 H), 3.90 (s, 3 H), 4.70 (d, *J* = 6.80 Hz, 2 H), 5.53 (t, *J* = 6.8 Hz, 1 H), 7.22 (m, 1 H), 7.41–7.35 (m, 2 H), 7.54 (s, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 8.39 (s, 1 H), 8.47 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.32 (CH_3), 25.91 (CH_3), 52.06 (CH_3), 65.32 (CH_2), 107.66 (CH), 111.21 (CH), 116.10 (CH), 119.27 (CH), 120.22 (CH), 120.75 (CH), 121.79 (Cq), 123.58 (Cq), 123.77 (Cq), 126.32 (CH), 133.16 (Cq), 139.02 (Cq), 139.47 (Cq), 144.34 (Cq), 168.07 (Cq).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{19}NO_3Na$: 332.1263; found: 332.1263.

Methyl 1-Hydroxy-4-(3-methyl-but-2-enyl)-9*H*-carbazole-3-carboxylate (7)
A solution of **15** (50 mg, 0.161 mmol) in *N*,*N*-diethylaniline (3 mL) was heated at reflux for 12 min. After cooling, the reaction mixture was acidified with 10% aq HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexanes–EtOAc, 3:1) to give **7**. Recrystallization of the obtained solid from hexane–EtOAc (4:1) provided white crystals.

Yield: 27 mg (54%); white solid; mp 195–196 °C (Lit.[24b] 196–198 °C).

IR (KBr): 1024, 1091, 1255, 1342, 1444, 1620, 1674, 3350 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 3 H), 1.90 (s, 3 H), 3.91 (s, 3 H), 4.28 (d, *J* = 4.80 Hz, 2 H), 5.28 (m, 1 H), 5.84 (br s, 1 H), 7.29 (m, 1 H), 7.51–7.43 (m, 3 H), 8.13 (d, *J* = 8.40 Hz, 1 H), 8.58 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.44 (CH_3), 25.69 (CH_3), 29.38 (CH_2), 52.03 (CH_3), 111.06 (CH), 112.81 (CH), 120.13 (CH), 120.52 (Cq), 122.90 (CH), 123.38 (CH), 123.89 (Cq), 123.93 (Cq), 125.78 (CH), 131.87 (Cq), 132.31 (Cq), 133.54 (Cq), 138.72 (Cq), 139.69 (Cq), 169.13 (Cq).

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