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THE FIRST TOTAL SYNTHESIS OF THE ANTIPLASMODIAL ALKALOID (±)-CASSIARIN C BASED ON A MICROWAVE-ASSISTED THERMAL AZAELECTROCYCLIC REACTION

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Abstract – A first total synthesis of the antiplasmodial alkaloid (±)-cassiarin C is described. The key step was a microwave-assisted thermal azaelectrocyclic reaction for the construction of the tricyclic pyrano[2,3,4-*ij*]isoquinoline core.

INTRODUCTION

The development of new chemotherapeutic agents against chloroquine-resistant and multiple-drug-resistant strains of malaria parasite is in high demand as more than two billion people living in tropical areas of high incidence according to the World Health Organization are exposed to the malaria parasite. Synthetic studies and evaluation of antimalarial natural products have been reported by many organic and/or medicinal chemists.[1]

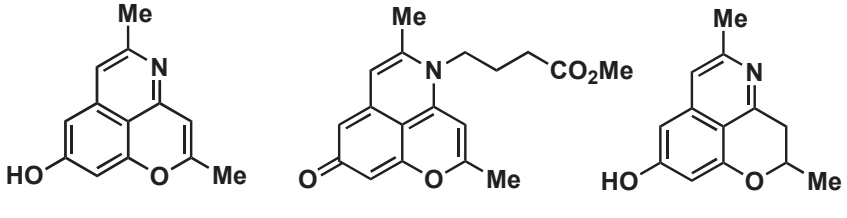


Figure 1

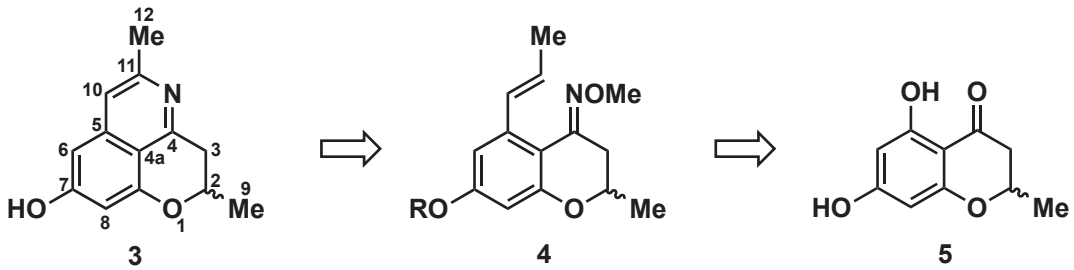
Cassia siamea is widely used in traditional medicine for treatment of periodic fever and malaria in Indonesia. Cassiarins A (**1**) and B (**2**) were isolated from the leaves of *Cassia siamea* by Morita and

co-workers in 2007.[2] These alkaloids possess an unprecedented tricyclic skeleton and exhibit potent antiplasmodial activity. The total synthesis of cassiarins is reported by four groups to date.[3] Honda's group achieved the first total synthesis of cassiarin A (**1**) using alkynylation by Sonogashira coupling and 6-endo-dig-cyclization to alkynes as key steps.[3a] Morita's group reported the synthesis and bioactivity of cassiarin A (**1**) and its derivatives derived from chromen-4-one.[3c] The total synthesis of cassiarin B (**2**) together with cassiarin A (**1**) from chromen-4-one was described by Yao's group.[3b] Furthermore, Thamyongkit's group achieved the synthesis of cassiarins A (**1**) and B (**2**) and their *N*-substituted derivatives by the condensation of barakol and amines.[3d] Three new closely related alkaloids, cassiarins C-E possessing a tricyclic 2,3-dihydropyrano[2,3,4-*ij*]isoquinoline core were recently isolated from the *Cassia siamea* flower by Morita and co-workers and also show antiplasmodial activity against *Plasmodium falciparum* 3D7.[4] Cassiarin C (**3**) has one stereogenic center, but the absolute configuration is not yet known. In addition, its total synthesis has not been reported.

We are performing the synthetic studies of fused pyridine ring systems based on a thermal electrocyclic reaction of an aza 6π-electron system.[5] To date, we have reported the construction of several fused pyridine ring systems, such as furo[3,2-*h*]isoquinoline,[6a-c] phenanthridine,[6d] benzo[*c*]phenanthridine,[6e,f] azaanthraquinone,[6g] and β-carboline alkaloids,[6h] using a microwave-assisted thermal electrocyclic reaction of a 1-aza 6π-electron system. We have also performed the synthetic studies of the antimalarial and antitumor alkaloids calothrixins A, B, and their derivatives.[7] As a next target compound, we focused on the synthesis of cassiarine C (**3**), which has a unique tricyclic framework and the antiplasmodial activity. In this paper, we describe the first total synthesis of (±)-cassiarin C (**3**).

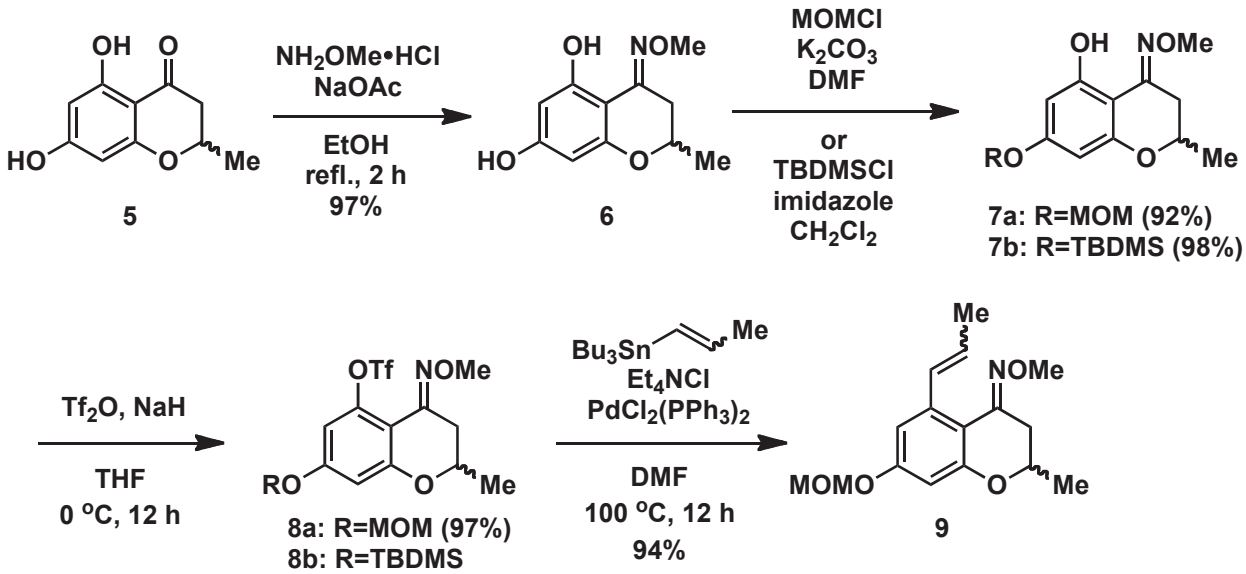
RESULTS AND DISCUSSION

To synthesize cassiarin C (**3**) according to the retro-synthetic scheme shown below (Scheme 1), we planned to construct a tricyclic pyranoisoquinoline core of **3** by a new bond formation between the C11 and N in **3** based on a microwave-assisted azaelectrocyclic reaction of a 1-azahexatriene **4**. We assumed that a 1-azahexatriene **4** might be derived from the known compound, 5,7-dihydroxy-2-methyl-chroman-4-one **5**.[8]



Scheme 1

To synthesize a precursor, 1-azahexatriene **4**, the known starting material, chroman-4-one **5**[8,9] was prepared from phloroglucinol according to Rao's method.[9] Treatment of **5** with *O*-methylhydroxylamine in the presence of AcONa gave the oxime ether **6** in 97% yield (Scheme 2). Regioselective protection of the C-7 hydroxy group of **6** using MOMCl and/or TBDMSCl in the presence of amines afforded the 7-MOM ether **7a** and the 7-TBDMS ether **7b** in 92% and 98% yields, respectively. Sequential treatment of **7a** or 7**b** with trifluoromethanesulfonic anhydride only yielded the corresponding triflate **8a** (97%), which was used in the Stille coupling reaction with 1-propenylstannane in the presence of $PdCl_2(PPh_3)_2$ to give the 5-propenylchromane **9** in 94% yield. The triflation of **7b** failed, because desilylation occurred.



Scheme 2

To obtain a tricyclic pyranoisoquinoline **10** from the 1-azahexatriene **9**, we next investigated a thermal azaelectrocyclic reaction under microwave-assisted or conventional conditions. Electrocyclic reactions of 1-azahexatriene **9** were performed by various conditions using toluene (100 °C), bromobenzene (150 °C), or 1,2-dichrolobenzene (180 °C) as the solvent (Table 1). Microwave-assisted conditions (entries 1,3,5) were more effective than conventional conditions for increasing the yield and reducing the reaction time (entries 2,4,8,9). In particular, the best yield of the product **10** was obtained by performing the reaction in 1,2-dichlorobenzene at 180 °C under microwave irradiation (entry 5). Heating of **9** for 1.5 h under the same conditions as entry 5 did not increase the yield of **10** (entry 6). Similarly, heating of **9** at 200 °C decreased the yield of **10** compared with that of entry 6 (entry 7). As the result, the microwave irradiation under thermal conditions seems to be the effective tool for 6π-azaelectrocyclic reaction.

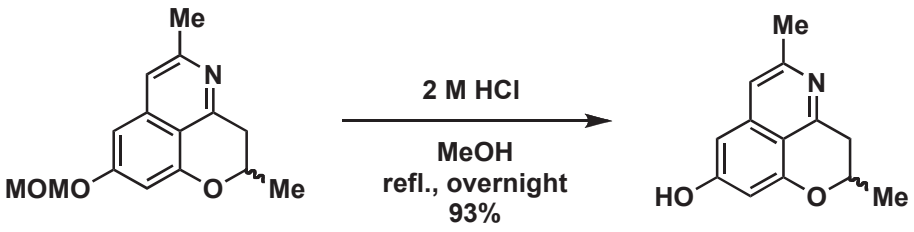
Table 1. Synthesis of Tricyclic Pyranoisoquinoline

9 10

Entry	Solvent	Time (h)	Temp (°C)*	MW	Yield (%) of 10
1	toluene	2	100	+	64
2	toluene	12	100	–	60
3	bromobenzene	2	150	+	61
4	bromobenzene	12	150	–	52
5	1,2-dichlorobenzene	45 min	180	+	78
6	1,2-dichlorobenzene	1.5	180	+	73
7	1,2-dichlorobenzene	1	200	+	63
8	1,2-dichlorobenzene	1	180	–	50
9	1,2-dichlorobenzene	6	180	–	65

* External temperature

Finally, treatment of *O*-MOM cassiarin C **10** with 2 M HCl in MeOH afforded (±)-cassiarin C (**3**) (Scheme 3). The spectroscopic data of our synthetic (±)-cassiarin C (**3**) were identical with those of reported previously natural cassiarin C.[4]



10 cassiarin C (3)

Scheme 3

CONCLUSION

The first total synthesis of (±)-cassiarin C (**3**) was established by constructing a pyrano[2,3,4-*ij*]isoquinoline ring with a microwave-assisted electrocyclic reaction of aza 6π-electron system as the key reaction. The target compound **3** was obtained in six steps in 60% overall yield from the readily accessible known starting material chroman-4-one **5**. This synthetic strategy is applicable to a series of other pyranoisoquinoline alkaloids. An asymmetric synthesis of (–)-cassiarin C (**3**) is now in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus MP-500D and are uncorrected. Infrared spectra were recorded with ATR method on a Shimadzu FTIR-8000 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). NMR spectra was measured with $CDCl_3$ unless otherwise noted. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.7). Low and high resolution mass spectra were recorded on JEOL JMS-700 and JMS-LCmate MS-MP30 spectrometers by direct inlet system. The reaction of microwave (MW) irradiation was carried out by Discover of CEM Co. Ltd. with 2450 MHz. Anhydrous THF, CH_2Cl_2, and DMF were used commercially available solvents (Cica reagents) for organic synthesis. 1,2-Dichlorobenzene, using for an MW-assisted electrocyclic reaction, was degassed before use. Silica gel 60N (63-210 μm, Kanto Ltd.) was used for column chromatography.

5,7-Dihydroxy-2-methylchroman-4-one *O*-methyloxime (6)

A mixture of the chroman-4-one **5** (200 mg, 1.03 mmol), $MeONH_2$•HCl (430 mg, 5.15 mmol), and AcONa (148 mg, 1.80 mmol) in EtOH (10 mL) was stirred at 80 °C for 2 h. After removal of solvent followed by addition of water, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc-hexane (3:7 v/v) as an eluent to give the *O*-methyloxime **6** (218 mg, 95%), mp 120-121 °C (EtOH). IR (ATR) ν: 3386 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (3H, d, *J* = 6.2 Hz), 2.34 (1H, dd, *J* = 17.1, 11.6 Hz), 3.22 (1H, dd, *J* = 17.1, 3.1 Hz), 3.94 (3H, s), 4.11-4.22 (1H, m), 5.14 (1H, br s), 5.95 (1H, d, *J* = 2.6 Hz), 6.04 (1H, d, *J* = 2.6 Hz), 10.88 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.8, 30.1, 62.3, 71.2, 95.6, 96.9, 98.0, 153.8, 158.5, 158.9, 159.6. MS (EI) *m*/*z*: 223 (M^+). HRMS (EI) calcd for $_{11}H_{13}NO_4$ 223.0845; found 223.0841.

5-Hydroxy-7-methoxymethyloxy-2-methylchroman-4-one *O*-methyloxime (7a)

A suspention of *O*-methyloxime **6** (180 mg, 0.81 mmol), K_2CO_3 (250 mg, 1.77 mmol), and chloromethyl methyl ether (0.15 mL, 1.77 mmol) in DMF (20 mL) was stirred at rt for 12 h. The reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the MOM ether **7a** (210 mg, 97%), mp 68-70 °C (Et_2O). IR (ATR) ν: 2935 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (3H, d, *J* = 6.2 Hz), 2.34

(1H, dd, *J* = 17.3, 11.7 Hz), 3.23 (1H, dd, *J* = 17.3, 3.0 Hz), 3.46 (3H, s), 3.94 (3H, s), 4.11-4.23 (1H, m), 5.12 (1H, d, *J* = 6.6 Hz), 5.15 (1H, *J* = 6.6 Hz), 6.15 (1H, d, *J* = 2.6 Hz), 6.24 (1H, d, *J* = 2.6 Hz), 10.8 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.8, 30.1, 56.1, 62.3, 71.1, 94.0, 95.9, 97.4, 98.8, 153.7, 158.2, 159.4, 160.1. MS (EI) *m*/*z*: 267 (M^+). HRMS (EI) calcd for $C_{13}H_{17}NO_5$ 267.1107; found 267.1092.

7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2-methylchroman-4-one *O*-methyloxime (7b)

A solution of *O*-methyloxime **6** (24 mg, 0.11 mmol), imidazole (29 mg, 0.43 mmol), and TBDMSCl (28 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 12 h. The reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the oily TBDMS ether **7b** (36 mg, 98%). mp 71-72 °C (Et_2O). IR (ATR) ν: 2931 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.21 (6H, s), 0.96 (9H, s), 1.43 (3H, d, *J* = 6.3 Hz), 2.33 (1H, dd, *J* = 17.5, 11.7 Hz), 3.22 (1H, dd, *J* = 17.5, 3.1 Hz), 3.94 (3H, s), 4.11-4.19 (1H, m), 5.95 (1H, d, *J* = 2.3 Hz), 6.05 (1H, d, *J* = 2.3 Hz), 10.8 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: -4.4, -4.4, 18.2, 20.9, 25.6, 30.2, 62.3, 71.1, 98.6, 100.1, 101.6, 153.9, 158.1, 159.1, 159.4. MS (EI) *m*/*z*: 337 (M^+). HRMS (EI) calcd for $C_{17}H_{27}NO_4Si$ 337.1709; found 337.1693.

7-Methoxymethyloxy-2-methyl-5-(trifluoromethylsulfonyloxy)chroman-4-one *O*-methyloxime (8a)

A solution of MOM ether **7a** (208 mg, 0.78 mmol) in THF (10 mL) was added to an ice-cooled suspention of NaH (47 mg, 1.17 mmol) in THF (10 mL) under an N_2 atmosphere, and then stirred at the same temperature for 30 min. A solution of *N*-phenylbis(trifluoromethanesulfonamide) (418 mg, 1.17 mmol) in THF (5 mL) was added to the reaction mixture at the same temperature. After being stirred at rt for 12 h, the mixture was quenched with water. The mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc-hexane (3:7 v/v) as an eluent to give the oily triflate **8a** (302 mg, 97%). IR (ATR) ν: 1627 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (3H, d, *J* = 6.9 Hz), 2.32 (1H, dd, *J* = 17.1, 11.3 Hz), 3.26 (1H, dd, *J* = 17.1, 3.5 Hz), 3.47 (3H, s), 4.03 (3H, s), 4.14-4.27 (1H, m), 5.15 (2H, s), 6.57 (1H, d, *J* = 2.5 Hz), 6.64 (1H, d, *J* = 2.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 30.1, 56.3, 62.3, 72.0, 94.5, 104.6, 105.4, 107.1, 120.8, 146.6, 147.3, 158.3, 158.9. MS (EI) *m*/*z*: 399 (M^+). HRMS (EI) calcd for $C_{14}H_{16}F_3NO_7S$ 399.0600; found 399.0607.

7-Methoxymethyloxy-2-methyl-5-(prop-1-en-1-yl)chroman-4-one *O*-methyloxime (9)

A mixture of triflate **8a** (305 mg, 0.76 mmol), propenylstannane (444 mg, 1.34 mmol), Et_4NCl (253 mg, 1.53 mmol), and $PdCl_2(PPh_3)_2$ (9 mg, 0.013 mmol) in DMF (10 mL) was stirred at 80 °C for 1.5 h under

N_2 atmosphere. The reaction mixture was quenched with aqueous solution of KF (30%), and then the mixture was stirred at rt for 2 h. The mixture was filtered off through Celite pad and the filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc-hexane (3:7 v/v) as an eluent to give the oily 5-propenylchromanone **9** (210 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (3H, d, *J* = 6.1 Hz), 1.81 (3H, dd, *J* = 7.1, 1.6 Hz), 2.35 (1H, dd, *J* = 16.7, 11.7 Hz), 3.22 (1H, dd, *J* = 16.7, 2.9 Hz), 3.47 (3H, s), 3.94 (3H, s), 4.17-4.08 (1H, m), 5.14 (1H, d, *J* = 6.8 Hz), 5.17 (1H, d, *J* = 6.8 Hz), 5.69 (1H, dq, *J* = 11.7, 7.1 Hz), 6.52 (1H, d, *J* = 2.7 Hz), 6.58 (1H, d, *J* = 2.7 Hz), 6.9 (1H, dd, *J* = 11.7, 1.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.6, 20.9, 29.7, 31.4, 56.1, 61.9, 71.4, 94.2, 103.1, 113.0, 124.0, 132.2, 137.9, 150.4, 157.5, 158.8. MS (EI) *m/z*: 291 (M^+). HRMS (ESI) calcd for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1549; found 292.1536.

7-Methoxymethyloxy-2,11-dimethyl-2,3-dihydropyrano[2,3,4-*ij*]isoquinoline (10)

An each mixture of the 5-propenylchromanone **9** (110 mg, 0.38 mmol) in 1,2-dichlorobenzene (15 mL) was stirred at 180 °C (external) under N_2 atmosphere under microwave irradiation. After removal of solvent, the residue was purified by column chromatography (silica gel) using EtOAc-hexane (1:1 v/v) as an eluent to give the oily 2,3-dihydropyranoisoquinoline **10** (76 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58 (3H, d, *J* = 6.2 Hz), 2.61 (3H, s), 3.26-3.08 (2H, m), 3.50 (3H, s), 4.57-4.48 (1H, m), 5.27 (2H, s), 6.67 (1H, d, *J* = 2.2 Hz), 6.83 (1H, d, *J* = 2.2 Hz), 7.21 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 24.4, 39.3, 56.3, 74.1, 94.2, 100.5, 102.3, 111.6, 116.3, 138.3, 151.9, 153.8, 156.5, 160.0 MS (EI) *m/z*: 259 (M^+). HRMS (EI) calcd for $C_{15}H_{17}NO_3$ 259.1208; found 259.1186.

Cassiarin C (3)

To a solution of 2,3-dihydropyranoisoquinoline **10** (50 mg, 0.19 mmol) in MeOH (5 mL) was added 2 M HCl (5 mL), and then heated at 50 °C for 12 h. After removal of solvent, the residue was adjusted to pH 8 with 2 M aqueous K_2CO_3, and the extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc-hexane (2:3 v/v) as an eluent to give the cassiarin C (**3**) (38 mg, 93%). mp 159-160 °C ($CHCl_3$). IR (ATR) ν: 2924 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD) δ: 1.54 (3H, d, *J* = 6.2 Hz), 2.52 (3H, s), 2.27-3.18 (2H, m), 4.41-4.53 (1H, m), 6.47 (1H, d, *J* = 2.0 Hz), 6.57 (1H, d, *J* = 2.0 Hz), 7.19 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 21.3, 23.4, 39.1, 75.1, 101.4, 103.3, 111.5, 117.1, 140.5, 151.1, 155.1, 158.4, 163.6. MS (EI) *m/z*: 215 (M^+). HRMS (EI) calcd for $C_{13}H_{13}NO_2$ 215.0946; found 215.0956.

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