Synthesis S. Ahn et al. Paper

Total Synthesis of the Natural Pyridocoumarins Goniothaline A and B

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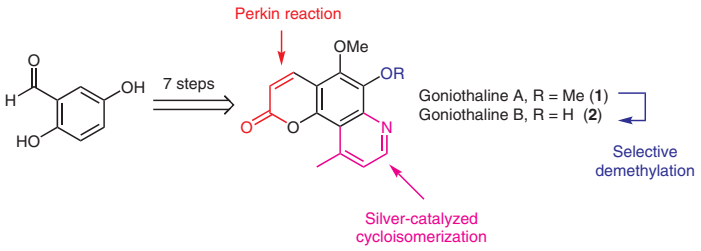

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Abstract In this paper, we report the first total synthesis of goniothaline A and B, which are rare natural pyridocoumarins isolated from *Goniothalamus australis*. The key feature of the synthesis of goniothaline A is high-yielding silver-catalyzed cycloisomerization to afford the pyridine moiety. In addition, goniothaline B, a natural 8-hydroxyquinoline derivative, is readily synthesized by the regioselective demethylation of goniothaline A.

Key words total synthesis, goniothaline, Perkin reaction, silver-catalyzed cycloisomerization, selective demethylation

Coumarins, including heterocycle-linked and fused coumarins, have been reported to possess diverse biological activities and hence are regarded as privileged scaffolds in drug discovery.[1] Consequently, much effort has devoted to not only acquire diverse natural and non-natural compounds bearing novel coumarin skeletons, but also develop efficient synthetic methods thereof.[2]

Goniothaline A (**1**) and B (**2**) are unprecedented natural pyridocoumarin derivatives isolated from *Goniothalamus australis*, an Australian rainforest plant (Figure 1).[3] Goniothaline A (**1**) possesses two methoxy groups at the 5- and 6-positions, whereas goniothaline B (**2**) has a hydroxy group instead of the methoxy group at the 6-position. The 8-hydroxyquinoline (8-HQ) moiety found in **2** has been considered as a privileged scaffold,[4] as many 8-HQs show therapeutically beneficial activities against neurodegenerative diseases, cancers, infective diseases, etc., by virtue of their metal-chelating properties.[4b] Goniothalines are expected to exhibit a diverse range of biological activities because of the 6-hydroxypyridocoumarin skeleton embedded with the privileged scaffolds coumarin and 8-HQ. The unique structure of **1** and **2** prompted us to investigate an efficient synthetic method that can be used in subsequent medicinal chemistry research.

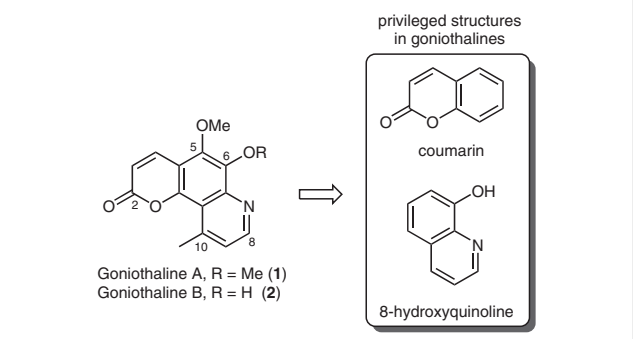
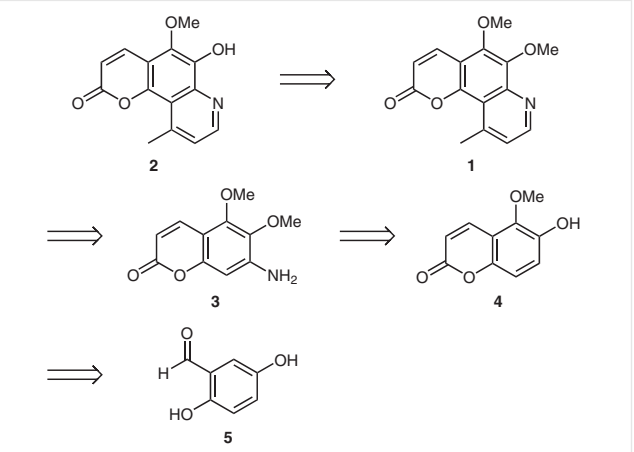


Figure 1 Structure of goniothaline A (**1**) and B (**2**), and embedded privileged structures

The retrosynthetic analysis for goniothalines is depicted in Scheme 1, which includes the efficient construction of the 5,6-dimethoxy-10-methylpyridocoumarin skeleton. Goniothaline B (**2**), a 5-hydroxy-6-methoxypyridocoumarin, was anticipated to be derived from goniothaline A (**1**) via selective demethylation of its 6-methoxy group, by the directing effect of the neighboring pyridine nitrogen.[5] 5,6-Dimethoxy-10-methylpyridocoumarin **1** was expected to be synthesized from 7-amino-5,6-dimethoxycoumarin **3** via synthetic methodologies for quinoline moiety such as the Skraup–Doebner–Miller reaction, Povarov reaction, or diverse metal-catalyzed reactions.[6]

Further, it was anticipated that **3** can be readily prepared from 6-hydroxy-5-methoxycoumarin **4** via regioselective nitration, *O*-methylation, and reduction of the nitro group. Hydroxycoumarin **4** could be accessed by cop-



Scheme 1 Retrosynthetic analysis of goniothaline A (**1**) and B (**2**)

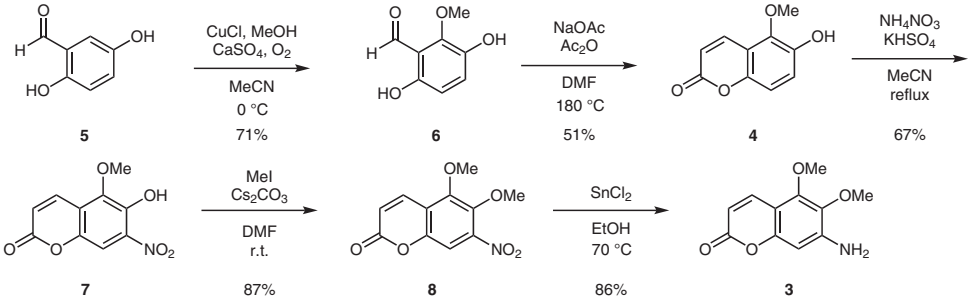
per-catalyzed oxidative methoxylation[7] and subsequent coumarin synthesis from the commercially available 2,5-dihydrobenzaldehyde (**5**).

As shown in Scheme 2, our synthesis commenced with the preparation of previously reported 3,6-dihydroxy-2-methoxybenzaldehyde (**6**) by copper-catalyzed oxidative methoxylation.[7] 2,5-Dihydroxybenzaldehyde (**5**) was stirred with CuCl and $CaSO_4$ under O_2 atmosphere to obtain a 2-methoxybenzoquinone intermediate that was subjected to reduction with $Na_2S_2O_4$ to provide hydroquinone **6**. This unstable compound was immediately used in the next step without further purification. Several sets of reaction conditions were investigated for the synthesis of coumarin **4**. Perkin reaction[8] of *o*-hydroxybenzaldehyde **6** using Ac_2O and NaOAc afforded coumarin **4** in the best yield (51%). Knoevenagel condensation (with Meldrum's acid)[9] and Wittig olefination[10] of **6** also gave **4**, but the yields decreased slightly to 47%.

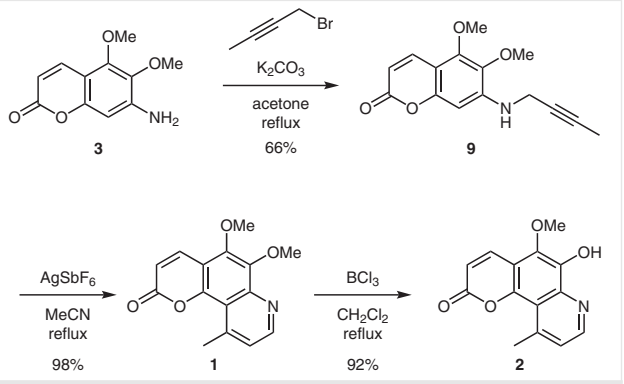
Next, to introduce a nitrogen moiety at the 7-position of 6-hydroxycoumarin **4**, we carried out nitration using several reported reaction conditions for the regioselective *ortho*-nitration of phenolic compounds.[11] When **4** was refluxed with 1.2 equiv of NH_4NO_3 and 1 equiv of $KHSO_4$ in acetonitrile,[11a,b] 7-nitrocoumarin **7** was obtained in best yield (67%) without the formation of the regioisomer 8-nitrocoumarin. The structure of **7** was confirmed by combined 2D-NMR analysis (see Supporting Information). We also could obtain **7** under in situ nitronium generation conditions, i.e., by using a combination of $NaNO_3$ and $KHSO_4$ in the presence of wet silica,[11b,c] although the yield did not exceed 52%. Further, we found that cerium ammonium nitrate (CAN)[11d] and nitric acid[11e] were unsuitable for the generation of **7** from **4**. Williamson etherification of **7** readily afforded dimethoxycoumarin **8**, which was subjected to nitro reduction using $SnCl_2$ to provide 7-aminocoumarin **3**, a key intermediate for constructing the pyridocoumarin skeleton of goniothalines.

With **3** in hand, we first attempted the Doebner–Miller reaction, an acid-catalyzed one-pot method for synthesizing quinoline from anilines and α,β-unsaturated carbonyl compounds.[12] When **3** was refluxed with methyl vinyl ketone in concentrated HCl[12b] or AcOH in the presence of $FeCl_3$,[12c] a mixture of unidentifiable products was obtained, possibly due to the acid-labile nature of the coumarin moiety.[6a] Therefore, we conceived a stepwise route via silver-catalyzed cycloisomerization,[13] as shown in Scheme 3. To prepare 7-(but-2-ynylamino)coumarin **9**, 1-bromobut-2-yne was added portionwise to the refluxing solution of 7-aminocoumarin **3** and K_2CO_3 in anhydrous acetone. Then, **9** was isolated in 66% yield (84% yield brsm) along with the unreacted **3** (20%) and dialkynylated byproduct (11%). Cycloisomerization of **9** using a catalytic amount of $AgSbF_6$[13] afforded the desired goniothaline A (**1**) in high yield (98%). The ^1H and ^{13}C NMR data of **1** were in agreement with those of the natural product.[3] We hypothesized that the nitrogen atom at the 7-position of **1** would serve as a directing group for the selective cleavage of the methyl ether at the 6-position to furnish goniothaline B (**2**).[5] As expected, **2** was obtained in high yield (92%) by refluxing **1** with 3 equiv of BCl_3 in CH_2Cl_2 for 4 hours. The spectral data of **2** were also consistent with the previously reported data.[3]

In summary, the first total synthesis of the natural pyridocoumarins, goniothaline A (**1**) and B (**2**), has been accomplished. Aminocoumarin **3** was prepared in moderated yield after intensive optimization of the nitration condition for hydroxycoumarin **4**. The key feature of the synthesis of **1**



Scheme 2 Preparation of 7-aminocoumarin intermediate **3**



Scheme 3 Completion of the synthesis of goniothaline A (**1**) and B (**2**)

is the silver-catalyzed isomerization. Unlike acid-catalyzed one-pot quinoline synthesis methods, our synthetic route provided the pyridocoumarin skeleton without decomposition of the acid labile **3**. In addition, 8-HQ derivative **2** was successfully synthesized from **1** via regioselective demethylation by the neighboring pyridine nitrogen. Because of its high efficiency, this synthesis protocol can be extended to various structurally related pyridocoumarins. Further synthesis of analogues and biological studies are in good progress in our laboratory, and the results will be reported in due course.

Unless noted otherwise, all starting materials and reagents were obtained commercially and were used without further purification. All solvents utilized for routine product isolation and chromatography were of reagent grade and glass-distilled, and reaction flasks were dried at 100 °C before use. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. TLC was performed using 0.25-mm silica gel plates (Merck). Mass spectra were obtained using an Agilent 6530 Q-TOF unit. Infrared spectra were recorded on a FT-IR spectrophotometer. ^{1}H and ^{13}C spectra were recorded on a Bruker Analytik AVANCE digital 400 (400 MHz) and AVANCE digital 500 (500 MHz) spectrometer in $CDCl_3$, CD_3OD, DMSO-d_6 and are referenced to the deuterated solvent.

6-Hydroxy-5-methoxy-2*H*-chromen-2-one (4)

3,6-Dihydroxy-2-methoxybenzaldehyde (6)

To a solution of 2,5-dihydroxybenzaldehyde (**5**; 1.0 g, 7.24 mmol) in MeCN (29 mL) were added MeOH (2.2 mL, 54.3 mmol, 7.5 equiv), anhyd $CaSO_4$ (14.49 g, 106.43 mmol, 14.7 equiv), and CuCl (3.58 g, 36.2 mmol, 5.0 equiv) at r.t. The mixture was stirred vigorously under an O_2 atmosphere at 0 °C for 7 h. To the mixture was added an aq soln of $NaHCO_3$ and $Na_2S_2O_4$ (83 mL; $NaHCO_3$: 1.46 g, 17.38 mmol; $Na_2S_2O_4$: 7.18 g, 41.27 mmol) at 0 °C, and then it was allowed to warm up to r.t. The mixture was stirred for 12 h at r.t. and then diluted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give methoxybenzaldehyde **6** (862 mg, 71%) as a yellow solid, which was used without further purification for next reaction step.

6-Hydroxy-5-methoxy-2*H*-chromen-2-one (4)

To a solution of benzaldehyde **6** (127 mg, 0.76 mmol) and NaOAc (186 mg, 2.27 mmol) in DMF (1.3 mL) was added Ac_2O (0.29 mL, 3.02 mmol, 4.0 equiv) at r.t. The mixture was stirred at 180 °C for 3 h and then allowed to cool to r.t., diluted with EtOAc, and quenched with 1 M HCl. The organic layer was washed with 1 M HCl and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue via flash column chromatography (silica gel, EtOAc/5% CH_2Cl_2 in *n*-hexane 1:5 to 1:2) afforded chromenone **4** (74 mg, 51%) as a yellow solid; R_f = 0.2 (EtOAc/*n*-hexane 1:2).

IR (neat): 3289, 1685, 1573, 1312, 1074 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 9.8 Hz, 1 H), 7.16 (d, *J* = 9.0 Hz, 1 H), 7.04 (d, *J* = 9.0 Hz, 1 H), 6.44 (d, *J* = 9.7 Hz, 1 H), 3.93 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0, 147.3, 145.8, 142.8, 136.6, 120.9, 115.6, 113.7, 111.8, 61.6.

HRMS (Q-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9O_4$: 193.0495; found: 193.0499.

6-Hydroxy-5-methoxy-7-nitro-2*H*-chromen-2-one (7)

To a solution of hydroxychromenone **4** (200 mg, 1.04 mmol) in MeCN (17 mL) were added NH_4NO_3 (100 mg, 1.25 mmol, 1.2 equiv) and $KHSO_4$ (142 mg, 1.04 mmol, 1.0 equiv) at r.t. The mixture was stirred for 30 min at this temperature, then it was heated at reflux for 19 h. The mixture was filtered through celite, and the filtercake was washed with MeCN and CH_2Cl_2. The combined filtrate and washes were concentrated in vacuo. Purification of the residue via flash column chromatography (silica gel, EtOAc/5% CH_2Cl_2 in *n*-hexane 1:5 to 1:3) afforded nitrochromenone **7** (166 mg, 67%) as a yellow solid; R_f = 0.3 (EtOAc/*n*-hexane 1:2).

IR (neat): 1763, 1532, 1466, 1290 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.47 (s, 1 H), 8.03 (d, *J* = 9.8 Hz, 1 H), 7.83 (s, 1 H), 6.57 (d, *J* = 9.8 Hz, 1 H), 4.12 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 146.1, 145.3, 144.7, 137.0, 135.2, 120.5, 120.3, 106.7, 62.2.

HR-MS (Q-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8NO_6$: 238.0346; found: 238.0350.

5,6-Dimethoxy-7-nitro-2*H*-chromen-2-one (8)

To a solution of hydroxychromenone **7** (100 mg, 0.42 mmol) and Cs_2CO_3 (647 mg, 2.11 mmol, 5.0 equiv) in DMF (2 mL) was added MeI (0.13 mL, 2.11 mmol, 5.0 equiv) at r.t. The mixture was stirred for 2 h at this temperature, and then it was diluted with EtOAc and quenched with water. The organic layer was washed with 1 M HCl and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue via flash column chromatography (silica gel, EtOAc/2% CH_2Cl_2 in *n*-hexane 1:4 to 1:3) afforded dimethoxychromenone **8** (92 mg, 87%) as a yellow solid; R_f = 0.4 (EtOAc/*n*-hexane 1:2).

IR (neat): 1766, 1574, 1521, 1415, 1352 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 9.7 Hz, 1 H), 7.45 (s, 1 H), 6.53 (d, *J* = 9.7 Hz, 1 H), 4.07 (s, 3 H), 3.99 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 151.0, 149.2, 146.4, 142.3, 137.2, 118.9, 117.6, 107.8, 62.6, 62.2.

HR-MS (Q-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}NO_6$: 252.0503; found: 252.0508.

7-Amino-5,6-dimethoxy-2*H*-chromen-2-one (3)

To a solution of nitrochromenone **8** (100 mg, 0.40 mmol) in EtOH (4 mL) was added $SnCl_2$ (380 mg, 2.0 mmol, 5.0 equiv), and the mixture was heated at 70 °C for 3 h. The mixture was cooled to r.t. and poured onto an ice/water mixture which was basified with $NaHCO_3$ until pH 8–9. The aqueous layer was extracted with EtOAc several times. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue via flash column chromatography (silica gel, EtOAc/1% CH_2Cl_2 in *n*-hexane 1:3 to 1:1) afforded aminochromenone **3** (78 mg, 86%) as a yellow solid; R_f = 0.25 (EtOAc/*n*-hexane 1:1).

IR (neat): 3356, 1715, 1623, 1259 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 9.6 Hz, 1 H), 6.39 (s, 1 H), 6.10 (d, *J* = 9.6 Hz, 1 H), 4.4 (s, 2 H), 3.97 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0, 152.3, 149.0, 145.2, 139.2, 136.0, 110.3, 105.3, 96.9, 61.5, 60.4.

HR-MS (Q-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{12}NO_4$: 222.0761; found: 222.0766.

7-(But-2-ynylamino)-5,6-dimethoxy-2*H*-chromen-2-one (9)

To a solution of aminochromenone **3** (10 mg, 0.045 mmol) and K_2CO_3 (14.4 mg, 0.104 mmol, 2.3 equiv) in acetone (0.4 mL) was added 1-bromobut-2-yne (6 mg, 0.045 mmol, 1 equiv) at r.t., and then the mixture was heated to reflux. After 19 h, 1-bromobut-2-yne (6 mg, 0.045 mmol, 1 equiv) was added to the mixture, and it was stirred for a further 30 h at the same temperature. The mixture was cooled to r.t., and then it was filtered and concentrated in vacuo. Purification of the residue via flash column chromatography (silica gel, EtOAc/4% CH_2Cl_2 in *n*-hexane 1:5 to 1:2) afforded 7-(but-2-ynylamino)chromenone **9** (8.2 mg, 66%) as a yellow gum along with unreacted **3** (2.0 mg, 20%) and dialkynylated byproduct (1.6 mg, 11%); R_f = 0.3 (EtOAc/*n*-hexane 1:2).

IR (neat): 1719, 1611, 1258, 772 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 9.5 Hz, 1 H), 6.39 (s, 1 H), 6.10 (d, *J* = 9.6 Hz, 1 H), 5.02 (s, 1 H), 3.95 (s, 3 H), 3.94–3.92 (m, 2 H), 3.84 (s, 3 H), 1.83–1.82 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.2, 152.8, 148.1, 145.2, 139.2, 135.9, 109.9, 104.6, 93.7, 61.5, 60.5, 33.45, 29.85, 14.29, 3.72.

HR-MS (Q-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}NO_4$: 274.1074; found: 274.1078.

Goniothaline A (1)

To a solution of 7-(but-2-ynylamino)chromenone **9** (10 mg, 0.037 mmol) in MeCN (1 mL) was added $AgSbF_6$ (1.0 mg, 3.7 µmol, 0.1 equiv) at r.t. The mixture was refluxed for 5 h, and then concentrated in vacuo. Purification of the residue via flash column chromatography (silica gel, Et_2O/CH_2Cl_2 1:20 to 1:10) afforded goniothaline A (**1**; 9.7 mg, 98%) as a light-brown gum; R_f = 0.1 (Et_2O/CH_2Cl_2 1:20). The spectral data were consistent with that previously reported.

IR (neat): 1731, 1622, 1367, 1226, 1083, 1039 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.83 (d, *J* = 4.4 Hz, 1 H), 8.28 (d, *J* = 9.7 Hz, 1 H), 7.44 (d, *J* = 4.4 Hz, 1 H), 6.63 (d, *J* = 9.8 Hz, 1 H), 4.10 (s, 3 H), 4.00 (s, 3 H), 2.97 (s, 3 H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 159.4, 151.1, 148.5, 146.3, 145.5, 145.4, 142.2, 139.7, 123.9, 115.8, 115.4, 111.5, 62.0, 61.9, 23.7.

HR-MS (Q-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}NO_4$: 272.0917; found: 272.0919.

Goniothaline B (2)

To a solution of goniothaline A (**1**; 10 mg, 0.37 mmol) in CH_2Cl_2 (1.8 mL) was added 1.0 M BCl_3 in CH_2Cl_2 (0.11 mL, 0.11 mmol, 3 equiv) at 0 °C. The mixture was heated to reflux for 4 h, and then it was cooled to r.t. and quenched with water. The organic layer was washed with water, brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue via flash column chromatography (silica gel, Et_2O/CH_2Cl_2 1:10 to 1:5) afforded goniothaline B (**2**; 8.7 mg, 92%) as a light-brown gum; R_f = 0.2 (Et_2O/CH_2Cl_2 1:6). The spectral data were consistent with that previously reported.

IR (neat): 3349, 1714, 1303, 1079 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.65 (br s, 1 H), 8.80 (d, *J* = 4.1 Hz, 1 H), 8.28 (d, *J* = 9.7 Hz, 1 H), 7.48 (d, *J* = 4.1 Hz, 1 H), 6.62 (d, *J* = 9.5 Hz, 1 H), 4.03 (s, 3 H), 2.99 (s, 3 H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 159.6, 149.8, 145.5, 144.5, 141.2, 139.8, 139.7, 137.8, 124.0, 115.5, 114.9, 112.1, 60.9, 23.5.

HR-MS (Q-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}NO_4$: 258.0761; found: 258.0765.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610909.

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