

Expedient Iodocyclization Approach Toward Polysubstituted 3*H*-Benzo[*e*]indoles

Guilherme M. Martins,^a Gilson Zeni,^a Davi F. Back,^a Teodoro S. Kaufman,^b and Claudio C. Silveira^{a,*}

^a Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS 97105-900, Brazil

Fax: (+55)-55-3220-8754; phone: (+55)-55-3220-8754; e-mail: silveira@quimica.ufsm.br

^b Instituto de Química Rosario (CONICET-UNR), Suipacha 531, Rosario, SF, S2002LRK, Argentina

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Abstract: A facile and expedient iodocyclization of 4-(2-prop-1-ynylphenyl)-1*H*-pyrroles towards the synthesis of polysubstituted 3*H*-benzo[*e*]indoles is reported. The transformation was optimized and the best results were obtained by using iodine (1.2 equiv.) in dichloromethane, and potassium carbonate as base. The starting 1,2,3,4-tetrasubstituted pyrroles were efficiently obtained by means of a nick-

el(II) chloride-promoted four-component (nitromethane, amine, 2-alkynylbenzaldehyde and ethyl acetate) reaction. Further functionalization of the resulting 5-iodoheterocycles was also explored.

Keywords: 3*H*-benzo[*e*]indoles; heterocycles; iodocyclization; phenylacetylenes; pyrroles

Introduction

The 3*H*-benzo[*e*]indoles are a small subfamily within the indoles, which is one of the most important heterocyclic ring systems among natural products and bioactive compounds.

This tricyclic skeleton is found among enzymes such as indoleamine 2,3-dioxygenase (IDO), monoamine oxidase (MAO) and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) inhibitors,^[1] intermediates toward antineoplastic agents, including analogues of duocarmycin and the indole antibiotic CC-1065, one of the most potent antineoplastic agents known, and also in the DNA-intercalating unit of hybrid bifunctional antitumor agents (Figure 1).^[2]

The 3*H*-benzo[*e*]indole motif is an integral part of core-modified, π -extended, expanded porphyrins, such as some naphthorubyrin and naphthosapphyrin derivatives,^[3a] being also found among fullerene derivatives,^[3b] drugs for treating Alzheimer's disease^[3c] and antimicrobials.^[3d,e]

In addition, some benzo[*e*]indoles have potential technological applications, this core being embodied in special photochromic materials^[4] and fluorescent multivalent carbocyanine molecular probes, useful for biomonitoring, chemosensing and optical imaging.^[5] This tricyclic skeleton is also found in materials for

the production of organic electroluminescent devices (OLEDs) and organic thin film transistors (OTFTs).^[6]

There are three main groups of methods that have been devised for accessing 3*H*-benzo[*e*]indoles. These involve (i) building the pyrrole ring on a naphthalene-type precursor,^[7] (ii) installing the benzo ring on

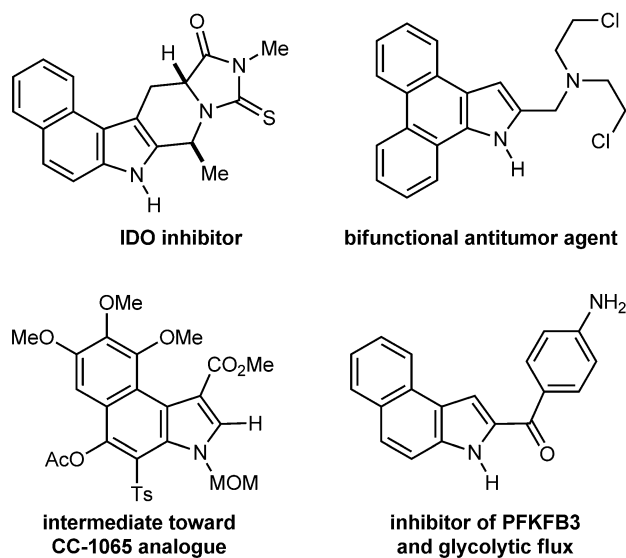


Figure 1. Selected examples of useful 3*H*-benzo[*e*]indole derivatives.

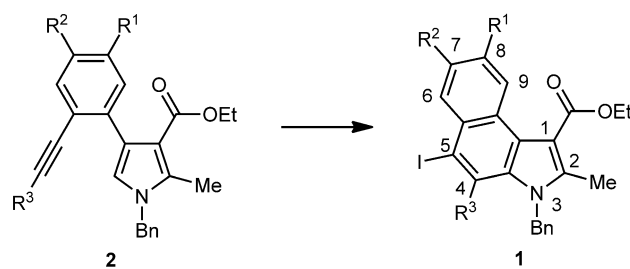
a pre-formed indole derivative,^[8] and (iii) constructing the required benzo ring from a pyrrole and an aryl moiety directly bound to its C-3 position^[9] or tethered to C-2.^[10] A variation of the latter alternative includes the use of the starting aryl and pyrrole moieties as separate chemical entities.^[11]

Compounds with the 3*H*-benzo[*e*]indole core have also resulted from the thermal rearrangement of 4,5-dihydro-1*H*-benzo[*g*]indole, and other reactions.^[12]

We have recently reported a multicomponent synthesis of polyfunctionalized pyrroles.^[13] We have also studied the functionalization of indoles under eco-friendly conditions^[14] and have been engaged in the synthesis of heterocycles attached to substituted indole moieties.^[15]

As part of our continued interest in the chemistry of pyrrole and indole derivatives, we focused our attention on exploring the ability of conveniently 3-substituted pyrroles to undergo intramolecular cyclization reactions, to afford more structurally complex products. Therefore, in continuation of these studies, here we wish to present the results of our iodocyclization-mediated synthesis of polysubstituted 3*H*-benzo[*e*]indoles (**1**) from 4-(2-prop-1-ynylphenyl)-1*H*-pyrroles (**2**), as shown in Scheme 1.

Indoles and fused indoles have been repeatedly accessed by means of iodocyclization reactions, mainly involving the construction of the heterocyclic ring by C–N bond formation^[16a–f] or by C-2 or C-3 functionalization of preformed indole derivatives.^[16g,h] However,



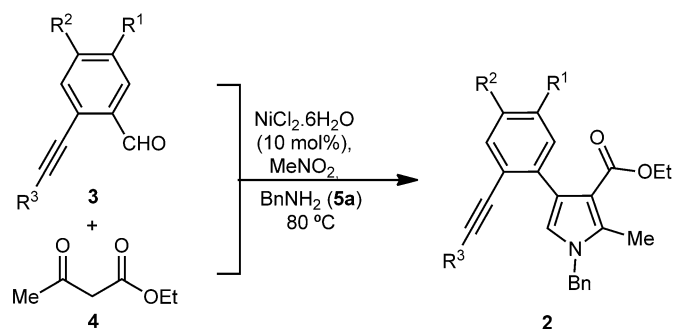
Scheme 1. Proposed iodocyclization strategy for the synthesis of polysubstituted 3*H*-benzo[*e*]indoles.

to the best of our knowledge, the strategy proposed herein represents the first iodocyclization approach toward building the homocyclic ring of polysubstituted indoles and complements other recently developed strategies, based on well-established π -activation catalysts (Au, Pt).^[17] Furthermore, the incorporation of an iodine atom into the products offers the possibility of rapidly increasing their molecular complexity through the incorporation of more rings or additional functionalities.^[18]

Results and Discussion

Initial attempts to access the required starting pyrroles (**2**), by use of our method,^[13a] proved to be problematic. However, the target compounds could be conveniently obtained, in moderate yields, by a modi-

Table 1. Four-component synthesis of the starting 1,2,3,4-tetrasubstituted 4-(2-prop-1-ynyl-phenyl)-1*H*-pyrroles **2a–j**.



Entry No,	Aldehyde	R ¹	R ²	R ³	Time [h]	Yield [%]	Product
1	3a	H	H	Ph	8	47	2a
2	3b	H	H	4-MeC ₆ H ₄	6	41	2b
3	3c	H	H	3-MeC ₆ H ₄	6	40	2c
4	3d	H	H	4-ClC ₆ H ₄	12	40	2d
5	3e	H	H	2-ClC ₆ H ₄	12	38	2e
6	3f	F	H	Ph	5	35	2f
7	3g	MeO	H	Ph	6	32	2g
8	3h	MeO	MeO	H	5	42	2h
9	3i	H	H	<i>n</i> -Bu	12	40	2i
10	3j	H	H	4-FC ₆ H ₄	6	31	2j
11	3a	H	H	Ph	6	45	2k ^[a]

^[a] β -Phenethylamine (**5b**) was employed as the amine component.

fication of the nickel(II)-mediated four-component reaction [2-alkynylbenzaldehyde (**3**),^[19] ethyl acetoacetate (**4**), primary amine (**5**) and MeNO₂] disclosed by Khan et al.^[20] Advantageously, this method avoided the need for the isolation and purification of the intermediates, thus minimizing the total reaction time, as well as waste and costs (Table 1).

Next, the proposed iodocyclization reaction was optimized, employing **2a** as model compound. The reaction gave the expected compound **1a** in 62% yield (Table 2, entry 1), along with 20% of **1'a**, as confirmed by comparison with an authentic sample (entry 17). This suggested the need for an added base to remove the HI formed. Thus, the reaction conditions were optimized by adjusting the relative amounts of iodine and base (entries 2–6).

After some experimentation, it was concluded that the use of NaHCO₃ (2 equiv.) and I₂ (1.2 equiv.) provided the best results, when the cyclization was run at

room temperature in CH₂Cl₂ (entry 3). Lowering the reaction temperature to 0 °C resulted in a diminished yield (entry 7), which was more noticeable when the process was conducted at –30 °C (entry 8).

The use of K₂CO₃ as base (entries 9–11) afforded still better results, being useful even when as little as 1.2 equiv. were employed (entry 9). It also confirmed that 2 equiv. furnished the optimal product yield (entry 11). On the other hand, the reaction did not take place in non-chlorinated solvents (entries 12–16) and compound **1'a** was isolated as the sole product when the cyclization was carried out under HI promotion at room temperature (41% yield, entry 17) or when catalytic amounts of TsOH were added to the reaction and the system was refluxed (41% yield, entry 18).

The alkynylpyrroles **2a–l** were cyclized under the optimized conditions (Table 3, entries 1–12), affording the expected products in good to excellent yields (61–96%) and short reaction times (0.5–2 h).

Small variations were observed among the yields of these products. Those containing chlorine as an electron-withdrawing group on the phenyl moiety not attached to the pyrrole ring (entries 4 and 5) were accessed in slightly lower yields than their analogues carrying methyl groups on this phenyl ring (entries 2 and 3).

On the other side, compound **2f**, which supports an electron-withdrawing group on its phenyl moiety attached to the pyrrole, cyclized more efficiently (90% yield) than its congeners **2g** and **2h** with an electron-donating group (entries 6–8), whereas the related **2j** which carries the fluoride on the other phenyl ring afforded **1j** in good yield (65%, entry 10).

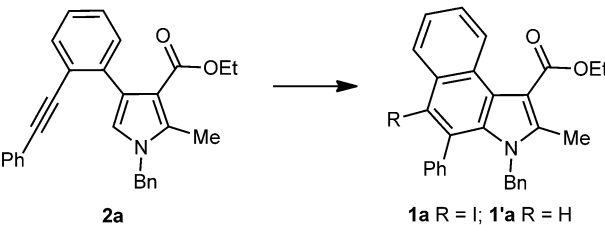
However, modifying the substituent attached to the pyrrolic nitrogen to a β-phenethyl group (**2k**) and the use of 1,2,4-trisubstituted pyrrole derivative **2l**, which lacks the 3-ethoxycarbonyl group, had essentially no effect on the efficiency of the iodocyclization process (entries 11 and 12, respectively).

Interestingly, compound **2i**, which carries an aliphatic substituent, furnished only a 61% yield of **1i** (entry 9). This result underscores the relevance of the structure of the disubstituted alkyne on the success of the transformation.

The single crystal X-ray analysis of compound **1a** (Figure 2) confirmed its structure and evidenced that the 3*H*-benzo[*e*]indole skeleton forms an essentially planar tricyclic core, where the C9'–C9''–C3'–N3 dihedral angle measures 172.6°.

Examination of the structure in Figure 2 also revealed that the aromatic rings of the *N*-benzyl moiety attached to C-4 are contained in quasi-parallel planes adopting almost perpendicular positions with regard to the tricyclic core, where the C26–C21–C4–C5, C15–C14–N3–C2 and N3–C14–C15–C20 dihedral angles are 95.5°, 89.9° and 176.8°, respectively.^[21]

Table 2. Optimization of the iodocyclization toward **1a**.^[a]

				
Entry No.	Solvent	Base [equiv.]	Iodine [equiv.]	Yield [%]
1	CH ₂ Cl ₂	–	1.2	62 ^[b]
2	CH ₂ Cl ₂	NaHCO ₃ (2.0)	2.0	80
3	CH ₂ Cl ₂	NaHCO ₃ (2.0)	1.2	84
4	CH ₂ Cl ₂	NaHCO ₃ (2.0)	1.0	81
5	CH ₂ Cl ₂	NaHCO ₃ (2.0)	1.2	82
6	CH ₂ Cl ₂	NaHCO ₃ (1.2)	1.2	83
7	CH ₂ Cl ₂	NaHCO ₃ (2.0)	1.2	80 ^[c]
8	CH ₂ Cl ₂	NaHCO ₃ (2.0)	1.2	63 ^[d]
9	CH ₂ Cl ₂	K ₂ CO ₃ (1.2)	1.2	90
10	CH ₂ Cl ₂	K ₂ CO ₃ (0.5)	1.2	82
11	CH ₂ Cl ₂	K ₂ CO ₃ (2.0)	1.2	93
12	CH ₃ CN	K ₂ CO ₃ (2.0)	1.2	– ^[e]
13	THF	K ₂ CO ₃ (2.0)	1.2	– ^[e]
14	DMF	K ₂ CO ₃ (2.0)	1.2	– ^[e]
15	H ₂ O	K ₂ CO ₃ (2.0)	1.2	– ^[e]
16	PEG-400	K ₂ CO ₃ (2.0)	1.2	– ^[e]
17	CH ₂ Cl ₂	–	–	41 ^[f,g]
18	CH ₂ Cl ₂	–	–	41 ^[g,h]

^[a] Pyrrole **2a** (0.25 mmol), base, I₂, solvent (2 mL), 0.5 h, room temperature.

^[b] Along with 20% **1'a** (by ¹H NMR).

^[c] At 0 °C.

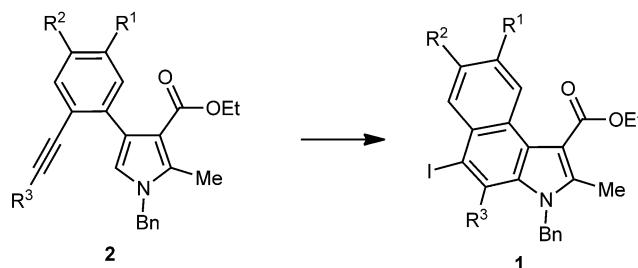
^[d] At –30 °C.

^[e] No products were formed.

^[f] With HI at room temperature.

^[g] The yield of **1'a** is given.

^[h] With TsOH under reflux.

Table 3. Synthesis of the 3*H*-benzo[*e*]indoles (**1a–k**) employing the iodocyclization of 4-(2-alkynylaryl)pyrroles (**2a–k**).^[a]

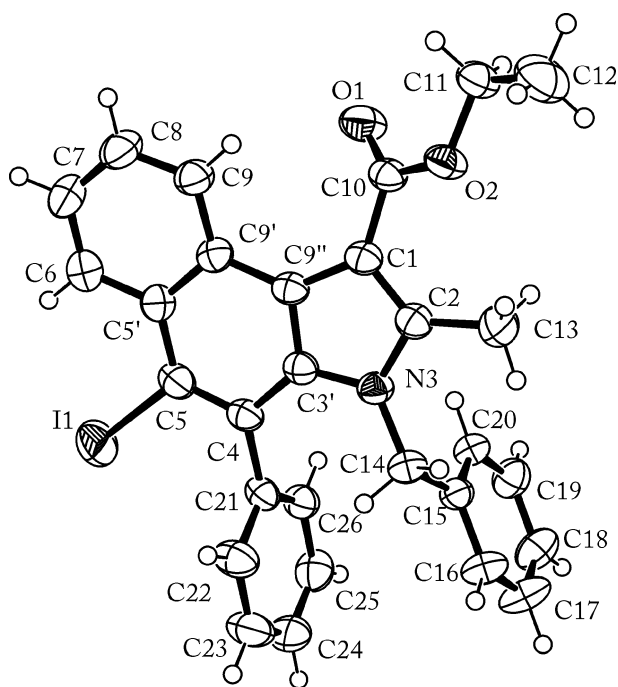
Entry No.	Pyrrole	R ¹	R ²	R ³	Time [h]	Product	Yield [%] ^[b]
1	2a	H	H	Ph	0.5	1a	93
2	2b	H	H	4-MeC ₆ H ₄	1	1b	96
3	2c	H	H	3-MeC ₆ H ₄	1	1c	94
4	2d	H	H	4-ClC ₆ H ₄	1	1d	90
5	2e	H	H	2-ClC ₆ H ₄	2	1e	89
6	2f	F	H	Ph	0.5	1f	93
7	2g	MeO	H	Ph	2	1g	89
8	2h	MeO	MeO	Ph	2	1h	73
9	2i	H	H	<i>n</i> -Bu	2	1i	61
10	2j	H	H	4-FC ₆ H ₄	1	1j	65
11	2k	H	H	Ph	0.5	1k	85 ^[c]
12	2l ^[d]	H	H	Ph	1	1l	90

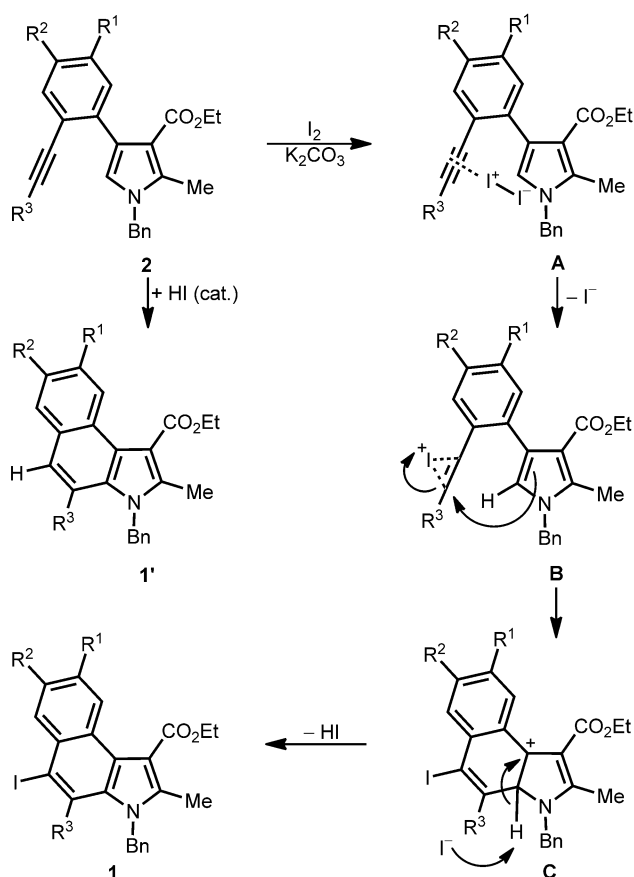
^[a] Pyrrole **2** (0.25 mmol), K₂CO₃ (2 equiv.), I₂ (1.2 equiv.), CH₂Cl₂ (2 mL), room temperature.

^[b] After purification by column chromatography.

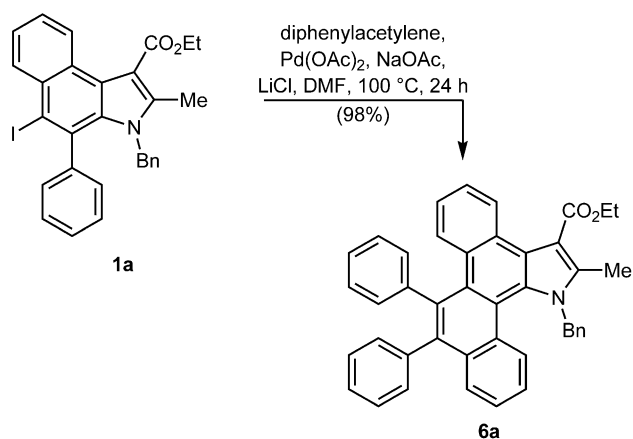
^[c] The *N*-substituent is PhCH₂CH₂.

^[d] Aldehyde **2l** lacks the 3-CO₂Et group.





Scheme 2. Proposed mechanism for the iodocyclization of the 4-(2-alkynylaryl)pyrrole derivatives **2**.



Scheme 3. Functionalization of the 3*H*-benzo[*e*]pyrrole **1a**.

Conclusions

In conclusion, we have developed an efficient synthesis of 3*H*-benzo[*e*]indoles by means of the iodocyclization of 4-(2-prop-1-ynylphenyl)-1*H*-pyrroles. The latter were conveniently accessed, in one-pot and in

moderate yield, by a nickel(II)-promoted four-component reaction.

The modular nature of the multicomponent transformation enables the inclusion of multiple points of diversification and, as demonstrated, the resulting iodocyclization products can be further functionalized, rapidly providing access to polycyclic compounds with increased structural complexity.

Experimental Section

General Procedure for the Synthesis of the 1,2,3,4-Tetrasubstituted Pyrroles **2a–k**

Benzylamine (10 mmol) and ethyl acetoacetate (10 mmol) were successively added to a mixture of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (10 mol%) in MeNO_2 (10 mL), magnetically stirred at room temperature. After ~10 min, formation of a precipitate was observed and the corresponding aldehyde (10 mmol) was added. The open system was heated at 80 °C for 5–12 h. After the reaction was completed, the system was cooled to room temperature and the products were extracted with EtOAc (3 × 100 mL), the organic phase was washed with water and brine, and dried over anhydrous MgSO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified *via* column chromatography on silica gel, eluting with EtOAc :hexane (5:95).

General Procedure for the Synthesis of the 3*H*-Benzo[*e*]indoles **1a–l**

Solid K_2CO_3 (0.5 mmol) was added to a solution of the pyrrole (0.25 mmol) in CH_2Cl_2 (2 mL) and the system was stirred at room temperature for 10 min. Then, it was treated dropwise with a solution of iodine (0.3 mmol) in CH_2Cl_2 (2 mL). After the reaction was completed, the product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were successively washed with 15% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL), water and brine, dried over MgSO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified *via* column chromatography on silica gel eluting with EtOAc :hexane (10:90).

Ethyl 11-Benzyl-12-methyl-5,6-diphenyl-11*H*-benzo[*e*]naphtho[2,1-*g*]indole-13-carboxylate (**6a**)

Diphenylacetylene (89 mg, 0.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mg, 5 mol%), NaOAc (41 mg, 0.5 mmol) and LiCl (10 mg, 0.25 mmol) were successively added to a stirred solution of **1a** (139 mg, 0.25 mmol) in DMF (1 mL). The system was heated at 100 °C for 24 h. After the reaction was completed, the products were extracted with EtOAc (4 × 25 mL) and successively washed with water (30 mL) and brine (3 × 10 mL). The extract was dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography on silica gel, eluting with hexane. The product was obtained as a yellow solid; yield: 145 mg (98%); mp 236–236.5 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.73 (ddd, J = 0.5, 1.4 and 8.3 Hz, 1H), 8.35–8.33 (m, 1H), 7.69–7.64 (m, 3H), 7.47–7.38 (m, 3H), 7.35–7.31 (m, 2H), 7.22–7.17 (m, 2H), 7.07–7.06 (m, 4H), 7.01–6.90

(m, 5H), 6.27 (d, $J=7.2$ Hz, 2H), 5.71 (d, $J=15.6$ Hz, 1H), 5.36 (d, $J=15.6$ Hz, 1H), 4.54–4.51 (m, 2H), 2.67 (s, 3H), 1.48 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 167.3, 143.6, 143.1, 139.5, 137.4, 136.4, 136.0, 132.5, 131.8, 131.5, 130.8, 130.5, 129.6, 128.8, 128.3, 128.1, 128.0, 127.5, 127.3, 126.9, 126.8, 126.6, 126.3, 126.1, 126.0, 125.9, 125.5, 125.0, 124.7, 123.1, 121.8, 121.5, 111.9, 60.5, 51.6, 14.4, 13.1; MS: m/z (rel. int. %) = 595 (M^+ , 17), 458 (10), 419 (23), 254 (14), 149 (13), 105 (100), 91 (84), 77 (45). HR-MS (ESI): m/z = 596.2583, calcd. for $\text{C}_{43}\text{H}_{33}\text{NO}_2$ ($[\text{M}+\text{H}]^+$): 596.2590.

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