# 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

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500275.

**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 acetoacetate) 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 antineoplasic agents known, and also in the DNA-intercalanting 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
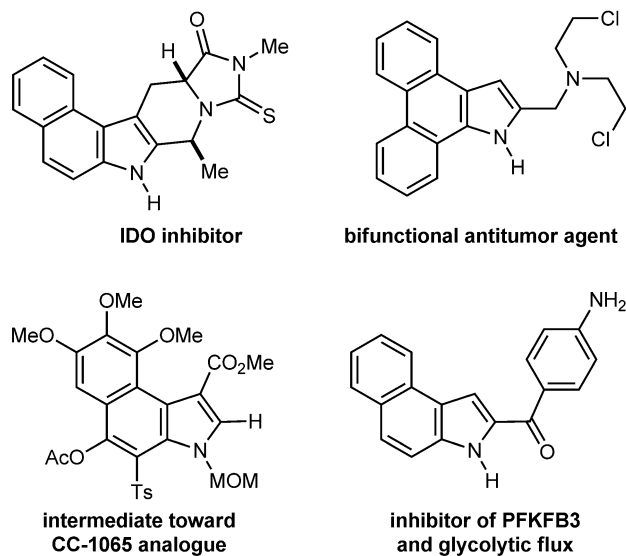


**Figure 1.** Selected examples of useful 3*H*-benzo[*e*]indole derivatives.

IDO inhibitor

bifunctional antitumor agent

intermediate toward CC-1065 analogue

inhibitor of PFKFB3 and glycolytic flux

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,
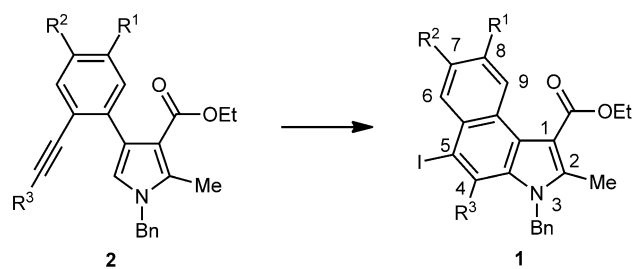


**Scheme 1.** Proposed iodocyclization strategy for the synthesis of polysubstituted 3*H*-benzo[*e*]indoles.

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**.
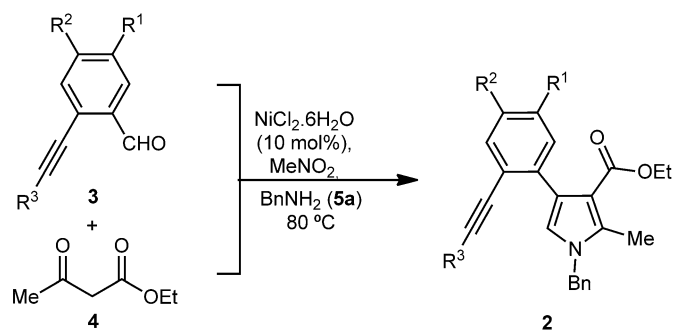


| Entry No, | Aldehyde | $R^1$ | $R^2$ | $R^3$ | Time [h] | Yield [%] | Product |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | H | H | Ph | 8 | 47 | **2a** |
| 2 | **3b** | H | H | 4-MeC$_6$H$_4$ | 6 | 41 | **2b** |
| 3 | **3c** | H | H | 3-MeC$_6$H$_4$ | 6 | 40 | **2c** |
| 4 | **3d** | H | H | 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 | *n*-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 re-action [2-alkynylbenzaldehyde (**3**),[19] ethyl acetoace-tate (**4**), primary amine (**5**) and $MeNO_2$] disclosed by Khan et al.[20] Advantageously, this method avoided the need for the isolation and purification of the inter-mediates, thus minimizing the total reaction time, as well as waste and costs (Table 1).

Next, the proposed iodocyclization reaction was op-timized, employing **2a** as model compound. The reac-tion 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 op-timized by adjusting the relative amounts of iodine and base (entries 2–6).

After some experimentation, it was concluded that the use of $NaHCO_3$ (2 equiv.) and $I_2$ (1.2 equiv.) pro-vided the best results, when the cyclization was run at

room temperature in $CH_2Cl_2$ (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 $K_2CO_3$ 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 promo-tion 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 elec-tron-withdrawing group on the phenyl moiety not at-tached to the pyrrole ring (entries 4 and 5) were ac-cessed 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 at-tached 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 af-forded **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 ali-phatic 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 3H-benzo[e]indole skeleton forms an essentially planar tricyclic core, where the C9′−C9″−C3′−N3 di-hedral angle measures 172.6°.

Examination of the structure in Figure 2 also re-vealed 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]



**2a**   **1a** R = I; **1′a** R = H
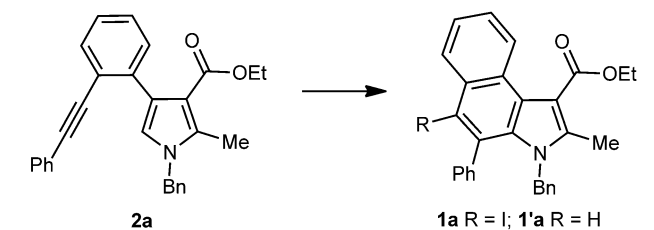
| Entry No. | Solvent | Base [equiv.] | Iodine [equiv.] | Yield [%] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | – | 1.2 | 62[b] |
| 2 | $CH_2Cl_2$ | $NaHCO_3$ (2.0) | 2.0 | 80 |
| 3 | $CH_2Cl_2$ | $NaHCO_3$ (2.0) | 1.2 | 84 |
| 4 | $CH_2Cl_2$ | $NaHCO_3$ (2.0) | 1.0 | 81 |
| 5 | $CH_2Cl_2$ | $NaHCO_3$ (2.0) | 1.2 | 82 |
| 6 | $CH_2Cl_2$ | $NaHCO_3$ (1.2) | 1.2 | 83 |
| 7 | $CH_2Cl_2$ | $NaHCO_3$ (2.0) | 1.2 | 80[c] |
| 8 | $CH_2Cl_2$ | $NaHCO_3$ (2.0) | 1.2 | 63[d] |
| 9 | $CH_2Cl_2$ | $K_2CO_3$ (1.2) | 1.2 | 90 |
| 10 | $CH_2Cl_2$ | $K_2CO_3$ (0.5) | 1.2 | 82 |
| 11 | $CH_2Cl_2$ | $K_2CO_3$ (2.0) | 1.2 | 93 |
| 12 | $CH_3CN$ | $K_2CO_3$ (2.0) | 1.2 | –[e] |
| 13 | THF | $K_2CO_3$ (2.0) | 1.2 | –[e] |
| 14 | DMF | $K_2CO_3$ (2.0) | 1.2 | –[e] |
| 15 | $H_2O$ | $K_2CO_3$ (2.0) | 1.2 | –[e] |
| 16 | PEG-400 | $K_2CO_3$ (2.0) | 1.2 | –[e] |
| 17 | $CH_2Cl_2$ | – | – | 41[f,g] |
| 18 | $CH_2Cl_2$ | – | – | 41[g,h] |

[a] Pyrrole **2a** (0.25 mmol), base, $I_2$, solvent (2 mL), 0.5 h, room temperature.
[b] Along with 20% **1′a** (by $^1$H NMR).
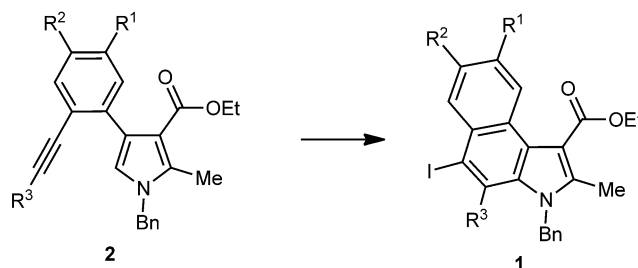[c] At 0°C.
[d] At −30°C.
[e] No products were formed.
[f] With HI at room temperature.
[g] The yield of **1′a** is given.
[h] With TsOH under reflux.

**Table 3.** Synthesis of the 3H-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 | n-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), K$_2$CO$_3$ (2 equiv.), I$_2$ (1.2 equiv.), CH$_2$Cl$_2$ (2 mL), room temperature.
[b] After purification by column chromatography.
[c] The N-substituent is PhCH$_2$CH$_2$.
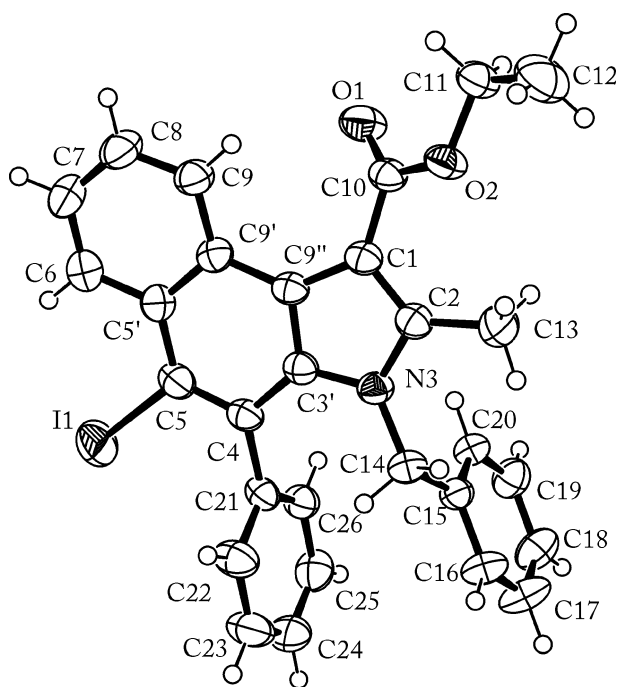[d] Aldehyde **2l** lacks the 3-CO$_2$Et group.



**Figure 2.** ORTEP projection of compound **1a**.[21]

A reaction mechanism (Scheme 2), where the key iodocyclization step involves the ring closure of the pyrrole as a nucleophilic aryl[22] was advanced based on those projected for analogous cyclizations involving I$_2$, ICl[23] or organometallic (Au, Pt, Ga, In, Fe) catalysis.[24]

In this proposal, it is assumed that iodine coordinates with the triple bond, thereby generating the intermediate **A**. In turn, the loss of iodide anion affords iodonium ion **B**, which is attacked intramolecularly by the nucleophilic C-5 carbon of the pyrrole, resulting in a 6-endo-digonal cyclization toward **C**.

Finally, elimination of HI from intermediate **C** and subsequent aromatization would drive the formation of the 3H-benzo[e]indole **1**. Although the reaction can take place with iodine alone, the addition of solid K$_2$CO$_3$ as a mild base serves to scavenge the HI as it is produced, preventing the formation of the acid-catalyzed side products (**1′**).

It was considered that the resulting 5-iodo derivatives **1** can be further functionalized for increasing their structural complexity, thus favorably contributing to broaden the scope of the iodocyclization process.

Luckily, it was observed that exposure of **1a** to diphenylacetylene under Pd(OAc)$_2$ catalysis in DMF gave rise to an alkyne annulation (Scheme 3). The use of 1.0 equiv. LiCl and 2.0 equiv. NaOAc efficiently provided the polycyclic derivative **6a** in 98% yield.[25]
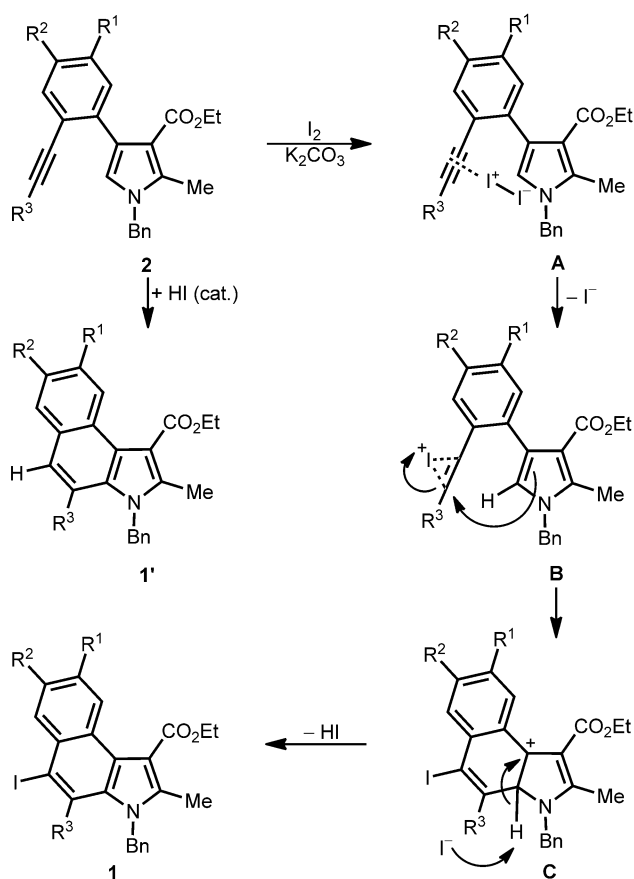
**Scheme 2.** Proposed mechanism for the iodocyclization of the 4-(2-alkynylaryl)pyrrole derivatives **2**.
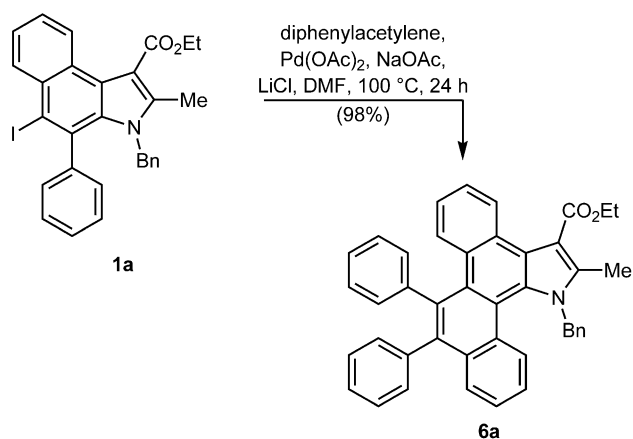


**Scheme 3.** Functionalization of the 3H-benzo[e]pyrrole **1a**.

## Conclusions

In conclusion, we have developed an efficient synthesis of 3H-benzo[e]indoles by means of the iodocyclization of 4-(2-prop-1-ynylphenyl)-1H-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 $NiCl_2 \cdot 6H_2O$ (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 3H-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 $Na_2S_2O_3$ (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-11H-benzo[e]naphtho[2,1-g]indole-13-carboxylate (6a)

Diphenylacetylene (89 mg, 0.5 mmol), $Pd(OAc)_2$ (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. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.73$ (ddd, $J = 0.5$, 1.4 and 8.3 Hz, 1 H), 8.35–8.33 (m, 1 H), 7.69–7.64 (m, 3 H), 7.47–7.38 (m, 3 H), 7.35–7.31 (m, 2 H), 7.22–7.17 (m, 2 H), 7.07–7.06 (m, 4 H), 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$_3$): $\delta =$ 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 C$_{43}$H$_{33}$NO$_2$ ([M+H]$^+$): 596.2590.

# Acknowledgements

# References

[1] a) M. Tanaka, X. Li, H. Hikawa, T. Suzuki, K. Tsutsumi, M. Sato, O. Takikawa, H. Suzuki, Y. Yokoyama, *Bioorg. Med. Chem.* **2013**, *21*, 1159–1165; b) P. Chand, J. A. Chesney, B. F. Clem, G. H. Tapolsky, S. Telang, J. O. Trent, WO Patent WO 2011/103557, 2011; c) M. Kai, A. Noda, H. Noda, S. Goto, *Chem. Pharm. Bull.* **1988**, *36*, 3604–3608.

[2] a) A. G. Neo, C. López, A. López, L. Castedo, G. Tojo, *Tetrahedron* **2013**, *69*, 11010–11016; b) L. Tietze, J. M. von Hof, WO Patent WO 2011/054837, **2011**; c) G. B. Jones, J. E. Mathews, *Tetrahedron* **1997**, *53*, 14599–14614.

[3] a) V. S. Shetti, S.-T. Kee, C.-H. Lee, *Chem. Asian J.* **2014**, *9*, 734–738; b) G. W. Wang, H.-T. Yang, C. B. Miao, Y. Xu, F. Liu, *Org. Biomol. Chem.* **2006**, *4*, 2595–2599; c) H. Bruderer, T. Godel, R. Imhof, R. Jakob-Roetne, U.S. Patent 5,318,967, **1994**; d) S. A. Samsoniya, M. V. Trapaidze, N. A. Kuprashvili, *Pharm. Chem. J.* **2009**, *43*, 92–94; e) S. A. Samsoniya, N. A. Esakiya, S. V. Dolidze, M. V. Trapaidze, Z. S. Lomtatidze, N. N. Suvorov, *Pharm. Chem. J.* **1991**, *25*, 40–43.

[4] S. Izumi, Y. Kawabata, Y. Takeda, J. Momoda, H. Nagoh, European Patent EP 1184379, **2000**.

[5] a) N. A. López, C. J. Abelt, *J. Photochem. Photobiol. A: Chem.* **2012**, *238*, 35–40; b) Y. Ye, S. Bloch, J. Kao, S. Achilefu, *Bioconjugate Chem.* **2005**, *16*, 51–61; c) Y. H. Lin, R. Weissleder, C. H. Tung, *Bioconjugate Chem.* **2002**, *13*, 605–610.

[6] a) F. Kakiuchi, J. Oguma, European Patent EP 2241563, **2009**; b) J.-S. Lee, European Patent EP 2772493, **2014**; c) O. Molt, C. Lennartz, E. Fuchs, K. Dormann, N. Langer, C. Schildknecht, J. Rudolph, G. Wagenblast, S. Watanabe, U.S. Patent 2011/0098473, **2011**; d) A. Facchetti, H. Usta, J. Wang, C. Huang, M. Denti, C. Newman, U.S. Patent 2013/0146851, **2013**.

[7] a) H.-T. Yang, X.-C. Liang, Y.-H. Wang, Y. Yang, X.-Q. Sun, C.-B. Miao, *J. Org. Chem.* **2013**, *78*, 11992–11998; b) X. Wang, J. Liu, H. Guo, C. Ma, X. Gao, K. Zhou, G. Huang, *Synthesis* **2012**, *44*, 1037–1042; c) J. Azizian, F. Sheikholeslami, J. Hosseini, M. Mohammadi, B.

Mirza, *J. Heterocycl. Chem.* **2012**, *49*, 413–416; d) T. D. Lash, B. E. Smith, M. J. Melquist, B. A. Godfrey, *J. Org. Chem.* **2011**, *76*, 5335–5345; e) G. W. Wang, H.-T. Yang, C.-B. Miao, Y. Xu, F. Liu, *Org. Biomol. Chem.* **2006**, *4*, 2595–2599; f) S. Selvi, S.-C. Pu, Y.-M. Cheng, J.-M. Fang, P.-T. Chou, *J. Org. Chem.* **2004**, *69*, 6674–6678; g) D. W. Yue, T. L. Yao, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 62–69; h) K. R. Roesch, R. C. Larock, *J. Org. Chem.* **2001**, *66*, 412–420; i) K. R. Roesch, R. C. Larock, *Org. Lett.* **1999**, *1*, 1551–1553; j) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652–7662.

[8] a) A. Bej, A. Chakraborty, A. Sarkar, *RSC Adv.* **2013**, *3*, 15812–15819; b) S. M. Bronner, K. B. Bahnck, N. K. Garg, *Org. Lett.* **2009**, *11*, 1007–1010; c) A. C. Kinsman, V. Snieckus, *Tetrahedron Lett.* **1999**, *40*, 2453–2456.

[9] a) R. Y. Huang, P. T. Franke, N. Nicolaus, M. Lautens, *Tetrahedron* **2013**, *69*, 4395–4402; b) D. G. Hulcoop, M. Lautens, *Org. Lett.* **2007**, *9*, 1761–1764; c) L. M. Hodges, M. L. Spera, M. W. Moody, W. D. Harman, *J. Am. Chem. Soc.* **1996**, *118*, 7117–7127.

[10] a) H. Ohno, M. Iuchi, N. Kojima, T. Yoshimitsu, N. Fujii, T. Tanaka, *Chem. Eur. J.* **2012**, *18*, 5352–5360; b) A. K. Yadav, I. Ila, H. Junjappa, *Eur. J. Org. Chem.* **2010**, 338–344; c) P. P. Singh, A. K. Yadav, I. Ila, H. Junjappa, *J. Org. Chem.* **2009**, *74*, 5496–5501; d) M. E. Hayes, H. Shinokubo, R. L. Danheiser, *Org. Lett.* **2005**, *7*, 3917–3920.

[11] S. Paria, O. Reiser, *Adv. Synth. Catal.* **2014**, *356*, 557–562.

[12] a) B. B. Trofimov, A. M. Vasil'tsov, I. A. Ushakov, A. V. Ivanov, E. Y. Schmidt, A. I. Mikhaleva, *Mend. Commun.* **2007**, *17*, 296–298; b) A. Padwa, H. Ku, A. Mazzu, *J. Org. Chem.* **1978**, *43*, 381–387.

[13] a) C. C. Silveira, S. R. Mendes, G. M. Martins, S. C. Schlösser, T. S. Kaufman, *Tetrahedron* **2013**, *69*, 9076–9085; b) C. C. Silveira, M. P. Fortes, S. R. Mendes, *Curr. Org. Chem.* **2012**, *16*, 1540–1548.

[14] a) J. B. Azeredo, M. Godoi, G. M. Martins, C. C. Silveira, A. L. Braga, *J. Org. Chem.* **2014**, *79*, 4125–4130; b) C. C. Silveira, S. R. Mendes, J. R. Soares, F. N. Victoria, D. M. Martinez, L. Savegnago, *Tetrahedron Lett.* **2013**, *54*, 4926–4929; c) C. C. Silveira, S. R. Mendes, L. Wolf, G. M. Martins, L. von Mühlen, *Tetrahedron* **2012**, *68*, 10464–10469.

[15] a) B. L. Kuhn, M. P. Fortes, T. S. Kaufman, C. C. Silveira, *Tetrahedron Lett.* **2014**, *55*, 1648–1652; b) M. M. Bassaco, M. P. Fortes, D. F. Back, T. S. Kaufman, C. C. Silveira, *RSC Adv.* **2014**, *4*, 60785–60797; c) M. P. Fortes, M. M. Bassaco, T. S. Kaufman, C. C. Silveira, *RSC Adv.* **2014**, *4*, 34519–34530; d) M. M. Bassaco, M. P. Fortes, T. S. Kaufman, C. C. Silveira, *RSC Adv.* **2015**, *5*, 21112–21124.

[16] a) B. Gabriele, R. Mancuso, R. C. Larock, *Curr. Org. Chem.* **2014**, *18*, 341–358; b) H. Song, Y. Liu, Q. Wang, *Org. Lett.* **2013**, *15*, 3274–3277; c) Z. He, H. Li, Z. Li, *J. Org. Chem.* **2010**, *75*, 4636–4639; d) R. Halim, P. J. Scammells, B. L. Flynn, *Org. Lett.* **2008**, *10*, 1967–1970; e) T. Yao, D. Yue, R. C. Larock, *J. Comb. Chem.* **2005**, *7*, 809–812; f) T. Yao, D. Yue, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 9985–9989; g) S. D. Gawande, V. Kavala, M. R. Zanwar, C.-W. Kuo, H.-N. Huang, C.-H.

He, T.-S. Kuo, C.-F. Yao, *Adv. Synth. Catal.* **2013**, *355*, 3022–3036; h) S. K. Sharma, A. K. Mandadapu, B. Kumar, B. Kundu, *J. Org. Chem.* **2011**, *76*, 6798–6805.

[17] a) Y. Li, J. Waser, *Angew. Chem.* **2015**, *127*, ####–####; *Angew. Chem. Int. Ed.* **2015**, *54*, 5438–5442; b) A. S. K. Hashmi, W. B. Yang, F. Rominger, *Chem. Eur. J.* **2012**, *18*, 6576–6580; c) B. Alcaide, P. Almendros, J. M. Alonso, M. T. Quiros, P. Gadzinski, *Adv. Synth. Catal.* **2011**, *353*, 1871–1876; d) Y. A. Qiu, W. Q. Kong, C. L. Fu, S. M. Ma, *Org. Lett.* **2012**, *14*, 6198–6201.

[18] N. A. Danilkina, A. E. Kulyashova, A. F. Khlebnikov, S. Bräse, I. A. Balova, *J. Org. Chem.* **2014**, *79*, 9018–9045.

[19] P. C. Too, S. Chiba, *Chem. Commun.* **2012**, *48*, 7634–7636.

[20] A. T. Khan, M. Lal, P. R. Bagdi, R. S. Basha, P. Saravanam, S. Patra, *Tetrahedron Lett.* **2012**, *53*, 4145–4150.

[21] CCDC 1045258 (**1a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[22] a) S. Akbar, K. Srinivasan, *Eur. J. Org. Chem.* **2013**, *9*, 1663–1666; b) T. Yao, M. A. Campo, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 3511–3517; c) C. T. Bui, B. L. Flynn, *Mol. Diversity* **2011**, *15*, 83–89.

[23] a) Y. Cheb, C. Huang, X. Liu, E. Perl, Z. Chen, J. Namgung, G. Subramaniam, G. Zhang, W. H. Hersh, *J. Org. Chem.* **2014**, *79*, 3452–3464; b) A. K. Verma, S. P. Shukla, J. Singh, V. Rustagi, *J. Org. Chem.* **2011**, *76*, 5670–5684; c) S. A. Worlikar, R. C. Larock, *Org. Lett.* **2009**, *11*, 2413–2416; d) S. A. Worlikar, T. Kesharwani, T. Yao, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 1347–1353; e) T. Kesharwani, S. A. Worlikar, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 2307–2312.

[24] a) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556–4575; b) M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485–3496; c) H. Inoue, N. Chatani, S. Murai, *J. Org. Chem.* **2002**, *67*, 1414–1417; d) B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347–2356.

[25] a) Z. Liu, R. C. Larock, *Angew. Chem.* **2007**, *119*, 2587–2590; *Angew. Chem. Int. Ed.* **2007**, *46*, 2535–2538; b) T. Yao, M. A. Campo, R. C. Larock, *Org. Lett.* **2004**, *6*, 2677–2680; c) R. C. Larock, M. J. Doty, Q. Tian, J. M. Zenner, *J. Org. Chem.* **1997**, *62*, 7536–7537.