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Three-Component Domino Reactions for Regioselective Formation of Bis-indole Derivatives

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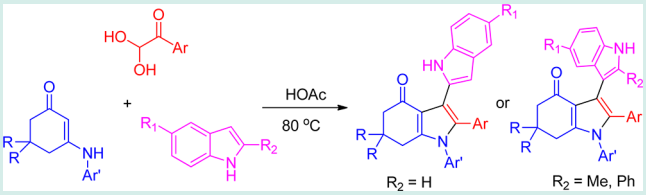
Supporting Information

ABSTRACT: A microwave-assisted regioselective reaction dealing with arylglyoxal monohydrate, diverse *N*-aryl enaminones, and indoles to achieve 3,2′- and 3,3′-bis-indoles by varying a substituted indole substrate is reported. The 2-unsubstituted indoles resulted in the 3,2′-bis-indole skeleton, whereas indoles bearing a methyl or phenyl group at C2 led to the 3,3′-bis-indoles with simultaneous formation of three sigma-bonds. The procedures feature excellent regioselectivity, short reaction times, convenient one-pot manner, and operational simplicity.



KEYWORDS: *multicomponent domino reaction, regioselective synthesis, indolation, enaminones, bis-indoles*

INTRODUCTION

The search for an efficient construction of indole skeletons of chemical and biomedical importance has been an active theme in organic synthesis.[1,2] Structurally diverse bis-indole skeletons commonly exist in nature and are represented by topsentins,[3] isoborreverine,[4] and indirubin (Figure 1)[5] which exhibit a broad range of biological activities. For example, topsentins and its dihydro analogues have shown antitumor, antiviral, and anti-inflammatory activities,[3] isoborreverine has exhibited antimalarial activity,[6] and indirubin and its analogues were found to target glycogen synthase kinase-3 (GSK-3),[7] and aurora kinases,[8] and acted as cyclin-dependent kinase (CDK) inhibitors[6] and dioxin receptor.[9] Thus, these complex architectures have inspired our interest in creating methodologies for their total synthesis.

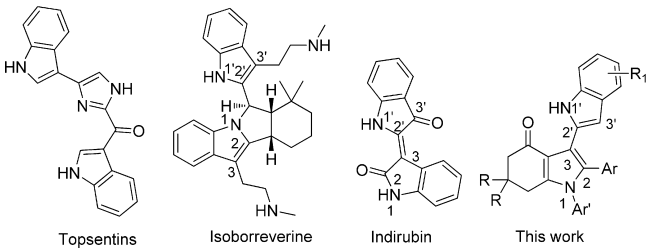


Figure 1. Structures of some bis-indole alkaloids.

Multicomponent domino reactions (MDRs) for use in total syntheses of natural products[10] or natural-like structures were one of the key tools that allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, and facile automation.[11] These reactions can avoid time-consuming and costly processes for purification of various precursors and isolation of intermediates, thereby minimized waste generation rendering the transformations green.[12] Recently, we have developed a series of new, multicomponent domino reactions (MDRs) that provide easy access to multiple functionalized ring structures of chemical and pharmaceutical importance.[13] We would like to report another new synthetic strategy for the regioselective preparation of polyfunctionalized bis-indoles through a three component domino reaction. This reaction was achieved from the readily available starting materials such as arylglyoxal monohydrate (Figure 2), *N*-aryl enaminones (Figure 3), and indoles (Figure 4) in HOAc under microwave heating (Scheme 1). The great aspect of the present domino reaction is shown by the fact that the synthesis of new polyfunctionalized bis-indoles, which connected through C3−C2′ bond of the two indole units, and its polyfunctionalities at C3 and C2′ positions were readily achieved via HOAc-promoted three-component

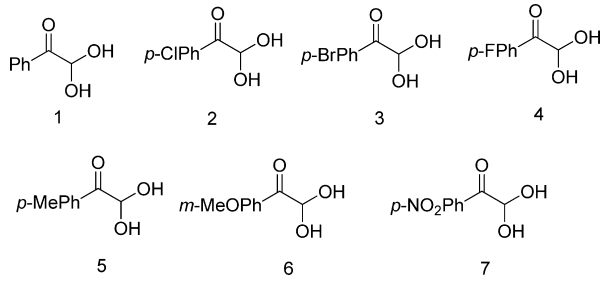


Figure 2. Diversity of arylglyoxal monohydrate **1**{*1*−*6*}.

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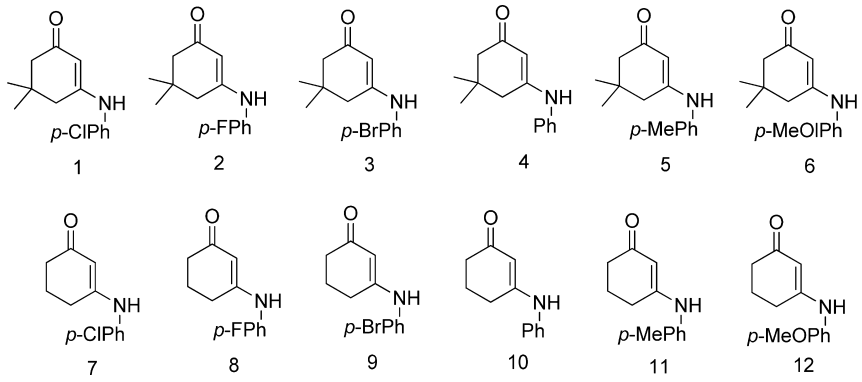


Figure 3. Diversity of enaminones **2**{*1*−*12*}.

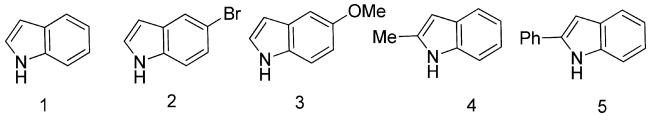
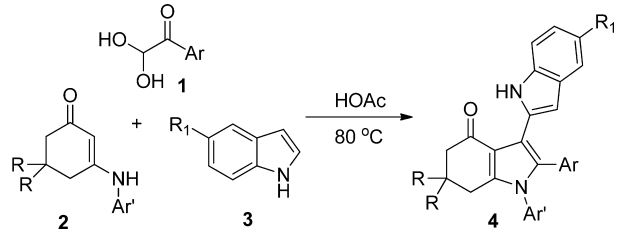


Figure 4. Diversity of substituted indoles **3**{*1*−*5*}.

Scheme 1. Regioselective Synthesis of Bis-Indoles 4

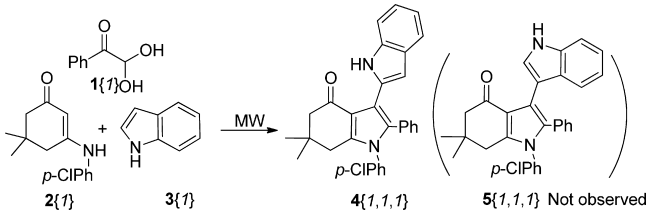


reaction in a single step, and regioselectivity was controlled well in an intermolecular manner.

RESULT AND DISCUSSION

Indole, possessing three nucleophilic centers, is an important type of nucleophile. Indeed, C-nucleophilicity at the C3 position is stronger than that of the C2 position, which has been described widely in the literature.[2] The utilization of its C2 position as a nucleophilic center to the preparation of 2-substituted indoles has been neglected. Arylglyoxal monohydrate, as readily available 1,2-biacceptors,[14] can provide two active sites (C−O and C═O bonds), which can be attacked by the electron-rich *β*-C atom and NH group in *β*-enaminones[15] for C−C and C−N bonds formation via [3 + 2] cyclization mechanism. Meanwhile, nucleophilic substitution between indole and arylglyoxal monohydrate occurs, in which functionalities at C3 and C2′ positions of two indole units can be realized through the control of an intermolecular hydrogen bond. Based on the above analysis, we started this study by subjecting a preformed *N*-*p*-ClPh substituted enaminones **2**{*1*} to the reaction with phenylglyoxal monohydrate **1**{*1*} and indole **3**{*1*} in HOAc at 80 °C under microwave irradiation. The reaction smoothly gave the desired product **4**{*1,1,1*} in 84% chemical yield. Indole **3** has two C-electrophilic centers, which may lead to two different products **4**{*1,1,1*} or **5**{*1,1,1*} (Table 1). In this reaction, only product **4**{*1,1,1*} was isolated; it is obvious that the reaction has high regioselectivity. An overview of the synthetic details is summarized in Table 1. This result prompted us to further optimize reaction conditions. The same reactions were

Table 1. Optimization for the Synthesis of 4{*1,1,1*} under MW



entry	solvent	*T* (°C)	time (min)[a]	yield (%)[c]
1	DMF	80	20	20
2	CH_2Cl_2	80	20	trace
3	EtCOOH	80	20	42
4	HCOOH	80	20	58
5	HOAc	80	20	84
6	HOAc	100	20	63
7	HOAc	80	60[b]	67

[a]Microwave (MW) Irradiation. [b]Classical Heating (CH) conditions. [c]Isolated yields.

performed in dimethylformamide (DMF) and CH_2Cl_2, and both cases scarcely proceeded. We reasoned that the acidic solvent can be used as a Brønsted acid promotor and improve the yield of the desired product **4**{*1,1,1*}. Next, this chemistry was carried out in EtCOOH and HCOOH. An incomplete reaction was observed using EtCOOH as an acidic solvent while HCOOH gave the 58% yield of **4**{*1,1,1*}. Therefore, HOAc proved to be a best case (Table 1, entry 5). Subsequently, the reaction was performed in HOAc and repeated many times at different temperatures in a sealed vessel under microwave (MW) irradiation for 20 min. The lower yield of product **4**{*1,1,1*} (63%) was obtained as the reaction temperature was increased to 100 °C. Subsequently, the identical reaction was investigated under classical heating (CH) conditions at 80 °C for 60 min, providing the desired product **4**{*1,1,1*} in 67% chemical yield (Table 1, entry 7).

With these optimized conditions in hand, we examined the scope of this MDR process by using various easily available starting materials. As revealed in Table 2, the reaction resulted in corresponding desired products in good to excellent yields. The regioselective transformation is easy to perform simply by subjecting a mixture of arylglyoxal monohydrate, various enaminones **2**, and indoles **3** in acetic acid to microwave heating. As shown in Table 2 (entries 1−6), we explored the enaminone substrate scope, phenylglyoxal monohydrate **1**{*1*} and indole **3**{*1*} were used as model substrates, with the results

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Table 2. Domino Synthesis of 3,2′-Bis-indoles 4 under MW

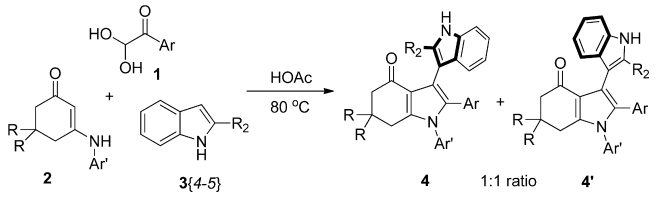
entry	4	time/min	yield/%
1	4{*1,1,1*}	20	84
2	4{*1,2,1*}	30	71
3	4{*1,3,1*}	20	81
4	4{*1,4,1*}	30	82
5	4{*1,5,1*}	24	77
6	4{*1,6,1*}	22	85
7	4{*1,1,2*}	30	83
8	4{*1,2,2*}	25	86
9	4{*1,3,2*}	28	81
10	4{*1,4,2*}	30	76
11	4{*7,4,2*}	28	88
12	4{*1,5,2*}	26	89
13	4{*1,6,2*}	28	83
14	4{*1,5,3*}	32	70
15	4{*1,6,3*}	28	65
16	4{*1,7,1*}	36	76
17	4{*1,8,1*}	38	75
18	4{*1,9,1*}	30	80
19	4{*1,10,1*}	36	63
20	4{*1,11,1*}	30	78
21	4{*1,12,1*}	30	82
22	4{*1,7,2*}	36	79
23	4{*1,8,2*}	34	73
24	4{*1,9,2*}	40	79
25	4{*1,10,2*}	36	68
26	4{*1,12,2*}	32	72

Table 3. Domino Synthesis of 3,3′-Bis-indoles 4 under MW

entry	4 and 4′	time/min	yield[a]/%
1	4{*1,1,4*}	30	73
2	4{*1,2,4*}	32	60
3	4{*1,4,4*}	30	79
4	4{*1,5,4*}	30	80
5	4{*1,6,4*}	32	78
6	4{*1,2,5*}	38	70
7	4{*2,1,5*}	35	78
8	4{*2,2,5*}	38	75
9	4{*3,1,5*}	34	79
10	4{*3,5,5*}	30	83
11	4{*4,2,5*}	28	78
12	4{*4,5,5*}	30	88
13	4{*5,5,5*}	38	71
14	4{*1,7,5*}	40	73
15	4{*1,9,5*}	38	75
16	4{*1,12,5*}	36	70

[a]Isolated yield of two isomers.

Scheme 2. Domino Synthesis of 3,3′-Bis-indoles 4



indicating the tolerance of some functional groups in the substrates **2** including ether and C−Cl (or F, Br) bonds. 4-Nitrophenylglyoxal monohydrate amine **1**{*7*} was also suitable for this three-component domino reaction (entry 11). The 5,5-unsubstituted enaminones **2**{*7*−*12*} were subjected to this reaction providing corresponding bis-indoles **4**{*1,7,1*}-**4**{*1,12,1*} in 63−82% yields. Next, we further examined the generality of this system. Various indole substrates **3** bearing either electron-donating or electron-withdrawing functional groups such as bromo or methoxyl were used to give the corresponding polysubstituted bis-indoles through metal-free intermolecular indolation. It is worth noting that functional groups like bromide and chloride were well tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions. This result is significant since there is no literature precedent for the synthesis of such highly functionalized 3,2′-bis-indoles.

Since bis-3-indoles show important bioactivities as selective inhibitors of cyclin-dependent-kinases (CDK4)[16] and anti-cancer agents,[17] we turned our attention to investigate several differently 2-substituted indoles to synthesize a series of polyfunctionalized bis-3-indoles. Next, the reactions of arylglyoxal monohydrate **1**, *N*-aryl enaminones **2** with 2-substituted indoles **3**{*4,5*} in acetic acid were performed under the conditions described above for a short period (28−40 min) (Table 3). In all these cases, the reactions proceeded smoothly to give the corresponding bis-3-indoles in good yields of 60−88% (Scheme 2). The bulkiness of 2-phenyl indoles **3**{*5*} did not hamper the reaction process. Several different *N*-substituents were compared and substituents bearing electron-withdrawing (4-ClPh **2**{*1*} and 4-FPh **2**{*2*}) or electron-donating (4-MeOPh, **2**{*6*}) groups were found to be suitable for this domino reaction. Impressively, the ^{1}H NMR analysis of the products **4**{*1,1,4*}−**4**{*1,12,5*} indicates the presence of a mixture of two isomers resulting from generation of axial chiral molecules due to large steric hindrance of 2-substituted indoles (Scheme 2). The ratio of the isomers was in 1:1 as demonstrated by ^{1}H NMR integration and HPLC analysis of the crude mixture (See Supporting Information). Indeed, the protocol provides a straightforward pathway to construct highly functionalized 3,2′- and 3,3′-bis-indoles. The resulting functionalities of these 3,2′- and 3,3′-bis-indoles offer a great flexibility for further structural modifications. These special 3,2′- and 3,3′-bis-indoles may be directly useful for drug design, discovery, and development.

In all cases, the functional complexity of the resulting products from this new reaction illustrates the remarkable regioselectivity of the sequence starting from very common and easily accessible starting materials. The structural elucidation and the attribution of regioselectivity were unequivocally determined by NMR spectroscopic analysis. To further ascertain structures of the newly synthesized bis-indole derivatives (**4**), single crystals of **4**{*1,5,3*} and **4**{*4,2,5*} were successfully obtained with their structures (Figures 5 and 6) unambiguously confirmed by X-ray diffraction analysis (see Supporting Information).

Similar to our previous multicomponent domino process,[12] the present reaction also showed *the following attractive characteristics*: (1) the environmentally friendly process in which water is the major byproduct; (2) the convenient workup which only needs simple filtration; (3) readily available starting materials of arylglyoxal monohydrate, preformed enaminones and indoles. Moreover, during these domino processes, the formation of indole skeleton and its indolation were readily achieved via regioselective three-component domino reaction

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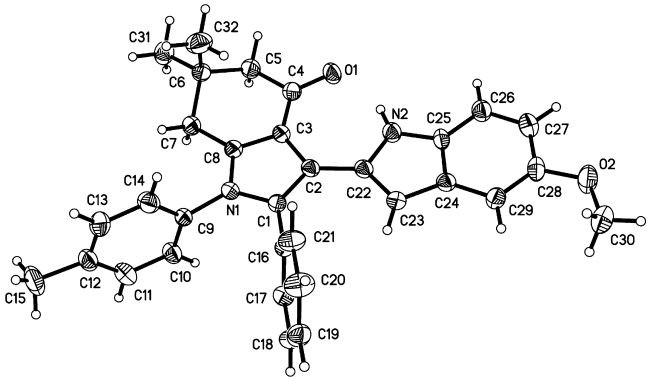


Figure 5. X-ray structure of product **4**{*1,5,3*}.

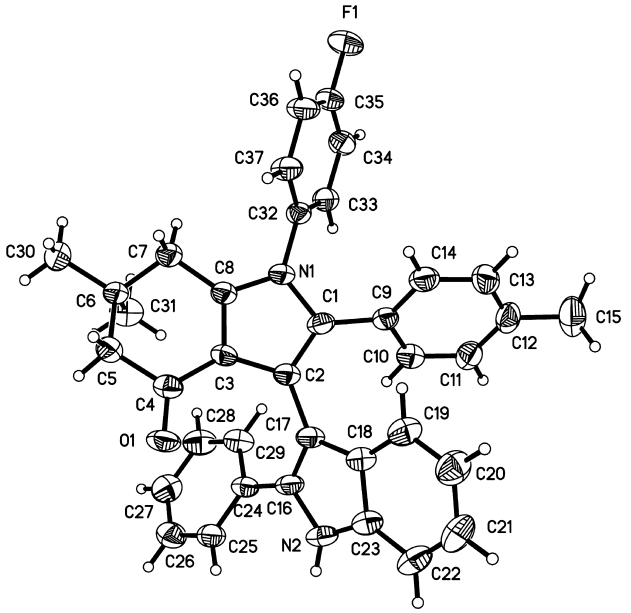


Figure 6. X-ray structure of product **4**{*4,2,5*}.

in a one-pot operation. *Up to three sigma-bonds were formed accompanied by the cleavage of C═O and C−O bonds of the aryl glyoxal via intermolecular indolation* (Scheme 3).

On the basis of all the above results, a possible mechanism has been proposed for the formation of bis-indoles as shown in Scheme 3. The reaction involves the ring closure cascade process that consist of initial protonation (**1** to **A**), nucleophilic substitution (**A** to **B**), and subsequent second protonation (**B** to **C**), second nucleophilic substitution (**C** to **D** and **E**), intramolecular cyclization and final dehydration (**E** to **4**). This regioselectivity is attributed to intramolecular hydrogen bond of intermediate **B**.

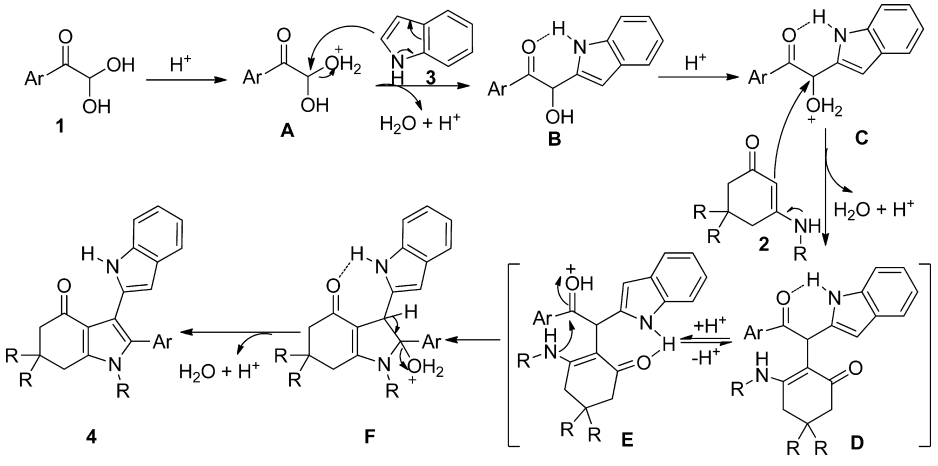
In conclusion, we have developed a three-component domino reaction (arylglyoxal monohydrates, enaminones, and indoles) as a novel method for regioselective synthesis of 3,2′- and 3,3′-bis-indoles by varying the substituted indole substrate. The reaction under acidic condition proceeds by selective [3 + 2] heterocyclization obtaining bis-indoles **4** in good yields, showing that the synthetic route allows us to build blocks of bis-indole derivatives with a wide diversity of substituents. This methodology is simple, practical, and is a regioselective alternative synthetic route to obtain good yields of bis-indole derivatives by microwave irradiation. Features of this strategy include the mild condition, convenient one-pot operation, and excellent regioselectivity. Further investigations are in progress in our laboratory to evaluate the process with a broader range of substrates, and to synthesize more complex products and test their biological activity.

EXPERIMENTAL PROCEDURES

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

Typical Procedure for the Preparation of Bis-indoles 4{*1,1,1*}. In a 10-mL reaction vial, phenylglyoxal monohydrate **1**{*1*} (0.153 g, 1 mmol), 3-((4-chlorophenyl)amino)-5,5-dimethylcyclohex-2-enone **2**{*1*} (0.25g, 1 mmol), indole **3**{*1*} (0.12 g, 1 mmol), and HOAc (1.5 mL) were mixed and then capped (the automatic mode stirring helped the mixing and uniform heating of the reactants). The mixture was heated for 20 min at 80 °C under microwave irradiation. Upon

Scheme 3. Reasonable Mechanism for the Product 4



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completion, monitored by TLC, the reaction mixture was cooled to room temperature. A suspension was formed which was then poured into water. The solid product was collected by Büchner filtration, subsequently washed with two different solvents of ethanol and ethylether in sequence to give the pure white solid (0.39 g, yield 84%). m.p.: 270−272 °C.

IR (KBr, ν, cm^{-1}): 3287, 1650, 1494, 1424, 1362, 1132, 1093, 1015, 834, 739, 700, 638, 519; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.91 (s, 1H, NH), 7.48 (d, J = 8.8 Hz, 2H, ArH), 7.31−7.27 (m, 3H, ArH), 7.14 (s, 1H, ArH), 7.04 (t, J = 3.2 Hz, 3H, ArH), 6.98−6.95 (m, 4H, ArH), 6.75 (t, J = 7.2 Hz, 1H, ArH), 2.59 (s, 2H, CH_2), 2.31 (s, 2H, CH_2), 1.08 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 192.2, 143.4, 136.1, 135.6, 132.7, 132.7, 131.4, 130.5, 129.9, 129.2, 127.6, 127.3, 126.9, 125.2, 120.3, 119.9, 118.1, 117.6, 113.9, 111.0, 1.7.6, 52.8, 36.5, 34.5, 28.1; HRMS (ESI): m/z calcd for: $C_{30}H_{25}ClN_2NaO$, 487.1548 $[M+Na]^+$, found: 487.1544.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data in CIF format. Further details on the experimental procedures and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Knölker, H.-J.; Reddy, K. R. Isolation and synthesis of biologically active carbazole alkaloids. *Chem. Rev.* **2002**, *102*, 4303−4427. (b) Jones, R. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, R. A., Reese, W., Eds.; Pergamon: New York, 1984; Vol. 4, p 201; (c) Hesse, M. *Indolalkaloide*; Chemie: Weinheim, Germany, 1974; (d) Sundberg, R. J. In *The Chemistry of Indoles*; Blomquist, A. T., Ed.; Academic: New York, 1970; (e) Remers, W. A. In *The Chemistry of Heterocyclic Compounds*; Houlihan,W. J., Ed.; Wiley-Interscience: New York, 1973; Vol. 25, Part I, Chapter 1; (f) Hibino, S.; Choshi, T. Simple indole alkaloids and those with a nonrearranged monoterpenoid unit. *Nat. Prod. Rep.* **2001**, *18*, 66−87. (g) Nishizawa, Y. The role of protein kinase C in cell surface signal transduction and tumor promotion. *Nature* **1984**, *308*, 693−698. (h) Nishizawa, Y. The molecular heterogeneity of protein kinase C and its implications for cellular regulation. *Nature* **1988**, *334*, 661−665. (i) Cacchi, S.; Fabrizi, G. Synthesis and functionalization of indoles through palladium-catalyzed reactions. *Chem. Rev.* **2005**, *105*, 2873−2920. (j) Humphrey, G. R.; Kuethe, J. T. Practical methodologies for the synthesis of Indoles. *Chem. Rev.* **2006**, *106*, 2875−2911.

(2) (a) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. Progress in palladium-based catalytic systems for the sustainable synthesis of annulated heterocycles: a focus on indole backbones. *Chem. Soc. Rev.* **2012**, *41*, 3929−3968. (b) Shiri, M. Indoles in multicomponent processes (MCPs). *Chem. Rev.* **2012**, *112*, 3508−3549. (c) Vicente, R. Recent advances in indole syntheses: New routes for a classic target. *Org. Biomol. Chem.* **2011**, *9*, 6469−6480. (d) Sapeta, K.; Lebold, T. P.; Kerr, M. A. Synthesis of highly substituted indoles via Diels-Alder/Plieninger indolization sequence: applications in total synthesis. *Synlett* **2011**, 1495−1514. (e) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. Organocatalytic strategies for the asymmetric functionalization of indoles. *Chem. Soc. Rev.* **2010**, *39*, 4449−4465.

(3) (a) Bartik, K.; Braekman, J.-C.; Daloze, D.; Stoller, C.; Huysecom, J.; Vandevyer, G.; Ottinger, R. Topsentins, new toxic bis-indole alkaloids from the marine sponge Topsentia genitrix. *Can. J. Chem.* **1987**, *65*, 2118−2121. (b) Tsuji, S.; Rinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. Topsentin, bromotopsentin, and dihydrodeoxybromotopsentin: antiviral and antitumor bis(indolyl)imidazoles from Caribbean deep-sea sponges of the family Halichondriidae. Structural and synthetic studies. *J. Org. Chem.* **1988**, *53*, 5446−5453. (c) Morris, S. A.; Andersen, R. J. Nitrogenous metabolites from the deep water sponge Hexadella sp. *Can. J. Chem.* **1989**, *67*, 677−681. (d) Murray, L. M.; Lim, T. K.; Hooper, J. N. A.; Capon, R. J. Isobromotopsentin: a new bis(indole) alkaloid from a deep-water marine sponge Spongosorites sp. *Aust. J. Chem.* **1995**, *48*, 2053−2058. (e) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J.-R.; Sim, C. J. New bis(Indole) alkaloids of the topsentin class from the sponge spongosorites genitrix. *J. Nat. Prod.* **1999**, *62*, 647−649.

(4) Tillequin, F.; Koch, M.; Bert, M.; Sevenet, T. Plants of new Caledonia. LV. Isoborreverine and borreverine, bis(indole) alkaloids from Flindersia fournieri. *J. Nat. Prod.* **1979**, *42*, 92−95.

(5) (a) Hoessel, R.; Leclerc, S.; Endicott, J.; Noble, M.; Lawrie, A.; Tunnah, P.; Leost, M.; Damiens, E.; Marie, D.; Marko, D.; Niederberger, E.; Tang, W.; Eisenbrand, G.; Meijer, L. Indirubin, the active constituent of a Chinese antileukemia medicine, inhibits cyclin-dependent kinases. *Nat. Cell Biol.* **1999**, *1*, 60−67. (b) Kritsanida, M.; Magiatis, P.; Skaltsounis, A.-L.; Peng, Y.; Li, P.; Wennogle, L. P. Synthesis and antiproliferative activity of 7-azaindirubin-3′-oxime, a 7-aza Isostere of the natural indirubin pharmacophore. *J. Nat. Prod.* **2009**, *72*, 2199−2202.

(6) (a) Fernandez, L. S.; Jobling, M. F.; Andrews, K. T.; Avery, V. M. Antimalarial activity of natural product extracts from papua new guinean and australian plants against plasmodium falciparum. *Phytother. Res.* **2008**, *22*, 1409−1412. (b) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M.; Flinderoles, A-C Antimalarial bis-indole alkaloids from Flindersia species. *Org. Lett.* **2009**, *11*, 329−332.

(7) Leclerc, S.; Garnier, M.; Hoessel, R.; Marko, D.; Bibb, J. A.; Snyder, G. L.; Greengard, P.; Biernat, J.; Mandelkow, E. M.; Eisenbrand, G.; Meijer, L. Indirubins inhibit glycogen synthase kinase-3β and CDK5/P25, two protein kinases involved in abnormal tau phosphorylation in Alzheimer's disease. A property common to most cyclin-dependent kinase inhibitors. *J. Biol. Chem.* **2001**, *276*, 251−260.

(8) Myrianthopoulos, V.; Magiatis, P.; Ferandin, Y.; Skaltsounis, A. L.; Meijer, L.; Mikros, E. An integrated computational approach to the phenomenon of potent and selective inhibition of aurora kinases B and C by a series of 7-substituted indirubins. *J. Med. Chem.* **2007**, *50*, 4027−4037.

(9) (a) Adachi, J.; Mori, Y.; Matsui, S.; Takigami, H.; Fujino, J.; Kitagawa, H.; Miller, C. A., 3rd; Kato, T.; Saeki, K.; Matsuda, T. Indirubin and indigo are potent aryl hydrocarbon receptor ligands present in human urine. *J. Biol. Chem.* **2001**, *276*, 31475−31478. (b) Kawanishi, M.; Sakamoto, M.; Ito, A.; Kishi, K.; Yagi, T. Construction of reporter yeasts for mouse aryl hydrocarbon receptor ligand activity. *Mutat. Res.* **2003**, *540*, 99−105.

(10) (a) Toure, B. B.; Hall, D. G. Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.* **2009**, *109*, 4439−4486. (b) Nicolaou, K. C.; Chen, J. S. The art of total synthesis through cascade reactions. *Chem. Soc. Rev.* **2009**, *38*, 2993−3009.

(11) (a) Tietze, L. F. Domino reactions in organic synthesis. *Chem. Rev.* **1996**, *96*, 115−136. (b) Tietze, L. F.; Brasche, G.; Gerike, K.

Domino Reactions in Organic Chemistry; Wiley-VCH: Weinheim, Germany, 2006. (c) Dömling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17−89. (d) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005. (e) Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (f) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Interfacial self-assembly of cell-like filamentous microcapsules. *Angew. Chem., Int. Ed.* **2011**, *50*, 6324−6327. (g) Tietze, L. F.; Kinzel, T.; Brazel, C. C. The domino multicomponent allylation reaction for the stereoselective synthesis of homoallylic alcohols. *Acc. Chem. Res.* **2009**, *42*, 367−378. (h) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. 1-Azadienes in cycloaddition and multicomponent reactions towards N-heterocycles. *Chem. Commun.* **2008**, 5474−5489. (i) Ganem, B. Strategies for innovation in multicomponent reaction design. *Acc. Chem. Res.* **2009**, *42*, 463−472. (j) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. Multicomponent reactions for the synthesis of heterocycles. *Chem.—Asian J.* **2010**, *5*, 2318−2335. (k) Duque, M.; del, M. S.; Allais, C.; Isambert, N.; Constantieux, T.; Rodriguez, J. ↓-Diketo building blocks for MCRs-based syntheses of heterocycles. *Top. Heterocycl. Chem.* **2010**, *2*, 227−277. (l) Li, M.; Cao, H.; Wang, Y.; Lv, X.-L.; Wen, L.-R. One-pot multicomponent cascade reaction of N,S-ketene acetal: solvent-free synthesis of imidazo[1,2-a] thiochromeno-[3,2-e]pyridines. *Org. Lett.* **2012**, *14*, 3470−3473.

(12) (a) Santra, S.; Andreana, P. R. A bioinspired Ugi/Michael/Aza-Michael cascade reaction in aqueous media: Natural-product-like molecular diversity. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418−9422. (b) Dömling, A.; Wang, W.; Wang, K. Chemistry and biology of multicomponent reactions. *Chem. Rev.* **2012**, *112*, 3083−3135. (c) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. From 2000 to mid-2010: A fruitful decade for the synthesis of pyrazoles. *Chem. Rev.* **2011**, *111*, 6984−7034. (d) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. A palladium-catalyzed three-component cross-coupling of conjugated dienes or terminal alkenes with vinyl triflates and boronic acids. *J. Am. Chem. Soc.* **2011**, *133*, 5784−5787. (e) Wang, J.; Wang, J.; Zhu, Y.; Lu, P.; Wang, Y. Copper-cascade catalysis: Synthesis of 3-functionalized indoles. *Chem. Commun.* **2011**, 3275−3277. (f) Isambert, N.; Duque, M.; del, M. S.; Plaquevent, J.-C.; Genisson, Y.; Rodriguez, J.; Constantieux, T. Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1347−1357. (g) Qiu, G.; Liu, G.; Pu, S.; Wu, J. A palladium-catalyzed three-component reaction for the preparation of quinazolin-4(3H)-imines. *Chem. Commun.* **2012**, 2903−2905.

(13) (a) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. Four-component domino reaction leading to multifunctionalized quinazolines. *J. Am. Chem. Soc.* **2009**, *131*, 11660−11661. (b) Jiang, B.; Yi, M.-S.; Shi, F.; Tu, S.-J.; Pindi, S.; McDowell, P.; Li, G. A multi-component domino reaction for the direct access to polyfunctionalized indoles via intermolecular allylic esterification and indolation. *Chem. Commun.* **2012**, 808−810. (c) Jiang, B.; Yi, M.-S.; Tu, M.-S.; Wang, S.-L.; Tu, S.-J. Brønsted acid-promoted divergent reactions of enaminones: Efficient synthesis of fused pyrroles with different substitution patterns. *Adv. Synth. Catal.* **2012**, *354*, 2504−2510. (d) Jiang, B.; Feng, B.-M.; Wang, S.-L.; Tu, S.-J.; Li, G. Domino constructions of pentacyclic indeno[2,1-c]quinolines and pyrano[4,3-b]oxepines by [4 + 1]/[3 + 2+1]/[5 + 1] and [4 + 3] multiple cyclizations. *Chem.—Eur. J.* **2012**, *18*, 9823−9826.

(14) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. Novel one-pot, three-component synthesis of new 2-alkyl-5-aryl-(1H)-pyrrole-4-ol in water. *J. Org. Chem.* **2008**, *73*, 2090−2095.

(15) (a) Stanovnik, B.; Svete, J. Synthesis of heterocycles from alkyl 3-(dimethylamino)propenoates and related Enaminones. *Chem. Rev.* **2004**, *104*, 2433−2480. (b) White, J. D.; Ihle, D. C. Tandem photocycloaddition-retro-Mannich fragmentation of Enaminones. A route to spiropyrrolines and the tetracyclic core of Koumine. *Org. Lett.* **2006**, *8*, 1081−1084. (c) Tu, S. J.; Jiang, B.; Jia, R. H.; Zhang, J. Y.; Zhang, Y.; Yao, C. S.; Shi, F. An efficient one-pot, three-component synthesis of indeno[1,2-b]quinoline −9,11(6H,10H)-dione, acridine-1,8(2H,5H)-dione and quinoline-3-carbonitrile derivatives from enaminones. *Org. Biomol. Chem.* **2006**, *4*, 3664−3668. (d) Huang, J.; Liang, Y.; Pan, W.; Dong, D. Efficient synthesis of highly substituted pyrrolin-4-ones *via* PIFA-mediated cyclization reactions of enaminones. *Org. Lett.* **2007**, *9*, 5345−5348. (e) Wang, G.-W.; Miao, C.-B. Environmentally benign one-pot multicomponent approaches to the synthesis of novel unsymmetrical 4-arylacridinediones. *Green Chem.* **2006**, *8*, 1080−1085. (f) Wu, X.-J.; Jiang, R.; Wu, B.; Su, X.-M.; Xu, X.-P.; Ji, S.-J. Nano-iron oxide as a recyclable catalyst for intramolecular C-N cross-coupling reactions under ligand-free conditions. One-pot synthesis of 1,4-dihydroquinoline derivatives. *Adv. Synth. Catal.* **2009**, *351*, 3150−3156.

(16) (a) Aubry, C.; Patel, A.; Mahale, S.; Chaudhuri, B.; Marechal, J.-D.; Sutcliffe, M. J.; Jenkins, P. R. The design and synthesis of novel 3-[2-indol-1-yl-ethyl]-1H-indole derivatives as selective inhibitors of CDK4. *Tetrahedron Lett.* **2005**, *46*, 1423−1425. (b) Ma, S.; Yu, S. $Sc(OTf)_3$-catalyzed indolylation of 1,2-allenic ketones: Controlled highly selective Synthesis of β-indolyl-α,β-unsaturated (E)-enones and β,β-bisindolyl ketones. *Org. Lett.* **2005**, *7*, 5063−5065.

(17) De Kruif, C. A.; Marsman, J. W.; Venekamp, J. C.; Falke, H. E.; Noordhoek, J.; Blaaubouer, B. J.; Wortelboer, H. M. Structure elucidation of acid reaction products of indole-3-carbinol: detection in vivo and enzyme induction in vitro. *Chem.-Biol. Interact.* **1991**, *80*, 303−315.