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Diastereoselective Synthesis of Biologically Active Cyclopenta[*b*]indoles

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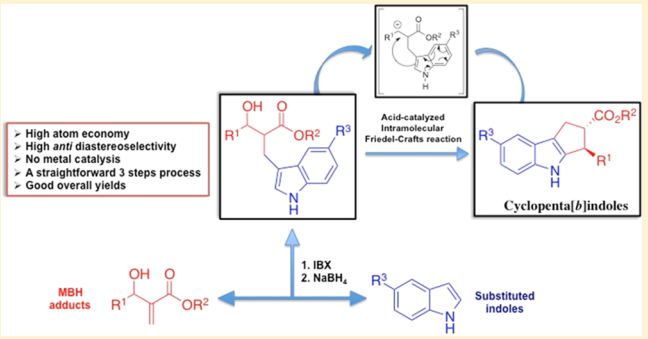
Supporting Information

ABSTRACT: The cyclopenta[*b*]indole motif is present in several natural and synthetic biologically active compounds, being directly responsible for the biological effects some of them present. We described herein a three step sequence for the synthesis of cyclopenta[*b*]indoles with a great structural diversity. The method is based on an oxidative Michael addition of suitable indoles on the double bond of Morita−Baylis−Hillman adducts mediated by a hypervalent iodine reagent (IBX) to form *β*-ketoesters, which were chemoselectively reduced with $NaBH_4$ in THF to give the corresponding *β*-hydroxyesters. The diastereoisomeric mixture was then treated with a catalytic amount of triflic acid (20 mol %) to give cyclopenta[*b*]indoles with overall yields ranging from 8 to 73% (for 2 steps). The acid-catalyzed cyclization step gave the required heterocycles, via an intramolecular Friedel−Crafts reaction, with high diastereoselectivity, where only the *trans* product was observed. A mechanistic study monitored by ESI-(+)-MS was also conducted to collect evidence about the mechanism of this reaction. The new molecules herein synthesized were also evaluated against a panel of human cancer cells demonstrating a promising antitumoral profile.



INTRODUCTION

The cyclopenta[*b*]indole nucleus (red backbone in Figure 1) is part of the carbon skeleton of various biologically active natural products.[1] For instance, Paspaline (**1**), a tremorgenic mycotoxin,[2] and the monoterpenoid alkaloid Yuehchukene (**2**) are products isolated from natural sources that bear such cyclopenta[*b*]indole moiety. Alkaloid **2** possesses abortive activity and affinity with the estrogen receptor.[3] Other biological functions, such as antagonist of the prostaglandin D2 receptor,[4] agonist of the progesterone receptor,[5] antioxidant[6] and insecticide[7] have been described for natural and synthetic compounds containing the cyclopenta[*b*]indole moiety.

Due to this great biological and synthetic relevance, various synthetic protocols have therefore been described to prepare of this heterocyclic nucleus. Cyclopenta[*b*]indoles have been synthesized using indole electrophilic substitution reactions,[8] Fischer synthesis,[9] [3 + 2]-cycloaddition,[10] [3,3]-sigmatropic rearrangement,[11] Yonemitsu condensation,[12] Dieckmann condensation,[13] Nazarov cyclization,[14] bismuth(III) catalyzed condensation,[15] Heck−Suzuki cascade,[16] vinylogous Michael addition/Friedel−Crafts reaction,[17] gold(I) catalyzed Rautenstrauch rearrangement,[18] and enzymatic synthesis.[19] Protocols to form the cyclopenta[*b*]indole nucleus via the Friedel−Crafts reaction have been however scarce.[20] In 2008, Li et al. developed a protocol to synthesize substituted fluorenes using an acid-catalyzed Friedel−Crafts reaction. The methodology was also extended to the synthesis of cyclopenta[*b*]indoles.[21] Some years later, Hamada et al.[22] reported the synthesis of various polycyclic cyclopenta[*b*]indoles in moderate to good yields using an intramolecular Friedel−Crafts reaction. Although efficient, this protocol has the disadvantage of employing a large excess (8 equiv) of trifluoroacetic acid.

Some years ago, Dorbec et al.[23] reported the synthesis of highly substituted indolotetralines and heterocyclic lignans using a strategy based on Michael addition, followed by a metal-catalyzed intramolecular Friedel−Crafts reaction. Although being elegant, his protocol also suffers from an important drawback. The starting material employed in his synthesis is methyl thuriferate. This highly substituted natural product can be

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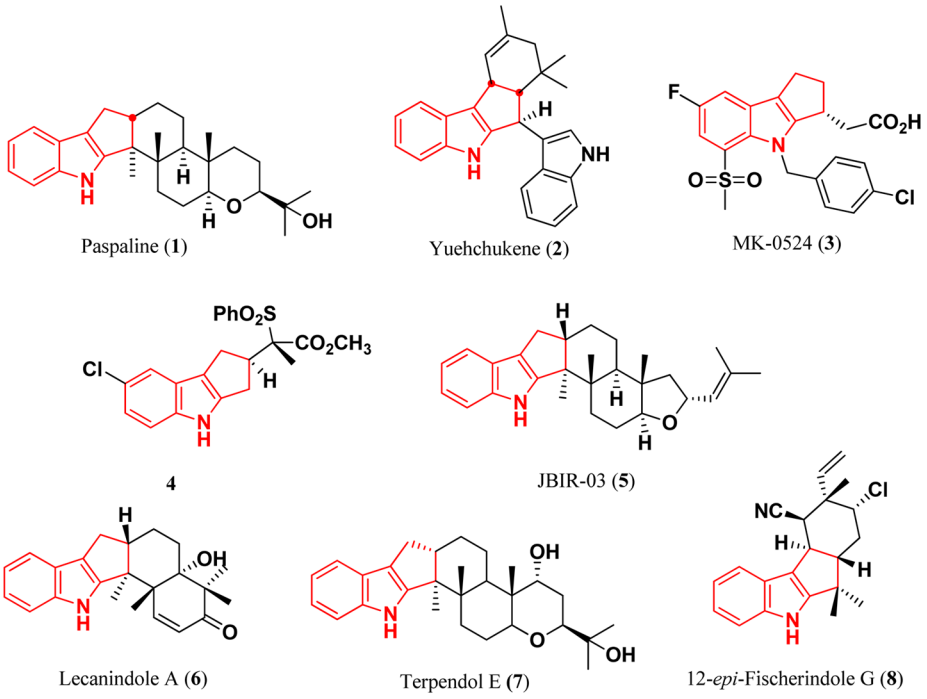
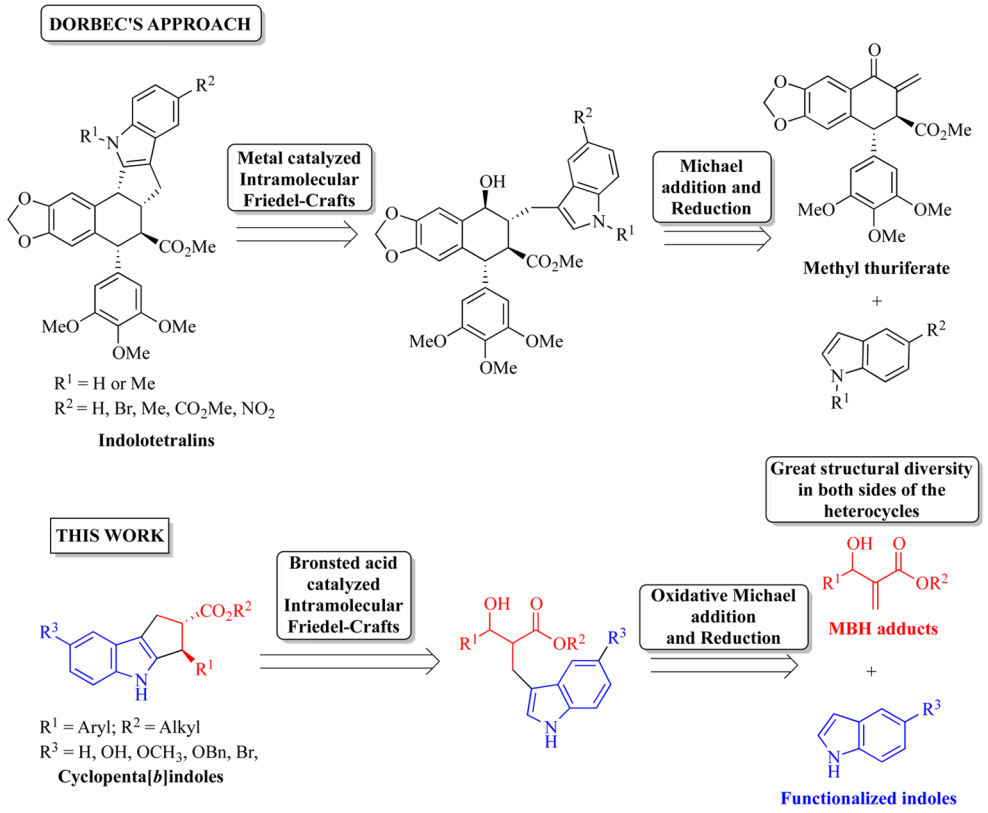


Figure 1. Examples of natural and synthetic biologically active molecules containing the cyclopenta[*b*]indole nucleus in their structure.

Scheme 1. Simple Approach for the Synthesis of Cyclopenta[*b*]indoles with Great Structural Diversity from MBH Adducts



obtained from natural sources (150 mg for each 15 kg of *Juniperus thurifera* leaves)[24] or by total synthesis.[25] But by being restricted to this building block, only the Michael donor can be structurally changed, which causes a severe restriction in terms of structural diversity (Scheme 1).

The biological and synthetic relevancy of the cyclopenta[*b*]-indoles calls therefore for the search of efficient and more comprehensive protocols for their preparation. Our interest in the biological profile of this particular class of hetero-cycles associated with our program aimed at exploring the

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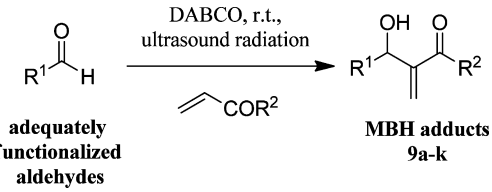
Morita−Baylis−Hillman adducts (MBH) as substrate for the development of synthetic methods have stimulated us to investigate an approach to prepare cyclopenta[*b*]indoles using a reaction sequence as short and as efficient as possible.

On the basis of a similar sequence of reactions, but now using MBH adducts as building blocks and a Brønsted acid as catalyst (Scheme 1), we report herein a highly diastereoselective method for the synthesis of cyclopenta[*b*]indoles with high structural diversity. The use of MBH adducts as starting material opens a great structural diversity associated with good chemical sustainability, since no metal catalyst is used.

RESULTS AND DISCUSSION

MBH adducts are small poly functionalized molecules which can normally be easily prepared from abundant and cheap materials.[26] The association of three contiguous functional groups in the structure of such small molecules transforms MBH adducts in most valuable building blocks; hence, they have been largely employed for the synthesis of many natural products and biologically active molecules.[27] We started therefore our sequence by preparing a designed set of MBH adducts by condensing several aldehydes with methyl or ethyl acrylate in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) as catalyst using ultrasound radiation.[27a] A broad diversity of such

Table 1. Synthesis of the MBH Adducts



entry	product	R^1	R^2	yield[a,b] (%)
1	**9a**	3-Cl-C_6H_4	OCH_3	83
2	**9b**	4-CH_3O-C_6H_4	OCH_3	71
3	**9c**	Piperonyl	OCH_3	70
4	**9d**	6-Br-Piperonyl	OCH_3	55
5	**9e**	C_6H_5	OCH_3	85
6	**9f**	4-O_2N-C_6H_4	OCH_3	90
7	**9g**	1,3-Thiazol-2-yl	OCH_3	93
8	**9h**	3,4-$(CH_3O)_2$-C_6H_3	OCH_3	70
9	**9i**	3,4,5-$(CH_3O)_3$-C_6H_2	OC_2H_5	70
10	**9j**	3,4,5-$(CH_3O)_3$-C_6H_2	OCH_3	71
11	**9k**	4-$C_6H_5CH_2OC_6H_4$	OCH_3	71
12	**9l**	*n*-Hexyl	OCH_3	70

[a]Yields refer to isolated and purified products (by flash column chromatography). [b]Acrylate (30 equiv) is used as reagent and solvent on these MBH reactions; thus, no additional solvent is required. After reaction completion, more than 95% of acrylate can be easily recovered by distillation under reduced pressure. However, these reactions can be also performed using 2−5 equiv of acrylate in methanol or acetonitrile solutions in lower yields and longer reaction times.

representative adducts could indeed be obtained in good to excellent yield (Table 1).

The MBH reaction worked well for all cases tested. After isolation and chromatographic purification, performed when necessary, the MBH adducts were properly characterized by spectroscopic and spectrometric methods. The spectral data were fully compatible for all proposed structures.

Indoles have already been used as Michael donors in Lewis acid catalyzed conjugated additions with electron-deficient olefins;[28] hence, we decided to test the behavior of the MBH adducts in this reaction. If successful, this reaction could lead to a direct route to cyclopenta[*b*]indoles. But despite several attempts under different experimental conditions, we are unable to obtain the desired addition product.

We noted however that in 2007, Yadav[29] developed an efficient method for the alkylation of indoles with MBH adducts via oxidative Michael addition using 2-iodoxybenzoic acid (IBX). We envisaged therefore that this methodology could provide the intermediate needed to access the cyclopenta[*b*]indole nucleus, and the experimental protocol proposed by Yadav was tested. For that, a mixture of a MBH adduct and nonsubstituted and 5-substituted indoles dissolved in acetonitrile was treated with 2-iodoxybenzoic acid (IBX, 1.2 equiv) under neutral conditions. After a few hours, we were indeed able to isolate the desired 2-methylindolyl-*β*-ketoesters (**10a−10r**) in good to excellent yields (Table 2).

The reactions summarized in Table 2 worked efficiently with almost all MBH adducts tested. The highest conversions were achieved for MBH adducts containing electron-deficient substituents in the aromatic portion, and also for those with electron-rich substituents. These results suggest that the electronic nature of the aryl ring is not crucial for the reaction. In general, the yields ranged from 53 to 95% and the reaction showed to be robust, admitting a diversity of substrates from indoles to MBH adducts. All the *β*-ketoesters were fully characterized by spectroscopic and spectrometric methods fully characterized by spectroscopic and spectrometric methods (see Supporting Information for details).

Next, to perform the intramolecular Friedel−Crafts reaction needed to generate a carbocation on the benzylic position, we envisaged that the best protocol would be via protonation with a strong acid followed by dehydration (Scheme 2). The *β*-ketoester **10a** was taken as model to test this sequence. That is, *β*-ketoester **10** was first chemoselectively reduced with $NaBH_4$ in the presence of methanol to afford a diastereoisomeric mixture of the corresponding *β*-hydroxyesters **10aa−10ab**, in almost quantitative yield (Scheme 2). We note that no diastereoselectivity was observed on this reduction step and the crude mixture was pure enough to be used for the next step with no need of any additional chromatographic purification.[30,31]

Separation of the diastereoisomers **10aa−10ab** was actually considered unnecessary since both isomers would form the same stable benzylic carbocation after acid-catalyzed dehydration. Using therefore the diastereoisomeric mixture of *β*-hydroxyester **10aa−10ab** as a model, different acids, solvents and temperatures were tested (Table 3).

Initially, we evaluated *p*-toluenesulfonic acid (PTSA) and toluene as solvent at room temperature, but no product was detected even after 2 days, with total recovery of the starting material. The same conditions were repeated, but now the reaction was kept under reflux in toluene for 5 h, and indeed the formation of cylopenta[*b*]indole **11a** was observed from the expected intramolecular Friedel−Crafts cyclization mixed with the compound **11aa** in a ratio of 1:2 (Table 3, entry 2) and in an overall yield of 30% (for two steps). The same behavior was observed when the reaction was run at 50 °C for 12 h. We also have evaluated different solvents and the first encouraging results appeared when the reaction was performed in benzene (Table 3, entry 8), affording the products **11a** and **11aa** in an overall yield of 23%. Note that now the Friedel−Crafts product **11a** was the major compound in the mixture (Table 3, compare

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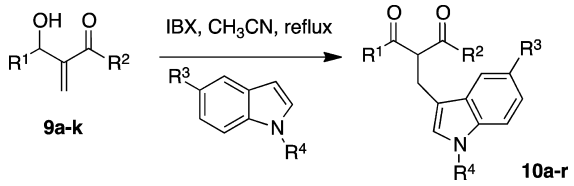
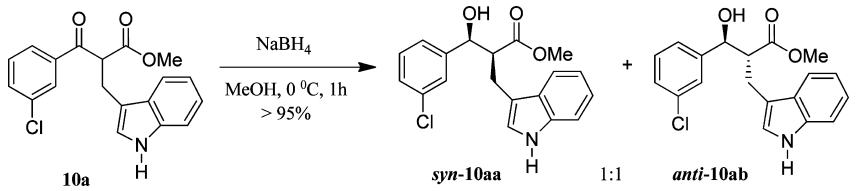
Table 2. Synthesis of 2-Methylindolyl β-Ketoesters from MBH Adducts



entry	product	R^1	R^2	R^3	R^4	yield[a,b] (%)
1	**10a**	3-Cl-C_6H_4	OCH_3	H	H	87
2	**10b**	4-CH_3O-C_6H_4	OCH_3	H	H	88
3	**10c**	4-CH_3O-C_6H_4	OCH_3	OCH_3	H	79
4	**10d**	4-$CH_3OC_6H_4$	OCH_3	$OCH_2C_6H_5$	H	72
5	**10e**	Piperonyl	OCH_3	H	H	61
6	**10f**	Piperonyl	OCH_3	$OCH_2C_6H_5$	H	69
7	**10g**	6-Br-Piperonyl	OCH_3	H	H	71
8	**10h**	C_6H_5	OCH_3	H	H	75
9	**10i**	C_6H_5	OCH_3	OCH_3	H	71
10	**10j**	4-O_2N-C_6H_4	OCH_3	H	H	90
11	**10k**	1,3-Thiazol-2-yl	OCH_3	H	H	74
12	**10l**	3,4-$(CH_3O)_2$-C_6H_3	OCH_3	$OCH_2C_6H_5$	H	53
13	**10m**	3,4,5-$(CH_3O)_3$-C_6H_2	OC_2H_5	Br	H	>95
14	**10n**	3,4,5-$(CH_3O)_3$-C_6H_2	OCH_3	$OCH_2C_6H_5$	CH_3	65
15	**10o**	3,4,5-$(CH_3O)_3$-C_6H_2	OCH_3	H	H	71
16	**10p**	3,4,5-$(CH_3O)_3$-C_6H_2	OCH_3	$OCH_2C_6H_5$	H	89
17	**10q**	4-$C_6H_5CH_2O$-C_6H_4	OCH_3	$OCH_2C_6H_5$	H	73
18	**10r**	*n*-Hexyl	OCH_3	OCH_3	H	62

[a]Yields refer to isolated and purified compounds. [b]In these reactions we used 1.2 equiv of IBX. We have decreased the amount of IBX; however, they were not completed. No further purification is needed.

Scheme 2. Chemoselective Reduction of β-Ketoester 10a



entries 3 and 8). For safety reasons, we therefore replaced benzene by toluene. We also tested sulfuric acid and Amberlyst as catalysts, but the α,β-ester **11aa** was the only product formed. Reactions using acetic acid as the catalyst also failed with the recovery of the starting material. The same behavior was observed when Lewis acid were employed (Table 3, entries 15 and 16). We also tested the conditions described by Dorbec[23] (see entry 15), but again, only the starting material was recovered. Finally, we tested trifluoromethanesulfonic acid (triflic acid) as catalyst, using toluene as the solvent, for a reaction performed at room temperature. After 4 h, the same mixture of compounds was formed in 31% of yield (for the two steps) but a mixture was formed in which the cyclization product was the major component (60:40, entry 13). Other attempts were performed, but either the starting material was recovered or the retro-Michael product was the major product isolated. We decided therefore to use triflic acid in toluene at room temperature as the standard protocol and test it with the whole set of β-hydroxy-esters.

Although the presence of cynnamic derivative **11aa** was still high, we decided to take the experimental conditions described on entry 13 (Table 3) as standard to evaluate the scope of our methodology. Due to high yield obtained in the chemoselective reduction of the β-ketoesters **10b−r** and the high degree of purity associated with these derivatives, the sequence was performed without any purification between the steps. The β-ketoesters **10a−r** were therefore reduced with $NaBH_4$. After isolation, the crude product was dissolved in anhydrous toluene and treated with trifluoromethanesulfonic acid (triflic acid, 20 mol %) at room temperature giving the corresponding cyclopenta[*b*]indoles **11b−11q** (Table 4). The overall yields ranging from 50 to 70% for those substrates for which the portion originated from the MBH adducts containing electron-donating substituent (Table 4, entries 1−6 and 11−15). In all cases, a unique diastereoisomer was detected. However, when the portion originated from MBH adducts contained an electron-withdrawing substituent, aromatic ring without substituents and heteroaromatic ring, the intramolecular Friedel−Crafts cyclization furnished the products with the lowest yields (Table 4, entries 7−10). Especially for the compound **11k** (Table 4, entry 10), the low yield would also be associated with the decomposition of the thiazole ring caused by the strong acid conditions used. Curiously, no conversion was observed for the *n*-hexyl (Table 4, entry 17) derivative and this failure might probably be related to the stabilization of a possible carbocation species. The presence of aromatic compounds having electro-withdrawing substituents, or an heteroaromatic compounds with alkyl groups seem to be limiting factors for this reaction.

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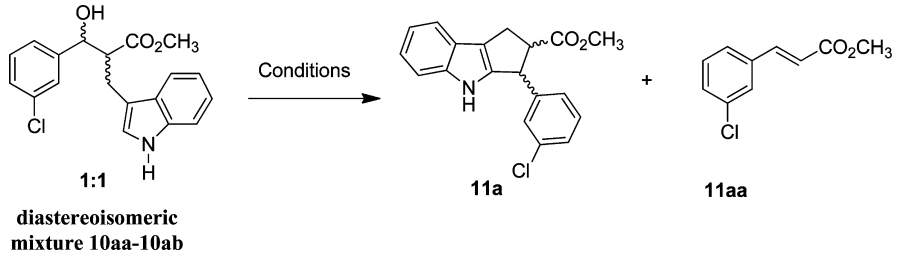
Table 3. Optimizing the Cyclization Reaction with β-Ketoesters 10aa−10ab under Acidic Conditions

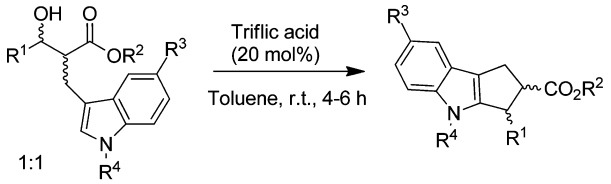


diastereoisomeric mixture 10aa-10ab

entry	acid[a]	solvent	temp. (°C)	time (h)	ratio **11a**:**11aa**
1	PTSA[b]	Toluene	25	48	SM[c]
2	PTSA	Toluene	Reflux	5	33:67
3	PTSA	Toluene	50	12	35:65
4	PTSA	Acetonitrile	Reflux	7	46:54
5	PTSA	Xylene	Reflux	0.5	0:100
6	PTSA	DMF	80	12	SM[c]
7	PTSA	DCM	Reflux	6	0:100
8	PTSA	Benzene	Reflux	5	56:44
9	H_2SO_4	Toluene	r.t.	0.5	0:100
10	H_2SO_4	CCl_4	r.t.	0.5	0:100
11	AcOH	Toluene	Reflux	12	SM[c]
12	Amberlyst	Toluene	Reflux	3	0:100
13	Triflic acid[d]	Toluene	r.t.	4	60:40
14	$KHSO_4$	Toluene	Reflux	60	23:77
15	$InCl_3$[e]	Acetonitrile	r.t.	12	SM[c]
16	$Sc(SO_3CF_3)_3$[e]	Acetonitrile	r.t.	10	SM[c]

[a]2 equiv of acid. [b]PTSA: *p*-toluenesulfonic acid. [c]SM: starting material recovered. [d]Reaction with 20 mol % of triflic acid. [e]Reaction with 10 mol % of Lewis acid.

Table 4. Synthesis of Cyclopenta[*b*]indole from α-Indolyl-β-hydroxyesters



diastereoisomeric mixture 10aa-10ab

11b-11q

entry	product	R^1	R^2	R^3	R^4	yield[c] (%)
1	**11b**	4-CH_3O-C_6H_4[a]	CH_3	H	H	62
2	**11c**	4-CH_3O-C_6H_4[a]	CH_3	4-OCH_3	H	67
3	**11d**	4-CH_3O-C_6H_4	CH_3	$OCH_2C_6H_5$	H	53
4	**11e**	Piperonyl[a]	CH_3	H	H	71
5	**11f**	Piperonyl	CH_3	$OCH_2C_6H_5$	H	55
6	**11g**	6-Br-Piperonyl[a]	CH_3	H	H	70
7	**11h**	C_6H_5[b]	CH_3	H	H	12[d]
8	**11i**	C_6H_5[b]	CH_3	OCH_3	H	8[d]
9	**11j**	4-O_2N-C_6H_4[b]	CH_3	H	H	10[d]
10	**11k**	1,3-Thiazol-2-yl[b]	CH_3	H	H	5[d]
11	**11l**	3,4-$(CH_3O)_2$-C_6H_3	CH_3	OH	H	58
12	**11m**	3,4,5-$(CH_3O)_3$-C_6H_2[a]	C_2H_5	Br	H	70
13	**11n**	3,4,5-$(CH_3O)_3$-C_6H_2	CH_3	$OCH_2C_6H_5$	CH_3	70
14	**11o**	3,4,5-$(CH_3O)_3$-C_6H_2	CH_3	H	H	50
15	**11p**	3,4,5-$(CH_3O)_3$-C_6H_2	CH_3	$OCH_2C_6H_5$	H	75
16	**11q**	4-$C_6H_5CH_2O$-C_6H_4	CH_3	$OCH_2C_6H_5$	H	73
17	**11r**	*n*-Hexyl[b]	CH_3	H	H	SM[e]

[a]Reaction carried out with 20 mol % of triflic acid. [b]Reaction carried out with 3 equiv of triflic acid. [c]Yields for 2 steps after silica gel column chromatography. [d]In these cases we observed the formation of the cynamate derivative. [e]Starting material recovered.

At this stage, we have already established an attractive approach to obtain cyclopenta[*b*]indoles with different substitution patterns in 3 steps from the MBH adducts using only 20 mol % of triflic acid in an intramolecular Friedel−Crafts step. This protocol

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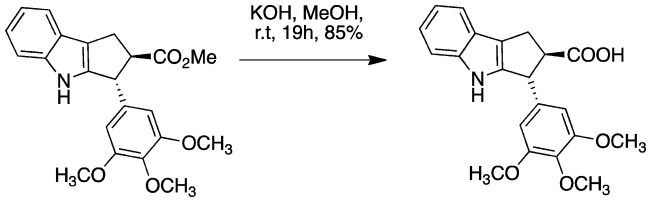
displays several advantages when compared to that described by Hamada et al.[22] First, we used only a small amount of acid catalysts and our protocol also display much higher atom economy, since all reagents are incorporated on the final group and only a water molecule is lost during the whole synthetic sequence. In addition, and to our delight, only one isomer was detected in the reaction medium, indicating the high degree of diastereoselection of this reaction. To determine the relative stereochemistry, two-dimensional NMR experiments were performed, indicating a *trans* relationship between the substituents in positions 2 and 3 of cyclopentane ring (for details see Supporting Information file).

Although these NOE data gave us relevant information about the relative stereochemistry of **11**, some doubts still remained since some increments are not conclusive. We tried therefore to get crystallographic data for these compounds. We observed that the carboxylic acids derived from them were crystalline. Therefore, **11o** was treated with KOH in methanol to provide the corresponding carboxylic acid **12**, in 85% yield, as a crystalline solid (Scheme 3).

Scheme 3. Preparation of Carboxylic Acid 12



The analysis of the crystallographic data of cyclopenta[*b*]-indole **12** allowed us to accurately determine its relative stereochemistry, which proved to be *trans* for all cases (see Supporting Information file for details concerning crystallographic data, pages S88−S90).[32]

We also tried to get corresponding *cis* diastereoisomers since their spectroscopic data could be considered as additional evidence to confirm the relative stereochemistry of **12**. A solution of diastereoisomer **11d** in toluene was treated with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) both at room temperature and at reflux for several hours or days, but only the presence of the *trans* diastereoisomer was detected. These data suggested that the *trans* diastereoisomer **12** is also the thermodynamic compound.

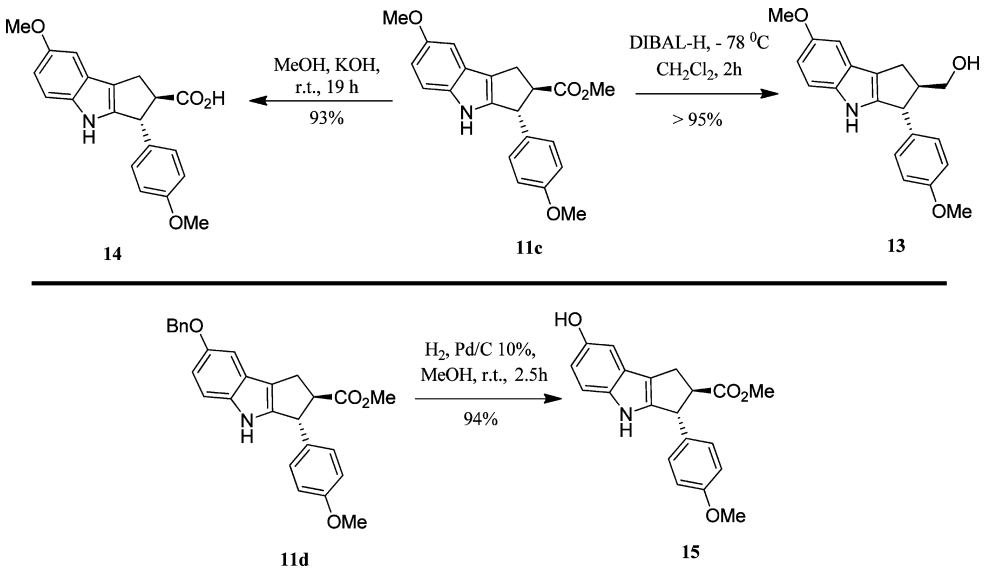
The heterocycles synthesized in this work are promising targets for biological assays. To increase therefore their structural diversity, we decide to try to implement some structural changes commonly employed in organic synthesis. For that we selected the cyclopenta[*b*]indoles **11c** and **11d** as models. The ester group of **11c** was therefore reduced in the presence of DIBAL-H to afford the corresponding hydroxymethyl alcohol derivative **13** in 95% yield and high diastereoselectivity. Treatment of ester **11c** on basic condition gave the carboxylic acid **14** in 93% yield. Alternatively, we removed the protecting group of the hydroxyl at C5 of **11d** to produce **15** (Scheme 4). All of these derivatives (**13**, **14** and **15**) should have increased water solubility, which might facilitate the biological evaluations.

Table 4 consistently shows that higher yields were obtained for systems having electron donor substituents in the aromatic ring. This trend points to the participation of a carbocation intermediate in the cyclization step. ESI(+)-MS, which has been shown to work as a powerful tool for the investigation of organic reaction mechanisms and to allows the interception and characterization of reaction intermediates,[33] was therefore used to try to intercept such putative intermediate.

The ESI(+)-MS monitoring was performed with **11c** due to the presence a methoxy group at the *para* position of the aromatic ring, which could stabilize the putative carbocation. But the protonated forms from **II** and the carbocation (**I**) are isobaric (*m*/*z* 322, Scheme 5); hence, it was necessary to differentiate them. Methanol was therefore thought to act as a nucleophilic compound to trap the carbocation.

After 5−10 min of reaction monitoring, what appeared to be key intermediates, that is, the two ions of *m*/*z* 130 (**III**) and *m*/*z* 322 (**I**) were detected (Figure 2) by ESI(+)-MS. To trap therefore the cationic species of *m*/*z* 322, if indeed formed, the ion was selected and methanol was injected into the collision cell of the instrument, and indeed the ion of *m*/*z* 354 (**IV**) was formed.

Scheme 4. Simple Chemical Transformations with Our Synthesized Cyclopenta[*b*]indoles



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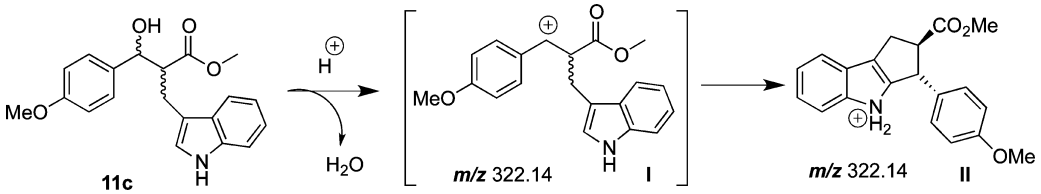
Scheme 5. ESI(+)-MS Monitoring of Compound 11c



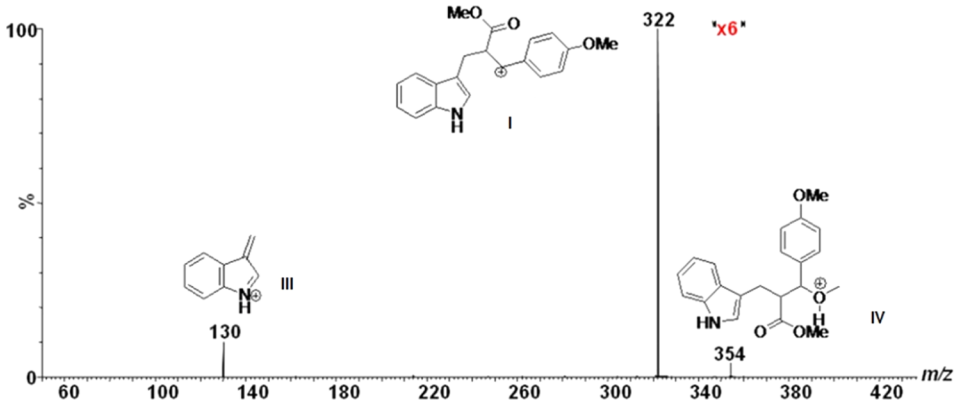
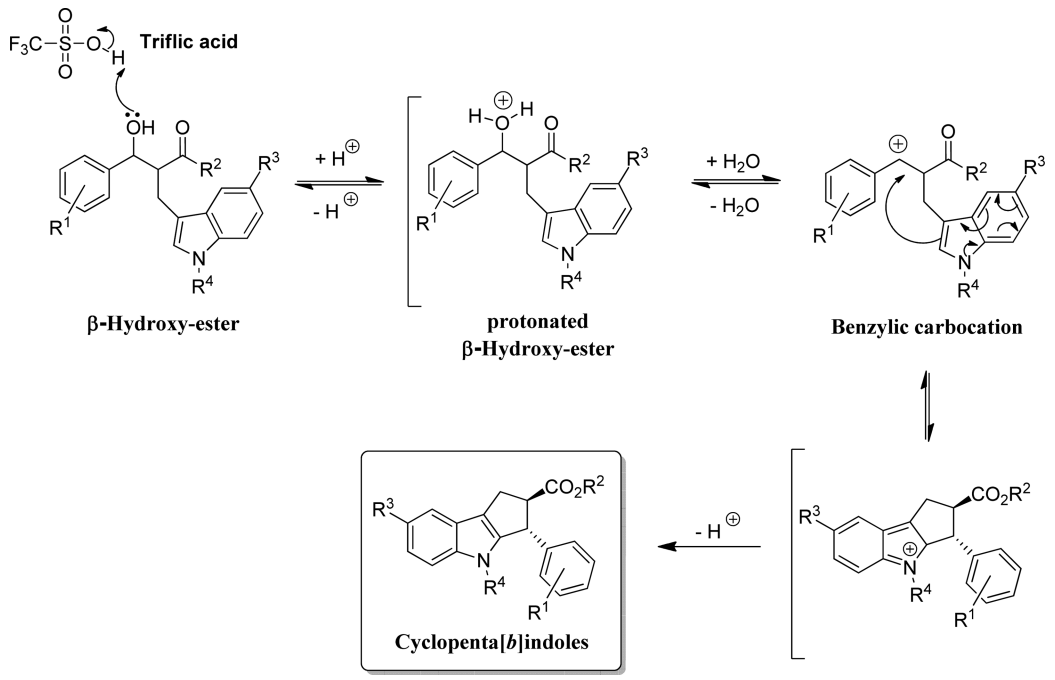
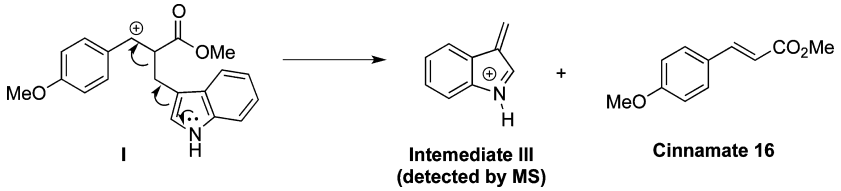


Figure 2. ESI(+)-MS/MS for the ion/molecule reaction of the carbocation II with methanol.

Scheme 6. Proposed Mechanism for the Synthesis of Cyclopenta[*b*]indoles from MBH Adducts



Scheme 7. Rationalizing the Formation of Cinnamate Derivative during the Intramolecular Friedel–Crafts Reaction



The Scheme 6 rationalizes a plausible mechanism for the cyclization reaction. The first step involves protonation of the benzylic hydroxyl group from the *β*-hydroxyester followed by the elimination of water and therefore affording a benzylic carbocation. The benzylic position interferes directly into the stability of this transient species and justifies the easiness for its

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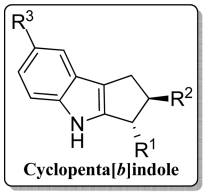
Table 5. TGI (Total Growth Inhibition) Values in μM, for Compounds 11a−11m, 13−15 and Doxorubicin (DOX)[a,b,c,d]



11a, R^1 = 3-Cl-C_6H_4; R^2 = CO_2CH_3; R^3 = H
11b, R^1 = 4-CH_3O-C_6H_4; R^2 = CO_2CH_3; R^3 = H
11c, R^1 = 4-CH_3O-C_6H_4; R^2 = CO_2CH_3; R^3 = CH_3O
11d, R^1 = 4-CH_3O-C_6H_4; R^2 = CO_2CH_3; R^3 = $C_6H_5CH_2O$
11e, R^1 = Piperonyl; R^2 = CO_2CH_3; R^3 = H
11g, R^1 = 6-Br-Piperonyl; R^2 = CO_2CH_3; R^3 = H
11h, R^1 = C_6H_5; R^2 = CO_2CH_3; R^3 = H
11i, R^1 = C_6H_5; R^2 = CO_2CH_3; R^3 = CH_3O
11j, R^1 = 4-O_2N-C_6H_4; R^2 = CO_2CH_3; R^3 = H
11k, R^1 = 1,3-thiazol-2-yl; R^2 = CO_2CH_3; R^3 = CH_3O
11m, R^1 = 3,4,5-(CH_3O)-C_6H_2; R^2 = CO_2CH_3; R^3 = Br
13, R^1 = 4-CH_3O-C_6H_4; R^2 = CH_2OH; R^3 = CH_3O
14, R^1 = 4-CH_3O-C_6H_4; R^2 = CO_2CH_3; R^3 = HO
15, R^1 = 4-CH_3O-C_6H; R^2 = CO_2H; R^3 = CH_3O

	U251	UACC-62	NCI-ADR/RES	786-0	NCI-H460	PC-3	OVCAR-3	HT-29	K562
DOX	19.30 ± 5.2	9.49 ± 2.64	46.00	135.55 ± 8.76	6.20 ± 2.24	3.96 ± 0.67	35.63 ± 7.66	6.27 ± 0.35	46.00
11a	21.92 ± 3.98	25.74 ± 4.27	>300	**109.95 ± 9.38**	223.31 ± 16.87	61.80 ± 16.04	**34.22 ± 9.33**	285.45 ± 0	>300
11b	81.98 ± 24.28	47.99 ± 29.81	>300	>300	>300	47.36 ± 11.61	**33.31 ± 12.313**	26.15 ± 1.69	>300
11c	>300	>300	>300	>300	>300	>300	>300	68.21 ± 8.25	>300
11d	>300	>300	>300	>300	>300	>300	>300	30.90 ± 2.46	>300
11e	18.65 ± 6.57	21.83 ± 4.65	>300	>300	48.95 ± 18.61	193.90 ± 12.48	59.22 ± 3.89	44.60 ± 16.96	>300
11g	64.15 ± 2.76	>300	>300	>300	20.71 ± 5.48	>300	>300	188.96 ± 14.36	89.05 ± 44.94
11h	68.14 ± 14.91	>300	74.36 ± 28.89	>300	96.81 ± 41.06	73.87 ± 15.23	92.65 ± 6.68	16.45 ± 3.64	4.27 ± 0.53
11i	16.13 ± 1.86	58.24 ± 7.06	>300	>300	22.59 ± 4.0	71.65 ± 1.57	66.34 ± 19.82	2.85 ± 0.063	0.77
11j	>300	>300	>300	>300	111.67 ± 23.38	>300	>300	91.21 ± 4.22	>300
11k	94.76 ± 12.31	116.76 ± 13.29	>300	128.48 ± 26.75	82.19 ± 10.75	102.23 ± 38.24	105.55 ± 1.34	123.01 ± 33.83	>300
11m	44.19 ± 7.95	277.03 ± 3.56	>300	>300	29.10 ± 10.91	61.90 ± 2.91	**31.10 ± 8.79**	24.54 ± 4.63	4.47 ± 1.4
13	44.43 ± 5.43	98.99 ± 30.45	>300	134.83 ± 35.99	42.86 ± 14.17	55.91 ± 4.39	43.39 ± 3.9324.04	24.04 ± 11.18	289.73 ± 71.59
14	>300	191.76 ± 33.51	>300	>300	>300	>300	>300	>300	90.42 ± 0.01
15	**6.70 ± 0.71**	**5.91 ± 1.5**	**7.10 ± 0.84**	**48.90 ± 6.93**	9.98 ± 2.71	11.55 ± 0.71	**2.82 ± 0.4**	9.24 ± 3.86	**22.98 ± 10.02**

[a]Results are expressed as mean of two independent experiments performed in triplicate ± standard error. [b]Concentration that elicits total growth inhibition (TGI) was determined from nonlinear regression analysis using ORIGIN 8.0 (OriginLab Corporations). [c]Doxorubicin (DOX) was the positive control. [d]Cell lines: Human tumor cell lines U251 (glioma), UACC-62 (melanoma), NCI-H460 (lung, nonsmall cells), HT-29 (colon), PC-3 (prostate), 786-0 (kidney), NCI-ADR/RES (ovarian expressing multiple drugs resistance phenotype), OVCAR-3 (ovary) and K562 (leukemia) were obtained from National Cancer Institute at Frederick MA-USA (see Supporting Information for experimental details).

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formation. The carbocation then undergoes nucleophilic attack of the indole C2 in a 5-*endo*-trig intramolecular Friedel−Crafts. After a rearomatization step, the cyclopenta[*b*]indole is formed.[34]

Likely during the cyclization step, the cynnamate derivative **16** would be formed. This product could be formed directly in the reaction medium by a decomposition of the carbocation intermediate **I** (Scheme 7). During the ESI(+)-MS monitoring study, a cation of *m*/*z* 130 was also detected. This stable cation seems to explain the formation of the cinnamate derivative. An alkyl migration from intermediate **I** could occurred to provide cinnamate derivative **16** and the indolylmethyl cation **III**.[35]

The high diastereoselectivity can also be rationalized as follow: initially the indole would approach the carbocation from the opposite side to the carbomethoxy group, which should contribute to decrease the steric hindrance. The superposition of the indole C2 orbital with the carbocation p orbital would form a five-membered ring as well as induce the carboxyl and phenyl groups to be on opposite sides, explaining the *trans*-stereochemistry observed for all cyclopenta[*b*]indoles synthesized in this work.

With this library of new heterocycles in hand and based on previous reports associating this structural motif to biological effects,[1−7] we decided to evaluate the behavior of these new compounds against a panel of human tumor cells using doxorubicin as control drug. The results are summarized in Table 5.

Some of the tested cyclopenta[*b*]indoles showed indeed antitumoral activity similar to the control drug, but with the advantage of better selectivity. For instance, the concentration of **11a** necessary to totally inhibit the growing of kidney cancer cells was slightly lower than that of doxorubicin, but **11a** was also quite selective for this cancer cell line. The same behavior was also observed with **11a**, **11b** and **11m**, which were selective against ovary cancer cell lines.

Among the tested cyclopenta[*b*]indoles, compound **15** proved to be the most potent and promising. For instance, the doxorubicin concentration (35.6 μM) necessary to totally inhibit the growing of the ovarian cancer cell lines (OVCAR-3) was 12 times higher than that of compound **15** (2.82 μM). The cyclopenta[*b*]indol **15** was also more potent than the control drug against most all cancer cell lines tested.

CONCLUSION

A diastereoselective approach for the synthesis of cyclopenta[*b*]indoles starting from the structurally diverse MBH adducts has been developed. The methodology presents several benefits in terms of sustainability, such as high atom economy, the use of a soft and environmental benign oxidant reagent (IBX) whereas avoiding the use of metal catalysis.[36]

It also increases the opportunities for structural diversity when preparing cyclopenta[*b*]indoles, simply by varying the substituents present both on indoles and many MBH adducts.[37] This seems to be the first report describing the use of MBH adducts as substrate for the synthesis of cyclopenta[*b*]indoles. Efforts to develop an asymmetric version of this approach are undergoing in our laboratory. Biological evaluations also showed promising antitumor profiles for the cyclopenta[*b*]indoles herein prepared, particularly for **15** which is a good candidate for a new antitumoral drug. Current studies in our laboratory have suggested that **15** may interacts with the colchicine binding-site on tubulin and consequently interfere with the cellular cycle division. A comprehensive biological evaluation of **15** and derivatives are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Methods. Chemicals were used as purchased unless otherwise noticed. Toluene was distilled from sodium immediately prior to use. Methanol was distilled from magnesium and catalytic amount of iodine. Acetonitrile was distilled from calcium hydride immediately prior to use. The reaction progress was monitored by thin layer chromatography on silica gel (aluminum foils) and spotted under UV light (254 nm), followed by staining with ethanolic 25% phosphomolibdic solution or aqueous $KMnO_4$. Purification by column chromatography was carried out with silica gel (70−230 or 230−400 Mesh). ^{1}H NMR spectra were measured at 250, 400, and 500 MHz and the ^{13}C NMR spectra at 62.5, 100, and 125 MHz, in $CDCl_3$ and acetone-d_6 at room temperature. Chemical shifts (δ) were reported in ppm and the coupling constants (*J*) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), doublet (d), double doublet (dd), double doublet doublet (ddd), triplet (t), double triplet (dt), quartet (q), quintuplet (qt), multiplet (m) and broad (br). The absorption spectra in the infrared region (IR) were obtained in FT-IR spectrophotometer with the frequencies expressed in cm^{-1}, and the samples applied to a cell of NaCl or KBr pellets. The mass spectra of high resolution were obtained on a device Q-ToF instrument configuration ESI-QqTof with a resolution of 5000 and 50.0 ppm accuracy in TOF mass analyzer. The compounds are named according to IUPAC rules using an adequate free program. Only spectroscopic data of unknown compounds were included in experimental section.

*Preparation of (±)-Methyl 2-{[4-(benzyloxy)phenyl](hydroxy)-methyl}prop-2-enoate (**9k**).* A mixture of the aldehyde 4-benzyloxybenzaldehyde (310 mg, 1.46 mmol), DABCO (106 mg, 0.95 mmol, 0.65 equiv) and methyl acrylate (3.8 g, 43.8 mmol, 30 equiv) was submitted to ultrasound radiation, at room temperature, for 25 h. During this time, water bath's temperature was kept around 35 °C. After that, the excess of methyl acrylate was removed under reduced pressure and the residue was dissolved in ethyl acetate (40 mL). The organic phase was washed with a diluted solution of HCl (10% v/v) (1 × 15 mL), distilled water (3 × 10 mL) and brine (1 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate, 70:30) to afford 309 mg (1.04 mmol, 71%) of MBH adduct **9k**, as a white amorphous solid. IR (neat) 3442, 1733, 735 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.08 (d, *J* = 5.1 Hz, 1H), 3.66 (s, 3H), 5.47 (d, *J* = 4.8 Hz, 1H), 5.84 (s, 1H), 6.29 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.31−7.38 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 51.8, 69.9, 72.5, 114.6, 125.4, 127.3, 127.9, 128.4, 133.7, 136.8, 142.1, 158.3, 166.6. HRMS (ESI, *m*/*z*) Calcd for $C_{18}H_{17}O_3$ $[M - H_2O]^+$ 281.1172, found 281.1201.

General Procedure for the Preparation of β-Ketoesters 10a−10r. A mixture of the MBH adduct (1 mmol), indole or substituted indole (1 mmol) and 2-iodoxybenzoic acid (IBX, 1.2 mmol) in acetonitrile (5 mL) was stirred under reflux for the time specified in Table 2. Evolution of the reactions was followed by thin layer chromatography (TLC). After completion, the solvent was removed under reduced pressure. The residue obtained was the purified by flash silica gel column chromatography using a gradient mixture of ethyl acetate/hexane (20:80) as eluent, to give the corresponding β-ketoesters **10a−10r**.

*(±)-Methyl 3-(3-chlorophenyl)-2-(1H-indol-3-ylmethyl)-3-oxopropanoate (**10a**).* Reaction Time: 6 h. Yield: 87% (297 mg, 0.87 mmol). Yellow oil. IR (film) 3411, 1738, 1688, 1221, 743 cm^{-1}. NMR ^{1}H (250 MHz, $CDCl_3$) δ 3.48 (d, *J* = 7.6 Hz, 2H), 3.65 (s, 3H), 4.71 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 7.10−7.18 (m, 2H), 7.21−7.33 (m, 2H), 7.47 (ddd, *J* = 1.0, 2.0, and 8.2 Hz, 1H), 7.59−7.63 (m, 1H), 7.73−7.77 (m, 1H), 7.87 (t, *J* = 1.8 Hz, 1H), 8.04 (broad s, 1H). NMR ^{13}C (62,5 MHz, $CDCl_3$) δ 24.7, 52.6, 54.9, 111.2, 112.0, 118.3, 119.6, 122.1, 122.8, 126.6, 126.9, 128.6, 129.9, 133.4, 135.0, 136.1, 137.7, 169.8, 194.0. HRMS (ESI, *m*/*z*) Calcd for $C_{19}H_{16}ClNNaO_3^+$ 364.0711, found 364.0686.

*(±)-Methyl 2-(1H-indol-3-ylmethyl)-3-(4-methoxyphenyl)-3-oxopropanoate (**10b**).* Reaction Time: 7 h. Yield: 88% (296 mg, 0.88 mmol). Brown oil. IR (neat) 3404, 1735, 1670, 1260, 744 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.50 (dd, *J* = 5.0 and 7.6 Hz, 2H), 3.65 (s, 3H), 3.84 (s, 3H), 4.75 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H),

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7.00 (s, 1H), 7.10−7.26 (m, 2H), 7.40−7.46 (m, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 9.0 Hz, 2H), 8.03 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 25.0, 52.7, 54.7, 55.7, 111.4, 112.8, 114.1, 118.7, 119.7, 122.2, 123.0, 127.4, 129.5, 131.3, 136.4, 164.1, 170.6, 193.7. HRMS (ESI, m/z) Calcd for $C_{20}H_{19}NNaO_4^+$ 360.1206, found 360.1193.

*(±)-Methyl 2-[(5-methoxy-1H-indol-3-yl)methyl]-3-(4-methoxyphenyl)-3-oxopropanoate (**10c**).* Reaction Time: 6 h. Yield: 79% (291 mg, 0.79 mmol). Brown oil. IR (neat) 3407, 2929, 1741, 1711, 1216, 797 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.46 (m, 2H), 3.65 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.73 (t, J = 7.2 Hz, 1H), 6.81−6.90 (m, 3H), 6.96 (d, J = 2.3 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.10 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.8, 52.4, 54.4, 55.4, 55.8, 100.3, 111.9, 112.1, 112.2, 113.8, 123.5, 127.5, 129.2, 131.0, 131.2, 153.9, 163.8, 170.4, 193.5. HRMS (ESI, m/z) Calcd for $C_{21}H_{21}NNaO_5^+$ 390.1312, found 390.1294.

*(±)-Methyl 2-{[5-(benzyloxy)-1H-indol-3-yl]methyl}-3-(4-methoxyphenyl)-3-oxopropanoate (**10d**).* Reaction Time: 8 h. Yield: 72% (319 mg, 0.72 mmol). Brown oil. IR (neat) 3410, 1736, 1673, 1265, 1175, 737 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.49 (dd, J = 3.6 and 7.1 Hz, 2H), 3.67 (s, 3H), 3.83 (s, 3H), 4.74 (t, J = 7.2 Hz, 1H), 5.13 (s, 2H), 6.87−6.97 (m, 4H), 7.19−7.54 (m, 7H), 7.95 (d, J = 8.9 Hz, 2H), 8.15 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.8, 52.4, 54.2, 55.4, 70.9, 102.0, 111.9, 112.0, 112.7, 113.8, 123.6, 127.4, 127.6, 127.7, 128.4, 129.1, 131.0; 131.4, 137.6, 153.1, 163.8, 170.4, 193.6. HRMS (ESI, m/z) Calcd for $C_{27}H_{25}NNaO_5^+$ 466.1625, found 466.1633.

*(±)-Methyl 3-(2H-1,3-benzodioxol-5-yl)-2-(1H-indol-3-ylmethyl)-3-oxopropanoate (**10e**).* Reaction Time: 6 h. Yield: 61% (214 mg, 0.61 mmol). Light yellow oil. IR (neat) 3407, 1734, 1672, 1443, 1258, 743 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.49 (dd, J = 2.7 and 7.1 Hz, 2H), 3.66 (s, 3H), 4.70 (t, J = 7.1 Hz, 1H), 6.00 (s, 2H), 6.77 (d, J = 8.7 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 7.13−7.19 (m, 2H), 7.32 (d, J = 7.1 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 7.54 (dd, J = 1.7 and 8.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 8.07 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.8, 52.5, 54.6, 101.9, 107.9, 108.3, 111.2, 112.4, 118.4, 119.4, 122.0, 122.8, 125.2, 127.1, 131.0, 136.1, 148.3, 152.2, 170.2, 193.0. HRMS (ESI, m/z) Calcd for $C_{20}H_{18}NO_5^+$ 352.1179, found 352.1190.

*(±)-Methyl 3-(2H-1,3-benzodioxol-5-yl)-2-{[5-(benzyloxy)-1H-indol-3-yl]methyl}-3-oxopropanoate (**10f**).* Reaction Time: 8 h. Yield: 69% (315 mg, 0.69 mmol). Brown oil. IR (neat) 3407, 1734, 1672, 1443, 1258, 743 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.61−7.33 (m, 7H), 7.22−7.17 (m, 2H), 6.97−6.88 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 6.00 (s, 2H), 5.12 (s, 2H), 4.64 (t, J = 7.2 Hz, 1H), 3.66 (s, 3H), 3.44 (d, J = 7.2 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 193.1, 170.2, 153.2, 152.2, 148.3, 137.7, 131.5, 131.1, 128.5, 127.8, 127.63, 127.5, 125.3, 123.6, 113.0, 112.3, 111.9, 108.3, 107.9, 102.1, 102.0, 71.0, 54.4, 52.5, 24.9. HRMS (ESI, m/z) Calcd for $C_{27}H_{24}NO_6^+$ 458.1598, found 458.1614.

*(±)-Methyl 3-(6-bromo-2H-1,3-benzodioxol-5-yl)-2-(1H-indol-3-ylmethyl)-3-oxopropanoate (**10g**).* Reaction Time: 12 h. Yield: 71% (305 mg, 0.71 mmol). Brown oil. IR (neat) 3409, 1738, 1698, 1479, 1244, 743 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.46 (d, J = 7.3 Hz, 2H), 3.66 (s, 3H), 4.69 (t, J = 7.3 Hz, 1H), 5.99 (s, 2H), 6.76 (s, 1H), 6.99 (s, 1H), 7.04 (d, J = 2.3 Hz, 1H), 7.11−7.18 (m, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.99 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.6, 52.5, 58.1, 102.4, 109.1, 111.1, 112.0, 112.1, 113.9, 118.5, 119.5, 122.1, 122.9, 127.0, 133.3, 136.1, 147.2, 150.3, 169.5, 196.9. HRMS (ESI, m/z) Calcd for $C_{20}H_{16}BrNNaO_5^+$ 452.0104, found 452.0100.

*(±)-Methyl 2-(1H-indol-3-ylmethyl)-3-oxo-3-phenylpropanoate (**10h**).* Reaction time: 8 h. Yield: 75% (230 mg, 0.75 mmol). Yellow oil. IR (neat) 3409, 1738, 1698, 1479, 1244, 743 cm^{-1}. NMR ^{1}H (250 MHz, $CDCl_3$) δ 3.53 (dd, J = 1,9 and 7.2 Hz, 1H), 3.63 (dd, J = 1.8 and 4.9 Hz, 1H), 3.67 (s, 3H), 4.81 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 2.3 Hz, 1H), 7.12−7.24 (m, 2H), 7.32−7.47 (m, 3H), 7.53−7.56 (m, 1H), 7.64−7.67 (m, 1H), 7.93−7.98 (m, 1H), 8.08 (br, 1H). NMR ^{13}C (62,5 MHz, $CDCl_3$) δ 24.9, 52.7, 55.0, 111.4, 112.6, 118.6, 119.7, 122.2, 123.0, 127.3, 128.8, 128.9, 133.7, 136.3, 136.4, 170.4, 195.3. HRMS (ESI, m/z) Calcd for $C_{19}H_{17}NNaO_3^+$ 330.1101, found 330.1098.

*(±)-Methyl 2-[(5-methoxy-1H-indol-3-yl)methyl]-3-oxo-3-phenylpropanoate (**10i**).* Reaction Time: 10 h. Yield: 71% (239 mg, 0.71 mmol). Yellow oil. IR (neat) 3409, 2999, 1737, 1683, 1596, 1216, 737 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3,48 (dd, J = 2.6 and 7.2 Hz, 2H), 3.67 (s, 3H), 3.88 (s, 3H), 4.77 (t, J = 7.2, 1H), 6.86 (dd, J = 2.4 and 8.8 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.41−7.46 (m, 2H), 7.53−7.59 (m, 1H), 7.92−7.98 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 25.0, 52.8, 54.9, 56.1, 100.6, 112.1, 112.4, 112.5, 123.7, 127.7, 128.86, 128.9, 131.5, 133.8, 136.5, 154.3, 170.4, 195.4. HRMS (ESI, m/z) Calcd for $C_{20}H_{19}NNaO_4^+$ 360.1206, found 360.1196.

*(±)-Methyl 2-(1H-indol-3-ylmethyl)-3-(4-nitrophenyl)-3-oxopropanoate (**10j**).* Reaction time: 8 h. Yield: 90% (317 mg, 0.9 mmol). Yellow oil. IR (neat) 3414, 1736, 1692, 1524, 1346, 745 cm^{-1}. NMR ^{1}H (250 MHz, $CDCl_3$) δ 3.54 (d, J = 7.3 Hz, 2H), 3.56 (s, 3H), 4.78 (t, J = 7.3 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 7.12−7.24 (m, 2H), 7.33 (d, J = 6.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.9 Hz, 3H), 8.21 (d, J = 8.9 Hz, 2H). NMR ^{13}C (62.5 MHz, $CDCl_3$) δ 24.7, 52.8, 55.2, 111.3, 111.8, 118.3, 119.7, 122.3, 122.8, 123.8, 126.9, 129.5, 136.1, 140.8, 150.3, 169.4, 194.1. HRMS (ESI, m/z) Calcd for $C_{19}H_{16}N_2NaO_5^+$ 375.0951, found 375.0971.

*(±)-Methyl 2-(1H-indol-3-ylmethyl)-3-oxo-3-(1,3-thiazol-2-yl)-propanoate (**10k**).* Reaction Time: 10 h. Yield: 74% (232 mg, 0.74 mmol). Yellow oil. IR (neat) 3411, 1736, 1685, 1435, 744 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.57 (m, 2H), 3.68 (s, 3H), 5.13 (t, J = 7.3 Hz, 1H), 7.06 (d, J = 2.1 Hz, 1H), 7.11−7.21 (m, 2H), 7.30−7.37 (m, 1H), 7.66 (d, J = 3.0 Hz, 1H), 7.75−7.72 (m, 1H), 8.01 (d, J = 3.0 Hz, 1H), 8.06 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.6; 52.7; 54.9; 111.3; 112.4; 119.0; 119.7; 122.2; 123.2; 127.1; 127.3; 136.3; 145.2; 166.0; 170.1; 188.9. HRMS (ESI, m/z) Calcd for $C_{16}H_{15}N_2O_3S^+$ 315.0798, found 315.0811.

*(±)-Methyl 2-{[5-(benzyloxy)-1H-indol-3-yl]methyl}-3-(3,4-dimethoxyphenyl)-3-oxopropanoate (**10l**).* Reaction Time: 8 h. Yield: 53% (251 mg, 0.53 mmol). Brown oil. IR (neat) 3245, 1736, 1675, 1440 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.64−7.10 (m, 9H), 7.03−6.85 (m, 2H), 6.79 (d, J = 8.5 Hz, 1H), 5.11 (s, 2H), 4.73 (t, J = 7.2 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.46 (dd, J = 7.1, 2.9 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 193.8, 170.4, 153.7, 153.2, 149.0, 137.6, 131.6, 129.5, 128.5, 127.8, 127.6, 127.5, 123.7, 123.5, 112.8, 112.1, 112.0, 110.7, 110.1, 102.2, 71.0, 56.0, 55.8, 54.1, 52.5, 25.0. HRMS (ESI, m/z) Calcd for $C_{28}H_{27}NNaO_6^+$ 496.1731, found 496.1727.

*(±)-Ethyl 2-[(5-bromo-1H-indol-3-yl)methyl]-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**10m**).* Reaction time: 12 h. Yield: 95% (464 mg, 0.95 mmol). Brown oil. IR (neat) 3445, 1727, 1671, 1584, 1127, 730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3H), 3.44 (dd, J = 1.9 and 7.0 Hz, 2H), 3.80 (s, 6H), 3.89 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 4.67 (t, J = 7.3 Hz, 1H), 7.01−7.29 (m, 6H), 7.77 (s, 1H), 8.12 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.3, 25.1, 54.8, 56.4, 61.1, 61.8, 106.2, 112.2, 113.0, 113.1, 121.2, 124.6, 125.2, 129.2, 131.8, 135.0, 143.0, 153.2, 169.8, 194.4. HRMS (ESI, m/z) Calcd for $C_{23}H_{24}BrNNaO_6^+$ 512.0679, found 512.0674.

*(±)-Methyl 2-{[5-(benzyloxy)-1-methyl-1H-indol-3-yl]methyl}-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**10n**).* Reaction time: 12 h. Yield: 65% (336 mg, 0.65 mmol). Brown oil. IR (neat) 3443, 1732, 1672, 1582, 1127, 730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.20 (dd, J = 8.7, 5.5 Hz, 2H), 7.14 (s, 2H), 7.00 (dd, J = 8.8, 2.2 Hz, 1H), 6.85 (s, 1H), 5.15 (s, 2H), 4.71 (t, J = 7.2 Hz, 1H), 3.92 (s, 3H), 3.78 (s, 6H), 3.73 (s, 3H), 3.67 (s, 3H), 3.48 (qd, J = 14.7, 7.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 170.3, 153.1, 153.0, 142.9, 137.6, 132.6, 131.7, 128.5, 128.4, 127.9, 127.7, 112.3, 110.2, 106.1, 102.5, 71.1, 60.9, 56.1, 54.7, 52.6, 32.8, 25.1. HRMS (ESI, m/z) Calcd for $C_{30}H_{31}NNaO_7^+$ 540.1993, found 540.1987.

*(±)-Methyl 2-[(1H-indol-3-yl)methyl]-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**10o**).* Reaction time: 8 h. Yield: 71% (282 mg, 0.71 mmol). Brown oil. IR (neat) 3447, 1728, 1669, 1588, 1127 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.72−7.60 (m, 1H), 7.38−7.04 (m, 5H), 6.96 (d, J = 2.3 Hz, 1H), 4.82−4.69 (m, 1H), 3.87 (s, 3H), 3.70 (d, J = 5.8 Hz, 9H), 3.67−3.35 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 194.6, 170.3, 152.9, 142.8, 136.2, 131.7, 127.1, 123.0, 122.1, 119.5, 118.3, 112.0, 111.4, 106.0, 60.9, 56.0, 54.3, 52.5,

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25.2. HRMS (ESI, m/z) Calcd for $C_{22}H_{23}NNaO_6$ 420.1418, found 420.1408.

*(±)-Methyl 2-{[5-(benzyloxy)-1H-indol-3-yl]methyl}-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**10p**).* Reaction time: 8 h. Yield: 89% (448 mg, 0.89 mmol). Brown oil. IR (neat) 3442, 1730, 1680, 1123, 731 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.46−3.52 (m, 2H), 3.69 (s, 9H), 4.72−4.78 (m, 1H), 5.11 (s, 2H), 6.92−6.95 (m, 2H), 7.09 (s, 2H), 7.18−7.22 (m, 2H), 7.34−7.39 (m, 3H), 7.48−7.51 (m, 2H), 8.32 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 25.2, 52.4, 54.1, 55.8, 60.7, 70.9, 102.0, 105.8, 111.4, 112.0, 112.4, 123.8, 127.3, 127.5, 127.7, 128.3, 131.5, 131.5, 131.6, 137.4, 142.6, 152.8, 153.1, 170.2, 194.6. HRMS (ESI, m/z) Calcd for $C_{29}H_{30}NO_7^+$ 504.2017, found 504.1997.

*(±)-Methyl 2-{[5-(benzyloxy)-1H-indol-3-yl]methyl}-3-[4-(benzyloxy)phenyl]-3-oxopropanoate (**10q**).* Reaction time: 5 h. Yield: 73% (379 mg, 0.73 mmol). Brown oil. IR (neat) 3445, 1737, 1129, 730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.53 (dd, J = 4.0 and 7.0 Hz, 1H), 3.68 (s, 3H), 4.77 (t, J = 7.0 Hz, 1H), 5.09 (s, 2H), 5.15 (s, 2H), 6.95−6.99 (m, 4H), 7.20−7.23 (m, 2H), 7.36−7.46 (m, 7H), 7.52−7.56 (m, 1H), 7.96 (d, J = 8.8 Hz, 2H), 8.18 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.8, 52.3, 54.2, 70.0, 70.8, 101.9, 111.9, 112.7, 114.6, 123.6, 127.3, 127.5, 127.7, 128.1, 128.4, 128.5, 129.3, 131.0, 131.4, 135.9, 137.5, 153.0, 162.9, 170.3, 193.5. HRMS (ESI, m/z) Calcd for $C_{33}H_{30}NO_5^+$ 520.2128, found 520.2132.

*(±)-Methyl 2-[(5-methoxy-1H-indol-3-yl)methyl]-3-oxononanoate (**10r**).* Reaction time: 10 h. Yield: 62% (215 mg, 0.62 mmol). Colorless viscous oil. IR (neat) 3445, 1727, 1671, 1584, 1127, 730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (t, J = 3.5 Hz, 3H), 1.21 (m, 5H), 1.48 (m, 2H), 1.63 (s, 1H), 2.33 (m, 1H), 2.51 (m, 1H), 3.30 (d, J = 7.6 Hz, 2H), 3.70 (s, 3H), 3.87 (s, 3H), 3.92 (t, J = 7.5 Hz, 1H), 6.85 (dd, J = 2.4 and 8.8 Hz, 1H), 6.98 (dd, J = 2.3 and 14.6 Hz, 2H), 7.23 (d, J = 8.8 Hz, 1H), 7.34 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9, 22.4, 23.2, 24.0, 28.5, 31.4, 42.8, 52.4, 55.9, 59.1, 100.4, 112.0, 112.3, 123.3, 127.4, 131.3, 154.1, 170.0, 205.5. HRMS (ESI, m/z) Calcd for $C_{20}H_{28}NO_4^+$ 346.2015, found 346.2032.

General Procedure for the Synthesis of Cyclopenta[*b*]indoles 11a−11q. To a solution of β-ketoesters **10a−r** (0.5 mmol) in MeOH (10 mL) was added $NaBH_4$ (1.5 mmol) in small portions at 0 °C. The resulting mixture was stirred for 1h at room temperature. Thus, the mixture was concentrated under vacuum. The crude residue was dissolved in ethyl acetate (30 mL) and washed with a saturated solution of ammonium chloride (NH_4Cl, 20 mL), H_2O (20 mL) and brine (20 mL), successively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was used in the next step without further purification. The β-hydroxyester (~0.5 mmol) was added in a dry round-bottom flask fitted with a stir bar. It was then dissolved in 15 mL of toluene. So, a solution of trifluoromethanesulfonic acid (triflic acid) in acetonitrile (20 mol %) was added at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for the time specified in Table 4. After, the mixture was diluted with an equivalent volume of ethyl acetate and washed with a saturated solution of sodium hydrogen carbonate ($NaHCO_3$, 30 mL), brine (30 mL) and dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the resulting oil was purified by flash chromatography (ethyl acetate: hexane 20:80) to give the corresponding cyclopenta[*b*]indoles.

*(±)-Methyl 3-(3-chlorophenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11a**).* Reaction time: 4 h. Yield: 18% (29 mg, 0.07 mmol). Brown oil. IR (film) 3394, 2950, 1731, 1434, 1264, 742 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.13 (ddd, J = 1.5, 6.8, and 14.4 Hz, 1H), 3.38 (ddd, J = 1.5, 6.8, and 14.4 Hz, 1H), 3.58−3.67 (m, 1H), 3.75 (s, 3H), 4.82 (d, J = 6.7 Hz, 1H), 7.11−7.15 (m, 3H), 7.22−7.30 (m, 4H), 7.48−7.51 (m, 1H), 7.72 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.7, 48.0, 52.1, 58.2, 111.8, 118.3, 118.9, 120.0, 121.6, 124.1, 126.1, 127.5, 127.8, 130.1, 134.7, 141.2, 141.9, 144.7, 174.5. HRMS (ESI, m/z) Calcd for $C_{19}H_{17}ClNO_2^+$ 326.0942, found 326.0961.

*Methyl (2E)-3-(3-chlorophenyl)prop-2-enoate (**11aa**).* Reaction time: 4 h. Yield: 13% (12.8 mg, 0.065 mmol). ^1H NMR (250 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.43 (d, J = 16 Hz, 1H), 7.26−7.38 (m, 2H), 7.50 (s, 1H), 7.60 (d, J = 16 Hz, 1H). HRMS (ESI, m/z) Calcd for $C_{10}H_{10}ClO_2^+$ 197.0364, found 197.0354.

*(±)-Methyl 3-(4-methoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11b**).* Reaction time: 0.5 h. Yield: 62% (99.8 mg, 0.31 mmol). Brown oil. IR (film) 3393, 1731, 1512, 1265, 738 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.13 (ddd, J = 1.5, 7.0, and 14.3 Hz, 1H), 3.37 (ddd, J = 1.5, 7.0, and 14.3 Hz, 1H), 3.58−3.67 (m, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 4.79 (d, J = 6.8 Hz, 1H), 6.84−6.87 (m, 2H), 7.11−7.23 (m, 4H), 7.25−7.28 (m, 1H), 7.48−7.52 (m, 1H), 7.73 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.7, 47.7, 52.0, 55.3, 58.6, 111.7, 114.2, 117.7, 118.7, 119.8, 121.3, 124.3, 128.8, 134.6, 141.1, 143.1, 158.8, 174.9. HRMS (ESI, m/z) Calcd for $C_{20}H_{20}NO_3^+$ 322.1438, found 322.1431.

*(±)-Methyl 7-methoxy-3-(4-methoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11c**).* Reaction time: 2 h. Yield: 67% (118 mg, 0.336 mmol). Brown oil. IR (film) 3372, 2951, 1731, 1511, 1247, 1214, 735 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.10 (ddd, J = 1.3, 7.0, and 14.2 Hz, 1H), 3.29−3.39 (m, 1H), 3.56−3.65 (m, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 3.86 (s, 3H), 4.75 (d, J = 6.7 Hz, 1H), 6.76−6.82 (m, 3H), 6.98 (d, J = 2.3 Hz, 1H), 7.11−7.16 (m, 3H), 7.76 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.6, 47.6, 51.9, 55.2, 55.8, 58.4, 101.1, 110.9, 112.2, 114.1, 117.3, 124.5, 128.7, 134.6, 136.1, 144,0, 154.1, 158.7, 174.9. HRMS (ESI, m/z) Calcd for $C_{21}H_{21}NNaO_4^+$ 374.1363, found 374.1350.

*(±)-Methyl 7-(benzyloxy)-3-(4-methoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11d**).* Reaction time: 5 h. Yield: 53% (120 mg, 0.28 mmol). Yellow oil. IR (film) 3374, 1731, 1585, 1247, 1176, 736 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.10 (ddd, J = 1.2, 7.1, and 14.2 Hz, 1H), 3.33 (m, 1H), 3.60 (dt, J = 7.1 and 14.1 Hz, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 4.77 (d, J = 6.7 Hz, 1H), 5.13 (s, 2H), 6.84−7.51 (m, 12H), 7.63 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.9, 47.9, 52.2, 55.5, 58.7, 71.2, 103.0, 111.9, 112.4, 114.4, 117.8, 124.8, 127.8, 128.0, 128.7, 129.0, 134.8, 136.5, 138.0, 144.3, 153.7, 159.0, 175.1. HRMS (ESI, m/z) Calcd for $C_{27}H_{25}NNaO_4^+$ 450.1676, found 450.1677.

*(±)-Methyl 3-(2H-1,3-benzodioxol-5-yl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11e**).* Reaction time: 4 h. Yield: 71% (119 mg, 0.355 mmol). Brown oil. IR (film) 3403, 1731, 1484, 1248 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.11 (dd, J = 6.9 and 14.3 Hz, 1H), 3.36 (dd, J = 6.9 and 14.3 Hz, 1H), 3.56−3.65 (m, 1H), 3.75 (s, 3H), 4.76 (d, J = 6.9 Hz, 1H), 5.92 (s, 2H), 6.69−6.74 (m, 3H), 7.11−7.15 (m, 2H), 7.25−7.28 (m, 1H), 7.48−7.51 (m, 1H), 7.80 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.6, 48.1, 52.0, 58.5, 101.0, 108.0, 108.3, 111.7, 117.8, 118.8, 119.8, 120.9, 121.3, 124.2, 136.4, 141.1, 142.7, 146.7, 148.0, 174.8. HRMS (ESI, m/z) Calcd for $C_{20}H_{18}NO_4^+$ 336.1230, found 336.1236.

*(±)-Methyl 3-(2H-1,3-benzodioxol-5-yl)-7-(benzyloxy)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11f**).* Reaction time: 6 h. Yield: 55% (121 mg, 0.274 mmol). Brown amorphous solid. IR (film) 3313, 1731, 1597, 1126 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.05 (ddd, J = 1.2, 7.0, and 10.6 Hz, 1H), 3.32 (ddd, J = 1.2, 8.9, and 11.6 Hz, 1H), 3.54−3.63 (m, 1H), 3.72 (s, 3H), 4.74 (d, J = 6.7 Hz, 1H), 5.12 (s, 2H), 5.92 (s, 2H), 6.70 (s, 1H), 6.73−6.74 (m, 2H), 6.88 (dd, J = 2.4 and 8.8 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.32−7.51 (m, 5H), 7.66 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.8, 48.4, 52.2, 58.6, 71.2, 101.2, 103.1, 108.2, 112.0, 112.4, 117.9, 121.1, 124.8, 127.7, 127.9, 128.7, 136.6, 137.9, 143.9, 147.0, 148.3, 153.7, 175.0. HRMS (ESI, m/z) Calcd for $C_{27}H_{24}NO_5^+$ 442.1649, found 442.1630.

*(±)-Methyl 3-(6-bromo-2H-1,3-benzodioxol-5-yl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11g**).* Reaction time: 2 h. Yield: 70% (145 mg, 0.35 mmol). Brown oil. IR (film) 3399, 3055, 1730, 1478, 738 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.17 (dd, J = 5.6 and 14.4 Hz, 1H), 3.28−3.37 (m, 1H), 3.50−3.58 (m, 1H), 3.76 (s, 3H), 5.23 (d, J = 5.2 Hz, 1H), 5.91 (s, 2H), 6.41 (s, 1H), 7.04 (s, 1H), 7.11−7.15 (m, 2H), 7.24−7.26 (m, 1H), 7.49−7.52 (m, 1H), 7.84 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.6, 47.8, 52.2, 57.2, 101.8, 108.4, 111.7, 112.7, 114.3, 118.6, 118.8, 119.8, 121.5, 124.1, 134.8, 141.3, 142.1, 147.4, 147.9, 174.9. HRMS (ESI, m/z) Calcd for $C_{20}H_{17}{}^{79}BrNO_4$ 414.0335; $C_{20}H_{17}{}^{81}BrNO_4$ 416.0315, found 414.0326; 416.0307.

*(±)-Methyl 3-phenyl-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11h**).* Reaction time: 24 h. Yield: 12% (17.5 mg, 0.06 mmol). Yellow oil. IR (film) 3396, 1730, 1169, 742 cm^{-1}. ^1H NMR (250 MHz,

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$CDCl_3$) δ 3.15 (ddd, J = 1.3, 6.9, and 14.4 Hz), 3.40 (ddd, J = 1.3, 9.1, and 14.4 Hz, 1H), 3.67 (dt, J = 7.0 and J = 9.0 Hz, 1H), 3.76 (s, 3H), 4.85 (d, J = 6.7 Hz, 1H), 7.10−7.18 (m, 2H), 7.29−7.37 (m, 6H), 7.50−7.53 (m, 1H), 7.75 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 29.0, 48.6, 52.2, 58.6, 111.9, 118.2 119.0, 120.1, 121.6, 124.5, 127.5, 128.0, 129.0, 141.3, 142.8, 143.0, 175.1. HRMS (ESI, m/z) Calcd for $C_{19}H_{17}NNaO_2^+$ 314.1151, found 314.1132.

*(±)-Methyl 7-methoxy-3-phenyl-1H,2H,3H,4H-cyclopenta[b]-indole-2-carboxylate (**11i**).* Reaction time: 19 h. Yield: 8% (12.8 mg, 0.04 mmol). Brown oil. IR (film) 3411, 1733, 1214, 735 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.12 (dd, J = 6.8 and 14.3 Hz, 1H), 3.36 (dd, J = 8.9 and 13.2 Hz, 1H), 3.66 (dt, J = 8.9 and 13.1 Hz, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 4.83 (d, J = 6.6 Hz, 1H), 6.80 (dd, J = 2.4 and 8.8 Hz 1H), 6.98 (d, J = 2.3 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.23−7.37 (m, 5H), 7.62 (broad s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 48.7, 52.3, 56.2, 58.6, 101.5, 111.3, 112.5, 118.1, 124.8, 127.5, 128.1, 129.1, 136.4, 142.8, 144.0, 154.5, 175.1. HRMS (ESI, m/z) Calcd for $C_{20}H_{20}NO_3^+$ 322.1438, found 322.1422.

*(±)-Methyl 3-(4-nitrophenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11j**).* Reaction time: 24 h. Yield: 10% (16.8 mg, 0.05 mmol). Yellow oil. IR (film) 1732, 1519, 1346 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.19 (ddd, J = 1.6, 6.8, and 14.3 Hz, 1H), 3.42 (ddd, J = 1.5, 8.8, and 14.5 Hz, 1H), 3.65 (dt, J = 6.6 and 8.9 Hz, 1H), 3.78 (s, 3H), 4.99 (d, J = 6.6 Hz, 1H), 7.13−7.22 (m, 2H), 7.30−7.34 (m, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.53 (m, 1H), 7.75 (broad s, 1H), 8.19 (d, J = 8.7 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.9, 48.3, 52.5, 58.5, 112.1, 119.2, 119.3 120.5, 122.2, 124.4, 129.0, 141.1, 141.5, 147.5, 147.9, 150.5, 174.4. HRMS (ESI, m/z) Calcd for $C_{19}H_{17}N_2O_4^+$ 337.1183, found 337.1162.

*(±)-Methyl 3-(1,3-thiazol-2-yl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11k**).* Reaction time: 24 h. Yield: 5% (7.5 mg, 0.025 mmol). Brown oil. IR (film) 3405, 1733 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.15 (ddd, J = 1.4 Hz, J = 6.9 Hz, J = 14.3 Hz,1H), 3.39 (ddd, J = 1.5, 9.0, 14.4 Hz, 1H), 3.67 (dt, J = 6.9 Hz, 1H), 3.76 (s, 3H), 4.86 (d, J = 6.6 Hz, 1H), 7.10−7.54 (m, 6H), 7.74 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 29.1, 48.6, 52.3, 58.6, 111.9, 119.0, 120.1, 121.6, 127.5, 128.1, 128.3, 129.1, 141.4, 142.8, 143.0, 175.1. HRMS (ESI, m/z) Calcd for $C_{16}H_{14}KN_2O_2S^+$: 337.0408, found 337.0402.

*(±)-Methyl 3-(3,4-dimethoxyphenyl)-7-hydroxy-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11l**).* Reaction time: 6 h. Yield: 58% (106.4 mg, 0.289 mmol). Brown oil. IR (film) 3343, 1729, 1597, 1123, 791 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06 (ddd, J = 0.8, 3.6, and 10.7 Hz, 1H), 3.95 (ddd, J = 0.8, 4.5, and 11.7 Hz, 1H), 3.59−3.64 (m, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 4.76 (d, J = 3.5 Hz, 1H), 6.71(dd, J = 1.2 and 4.3 Hz, 1H), 6,75 (d, J = 0.8 Hz, 1H), 6.79−6.82 (m, 2H), 6.91 (d, J = 1.2 Hz, 1H), 7.13 (d, J = 4.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 48.4, 52.2, 56.2, 58.6, 103.9, 110.8, 111.0, 111.6, 112.4, 117.4, 120.2, 125.2, 135.1, 136.5, 144.6, 148.5, 149.5, 149.9, 175.1. HRMS (ESI, m/z) Calcd for $C_{21}H_{21}NNaO_5^+$ 390.1312, found 390.1308.

*(±)-Ethyl 7-bromo-3-(3,4,5-trimethoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11m**).* Reaction time: 5 h. Yield: 72% (165 mg, 0.348 mmol). Brown solid. mp 183−185 °C. IR (film) 3340, 1728, 1593, 1128, 795 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 3.02−3.11 (m, 1H), 3.30−3.40 (m, 1H), 3.58−3.67 (m, 1H) 3.75 (s, 6H), 3.83 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.76 (d, J = 7.0 Hz, 1H), 6.40 (s, 2H), 7.16−7.26 (m, 2H), 7.63 (s, 1H), 8.32 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.5, 28.9, 48.8, 56.3, 58.6, 60.9, 61.1, 104.7, 113.1, 113.3, 117.4, 121.6, 124.2, 126.1, 138.3, 140.0, 144.5, 153.6, 174.4. HRMS (ESI, m/z) Calcd for $C_{23}H_{24}BrNNaO_5^+$ 496.0730, found 496.0731.

*(±)-Methyl 7-(benzyloxy)-4-methyl-3-(3,4,5-trimethoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11n**).* Reaction time: 4 h. Yield: 70% (176 mg, 0.35 mmol). Brown oil. IR (film) 3345, 1732, 1595 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.13 (dd, J = 1.2, and 7.2 Hz, 1H), 3.26 (s, 3H), 3.27−3.28 (m, 1H), 3.59−3.63 (m, 1H), 3.75 (s, 3H), 3.78 (s, 6H), 3.84 (s, 3H), 4.77 (d, J = 1.2 Hz, 1H), 5.12 (s, 2H), 6.44 (s, 2H), 6.91 (dd, J = 1.1 and 4.4 Hz, 1H), 7.05 (d, J = 1.1 Hz, 1H), 7.13 (d, J = 4.4 Hz, 1H), 7.32 (t, J = 3.7 Hz, 1H), 7.37 (d, J = 3.7 Hz, 2H), 7.41 (d, J = 3.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 30.9, 48.5, 52.3, 56.4, 58.6, 61.1, 71.2, 103.0, 104.7, 110.4, 111.5, 115.9, 124.1, 127.7, 128.0, 128.7, 137.2, 137.5, 138.0, 138.7, 145.2, 153.4, 153.8, 175.2. HRMS (ESI, m/z) Calcd for $C_{30}H_{31}NNaO_6^+$ 524.2044, found 524.2048.

*(±)-Methyl 3-(3,4,5-trimethoxyphenyl)-1H,2H,3H,4H-cyclopenta-[b]indole-2-carboxylate (**11o**).* Reaction time: 6 h. Yield: 50% (92.2 mg, 0.25 mmol). Brown oil. IR (film) 3356, 1732, 1603 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.10 (ddd, J = 1.6, 7.4, and 11.2 Hz, 1H), 3.95 (ddd, J = 1.6, 9.0, and 12.3 Hz, 1H), 3.61−3.70 (m, 1H), 3.76 (s, 9H), 3.84 (s, 3H), 4.79 (d, J = 7.4 Hz, 1H), 6.44 (s, 2H), 7.12−7.16 (m, 2H), 7.29−7.33 (m, 1H), 7.49−7.53 (m, 1H), 8.07 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 29.2, 48.9, 52.2, 56.3, 58.6, 61.1, 104.8, 112.0, 117.9, 118.9, 120.0, 121.5, 124.4, 138.5, 141.4, 143.0, 153.6, 175.0. HRMS (ESI, m/z) Calcd for $C_{22}H_{23}NNaO_5$ 404.1468, found 404.1467.

*(±)-Methyl 7-(benzyloxy)-3-(3,4,5-trimethoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11p**).* Reaction time: 6 h. Yield: 75% (182.6 mg, 0.375 mmol). Brown oil. IR (film) 3328, 1731, 1138, 785 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.05 (dd, J = 7.3 and 13.8 Hz, 1H), 3.33 (dd, J = 9.2 and 14.1 Hz, 1H), 3.57−3.66 (m, 1H), 3.71 (s, 6H), 3.73 (s, 3H), 3.81 (s, 3H), 4.73 (d, J = 7.1 Hz, 1H), 5.10 (s, 2H), 6.40 (s, 2H), 6.86 (dd, J = 2.2 and 8.8 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.30−7.40 (m, 3H), 7.45−7.48 (m, 2H), 8.24 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.8, 48.6, 51.9, 55.9, 58.2, 60.6, 70.9, 102.6, 104.5, 111.6, 112.3, 117.2, 124.4, 127.4, 127.7, 128.4, 136.4, 136.7, 137.6, 138.3, 143.7, 153.2, 153.3, 174.8. HRMS (ESI, m/z) Calcd for $C_{29}H_{30}NO_6^+$ 488.2068, found 488.2056.

*(±)-Methyl 7-(benzyloxy)-3-[4-(benzyloxy)phenyl]-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**11q**).* Reaction Time: 6 h. Yield: 73% (183.6 mg, 0.365 mmol). Brown oil. IR (film) 3340, 1732, 1135, 788 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.03 (dd, J = 7.0 and 14.2 Hz, 1H), 3.27 (dd, J = 9.1 and 14.2 Hz, 1H), 3.50−3.59 (m, 1H), 3.68 (s, 3H), 4.97 (s, 2H), 5.06 (s, 2H), 6.80−6.89 (m, 3H), 7.02−7.10 (m, 4H), 7.28−7.46 (m, 10H), 7.58 (broad s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.6, 47.6, 51.9, 58.4, 69.9, 70.9, 102.7, 111.6, 112.2, 115.0, 117.4, 124.5, 127.4, 127.5, 127.7, 127.9, 128.4, 128.5, 128.8, 134.9, 136.3, 136.9, 137.7, 144.0, 153.3, 157.9, 174.8. HRMS (ESI, m/z) Calcd for $C_{33}H_{30}NO_4^+$ 504.2169, found 504.2195.

*Preparation of (±)-3-(3,4,5-Trimethoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylic acid (**12**).* To a solution of **11o** (76.2 mg, 0.2 mmol) in MeOH (10 mL) was added KOH (45 mg, 0.8 mmol, 4 equiv). The resulting mixture was stirred at room temperature for 19h. After that, the reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in ethyl acetate (20 mL) and washed with HCl 10% (1 × 25 mL), distilled H_2O (2 × 25 mL) and brine (1 × 25 mL), successively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give carboxylic acid **12**, in 93% yield (68.3 mg, 0.186 mmol), as a yellow solid. mp 240−242 °C. IR (film) 3353, 1695, 1606, 1243, 738 cm^{-1}. ^{1}H NMR (400 MHz, MeOD) δ 3.07(dd, J = 6.8 and 14.0 Hz, 1H), 3.38(dd, J = 6.8 and 14.0 Hz, 1H), 3.59−3.65 (m, 1H), 3.77 (s, 3H), 3.79 (s, 6H), 4.77 (d, J = 6.8 Hz, 1H), 6.58 (s, 2H), 7.01−7.08 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, MeOD) δ 29.9, 50.4, 56.7, 60.3, 61.2, 106.0, 112.9, 118.1, 119.4, 120.2, 121.9, 125.6, 138.2, 141.0, 143.3, 144.5, 154.9, 178.6. HRMS (ESI, m/z) Calcd for $C_{21}H_{21}NNaO_5^+$ 390.1312, found 390.1309.

*Preparation of (±)-[7-Methoxy-3-(4-methoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indol-2-yl]methanol (**13**).* To a solution of **11c** (38.6 mg, 0.11 mmol) in anhydrous dichlorometane (5 mL), at −78 °C, under nitrogen atmosphere, was added a solution of diisobutylaluminum hydride (DIBAL-H, solution 1.5 mol/L in toluene, 0.33 mmol). The reaction was stirred at the same temperature for 2h. After that, a saturated aqueous solution of sodium acetate was added into the reaction medium and the mixture was stirred for more 15 min. So, the reaction was diluted with ethyl ether (10 mL) and with a saturated solution of ammonium chloride. The resulting mixture was then stirred, at room temperature, for more 60 min. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the corresponding alcohol **13**, as viscous brown oil, with a yield >95% (34.8 mg, 0.107 mmol). IR (film) 3404, 1610, 1246, 735 cm^{-1}.

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^{1}H NMR (250 MHz, $CDCl_3$) δ 1.58 (br, 1H), 2.66 (dd, J = 5.6 and 14.1 Hz, 1H), 2.89−3.01 (m, 1H), 3.13 (dd, J = 8.2 and 14.0, 1H), 3.79 (s, 3H), 3.85 (s, 2H), 3.87 (s, 3H), 4.20 (d, J = 5.5 Hz, 1H), 6.78 (dd, J = 2.5 and 8.8 Hz, 1H), 6.84 (d, J = 8.6 Hz 2H), 6.98 (d, J = 2.1 Hz, 1H), 7.09−7.16 (m, 3H), 7.59 (br, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 27.4, 47.5, 55.3, 55.9, 57.6, 65.9, 101.2, 110.7, 112.1, 114.1, 118.5, 124.9, 128.7, 135.8, 136.0, 145.1, 154.2, 158.5. HRMS (ESI, m/z) Calcd for $C_{20}H_{22}NO_3^+$ 324.1594, found 324.1626.

*Preparation of (±)-7-(Hydroxy)-3-(4-methoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylic acid (**14**).* To a solution of **11c** (0.07 g, 0.2 mmol) in a mixture methanol:H_2O (9:1, 5 mL) was added potassium hydroxide (KOH, 0.045 g, 0.08 mmol, 4 equiv). The resulting mixture was stirred at room temperature for 19 h. After that, the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and the organic phase was washed with HCl 10% (3 × 10 mL), distilled H_2O (4 × 20 mL) and brine (2 × 20 mL), successively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give carboxylic acid **14** in 93% yield (0.062g g, 0.18 mmol), as a brown solid. mp 96−97 °C. IR (film) 3353, 1704, 1606, 1248, 736 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 (br, 1H), 7.15 (d, J = 8.5 Hz, 3H), 6.97 (s, 1H), 6.77−6.85 (d, J = 8.6 Hz, 3H), 4.75 (d, J = 6.5 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.58−3.59 (m, 1H), 3.31−3.41 (m, 1H), 3.15 (dd, J = 6.7 and 14.2 Hz, 1H).^{13}C NMR (62.5 MHz, $CDCl_3$) δ 180.2, 159.1, 154.5, 144.1, 136.4, 134.6, 129.0, 124.8, 117.7, 114.5, 112.5, 111.3, 101.4, 58.4, 56.2, 55.5, 47.8, 28.7. HRMS (ESI, m/z) Calcd for $C_{20}H_{18}NO_4^-$ 336.1241, found 336.1239 (negative mode).

*Preparation of (±)-Methyl 7-(hydroxy)-N-methyl-3-(4-methoxyphenyl)-1H,2H,3H,4H-cyclopenta[b]indole-2-carboxylate (**15**).* To a stirred solution of **11d** (0.051 g, 0.12 mmol) in methanol (10 mL) was added Pd/C 10% (0.01 g). The reaction flask was corked with a rubber septum and the atmosphere was changed with nitrogen (3 times) and finally hydrogen. The reaction was then stirred under hydrogen atmosphere for 3h. After that, the mixture was filtered on a plug of silica and the solvent was removed to give **15**, as a gray solid (0.038 g, 0.113 mmol), in 94% yield. mp 91−92 °C. IR (film) 3465, 3397, 1716, 1245, 736 cm^{-1}. ^{1}H NMR [250 MHz, $(CD_3)_2CO$] δ 8.97 (bs, 1H), 7.19−7.26 (m, 3H), 6.93−7.01 (m, 3H), 6.72 (dd, J = 2.4 and 8.7 Hz, 1H), 6.53 (bs, 1H), 4.76 (d, J = 6.2 Hz, 1H), 3.87 (s, 1H), 3.80 (s, 3H), 3.56−3.71 (m, 1H), 3.30−3.41 (m, 1H), 3.11 (ddd, J = 1.2, 6.5, and 14.3 Hz, 1H). ^{13}C NMR [62.5 MHz, $(CD_3)_2CO$] δ 188.3, 180.1, 174.3, 165.9, 164.6, 158.3, 154.5, 146.9, 145.8, 143.6, 141.8, 139.9, 132.6, 87.6, 84.5, 81.1, 77.4, 57.6. HRMS (ESI, m/z) Calcd for $C_{20}H_{20}NO_4^+$ 338.1387, found 338.1377.

Biological Assays. *In Vitro Antiproliferative Assay. Cell Lines.* Human tumor cell lines U251 (glioma), UACC-62 (melanoma), NCI-H460 (lung, nonsmall cells), HT-29 (colon), PC-3 (prostate), 786-0 (kidney), NCI-ADR/RES (ovarian expressing multiple drugs resistance phenotype), OVCAR-3 (ovary) and K562 (leukemia) were obtained from National Cancer Institute at Frederick MA-USA.

Cell Culture. Stock cultures were grown in medium RPMI 1640 (GIBCO BRL) supplemented with 5% fetal bovine serum (FBS, GIBCO) and 100 U/mL penicillin, 100 μg/mL streptomycin at 37 °C with 5% CO_2.

Antiproliferative Assay. Cells in 96 well plates (100 μL cells/well) were exposed to **11a−e**, **11g−11k**, **11m**, **13**, **14**, **15** in concentrations 0.25, 2.5, 25, and 250 μg/mL in DMSO/RPMI at 37 °C, 5% of CO_2 in air for 48 h. Doxorubicin was used as positive control (0.025, 0.25, 2.5, and 25 μg/mL). Final DMSO concentration did not affect cell viability (0.1%). Afterward cells were fixed with 50% trichloroacetic acid and cell growth determined by spectrophotometric quantification (540 nm) of cellular protein content using sulforhodamine B assay1, 2).[38] The TGI (concentration that produces total growth inhibition or cytostatic effect) were determined through nonlinear regression analysis using the concentration−response curve for each cell line (Table 1) in software ORIGIN 8.0 (OriginLab Corporation).[39] Results were expressed in μM, as mean of two independent experiments performed in triplicate ± standard error.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01270.

Crystal data (CIF)

Copies of all NMR spectra (^{1}H and ^{13}C) of the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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