Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Liu, L. Wang, X. wang, L. Xu, Z. Hao and J. Xiao, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB01953F.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

DOI: 10.1039/C6OB01953F

Journal Name

ARTICLE

Fluorinated Alcohol-Mediated [4+3] Cycloaddition Reaction of Indolyl Alcohols with Cyclopentadiene

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jian Liu, Liang Wang, Xiaoxiao Wang, Lubin Xu, Zhihui Hao and Jian Xiao*

This paper describes an efficient [4+3] cycloaddition reaction of 3-indolylmethanols with cyclopentadiene in hexafluoroisopropanol, featuring catalyst-free, low cost, wide substrate scope and mild reaction condition. This methodology provides the first additive-free [4+3] cycloaddition reactions of indolyl alcohols, offering green and efficient methods for synthesis of cyclohepta[b]indole derivatives.

Introduction

Indole nucleus, known as a "privileged pharmacophore", is ubiquitous in a vast number of natural alkaloids, pharmaceuticals, agrochemicals as well as materials.[1] Among the family of indole derivatives, cyclohepta[b]indoles have distinguished themselves as core structural motifs in many natural products such as silicine (A)[2] and ervitsine (B).[3] Moreover, a variety of pharmacologically important agents contain this skeleton, such as A-FABP inhibitor (C),[4] antitubercular agent (D)[5] and SIRT1 inhibitor (E).[6]

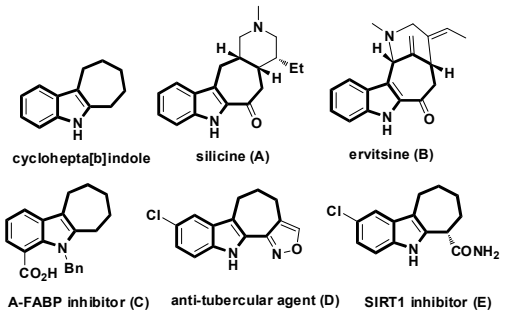


Figure 1. Representative compounds containing cyclohepta[b]indoles

In light of the biological importance of cyclohepta[b]indole derivatives and their application as potential therapeutics, the synthesis of these compounds have attracted great interest from the synthetic community and pharmaceutical industry. Notebly, much effort has been devoted to develop efficient synthetic methods for construction of the indole-fused seven-membered rings.[7] Recent progress has witnessed the [4+3] cycloaddition reactions as efficient protocols to build such seven-membered rings.[8] Quite recently, Tang reported a novel indole annulation/[4+3] cycloaddition sequence for the synthesis of various substituted cyclohepta[b]indoles via reaction of vinyl metal carbene with diene.[9] Inspired by $TiCl_4$-promoted [4+3] cycloadditions of 2-furfuryl alcohols with dienes,[10] Wu and co-workers developed the gallium(III) salts-catalyzed three-component [4+3] cycloadditions, furnishing a diverse library of cyclohepta[b]indole analogues in high yields.[11] Subsequently, a Ag(I)-catalyzed tandem hydroamination/[4+3] cycloaddition,[12a] boronic acid-catalyzed [4+3] cycloaddition of allylic alcohols with dienes[12b] as well as $ZnCl_2$-promoted reaction of heterocyclic alcohols with conjugated dienes[12c] were also developed to synthesize these significant frameworks. However, all these methods suffered from the employment of harsh reaction conditions, toxic acid catalysts, especially the transition metal catalysts, which are environmentally detrimental and troublesome in the final product purification, especially in pharmaceutical industries. Notably, the employment of metallic catalysts is indispensable in most cases, hence, it's highly desirable to develop mild condition, metal-free or even catalyst-free strategies for construction of cyclohepta[b]indole derivatives.

Fluorinated alcohols have distinguished themselves as magic solvents in organic synthesis with unique properties such as high H-bonding donor ability, high ionizing power and low nucleophilicity. These properties enable them to easily generate cationic intermediates with alcohols, thereby promoting reactions in the absence of acidic catalysts.[13-14] In addition to Friedel-Crafts alkylation, benzylation and acylation reaction,[14m-q] fluorinated alcohols also played significant roles in [3+2][15] and [4+3][16] cycloadditions of the aza-oxyallyl or diaza-oxyallyl cations with 1,3-disubstituted indoles and dienes. However, in these cycloaddition reactions, additional reagents or catalysts were still needed in addition to fluorinated alcohols. In the course of our research on fluorinated alcohol-mediated reactions, we developed an efficient trifluoroethanol (TFE)-mediated S_N1-type reaction of 3-indolylmethanols at room temperature, providing a green and efficient method for synthesis of diverse 3-indolyl substituted derivatives.[17a-b] We have also reported an asymmetric

College of Chemistry and Pharmaceutical Sciences, Qingdao Agricultural University, Qingdao, 266109, China. E-mail: chemjianxiao@163.com
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

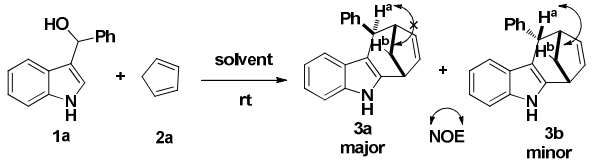
View Article Online
DOI: 10.1039/C6OB01953F

intermolecular α-alkylation of aldehydes in TFE.[17c] These works demonstrated that alkylideneindoleninium ions could be generated *in situ* from 3-indolylmethanols in fluorinated alcohols, which was dramatically different from the previous protocols under acidic conditions.[18] We surmised that the additive-free [4+3] cycloaddition of 3-indolylmethanols with dienes might be feasible with fluorinated alcohols as solvents. As our continuous work on fluorinated alcohol-mediated reactions,[17] herein we report the first catalyst-free [4+3] cycloaddition of 3-indolylmethanols with cyclopentadiene using hexafluoroisopropanol (HFIP) as a solvent at room temperature. The products could be easily obtained through straightforward evaporation of the solvent (bp 58 ℃) and simple purifications. This strategy features catalyst-free, mild reaction condition, low cost, wide substrate scope and convenient workup.

Results and discussion

Initially, cyclopentadiene **2a** and 3-indolylmethanol **1a** were selected as the model substrates to test our hypothesis. Gratifyingly, this reaction proceeded smoothly to afford the desired cycloaddition product **3a** in 81% yield and moderate diastereoselectivity (79:21) in HFIP after two hours at room temperature (Table 1, entry 1). The relative configuration of the major diastereomer of product **3a** was unambiguously determined by NOESY (see Supporting Information). The less acidic trifluoroethanol (TFE) could also promote this reaction, albeit with lower yield (Table 1, entry 2). Subsequently, various protonic solvents and aprotic solvents were examined, whereas no transformation was observed (Table 1, entries 3-8). Considering that hot water could act as "unqiue acid" to promote the reactions with alcohols,[14g,17] water was also evaluated as a solvent at 80 °C, however, only trace of product was detected (Table 1, entry 9). Interestingly, addition of catalytic acetic acid (20 mol%) to the water solution could furnish **3a** in moderate yield (Table 1, entry 10). However, the aqueous solution of HFIP (20 mol%) does not promote this reaction and the reactants remained intact (Table 1, entry 11), which might attribute to the disorderd hydrogen bonding.

Table 1. Optimization of reaction conditions[a]

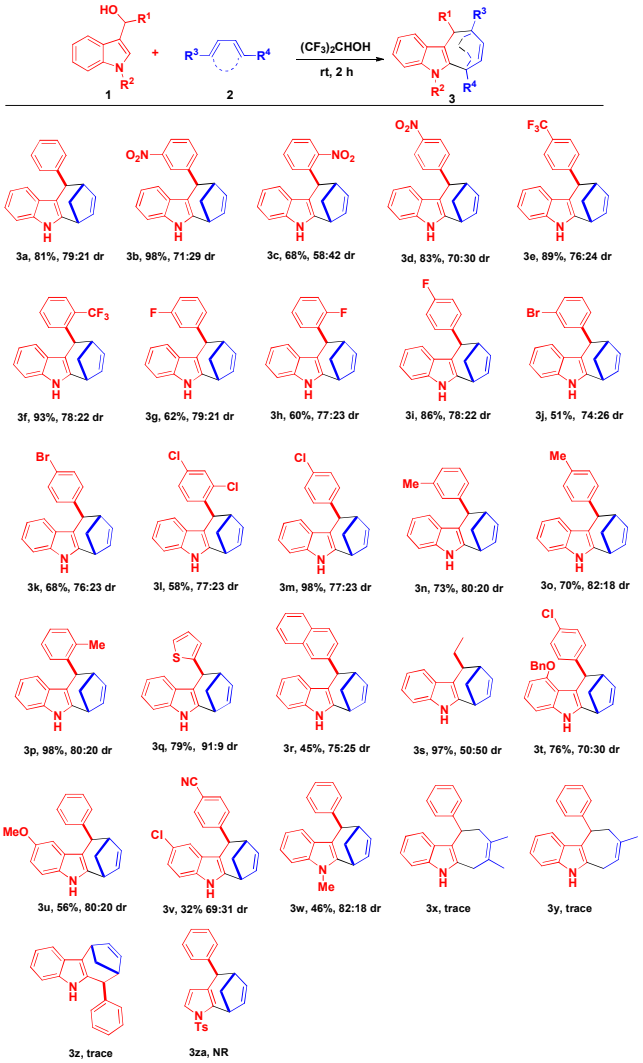


Entry	Solvent	Catalyst	Time (h)	Yield (%)[b]	Dr[c]
1	HFIP	-	2	81	79:21
2	TFE	-	2	53	70:30
3	IPA	-	24	N.R.	-
4	EtOH	-	24	N.R.	-
5	DCM	-	24	N.R.	-
6	DCE	-	24	N.R.	-
7	DMSO	-	24	N.R.	-
8	DMF	-	24	N.R.	-
9[d]	H_2O	-	24	trace	-
10	H_2O	20% HOAc	24	62	81:19
11[e]	H_2O	20% HFIP	24	N.R.	-
12[e]	AcOH	-	2	37	82:18

[a] Reaction conditions: 0.1 mmol of **1a**, 0.5 mmol of **2a**, 2 mL of solvent, at room temperature. [b] Isolated yield after column chromatography. [c] Dr was determined by ^{1}H NMR after purification. [d] Reaction was performed at 80 ℃. [e] Reaction was performed at 100 ℃.

Lastly, this reaction could proceed in acetic acid alone, albeit with lower yield (Table 1, entry 12). Hence, HFIP was shown to be the optimal solvent in terms of yield and reaction efficiency.

With the optimized reaction condition in hand, a variety of electronically and sterically diverse 3-indolylmethanols were subjected to this reaction to investigate the generality of this protocol (Scheme 1). At the outset, the generality for the aryl substituent of (1*H*-indol-3-yl)(aryl)methanols **1** was evaluated (Scheme 1, **3a-3r**). Both the electron-withdrawing groups (**3b-3m**) and electron-donating groups (**3n-3p**) on the phenyl ring were all well tolerated, providing the corresponding products in good to excellent yields. All the (1*H*-indol-3-yl)(aryl)methanols bearing *ortho*, *para* and *meta*-substituted phenyl groups and even 2,4-disubstituted phenyl group were ideal reaction partners with different reactivity. In term of the nitro substituted substrates, the highest yield could be achieved with nitro group substituted at *meta* position (**3b**), whereas the substrates substituted at *ortho* and *para* positions only gave the lower yield (**3c**, **3d**), which might be



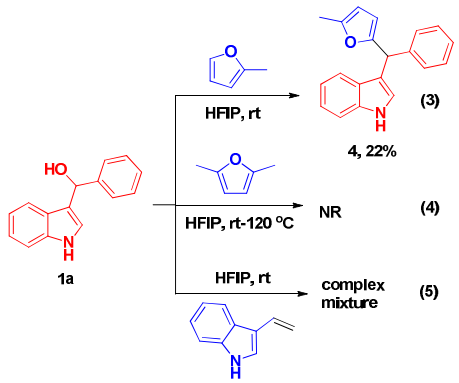
Scheme 1. Substrate scope of [4+3] cycloaddition reaction of 3-indolylmethanols with dienes. Reaction conditions: 0.1 mmol of **1**, 0.5 mmol of **2** in 2 mL of HFIP at room temperature.

View Article Online
DOI: 10.1039/C6OB01953F

ascribed to the strong destabilization of the cationic intermediate by nitro group. As to other substituents, e.g. fluoro, chloro, methyl, etc., however, the impacts of the types and positions on the yields were perplexing. In addition to phenyl groups, other heteroaryl substituents such as thienyl group as well as 2-naphthyl group, were also well tolerated, furnishing **3q** and **3r** in 79% and 45% yields, respectively. Moreover, the alkyl substituted 3-indolylmethanol was also ideal precursor for this transformation, giving rise to **3s** in 97% yield.

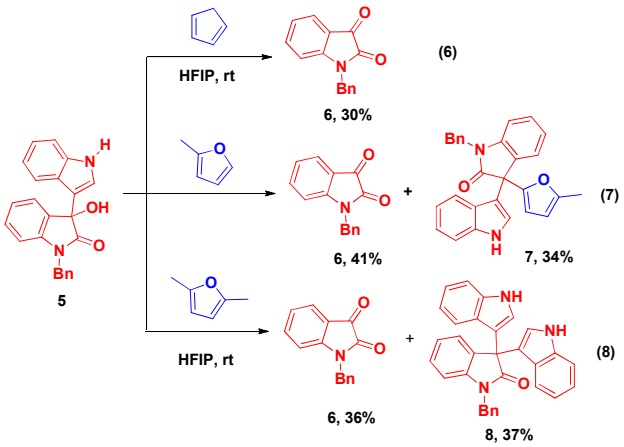
The impact of the substituents on indole ring on the yields was investigated subsequently. The substrates with electron-donating groups (**3t-3u**) on the indole moieties furnished the desired products in good yields, while in sharp contrast, product 3v was only obtained in 32% yield with chloro substituent. Protection of N-H with methyl group resulted in lower yield (3w) compared with unprotected 3-indolylmethanol (**3x**), which might be ascribed to the increased steric hindrance by introduction of methyl group. In addition to cyclopentadiene, other conjugate linear dienes were also subjected to this reaction, however, only trace of products were observed (**3x-3z**). Finally, the substrate with a pyrrole moiety instead of an indole was examined, however, the reaction did not proceed at all.

Afterwards, mono- and di-substituted furans and Indole-derived diene were employed as substrates to examine the feasibility of this reaction (Scheme 2). When 2-methylfuran was subjected to this reaction, only Friedel–Crafts product **4** was isolated (Scheme 2, eq 3), and no reaction was observed for 2,5-dimethylfuran, even increasing the reaction temperature (Scheme 2, eq 4). Reaction of **1a** with Indole-derived diene produced complex mixture at room temprature (Scheme 2, eq 5).



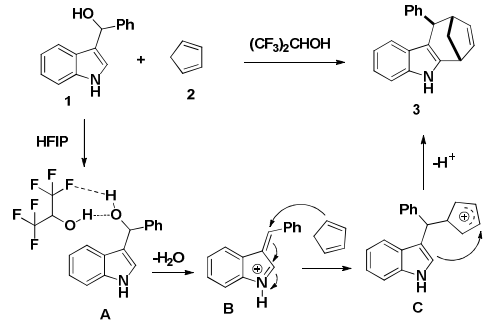
Scheme 2. Substituted furan and Indole-derived diene were used as substrates

Next, isatin-derived 3-indolylmethanol **5** was also tested for this reaction. Surprisingly, subjection of isatin-derived 3-indolylmethanol **5** to the reaction resulted in retro-addition product to afford benzyl protected-isatin **6** instead of the desired cyclization product (Scheme 3, eq 6). Similarly, reaction of 2-methylfuran with **5** produced **6** and Friedel–Crafts product **7** in 41% and 34% yields, respectively. When 2,5-dimethylfuran was employed as substrate, in addition to retro-addition product **6** was isolated in 36% yield, product 8 could also be obtained in 37% yield.



Scheme 3. Isatin-derived 3-indolylmethanol were used as substrates

On the basis of the above observations, a plausible mechanism is outlined to account for the [4+3] cycloaddition reaction (Scheme 4). Dual H-bonds are formed between HFIP and 3-indolylmethanol **1** as shown in intermediate **A**.[20] One is H-bonding interactions between positively charged hydroxylic hydrogen in HFIP and the negatively charged oxygen of the departing OH group, and the other is between the negatively charged fluorine atom and the positively charged hydrogen of the departing OH moiety. The dual H-bonding interactions renders HFIP a complementary charge template, leading to the decrease of the reaction barrier and stabilization of the transition state.[19c] The electron density of the oxygen of the departing OH moiety can be decreased via the dual H-bonding interactions, resulting in the significantly weakened C-O bond. Alkylideneindoleninium intermediate **B** can be generated via C-O bond cleavage, which is stabilized by the hydrogen bonding network of HFIP. As manifested by the previous work,[10-11] the following stepwise [4+3] cyclization might be initiated by the nucleophilic addition of cyclopentadiene to the alkylideneindoleninium intermediate **B**, producing intermediate **C**, which is followed by the intramolecular Friedel-Crafts alkylation reaction to furnish product **3**.



Scheme 4. Proposed mechanism of [4+3] cycloaddition reaction in HFIP.

Conclusions

In summary, we have developed a novel and efficient [4+3] cycloaddition reaction of 3-indolylmethanols with cyclopentadiene in HFIP, which features catalyst-free, low cost, wide substrate scope and mild reaction condition. This

View Article Online
DOI: 10.1039/C6OB01953F

methodology provides the first catalyst-free and additive-free [4+3] cycloaddition reactions of indolyl alcohols, offering green and efficient methods for synthesis of cyclohepta[b]indole derivatives.

Experimental

General Method for Preparation of Cyclohepta[b]indoles:

To a 25 mL pressure tube equipped with a magnetic stirrer bar were added HFIP (2 mL), 3-indolylmethanol **1a** (0.1 mmol) and cyclopentadiene **2a** (0.5 mmol). The mixture was then stirred at room temperature. Reaction was monitored by TLC until 1a was consumed up. The solvent was then removed in vacuo and the residue was purified by column chromatography on silica gel to afford the desired product **3a**.

10-Phenyl-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta-[b]indole (3a)

White solid; yield 81%; 79:21 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 141.5, 140.8, 140.7, 140.5, 140.0, 134.9, 132.4, 130.9, 128.6, 128.5, 128.4, 128.3, 128.0, 126.1, 126.1, 120.5, 120.3, 119.5, 119.3, 118.8, 118.6, 110.7, 110.62, 106.9, 105.6, 48.9, 47.7, 44.4, 43.4, 42.3, 39.0, 39.0, 37.6; HRMS (ESI) calcd for $[M+H]^+$ 272.1361, found 272.1368.

10-(3-Nitrophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclo-hepta[b]indole (3b).

Brown solid, yield 98%, 71:29 dr.; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 189.9, 148.7, 148.5, 147.8, 144.0, 141.8, 141.1, 140.7, 135.1, 134.8, 134.7, 132.0, 130.5, 129.9, 129.4, 129.0, 128.7, 128.1, 127.7, 124.6, 123.5, 123.4, 121.6, 121.5, 121.0, 120.8, 119.9, 119.7, 118.2, 118.1, 111.1, 111.0, 105.5, 104.3, 48.8, 47.4, 44.5, 43.1, 42.2, 39.0, 38.9, 37.5; HRMS (ESI) calcd for $[M+H]^+$ 317.1212, found 317.1219.

10-(2-Nitrophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclo-hepta[b]indole (3c).

Brown solid; yield 68%; 58:42 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 162.7, 150.1, 149.4, 141.4, 141.0, 141.0, 140.0, 139.7, 135.7, 135.1, 134.7, 133.0, 132.8, 132.2, 131.6, 130.6, 127.9, 127.5, 127.3, 127.2, 125.0, 124.3, 120.9, 120.8, 119.8, 119.7, 118.1, 118.1, 110.9, 106.3, 104.8, 47.4, 45.4, 44.7, 39.2, 38.9, 38.1, 38.0, 37.7; HRMS (ESI) calcd for $[M+H]^+$ 317.1212, found 317.1218.

10-(4-Nitrophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclo-hepta[b]indole (3d).

Yellow solid; yield 83%; 70:30 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 153.1, 149.8, 146.8, 146.7, 141.6, 141.0, 140.7, 135.0, 134.7, 132.0, 130.0, 129.4, 129.2, 128.1, 127.7, 123.9, 123.6, 121.0, 120.9, 119.9, 119.8, 118.3, 118.1, 111.0, 105.6, 104.4, 48.8, 47.4, 44.5, 43.4, 42.5, 39.1, 39.0, 37.7; HRMS (ESI) calcd for $[M+H]^+$ 317.1212, found 317.1219.

10-(4-(Trifluoromethyl)phenyl)-5,6,9,10-tetrahydro-6,9-methanocyclohepta[b]indole (3e).

Yellow solid; yield 89%; 76:24 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 149.5, 145.8, 141.1, 141.0, 140.4, 135.0, 132.1, 130.4, 128.8, 128.7, 128.6, 128.5, 128.3, 128.3, 128.0, 127.9, 127.8, 125.6, 125.4, 125.4, 125.4, 125.3, 125.1, 125.0, 125.0, 125.0, 123.4, 120.8, 120.6, 119.7, 119.6, 118.5, 118.3, 110.9, 105.9, 104.7, 48.8, 47.5, 44.4, 43.2, 42.3, 39.0, 38.9, 37.6, 27.0; HRMS (ESI) calcd for $[M+H]^+$ 340.1235, found 340.1227.

10-(2-(Trifluoromethyl)phenyl)-5,6,9,10-tetrahydro-6,9-methanocyclohepta[b]indole (3f).

White solid; yield 93%; 78:22 dr.; ^{1}H NMR(500 MHz, $CDCl_3$) *δ* 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 144.1, 140.6, 140.5, 140.3, 140.3, 139.6, 134.9, 134.7, 132.6, 131.9, 131.3, 131.1, 130.7, 130.5, 128.4, 128.2, 128.0, 127.9, 127.7, 126.3, 126.2, 126.1, 126.1, 125.7, 125.7, 125.6, 125.6, 124.1, 121.9, 120.7, 120.5, 119.6, 119.5, 118.2, 110.8, 107.5, 105.8, 47.5, 46.1, 44.9, 38.9, 38.8, 38.1, 37.1; HRMS (ESI) calcd for $[M+H]^+$ 340.1235, found 340.1226.

10-(3-Fluorophenyl)-5,6,9,10-tetrahydro-6,9-methanocyclo-hepta[b]indole (3g).

Brown solid; yield 62%; 79:21 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* =

View Article Online
DOI: 10.1039/C6OB01953F

4.5 Hz, 1H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 164.1, 163.9, 162.1, 161.9, 148.2, 148.2, 144.5, 144.4, 140.9, 140.8, 140.8, 140.2, 134.9, 134.6, 132.4, 132.2, 131.0, 130.6, 129.7, 129.7, 129.4, 129.3, 128.9, 128.4, 128.01, 124.1, 124.1, 124.0, 124.0, 120.6, 120.5, 119.6, 119.5, 118.6, 118.4, 115.4, 115.2, 115.2, 115.0, 113.1, 113.1, 113.0, 112.9, 110.8, 106.3, 105.1, 48.8, 47.5, 44.5, 43.2, 42.2, 39.0, 38.9, 37.7; HRMS (ESI) calcd for $[M+H]^+$ 290.1267, found 290.1257.

10-(2-Fluorophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta[b]indole (3h).

Brown solid; yield 60%; 77:23 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 162.1, 160.2, 141.4, 141.3, 140.6, 140.1, 134.9, 134.6, 132.3, 131.9, 131.8, 131.0, 130.9, 130.5, 130.5, 130.3, 130.2, 128.9, 128.3, 127.9, 127.7, 127.6, 127.5, 123.9, 123.9, 123.4, 123.4, 120.6, 120.4, 119.6, 119.4, 118.6, 118.4, 115.0, 114.9, 110.7, 105.5, 104.3, 46.7, 45.0, 44.1, 39.0, 38.8, 38.0, 35.3, 35.2; HRMS (ESI) calcd for $[M+H]^+$ 290.1267, found 290.1258.

10-(4-Fluorophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta[b]indole (3i).

Brown solid; yield 86%; 78:22 dr.; ^{1}H NMR(500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 160.5, 141.0, 140.9, 140.8, 140.8, 140.8, 140.1, 137.1, 137.1, 134.9, 134.6, 132.4, 132.3, 131.0, 130.7, 129.9, 129.8, 129.7, 129.7, 128.9, 128.4, 128.1, 120.6, 120.4, 119.6, 119.4, 118.6, 118.4, 115.2, 115.0, 114.8, 114.7, 110.8, 106.7, 105.4, 48.9, 47.7, 44.4, 42.6, 41.6, 38.9, 38.9, 37.5; HRMS (ESI) calcd for $[M+H]^+$ 290.1267, found 290.1258.

10-(3-Bromophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclo-hepta[b]indole (3j).

Brown solid; yield 51%; 74:26 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 144.2, 141.1, 140.9, 140.9, 140.3, 135.0, 134.7, 132.3, 131.6, 131.4, 130.6, 130.1, 129.7, 129.4, 129.4, 128.4, 128.1, 127.3, 127.1, 122.7, 122.3, 120.8, 120.6, 119.8, 119.6, 118.65, 118.5, 110.8, 106.2, 104.9, 48.9, 47.6, 44.6, 43.2, 42.2, 39.1, 39.0, 37.7; HRSM (ESI) calcd for $[M+H]^+$ 350.0466, found 350.0475.

10-(4-Bromophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclo-hepta[b]indole (3k).

Brown solid; yield 68%; 76:23 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (m, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 141.0, 140.9, 140.9, 140.6, 140.3, 135.0, 134.7, 132.3, 131.5, 131.2, 130.60, 130.4, 130.2, 128.4, 128.1, 120.8, 120.6, 119.9, 119.9, 119.7, 119.6, 118.7, 118.5, 110.8, 110.8, 106.3, 105.1, 48.9, 47.6, 44.5, 42.9, 41.9, 39.1, 38.9, 37.6; HRMS (ESI) calcd for $[M+H]^+$ 350.0466, found 350.0475.

10-(2, 4-Dichlorophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta[b]indole (3l).

Yellow solid; yield 58%; 77:23 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 141.3, 140.6, 140.0, 134.9, 134.4, 132.4, 132.2, 131.4, 129.4, 127.9, 127.0, 120.8, 119.7, 118.2, 110.8, 104.5, 45.7, 39.1, 38.8, 37.8, 31.6, 22.7, 14.1; HRMS (ESI) calcd for $[M+H]^+$ 340.0582, found 340.0576.

10-(4-Chlorophenyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclo-hepta[b]indole (3m).

Yellow solid; yield 98%, 77:23 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 143.9, 141.0, 140.9, 140.9, 140.3, 140.11, 135.0, 134.7, 132.3, 131.8, 131.1, 131.0, 130.6, 129.9, 129.8, 129.6, 128.6, 128.4, 128.3, 128.1, 120.7, 120.6, 119.7, 119.6, 118.7, 118.5, 110.9, 110.8, 106.4, 105.2, 48.9, 47.7, 44.5, 42.9, 41.8, 39.0, 38.9, 37.6; HRMS (ESI) calcd for $[M+H]^+$ 306.0971, found 306.0963.

10-(M-tolyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta-[b]indole (3n).

Brown solid; yield 73%; 80:20 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 140.4, 139.6, 139.5, 139.4, 138.8, 136.7, 136.3, 133.9, 133.5, 131.4, 131.3, 129.9, 129.9, 128.1, 128.0, 127.8, 127.6, 127.3, 127.1, 126.7, 125.8, 125.8, 124.5, 124.4, 119.4, 119.2, 118.4, 118.2, 117.8, 117.6, 109.5, 105.9, 104.6, 47.9, 46.7, 43.4, 42.4, 41.2, 37.9, 37.9, 36.6, 20.5, 18.2; HRMS (ESI) calcd for $[M+H]^+$ 286.1517, found 286.1525.

10-(P-tolyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta-[b]indole (3o).

View Article Online
DOI: 10.1039/C6OB01953F

Brown solid; yield 70%; 82:18 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J*= 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 139.7, 139.6, 139.4, 138.8, 137.3, 134.4, 133.9, 133.5, 131.4, 129.9, 128.0, 127.6, 127.6, 127.3, 127.2, 119.4, 119.2, 118.4, 118.2, 117.8, 117.5, 109.6, 106.0, 104.7, 48.0, 46.7, 43.4, 42.0, 40.8, 38.0, 37.9, 36.6, 20.0; HR MS (ESI) calcd for $[M+H]^+$ 286.1517, found 286.1525.

10-(O-tolyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta-[b]indole (3p).

Brown solid; yield 98%; 80:20 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 140.4, 139.6, 139.5, 139.4, 138.8, 136.7, 136.3, 133.9, 133.5, 131.4, 131.3, 129.9, 128.1, 128.0, 127.9, 127.8, 127.6, 127.3, 127.1, 126.8, 125.8, 125.8, 124.5, 124.4, 119.3, 119.2, 118.3, 118.2, 117.8, 117.6, 109.5, 105.9, 104.6, 47.9, 46.7, 43.4, 42.4, 41.2, 37.9, 37.9, 36.6, 20.5, 18.2; HRMS (ESI) calcd for $[M+H]^+$ 286.1517, found 286.1524.

10-(Thiophen-2-yl)-5, 6, 9, 10-tetrahydro-6,9-methanocyclo-hepta[b]indole (3q).

Black solid; yield 79%; 91:9 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.8, 140.1, 139.2, 133.7, 131.3, 130.8, 130.1, 129.9, 127.8, 127.4, 125.5, 125.2, 123.5, 123.4, 122.2, 122.0, 119.5, 119.4, 118.5, 118.4, 117.7, 117.4, 109.6, 105.2, 64.6, 48.2, 38.0, 37.6, 36.5, 29.6, 18.2, 12.7; HRMS (ESI) calcd for $[M+H]^+$ 278.0925, found 278.0916.

10-(Naphthalen-1-yl)-5, 5a, 6, 9, 10, 10a-hexahydro-6, 9-methanocyclohepta[b]indole (3r)

White solid; yield 45%; 75:25 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.68 (dd, *J* = 8.2, 4.4 Hz, 1H), 7.64 (s, 1H), 7.47 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.85 (dd, *J* = 11.0, 3.8 Hz, 1H), 6.50 (dd, *J* = 5.5, 2.8 Hz, 1H), 6.45 (dd, *J* = 5.4, 2.7 Hz, 1H), 6.08 (dd, *J* = 5.4, 3.0 Hz, 1H), 5.37 (dt, *J* = 8.7, 4.3 Hz, 1H), 4.60 (d, *J* = 4.9 Hz, 1H), 4.17 (s, 1H), 3.49 (dd, *J* = 4.3, 2.9 Hz, 1H), 3.44 (dt, *J* = 6.9, 3.5 Hz, 1H), 3.31 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.01 (dd, *J* = 7.9, 4.5 Hz, 1H), 2.51 – 2.44 (m, 1H), 2.31 (d, *J* = 9.6 Hz, 1H), 2.27 (d, *J* = 10.1 Hz, 1H), 2.01 (dt, *J* = 9.9, 4.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.86, 140.81, 140.77, 140.59, 140.00, 134.97, 134.60, 133.69, 133.54, 132.46, 132.37, 132.31, 130.87, 128.61, 128.28, 127.94, 127.87, 127.79, 127.59, 127.57, 127.47, 127.42, 127.33, 126.71, 126.48, 125.74, 125.60, 125.21, 125.11, 120.53, 120.36, 119.54, 119.41, 118.80, 118.66, 110.64, 110.61, 106.77, 105.51, 48.75, 47.83, 44.50, 43.59, 42.50, 39.06, 38.99, 37.69. HRMS (ESI) calcd for $[M+H]^+$ 323.1674, found 323.1628.

10-Ethyl-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta[b]-indole (3s).

White solid; yield 97%; 50:50 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 2H), 7.48 (m , 1H), 7.45 (m, 1H), 7.20 (m, 2H), 7.04 (m, 4H), 6.42 (m, 1H), 6.28 (m, 1H), 5.85 – 5.77 (m, 2H), 3.27 (s, 1H), 3.22 (m, 2H), 3.06 (d, *J* = 11.2 Hz, 1H), 2.92 (s, 1H), 2.55 (d, *J* = 10.0 Hz, 1H), 2.36 (d, *J* = 4.6 Hz, 1H), 2.07 (t, *J* = 9.5 Hz, 2H), 1.98 (d, *J* = 9.3 Hz, 1H), 1.64 – 1.39 (m, 2H), 1.35 – 1.26 (m, 2H), 1.13 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 142.0, 141.5, 137.4, 137.2, 134.6, 133.4, 131.0, 130.9, 122.6, 122.5, 121.8, 121.1, 120.7, 113.3, 111.1, 111.0, 46.3, 44.5, 44.2, 41.6, 41.5, 40.9, 40.4, 30.4, 25.8, 15.0, 14.6; HRMS (ESI) calcd for $[M+H]^+$ 224.1361, found 224.1369.

10-(4-(Benzyloxy)phenyl)-5, 6, 9, 10-tetrahydro-6, 9-methano-cyclohepta[b]indole (3t).

Brown oil; yield 76%; 70:30 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 – 7.17 (m, 7H), 7.04 (dd, *J* = 15.0, 7.4 Hz, 2H), 6.90 (q, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 13.8 Hz, 1H), 6.42 (m, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 4.43 (s, 1H), 4.01 (s, 1H), 3.46 (s, 1H), 3.41 (s, 1H), 3.23 (s, 1H), 2.90 (d, *J* = 22.6 Hz, 1H), 2.44 (s, 1H), 2.28 – 2.23 (m, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.00 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 146.2, 142.5, 141.0, 139.4, 139.4, 139.0, 137.3, 137.2, 136.4, 136.0, 132.1, 131.9, 130.7, 130.5, 129.6, 128.2, 128.1, 128.0, 127.7, 127.5, 121.4, 121.2, 118.9, 118.6, 106.3, 104.9, 104.3, 104.2, 101.2, 101.0, 69.7, 69.6, 48.9, 47.1, 44.4, 43.1, 42.9, 39.0, 38.8, 36.7; HRMS (ESI) calcd for $[M+H]^+$ 412.1390, found 412.1382.

2-Methoxy-10-phenyl-5, 6, 9, 10-tetrahydro-6, 9-methanocyclo-hepta[b]indole (3u).

Brown oil; yield 46%, 82:18 dr.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 5H), 7.20 (s, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.88 (dd, *J* = 19.9, 13.3 Hz, 2H), 6.71 (d, *J* = 7.2 Hz, 1H), 6.45 (s, 1H), 6.39 (m, 1H), 6.03 (m, 1H), 5.38 (s, 1H), 4.44 (s, 1H), 4.02 (s, 1H), 3.76 (s, 3H), 3.64 (s, 1H), 3.59 (s, 1H), 3.23 (s, 1H), 2.93 (s, 1H), 2.25 – 2.20 (m, 1H), 2.17 (d, *J* = 9.9 Hz, 1H), 2.04 (m, *J* = 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 142.2, 141.6, 140.0, 139.4, 136.4, 136.1, 132.3, 130.9, 128.5, 128.4, 128.3, 127.9, 127.9, 126.1, 126.0, 120.0, 119.8, 119.0, 118.8, 118.7, 118.6, 108.8, 104.7, 48.9, 47.8, 44.3, 43.5, 42.3, 37.6, 37.0, 36.9; HRMS (ESI) calcd for $[M+H]^+$ 302.1467, found 302.1436.

4-(2-Chloro-5,5a, 6, 9, 10, 10a-hexahydro-6, 9-methanocyclohepta[b]indol-10-yl)benzonitrile (3v)

White solid; yield 32%; 69:31 dr ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.60 – 7.57 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 3.4 Hz, 1H), 7.21 (d, *J* = 3.4 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 7.01 (t, *J* = 2.0 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 1.9 Hz, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 6.49 (dd, *J* = 5.6, 2.8 Hz, 1H), 6.45 (dd, *J* = 5.4, 2.7 Hz, 1H), 6.05 (dd, *J* = 5.4, 3.0 Hz, 1H), 5.28 (dd, *J* = 5.6, 2.9 Hz, 1H), 4.43 (d, *J* = 4.9 Hz, 1H), 4.01 (s, 1H), 3.52 – 3.49 (m, 1H), 3.46 (dd, *J* = 4.2, 3.0

View Article Online
DOI: 10.1039/C6OB01953F

Hz, 1H), 3.21 (td, *J* = 4.9, 3.1 Hz, 1H), 2.89 (t, *J* = 3.2 Hz, 1H), 2.48 (dt, *J* = 9.7, 4.8 Hz, 1H), 2.27 – 2.23 (m, 1H), 2.09 (d, *J* = 10.3 Hz, 1H), 2.02 (dt, *J* = 16.0, 5.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 150.47, 146.83, 142.63, 142.55, 141.05, 140.41, 133.27, 132.96, 132.43, 132.18, 132.12, 130.27, 129.20, 129.16, 128.96, 128.85, 125.52, 125.37, 121.02, 120.86, 119.21, 119.13, 117.51, 117.41, 111.81, 111.77, 110.23, 110.16, 105.34, 104.14, 48.58, 47.20, 44.25, 43.20, 42.36, 38.92, 38.85, 37.33. HRMS (ESI) calcd for $[M+H]^+$ 332.1093, found 332.1052.

5-Methyl-10-phenyl-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohepta[b]indole (3w)

Brownness oil, yield 46%, 82:18 d. r.^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.30 – 7.23 (m, 5H), 7.20 (s, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.88 (dd, *J* = 19.9, 13.3 Hz, 2H), 6.71 (d, *J* = 7.2 Hz, 1H), 6.45 (s, 1H), 6.39 (m, 1H), 6.03 (m, 1H), 5.38 (s, 1H), 4.44 (s, 1H), 4.02 (s, 1H), 3.76 (s, 3H), 3.64 (s, 1H), 3.59 (s, 1H), 3.23 (s, 1H), 2.93 (s, 1H), 2.25 – 2.20 (m, 1H), 2.17 (d, *J* = 9.9 Hz, 1H), 2.04 (m, *J* = 4.9 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$) *δ* 145.49, 142.21, 141.64, 140.04, 139.42, 136.42, 136.06, 132.33, 130.85, 128.54, 128.41, 128.28, 127.92, 127.90, 126.05, 125.98, 120.03, 119.84, 118.96, 118.82, 118.71, 118.55, 108.79, 104.74, 48.91, 47.75, 44.32, 43.50, 42.33, 37.58, 37.02, 36.86 ; HRMS (ESI) calcd for $[M+H]^+$ 285.1517, found 285.1510.

Acknowledgements

We are grateful to the Natural Science Foundation of Shandong Province for Distinguished Young Scholars (JQ201604) and General Project (ZR2016BM07). Financial supports from Qingdao Special Research Foundation of Science and Technology (16-6-2-29-nsh) and Talents of High Level Scientific Research Foundation (Nos. 6631112323, 6631115015) of Qingdao Agricultural University are also gratefully acknowledged. We thank Prof Teck-Peng Loh (University of Science and Technology of China and Nanyang Technological University) for HRMS determination.

Notes and references

1 (a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875; (b) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.*, 2009, **48**, 9608; (c) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; (d) M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep.*, 2000, **17**, 175; (e) S. Hibino, T. Chozi, *Nat. Prod. Rep.*, 2001, **18**, 66.

2 A. Shafiee, A. Ahond, A. M. Bui, Y. Langlois, C. Riche, P. Potier, *Tetrahedron Lett*., 1976, **17**, 921

3 M. Andriantsiferana, R. Besselievre, C. Riche, H. P. Husson, *Tetrahedron. Lett*., 1977, **18**, 2587.

4 T. Barf, F. Lehmann, K. Hammer, S. Haile, E. Axen, C. Medina, J. Uppenberg, S. Svensson, L. Rondahl, T. Lundbaeck, *Bioorg. Med. Chem. Lett*., 2009, **19**, 1745.

5 E. Yamuna, R. A. Kumar, M. Zeller, K. J. R. Prasad, *Eur. J. Med. Chem*., 2012, **47**, 228.

6 A. D. Napper, J. Hixon, T. McDonagh, K. Keavey, J. F. Pons, J. Barker, W. T. Yau, P. Amouzegh, A. Flegg, E. Hamelin, R. J. Thomas, M. Kates, S. Jones, M. A. Navia, J. O. Saunders, P. S. DiStefano, R. Curtis, *J. Med. Chem*., 2005, **48**, 8045.

7 For reviews, see: (a) B. Robinson, *Chem. Rev*., 1969, **69**, 227; (b) M. Inman, C. J. Moody, *Chem. Commun*., 2011, **47**, 788. For examples, see: (c) M. C. Willis, G. N. Brace, I. P. Holmes, *Angew. Chem. Int. Ed*., 2005, **44**, 403; (d) J. Barluenga, A. Jiménez-Aquino, C. Valdés, F. Aznar, *Angew. Chem. Int. Ed*., 2007, **46**, 1529; (e) K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem. Int. Ed*., 2011, **50**, 1702; (f) C. Liu, R. A. Widenhoefer, *J. Am. Chem. Soc*., 2004, **126**, 10250; (g) J. R. Ragains, J. D.Winkler, *Org. Lett*., 2006, **8**, 4437; (h) A. C. Silvanus, S. J. Heffernan, D. J. Liptrot, G. Kociok-Kçhn, B. I. Andrews, D. R. Carbery, *Org. Lett*., 2009, **11**, 1175; (i) O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, A. E. Kaplun, I. V. Trushkov, M. Y. Melnikov, *Adv. Synth. Catal*., 2011, **353**, 1125.

8 (a) M. Harmata, *Chem. Commun*., 2010, **46**, 8886; (b) M. Harmata, *Acc. Chem. Res*., 2001, **34**, 595; (c) M. Harmata, *Adv. Synth. Catal*., 2006, **348**, 2297; (d) M. A. Battiste, P. M. Pelphrey, D. L. Wright, *Chem. Eur. J*., 2006, **12**, 3438.

9 D.-X. Shu, W.-Z. Song, X.-X. Li, W.-P. Tang, *Angew. Chem. Int. Ed*., 2013, **52**, 3237.

10 J. M. Winne, S. Catak, M. Waroquier, V. V. Speybroeck, *Angew. Chem. Int. Ed*., 2011, **50**, 11990.

11 X. Han, H. Li, R. P. Hughes, J. Wu, *Angew. Chem. Int. Ed*., 2012, **51**, 10390.

12 (a) J. Zhang, J. D. Shao, J.-J. Xue, Y.-X. Wang, Y. Li, *RSC Adv*., 2014, **4**, 63850; (b) K.-S. Cao, H.-X. Bian, W. H. Zheng, *Org. Biomol. Chem*., 2015, **13**, 6449; (c) W. Gong, Y. Liu, J. Zhang, Y. Jiao, J. Xue, Y. Li, *Chem. Asian J*., 2013, **8**, 546.

13 For reviews, see: (a) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett*., 2004, 18; (b) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis,* 2007, 2925; (c) T. Dohi, N. Yamaoka, Y. Kita, *Tetrahedron*, 2010, **66**, 5775; (d) T. Sugiishi, M. Matsugi, H. Hamamoto, H. Amii, *RSC Adv*., 2015, **5**, 17269; (e) J. Wencel-Delord, F. Colobert, *Org. Chem. Front*., 2016, **3**, 394.

14 For selected examples, see: (a) A. Berkessel, J. A. Adrio, *J. Am. Chem. Soc*., 2006, **128**, 13412; (b) D. Vuluga, J. Legros, B. Crousse, A. M. Z. Slawin, C. Laurence, P. Nicolet, D. Bonnet-Delpon, *J. Org. Chem.*, 2011, **76**, 1126; (c) A. Laskavy, L. J. W. Shimon, L. Konstantinovski, M. A. Iron, R. Neumann, *J. Am. Chem. Soc.*, 2010, **132**, 517; (d) N. V. Dubrovina, I. A. Shuklov, M. N. Birkholz, D. Michalik, R. Paciello, A. Börner, *Adv. Synth. Catal.*, 2007, **349**, 2183; (e) L. N. Wang, S. L. Shen, J. Qu, *RSC Adv.*, 2014, **4**, 30733; (f) D. Petruzziello, A. Gualandi, S.Grilli, P. G. Cozzi, *Eur. J. Org. Chem.,* 2012, 6697; (g) P. G. Cozzi, L. Zoli, *Angew. Chem. Int. Ed.*, 2008, **47**, 4162; (h) J. E. Rice, M. Fujiwara, P. Dubois, J. L. Hedrick, *Angew. Chem. Int. Ed.*, 2009, **48**, 5170; (i) M. Westermaier, H. Mayr, *Chem. Eur. J.*, 2008, **14**, 1638; (j) X. Mo, J. Yakiwchuk, J. Dansereau, J. Adam McCubbin, DG. Hall, *J. Am. Chem. Soc.*, 2015, **137**, 9694; (k) A.Volbeda, H. A. V. Kistemaker, H. S. Overkleeft, G. A. van der Marel, D. V. Filippov, J. D. C. Codée, *J. Org. Chem.*, 2015, **80**, 8796; (l) L.-R. Wen, T. He, M.-C. Lan, M. Li, *J. Org. Chem.*, 2013, **78**, 10617; (m) G. X. Li, J. Qu, *Chem. Commun.,* 2010, **46**, 2653; (n) P. Trillo, A. Baeza, C. Nájera, *J. Org. Chem.*, 2012, **77**, 7344; (o) Y. Tian, X. Xu, L. Zhang, J. Qu, *Org. Lett.,* 2016, **18**, 268; (p) H. F. Motiwala, R. H. Vekariya, J. Aubé, *Org. Lett.*, 2015, **17**, 5484; (q) P. A. Champagne, Y. Benhassine, J. Desroches, J.-F. Paquin, *Angew. Chem. Int. Ed.*, 2014, **53**, 13835.

15 (a) A. Acharya, D. Anumandla, C. S. Jeffrey, *J. Am. Chem. Soc*., 2015, **137**, 14858; (b) M. C. DiPoto, R. P. Hughes, J. Wu, *J. Am. Chem. Soc.*, 2015, **137**, 14861; (c) D.

View Article Online
DOI: 10.1039/C6OB01953F

Anumandla, A. Acharya, C. S. Jeffrey, *Org. Lett*., 2016, **18**, 476.

16 (a) D. Anumandla, R. Littlefield, C. S. Jeffrey, *Org. Lett*., 2014, **16**, 5112; (b) C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff, C. R. Carson, *J. Am. Chem. Soc*., 2011, **133**, 7688; (c) K. L. Barnes, A. K. Koster, C. S. Jeffrey, *Tetrahedron Lett*., 2014, **55**, 4690; (d) A. Acharya, J. A. Eickhoff, C. S. Jeffrey, *Synthesis*, 2013, **45**, 1825; (e) A. Acharya, J. A. Eickhoff, K. Chen, V. J. Catalano, C. S. Jeffrey, *Org. Chem. Front*., 2016, **3**, 330.

17 (a) H. Wen, L. Wang, L.-B. Xu, Z. Hao, C.-L. Shao, C.-Y. Wang, J. Xiao, *Adv. Synth. Catal.,* 2015, **357**, 4023; (b) J. Xiao, H. Wen, L. Wang, L. Xu, Z. -H. Hao, C.-L. Shao, C.-Y. Wang, *Green Chem*., 2016, **18**, 1032; (c) J. Xiao, K. Zhao, T. P. Loh, *Chem. Commun.*, 2012, **48**, 3548.

18 For reviews, see: (a) A. Palmieri, M. Petrini, R. R. Shaikh, Org. Bio*mol. Chem.,* 2010, **8**, 1259; (b) L. Wang, Y. Chen, J. Xiao, *Asian J. Org. Chem.,* 2014, **3**, 1036; (c) S. Zhu, L. Xu, Z Hao, L. Wang, J. Xiao, *Chin. Org. Chem.,* 2016, 36, 1229; (d) H. Wu, Y. He, F. Shi, *Synthesis*, 2015, **47**, 1990. For representative examples, see: (e) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.,* 2008, **47**, 8707; (f) J. Xiao, *Org. Lett.,* 2012, **14**, 1716; (g) J. Xiao, K. Zhao, T. P. Loh, *Chem. Asian J.,* 2011, **6**, 2890; (h) M.-H. Zhuo, Y.-J. Jiang, Y.-S. Fan, Y. Gao, S. Liu, S. Zhang, *Org. Lett.,* 2014, **16**, 1096; (i) X. Han, J. Wu, *Angew. Chem. Int. Ed.*, 2013, **52**, 4637; (j) B. Xu, Z. L. Guo, W. Y. Jin, Z. P. Wang, Y. G. Peng, Q. X. Guo, *Angew. Chem. Int. Ed.*, 2012, **51**, 1059; (k) C. Guo, J. Song, S.-W. Luo, L.-Z. Gong, *Angew. Chem. Int. Ed.,* 2010, **49**, 5558; (l) X.-X. Sun, B.-X. Du, H.-H. Zhang, L. Ji, F. Shi, *Chem. Cat. Chem.,* 2015, **7**, 1211; (m) F. Shi, H.-H. Zhang, X.-X. Sun, J. Liang, T. Fan, S.-J. Tu, *Chem. Eur. J.,* 2015, **21**, 3465; (n) W. Dai, H. Lu, X. Li, F. Shi, S.-J. Tu, *Chem. Eur. J.,* 2014, **20**, 11382; (o) Y. Liu, H.-H. Zhang, Y.-C. Zhang, Y. Jiang, F. Shi, S.-J. Tu, *Chem. Commun.,* 2014, **50**, 12054; (p) W. Tan, X. Li, Y.-X. Gong, M.-D. Ge, F. Shi, *Chem. Commun.,* 2014, **50**, 15901; (q) W. Tan, B.-X. Du, X. Li, X. Zhu, F. Shi, S.-J. Tu, *J. Org. Chem.,* 2014, **79**, 4635; (r) L.-J. Zhou, Y.-C. Zhang, J.-J. Zhao, F. Shi, S.-J. Tu, *J. Org. Chem.,* 2014, **79**, 10390; (s) X. Li, W. Tan, Y.-X. Gong, F. Shi, *J. Org. Chem.*, 2015, **80**, 1841. (a) P. G. Cozzi and L. Zoli, Green Chem., 2007, 9, 1292;

19 (a) R. Ben-Daniel, S. P. d. Visser, S. Shaik, R. Neumann, *J. Am. Chem. Soc.*, 2003, **125**, 12116; (b) A. Berkessel, Jens A. Adrio, D. Hüttenhain, J. M. Neudörfl, *J. Am. Chem. Soc.,* 2006, **128**, 8421; (c) S. P. d. Visser, J. Kaneti, R. Neumann, S. Shaik, *J. Org. Chem.,* 2003, **68**, 2903; (d) K. Neimann, R. Neumann, *Org. Lett.,* 2000, **2**, 2861.