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Synthesis of bis(indolyl)alkanes by a site-selective gold-catalyzed addition of indoles to butynol derivatives

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ABSTRACT

A new site-selective hydroarylation reaction of alkynes catalyzed by gold complexes and directed by an internal hydroxyl group has been developed. Thus, the treatment of 3-butyn-1-ol derivatives with indoles and a catalytic amount of an *in situ* formed cationic gold complex leads to the formation of bis(indolyl)alkane derivatives. Particularly interesting is the reaction with terminal alkynes as the double addition of the indol occurs at the terminal carbon of the triple bond. The reaction conditions are very mild and the final bis(indolyl)alkanes are obtained in high yields.

1. Introduction

A large variety of biologically active natural products contain the indole system as a central element of their structure [1]. More specifically, numerous bis(indolyl)alkanes have been isolated from several terrestrial and marine natural source and the range of biological activities possessed by individual members of this series includes coronary dilatory properties, genotoxicity and antibacterial activity [2]. However, the discovery of important anti-carcinogenic properties of some bis(indolyl)alkanes have brought to the forefront the importance of these compounds [3]. Thus, a significant effort from the synthetic community has been directed in recent years to the production of this kind of molecules. Almost all procedures described in the literature to access these compounds are based on the condensation reaction of indoles with aldehydes or ketones in the presence of protic or Lewis acids [4]. However, Echavarren et al. have recently published an interesting gold-catalyzed synthesis of bisindolyl derivatives by reaction of alkynes and indoles (Scheme 1) [5]. This process supposes a formal double addition of the indole to the alkyne. It is important to remark that this double addition of the indole always occurs at the internal carbon of the triple bond. Interestingly, when 4-pentyn-1-ol or 5-hexyn-1-ol are used as the alkyne counterpart, the corresponding tetrahydrofurane or tetrahydropyrane derivatives are obtained (Scheme 1) [6].

During our ongoing investigations on the development of new platinum and gold-catalyzed processes [7], we have found that bisindolyl derivatives are also available from alkynols derived from 3-butyn-1-ol. In contrast to those results found by Echavarren for terminal alkynes, the double addition of the indole occurs at the terminal carbon of the triple bond [8]. Details on this hydroxy-directed gold catalyzed double hydroarylation reaction of terminal and internal alkynes are given in this communication [9].

2. Results and discussion

We initiated our investigations with the reaction of terminal butynol derivative **1a** and *N*-methylindol **2** in the presence of a cationic gold(I) complex, *in situ* generated by reaction of 5 mol% of $(Ph_3P)AuCl$ and 5 mol% of $AgSbF_6$, in dichloromethane as solvent at room temperature (Table 1, entry 1). This reaction led to the formation of the bis(indolyl)alkane derivative **3a** in 77 yield. Surprisingly, compound **3a** was obtained as a single regioisomer and formation of the expected bis(indolyl)alkane where the addition of the indoles occurred at the internal carbon of the triple bond was not obtained [5]. This result is also in contrast to the results observed by Cheng et al. by using similar starting materials but platinum catalysts as they isolated tetrahydrofurane derivatives [6]. In view of this differential behaviour we further study the scope of the reaction by using a range of 3-butyn-1-ol derivatives **1a–f** (Table 1). In all cases we obtained the corresponding bis(indolyl)alkane **3** in high yield and as single regioisomers.

All these examples represent a clear example of site-selective carbon–carbon bond formation across terminal alkynes. However, much more challenging is the site-selectivity with internal alkynes and in particular in those cases where both substituents of the

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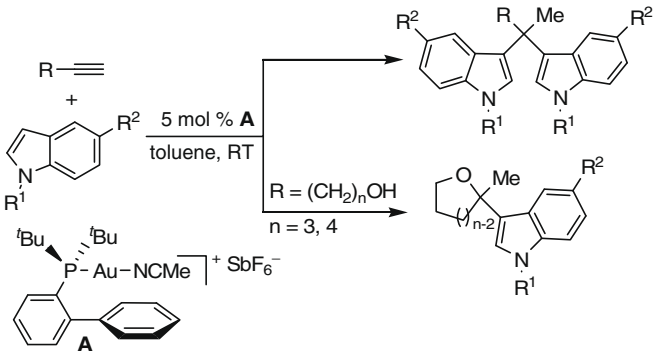
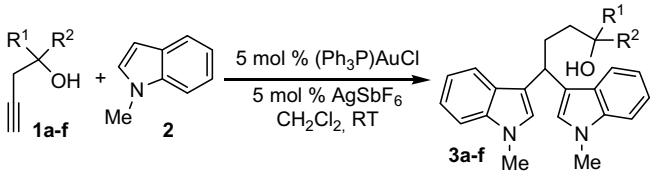


Scheme 1. Gold(I)-catalyzed reaction of indoles and alkynes (see Refs. [5,6]).

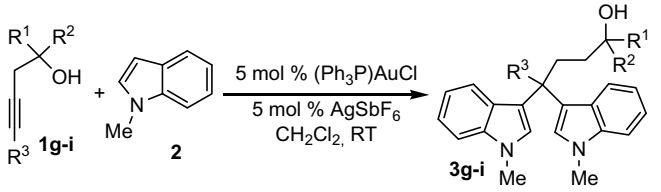
Table 1
Gold(I)-catalyzed reaction of 3-butyn-1-ol derivatives **1a-f** and indol **2**.



Entry	Alkynol	R^1	R^2	Product	Yield (%)[a]
1	**1a**	Me	H	**3a**	77
2	**1b**	^{i}Pr	H	**3b**	84
3	**1c**	Ph	H	**3c**	78
4	**1d**	$H_2C{=}CH(CH_2)_2$	Ph	**3d**	87
5	**1e**	Ph	Me	**3e**	70
6	**1f**	$-(CH_2)_5-$		**3f**	85

[a] Yield of isolated product **3** based on starting alkynol **1**.

Table 2
Gold(I)-catalyzed reaction of internal alkynol derivatives **1g–i** and indol **2**.

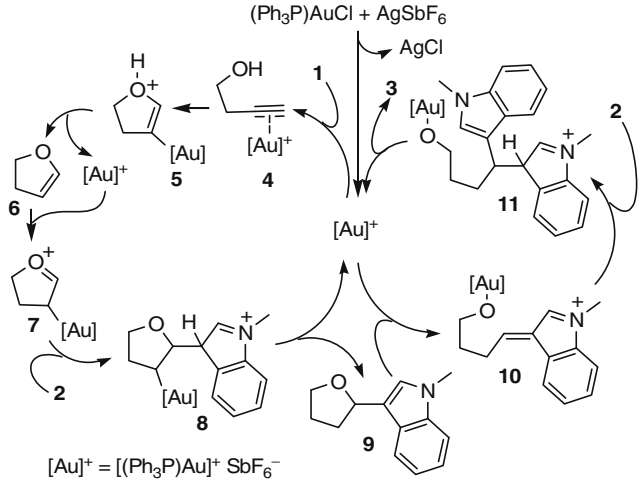


Entry	Alkynol	R^1	R^2	R^3	Product	Yield (%)[a]
1	**1g**	H	H	Me	**3g**	92
2	**1h**	Me	H	Bu	**3h**	87
3	**1i**	Me	H	$(CH_2)_2Ph$	**3i**	80

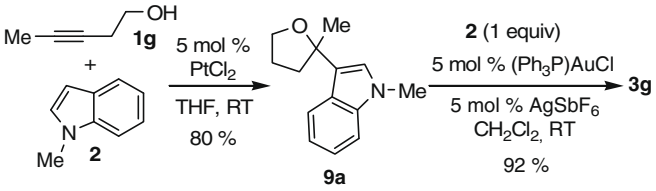
[a] Yield of isolated product **3** based on starting alkynol **1**.

triple bond are very similar. In order to check the regioselection across the internal alkyne in the above synthesis of bis(indolyl)alkane derivatives we performed a set of experiments with homopropargylic alcohols **1g–i** (Table 2). As shown, these reactions led to the corresponding products **3g–i** in high yield and most important as single regioisomers. In all cases, the new carbon–carbon bonds are formed at the site distal to the free hydroxyl group independently of the substitution on the alkyne.

A catalytic mechanism that explains the formation of products **3** is shown in Scheme 2. In first place, we suppose the formation of a reactive cationic gold complex from $(Ph_3P)AuCl$ by reaction with $AgSbF_6$.



Scheme 2. Mechanism of formation of bis(indolyl)alkane derivatives **3**. For clarity the substituents of the alkynol derivative are not considered.



Scheme 3. Isolation of intermediate **9a** and further reaction with indole **2** to give **3g**.

The first step of the catalytic cycle is the coordination of the metallic complex to the triple bond of the starting alkynol **1** to form intermediate **4**. Intramolecular addition of the hydroxyl group to the terminal carbon of the triple bond generates **5**. Protodemetallation of the latter affords the enol ether **6** and releases the catalytic species. After an initial coordination of the catalyst to the double bond of the enol ether **6**, the oxonium intermediate **7** is formed. Further nucleophilic attack of the indol **2** affords the intermediate **8** that evolves through aromatization and protodemetallation to give the tetrahydrofurane derivative **9**. Coordination of the gold complex to the oxygen of the tetrahydrofurane favours the opening of the tetrahydrofurane ring to form the intermediate **10**. A second nucleophilic attack of the indol **2** affords the intermediate **11** that after aromatization and protodemetallation steps gives rise to the final product **3** releasing the catalytic species.

The role of enol tetrahydrofurane **9** as an intermediate of the reaction is supported by the following experiment. 3-Pentyn-1-ol (**1g**) was treated with one equivalent of indol **2** in the presence of 5 mol% of $PtCl_2$ in THF under the conditions reported by Cheng et al. [6], to obtain the expected tetrahydrofurane derivative **9a** in 80% yield (Scheme 3). Compound **9a** was isolated and characterized and then reacted with **2** under our gold-catalyzed conditions previously described to give the bis(indolyl)alkane derivative **3g** in 92% yield.

3. Conclusions

Overall, a new site-selective hydroarylation reaction of alkynes catalyzed by gold complexes and directed by an internal hydroxyl group has been developed and applied to the synthesis of bis(indolyl)alkanes. Remarkably, when terminal alkynes are used the double addition of the indol occurs at the terminal carbon of the triple bond. When internal alkynes are used, the double addition occurs at the carbon distal to free hydroxyl group. The reaction conditions

are very mild, high yields are achieved and so, the methodology here described could be applied to the synthesis of biologically interesting bis(indolyl)alkanes. Moreover, we speculate that this site-selective strategy could be further exploited in other carbon–carbon bond-forming reactions.

4. Experimental

4.1. General consideration

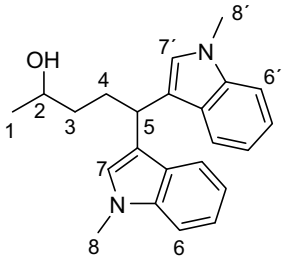
^{1}H NMR spectra were recorded on a Bruker AV-600 (600 MHz), Bruker AMX-400 (400 MHz) or Bruker DPX-300 (300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the residual solvent resonance as the internal standard ($CHCl_3$: δ 7.26, THF δ 3.58, 1.73, acetone δ 2.05). Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, dt: double triplet, ddd: double doublet of doublets, ddt: double doublet of triplets, t: triplet, td: triplet of doublets, m: multiplet), coupling constants (J in Hz), integration and assignment. ^{13}C NMR spectra were recorded on a Bruker AV-600 (150 MHz), Bruker AMX-400 (100 MHz) or Bruker DPX-300 (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$: δ 76.95, THF-d_8 δ 67.4, 25.3, acetone-d_6 δ 206.0, 29.8). High-resolution mass spectrometry was carried out on a Finnigan-Mat 95 spectrometer. All reactions were conducted in dried glassware under an inert atmosphere of argon. Solvent (dichloromethane) was dried over sodium hydride and was used freshly distilled.

4.2. General procedure for the synthesis of bis(indolyl)alkanes **3**

To a colorless solution of $(Ph_3P)AuCl$ (25 mg, 0.05 mmol) in dichloromethane (2 mL) at room temperature the corresponding butyn-1-ol **1** (1 mmol), and the indole **2** (289 mg, 2.2 mmol) were added. The mixture was cooled to 0 °C and $AgSbF_6$ (17 mg, 0.05 mmol) was added. The resulting slurry was warmed to room temperature and stirred until complete conversion (monitored by TLC). After removing of the solvent, the crude was purified by flash column chromatography on silica gel using hexane:ethyl acetate 2:1 as eluent to yield pure compounds **3**.

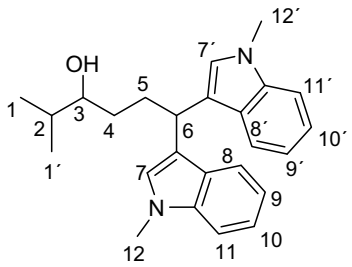
4.3. Spectral data for bis(indolyl)alkanes **3**

4.3.1. 5,5-Bis(1-methyl-1H-indol-3-yl)pentan-2-ol (**3a**)



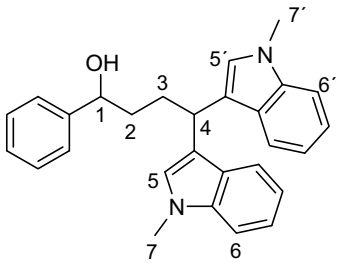
Colorless oil. R_f 0.05 (hexane:ethyl acetate, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.62 and 7.61 (2×d, J = 7.8 Hz, 2H; $H_{6,6'}$), 7.29–7.02 (m, 6H), 6.86 and 6.84 (2×s, 2H; $H_{7,7'}$), 4.47 (t, J = 7.4 Hz, 1H; H_5), 3.72–3.60 (m, 1H; H_2), 3.67 (s, 6H; $H_{8,8'}$), 2.37–2.16 (m, 2H; H_4), 1.62–1.49 (m, 2H; H_3), 1.14 (d, J = 6.1 Hz, 3H; H_1). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.1, 126.1, 121.1, 119.5, 118.3, 109.0, 68.1, 37.9, 33.75, 32.4, 32.2, 23.3. HRMS calcd. for $C_{23}H_{24}N_2$ $(M-H_2O)^+$ 328.1934, found 328.1929.

4.3.2. 6,6-Bis(1-methyl-1H-indol-3-yl)-2-methyl-hexan-3-ol (**3b**)



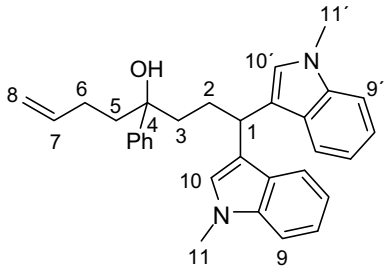
Colorless oil. R_f 0.06 (hexane:ethyl acetate, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 and 7.64 (2×d, J = 8.0 Hz, 2H; $H_{11,11'}$), 7.30(d, J = 8.0 Hz, 2H; $H_{8,8'}$), 7.22 (t, J = 7.6 Hz, 2H; $H_{10,10'}$), 7.07 (t, J = 7.6 Hz, 2H; $H_{9,9'}$), 6.91 and 6.87 (2×s, 2H; $H_{7,7'}$), 4.51 (t, J = 7.5 Hz, 1H; H_6), 3.74 and 3.73 (2×s, 6H; $H_{12,12'}$), 3.45 (dt, J = 7.8, 5.0 Hz, 1H; H_3), 2.50–2.18 (m, 2H), 1.74–1.43 (m, 3H), 0.89 and 0.88 (2×d, J = 6.8 Hz, 6H; $H_{1,1'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.2, 127.4, 127.3, 126.1, 126.1, 121.2, 119.6, 119.5, 119.0, 118.6, 118.3, 109.0, 33.8, 33.2, 33.1, 32.5, 32.5, 19.0, 16.8. HRMS calcd. for $C_{25}H_{30}N2O$ 378.2358, found 374.2359.

4.3.3. 4,4-Bis(1-methyl-1H-indol-3-yl)-1-phenylbutan-1-ol (**3c**)



Colorless oil. R_f 0.08 (hexane:ethyl acetate, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.64 and 7.61 (2×d, J = 7.8 Hz, 2H; $H_{6,6'}$), 7.45–7.20 (m, 9H), 7.13–7.05 (m, 2H), 6.84 and 6.81 (2×s, 2H; $H_{5,5'}$), 4.76 (t, J = 6.7 Hz, 1H; H_4), 4.54 (t, J = 7.4 Hz, 1H; H_1), 3.74 (s, 6H; $H_{7,7'}$), 2.48–2.33 (m, 1H), 2.31–2.16 (m, 1H), 2.08–1.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.5, 137.1, 128.2, 127.3, 126.1, 125.9, 121.1, 119.5, 118.5, 118.3, 108.9, 74.5, 37.4, 33.6, 32.5, 31.9. HRMS calcd. for $C_{28}H_{28}N_2O$ 408.2202, found 408.2202.

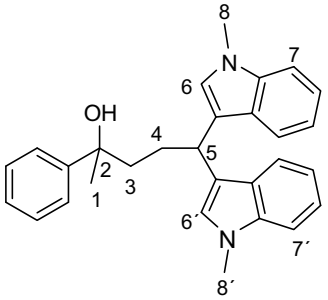
4.3.4. 1,1-Bis(1-methyl-1H-indol-3-yl)-4-phenyloct-7-en-4-ol (**3d**)



Colorless oil. R_f 0.02 (hexane:ethyl acetate, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55 and 7.44 (2×d, J = 8.0 Hz, 2H; $H_{9,9'}$), 7.28–7.13 (m, 7H), 7.07–6.95 (m, 3H), 6.66 and 6.63 (2×s, 2H; $H_{10,10'}$), 5.73 (ddt, J = 16.9, 10.7, 6.0 Hz, 1H; H_7), 4.90 (d, J = 10.7 Hz, 1H; H_{8cis}), 4.88 (d, J = 16.9 Hz, 1H; H_{8trans}), 4.39 (t,

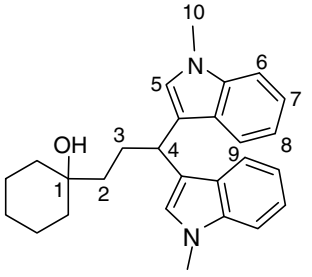
J = 7.0 Hz, 1H; H_1), 3.64 and 3.62 (2×s, 6H; $H_{11,11'}$), 2.04–1.90 (m, 4H), 1.89–1.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.70, 138.78, 137.07, 127.93, 127.29, 127.22, 126.20, 126.09, 125.35, 121.15, 119.53, 119.44, 118.76, 118.34, 118.29, 114.31, 108.98, 108.93, 77.12, 41.95, 41.61, 33.84, 32.45, 29.79, 27.90. HRMS calcd. for $C_{32}H_{34}N_2O$ 462.2666, found 462.2665.

*4.3.5. 5,5-Bis(1-methyl-1H-indol-3-yl)-2-phenylpentan-2-ol (**3e**)*



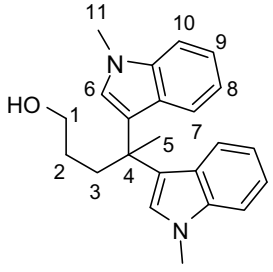
Colorless oil. R_f 0.18 (hexane:ethyl acetate, 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43 and 7.37 (2×d, J = 7.9 Hz, 2H; $H_{7,7'}$), 7.30–7.03 (m, 9H), 6.96–6.97 (m, 2H), 6.57 and 6.55 (2×s, 2H; $H_{6,6'}$), 4.28 (t, J = 7.1, 1H; H_5), 3.57 and 3.56 (2×s, 6H; $H_{8,8'}$), 1.93–1.84 (m, 4H; $H_{3,4}$), 1.41 (s, 3H; H_1). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.6, 137.1, 127.9, 127.3, 127.2, 126.3, 126.1, 124.8, 121.2, 119.5, 119.4, 118.7, 118.4, 118.3, 108.9, 74.8, 42.6, 33.9, 32.5, 30.4, 30.3. HRMS calcd. for $C_{29}H_{30}N_2O$ 422.2353, found 422.2353.

*4.3.6. 1-[3,3-Bis(1-methyl-1H-indol-3-yl)propyl]cyclohexanol (**3f**)*



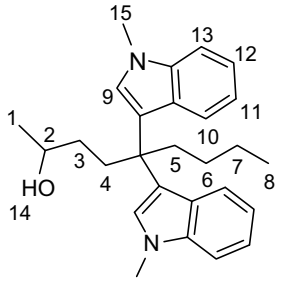
Colorless oil. R_f 0.17 (hexane:ethyl acetate, 5:1). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.54 (d, J = 7.9 Hz, 2H; H_6), 7.18 (d, J = 7.9 Hz, 2H; H_9), 7.11 (t, J = 7.9 Hz, 2H; H_7), 6.97 (t, J = 7.9 Hz, 2H; H_8), 6.78 (s, 2H; H_5), 4.35 (t, J = 7.6 Hz, 1H; H_4), 3.61 (s, 6H; H_{10}), 2.21 (td, J = 7.8, 7.6 Hz, 2H; H_3), 1.54–1.31 (m, 10H), 0.84–0.77(m 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.1, 127.4, 126.1, 121.2, 119.5, 118.9, 118.3, 108.9, 71.4, 41.1, 37.3, 34.2, 32.5, 29.5, 25.7, 22.1. HRMS calcd. for $C_{27}H_{32}N_2O$ 400.2515, found 400.2517.

*4.3.7. 4,4-Bis(1-methyl-1H-indol-3-yl)pentan-1-ol (**3g**)*



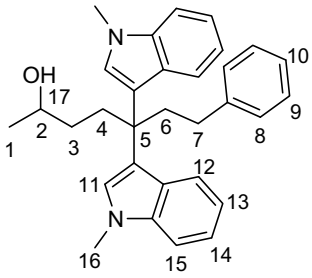
Colorless oil. R_f 0.01 (hexane:ethyl acetate, 5:1). ^1H NMR (400 MHz, THF-d_8) δ = 7.36 (d, J = 7.9 Hz, 2H; H_7), 7.27 (d, J = 7.9 Hz, 2H; H_{10}), 7.09 (s, 2H; H_6), 6.97 (t, J = 7.9 Hz, 2H; H_8), 6.77 (t, J = 7.9 Hz, 2H; H_9), 3.78 (s, 6H; H_{11}), 3.47 (td, J = 6.4, 5.3 Hz, 2H; H_1), 3.36 (t, J = 5.3 Hz, 1H; OH), 2.52–2.40 (m, 2H; H_3), 1.88 (s, 3H; H_5), 1.49–1.36 (m, 2H; H_2). ^{13}C NMR (100 MHz, THF-d_8) δ = 139.05, 128.15, 126.98, 123.76, 122.06, 121.47, 118.66, 109.75, 63.63, 39.11, 38.29, 32.68, 29.70, 28.19. HRMS calcd. for $C_{23}H_{26}N_2O$ 346.2045, found 346.2043.

*4.3.8. 5,5-Bis(1-methyl-1H-indol-3-yl)nonan-2-ol (**3h**)*



White solid. M.p.: 177.3–178.1 °C. R_f 0.25 (hexane:ethyl acetate, 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.31 and 7.28 (2×s, 2H; H_9), 7.27–7.22 (m, 4H; $H_{10,13}$), 6.97 (dd, J = 7.1, 0.9 Hz, 2H; H_{12}), 6.66 (dd, J = 0.9, 7.1, 2H; H_{11}), 3.80 and 3.79 (2×s, 6H; NMe), 3.69–3.58 (m, 1H; H_2), 3.38 (d, J = 4.6 Hz, 1H; H_{14}), 2.56 (ddd, J = 12.7, 4.6, 4.4 Hz, 1H; H_{4a}), 2.40–2.29 (m, 3H; $H_{4b,5}$), 1.39–1.11 (m, 6H; $H_{3,6,7}$), 1.07 (d, J = 6.1 Hz, 3H; H_1), 0.83 (t, J = 7.3 Hz, 3H; H_8). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.75, 127.97, 127.54, 122.48, 122.44, 121.79, 121.44, 118.44, 109.86, 68.48, 41.83, 36.97, 34.74, 33.41, 32.81, 26.82, 24.13, 24.05, 14.54. HRMS calcd. for $C_{27}H_{34}N_2O$ 402.2680, found 402.2671.

*4.3.9. 5,5-Bis(1-methyl-1H-indol-3-yl)-7-phenylheptan-2-ol (**3i**)*



White solid. M.p.: 167.8–168.2 °C. R_f 0.20 (hexane:ethyl acetate, 2:1). ^1H NMR (300 MHz, acetone-d_6) δ = 7.34 (s, 2H; H_{11}), 7.28 (d, J = 8.0 Hz, 2H; H_{15}), 7.24 (d, J = 8.0 Hz, 2H; H_{12}), 7.20 (d, J = 7.4 Hz, 2H; H_9), 7.11 (t, J = 7.4 Hz, 1H; H_{10}), 7.02 (d, J = 7.4 Hz, 2H; H_8), 6.98 (t, J = 8.0 Hz, 2H; H_{14}), 6.67 (t, J = 8.0 Hz, 2H; H_{13}), 3.74 (s, 6H; H_{16}), 3.66 (sextet, J = 6.1 Hz, 1H; H_2), 3.37 (d, J = 4.8 Hz, 1H; H_{17}), 2.68–2.58 (m, 3 H; $H_{4a,6}$), 2.47–2.34 (m, 3H; $H_{4b,7}$), 1.42–1.31 (m, 1H; H_{3a}), 1.30–1.20 (m, 1H; H_{3b}), 1.07 (d, J = 6.1 Hz, 3H; H_1). ^{13}C NMR (75 MHz, acetone-d_6) δ = 144.6, 139.0, 129.5, 129.3, 128.1, 127.9, 126.5, 122.3, 122.2, 122.0, 121.8, 118.9, 110.2, 68.7, 42.3, 40.2, 35.0, 33.5, 33.1, 31.7, 24.5, 14.6. HRMS calcd. for $C_{31}H_{34}N_2O$ 450.2672, found 450.2671.

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