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5-Hydroxy Indoles by Intramolecular Alkynol-Furan Diels-Alder Cycloaddition[‡]

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Abstract

A convergent approach provides a convenient access to synthetically and biologically useful 3,4-disubstituted 5-hydroxy indoles. The one-pot procedure uses microwave heating to initiate an intramolecular [4+2]-cycloaddition of an alkynol segment onto a furan followed by a fragmentation, aromatization and *N*-Boc deprotection cascade. Yields range from 15–75%, with aromatic substituents providing better conversions. 4-Trimethylsilylated analogs undergo a 1,3-silotropic rearrangement to give the *O*-TMS ethers.

INTRODUCTION

Second only to pyridines, indoles are among the most common aromatic scaffolds present in bioactive molecules.¹ The 5-hydroxy indole moiety alone has currently >11,000 substructure hits from >100,000 literature references in SciFinder. In addition to their prominence in the neurotransmitter serotonin and its many analogs, 5-hydroxy indoles are found in a vast array of pharmacologically active agents and natural products (Figure 1). Furthermore, the hydroxy group can be readily converted to derivatives that allow scaffold extensions cross-coupling or nucleophilic addition reactions of the indole nucleus.²

The Nenitzescu reaction is frequently used for the construction of 5-hydroxy indoles.³ Alternative protocols include the coumarin-indole transformation,⁴ and the Pd-catalyzed coupling of 2-iodoanilines with alkynes (Scheme 1).⁵ All of these protocols start with a functionalized 6-membered ring and add the pyrrole moiety in a linear sequence. We have recently reported an alternative strategy for a convergent indole synthesis that uses an intramolecular Diels-Alder furan (IMDAF) cycloaddition to assemble both benzene and pyrrole moieties simultaneously.^{6,7} We are now reporting an extension of this procedure to the direct preparation of 5-hydroxy indoles.

[‡]Dedicated to the memory of Professor Robert E. Ireland.

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Supporting Information. Copies of ¹H NMR spectra for **14e**, **14i**, **14k**, **14l**, **14m**, **14n**, **14o**, **14p**, and **14q**, and copies of ¹H NMR and ¹³C NMR spectra for all other compounds, except the commercial compounds **14a** and **14b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

In our previous reaction sequence,⁶ the 1,2-addition of lithiated **1** to enone **2** provided the allylic alcohol **3** (Scheme 2). Microwave heating of **3** led to the tricyclic IMDAF product **4** and subsequently through sequential elimination of two equivalents of water via **5** and **6** led to indoles **7**. We reasoned that the use of an alkynone in place of the enone would give us the opportunity to branch out from this reaction pathway, eliminate the bridging oxygen atom in **4** to give **8**, aromatize the intermediate at an earlier stage to give phenol **9**, and finally only eliminate a single molecule of water and, concomitantly, the *N*-protective group⁸ to yield 5-hydroxy indole **10**.

RESULTS AND DISCUSSION

The hypothesis that an alkynyl intermediate **3** would lead to the formation of 5-hydroxy indole **10** was readily put to test. Furanyl stannane **13** was prepared from iodide **11**⁹ and *N*-Boc-2-aminofuran **12**¹⁰ in the presence of NaH (Scheme 3). Stannane **13** underwent a rapid transmetalation (5 min) to **1** with *n*-Bu Li at -78 °C; and after the addition of 1 equivalent of 1,3-diphenylprop-2-yn-1-one **14a**, the tertiary alcohol **15** was isolated in 57% yield. Microwave heating to 220 °C for 1 h effected the desired IMDAF process and aromatization to give 5-hydroxy indole **16a** in 74% yield after chromatographic purification of the reaction mixture on SiO₂. The Boc group was cleaved off under the thermal conditions⁸. Interestingly, the ethoxycarbonyl protective group^{7c} on nitrogen led to lower yields, possibly due to an *N* → *O* acyl shift in intermediate **3**.

In order to further investigate the scope of this new process, we converted commercially available carbonyl compounds into ynones **14b-e** according to literature protocols.^{11,12} The lithium reagent derived from stannane **13** was then added to these ynones to give the corresponding alkynols **15b-e** in unoptimized 44-52% yield. As shown in Table 1, microwave irradiation of **15b-e** in *o*-dichlorobenzene for 1 h produced the expected 5-hydroxy indoles **16b-e** in moderate (36%) to good (63%) yields.

The reaction tolerated both aromatic and heteroaromatic groups (i.e. phenyl, **16a**, and thiophene, **16b**) as well as branched and cyclic aliphatic substituents (i.e. *n*-hexyl, **16c**, phenethyl, **16d**, and *c*-hexyl, **16e**) at the R¹-position. We explored fewer variations of the R² groups, but as the *n*-butyl derivative **16e** demonstrated, aliphatic groups appear to be acceptable substituents at R². The lowest yield, 36%, was obtained with R¹ and R² both being aliphatic residues, which could indicate that either indole stabilization through conjugative substituents at R¹ and R² or the presence of sterically bulky groups such as phenyl rings promotes product formation. Therefore, we tested silylated alkynes derived from silyl ketones as substrates that provide steric shielding in the absence of π -electron resonance effects.

When the four trimethylsilyl (TMS) alkynols **15f-i**¹³ were subjected to the microwave mediated cycloaddition conditions at 180 °C, the cycloaddition occurred smoothly and provided indole products in good yields (Scheme 4 and Table 2). However, rather than the expected 4-trimethylsilyl derivatives **16f-i**, a mixture of 5-trimethylsilyloxy indoles **17f-i** and the corresponding 5-hydroxy indoles **16f-i** were isolated. Presumably, the TMS-ethers result from a 1,3-silotropic C to O rearrangement,¹⁴ induced by the thermal conditions and rendered quantitative by the strong O-Si bond. In order to generate a homogeneous product fraction, the crude reaction mixtures were treated with 2% HCl in MeOH to desilylate **17f-i** to cleanly afford the 5-hydroxy indole products **16f-i**.

As a further test of this methodology, the reaction sequence was extended to aldehyde substrates, and the secondary alkynols **15j-q** were prepared¹⁶ in unoptimized 20-57% yields by addition of lithiated **13** to ynals **14j-q** (Scheme 5). As expected, the microwave

conditions promoted cycloadditions to ultimately afford the 4-substituted-5-hydroxy indoles **16j-q**. Similar to our previous observations, aromatic substrates gave better isolated yields compared to the alkyl substituted alkynols (Table 3).

Indoles with 4-aryl residues **16j-n** were isolated in 42-64% yield, and no obvious trend for electron-withdrawing or -donating substituents was observed. The two alkyl-chain containing products **16o** and **16p** were formed in low (15-20%) yields, and the 3-chloropropyl analog **16p** partially cyclized and produced an additional 7% of the corresponding pyran **18**. The cyclized ether¹⁷ could also be obtained in 53% by treatment of isolated **16p** with NaH in THF. Finally, the cyclohexene derivative **15q** led to the introduction of a 4-alkene group in **16q**, but the yield (23%) was similarly low as observed for aliphatic substrates. Nonetheless, this methodology allows for the rapid introduction of a diverse range of substituents at carbons 3 and 4 of the 5-hydroxy indole scaffold.

CONCLUSION

The use of alkynones and alkynals as starting materials extends our microwave-assisted IMDAF-aromatization cascade reaction to the direct formation of synthetically and biologically valuable 5-hydroxy indoles. The requisite substituted alkynes are readily available, and the methodology represents an unusual convergent formation of both the benzene and the pyrrole subunits of the indole ring system. Yields range from 15-75%, and the efficiency of the conversion benefits from aromatic substituents that can stabilize the charged and/or reactive intermediates **4**, **8** and **9** in the cascade indole formation process. We also observed an interesting 1,3-silotropic rearrangement of 4-silylated intermediates **16'**. Overall, due to the straightforward access to ynones and ynals, the convergent nature of the retrosynthetic disconnection, and the convenient thermal reaction conditions, this new reaction provides a significant alternative to other common methods for 5-hydroxy indole construction, especially for projects where a diverse range of 3- and 4-substitutions is desired.

EXPERIMENTAL SECTION

General Information

Microwave reactions were performed at 200-250 W using a Biotage Initiator. Ketones **14a** and **14b** are commercially available and were used without further purification. Ketones **14c**,^{11,18} **14d**,^{11,19} **14e**,^{12,20} **14f**,^{21,22} **14g**,^{21,23} **14h**,²¹ **14i**,^{21,24} and aldehydes **14j**,²⁵ **14k**,^{11,26} **14l**,^{11,27} **14m**,^{11,28} **14n**,^{11,29} **14o**,²⁵ **14p**,^{25,30} and **14q**^{25,31} were prepared according to literature procedures.

1-(Benzofuran-2-yl)-3-(trimethylsilyl)prop-2-yn-1-one (**14h**)

According to a literature protocol,²¹ **14h** was obtained as a yellow oil (2.50 g, 84%): IR (neat) 2963, 2158, 1630, 1548 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆) δ 7.94 (s, 1 H), 7.88 (d, *J* = 7.6 Hz, 1 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.60 (ddd, *J* = 1.2, 7.0, 7.0 Hz, 1 H), 7.40 (ddd, *J* = 0.9, 8.0, 8.0 Hz, 1 H), 0.34 (s, 9 H); ¹³C NMR (100 MHz, acetone-d₆) δ 165.9, 157.3, 154.0, 130.3, 127.9, 125.3, 124.9, 118.9, 113.2, 101.1, 99.7, -0.78; HRMS (TOF APCI+) *m/z* calcd for C₁₄H₁₅O₂Si (M+H) 243.0841, found 243.0865.

General Protocol A. *tert*-Butyl furan-2-yl(2-hydroxy-2,4-diphenylbut-3-ynyl)carbamate (**15a**)

A flame dried 25-mL round bottom flask was charged with a solution of furanyl-stannane **13** (0.608 g, 1.25 mmol) in dry THF (4 mL). The solution was cooled to -78 °C and treated with BuLi (1.0 mL, 1.6 M in hexanes) using a syringe pump over 10 min. The reaction mixture was then treated with alkyne **14a** (0.253 g, 1.23 mmol) in THF (4 mL) via syringe pump

over 10 min. After 1 h, the orange solution was diluted with satd. NH_4Cl , extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (nt) (ISCO-Companion, 0-100% EtOAc/hexanes, 25 min gradie) to give alcohol **15a** (0.29 g, 0.72 mmol, 57%) as a yellow oil; IR (neat) 3395, 2982, 1713, 1681 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6) δ 7.73 (d, J = 7.2 Hz, 2 H), 7.44-7.28 (m, 8 H), 7.24 (dd, J = 1.0, 2.2 Hz, 1 H), 6.32 (dd, J = 2.4, 3.2 Hz, 1 H), 6.02 (br s, 1 H), 5.39 (br s, 1 H), 4.16-4.04 (m, 2H), 4.07 (d, J = 14.2 Hz, 1 H), 1.29 (s, 9 H); ^{13}C NMR (75 MHz, acetone- d_6) δ 150.0, 144.2, 138.9, 132.6, 129.4, 129.3, 128.8, 128.5, 127.1, 123.8, 111.7, 91.9, 86.4, 81.7, 73.8, 60.8, 28.2; HRMS (TOF ES+) m/z calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_4\text{Na}$ ($\text{M}+\text{Na}$) 426.1681, found 426.1698.

***tert*-Butyl furan-2-yl(2-hydroxy-4-phenyl-2-(thiophen-2-yl)but-3-ynyl)carbamate (15b)**

According to General Protocol A, **15b** was obtained as a yellow oil (0.350 g, 52%, SiO_2 , EtOAc:hexanes, 1:6): IR (neat) 3384, 2982, 2918, 1713, 1681 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6) δ 7.46-7.37 (m, 6 H), 7.27-7.25 (m, 2 H), 7.01 (dd, J = 3.6, 4.4 Hz, 1 H), 6.34 (dd, J = 2.4, 3.2 Hz, 1 H), 6.08 (br s, 1 H), 5.78 (br s, 1 H), 4.20 (s, 2 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, acetone- d_6) δ 149.8, 149.1, 138.9, 132.6, 132.4, 129.5, 129.3, 127.5, 126.1, 125.7, 123.5, 111.8, 91.2, 86.0, 81.8, 60.8, 28.2; HRMS (TOF ES+) m/z calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_4\text{SNa}$ ($\text{M}+\text{Na}$) 432.1245, found 432.1281.

***tert*-Butyl furan-2-yl(2-hydroxy-2-(phenylethynyl)octyl)carbamate (15c)**

According to General Protocol A, **15c** was obtained as a yellow oil (0.225 g, 44%, SiO_2 , EtOAc:hexanes, 1:6): IR (neat) 3422, 2956, 2931, 2855, 1718, 1686, 1591 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6) δ 7.34-7.32 (m, 5 H), 7.27 (br s, 1 H), 6.35 (s, 1 H), 6.14 (s, 1 H), 4.53 (br s, 1 H), 3.91 (s, 2 H), 1.72-1.51 (m, 4 H), 1.39 (s, 9 H), 1.29 (br s, 6 H), 0.87 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, acetone- d_6) δ 150.2, 139.0, 132.5, 129.2, 129.1, 124.1, 111.8, 102.9, 92.2, 85.4, 81.8, 72.1, 58.5, 40.8, 32.6, 28.3, 24.9, 23.3, 14.4; HRMS (TOF ES+) m/z calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_4\text{Na}$ ($\text{M}+\text{Na}$) 434.2307, found 434.2281.

***tert*-Butyl furan-2-yl(2-hydroxy-2-phenethyl-4-phenylbut-3-ynyl)carbamate (15d)**

According to General Protocol A, **15d** was obtained as a yellow oil (0.310 g, 47%, SiO_2 , EtOAc:hexanes, 1:6): IR (neat) 3409, 3054, 2976, 2928, 1712, 1591 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6) δ 7.43-7.16 (m, 11 H), 6.37 (dd, J = 2.0, 3.2 Hz, 1 H), 6.17 (dd, J = 0.8, 3.2 Hz, 1 H), 4.78 (br s, 1 H), 4.01 (s, 2 H), 3.00-2.85 (m, 2 H), 2.06-1.99 (m, 2 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, acetone- d_6) δ 150.2, 143.3, 139.1, 132.6, 129.3, 129.23, 129.20, 126.6, 124.0, 111.8, 103.0, 91.8, 85.8, 81.8, 71.8, 58.3, 42.9, 31.4, 28.3; HRMS (TOF ES+) m/z calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_4\text{Na}$ ($\text{M}+\text{Na}$) 454.1994, found 454.2024.

***tert*-Butyl 2-cyclohexyl-2-hydroxyoct-3-ynyl(furan-2-yl)carbamate (15e)**

According to General Protocol A, **15e** was obtained as a yellow oil (0.438 g, 49%, SiO_2 , EtOAc:hexanes, 1:9): IR (neat) 3422, 3285, 2931, 2855, 1694, 1590 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6) δ 7.31 (dd, J = 0.8, 1.6 Hz, 1 H), 6.39 (dd, 1 H, J = 2.4, 3.2 Hz, 1 H), 6.13 (dd, J = 0.8, 3.2 Hz, 1 H), 4.15 (br s, 1 H), 3.89 (d, J = 14.4 Hz, 1 H), 3.79 (d, J = 14.4 Hz, 1 H), 2.16 (app t, J = 6.8 Hz, 2 H), 2.03-2.01 (m, 1 H), 1.75-1.63 (m, 4 H), 1.49-1.44 (m, 13 H), 1.22-1.13 (m, 6 H), 0.91 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, acetone- d_6) δ 150.3, 139.0, 111.9, 111.7, 102.8, 86.3, 81.8, 81.7, 74.7, 57.1, 46.4, 31.7, 28.8, 28.4, 28.3, 27.5, 27.3, 27.1, 27.0, 22.6, 18.9, 13.9; HRMS (EI) m/z calcd for $\text{C}_{23}\text{H}_{35}\text{NO}_4\text{Na}$ ($\text{M}+\text{Na}$) 412.2464, found 412.2472.

***tert*-Butylfuran-2-yl(2-hydroxy-2-phenyl-4-(trimethylsilyl)but-3-ynyl)carbamate (15f)**

According to General Protocol A, **15f** was obtained as a yellow oil (0.335 g, 58%, SiO₂, EtOAc:hexanes, 1:6): IR (neat) 3390, 2956, 2918, 1713, 1681 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 7.66 (d, *J* = 7.2 Hz, 2 H), 7.34 (dd, *J* = 6.8, 7.2 Hz, 2 H), 7.29-7.26 (m, 2 H), 6.34 (s, 1 H), 5.96 (br s, 1 H), 5.34 (br s, 1 H), 4.00 (s, 2 H), 1.30 (s, 9 H), 0.14 (s, 9 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 149.8, 143.8, 138.7, 128.6, 128.4, 127.1, 111.7, 108.2, 102.7, 90.3, 81.7, 73.5, 60.8, 28.2, 0.09; HRMS (TOF ES+) *m/z* calcd for C₂₂H₂₉NO₄SiNa (M+Na) 422.1764, found 422.1778.

***tert*-Butylfuran-2-yl(2-hydroxy-2-(naphthalen-2-yl)-4-(trimethylsilyl)but-3-ynyl)carbamate (15g)**

According to General Protocol A, **15g** was obtained as a yellow oil (0.413 g, 60%, SiO₂, EtOAc:hexanes, 1:9): IR (neat) 3395, 2956, 2140, 1718, 1681 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.18 (d, *J* = 1.5 Hz, 1 H), 7.90-7.83 (m, 3 H), 7.72 (dd, *J* = 1.8, 8.7 Hz, 1 H), 7.52-7.49 (m, 2 H), 7.13 (br s, 1 H), 6.26 (br s, 1 H), 5.78 (br s, 1 H), 4.09 (s, 2 H), 1.41 (s, 9 H), 0.22 (s, 9 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 148.9, 140.4, 137.8, 133.1, 133.0, 128.2, 127.5, 127.4, 126.03, 125.99, 125.0, 124.6, 110.8, 107.3, 101.9, 89.8, 80.8, 72.7, 59.6, 27.2, -0.74; HRMS (TOF ES+) *m/z* calcd for C₂₆H₃₁NO₄SiNa (M+Na) 472.1920, found 472.1915.

***tert*-Butyl-2-(benzofuran-2-yl)-2-hydroxy-4-(trimethylsilyl)but-3-ynyl(furan-2-yl)carbamate (15h)**

According to General Protocol A, **15h** was obtained as a yellow oil (0.151 g, 58%, SiO₂, ISCO-Companion, 0-100% EtOAc/hexanes, 15 min gradient): IR (neat) 3377, 2969, 1718, 1681 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 7.59 (d, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.28 (ddd, *J* = 1.2, 7.2, 7.2 Hz, 1 H), 7.26-7.21 (m, 1 H), 7.16 (dd, *J* = 0.8, 1.6 Hz, 1 H), 6.89 (d, *J* = 0.8 Hz, 1 H), 6.22 (br s, 1 H), 5.94 (br s, 1 H), 5.64 (br s, 1 H), 4.25 (s, 2 H), 1.27 (s, 9 H), 0.17 (s, 9 H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 158.0, 156.0, 149.3, 138.7, 129.0, 125.1, 123.6, 122.0, 112.0, 111.5, 105.3, 105.2, 103.0, 90.8, 81.7, 69.6, 57.4, 28.1, -0.06; HRMS (TOF ES+) *m/z* calcd for C₂₄H₂₉NO₅SiNa (M+Na) 462.1713, found 462.1749.

***tert*-Butyl-2-cyclopropyl-2-hydroxy-4-(trimethylsilyl)but-3-ynyl(furan-2-yl)carbamate (15i)**

According to General Protocol A, **15i** was obtained as a yellow oil (0.139 g, 52%, SiO₂, ISCO-Companion, 0-100% EtOAc/hexanes, 15 min gradient): IR (neat) 3427, 2974, 1718 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (dd, *J* = 1.2, 2.0 Hz 1 H), 6.33 (dd, *J* = 2.4, 3.6 Hz, 1 H), 6.06 (br s, 1 H), 3.96 (br s, 2 H), 1.45 (s, 9 H), 1.15-1.08 (m, 1 H), 0.71-0.66 (m, 1 H), 0.49-0.45 (m, 3 H), 0.12 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 148.9, 137.9, 110.9, 103.6, 101.7, 89.8, 82.2, 73.4, 59.0, 28.1, 18.2, 1.58, 1.35, -0.14; HRMS (TOF ES+) *m/z* calcd for C₁₉H₂₉NO₄SiNa (M+Na) 386.1764, found 386.1757.

***tert*-Butyl furan-2-yl(2-hydroxy-4-phenylbut-3-ynyl)carbamate (15j)**

According to General Protocol A, **15j** was obtained as a yellow oil (0.210 g, 43%, SiO₂, EtOAc:hexanes, 1:6): IR (neat) 3422, 2974, 2931, 1705, 1625 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.42 (m, 2 H), 7.32-7.26 (m, 3 H), 7.22 (s, 1 H), 6.37 (s, 1 H), 6.11 (br s, 1 H), 4.86-4.83 (m, 1 H), 4.00 (dd, *J* = 8.0, 14.4 Hz, 1 H), 3.88 (dd, *J* = 3.6, 14.4 Hz, 1 H), 1.47 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.2, 138.3, 134.8, 131.7, 128.4, 128.2, 122.3, 111.0, 101.8, 87.3, 82.1, 62.3, 54.8, 28.0; HRMS (EI) *m/z* calcd for C₁₉H₂₁NO₄Na (M+Na) 350.13968, found 350.1361.

***tert*-Butyl-furan-2-yl(2-hydroxy-4-(3-methoxyphenyl)but-3-ynyl)carbamate (15k)**

According to General Protocol A, **15k** was obtained as a yellow oil (0.250 g, 57%, SiO₂, EtOAc:hexanes, 1:6): IR (neat) 3459, 2982, 1712, 1599 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.22 (app t, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 7.6 Hz, 1 H), 6.96 (s, 1 H), 6.89 (dd, *J* = 2.4, 8.4 Hz, 1 H), 6.37 (app t, *J* = 2.8 Hz, 1 H), 6.11 (br s, 1 H), 4.84 (dd, *J* = 4.0, 7.6 Hz, 1 H), 4.00 (dd, *J* = 8.0, 14.4 Hz, 1 H), 3.88 (dd, *J* = 4.0, 14.4 Hz, 1 H), 3.80 (s, 3 H), 1.47 (s, 9 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 160.5, 149.8, 139.2, 130.4, 124.8, 117.3, 115.7, 111.8, 89.8, 85.4, 81.6, 61.5, 55.7, 55.0, 28.3; HRMS (TOF ES+) *m/z* calcd for C₂₀H₂₃NO₅Na (M+Na) 380.1474, found 380.1477.

***tert*-Butyl furan-2-yl(2-hydroxy-4-(*p*-tolyl)but-3-yn-1-yl)carbamate (15l)**

According to General Protocol A, **15l** was obtained as a yellow oil (0.144 g, 52%, SiO₂, EtOAc:hexanes, 1:15): ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, *J* = 8.0 Hz, 2 H), 7.19 (dd, *J* = 0.8, 2.0 Hz, 1 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 6.34 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.08 (br s, 1 H), 4.83-4.78 (m, 1 H), 3.97 (dd, *J* = 8.0, 14.4 Hz, 1 H), 3.85 (dd, *J* = 4.0, 14.4 Hz, 1 H), 2.34 (s, 3 H), 1.61 (br s, 1 H), 1.45 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.0, 148.2, 138.4, 138.2, 131.6, 128.9, 119.3, 110.9, 101.8, 86.9, 85.8, 81.9, 62.0, 54.7, 28.0, 21.3; HRMS (TOF ES+) *m/z* calcd for C₂₀H₂₃NO₄Na (M+Na) 364.1525, found 364.1494.

***tert*-Butyl furan-2-yl(2-hydroxy-4-(4-(trifluoromethyl)phenyl)but-3-yn-1-yl)carbamate (15m)**

According to General Protocol A, **15m** was obtained as a yellow oil (0.067 g, 26%, SiO₂, EtOAc:hexanes, 1:15): ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, *J* = 8.5 Hz, 2 H), 7.49 (d, *J* = 8.5 Hz, 2 H), 7.18 (dd, *J* = 1.0, 2.0 Hz, 1 H), 6.34 (dd, *J* = 2.0, 3.0 Hz, 1 H), 6.07 (br s, 1 H), 4.84 (dd, *J* = 4.0, 8.0 Hz, 1 H), 3.98 (dd, *J* = 8.0, 14.5 Hz, 1 H), 3.89 (dd, *J* = 4.0, 14.5 Hz, 1 H), 1.44 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 148.2, 138.4, 132.0, 130.2 (q, *J* = 32.5 Hz), 126.2, 125.2 (q, *J* = 3.8 Hz), 123.8 (d, *J* = 270.5 Hz), 111.1, 101.8, 90.1, 84.4, 82.2, 62.2, 60.4, 54.6, 28.1; HRMS (TOF ES+) *m/z* calcd for C₂₀H₂₁F₃NO₄ (M+H) 396.1423, found 396.1404.

***tert*-Butyl (4-(4-fluorophenyl)-2-hydroxybut-3-yn-1-yl)(furan-2-yl)carbamate (15n)**

According to General Protocol A, **15n** was obtained as a yellow oil (0.042 g, 20%, SiO₂, EtOAc:hexanes, 1:15): ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.36 (m, 2 H), 7.19 (dd, *J* = 0.8, 2.0 Hz, 1 H), 7.02-6.96 (m, 2 H), 6.34 (dd, *J* = 2.0, 4.0 Hz, 1 H), 6.07 (br s, 1 H), 4.80 (dd, *J* = 4.0, 8.0 Hz, 1 H), 3.97 (dd, *J* = 8.0, 14.4 Hz, 1 H), 3.86 (dd, *J* = 4.0, 14.4 Hz, 1 H), 3.25-3.21 (m, 1 H), 1.45 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 162.6 (d, *J* = 248.8 Hz), 148.2, 138.4, 133.7 (d, *J* = 8.8 Hz), 118.4, 115.5 (d, *J* = 21.2 Hz), 111.0, 101.8, 87.1, 84.8, 82.2, 62.3, 54.8, 28.1; HRMS (TOF ES+) *m/z* calcd for C₁₉H₂₀FNO₄Na (M+Na) 368.1274, found 368.1258.

***tert*-Butyl furan-2-yl(2-hydroxy-7-methyloct-3-ynyl)carbamate (15o)**

According to General Protocol A, **15o** was obtained as a yellow oil (0.073 g, 54%, SiO₂, ISCO-Companion, 0-100% EtOAc/hexanes, 20 min gradient): IR (neat) 3429, 2933, 2881, 1714, cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 7.29 (d, *J* = 1.2 Hz, 1 H), 6.38 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.10 (d, *J* = 2.8 Hz, 1 H), 4.50-4.41 (m, 2 H), 3.68 (d, *J* = 6.4 Hz, 2 H), 2.19 (ddd, *J* = 2.0, 7.2, 7.2 Hz, 2 H), 1.67 (sept, *J* = 6.8 Hz, 1 H), 1.42 (s, 9 H), 1.36 (d, *J* = 7.2 Hz, 1 H), 1.33 (d, *J* = 7.2 Hz, 1 H), 0.87 (d, *J* = 6.4 Hz, 6 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 149.9, 139.1, 111.8, 102.6, 85.9, 81.4, 80.7, 61.2, 55.5, 38.4, 28.3, 27.8, 22.5, 17.2; HRMS (TOF ES+) *m/z* calcd for C₁₈H₂₇NO₄Na (M+Na) 344.1838, found 344.1830.

tert-Butyl-7-chloro-2-hydroxyhept-3-ynyl(furan-2-yl)carbamate (15p)

According to General Protocol A, **15p** was obtained as a yellow oil (0.089 g, 52%, SiO₂, ISCO-Companion, 0-100% EtOAc/hexanes, 15 min gradient): IR (neat) 3440, 2969, 1705, 1617 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.19 (s, 1 H), 6.35 (app t, *J* = 2.4 Hz, 1 H), 6.05 (br s, 1 H), 4.58-4.55 (m, 1 H), 3.84 (dd, *J* = 8.4, 14.4 Hz, 1 H), 3.73 (dd, *J* = 4.4, 14.4 Hz, 1 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 2.38 (ddd, *J* = 2.0, 6.8, 6.8 Hz, 2 H), 1.94 (ddd, *J* = 6.8, 6.8, 13.2 Hz, 2 H), 1.45 (s, 9 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 149.8, 111.8, 84.2, 81.7, 81.5, 61.1, 55.3, 44.5, 32.3, 28.3, 16.6; HRMS (TOF ES+) *m/z* calcd for C₁₆H₂₂ClNO₄Na (M+Na) 350.1135, found 350.1100.

tert-Butyl 4-cyclohexenyl-2-hydroxybut-3-ynyl(furan-2-yl)carbamate (15q)

According to General Protocol A, **15q** was obtained as a yellow oil (0.313 g, 38%, SiO₂, EtOAc:hexanes, 1:6): IR (neat) 3435, 2982, 1705, 1612 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.16 (dd, *J* = 0.8, 2.0 Hz, 1 H), 6.32 (dd, *J* = 2.4, 3.2 Hz, 1 H), 6.08-6.05 (m, 2 H), 4.69-4.65 (m, 1 H), 3.87 (dd, *J* = 8.0, 14.4 Hz, 1 H), 3.73 (dd, *J* = 8.0, 14.4 Hz, 1 H), 2.07-2.04 (m, 4 H), 1.62-1.52 (m, 4 H), 1.43 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.2, 138.3, 135.6, 119.9, 110.9, 101.7, 84.6, 81.9, 62.1, 54.8, 28.9, 28.0, 25.5, 22.1, 21.4; HRMS (TOF ES+) *m/z* calcd for C₁₉H₂₅NO₄Na (M+Na) 354.1681, found 354.1674.

General Protocol B. 3,4-Diphenyl-1 *H*-indol-5-ol (16a)

A solution of alcohol **15a** (0.087 g, 0.21 mmol) in *o*-DCB (2.1 mL) was subjected to microwave irradiation at 220 °C for 60 min. The crude solution was purified by chromatography on SiO₂ (0-20%, EtOAc/hexanes) to give indole **16a** (0.046 g, 74%) as a light brown solid: Mp 184-185 °C; IR (neat) 3504, 3403, 3054, 1599 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 10.32 (br s, 1 H), 7.37 (d, *J* = 8.8 Hz, 1 H), 7.28 (d, *J* = 2.8 Hz, 1 H), 7.12-7.10 (m, 2 H), 7.08 (s, 1 H), 7.03-6.99 (m, 3 H), 6.96-6.82 (m, 6 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 148.0, 137.2, 132.9, 131.5, 129.5, 127.7, 127.4, 126.5, 125.6, 125.3, 124.9, 119.5, 119.0, 112.9, 112.0; HRMS (TOF APCI+) *m/z* calcd for C₂₀H₁₆NO 286.1232 (M+H), found 286.1226.

4-Phenyl-3-(thiophen-2-yl)-1 *H*-indol-5-ol (16b)

According to General Protocol B, **16b** was obtained as a brown solid (0.057 g, 61%, SiO₂, EtOAc:hexanes, 1:6): Mp 166-167 °C; IR (neat) 3528, 3390, 3067, 1574 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 10.42 (br s, 1 H), 7.37 (d, *J* = 8.8 Hz, 1 H), 7.36 (s, 1 H), 7.19-7.16 (m, 2 H), 7.13-7.09 (m, 4 H), 7.01 (dd, *J* = 1.2, 5.2 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 1 H), 6.55 (dd, *J* = 3.6, 5.2 Hz, 1 H), 6.04 (dd, *J* = 1.2, 3.6 Hz, 1 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 148.5, 138.7, 137.3, 132.9, 131.5, 128.0, 127.2, 127.1, 126.9, 126.6, 125.8, 123.7, 120.0, 113.4, 112.4, 111.0; HRMS (TOF ES+) *m/z* calcd for C₁₈H₁₃NOSK (M+K) 330.0355, found 330.0370.

3-Hexyl-4-phenyl-1 *H*-indol-5-ol (16c)

According to General Protocol B, **16c** was obtained as a brown oil (0.054 g, 58%, SiO₂, EtOAc:hexanes, 1:6): IR (neat) 3535, 3472, 3403, 1725, 1591 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 9.76 (br s, 1 H), 7.44-7.32 (m, 5 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 2.09-2.03 (m, 2 H), 1.21-1.01 (m, 6 H), 0.97-0.89 (m, 2 H), 0.81 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 146.4, 137.4, 131.8, 130.7, 127.1, 126.2, 125.6, 123.0, 118.8, 115.8, 111.0, 110.6, 31.1, 30.8, 26.2, 22.0, 13.1; HRMS (TOF ES+) *m/z* calcd for C₂₀H₂₄NO 294.1858 (M+H), found 294.1841.

3-Phenethyl-4-phenyl-1H-indol-5-ol (16d)

According to General Protocol B, **16d** was obtained as a brown solid (0.063 g, 63%, SiO₂, EtOAc:hexanes, 1:6): Mp 102-103 °C; IR (neat) 3528, 3409, 3067, 3054, 1559 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 9.87 (br s, 1 H), 7.49-7.40 (m, 5 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 7.18-7.14 (m, 2 H), 7.10-7.06 (m, 2 H), 6.92 (s, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.83-6.81 (m, 2 H), 2.49-2.37 (m, 4 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 147.6, 143.1, 138.6, 132.9, 131.8, 128.8, 128.5, 128.4, 127.4, 126.4, 125.9, 124.7, 119.7, 116.0, 112.1, 111.7, 38.6; HRMS (EI) *m/z* calcd for C₂₂H₁₉NO 313.1467 (M⁺), found 313.1464.

4-Butyl-3-cyclohexyl-1H-indol-5-ol (16e)

According to General Protocol B, **16e** was obtained as a brown oil (0.050 g, 36%, SiO₂, 0-10%, EtOAc:hexanes): IR (neat) 3395, 1681 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 9.64 (br s, 1 H), 7.26 (s, 1 H), 7.02 (d, *J* = 2.4 Hz, 1 H), 7.00 (d, *J* = 8.4 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 3.00-2.87 (m, 4 H), 2.07-2.04 (m, 3 H), 1.87-1.76 (m, 3 H), 1.64-1.58 (m, 2 H), 1.54-1.43 (m, 7 H), 1.00 (t, *J* = 6.8 Hz, 3 H); ¹³C NMR δ 148.1, 132.8, 126.1, 123.1, 121.5, 119.7, 112.0, 109.5, 36.9, 36.7, 34.0, 29.0, 27.9, 27.0, 26.7, 23.7, 14.3; HRMS (EI) *m/z* calcd for C₁₈H₂₅NO (M⁺) 271.1936, found 271.1928.

General Protocol C. 3-Phenyl-1H-indol-5-ol (16f).¹⁵

A solution of alcohol **15f** (0.057 g, 0.14 mmol) in *o*-DCB (1.0 mL) was subjected to microwave irradiation at 180 °C for 30 min. The reaction mixture was cooled to 0 °C and treated with dry methanolic HCl (2%, 0.2 mL). After 5 min, the solution was concentrated and the crude residue was purified by chromatography on SiO₂ (ISCO-Rf, 0-100%, EtOAc/hexanes; 12 min gradient) to give indole **16f** (0.019 g, 63%) as a light brown oil: IR (neat) 3385, 1687 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆) δ 10.26 (br s, 1 H), 7.76 (s, 1 H), 7.67 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.55 (d, *J* = 2.7 Hz, 1 H), 7.42 (app t, *J* = 7.8 Hz, 2 H), 7.38 (d, *J* = 2.4 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.25-7.19 (m, 1 H), 6.79 (dd, *J* = 2.4, 8.7 Hz, 1 H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 152.2, 137.2, 132.7, 129.2, 127.2, 126.9, 125.7, 123.9, 116.8, 112.8, 112.5, 103.9; HRMS (TOF ES⁺) *m/z* calcd for C₁₄H₁₂NO (M+H) 210.0919, found 210.0925.

3-(Naphthalen-2-yl)-1H-indol-5-ol (16g)

According to General Protocol C, **16g** was obtained as a brown oil (0.028 g, 60%, SiO₂, Flash-system, 0-100%, EtOAc/hexanes; 15 min gradient): IR (neat) 3390, 1699 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆) δ 10.27 (br s, 1 H), 8.12 (s, 1 H), 7.88 (d, *J* = 8.7 Hz, 2 H), 7.84-7.79 (m, 2 H), 7.72 (s, 1 H), 7.64 (d, *J* = 2.7 Hz, 1 H), 7.47-7.44 (m, 2 H), 7.41-7.35 (m, 2 H), 7.30 (d, *J* = 8.7 Hz, 1 H), 6.77 (dd, *J* = 2.4, 8.7 Hz, 1 H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 152.4, 134.9, 134.8, 132.8, 132.4, 128.7, 128.2, 127.1, 126.7, 126.6, 125.5, 124.7, 124.4, 116.6, 112.9, 112.6, 104.2; HRMS (TOF ES⁺) *m/z* calcd for C₁₈H₁₃NO (M⁺) 259.0997, found 259.0970.

3-(Benzofuran-2-yl)-1H-indol-5-ol (16h)

According to General Protocol C, **16h** was obtained as a light orange solid (0.022 g, 63%, SiO₂, ISCO-Rf, 0-100%, EtOAc/hexanes; 15 min gradient): Mp 169-172 °C; IR (neat) 3364, 3295, 1629 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆) δ 10.55 (br s, 1 H), 7.94 (s, 1 H), 7.88 (d, *J* = 3.0 Hz, 1 H), 7.62-7.53 (m, 1 H), 7.52-7.50 (m, 2 H), 7.38 (d, *J* = 8.7 Hz, 1 H), 7.25-7.21 (m, 2 H), 6.95 (d, *J* = 1.0 Hz, 1 H), 6.86 (dd, *J* = 2.4, 8.7 Hz, 1 H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 154.6, 154.3, 152.8, 132.3, 130.7, 126.0, 125.1, 123.4, 123.3, 120.5, 113.1, 110.8, 107.2, 104.7, 98.6; HRMS (TOF ES⁺) *m/z* calcd for C₁₆H₁₁NO₂ (M⁺) 249.0790, found 249.0783.

3-Cyclopropyl-1*H*-indol-5-ol (16i)

According to General Protocol C, **16i** was obtained as a light yellow oil (0.018 g, 47%, SiO₂, Flash-system, 0-100%, EtOAc/hexanes; 15 min gradient): IR (neat) 3435, 3364, 1581 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 9.56 (br s, 1 H), 7.50 (s, 1 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.89 (d, *J* = 1.6 Hz, 1 H), 6.63 (dd, *J* = 2.0, 8.4 Hz, 1 H), 1.83-1.76 (m, 1 H), 0.78-0.74 (m, 2 H), 0.52-0.50 (m, 2 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 151.1, 132.3, 129.7, 122.2, 117.6, 112.2, 112.0, 103.4, 6.6, 6.0; HRMS (TOF ES+) *m/z* calcd for C₁₁H₁₂NO (M+H) 174.0919, found 174.0913.

General Protocol D. 4-Phenyl-1*H*-indol-5-ol (16j)

A solution of alcohol **15j** (0.052 g, 0.16 mmol) in 1,2-dichloroethane (1.0 mL) was subjected to microwave irradiation at 180 °C for 30 min. The crude solution was concentrated and purified by chromatography on SiO₂ (Flash-system, 0-100% EtOAc:hexanes, 15 min gradient) to give **16j** as a light brown oil (0.016 g, 48%): IR (neat) 3535, 3409, 3045, 2918, 1580 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 9.95 (br s, 1 H), 7.48 (d, *J* = 7.6 Hz, 2 H), 7.31 (app t, *J* = 7.6 Hz, 2 H), 7.20-7.15 (m, 2 H), 7.13-7.11 (m, 2 H), 6.73 (d, *J* = 8.8 Hz, 1 H), 6.14 (br s, 1 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 145.9, 135.6, 130.9, 129.9, 129.3, 127.8, 127.7, 125.1, 117.8, 111.9, 111.3, 101.6; HRMS (TOF APCI+) *m/z* calcd for C₁₄H₁₂NO (M+H) 210.0919, found 210.0895.

4-(3-Methoxyphenyl)-1*H*-indol-5-ol (16k)

According to General Protocol D, **16k** was obtained as a light brown oil (0.015 g, 42%, SiO₂, Flash-system, 0-100%, EtOAc/hexanes; 15 min gradient): IR (neat) 3528, 3403, 2924, 1712, 1580 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) δ 10.11 (br s, 1 H), 7.37 (t, *J* = 8.4 Hz, 1 H), 7.30-7.26 (m, 3 H), 7.20-7.18 (m, 2 H), 6.90 (dd, *J* = 2.4, 8.0 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 1 H), 6.30 (app t, *J* = 2.4 Hz, 1 H), 3.85 (s, 3 H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 160.5, 147.7, 140.1, 132.3, 129.8, 129.4, 126.3, 123.6, 118.8, 116.8, 113.2, 112.9, 112.0, 101.6, 55.5; HRMS (TOF ES+) *m/z* calcd for C₁₅H₁₃NO₂ (M+) 239.0946, found 239.0940.

4-(*p*-Tolyl)-1*H*-indol-5-ol (16l)

According to General Protocol D, **16l** was obtained as a light brown solid (0.011 g, 47%, SiO₂, EtOAc:hexanes, 1:8): Mp 112-114 °C; IR (neat) 3523, 3409, 3021, 2917 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.11 (br s, 1 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.27 (dd, *J* = 0.5, 8.5 Hz, 1 H), 7.17 (app t, *J* = 3.0 Hz, 1 H), 6.94 (d, *J* = 9.0 Hz, 1 H), 6.32 (ddd, *J* = 1.0, 2.0, 3.0 Hz, 1 H), 5.00 (br s, 1 H), 2.45 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 146.0, 137.4, 132.5, 130.9, 130.0, 129.8, 127.9, 125.0, 117.8, 111.9, 111.1, 101.7, 21.3; HRMS (TOF ES+) *m/z* calcd for C₁₅H₁₄NO (M+H) 224.1075, found 224.1074.

4-(4-(Trifluoromethyl)phenyl)-1*H*-indol-5-ol (16m)

According to General Protocol D, **16m** was obtained as a light brown solid (0.013 g, 64%, SiO₂, EtOAc:hexanes, 1:8): Mp 140-142 °C; IR (neat) 3491, 2922 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.17 (br s, 1 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.32 (dd, *J* = 0.5, 8.5 Hz, 1 H), 7.21 (app t, *J* = 3.0 Hz, 1 H), 6.92 (d, *J* = 9.0 Hz, 1 H), 6.31 (ddd, *J* = 1.0, 2.5, 3.0 Hz, 1 H), 4.76 (br s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 145.9, 139.9, 131.0, 130.4, 129.5 (q, *J* = 32.2 Hz), 127.7, 126.0 (q, *J* = 3.6 Hz), 125.5, 124.2 (q, *J* = 270.1 Hz), 116.7, 112.3, 112.0, 101.4; HRMS (TOF ES+) *m/z* calcd for C₁₅H₁₁NOF₃ (M+H) 278.0793, found 278.0794.

4-(4-Fluorophenyl)-1H-indol-5-ol (16n)

According to General Protocol D, **16n** was obtained as a brown solid (0.006 g, 44%, SiO₂, EtOAc:hexanes, 1:8): Mp 145-148 °C; IR (neat) 3491, 3409, 2919 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.13 (br s, 1 H), 7.57-7.53 (m, 2 H), 7.29 (dd, *J* = 1.0, 9.0 Hz, 1 H), 7.25-7.21 (m, 2 H), 7.18 (app t, *J* = 3.0 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.28 (ddd, *J* = 1.0, 2.0, 3.0 Hz, 1 H), 4.80 (br s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 162.3 (d, *J* = 245.0 Hz), 146.0, 131.8 (d, *J* = 7.5 Hz), 131.5 (d, *J* = 2.5 Hz), 130.9, 128.0, 125.2, 116.9, 116.2 (d, *J* = 24.2 Hz), 112.1, 111.4, 101.5; HRMS (TOF ES+) *m/z* calcd for C₁₄H₁₁NOF (M+H) 228.0825, found 228.0827.

4-Isopentyl-1H-indol-5-ol (16o)

According to General Protocol D, **16o** was obtained as a brown oil (0.005 g, 15%, SiO₂, ISCO-Rf, 0-100%, EtOAc/hexanes; 15 min gradient): IR (neat) 3405, 2974, 1686 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆) δ 9.92 (br s, 1 H), 7.31 (s, 1 H), 7.23 (app t, *J* = 2.0 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 6.41 (br s, 1 H), 2.90 (t, *J* = 8.0 Hz, 2 H), 1.77 (sept, *J* = 6.8 Hz, 1 H), 1.59-1.53 (m, 2 H), 0.99 (d, *J* = 6.4 Hz, 6 H); ¹³C NMR (75 MHz, acetone-d₆) δ 148.0, 132.0, 129.7, 125.3, 118.9, 112.5, 109.5, 100.3, 39.7, 28.9, 25.5, 22.9; HRMS (TOF ES-) *m/z* calcd for C₁₃H₁₆NO (M-H) 202.1232, found 202.1229.

4-(3-Chloropropyl)-1H-indol-5-ol (16p)

According to General Protocol D, **16p** was obtained as a brown oil (0.007 g, 20%, SiO₂, Flash-system, 0-100%, EtOAc/hexanes; 15 min gradient): IR (neat) 3409, 2934, 1705 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆) δ 9.99 (br s, 1 H), 7.50 (s, 1 H), 7.26 (app t, *J* = 2.8 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 6.47 (app s, 1 H), 3.66 (t, *J* = 6.8 Hz, 2 H), 3.04 (t, *J* = 7.6 Hz, 2 H), 2.15 (pent, *J* = 7.2 Hz, 2 H); ¹³C NMR (75 MHz, acetone-d₆) δ 148.3, 131.9, 129.9, 125.6, 116.9, 112.4, 110.1, 100.2, 45.7, 33.7, 24.9; HRMS (TOF ES+) *m/z* calcd for C₁₁H₁₃NOCl (M+H) 210.0686, found 210.0657.

4-Cyclohexenyl-1H-indol-5-ol (16q)

According to General Protocol B, **16q** was obtained as a brown oil (0.021 g, 23%, SiO₂, EtOAc:hexanes, 1:6): IR (neat) 3403, 2931, 1705, 1612 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆) δ 9.94 (br s, 1 H), 7.19 (t, *J* = 2.8 Hz, 1 H), 7.12 (dd, *J* = 0.8, 8.8 Hz, 1 H), 6.84 (s, 1 H), 6.70 (d, *J* = 8.8 Hz, 1 H), 6.30-6.29 (m, 1 H), 5.76-5.76 (m, 1 H), 2.41-2.37 (m, 2 H), 2.24-2.20 (m, 2 H), 1.82-1.78 (m, 4 H); ¹³C NMR (100 MHz, acetone-d₆) δ 147.1, 135.9, 132.1, 128.9, 127.6, 125.6, 121.3, 112.6, 110.9, 101.5, 26.3, 23.9, 23.2; HRMS (TOF ES+) *m/z* calcd for C₁₄H₁₅NO 213.1154, found 213.1171.

3,7,8,9-Tetrahydropyrano[3,2-e]indole (18)¹⁷

A solution of phenol **16p** (0.023 g, 0.11 mmol) in THF (1.5 mL) was treated with NaH (0.008 g, 0.20 mmol, 60% dispersion) followed by TBAI (0.045 g, 0.19 mmol) at room temperature. After 30 min, the solution was diluted with brine and extracted with diethyl ether. The organic layers were dried (Na₂SO₄) filtered and concentrated. The crude residue was purified by chromatography on SiO₂ (ISCO-Rf, 0-100% EtOAc/hexanes, 15 min gradient) to give pyran **18** (0.010 g, 53%) as a light yellow semi-solid: IR (neat) 3428, 2934, 1493 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆) δ 9.91 (br s, 1 H), 7.11 (app t, *J* = 2.8 Hz, 1 H), 6.99 (d, *J* = 8.8 Hz, 1 H), 6.43 (d, *J* = 8.8 Hz, 1 H), 6.21 (br s, 1 H), 3.99 (t, *J* = 5.2 Hz, 2 H), 2.76 (t, *J* = 6.8 Hz, 2 H), 2.72-2.68 (m, 2 H); ¹³C NMR (75 MHz, acetone-d₆) δ 148.9, 131.4, 128.7, 125.3, 112.9, 112.2, 110.4, 99.7, 66.4, 23.1, 22.5; HRMS (TOF ES+) *m/z* calcd for C₁₁H₁₂NO (M+H) 174.0919, found 174.0895.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Representative biologically active 5-hydroxy indoles.

Scheme 1.
Methods for Formation of 5-Hydroxy Indoles

Scheme 2.

Proposed Reaction Pathways for Indole and 5-Hydroxy Indole Formation by Intramolecular Diels-Alder Reaction with Furans

Scheme 3.^a Formation of Propargyl Alcohol and Thermal Cycloaddition Reaction

Scheme 4.

^a Formation of 3-Substituted 5-Hydroxy Indoles from Silylated Alkynones.

Scheme 5.

^a Formation of 4-Substituted 5-Hydroxy Indoles from Alkynals.

Table 1

Synthesis of 5-Hydroxy Indoles 16b-e from Tertiary Alkynols 15b-e

entry	15	[%] ^a	R ¹	R ²	16	[%] ^b
1	b	52	2-thiophenyl	Ph	b	61
2	c	44	<i>n</i> -hexyl	Ph	c	58
3	d	47	CH ₂ CH ₂ Ph	Ph	d	63
4	e	49	<i>c</i> -hexyl	<i>n</i> -butyl	e	36

^aYields of isolated alkynols **15**.

^bYields of isolated furans **16**.

Table 2

Synthesis of 5-Hydroxy Indoles 16f-i from Tertiary Alkynols 15f-i.

entry	15	[%] ^a	R ¹	16	[%] ^b
1	f	58	Ph	f	63
2	g	60	2-naphthyl	g	60
3	h	58	2-benzofuryl	h	63
4	i	52	c-propyl	i	47

^aYields of isolated alkynols **15**.

^bYields of isolated furans **16**.

Table 3

Synthesis of 5-Hydroxy Indoles 16j-q from Secondary Alkynols 15j-q.

entry	15	[%] ^a	R ²	16	[%] ^b
1	j	43	Ph	j	48
2	k	57	3-OMePh	k	42
3	l	52	4-MePh	l	47
4	m	26	4-CF ₃ Ph	m	64
5	n	20	4-F-Ph	n	44
6	o	54	(CH ₂) ₂ CH(CH ₃) ₂	o	15
7	p	52	(CH ₂) ₃ Cl	p	20 ^c
8	q	38	1-cyclohexene	q	23

^aYields of isolated alkynols **15**.

^bYields of isolated furans **16**.

^cThe pyran-containing indole product **18**¹⁷ was also isolated in 7% (see Supporting Information).