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Total Synthesis of (+)-Conolidine by the Gold(I)-
Catalyzed Cascade Cyclization of a Conjugated Enyne

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Abstract: A total synthesis of (+)-conolidine has been achieved via the gold(I)-catalyzed cascade cyclization of a conjugated enyne. Remarkably, this strategy allowed for the simultaneous formation of the indole ring and the ethylidene-substituted piperidine moiety of (+)-conolidine under homogenous gold catalysis in an enantioselective manner (88–91% ee).

Conolidine (1), which belongs to the C5-nor stemmadenine family of alkaloids, was first isolated from *Tabernaemontana divaricata* by Kam *et al.* in 2004 (Figure 1).1 This group only managed to isolate 0.0013 g of conolidine from the stem bark of this small flowering plant. Since Bohn, Micalizio, and co-workers accomplished the first asymmetric total synthesis of conolidine (1) in 2011, there has been considerable interest in its unique analgesic activity, which differs from that of many common opioids, including morphine.2 Although several efficient methods have been reported for the synthesis of C5-nor stemmadenine-type indoles,2-4 the development of a diversity-oriented route suitable for evaluating the structure-activity relationships of these compounds is still highly desired.
Homogeneous gold catalysis has attracted considerable attention because of the strong $\pi$-acidity of gold, as well as its potential to stabilize cationic reaction intermediates.\textsuperscript{5} The versatile reactivity of gold catalysts has allowed for the design of several eloquent cascade reactions for the direct step- and atom-economical synthesis of complex molecules.\textsuperscript{6} Nowadays, homogeneous gold catalysis is recognized as one of the most effective strategies for the electrophilic activation of alkynes for the synthesis of natural products.\textsuperscript{6f}

We recently reported the gold(I)-catalyzed bis-cyclization of conjugated diynes 2 ($R' = H, \text{--}N\text{uH} = \text{CH}_2\text{OH}$) as an efficient strategy for the construction of fused indoles 3 and 4 (Scheme 1).\textsuperscript{7} In this reaction, the initial indole formation occurred via a 5-$\text{endo}$-$\text{dig}$ cyclization, which was followed by a 7-$\text{endo}$-$\text{dig}$ cyclization to give the fused indole 3 as the major product. Based on this reaction, we designed a strategy for the synthesis of (+)-conolidine (1) (Scheme 2, strategy I). It was envisaged that the known conolidine precursor \textsuperscript{7}2,4 could be prepared by the gold(I)-catalyzed cascade cyclization of conjugated diyne 10. In this sense, the bis-cyclization reaction would allow for the formation of a fused indole (path a and b), which would be followed by a third cyclization to give the piperidine moiety. One of the potential issues with this strategy would be controlling the regioselectivity of the second cyclization step. In particular, the 6-$\text{exo}$-$\text{dig}$ cyclization (path b) would need to be favored over the 7-$\text{endo}$-$\text{dig}$ pathway (path b’) to allow for the introduction of the oxygen atom at the appropriate carbon of the product. We also designed a second strategy (strategy II) using a conjugated enyne 11 bearing a silyl enol ether.\textsuperscript{8} Notably, this strategy would avoid the need to control the regioselectivity of the second cyclization described in strategy I by introducing the oxygen atom of the conolidine as a silyl ether. It was also envisaged that the nucleophilicity of

Figure 1. Stemmadenine-based alkaloids
the enol ether would be increased following the formation of the indole, leaving it better equipped to promote the subsequent formation of the piperidine ring. Furthermore, the use of a chiral auxiliary (in strategy I) or chiral gold complex would allow for the asymmetric induction of these key steps. Both of these strategies involve the use of readily accessible synthons 12–16, and can therefore be considered as diversity-oriented convergent syntheses. Herein, we report the total synthesis of (+)-conolidine (1) based on the catalytic asymmetric cyclization of the enol ether-type substrate 11 (strategy II).

**Scheme 1.** Previous Work: Gold(I)-Catalyzed Intra-molecular Consecutive Cyclizations of a Conjugated Diyne

![Scheme 1](image)

**Scheme 2.** Retrosynthetic Analysis of Conolidine Based on the Gold(I)-Catalyzed Cascade Reaction of Conjugated Alkynes

![Scheme 2](image)
Strategy I. We initially conducted a series of model experiments using conjugated diynes 2a–c to evaluate the possibility of controlling the regioselectivity in strategy I (Scheme 3). The reaction of 2a bearing a phenylglycinol moiety gave the desired isomer 4a as a minor product (4a/3a = 29:71). In contrast, substrate 2b bearing a vicinal phenyl group and substrate 2c bearing a carboxylic acid preferentially afforded the corresponding 6-exo-products (4/3 = 71:29–80:20). Based on these results, we prepared the corresponding alcohol and carboxylic acid substrates 10a and 10b as the most suitable candidates for the synthesis of conolidine.

Scheme 3. Model Experiment for Control of the Regioselectivity in the Second Cyclization
The *erythro*-isomer of (±)-2b was used.

Our initial efforts towards the preparation and subsequent gold(I)-catalyzed cyclization of the conjugated diynes 10a and 10b are shown in Scheme 4. The alkylation of tosylamide 17 with 1-bromobut-2-yne (18) gave diyne 19. The iodination of the terminal alkyne moiety in 19 with NIS and AgNO₃, followed by the subsequent Cadiot–Chodkiewicz coupling of the resulting iodoalkyne with 13a or 13b gave the amino alcohol- and amino acid-type substrates (±)-10a and 10b (after hydrolysis), respectively. Unfortunately, however, the subsequent reaction of 10a with IPrAuCl/AgOTf (10 mol %) and EtOH (2 equiv) in 1,2-DCE at 50 °C for 2 h gave a complex mixture of unidentified products. In contrast, the reaction of 10b under the same conditions led to the formation of the bis-cyclization products 20b and 20b’ with good regioselectivity for the former of these two products (20b/20b’ = 90/10). It is noteworthy, however, that these compounds were formed in low yields (<31%) because of their poor stability. Disappointingly, all of our other attempts to promote the formation of the piperidine using 10b and 20b/20b’ resulted in failure, most likely because of the poor nucleophilicity of the enol ether moiety of 20b bearing an electron-withdrawing group. Based on these results, we discarded strategy I and focused our efforts on strategy II using the conjugated enynes 11a and 11b.

**Scheme 4.** Unsuccessful Attempts at the Gold(I)-Catalyzed Cyclization of the Conjugated Diynes 10a and 10b (Strategy I)
Strategy II. Conjugated enynes 11a and 11b bearing different silyl enol ether moieties were prepared according to route shown in Scheme 5. The alkylation of tosylamide 21 with ethyl 4-bromobutanoate (22) gave ester 23, which was reduced with DIBAL to give the corresponding aldehyde. The subsequent 1,2-addition of lithium (trimethylsilyl)acetylide (15) to this aldehyde, followed by the removal of the TMS group with TBAF afforded the terminal alkyne 25 in excellent yield. The Sonogashira coupling reaction of alkyne 25 with o-iodoaniline (16) provided alkynylaniline 26 in 90% yield. The oxidation of 26 with MnO₂ gave the corresponding ketone 27 in 71% yield, which was treated with TIPSOTf or TBSOTf in the presence of Et₃N to give the conjugated enyne-type silyl enol ethers 11a and 11b in 75 and 81% yields, respectively. It is noteworthy that the (E)- and (Z)-isomers¹² of 11 could be separated, as necessary, by column chromatography over silica gel followed by PTLC (see Supporting Information).

Scheme 5. Preparation and Gold-Catalyzed Cyclization of the Conjugated Enynes 11a and 11b
We then investigated the gold(I)-catalyzed cascade reaction of the enol ether-type conjugated enynes 11a and 11b (Table 1). The treatment of enyne 11a with L1Au(MeCN)SbF6 (5 mol %) (Figure 2) in toluene-d8 at room temperature afforded the desired product 9 (16%), as well as the two monocyclization products 28 (34%) and 29 (14%). To drive the reaction to completion, we investigated the use of an additive as a proton source as well as silyl scavenger. Fortunately, the addition of H2O improved the yields of 9 to 38% (entry 2). In contrast, the use of MeOH was less efficient (entry 3). The use of an IPr ligand was found to be unsuitable for this reaction (entry 4). Similarly, several other experiments using NaBARF8h (Figure 2) as the counter anion (entry 5), CD2Cl2 as a solvent (entry 6) or the TBS ether 11b as a substrate (entry 7) did not improve the yield.

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>additive</th>
<th>R</th>
<th>time (h)</th>
<th>yield(%)</th>
<th>9</th>
<th>28</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>–</td>
<td>TIPS</td>
<td>24</td>
<td>16</td>
<td>34</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td>H2O</td>
<td>TIPS</td>
<td>24</td>
<td>38</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>L1</td>
<td>MeOH</td>
<td>TIPS</td>
<td>19</td>
<td>29</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>IPr</td>
<td>H2O</td>
<td>TIPS</td>
<td>24</td>
<td>3</td>
<td>45</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
We then proceeded to investigate the enantioselective gold(I)-catalyzed cascade reaction of the conjugated enyne 11a (Table 2). Based on a related study reported by Toste and co-workers involving the asymmetric carbocyclization of a silyl enol ether,8h we investigated the use of biarylphosphine-type dinuclear chiral gold complexes to affect this reaction (Figure 2). The treatment of the conjugated enyne 11a with (R)-DTBM-SEGPHOS(AuCl)2 (5 mol %)/AgSbF6 (10 mol %) resulted in the formation of the undesired ketone 29 as the major product (entry 1). The use of (R)-MeO-DTBM-BIPHEP gave the desired product (S)-9 in 13% yield and 89% ee (entry 2). An increase in catalyst loading (10 mol % for the bimetallic gold complex) led to a slight decreased in the yield to 10%, as well as a decrease in the ee to 76% (entry 3). Expecting that the sterically less hindered (Z)-isomer has better reactivity, we examined the reaction of the both isomers, (Z)- and (E)-11a. Interestingly, the use of (Z)-11a led to an improvement in the yield of (S)-9 to 32% (entry 5), whereas the reaction of (E)-11a failed to afford the desired product (entry 4). Taken together,
these results suggested that it was only possible to generate the desired product 9 from the Z-isomer of 11a when a E/Z mixture of 11a was used as the substrate (entries 1–3). The use of 11a in conjunction with a decreased loading of H2O (1.0 equiv) led to an improvement in the ee to 91%, although the yield dropped to 18% (entry 6).

Table 2. Enantioselective Gold(I)-Catalyzed Cyclization

<table>
<thead>
<tr>
<th>entry</th>
<th>Z/E (11)</th>
<th>catalyst</th>
<th>time (h)</th>
<th>yield of 9 (%)b</th>
<th>% ee[c]</th>
<th>[[(S)-9]]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/47</td>
<td>(R)-DTBM-SEGPHOS(AuCl)2/AgSbF6</td>
<td>24</td>
<td>N.D. d,e</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>53/47</td>
<td>(R)-MeO-DTBM-BIPHEP(AuCl)2/AgSbF6</td>
<td>19</td>
<td>13</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>53/47</td>
<td>(R)-MeO-DTBM-BIPHEP(AuCl)2/AgSbF6</td>
<td>19</td>
<td>ca.10</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>E only</td>
<td>(R)-MeO-DTBM-BIPHEP(AuCl)2/AgSbF6</td>
<td>20</td>
<td>N.D. e</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Z only</td>
<td>(R)-MeO-DTBM-BIPHEP(AuCl)2/AgSbF6</td>
<td>17</td>
<td>32</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>6g</td>
<td>83/17</td>
<td>(R)-MeO-DTBM-BIPHEP(AuCl)2/AgSbF6</td>
<td>14</td>
<td>18</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

a Unless otherwise noted, these reactions were carried out using 11a in toluene (0.2 M) at room temperature in the presence of H2O (1.5 equiv) with a catalyst loading of 5 (for the bimetallic gold complex) and 10 mol % (for AgSbF6). b Isolated yields. c Determined by chiral HPLC. d Ketone 29 was obtained as the major product. e N.D. = not detected. f The catalyst loading was increased to 10 and 20 mol %. g Using H2O (1.0 equiv).

Finally, we investigated the conversion of the bis-cyclization product (S)-9 (91% ee) to (+)-conolidine (1). The treatment of (S)-9 with Na/naphthalene resulted in the cleavage of the Ts protecting group to give the known conolidine precursor 7 in 60% yield (Scheme 6). According to the procedure reported by Bohn, Micalizio, and co-workers,2 we obtained (+)-conolidine (1) in 34% yield and 84% ee. The spectroscopic and specific optical rotation data for the synthetic conolidine were identical to those reported in the literature.1,2

Scheme 6. Total Synthesis of (+)-Conolidine
In conclusion, we have achieved the total synthesis of (+)-conolidine based on the gold(I)-catalyzed cascade cyclization of a conjugated enyne. This study has shown that the feasibility of catalytic asymmetric reactions involving chiral gold(I) complexes for the construction of stemmadenine-type scaffolds.

**Experimental Section**

**General Methods.** For open column chromatography, silica gel or NH₂ silica gel was employed. Thin layer chromatography was performed on TLC silica gel 60 F₂₅₄ or NH₂ silica gel 60 F₂₅₄ plate (layer thickness 0.25 mm), which were developed using standard visualizing agents: UV fluorescence (254 nm) and anisaldehyde with heating. Melting points were measured by a hot stage melting point apparatus (uncorrected). In ¹H NMR spectra, chemical shifts are reported in δ (ppm) relative to TMS as internal standard. In ¹³C NMR spectra, chemical shifts are referenced to the residual solvent signal. ¹H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s).

The compounds 16, 18, 22, and (R)-DTBM-SEGPHOS(AuCl)₂ were obtained commercially and used without further purification. The known compounds S₁,¹⁴ S₄,¹⁵ S₇,¹⁶ 17,⁹ 21,¹¹ and (R)-MeO-BIPHES(AuCl)₂¹⁷,¹⁸ were prepared according to the literature. Structures of S₁–S₉ are shown in Schemes S₁–S₃ (Supporting Information).

**Preparation of Starting Materials.**

**(R)-2-Phenyl-2-({2-[((trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol (S₂).** The coupling of
S1 and trimethylsilylacetylene was carried out according to the reported method\textsuperscript{19} as follows: to a stirred suspension of S1 (1.42 g, 4.86 mmol), PdCl\textsubscript{2}(PhCN)\textsubscript{2} (112 mg, 0.29 mmol) and CuI (55.6 mg, 0.29 mmol) in dry 1,4-dioxane (10 mL) under argon were added diisopropylamine (3.4 mL, 24.2 mmol), trimethylsilylacetylene (0.7 mL, 5.06 mmol) and tri(tert-butyl)phosphine (0.2 mL, 0.85 mmol). After stirring at 50 °C for 12 h, the reaction mixture was diluted with EtOAc and filtered through a short pad of silica gel. The filtrate was concentrated \textit{in vacuo} and the residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford S2 (976 mg, 65\%) as amber oil: [\(\alpha\)]\textsubscript{29}D 242 (c 0.51, CHCl\textsubscript{3}); IR (neat): 3393 (OH), 2143 (C≡C); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 0.30 (s, 9H), 1.69 (br s, 1H), 3.80-3.83 (br m, 1H), 3.96-4.00 (br m, 1H), 4.56-4.57 (br m, 1H), 5.52-5.53 (br m, 1H), 6.38 (d, \(J = 8.6\) Hz, 1H), 6.57-6.58 (m, 1H), 7.00-7.04 (m, 1H), 7.25-7.35 (m, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\): 0.0 (3C), 59.3, 67.3, 100.7, 101.8, 108.0, 110.9, 116.6, 126.5 (2C), 127.6, 128.7 (2C), 129.9, 131.7, 139.7, 148.4; HRMS (FAB) calcd for C\textsubscript{19}H\textsubscript{24}NOSi (MH\textsuperscript{+}) 310.1622, found 310.1620.

\((R)-2-[(2-Ethynylphenyl)amino]-2-phenylethan-1-ol (S3).\) The desilylation of S2 was carried out according to the reported method\textsuperscript{20} as follows: K\textsubscript{2}CO\textsubscript{3} (1.08 g, 8.0 mmol) was added to the solution of S2 (804 mg, 2.60 mmol) in MeOH (26 mL). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO\textsubscript{4}, and concentrated \textit{in vacuo}. The residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford S3 (445 mg, 72\%) as pale amber powder: mp 79 °C; [\(\alpha\)]\textsubscript{26}D 240 (c 1.06, CHCl\textsubscript{3}); IR (neat): 3401 (OH), 3253 (C≡CH), 2089 (C≡C); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 1.66 (dd, \(J = 7.5, 5.2\) Hz, 1H), 3.50 (s, 1H), 3.82-3.87 (m, 1H), 3.97-4.03 (m, 1H), 4.60 (dd, \(J = 10.4, 6.4\) Hz, 1H), 5.47-5.48 (br m, 1H), 6.39 (d, \(J = 8.7\) Hz, 1H), 6.59-6.61 (m, 1H), 7.04-7.06 (m, 1H), 7.27-7.30 (m, 1H), 7.31-7.38 (m, 5H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\): 59.4, 67.3, 80.6, 83.3, 106.9, 111.1, 116.8, 126.6 (2C), 127.7, 128.9 (2C), 130.2, 132.6, 139.6, 148.4; HRMS (FAB) calcd for C\textsubscript{16}H\textsubscript{18}NO (MH\textsuperscript{+}) 238.1226, found 238.1232.

\((R)-2-Phenyl-2-[[2-(phenylbuta-1,3-diyn-1-yl)phenyl]amino]ethan-1-ol (2a).\) The coupling
of S3 and ethynylbenzene was carried out according to the reported method\textsuperscript{21} as follows: a mixture of S3 (432 mg, 1.82 mmol), ethynylbenzene (1.0 mL, 9.11 mmol), Cu(OAc)\textsubscript{2}·H\textsubscript{2}O (36.3 mg, 0.18 mmol) and piperidine (0.5 mL, 5.06 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (9 mL) was stirred in open atmospheric air at room temperature for 5 h. The reaction mixture was concentrated \textit{in vacuo} and the residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford 2a (349 mg, 57\%) as amber oil: [\alpha]\textsubscript{26}D 470 (c 1.00, CHCl\textsubscript{3}); IR (neat): 3391 (OH), 2208 (C≡C), 2140 (C≡C); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 1.71-1.73 (m, 1H), 3.86-3.89 (m, 1H), 3.99-4.04 (m, 1H), 4.60-4.62 (m, 1H), 5.45-5.47 (br m, 1H), 6.38 (d, \(J = 8.1\) Hz, 1H), 6.60-6.62 (m, 1H), 7.05-7.07 (m, 1H), 7.27-7.31 (m, 1H), 7.33-7.39 (m, 8H), 7.56-7.57 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\): 59.4, 67.2, 74.0, 78.5, 79.7, 83.0, 106.5, 111.3, 117.0, 121.8, 126.6 (2C), 127.7, 128.4 (2C), 128.8 (2C), 129.1, 130.7, 132.4 (2C), 133.4, 139.4, 149.4; HRMS (FAB) calcd for C\textsubscript{24}H\textsubscript{20}NO (MH\textsuperscript{+}) 338.1539, found 338.1537.

\((\pm)-(1R,2S)-2-[(2-Bromophenyl)amino]-1,2-diphenylethan-1-ol \ [(\pm)-S5]\). The reaction of 2-bromoiodobenzene and (\pm)-S4 was carried out according to the reported method\textsuperscript{14} as follows: a mixture of 2-bromoiodobenzene (0.9 mL, 7.01 mmol), (\pm)-S4 (1.72 g, 8.06 mmol), NaOH (600 mg, 15.0 mmol), and CuI (35.7 mg, 0.19 mmol) was stirred under argon at 90 °C for 13 h. The reaction mixture was diluted with EtOAc, washed water and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. The residue was chromatographed on silica gel (hexane/EtOAc = 10/1) to afford (\pm)-S5 (2.06 g, 80\%) as pale amber powder: mp 100 °C; IR (neat): 3398 (OH), 1321 (NH); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 2.37-2.39 (br m, 1H), 4.67-4.69 (m, 1H), 5.06-5.07 (m, 1H), 5.14-5.16 (br m, 1H), 6.35 (d, \(J = 8.0\) Hz, 1H), 6.48 (t, \(J = 7.7\) Hz, 1H), 6.93 (t, \(J = 7.7\) Hz, 1H), 7.11-7.12 (m, 4H), 7.23-7.24 (m, 3H), 7.27-7.28 (m, 3H), 7.35-7.37 (m, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\): 64.4, 78.0, 110.5, 112.8, 118.0, 126.5 (2C), 127.1 (2C), 127.7, 128.0, 128.2, 128.3 (2C), 128.6 (2C), 132.2, 139.6, 140.4, 143.9. \textit{Anal. calcd for C\textsubscript{20}H\textsubscript{18}BrNO: C, 65.23; H, 4.93; N, 3.80. Found: C, 65.48; H, 4.89; N, 3.79.}

\((\pm)-(1R,2S)-1,2-Diphenyl-2-[(2-[(trimethylsilyl)ethynyl]phenyl)amino]ethan-1-ol \ [(\pm)-S6]\). According to the procedure described for the preparation of S2, (\pm)-S5 (2.95 g, 8.01 mmol) was
converted to (±)-S6 (2.72 g, 88%). Column chromatography: silica gel (hexane/EtOAc = 10/1): dark brown oil; IR (neat): 3298 (OH), 2140 (C≡C), 1252 (NH); $^1$H NMR (500 MHz, CDCl$_3$) δ: 0.31 (s, 9H), 2.30-2.31 (br m, 1H), 4.73-4.74 (br m, 1H), 5.10-5.11 (br m, 1H), 5.57-5.58 (br m, 1H), 6.36 (d, $J = 8.0$ Hz, 1H), 6.53-6.54 (m, 1H), 6.97-6.99 (m, 1H), 7.09-7.11 (m, 4H), 7.22-7.27 (m, 7H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 0.0 (3C), 63.2, 76.9, 100.2, 101.7, 108.0, 110.8, 116.5, 126.3 (2C), 127.4, 127.6 (2C), 127.7, 127.96 (2C), 128.02 (2C), 129.7, 132.0, 137.9, 139.7, 147.8; HRMS (FAB) calcd for C$_{25}$H$_{28}$NOSi (MH$^+$) 386.1935, found 386.1927.

(±)-(1$^R$,2$^S$)-2-[(2-Ethynylphenyl)amino]-1,2-diphenylethan-1-ol [(±)-13a]. According to the procedure described for the preparation of S3, (±)-S6 (1.44 g, 3.74 mmol) was converted into (±)-13a (852 mg, 73%). Column chromatography: silica gel (hexane/CHCl$_3$= from 1/1 to 1/2): amber oil; IR (neat): 3396 (OH), 3292 (C≡CH), 2094 (C≡C); $^1$H NMR (500 MHz, CDCl$_3$) δ: 2.54-2.55 (br m, 1H), 3.38 (s, 1H), 4.70-4.71 (br m, 1H), 5.02-5.03 (br m, 1H), 5.44-5.45 (br m, 1H), 6.30 (d, $J = 8.6$ Hz, 1H), 6.52-6.53 (m, 1H), 6.94-6.98 (m, 1H), 7.06-7.08 (m, 4H), 7.17-7.28 (m, 7H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 63.1, 77.2, 80.6, 83.1, 107.0, 111.1, 116.7, 126.6 (2C), 127.55, 127.63 (2C), 128.0, 128.1 (2C), 128.2 (2C), 130.1, 131.2, 138.3, 139.5, 148.2; HRMS (FAB) calcd for C$_{22}$H$_{20}$NO (MH$^+$) 314.1539, found 314.1535.

(±)-(1$^R$,2$^S$)-1,2-Diphenyl-2-[[2-(phenylbuta-1,3-diyn-1-yl)phenyl]amino]ethan-1-ol [(±)-2b]. According to the procedure described for the preparation of 2a, (±)-13a (430 mg, 1.37 mmol) was converted into (±)-2b (337 mg, 59%). Column chromatography: silica gel (hexane/CHCl$_3$= 1/1 to CHCl$_3$ only): brown powder; mp 122–124 °C; IR (neat): 3401 (OH), 2209 (C≡C), 2141 (C≡C); $^1$H NMR (500 MHz, CDCl$_3$) δ: 2.43-2.43 (br m, 1H), 4.72-4.73 (br m, 1H), 5.05-5.06 (br m, 1H), 5.45-5.46 (br m, 1H), 6.29 (d, $J = 8.6$ Hz, 1H), 6.54 (t, $J = 7.4$ Hz, 1H), 6.98 (t, $J = 7.4$ Hz, 1H), 7.16 (d, $J = 6.9$ Hz, 4H), 7.26-7.30 (m, 3H), 7.36-7.41 (m, 3H), 7.59-7.60 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 63.4, 74.1, 77.5, 78.5, 79.9, 82.9, 106.6, 111.2, 116.9, 122.0, 126.6 (2C), 127.2 (2C), 127.8, 128.2, 128.4 (2C), 128.5 (2C), 128.6 (2C), 129.2, 130.7, 132.4 (2C), 132.9, 138.5, 139.2, 149.3; HRMS (FAB) calcd for C$_{30}$H$_{24}$NO (MH$^+$) 414.1852, found 414.1860.
Ethyl 2-Phenyl-2-((2-[[trimethylsilyl]ethynyl]phenyl)amino)acetate [(±)-S8]. To a stirred suspension of (±)-S7 (2.59 g, 6.78 mmol), PdCl2(PPh3)2 (119 mg, 0.17 mmol) and CuI (32.3 mg, 0.17 mmol) in THF (14 mL) under argon was added trimethylsilylacetylene (1.0 mL, 7.46 mmol) and Et3N (4.3 mL, 33.9 mmol). After stirring at rt for 3 h, the reaction mixture was diluted with EtOAc and filtered through a short pad of silica gel. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/CHCl3 = 3/1) to afford (±)-S8 (2.10 g, 88%) as amber oil: IR (neat): 2145 (C≡C), 1736 (C=O); 1H NMR (500 MHz, CDCl3) δ: 0.31 (s, 9H), 1.21 (t, J = 7.2 Hz, 3H), 4.13-4.16 (m, 1H), 4.23-4.26 (m, 1H), 5.09 (d, J = 5.7 Hz, 1H), 6.04-6.05 (br m, 1H), 6.29 (d, J = 8.6 Hz, 1H), 6.58-6.59 (m, 1H), 7.02-7.03 (m, 1H), 7.30 (d, J = 6.9 Hz, 2H), 7.34-7.36 (m, 2H), 7.50 (d, J = 6.9 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ: 0.00 (3C), 14.0, 60.4, 61.7, 100.8, 108.1, 101.5, 110.3, 116.8, 127.0 (2C), 128.2, 128.7 (2C), 129.8, 131.8, 137.4, 147.2, 171.0; HRMS (FAB) calcd for C21H26NO2Si (MH+) 352.1733, found 352.1726.

Ethyl 2-[(2-Ethynylphenyl)amino]-2-phenylacetate [(±)-13b]. According to the procedure described for the preparation of S3, (±)-S8 (5.27 g, 15.0 mmol) was converted into (±)-13b (2.99 g, 71%). Column chromatography: silica gel (hexane/EtOAc = 20/1) The product was recrystallized from CHCl3–hexane: white powder; mp 100 °C; IR (neat): 3264 (C≡CH), 2095 (C≡C), 1723 (C=O); 1H NMR (500 MHz, CDCl3) δ: 1.22 (t, J = 7.2 Hz, 3H), 3.51 (s, 1H), 4.15 (dq, J = 11.0, 7.0 Hz, 1H), 4.24 (dq, J = 11.0, 7.0 Hz, 1H), 5.11 (d, J = 5.7 Hz, 1H), 6.03-6.04 (br m, 1H), 6.30 (d, J = 8.6 Hz, 1H), 6.61 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H), 7.05-7.07 (m, 1H), 7.29-7.31 (m, 1H), 7.35-7.37 (m, 3H), 7.49-7.51 (m, 2H); 13C NMR (125 MHz, CDCl3) δ: 14.0, 60.3, 61.9, 80.3, 83.2, 107.1, 110.5, 117.0, 127.1 (2C), 128.3, 128.8 (2C), 130.1, 132.6, 137.3, 147.3, 171.2. Anal. calcd for C18H17NO2: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.36; H, 6.11; N, 5.00.

Ethyl 2-[(2-(Hepta-1,3-diyn-1-yl)phenyl)amino]-2-phenylacetate [(±)-S9]. According to the procedure described for the preparation of 2a, (±)-13b (836 mg, 3.0 mmol) was converted into S9 (621 mg, 60%). Column chromatography: silica gel (hexane/EtOAc = 10/1): brown powder; mp 83–84 °C; IR (neat): 2236 (C≡C), 2139 (C≡C), 1733 (C=O); 1H NMR (500 MHz, CDCl3) δ: 1.04 (t,
J = 7.4 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.63 (qt, J = 7.4, 7.2 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 4.14-4.27 (m, 2H), 5.09 (d, J = 6.3 Hz, 1H), 5.99-6.00 (br m, 1H), 6.28 (d, J = 8.0 Hz, 1H), 6.58-6.59 (m, 1H), 7.02-7.04 (m, 1H), 7.32-7.34 (m, 4H), 7.50 (d, J = 7.4 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ: 13.6, 14.0, 21.7, 21.8, 60.4, 61.9, 65.2, 71.2, 80.3, 86.0, 107.1, 110.6, 117.1, 127.1 (2C), 128.3, 128.8 (2C), 130.2, 133.3, 137.2, 148.1, 171.0; HRMS (FAB) calcd for C23H24NO2 (MH+) 346.1802, found 346.1804.

2-{(2-(Hepta-1,3-diyn-1-yl)phenyl)amino}-2-phenylacetic acid [(±)-2c]. To a stirred suspension of (±)-S9 (86.9 mg, 0.25 mmol) in EtOH (5 mL) was added THF until (±)-S9 dissolved (ca. 2 mL), and 0.4 N NaOH aq. (19 mL) was added to the reaction mixture. After stirring at rt for 40 min, the reaction mixture was diluted with CH2Cl2, washed with water, 1N HCl aq., and brine, dried over Na2SO4, and concentrated in vacuo. The residue was recrystallized from CH2Cl2–hexane to afford (±)-2c (43.3 mg, 54%): white solid; mp 164–166 °C; IR (neat): 3394 (O H), 2238 (C≡C), 2147 (C≡C), 1709 (C=O); 1H NMR (500 MHz, CDCl3) δ: 1.04 (t, J = 7.4 Hz, 3H), 1.63 (qt, J = 7.4, 6.9 Hz, 2H), 2.37 (t, J = 6.9 Hz, 2H), 5.14 (s, 1H), 6.30-6.32 (m, 1H), 6.61-6.63 (m, 1H), 7.04-7.08 (m, 1H), 7.35-7.37 (m, 4H), 7.51-7.52 (m, 2H); 13C NMR (125 MHz, CDCl3) δ: 13.5, 21.68, 21.74, 60.2, 65.1, 71.0, 80.4, 86.2, 107.3, 110.6, 117.6, 127.2 (2C), 128.8, 129.1 (2C), 130.3, 133.4, 136.4, 147.8, 175.8; HRMS (FAB) calcd for C21H20NO2 (MH+) 318.1489, found 318.1485.

N-(But-2-yn-1-yl)-N-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (19). A mixture of 17 (4.47 g, 20.0 mmol) and Cs2CO3 (16.3 g, 50.0 mmol) in dry DMF (100 mL) was stirred in open atmospheric air at 0 ºC. After stirring at the same temperature for 0.5 h, 1-bromobut-2-yne (18) (2.7 mL, 29.8 mmol) was added to the mixture. The mixture was stirred for 0.5 h. The mixture was diluted with Et2O, washed with water and brine, dried over MgSO4, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford 19 (5.33 g, 97%) as colorless oil: IR (neat): 3288 (C≡CH), 2224 (C≡C), 2120 (C≡C), 1343 (S=O), 1156 (S=O); 1H NMR (500 MHz, CDCl3) δ: 1.58 (t, J = 2.1 Hz, 3H), 2.01 (t, J = 2.5 Hz, 1H), 2.42 (s, 3H), 2.51 (td, J = 7.4, 2.5 Hz, 2H), 3.35 (t, J = 7.4 Hz, 2H), 4.12 (q, J = 2.1 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H),
7.73 (d, J = 8.0 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ: 3.2, 18.9, 21.4, 37.7, 45.3, 70.1, 71.7, 80.8, 81.7, 127.6 (2C), 129.3 (2C), 135.9, 143.3; HRMS (FAB) calcd for C15H18NO2S (MH+) 276.1058, found 276.1059.

N-(But-2-yn-1-yl)-N-[6-((1R,2S)-2-hydroxy-1,2-diphenylethyl]amino]phenyl]hexa-3,5-diyn-1-yl]-4-methylbenzenesulfonamide [(±)-10a]. A mixture of 19 (1.10 g, 4.0 mmol), AgNO3 (203 mg, 1.20 mmol), and NIS (1.26 g, 5.60 mmol) in acetone (100 mL) was stirred in open atmospheric air at room temperature under dark. After stirring at the room temperature for 1 h, the mixture was concentrated in vacuo. The residue was diluted with CHCl3, washed with water and brine, dried over MgSO4, and concentrated in vacuo. This crude iodide 12 was used for the next reaction without further purification. According to the reported method,22 the copper-mediated coupling of (±)-13a and 12 was conducted as follows: 12, (±)-13a (0.63 g, 2.02 mmol), and CuCl (60.0 mg, 0.60 mmol) in piperidine (7.0 mL) was stirred at room temperature under argon for 3 h. The reaction mixture was quenched with aqueous saturated NH4Cl, diluted with Et2O, washed with brine, dried over Na2SO4, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc =10/1) to afford (±)-10a (0.31 g, 19% based on (±)-13a) as pale amber amorphous: IR (neat): 3396 (OH), 2230 (C≡C), 2214 (C≡C), 1327 (S=O), 1157 (S=O); 1H NMR (500 MHz, CDCl3) δ: 1.58 (t, J = 2.0 Hz, 3H), 2.40 (s, 3H), 2.59 (br s, 1H), 2.77 (t, J = 7.4 Hz, 2H), 3.44 (t, J = 7.4 Hz, 2H), 4.14-4.15 (br m, 2H), 4.69-4.70 (br m, 1H), 5.07 (br s, 1H), 5.48-5.49 (br m, 1H), 6.26 (d, J = 8.6 Hz, 1H), 6.51 (t, J = 7.2 Hz, 1H), 6.94-6.97 (m, 1H), 7.11-7.11 (m, 4H), 7.24-7.28 (m, 9H), 7.75 (d, J = 8.0 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ: 3.3, 20.3, 21.4, 37.9, 45.2, 63.1, 67.0, 71.7, 72.5, 77.2, 79.8, 81.8, 81.9, 106.3, 111.1, 116.7, 126.5 (2C), 127.55, 127.58 (2C), 127.7 (2C), 128.0, 128.15 (2C), 128.22 (2C), 129.4 (2C), 130.4, 132.8, 135.6, 138.3, 139.3, 143.5, 149.3; HRMS (FAB) calcd for C37H35N2O3S (MH+) 587.2368, found 587.2363.

Ethyl 2-[[2-(6-[[N-(But-2-yn-1-yl)-4-methylphenyl]sulfonamide]hexa-1,3-diyn-1-yl]phenyl]amino]-2-phenylacetate [(±)-S10]. According to the procedure described for the preparation of (±)-10a, (±)-13b (12.0 g, 3.0 mmol) was converted to (±)-S10 (0.80 g, 73%) by the
reaction with 12 in the presence of CuCl (59.4 mg, 0.6 mmol) in piperidine (7 mL) at room temperature for 4 h. Column chromatography: silica gel (hexane/EtOAc = 3/1); yellow oil; IR (neat): 2226 (C≡C), 2146 (C≡C), 1735 (C=O), 1328 (S=O), 1158 (S =O); 1H NMR (500 MHz, CDCl3) δ: 1.22 (t, J = 7.2 Hz, 3H), 1.61 (t, J = 2.3 Hz, 3H), 2.41 (s, 3H), 2.71-2.74 (m, 2H), 3.39-3.42 (m, 2H), 4.12-4.27 (m, 4H), 5.09 (d, J = 5.7 Hz, 1H), 5.98 (d, J = 5.7 Hz, 1H), 6.28 (d, J = 8.6 Hz, 1H), 6.57-6.60 (m, 1H), 7.02-7.05 (m, 1H), 7.30-7.35 (m, 6H), 7.49 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ: 3.3, 13.9, 20.3, 21.4, 38.0, 45.2, 60.3, 61.9, 66.8, 71.8, 72.2, 79.8, 81.8, 81.9, 106.6, 110.6, 117.1, 127.0 (2C), 127.7 (2C), 128.3, 128.8 (2C), 129.4 (2C), 130.4, 133.3, 135.8, 137.1, 143.4, 148.2, 170.9; HRMS (FAB) calcd for C33H33N2O4S (MH+) 553.2161, found 553.2155.

2-[[2-(6-[[N-(But-2-yn-1-yl)-4-methylphenyl]sulfonamide]hexa-1,3-diyn-1-yl]phenyl]amino]-2-phenylacetic Acid [(±)-10b]. THF (ca. 2 mL) was added to the mixture (±)-S10 (0.15 g, 0.27 mmol) and 0.4N NaOH (2 mL) in EtOH (4 mL). After stirring at the room temperature for 0.5 h, the reaction mixture was diluted with CH2Cl2, washed with water, 1N HCl, and brine, dried over Na2SO4, and concentrated in vacuo to afford (±)-10b (0.14 g, 95%) as brown powder; mp 64–65 ºC; IR (neat): 3386 (OH), 2309 (C≡C), 2145 (C≡C), 1715 (C=O), 1326 (S=O), 1157 (S=O); 1H NMR (500 MHz, CDCl3) δ: 1.60 (br s, 3H), 2.42 (s, 3H), 2.71-2.72 (br m, 2H), 3.39-3.41 (br m, 2H), 4.12 (br s, 2H), 5.12 (br s, 1H), 6.31-6.32 (br m, 1H), 6.61-6.63 (m, 1H), 7.06-7.07 (m, 1H), 7.29-7.37 (m, 7H), 7.50-7.52 (m, 2H), 7.75 (d, J = 8.0 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ: 3.3, 20.3, 21.5, 37.9, 45.1, 60.2, 66.8, 71.8, 72.2, 79.8, 81.9, 82.1, 106.6, 110.7, 117.4, 127.2 (2C), 127.7 (2C), 128.6, 129.0 (2C), 129.4 (2C), 130.5, 133.5, 135.7, 136.5, 143.5, 148.0, 176.0; HRMS (FAB) calcd for C31H29N2O4S (MH+) 525.1848, found 525.1849.

Ethyl 4-[[N-(But-2-yn-1-yl)-4-methylphenyl]sulfonamide]butanoate (23). The coupling of 21 and ethyl 4-bromobutanoate (22) was carried out according to the reported method as follows: a mixture of 21 (448 mg, 2.0 mmol) and NaH (48.0 mg, 2.4 mmol) in dry DMF (5 mL) was stirred at room temperature for 0.5 h under argon. 4-Bromobutanoate (22) (0.17 mL, 2.4 mmol) was added
to the reaction mixture. The mixture was stirred for 3 h. The mixture was quenched with aqueous saturated NH₄Cl, diluted with EtOAc, washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 10/1) to afford 23 (0.68 g, 100%) as pale yellow oil: IR (neat): 1730 (C=O), 1345 (S=O), 1157 (S=O); ¹H NMR (500 MHz, CDCl₃) δ: 1.26 (t, J = 7.2 Hz, 3H), 1.54 (t, J = 2.3 Hz, 3H), 1.88 (tt, J = 6.6, 6.6 Hz, 2H), 2.40-2.41 (m, 5H), 3.21 (t, J = 6.6 Hz, 2H), 4.05 (q, J = 2.3 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 3.2, 14.2, 21.5, 22.7, 31.1, 36.8, 45.5, 60.5, 71.6, 81.6, 127.8 (2C), 129.2 (2C), 136.0, 143.2, 173.1; HRMS (FAB) calcd for C₁₇H₂₄NO₄S (MH⁺) 338.1426, found 338.1423.

N-(But-2-yn-1-yl)-N-[4-hydroxy-6-(trimethylsilyl)hex-5-yn-1-yl]-4-methylbenzenesulfonamide (24). Alkynylation was carried out according to the reported method as follows: to a mixture of 23 (2.70 g, 8.0 mmol) in dry CH₂Cl₂ (40 mL) was added 1M DIBAL in toluene (9 mL, 8.7 mmol) at –78 ºC under argon. After stirring at the same temperature for 1 h, the reaction was quenched with MeOH (1 equiv) and H₂O (6 equiv) at –78 ºC, and the resulting slurry was allowed to warm to room temperature. It was then filtered through MgSO₄ and Celite and the solvent was evaporated under reduced pressure to leave aldehyde 14 as a yellow liquid. This crude material was used for the next reaction without further purification. To a mixture of trimethylsilylacetylene (1 mL, 7.20 mmol) in dry THF (36 mL) at –78 ºC under argon was added n-BuLi in THF (2.6M solution in n-BuLi; 3.1 mL, 8.0 mmol) dropwise, and the mixture was stirred at –78 ºC for 0.5 h to afford a solution of lithium trimethylsilylacetylide (15), to which the solution of 14 in THF (18 mL) was slowly added. After stirring at –78 ºC for 2 h, the reaction mixture was cooled to room temperature, quenched with aqueous saturated NH₄Cl, diluted with Et₂O, washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc =3/1) to afford 24 (2.81 g, 90%) as colorless oil: IR (neat): 3511 (OH), 2223 (C≡C), 2170 (C≡C), 1345 (S=O), 1158 (S=O); ¹H NMR (500 MHz, CDCl₃) δ: 0.17 (s, 9H), 1.53 (t, J = 2.3 Hz, 3H), 1.72-1.77 (m, 4H), 2.03-2.04 (br m, 1H), 2.42 (s, 3H), 3.20-3.21 (br m, 2H),
4.06 (q, \( J = 2.3 \) Hz, 2H), 4.42-4.43 (br m, 1H), 7.28-7.30 (m, 2H), 7.72-7.73 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 0.0 (3C), 3.4, 21.7, 23.1, 34.4, 36.6, 45.8, 62.5, 71.7, 81.7, 89.9, 106.4, 128.0 (2C), 129.4 (2C), 136.1, 143.3; HRMS (FAB) calcd for C\(_{20}\)H\(_{30}\)NO\(_3\)SSi (MH\(^+\)) 392.1716, found 392.1710.

\( N \)-(But-2-yn-1-yl)-\( N \)-(4-hydroxyhex-5-yn-1-yl)-4-methylbenzenesulfonamide (25).\) To a mixture of 24 (4.48 g, 11.4 mmol) in dry THF (23 mL) at 0 °C under argon was added 1M TBAF in THF (11.5 mL, 11.4 mmol) dropwise, and the mixture was stirred at room temperature for 0.7 h. The mixture was diluted with CH\(_2\)Cl\(_2\), washed with water and brine, dried over Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo}. The residue was chromatographed on silica gel (hexane/EtOAc =5/1) to afford 25 (3.42 g, 94%) as pale amber oil: IR (neat): 3516 (OH), 3284 (C ≡H), 2225 (C≡C), 2114 (C≡C), 1327 (S=O), 1156 (S=O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 1.54 (br s, 3H), 1.72-1.81 (m, 4H), 2.31 (br s, 1H), 2.42 (s, 3H), 2.48-2.48 (br m, 1H), 3.21 (t, \( J = 6.6 \) Hz, 2H), 4.06-4.06 (br m, 2H), 4.45 (br s, 1H), 7.29 (d, \( J = 8.0 \) Hz, 2H), 7.72 (d, \( J = 8.0 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 3.3, 21.4, 22.8, 34.1, 36.5, 45.6, 61.6, 71.5, 73.1, 81.6, 84.5, 127.8 (2C), 129.2 (2C), 135.8, 143.2; HRMS (FAB) calcd for C\(_{17}\)H\(_{22}\)NO\(_3\)S (MH\(^+\)) 320.1320, found 320.1318.

\( N \)-(6-(2-Aminophenyl)-4-hydroxyhex-5-yn-1-yl)-\( N \)-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (26).\) Et\(_3\)N (1.5 mL, 12.0 mmol) was added to a stirred mixture of 25 (0.97 g, 3.02 mmol), 2-iodoaniline (16) (0.66 g, 3.03 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (53.1 mg, 0.08 mmol) and CuI (28.8 mg, 0.15 mmol) in CH\(_3\)CN (20 mL) under argon. After stirring at room temperature for 1.5 h, the mixture was diluted with EtOAc, washed with aqueous saturated NH\(_4\)Cl and brine, dried over Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo}. The residue was chromatographed on silica gel (hexane/EtOAc =2/1) to afford 26 (1.11 g, 90%) as colorless oil: IR (neat): 3379 (OH), 2301 (C≡C), 2218 (C≡C), 1328 (S=O), 1306 (NH), 1156 (S=O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 1.52 (t, \( J = 2.3 \) Hz, 3H), 1.78-1.90 (m, 4H), 2.40 (s, 3H), 2.49 (br s, 1H), 3.24 (t, \( J = 6.6 \) Hz, 2H), 4.06 (q, \( J = 2.3 \) Hz, 2H), 4.24 (br s, 2H), 4.70-4.72 (br m, 1H), 6.65-6.68 (m, 2H), 7.09-7.13 (m, 1H), 7.23-7.27 (m, 3H), 7.72 (d, \( J = 8.0 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 3.2, 21.4, 23.2, 34.6, 36.7, 45.8, 62.5,
According to the reported method,\textsuperscript{25} oxidation of 26 was conducted as follows: a mixture of 26 (421 mg, 1.03 mmol) and MnO\textsubscript{2} (882 mg, 10.3 mmol) in dry CHCl\textsubscript{3} (10 mL) was stirred under reflux for 0.5 h. The reaction mixture was cooled to room temperature, filtered through Celite, and concentrated \textit{in vacuo}. The residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford 27 (297 mg, 71\%) as orange amber oil: IR (neat): 2300 (C≡C), 2180 (C≡C), 1658 (C=O), 1342 (S=O), 1330 (NH), 1156 (S=O); \textit{1H NMR} (500 MHz, CDCl\textsubscript{3}) δ: 1.54 \textit{(t, } J = 2.3 Hz, 3H), 1.99 \textit{(tt, } J = 7.0, 7.0 Hz, 2H), 2.41 \textit{(s, 3H)}, 2.82 \textit{(t, } J = 7.2 Hz, 2H), 3.22 \textit{(t, } J = 6.6 Hz, 2H), 4.05 \textit{(q, } J = 2.3 Hz, 2H), 4.47 \textit{(br s, 2H)}, 6.68-6.69 \textit{(m, 2H)}, 7.20-7.24 \textit{(m, 1H)}, 7.28 \textit{(d, } J = 8.6 Hz, 2H), 7.36-7.37 \textit{(m, 1H)}, 7.72 \textit{(d, } J = 8.0 Hz, 2H); \textit{13C NMR} (125 MHz, CDCl\textsubscript{3}) δ: 3.2, 21.4, 21.9, 37.0, 42.1, 45.5, 71.5, 81.7, 89.1, 94.1, 103.4, 114.5, 117.8, 127.8 (2C), 129.2 (2C), 132.5, 133.8, 135.7, 143.3, 105.3, 186.5; HRMS (FAB) calcd for C\textsubscript{23}H\textsubscript{25}N\textsubscript{2}O\textsubscript{3}S (MH\textsuperscript{+}) 409.1586, found 409.1590.

\textbf{(E)- and (Z)-N-[6-(2-Aminophenyl)-4-oxohex-5-yn-1-yl]-N-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (11a).} TIPSOTf (0.9 mL, 3.24 mmol) was added dropwise to a mixture of 27 (883 mg, 2.16 mmol) and Et\textsubscript{3}N (0.8 mL, 6.84 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (36 mL) at –78 \degree C under argon, and the mixture was stirred for 2 h. The mixture allowed to warm slowly to room temperature. The mixture was diluted with EtOAc, washed with 3N HCl twice, water, aqueous saturated NaHCO\textsubscript{3} and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. The residue was chromatographed on silica gel (hexane/EtOAc =5/1) to afford 11a (921 mg, 75\%, Z/E = 85/15, determined by \textit{1H NMR}).\textsuperscript{11} Both products were isolated by column chromatography on silica gel followed by PTLC (silica gel) with hexane/EtOAc (10/1). Compound (Z)-11a (more polar isomer): amber oil; IR (neat): 2193 (C=C), 1616 (SiOC=C); \textit{1H NMR} (500 MHz, CDCl\textsubscript{3}) δ: 1.12 (d, \textit{J = 7.4 Hz, 18H}), 1.27-1.36 (m, 3H), 1.54 (t, \textit{J = 2.3 Hz, 3H}), 2.41 (s, 3H), 2.47-2.53 (m, 2H), 3.22 (t, \textit{J =
7.4 Hz, 2H), 4.09 (q, \( J = 2.3 \) Hz, 2H), 4.19 (br s, 2H), 5.09 (t, \( J = 7.2 \) Hz, 1H), 6.67-6.69 (m, 2H), 7.11-7.14 (m, 1H), 7.21 (d, \( J = 6.9 \) Hz, 1H), 7.28 (d, \( J = 8.0 \) Hz, 2H), 7.74 (d, \( J = 8.0 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 3.2, 12.9 (3C), 18.0 (6C), 21.5, 24.4, 36.7, 45.3, 71.8, 81.4, 83.7, 92.3, 107.1, 114.3, 114.8, 117.8, 127.8 (2C), 129.2 (2C), 129.9, 131.9, 134.1, 136.1, 143.1, 148.0; HRMS (FAB) calcd for C\(_{32}\)H\(_{45}\)N\(_2\)O\(_3\)SSi (MH\(^+\)) 565.2920, found 565.2919. Compound (\(E\))-11a (less polar isomer): amber oil; IR (neat): 2191 (C≡C), 1616 (SiOC=C); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 1.13 (d, \( J = 7.4 \) Hz, 18H), 1.27 (m, 3H), 1.51 (t, \( J = 2.3 \) Hz, 3H), 2.40 (s, 3H), 2.51-2.54 (m, 2H), 3.21 (t, \( J = 7.4 \) Hz, 2H), 4.10 (q, \( J = 2.3 \) Hz, 2H), 4.27 (br s, 2H), 5.30 (t, \( J = 8.0 \) Hz, 1H), 6.67-6.70 (m, 2H), 7.11-7.14 (m, 1H), 7.26-7.27 (m, 3H), 7.72 (d, \( J = 8.0 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 3.2, 12.5 (3C), 17.9 (6C), 21.5, 27.4, 37.0, 45.9, 71.8, 81.6, 89.1, 89.8, 107.0, 114.4, 114.6, 117.7, 127.8 (2C), 129.2 (2C), 130.0, 132.1, 135.8, 136.0, 143.1, 148.0; HRMS (FAB) calcd for C\(_{32}\)H\(_{45}\)N\(_2\)O\(_3\)SSi (MH\(^+\)) 565.2920, found 565.2913.

\((E)-\) and \((Z)-\)N-{6-(2-Aminophenyl)-4-[(tert-butyldimethylsilyl)oxy]hex-3-en-5-yn-1-yl}-N-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (11b). TBSOTf (0.2 mL, 0.81 mmol) was added dropwise to a mixture of 27 (166 mg, 0.41 mmol) and Et\(_3\)N (0.1 mL, 0.81 mmol) in dry CH\(_2\)Cl\(_2\) (0.8 mL) at 0 °C under argon and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with 1N HCl, water, aqueous saturated NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc =5/1) to afford 11b (171 mg, 81%, \( Z/E = 73/27 \), determined by \(^{1}\)H NMR).\(^{11}\) Both products were isolated by column chromatography on silica gel followed by PTLC (silica gel) with hexane/EtOAc (10/1). Compound (\(Z\))-11b (more polar isomer): reddish amber oil; IR (neat): 2193 (C≡C), 1616 (SiOC=C); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 0.26 (s, 6H), 0.96 (s, 9H), 1.54 (t, \( J = 2.3 \) Hz, 3H), 2.41 (s, 3H), 2.45 (dt, \( J = 7.4, 7.4 \) Hz, 2H), 3.21 (t, \( J = 7.4 \) Hz, 2H), 4.09 (q, \( J = 2.3 \) Hz, 2H), 4.20 (br s, 2H), 5.13 (t, \( J = 7.4 \) Hz, 1H), 6.67-6.69 (m, 2H), 7.12-7.13 (m, 1H), 7.25-7.28 (m, 3H), 7.73 (d, \( J = 8.6 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): –4.1 (2C), 3.2, 18.1, 21.5, 24.3, 25.7 (3C), 36.7, 45.3, 71.7, 81.5, 84.3, 92.1, 107.0, 114.3, 115.2, 117.8, 127.8 (2C), 129.2 (2C), 129.9, 131.9, 133.8,
Compound (E)-11b (less polar isomer): reddish amber oil; IR (neat): 2193 (C≡C), 1616 (SiOC=C); 
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 0.23 (s, 6H), 0.96 (s, 9H), 1.51 (t, \(J = 2.3\) Hz, 3H), 2.40 (s, 3H), 2.52 (dt, \(J = 7.6, 7.6\) Hz, 2H), 3.22 (t, \(J = 2.3\) Hz, 2H), 4.10 (q, \(J = 2.3\) Hz, 2H), 4.27 (br s, 2H), 5.27 (t, \(J = 8.0\) Hz, 1H), 6.66-6.70 (m, 2H), 7.11-7.14 (m, 1H), 7.25-7.29 (m, 3H), 7.72 (d, \(J = 8.6\) Hz, 2H); 
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): –4.4 (2C), 3.2, 18.1, 21.5, 25.6 (3C), 27.3, 37.0, 45.9, 71.8, 81.6, 89.4, 89.7, 107.0, 114.4, 115.1, 117.7, 127.8 (2C), 129.2 (2C), 130.1, 132.1, 135.4, 136.0, 143.1, 148.0; HRMS (FAB) calcd for C\(_{29}\)H\(_{39}\)N\(_2\)O\(_3\)SSi (MH\(^+\)) 523.2451, found 523.2454.

2. Gold(I)-Catalyzed Cascade Reactions.

General Procedure A: Synthesis of (R)-2,5-Diphenyl-4,5-dihydro-[1,4]oxazepino[4,5-a]indole (3a) and (R, Z)-1-Benzylidene-4-phenyl-3,4-dihydro-1\(H\)-[1,4]oxazino[4,3-a]indole (4a).

A screw-cap test tube was charged with 2a (33.7 mg, 0.10 mmol), IPrAuCl (3.1 mg, 5.0 µmol) and AgOTf (1.3 mg, 5.0 µmol). Dry 1,2-DCE (1.5 mL) was added to the screw-cap test tube. After stirring at 50 °C for 5 h, the reaction mixture was concentrated \textit{in vacuo} and chromatographed on NH\(_2\) silica gel (hexane/CHCl\(_3\) = 2/1), and the collected solid was rinsed with hexane to afford an inseparable mixture of 3a/4a (29.0 mg, 86%, 3a/4a = 71/29, determined by \(^1\)H NMR): greenish gray powder; mp 198–200 °C; IR (neat) 1627 (CH\(_2\)OC=C); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): (Major isomer 3a) 4.70 (dd, \(J = 12.6, 1.1\) Hz, 1H), 5.00 (dd, \(J = 12.6, 3.7\) Hz, 1H), 5.89 (br m, 1H), 6.47 (s, 1H), 6.55 (s, 1H), 7.04-7.08 (m, 3H), 7.11-7.17 (m, 2H), 7.19-7.35 (m, 6H), 7.58-7.58 (m, 1H), 7.63-7.64 (m, 2H); (Minor isomer 4a): 4.57-4.61 (m, 2H), 5.50-5.50 (br m, 1H), 6.37 (s, 1H), 6.94 (s, 1H), 6.98 (d, \(J = 8.0\) Hz, 1H), 7.11-7.17 (m, 5H), 7.19-7.35 (m, 6H), 7.69 (d, \(J = 7.4\) Hz, 2H); 
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): (Major isomer 3a): 61.3, 73.3, 96.6, 102.8, 109.1, 120.19, 120.20, 121.7, 125.5 (2C), 126.5 (2C), 127.7, 128.2 (2C), 128.3, 128.5, 128.6 (2C), 136.0, 136.6, 138.1, 138.4, 153.4; (Minor isomer 4a): 55.3, 70.6, 97.7, 105.5, 109.6, 120.8 (2C), 122.2 (2C), 126.1 (2C), 136.0, 143.1, 148.0; HRMS (FAB) calcd for C\(_{29}\)H\(_{39}\)N\(_2\)O\(_3\)SSi (MH\(^+\)) 523.2451, found 523.2454.
127.8, 128.2 (2C), 128.3, 128.46, 128.47, 128.7, 128.9, 130.6, 135.7, 135.9, 138.1, 144.7; HRMS (ESI) calcd for C24H20NO (MH+): 338.1545; found: 338.1550.

(±)-(4R,5S)-2,4,5-Triphenyl-4,5-dihydro-[1,4]oxazepino[4,5-a]indole (3b) and (±)-(3R,4S)-1-[(Z)-Benzyldiene]-3,4-diphenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (4b). By use of the General Procedure A, 2b (41.4 mg, 0.10 mmol) was converted to 3b/4b (37.9 mg, 92%, 3b/4b = 29/71, determined by 1H NMR) by the reaction in the presence of IPrAuCl (3.1 mg, 5.0 µmol) and AgOTf (1.3 mg, 5.0 µmol) in dry 1,2-DCE (1.0 mL) at 50 °C for 2.5 h. Both the products were isolated by PTLC (NH2 silica gel) with hexane/Et2O (3/1). Compound 3b (less polar isomer): white solid; mp >250 °C; IR (neat): 1642 (CHOC=C); 1H NMR (500 MHz, CDCl3) δ: 5.90 (d, J = 6.9 Hz, 2H), 6.61 (s, 1H), 6.64 (s, 1H), 6.82 (d, J = 6.9 Hz, 2H), 7.05-7.12 (m, 5H), 7.15-7.18 (m, 1H), 7.23-7.24 (m, 2H), 7.32-7.36 (m, 6H), 7.59-7.60 (m, 1H), 7.69-7.70 (m, 2H); 13C NMR (125 MHz, CDCl3) δ: 67.5, 83.4, 97.2, 103.0, 109.2, 120.19, 120.24, 121.8, 125.7 (2C), 126.6 (2C), 127.71 (2C), 127.73, 127.9, 128.0, 128.25 (2C), 128.34 (2C), 128.4 (2C), 128.6, 135.7, 135.9, 136.4, 138.1, 138.4, 152.7; HRMS (FAB) calcd for C30H24NO (MH+) 414.1852, found 414.1861. Compound 4b (more polar isomer): pale yellow solid; mp 168–172 °C; IR (neat): 1632 (CH2OC=C); 1H NMR (500 MHz, CDCl3) δ: 5.54-5.55 (br m, 1H), 5.76-5.77 (br m, 1H), 6.48 (s, 1H), 6.70-6.70 (m, 2H), 7.00 (d, J = 8.6 Hz, 1H), 7.04-7.05 (m, 2H), 7.09-7.18 (m, 7H), 7.26-7.33 (m, 5H), 7.65-7.67 (m, 1H), 7.75 (d, J = 7.4 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ: 60.9, 80.3, 97.5, 105.8, 109.1, 120.82, 120.84, 122.3, 126.1, 126.5 (2C), 127.881 (2C), 127.886 (2C), 128.0, 128.17 (2C), 128.22, 128.35 (2C), 128.38, 128.8 (2C), 130.3, 134.8, 135.6, 135.7, 136.2, 144.9; HRMS (FAB) calcd for C30H24NO (MH+) 414.1852, found 414.1859.

5-Phenyl-2-propyl-[1,4]oxazepino[4,5-a]indol-4(5H)-one (3c) and (Z)-1-Butylidene-4-phenyl-1H-[1,4]oxazino[4,3-a]indol-3(4H)-one (4c). By use of the General Procedure A, 2c (31.7 mg, 0.10 mmol) was converted to 3c/4c (11.1 mg, <35%, 3c/4c = 20/80, determined by 1H NMR) by the reaction in the presence of IPrAuCl (3.1 mg, 5.0 µmol) and AgOTf (1.3 mg, 5.0 µmol) in dry 1,2-DCE (1.0 mL) at 50 °C for 3 h. The products were separated by PTLC (NH2 silica gel) with
hexane/ Et₂O (3/1). Compound 3c (less polar isomer): unstable pale amber oil; IR (neat): 1749 (C=O); ¹H NMR (500 MHz, CDCl₃) δ: 0.62 (t, J = 7.4 Hz, 3H), 1.10-1.19 (m, 1H), 1.33-1.43 (m, 1H), 1.95-2.01 (m, 1H), 2.11-2.17 (m, 1H), 5.96 (s, 1H), 6.55 (s, 1H), 6.67-6.69 (m, 2H), 6.76 (s, 1H), 7.19-7.29 (m, 5H), 7.43 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 13.0, 19.9, 37.0, 62.9, 102.3, 102.9, 108.7, 120.8, 121.1, 122.6, 124.6 (2C), 128.5, 128.9 (3C), 132.3, 133.0, 136.9, 149.0, 164.2; HRMS (FAB) calcd for C₂₁H₂₀NO₂ (MH⁺) 318.1489, found 318.1484. Compound 4c (more polar isomer): unstable yellow oil; IR (neat): 1760 (C=O); ¹H NMR (500 MHz, CDCl₃) δ: 0.93 (t, J = 7.4 Hz, 3H), 1.47-1.51 (m, 2H), 2.29-2.41 (m, 2H), 5.69 (t, J = 7.7 Hz, 1H), 6.24 (s, 1H), 6.82 (s, 1H), 7.04-7.06 (m, 3H), 7.10-7.17 (m, 2H), 7.28-7.28 (m, 3H), 7.63 (d, J = 7.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 13.7, 22.4, 26.6, 59.2, 97.5, 109.7, 112.4, 121.0, 121.4, 122.8, 126.1 (2C), 127.1, 129.0, 129.1, 129.2 (2C), 134.65, 134.74, 139.5, 163.1; HRMS (FAB) calcd for C₂₁H₂₀NO₂ (MH⁺) 318.1489, found 318.1484.

(Z)-N-(But-2-yn-1-yl)-4-methyl-N-[3-(3-oxo-4-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-ylidene)propyl]benzenesulfonamide (20b). A screw-cap test tube was charged with (±)-10b (52.5 mg, 0.1 mmol), IPrAuCl (6.2 mg, 0.01 mmol) and AgOTf (2.6 mg, 0.01 mmol). Dry 1,2-DCE (1 mL) was added to the screw-cap test tube. After stirring at 50 °C for 27 h, the mixture was concentrated in vacuo and chromatographed on NH₂ silica gel (hexane/CHCl₃ = 3/1) to afford 20b/20b’ (16.3 mg, <31%, 20b/20b’ = 90/10, determined by ¹H NMR) as an isomeric mixture of unstable compounds. The major isomer 20b was isolated by PTLC (silica gel) with hexane/Et₂O (3/1): unstable yellow oil; IR (neat): 2225 (C=C), 1765 (C=O), 1345 (S=O), 1157 (S=O); ¹H NMR (500 MHz, CDCl₃) δ: 1.53 (t, J = 2.3 Hz, 3H), 2.40 (s, 3H), 2.61-2.65 (m, 2H), 3.33-3.34 (m, 2H), 3.99-4.10 (m, 2H), 5.73 (t, J = 7.4 Hz, 1H), 6.25 (s, 1H), 6.87 (s, 1H), 7.05-7.07 (m, 3H), 7.11-7.17 (m, 2H), 7.27-7.30 (m, 5H), 7.64-7.66 (m, 1H), 7.72 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 3.2, 21.5, 23.0, 36.7, 45.2, 59.2, 71.5, 81.9, 98.5, 107.6, 109.7, 121.3, 121.5, 123.06, 126.13 (2C), 126.4, 127.8 (2C), 128.9, 129.2, 129.27 (2C), 129.31 (2C), 134.65, 134.71, 135.9, 140.9, 143.3, 162.8; HRMS (FAB) calcd for C₃₁H₂₉N₂O₄S (MH⁺) 525.1848, found 525.1851.
Gold(I)-Catalyzed Cyclization of the Conjugated Enyne (Table 1): \((E)-(3\text{-Ethylidene-1-tosylpiperidin-4-yl})(1H\text{-indol-2-yl})\text{methanone } ([\pm]-9)\). The experiments shown in Table 1 were carried out as follows: \(11a\) (56.5 mg, 0.1 mmol; \(Z/E = 79:21\)) or \(11b\) (52.3 mg, 0.1 mmol; \(Z/E = 71:29\)) were treated with JohnPhosAu(MeCN)SbF\(_6\) (3.9 mg, 5.0 µmol) or IPrAuCl (3.1 mg, 5.0/5.0 µmol; 5 mol %)/AgSbF\(_6\) (1.7 mg, 5.0 µmol; 5 mol %) in toluene-\(d_8\) (0.5 mL, 0.2 M) at room temperature in the presence of an additive (1.5 equiv) and mesitylene (1.0 equiv) as an internal standard. After completion of the reaction (monitored by TLC), the reaction mixtures were analyzed by \(^1\)H NMR to determine the yields of \((\pm)-9, 28\), and 29 based on the internal standard. Pure \((\pm)-9\) was obtained as follows: a screw-cap test tube was charged with \(11a\) (293 mg, 0.52 mmol, \(Z/E = 93/7\)) and JohnPhosAu(MeCN)SbF\(_6\) (20 mg, 25.9 µmol). H\(_2\)O (14 µL, 0.8 mmol) and dry toluene (2.6 mL) were added to the mixture. After stirring at room temperature for 24 h, the mixture was concentrated in vacuo and chromatographed on NH\(_2\) silica gel (hexane/EtOAc = 5/1). The product was recrystallized from CHCl\(_3\)–hexane to afford \((\pm)-9\) (64.1 mg, 30%) as white solid: mp 183–186 °C; IR (neat): 3343 (NH), 1643 (C=O), 1341 (S=O), 1162 (S=O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 1.72 (dd, \(J = 6.9, 1.7\) Hz, 3H), 2.06-2.11 (m, 1H), 2.15-2.16 (m, 1H), 2.44 (s, 3H), 2.86 (ddd, \(J = 12.2, 12.0, 3.2\) Hz, 1H), 3.43-3.45 (br m, 1H), 3.71-3.74 (br m, 1H), 4.09-4.11 (br m, 1H), 4.43-4.43 (br m, 1H), 5.72 (q, \(J = 6.7\) Hz, 1H), 7.14-7.17 (m, 1H), 7.25 (d, \(J = 2.3\) Hz, 1H), 7.33-7.36 (m, 4H), 7.66 (d, \(J = 8.0\) Hz, 2H), 7.70 (d, \(J = 9.2\) Hz, 1H), 8.86 (br s, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 13.3, 21.6, 28.5, 41.2, 43.2, 52.3, 109.4, 112.0, 121.2, 123.2, 124.8, 126.7, 127.4, 127.7 (2C), 129.7 (2C), 129.9, 133.5, 133.8, 137.3, 143.5, 192.6; HRMS (FAB) calcd for C\(_{23}\)H\(_{25}\)N\(_2\)O\(_3\)S (MH\(^+\)) 409.1586, found 409.1577.

\((Z)-N\{4-(1H-\text{Indol-2-yl})-4-[(\text{triisopropylsilyl})\text{oxy}]\text{but-3-en-1-yl}\}-N-(\text{but-2-yn-1-yl})-4\)-methylbenzenesulfonamide (28). Amber oil: IR (neat): 3386 (NH), 2225 (C≡C), 1650 (SiOC=C), 1341 (S=O), 1157 (S=O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 1.09 (d, \(J = 6.9\) Hz, 18H), 1.18-1.21 (m, 3H), 1.56 (t, \(J = 2.3\) Hz, 3H), 2.40 (s, 3H), 2.54 (q, \(J = 7.3\) Hz, 2H), 3.27 (t, \(J = 7.4\) Hz, 2H), 4.11 (q, \(J = 2.3\) Hz, 2H), 5.13 (t, \(J = 6.9\) Hz, 1H), 6.54-6.54 (br m, 1H), 7.08-7.10 (m, 1H), 7.16-7.18 (m, 1H).
1H), 7.26 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 8.15 (br s, 1H); 13C NMR (125 MHz, CDCl3) δ: 3.3, 13.6 (3C), 17.9 (6C), 21.5, 24.5, 36.8, 45.8, 71.8, 81.5, 100.1, 106.4, 110.8, 119.9, 120.6, 122.2, 127.8 (2C), 128.5, 129.2 (2C), 135.7, 136.0, 136.7, 143.2, 144.8; HRMS (FAB) calcd for C32H45N2O3SSi (MH+) 565.2920, found 565.2927.

N-[1H-Indol-2-yl]-4-oxobutyl]-N-(but-2-yn-1-yl)-4-methylbenzenesulphonamide (29).
White powder: mp 120–121 °C; IR (neat): 3326 (NH), 2224 (C≡C), 1649 (C=O), 1340 (S=O), 1157 (S=O); 1H NMR (500 MHz, CDCl3) δ: 1.53 (t, J = 2.3 Hz, 3H), 2.01-2.07 (m, 2H), 2.41 (s, 3H), 3.08 (t, J = 7.4 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H), 4.08-4.08 (br m, 2H), 7.15-7.17 (m, 1H), 7.25-7.28 (m, 3H), 7.34-7.36 (m, 1H), 7.41-7.43 (m, 1H), 7.72-7.74 (m, 3H), 9.01 (br s, 1H); 13C NMR (125 MHz, CDCl3) δ: 3.2, 21.4, 22.0, 34.9, 36.9, 45.8, 71.7, 81.7, 109.4, 112.1, 120.9, 123.1, 126.3, 127.6, 127.8 (2C), 129.3 (2C), 134.9, 135.9, 137.1, 143.3, 192.2; HRMS (FAB) calcd for C23H25N2O3S (MH+) 409.1586, found 409.1590.

Enantioselective Cyclization of Conjugated Enyne (Table 2): Synthesis of (S,E)-(3-Ethylidene-1-tosylpiperidin-4-yl)(1H-indol-2-yl)methanone [(S)-9]. (R)-MeO-DTBM-BIPHEP(AuCl)2 (8.1 mg, 5.0 μmol; 5 mol %) and AgSbF6 (3.4 mg, 0.01 mmol; 10 mol %) was dissolved in toluene (0.1 mL) and stirred for 10 min at room temperature. A solution of (Z)-11a (56.5 mg, 0.1 mmol) in toluene (0.4 mL) was transferred to the catalyst mixture. The mixture was stirred at room temperature for 17 h. The mixture was concentrated and purified on PTLC (silica gel) with hexane/EtOAc (3/1) to afford (S)-9 as a white amorphous solid {13.1 mg, 32% yield, 88% ee [HPLC, Chiralcel-OD-H column eluting under condition with 40% i-PrOH/n-hexane over 30 min at 0.75 mL/min, t1 = 12.66 min (major isomer), t2 = 16.60 min (minor isomer)]}: [α]26D −2.1 (c 0.92, CHCl3); IR (neat): 3334 (NH), 1641 (C=O), 1341 (S=O), 1159 (S=O); 1H NMR (500 MHz, CDCl3) δ: 1.71 (dd, J = 6.9, 1.7 Hz, 3H), 2.03-2.10 (m, 1H), 2.14-2.17 (m, 1H), 2.40 (s, 3H), 2.88 (ddd, J = 12.3, 12.3, 2.9 Hz, 1H), 3.47-3.49 (br m, 1H), 3.71-3.74 (br m, 1H), 4.10-4.13 (br m, 1H), 4.43-4.44 (br m, 1H), 5.71 (q, J = 6.9 Hz, 1H), 7.13-7.16 (m, 1H), 7.32-7.34 (m, 4H), 7.65 (d, J =
3. Total Synthesis of (+)-Conolidine (Scheme 6).

(S,E)-(3-Ethylidene-4-piperidinyl)(1H-indol-2-yl)methanone (7). According to the reported method, removal of the tosyl group was carried out as follows: sodium (27.7 mg, 1.20 mmol) was added to a solution of naphthalene (193 mg, 1.50 mmol) in THF (1.5 mL) at room temperature and the mixture stirred for 30 min. The resulting dark green/blue solution (ca. 0.8 M in THF) was added dropwise to a solution of (S)-9 (49.2 mg, 0.12 mmol, 91% ee) in THF (1.2 mL) at 0 °C until dark green/blue color persisted. Saturated aqueous NaHCO₃ was added and the solution was allowed to warm slowly to room temperature. The aqueous layer was then extracted with CH₂Cl₂ and the organic layers were washed with brine, combined, dried over K₂CO₃ and filtered. Concentration under reduced pressure and recrystallization from CH₂Cl₂–hexane afforded (+)-7 (18.5 mg, 60%): mp 205–210 °C; [α]²⁸D = +41.0 (c 0.26, MeOH), comparable to the report by Bohn et al. (2011): [α]²⁸D = +45.0 (c 0.24, MeOH); IR (neat): 3345 (NH), 1627 (C=O); ¹H NMR (500 MHz, CDCl₃) δ:

1.72 (dd, J = 6.9, 1.7 Hz, 3H), 1.87-1.95 (m, 1H), 2.20-2.22 (br m, 1H), 2.97-3.00 (br m, 1H), 3.15 (ddd, J = 12.6, 12.6, 2.9 Hz, 1H), 3.33 (d, J = 12.6 Hz, 1H), 3.49 (s, 1H), 3.72 (d, J = 12.6 Hz, 1H), 4.53-4.54 (br m, 1H), 5.54 (q, J = 6.7 Hz, 1H), 7.15-7.17 (m, 1H), 7.28 (s, 1H), 7.34-7.36 (m, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 9.16 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ:

13.0, 31.5, 43.0, 43.2, 53.1, 108.9, 112.1, 120.8, 121.0, 123.1, 126.3, 127.6, 134.4, 135.1, 137.1, 193.6; HRMS (FAB) calcd for C₁₆H₁₉N₂O (MH⁺) 255.1497, found 255.1490.

(+)-Conolidine (1). According to the Bohn’s procedure, the amine (+)-7 (16.0 mg, 0.06 mmol), paraformaldehyde (6.8 mg, 0.23 mmol), and TFA (14.5 µL, 0.19 mmol) were dissolved in dry MeCN (1.2 mL) and the reaction mixture heated under reflux for 2 h. TFA (14.5 µL) was added and
the mixture was stirred for further 3 h. The mixture was concentrated in vacuo and the crude product was made basic with aqueous saturated NaHCO₃ (to pH 9.0) and extracted with CH₂Cl₂ three times. The resultant orange solution was dried over Na₂SO₄, concentrated in vacuo and chromatographed on NH₂ silica gel (MeOH/CHCl₃ = 99/1) to afford (+)-conolidine (I) (5.7 mg, 34%, 84% ee [HPLC, Chiralcel-AD-H column eluting under condition with 80% i-PrOH/n-hexane over 25 min at 0.75 mL/min, $t_1 = 14.25$ min (minor isomer), $t_2 = 16.95$ min (major isomer)]): mp 178–180 °C; $[\alpha]^{28}_D = +31.5$ (c 0.24, CHCl₃), comparable to the report by Kam et. al. (2004)¹: $[\alpha]_D = +32.0$ (c 0.16, CHCl₃), Bohn et. al. (2011)¹⁶: $[\alpha]^{27}_D = +28.1$ (c 0.16, CHCl₃); IR (neat): 2914 (NH), 1634 (C=O); ¹H NMR (500 MHz, CDCl₃) δ: 1.51-1.52 (br m, 3H), 2.04-2.06 (m, 1H), 2.10-2.18 (m, 1H), 3.06-3.13 (m, 1H), 3.30-3.33 (br m, 1H), 3.41 (ddd, $J = 13.7$, 8.6, 2.9 Hz, 1H), 3.85-3.88 (br m, 1H), 3.97-3.98 (br m, 1H), 4.29 (d, $J = 18.3$ Hz, 1H), 4.78 (d, $J = 18.3$ Hz, 1H), 5.47 (q, $J = 6.9$ Hz, 1H), 7.11 (ddd, $J = 16.0$, 8.0, 4.0 Hz, 1H), 7.32-7.37 (m, 2H), 7.57 (d, $J = 8.0$ Hz, 1H), 9.02 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 12.7, 22.9, 44.2, 48.1, 53.3, 55.0, 111.7, 120.1, 120.5, 120.8, 122.9, 126.5, 127.9, 130.1, 133.5, 136.1, 193.5; HRMS (FAB) calcd for C₁₇H₁₉N₂O (MH⁺) 267.1497, found 267.1494.

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Supporting Information Available.

Additional synthetic schemes (preparation of 2a–c), NMR spectra, and HPLC chromatograms. This material is available freely via the Internet at http://pubs.acs.org.
References


(4) During the course of this study, a similar approach was recently reported for construction of the ethylidene-piperidine moiety and used to synthesize (±)-conolidine and (±)-apparicine: Takanashi, N.; Suzuki, K.; Kitajima, M.; Takayama, H. *Tetrahedron Lett.* **2016**, *57*, 375.


(13) The geometry of 28 was confirmed by an NOE between the protons on the indole 3-position and vinylic carbon.  


