# A Cobalt-Catalyzed Entry Into the Ergot Alkaloids: Total Syntheses of (±)-Lysergene and (±)-LSD

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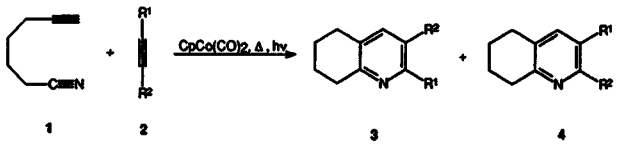
**Abstract:** Cocyclization of 4-ethynyl-3-indoleacetonitriles with alkynes in the presence of $CpCo(CO)_2$ gives rise to the ergoline derivatives **6-9**, two of which were transformed into racemic lysergene and LSD, respectively.

The powerful physiological activity of the ergot alkaloids, in conjunction with their structural variety, has made this class of compounds a continuing target on which to test the utility of novel synthetic methodology.[1,2] We report the rapid construction of the ergoline skeleton via an A,B→C,D ring assembly (Scheme 2) that relies on the $\eta^5$-cyclopentadienylcobalt-catalyzed cocyclization of α,ω-alkynenitriles with alkynes to give annelated [*b*]pyridines (Scheme 1).[3]

At the outset of this work, it was hoped that the substitution pattern in ring D would be set by employing the bulky trialkylsilylgroup as a regiodirecting substituent in the alkyne partner **2** of the [2+2+2]cycloaddition, thus, in particular, enforcing the emergence of an alkoxycarbonyl or carbamoyl function at C-9 (see structure **6**), a feature typical of lysergic acid and its derivatives. Such control had been established earlier only for alkyl juxtaposing silyl, a state manqué rectified here by the results summarized in Scheme 1, Table I.




**1** **2** **3** **4**

Scheme 1

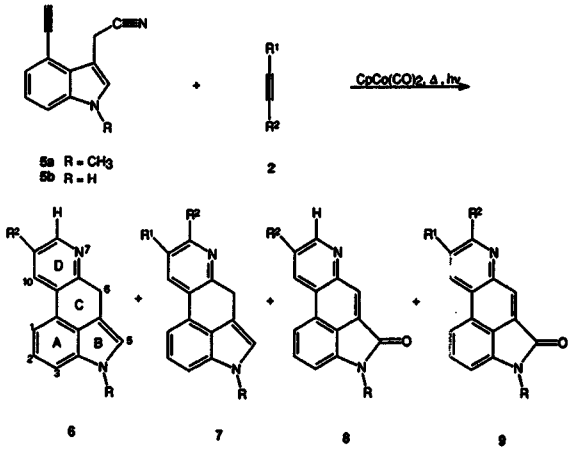
Table I. Results of the Cocyclization of **1** with **2** [a,b]

| Solvent | Alkyne | Ratio 3:4[c] | Yield, %[d] |
|---|---|---|---|
| benzene | **2a** $R^1 = Si(CH_3)_3$, $R^2 = CO_2CH_3$ | 1.1:1 | 82 |
| benzene | **2b** $R^1 = Si(CH_2CH_3)_3$, $R^2 = CO_2CH_3$ | 1:1 | 78 |
| benzene | **2c** $R^1 = Si[CH(CH_3)_2]_3$, $R^2 = CO_2CH_3$ | 1.7:1 | 67 |
| benzene | **2d** $R^1 = Si(CH_3)_3$, $R^2 = CON(CH_2CH_3)_2$[e] | 1.4:1 | 87 |
| 1,3-dimethylbenzene | **2e** $R^1 = Si(CH_2CH_3)_3$, $R^2 = OCH_3$ | >95:(1) | 43 |
| 1,3-dimethylbenzene | **2f** $R^1 = Si(CH_2CH_3)_3$, $R^2 = H$ | >95:(1) | 26 |
| 1,3-dimethylbenzene | **2g** $R^1 = Si(CH_3)_3$, $R^2 = CH_3$ | >95:(1) | 70[f] |

[a]High dilution (syringe pump addition) conditions, reflux, irradiation with a GE-ELH slide projector lamp, ~10% catalyst. See also Experimental and references 3,4. [b]All new compounds gave satisfactory analytical and/or spectral data. [c]By NMR or g.c. Regiochemical assignments were corroborated by protodesilylation. [d]After separation by column chromatography (silica gel). [e]Reference 9. [f]Reference 3a.

The data show that, while the relevant cyclizations proceed efficiently, electronic and steric factors seem to compete, a finding precedented by related cyclizations featuring heteroaromatic α,ω-enynes.[4] In all these cases it appears that the regiochemistry is established in a common alkyne coupling step to an intermediate metallacyclopentadiene species.[3b,5] Surprisingly, changing the size of the trialkylsilyl group is of little consequence (Table I).

An exploration of the utility of this cyclization in the synthesis of the ergot framework is summarized in Scheme 2, Table II.[12] The requisite 4-ethynyl-3-indoleacetonitriles **5** were prepared readily by adaptation of literature procedures[6] via the 4-bromoprecursors,[7] followed by Pd-catalyzed trimethylsilylethynylation-deprotection.[8,12]




**5a** R = $CH_3$
**5b** R = H

**2**

**6** **7** **8** **9**

Scheme 2

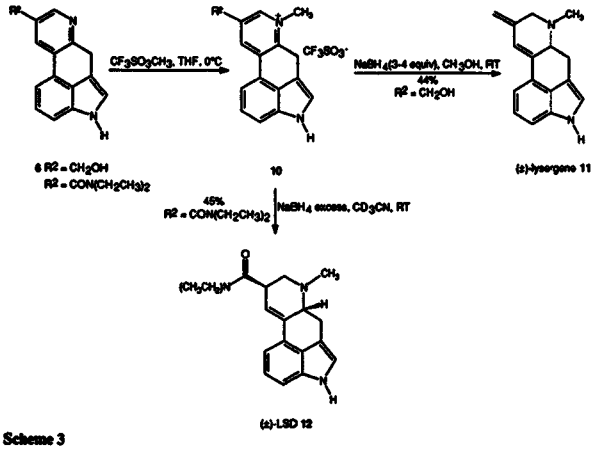
Table II. Results of the Cocyclization of **2** with **5** [a,b]

| Indole Precursor 5 | Cocyclization Partner 2 | Products (% yield) 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|
| 5a | 2h $R^1 = R^2 = Si(CH_3)_3$ | 6 | 0 | 33 | trace[c] |
| 5a | 2g $R^1 = Si(CH_3)_3$, $R^2 = CH_3$ | 6 | 0 | 12 | 0 |
| 5a | 2d $R^1 = Si(CH_3)_3$, $R^2 = CON(CH_2CH_3)_2$[d] | 0 | 13 | 9 | trace |
| 5b | 2d | 17 | 33 | trace | trace |
| 5b | 2i $R^1 = Si(CH_3)_3$, $R^2 = CH_2OH$[e] | 38 | 11 | 0 | 0 |
| 5b | 2j $R^1 = Si(CH_3)_3$, $R^2$ =  | 10 | 41 | trace | trace |

[a]High dilution (syringe pump addition) conditions, methylbenzene (RT) or THF (reflux), irradiation with a GE-ELH slide projector lamp, 1 equiv. of catalyst. See also Experimental. [b]All new compounds gave satisfactory analytical and/or spectral data. [c]By NMR spectroscopy of crude product mixture. [d]Reference 9. [e]Reference 10. [f]Reference 11.

Several aspects of the results are noteworthy: 1. the total yields of cycloaddition products are only moderate (18-51%), undoubtedly because of the sensitivity of C-6 in **6** and **7** to autoxidation and the propensity of the trimethylsilylgroup at C-8 to hydrolyze;[13] 2. products of **6** and **8** are formed by protodesilylation of their precursors at C-8 on column chromatography (silica gel), the latter compound being observable only in the crude reaction mixture; 3. the indoloquinolines **6** and **7** quantitatively converted to the indoloquinolones **8** and **9**, respectively, on standing in air; 4. equimolar quantities of catalyst were used in millimolar runs to make up for depletion of CpCo by traces of air and side reactions;[3,4,14] 5. the location of the ring-carbonyl oxygen in **8** and **9** at C-5 was evident from spectral data[15] and was confirmed by long range correlation $^1H$-$^{13}C$ NMR experiments;[16] 6. as in the model cooligomerizations of **1**, those of **5** exhibit only modest regioselectivity when the trimethylsilylgroup on **2** is paired with a substituent endowed with electron-withdrawing qualities (**2d**, **2i**, **2j**); 7. despite the specific limitations of the reaction of **5** and **2**, it is clear that the method provides a short alternative to existing methodologies and potential access to novel structures.

With the tetracycles of the type **6-9** in hand, it remained to realize a synthetic connection to some molecules of established synthetic-medicinal interest. Thus, **6** (R = H, $R^2 = CH_2OH$; green crystals, m.p. 193-194°C) was methylated to **10** (72%, orange powder, m.p. 174-175°C dec) and reduced according to Scheme 3[12] to furnish (±)-lysergene **11**, identical ($^1H$ NMR, MS, UV, TLC) with authentic material.[17]



Scheme 3

Similarly, **6** [R = H, $R^2 = CON(CH_2CH_3)$][12] was converted to **10** (32%, orange powder, m.p. 185-186°C dec) and then (±)-LSD **12**, identified by NMR comparisons[18] and mass spectrometry.[19,20] For the purposes of comparison with other routes, both compounds were made starting from commercial 4-bromoindole in seven steps, respectively, in overall yields of 12% for **11** and 1.1% for **12**.

**Experimental**

A solution of **5** (1.50 mmol) in THF (4 mL) and another solution of [$CpCo(CO)_2$] (0.30g, 1.68 mmol) and **2** (4-8 mmol) in THF (3 mL) were slowly added over 12h via two separate syringe pumps to stirred THF (5 mL) in a round-bottomed flask under $N_2$, equipped with a reflux condenser and submerged in an oil bath at 65-70°C. The reaction vessel was irradiated with a Sylvania ELH 300 W tungsten slide projector lamp. The volatile components were removed by vacuum transfer and the residue chromatographed on silica gel eluting with $CH_2Cl_2$-$CH_3OH$ (100:0 to 95:5).

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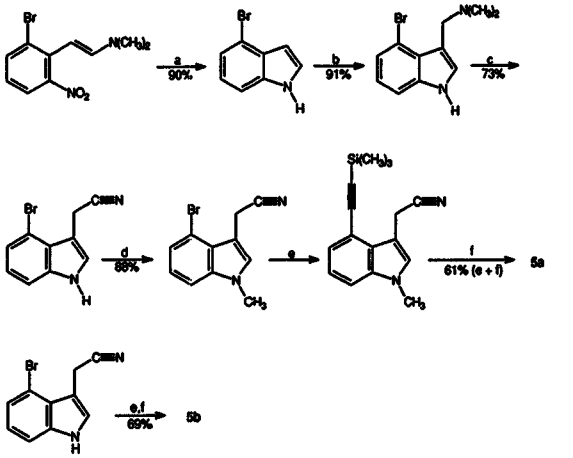

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(12) For example, **5b**: light brown powder, m.p. 168-169°C ($CH_2Cl_2$-petroleum ether); IR (KBr): $\tilde{\nu}$ = 3320, 2250, 1400, 1340, 755 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.25 (br s, N*H*), 7.37 (d, *J* = 8.3 Hz, 1H), 7.32-7.29 (m, 2H), 7.15 (dd, *J* = 7.8, 7.7 Hz, 1H), 4.22 (s, 2H), 3.32 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 136.3, 126.1, 125.6, 124.1, 122.5, 118.8, 112.7, 105.9, 82.6, 80.5, 15.3; MS (70 eV):*m/z* 180 ($M^+$, 100), 179 (92), 152 (37), 126 (15). **8** [R = $CH_3$, $R^2$ = $Si(CH_3)_3$]: yellow crystals, m.p. 199-200°C ($CH_3OH$); IR (KBr): $\tilde{\nu}$ 2955, 1698, 1695, 1617, 1493, 1387, 1301, 1242, 1068, 973 $cm^{-1}$; UV ($CH_3OH$): $\lambda_{max}$ (log ε) 225 (4.44), 249 (4.40), 295 (4.23), 348 (3.31), 388 (3.35) nm; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 9.08 (s, 1H), 8.89 (s, 1H), 8.47 (s, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 8.3, 7.2 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 3.39 (s, 3H), 0.43 (s, 9H); $^{13}C$ NMR and DEPT (125 MHz, $CDCl_3$, numbering as in an indolo[4,3-*fg*]quinoline derivative, see structure **6**): δ = 167.3 (C=O), 154.0 (C-8), 149.5 (C-6a), 140.4 (C-13), 136.8 (C-10), 135.4 (C-9), 129.5 (C-2), 138.5 (C-5a or C-10a), 127.8 (C-6), 126.7 (C-5a or C-10a), 125.8 (C-11), 121.1 (C-12), 115.7 (C-3), 105.6 (C-1), 26.5 ($CH_3$), -1.2 [$Si(CH_3)_3$]; MS (70 eV):*m/z* 306 ($M^+$, 65), 292 (25), 291 (100), 145 (30). **6** [R = H, $R^2$ = $CON(CH_2CH_3)_2$]: greenish-yellow crystals, m.p. 150-152°C ($CH_3OH$-$CH_2Cl_2$); IR (KBr): $\tilde{\nu}$ 1627, 1487, 1480, 1466, 1428, 1285, 849, 757 $cm^{-1}$; UV ($CH_3OH$): $\lambda_{max}$ (log ε) 238

sh (4.36), 360 (3.78) nm; $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 2.0 Hz, 1H), 8.30 (br s, N*H*), 8.14 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.18 (m, 2H), 6.96 (br d, *J* = 1.7 Hz, 1H), 4.50 (d, *J* = 0.6 Hz, 2H), 3.60-3.35 (m, 4H), 1.28-1.17 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 169.0, 157.0, 144.1, 133.8, 130.5, 128.6, 128.2, 125.6, 123.9, 122.9, 118.8, 111.4, 111.1, 109.3, 43.4, 39.6, 31.1, 14.3, 12.8; MS (70eV):*m/z* 305 ($M^+$, 100), 304 (41), 233 (92), 205 (57), 178 (31); HRMS calcd for $C_{19}H_{19}N_3O$ 305.1527, found 305.1528. **7** [R = H, $R^1$ = $Si(CH_3)_3$, $R^2$ = $CON(CH_2CH_3)_2$]: yellow-green oil (rapidly oxidizing to **9**); $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.75 (br s, N*H*), 8.34 (s, 1H), 7.36 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.14 (m, 2H), 6.89 (br d, *J* = 1.9 Hz, 1H), 4.44 (d, *J* = 0.6 Hz, 2H), 3.56 (q, *J* = 7.2 Hz, 2H), 3.20 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 0.35 (s, 9H). **8** [R = H, $R^2$=$CON(CH_2CH_3)_2$]: yellow-green crystals, m.p. 290-292° C ($CH_3OH$); IR (KBr): $\tilde{\nu}$ 3435, 1723, 1631, 1468, 1074, 784, 752 $cm^{-1}$; UV($CH_3OH$): $\lambda_{max}$ (log ε) 220 (4.48), 248 (4.42), 291 (4.28), 346 sh (3.41), 362 sh (3.43), 390 (3.48) nm; $^1$H NMR (300 MHz, $CDCl_3$): δ = 9.03 (d, *J* = 1.8 Hz, 1H), 8.91 (d, *J* = 1.8 Hz, 1H), 8.56 (s, 1H), 8.06 (br s, N*H*), 8.01 (d, *J* = 8.4 Hz, 1 H), 7.61 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 3.60-3.40 (m, 4H), 1.30-1.15 (m, 6H); MS (70eV):*m/z* 319 ($M^+$, 48), 318 (35), 247 (100), 219 (50), 192 (25), 164 (39). **9** [R = H, $R^1$ = $(CH_3)_3Si$, $R^2$ = $CON(CH_2CH_3)_2$]: yellow-green crystals, m.p. 267-268°C ($CH_3OH$); IR(KBr): $\tilde{\nu}$ 2966, 1698, 1632, 1430, 1379, 1249, 858, 844 $cm^{-1}$; UV($CH_3OH$):$\lambda_{max}$ (log ε) 231 (4.24), 253 (4.26), 287 (4.12), 348 sh (3.21), 365 sh (3.23), 391 (3.28) nm; $^1$H NMR (300 MHz, $CDCl_3$): δ = 9.12 (s, 1H), 8.58 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.95 (br s, N*H*), 7.67 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 3.65 (q, *J* = 7.1 Hz, 2H), 3.27 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.45 (s, 9H); MS (70eV):*m/z* 391 ($M^+$,4), 376 (39), 320 (16), 111 (17), 73 (17), 72 (100).


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