

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

Carlos Saá,^{*a} Dallas D. Crotts, Gishun Hsu, K. Peter C. Vollhardt^{*b}

^aDepartamento de Química Orgánica, Universidad de Santiago de Compostela, Augas Férreas-Fingoi, 27002 Lugo, Spain

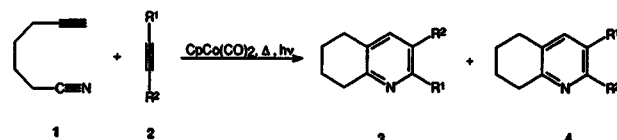
^bDepartment of Chemistry, University of California-Berkeley and the Chemical Sciences Division, Lawrence Berkeley Laboratory, Berkeley, California 94720, USA

Received 22 April 1994

Abstract: Cocyclization of 4-ethynyl-3-indoleacetonitriles with alkynes in the presence of $\text{CpCo}(\text{CO})_2$ 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 η^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 trialkylsilyl group as a regiodirecting substituent in the alkyne partner 2 of the [2+2+2]cycloaddition, thus, in particular, enforcing the emergence of an alkoxy-carbonyl 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.



Scheme 1

Table I. Results of the Cocyclization of 1 with 2 ^{a,b}

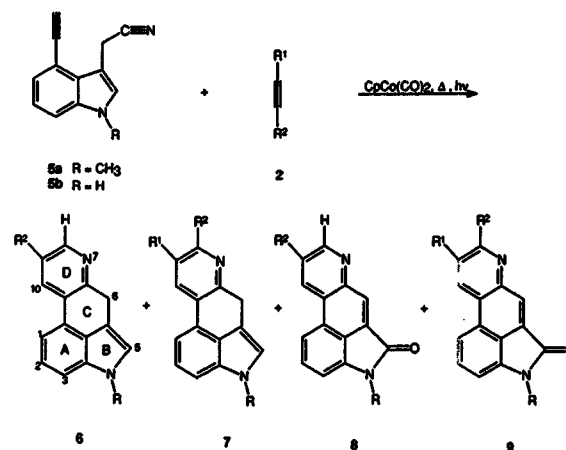
Solvent	Alkyne	Ratio 3:4 ^c	Yield, % ^d
benzene	2a R ¹ = Si(CH ₃) ₃ , R ² = CO ₂ CH ₃	1.1:1	82
benzene	2b R ¹ = Si(CH ₂ CH ₃) ₃ , R ² = CO ₂ CH ₃	1:1	78
benzene	2c R ¹ = Si(CH ₂ CH ₃) ₂ , R ² = CO ₂ CH ₃	1.7:1	67
benzene	2d R ¹ = Si(CH ₃) ₃ , R ² = CON(CH ₂ CH ₃) ₂ ^e	1.4:1	87
1,3-dimethylbenzene	2e R ¹ = Si(CH ₂ CH ₃) ₃ , R ² = OCH ₃	>95:1	43
1,3-dimethylbenzene	2f R ¹ = Si(CH ₂ CH 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

^aHigh dilution (syringe pump addition) conditions, reflux, irradiation with a GE-ELH slide projector lamp, ~10% catalyst. See also Experimental and references 3,4. ^bAll new compounds gave satisfactory analytical and/or spectral data. ^cBy NMR or g.c. Regiochemical assignments were corroborated by protodesilylation. ^dAfter separation by column chromatography (silica gel). ^eReference 9. ^fReference 3a.

The data show that, while the relevant cyclizations proceed efficiently, electronic and steric factors seem to compete, a finding preceded 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 procedures⁶ via the 4-bromoprecursors,⁷ followed by Pd-catalyzed trimethylsilyl-ethynylation-deprotection.^{8,12}



Scheme 2

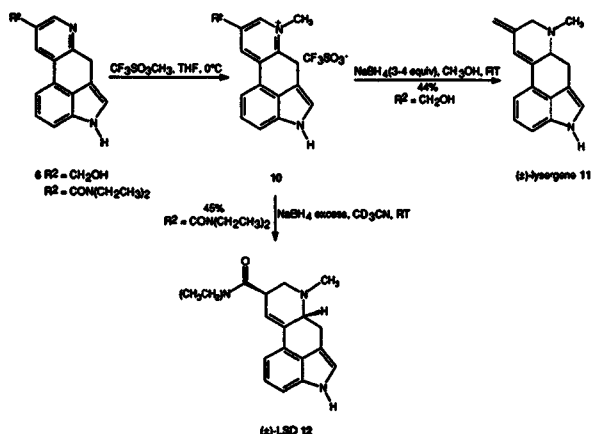
Table II. Results of the Cocyclization of 2 with 5 ^{a,b}

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 ₂ CH ₃) ₃ , R ² = CH ₃	6	0	12	0
5a	2d R ¹ = Si(CH ₃) ₃ , R ² = CON(CH ₂ CH ₃) ₂ ^d	0	13	9	trace
5b	2d	17	33	trace	trace
5b	2i R ¹ = Si(CH ₃) ₃ , R ² = CH ₂ OH ^e	38	11	0	0
5b	2j R ¹ = Si(CH ₃) ₃ , R ² = CH(CH ₂) ₂ OCH ₃ ^f	10	41	trace	trace

^aHigh 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. ^bAll new compounds gave satisfactory analytical and/or spectral data. ^cBy NMR spectroscopy of crude product mixture. ^dReference 9. ^eReference 10. ^fReference 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 trimethylsilyl group 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 indoloquinolones 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 data¹⁵ and was confirmed by long range correlation ¹H-¹³C NMR experiments;¹⁶ 6. as in the model coelomerizations of 1, those of 5 exhibit only modest regioselectivity when the trimethylsilyl group 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 312 to furnish ($\pm$)-lysergine 11, identical (1H NMR, MS, UV, TLC) with authentic material.¹⁷



Scheme 3

Similarly, 6 [$R = H$, $R^2 = CON(CH_2CH_3)_2$]12 was converted to 10 (32%, orange powder, m.p. 185-186°C dec) and then ($\pm$)-LSD 12, identified by NMR comparisons¹⁸ 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

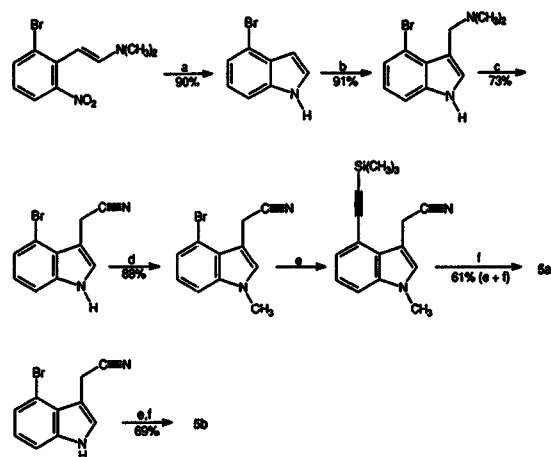
A solution of 5 (1.50 mmol) in THF (4 mL) and another solution of $[CpCo(CO)_2]$ (0.30g, 1.68 mmol) and 2 (4-8 mmol) in THF (3 mL) were slowly added over 12h via two separate syringe pumps to stirred THF (5 mL) in a round-bottomed flask under N_2 , equipped with a reflux condenser and submerged in an 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).

Acknowledgement. This work was supported by the National Institutes of Health (GM22479). C. S. thanks NATO for a postdoctoral fellowship (1987-1988). We are grateful to Prof. I. Ninomiya for providing us with an authentic sample of lysergine and to Prof. H. G. Floss for helpful correspondence.

References and Notes

- (1) For a review, see: Ninomiya, I.; Kiguchi, T. in *The Alkaloids*, Vol. 38; Brossi, A., Ed.; Academic: New York, NY, 1990; p1.
- (2) For some recent references, see: Ozlu, Y.; Cladingboel, D. E.; Parsons, P. J. *Synlett* 1993, 357; Kozikowski, A. P.; Chen, C.; Wu, J.-P.; Shibuya, M.; Kim, C.-G.; Floss, H. G. *J. Am. Chem. Soc.* 1993, 115, 2482; Semmelhack, M. F.; Knochel, P.; Singleton, T. *Tetrahedron Lett.* 1993, 34, 5051; Eich, E. *Pharm. Ztg.* 1992, 137, 9, 18, 22.
- (3) (a) Brien, D. J.; Naiman, A.; Vollhardt, K. P. C. *J. Chem. Soc., Chem. Commun.* 1982, 133. (b) Vollhardt, K. P. C. *Angew. Chem.* 1984, 96, 525; *Angew. Chem., Int. Ed. Engl.* 1984, 23, 539; *Lect. Heterocycl. Chem.* 1987, 9, 59. (c) For leading references, see: Viljoen, J. S.; du Plessis, J. A. K. *J. Mol. Cat.* 1993, 79, 75.

- (4) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* 1986, 108, 2091; Sheppard, G. S.; Vollhardt, K. P. C. *J. Org. Chem.* 1986, 51, 5496; Boese, R.; Knölker, H.-J.; Vollhardt, K. P. C. *Angew. Chem.* 1987, 99, 1067; *Angew. Chem., Int. Ed. Engl.* 1987, 26, 1035.
- (5) Vollhardt, K. P. C. in *Inorganic Reactions and Methods*, Vol. 12A; Hagen, A. P.; Zuckerman, J. J., Eds.; Verlag Chemie: New York, NY, 1991; p247.
- (6) Clark, R. D.; Repke, D. B. *Heterocycles* 1984, 22, 195.
- (7) Somei, M.; Kizu, K.; Kunimoto, M.; Yamada, F. *Chem. Pharm. Bull.* 1985, 33, 3696.
- (8) Kalinin, V. N. *Synthesis* 1992, 413. See also: Galambos, G.; Szántay Jr., C.; Tamás, J.; Szántay, C. *Heterocycles* 1993, 36, 2241.



(a) Fe powder, CH_3COOH , silica gel, $C_6H_5-C_6H_5$; (b) 40%aq $(CH_3)_2NH$, 37%aq $HCHO$, CH_3COOH ; (c) KCN , $DMF-H_2O$; (d) 1. NaH , DMF ; 2. CH_3I , DMF ; (e) $(CH_3)_3SiC\equiv CH$, CuI 3%, $PdCl_2[P(C_6H_5)_3]_2$, $(CH_3CH_2)_2N$, 120-125°C (pressure bomb), 15h; (f) K_2CO_3 , CH_3OH .

- (9) Safronova, L. P.; Medvedeva, A. S.; Vyazankin, N. S. *J. Gen. Chem.* 1983, 53, 1177.
- (10) Ahmed, M.; Barley, G. C.; Hearn, M. T. W.; Jones, E. R. H.; Thaller, V.; Yates, J. A. *J. Chem. Soc., Perkin Trans. 1* 1974, 1981.
- (11) Kruithof, K. J. H.; Schmitz, R. F.; Klumpp, G. W. *J. Chem. Soc., Chem. Commun.* 1983, 239.
- (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, NH), 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): λ_{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): λ_{max} (log ϵ) 238

sh (4.36), 360 (3.78) nm; ^1H NMR (300 MHz, CDCl_3): δ = 8.42 (d, J = 2.0 Hz, 1H), 8.30 (br s, NH), 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 $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$ 305.1527, found 305.1528. **7** [R = H, R^1 = $\text{Si}(\text{CH}_3)_3$, R^2 = $\text{CON}(\text{CH}_2\text{CH}_3)_2$]: yellow-green oil (rapidly oxidizing to **9**); ^1H NMR (300 MHz, CDCl_3): δ = 8.75 (br s, NH), 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 = $\text{CON}(\text{CH}_2\text{CH}_3)_2$]: 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): λ_{max} (log ϵ) 220 (4.48), 248 (4.42), 291 (4.28), 346 sh (3.41), 362 sh (3.43), 390 (3.48) nm; ^1H 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, NH), 8.01 (d, J = 8.4 Hz, 1H), 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 = $(\text{CH}_3)_3\text{Si}$, R^2 = $\text{CON}(\text{CH}_2\text{CH}_3)_2$]: 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): λ_{max} (log ϵ) 231 (4.24), 253 (4.26), 287 (4.12), 348 sh (3.21), 365 sh (3.23), 391 (3.28)

nm; ^1H 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, NH), 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).

- (13) Brown, R. S.; Slebocka-Tilk, H.; Buschek, J. M.; Ulan, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 5979.
- (14) Fritch, J. R.; Vollhardt, K. P. C. *Isr. J. Chem.* **1985**, *26*, 131; Gesing, E. R. F.; Tane, J. P.; Vollhardt, K. P. C. *Angew. Chem.* **1980**, *92*, 1057; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1023; Gesing, E. R. F.; Vollhardt, K. P. C. *J. Organomet. Chem.* **1981**, *217*, 105.
- (15) Gómez, B.; Guitián, E.; Castedo, L. *Synlett* **1992**, 903.
- (16) Bax, A.; Morris, G. A. *J. Magn. Res.* **1981**, *42*, 501.
- (17) Kiguchi, T.; Hashimoto, C.; Ninomiya, I. *Heterocycles* **1984**, *22*, 43.
- (18) Bach, N. J.; Boaz, H. E.; Kornfeld, E. C.; Chang, C.-J.; Floss, H. G.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1974**, *39*, 1272. See also: Rebek Jr., J.; Tai, D. F.; Shue, J.-K. *J. Am. Chem. Soc.* **1984**, *106*, 1813; Ninomiya, I.; Hashimoto, C.; Kiguchi, T.; Naito, T. *J. Chem. Soc., Perkin Trans. I* **1985**, 941.
- (19) Inoue, T.; Nakahara, Y.; Niwaguchi, T. *Chem. Pharm. Bull.* **1972**, *20*, 409; Cornell, R. R.; Fenselau C. *Arch. Mass Spectral Data* **1971**, *2*, 696.
- (20) The NMR spectrum also contained signals (~20%) tentatively assigned to ($\pm$)iso-LSD: Černý, A.; Semonský, M. *Coll. Czech. Chem. Commun.* **1962**, *27*, 1585; Stoll, A.; Hofmann, A. *Helv. Chim. Acta* **1955**, *38*, 421; **1943**, *26*, 944.