Registry No. **2**, 2166-14-5; **3a**, 23900-50-7; **3b**, 92144-06-4; **3c**, 71124-72-6; **3d**, 2166-27-0; **3e**, 92144-07-5; **3f**, 92144-08-6; **3g**, 92144-09-7; **3h**, 92144-10-0; **4b**, 92144-11-1; **4c**, 37813-95-9; **4d**, 92184-43-5; **5a**, 78331-70-1; **5b**, 91248-34-9; **5c**, 25473-58-9; **5d**, 92144-12-2; **5e**, 92144-13-3; **5f**, 92144-14-4; **5g**, 92144-15-5; **5h**, 92144-16-6; **6a**, 822-51-5; **6b**, 488-92-6; **6d**, 27649-43-0; **7**, 1257-25-6; $CH_3CH{=}C(OSiEt_3)CH_3$, 53379-23-0; $CH_3C{\equiv}CCH_3$, 503-17-3; $PhC(OSiMe_3){=}CH_2$, 13735-81-4; $(MeO)_2C{=}CH_2$, 922-69-0; $PhCH_2OC(=CH_2)OSiMe_2$-*t*-Bu, 92144-04-2; $CH_3C(O)CH{=}C(OCH_3)_2$, 50473-61-5; 4-(1-ethyl-1-propenyl)morpholine, 13654-48-3; 1-(1-ethyl-1-propenyl)pyrrolidine, 13750-57-7; 1-(1-phenyl-1-ethenyl)pyrrolidine, 3433-56-5; 8-(methoxycarbonyl)-3-morpholino-8-azabicyclo[3.2.1]oct-2-ene, 92144-05-3; 1-(1-cyclohexenyl)pyrrolidine, 1125-99-1; 4-(1-phenylethenyl)morpholine, 7196-01-2; 3,4-dimethyl-1*H*-pyrrole-2,5-dicarboxylic acid, 92144-17-7; *N*-(methoxycarbonyl)nortropin-3-one, 53416-88-9; 3-morpholino-3,4-dihydro-1,2-diazine, 92184-44-6; 4-phenyl-1,2-diazine-3,6-dicarboxylic acid, 92144-18-8.

Preparation and Reactions of 4-(Trimethylsilyl)indole

Anthony G. M. Barrett*

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Daniel Dauzonne, Ian A. O'Neil, and Alain Renaud

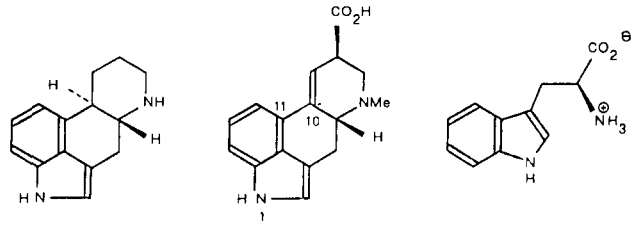
Department of Chemistry, Imperial College, London SW7 2AY, England

Received May 14, 1984

Indole or 1-(trimethylsilyl)indole was reacted sequentially with lithium–chlorotrimethylsilane and with 1,4-benzoquinone to produce 1,4-bis(trimethylsilyl)indole (50% and 55%, respectively). Methanolysis gave 4-(trimethylsilyl)indole which reacted with electrophiles at C-3. However, the derivative 1-acetyl-4-(trimethylsilyl)indole reacted with acetyl, 2-chloropropanoyl, or propenoyl chlorides via clean C-4 ipso substitution. Attempts to extend the reaction to a useful synthesis of derivatives of 5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole, a lysergic acid synthon, were prevented by low yields.

Introduction

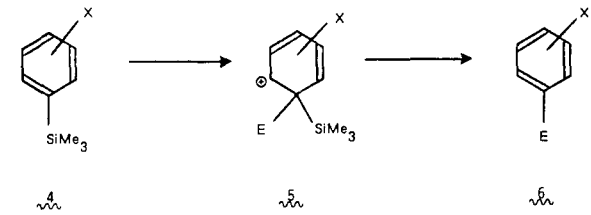
The ergot alkaloids are a group of biologically active metabolites produced by various species of the fungus *Claviceps*. these clinically important compounds are widely applied in the treatment of hypertension, migraine, prolactin dependent disorders, and postpartum hemorrnage.[1] The parent unit present in all the ergot alkaloids is the ergoline ring system **1**. An example is lysergic acid



1 **2** **3**

(**2**) which is obtained by the alkaline hydrolysis of the ergot peptide alkaloids. Several synthesis of this pivotal molecule **2** have been recorded.[1-3] In the total synthesis of **2** it is necessary to decide how to establish the single C-10 to C-11 carbon–carbon bond. Clearly in concise syntheses of **2**, indole precursors including L-tryptophan (**3**) are attractive starting materials. There is, however, a major problem in using indole precursors: the C-4 (indole numbering) center is considerably less reactive toward electrophiles than either C-3 or C-2. Thus, when lysergic acid (**2**) has been prepared from indole derivatives, one of two strategies has been adopted. Either the indole is already C-4 functionalized or the indole precursor is masked at the indoline oxidation level. Examples of these two strategies are the elegant synthesis and use of indole-4-carboxaldehyde by Kozikowski[4] and the succinct synthesis of **2** from 2,3-dihydro-L-tryptophan reported by Rebek.[3]

Scheme I



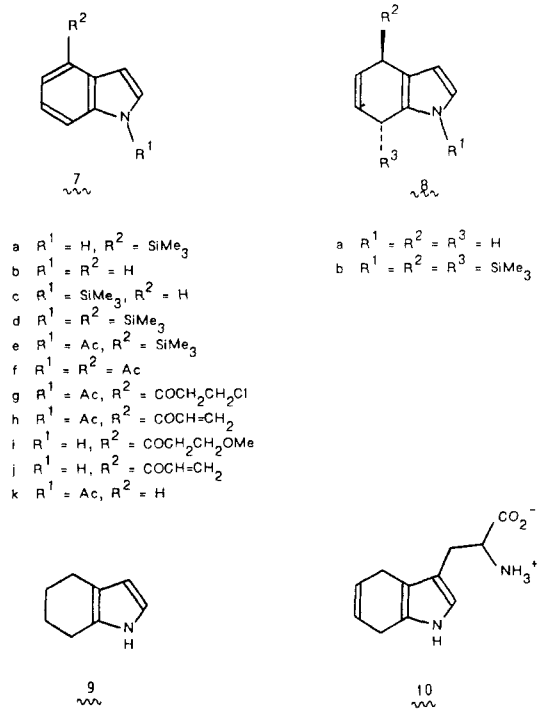
4 **5** **6**

A tenet of organosilicon chemistry is the generalization that "a silicon–carbon bond stabilizes a carbonium ion β to it".[5] For example diverse aryltrimethylsilanes[4] undergo ipso substitution by electrophiles to produce **6** on account of preferential formation of the Wheland intermediate **5** (Scheme I). This ipso attack may overwhelm the effects of other directing substituents. Thus 2-(trimethylsilyl)-benzoic acid reacted with bromine to produce 2-bromobenzoic acid, whereas 3-(trimethylsilyl)toluene gave 3-methylbenzophenone on Friedel–Crafts benzoylation. In principle, such a reversal of the aromatic electrophilic substitution pattern mediated by a trimethylsilyl group should be applicable to indole chemistry. Indeed the production of 4-(trimethylsilyl)indole (**7a**) should be of relevance to C-4 electrophilic substitution and ultimately to lysergic acid (**2**) total synthesis.

In 1960 Smith reported[6] that indole (**7b**) was reduced under Birch conditions to produce an inseparable mixture of 4,7-dihydro- and 4,5,6,7-tetrahydroindoles (**8a** and **9**).

(1) Stadler, P. A.; Stütz, P. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, p 1.
(2) Horwell, D. C. *Tetrahedron* **1980**, *36*, 3123. Oppolzer, W.; Francotte, E.; Battig, K. *Helv. Chim. Acta* **1981**, *64*, 478. Kiguchi, T.; Hashimoto, C.; Naito, T.; Ninomiya, I. *Heterocycles* **1982**, *19*, 2279.
(3) Rebek, J. Jr.; Tai, D. B. *Tetrahedron Lett.*, **1983**, *24*, 859. Rêbek, J. Jr.; Tai, D. B.; Shue, Y.-K. *J. Am. Chem. Soc.*, **1984**, *106*, 1813.
(4) Kozikowski, A. P. *Heterocycles*, **1981**, *16*, 267.
(5) Fleming, I. In "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds.; Pergammon Press: Oxford, 1979; Vol. 3, p 539.
(6) O'Brien, S.; Smith, D. C. C. *J. Chem. Soc.* **1960**, 4609.

0022-3263/84/1949-4409$01.50/0 © 1984 American Chemical Society

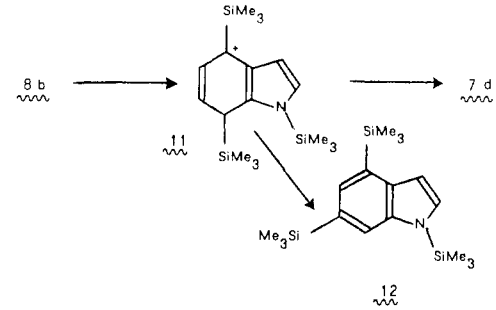


Subsequently, Remers[7] and Helmkamp[8] studied the reaction more carefully and defined conditions for the purification of **8a** and related systems.[9] Intriguingly, L-tryptophan (**3**) has also been smoothly Birch reduced to produce 4,7-dihydro-L-tryptophan.[10] Since the Birch reduction of an aromatic substrate proceeds via the radical anion and cyclohexadienyl anion[11] there is, of course, the opportunity to intercept these intermediates by electrophiles other than a proton source. Laguerre and others[12] have reduced carbocyclic aromatic substrates by using chlorotrimethylsilane and lithium in THF solution. Thus, under these conditions, benzene was converted into 2,5-bis(trimethylsilyl)-1,4-cyclohexadiene which on air oxidation gave 1,4-bis(trimethylsilyl)benzene. Clearly the Birch reduction of indole (**7b**) under silylating conditions should provide a method for the activation of the C-4 center.

Results and Discussion

Synthesis of 1,4-Bis(trimethylsilyl)indole (7d). 1-(Trimethylsilyl)indole (**7c**), chlorotrimethylsilane, and lithium metal in THF solution were ultrasonically agitated for 4 h at 5–10 °C and overnight at 45 °C. Evaporation of the solvent gave an off-white solid that was air sensitive and presumably contained lithium chloride and **8b**. Without purification this was directly oxidized using 1,4-benzoquinone in dichloromethane solution. Chromatography gave 1,4-bis(trimethylsilyl)indole (**7d**) (55%). The structural assignment of **7d** was in full agreement with all spectral and microanalytical data. The ^1H high-resolution NMR spectrum was especially informative. Thus the chemical shifts and coupling constants for the aromatic protons were fully consistent with the 1,4-disubstitution pattern. In addition, when difference NOE experiments were used, the N–$SiMe_3$ group was shown to be close to H-2 and H-7 whereas the C–$SiMe_3$ was close to both H-3 and H-5.[13] As an alternative procedure indole (**7b**) was reduced by using chlorotrimethylsilane and lithium metal in THF solution followed by oxidation using 1,4-benzoquinone in dichloromethane to produce **7d** (50%). In either preparation of **7d** it was found to be essential to ultrasonically agitate the mixture during the reduction step. Without this efficient mixing the rate and yield of reduction was decreased.

Scheme II

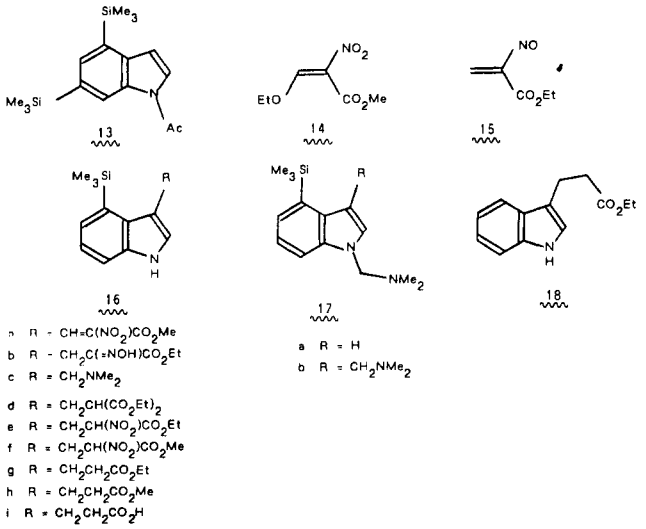


The mechanism describing the formation of **7d** requires further comment. Prior to oxidation using 1,4-benzoquinone the intermediate was assigned as the 4,7-dihydroindole derivative **8b** with the two trimethylsilyl groups trans. Although this was not authenticated, the assignment was consistent with precedent.[12] In the aromatization reaction one hydrogen must be removed from C-4 and one trimethylsilyl group from C-7. The oxidation step is most reasonably depicted as in Scheme II. Thus electron transfer followed by proton transfer and second electron transfer from **8b** to the quinone should provide **11** and the hydroquinone monoanion. Clearly in this process the less hindered C-4 hydrogen is transferred. Finally the hydroquinone monoanion desilylates **11** at C-7 to produce the product **7d**. In the overall transformation preferential loss of the C-7 trimethylsilyl group follows from release of steric congestion with the N-substituent. In addition, the loss of one hydrogen and one silyl group follows from their cis disposition in **8b** and syn selectivity in their removal. Both these proposals have precedent. Thus Laguerre reported that *m*-xylene was converted into 1-(trimethylsilyl)-3,5-dimethylbenzene on reductive silylation and reoxidation.[12] Secondly, Fleming reported that the DDQ oxidation of *trans*-3,6-dideuterio-1,4-cyclohexadiene was syn stereospecific giving monodeuteriobenzene only.[14] In support of the intermediacy of **11** we have isolated **12**, vide infra, as a minor product formed in the conversion of **8b** into **7d**. Clearly **12** must have arisen from **11** via a 1,2-trimethylsilyl group migration.[14]

Reactions of 1,4-Bis(trimethylsilyl)indole (7d). On brief warming the methanol solution **7d** was converted into 4-(trimethylsilyl)indole (**7a**) (98%). The structure of this material was confirmed by an X-ray crystallographic study[15] and this, of course, completely secured the structure of **7d**. On reaction with sodium hydride followed by acetyl chloride **7a** was converted into the acetyl derivative **7e** (96%). In a subsequent preparation of **7e** on a large scale, crude **7a** was acetylated and the major component

(7) Remers, W. A.; Gibs, G. J.; Pidacks, C.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 279.
(8) Ashmore, J. W.; Helmkamp, G. K. *Org. Prep. Proced. Int.* **1976**, *8*, 223.
(9) Teuber, H. J.; Schmitt, G. *Chem. Ber.* **1969**, *102*, 713. Remers, W. A.; Weiss, M. J. *Tetrahedron Lett.* **1968**, 81. Remers, W. A.; Gibs, G. J.; Pidacks, C.; Weiss, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5513. Remers, W. A.; Gibs, G. J.; Pidacks, C.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 279.
(10) Yonemitsu, O.; Cerutti, P.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 3941.
(11) Birch, A. J. *Q. Rev.*, **1950**, *4*, 49.
(12) Lacquerre, M.; Dunogues, J.; Calas, R.; Duffaut, N. *J. Organomet. Chem.*, **1976**, *112*, 49. Bikkofer, L.; Ramadan, N. *Ibid.* **1972**, *44*, C41.
(13) We thank David Neuhaus for these measurements.
(14) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415.
(15) Barrett, A. G. M.; Dauzonne, D.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 636.

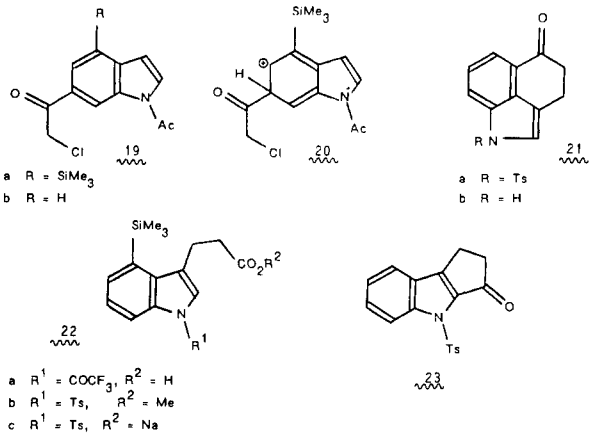
7e isolated by recrystallization. Chromatography of the mother liquor gave a minor byproduct **13**. Clearly this product was formed by the impurity **12** present in crude **7d**. The assignment of the structure **13** was secured principally by the ^{1}H NMR spectrum [δ 8.68 (br s, 1 H, 7-H)].



Both 4-(trimethylsilyl)indole (**7a**) and 1,4-bis(trimethylsilyl)indole (**7d**) reacted with electrophiles at C-3 not via ipso substitution at C-4. Thus **7a** reacted with methyl 3-methoxy-2-nitropropenoate (**14**)[16] or ethyl 2-nitrosopropenoate (**15**)[17] to produce the expected[16-18] C-3 substituted indole derivatives **16a** (43%) and **16b** (36%). In addition, **7d** reaction with dimethylmethyleneammonium chloride[19] in dichloromethane solution to produce **16c** (20–60%), as the major compound, and two additional products tentatively identified as **17a** and **17b**.

Again when standard indole chemistry[18,20] was used, 4-(trimethylsilyl)gramine (**16c**) was converted into **16d** (97%), **16e** (99%), and **16f** (97%). Subsequent tri-*n*-butylstannane reduction[21] of **16e** and **16f** gave **16g** (32%) and **16h** (76%), respectively. In these radical denitrations, purification of the product was most efficiently carried out on alumina, not silica. This was due to the instability of the byproduct tributyltin nitrite[21] on the second support. As an alternative, ester **16g** was prepared directly from 4-(trimethylsilyl)indole (**7a**) by reaction with ethyl acrylate and aluminum chloride.[18] This reaction, with several Lewis acids, gave low yields (≤15%) because of competitive protodesilylation to give **18**.

The Friedel–Crafts Acylation of 4-(Trimethylsilyl)indole (7a). Since 4-(trimethylsilyl)indole (**7a**) and 1,4-bis(trimethylsilyl)indole (**7d**) both reacted with electrophiles at C-3, it was necessary to deactivate this position to allow for ipso substitution at C-4. Thus the reaction of 1-acetyl-4-(trimethylsilyl)indole (**7e**) with acylating reagents was investigated. Acetyl chloride, **7e**, and aluminum chloride reacted smoothly together to produce 1,4-diacetylindole (**7f**) (95%). Again the N-1, C-4 substitution pattern followed directly from the ^{1}H NMR spectrum [δ 7.44 (dd, 1 H, J = 8.5, 7.5 Hz, 6-H), 8.66 (ddd, 1 H, J = 8.5, 1, 1 Hz, 7-H)]. Both 3-chloropropanoyl chloride and propenoyl chloride reacted with **7e** and aluminum chloride to produce the same product **7g** (75%, 60%, respectively). Clearly both **7f** and **7g** were formed via clean ipso substitution. Chloroacetyl chloride, however, reacted with **7e** to give a mixture of compounds. Chromatography gave the C-6 ketones **19a** (37%) and **19b** (46%). Presumably in this case ipso substitution was suppressed by steric congestion and reaction took place via **20** with **19b** being formed via late protodesilylation. The ^{1}H NMR spectrum of **19a** was fully consistent with the N-1, C-4, C-6 substitution pattern [δ 8.07 (d, 1 H, J = 1.3 Hz, 5-H), 9.09 (s, 1 H, 7-H)].



Preparation of Ketone 21a. Uhle's ketone (**21b**) is a pivotal intermediate in the early syntheses of lysergic acid (**2**). Prompted by this fact, we set out to explore its preparation from 4-(trimethylsilyl)indole (**7a**). Initially we sought to cyclize **7g**. Under diverse basic conditions **7g** was converted into **7h**, **7i**, or **7j**. Neither under these conditions nor under Lewis acidic conditions were any derivatives of **21** produced. Thus we examined the preparation of **21** from **7a** with reversal of order in the C–C bond formation reactions. Ester **16e** was reacted sequentially with tributylstannane and sodium hydroxide to produce **16i** (53%) on acidification. This was converted into **22a** (31%) by sequential reaction with sodium hydride and trifluoroacetic anhydride. Attempted cyclization of **22a** using oxalyl chloride followed by aluminum chloride did not produce isolable quantities of **21b**. However, the toluene-4-sulfonate **22c** was successfully cyclized. Ester **16h** was converted into **22c** by sequential reaction with potassium hydride, toluene-4-sulfonyl chloride, and methanolic sodium hydroxide. On reaction with diethyl chlorophosphate and aluminum chloride **22c** was converted into a mixture of compounds. Chromatography gave two cyclic products **21a**[22] (5%) and **23** (34%). Clearly, the angle strain associated with the production of **21a** is sufficient to overwhelm the combined directing influence of the *N*-toluene-4-sulfonyl group and the 4-trimethylsilyl substituent. Thus, although we have been able to prepare **21a**, the yield is extremely poor.

Further Reductions Using Lithium–Chlorotrimethylsilane. In addition to our studies on indole, we briefly examined the reduction of pyridine, 2,6-dimethylpyridine, quinoline, and *N*,*N*-dimethylbenzamide.

(16) Kamlet, M. J. *J. Org. Chem.* **1956**, *24*, 714. Hangartner, U.; Valentine, D., Jr.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townesend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741.

(17) Gilchrist, T. L.; Lingham, D. A.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, 1089. Roberts, T. G. Ph.D. Thesis, University of Liverpool, **1979**.

(18) Brown, R. J.; Joule, J. A. In "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 4, p 411.

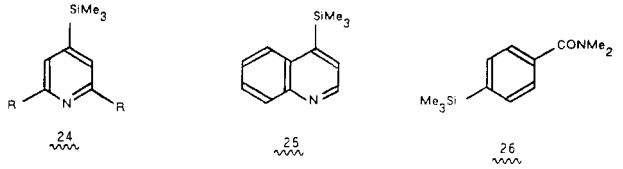
(19) Bohme, H.; Hartke, K. *Chem. Ber.* **1960**, *93*, 1305. Kinast, G.; Tietze, L. F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239.

(20) Somei, M.; Karasawa, Y.; Kaneko, C. *Chem. Lett.* **1980**, 813.

(21) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, 1705.

(22) Bowman, R. E.; Evans, D. D.; Guyett, J.; Nagy, J. G. H.; Weale, J.; Weyell, D. J.; White, A. C. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1926.

Thus reaction of these aromatic substrates with lithium and chlorotrimethylsilane followed by 1,4-benzoquinone or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave respectively **24a**[23] (74%), **24b** (42%), **25**[23] (35%), and **26** (42%). Although these yields are modest, the reaction provides an alternative procedure for heteroarene ring silylation.



a R = H
b R = Me

Conclusion

The reduction of indole (**7b**) with lithium and chlorotrimethylsilane followed by 1,4-benzoquinone oxidation provided a convenient method for the production of 4-(trimethylsilyl)indole (**7a**). This product reacted with electrophiles at C-3. Alternatively the derived 1-acetyl-4-(trimethylsilyl)indole (**7e**) usually underwent intermolecular Friedel–Crafts acylation via ipso substitution at C-4. Although the Uhle's ketone derivative **21a** was prepared from **7a**, the procedure was inapplicable to lysergic acid (**2**) synthesis on account of poor yields.

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. Reactions were carried out under dry argon or nitrogen. All solvents and reagents were purified and dried before use. Ultrasonication was carried out in a PUL55 Kerry QH Ultrasonic Bath (Kerry Ultrasonics Ltd., England). Organic extracts were concentrated by rotary evaporation under reduced pressure at ≤40 °C. Unless stated to the contrary, chromatography refers to flash chromatography on Merck Kieselgel H.

1-(Trimethylsilyl)indole (7c). Indole (**7b**) (23.4 g) and NaH (7.2 g) in THF (100 mL) were mixed together in an ultrasonic bath overnight when the temperature increased from 20 to 45 °C. Me_3SiCl (38 mL) in THF (50 mL) was added dropwise at 0 °C and the mixture refluxed for 5 h. After evaporation the residue was leached with hexane and the extract filtered. Evaporation gave **7c**[24] (35.2 g, 93%) which on distillation gave pure **7c** (32.6 g, 86%), bp 68–70 °C (0.06 mmHg).

1,4-Bis(trimethylsilyl)indole (7d). Method A. Me_3SiCl (4.05 ml) was added dropwise with stirring to 1-(trimethylsilyl)indole (**7c**) (2.0 g) in THF (30 mL) at 0 °C. Lithium (186 mg) cut into 20 clean pieces was added and the mixture agitated in an ultrasonic bath at 5–10 °C for 4 h and subsequently overnight at 45 °C. The THF was evaporated in vacuo and replaced by CH_2Cl_2 (10 mL). It was essential to maintain a nitrogen atmosphere during this solvent change. The mixture was cooled to 0 °C and *p*-benzoquione (1.72 g) in CH_2Cl_2 (20 mL) was added. After the reaction had stirred 3 h, the CH_2Cl_2 was removed under reduced pressure, the residue was leached with hexane, and the extract was directly filtered through silica (35 g) eluting with hexane (60 mL) and CH_2Cl:hexane (1:9, 130 mL). The combined filtrates were evaporated to leave a mixture of **7c** and **7d** (2.53 g, 3:7). This was flash chromatographed on silica (70 g) to give [eluant hexane–hexane:CH_2Cl_2 (9:1)] pure 1,4-bis(trimethylsilyl)indole (7d) (1.52 g, 55%): mp 62.5–63.5 °C (from hexane); IR (Nujol) 1510, 1400, 1290, 1260, 1160, 915, 850, 760 cm^{-1}; NMR ($CDCl_3$) δ 0.38 (s, 9 H), 0.53 (s, 9 H), 6.68 (dd, 1 H, J = 3.5, 1 H, J = 3.5, 1 Hz), 7.12 (dd, 1 H, J = 9, 8 Hz), 7.15 (d, 1 H, J = 3.5 Hz), 7.25 (dd, 1 H, J = 8, 1 Hz), 7.47 (dt, J = 4, 1 Hz); mass spectrum m/e 261 ($M^{+}\cdot$), 246. Anal. Calcd for $C_{14}H_{23}NSi_2$: C, 64.28; H, 8.87; N, 5.36. Found: C, 64.28; H, 8.93;, N, 5.33.

Method B. When exactly the same procedure was used, reaction of indole (**7b**) (1.24 g), Li (0.297 g), Me_3SiCl (4.6 g), and *p*-benzoquinone (2.3 g)) gave **7d** (1.39 g, 50%) identical with the previous sample.

4-(Trimethylsilyl)indole (7a). 1,4-Bis(trimethylsilyl)indole (**7d**) (2.61 g) in dry MeOH (50 mL) was refluxed for 5 min, evaporated to dryness, redissolved in MeOH (50 mL), reevaporated, redissolved in hexane, and reevaporated to give **7a** (1.85 g, 98%). Recrystallization from MeOH–H_2O gave **7a** (1.70 g, 90%) as white plates: mp 63.5–64 °C; IR (CH_2Cl_2) 3400, 1400, 1250, 940, 840, 760, 735 cm^{-1}; NMR ($CDCl_3$) δ 0.41 (s, 9 H), 6.68 (m, 1 H), 7.20 (dd, 1 H, J = 8, 7 Hz), 7.23 (m, 1 H), 7.29 (dd, 1 H, J = 7, 1.5 Hz), 7.40 (dt, 1 H, J = 7, 1.5 Hz), 8.0–8.3 (m, 1 H); mass spectrum, m/e 189 ($M^{+}\cdot$), 174. Anal. Calcd for $C_{11}H_{15}NSi$: C, 69.76; H, 7.99; N, 7.40. Found: C, 69.79; H, 8.04; N, 7.40.

1-Acetyl-4-(trimethylsilyl)indole (7e). NaH (0.252 g), 4-(trimethylsilyl)indole (**7a**) (1.325 g), and THF (30 mL) were ultrasonically agitated overnight when the temperature increased from 20 to 40 °C. After cooling to −78 °C, AcCl (0.825 g) in THF (5 mL) was added dropwise with stirring. The mixture was warmed up to room temperature (1 h) and evaporated to dryness. The residue was extracted with CH_2Cl_2 (30 mL), treated with charcoal, filtered, and evaporated to leave **7e** (1.550 g, 96%). Recrystallization from hexane gave **7e** as colorless needles: mp 123–124 °C; IR ($CHCl_3$) 1690, 1530, 1400–1360, 1320, 1250 cm^{-1}; NMR ($CDCl_3$) δ 0.39 (s, 9 H), 2.64 (s, 3 H), 6.77 (dd, 1 H, J = 4, 0.5 Hz), 7.34 (d, 1 H, J = 8, 7 Hz), 7.42 (dd, 1 H, J = 7, 1.5 Hz), 7.46 (d, 1 H, J = 4 Hz), 8.48 (br d, 1 H, J = 8 Hz); mass spectrum, m/e 231 ($M^{+}\cdot$), 216, 189, 174. Anal. Calcd for $C_{13}H_{17}NOSi$: C, 67.49; H, 7.41; N, 6.05. Found C, 67.38; H, 7.43; N, 5.99.

1-Acetyl-4,6-bis(trimethylsilyl)indole (13). Crude unchromatographed 1,4-bis(trimethylsilyl)indole (**7d**) (9.62 g) was reacted with methanol, sodium hydride, and acetyl chloride without purification of intermediates. Recrystallization of the crude product gave **7e** (3.75 g). Chromatography of the mother liquor on silica (eluant CH_2Cl_2:hexane 7:3) gave, in addition to **7e** and **7k**, crude 1-acetyl-4,6-bis(trimethylsilyl)indole (**13**) (0.5 g). Repeated recrystallization from cyclohexane gave **13** as an analytically pure sample: mp 122.5–124 °C; NMR ($CDCl_3$) δ 0.33 (s, 9 H), 0.40 (s, 9 H), 2.64 (s, 3 H), 6.75 (dd, 1 H, J = 4, 0.5 Hz), 7.45 (d, 1 H, J = 4 Hz), 7.56 (d, 1 H, J = 0.5 Hz), 8.68 (br s, 1 H); mass spectrum, m/e 303, ($M^{+}\cdot$), 288, 246. Anal. Calcd for $C_{16}H_{25}NOSi_2$: C, 63.27; H, 8.31; N, 4.66. Found: C, 63.31; H, 8.30; N, 4.61.

Methyl 2-Nitro-3-[4-(trimethylsilyl)indol-3-yl]propenoate (16a). A mixture of 4-(trimethylsilyl)indole (**7a**) (0.189 g) and methyl 3-ethoxy-2-nitropropenoate (**14**)[16] (0.145 g) were stirred under argon at room temperature for 24 h. A further equivalent of **14** (0.145 g) was added and the mixture stirred for a further 24 h. The crude material was chromatographed on Silica H (10 g) eluting with CH_2Cl_2 to give **16a** (0.138 g, 43%): mp 176–179 °C with resolidification, second mp 195–202 °C (from CCl_4:benzene); IR (Nujol) 3390, 1710, 1615, 1520, 1290, 1270, 1250, 1145, 1125, 1105, 835, 750 cm^{-1}; NMR ($CDCl_3$) δ 0.339, 0.345 (2 s, 9 H), 3.942, 3.975 (2 s, 3 H) 7.275–8.586 (complex, 5 H), 8.75, 8.83 (br, 1 H); mass spectrum, m/e 320, 319, 318 ($M^{+}\cdot$), 305, 304, 303, 286, 272, 259, 243, 229, 218, 202, 184, 168, 154, 141, 127. Anal. Calcd for $C_{15}H_{18}N_2O_4Si$: C, 56.56; H, 5.70. Found: C, 56.65; H, 5.79.

Ethyl 2-(Hydroxyimino)-3-[4-(trimethylsilyl)indol-3-yl]-propanoate (16b). 4-(Trimethylsilyl)indole (**7a**) (0.47 g) was dissolved in dry CH_2Cl_2 (60 mL). Ethyl 3-bromo-2-(hydroxyimino)propanoate[17] (0.58 g) was added to the solution followed by Na_2CO_3 (1.50 g). The solution was stirred at room temperature for 16 h, filtered through Celite, and evaporated in vacuo. The residue was chromatographed on Silica H (20 g) eluting with Et_2O:hexanes (70:30) to give **16b** (0.29 g, 36%): mp 201–204 °C (from EtOAc); IR (Nujol) 3460, 3250 (br), 1720, 1260, 1230, 1215, 1130, 1015, 955, 850, 760 cm^{-1}; NMR [$(CD_3)_2CO$] δ 0.47 (s, 9 H), 1.20 (t, 3 H, J = 7 Hz), 4.17 (q, 2 H J = 7 Hz), 4.25 (d, 2 H, J = 1 Hz), 6.88 (s, 1 H), 7.07 (dd, 1 H, J = 7.9, 7.3 Hz), 7.25 (dd, 1 H, J = 7.3, 1.3 Hz), 7.42 (dd, 1 H, J = 7.9, 1.3 Hz); mass spectrum, m/e 318, 303, 301, 229, 228, 227, 204, 202, 186, 185, 184, 183, 174, 155. Anal. Calcd for $C_{16}H_{22}N_2O_2Si$: C, 60.35; H, 6.96; N, 8.80. Found: C, 60.71; H, 7.25; N, 8.80.

3-[(Dimethylamino)methyl]-4-(trimethylsilyl)indole (16c). *N,N*-Dimethylmethyleneammonium chloride[19] (131 mg) was

(23) Fischer, A.; Morgan, M. W.; Eaborn, C. *J. Organomet. Chem.* **1977**, *136*, 323.
(24) Birkofer, L.; Richter, P.; Ritter, A. *Chem. Ber.* **1960**, *93*, 2804. Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324.

added to 1,4-bis(trimethylsilylindole (**7d**) (261 mg) in dry CH_2Cl_2 (10 mL). After the reaction was stirred for 4 h, aqueous K_2CO_3 (10%, 8 mL) was added and the organic layers were washed, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica (12 g) gave the following in sequence of polarity (eluant CH_2Cl_2:EtOAc 9:1 and MeOH). An oil (25 mg) probably **17a**: NMR ($CDCl_3$, 60 MHz) 0.40 (s, 9 H), 2.22 (s, 6 H), 4.6 (s, 2 H), 6.53 (d, 1 H, J = 3 Hz), 7.0–7.55 (m, 4 H). This was followed by **16c** (120 mg, 48%) as a white crystalline solid: mp 122–133 °C dec (from hexane); IR (CH_2Cl_2) 3460, 1390, 1100, 1015, 940, 840 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 0.43 (s, 9 H), 2.31 (s, 6 H), 3.71 (s, 2 H), 6.98–7.40 (m, 4 H), 8.25–8.65 (m, 1 H); mass spectrum, m/e 246 ($M^{+\cdot}$), 231, 202, 186. Anal. Calcd for $C_{14}H_{22}N_2Si$: C, 68.24; H, 8.99; N, 11.37. Found: C, 68.26; H, 8.95; N, 11.10. The final eluted material was an oil (35 mg) probably **17b**: NMR ($CDCl_3$, 60 MHz) 0.42 (s, 9 H), 2.28 (s, 6 H), 2.3 (s, 6 H), 3.7 (s, 2 H), 4.67 (s, 2 H), 7.05–7.58 (m, 4 H). The yield of **16c** in this experiment varied from 20–60% with variation in time of reaction and ratio of *N,N*-dimethylmethyleneammonium chloride:**7d**.

Ethyl 2-(Ethoxycarbonyl)-3-[4-(trimethylsilyl)indol-3-yl]propanoate (16d). The gramine derivative **16c** (105 mg), diethyl malonate (82 mg), tri-*n*-butylphosphine[20] (24.2 mg), and MeCN (10 mL) were refluxed for 4 h and evaporated, and the residue was chromatographed on silica (7 g) to give (eluant CH_2Cl_2) **16d** (140 mg, 91%): mp 83.5–85.5 °C (from hexane); IR (CH_2Cl_2) 3460, 1740, 1725, 1150, 1035, 940, 840 cm^{-1}; NMR ($CDCl_3$) δ 0.49 (s, 9 H), 1.21 (t, 6 H, J = 7 Hz), 3.42–3.90 (m, 3 H), 4.15 (q, 4 H, J = 7 Hz), 6.97 (br d, 1 H, J = 3 Hz), 7.05–7.45 (m, 3 H), 8.05–8.45 (br m, 1 H); mass spectrum, m/e 361 ($M^{+\cdot}$), 346, 272, 202, 130. Anal. Calcd for $C_{19}H_{27}NO_4Si$: C, 63.13; H, 7.53; N, 3.87. Found: C, 63.15; H, 7.58; N, 3.87.

Ethyl 2-Nitro-3-[4-(trimethylsilyl)indol-3-yl]propanoate (16e). The gramine derivative **16c** (284 mg), ethyl nitroacetate (160 mg), and MeCN (30 mL) were refluxed together overnight. Evaporation and chromatography of the residue on silica (12 g) gave (eluant CH_2Cl_2) the nitroacetate derivative **16e** (380 mg, 99%) as a yellow oil: NMR ($CDCl_3$, 60 MHz), 0.48 (s, 9 H), 1.27 (t, 3 H, J = 7 Hz), 3.82 (d, 2 H, J = 8 Hz), 4.24 (q, 2 H, J = 7 Hz), 5.38 (t, 1 H, J = 8 Hz), 6.89 (br d, 1 H, J = 3 Hz), 7.02–7.33 (m, 3 H), 8.0–8.4 (br m, 1 H); mass spectrum, m/e 334 ($M^{+\cdot}$), 320, 288, 273, 201, 199.

Ethyl 3-[4-(Trimethylsilyl)indol-3-yl]propanoate (16g). Method 1. Bu_3SnH (277 mg), **16e** (252 mg), and $Me_2C(CN)$-N=NC(CN)Me_2 (25 mg) in PhH (10 mL) were refluxed for 6 h when more Bu_3SnH (115 mg) was added and the reflux was continued overnight.[21] Evaporation and chromatography on silica (12 g) gave (eluant CH_2Cl_2) ester **16g** (70 mg, 32%): mp 94–95.5 °C (from hexane); IR (CH_2Cl_2) 3460, 1720, 1370, 1335, 1180–1160, 1110, 1040, 945, 840 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 0.48 (s, 9 H), 1.22 (t, 3 H), 2.48–2.82 (br t, 2 H, J = 8 Hz), 2.98–3.40 (br t, 2 H, J = 8 Hz), 4.09 (q, 2 H, J = 7 Hz), 6.90 (br s, 1 H), 7.0–7.6 (m, 3 H), 7.85–8.25 (br m, 1 H); mass spectrum, m/e 289 ($M^{+\cdot}$), 274, 244, 200. Anal. Calcd for $C_{16}H_{23}NO_2Si$: C, 66.39; H, 8.01; N, 4.84. Found: C, 66.50; H, 8.08; N, 4.86.

Method 2. $AlCl_3$ (1.33 g) and ethyl acrylate (1.0 g) were added to 4-(trimethylsilyl)indole (**7a**) (0.378 g) in dry CH_2Cl_2 (20 mL) and the mixture was stirred at room temperature for 10 h. The mixture was washed with H_2O, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica (12 g) gave (eluant CH_2Cl_2) **16g** (86 mg, 15%).

Methyl 2-Nitro-3-[4-(trimethylsilyl)indol-3-yl]propanoate (16f). As for ester **16e** reaction of **16c** (0.49 g) with methyl nitroacetate (0.25 g) in dry MeCN (40 mL) gave **16f** (0.595 g, 97%) as a yellow oil: IR (CH_2Cl_2) 3460, 1760, 1570, 1220, 1100, 1015, 850 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 0.45 (s, 9 H), 3.8 (s, 3 H), 3.85 (d, 2 H, J = 7 Hz), 5.43 (t, 1 H, J = 7 Hz), 6.9 (d, 1 H, J = 3 Hz), 7.1–7.5 (m, 3 H), 8.05–8.3 (br m, 1 H); mass spectrum, m/e 320 ($M^{+\cdot}$), 259.

Methyl 3-[4-(Trimethylsilyl)indol-3-yl]propanoate (16h). Nitro ester **16f** (1.2 g), Bu_3SnH (2.5 mL), $Me_2C(CN)N$=NC-(CN)Me_2 (0.35 g), and PhH (100 mL) were refluxed for 4 h. Evaporation and chromatography on alumina (110 g) gave (eluant CH_2Cl_2:hexane 1:1) ester **16h** (0.78 g, 76%): mp 108–109 °C (from cyclohexane); IR ($CHCl_3$) 3490, 1760, 1570, 1150 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 0.45 (s, 9 H), 2.7 (t, 2 H, J = 7.5 Hz), 3.25 (t, 2 H, J = 7.5 Hz), 3.7 (s, 3 H), 6.9–7.5 (m, 4 H), 8.1 (br m, 1 H); mass spectrum, m/e 275 ($M^{+\cdot}$), 202, 186. Anal. Calcd for $C_{15}H_{21}NO_2Si$: C, 65.41; H, 7.68; N, 5.08. Found: C, 65.25; H, 7.86; H, 5.11.

1,4-Diacetylindole (7f). 1-Acetyl-4-(trimethylsilyl)indole (**7e**) (0.231 g) in dry CH_2Cl_2 (5 mL) was added to a solution of $AlCl_3$ (0.667 g) in dry CH_2Cl_2 (10 mL) under N_2. The mixture was stirred overnight at room temperature when HCl–H_2O (0.25 M, 20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue on silica (6 g) gave (eluant CH_2Cl_2) 1,4-diacetylindole (**7f**) (0.191 g, 95%): mp 110–113 °C (from cyclohexane); IR (CH_2Cl_2) 1710, 1675, 1580; 1530, 1380, 1320, 1180, 980, 935 cm^{-1}; NMR (Me_2CO-d_6) δ 2.66 (s, 3 H), 2.71 (s, 3 H), 7.41 (dd, 1 H, J = 4, 1 Hz), 7.44 (dd, 1 H, J = 8.5, 7.5 Hz), 7.91 (d, 1 H, J = 4 Hz), 7.95 (dd, 1 H, J = 7.5, 1 Hz), 8.66 (ddd, 1 H, J = 8.5, 1, 1 Hz); mass spectrum, m/e 201 ($M^{+\cdot}$), 159, 144, 116. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.58; H, 5.51; N, 6.93.

1-Acetyl-4-(3-chloropropanoyl)indole (7g). Method 1. Reaction of **7e** (0.23 g), $AlCl_3$ (0.667 g), and $ClCH_2CH_2COCl$ (0.635 g) in CH_2Cl_2 (15 mL) gave on workup and chromatography on silica (8 g) (eluant CH_2Cl_2:pentane 7:3) **7g** (0.186 g, 75%): mp 120–122 °C (from cyclohexane); IR (CH_2Cl_2) 1710, 1670, 1580, 1535, 1320, 1170, 1120, 1010, 930 cm^{-1}; NMR ($CDCl_3$) δ 2.67 (s, 3 H), 3.57 (t, 2 H, J = 6.5 Hz), 3.97 (t, 2 H, J = 6.5 Hz), 7.43 (dd, 1 H, J = 8, 8 Hz), 7.51 (dd, 1 H, J = 4, 0.5 Hz), 7.57 (d, 1 H, J = 4 Hz), 7.84 (dd, 1 H, J = 8, 0.5 Hz), 8.74 (br d, 1 H, J = 8 Hz); mass spectrum, m/e 251, 249 ($M^{+\cdot}$), 213, 209, 207, 186, 144, 116. Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found C, 62.47; H, 5.00; N, 5.38.

Method 2. Reaction of 1-acetyl-4-(trimethylsilyl)indole (**7e**) (200 mg) in CH_2Cl_2 (5 mL) with CH_2=CHCOCl (392 mg) and $AlCl_3$ (577 mg) in CH_2Cl_2 (10 mL) gave on HCl–H_2O workup **7g** (130 mg, 60%).

1-Acetyl-6-(chloroacetyl)-4-(trimethylsilyl)indole (19a). Anhydrous $AlCl_3$ (0.667 g) was suspended in dry CH_2Cl_2 (10 mL) under argon. $ClCH_2COCl$ (0.565 g, 0.39 mL) was added and the resulting solution stirred until all the aluminum chloride was solubilized. A solution of 1-acetyl-4-(trimethylsilyl)indole **7e** (0.231 g) in dry CH_2Cl_2 (5 mL) was added dropwise and the resulting solution stirred at room temperature for 15 h. Hydrochloric acid (20 mL, 0.25) was added and the organic phase separated after washing. The CH_2Cl_2 was evaporated in vacuo and the residue chromatographed on silica H (20 g) eluting with CH_2Cl_2 to give **19a** (0.114 g, 37%): mp 194–196 °C; IR (nujol) 1715, 1680, 1585, 1515, 1400, 1330, 1295, 1240, 1210, 1190, 1130, 1105, 955, 870, 840, 790 cm^{-1}; NMR ($CDCl_3$) δ 0.42 (s, 9H), 2.69 (s, 3 H), 4.83 (s, 2 H), 6.83 (br d, 1 H, J = 4 Hz), 7.66 (d, 1 H, J = 3 Hz), 8.07 (d, 1 H, J = 1.3 Hz), 9.09 (s, 1 H); mass spectrum, m/e 307 ($M^{+\cdot}$) 292, 259, 258, 250, 235, 224, 217, 216, 202, 186, 172, 158, 144. Anal. Calcd for $C_{15}H_{18}ClNO_2Si$: C, 58.52; H, 5.89; N, 4.55. Found: C, 58.44; H, 5.85; N, 4.54. Further elution (CH_2Cl_2) of the chromatographic column gave crude **19b** (0.108 g, 46%): mp 186–188 °C; IR (nujol) 1715, 1695, 1525, 1340, 1320, 1255, 1215, 1150, 1120, 1040, 950, 835, 785, 760, 740 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (s, 3 H), 4.84 (s, 2 H), 6.72 (d, 1 H, J = 4.0 Hz), 7.63 (d, 1 H, J = 4.0 Hz), 7.67 (d, 1 H, J = 8.0 Hz), 7.95 (dd, 1 H, J = 8.0, 1.2 Hz), 9.08 (s, 1 H); mass spectrum, m/e 235 ($M^{+\cdot}$), 193, 186, 145, 144, 130, 116, 115, 100, 89.

1-Acetyl-4-propenoylindole (7h). NaOH in H_2O (2 M, 0.5 mL) was added to **7g** (249 mg) in THF (20 mL) and the mixture refluxed for 6 h. After evaporation water (10 mL) was added to the residue and the mixture extracted with CH_2Cl_2 (25 mL, 2 × 15 mL). The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica (8 g) gave (eluant CH_2Cl_2:hexane 7:3) **7h** (0.178 g, 84%): mp 105–108 °C (from cyclohexane); IR (CH_2Cl_2) 1710, 1660, 1320, 1180, 1125 cm^{-1}; NMR ($CDCl_3$) δ 2.69 (s, 3 H), 5.95 (dd, 1 H J = 11, 1.5 Hz), 6.44 (dd, 1 H, J = 17, 1.5 Hz), 7.23 (dd, 1 H, J = 17, 11 Hz), 7.41 (dd, 1 H, J = 3.5, 0.5 Hz), 7.43 (dd, 1 H, J = 8, 8 Hz), 7.56 (d, 1 H, J = 3.5 Hz), 7.81 (dd, 1 H, J = 8, 0.7 Hz), 8.72 (br d, 1 H, J = 8 Hz); mass spectrum, m/e 213 ($M^{+\cdot}$), 171, 144, 116. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.47; H, 5.31; N, 6.55.

4-(3-Methoxypropanoyl)indole (7i). K_2CO_3 (34 mg) and **7h** (50 mg) in MeOH–Me_2CO (7:3, 5 mL) were stirred at room temperature for 30 min. HOAc (53 mg) was added and solvents were removed under reduced pressure. The residue in CH_2Cl_2 was washed twice with H_2O, dried ($MgSO_4$), and evaporated to leave **7i** (52 mg): mp 94–95 °C (from cyclohexane); IR (CH_2Cl_2) 3460, 1665, 1500, 1340, 1115, 1040 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 3.35 (s, 3 H), 3.33 (t, 2 H, J = 6 Hz), 3.85 (t, 2 H, J = 6 Hz), 7.0–7.85 (m, 5 H), 8.3–8.8 (br m, 1 H); mass spectrum, m/e 203 ($M^{+\cdot}$), 171, 144, 116, 89. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.69; H, 6.45; N, 6.64.

4-Propenylindole (7j). As in the foregoing experiment, reaction of **7g** (129 mg) with K_2CO_3 (72 mg) in MeOH–Me_2CO (7:3, 10 mL) for 0.5 h at room temperature, quenching with HOAc (0.3 mL), and workup gave 4-propenoylindole (**7j**) (86 mg, 97%) as an unstable yellow oil: NMR ($CDCl_3$, 60 MHz) 5.81 (dd, 1 H, J = 11, 2.5 Hz), 6.37 (dd, 1 H, J = 17, 2.5 Hz), 6.83–7.78 (m, 6 H), 8.8–9.4 (br m, 1 H); mass spectrum, m/e 171 ($M^{+\cdot}$), 144, 116.

3-[1-(Trifluoroacetyl)-4-(trimethylsilyl)indol-3-yl]propanoic Acid (22a). The crude ester **16g**, prepared from the Bu_3SnH denitration of **16e** (433 mg), was refluxed with aqueous NaOH (1 M, 6.5 mL) and MeOH (25 mL) for 30 min. After evaporation of the MeOH the residue was dissolved in H_2O (15 mL) and CH_2Cl_2 (10 mL). H_3PO_4–H_2O (10%) was cautiously added to the aqueous layer to pH 2.6 maintaining the temperature at 0 °C. This was saturated with NH_4Cl and extracted with EtOAc (4 × 20 mL). After drying ($MgSO_4$), the organic layer was evaporated and the residue was chromatographed on SiO_2 (10 g) to give (eluant EtOAc:CH_2Cl_2 4:6) the crude carboxylic acid **16i** (158 mg, 53%): NMR (Me_2CO-d_6, 60 MHz) δ 0.42 (s, 9 H), 2.5–2.9 (br t, 2 H, J = 8 Hz), 3.05–3.42 (br t, 2 H, J = 8 Hz), 6.82–7.55 (m, 4 H), 9.7–10.15 (m, 1 H). The crude product **16i** (158 mg) was dissolved in DMF (2.5 mL) and NaH (44 mg) was added. After ultrasonic agitation for 2 h the mixture was cooled down to −50 °C when trifluoracetic anhydride (260 μL) was added. The mixture was warmed up to room temperature and the solvent removed under reduced pressure. Chromatography on silica gave (eluant CH_2Cl_2:EtOAc 9:1) the N-trifluoroacetyl derivative **22a** (67 mg, 31%): mp 170–173 °C (from cyclohexane); IR (CH_2Cl_2) 3500–2500, 1725, 1200, 1160, 910 and 840 cm^{-1}; NMR (Me_2CO-d_6, 60 MHz) δ 0.48 (s, 9 H), 2.4–3.0 (br t, 2 H, J = 6 Hz), 3.0–3.37 (br t, 2 H, J = 6 Hz), 7.17–7.7 (m, 3 H), 8.42 (dd, 1 H, J = 8, 1.5 Hz); mass spectrum, m/e 357 ($M^{+\cdot}$), 342, 226. Anal. Calcd for $C_{16}H_{18}F_3NO_3Si$: C, 53.77; H, 5.08; N, 3.92. Found: C, 53.61; H, 5.32; N, 3.87.

Methyl 3-[4-(Trimethylsilyl)-1-(tolyl-4-sulfonyl)indol-3-yl]propanoate (22b). Ester **16h** (50 mg) in THF (1.5 mL) was added to KH (35% in oil, 36 mg) in THF at −50 °C. The mixture was stirred at −30 °C for 45 min when TsCl (52 mg) in THF (1 mL) was added. The yellow suspension was stirred at room temperature for 30 min. After evaporation the residue was dissolved in Et_2O, washed with pH 4 buffer, aqueous $NaHCO_3$ (10%), and H_2O, dried (Na_2SO_4), and evaporated. Chromatography on silica (4 g) gave (eluant CH_2Cl_2:hexane 85:15) the N-tosyl derivative **22b** (75 mg, 94%) as an oil: IR ($CHCl_3$) 1730, 1450, 1380, 1170 cm^{-1}; NMR ($CDCl_3$, 60 MHz), 0.4 (s, 9 H), 2.3 (s, 3 H), 2.7 (m, 2 H), 3.1 (m, 2 H), 3.65 (s, 3 H), 7.1 (d, 2 H, J = 8 Hz), 7.3 (m, 3 H), 7.65 (d, 2 H, J = 8 Hz), 8.0 (dd, 1 H, J = 8, 1.5 Hz); mass spectrum, m/e 429 ($M^{+\cdot}$), 414, 340.

Cyclization of the Indolepropanoic Acid Derivative 22c. Methyl ester **22b** (156 mg) was dissolved in MeOH (1.6 mL), aqueous NaOH (1 M, 0.4 mL) was added, and the mixture was heated at 60 °C for 3 h. After evaporation the residue was suspended in PhH and reevaporated (twice). The solid was dried overnight under vacuum. CH_2Cl_2 (15 mL) followed by $(EtO)_2P(O)Cl$ (53 μL) were added at 0 °C and the mixture was stirred at room temperature for 30 min. Freshly resublimed $AlCl_3$ (97 mg) was added and the mixture was stirred overnight at room temperature. Water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica (8 g) gave (eluant CH_2Cl_2:EtOAc 1:0, 95:5, 1:1) the following in order of increasing polarity. **21a** (6 mg, 5%): mp 142–143 °C (from hexane) (lit.[22] mp 143–144 °C); IR ($CDCl_3$) 1690, 1435, 1360, 1300, 1180, 1110, 1030 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (s, 3 H), 2.85 (t, 2 H, J = 8 Hz), 3.2 (dt, 2 H, J = 8, 1.5 Hz), 7.25 (d, 2 H, J = 8 Hz), 7.35 (t, 1 H, J = 1.5 Hz), 7.45 (t, 1 H, J = 8 Hz), 7.7 (dd, 1 H, J = 8, 0.6 Hz), 7.8 (d, 2 H, J = 8 Hz), 8.1 (dd, 1 H, J = 8, 0.6 Hz); mass spectrum, m/e impurities 397, 382, 333, 325 ($M^{+\cdot}$), 170, 155, 114. **23** (49 mg, 34%): mp 153–154 °C (from hexane); IR (CH_2Cl_2) 1705, 1370, 1180, 1120, 1050, 840 cm^{-1}; NMR ($CDCl_3$) δ 0.4 (s, 9 H), 2.35 (s, 3 H), 3.0 (m, 2 H), 3.15 (m, 2 H), 7.25 (d, 2 H, J = 8.3 Hz), 7.5 (m, 2 H), 8.05 (d, 2 H, J = 8.3 Hz), 8.45 (dt, 1 H, J = 9.5, 3.8 Hz); mass spectrum, m/e 397 ($M^{+\cdot}$), 382. Anal. Calcd for $C_{21}H_{23}NO_3SSi$: C, 63.43; H, 5.84. Found: C, 63.47; H, 5.98.

Preparation of 4-(Trimethylsilyl)pyridine (24a). Dry pyridine (0.79 g, 0.81 mL) in dry THF (130 mL) under argon was cooled to 0 °C and Me_3SiCl (2.72 g, 3.17 mL) was added dropwise followed rapidly by lithium metal (0.146 g) freshly cut into ~30 pieces. The solution was ultrasonically stirred at 0 °C until the metal had dissolved. A solution of DDQ (2.26 g) in dry THF (15 mL) was added dropwise and the solution stirred at 0 °C for a further 1 h. The THF was then carefully evaporated in vacuo. The residue was extracted with Et_2O (4 × 40 mL) and the extracts were filtered through alumina (5 g). The Et_2O was evaporated in vacuo to yield **24a**[23] (1.11 g, 74%): bp 68 °C (8 mmHg); IR (neat) 3050, 2950, 2900, 1580, 1400, 1315, 1250, 1125, 840, 800, 755, 730 cm^{-1}; NMR ($CDCl_3$) δ 0.35 (s, 9 H), 7.40 (dd, 2 H, J = 7, 2 Hz), 8.60 (dd, 2 H, J = 7, 2 Hz); mass spectrum, m/e 151, 136, 106, 83, 75, 73.

2,6-Dimethyl-4-(trimethylsilyl)pyridine (24b). Redistilled 2,6-dimethylpyridine (1.07 g, 1.16 mL) was dissolved in dry THF (30 mL) under argon with stirring. The solution was cooled to 0 °C and Me_3SiCl (2.72 g, 3.17 mL) was added dropwise followed by lithium metal (0.146 g) freshly cut into ~25 pieces. The solution was ultrasonically stirred at 0 °C until all the metal had dissolved. A solution of DDQ (2.26 g) in dry THF (20 mL) was added dropwise and the resulting solution stirred at 0 °C for 15 min. The THF was evaporated in vacuo and the residue extracted with Et_2O (4 × 40 mL). The extracts were concentrated and chromatographed on alumina (15 g, neutral grade 3) to give **24b** (0.75 g, 42%): IR (CH_2Cl) 2910, 1585, 1530, 1375, 1135, 1030, 980, 940 cm^{-1}; NMR ($CDCl_3$) δ 0.48 (s, 9 H), 2.75 (s, 6 H), 7.22 (s, 2 H); mass spectrum, m/e 179 ($M^{+\cdot}$), 166, 165, 164, 97, 83, 73. A sample was converted into its toluene-4-sulfonate salt: mp 124–126 °C. Anal. Calcd for $C_{17}H_{25}NO_3SSi$: C, 58.06; H, 7.17. Found: C, 58.27; H, 7.19

4-(Trimethylsilyl)quinoline (25). Redistilled quinoline (2.58 g, 2.36 mL) was dissolved in dry THF (60 mL) under argon at 0 °C with stirring. Me_3SiCl (6.79 g, 7.93 mL) was added dropwise followed by lithium metal (0.43 g) freshly cut into ~100 pieces. The solution was stirred at 0 °C until all the metal had dissolved. The THF was removed under reduced pressure and the residue was taken up in dry CH_2Cl (40 mL) with the careful exclusion of air. The solution was cooled to 0 °C, a solution of p-benzoquinone (2.38 g) in dry CH_2Cl_2 (40 mL) was evaporated in vacuo, the residue was extracted with hexanes (4 × 30 mL), and the extracts were filtered through Celite and concentrated. The residue was chromatographed on silica gel (30 g) to give **25**[23] (1.47 g, 35%): bp 102–104 °C (0.2 mm); IR (neat) 3100, 2970, 2900, 1560, 1505, 1475, 1420, 1260, 1210, 1160, 1140, 1065, 1025, 990, 850, 805, 775, 700, 625 cm^{-1}; NMR ($CDCl_3$) δ 0.48 (s, 9 H), 7.50–8.20 (m, 5 H), 8.85 (d, 1 H); mass spectrum, m/e 201 ($M^{+\cdot}$), 187, 186, 170, 156.

***N*,*N*-Dimethyl-4-(trimethylsilyl)benzamide (26).** *N*,*N*-Dimethylbenzamide (1.49 g) was dissolved in dry THF (30 mL) under argon with stirring. The solution was cooled to 0 °C and Me_3SiCl (3.26 g, 3.81 mL) was added, followed by lithium metal (0.21 g) freshly cut into ~30 pieces. The solution was ultrasonically stirred at 0 °C until all the metal had dissolved. The THF was removed under reduced pressure and the residue was taken up in dry CH_2Cl_2 (20 mL) with the careful exclusion of air. The solution was cooled to 0 °C, a solution of p-benzoquinone (1.08, g) in dry CH_2Cl_2 (20 mL) was added dropwise, and the resulting solution was stirred at 0 °C for 3 h. The CH_2Cl_2 was evaporated in vacuo and the residue extracted with hexanes (3 × 40 mL). The extracts were filtered through Celite and concentrated. Chromatography of the residue on silica gel (25 g) with Et_2O:hexanes (80:20) gave *N*,*N*-dimethyl-4-(trimethylsilyl)benzamide (**26**) (0.98 g, 42%): mp 45–47 °C (from Et_2O at −60 °C); IR (KBr) 3040, 2985, 2885, 1645, 1515, 1495, 1465, 1400, 1255,

1225, 1200, 1150, 1120, 1080, 1030, 860, 755, 700, 675, 630 cm^{-1}; NMR ($CDCl_3$) δ 0.32 (s, 9 H), 3.05 (s, 6 H), 7.45 (q, 4 H); mass spectrum, m/e 221 ($M^{+\cdot}$), 220, 207, 206, 178, 177, 149, 102. Anal. Calcd for $C_{12}H_{19}NOSi$: C, 65.09; H, 8.67; N, 6.34. Found: C, 64.91; H, 8.69.

Acknowledgment. We thank the Royal Society, Service de Chimie de L'Institut Curie, ER No. 213 C.N. R.S., Centre de Recherche Delalande, and the Science and Engineering Research Council all for financial support. We also thank Steven D. Barker and Mark A. Russell for obtaining several items of data, and David C. Horwell (Lilly Research) for a sample of Uhle's ketone.

Registry No. **2**, 82-58-6; **7a**, 82645-11-2; **7b**, 120-72-9; **7c**, 17983-42-5; **7d**, 83188-11-8; **7e**, 83188-12-9; **7f**, 83188-13-0; **7g**, 83188-14-1; **7h**, 92012-86-7; **7i**, 92012-87-8; **7j**, 92012-88-9; **7k**, 576-15-8; **8b**, 92012-89-0; **12**, 92012-90-3; **13**, 92012-91-4; **14**, 70290-55-0; **15**, 87497-88-9; **16a**, 92012-92-5; **16b**, 92012-93-6; **16c**, 92012-94-7; **16d**, 92012-95-8; **16e**, 92012-96-9; **16f**, 92012-97-0; **16g**, 92012-98-1; **16h**, 92012-99-2; **16i**, 92013-00-8; **17a**, 92013-01-9; **17b**, 92013-02-0; **18**, 40641-03-0; **19a**, 92013-03-1; **19b**, 92013-04-2; **21a**, 37945-46-3; **21b**, 3744-82-9; **22a**, 92013-05-3; **22b**, 92013-06-4; **22c**, 92013-07-5; **23**, 92013-08-6; **24a**, 18301-46-7; **24b**, 92013-09-7; **25**, 65094-40-8; **26**, 34906-65-5; Me_3SiCl, 75-77-4; AcCl, 75-36-5; $CH_3C(=NOH)CO_2Et$, 20591-87-1; $CH_2=NMe_2^+Cl^-$, 30354-18-8; $CH_2(CO_2Et)_2$, 105-53-3; Bu_3P, 998-40-3; $O_2NCH_2CO_2Et$, 626-35-7; Bu_3SnH, 688-73-3; $Me_2C(CN)N=NC(CN)Me_2$, 78-67-1; $CH_2=CHCO_2Et$, 140-88-5; $O_2NCH_2CO_2Me$, 2483-57-0; $Cl(CH_2)_2COCl$, 625-36-5; $CH_2=CHCOCl$, 814-68-6; $ClCH_2COCl$, 79-04-9; $(CF_3CO)_2O$, 407-25-0; TsCl, 98-59-9; $(EtO)_2P(O)Cl$, 814-49-3; $C_6H_5CONMe_2$, 611-74-5; pyridine, 110-86-1; 2,6-dimethylpyridine, 108-48-5; quinoline, 91-22-5.

Synthesis and Reactions of Some 1-Substituted 1,2-Diazetidinones

Edward C. Taylor* and Huw M. L. Davies

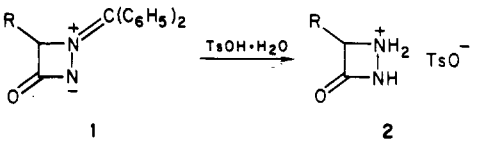
Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received January 5, 1984

A number of 1,2-diazetidin-3-ones variously substituted at N-1 have been prepared by sodium borohydride reduction of, or addition of methylmagnesium bromide to, 3-oxo-1,2-diazetidinium inner salts (formed by condensation of 3-oxo-1,2-diazetidinium tosylate with carbonyl compounds). 1-Cinnamyl-1,2-diazetidin-3-ones, silylated at N-2, underwent base-promoted alkylation and aldol reactions at C-4. Some unusual dimerization and fragmentation reactions of these aza-β-lactam derivatives have been observed.

We have recently described a convenient, high-yield synthesis of the novel four-membered heterocycle 3-oxo-1,2-diazetidinium tosylate (**2**) by hydrolysis of 1,1-diphenylmethylene-3-oxo-1,2-diazetidinium inner salt **1** (available in two steps from benzophenone hydrazone) with *p*-toluenesulfonic acid monohydrate (Scheme I).[1] With the ultimate objective of introducing substituents into the diazetidinone ring system capable of eventual intramolecular cyclization to give bridgehead aza analogues of the β-lactam antibiotics, we have initiated a program aimed at functionalization of **2** at N-1, N-2, and C-4. We have already described our unexpected results[2] when one of the normal strategies for the synthesis of carbapenems from monocyclic β-lactams, the intramolecular carbene insertion reaction,[3] was applied to the aza-β-lactam system. Other strategies based on intramolecular Wittig,[4] Horner–Emmons,[5] aldol,[6] or Dieckmann cyclizations[7] would require as precursors a side-chain aldehyde. In order to apply the latter three procedures to the preparation of bicyclic 1,2-diazetidin-3-ones (aza-β-lactams), we have prepared a number of 1,2-diazetidin-3-ones with latent aldehyde substituents at position 1. We also report our initial results

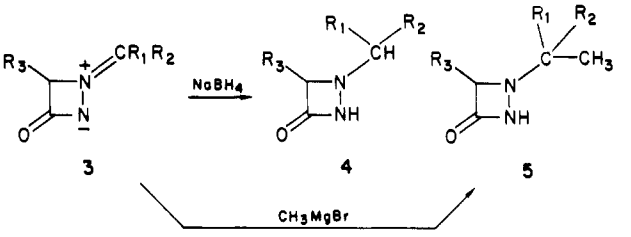
Scheme I[a]



1 2

[a] a, R = H; b, R = CH_3; c, R = C_2H_5.

Table I. Synthesis of 1-Substituted 1,2-Diazetidin-3-ones



3 4 5

starting material	R_1	R_2	R_3	yield, % 4	5
3a	C_6H_4Cl-4	H	H	78	
3b	$CH=CHC_6H_5$	H	H	82	
3c	$CH=CHC_6H_5$	H	CH_3	95	
3d	$CH=CHC_6H_5$	H	CH_2CH_3	95	
3e	$CH_2C_6H_5$	CH_3	H	72	44
3f	$CH_2CH(OCH_3)_2$	CH_3	H	81	73
3g	$CH(OCH_3)_2$	CH_3	H		12
3h			H		36
3i	$CH=CHC_6H_5$	CH_3	H		70
3j	$CH=CHC_6H_5$	CH_3	CH_3		81

(1) Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 7743.
(2) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113.
(3) (a) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, 4233. (b) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31. (c) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193. (d) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(4) (a) Scartazzini, v. R.; Peter, H.; Bickel, H.; Heusler, K.; Woodward, R. B. *Helv. Chim. Acta* **1972**, *55*, 408. (b) Scartazzini, v. R.; Gosteli, J.; Bickel, H.; Woodward, R. B. *Helv. Chim. Acta* **1972**, *55*, 2567. (c) Ernest, T.; Gosteli, J.; Greengrass, W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.
(5) (a) Venugopalan, B.; Hamlet, A. B.; Durst, T. *Tetrahedron Lett.* **1981**, *22*, 191. (b) Sharma, R.; Stoodley, R. J. *Tetrahedron Lett.* **1981**, *22*, 2025.
(6) (a) Shibuya, M.; Kubota, S. *Tetrahedron Lett.* **1980**, 21, 4009. (b) Shibuya, M.; Kuretani, M.; Kubota, S. *Tetrahedron* **1982**, *38*, 2659. (c) Foxton, M. W.; Mearman, R. C.; Newall, C. E.; Ward, P. *Tetrahedron Lett.* **1981**, *22*, 2497. (d) Chu, D. T. W.; Hengeueld, J. E.; Lester, D. *Tetrahedron Lett.* **1983**, *24*, 139.
(7) (a) Shibuya, M.; Kubota, S. *Tetrahedron Lett.* **1981**, *22*, 3611. (b) Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883.

0022-3263/84/1949-4415$01.50/0 © 1984 American Chemical Society