N-(Triisopropylsilyl)pyrrole. A Progenitor "Par Excellence" of 3-Substituted Pyrroles†

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A very effective strategy has been devised for the synthesis of 3-substituted pyrroles based on the use of the triisopropylsilyl (TIPS) moiety as a sterically demanding nitrogen substituent to obstruct the attack of electrophilic reagents at the α positions. 1-(Triisopropylsilyl)pyrrole (1) undergoes highly preferential kinetic electrophilic substitution at the β position with a variety of electrophiles (Br^+, I^+, NO_2^+, RCO^+, etc.) and fluoride ion induced desilylation of the products provides the corresponding 3-substituted pyrroles in good overall yields. Competitive trifluoroacetylation experiments demonstrate that substitution of TIPS-pyrrole at the α positions is decelerated by a factor of $>10^4$, vs pyrrole at the same sites, without affecting reactivity at the β positions. 1-(Triisopropylsilyl)-3-bromopyrrole (2) is readily converted into the 3-lithio compound 44 by bromine–lithium interchange with alkyllithium reagents. This previously unavailable, formal equivalent of 3-lithiopyrrole is itself an excellent source of a wide range of β-substituted pyrroles, many of which would not be directly preparable from 1. TIPS-pyrrole can be 3,4-dihalogenated and these compounds undergo sequential halogen–metal interchange trapping reactions. This process is exemplified by an efficient, three-step synthesis of the antibiotic verrucarin E (63) from the dibromo compound 5.

It has long been known that pyrrole undergoes predominant or exclusive kinetic electrophilic substitution at the $\alpha(2)$ position[1] with most electrophilic reagents[2] in solution.[3] Consequently, it has been the objective of numerous investigations to devise means of synthesizing the much less readily accessible $\beta(3)$-substituted pyrroles and a number of processes now exist that provide access to such compounds.[4] Three of the more notably successful of these processes are (a) utilization of a removable deactivating 2-substituent (usually acyl) to direct the entry of an electrophile to the $4(\beta)$ position,[5] (b) acid-mediated isomerization of the easily preparable α isomers,[6] and (c) direct substitution of *N*-(phenylsulfonyl)pyrrole with certain electrophiles, first described by Anderson et al.[7] and Rokach and co-workers.[8] Method a is historically the first and the most intensively studied of the synthetic routes to 3-substituted pyrroles.[4] It is quite broad in scope but removal of the directing substituent is frequently not inconsequential. The acid-induced isomerization of 2-substituted pyrroles is remarkably general and sometimes occurs under surprisingly mild conditions.[9] Its main drawback is that an apparent equilibrium mixture of the α and β isomers is often produced, although such mixtures usually are easily separated by column chromatographic techniques. The Friedel–Crafts acylation of 1-(phenylsulfonyl)pyrrole and subsequent removal of the nitrogen substituent under alkaline conditions is an excellent route to 3-acylpyrroles. Unfortunately some electrophilic reagents do not react with this substrate at all and others give unfavorable β:α product ratios.[4,7]

Another approach to the synthesis of 3-substituted pyrroles is based on the use of a bulky group on nitrogen, such as a *tert*-butyl[10] or a trityl[11] moiety, to obstruct electrophilic attack at the α position. Substantial selectivity for C-3 is indeed observed in these cases but the process is of limited value because removal of the nitrogen substituent is impossible or the conditions necessary for N-dealkylation ($Na/MeOH/NH_3$ for trityl) are incompatible with the survival of many functional groups. The concept is nevertheless valid and a sterically demanding,

Figure 1. Global energy minimum of TIPS-pyrrole with van der Waals dot surface. Higher energy conformations generally increased steric bulk about the pyrrole ring.

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(1) (a) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977. (b) Gossauer, A. *Die Chemie der Pyrrole*; Springer-Verlag: Berlin, 1974.

(2) The predominant β-trimethylsilylation of *N*-methyl- or *N*-benzylpyrrole with trimethylsilyl trifluoromethanesulfonate (TMS triflate) in triethylamine is the only exception to this rule (Majchrzak, M. W.; Simchen, G. *Tetrahedron* **1986**, *42*, 1299. Frick, V.; Simchen, G. *Synthesis* **1984**, 929. This result has been interpreted to support certain theoretical calculations (ref 1a, pp 40–45, and Catalan, J.; Yáñez, M. *J. Am. Chem. Soc.* **1984**, *106*, 421 and references cited therein), which predict that the reaction of pyrrole with hard electrophiles (e.g., TMS triflate) will be charge density controlled and occur predominantly at the β position.

(3) In contrast, in the gas phase, pyrrole and *N*-methylpyrrole undergo predominant attack at the β position by radiolytically generated dimethylfluoronium ion and *tert*-butyl cation (Angelini, G.; Sparpani, C.; Speranza, M. *J. Am. Chem. Soc.* **1982**, *104*, 7084. Margonelli, A.; Sperenza, M. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1491. These data are also in agreement with calculations that indicate that the highest net negative charge in pyrrole resides at the β carbons and that hard electrophiles should be preferentially directed thereto (Abronin, I. A.; Belenkii, L. I.; Gol'dfarb, Y. L. *New Trends in Heterocyclic Chemistry*; Elsevier: Amsterdam, 1979. Ridd, J. *Phys. Methods Heterocycl. Chem.* **1971**, *4*, 55. Catalan, J.; Yáñez, M. *J. Chem. Soc. Perkin Trans. 2* **1979**, 1672. Palmer, M. H.; Gaskell, A. G. *Theoret. Chim. Acta* **1971**, *23*, 52. Kramling, R. W.; Wagner, E. L. *Theoret. Chim. Acta* **1969**, *15*, 43. See also, citations in ref 2.

(4) Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.

(5) Loader, C. E.; Anderson, H. J. *Can. J. Chem.* **1981**, *59*, 2673 and references therein.

(6) DeSales, J.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 3668 and references therein.

(7) Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896.

(8) (a) Rokach, J.; Hamel, P.; Kakushima, M.; Smith, G. M. *Tetrahedron Lett.* **1981**, *22*, 4899. (b) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.

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Table I. Reaction of *N*-(Triisopropylsilyl)pyrroles with Electrophilic Reagents

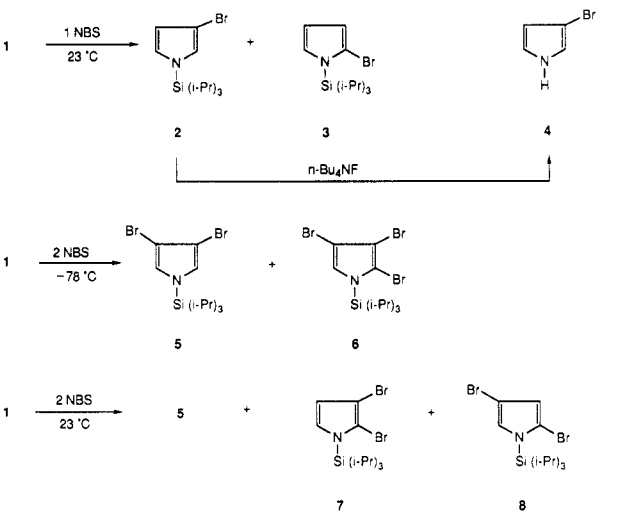
substr	reagent (mol)	*T*, °C	% yield	products (%)	product ratios[a]
1	NBS (1)	−20	74	**2** (85), **3** (15)	**2:3** (5.7)
1	NBS (1)	−78	93	**2** (96.2), **3** (3.8)	**2:3** (25.3)[b]
1	NBS (1)	23		**2** (68.7), **3** (31.3)	**2:3** (2.2)[b]
1	NBS (2)	−78	82	**5** (95), **6** (5)	**5:6** (19)
1	NBS (2)	23	92	**5** (17), **7** (62), **8** (21)	**7:5** (3.7)
2	NBS (1)	23	90	**5** (30), **7** (70)	**7:5** (2.3)
1	NBS (3)	−78	89	**6** (89)	
1	NCS (1)/THF	23	>95	**9** (68), **10** (11)	**9:10** (6.2)
1	NCS (1)/DMF	23	>95	**9** (38), **11** (28), **12** (6)	**9:11** (1.4)
1	$I_2/Hg(OAc)_2$ (1)	−25	61	**13** (61)	
1	$I_2/Hg(OAc)_2$ (2)	0	69	**14** (69)	
1	$Cu(NO_3)_2/Ac_2O$ (2)	23	85	**16** (77), **17** (8)	**16:17** (11)
1	EtOCOCOCl/Py (1)	25	88	**19** (79), **20** (9)	**19:20** (8.7)[c]
1	EtOCOCOCl/Py (3)	73	64	**21** (64)	
1	CCl_3COCl/Py (1.5)	25	75	**22** (75)	
1	$PhCOCl/AlCl_3$ (1.1)	0 → 23	48	**23** (48)	
1	$PhCH_2COCl/AlCl_3$ (1.1)	0 → 23	44	**24** (44)	
1	**27** (1.1)	40	97	**29** (>96), **α** (<4)[d]	**29:α**(>24)[d]
1	$(CF_3CO)_2O$/Py (3)	23	97	**31** (73), **33** (~1)	**31:33** (49)
1	$ClSO_2NCO$/DMF (1)	−78 → 0	95	**37** (14), **38** (81)	**38:37** (6)
1	$(SCN)_2$ (1)	−78	98	**39** (98)	
	4-MeC_6H_4SOCl/py (1.1)	0	62	**41** (48), **42** (14)	**41:42** (3.4)[c]

[a] Ratio determined by NMR integration unless indicated otherwise. [b] Capillary VPC on SE 30. [c] Ratio by isolation. [d] Ratio determined by NMR after hydrolysis to **30** and pyrrole-2-carboxaldehyde.

stable, easily cleavable N-substituent would have considerable synthetic value.

The remarkable steric requirements of the triisopropylsilyl moiety were first recorded by Corey et al.[12] Examination of a CPK model of *N*-(triisopropylsilyl)pyrrole (**1**, TIPS-pyrrole) suggested that the α positions of the pyrrole nucleus would be significantly encumbered. Indeed, molecular modeling studies indicate that the steric shielding of these positions would not be alleviated in any of the energetically accesible conformations. Figure 1, a stereoscopic view of the lowest energy conformation of **1** with van der Waals surface,[13] shows that the hydrogen atoms of the isopropyl groups virtually encapsulate the α positions and that access of an electrophile thereto is likely to be strongly impeded. This expectation and the known facile tetraalkylammonium fluoride induced cleavage of trialkylsilyl moieties[14] made a study of TIPS-pyrrole as a progenitor of β-substituted pyrroles doubly attractive. This paper shows that **1** is an exceptionally versatile, and in many instances the preferred, starting material for the synthesis of a broad range of β-functionalized pyrroles.[15-17,21]

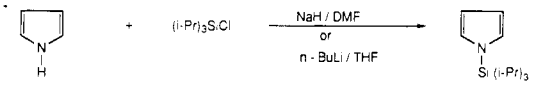
Scheme I



TIPS-pyrrole is easily prepared, in high yield, from the sodium or lithium salt of pyrrole and triisopropylsilyl chloride. It is a colorless, mobile liquid at room temperature (mp ~ 5 °C), which is indefinitely stable under ambient conditions. The ^1H NMR spectrum of the ring protons shows two apparent triplets centered at δ 6.80 and 6.32 for the α and β protons, respectively, which is little different from that of pyrrole itself (δ 6.73 and 6.17),[23]

(9) Carmona, O.; Greenhouse, R.; Landeros, R.; Muchowski, J. M. *J. Org. Chem.* **1980**, *45*, 5336.
(10) Candy, C. F.; Jones, R. A.; Wright, P. H. *J. Chem. Soc. C* **1970**, 2563. Chadwick, D. J.; Meakins, G. D.; Rhodes, C. A. *J. Chem. Res., Synop.* **1980**, 42; *J. Chem. Res., Miniprint* **1980**, 0878.
(11) Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans 1* **1983**, 93.
(12) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(13) Local minima were located by using the CSEARCH algorithm in SYBYL 5.3 and optimized by using MAXIMIN2 and MOPAC 5.0 as supplied with this version of SYBYL. The dot surface shown was determined by using the default van der Waals parameters.
(14) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(15) For preliminary communications, see: (a) Muchowski, J. M.; Solas, D. R. *Tetrahedron Lett.* **1983**, *24*, 3455. (b) Muchowski, J. M.; Naef, R. *Helv. Chim. Acta* **1984**, *67*, 1168.
(16) For other examples where the TIPS group has been used to alter the regioselectivity of a reaction, see: (a) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (b) Nechvatal, G.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1982**, 467. (c) Mastens, N. F.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, 955. (d) Muchowski, J. M.; Naef, R.; Maddox, M. L. *Tetrahedron Lett.* **1985**, *26*, 5375. (e) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, *27*, 3223. (f) Tanaka, K.; Funaki, I.; Kaji, A.; Minami, K.; Sawada, M.; Tanaka, T. *J. Am. Chem. Soc.* **1988**, *110*, 7185.
(17) The *tert*-butyldiphenylsilyl[18] and triphenylsilyl[19] moieties are stated to be ineffective in shielding the α positions of pyrrole against electrophiles. Surprisingly, however, *N*-(*tert*-butyldimethylsilyl)pyrrole was reported[20] to be acylated exclusively at the β position by acyl chlorides in the presence of aluminum chloride.
(18) Kozikowski, A. P.; Cheng, X.-M. *J. Org. Chem.* **1984**, *49*, 3239.
(19) Ksander, K.; Bold, G.; Lattmann, R.; Lehmann, C.; Früh, T.; Xiang, Y.-B.; Inomata, K.; Buser, H.-P.; Schreiber, J.; Zass, E.; Eschenmoser, A. *Helv. Chim. Acta* **1987**, *70*, 1115.
(20) Simchin, G.; Majchrzak, M. W. *Tetrahedron Lett.* **1985**, *26*, 5035.
(21) After the appearance of our preliminary communications, Kozikowski and Cheng[18] and Stefan et al.[22] published results, which were similar in several respects to those described by us, on the generation of 3-lithio-1-(triisopropylsilyl)pyrrole (**44**) and the synthesis of 3-substituted pyrroles therefrom.
(22) Stefan, K.-P.; Schuhmann, W.; Parlar, H.; Korte, F. *Chem. Ber.* **1989**, *122*, 169.

indicating that N-silylation has had no significant electronic effect on the pyrrole nucleus.



I. Reaction of TIPS-pyrrole with Electrophilic Reagents. When these studies were initiated, it was recognized that the success of this potential synthesis of 3-substituted pyrroles was contingent upon either the selection of electrophilic reagents that were poor silylophiles or the discovery of conditions under which the rate of electrophilic substitution of **1** was substantially greater than that of its desilylation. As shown below, both of these options were realized.

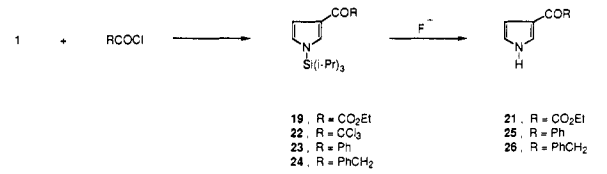
A. Halogenation. 1. Bromination. The bromination of **1** was studied by using *N*-bromosuccinimide (NBS) in THF solution since, under these conditions, desilylation was considered to be exceedingly unlikely. The reaction of TIPS-pyrrole with 1 equiv of NBS, essentially under the conditions reported by Gilow and Burton[24] (ca. −20 °C), occurred rapidly to give a 5.7:1 mixture (see Table I and Scheme I) of monobrominated compounds, the major and minor components of which are obviously the β and the α (independently prepared from 2-bromopyrrole) isomers **2** and **3**, as deduced from their NMR spectral characteristics (see Experimental Section). When the reaction temperature was maintained at −78 °C the β:α isomer ratio increased to 25 and 3-bromo-1-TIPS-pyrrole (**2**), of more than 96% purity, could be isolated in over 90% yield. At room temperature (22 °C) the β:α ratio plummeted to ca. 2. Thus, the highly preferential formation of **2** at low temperature is indubitably a consequence of kinetic control.

Bromination of **1** with 2 equiv of NBS at −78 °C gave a 19:1 mixture of the 3,4-dibromo and 2,3,4-tribromo compounds **5** and **6**, from which **5** could be obtained in high yield by crystallization.[25] When this reaction was effected at 22 °C, the product consisted of a 17:62:21 mixture (NMR) of the dibromo compounds **5**, **7**, and **8**, which was not readily separable. If, however, 3-bromo-1-TIPS-pyrrole was reacted with 1 equiv of NBS at 23 °C, a 2.3:1 mixture of **7** and **5** was produced, from which **7** could be obtained pure in satisfactory yield, after removal of **5** by low temperature crystallization. The predominant formation of **7** under these conditions was unexpected and is a striking indication of the powerful directing effect[26] (to C-2) exerted by the bromine substituent at C-3.

Bromination of **1** with 3 equiv of NBS at −78 °C gave the crystalline, 2,3,4-tribromo compound **6** as the sole product.

At this point it is worth noting that whereas bromopyrroles, especially the mono- and dibromopyrroles, are notoriously unstable,[24,27] the corresponding triisopropylsilylated compounds can be stored, without appreciable decomposition, under ambient conditions for weeks and indefinitely at 0 °C. Desilylation of **2** (1 equiv n-Bu_4NF in THF at room temperature for 5 min) gave 3-bromopyrrole (**4**, 65%), which, as expected, was very prone to decomposition at room temperature.

Scheme II



2. Chlorination. No conditions were found for the selective β-chlorination of TIPS-pyrrole with *N*-chlorosuccinimide (NCS). In THF as the solvent, a 6.8:1 mixture (Table I, Scheme II) of the 2-chloro and the 2,3,5-trichloro compounds **9** and **10** was formed very slowly at 23 °C (no reaction at −10 °C). In DMF solution, chlorination at 23 °C occurred much more rapidly (no reaction at −10 °C) to give a 19:14:3 mixture of the 2-chloro, 3-chloro, and 2,3-dichloro compounds **9**, **11**, and **12**. A substantial amount of starting material was present in both cases. No other chlorinating agents were studied, but the much more favorable β:α ratio in the latter case suggests that a more reactive reagent, e.g., sulfuryl chloride, might substantially increase the β-isomer content.

3. Iodination. Selective mono- or diiodination of **1** could be effected with iodine in the presence of mercuric acetate[28] (Table I). Thus, at −25 °C and using equimolar quantities of all three reactants, the sole product was the 3-iodo compound **13**. Iodination with 2 equiv each of iodine and the mercuric salt, at 0 °C, produced the crystalline 3,4-diiodopyrrole derivative **14** (~70%), which was desilylated with fluoride ion (90%) to 3,4-diiodopyrrole (**15**).[29] It is not known whether these iodinations occurred directly or via intermediate acetoxymercuri compounds.

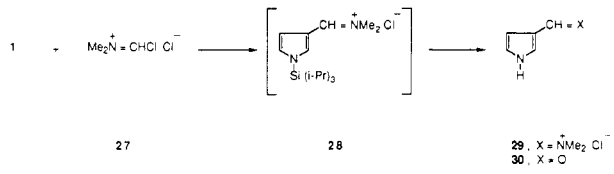
B. Nitration. The nitration of TIPS-pyrrole, at 23 °C, with acetyl nitrate, generated from cupric nitrate trihydrate in acetic anhydride,[30] gave a 11:1 mixture of 3-nitro-1-(triisopropylsilyl)pyrrole (**16**, Table I) and 2-nitropyrrole (**17**), from which **16** could be isolated in 77% yield. The small amount of 2-nitropyrrole that was obtained may well have been derived from the nitration of pyrrole itself since acetic acid (3 molar equiv of which are produced for each equivalent of acetyl nitrate generated from cupric acetate trihydrate) slowly desilylates TIPS-pyrrole at room temperature. Desilylation of **16** in the usual way gave 3-nitropyrrole (**18**) in high yield. This is the best available synthesis of this compound to date.

C. Acylation. 1. Acyl Halides. With the very reactive acyl halides, ethyl oxalyl chloride and trichloroacetyl chloride, acylation occurred slowly at room temperature, in 1,2-dichloroethane solution. The 3-acylpyrroles **19** and **22** (Scheme II, Table I) were formed as the major or exclusive products provided that pyridine was present to retard the rate of hydrogen chloride induced desilylation. It is not known if the small amount of ethyl 2-pyrrolylglyoxalate (**20**) was derived from the direct acylation of **1** or indirectly by desilylation of **1** to pyrrole and subsequent acylation. Acylation with ethyl oxalyl chloride at 73 °C resulted in the isolation of the product of desilylation, ethyl 3-pyrrolylglyoxalate (**21**), in 64% yield.

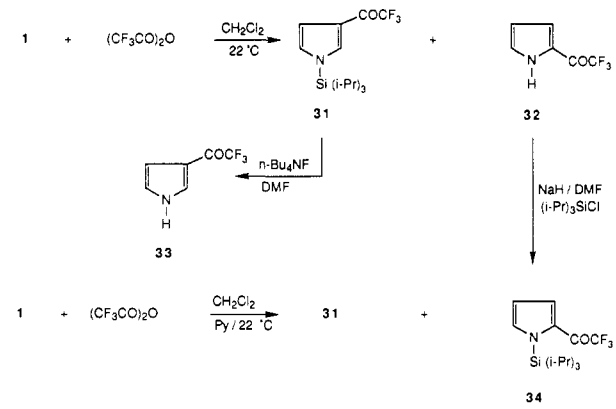
Acylation with the less electrophilic acyl halides, benzoyl chloride or phenylacetyl chloride, occurred rapidly in dichloromethane solution (0 → 23 °C) in the presence of an equimolar amount of aluminum chloride. Surprisingly,

(23) See ref 1, p 473, and articles cited therein.
(24) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221. It is of considerable significance that *N*-(trimethylsilyl)pyrrole is brominated exclusively at the α position under these conditions (Solas, D.; Muchowski, J. M. Unpublished data).
(25) It was previously reported[15b] that a 1:1 mixture of **5** and **7** was produced under these conditions, an observation that was, no doubt, a result of inadequate control of the reaction temperature.
(26) Reference 1a, pp 151, 153.
(27) Cordell, G. A. *J. Org. Chem.* **1975**, *40*, 3161.
(28) Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985.
(29) (a) Farnier, C.; Fournari, P. *J. Heterocycl. Chem.* **1975**, *12*, 373. (b) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1985**, *50*, 425.
(30) Windgassen, R. J.; Saunders, W. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1959**, *81*, 1459.

Scheme III



Scheme IV



desilylation did not occur under these conditions, and the 3-acylpyrroles **23** and **24** were obtained as the sole products in modest yields (ca. 45%). Similar results had already been reported in 1985 by Simchin and Majchrzak[20] for *N*-(*tert*-butyldimethylsilyl)pyrrole. The 3-acylpyrroles **25** and **26** were readily obtained on fluoride ion induced desilylation of **23** and **24**.

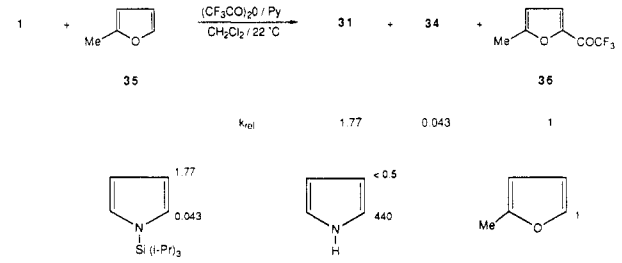
2. Vilsmeier–Haack Reagent. Brief (0.5 h) reaction of TIPS-pyrrole with a slight excess of *N*,*N*-dimethylchloroformiminium chloride (**27**), in dichloromethane at reflux temperature, gave a product (97% yield), greater than 96% of which was the β-substituted iminium salt **29** (Scheme III, Table I).[31] The high regioselectivity of this reaction and the absence of the silyl moiety in **29** indicate that the rate of formation of the primary product **28** is substantially greater than the hydrogen chloride induced desilylation of TIPS-pyrrole and presumably also of **28**.

Alkaline hydrolysis of **29** gave pyrrole-3-carboxaldehyde (**30**), in ca. 70% yield, as well as a minor amount (~3%) of pyrrole-2-carboxaldehyde. This is one of the most efficient syntheses of **30** known.

3. Trifluoroacetic Anhydride. The trifluoroacetylation of 1 was examined in detail from both preparative and mechanistic standpoints. TIPS-pyrrole reacted with a 10-fold excess of trifluoroacetic anhydride (TFA), in dichloromethane solution at 25 °C, to give a 6.2:1 mixture of 3-(trifluoroacetyl)-1-TIPS-pyrrole (**31**) and 2-(trifluoroacetyl)pyrrole (**32**) (Scheme IV, Table I). Compound **32** was clearly derived from pyrrole itself, since examination of the course of the reaction of an equimolar mixture of the reactants by VPC revealed the presence of pyrrole as well as **31** and **32**. The desilylation of 1 could be completely suppressed by conducting this reaction in the presence of an excess of pyridine, in which case a 49:1 mixture of **31** and 2-(trifluoroacetyl)-1-TIPS-pyrrole (**34**) was formed. The latter compound (independently prepared from **32** and triisopropyl chloride) was not isomerized to the β isomer **31** under these conditions. When the trifluoroacetylation in the presence of excess pyridine was carried out on a preparative scale (see Experimental Section), 3-(trifluoroacetyl)-1-(triisopropylsilyl)pyrrole (**31**)

(31) Bray, B. L.; Muchowski, J. M. *J. Org. Chem.* **1988**, *53*, 6115.

Scheme V



could be isolated in 73% yield (Table I). On desilylation with tetra-*n*-butylammonium fluoride in DMF, **31** was transformed into, the previously unreported, 3-(trifluoroacetyl)pyrrole (**33**).

Competitive reactions of 1 and 2-methylfuran (**35**) with trifluoroacetic anhydride, in the presence of excess pyridine (dichloromethane, 22 °C), were carried out by using a modification of the procedure of Clementi et al.[32] (see Experimental Section). The relative rates for the formation of **31**, **34**, and **36** (shown in Scheme V) were calculated according to the Shaw–Ingold expression (eq 1),[33] where

$$k_{rel} = \frac{\log ([A_t]/[A_0])}{\log ([B_t]/[B_0])} \quad (1)$$

A and B refer to 1 and **35** and A_t and B_t are the amount of the reactants remaining at time t taken as the amount present initially minus the amount of product formed. Since the reactivity of 2-methylfuran relative to pyrrole is known,[32] the k_{rel} values for trifluoroacetylation of 1 at C-2 and C-3 compared to pyrrole itself could be calculated.[34] In addition, careful reexamination of the trifluoroacetylation of pyrrole[35] by GLPC showed that, besides 2-trifluoroacetylpyrrole, a product with the same retention time as 3-(trifluoroacetyl)pyrrole (**33**),[36] was formed in about 0.1% yield. Thus an upper limit on the relative reactivity of pyrrole at C-3 could be established.[36]

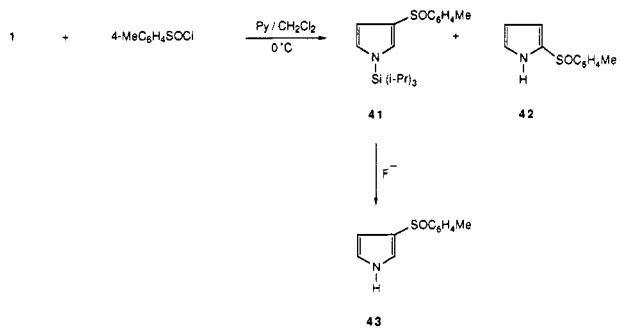
These results demonstrate that the trifluoroacetylation of 1-(triisopropylsilyl)pyrrole at C-2 is more than 10^4 times less favored than the trifluoroacetylation of pyrrole at the same position. Significantly, the trifluoroacetylation of 1 at C-3 is >40 times faster than at C-2 and only ca. 250 times slower than the trifluoroacetylation of pyrrole at C-2. Thus, the triisopropylsilyl moiety admirably serves the purpose of hindering access of most electrophilic species to C-2 without affecting the reactivity at C-3.[36]

D. Other Electrophiles. 1. Chlorosulfonyl Isocyanate. The reaction of chlorosulfonyl isocyanate with 1, in the presence of DMF,[5] occurred preferentially at C-2, even at −78 °C (Table I). Under these conditions, a 1:6 mixture of the nitriles **37** and **38** was formed, from which the 2-cyano compound **38** could be isolated in over 80% yield. The unusually high preponderance of the α isomer in this reaction and in the thiocyanation reaction described below is not understood.

2. Thiocyanogen. The thiocyanation of 1-(triisopropylsilyl)pyrrole, at −78 °C, according to the procedure of Matteson and Snyder[37] [$(SCN)_2$], occurred exclusively

(32) Clementi, S.; Marino, G. *Tetrahedron* **1969**, *25*, 4599.
(33) Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* **1927**, 2918.
(34) This calculation assumes that the difference in temperature (22 °C vs 75 °C) and solvent (CH_2Cl_2 vs $ClCH_2CH_2Cl$) do not significantly affect these relative rates.
(35) Cooper, W. D. *J. Org. Chem.* **1958**, *23*, 1382.
(36) Because of the low yield of this product, its identity could not be established unequivocally by isolation. For the same reason, the relability of this K_{rel} value is probably not better than <0.5 ± 1.0 and thus the apparent greater reactivity of 1 vs pyrrole at C-3 is also open to question.

Scheme VI



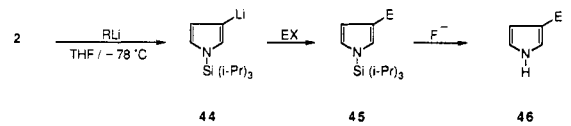
at the α position (Table I). The identity of this product (**39**) was confirmed by its NMR spectral characteristics and by conversion to 2-(methylthio)pyrrole[38] (**40**, see Experimental Section). The reactivity of other thiocyanation reagents (see ref 1a, pp 142–3) toward **1** was not examined.

3. *p*-Toluenesulfinyl Chloride. The highly electrophilic arenesulfinyl chlorides are reported[9] to arylsulfinylate pyrroles under mild conditions. Not surprisingly, *p*-toluenesulfinyl chloride reacted with **1**, at 0 °C in the presence of pyridine, to give a 3.5:1 mixture of the β-suubstituted product **41** and 2-(*p*-tolylsulfinyl)pyrrole (**42**) (Scheme VI, Table I). Once again, it is not known if the α-substituted product **42** was derived directly from **1** or indirectly via pyrrole. The identity of **41** was confirmed by desilylation to 3-(*p*-tolylsulfinyl)pyrrole (**43**).[9]

II. Halogen–Metal Interchange of *N*-(Triisopropylsilyl)bromopyrroles. The first reported 3-metalated pyrrole derivative was described by Anderson and Griffiths,[39] who generated 1-benzyl-3-lithiopyrrole from the bromo compound and metallic lithium. Chadwick and co-workers[40] have shown that 4,4-dimethyl-2-(*N*-methylpyrrol-2-yl)oxazoline can be selectively monolithiated at C-3. The usefulness of both of the above lithium reagents is minimal because removal of the N-substituent is not possible. *N*-(Trimethylsilyl)pyrrole is lithiated to a considerable degree at C-3 with excess *tert*-butyllithium in pentane,[41] but the 2-lithio species is formed as well. Finally, Farnier and Fournari[29a] and Sundberg and Pearce[29b] have shown that certain 3-halopyrroles can be made to undergo halogen–lithium interchange with alkyllithium reagents at low temperature. This is unlikely to be a generally useful process because of the instability of N-unsubstituted halopyrroles and because at least some halopyrroles of this type do not undergo the halogen–lithium exchange reaction.[42]

A. Lithiation. 1. 1-(Triisopropylsilyl)-3-bromopyrrole. The facile accessibility of the monobromo compound **2** was of obvious importance because it was expected that the lithio compound derived therefrom would serve as a source of a wide variety of 3-substituted pyrroles. Indeed, the lithiation of **2** was easily accomplished by bromine–lithium exchange with 1 equiv of *n*-butyllithium or 2 equiv of *tert*-butyllithium in THF at −78 °C (0.5 h). The lithiopyrrole derivative **44** reacted with a broad spectrum of electrophilic reagents (Table II) much like a typical aryllithium compound. The electrophilic reagents examined included alkyl halides (benzyl bromide gave bibenzyl), various carbonyl compounds, carbon dioxide, and trimethylsilyl chloride.[41] In most cases, the products **45** were obtained in very good yields; in some instances these products were desilylated with tetrabutylammonium fluoride to the 3-substituted pyrroles **46**. It is thus clear that **2** is an exceedingly useful, formal equivalent of 3-lithiopyrrole.

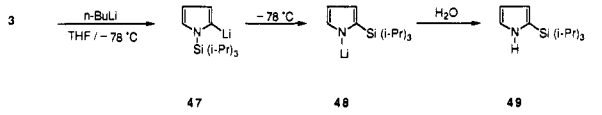
Table II. Synthesis of 3-Substituted Pyrroles from 3-Lithio-1-(triisopropylsilyl)pyrrole



RLi (equiv)	electrophile	E in products	45	46
t-BuLi (2)	MeI	Me	92	
n-BuLi (1)	*n*-BuBr	*n*-Bu	40	
t-BuLi (2)	*n*-$C_{18}H_{37}I$	*n*-$C_{18}H_{37}$	88	76
t-BuLi (2)	2-MeBuBr[a]	2-MeBu	40	
t-BuLi (2)	Me_3SiCl	Me_3Si	87	
t-BuLi (2)	CO_2 (gas)	COOH	88	88
n-BuLi (1)	DMF	CHO	82	86
t-BuLi (2)	HCHO (gas)	CH_2OH	73	
n-BuLi (1)	PhCHO	CHOHPh	48	
t-BuLi (2)	Cyclohexanone	cyclohexen-1-yl[b]	69	
t-BuLi (2)	MeCON(OMe)Me	COMe	61	84

[a] $CH_3CH_2CH(CH_3)CH_2Br$. [b] The primary product was heated at 150 °C (45 min) to effect dehydration.

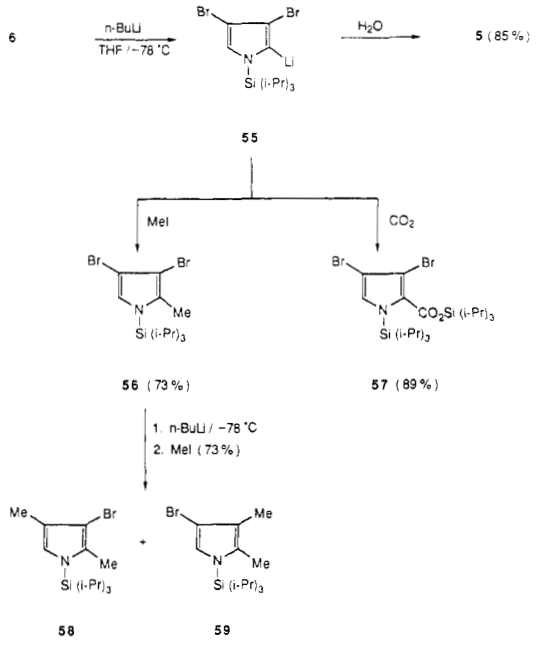
Scheme VII



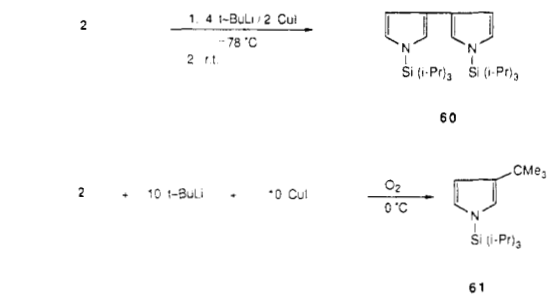
2. 1-(Triisopropylsilyl)-2-bromopyrrole. The notable synthetic utility of 1-(triisopropylsilyl)-3-lithiopyrrole suggested that 1-triisopropyl-2-bromopyrrole (**3**) might be a useful formal equivalent of 2-lithiopyrrole. The generation of 1-(triisopropylsilyl)-2-lithiopyrrole (**47**) was readily accomplished by bromine–lithium exchange with *n*-butyllithium in THF solution at −78 °C (Scheme VII). In contrast to the 3-lithio species **44**, which was stable at −78 °C, the α-lithio compound underwent rapid (50% rearranged after 40 min) isomerization[43,44] at this temperature to 1-lithio-2-(triisopropylsilyl)pyrrole (**48**). At −100 °C, the rearrangement was much slower (<2% in 1 h) and therefore the reactions with electrophilic reagents were initiated at this temperature. Nevertheless, only the most reactive reagents gave the desired products. For example, methyl iodide, carbon dioxide, and benzaldehyde provided 2-methyl-1-(triisopropylsilyl)pyrrole (**50**), triisopropylsilyl pyrrole-2-carboxylate (**51**), and 2-(1-hydroxybenzyl)-1-(triisopropylsilyl)pyrrole (**52**) respectively, **50**, **51** and **52**, whereas less electrophilic reagents, such as 2-iodobutane, gave **49** (74%) and **1** (11%) as the exclusive products. The identity of compound **51** was confirmed by fluoride ion induced desilylation to pyrrole-2-carboxylic acid (**53**), that of the very unstable alcohol **52** was established by reduction to 2-benzylpyrrole (**54**) with sodium borohydride in boiling 2-propanol.[45]

(37) Matteson, D. S.; Snyder, H. R. *J. Org. Chem.* **1957**, *22*, 1500.
(38) Gronowitz, S.; Hoernfeldt, A. B.; Gestbloom, B.; Hoffman, R. *Arkiv Kemi* **1961**, *18*, 151.
(39) Anderson, H. J.; Griffiths, S. J. *Can. J. Chem.* **1967**, *45*, 2227.
(40) Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. *J. Chem. Soc., Perkin Trans 1.* **1982**, 1342.
(41) Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1833.
(42) 2-Bromopyrrole is not lithiated on carbon even with excess *tert*-butyllithium. Naef, R.; Muchowski, J. M. Unpublished data.
(43) In view of the fact that **44** shows no tendency to undergo N to C silyl migration, it is probable that the rearrangement of **47** to **48** is intramolecular.
(44) This remarkably facile transposition was quite unexpected since it is reported that 1-(trimethylsilyl)- and 1-(triethylsilyl)-2-lithiopyrrole are only slowly isomerized in pentane at reflux temperature.[41]

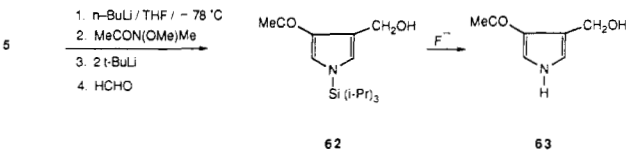
Scheme VIII



Scheme IX



Scheme X



The Grignard reagent corresponding to **47**, generated from the lithium compound and ethereal magnesium bromide at −100 °C, was much less prone to undergo N to C silyl migration (slow at 50 °C), but the spectrum of reactivity toward electrophiles did not differ significantly from that of the lithium compound.

3. N-Silylated Polybromopyrroles. The monolithiation of the tribromo compound **6** was effected with *n*-butyllithium under conditions identical with those used to generate **44**. The 2-lithio species **55** (Scheme VIII) was formed exclusively (99%) as determined by protonolysis to 1-(triisopropylsilyl)-3,4-dibromopyrrole (**5**). This lithium compound also reacted satisfactorily with methyl iodide and carbon dioxide; less reactive electrophiles were not studied.

It is surprising that halogen–metal interchange of the most hindered bromine atom of **6** should occur exclusively. This may be a kinetic phenomenon since lithiation of an equimolar mixture of the monobromo compounds **2** and **3** with a deficiency of *n*-butyllithium (−78 °C, 1 min), followed by methyl iodide trapping, gave a 5.5:1 mixture of the α- and β-methyl compounds **50** and **45** (Table II, E = Me). In contrast, monolithiation of the 3,4-dibromo compound **56** occurred selectively at the least hindered bromine atom, as deduced by the formation of a 3:1 mixture of the dimethyl compounds **58** and **59** upon reaction with methyl iodide. It is also noteworthy that the monolithio compound **55** showed no tendency toward isomerization of the kind observed for **47**, a result which, at least in part, may be of steric origin.

4. Copper-Induced Coupling Reactions. A cursory examination of the possibility of effecting copper(I)-induced hetero and homo coupling reactions[46] was made. Thus **2** was lithiated in the presence of cuprous iodide and the "copper species" thus obtained was warmed to room temperature to effect its decomposition. The 3,3-bipyrrolyl compound **60** was formed in good yield (Scheme IX). When a 8:1 mixture of *tert*-butyllithium and **2**, containing excess cuprous iodide, was kept at 0 °C in an oxygen atmosphere, the cross-coupled product **61** was isolated in ca. 60% yield. In neither case is the nature of the copper-containing species known.

5. Synthesis of Verrucarin E. Verrucarin E (**63**) is a 3,4-disubstituted pyrrole derivative with weak antibiotic activity, isolated from *Myrothecium verrucaria*,[47] which has been synthesized on several occasions.[48-50] A simple synthesis of this compound was devised on the basis on the readily available 3,4-dibromo compound **5** as the starting material (Scheme X). Thus, after sequential reaction of **5**, in one pot, with *n*-butyllithium (1 equiv), *N*-methoxy-*N*-methylacetamide,[51] *tert*-butyllithium (2 equiv), and excess gaseous formaldehyde, the 3-acetyl-4-hydroxymethyl compound **62** was isolated in ca. 44% overall yield. Desilylation of **62** gave crystalline verrucarin E with NMR spectral properties very similar to those reported.[50] This synthesis compares quite favorably with the most efficient[50] of the syntheses of verrucarin E published to date.

III. Summary. In summation, a most useful strategy has been devised for the synthesis of 3-substituted pyrroles on the basis of the kinetic electrophilic substitution of 1-(triisopropylsilyl)pyrrole (**1**) at the β position and subsequent fluoride ion induced desilylation. This now becomes the preferred route, indeed, in some instances the only route, to 3-monosubstituted pyrroles. This process is extendable to the introduction of substituents at both β positions. This is because **1** can be 3,4-dihalogenated and then transformed, by standard sequential halogen–metal interchange–electrophile trapping sequences, to 3,4-disubstituted pyrroles.

Since these results were communicated in preliminary form,[15] several investigators have taken advantage of the principles discussed in detail herein. Kozikowski et al.[52] have utilized **2** as a starting material for the synthesis of 1-ethoxycarbonyl)-7-ethylindole and Eschenmoser and co-workers[19] have shown that **1** is converted into the 3,4-bis(dimethylamino)methyl compound with excess *N*,*N*-

(45) Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985**, *50*, 2961.
(46) (a) Bahr, G., Burba, P. In *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed.; G. Thieme: Stuttgart, 1970; Vol 13/1, pp 735–761. (b) Normant, J. F. *Synthesis* **1970**, 63.
(47) Fetz, E.; Tamm, C. *Helv. Chim. Acta* **1966**, *49*, 349.
(48) Pfäffli, P.; Tamm, C. *Helv. Chim. Acta* **1969**, *52*, 1911.
(49) Groves, J. K.; Cundasawmy, N. E.; Anderson, H. J. *Can. J. Chem.* **1973**, *51*, 1089.
(50) Gossauer, A.; Suhl, K. *Helv. Chim. Acta* **1976**, *59*, 1698.
(51) Nahm, M. S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(52) Kozikowski, A. P.; Cheng, X.-M.; Li, C.-S.; Scripko, J. G. *Isr. J. Chem.* **1986**, *27*, 61.

dimethylmethyleneammonium iodide (Eschenmoser's salt)[53] in boiling acetonitrile solution. In addition, 1-(triisopropylsilyl)-3-nitropyrrole (16) has been used as a source of 2-alkyl-3-nitropyrroles[54] and various 3-substituted pyrroles have been prepared[22] via the lithium compound 44. 1-(Triisopropylsilyl)pyrrole is already proving its synthetic worth!

Experimental Section

General Information. The melting points were determined in a Mel-Temp or a Thomas-Hoover Uni-Melt apparatus and are not corrected. The infrared spectra were obtained with a Sargent-Welch Model 3-200 infrared spectrophotometer, a Perkin-Elmer Model 1420 infrared spectrophotometer, or a Nicolet 5 PC FT infrared spectrophotometer. The NMR spectra were measured in $CDCl_3$, unless stated otherwise, on a Varian EM-390, a Bruker WM-300, or a Bruker AM-500 NMR spectrometer and are expressed as parts per million (δ) from internal tetramethylsilane. When exchangeable protons were present, the coupling constants reported are those obtained after deuterium oxide exchange. The high resolution mass spectra were obtained with a Finnigan MAT 311A mass spectrometer.

THF was distilled from sodium/benzophenone ketyl. Anhydrous DMF (Aldrich) was stored over activated 4A molecular sieves before use. Dichloromethane was dried by removal of the water azeotrope by distillation. 1,2-Dichloroethane was dried by distillation from phosphorus pentoxide. Dry pyridine was obtained by distillation from barium oxide. *N*-Bromosuccinimide was recrystallized from benzene. Pyrrole (Aldrich) was distilled before use.

Reactions requiring anhydrous conditions were conducted in oven-dried (130 °C) glassware under a positive pressure of nitrogen or argon.

***N*-(Triisopropylsilyl)pyrrole (1). (a) Sodium Hydride Method.** Pyrrole (5.0 mL, 4.82 g, 72 mmol) was added dropwise at 0 °C to a mechanically stirred suspension of sodium hydride (3.17 g of a 60% dispersion in mineral oil, 79 mmol) in anhydrous DMF (100 mL). When hydrogen evolution (foaming) had ceased (ca. 1.25 h), triisopropylsilyl chloride (15.3 mL, 13.9 g, 72 mmol) was added dropwise and stirring at 0 °C was then continued for 0.75 h. The reaction mixture was partitioned between ether and water, and the ether phase was washed with water, dried over sodium sulfate, and evaporated in vacuo. Kugelrohr distillation of the residue gave an oil (15.90 g, 99% yield), bp 125 °C/11 mm, mp 5 °C; ^{1}H NMR δ 1.09 (d, 18 H, J = 7.4 Hz, Me), 1.45 (sept, 3 H, J = 7.4 Hz, CH), 6.32 (t, 2 H, H-3,4), 6.80 (t, 2 H, H-2,5). Anal. Calcd for $C_{13}H_{25}NSi$: C, 69.88; H, 11.28; N, 6.27. Found: C, 69.93; H, 11.34; N, 6.14.

(b) *n*-Butyllithium Method. A solution of *n*-butyllithium in hexane (103 mL of a 1.6 M solution, 164 mmol) was added dropwise to a stirred solution of pyrrole (10.0 g, 149 mmol) in anhydrous THF (250 mL) at −78 °C. Ten minutes thereafter, triisopropylsilyl chloride (31.9 mL, 28.7 g, 149 mmol) was added and the reaction mixture was warmed to room temperature over a 0.5-h period. The solvent was then removed in vacuo, water was added to the residue, and the product was extracted into ether. After a workup identical with that described in (a), Kugelrohr distillation gave the product (30.8 g, 92% yield).

3-Bromo-1-(triisopropylsilyl)pyrrole (2). Freshly purified[55] NBS (*N*-bromosuccinimide; 3.2 g, 18 mmol) was added to a stirred solution of *N*-(triisopropylsilyl)pyrrole (4.0 g, 18 mmol) in anhydrous THF (40 mL) at −78 °C. The reaction mixture was kept at −78 °C for 1–2 h and then left to reach room temperature (ca. 1 h). Pyridine (0.5 mL) and hexane (40 mL) were added, the resulting suspension was filtered through a plug of neutral alumina, and the filtrate was evaporated in vacuo. Kugelrohr distillation of the residue gave an oil (5.0 g, 93%), bp 100 °C/0.1 mm, which by capillary VPC (SE 30) contained 3% of the α-isomer **3** as the only contaminant: ^{1}H NMR δ 1.08 (d, 18 H, J = 7.50 Hz, Me), 1.42 (sept, 3 H, J = 7.50 Hz, CH), 6.26 (dd, 1 H, $J_{2,4}$ = 1.41 Hz, $J_{4,5}$ = 2.83 Hz, H-4), 6.65 (t, 1 H, H-5), 6.70 (dd, 1 H, $J_{2,4}$ = 1.41 Hz, $J_{2,5}$ = 2.25 Hz, H-2). Anal. Calcd for $C_{13}H_{24}BrNSi$: C, 51.65; H, 8.00; N, 4.63. Found: C, 51.52; H, 8.17; N, 4.72.

This and the other brominations described herein have been repeated many times without encountering the problem described by Stefan et al.[22] In every case, recrystallized NBS and THF distilled from sodium/benzophene were used.

2-Bromo-1-(triisopropylsilyl)pyrrole (3). NBS (20.95 g, 118 mmol) was added to a solution of freshly distilled pyrrole (8.2 mL, 7.90 g, 118 mmol) in anhydrous THF (500 mL) at −78 °C. The cooling bath was removed and the reaction mixture was stored in the refrigerator (−12 °C) for 15 h. Anhydrous DMF (140 mL) was added, and this solution was cooled to −20 °C and added to a suspension of sodium hydride [prepared from 11.78 g (245 mmol) of a 50% dispersion in mineral oil, which was washed with hexane] in anhydrous THF (60 mL). After 3 h at this temperature, triisopropylsilyl chloride (27.7 mL, 25.0 g, 130 mmol) was added. When the addition was completed, stirring was continued for 10 min and then triethylamine (2 mL) and hexane (250 mL) were added. The mixture was filtered through Celite and the filtrate was evaporated in vacuo (T < 15 °C). The residue was partitioned between hexane and water, and the organic phase was washed with saturated sodium chloride solution and evaporated in vacuo. The residue was filtered through a column of neutral alumina, deactivated with 3 wt % triethylamine, using hexane as the solvent. The crude product (25.2 g) was purified to homogeneity by chromatography over silica gel (deactivated with 3 wt % triethylamine) using hexane as the eluant. 2-Bromo-1-(triisopropylsilyl)pyrrole was obtained as a colorless oil (20.6 g, 58% yield): ^{1}H NMR δ 1.14 (d, 18 H, J = 7.52 Hz, Me), 1.70 (sept, 3 H, J = 7.52 Hz, CH), 6.21 (t, 1 H, H-4), 6.27 (dd, 1 H, $J_{3,4}$ = 3.27 Hz, $J_{3,5}$ = 1.71 Hz, H-3), 6.81 (dd, 1 H, $J_{4,5}$ = 3.12 Hz, $J_{3,5}$ = 1.71 Hz, H-5). Anal. Calcd for $C_{13}H_{24}BrNSi$: C, 51.65; H, 8.00. Found: C, 52.09; H, 8.16.

3-Bromopyrrole (4). A solution of tetra-*n*-butylammonium fluoride (0.33 mL of a 1 M solution, 0.33 mmol) in THF was added to a stirred solution of **2** (0.100 g, 0.33 mmol) in THF (1.0 mL). After 5 min at room temperature, the solution was diluted with ether, and the organic phase was washed with water and dried ($MgSO_4$). Removal of the solvent in vacuo gave a very unstable oil (0.031 g, 65% yield): ^{1}H NMR δ 6.15 (dd, 1 H, $J_{2,4}$ = 1.51 Hz, $J_{4,5}$ = 2.89 Hz, H-4), 6.62 (dd, 1 H, $J_{2,5}$ = 2.15 Hz, $J_{4,5}$ = 2.89 Hz, H-5), 6.68 (dd, 1 H, $J_{2,4}$ = 1.51 Hz, $J_{2,5}$ = 2.15 Hz, H-2); HRMS calcd for C_4H_4BrN 144.9527, found 144.9530.

3,4-Dibromo-1-(triisopropylsilyl)pyrrole (5). NBS (4.0 g, 22.5 mmol) was added to a stirred solution of **1** (2.5 g 11.2 mmol) in anhydrous THF (35 mL) at −78 °C. After 1 h at −78 °C the reaction mixture was left to reach room temperature (0.5 h), it was poured into 10% aqueous sodium bicarbonate solution (30 mL), and the product was extracted into ether. The extract was washed with saturated sodium chloride solution, dried over potassium carbonate, and evaporated in vacuo. The residue (4.13 g) was crystallized from pentane at 0 °C to give the product (3.33 g, 78%) as a solid: mp 77 °C; NMR δ 1.09 (d, 18 H, J = 7.48 Hz, Me), 1.40 (sept, 3 H, J = 7.48 Hz, CH), 6.72 (s, 2 H, H-2,5). Anal. Calcd for $C_{13}H_{23}Br_2NSi$: C, 40.96; H, 6.08; N, 3.67. Found: C, 40.69; H, 6.36; N, 3.48.

2,3,4-Tribromo-1-(triisopropylsilyl)pyrrole (6). NBS (37.4 g, 210 mmol) was added to a stirred solution of **1** (9.30 g, 42 mmol) in anhydrous THF (100 mL) at −78 °C. After 3 h at this temperature, hexane (100 mL) was added and the mixture was filtered through a plug of neutral alumina. The filtrate was evaporated in vacuo and the residue was passed over a short column of silica gel, using hexane as the eluting solvent. Evaporation of the solvent gave a solid, which was recrystallized at low temperature (−78 °C) from pentane. The tribromo compound **6** was obtained as a colorless solid (17.1 g, 89% yield): mp 46 °C; ^{1}H NMR δ 1.14 (d, 18 H, J = 7.56 Hz, Me), 1.68 (sept, 3 H, J = 7.56 Hz, CH), 6.87 (s, 1 H, H-5). Anal. Calcd for $C_{13}H_{22}Br_3NSi$: C, 33.93; H, 4.82; N, 3.04. Found: C, 34.09; H, 5.08; N, 2.82.

2,3-Dibromo-1-(triisopropylsilyl)pyrrole (7). NBS (0.905 g, 5.08 mmol) was added to a stirred solution of **2** (1.54 g, 5.08 mmol) in anhydrous THF at 23 °C. After 1 h at this temperature, the reaction mixture was worked up as described for **5** to give a

(53) Rochin, C.; Babot, O.; Dunogues, J.; Dubondin, F. *Synthesis* **1986**, 228.
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mixture of **5** and **7** (1.89 g). The 3,4-dibromo compound was removed by crystallization from pentane, first at −20 °C and then at −78 °C. The filtrate was evaporated in vacuo and the residue was Kugelrohr distilled at 109 °C/0.15 mm to give **7** as an oil (0.89 g, 46% yield): ^{1}H NMR δ 1.14 (d, 18 H, J = 7.54 Hz, Me), 1.69 (sept, 3 H, J = 7.54 Hz, CH), 6.31 (d, 1 H, $J_{4,5}$ = 3.26 Hz, H-4), 6.80 (d, 1 H, $J_{4,5}$ = 3.26 Hz, H-5); HRMS calcd for $C_{13}H_{23}Br_2NSi$ 380.9946, found 380.9902.

3-Iodo-1-(triisopropylsilyl)pyrrole (13). A solution of iodine (0.569 g, 2.24 mmol) in anhydrous dichloromethane (100 mL) was added dropwise, over a 1.5-h period, to a stirred solution of **1** (0.500 g, 2.24 mmol) in dichloromethane (50 mL) containing suspended mercuric acetate (0.714 g, 2.34 mmol) at −25 °C. The reaction mixture was stirred at −25 °C for 3.5 h and then the solvent was removed in vacuo. Hexane was added to the residue, the mixture was filtered, and the filtrate was evaporated in vacuo. The residual oil was purified by flash chromatography on silica gel, using hexane as the eluting solvent. The product (0.475 g, 61%) contained the starting material as the only impurity (~6%). An analytical specimen was obtained by Kugelrohr distillation at 160 °C/3 mm: ^{1}H NMR δ 1.08 (d, 18 H, J = 7.37 Hz, Me), 1.42 (sept, 3 H, J = 7.37 Hz, CH), 6.36 (dd, 1 H, $J_{2,4}$ = 1.32 Hz, $J_{4,5}$ = 2.73 Hz, H-4), 6.66 (t, 1 H, H-5), 6.79 (dd, 1 H, $J_{2,4}$ = 1.32 Hz, $J_{2,5}$ = 2.06 Hz, H-2). Anal. Calcd for $C_{13}H_{24}INSi$: C, 44.69; H, 6.93; N, 4.01. Found: C, 44.83; H, 6.95; N, 3.96.

3,4-Diiodo-1-(triisopropylsilyl)pyrrole (14). A solution of iodine (1.14 g, 4.48 mmol) in anhydrous dichloromethane (200 mL) was added dropwise, over a 1-h period, to a stirred solution of **1** (0.500 g, 2.24 mmol) in dichloromethane (80 mL) containing suspended mercuric acetate (1.43 g, 4.48 mmol) at 0 °C. After a further 1 h at 0 °C, the reaction mixture was worked up as described for **13** to give a solid (1.11 g), which was purified by column chromatography on activity II neutral alumina (50 g), using hexane as the eluate. The diiodo compound **14** was obtained as a solid (0.730 g, 69% yield), which on crystalllization from hexane had mp 75–78 °C: ^{1}H NMR δ 1.08 (d, 18 H, J = 7.49 Hz, Me), 1.41 (sept, 3 H, J = 7.49 Hz, CH), 6.79 (s, 2 H, H-2,5). Anal. Calcd for $C_{23}H_{23}I_2NSi$: C, 32.85; H, 4.88; N, 2.95. Found: C, 32.73; H, 4.82; N, 2.86.

3,4-Diiodopyrrole (15). The desilylation of **14** was effected in the same manner as described for the desilylation of **3** except that the reaction time was 15 min. The crude product was purified by flash chromatography on silica gel, using hexane–ethyl acetate (3:1) as the eluting solvent. The solid product (90% yield), on crystallization from hexane, at −78 °C, had mp 39–40 °C (lit.[29] mp 40 °C).

3-Nitro-1-(triisopropylsilyl)pyrrole (16). A solution of **1** (0.640 g, 2.86 mmol) and cupric nitrate trihydrate (0.725 g, 3.00 mmol) in acetic anhydride (18 mL) was stirred at 25 °C for 1 h and then poured into saturated aqueous sodium bicarbonate (200 mL). The products were extracted into ether, and the extract was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo. The residue was subjected to flash chromatography on silica gel, using hexane–ethyl acetate (12:1 to 4:1) to elute the products. Compound **16** (0.590 g, 77%) and 2-nitropyrrole (**17**, 0.025 g, 8%, identified by its NMR spectrum) were obtained as solids. Crystallization of **16** from hexane–ethyl acetate gave an analytical specimen: mp 52–54 °C; ^{1}H NMR δ 1.11 (d, 18 H, J = 7.50 Hz, Me), 1.48 (sept, 3 H, J = 7.50 Hz, CH), 6.65 (dd, 1 H, $J_{2,5}$ = 2.31 Hz, $J_{4,5}$ = 3.19 Hz, H-5), 6.83 (dd, 1 H, $J_{2,4}$ = 1.48 Hz, $J_{4,5}$ = 3.19 Hz, H-4), 7.60 (dd, 1 H, $J_{2,4}$ = 1.48 Hz, $J_{2,5}$ = 2.31 Hz, H-2). Anal. Calcd for $C_{13}H_{24}N_2O_2Si$: C, 58.17; H, 9.01; N, 10.43. Found: C, 58.17; H, 9.09; N, 10.51.

3-Nitropyrrole (18). The desilylation of **16** was carried out as described for the synthesis of **4**. The crude product was purified by centrifugally accelerated thin layer chromatography on silica gel, using hexane–ethyl acetate (1:4) to elute the product, mp 95–96 °C (lit.[56] mp 101 °C), in quantitative yield.

Ethyl 1-(Triisopropylsilyl)-3-pyrrolylglyoxalate (19). A solution of pyridine (1.17 g, 14.8 mmol) in anhydrous dichloromethane (10 mL) was added to a stirred solution of ethyl oxalyl chloride (2.02 g, 14.8 mmol) in the same solvent (10 mL) at −20 °C, and then 1-(triisopropylsilyl)pyrrole (**1**, 1.00 g, 4.48 mmol) dissolved in dichloromethane (15 mL) was added thereto. The solution was left to come to room temperature and after 48 h the reaction mixture was poured into cold saturated aqueous sodium bicarbonate. The product was extracted into ether, and the extract was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by centrifugally accelerated TLC using a gradient of hexane–ethyl acetate (10:1) to pure ethyl acetate to elute the 3-substituted compound **19** (1.14 g, 79%) and 2-substituted compound (0.071 g, 9%, identical with an authentic specimen[57]). A sample of **19** on crystallization from hexane had mp 48–49 °C: IR (KBr) 1745, 1660 cm^{-1}; ^{1}H NMR δ 1.12 (d, 18 H, J = 7.46 Hz, CH Me_2) 1.41 (t, 3 H, J = 7.15 Hz, CH_2CH_3), 1.49 (sept, 3 H, J = 7.46 Hz, CH), 4.39 (q, 2 H, J = 7.15 Hz, CH_2), 6.76 (dd, 1 H, $J_{2,5}$ = 2.03 Hz, $J_{4,5}$ = 2.89 Hz, H-5), 6.89 (dd, 1 H, $J_{2,4}$ = 1.27 Hz, $J_{4,5}$ = 2.89 Hz, H-4), 7.82 (t, 1 H, H-2). Anal. Calcd for $C_{17}H_{29}NO_3Si$: C, 63.11; H, 9.04; N, 4.33. Found: C, 62.98, H, 8.70; N, 4.56.

Ethyl 3-Pyrrolylglyoxalate (21). A solution of **1** (13.0 g, 58 mmol), ethyl oxalyl chloride (23.9 g, 175 mmol), and pyridine (14.1 mL, 13.8 g, 175 mmol) in anhydrous 1,2-dichloroethane (100 mL) was heated at 73 °C for 16 h. The reaction mixture was cooled and poured into saturated aqueous ammonium chloride solution. The organic phase was separated and combined with a dichloromethane extract of the aqueous phase, and the combined organic phases were washed with saturated salt solution and dried (Na_2SO_4). The solvents were removed in vacuo and the residue was purified by column chromatography on silica gel (70 g), using hexane–ethyl acetate (4:1) as the eluting solvent. The product **21** was obtained as a solid (5.8 g, 60% yield), which, after crystallization from hexane–ethyl acetate, had mp 91–92 °C: IR (KBr) 3250, 1730, 1635 cm^{-1}; ^{1}H NMR δ 1.41 (t, 3 H, J = 7.16 Hz, Me), 4.39 (q, 2 H, J = 7.16 Hz, CH_2), 6.82 (dd, 1 H, $J_{2,5}$ = 1.84 Hz, $J_{4,5}$ = 3.12 Hz, H-5), 6.84 (dd, 1 H, $J_{2,4}$ = 1.51 Hz, $J_{4,5}$ = 3.12 Hz, H-4), 7.87 (t, 1 H, H-2). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43. Found: C, 57.30; H, 5.54.

Ethyl 3-pyrrolylglyoxalate (**21**) could also be prepared, in over 95% yield, by fluoride ion induced desilylation of **19**.

3-(Trichloroacetyl)-1-(triisopropylsilyl)pyrrole (22). A solution of *N*-(triisopropylsilyl)pyrrole (**1**, 5.00 g, 22.4 mmol) in anhydrous 1,2-dichloroethane (100 mL) containing anhydrous pyridine (2.67 g, 33 mmol) and trichloroacetyl chloride (4.91 g, 27 mmol) was stirred at room temperature for 96 h. The reaction mixture was worked up in the manner described for the synthesis of **21**. The crude product was purified by column chromatography on silica gel (300 g), using hexane–ethyl acetate (9:1) to elute the solid product (6.21 g, 75% yield) as well as some (1.0 g) starting material. Crystallization of the above solid from hexane–dichloromethane gave **22** with mp 65 °C: IR ($CHCl_3$) 1675 cm^{-1}; ^{1}H NMR δ 1.20 (d, 18 H, J = 7.5 Hz, Me), 1.50 (sept, 3 H, J = 7.5 Hz, CH), 6.75 (dd, 1 H, $J_{2,5}$ = 2.1 Hz, $J_{4,5}$ = 3.0 Hz, H-5), 6.95 (dd, 1 H, $J_{2,4}$ = 1.5 Hz, $J_{4,5}$ = 3.0 Hz, H-4), 7.80 (t, 1 H, H-2). Anal. Calcd for $C_{15}H_{24}NCl_3OSi$: C, 48.84; H, 6.55; Cl, 28.84; N, 3.79. Found: C, 48.89; H, 6.48; Cl, 28.86; N, 3.83.

3-Benzoyl-1-(triisopropylsilyl)pyrrole (23). Benzoyl chloride (1.40 g, 10 mmol) was added slowly to a stirred slurry of aluminum chloride (1.5 g, 11 mmol) in anhydrous dichloromethane (20 mL) at 0 °C. After 0.25 h, a solution of **1** (2.23 g, 10 mmol) in dichloromethane (5 mL) was added. The mixture was stirred for 0.5 h at 0 °C and 0.5 h at 25 °C and then poured into an ice–water mixture. The organic phase was separated and combined with a dichloromethane extract of the aqueous phase. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residual material was subjected to flash chromatography on silica gel, using gradient elution with hexane–ethyl acetate (10:1 to 3:1) to elute the starting material (0.64 g) and the solid product (1.60 g, 48%). Crystallization of the solid from hexane gave pure **23**: mp 94–96 °C; IR (KBr) 1630 cm^{-1}; ^{1}H NMR δ 1.11 (d, 18 H, J = 7.50 Hz, Me) 1.47 (sept, 3 H, J = 7.50 Hz, CH), 6.79 (dd, 1 H, $J_{2,5}$ = 2.06 Hz, $J_{4,5}$ = 2.93 Hz, H-5), 6.81 (dd, 1 H $J_{2,4}$ = 1.51 Hz, $J_{4,5}$ = 2.93 Hz, H-4), 7.33 (t, 1 H, H-2), 7.48 (m, 3 H), 7.85 (m, 2 H). Anal. Calcd for $C_{20}H_{29}NOSi$: C, 73.34; H, 8.92; N, 4.27. Found: C, 73.51; H, 9.06; N, 4.27.

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3-(Phenylacetyl)-1-(triisopropylsilyl)pyrrole (24). This compound was prepared in exactly the same manner as described for **23**, except that the eluting solvent was hexane–ethyl acetate (12:1). In addition to starting material (31%), compound **24** was isolated in 44% yield as an oil: IR (neat) 1655 cm^{-1}; ^1H NMR δ 1.08 (d, 18 H, J = 7.46 Hz, Me), 1.45 (sept, 3 H, J = 7.46 Hz, CH) 4.05 (s, 2 H, CH_2), 6.71 (t, 1 H, H-5) 6.73 (dd, 1 H, $J_{2,4}$ = 1.34 Hz, $J_{4,5}$ = 3.00 Hz, H-4), 7.18–7.31 (m, 5 H, C_6H_5), 7.38 (t, 1 H, H-2). This material was not characterized further. Instead it was desilylated to the known ketone **26** (see below).

3-Benzoylpyrrole (25). Compound **23** was desilylated in the usual way at room temperature (0.5 h). The crude product was purified by flash chromatography on silica gel, using hexane–ethyl acetate (3:1) as the eluting solvent. The product **23**, mp 98–100 °C (lit.[58] mp 99.5–100 °C) was obtained in 97% yield.

3-(Phenylacetyl)pyrrole (26). This compound was prepared in a manner identical with that described for **25**. The crude product was freed of triisopropylfluorosilane by washing with hexane followed by crystallization from hexane–ethyl acetate. Pure **26**, obtained in 94% yield, had mp 118–120 °C (lit.[45] mp 121–123 °C).

Pyrrole-3-carboxaldehyde (30). The iminium salt **29**[31] (2.10 g, 13.2 mmol) was added to 5% aqueous sodium hydroxide solution (200 mL), and the solution was stirred at room temperature for 4 h. The solution was exhaustively extracted with dichloromethane, and the extract was dried over potassium carbonate and evaporated in vacuo. The residue was subjected to flash chromatography on silica gel, using hexane–ethyl acetate (3:1 to 1:1) to elute a small amount of pyrrole-2-carboxaldehyde (0.035 g, 3% yield) and pyrrole-3-carboxaldehyde (0.870 g, 69% yield). The aldehyde **30** had mp 68 °C (lit.[59] mp 63–65 °C). This compound was identical with a sample, prepared in 86% yield, by the desilylation of **45** (E = CHO).

3-(Trifluoroacetyl)-1-(triisopropylsilyl)pyrrole (31). Pyridine (50 g, 75 mmol) was added to a stirred solution of trifluoroacetic anhydride (10 mL, 14.9 g, 71 mmol) in anhydrous dichloromethane (100 mL). Immediately thereafter, 1-(triisopropylsilyl)pyrrole (5.50 g, 24.7 mmol) dissolved in dichloromethane (15 mL) was added. The solution was left to come to room temperature and stirring was continued for 3 h. The reaction mixture was poured into dilute aqueous sodium bicarbonate solution, and the organic phase was separated and combined with a dichloromethane extract of the aqueous phase. The organic phase was washed with bicarbonate solution, dried with Drierite, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel, using hexane–ethyl acetate (95:5) as the eluting solvent. Compound **31** was obtained as an oil (5.76 g, 73% yield): IR (CCl_4) 1685 cm^{-1}; ^1H NMR δ 1.13 (d, 18 H, J = 7.50 Hz, Me), 1.50 (sept, 3 H, J = 7.50 Hz, CH), 6.79 (dd, 1 H, $J_{2,5}$ = 1.95 Hz, $J_{4,5}$ = 2.85 Hz, H-5), 6.85 (m, 1 H, H-4), 7.61 (m, H-2). Anal. Calcd for $C_{15}H_{24}F_3NOSi$: C, 56.40; H, 7.59; N, 4.38. Found: C, 56.59; H, 7.68; N, 4.41.

3-(Trifluoroacetyl)pyrrole (33). The desilylation of **31** was effected in the usual manner (10 min) in DMF solution. The crude product was sublimed at 120 °C/10 mm and the sublimate was triturated with pentane to remove an oily impurity. Resublimation gave pure **33** (67% yield): mp 111–112 °C; IR ($CHCl_3$) 3460, 1692 cm^{-1}; ^1H NMR (acetone-d_6) 6.71 (dd, 1 H, $J_{2,5}$ = 1.93 Hz, $J_{4,5}$ = 2.85 Hz, H-5), 7.01 (m, 1 H, H-4), 7.79 (m, 1 H, H-2). Anal. Calcd for $C_6H_4F_3NO$: C, 44.19; H, 2.47; N, 8.59. Found: C, 44.06; H, 2.23; N, 8.34.

2-(Trifluoroacetyl)-1-(triisopropylsilyl)pyrrole (34). A solution of 2-(trifluoroacetyl)pyrrole[35] (2.00 g, 12 mmol) in anhydrous DMF (15 mL) was added, at 0 °C, to a stirred suspension of sodium hydride (0.60 g, 50% dispersion in mineral oil, 12 mmol) in DMF (30 mL). When hydrogen evolution had subsided, triisopropylsilyl chloride (2.9 g, 15 mmol) was added, and the reaction mixture was allowed to reach room temperature. After 1.5 h, the solution was poured into dilute sodium bicarbonate solution, the product was extracted into ether, and the extract was washed successively with sodium bicarbonate solution and saturated sodium chloride solution and then dried over Drierite. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel, using hexane–ethyl acetate (95:5) as the eluting solvent. The product **34** was obtained as an oil (3.05 g, 80% yield): IR ($CHCl_3$) 1665 cm^{-1}; ^1H NMR δ 1.11 (d, 18 H, J = 7.50 Hz, Me), 1.75 (sept, 3 H, J = 7.50 Hz, CH), 6.45 (dd, 1 H, $J_{3,4}$ = 3.57 Hz, $J_{4,5}$ = 2.52 Hz, H-4), 7.44 (m, 2 H, H-3,5). Anal. Calcd for $C_{15}H_{24}F_3NOSi$: C, 56.40; H, 7.59; N, 4.38. Found: C, 56.60; H, 7.73; N, 4.32.

Reaction of 1-(Triisopropylsilyl)pyrrole (1) with Chlorosulfonyl Isocyanate. Chlorosulfonyl isocyanate (1.42 g, 10 mmol) was added to a stirred solution of **1** (2.23 g, 10 mmol) in dry 1:1 DMF–acetonitrile (10 mL) at −78 °C. The reaction mixture was left to warm to 0 °C, and then it was partitioned between water and ether. The ether phase was dried and the solvent was removed in vacuo. The residue was subjected to column chromatography on silica gel to give the 2-cyano **38** (2.06 g, 81% yield) and the 3-cyano **37** (oil, 0.34 g, 16%) compounds as oils.

The β-isomer **37** was characterized spectroscopically: ^1H NMR δ 1.10 (d, 18 H, J = 7.5 Hz, Me), 1.46 (sept, 3 H, J = 7.5 Hz, CH), 6.54 (dd, 1 H, $J_{2,4}$ = 1.39 Hz, $J_{4,5}$ = 2.85 Hz, H-4), 6.73 (dd, 1 H, $J_{2,5}$ = 2.10 Hz, $J_{4,5}$ = 2.85 Hz, H-5), 7.25 (dd, 1 H, $J_{2,4}$ = 1.39 Hz, $J_{2,5}$ = 2.10 Hz, H-2).

The α-isomer **38**: IR ($CHCl_3$) 2230 cm^{-1}; ^1H NMR δ 1.14 (d, 18 H, J = 7.5 Hz, Me), 1.73 (sept, 3 H, J = 7.5 Hz, CH), 6.32 (dd, 1 H, $J_{3,4}$ = 3.52 Hz, $J_{4,5}$ = 2.70 Hz, H-4), 6.96 (dd, 1 H, $J_{3,5}$ = 1.37 Hz, $J_{4,5}$ = 2.70 Hz, H-5), 7.02 (dd, 1 H, $J_{3,4}$ = 3.52 Hz, $J_{3,5}$ = 1.37 Hz, H-3). Anal. Calcd for $C_{14}H_{24}N_2Si$: C, 67.68; H, 9.74; N, 11.28. Found: C, 67.50; H, 9.46; N, 11.02.

Thiocyanation of 1-(Triisopropylsilyl)pyrrole. A solution of bromine (1.4 g, 9 mmol) in methanol (6 mL) was prepared at −78 °C, and the cold solution was added dropwise to a stirred slurry of potassium thiocyanate (1.8 g, 19 mmol) in methanol (6 mL) at −78 °C. After 20 min, a solution of **1** (2.0 g, 9 mmol) in methanol (20 mL) was added. The solution was warmed to −40 °C and 0.5 h; thereafter it was poured into an ice–water mixture. The product was extracted into ether, and the extract was washed successively with saturated solutions of sodium bisulfite and sodium chloride and then dried ($MgSO_4$). The solvent was removed in vacuo to give the thiocyano compound **39** as an oil (2.45 g, 98% yield). This material had the expected NMR spectrum (60 MHz). The identity thereof was confirmed by desilylation in the usual way, followed by methylation under alkaline conditions.[60] The 2-methylthio compound **40** (88% yield overall) was spectroscopically identical with an authentic specimen.[61]

3-(*p*-Tolylsulfinyl)-1-(triisopropylsilyl)pyrrole (41). A solution of **1** (1.00 g, 4.48 mmol) in anhydrous dichloromethane (13 mL) was added to a stirred solution of *p*-toluenesulfinyl chloride (0.86 g, 4.93 mmol) in dichloromethane (13 mL) containing pyridine (0.78 g, 9.86 mmol) at 0 °C. After 2 h at 0 °C, the reaction mixture was poured into saturated sodium bicarbonate solution, the organic phase was separated and combined with an ether extract of the aqueous phase. The combined extracts were dried and evaporated in vacuo. The residual mixture was separated by centrifugally accelerated TLC on silica gel by gradient elution [hexane–ethyl acetate (9:1) to pure ethyl acetate]. In this way there was obtained the starting material (0.30 g), compound **41** (0.78 g, 48%), and 2-(*p*-tolylsulfinyl)pyrrole[9] (**42**, 0.13 g, 14%). Compound **41** had mp 96–97 °C; ^1H NMR δ 1.10 (d, 18 H, J = 7.5 Hz, Me), 1.45 (sept, 3 H, J = 7.5 Hz, CH), 2.41 (s, 3 H, Ar*Me*), 6.25 (dd, 1 H, $J_{2,4}$ = 1.47 Hz, $J_{4,5}$ = 2.91 Hz, H-4), 6.75 (dd, 1 H, $J_{2,5}$ = 2.10 Hz, $J_{4,5}$ = 2.91 Hz, H-5), 7.19 (dd, 1 H, $J_{2,4}$ = 1.47 Hz, $J_{2,5}$ = 2.10 Hz, H-2), 7.27 (d, 2 H, J = 8.2 Hz, H-3′,5′), 7.51 (d, 2 H, J = 8.2 Hz, H, 2′,6′). Anal. Calcd for $C_{20}H_{31}NOSSi$: C, 66.24; H, 8.62; N, 3.86. Found: C, 66.58; H, 8.81; N, 4.10.

3-(*p*-Tolylsulfinyl)pyrrole (43). This compound was prepared in >95% yield by desilylation of **41** in the usual manner. Compound **43** had mp 148–150 °C (lit.[9] mp 151–151.5 °C).

Generation of 3-Lithio-1-(triisopropylsilyl)pyrrole (44) and Trapping with Electrophilic Reagents. A solution of 1.5 M *n*-butyllithium in hexane (3.3 mL, 5 mmol) or 2 M *tert*-butyllithium in pentane (5 mL, 10 mmol) was added, at −78 °C, to

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a solution of 3-bromo-1-(triisopropylsilyl)pyrrole (1.51 g, 5 mmol) in anhydrous THF (25 mL). After 15 min at −78 °C, the electrophilic reagent (5–10 mmol, see Table II) was added and 15 min thereafter the reaction was removed from the cooling bath and left to come to room temperature. The reaction mixture was quenched with water and extracted with ether. The extract was dried ($MgSO_4$) and evaporated in vacuo. The residue was then purified in the manner indicated below.

3-Methyl-1-(triisopropylsilyl)pyrrole (45, E = Me): purification by column chromatography on silica gel using hexane–ethyl acetate (4:1); oil; ^{1}H NMR δ 1.09 (d, 18 H, J = 7.44 Hz, Me_2CH), 1.40 (sept, 3 H, J = 7.44 Hz, CH), 2.13 (d, m, 3 H, J = 0.4 Hz, Me), 6.16 (m, 1 H, $J_{2,4}$ = 1.2 Hz, $J_{4,5}$ = 2.4 Hz, H-4), 6.55 (m, 1 H, $J_{2,4}$ = 1.2 Hz, $J_{2,5}$ = 2.1 Hz, H-2), 6.71 (t, 1 H, H-5). Anal. Calcd for $C_{14}H_{27}NSi$: C, 70.81; H, 11.46; N, 5.90. Found: C, 70.87; H, 11.66; N, 5.84.

3-*n*-Butyl-1-(triisopropylsilyl)pyrrole (45, E = n-Bu): purification by Kugelrohr distillation, 110 °C/0.3 mm; ^{1}H NMR δ 0.91 (t, 3 H, J = 7.3 Hz, Me), 1.09 (d, 18 H, J = 7.4 Hz, Me_2CH), 1.36 (m, 2 H, CH_2), 1.42 (sept, 3 H, J = 7.4 Hz, CH), 1.56 (m, 2 H, CH_2), 2.48 (t, 2 H, J = 7.6 Hz, CH_2C), 6.14 (m, 1 H, H-4), 6.51 (m, H-2), 6.69 (t, 1 H, H-5). Anal. Calcd for $C_{17}H_{33}NSi$: C, 73.04; H, 11.90; N, 5.01. Found: C, 72.88; H, 11.76; N, 5.30.

3-*n*-Octadecyl-1-(triisopropylsilyl)pyrrole (45, E = *n*-$C_{18}H_{37}$): purification by column chromatography on silica gel [hexane–ethyl acetate (9:1)]; glass; ^{1}H NMR δ 0.88 (t, 3 H, J = 7.5 Hz, CH_2Me), 1.08 (d, 18 H, J = 7.4 Hz, $CHMe_2$), 1.25 (m, 30 H, $(CH_2)_{15}$), 1.43 (sept, 3 H, J = 7.4 Hz, CH), 1.57 (m, 2 H, CH_2), 2.47 (t, 2 H, J = 7 Hz, CH_2C), 6.14 (dd, 1 H, $J_{2,4}$ = 1.4 Hz, $J_{4,5}$ = 2.4 Hz, H-4), 6.51 (m, 1 H, H-2), 6.69 (t, 1 H, H-5). Anal. Calcd for $C_{31}H_{61}NSi$: C, 78.24; H, 12.92; N, 2.94. Found: C, 78.25; H, 13.09; N, 2.48.

3-(2-Methylbut-1-yl)-1-(triisopropylsilyl)pyrrole (45, E = 2-MeBu): purification as for *n*-octadecyl compound; oil; ^{1}H NMR δ 0.83–0.92 (m, 5 H, CH*MeEt*), 1.08 (d, 18 H, J = 7.5 Hz, $CHMe_2$), 1.42 (sept, 3 H, J = 7.5 Hz, $CHMe_2$), 1.57 (m, 2 H, *CH*MeEt), 2.26 (dd, 1 H, J_{AB} = 14.00 Hz, J_{AX} = 7.70 Hz, CHC), 2.48 (dd, 1 H, J_{AB} = 14.00 Hz, J_{BX} = 5.90 Hz, CHC), 6.11 (dd, 1 H, $J_{2,4}$ = 1.42 Hz, $J_{4,5}$ = 2.55 Hz, H-4) 6.50 (m, 1 H, H-2), 6.69 (t, 1 H, H-5). Anal. Calcd for $C_{18}H_{35}NSi$: C, 73.64; H, 12.02; N, 4.77. Found: C, 73.62; H, 11.94; N, 4.97.

3-(Trimethylsilyl)-1-(triisopropylsilyl)pyrrole (45, E = Me_3Si): purification by column chromatography on silica gel [hexane–ethyl acetate (4:1)]; oil; ^{1}H NMR δ 0.20 (m, 9 H, Me_3Si), 1.11 (d, 18 H, J = 7.5 Hz, Me), 1.46 (sept, 3 H, J = 7.5 Hz, CH), 6.40 (dd, 1 H, $J_{2,4}$ = 1.32 Hz, $J_{4,5}$ = 2.49 Hz, H-4), 6.83 (dd, 1 H, $J_{2,5}$ = 1.90 Hz, $J_{4,5}$ = 2.49 Hz, H-5), 6.90 (dd, 1 H, $J_{2,4}$ = 1.32 Hz, $J_{2,5}$ = 1.90 Hz, H-2). Anal. Calcd for $C_{16}H_{33}NSi_2$: C, 65.01; H, 11.25; N, 4.74. Found: C, 64.88; H, 11.08; N, 4.76.

1-(Triisopropylsilyl)pyrrole-3-carboxylic Acid (45, E = COOH). After generation of **44**, excess dry CO_2 was bubbled through the solution (~15 min). Purification was by crystallization from ethyl acetate at −20 °C: mp 162 °C; IR (KBr) 3600–2300 (br), 1670 cm^{-1}; ^{1}H NMR δ 1.11 (d, 18 H, J = 7.46 Hz, Me), 1.48 (sept, 3 H, J = 7.46 Hz, CH), 6.73 (dd, 1 H, $J_{2,5}$ = 1.95 Hz, $J_{4,5}$ = 2.66 Hz, H-5), 6.75 (dd, 1 H, $J_{2,4}$ = 1.43 Hz, $J_{4,5}$ = 2.66 Hz, H-4), 7.50 (dd, 1 H, $J_{2,4}$ = 1.43 Hz, $J_{2,5}$ = 1.95 Hz, H-5). Anal. Calcd for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.23. Found: C, 62.79; H, 9.47; N, 5.24.

1-(Triisopropylsilyl)pyrrole-3-carboxaldehyde (45, E = CHO): purification by column chromatography on silica gel [hexane–ethyl acetate (7:3)]; oil; IR (CCl_4) 1685 cm^{-1}; ^{1}H NMR δ 1.12 (d, 18 H, J = 7.5 Hz, Me), 1.49 (sept, 3 H, J = 7.5 Hz, CH), 6.75 (m, 1 H, $J_{2,4}$ = 1.4 Hz, $J_{4,5}$ = 2.9 Hz, $J_{4,CHO}$ = 1.6 Hz, H-4), 6.78 (m, 1 H, $J_{2,5}$ = 2.0 Hz, $J_{4,5}$ = 2.9 Hz, $J_{5,CHO}$ = 1.4 Hz, H-5), 7.41 (dd, 1 H, $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 2.0 Hz, H-2), 9.84 (m, 1 H, CHO).

3-(Hydroxymethyl)-1-(triisopropylsilyl)pyrrole (45, E = CH_2OH). After generation of **44**, excess monomeric formaldehyde was bubbled through the reaction mixture (~15 min), and 0.5 h thereafter the reaction was poured into 2 N sodium carbonate solution. Purification was by column chromatography on silica gel [hexane–ethyl acetate (4:1)]: solid, mp 37 °C; ^{1}H NMR δ 1.09 (d, 18 H, J = 7.43 Hz, Me), 1.42 (sept, 3 H, J = 7.43 Hz, CH), 4.59 (s, 2 H, CH_2), 6.33 (dd, 1 H, $J_{2,4}$ = 1.48 Hz, $J_{4,5}$ = 2.60 Hz, H-4), 6.75 (m, 2 H, H-2,5). Anal. Calcd for $C_{14}H_{27}NOSi$: C, 66.34; H, 10.74; N, 5.52. Found: C, 66.45; H, 10.72; N, 5.50.

3-(1-Hydroxybenzyl)-1-(triisopropylsilyl)pyrrole (45, E = CHOHPh). After the addition of benzaldehyde, the reaction mixture was stirred for 3 h at −78 °C. Purification was by column chromatography on silica gel [hexane–ethyl acetate–triethylamine (2:2:1)]: mp 132 °C; ^{1}H NMR δ 1.07 (d, 18 H, J = 7.5 Hz, Me), 1.39 (sept, 3 H, J = 7.5 Hz, CH), 5.44 (s, 1 H, *CH* Ph), 6.21 (dd, 1 H, $J_{2,4}$ = 1.34 Hz, $J_{4,5}$ = 2.67 Hz, H-4), 6.57 (m, 1 H, H-2), 6.70 (t, 1 H, H-5), 7.19–7.32 (m, 3 H), 7.46 (m, 2 H). Anal. Calcd for $C_{20}H_{31}NOSi$: C, 72.89; H, 9.48; N, 4.25. Found: C, 72.93; H, 9.32; N, 4.07.

3-(Cyclohex-1-enyl)-1-(triisopropylsilyl)pyrrole (45, E = Cyclohex-1-enyl). The crude alcohol was heated at 150 °C for 0.75 h to effect dehydration and the olefinic product was Kugelrohr distilled, 170 °C/0.3 mm, and then further purified by column chromatography on silica gel [hexane–ether (98:2)]: oil; ^{1}H NMR δ 1.09 (d, 18 H, J = 7.48 Hz, Me), 1.43 (sept, 3 H, J = 7.48 Hz, CH), 1.65 (m, 2 H, CH_2), 1.74 (m, 2 H, CH_2), 2.17 (m, 2 H, CH_2C=), 2.25 (m, 2 H, CH_2C=), 6.01 (m, 1 H, CH=C), 6.43 (t, 1 H, H-4), 6.71 (d, 2 H, H-2,5). Anal. Calcd for $C_{19}H_{33}NSi$: C, 75.18; H, 10.96; N, 4.61. Found: C, 74.99; H, 10.84; N, 4.42.

3-Acetyl-1-(triisopropylsilyl)pyrrole (45, E = COMe): purification by column chromatography on silica gel [hexane–ethylacetate (9:1)]; mp 69 °C; IR (CCl_4) 1675 cm^{-1}; ^{1}H NMR δ 1.11 (d, 18 H, J = 7.43 Hz, Me), 1.48 (sept, 3 H, J = 7.43 Hz, CH), 2.43 (s, 3 H, COMe), 6.72 (dd, 1 H, $J_{2,4}$ = 1.44 Hz, $J_{4,5}$ = 2.80 Hz, H-4), 6.73 (t, 1 H, H-5), 7.39 (t, 1 H, H-2). Anal. Calcd for $C_{15}H_{27}NOSi$: C, 67.87; H, 10.25; N, 5.28. Found: C, 68.02; H, 10.24; N, 5.41.

3-*n*-Octadecylpyrrole (46, E = *n*-$C_{18}H_{37}$). The silyl compound **45** (E = *n*-$C_{18}H_{37}$) was desilylated in the usual way to give a solid, which on crystallization from pentane at −20 °C had mp 53 °C: ^{1}H NMR δ 0.88 (t, 3 H, J = 6.8 Hz, Me) 1.26 (m, 28 H, $(CH_2)_{14}$), 1.68 (m, 2 H, CH_2), 2.48 (t, 2 H, J = 7.3 Hz, CH_2C), 6.09 (m, 1 H, H-4), 6.56 (m, 1 H, H-2), 6.71 (dd, 1 H, $J_{4,5}$ = 2.68 Hz, $J_{2,5}$ = 2.02 Hz, H-5). Anal. Calcd for $C_{22}H_{41}N$: C, 82.68; H, 12.93; N, 4.38. Found: C, 82.52; H, 12.96; N, 4.36.

Pyrrole-3-carboxylic acid (46, E = COOH) was obtained as a solid, mp 149 °C (lit.[62] mp 150–150.5 °C), by desilylation of **45** (E = COOH).

3-Acetylpyrrole (46, E = MeCO) was obtained by desilylation in the usual way as a solid, mp 111–112 °C (lit.[63] mp 114–115 °C), after crystallization from carbon tetrachloride.

Generation of 2-Lithio-1-(triisopropylsilyl)pyrrole (47) and Trapping with Electrophilic Reagents. A solution of 1.5 M *n*-butyllithium in hexane (3.3 mL, 4.95 mmol) was added to a stirred solution of 2-bromo-1-(triisopropylsilyl)pyrrole (**3**, 1.51 g, 5.0 mmol) in anhydrous THF (50 mL) cooled to −100 °C. After 0.25 h, the electrophile [MeI (10 mmol), CO_2 (gas, 10 min), PhCHO (7.5 mmol)] was added, and after 0.25 h the cooling bath was removed. When the reaction temperature had reached ambient, triethylamine (1.0 mL) was added, the solvent was removed in vacuo, and then the residue was partitioned between water and ether or ethyl acetate. The extract was washed with saturated sodium chloride solution, dried, and evaporated in vacuo. The residue was then purified as described below.

2-Methyl-1-(triisopropylsilyl)pyrrole (50): purification by centrifugally accelerated TLC on silica gel [hexane to hexane–ether (10:1)]; oil (91% yield); ^{1}H NMR δ 1.12 (d, 18 H, J = 7.5 Hz, $CHMe_2$), 1.52 (sept, 3 H, J = 7.5 Hz, CH), 2.32 (d, 3 H, $J_{Me,3}$ = 0.7 Hz, Me), 6.01 (m, 2 H, H-3), 6.15 (t, 1 H, H-4), 6.73 (dd, 1 H, $J_{3,5}$ = 1.57 Hz, $J_{4,5}$ = 2.89 Hz, H-5). Anal. Calcd for $C_{14}H_{27}NSi$: C, 70.81; H, 11.46; N, 5.90. Found: C, 70.76; H, 11.22; N, 5.88.

Triisopropylsilyl Pyrrole-2-carboxylate (51) and Pyrrole-2-carboxylic Acid (53). Purification of **51** was by centrifugally accelerated TLC [hexane to hexane ethyl acetate (7:3)]: solid (89%), identified by desilylation to pyrrole-2-carboxylic acid (**53**, 86% yield), identical in all respects to a commercial sample.

2-(Triisopropylsilyl)pyrrole (49). When the lithio compound was reacted with 2-iodobutane, a mixture of **49** (oil, 73.5%) and **1** (11%) was obtained, which was separated by centrifugally accelerated TLC on silica gel [hexane to hexane–ethyl acetate (95:5)]: IR (CCl_4) 3492 cm^{-1}; ^{1}H NMR δ 1.09 (d, 18 H, J = 7.3 Hz, Me), 1.27 (sept, 3 H, J = 7.3, CH), 6.32 (m, 1 H, H-4), 6.48

(62) Rapoport, H.; Wilson, C. D. *J. Org. Chem.* **1961**, *26*, 1102.
(63) Loader, C. E.; Anderson, H. J. *Tetrahedron* **1969**, *25*, 3979.

(m, 1 H, H-3), 7.02 (m, 1 H, H-5); HRMS calcd for $C_{13}H_{25}NSi$ 223.1756, found 223.1753. Anal. Calcd for $C_{13}H_{25}NSi$: C, 69.88; H, 11.28; N, 6.27. Found: C, 69.36; H, 11.16; N, 6.13.

2-(1-Hydroxybenzyl)-1-(triisopropylsilyl)pyrrole (52) and 2-Benzylpyrrole (54). Purification of **52** was by column chromatography on silica gel [hexane–ethyl acetate (9:1)]; oil (72% yield); IR (CCl_4) 3595 cm^{-1}; ^1H NMR δ 1.16, 1.17 (doublets, 18 H, J = 7.5 Hz, Me), 1.66 (sept, 3 H, J = 7.5 Hz, $CHMe_2$), 2.74 (bs, 1 H, OH) 5.90 (bs, 1 H, CHO), 5.92 (dd, 1 H, $J_{3,5}$ = 1.42 Hz, $J_{3,4}$ = 3.28 Hz, H-3), 6.17 (t, 1 H, H-4), 6.86 (dd, 1 H, $J_{3,5}$ = 1.42 Hz, $J_{4,5}$ = 2.80 Hz, H-5), 7.26–7.36 (m, 3 H), 7.45 (m, 2 H). This compound was not characterized further. Instead, a solution of **52** (0.206 g, 0.60 mmol) in 2-propanol (15 mL) containing sodium borohydride (0.150 g, 4 mmol) was heated at reflux temperature for 24 h. The solution was poured into water, the product was extracted with ethyl acetate, and the extract was washed with saturated sodium chloride and dried. The solvent was removed in vacuo and the residue was purified by centrifugally accelerated TLC, using hexane–ethyl aceetate (95:5) as the eluting solvent. 2-Benzylpyrrole (**54**) (0.085 g, 90%), identical in all respects with a specimen prepared by reduction of 2-benzoylpyrrole was obtained.[45]

Generation of 2-Lithio-3,4-dibromo-1-(triisopropylsilyl)-pyrrole (55) and Trapping with Electrophilic Reagents. A 1.57 M solution of *n*-butyllithium in hexane (3.2 mL, 5.0 mmol) was added to a stirred solution of the tribromo compound **6** (2.30 g, 5 mmol) in anhydrous THF (30 mL) cooled to −78 °C. After 0.25 h, the electrophilic reagent (excess) was introduced, and after a further 0.25 h the cooling bath was removed. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution or dilute sulfuric acid solution (for **57**) and extracted with ether or dichloromethane (**57**). The extract was dried, evaporated in vacuo, and then worked up as described below.

3,4-Dibromo-1-(triisopropylsilyl)pyrrole (5): purification by crystallization from pentane at −78 °C; mp 77 °C (85% yield), identical with that obtained by dibromination of **1**.

2-Methyl-3,4-dibromo-1-(triisopropylsilyl)pyrrole (56): purification by crystallization from pentane at −20 °C; mp 63 °C (73% yield); ^1H NMR δ 1.12 (d, 18 H, J = 7.48 Hz, $CHMe_2$), 1.49 (sept, 3 H, J = 7.48 Hz, CH), 2.31 (s, 3 H, Me), 6.74 (s, 1 H, H-5). Anal. Calcd for $C_{14}H_{25}Br_2NSi$: C, 42.54; H, 6.38; N, 3.54. Found; C, 42.48; H, 6.64; N, 3.59.

Triisopropylsilyl 3,4-dibromopyrrole-2-carboxylate (57): purification by column chromatography on silica gel [hexane–ethyl acetate (2:1)]; solid, mp 139 °C (89% yield); IR (KBr) 3280, 1660 cm^{-1}; ^1H NMR δ 1.14 (d, 18 H, J = 7.4 Hz, Me), 1.42 (sept, 3 H, J = 7.4 Hz, CH), 6.99 (s, 1 H, H-5). Anal. Calcd for $C_{14}H_{23}Br_2NO_2Si$: C, 39.54; H, 5.45; N, 3.29. Found: C, 39.83; H, 5.45; N, 3.06.

2,4-Dimethyl-3-bromo-1-(triisopropylsilyl)pyrrole (58) and 2,3-Dimethyl-4-bromo-1-(triisopropylsilyl)pyrrole (59). Compound **56** was lithiated in the same manner as described for **6** and reacted with methyl iodide (2 equiv). The crude product was purified by column chromatography on silica gel, using hexane–ether (95:5) as the eluant. The product, a 3:1 mixture (NMR) of **58** and **59**, was obtained as a glass (73% yield). The NMR spectrum showed, besides the absorptions of the isopropyl groups at 1.11 (d, 18 H, J = 7.5 Hz) and 1.49 (sept, J = 7.5 Hz), that the high field methyl absorption of the major isomer was long-range coupled to H-5. For **58**: δ 2.02 (d, J = 0.90 Hz, 4-Me), 2.27 (s, 3-Me), 6.50 (d, J = 0.9 Hz, H-5). For **59**: δ 1.97 (s, Me), 2.22 (s, Me), 6.66 (s, H-5). Anal. Calcd for $C_{15}H_{28}BrNSi$: C, 54.53; H, 8.54; N, 4.24. Found: C, 54.64; H, 8.56; N, 3.97.

1,1′-Bis(triisopropylsilyl)-3,3′-bipyrrolyl (60). A solution of 2 M *tert*-butyllithium in pentane (2 mL, 4 mmol) was added to a stirred solution of **2** (0.302 g, 1 mmol) in anhydrous THF (10 mL) containing suspended cuprous iodide (0.381 g, 2 mmol) at −78 °C. After ca. 10 min the cooling bath was removed and the reaction mixture was left to come to room temperature where stirring was continued for 2 h. The reaction mixture was washed with saturated aqueous cupric sulfate, and the organic phase was diluted with ether, dried, and evaporated in vacuo. Column chromatographic purification of the residue on silica gel, using hexane as the eluate, gave **60** as a solid (0.169 g, 76% yield): mp 132 °C; ^1H NMR δ 1.13 (d, 36 H, J = 7.5 Hz, Me), 1.47 (sept, 6 H, J = 7.5 Hz, CH), 6.45 (dd, 2 H, $J_{2,4}$ = 1.44 Hz, $J_{4,5}$ = 2.70 Hz, H-4,4′), 6.75 (t, 2 H, H-2,2′), 6.88 (t, 2 H, H-5,5′). Anal. Calcd for $C_{26}H_{48}N_2Si_2$: C, 70.20; H, 10.88; N, 6.30. Found: C, 70.15; H, 11.13; N, 6.30.

3-*tert*-Butyl-1-(triisopropylsilyl)pyrrole (61). A 2 M solution of *tert*-butyllithium in pentane (10 mL, 20 mmol) was added to a stirred solution of **2** (0.604 g, 2 mmol) in anhydrous THF (10 mL) containing suspended cuprous iodide (1.90 g, 10 mmol) at −78 °C. The cooling bath was removed, and after the reaction temperature had reached 0 °C, oxygen was bubbled through the mixture for about 10 min. The reaction mixture was poured into dilute ammonium chloride solution and extracted with hexane, and the extract was dried and evaporated in vacuo. The residue was purified by column chromatography on silica gel, using hexane–ether (98:2) as the eluant. Compound **61** was obtained as an oil (0.330 g, 59% yield): ^1H NMR δ 1.09 (d, 18 H, J = 7.37 Hz, Me), 1.24 (s, 9 H, *t*-Bu), 1.41 (sept, 3 H, J = 7.37 Hz, CH), 6.21 (dd, 1 H, $J_{2,4}$ = 1.51 Hz, $J_{4,5}$ = 2.67 Hz, H-4), 6.50 (t, 1 H, H-2), 6.68 (t, 1 H, H-5). Anal. Calcd for $C_{17}H_{35}NSi$: C, 73.04; H, 11.90; N, 5.01. Found: C, 72.99, H, 12.08; N, 5.14.

3-Acetyl-4-(hydroxymethyl)-1-(triisopropylsilyl)pyrrole (62). A 1.6 M solution of *n*-butyllithium in hexane (1.85 mL, 2.96 mmol) was added to a stirred solution of the dibromo compound **5** (1.14 g, 3 mmol) in anhydrous THF (25 mL) at −78 °C. After 0.25 h, *N*-methyl-*N*-methoxyacetamide (0.31 g, 3 mmol) was added, and the reaction mixture was warmed to −30 °C. After 0.5 h, the solution was cooled to −78 °C and a solution of 2 M *tert*-butyllithium in pentane (3 mL, 6 mmol) was added. The solution was stirred for 0.5 h at −78 °C and then an excess of formaldehyde gas (obtained by thermal depolymerization of paraformaldehyde) was bubbled into the solution. After 10 min the reaction mixture was poured into dilute sodium carbonate solution and the product was extracted into ether. The extract was dried and evaporated in vacuo. The residue was purified by column chromatography on silica gel, using hexane–ethyl acetate (1:1) to elute compound **62** (0.51 g, 58%) as a solid: mp 91 °C; IR (CCl_4) 3465 (br), 1652 cm^{-1}; ^1H NMR δ 1.11 (d, 18 H, J = 7.50 Hz, $CHMe_2$), 1.47 (sept, 3 H, J = 7.50 Hz, CH), 2.47 (s, 3 H, MeCO), 4.80 (s, 2 H, CH_2), 6.65 (d, 1 H, $J_{2,5}$ = 2.06 Hz, H-5), 7.30 (d, 1 H, $J_{2,5}$ = 2.06 Hz, H-2). Anal. Calcd for $C_{16}H_{29}NSiO_2$: C, 65.03; H, 9.89; N, 4.74. Found: C, 64.86; H, 9.91; N, 4.71.

3-Acetyl-4-(hydroxymethyl)pyrrole (Verrucarin E, 63). Compound **62** was deprotected in the usual way and the crude product was purified by column chromatography on silica gel to give a solid (76% yield): mp 90 °C (lit.[50] mp 91 °C); NMR δ 2.47 (s, 3 H, Me), 4.58 (s, 2 H, CH_2), 6.72 (d, 1 H, $J_{2,5}$ = 1.75 Hz, H-5), 7.40 (d, 1 H, $J_{2,5}$ = 1.75 Hz, H-2).

Competitive Trifluoroacetylation of *N*-(Triisopropylsilyl)pyrrole (1) and 2-Methylfuran (35). A solution that was ca. 0.3 M in trifluoroacetic anhydride and 0.4 M in pyridine was prepared from the anhydride (1.19 g, 5.68 mmol) and pyridine (0.579 g, 8.63 mmol) in dichloromethane (20 mL). To an aliquot (2 mL) of this solution was added a solution of **1** (0.0500 g, 0.224 mmol) and **35** (0.0246 g, 0.300 mmol). The solution was kept at 22 °C for 2.5 h, poured into dilute sodium bicarbonate solution, and extracted twice with dichloromethane. 4-*tert*-Butylcyclohexanone (0.0307 g, 0.199 mmol) was added as an internal standard and the product mixture was analyzed by VPC with a 1-m SE-30 column and found to contain 0.183, 0.00796, and 0.162 mmol of the trifluoroacetyl compounds **31**, **34**, and **36**, respectively. In other experiments, a similar procedure was followed except that aliquots of the reaction solution were withdrawn and analyzed at time intervals ranging from 0.33 to 20 h. The product yields were used to calculate k_{rel} values by the Shaw–Ingold expression.[33]

Registry No. **1**, 87630-35-1; **2**, 87630-36-2; **3**, 130408-79-6; **4**, 87630-40-8; **5**, 93362-54-0; **6**, 93362-20-0; **7**, 93362-53-9; **8**, 130408-80-9; **9**, 130408-81-0; **10**, 130408-82-1; **11**, 130408-83-2; **12**, 130408-84-3; **13**, 117270-91-4; **14**, 130408-85-4; **15**, 56821-81-9; **16**, 87630-39-5; **17**, 5919-26-6; **18**, 5930-94-9; **19**, 87630-37-3; **21**, 87630-41-9; **22**, 130408-86-5; **23**, 90971-77-0; **24**, 130408-87-6; **25**, 7126-41-2; **26**, 96999-24-5; **29**, 117067-97-7; **30**, 7126-39-8; **31**, 130408-88-7; **32**, 2557-70-2; **33**, 130408-89-8; **34**, 130408-90-1; **37**, 130408-91-2; **38**, 130408-92-3; **39**, 130408-93-4; **40**, 53391-61-0; **41**, 87630-38-4; **42**, 75421-80-6; **43**, 75421-89-5; **45** (E = Me), 90971-71-4; **45** (E = *n*-Bu), 117270-80-1; **45** (E = n-$C_{18}H_{37}$), 93362-47-1; **45** (E = $CH_2CH(CH_3)CH_2CH_3$), 130409-04-0; **45** (E = TMS),

93362-48-2; **45** (E = CO_2H), 93362-49-3; **45** (E = CHO), 90971-76-9; **45** (E = CH_2OH), 93362-50-6; **45** (E = CH(OH)Ph), 90971-75-8; **45** (E = cyclohexene), 93362-51-7; **45** (E = Ac), 93362-52-8; **46** (E = $C_{18}H_{27}$), 93362-22-2; **46** (E = CO_2H), 931-03-3; **46** (E = CHO), 7126-39-8; **46** (E = Ac), 1072-82-8; **49**, 130408-94-5; **50**, 130408-95-6; **51**, 130408-96-7; **52**, 130408-97-8; **53**, 634-97-9; **54**, 33234-48-9; **56**, 130408-98-9; **57**, 130408-99-0; **58**, 130409-00-6; **59**, 130409-01-7; **60**, 130409-02-8; **61**, 130409-03-9; **62**, 93362-25-5; **63**, 24445-13-4; $(i\text{-}Pr)_3SiCl$, 13154-24-0; n-$C_{18}H_{37}I$, 629-93-6; $H_3CCH_2CH(CH_3)CH_2Br$, 10422-35-2; AcN(OMe)Me, 78191-00-1; pyrrole, 109-97-7; ethyl oxalyl chloride, 4755-77-5; phenylacetyl chloride, 103-80-0; 4-toluenesulfinyl chloride, 10439-23-3; cyclohexanone, 108-94-1.

Selective Reductions. 46. Effect of the Steric Requirement at the 2-Position of Apopinene on Chiral Reductions. *B*-(Iso-2-ethylapopinocampheyl)- and *B*-(Iso-2-*n*-propylapopinocampheyl)-9-borabicyclo[3.3.1]nonanes as Improved Reagents for the Chiral Reduction of α,β-Acetylenic Ketones and α-Keto Esters

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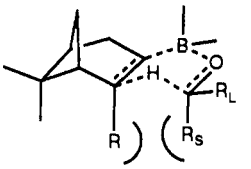
B-(Iso-2-ethylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (Eapine-Borane, **7**), and *B*-(Iso-2-*n*-propylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (Prapine-Borane, **9**), prepared via the hydroboration of 2-ethylapopinene (**6**) or 2-*n*-propylapopinene (**8**), respectively, with 9-borabicyclo[3.3.1]nonane, reduce prochiral α,β-acetylenic ketones and α-keto esters to the corresponding alcohols with significantly higher optical induction than does Alpine-Borane (**1**). (-)-2-*n*-Propylapopinene was synthesized by treating nopyl tosylate with dimethyl cuprate prepared in situ from methyllithium and cuprous iodide. (+)-2-*n*-Propylapopinene was synthesized by Schlosser metalation of (+)-α-pinene followed by treatment with ethyl iodide. 4-Phenyl-3-butyn-2-one was reduced to the corresponding propargylic alcohol in 89% ee and 96% ee by Eapine-Borane and Prapine-Borane, respectively, as compared to 82% ee with Alpine-Borane. Similar improved results were realized in the reduction of other acetylenic ketones by Eapine-Borane and Prapine-Borane. Similar improvements in the optical yields were realized in the reduction of α-keto esters by Eapine-Borane. For example, while Alpine-Borane produced methyl and ethyl lactate in 92% and 91% ee, respectively, Eapine-Borane gave these alcohols in 97% and 96% ee, respectively. Unfortunately, Prapine-Borane shows no improvement in percent ee for the reduction of α-keto esters. The increase in the percent ee realized is tentatively attributed to the increased steric requirements of the alkyl group at the 2-position of apopinene.

Introduction

A branch of asymmetric synthesis that has been actively pursued during the last decade is the asymmetric reduction of prochiral ketones.[2] Various reagents have been developed in the past which provide the product alcohols in good to excellent enantiomeric excess (ee). A compilation of the available literature data showed the absence of a single reagent which is equally effective for all classes of ketones.[3] Moreover, no strategic modifications based on observed results have been made. Consequently, we set out to design chiral organoborane reagents based on the knowledge of the behavior of available reducing agents.

Midland's *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane, **1**), introduced a decade ago, proved very efficient for the chiral reduction of α-deuterio aldehydes,[4] α,β-acetylenic ketones,[5] α-keto esters,[6] and

Scheme I



α-halo ketones,[7] all of which undergo relatively rapid reduction. However, the reagent proved ineffective for the chiral reduction of slower reacting ketones, such as aralkyl and dialkyl ketones. This variation in the chiral inductions of slow versus fast reacting ketones was attributed to the dissociation of the reagent into its components, α-pinene and 9-BBN with the less reactive ketones resulting in achiral reduction.[8] The dehydroboration is suppressed

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