1 molar equiv of imidoyl chloride **1d** and 10 mol % of chlorosulfuric acid. After 24 h at room temperature, GLC showed no evidence of ketimine **3d**. In the second experiment, equimolar quantities of imidoyl chloride **1b** and pyrrole **2a** were treated with a catalytic amount of chlorosulfuric acid. The reaction was allowed to proceed to 85% conversion and then treated with imidoyl chloride **1d**. The reaction was allowed to proceed until only traces of pyrrole were observed by GLC. At this point, the ratio of ketimine **3b** to **3d** was found to be 86:14.

All the perchlorate salts prepared in this study gave ^{1}H NMR spectra that were consistent with the ketiminium salt being a mixture of *E* and *Z* isomers. The isomer ratio varied from ~3:1 in the case of **3e** to ~28:1 for **3b**. The structure of the major isomer for each of the compounds has not been definitely established.[8]

Discussion

Ketimines have been prepared through the condensation of ketones with amines in the presence of titanium tetrachloride,[9] through the condensation of nitriles with organometallic reagents,[10] and several other miscellaneous methods.[11] The current reaction makes ketimines derived from pyrroles available under essentially neutral conditions which are compatible with a variety of functional groups.

Experimental conditions are undemanding. Unlike the Vilsmeier–Haack reaction, this condensation need not be run under strictly anhydrous conditions[7b] in order to obtain good yields of clean products. If the imidoyl halide is used in excess, water is removed through the formation of amide. The resulting amide byproduct does not interfere with the condensation reaction.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded on Perkin-Elmer 727B or 283 spectrophotometers. Unless noted otherwise, ^{1}H NMR spectra were obtained on JEOL JNM-FX60Q (60 MHz) or Perkin-Elmer R32 (90 MHz) instruments with $CDCl_3$ as solvent and Me_4Si as internal reference (20 mg of compound in 0.3 mL of solvent). GLC analyses were performed on a Perkin-Elmer Sigma 2B instrument equipped with flame-ionization detectors. All GLC analyses were performed with 6-ft, 3% SE-30 on 100–200-mesh Chromosorb W glass columns, temperature programmed 2 min 125–260 °C, 10 °C/min, with dodecane as internal standard.

Experiments in $CHCl_3$ were run with either MCB OmniSolv grade chloroform or chloroform with the alcohol stabilizer removed by elution through an activity I alumina column. Chloroform with no stabilizer was stored in amber bottles under argon in a refrigerator at 0 °C prior to use.

Preparation of Benzimidoyl Chlorides 1a–e. The procedure is a modification of that reported by Bartholomew and Kay.[12] The *N*-methylbenzamide (84.5 mmol) and thionyl chloride (33 g, 278 mmol) were placed in a 50-mL, round-bottom flask equipped with a magnetic stirrer, heating mantle, and condensor attached to a trap containing aqueous base. The reaction was stirred and heated at reflux until gas evolution ceased (1–3 h depending upon the amide). The excess thionyl chloride was distilled at ~15 mmHg. The benzimidoyl chlorides were purified by distillation as shown in Table I. In the case of *N*-methyl-4-nitrobenzimidoyl chloride, purification was effected through recrystallization from petroleum ether.

Preparation of Ketimines 3a–f. The appropriate *N*-methylbenzimidoyl chloride (35 mmol) was placed in a dry, 50-mL, round-bottom flask and treated with chloroform (13 mL) and chlorosulfuric acid (0.42 g, 3.6 mmol). The appropriate pyrrole (35 mmol) was added dropwise with stirring over a period of about 5 min, and the reaction was stirred overnight. The orange reaction mixture was quenched into saturated aqueous sodium bicarbonate, the phases were separated, and the organic phase was washed with saturated sodium bicarbonate and water then dried over sodium sulfate, and filtered. The chloroform was removed under reduced pressure. The residue was dissolved in absolute ethanol (~20 mL), cooled, and treated with 70% perchloric acid (5.5 g, 38 mmol). The resulting solution was cooled, stirred, and treated with diethyl ether to induce crystallization. The solid was isolated by filtration, washed with cold ethanol, and air-dried.[13] The IR spectra typically show absorption bands between 1730 and 1745 cm^{-1} and between 1598 and 1608 cm^{-1}. Melting points are given in Table I.

Registry No. **1a**, 78554-86-6; **1b**, 55174-52-2; **1c**, 21737-87-1; **1d**, 39887-78-0; **1e**, 64594-45-2; **2a**, 84145-71-1; **2b**, 51856-79-2; **3a**, 87937-72-2; **3a**·$HClO_4$, 87937-73-3; **3b**, 87937-74-4; **3b**·$HClO_4$, 87937-75-5; **3c**, 87937-76-6; **3c**·$HClO_4$, 87937-77-7; **3d**, 87937-78-8; **3d**·$HClO_4$, 87937-79-9; **3e**, 87937-80-2; **3e**·$HClO_4$, 87937-81-3; **3f**, 87937-82-4; **3f**·$HClO_4$, 87937-83-5; 4-methoxy-*N*-methylbenzamide, 3400-22-4; *N*,4-dimethylbenzamide, 18370-11-1; *N*-methylbenzamide, 613-93-4; 4-chloro-*N*-methylbenzamide, 6873-44-5; *N*-methyl-4-nitrobenzamide, 2585-23-1; thionyl chloride, 7719-09-7.

Supplementary Material Available: Table II, giving IR, UV, and ^{1}H NMR data for ketimine salts **3a–f**, and Table III, giving IR and ^{1}H NMR data for benzimidoyl chlorides **1a–e** (2 pages). Ordering information is given on any current masthead page.

(8) *E*/*Z* isomeric mixtures have been well-documented for a number of ketimines and aldimines as the free bases (see W. B. Jennings, V. E. Wilson, D. R. Boyd, and P. B. Coulter, *Org. Magn. Reson.*, **21**, 279 (1983) and references therein). Work is continuing to establish the structure of the major isomer and to determine substituent effects in this system.

(9) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967).

(10) (a) F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.*, **9**, 725 (1972); (b) P. L. Pickard and D. J. Vaughan, *J. Am. Chem. Soc.*, **72**, 876 (1950).

(11) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(12) D. Bartholomew and I. T. Kay, *Tetrahedron Lett.*, **30**, 2827 (1979).

(13) No shock sensitivity was observed with any of these compounds; however, due care should be exercised in their preparation and handling.

Absolute Configuration of (–)-Vincatine, the Unique 2,16-Seco *Aspidosperma* Alkaloid

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In our continuing study of the chemistry in indole alkaloids,[1] our attention was drawn by (–)-vincatine (VCT, **1**,[2] Chart I) which represents a unique type of alkaloid formally derived from a ring-C-cleaved *Aspidosperma* skeleton. Prompted by the natural occurrence of VCT and of both antipodal vincadifformines (VDF, **2a,b**) in *Vinca minor* L., we set out to correlate **2a,b** → **1** in order to clear up the stereochemistry, relative and absolute, of VCT. While our work was in progress, Ali and Pakrashi[3a] described the results of a similar study. Our findings led to the assignment of the 7*R*,20*S*,21*R* configuration for (–)-

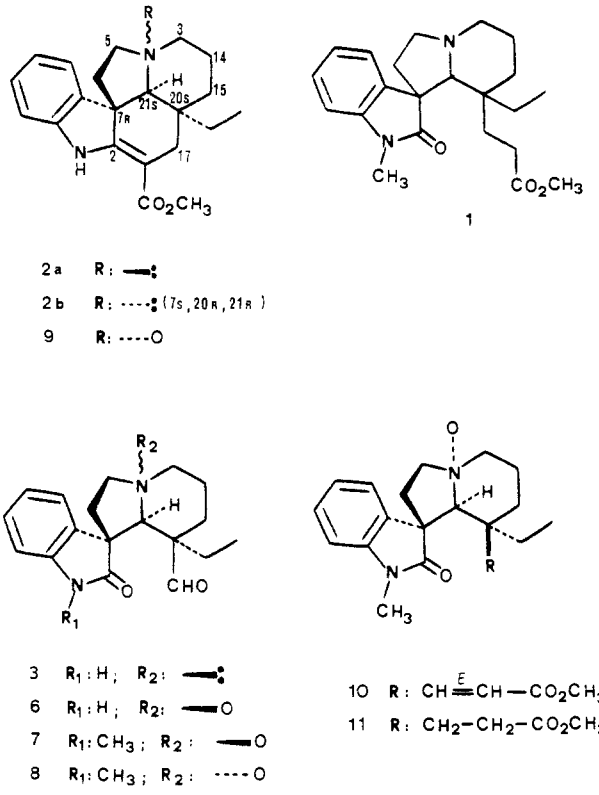
(1) Part of this paper was presented as a communication at the 12th IUPAC International Symposium on the Chemistry of Natural Products at Tenerife, Spain, Sept 21–27 1980.

(2) (a) Döpke, W.; Meisel, H.; Fehlhaber, H. W. *Tetrahedron Lett.* **1969**, 1701. For synthetic studies on VCT, see: Castedo, L.; Harley-Mason, J.; Caplan, M. *Chem. Commun.* **1969**, 1444. Hugel, G.; Laronze, J. Y.; Laronze, J.; Lévy, J. *Heterocycles* **1981**, *16*, 581.

(3) (a) Ali, E.; Roy, S.; Chakraborty, P. K.; Pakrashi, S. C. *Tetrahedron Lett.* **1983**, *24*, 2497. (b) Ali, E.; Chakraborty, P. K.; Chakravarty, A. K.; Pakrashi, S. C. *Heterocycles* **1982**, *9*, 1667.

0022-3263/84/1949-0547$01.50/0

Chart I



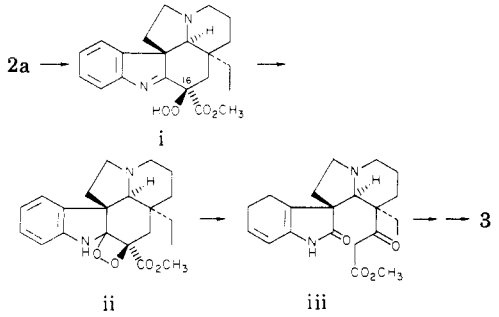
vincatine, rather than the enantiomeric configuration (7*S*,20*R*,21*S*) assigned by Indian workers.

Our approach to VCT was based on the discovery that *t*-BuOK-catalyzed autoxidation of the most abundant (−)-VDF **2a** in *tert*-butyl alcohol at room temperature (15 min) gave the tetracyclic aldehyde **3** in 84% isolated yield.[4] This oxindole proved to be stereochemically labile. In fact, on being allowed to stand in $CHCl_3$ (2 h, room temperature) a mixture of at least three closely eluted diastereomers (HPLC) was detected. Difficulties were encountered during attempts to separate this mixture due to the ease with which they interconverted, presumably through the intermediacy of nonstereodiscerning iminium intermediates **4** and **5** (retro-Mannich–Mannich sequence below).

In light of the above considerations, it became clear that maintainance of all chiral centers in the known configuration would necessitate prior protection at N-4. Thus, oxidation of **3** with *m*-chloroperbenzoic acid in CH_2Cl_2 at 0 °C (20 min) gave rise efficiently and exclusively to *N*-oxide **6**. The ^1H NMR spectrum (Me_2SO-d_6) of **6** showed a typical value (δ 7.28) for H-9 (vs. δ 7.34 in **3**) in contrast to the general observation that this proton is diamagnetically deshielded by a through-space interaction with the α-oriented *N*-oxide function in other oxindole *N*-oxides.[5] This observation dictates that in **6** the N–O bond and the oxindole carbonyl occur on the same side of the molecule (4*R* absolute configuration) and we denote **6** as *syn*-oxide. This was then converted into NMe derivative **7**[6] by treatment with dimethyl sulfate in *t*-BuOK–*t*-BuOH. Attemped olefination of **7** by reaction with methyl (triphenylphosphoranylidene)acetate as well as with trimethyl phosphonoacetate–NaH was unsuccessful. The reluctance of **7** to undergo olefination, even at high temperatures, likely stemmed from the 1,6 n,π nonbonding interaction[7] between the *N*-oxide and carbonyl. In an effort to minimize this apparent steric congestion, we next attempted the synthesis of *anti*-oxide **8**, which takes advantage of the stereochemical outcome of N-oxidation of (−)-VDF **2a** to give **9**.[8] Indeed, exposure of **9** to triplet oxygen in *t*-BuOH in the presence of *t*-BuOK followed by quenching of the reaction mixture with dimethyl sulfate afforded **8**, which was clearly distinguishable spectrally and chromatographically from **7** (see Experimental Section). The *anti*-oxide **8**, gratifyingly, reacted with trimethyl phosphonoacetate–NaH in refluxing DME to give acrylic ester **10** with complete *E* stereoselectivity.

When we considered the task of converting **10** into VCT, our stereoconservative approach from (−)-VDF **2a** demanded chemical discrimination between the acrylic moiety and *N*-oxide function, namely, saturation of the double bond must *precede* removal of the *N*-oxide function. Attempts at chemoselective reduction of **10** to **11** were uniformly unsuccessful; however, use of a diimide (methanol–dipotassium azodicarboxylate–acetic acid)[9,10] circumvented this problem, affording the pure *N*-oxide **11**, albeit in modest yield. Exposure of **11** to W-2 Raney nickel in DME at room temperature resulted in almost instantaneous reduction to a single compound (TLC). We were surprised to find that the ^1H NMR spectrum (300 MHz, $CDCl_3$) exhibited, inter alia, four pairs of sharp methoxy signals and H-18 triplets at δ 3.62–0.49, 3.54–0.72, 3.47–0.68, and 3.60–0.46 corresponding to the four diastereomeric oxindoles **12–15** in a 35:10:4:1 ratio, respectively, as previously reported by Pakrashi.[3b] Although the theoretical justification of the well-known scrambling of stereochemistry in oxindoles[11] is still open to question,

(4) A possible rationale for the formation of **3** is depicted below. Fragmentation of the dioxetane ii, obtained by the cyclization of the initial formed 16-hydroperoxide i, would yield the α-keto ester iii, the precursor of the observed product (via an α-hydroperoxy ketone).



(5) Phillipson, J. D.; Rungsiyakul, D.; Shellard, E. J. *Phytochemistry* **1973**, *12*, 2043.

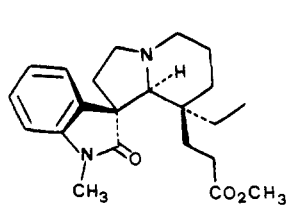
(6) No change in the TLC and ^1H NMR spectrum was seen when **6** and **7** were refluxed in chloroform for 12 h.

(7) For calssification of nonbonding interaction, see: Martin, H. D.; Meyer, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 283.

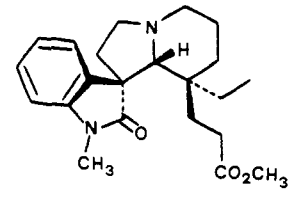
(8) For preparation of (−)-VDF *N*(4)-oxide see: Hugel, G.; Lêvy, J.; Le Men, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *274*, 1350. For the stereochemistry at N(4) see: Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1371.

(9) Hamersma, J. W.; Snyder, E. I. *J. Org. Chem.* **1965**, *30*, 3985.

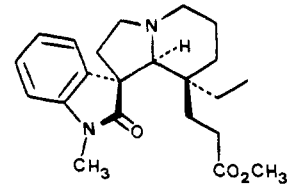
(10) Moriwaki, M.; Yamamoto, Y.; Oda, J.; Inouye, Y. *J. Org. Chem.* **1976**, *41*, 300.



13



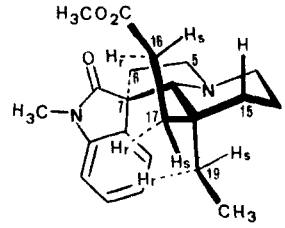
14



15

interestingly, isomerization at C-7 and/or C-21 for **12–15** was observed under the conditions which normally did not effect such changes in the oxindole alkaloids.[12] Fortunately, careful fractional recrystallization[13] of the above mixture from EtOH afforded the diastereomerically pure **12** [checked by 300-MHz ^{1}H NMR (see Table I) and 50.4-MHz ^{13}C NMR spectra] as a nicely crystalline compound, mp 109 °C. Apart from absolute stereochemistry, the above data revealed our compound to be identical with the one synthesized by Pakrashi et al.,[3b] and it was identified as vincatine. The knowledge of the 20*S* configuration of the starting (−)-VDF **2a** combined with the complete conservation of this chirality throughout our synthesis, with the observance of long-range coupling across four σ bonds (J = 1.0 Hz) between *pro-R* H-19 and H-15β and with CD data in comparison with those of known oxindoles,[14] support a 7*R*,20*S*,21*R* configuration for **12**, i.e., enantiomeric to that prepared by Pakrashi. In fact, the two compounds exhibit CD curves which are mirror images of each other (see Experimental Section). In our opinion, compound **12** must be regarded as the most likely candidate to represent the absolute stereochemistry of vincatine isolated from *Vinca minor* L. The apparent discrepancy between the optical rotation observed for **12** [$[\alpha]^{20}_D$ −2.4° (*c* 0.8, $CHCl_3$)] vs. that reported for natural material (lit.[2] −13°) can be rationalized in terms of the innate propensity of **12** to undergo facile isomerization in solution. For example, on being allowed to stand in chloroform at 35 °C, the synthetic **12** led to a stationary mixture (after 6 h, $[\alpha]^{20}_D$ −12.4°) composed of the diastereomers **13–15** and starting material in a ratio of 21:7:1:71 (^{1}H NMR). Hence, the $[\alpha]_D$ observed by Döpke[2] for natural VCT could be attributed to isomerization during extraction and purification procedure from the natural source. Although a direct comparison was impossible since Döpke's samples are lost, on the basis of our evidence, natural VCT has the 7*R*,20*S*,21*R* configuration, and it appears reasonable to assume its biogenetic derivation from (−)-vincadifformine.[15] Finally, the opposite conclusion about the absolute configuration of VCT as 7*S*,20*R*,21*S*, reached by an Indian group[3a] and based on the disconcerting levorotatory(!) $[\alpha]_D$ value −11.7° (*c* 0.8, $CHCl_3$), seems to be inconsistent and must be regarded with suspicion.

Table I. ^{1}H NMR Chemical Shifts at 300 MHz for 12[a]



12

proton	shift	J,[b] Hz
5α	3.38	$J_{5,5} = J_{5,6} = 9.0$,
5β	2.48	$J_{5,6} = 4.8$, $J_{5,6} = 6.8$,
6α	1.83	$J_{5,6} = 10.0$, $J_{6,6} = 12.8$
6β	2.26	
16*R*	2.42	$J_{16R,16S} = 15.6$, $J_{16R,17R} = 4.2$,
16*S*	2.09	$J_{16R,17S} = 12.5$,
17*R*	0.98	$J_{16S,17R} = 12.0$, $J_{16S,17S} = 5.5$,
17*S*	1.41	$J_{17R,17S} = 14.5$
19*R*	0.24	$J_{19R,18} = 7.2$, $J_{19R,19S} = 15.0$,
19*S*	1.85	$J_{19S,18} = 7.2$,
18	0.49	$J_{19R,15\beta} = 1.0$ Hz (W path)

[a] In $CDCl_3$; chemical shifts (δ values) are in parts per million from Me_4Si, data of other protons are given in the Experimental Section; computer-simulated spectra (PANIC software) generated from the parameters in the table were superimposable on the pertinent regions of the experimental spectra. [b] Coupling constants confirmed by double resonance.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer, ultraviolet spectra on a Perkin-Elmer 554 UV–vis spectrophotometer, and ^{1}H NMR spectra on Bruker WP-80 (80 MHz), Varian XL-200 (200 MHz), and Bruker CXP-300 (300 MHz) instruments. ^{13}C NMR spectra were obtained on a Varian XL-100 (25.2 MHz). Chemical shifts are expressed in part per milion downfield from internal Me_4Si, and coupling constants (J values) are given in hertz. Optical rotations were obtained with a Perkin-Elmer 141 polarimeter. Circular dichroism spectra were recorded on a Jobin-Yvon Dichrograph III. Mass spectra (EI) were recorded on Varian 112 and CH-7 spectrometers (temperature of registration is given). HPLC was performed on a Perkin-Elmer HPLC system (2/2 dual pump module, LC-85 spectrophotometric UV detector, and a Merck LiChrosorb RP-18 column) with methanol/water as the mobile phase. TLC was performed on 0.25-mm-thick layers of silica gel GF_{254} (Merck) on glass plates. Solvent systems were (A) benzene–ethanol–ammonia (d = 0.88) (89:10:1) and (B) chloroform–methanol–ammonia (*d* = 0.88) (40:10:1). Compounds were detected on developed chromatograms by fluorescence quenching at λ 254 or 365 nm and later visualized with Dragendorff's reagent. The R_f (solvent system A or B) and color (spray on TLC) of the products are given. Potassium *tert*-butoxide was purchased from Aldrich Chemical Co. and was used as received; 98% MCPBA was obtained from commercially available material washed with phosphate buffer (pH 7.5), filtered, and dried under reduced pressure at room temperature.

Autoxidation of (−)-Vincadifformine (2a): Tetracyclic Aldehyde 3. A solution of potassium *tert*-butoxide (2.0 g, 17.8 mmol) in *tert*-butyl alcohol (15 mL) was added dropwise to a stirred solution of (−)-vincadifformine **2a** (2.0 g, 5.9 mmol) in *tert*-butyl alcohol (50 mL) at room temperature with oxygen gas bubbled through the solution (10 L/h) during 15 min. After the addition was completed, H_3PO_4 (10%) was added until pH 7 and the mixture extracted with ethyl acetate. Solvent removal gave a residue which was recrystallized from *tert*-butyl alcohol to yield 1.49 g (84%) of **3**: mp 142 °C; R_f 0.35 (A, orange); UV (MeOH) λ_{max} 227, 254, 285 (log ε 4.15, 3.94, 3.32); IR ($CHCl_3$) 3440, 2490,

(11) See, for example: Wenkert, E.; Bindra, J. S.; Chang, C.-J.; Cochran, D. W.; Rearick, D. E. *J. Org. Chem.* **1974**, *39*, 1662.

(12) For a pertinent review on the isolation and chemistry of oxindole alkaloids, see: Bindra, J. S. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, London, 1973; Vol. XIV, p 84.

(13) Several attempts to separate the respective diastereomers by standard column chromatography over silica gel or by HPLC were unsuccessful.

(14) Beecham, A. F.; Hart, N. K.; Johns, I. R.; Lamberton, J. A. *Aust. J. Chem.* **1968**, *21*, 491 and references quoted therein.

(15) ur-Rahman, A.; Basha, A. In "Biosynthesis of Indole Alkaloids"; Clarendon Press: Oxford, 1983; p 116.

1720, 1710, 1620 cm^{-1}; mass spectrum (70 eV, 150 °C), m/z (relative intensity) 298 (M^+·, 13.3), 270 (3.9), 269 (3.3),160 (3.2), 159 (9.4), 124 (100); ^1H NMR (200 MHz, $CDCl_3$) 10.60 (1 H, br s, CHO), 9.70 (1 H, br s, N(1)H), 7.27 (1 H, dd, J = 7.0, 1.0 Hz, H-9), 7.20–7.10 (2 H, 2 dt, J = 7.0, 1.0 Hz, H-10, H-11), 7.02 (1 H, dd, J = 7.0, 1.0 Hz, H-12), 2.66 (1 H, s, H-21), 0.40 (3 H, t, J = 7.0 Hz, H-18); ^{13}C NMR ($CDCl_3$) 182.4 (C-2), 54.6 (C-3), 55.3 (C-5), 37.9 (C-6), 55.3 (C-7), 135.8 (C-8), 122.6 (C-9, C-10), 128.1 (C-11), 110.7 (C-12), 140.2 (C-13), 22.1 (C-14), 24.5 (C-15), 208.0 (C-17), 7.3 (C-18), 33.8 (C-19), 50.7 (C-20), 79.1 (C-21); CD (EtOH) $\Delta\epsilon$ +1.40 (310 nm), +1.50 (290), 0 (272), −5.45 (258), 0 (245), +4.60 (235), 0 (228), −26.1 (210). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.53; H, 7.39; N, 9.49.

Oxidation of Tetracyclic Aldehyde 3 with MCPBA: *N*(4)-Oxide (Syn) Derivative 6. MCPBA (591 mg, 3.35 mmol) was added over a 20-min period to a stirred solution of **3** (1.0 g, 3.35 mmol) in dry dichloromethane (75 mL) under a nitrogen atmosphere at 0 °C. The mixture was stirred continuously for 15 min at room temperature, after which the solvent was removed under reduced pressure (<30 °C). The residue was charged onto a column of activated Dowex 1-X8 (3.0 g, 100/200 mesh, washed with methanol) to obtain, after removal of the solvent, the pure *N*(4)-oxide (syn) **6**: 893 mg (85%); amorphous solid; R_f 0.22 (B, orange); UV (MeOH) λ_{max} 224, 258, 290 (log ϵ 4.27, 4.00, 3.31); IR ($CHCl_3$) 3440, 1720, 1715, 1620 cm^{-1}; mass spectrum (70 eV, 200 °C), m/z (relative intensity) 314 (M^+·,3), 298 (8), 270 (12), 253 (60), 211 (14), 124 (100); ^1H NMR (80 MHz,Me_2SO-d_6) 8.17 (1 H, s, CHO), 7.28 (1 H, br d, J = 7.0 Hz, H-9), 7.20–6.87 (3 H, m, aromatic), 4.30 (1 H, s, H-21), 0.48 (3 H, t, J = 7.3 Hz, H-18); CD (EtOH) $\Delta\epsilon$ -1.2 (320 nm), 0 (307), +2.36 (284), 0 (270), −1.12 (263), 0 (256), +4.5 (238), 0 (230), −16.9 (214).

Methylation of Aldehyde *N*(4)-Oxide (Syn) 6 to Derivative 7. A mixture of 1.05 g (3.35 mmol) of **6** and 752 mg (6.7 mmol) of potassium *tert*-butoxide in 30 mL of dry *tert*-butyl alcohol was treated at room temperature with dimethyl sulfate (348 μL, 3.68 mmol). The resulting mixture was stirred under a nitrogen atmosphere for 12 h and then diluted with ethyl acetate (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). After separation of the organic layer was washed with water, dried (Na_2SO_4), and evaporated in vacuo. Recrystallization of the residue from ethyl acetate–ethanol (4:1) gave the pure *N*(1)-methyl derivative **7**: 912 mg (83%); mp 139 °C dec; R_f 0.29 (B, orange); UV (MeOH) λ_{max} 222, 258, 285 (log ϵ 4.45, 4.03, 3.38); IR ($CHCl_3$) 2790, 1710, 1612 cm^{-1}; mass spectrum (70 eV, 200 °C) m/z (relative intensity) 328 (M^+·,1.5), 284 (16), 267 (100), 124 (53); ^1H NMR (80 MHz, $CDCl_3$) 10.22 (1 H, s, CHO), 7.37 (1 H, br d, J = 7.0 Hz, H-9), 7.25 (2 H, m, H-10, H-11), 6.80 (1 H, br d, J = 7.0 Hz, H-12), 3.80 (1 H, s, H-21), 3.25 (3 H, s, NCH_3), 0.42 (3 H, t, J = 7.0 Hz, H-18); ^{13}C NMR ($CDCl_3$) 176.8 (C-2), 65.5 (C-3), 66.7 (C-5), 37.1 (C-6), 54.0 (C-7), 134.6 (C-8), 123.7* (C-9), 121.8* (C-10), 129.2 (C-11), 108.7 (C-12), 141.7 (C-13), 18.3 (C-14), 22.9 (C-15), 197.7 (C-17), 7.0 (C-18), 29.0 (C-19), 52.8 (C-20), 90.6 (C-21), 27.0 (NCH_3) (an asterick indicates assignments may be interchanged); CD (EtOH) $\Delta\epsilon$ +0.13 (298 nm), 0 (282), −2.9 (260), 0 (248), +6.4 (231), 0 (220), −10.2 (210). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 68.75; H, 7.42; N, 8.55.

Autoxidation and N(1)-Methylation of Vincadifformine *N*(4)-Oxide (9) to Tetracyclic Aldehyde *N*(1)-Methyl *N*(4)-Oxide (Anti) 8. By use of a procedure similar to that described above for preparing the aldehyde **3**, 1.416 g (4.0 mmol) of vincadifformine *N*(4)-oxide (**9**) was reacted with 1.795 g (16.0 mmol) of potassium *tert*-butoxide in 34 mL of *tert*-butyl alcohol. When the addition was complete (20 min), dimethyl sulfate (416 μL, 4.4 mmol) was added to the reaction mixture over a 10-min period. The resulting solution was stirred at room temperature for 10 h and then diluted with chloroform (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). After separation the organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a residue which was crystallized from ethanol to yield **8**: 892 mg (68%); mp 120 °C; R_f 0.50 (B, orange); UV (MeOH) λ_{max} 224, 260, 290 (log ϵ 4.37, 4.07, 3.32); IR ($CHCl_3$) 2740, 1720, 1710, 1612 cm^{-1}; mass spectrum (70 eV, 200 °C), m/z (relative intensity) 328 (M^+·, 2.5), 282 (14), 268 (18), 266 (80), 124 (100); ^1H NMR (80 MHz, $CDCl_3$) 8.50 (1 H, s, CHO), 7.85 (1 H, dd, J = 7.0, 1.0 Hz, H-9), 7.40 (1 H, dt, J = 7.0, 1.0 Hz, H-11), 7.20 (1 H, dt, J = 7.0, 1.0 Hz, H-10), 6.76 (1 H, dd, J = 7.0, 1.0 Hz, H-12), 4.50 (1 H, s, H-21), 3.17 (3 H, s, NCH_3), 0.66 (3 H, t, J = 7.3 Hz, H-18); ^{13}C NMR ($CDCl_3$) 176.1 (C-2), 60.3 (C-3), 69.1 (C-5), 53.1 (C-7), 123.5* (C-9), 124.4* (C-10), 198.6 (C-17), 8.2 (C-18), 26.5 (NCH_3) (an asterick indicates assignments may be interchanged); CD (EtOH) $\Delta\epsilon$ −0.14 (325), 0 (318), +2.24 (293), +0.95 (275), +1.3 (272), +0.63 (260), +3.07 (236), 0 (228), −14.4 (213). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 68.98; H, 7.30; N, 8.57.

Preparation of the Acrylate 10 from 8. To a stirred 0 °C suspension of 363 mg (23.5 mmol) of NaH in 100 mL of dry dimethoxyethane (DME) under an argon atmosphere was added 3.5 mL (23.5 mmol) of trimethyl phosphonoacetate (Aldrich). After 30 min, 7.0 g (21.3 mmol) of aldehyde **8** in 150 mL of dry DME was added over 2 min. The solution was stirred at reflux for 12 h, and then the solvent was evaporated. The remaining residue was dissolved in dichloromethane (200 mL). After being washed with saturated $NaHCO_3$ solution (30 mL) and saturated NaCl solution (2 × 30 mL) the solution was dried over Na_2SO_4. After evaporation of the solvent, the residue was triturated with hexane to give 6.3 g (77%) of **10** as amorphous white solid: R_f 0.53 (B, orange); UV (MeOH) λ_{max} 224, 258, 285 (log ϵ 4.47, 4.00, 3.45); IR ($CHCl_3$) 1725, 1708, 1615 cm^{-1}; mass spectrum (70 eV, 180 °C), m/z (relative intensity) 384 (M^+·, 8), 368 (18), 353 (13), 279 (10), 215 (10), 208 (100); ^1H NMR (80 MHz, $CDCl_3$) 7.60 (1 H, dd, J = 7.0, 1.0 Hz, H-9), 7.20 (2 H, m, H-10, H-11), 6.72 (1 H, dd, J = 7.0, 1.0 Hz, H-12), 5.92 and 5.49 (2 H, AB system, J = 16.0 Hz, H-17 and H-16), 3.52 (3 H, s, CO_2CH_3), 3.09 (3 H, br s, NCH_3), 0.55 (3 H, t, J = 7.0 Hz, H-18); ^{13}CNMR ($CDCl_3$) 176.9 (C-2), 60.2 (C-3), 69.4 (C-5), 54.0 (C-7), 124.0* (C-9), 122.5* (C-10), 120.4 (C-16), 148.3 (C-17), 8.1 (C-18), 165.8 (CO_2CH_3), 26.2 (NCH_3) (an asterisk indicates assignments may be interchanged); CD (EtOH) $\Delta\epsilon$ +0.47 (299 nm), 0 (284), −3.9 (262), −0.72 (243), −28.1 (222), 0 (214), +35.3 (205).

Reduction of the Acrylate 10 to 11. Potassium azodicarboxylate (1.23 g, 6.3 mmol) in methanol (100 mL) was added to a stirred solution of the acrylate **10** (1.15 g, 3.0 mmol) in methanol (100 mL), and a solution of methanol (10 mL) containing distilled acetic acid (0.36 mL, 6.3 mmol) was slowly added to the mixture at room temperature in a nitrogen atmosphere. After 2 h of stirring a second portion of distilled AcOH (0.286 mL, 5.0 mmol) in methanol (10 mL) was added. The reaction mixture was stirred for a total 10 h until the yellow color had almost disappeared. The solvent was removed at reduced pressure to leave a residue which was taken up in chloroform (200 mL), washed with saturated $NaHCO_3$ and water, and dried (Na_2SO_4), and the solvent was removed to give 0.73 g of residue. Flash chromatography (Chloroform–methanol–ammonia (*d* 0.88), 82:17:1) afforded pure **11**: 440 mg (38%); foam; R_f 0.50 (B, orange); UV (MeOH) λ_{max} 222, 256, 284 (log ϵ 4.54, 4.04, 3.47); IR ($CHCl_3$) 1735, 1710, 1615 cm^{-1}; mass spectrum (70 eV, 180 °C), m/z (relative intensity) 386 (M^+·, 5), 370 (22), 355 (18), 327 (14); ^1H NMR (80 MHz, $CDCl_3$) 7.57 (1 H, br d, J = 7.0 Hz, H-9), 7.22 (2 H, br t, J = 7.0 Hz, H-10, H-11), 6.74 (1 H, br d, J = 7.0 Hz, H-12), 3.59 (3 H, s, CO_2CH_3), 3.17 (3 H, s, NCH_3), 0.52 (3 H, t, J = 7.0 Hz, H-18); CD (EtOH) $\Delta\epsilon$ +0.44 (298 nm), 0 (284), −4.1 (261), −0.77 (243), −24.2 (221).

Reduction of 11 with W-2 Raney Nickel To Give 12–15. The *anti*-oxide **11** (386 mg, 1.0 mmol) was dissolved in DME (50 mL) to which was added a suspension of W-2 Raney nickel in DME with vigorous stirring. The resulting mixture was filtered on a short column of Celite and thoroughly washed with DME. The combined solutions were concentrated to give a slightly yellow oil (410 mg). Removal of the remainder of the solvent at 0.1 mm caused the oil to deposit a mass of white crystals: 350 mg (95%); R_f 0.57 (A, orange); UV (MeOH) λ_{max} 212, 255, 282 (log ϵ 4.54, 4.08, 3.47); IR ($CHCl_3$) 1735, 1710, 1615 cm^{-1}; mass spectrum (70 eV, 150 °C), m/z (relative intensity) 370 (M^+·, 10). ^1H NMR (300 MHz, $CDCl_3$) displayed four sharp carbomethoxy signals at δ 3.62, 3.54, 3.47, and 3.60, four NCH_3 signals at δ 3.19, 3.20, 3.21, and 3.22, and four H-18 triplets (J = 7 Hz) at δ 0.49, 0.72, 0.68, and 0.46 corresponding to the four diastereomeric oxindoles **12–15** in a 35:10:4:1 ratio, respectively. Fractional recrystallization of this material from EtOH gave pure **12**: 35 mg; mp 109 °C; $[\alpha]^{20}_D$ −2.4° (*c* 0.8, $CHCl_3$); mass spectrum (70 eV, 180 °C), m/z (relative intensity) 370 (M^+·, 100), 297 (21), 215 (16), 211 (20), 182 (43), 173 (10), 124 (52); ^1H NMR (300 MHz, $CDCl_3$) 7.41 (1 H, br dd, J = 7.5, 1.0 Hz, H-9), 7.22 (1 H, dt, J = 7.5, 1.2 Hz, H-11), 6.98

(1 H, dt, J = 7.5, 1.2 Hz, H-10), 6.81 (1 H, br d, J = 7.5, H-12), 3.62 (3 H, s, CO_2CH_3), 3.21 (1 H, br dt, J = 12.0, 2.3 Hz, H-3α), 3.19 (3 H, s, NCH_3), 2.65 (1 H, s, H-21), 2.04 (1 H, ddd, J = 12.0, 11.0, 3.5 Hz, H-3β), 1.57 (1 H, m, H-14α), 1.40 (2 H, m, H-14β, H-15α), 0.91 (1 H, br dt, J = 12.5 3.5, 1.0 Hz, H-15β); ^{13}C NMR (50.4 MHz, $CDCl_3$; the chemical shift values in parentheses are those reported in ref 3a) 179.3 (179.4, C-2), 53.8 (53.8, C-3), 55.1 (55.2, C-5), 36.5 (36.5, C-6), 55.2 (55.1, C-7), 133.7 (134.0, C-8), 126.8 (126.9, C-9), 121.7 (121.8, C-10), 127.3 (127.5, C-11), 107.7 (107.8, C-12), 142.3 (142.4, C-13), 21.4 (21.4, C-14), 31.2 (31.2, C-15), 28.0 (28.0, C-16), 30.9 (30.9, C-17), 7.8 (7.9, C-18), 26.3 (26.3, C-19), 39.2 (39.3, C-20), 76.6 (76.7, C-21), 174.3 (174.4, CO_2CH_3), 51.3 (51.2, OCH_3), 26.3 (26.3, NCH_3); CD (MeOH) $\Delta\epsilon$ +2.23 (287 nm), +5.54 (260), 0 (249), −10.42 (231) [lit.[3a] (THF) $\Delta\epsilon$ −3.22 (287 nm), −8.51 (260), 0 (250), +13.6 (238). Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.26; H, 8.19; N, 7.50.

Equilibration of 12 in Chloroform. A 2-mL sample of a 2 × 10^{-2} M solution of **12** in $CDCl_3$ was kept at 35 °C. At 0.5, 1.6, 4.0, and 6.0 h, a ^{1}H NMR spectrum of the sample was recorded and the optical rotation measured. Ratios of **12/13/14/15** calculated from the areas of methoxy peaks and $[\alpha]^{20}_D$ at the appropriate time are reported: 0.5 h (92:5:3:1), −7.4°; 1.6 h (83:10:5:1), −10.2°; 4.0 h (72:20:7:1), −11.9°; 6.0 h (71:21:7:1), −12.4°. No change in optical rotation of the solution was observed after this time.

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Registry No. **2a**, 3247-10-7; **3**, 88377-49-5; **6**, 88377-50-8; **7**, 88377-51-9; **8**, 88424-28-6; **9**, 79854-75-4; **10**, 88377-52-0; **11**, 88377-53-1; **12**, 23185-53-7; **13**, 88424-29-7; **14**, 88424-30-0; **15**, 88424-31-1; trimethyl phosphonoacetate, 5927-18-4.

Regioselective Functionalization of Heterocyclic Rings: Synthesis and Reactions of 1-Methyl-2-(trimethylsiloxy)pyrrole and 2-(Trimethylsiloxy)thiophene

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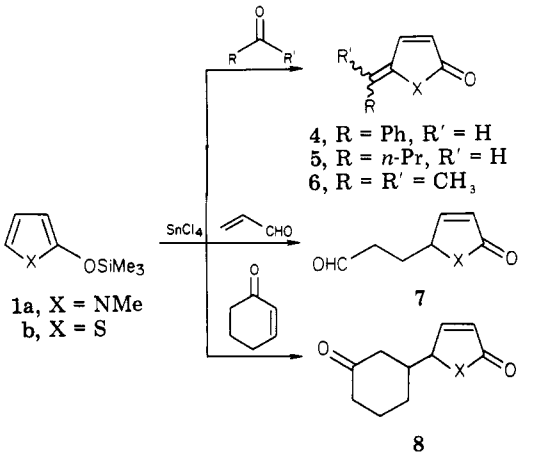
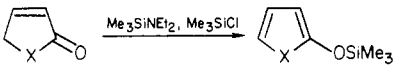
Recently we reported a novel synthesis of 2-(trimethylsiloxy)furan and its regiospecific functionalization with representative nucleophilic and electrophilic reagents.[1] We now report the synthesis of the previously unknown 1-methyl-2-(trimethylsiloxy)pyrrole (**1a**) and 2-(trimethylsiloxy)thiophene (**1b**) and their use as synthetic units for the preparation of regioselectively substituted unsaturated lactams and thiolactones.

Our approach involved interaction of amino and thiosilanes with 1-methylpyrrol-2(5*H*)-one (**2a**) and thiophen-2(5*H*)-one (**2b**). Thus, addition of (diethylamino)trimethylsilane (Me_3SiDEA) to an equimolar amount of

Scheme I



pyrrolone **2a**, under mild conditions, gave **1a** in 70% yield (eq 1). From **2b**, following the same procedure, **1b** was



(1)

2a, X = NMe
b, X = S

1

detected in the reaction mixture at −78 °C but rapidly decomposed at room temperature, probably owing to the presence of diethylamine produced during the reaction. Addition of 2 equiv of trimethylchlorosilane (Me_3SiCl) and 1.2 equiv of Me_3SiDEA to **2b** gave **1b** in 65% yield, after distillation, as a colorless oil that could be kept indefinitely under an inert atmosphere.

In contrast with the behavior of 2(5*H*)-furanone with the same reagents, no products of nucleophilic substitution at position 4 were isolated in these reactions with **2a** and **2b**. The action of $PhSSiMe_3$ on **2a** and **2b** again resulted in the formation of **1a** and **1b**, but sizable amounts of the 4-substituted products **3a** and **3b** were also recovered from the reaction mixture[2] (eq 2); with $Me_3SiSSiMe_3$ and

(2)

3a, X = NMe
b, X = S

2

1

Me_3SiSMe, on the other hand, siloxy compounds **1a** and **1b** were predominant, and only trace amounts of the corresponding 4-substituted products were detected by ^{1}H NMR analysis.

Both **1a** and **1b** behave as heterocyclic analogues of siloxy dienes; in the presence of $SnCl_4$ or $AlCl_3$[3] as Lewis acid catalysts, they reacted with various carbon electrophiles to give, after a hydrolytic workup, methylenepyrrolones or -thiophenones **4a,b** with benzaldehyde, **5a,b** with butyraldehyde, and **6a,b** with acetone (Scheme I). Compounds **4a** and **5a** were mixtures of *Z* and *E* isomers in an approximate 1:1 ratio as revealed by ^{1}H NMR spectra: in fact, the signals of the unsaturated and heteroaromatic protons showed a multiplicity which was unaffected by spin decoupling experiments, suggesting the presence of two geometrical isomers. No attempts were

(1) Fiorenza, M.; Ricci, A.; Romanelli, N.; Taddei, M.; Dembech, P.; Seconi, G. *Heterocycles* **1982**, *19*, 2327.

(2) On carrying out the reaction with PhSH and **2a** or **2b**, without solvent, **3b** was obtained after 6 h at 100 °C in 75% yield, but **3a** was identified in a complex reaction mixture arising after warming at 100 °C for 2 h.

(3) Attempts to use a fluoride ion catalyst led to complex products and were abandoned.

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