(3), 392 (5), 316 (9), 285 (6), 277 (12), 259 (10), 43 (100).

24-Methyl-5α-cholesta-7,22-diene-2α,3β,5α,6β,9α,11α,19-heptol 11-acetate (8): yield 8.2 × 10^{-4} %; mp 213 °C; $[\alpha]^{25}_D$ −32.2° (c 1.0 EtOH); ^{1}H NMR (250 MHz, pyridine-d_5) δ 0.82 (6 H, dd, J = 2.9, 6.1, H-26, H-27), 0.92 (3 H, d, J = 6.7, H-28), 1.02 (3 H, d, J = 6.1, H-21), 1.08 (3 H, s, H-18), 1.82 (1 H, m, H-24), 1.94 (3 H, s, acetate methyl), 2.03 (1 H, m, H-20), 2.22 (1 H, m, H-12α), 2.54 (2 H, m, H-4α, H-12β), 2.80 (1 H, dd, J = 4.0, 13.0, H-1β), 3.13 (2 H, m, H-4β, H-14), 3.26 (1 H, dd, J = 12.8, H-1α), 4.28 (1 H, d, J = 12.6, H-19), 4.42 (2 H, m, H-2 and H-6), 4.68 (1 H, d, J = 12.5, H-19), 4.80 (1 H, m, H-3), 5.16 (2 H, m, H-22, H-23), 5.89 (1 H, d, J = 4.4, H-7), 6.32 (1 H, dd, J = 3.9, 10.9, H-11); FAB-MS, m/z (relative intensity) 621 (M + Rb^+, 11); LRMS (EI), m/z (relative intensity) 518 (1), 500 (4), 482 (2), 470 (2), 458 (16), 440 (15), 428 (12), 410 (11), 392 (7), 316 (20), 303 (6), 285 (12), 269 (13), 261 (21), 43 (100).

5α-Cholest-7-ene-2α,3β,5α,6β,9α,11α,19-heptol 11-acetate (9): yield 1.5 × 10^{-3} %; mp 211–220 °C; $[\alpha]^{25}_D$ −40.9° (c 1.1, EtOH); ^{1}H NMR (250 MHz, pyridine-d_5) δ 0.82 (6 H, d, J = 6.6, H-26, H-27), 0.93 (3 H, d, J = 4.6, H-21), 1.06 (3 H, s, H-18), 1.91 (3 H, s, acetate methyl), 2.22 (1 H, dd, J = 11.5, 11.5, H-12α), 2.58 (2 H, m, H-4α, H-12β), 2.82 (1 H, dd, J = 4.6, 13.4, H-1β), 3.10 (2 H, m, H-4β, H-14), 3.27 (1 H, dd, J = 12.9, 12.7, H-1α), 4.29 (1 H, d, J = 12.6, H-19), 4.43 (2 H, m, H-2 and H-6), 4.70 (1 H, d, J = 12.5, H-19), 4.83 (1 H, m, H-3), 5.89 (1 H, d, J = 4.6, H-7), 6.32 (1 H, dd, J = 4.4, 11.1, H- 11); FAB-MS, m/mz (relative intensity) 609 (M + Rb^+, 8); LRMS (EI), m/z (relative intensity) 506 (0.1), 488 (0.4), 470 (0.5), 446 (1), 428 (2), 410 (1), 398 (2), 380 (1), 304 (1), 285 (1), 261 (2), 43 (100).

24-Ethyl-5α-cholesta-7,22-diene-2α,3β,5α,6β,9α,11α,19-heptol 11,19-diacetate (10): yield 2.1 × 10^{-3} %; mp 147 °C; $[\alpha]^{25}_D$ −47.5° (c 1.6, EtOH); ^{1}H NMR (250 MHz, pyridine-d_5) δ 0.78–0.93 (12 H, overlapping multiplet and singlet, H-18, H-26, H-27, H-29), 1.03 (3 H, d, J = 6.4, H-21), 1.50 (3 H, overlapping signals, m, H-28, H-24), 1.97 (1 H, m, H-20), 2.01, 2.04 (6 H, s, acetate methyls), 2.17 (1 H, m, H-12α), 2.59 (2 H, m, H-4α, H-12β), 3.02 (1 H, m, H-14), 3.15 (3 H, m, H-1, H-4β), 4.37 (1 H, m, H-2), 4.43 (1 H, d, J = 4.8 H-6), 4.80 (1 H, m, H-3), 4.90 (1 H, d, J = 13.6, H-19), 4.95 (1 H, dd, J = 8.4, H-23), 5.08 (1 H, dd, J = 8.3, 15, H-22), 5.30 (1 H, d, J = 13.6, H-19), 5.46 (1 H, dd, J = 4.4, 11.1, H-11), 5.95 (1 H, d, J = 4.9, H-7); FAB-MS, m/z (relative intensity) 677 (M + Rb^+, 25); acc. mass (EI), m/z (relative intensity) 574.3500 (M − 18^+), calcd for $C_{33}H_{50}O_8$, 574.3506; LRMS (EI), m/z (relative intensity) 556 (0.6), 538 (1), 514 (3), 496 (5), 472 (5), 454 (10), 436 (3), 424 (4), 406 (4), 357 (6), 330 (11), 315 (11), 303 (11), 291 (6), 261 (11), 43 (100).

5α-Cholest-7-ene-2α,3β,5α,6β,9α,11α,19-heptol (4): yield 7.9 × 10^{-4} %; mp 250 °C dec; $[\alpha]^{25}_D$ −24.2° (c 1.2, EtOH); ^{1}H NMR (same as hydrolysis product of 3); FAB-MS, m/z (relative intensity) 567 (M + Rb^+, 13).

Ozonolysis of Sterols 5, 8, and 10 and Stigmasterol. Each sterol (5, 8, 10, and stigmasterol, 120 μg) was ozonized and converted to aldehydes by using triphenylphosphine according to the method described by Beroza and Bierl.[20] The aldehyde fragments were analyzed by GC/MS. 5: m/z (relative intensity) 86 (M^+, 6). 8: m/z 100 (M^+, 8). 10: m/z 114 (M^+, 2). Stigmasterol: m/z, 114 (M^+, 2).

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Registry No. 3, 114395-61-8; 4, 114395-62-9; 5, 114395-63-0; 6, 114395-64-1; 7, 114395-65-2; 8, 114395-66-3; 9, 114395-67-4; 10, 114422-36-5.

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5-Unsubstituted 2-Pyrrolecarboxaldehydes for Porphyrin Synthesis and the Cyanovinyl Protecting Group

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(Cyanovinyl)pyrroles (13) derived from the Knoevenagel condensation of benzyl 5-formyl-2-pyrrolecarboxylates (12) with methyl cyanoacetate were employed in a facile sequence of four steps to produce, regioselectively, 5-unsubstituted 2-pyrrolecarboxaldehydes (5), important intermediates for porphyrin synthesis. Each step proceeded in 90–95% yield, making 5 available smoothly from benzyl 5-methyl-2-pyrrolecarboxylates (10) in seven steps, with an overall yield of 66–72%. Improved preparations are given for 5, available more conveniently by traditional methods.

Introduction

In the course of our synthetic approaches to a wide range of dimeric porphyrins,[2] we have attempted to improve the synthetic methodology of octaalkylporphyrins generally. The highest yielding known regioselective synthesis of such porphyrins was discovered by Johnson et al.[3] This entails a stepwise condensation of a 5′-(bromomethyl)-5-bromo-2,2′-dipyrromethenium bromide (1) with a 5′-unsubstituted 5-methyl-2,2′-dipyrromethenium bromide (2). The first stage is a Friedel–Crafts coupling with $SnCl_4$ in CH_2Cl_2 to afford, after workup with methanolic HBr, a crystalline 1-bromo-19-methyl-5,15-biladienium dibromide (3), often in yields exceeding 90%. This, when refluxed briefly in *o*-dichlorobenzene,[3a] or (usually better) kept for several days in the dark in dimethyl sulfoxide–pyridine,[3b] cyclizes to the final porphyrin (4), also in very high (80+%) yield (Scheme I).

Since these two reactions are so inherently efficient and convenient, we have devoted considerable effort to improving the access to the obligatory components, 1 and 2. We have already reported our improvement of the Kleinspehn[4] synthesis of ethyl 2-pyrrolecarboxylates (7) from

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(2) (a) Paine, J. B., III; Dolphin, D. *Can. J. Chem.* **1978**, *56*, 1710–1712. (b) Dolphin, D.; Hiom, J.; Paine, J. B., III. *Heterocycles* **1981**, *16*, 417–447.

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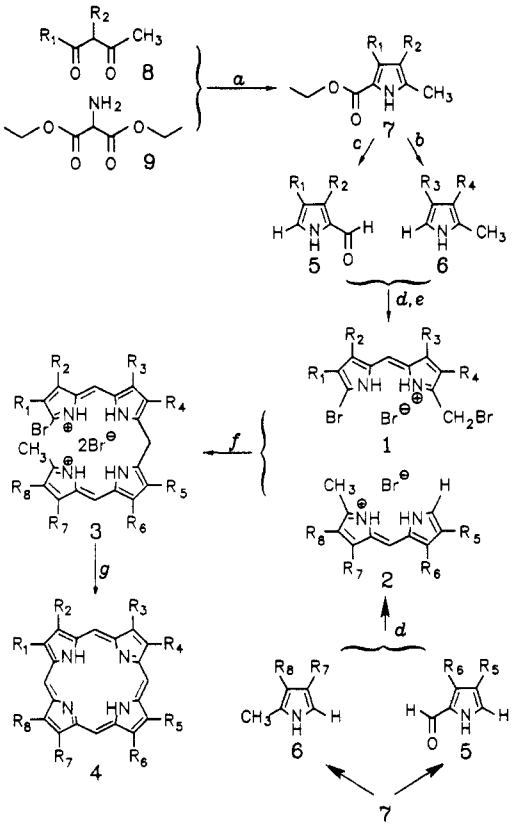
Scheme I



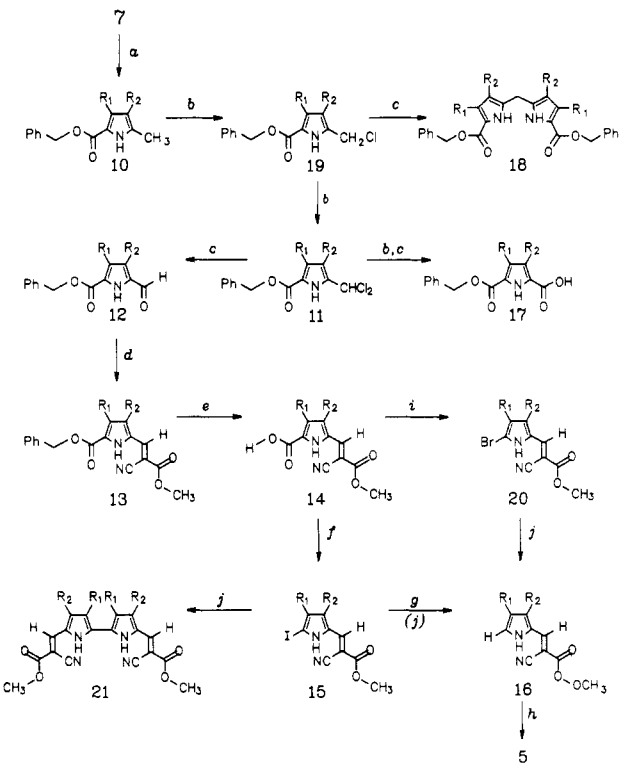
[a] CH_3CO_2H (boiling). [b] (i) NaOH; (ii) CH_3CO_2H to pH 7; (iii) steam distillation. [c] This paper. [d] 48% HBr/CH_3OH. [e] $2Br_2$/TFA, CH_2Cl_2, room temperature, 3 days. [f] (i) $SnCl_4/CH_2Cl_2$, room temperature, 1 h; (ii) HBr/CH_3OH. [g] O_2/DMSO, C_5H_5N, ca. 7–14 days.

1,3-diketones (**8**) and diethyl aminomalonate (**9**),[5] and the bromination of 2,2′-dipyrromethenes to give **1** is presented in the following paper.[6] Here, we present details of the synthesis of 5-unsubstituted 2-pyrrolecarboxaldehydes (**5**), the most generally reliable precursors to **2**.

Inasmuch as the ad hoc synthesis of **5** from β-keto ester cyanohydrins developed by Plieninger et al.[7] and von Dobeneck et al.[8] is insufficiently general and requires specialized equipment (high-temperature and high-pressure hydrogenators), we have confined our attention to sequences derived from that most widely accessible class of pyrroles, the 5-methyl-2-pyrrolecarboxylate esters (**7**, **10**),[5,9] via their immediate oxidation products, the 5-formyl-2-pyrrolecarboxylate esters (**12**) (Scheme II).

Further transformations of **12** have been performed upon the unprotected aldehydes,[10] but with significantly lowered yields, due to the vulnerability of the formyl group to oxidation, reduction, or acid-induced cleavage. Such protecting groups as have been[11a] applied to the problem

Scheme II



a, R_1 = Me; R_2 = Et
b, R_1 = Et; R_2 = Me
c, R_1 = Me; R_2 = n-C_8H_{17}

[a] $PhCH_2OH$, $PhCH_2ONa$, 200 °C. [b] SO_2Cl_2/CH_2Cl_2, 0 °C. [c] H_2O/THF. [d] $NCCH_2CO_2CH_3$/toluene, Et_3N, 100 °C. [e] H_2/Pd–C, THF, Et_3N, room temperature. [f] ICl, CH_3CO_2Na/CH_3CO_2H, 70 °C. [g] Zn, CH_3CO_2H, room temperature to 55 °C. [h] NaOH/CH_3OH, H_2O, 65–100 °C. [i] Br_2, CH_3CO_2Na/CH_3CO_2H, 70 °C. [j] H_2/Pd–C, CH_3CO_2Na, THF, room temperature.

(acetals,[11a] thioacetals,[12] oximes,[13] Girard hydrazones,[14] etc.) have often been difficult to apply, insufficiently stabilizing, or—worst of all—difficult to remove. Most have required acidic conditions to effect deprotection, conditions under which the desired product (**5**) is especially vulnerable.

5-Unsubstituted 2-Pyrrolecarboxaldehydes from (Cyanovinyl)pyrroles

The use of cyanovinyl protecting groups avoids many of these difficulties (Scheme II). The *tert*-butyl esters emphasized in our earlier report[15,16] of the chemistry of cyanovinyl-substituted pyrroles have been largely supplanted by the more generally available *benzyl* esters (**10**). These are readily obtained by base-catalyzed transesterification of the corresponding ethyl esters (**7**)[5,9,15–17] and, unlike the analogous *tert*-butyl esters, can be oxidized efficiently by inexpensive sulfuryl chloride. Lead tetraacetate, required to oxidize the 5-methyl group of the acid-labile *tert*-butyl 2-pyrrolecarboxylates,[15,16] is less

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economical and unduly toxic.

Under "high-dilution" conditions in CH_2Cl_2 at 0 °C, benzyl esters (**10**) are oxidized reasonably selectively by 2 equiv of SO_2Cl_2 to the corresponding 5-(dichloromethyl)pyrroles (**11**). These are hydrolyzed smoothly in crude form to the corresponding aldehydes (**12**) upon treatment with aqueous tetrahydrofuran. The most significant impurities, other than the readily removed 5-carboxylic acids (**17**), are the symmetrical dipyrromethanes (**18**) that result from the self-condensation of the surviving intermediary 5-(chloromethyl)pyrroles (**19**). Since **18** are very similar in polarity to **12**, they are difficult to remove chromatographically.[18] A potentially tedious purification of **12** can be avoided, however, since even the crude aldehydes (**12**) can be smoothly reacted with cyanoacetate esters[19] or malononitrile[20] and the (cyanovinyl)pyrrole products such as **13** isolated by simple crystallization. The products **13** crystallize extremely well, free of contamination and in high yield, unlike their far more soluble aldehyde precursors (**12**). Yields of **13** from **10** typically range from 80 to 90% overall for the three steps! The bright yellow (and yellow fluorescent) products are also highly nonpolar, making chromatographic purification especially facile, if required.

The catalytic hydrogenolysis of the (cyanovinyl)pyrrole benzyl esters (**13**) is effected with 10% Pd–C catalyst in tetrahydrofuran at room temperature and atmospheric pressure. This reduction requires some care since the cyanovinyl group is also reducible,[21] albeit at a far slower rate than the benzyl ester. The hydrogen uptake slows dramatically after the first equivalent has been consumed, and the reaction must be terminated at this point to ensure maximum yield. Problems can arise if a *particular batch* of catalyst is too reactive: a new batch of catalyst should be examined for suitability before committing a large quantity of substrate. Since the product (**14**) is sensitive to aqueous base[22] and difficult to recover from aqueous solution by either precipitation or extraction, it is recovered from the hydrogenation solution by simple crystallization. The carboxylic acid **14** is readily obtained pure in 90–95% yield. The product **14** is indefinitely stable in the dark, but may undergo gradual photochemical bleaching (with unknown structural consequences) when exposed to bright light for extended periods. Pyrrole **14** cannot be decarboxylated thermally and gives a stable parent ion in the mass spectrometer. The indirect halogenative decarboxylations must therefore be used.

The principle stumbling blocks in the use of (cyanovinyl)pyrroles had been the halogenative decarboxylation–hydrogenative dehalogenation steps. Despite the use of a wide range of conditions, brominative decarboxylation[22] rarely gave yields much above 60%. The resulting 5-bromopyrroles (**20**), however, debrominated readily with H_2 and 10% Pd–C in the presence of sodium acetate to give **16**. By contrast, by modifying our earlier conditions[15] from the use of a *solution* of **14** at 115 °C to a *slurry* of **14** at 70 °C, light-colored iodopyrrole (**15**) could be obtained readily in 90–95% yield by the use of a moderate excess of ICl in sodium acetate buffered glacial acetic acid. Unfortunately, the resulting iodopyrroles (**15**) quickly poisoned the hydrogenation catalysts (Pd or Pt), with considerable formation of the corresponding 2,2′-bipyrrole (**21**). The bipyrrole **21** was also formed, to a much slighter extent, upon the hydrogenolysis of **20**, but in quantities sufficient to impart a bright orange color to what would normally be a lemon yellow material (**16**).

These excellent iodination yields could finally be taken full advantage of when we found that *zinc dust* in glacial acetic acid reacted spontaneously with **15** at *room temperature* to give **16**. In the presence of excess Zn, this reduction went to completion in minutes, without *any* bipyrrole (**21**) formation and in 93–97% yield. This reduction is far more facile than that of analogous 5-iodo-2-pyrrolecarboxylate esters[23] (such as **32**), which require hours of reflux to deiodinate with zinc or the use of Zn/NH_4Cl in refluxing ethanol, as employed by Badger.[22] The strongly electron-withdrawing propensity of the cyanovinyl group is undoubtedly responsible—greatly easing the acceptance of electrons from the metal by the aromatic system. The products (**16**) can be employed in dipyrromethane synthesis[15] or deprotected as follows.

The deprotection step to give **5** requires the use of excess caustic alkali[24] and proceeds to completion at 100 °C. By use of an inert atmosphere to minimize potential autoxidation of intermediates, deprotection yields routinely range from 92 to 98%. The strong base limits the use of cyanovinyl protecting groups to pyrroles whose substituents are either inert to strong base or else easily repaired thereafter. *However, where applicable, the cyanovinyl protecting groups are the protecting groups of choice* and nicely complement the alternative methods, whose yields are especially poor with the simple alkyl-substituted pyrroles that perform so well here. Overall yields for the three sequences detailed in the Experimental Section (or in the Supplementary Material) range from 66 to 72% from the benzyl 5-methyl-2-pyrrolecarboxylates (**10**) to **5**, despite the large number of steps (seven) or purified intermediates (four).

The yields are sufficiently high as to allow the successful application of this sequence to *dimeric* pyrroles[25] such as **10** (where $R_1 = CH_3$, $R_2 = -(CH_2)_8-$). It will be noted that the sequence can be readily performed on a respectable scale, with inexpensive reagents and purification techniques.

Of the choice of cyanovinyl protecting groups, we have settled on the methyl cyanoacrylates. These are more reactive than their 2,2′-dicyanovinyl analogues[26] and more conveniently soluble. Their variable content of *E* and *Z*[27] isomers makes their melting points a poor criterion of purity but has negligible effect on their manipulations, which can be performed as if on a homogeneous material.

(18) These can be visualized on a TLC plate with Br_2 vapor, which turns them orange-red. Cf: Clezy, P. S.; Liepa, A. J. *Aust. J. Chem.* **1970**, *23*, 2443–2459. They generally occupy the leading edge of the main formylpyrrole product spot (silica gel plates).

(19) If effected in an *alcoholic* solvent, this must correspond to the cyanoacetate *ester* used, or else partial transesterification will be observed (Paine, J. B., III, unpublished results[15a]).

(20) We have observed (Paine, J. B., III, unpublished results[15a]) that *pyrrolecyanoacrylates* react with malononitrile (base catalysis) to afford the corresponding 2-(2,2-dicyanovinyl)pyrrole, presumably by a Michael–retro-Michael reaction sequence.

(21) Howarth, T. T.; Jackson, A. H.; Judge, J.; Kenner, G. W.; Newman, D. J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 490–501.

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(25) (a) Paine, J. B., III; Dolphin, D., unpublished results. (b) Awruch, J.; Frydman, B. *Tetrahedron* **1986**, *42*, 4137–4146 (87% yield, benzyl ester). (c) In our experience, large-scale (2–6 mol) diborane reductions, invariably run at high concentration (≥1 M), give lower yields (60–70%) since the temperature becomes difficult to control. Possible side reactions include competing elimination to give vinylpyrroles, which can be hydroborated under the reaction conditions.

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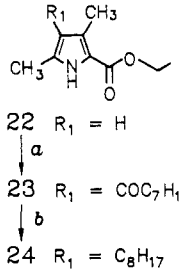
Scheme III



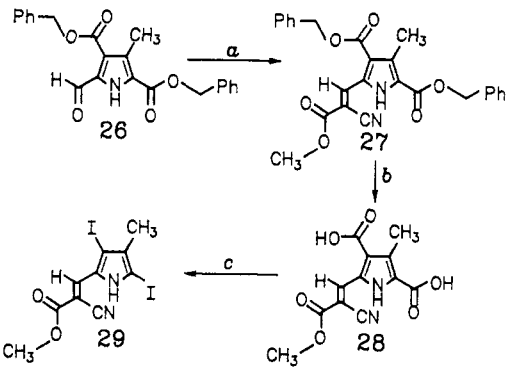
[a] $C_7H_{15}COCl/SnCl_4$, CH_2Cl_2, 0–40 °C. [b] $NaBH_4$, $BF_3{\cdot}OEt_2$/THF, 0 °C.

Although chromatographic separation of the two isomers appears to be possible, it would be pointless to perform in the course of their employment *as a protecting group ultimately to be removed*, especially since the *E:Z ratio changes along the sequence*, with the less stable *Z* isomer reaching a maximum at the iodopyrrole stage (**15**). The methyl esters are well behaved and generally present the simplest possible NMR spectra.

This sequence was pioneered with the esters of cryptopyrrole-2-carboxylic acid (**7**, **10**, $R_1 = CH_3$, $R_2 = CH_2CH_3$). These are most readily available by direct ring synthesis from 3-ethyl-2,4-pentanedione, with the benzyl esters being obtained directly with the use of benzyl oximinoacetoacetate[28] or indirectly by base-catalyzed transesterification[17] of the ethyl esters, derived by the use of ethyl oximinoacetoacetate,[3a] diethyl oximinomalonate,[4] or (best) diethyl aminomalonate[5] (**9**). Alternatively, they can be prepared via diborane reduction[25,29] of the corresponding 4-acetylpyrroles, Knorr products from the reaction of 2,4-pentanedione itself with oximinoacetoacetate esters.[9] Since benzyl acetoacetate[30] itself requires synthesis, no steps are saved by employing it in preference to the later transesterification of pyrrole ethyl esters—unless side-chain esters are present—and even then, yields are usually inferior to any procedure using diethyl aminomalonate (**9**) as such.[5] Although the method to be chosen must reflect the circumstances of a particular laboratory, our personal preference originally was to perform large-scale (up to 5 mol) diborane reductions of benzyl 4-acetyl-3,5-dimethyl-2-pyrrolecarboxylate, which typically gave 70% yields at the high concentrations used, due to difficulty of temperature control on such a scale. Since our development of the aminomalonate procedure,[5] we have relied on the high-temperature transbenzylation of ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate to provide the starting material **10a**. The procedure for the synthesis of **10c** can be applied to that of **10a**, except that **10a** can be expected to crystallize from the quenching solution. The resulting final product, 3-ethyl-4-methyl-2-pyrrolecarboxaldehyde (**5a**) figured prominently in our work with porphyrin dimers.[2]

The isomeric aldehyde 4-ethyl-3-methyl-2-pyrrolecarboxaldehyde (**5b**) was prepared similarly from ethyl 3-ethyl-4,5-dimethyl-2-pyrrolecarboxylate (**7b**), derived in 70% yield from 3-ethyl-2,4-hexanedione (**8b**) and diethyl aminomalonate (**9**).[5] Such minor ethyl 5-ethyl-3,4-dimethyl-2-pyrrolecarboxylate impurity as is contained in **7b** so prepared is quickly eliminated by the reactions that functionalize the 5-methyl substituent of **7b**. The experimental details for this sequence appear in the Supplementary Material.

Scheme IV



[a] $NCCH_2CO_2CH_3$/toluene, Et_3N, 100 °C. [b] $2H_2$/Pd–C, THF, Et_3N, 1 atm, room temperature. [c] 2ICl, $2CH_3CO_2Na/CH_3CO_2H$, 70 °C.

In order to produce dimeric porphyrins of enhanced solubility, *n*-octyl side chains were introduced into the sequence via an efficient acylation procedure[2a,31] ($SnCl_4$–CH_2Cl_2) employing octanoyl chloride and the readily available ethyl 3,5-dimethyl-2-pyrrolecarboxylate[4,5] (**22**). The resulting 4-(1-oxooctyl) substituent was reduced to *n*-octyl by the use of diborane[2a,29] (Scheme III). The Experimental Section details the methodological changes required to accommodate derivatives of increased lipophilicity.

Although the yields remain to be optimized in this series, we found that dibenzyl 5-(2-cyano-2-(methoxycarbonyl)-ethenyl)-3-methyl-2,4-pyrroledicarboxylate (**27**) hydrogenated cleanly to lose *both* benzyl esters before any protecting-group reduction occurred. The product (**28**) gave the diiodopyrrole (**29**) under the usual iodination conditions. The pyrrole **27** could be obtained from **26** under Knoevenagel conditions which *excluded* alcoholic solvents, to prevent an otherwise reported transesterification[21] (Scheme IV). The experimental details appear in the Supplementary Material.

Yields have likewise to be optimized with dimer pyrroles, but the feasibility of the transformations has been demonstrated.[25]

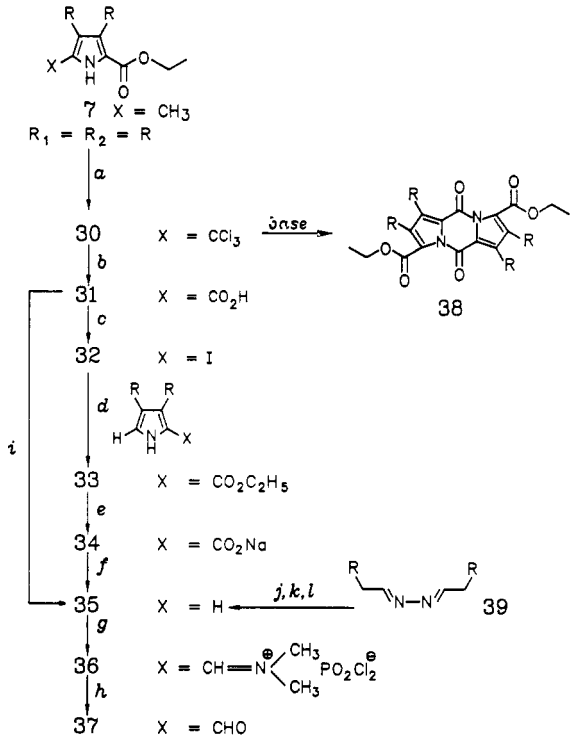
Nonregioselective Synthesis of 5-Unsubstituted 2-Pyrrolecarboxaldehydes (Scheme V)

Although the above sequence has been performed with pyrroles bearing *identical* β-substituents (3,4-dimethyl[15] and 3,4-diethylpyrroles[25a,27]), the inherent regioselectivity is wasted (unless specifically labeled derivatives are required). We have made some improvements in the nonregioselective synthesis of such 2-pyrrolecarboxaldehydes, via degradation of ethyl 5-methyl-2-pyrrolecarboxylates (**7**).

The oxidation of **7** can be effected rapidly with *3* equiv of SO_2Cl_2 in CH_2Cl_2[16] to give the 5-(trichloromethyl)pyrrole (**30**). The trichloromethyl group of **30** can be hydrolyzed under *acidic conditions*,[16] which prevent the possible losses caused by the formation of dipyrrolopyrazinediones (pyrrocolls)[32] (**38**), in aqueous acetone, to give the 5-(ethoxycarbonyl)-2-pyrrolecarboxylic acids (**31**), which generally crystallize directly from the reaction mixture in an

(28) Johnson, A. W.; Markham, E.; Price, R.; Shaw, K. B. *J. Chem. Soc.* **1958**, 4254–4257.
(29) (a) Rattini, G. A.; Sleiter, G. *Liebigs Ann. Chem.* **1975**, 1677–1689. (b) Whitlock, H. W.; Hanauer, R. *J. Org. Chem.* **1968**, *33*, 2169–2171.
(30) (a) Baker, B. R.; Schaub, R. E.; Querry, M. Y.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 77–96. (b) Bacon, R. F. *Am. Chem. J.* **1905**, *33*, 79.
(31) Robinson, J. A.; McDonald, E.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1699–1709.
(32) Cavaleiro, J. A. S.; Rocha Gonsalves, A. M. d'A.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2471–2478.

Scheme V



a, R = Me
b, R = Et

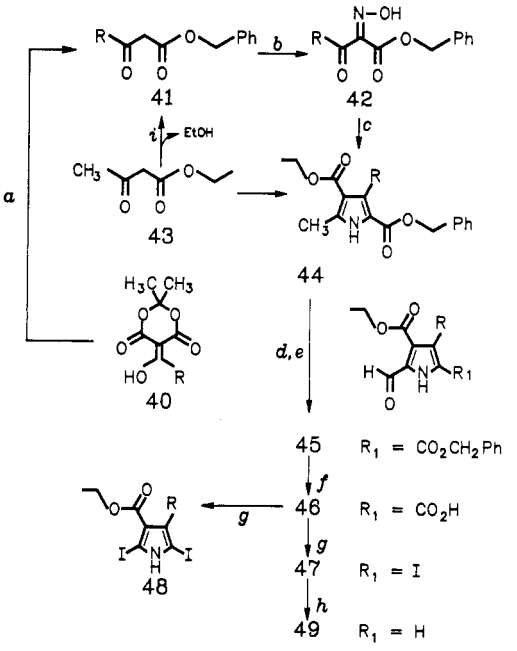
[a] $3SO_2Cl_2/CH_2Cl_2$, 0 °C. [b] H_2O/CH_3COCH_3. [c] I_2, $KHCO_3$/$ClCH_2CH_2Cl$, H_2O, 75 °C. [d] HI, H_3PO_2/CH_3CO_2H, H_2O. [e] NaOH/CH_3OH, H_2O. [f] CH_3CO_2H to pH 7; then steam distillation. [g] $POCl_3$, DMF/CH_2Cl_2, 0 °C. [h] $NaHCO_3$, H_2O, 0–65 °C. [i] NaOH, H_2O, 180 °C. [j] PhCOCl, C_5H_5N/C_6H_6. [k] Xylene, 140 °C. [l] H_2NNH_2/*i*-PrOH, 80 °C.

easily filtered form. Such half-esters have been converted directly to 3,4-dialkylpyrroles (**35**) by alkali fusion,[24b,33] but the yields were often low. We find that the indirect stepwise decarboxylation is far more efficient and reliable. Since the ultimate 3,4-dialkylpyrrole (**35**) comes to be isolated by steam distillation, it is unnecessary to purify any of the intermediates.

Thus, the half-ester (**31**) is subjected to our two-phase iodinative decarboxylation,[15a,16] using *crystalline* iodine, added to an aqueous bicarbonate solution of **31** in the presence of 1,2-dichloroethane to control the temperature and extract the product (**32**).[9] The resulting iodopyrrole (**32**), purified or not, can be deiodinated smoothly with $HI–H_3PO_2$ in *acetic acid* (a far superior solvent for this reaction to ethanol).[34] Whether isolated by crystallization or extraction, the resulting 5-unsubstituted 2-pyrrolecarboxylate ester (**33**) can be saponified by an *exactly known* excess of NaOH. Exact neutralization of the base with acetic acid, followed by steam distillation, allows the isolation of pure 3,4-dialkylpyrrole (**35**) in excellent yield.[34]

3,4-Dialkylpyrroles (**35**) react smoothly with excess $POCl_3$–DMF[3a,26,35] in CH_2Cl_2 at 0 °C, giving, unlike analogous 2,3,4-trialkylpyrroles (**6**), negligible colored byproduct. The resulting iminium salts (**36**) liberate the corresponding aldehydes (**37** = **5**, $R_1 = R_2$) in high yield, when warmed with excess aqueous $NaHCO_3$. (Ammonia[15b] should *never* be used for this hydrolysis: it gives an im-

Scheme VI



a, R = Me
b, R = Et

[a] $PhCH_2OH$/toluene, 110 °C. [b] $NaNO_2$, CH_3CO_2H, H_2O, room temperature. [c] 2Zn, $4CH_3CO_2H$. [d] $2SO_2Cl_2/CH_3CO_2H$. [e] H_2O/CH_3CO_2H or C_2H_5OH. [f] H_2/Pd–C, THF, Et_3N, room temperature. [g] KI_3 or NaI_3, $KHCO_3$, or $NaHCO_3/H_2O$, $CHCl_3$, reflux. [h] H_2, CH_3CO_2Na/Pd–C, C_2H_5OH, H_2O, 1 atm, room temperature. [i] R = Me: $PhCH_2OH$, ca. 150 °C.

mediate red color, which signals severe losses to polymer formation.) Since the PO_2Cl_2 counterion initially present during the workup resists hydrolysis in the cold, a false end point is usually noted as $NaHCO_3$ is added to the reaction. As the solution warms to around 40 °C, PO_2Cl_2 is hydrolyzed, with a precipitous drop in pH, unless sufficient base is present.[34] Overall yields of **5** from **31** are often as high as 70–80% by this sequence, far higher than any heretofore reported.[3a,26] Experimental details may be found in the Supplementary Material.

A recent report by Bottaro and Baldwin[36] has made 3,4-dialkylpyrroles (**35**) accessible, at long last,[37] from easily prepared aldazines (**39**). A steam-distillative modification of the workup of the intermediate *N*-benzoylpyrrole would undoubtedly prove beneficial. The above sequence is not diminished in importance by this development, since the intermediates therein are often required in their own right for other purposes, and the formylation procedure succeeds independently of the provenance of the dialkylpyrrole (**35**).

Unprotected Regioselective Synthesis of 2-Pyrrolecarboxaldehydes (Scheme VI)

When β-ester substituents are present, particulary if *directly* appended to the pyrrole ring, the use of cyanovinyl protecting groups becomes difficult. Such esters, however, exert a stabilizing influence upon some of the intermediates encountered when degrading unprotected 2-pyrrolecarboxaldehydes. This is particularly true in pyrroles of the Knorr type of substitution pattern, the 5-methyl-2,4-pyrroledicarboxylate esters (**44**) (Scheme VI). For ease in regioselective manipulation, *benzyl* esters are incorporated

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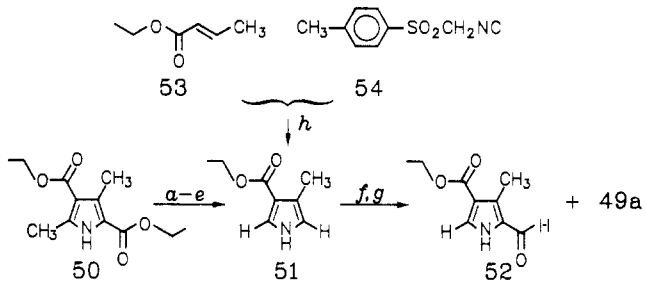
(34) Wijesekera, T. P.; Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1985**, *50*, 3832–3838.
(35) Johnson, A. W.; Kay, I. T. *J. Chem. Soc.* **1965**, 1620–1629.
(36) Baldwin, J. E.; Bottaro, J. C. *J. Chem. Soc., Chem. Commun.* **1982**, 624.
(37) Paine, J. B., III; Kirshner, W. B.; Moskowitz, D. W.; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 3857–3860.

Scheme VII



[a] $3SO_2Cl_2$, Br_2/CH_3CO_2H, Ac_2O, 0–5 °C. [b] H_2O/CH_3CO_2H. [c] $2NaOH/H_2O$, C_2H_5OH, ca. 100 °C. [d] $2NaI_3$. [e] HI, H_3PO_2/CH_3CO_2H, H_2O, below 40 °C. [f] $POCl_3$, DMF/CH_2Cl_2, 0 °C. [g] $NaHCO_3$, H_2O, room temperature. [h] NaH/Et_2O, DMSO.

into the 2-position by direct Knorr synthesis[17,28] from a nitrosated benzyl 3-oxoalkanoate (**41**), a class of compounds available by uncatalyzed transesterification of ethyl 3-oxoalkanoates with benzyl alcohol[30,38] or from the benzyl alcoholysis of acyl-Meldrum's acids[39] (**40**).

Corwin's conditions[40] ($2SO_2Cl_2$ in warm acetic acid) are employed to oxidize the 5-methyl substituent to the dichloromethyl stage, with hydrolysis to the 5-formylpyrrole (**45**) occurring either during or subsequent to the oxidation.

Catalytic hydrogenation of **45** leaves the 5-formyl substituent intact,[41] and the resulting 5-formyl-2-pyrrolecarboxylic acid (**46**) is treated, slowly, with I_3^- in bicarbonate-buffered H_2O–$CHCl_3$. Even under conditions of *slow* I_2 addition, *two* products are formed. The principal product is the desired 5-iodo-2-pyrrolecarboxaldehyde (**47**), but the 2,5-diiodopyrrole (**48**)[42b] is formed as well. Since **48** still bears a stabilizing ester group, it survives the reaction and can be isolated. On storage, however, even in the dark, it soon decomposes autocatalytically. Without such a stabilizing substituent, 2,5-diiodopyrroles do not even survive the reaction mixture, accounting for the messy iodinations usually seen with unprotected 2-pyrrolecarboxaldehydes. The two products (**47**, **48**) can be separated by crystallization or chromatography, depending on the solubility characteristics. Corwin's workup[43] with dilute NaOH is not required. Intermediate **47** is stable to prolonged storage in the dark.

Pyrrole **47** hydrogenated smoothly with 10% Pd–C[43] and sodium acetate buffering, to give good yields of **49**. The novel ethyl 3-ethyl-2-formyl-3-pyrrolecarboxylate (**49b**) was prepared to aid in the ^{13}C NMR assignments of a wide range of ester-substituted 2,2′-dipyrromethenes, biladienes, and porphyrins, to be reported elsewhere. The experimental details for this sequence appear in the Supplementary Material.

Ethyl 5-formyl-4-methyl-3-pyrrolecarboxylate[43] (**52**) was prepared by the Vilsmeier formylation of ethyl 4-methyl-3-pyrrolecarboxylate (**51**).[44] Despite the presence of the deactivating ethoxycarbonyl substituent, this formylation was not entirely selective, and the resulting **52** had to be recrystallized several times to eliminate **49a**. The experimental procedure appears in the Supplementary Material. Precursor **51** had been prepared via the standard degradation of Knorr's pyrrole[42] (**50**). It is now much more readily available from ethyl crotonate (**53**) and (*p*-toluenesulfonyl)methyl isocyanide[44] (**54**) (Scheme VII).

Experimental Section

Reagents were employed as received, unless otherwise indicated. NMR spectra were recorded with a Varian CFT-20 or Bruker WP 400 (10-mm tubes) for ^{13}C and Varian XL-100 or Bruker WP400 (5-mm tubes) for ^1H. Assignments of ^{13}C and ^1H NMR chemical shifts were made, unambiguously, by direct comparison of data from a large number of *close* analogues, related by methyl–ethyl substitution, since 2D NMR was unavailable to us at the time. All NMR spectra were obtained in $CDCl_3$ to ensure the validity of comparisons. Since the chemical shift of $CDCl_3$ varies with the concentration of solute, we usually report the chemical shift of this solvent. The higher deshieldings are associated with the higher concentrations. Low-solubility compounds, for which $\delta(CDCl_3) \leq 77.05$, were examined at 100.6 MHz. Melting points (uncorrected) were obtained with a Thomas-Hoover capillary immersion apparatus or a Thomas micro hot stage. Microanalyses were performed by Peter Borda at UBC.

Benzyl 5-[(*E*)-2-Cyano-2-(methoxycarbonyl)ethenyl]-4-ethyl-3-methyl-2-pyrrolecarboxylate (13a). An ice-cooled magnetically stirred solution of benzyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate[17,25,28] (**10a**) (128.9 g, 0.50 mol) in CH_2Cl_2 (400 mL) was treated, slowly dropwise, under N_2, with a solution of SO_2Cl_2 (138.8 g, 84.2 mL, 1.03 mol) in CH_2Cl_2 (1500 mL) over 5 h.

The solvent was removed with a rotary evaporator (water bath at 40–50 °C). The resulting greenish oil [the 5-(dichloromethyl)pyrrole (**11a**)], dissolved in tetrahydrofuran (500 mL), was treated all at once with H_2O (200 mL) and swirled to mix. After the exothermic reaction had subsided, the mixture was refluxed for ca. 10 min (steam bath). The organic phase was isolated. The aqueous phase was extracted once with ethyl acetate (250 mL). The organic phases were evaporated in vacuo.

The resulting crude 5-formylpyrrole (**12a**)[45] was heated (steam bath) in toluene (400 mL) with methyl cyanoacetate (50 g, 0.51 mol) and triethylamine (10 mL) until TLC (CH_2Cl_2, silica GF) showed complete reaction (ca. 2 h).

The toluene was removed (rotary evaporator) until crystals apeared. Methanol (300 mL) was added, and the rotary evaporation was continued until a thick slurry resulted. The golden chunky crystals were filtered off, washed with methanol and then hexanes, and dried. Yield 147.7 g (83.7%). A second crop was obtained from the filtrates: 5.35 g (3.0%). Total 153.05 g (86.7%). Recrystallization can be effected conveniently on a rotary evaporator, using the solvent pairs CH_2Cl_2–CH_3OH or THF–CH_3OH to give product less likely to slow the following hydrogenation step; mp 124.5 –125.0 °C. The X-ray structure is reported elsewhere.[27]

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.24; H, 5.78; N, 7.91.

^1H NMR ($CDCl_3$) δ 1.09 (3 H, t, J = 7 Hz, 4-Et), 2.25 (3 H, s, 3-Me), 2.55 (2 H, q, J = 7 Hz, 4-Et), 3.82 (3 H, s, CH_3O), 5.31 (2 H, s, $ArCH_2O$), 7.24–7.50 (5 H, m, Ar), 7.97 (1 H, s, vinyl), 10.22 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$) δ 163.32 (CO_2Me), 159.78 (CO_2Bz), 139.88 (4), 138.88 (CH=C), 135.56 (Ar-1), 128.66 (2 C, Ar), 128.37 (Ar-4), 128.16 (2C, Ar), 126.69 (3), 126.20 (2), 124.93 (5), 117.84 (CN), 94.60 (CH=C), 66.64 ($ArCH_2O$), 53.05 (CH_3O), 17.41 (4-CH_3CH_2), 16.04 (4-CH_3CH_2), 9.74 (3-CH_3).

5-[(*E*)-2-Cyano-2-(methoxycarbonyl)ethenyl]-4-ethyl-3-methyl-2-pyrrolecarboxylic Acid (14a). A solution of the preceding benzyl ester (**13a**) (152.9 g, 0.43 mol) and triethylamine (0.5 mL) in tetrahydrofuran (1150 mL) was stirred with 10% Pd–C

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(39) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087–2088.
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(41) (a) Clezy, P. S.; Liepa, A. J. *Aust. J. Chem.* **1971**, *24*, 1933–1948. (b) Jones, R. V. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 531–534.
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(43) Corwin, A. H.; Kleinspehn, G. G. *J. Am. Chem. Soc.* **1953**, *75*, 2089–2095.
(44) (a) Smith, K. M., personal communication. (b) Van Leusen, A. M.; Siderius, H.; Hoogenboom, B. G.; van Leusen, D. *Tetrahedron Lett.* **1971**, 5337–5340.
(45) Jackson, A. H.; Kenner, G. W.; Warburton, D. *J. Chem. Soc.* **1965**, 1328–1337.

(2.6 g) under H_2 (1 atm, room temperature) until 1 equiv (typically 25 L/mol when corrected for temperature and solvent vapor pressure; here 9960 mL) had been consumed. The rate of H_2 consumption then slowed dramatically (time, ca. 90 min).

The catalyst was promptly removed by filtration and rinsed with hot THF. The filtrates were concentrated (rotary evaporator) until crystals appeared. Methanol (300 mL) was added and the rotary evaporation continued until a thick slurry resulted. The dense pale yellow powdery product was filtered off and rinsed with methanol, ethyl ether, and hexane. Yield 103.9 g (91.3%). Acetic acid (2 mL) was added to the filtrates, which upon concentration in vacuo gave a second crop: 5.27 g (4.6%). Total 109.2 g (95.9%).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.52; H, 5.41; N, 10.57. Mass spectrum: m/z 262 M+ (calcd = obsd).

Methyl (*E*)-2-Cyano-3-(3-ethyl-5-iodo-4-methyl-2-pyrrolyl)propenoate (15a). A suspension of the preceding 5-carboxypyrrole (**14a**) (104.1 g, 0.397 mol) and anhydrous sodium acetate (62.4 g, 0.76 mol) in glacial acetic acid (750 mL) in a 4-L Erlenmeyer flask was stirred magnetically at 70–80 °C and treated, over 20 min, with a steady stream of a solution of ICl (76.9 g, 0.47 mol) in glacial acetic acid (200 mL). The starting material dissolved with perceptible gas evolution; a fine precipitate of NaCl formed in its place.

The brown I_2 color was discharged by the dropwise addition of minimal aqueous $NaHSO_3$, and then H_2O was added until the product began to crystallize. After 10 min, further H_2O was added to dilute the mixture to 4 L.

The deep yellow solids were filtered off, washed with H_2O until the rinsings were colorless, and dried in air. Yield 126.0 g (92.1%). It was generally employed in the next step without further purification. A sample was recrystallized for analysis, mp 158–168 °C (varies widely with change in isomer ratio).

Anal. Calcd for $C_{12}H_{13}IN_2O_2$: C, 41.88; H, 3.81; N, 8.14; I, 36.87. Found: C, 41.75; H, 3.63; N, 7.97; I, 36.77.

^{1}H NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 7.6 Hz, 3-Et), 2.02 (3 H, s, 4-Me), 2.64 (2 H, q, J = 7.6 Hz, 3-Et), 3.88 (3 H, s, CH_3O), 7.83 (1 H, s, vinyl), 9.63 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.17) δ (dominant *E* isomer) 164.19 (C=O), 140.16 (3), 137.12 (*C*H=C), 127.96 (2), 127.27 (4), 119.01 (CN), 89.66 (CH=*C*), 84.74 (5), 52.75 (CH_3O), 18.30 (3-CH_3*C*H_2), 15.93 (3-*C*H_3CH_2), 11.80 (4-CH_3); (minor *Z* isomer) 166.86 (C=O), 137.80 (*C*H=C), 89.49 (CH=*C*), 53.93 (CH_3O) (other peaks coincide).

Methyl (*E*)-2-Cyano-3-(3-ethyl-4-methyl-2-pyrrolyl)-propenoate (16a). A thorough mixture of the preceding iodopyrrole (**15a**) (163.2 g, 0.47 mol) and zinc dust (155.9 g, 2.38 mol) was treated in a 3-L Erlenmeyer flask with glacial acetic acid (1015 mL). The mixture was swirled manually for several minutes until a spontaneous reaction set in, and the pyrrole dissolved as the temperature rose to 50–55 °C. Agitation was continued (magnetic stirrer) for 20 min *without* application of external heat.

The zinc dust was filtered off and rinsed with methanol until the rinsings were colorless. Water (to 3-L total volume) was filtered through next, causing crystallization of product. This was filtered off, washed with H_2O, and dried in air. Yield 96.5 g (93.3%). The filtrates were extracted with CH_2Cl_2 to give, after evaporation of solvent and crystallization from ethanol, a second crop: 4.0 g (3.8%). Total 100.5 g (97.1%).

The solids were recrystallized from ethanol after a hot filtration in crops of 81.3 and 15.3 g. Combined purified yield 96.6 g (93.4%), as yellowish blades; mp 145.5–147.0 °C.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.13; H, 6.27; N, 12.87.

^{1}H NMR ($CDCl_3$) δ 1.14 (3 H, t, J = 7.5 Hz, 3-Et), 2.08 (3 H, d, J = 1 Hz, 4-Me), 2.63 (2 H, q, J = 7.5 Hz, 3-Et), 3.88 (3 H, s, CH_3O), 7.03 (1 H, br d, J = 3.5 Hz, 5-H), 8.00 (1 H, s, vinyl), 9.74 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.37) δ 164.79 (C=O), 140.96 (3), 139.19 (*C*H=C), 128.74 (5), 124.03 (2), 121.19 (4), 119.31 (CN), 87.99 (CH=*C*), 52.65 (CH_3O), 17.71 (3-CH_3*C*H_2), 16.13 (3-*C*H_3CH_2), 9.72 (4-CH_3).

3-Ethyl-4-methyl-2-pyrrolecarboxaldehyde (5a). A boiling solution of the preceding pyrrolylcyanoacrylate (**16a**) (80.7 g, 0.37 mol) in methanol (500 mL) was treated, under N_2, with a solution of NaOH (75.9 g, 1.90 mol) in H_2O (450 mL) over several minutes. The mixture was refluxed for 20 min and then the methanol was distilled off (caution: foaming), being replaced, as needed, by additional H_2O.

Oily product began to separate when the vapor temperature reached 100 °C. Boiling was continued until the aqueous phase was colorless (ca. 2 h). On cooling, the brown oil solidified. It was filtered off, washed with H_2O, and dried. Yield 47.0 g (92.7%). It was employed as such in dipyrromethene synthesis. The aqueous methanolic distillates were concentrated on the rotary evaporator, giving 2.07 g of additional product as pale pinkish-white crystals, mp 74.5–76.0 °C (lit.[11b] mp 75–76 °C). Total yield 49.08 g (96.76%).

The "distilled" material was analyzed. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.12; H, 8.02; N, 10.19.

^{1}H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7.5 Hz, 3-Et), 2.04 (3 H, d, J = 1 Hz, 4-Me), 2.74 (2 H, q, J = 7.5 Hz, 3-Et), 6.89 (1 H, d, J = 2.5 Hz, 5-H), 9.58 (1 H, d, J = 1 Hz, CHO), 10.09 (1 H, v br "s", NH).

^{13}C NMR ($CDCl_3$ at 77.20) δ 177.42 (CHO), 138.43 (3), 128.99 (2), 126.21 (5), 120.11 (4), 17.13 (3-CH_3*C*H_2), 16.54 (3-*C*H_3CH_2), 9.39 (4-CH_3).

Ethyl 3,5-Dimethyl-4-(1-oxooctyl)-2-pyrrolecarboxylate (23). Anhydrous $SnCl_4$ (133 mL) was added in a steady stream over 3 min to an ice-cooled magnetically stirred solution of ethyl 3,5-dimethyl-2-pyrrolecarboxylate[4,5] (**22**) (175.0 g, 1.05 mol) and octanoyl chloride (174.9 g, 1.08 mol, Aldrich) in CH_2Cl_2 (815 mL), under N_2, in a 4-L ₹29/42 heavy-wall Erlenmeyer flask (Ace Glass). The vigorous reaction (boiling; evolution of HCl) soon subsided. When, after 20 min, TLC inspection (CH_2Cl_2, silica GF) showed only traces of remaining **22**, the mixture was quenched into magnetically stirred concentrated HCl (50 mL)–H_2O (1000 mL).

The mixture was stirred vigorously for 15 min to ensure the removal of Sn(IV) from the organic phase. After warming (steam bath) to dissolve crystallized product, the organic phase was isolated, filtered, and concentrated in vacuo.

A solution of the residue in boiling ethanol (500 mL, 100%) was filtered hot (with minor ethanol rinsings) and diluted with H_2O (250 mL). The product was allowed to crystallize undisturbed and cooled to 0 °C only at the end. The solid mass was slurried, filtered, and washed with 50% (v/v) aqueous ethanol and then H_2O. Yield 290.7 g (94.7%); mp 79–81 °C.

Anal. Calcd for $C_{27}H_{27}NO_3$: C, 69.59; H, 9.29; N, 4.77. Found: C, 69.83; H, 9.08; N, 4.79.

^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6 Hz, octyl-8), 1.31 (8 H, br s, octyl), 1.38 (3 H, t, J = 7 Hz, ester), 1.69 (2 H, m, octyl), 2.54 (3 H, s, 5-Me), 2.59 (3 H, s, 3-Me), 2.74 (2 H, t, J = 7.5 Hz, octyl-2), 4.35 (2 H, q, J = 7 Hz, ester), 9.68 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.20) δ 198.65 (1′, C=O), 162.33 (*C*O_2Et), 138.41 (5), 129.25 (3), 123.64 (4), 118.13 (2), 60.44 (CH_3*C*H_2O), 43.00 (2′), 31.80 (6′), 29.52 (4′), 29.35 (5′), 24.45 (3′), 22.68 (7′), 14.96 (5-CH_3), 14.47 (*C*H_3CH_2O), 14.08 (8′), 12.80 (3-CH_3).

Ethyl 3,5-Dimethyl-4-octyl-2-pyrrolecarboxylate (24). Boron trifluoride ethyl ether complex (186.5 mL, 1.52 mol) was added, *cautiously* dropwise, over 50 min to an ice-cooled mechanically stirred solution/suspension of ethyl 3,5-dimethyl-4-(1-oxooctyl)-2-pyrrolecarboxylate (**23**) (190.6 g, 0.65 mol) and $NaBH_4$ (40.92 g, 1.08 mol) in tetrahydrofuran (THF) (1500 mL) under N_2.

A test sample was quenched in H_2O: vigorous effervescence showed that B_2H_6 was still present in excess. TLC examination (CH_2Cl_2, silica GF) showed absence of **23**.

Excess glacial acetic acid (130 mL) was added dropwise (*Caution*: evolution of H_2) to destroy remaining B_2H_6.[47] Water

(46) Ellis, J.; Jackson, A. H.; Jain, A. C.; Kenner, G. W. *J. Chem. Soc.* **1964**, 1935–1949.

(47) Acetic acid is superior to H_2O for destroying excess B_2H_6, since H_2 evolution is decreased by two-thirds *and* the viscosity of the reaction mixture remains low.

(48) Bullock, E.; Johnson, A. W.; Markham, E.; Shaw, K. B. *J. Chem. Soc.* **1958**, 1430–1440.

(1500 mL) was then added, slowly at first since any *lumps* of $NaBH_4$ remaining would now effervesce.

The organic phase was isolated. The aqueous phase was extracted once with ethyl acetate. The combined organic phases were concentrated in vacuo. A solution of the residue in boiling ethanol (400 mL, 100%) was filtered hot (with minor ethanol rinsings) and diluted with H_2O (100 mL). The product crystallized as the solution cooled, being finally cooled to 0 °C.

The product was filtered and washed with 60% (v/v) aqueous ethanol (500 mL) and then H_2O. Yield 158.3 g (87.2%); mp 55.0–56.7 °C.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.31; H, 10.50; N, 5.08.

^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 6 Hz, octyl-8), 1.22 (12 H, br s, octyl), 1.29 (3 H, t, J = 7.5 Hz, ester), 2.14 (3 H, s, 5-Me), 2.21 (3 H, s, 3-Me), 2.31 (2 H, t, J = 7.5 Hz, octyl-1), 4.25 (2 H, q, J = 7.5 Hz, ester), 9.35 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.14) δ 162.21 (C=O), 129.94 (5), 126.95 (3), 122.39 (4), 116.87 (2), 59.55 (CH_3CH_2O), 32.01 (6′), 30.98 (2′), 29.60 (2 C, 3′, 4′), 29.44 (5′), 24.14 (1′), 22.74 (7′), 14.62 (CH_3CH_2O), 14.09 (8′), 11.41 (5-CH_3), 10.72 (3-CH_3).

Benzyl 3,5-Dimethyl-4-octyl-2-pyrrolecarboxylate (10c). A solution of ethyl 3,5-dimethyl-4-octyl-2-pyrrolecarboxylate (**24**) (139.5 g, 0.5 mol) in benzyl alcohol (250 mL, distilled from K_2CO_3 at atmospheric pressure to remove H_2O and benzoic acid) was refluxed under N_2 (2-L heavy-wall Erlenmeyer flask; magnetic stirrer–hotplate). When the vapor temperature atop the flask exceeded 200 °C, a solution of Na in anhydrous benzyl alcohol was added *cautiously* in 1-mL portions until a vigorous evolution of ethanol was apparent. Thereafter, further portions of catalyst were added over several-minute intervals, until no futher effect was noted, and the vapor temperature atop the flask again exceeded 200 °C.

With the *hot* reaction vessel held firmly by a clamp and supported from below by an enameled steel bowl, the hot solution was immediately poured *cautiously* into a quenching mixture of magnetically stirred methanol (820 mL)–H_2O (225 mL)–acetic acid (21 mL). The reaction vessel was rinsed with benzyl alcohol (50 mL) while still hot.

The oily product was extracted into petroleum ether (bp 40–60 °C, 400 mL, then 300 mL). The combined organic phases were extracted with 80% (v/v) aqueous methanol (500 mL) to remove benzyl alcohol. The solvent was removed in vacuo and the residue crystallized from ethanol (600 mL, 100%)–H_2O (80 mL). The product was rinsed with 72% (v/v) aqueous ethanol and then H_2O. First crop: 138.4 g (81.2%); second crop: 11.4 g. Total 149.8 g (87.8%); mp 61.0–61.5 °C.

Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.11; H, 9.11; N, 4.06.

^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 6 Hz, octyl-8), 1.24 (12 H, br s, octyl), 2.08 (3 H, s, 5-Me), 2.22 (3 H, s, 3-Me), 2.30 (2 H, t, J = 7 Hz, octyl-1), 5.23 (2 H, s, ArCH_2), 7.21–7.34 (5 H, m, Ar), 9.26 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.10) δ 161.75 (C=O), 136.89 (Ar-1), 130.33 (5), 128.50 (2 C, Ar), 127.94 (3 C, Ar), 127.55 (3), 122.54 (4), 116.44 (2), 65.36 (ArCH_2O), 31.97 (6′), 30.92 (2′), 29.55 (2 C, 3′, 4′), 29.39 (5′), 24.08 (1′), 22.70 (7′), 14.10 (8′), 11.40 (5-CH_3), 10.86 (3-CH_3).

Benzyl 5-Formyl-3-methyl-4-octyl-2-pyrrolecarboxylate (12c). A magnetically stirred, ice-cooled solution of benzyl 3,5-dimethyl-4-octyl-2-pyrrolecarboxylate (**10c**) (102.4 g, 0.30 mol) in CH_2Cl_2 (600 mL) was treated, slowly dropwise, over 4 h, under N_2, with a solution of SO_2Cl_2 (83.5 g, 51 mL, 0.62 mol) in CH_2Cl_2 (750 mL).

The resulting solution was stirred for 1 h and then treated with H_2O (500 mL) and left stirring at room temperature overnight. The organic phase was isolated and concentrated in vacuo. A solution of the residue in tetrahydrofuran (500 mL) was treated, all at once, with H_2O (200 mL) and refluxed gently (steam bath) for 30 min. The organic phase was isolated. The aqueous phase was extracted once with ethyl acetate (200 mL). The combined organic phases were concentrated in vacuo. The residue was dissolved in toluene (250 mL), decanted from residual H_2O, and reconcentrated in vacuo. The resulting crude oily product was employed as such in the next step.

A sample from another preparation (0.2 mol) was recrystallized for analysis, twice from ethanol and once from hexane, to afford fluffy white solids in 18.8% yield. (The combined filtrates were scavenged with methyl cyanoacetate as for the following preparation, to give an additional 61% of product.); mp 53.0–53.5 °C.

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.54; H, 8.19; N, 3.98.

^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6 Hz, octyl-8), 1.26 (12 H, br s, octyl), 2.28 (3 H, s, 3-Me), 2.69 (2 H, t, J = 7 Hz, octyl-1), 5.33 (2 H, s, ArCH_2), 7.28–7.46 (5 H, m, Ar), 9.73 (1 H, s, CHO), 9.93 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.13) δ 179.31 (CHO), 160.81 (CO_2Bz), 135.69 (Ar-1), 135.16 (4), 130.28 (5), 128.66 (2 C, Ar), 128.46 (3 C, Ar), 126.94 (3), 124.35 (2), 66.63 (ArCH_2O), 31.75 (2 C, 2′, 6′), 29.40 (3 C, 3′, 4′, 5′), 23.50 (1′), 22.68 (7′), 14.07 (8′), 9.92 (3-CH_3).

Benzyl 5-[(*E*)-2-Cyano-2-(methoxycarbonyl)ethenyl]-3-methyl-4-octyl-2-pyrrolecarboxylate (13c). A solution of the preceding crude aldehyde (**12c**) (0.30 mol), methyl cyanoacetate (30 mL), and triethylamine (8 mL) in toluene (250 mL) was warmed (steam bath) until TLC examination (CH_2Cl_2, silica GF) showed the absence of **12c** (1 h). The solvent was removed in vacuo and the residue crystallized from ethanol (300 mL). The fluffy yellow solids were rinsed with 100% and then 70% (v/v) ethanol. Yield 103.7 g (79.2%). A second crop, 9.2 g (7%), was recovered from ethanol (150 mL). Total 112.9 g (86.2%).

Another preparation, chromatographed (CH_2Cl_2, silica), was analyzed; mp 75.5–84.5 °C.

Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.75; H, 7.49; N, 6.45.

^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6 Hz, octyl-8), 1.23 (12 H, br s, octyl), 2.24 (3 H, s, 3-Me), 2.55 (2 H, t, J = 7 Hz, octyl-1), 3.82 (3 H, s, CH_3O), 5.31 (2 H, s, ArCH_2), 7.24–7.50 (5 H, m, Ar), 7.98 (1 H, s, vinyl), 10.22 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.13) δ 163.38 (CO_2Me), 159.81 (CO_2Bz), 139.23 (CH=C), 138.51 (4), 135.54 (Ar-1), 128.64 (2 C, Ar), 128.37 (Ar-4), 128.18 (2 C, Ar), 126.96 (3), 126.16 (2), 125.39 (5), 117.91 (CN), 94.49 (CH=C), 66.64 (ArCH_2O), 53.00 (CH_3O), 31.84 (6′), 31.51 (2′), 29.33 (3 C, 3′, 4′, 5′), 24.09 (1′), 22.65 (7′), 14.06 (8′), 9.96 (3-CH_3).

5-[(*E*)-2-Cyano-2-(methoxycarbonyl)ethenyl]-3-methyl-4-octyl-2-pyrrolecarboxylic Acid (14c). A solution of the preceding benzyl ester (**13c**) (131.0 g, 0.30 mol) and triethylamine (1 mL) in tetrahydrofuran (750 mL) was stirred with 10% Pd–C (4 g) under H_2 (1 atm, room temperature) until the rate of H_2 consumption fell appreciably after the first equivalent (7300 mL at room temperature) had reacted (90 min). A standard hydrogenator manifold was employed, with a 1-L buret, which needed constant attention until the rapid reaction was over.

The catalyst was filtered off at once and washed with ethanol until the rinsings were colorless. The solvent was removed in vacuo (*Caution*: foaming), and chased with acetic acid (100 mL). The solids were slurried in glacial acetic acid (150 mL) and diluted gradually with H_2O (4 × 100 mL). The solids were filtered off, washed with H_2O, and dried. Yield 100.9 g (97%); mp mostly 117–119.5 °C (some needles crystallized from the melt and remelted sharply at 126–126.5 °C).

Anal. (first crop) Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.95; H, 7.53; N, 8.02.

^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6 Hz, octyl-8), 1.28 (12 H, br s, octyl), 2.33 (3 H, s, 3-Me), 2.60 (2 H, t, J = 7 Hz, octyl-1), 3.91 (3 H, s, CH_3O), 8.04 (1 H, s, vinyl), 9.07 (1 H, v br s, CO_2H), 10.24 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.10) δ 165.78 (CO_2H), 163.32 (CO_2Me), 139.29 (CH=C), 138.56 (4), 128.28 (3?), 126.14 (2?), 125.41 (5), 117.66 (CN), 95.32 (CH=C), 53.22 (CH_3O), 31.85 (6′), 31.53 (2′), 29.37 , 29.35, 29.24 (3 C, 3′, 4′, 5′), 24.10 (1′), 22.66 (7′), 14.09 (8′), 10.07 (3-CH_3).

Methyl (*E*)-2-Cyano-3-(5-iodo-4-methyl-3-octyl-2-pyrrolyl)propenoate (15c). A magnetically stirred suspension of the preceding carboxypyrrole (**14c**) (97.2 g, 0.28 mol) and anhydrous sodium acetate (76.8 g, 0.94 mol) in glacial acetic acid (500 mL) was treated at 60–70 °C, dropwise, with a solution of ICl (60.9 g, 0.38 mol) in glacial acetic acid (200 mL) over 35 min.

(49) Grigg, R.; Johnson, A. W.; Wasley, J. W. F. *J. Chem. Soc.* **1958**, 359–366.

(50) Eisner, U.; Lichtarowicz, A.; Linstead, R. P. *J. Chem. Soc.* **1957**, 733–739.

When TLC examination (CH_2Cl_2, silica GF) suggested traces of remaining **14c**, further ICl (10.9 g, 0.07 mol) in acetic acid (31 mL) was added.

Aqueous $NaHSO_3$ was added in small portions until the I_2 was reduced. H_2O and ice were added to dilute the mixture to 2 L. The crystalline product was filtered off, washed with H_2O, and heated in ethanol (500 mL, 100%). Minor persistent solids, 5.3 g, were filtered from the hot solution. (These proved to be a relatively pure sample of the *E* isomer, mp 130–133.5 °C, analyzed below.) The filtrates, 800 mL, including rinsings, afforded main crop of 90.7 g on cooling, filtering, and rinsing with 70% (v/v) aqueous ethanol. The combined filtrates were extracted into CH_2Cl_2, and the solvent was removed in vacuo. The residue was chromatographed over silica (201 g, Woelm Akt I) with CH_2Cl_2. The clean lemon yellow eluates afforded an additional 9.9 g. Combined yield 105.9 g (88%).

Anal. Calcd for $C_{18}H_{25}IN_2O_2$: C, 50.48; H, 5.88; N, 6.54; I, 29.63. Found: C, 50.49; H, 5.90; N, 6.51; I, 29.44.

^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6 Hz, octyl-8), 1.29 (12 H, br s, octyl), 2.02 (3 H, s, 4-Me), 2.61 (2 H, t, J = 7 Hz, octyl-1), 3.89 (3 H, s, CH_3O), 3.92 (3 H, minor isomer, CH_3O), 7.17 (1 H, s, minor isomer, vinyl), 7.86 (1 H, s, vinyl), 9.70 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.10) δ (principal isomer, *E*) 164.17 (C=O), 138.79 (3), 137.31 (*C*H=C), 128.45 (2), 127.48 (4), 119.05 (CN), 89.58 (CH=*C*), 84.53 (5), 52.73 (CH_3O), 31.84 (6′), 31.34 (2′), 29.36 (3 C, 3′, 4′, 5′), 25.00 (1′), 22.63 (7′), 14.06 (8′), 11.99 (4-CH_3); (minor isomer, *Z*) 166.89 (C=O), 137.99 (*C*H=C), 129.80 (2?), 119.43 (CN), 89.44 (CH=*C*), 85.85 (5), 52.94 (CH_3O), 31.64 (2′) (other peaks coincide).

Methyl (*E*)-2-Cyano-3-(4-methyl-3-octyl-2-pyrrolyl)-propenoate (16c). A thorough mixture of the preceding iodopyrrole (**15c**) (103.9 g, 0.24 mol) and zinc dust (103.3 g, 1.58 mol) in a 3-L Erlenmeyer flask was treated with glacial acetic acid (500 mL), and the mixture was agitated manually for several min. The slurry soon warmed spontaneously to around 55 °C, and the pyrrole dissolved.

Magnetic stirring now became possible and was maintained *without application of external heat* for 10–15 min after the dissolution of **15c**. The excess zinc was filtered off and washed thoroughly with methanol, until rinsings were colorless, and then H_2O. Product crystallized from the filtrates. This was filtered off, washed with 50% aqueous ethanol, and dried. Yield 69.4 g (94.7%). On standing, the filtrates deposited additional product (2.6 g).

The combined solids were recrystallized from ethanol–H_2O. Yield 63.1 g (86%); mp 79–101 °C. The product in the filtrates was isolated by extraction (CH_2Cl_2) and chromatography (CH_2Cl_2) over silica gel (101 g, Woelm Akt I). Yield, after crystallization from ethanol (150 mL, 100%)–H_2O (25 mL), 6.9 g. Total recovery 70.0 g (95.5%). Anal. (first crop) Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.58; H, 8.60; N, 9.31.

^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6 Hz, octyl-8), 1.25 (12 H, br s, octyl), 2.01 (3 H, s, 4-Me), 2.55 (2 H, t, J = 7 Hz, octyl-1), 3.80 (3 H, s, CH_3O), 7.00 (1 H, d, J = 3 Hz, 5-H), 7.26 (1 H, s, minor isomer, vinyl), 7.95 (1 H, s, vinyl), 9.80 (H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.21) δ (major isomer, *E*) 164.73 (C=O), 139.46 (2 C, 3, *C*H=C), 128.46 (5), 124.57 (2), 121.47 (4), 119.38 (CN), 87.90 (CH=*C*), 52.58 (CH_3O), 31.92 (6′), 31.57 (2′), 29.46 (3 C, 3′, 4′, 5′), 24.45 (1′), 22.70 (7′), 14.08 (8′), 9.85 (4-CH_3).

4-Methyl-3-octyl-2-pyrrolecarboxaldehyde (5c). A boiling solution of the preceding octylpyrrolecyanoacrylate (**16c**) (68.0 g, 0.225 mol) in methanol (500 mL) was treated with NaOH (40.1 g, 1 mol) in H_2O (100 mL) under N_2. Methanol was distilled off over an hour, as H_2O was added periodically to maintain the volume (*Caution*: foaming). The distillates were saved to recover minor volatile product.

At 100 °C, a brown oily phase separated, leaving a nearly colorless aqueous phase. The product solidified on cooling overnight. Yield 52.12 g (104.7%; some incompletely hydrolyzed precursor had been extracted into the product phase). The product was recrystallized from methanol, giving successive crops of 35.1, 7.9, and 3.9 g. Total 46.9 g (94.1%); mp 78.0–79.5 °C.

Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.68; H, 10.68; N, 6.26.

^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6 Hz, octyl-8), 1.24 (12 H, br s, octyl), 1.98 (3 H, s, 4-Me), 2.66 (2 H, t, J = 7.5 Hz, octyl-1), 6.83 (1 H, d, J = 2 Hz, 5-H), 9.52 (1 H, s, CHO), 10.04 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.07) δ 177.51 (CHO), 136.74 (3), 129.53 (2), 125.69 (5), 120.39 (4), 31.92 (2 C, 2′, 6′), 29.50 (3 C, 3′, 4′, 5′), 23.83 (1′), 22.71 (7′), 14.09 (8′), 9.64 (4-CH_3).

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Registry No. **5a**, 32928-30-6; **5b**, 19711-71-8; **5c**, 113998-96-2; **7** (R_1 = R_2 = CH_3), 2199-46-4; **10a**, 1925-61-7; **10b**, 61538-85-0; **10c**, 113998-88-2; **11a**, 13219-63-1; **12a**, 965-20-8; **12c**, 113998-89-3; **13a**, 98619-41-1; **13b**, 113998-77-9; **13c**, 113998-90-6; **14a**, 113998-78-0; **14b**, 113998-79-1; **14c**, 113998-91-7; **15a**, 113998-80-4; (*Z*)-**15a**, 113998-81-5; **15b**, 113998-82-6; (*Z*)-**15b**, 113998-83-7; **15c**, 113998-92-8; (*Z*)-**15c**, 113998-93-9; **16a**, 113998-84-8; **16b**, 113998-85-9; (*Z*)-**16b**, 113998-86-0; **16c**, 113998-94-0; (*Z*)-**16c**, 113998-95-1; **22**, 2199-44-2; **23**, 63892-47-7; **24**, 113998-87-1; **26**, 52649-13-5; **27**, 113998-97-3; **28**, 113998-98-4; **29**, 113998-99-5; (*Z*)-**29**, 113999-00-1; **30**, 113999-01-2; **31a**, 85057-78-9; **31b**, 109162-14-3; **32a**, 4391-95-1; **32b**, 113999-02-3; **33a**, 938-75-0; **33b**, 97336-41-9; **35b**, 16200-52-5; **37a**, 822-51-5; **37b**, 1006-26-4; **41b**, 4949-45-5; **42b**, 114130-25-5; **44b**, 113999-03-4; **45b**, 113999-04-5; **46a**, 5448-14-6; **46b**, 113999-05-6; **47a**, 49569-11-1; **47b**, 113999-06-7; **48b**, 114031-41-3; **49a**, 42953-50-4; **49b**, 113999-07-8; **51**, 2199-49-7; **52**, 6339-66-8; methyl cyanoacetate, 105-34-0; octanoyl chloride, 111-64-8; 3,4-dimethyl-2-pyrrolecarboxylic acid, 89776-55-6; 3,4-dimethylpyrrole, 822-51-5; malononitrile, 109-77-3; 2-(2,2-dicyanoethenyl)-3,4-diethylpyrrole, 59435-31-3; ethyl acetoacetate, 141-97-9.

Supplementary Material Available: NMR chemical shift data and detailed synthetic procedures for **13b**, **14b**, **15b**, **16b**, **5b**, **27**, **28**, **29**, **31a**, **32a**, **33a**, **35a**, **37a**, **32b**, **33b**, **35b**, **37b**, **44b**, **45b**, **46b**, **47b**, **48b**, **49b**, **52**, **47a**, and **49a** (14 pages). Ordering information is given on any current masthead page.