(26) on the basis of its spectral properties: IR (neat) 3080, 3010, 2920, 1730, 1680, 1600, 1585, 1450, 1315, 1295, 1265, 1235, 1200, 1010, 890, 770, and 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, 1 H, J = 9.9 Hz), 1.77 (d, 1 H, J = 9.9 Hz), 2.06-2.18 (m, 1 H), 2.23-2.37 (m, 1 H), 2.60-2.70 (m, 1 H), 2.84 (br s, 1 H), 2.91 (br d, 2 H, J = 4.5 Hz), 3.45 (s, 1 H), 7.47 (t, 2 H, J = 8.0 Hz), 7.56 (t, 1 H, J = 7.0 Hz), and 7.94 (d, 2 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.2, 35.6, 38.6, 39.0, 39.9, 46.1, 47.0, 128.5, 128.7, 133.3, 135.2, 196.8, and 213; HRMS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.1001.

Preparation and Rhodium(II) Acetate Catalyzed Reaction of *cis*-2-Benzoyl-1-(diazoacetyl)cyclopentane (28). A solution containing 1.03 g of *cis*-2-benzoylcyclopentanecarboxylic acid[56] and 0.51 mL of methyl chloroformate in 30 mL of ether and 15 mL of tetrahydrofuran was treated with 0.92 mL of triethylamine. After being stirred for 2 h under a nitrogen atmosphere, the solution was filtered and was then treated with an excess of diazomethane in ether. The reaction mixture was slowly allowed to warm from 0 °C to room temperature over a 12-h interval. The solvent was removed under reduced pressure, and the resulting oil was purified via silica gel flash chromatography using a 3:1 hexane-ethyl acetate mixture as the eluent. The first component eluted from the column contained 0.8 g of hexahydro-2-oxa-3-methoxy-3-phenylpentalen-1-one: IR (neat) 2960, 2890, 1800, 1775, 1455, 1265, 1175, 960, 770, and 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.1-1.4 (m, 3 H), 1.8-2.0 (m, 3 H), 3.13 (dt, 1 H, J = 7.4 Hz and 7.2 Hz), 3.32 (dt, 1 H, J = 8.4 and 3.3 Hz), 3.50 (s, 3 H), and 7.2-7.4 (m, 5 H).

The second material eluted from the column contained 0.17 g (15%) of *cis*-2-benzoyl-1-(diazoacetyl)cyclopentane (**28**): IR (neat) 2980, 2130, 1680, 1635, 1450, 1375, and 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60-2.10 (m, 6 H), 3.01 (q, 1 H, J = 8.0 Hz), 4.01 (dt, 1 H, J = 7.7 and 7.0 Hz), 5.20 (s, 1 H), 7.33-7.48 (m, 3 H), and 7.82-7.85 (m, 2 H).

To a solution containing 90 mg of *cis*-2-benzoyl-1-(diazoacetyl)cyclopentane (**28**), 0.05 mL of dimethyl acetylenedicarboxylate, and 5 mL of benzene was added 3 mg of rhodium(II) acetate. The solution was stirred at room temperature under a nitrogen atmosphere for 4.5 h. After filtration, the solvent was removed under reduced pressure and the resulting residue was purified via silica gel flash chromatography using a 10:1 hexane-ethyl acetate mixture as the eluent. The major fraction contained a yellow oil (75%), whose structure was assigned as dimethyl 1,2,3,3a,4,7,8,8a-octahydro-4-phenyl-8-oxo-4,7-epoxyazulene-5,6-dicarboxylate (**30**): IR (neat) 2980, 1730, 1660, 1450, 1435, 1330, 1255, 1145, 1020, and 755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80-1.70 (m, 4 H), 1.9-2.1 (m, 2 H), 3.14 (ddd, 1 H, J = 8.7, 8.6, and 5.5 Hz), 3.2-3.4 (m, 1 H), 3.65 (s, 3 H), 3.74 (s, 3 H), 5.10 (s, 1 H), and 7.2-7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.4, 28.7, 28.9, 46.1, 46.8, 52.6, 86.0, 92.9, 125.4, 128.1, 128.3, 131.7, 137.5, 151.2, 160.8, 164.4, and 202.2; UV (95% ethanol) 240 (ϵ 7100) and 322 nm (560); HRMS calcd for $C_{20}H_{20}O_6$ 356.1259, found 356.1246.

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Synthesis of Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles by Double Fischer Indolizations

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A synthesis of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles (**16**) based on a double Fischer indolization of the bis(phenylhydrazones) (**10**), employing polyphosphoric acid trimethylsilyl ester (PPSE) as the cyclization agent, is described. The bis(phenylhydrazones) (**10**) were prepared by a Diels-Alder reaction of 2,3-bis[(trimethylsilyl)oxy]butadiene (**6**) with the dienophiles **7** followed by reaction with the appropriate substituted phenylhydrazines (**9**). By use of this methodology arcyriaflavin A (**4a**) and the aglycon (**16d**) of the antitumor alkaloid rebeccamycin as well as a number of analogues of this class of alkaloids have been prepared.

The classical Fischer indole synthesis has been and still is the most frequently used method for the preparation of indoles.[1] Its versatility has continuously been expanded by the introduction of a wide range of new catalysts, which has allowed construction of more sensitive substances and improved yields and selectivity.

In our efforts[2] to explore new routes[3] to indolocarbazole alkaloids,[4-9] such as the protein kinase inhibitors staurosporine (**1**)[10] and K-254a (**2**),[11] the antitumoral rebeccamycin (**3**),[12] and the arcyriaflavins (**4**),[4,13] it was desirable

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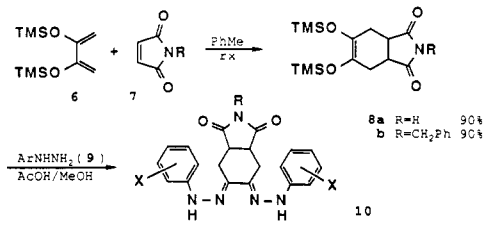
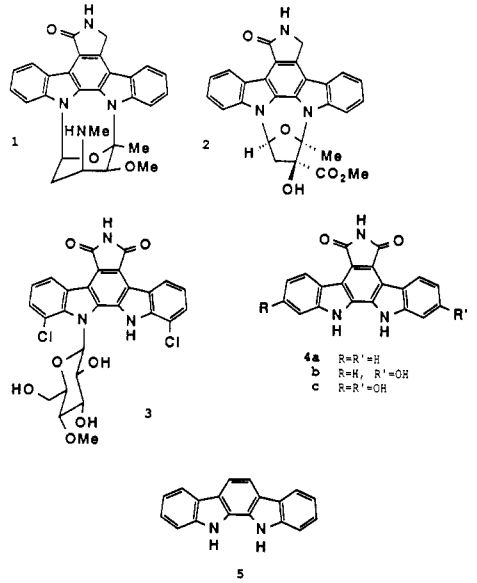
Scheme I



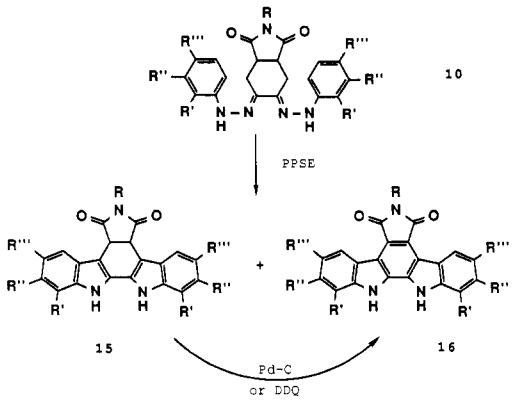
to investigate if a process based on a double Fischer indolization could be utilized. As indolo[2,3-a]carbazole (**5**)



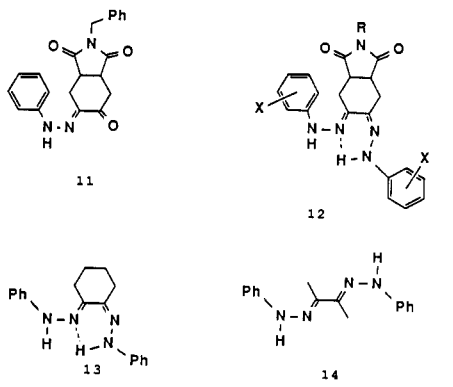
is readily prepared from 1,2-cyclohexanedione[14] by the Fischer indole synthesis, this approach might seem straightforward. The use of conventional catalysts (HCl/EtOH, H_2SO_4, PPA, $BF_3{\cdot}OEt_2$/AcOH, etc.)[1] in the cyclization of **10a** was, however, found to give complex mixtures. In this paper we describe the use of polyphosphoric acid trimethylsilyl ester (PPSE) to perform an efficient double Fischer indolization. PPSE has been successfully employed in a number of different syntheses,[15-17] but only one example of a Fischer indole synthesis (2-ethyl-3-methylindole from diethyl ketone) has been documented.[17] Although the yield was high, PPSE does not offer any real advantage in this particular case.

The required bis(phenylhydrazones) (**10**) were prepared according to Scheme I. Reaction of 2,3-bis[(trimethylsilyl)oxy]butadiene (**6**) with the maleimides **7** readily yielded the cycloadducts **8**,[18] which can be regarded as bis(trimethylsilyl)-protected α-hydroxy ketones. The latter react as such[1] with 3 equiv of arylhydrazines (**9**) to give the 1,2-bis(phenylhydrazones) (**10**). In the reaction of **8a** with phenylhydrazine (**9a**) we were also able to isolate a small amount of the α-oxoarylhydrazone **11**, which on reaction with 1 equiv of (2-chlorophenyl)hydrazine afforded the unsymmetrical bis(phenylhydrazone) **10m**. The ^1H NMR spectra of the bis(phenylhydrazones) revealed that they exist in the chelated form (**12**), causing a large downfield shift of the chelated proton. This phenomenon has previously been observed for sugar osazones[19] and for the bis(phenylhydrazone) of 1,2-cyclohexanedione (**13**).[20] The bis(phenylhydrazone) of biacetyl (**14**),[20] on the other hand, exists in the symmetrical form.

Scheme II[a]



[a] **a**, R = CH_2Ph, R′ = R″ = R‴ = H; **b**, R = R′ = R″ = R‴ = H [**16b**, arcyriaflavin A (**4a**)]; **c**, R′ = OMe, R = R″ = R‴ = H; **d** R′ = Cl, R = R″ = R‴ = H; **e**, R″ = OMe, R = R′ = R‴ = H; **f**, R″ = Br, R = R′ = R‴ = H; **g**, R‴ = OMe, R = R′ = R″ = H; **h**, R‴ = F, R = R′ = R″ = H; **i**, R‴ = Cl, R = R′ = R″ = H; **j**, R‴ = Br, R = R′ = R″ = H; **k**, R‴ = NO_2, R = R′ = R″ = H; **l**, R′ = R‴ = Cl, R = R″ = H.



Compound **10a** was employed as a model substrate in the Fischer indolization reaction as the desired product

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16a is known and easily prepared by other routes.[2,5] It was found that indolization of **10a** with PPSE, neat or with sulfolane[15] as cosolvent (130 °C, 2 h), afforded the dihydroindolocarbazole **15a** together with some of the fully aromatized compound **16a**. These reaction conditions were found to be unsatisfactory, however. Starting material was recovered when the reaction was performed without solvent due to difficulties in obtaining homogeneous reaction mixtures, and the use of sulfolane was problematic as it was difficult to extract or filter aqueous solutions containing sulfolane. From the reaction mixtures of certain bis(phenylhydrazones) it was difficult to obtain products free from sulfolane (even after chromatography!). The problems were finally solved by replacement of sulfolane with nitromethane, a solvent that apparently has not been used in PPSE-promoted reactions.

Usually, mixtures of **15** and the fully aromatized product **16** were formed (Scheme II). It was found in some cases that complete aromatization could be affected on prolonged treatment with PPSE/$MeNO_2$, but it was usually more convenient to prepare the fully aromatized indolocarbazoles by dehydrogenation of the crude reaction mixtures with Pd–C in refluxing diglyme or with DDQ, especially for the methoxy-substituted compounds, which decomposed during long reaction times. The dihydro compounds **15c–d**, having substituents in the ortho positions, aromatized more reluctantly, most likely as a consequence of the strain encountered from the ortho substituents when the molecule is forced into a nearly planar configuration. As expected, **10e**, which is principle can give products with substituents in the indolic 4- and/or 6-positions, gave **15e**/**16e**. Severe steric repulsion between the methoxy groups and the carbonyl oxygens would be the result in the alternative cyclization. In the case of **10f** and **10l**, mixtures of indolopyrrolocarbazoles were formed, probably as a result of migration or loss of the halogen substituents, a well-known phenomenon in the Fischer indole synthesis.[1] Finally, the bis(hydrazone) **10k**, with its strongly electron-withdrawing nitro groups, was virtually inert under the cyclization conditions employed.

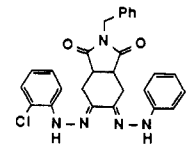
The difference between **16**, which are planar molecules, and **15**, which are nonplanar, is reflected in their ^1H NMR spectra. While the aromatic protons in **15** have normal shifts, the protons in the indolic 4-position in **16** are shifted ~1 δ unit downfield as they are forced in proximity to the magnetic field of the carbonyl groups.

Finally it should be mentioned that **13** readily gave the unsubstituted indolo[2,3-*a*]carbazole **5** with PPSE/$MeNO_2$. It was not possible, however, to synthesize 2,2′-biindolyl from **14** employing these conditions.

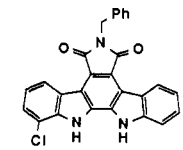
In summary, a short and very efficient synthesis of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles such as arcyriaflavin A (**4a**) and the rebeccamycin aglycon (**16d**) has been developed. Both compounds have been synthesized previously by other routes.[4,7a] The new approach is applicable in the synthesis of a large number of substituted compounds and does not require expensive or inaccessible starting materials. The use of α-oxoarylhydrazones **11** or analogoues thereof as starting materials also makes this route attractive for the synthesis of unsymmetrically substituted indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles (e.g. **16m**). It should also be possible to further expand the versatility of this approach to the synthesis of analogues of the indolocarbazole alkaloids by using different dienophiles in the reaction with **6**.

Experimental Section

All reactions were performed under a positive pressure of nitrogen. Hexanes and EtOAc used for chromatography were distilled. Sulfolane and nitromethane were dried over 4-Å molecular sieves. All arylhydrazines, except **9d**,[21] were commercially available or prepared from the commercially available hydrochlorides. Melting points were determined on a Reichert WME Kofler hot stage and are uncorrected. ^1H NMR spectra were recorded on a Bruker VP-200 (200 MHz) instrument. IR spectra (KBr disks) were obtained by using a Perkin-Elmer 257 instrument or a Perkin-Elmer FT-IR 1710. MS (70 eV) were obtained with a LKB-9000 spectrometer.



10m



16m

***N*-Benzyl-5,6-bis[(trimethylsilyl)oxy]-3a,4,7,7a-tetrahydroisoindole-1,3-dione (8a).** A mixture of *N*-benzylmaleimide (**7a**)[22] (4.68 g, 25 mmol), **6**[18f,g] (5.76 g, 25 mmol), and dry toluene (25 mL) was refluxed for 24 h, cooled, and concentrated. Distillation (bulb-to-bulb, 180 °C, 0.05 mbar) gave **8a** (9.39 g, 90%) as a white solid: mp 114–117 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4–7.2 (5 H, m), 4.63 (2 H, s), 3.0 (2 H, m), 2.5 (4 H, m), and 0.11 (18 H, s); IR 3185, 3073, 2960, 2902, 1783, 1709, 1362, 1344, 1268, 1251, 1235, 1196, 1011, 920, 906, 876, 851 cm^{-1}. An analytical sample was obtained by redistillation (bulb-to-bulb). Found: C, 60.25; H, 7.36; N, 3.25. Calcd: C, 60.40; H, 7.48; N, 3.35.

5,6-Bis[(trimethylsilyl)oxy]-3a,4,7,7a-tetrahydroisoindole-1,3-dione (8b) was prepared as above from maleimide (2.43 g, 25 mmol). Bulb-to-bulb distillation (170 °C, 0.05 mbar) gave **8b** (7.39 g, 90%) as a white solid: mp 120–122 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00 (1 H, s), 3.02 (2 H, m), 2.44 (4 H, m), and 0.07 (18 H, s); IR 3090, 3064, 3036, 2958, 2903, 1698, 1428, 1404, 1343, 1250, 1235, 1193, 962, 903, 846 cm^{-1}. An analytical sample was obtained by redistillation (bulb-to-bulb). Found: C, 51.16; H, 7.79; N, 4.30. Calcd: C, 51.34;, H, 7.69; N, 4.27.

Preparation of Bis(arylhydrazones) (10). General Procedure. A mixture of the appropriate arylhydrazine (**9**) (16 mmol), **8** (5 mmol), MeOH (10 mL), and AcOH (10 mL) was refluxed for 6 h and allowed to cool. The products were obtained after flash chromatography, following an ordinary extractive workup procedure with EtOAc (**10a**/**11**), or precipitated from the reaction mixture (**10b–l**). All compounds were yellow solids.[23]

10a and the Monophenylhydrazone 11. Flash chromatography (CH_2Cl_2/1% MeOH) yielded the following. (a) Compound **11** (0.20 g, 11%) as a yellow foam that crystallized on trituration with Et_2O: mp 132–133 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 10.77 (1 H, s), 7.4–7.0 (10 H, m), 4.62 (2 H, s) 3.3 (2 H, m), 3.1 (2 H, m), and 2.8 (2 H, m); IR 1770, 1695, 1525, 1400, 1345, 1225, 1155, 1125, 960, 760, 705, and 700 cm^{-1}; MS 361 (M^+). Found: C, 69.82; H, 5.35; N, 11.86. Calcd: C, 69.79; H, 5.30; N, 11.63. (b) The bis(hydrazone) **10a** (0.81 g, 60%): sinters at ~115 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 12.43 (1 H, s), 7.60 (1 H, s), 7.4–6.9 (15 H, m), 4.59 (2 H, q), 3.3 (2 H, m), and 3.0 (4 H, m); IR 3330, 1780, 1690, 1600, 1575, 1500, 1250, 1160, 965, 755, and 695 cm^{-1}; MS 451 (M^+).

10b: yield 91%; mp 263–265 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 12.57 (1 H, s), 11.20 (1 H, s), 9.93 (1 H, s), 7.3–7.0 (8 H, m), 6.9–6.7 (2 H, m), 3.14 (4 H, m), and 2.75 (2 H, m); IR 3340, 3200 (broad), 3050, 1775, 1695, 1590, 1500, 1360, 1250, 1155, 1045, 755, and 695 cm^{-1}; MS 361 (M^+).

10c: yield 66%; mp 246–248 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 12.03 (1 H, s), 11.26 (1 H, s), 8.62 (1 H, s), 7.5–7.4 (2 H, m), 7.1–6.8 (6 H, m), 3.91 (3 H, s), 3.85 (3 H, s), 3.3–3.1 (4 H, m), and 2.9–2.7 (2 H, m); IR 3370, 3180 (broad), 3050, 1780, 1700, 1600, 1575, 1510, 1255, 1220, 1160, 1015, and 745 cm^{-1}.

10d: yield 59%; mp 261–263 °C; ^1H NMR (200 MHz,

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(23) The bis(arylhydrazones) **10** were used without any further purification. Attempted recrystallization caused some decomposition. Acceptable elemental analytical data could not be obtained.

DMSO-d_6) δ 12.24 (1 H, s), 11.27 (1 H, s), 8.99 (1 H, s), 7.6–6.8 (8 H, m), 3.2 (4 H, m), and 2.8 (2 H, m); IR 3370, 3150 (broad), 3060, 1780, 1710, 1600, 1585, 1490, 1355, 1240, 1150, 1035, and 750 cm^{-1}.

10e: yield 72%; mp 249–250 °C; ^1H NMR (200 MHz, CD_3CN) δ 12.58 (1 H, s), 8.9 (1 H, s), 8.51 (1 H, s), 7.3–7.1 (2 H, m), 6.7 (4 H, m), 6.6–6.4 (2 H, m), 3.79 (6 H, d), 3.3 (4 H, m), and 2.8 (2 H, m); IR 3320, 3180 (broad), 1780, 1700, 1605, 1585, 1155, 1045, 1010, 760, and 690 cm^{-1}.

10f: yield 43%; mp 260 °C dec; ^1H NMR (200 MHz, DMSO-d_6) δ 12.52 (1 H, s), 11.26 (1 H, s), 10.20 (1 H, s), 7.3–7.0 (8 H, m), 3.2 (4 H, m), and 2.8 (2 H, m).

10g: yield 36%; mp 255–257 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 12.55 (1 H, s), 11.263 (1 H, s), 9.76 (1 H, s), 7.1–6.9 (8 H, m), 3.74 (3 H, s), 3.70 (3 H, s), 3.2 (4 H, m), and 2.8 (2 H, m).

10h: yield 73%; mp >300 °C dec; ^1H NMR (200 MHz, DMSO-d_6) δ 12.53 (1 H, s), 11.27 (1 H, s), 9.99 (1 H, s), 7.3–7.1 (8 H, m), 3.2 (4 H, m), and 2.8 (2 H, m); IR 3330, 3180 (broad), 3080, 1775, 1690, 1585, 1505, 1355, 1260, 1190, 1045, 830, 760, and 745 cm^{-1}.

10i: yield 52%; mp >300 °C dec; ^1H NMR (200 MHz, DMSO-d_6) δ 12.60 (1 H, s), 11.34 (1 H, s), 10.20 (1 H, s), 7.5–7.1 (8 H, m), 3.3 (4 H, m), and 2.9–2.8 (2 H, m); IR 3330, 3190 (broad), 3070, 1780, 1700, 1585, 1490, 1345, 1255, 1160, 1090, 1045, and 820 cm^{-1}.

10j: yield 55%; mp >300 °C dec; ^1H NMr (200 MHz, DMSO-d_6) δ 12.53 (1 H, s), 11.27 (1 H, s), 10.44 (1 H, s), 7.53 (2 H, d), 7.42 (2 H, d), 7.07 (4 H, m), 3.2 (4 H, m), and 2.8 (2 H, m); IR 3340, 3190 (broad), 3070, 1780, 1695, 1580, 1490, 1350, 1255, 1150, 1070, 1045, 820, and 810 cm^{-1}.

10k: yield 53%; mp >300 °C dec; ^1H NMR (200 MHz, DMSO-d_6) δ 12.73 (1 H, s), 11.33 (1 H, s), 10.88 (1 H, s), 8.32 (2 H, d), 8.20 (2 H, d), 7.3–7.2 (4 H, m), 3.3 (4 H, m), and 2.9 (2 H, m).

10l: yield 55%; mp 302–304 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 12.35 (1 H, s), 11.31 (1 H, s), 9.22 (1 H, s), 7.6–7.3 (6 H, m), 3.2 (4 H, m), and 3.0–2.8 (2 H, m); IR 3330, 3190 (broad), 3080, 1775, 1710, 1590, 1490, 1270, 1160, 1095, 1015, 820, and 800 cm^{-1}.

10m. A mixture of **11** (140 mg, 0.39 mmol), (2-chlorophenyl)hydrazine (60 mg, 0.4 mmol), AcOH (2 mL), and MeOH (2 mL) was refluxed for 3 h, allowed to cool to room temperature, and refrigerated to give **10m**: yield 91 mg (48%); mp 248–250 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 12.05 (1 H, s), 9.90 (1 H, s), 7.55 (1 H, dd), 7.4–7.2 (6 H, m), 7.0–6.8 (7 H, m), 3.4 (4 H, m), and 2.8 (2 H, m).

PPSE-Induced Indolization of the Bis(arylhydrazones) 10. General Procedure. PPSE was prepared[15] by refluxing a mixture of P_2O_5 (0.7 g, 5 mmol), hexamethyldisiloxane (1.7 mL, 8 mmol), and CH_2Cl_2 (5 mL) for 30 min whereafter the flask was equipped with a distillation head and the volatile materials were removed by gradually increasing the temperature at 160 °C. The bis(hydrazone) **10** (1 mmol) was added in one portion at 130 °C, immediately followed by $MeNO_2$ (5 mL). The mixture was heated at 130 °C for 1–43 h (see below), allowed to cool, and poured into water.

Preparation of 6-Benzylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (16a) and the Corresponding 4c,7a-Dihydro Derivative (15a) from the Bis(phenylhydrazone) 10a. After being heated for 2 h with PPSE/$MeNO_2$ the mixture was poured into water and extracted twice with EtOAc. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc/hexanes, 2:1) gave the following. (a) Compound **15a** (0.31 g, 74%) as a pale yellow solid, which partly aromatized on attempted recrystallization: mp 205–210 °C; MS 417 (M^+). (b) Compound **16a** (0.05 g, 12%) as a yellow solid: mp 308–310 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 11.72 (2 H, s), 8.97 (2 H, d), 7.80 (2 H, d), 7.56 (2 H, m), 7.4–7.3 (7 H, m), and 4.89 (2 H, s); MS 415 (M^+, 100). This product was identical with samples prepared by other routes.[2a,5]

Dehydrogenation of the 4c,7a-Dihydro Derivative 15a to 16a. The dihydro compound **15a** (0.21 g, 0.5 mmol) was refluxed in diglyme (5 mL) containing a catalytic amount of Pd–C (10%) for 15 h. The mixture was allowed to cool, filtered through Celite, and poured into water. On standing a precipitate formed, which was collected by filtration and dried to give **16a** (0.19 g, 82%).[24]

4c,7a-Dihydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)-dione (15b). After **10b** was heated for 2 h with PPSE/$MeNO_2$, the mixture was poured into water and extracted three times with EtOAc. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (CH_2Cl_2/MeOH, 95:5) gave **15b** (0.21 g, 64%) as an orange foam, which partly aromatized on attempted recrystallization: ^1H NMR (200 MHz, DMSO-d_6) δ 11.52 (1 H, s), 11.03 (2 H, s), 7.86 (2 H, d), 7.49 (2 H, d), 7.09 (4 H, m), and 4.82 (2 H, s); IR 3550 (broad), 3320 (broad), 3050, 1765, 1690, 1600, 1435, 1335, 1250, 1150, 1010, and 745 cm^{-1}. MS: 327 (M^+, 100), 325 (33), 256 (89), 255 (53), 128 (41).

Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (Arcyriaflavin A) (4a).[4d] After **10b** was heated for 2 h with PPSE/$MeNO_2$, the mixture was poured into water with water, and the solid formed was collected by filtration and dried. The solid, diglyme (10 mL), and a catalytic amount of Pd–C (10%) were heated at reflux for 24 h. The mixture was filtered hot, and the orange filtrate was allowed to cool and poured into water. The precipitate formed was collected by filtration and dried (200 °C, 0.05 mbar) to give **4a** (0.22 g, 68%) as an orange solid: mp >360 °C (lit.[4d] mp >300 °C); ^1H NMR (200 MHz, DMSO-d_6) δ 11.73 (2 H, s), 10.95 (1 H, s), 9.00 (2 H, d), 7.82 (2 H, d), 7.56 (2 H, m), and 7.36 (2 H, m); IR 3500–3000 (br), 1744, 1680, 1565, 1404, 1331, 1246, 1013, 810, 748 cm^{-1}.

16c. After **10c** was heated for 1 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried. The solid, DDQ (0.23 g, 1 mmol), and EtOAc (25 mL) were refluxed for 24 h. The mixture was cooled and filtered, and the solid was washed thouroughly with EtOAc and dried (200 °C, 0.05 mbar) to give **16c** (0.26 g, 60%) as a brown solid: mp >360 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 11.72 (2 H, s), 10.97 (1 H, s), 8.53 (2 H, d), 7.29 (2 H, t), 7.16 (2 H, d), and 4.09 (6 H, m).

1,11-Dichloroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)-dione (the Aglycon of Rebeccamycin) (16d).[7] After **10d** was heated for 22 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried. The solid, DDQ (0.23 g, 1 mmol), and EtOAc (25 mL) were refluxed for 24 h. The mixture was cooled and filtered, and the solid was washed thouroughly with EtOAc and dried (200 °C, 0.05 mbar) to give **16d** (0.31 g, 79%) as golden yellow needles: mp >360 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 11.86 (2 H, s), 11.11 (1 H, s), 8.87 (2 H, d), 7.64 (2 H, d), and 7.35 (2 H, m). An analytical sample was obtained from DMF. Found: C, 61.24; H, 2.42; N, 10.52; Cl, 18.06. Calcd: C, 60.93; H, 2.28; N, 10.66; Cl, 17.99

Repetition of this experiment (10-mmol scale) gave 3.30 g (84%) of **16d** after recrystallization from DMF.

16e. After **10e** was heated for 2 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried. The solid, diglyme (10 mL), and a catalytic amount of Pd–C (10%) were heated at reflux for 24 h. The mixture was filtered hot, and the deep red solution was allowed to cool and poured into water. The precipitate formed was collected by filtration and dried (200 °C, 0.05 mbar) to give **16e** (0.19 g, 49%) as an orange solid: mp 252–254 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 11.49 (2 H, s), 10.85 (1 H, s), 8.79 (2 H, d), 7.29 (2 H, s), 6.94 (2 H, d), and 3.90 (6 H, s).

Indolization of 10f. After **10f** was heated for 20 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried to give an orange solid (0.50 g). ^1H NMR analysis revealed a mixture of isomers.

16g. After **10g** was heated, for 1 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried. The solid, DDQ (0.23 g, 1 mmol), and EtOAc (25 mL) were refluxed for 24 h. The mixture was filtered hot, and the solid was washed thouroughly with hot EtOAc and dried (200 °C, 0.05 mbar) to give **16g** (0.18 g 47%) as a brown solid: ^1H NMR (200 MHz, DMSO-d_6) δ 11.60 (2 H, s), 10.92 (1 H, s), 8.53 (2 H, s), 7.69 (2 H, d), 7.16 (2 H, d), and 3.90 (6 H, s); MS 385 (M^+, 100), 370 (19), 342 (8), 284 (12), 192 (10). Found:

(24) No cleavage of the benzyl group was observed.

C, 68.20; H, 3.85; N, 10.90. Calcd: C, 68.56; H, 3.92; N, 10.91.

16h. After **10h** was heated for 18 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried. The solid, diglyme (10 mL), and a catalytic amount of Pd-C (10%) were heated at reflux for 20 h. The mixture was allowed to cool, filtered, and poured into water. The precipitate formed was collected by filtration and dried (200 °C, 0.05 mbar) to give **16h** (0.22 g, 61%) as a red-brown solid: ^1H NMR (200 MHz, DMSO-d_6) δ 11.85 (2 H, s), 11.09 (1 H, s), 8.66 (2 H, dd), 7.9-7.8 (2 H, m), and 7.5-7.4 (2 H, m); MS 361 (M^+, 100), 290 (26), 180 (13), 145 (19).

Repetition of this experiment (10-mmol scale) gave the product in 80% yield after recrystallization from DMF.

16i. After **10i** was heated for 16 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried. the solid, diglyme (10 mL), and a catalytic amount of Pd-C (10%) were heated at reflux for 20 h. The mixture was filtered hot and allowed to cool. The precipitate formed was collected by filtration and dried (200 °C, 0.05 mbar) to give **16i** (0.18 g) as an orange crystalline solid: mp >360 °C. The analytical sample was recrystallized from DMF. Found: C, 61.20; H, 2.34; N, 10.37; Cl, 18.08. Calcd: C, 60.93; H, 2.28; N, 10.66; Cl, 17.99. A second crop (0.11 g) was obtained by pouring the filtrate into water and collecting the solid that formed: total yield 74%; ^1H NMR (200 MHz, DMSO-d_6) δ 11.98 (2 H, s), 11.16 (1 H, s), 8.98 (2 H, s), 7.88 (2 H, d), and 7.59 (2 H, m). MS 393 (M^+, 100), 358 (19), 323 (12), 287 (8). Peaks containing ^{37}Cl are not listed.

16j. After **10j** was heated for 20 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried. The solid was washed several times with hot EtOAc and dried (200 °C, 0.05 mbar) to give **16j** (0.36 g, 78%) as an golden-yellow solid: mp >360 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 11.94 (2 H, s), 11.14 (1 H, s), 9.10 (2 H, s), 7.81 (2 H, d), and 6.68 (2 H, d).

Indolization of 10l. After **10l** was heated for 43 h with PPSE/$MeNO_2$, the mixture was poured into water, and the solid formed was collected by filtration and dried to give an orange solid (0.47 g). ^1H NMR analysis revealed a mixture of isomers.

1-Chloroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (16m). After **10m** (64 mg, 0.13 mmol) was heated for 2 h with PPSE/$MeNO_2$, the mixture was poured into water and extracted twice with EtOAc. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to give an orange oil, which was refluxed with Pd-C (catalyst) and diglyme (2 mL) for 8 h, allowed to cool, filtered, and poured into water. The mixture was extracted twice with EtOAc. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to give an orange material, which was triturated with acetone to give **16m** (14 mg, 24%) as an orange solid, mp >360 °C.

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Registry No. **4a**, 118458-54-1; **6**, 31411-71-9; **7a**, 1631-26-1; **7** (R = H), 541-59-3; **8a**, 118458-37-0; **8b**, 118458-36-9; **9a**, 100-63-0; **9c**, 18312-46-4; **9d**, 10449-07-7; **9e**, 15384-39-1; **9f**, 40887-80-7; **9g**, 3471-32-7; **9h**, 371-14-2; **9i**, 1073-69-4; **9j**, 589-21-9; **9k**, 100-16-3; **9l**, 13123-92-7; **10a**, 118458-38-1; **10b**, 118458-40-5; **10c**, 118458-41-6; **10d**, 118458-42-7; **10e**, 118458-43-8; **10f**, 118458-44-9; **10g**, 118458-45-0; **10h**, 118458-46-1; **10i**, 118458-47-2; **10j**, 118458-48-3; **10k**, 118458-49-4; **10l**, 118458-50-7; **10m**, 118458-51-8; **11**, 118458-39-2; **15a**, 118458-52-9; **15b**, 118458-53-0; **16a**, 87259-91-4; **16c**, 118458-55-2; **16d**, 118458-56-3; **16e**, 118458-57-4; **16g**, 118458-58-5; **16h**, 118458-59-6; **16i**, 118458-60-9; **16j**, 118458-61-0; **16m**, 118458-62-1.

Investigation of the Synthesis of Ortho-Substituted Tetraphenylporphyrins

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Ortho-disubstituted tetraphenylporphyrins such as tetramesitylporphyrin have been widely used in model systems, but these "sterically hindered" porphyrins have been difficult to synthesize under mild as well as forcing conditions. Mesitaldehyde is highly discriminating in its exacting requirements for catalysis, but little steric hindrance is observed when these catalytic requirements are satisfied. A key feature of these catalytic conditions involves BF_3-ethanol cocatalysis. Application of these conditions to 14 ortho-substituted benzaldehydes resulted in a clear reactivity pattern: cocatalysis gave improved yields with 2-alkyl-, 2-alkoxy-, and 2,6-dialkoxybenzaldehydes, but six *o*-halogen-substituted benzaldehydes showed little or no increase. Four ortho-disubstituted aldehydes failed to react under any conditions. The structural effects of substituents can be partly understood by examining the packing of the aldehyde ortho substituents about the tetrahedral meso carbon in the porphyrinogen, the precursor to the porphyrin.

Introduction

Few classes of synthetic porphyrins have aroused more interest yet remained more difficult to prepare than the sterically hindered porphyrins.[1] Tetramesitylporphyrin, the test case for gauging the success of new methods for preparing sterically hindered porphyrins, has been prepared in yields of 1-6% by reaction of mesitaldehyde and pyrrole at >170 °C for 2-3 days in the presence of added metal salts.[2-6] That forcing conditions might be required to overcome steric hindrance with mesitaldehyde is hardly surprising; the concept of steric hindrance was first pos-

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