Porphyrin Analogues

Reductive N Alkylation of Cyclo[8]pyrroles**

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Cyclo[8]pyrrole (**1**), although lacking bridging meso carbon atoms, may be considered as a larger analogue of porphyrin (**2**) in that it is flat and aromatic (see Scheme 1).[1] For this reason, we have been interested in exploring the chemical behavior of cyclo[8]pyrrole and contrasting it to that of the porphyrins. In previous work, we have found that cyclo[8]pyrrole in its diprotonated form may be reduced electrochemically to produce a formally antiaromatic 32-π-electron species under conditions that are much less forcing than those needed to reduce typical porphyrins.[2] Here we report that cyclo[8]pyrrole, upon treatment with NaH and an alkyl halide, undergoes chemical reduction to produce an octa-N-

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Supporting information for this article (experimental details describing the synthesis of **3a** and **3b** and spectroelectrochemical/ESR/X-ray diffractions results) is available on the WWW under http://www.angewandte.org or from the author.

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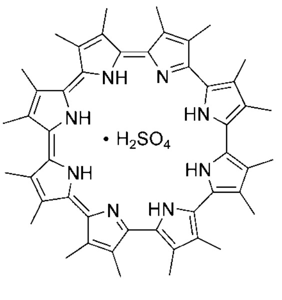
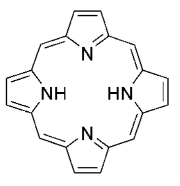


1a



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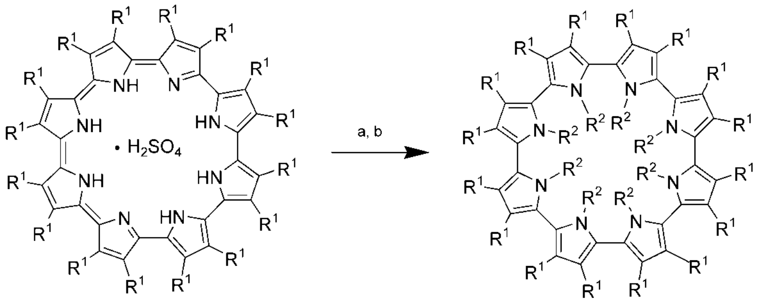


1

3

1a: R^1 = Me
1b: R^1 = Et

3a: R^1 = Et, R^2 = Me
3b: R^1 = Me, R^2 = Et
3c: R^1 = Me, R^2 = Bn

Scheme 1. Reaction sequence used to effect the reduction and N alkylation of cyclo[8]pyrroles **1**. a) NaH, THF, Ar, room temperature; b) R^2X, Ar, reflux, 12 h. R^2 = Me, Et, or Bn, Bn = benzyl.

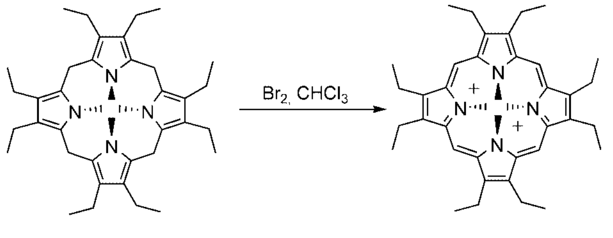
alkylated product, **3**. This reaction sequence is to the best of our knowledge without precedent in the literature regarding porphyrins. Furthermore, in the case of larger substituents, the synthesized products, namely **3b** and **3c**, are without direct analogy in the case of simple porphyrins/porphyrinogens.[3]

N,N′,N″,N‴-(tetramethyl)octaethylporphyrinogen (**4**), the porphyrin analogue of **3a**, was reported in a doctoral dissertation from the group of Professor Franck in 1986.[4] However, in contrast to **3a** (see below), **4** was not produced through reductive alkylation, but rather it was generated by the cyclization of N-substituted diethylpyrrole. Compound **4** is not only a direct analogue of **3a**, but it is also a historically important intermediate in porphyrin chemistry. In particular, Vogel et al. used it to produce the long-sought-after *N,N′,N″,N‴*-(tetramethyl)octaethylporphyrin dication (**5**) in 1989 (Scheme 2).[5]

Nonetheless, our own efforts to produce this nonaromatic, tetrapyrrolic macrocycle by using the reductive alkylation procedure to generate **3** failed to give isolable quantities of product.[6] This difference in reaction behavior thus highlights an important difference between porphyrin (**2**) and cyclo[8]pyrrole (**1**). It also underscores the fact that compounds **3** represent a new, potentially interesting class of functionalized oligopyrroles. Scheme 1 summarizes the chemistry involved in the conversion of **1** into **3**. Briefly, treatment of **1** with NaH under an inert atmosphere, followed by addition of an alkylating agent (methyl iodide, ethyl iodide, and benzyl bromide in the case of **3a**, **3b**, and **3c**, respectively), and heating the mixture at reflux for 12 h produces the corresponding N-alkylated derivatives **3** in 64–70% yield. In contrast to the diprotonated form of **1**, which dissolves in organic solvents to produce solutions that are yellow–brown in color, the products obtained in this way were essentially colorless. Such a lack of color is consistent with the absence of an extended conjugation pathway. Evidence for the proposed lack of aromaticity came from the ^{1}H NMR spectroscopic data. In contrast to the observations reported by Vogel for **5** ($\delta = -4.59$ ppm for the protons of the CH_3 group—a result of the diamagnetic ring current),[5] the signals of the N-alkylated fragments were not shifted upfield (e.g. for **3a**, the signals for the protons from CH_3 appear at $\delta = 2.65$ ppm).

Further support for the nonaromatic and unconjugated nature of **3** comes from solid-state X-ray diffraction structural analyses (Figure 1, A–C).[7–9] The structures of **3a**, **3b**, and **3c** reveal that the eight nitrogen substituents adopt an alternating up–down orientation. As a result, the macrocycle as a whole is highly distorted from planarity and appears to be almost bowl-like in nature. Whereas **3a** shows N_1-$C_{\alpha 1}$-$C_{\alpha 2}$-N_2 torsional angles of 67° (average), **3b** and **3c** are both characterized by smaller torsional angles (61° and 58°, respectively). Nonetheless, the alkyl fragments in **3b** and **3c** are located almost perpendicular to the mean plane of the heterocyclic ring. The compounds reveal bond lengths of approximately 1.37 Å for the C_α–C_β bonds in all three cases, whereas the C_β–$C_{\beta'}$ bond lengths are in the range of 1.40–1.42 Å. This nonequivalence in bond lengths is consistent with localized pyrrole aromaticity and stands in contrast to what is seen in the aromatic precursor **1** in which the pyrrolic C–C bond lengths are much more similar.[1] Furthermore, the C–C distances between adjacent pyrrole units in **3** are of the order of 1.46 Å, as expected for an electron-localized system that lacks extensive conjugation.

The hallmark of porphyrinogen systems is their ability to undergo oxidation to the corresponding aromatic systems: for example, the conversion of porphyrinogen **4** to the dication **5**. To test whether this might be possible with the reduced



4

5

Scheme 2. Oxidation of the N-tetramethylated porphyrinogen **4** to the aromatic dication **5**. For details, see reference [5].

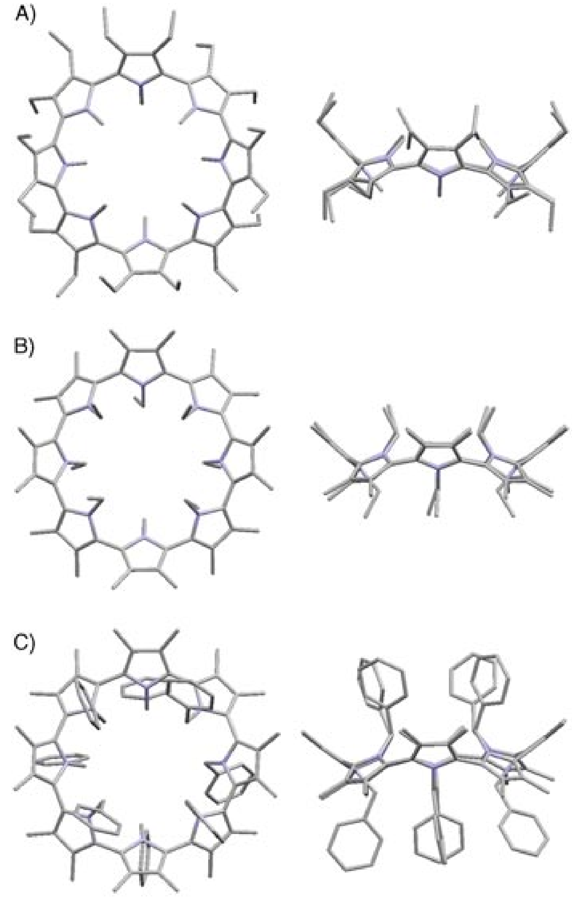


Figure 1. Single crystal X-ray diffraction analyses. Top and side views of mercury-rendered wire-frame structures of A) **3a**,[7] B) **3b**,[8] and C) **3c**.[9] Hydrogen atoms are removed for clarity; half a molecule of methylene chloride (**3a**) and one molecule of methylene chloride and half a molecule of benzene (**3c**) have also been omitted. Blue N.

cyclo[8]pyrrole derivative **3a**, a series of electrochemical and spectroelectrochemical studies were carried out in CH_2Cl_2 containing tetra-*n*-butylammonium perchlorate (TBAP, 0.1 or 0.2 M). Three reversible oxidations are observed at $E_{1/2} = 0.52$, 0.94, and 1.33 V, the first of which is a two-electron-transfer process. No reductions are seen under these experimental conditions up to a potential of −2.0 V vs SCE (saturated calomel electrode; see Figure 2A).

The N-alkylated macrocycle **3a** displays no significant absorption bands in the region $\lambda = 325$–1100 nm. However, upon two-electron oxidation of this species at 0.70 V in a thin-layer spectroelectrochemical cell, an initial product was observed and is assigned as the dication $\mathbf{3a}^{2+}$, which is characterized by a spectrum with two bands at $\lambda = 415$ and 1036 nm, respectively (see curve b in Figure 2B). The λ_{max} of these bands correspond to the Soret and Q-type bands seen for the diprotonated form of the 30-π-electron cyclo[8]pyrrole (**1a**). Upon further oxidation of $\mathbf{3a}^{2+}$ in a thin-layer cell at 1.10 V, a high intensity Q type band at $\lambda = 917$ nm is observed (see curve c in Figure 2B). This spectrum is assigned to the π-cation radical, $\mathbf{3a}^{3+}$, which has one unpaired electron as inferred from ESR measurements. Similar spectra were obtained upon bulk controlled-potential electrolysis. A summary of the spectral data is given in Table 1.[11]

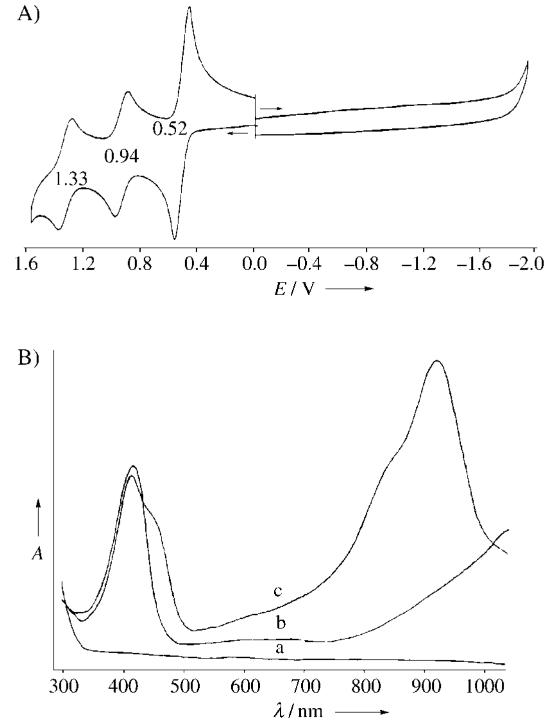


Figure 2. A) Cyclic voltammograms (vs SCE) of **3a** (in CH_2Cl_2 with TBAP (0.1 M)) and B) UV/Vis spectra of **3a** a) before and b) after the first two-electron oxidation at 0.70 V and c) after the second one-electron oxidation at 1.10 V (in CH_2Cl_2 with TBAP (0.2 M)).

Table 1: UV/Vis spectral data of 30-π-electron systems, determined from thin-layer spectroelectrochemistry in CH_2Cl_2.

compound	λ_{max} [nm] Soret band	 Q band
cyclo[8]pyrrole **1a**	431[a]	1112[a]
N-methylated cyclo[8]pyrrole dication $\mathbf{3a}^{2+}$	415	> 1040[b]
radical π cation $\mathbf{3a}^{3+}$	415[c]	917[c]
N-benzylated cyclo[8]pyrrole dication $\mathbf{3c}^{2+}$	450	> 1040[b]

[a] Taken from reference [1]. [b] Lower limit: the exact determination was limited by the spectral response of the instrument. [c] Shoulders are also observed at 447 nm and 845 nm.

Upon bulk controlled-potential electrolysis of **3a** at 0.70 V in CH_2Cl_2 containing TBAP (0.2 M) for 15 min, a strong signal in the ESR spectrum at $g = 2.004$ was observed (see Supporting Information). However, when the controlled-potential electrolysis was carried out for a longer time (45 min), the intensity of the signal of the ESR spectrum decreased and became negligible. This leads us to suggest that a comproportionation reaction occurs between the neutral compound, **3a**, and the oxidized species, presumably $\mathbf{3a}^{2+}$, which is produced as the result of a two-electron oxidation. This comproportionation reaction gives rise to **3a**$^+$, which exhibits an ESR signal. The final product, **3a**$^{2+}$, is expected to be ESR-inactive provided that the two holes (unpaired spins), which are produced upon oxidation, are paired. Further oxidation at 1.10 V leads to the formation of a species with a strong ESR signal at $g = 2.007$ and $\Delta H = 7.8$ G (see Supporting Information). Such values are consistent with a π-cation radical and leads us to propose that the product of this oxidative process is the triply oxidized species, **3a**$^{3+}$.

Currently, we are working to affirm the results of spectroelectrochemistry by chemical oxidation. We have found, for instance, that treatment of colorless solutions of **3a** in methylene chloride with perchloric acid, acidic aqueous solutions of chromate and bromate under heterogeneous conditions, or with bromine (but not with iodine) under homogeneous conditions gives rise to a compound (or a mixture of compounds) whose spectrum also resembles that of the acid salt **1a**. Unfortunately, the spectral features ascribed to the presumed compound produced in this way, namely **3a**$^{2+}$, begin to fade over the course of 0.5 h which leads us to infer that the product is not stable under these conditions at ambient temperature. Nonetheless, these findings, when considered in conjunction with the results of the bulk electrolysis experiments described above, suggest that it might be possible to isolate dicationic products of general structure **3**$^{2+}$ or even their more-oxidized radical-cation analogues **3**$^{3+}$ under appropriate conditions. Efforts are currently directed to this end. We are also working to test the generality of the reductive alkylation procedure of Scheme 1 by applying it, for example, to other expanded porphyrin systems.[12] Besides this, we are exploring the use of **3**, with its unique "four up, four down" orientation, as a possible scaffold for further synthetic elaboration, such as in the construction of self-assembled arrays and polytopic receptor systems.

Experimental Section

Unless otherwise noted, solvents and reagents were reagent-grade and were used without further purification. Tetrahydrofuran (THF) was dried by passage through two columns of activated alumina. The bipyrrolic precursors were prepared as described previously.[13] ^{1}H and ^{13}C NMR spectra were measured at 25 °C on a Varian Unity Innova at 300 and 400 MHz, respectively. UV/Vis spectra were recorded on a Beckman DU 640B spectrophotometer. High-resolution CI and FAB mass spectra were measured with a VG ZAB2-E mass spectrometer.

3c: Under an argon atmosphere, sodium hydride (60% suspension in mineral oil; 95 mg, 2.38 mmol) was added to a solution of cyclo[8]pyrrole **1a** (49.2 mg, 58.5 μmol) in dry THF (20 mL), and the mixture was stirred at room temperature for 30 min. Then, benzyl bromide (335 μL, 2.8 mmol) was added, and the solution was heated under reflux for 12 h. The solution was allowed to cool to room temperature, then aqueous NaOH solution (1 M, 10 mL) was added along with CH_2Cl_2 (20 mL). After stirring this mixture for 20 min, the phases were separated, and the aqueous phase was extracted further with CH_2Cl_2 (10 mL). The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The residue was passed through a short plug of silica gel using CH_2Cl_2 as the eluent. Compound **3c** was isolated as a white–amber-colored crystalline product (66 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.68$ (s, 48 H, CH_3), 5.09 (s, 16 H, benzyl-CH_2), 6.34–6.37 (m, 16 H, phenyl-H), 6.83–6.88 (m, 16 H, phenyl-H), 6.94–6.99 ppm (m, 8 H, phenyl-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.82$, 48.91, 121.08, 123.96, 126.50, 126.67, 127.76, 138.17 ppm. HRMS (FAB); m/z: calcd for $C_{104}H_{104}N_8$: 1464.8384; found: 1464.8410 ([M^+]).

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Keywords: aromaticity · electrochemistry · nitrogen heterocycles · porphyrinoids · redox chemistry

[1] D. Seidel, V. Lynch, J. L. Sessler, *Angew. Chem.* **2002**, *114*, 1480–1483; *Angew. Chem. Int. Ed.* **2002**, *41*, 1422–1425.

[2] T. Köhler, D. Seidel, V. Lynch, F. O. Arp, Z. Ou, K. M. Kadish, J. L. Sessler, *J. Am. Chem. Soc.* **2003**, *125*, 6872–6873.

[3] During the course of this work, the preparation and full structural characterization of a tetra-N-benzylated *meso*-tetrakis(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)porphyrinogen, obtained from the four-fold N alkylation of the parent *meso*-tetra(oxocyclohexadienylidene)porphyrinogen (generated by oxidation of the corresponding *meso*-substituted (4-hydroxyphenyl)porphyrin), was reported. However, this procedure apparently cannot be successfully applied to produce the corresponding unoxidized (that is, "normal") porphyrinogen starting from, for example, *meso*-unsubstituted porphyrins. See J. P. Hill, I. J. Hewitt, C. E. Anson, A. K. Powell, A. L. McCarty, P. A. Karr, M. E. Zandler, F. D'Souza, *J. Org. Chem.* **2004**, 69, 5861–5869. For a recent review about hydroporphyrins and reduced species, see: a) M. O. Senge, J. Richter, *J. Porphyrins Phthalocyanines* **2004**, *8*, 934–953; b) L. R. Milgrom, *Tetrahedron* **1983**, *39*, 3895–3898; c) L. R. Milgrom, J. P. Hill, G. Yahioglu, *J. Heterocycl. Chem.* **1995**, *32*, 97–101; d) E. Dolusic, S. Toppet, S. Smeets, L. van Meervelt, B. Tinant, W. Dehaen, *Tetrahedron* **2003**, *59*, 395–400.

[4] M. Gosmann, PhD Thesis, Universität Münster (Germany) **1986**.

[5] E. Vogel, P. Röhrig, M. Sicken, B. Knipp, A. Herrmann, M. Pohl, H. Schmickler, J. Lex, *Angew. Chem.* **1989**, *101*, 1683–1687; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1651–1655; .

[6] That porphyrins may be reduced to produce porphyrinogens (and other reduced species) is historically well appreciated. See, for instance: H. Fischer, H. Orth, *Die Chemie des Pyrrols*, Band *II, II.* Haelfte, Akad. Verlagsgesellschaft, Leipzig, **1940**. However, conversion of these species to **4** and its analogues is apparently problematic. For instance, our attempts to N alkylate calix[4]pyrrole (*meso*-octamethylporphyrinogen) by treatment with excess *n*-butyllithium followed by ethyl bromoacetate did not result in an N-alkylated product analogous to **4**. Rather, very effective β-pyrrolic C alkylation was observed. See P. A. Gale, J. L. Sessler, W. E. Allen, N. A. Tvermoes, V. Lynch, *Chem. Commun.* **1997**, 665–666.

[7] Structural data for compound **3a**: Single crystals suitable for X-ray diffraction studies of compound **3a**·0.5 CH_2Cl_2 were obtained by slow evaporation of its solution in methylene chloride and methanol. Data were collected on a Nonius Kappa CCD diffractometer by using a graphite monochromator with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). $C_{72.50}H_{105}ClN_8$, $M_r = 1124.09$, monoclinic, space group $P21/n$, $a = 16.7530(5)$ Å, $b = 24.4090(6)$ Å, $c = 18.3380(9)$ Å, $\alpha = 90.000(2)°$, $\beta = 112.488(2)°$, $\gamma = 90.000(11)°$, $V = 6928.6(4)$ Å^3, $Z = 4$. Full matrix least-squares on F^2 was used as the refinement method. Final $R1$ $(I > 2\sigma(I)) = 0.1093$; $wR2$(all data) $= 0.1932$.[10]

[8] Structural data for compound **3b**: Single crystals suitable for X-ray diffraction studies of compound **3b** were obtained by vapor diffusion of methylene chloride into a solution of the macrocycle in methanol. Data were collected on a Nonius Kappa CCD

diffractometer by using a graphite monochromator with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). $C_{64}H_{88}N_8$, $M_r = 969.42$, orthorhombic, space group *Pbcn*, $a = 12.6903(1)$ Å, $b = 28.1058(3)$ Å, $c = 17.2872(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 6165.84(11)$ Å^3, $Z = 4$. Full matrix least-squares on F^2 was used as the refinement method. Final $R1$ ($I > 2\sigma(I)$) = 0.1445; $wR2$(all data) = 0.1534.[10]

[9] Structural data for compound **3c**: Single crystals suitable for X-ray diffraction studies of compound **3c**·CH_2Cl_2·0.5 C_6H_{14} were obtained by vapor diffusion of *n*-hexane into a solution of the macrocycle in methylene chloride. The data were collected on a Nonius Kappa CCD diffractometer by using a graphite monochromator with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). $C_{108}H_{113}Cl_2N_8$, $M_r = 1593.96$, orthorhombic, space group *Pbca*, $a = 26.5693(3)$ Å, $b = 24.2573(3)$ Å, $c = 28.3957(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 18301.0(4)$ Å^3, $Z = 8$. Full-matrix-block least-squares on F^2 was used as the refinement method. Final $R1$ ($I > 2\sigma(I)$) = 0.0560; $wR2$ (all data) = 0.1462.[10]

[10] For further details on the crystal-structure data and structure refinements for **3a**, **3b**, and **3c**, see the Supporting Information. CCDC-248431 (**3a**), CCDC-248429 (**3b**), and CCDC-248430 (**3c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] Spectral features similar to those seen in the case of the thin-cell spectroelectrochemical studies are observed after carrying out both the first two-electron and second one-electron oxidations by bulk electrolysis. However, the shoulder at 447 nm seen in Figure 2B was not seen in the case of the latter experiments. We are currently exploring the significance of this finding.

[12] In preliminary work, we have found that the reaction sequence used to produce **3a** from **1a** could be successfully applied to cyclo[6]pyrrole[2] to produce the corresponding reduced hexa-N-methylated macrocycle—the smaller homologue of **3a**.

[13] J. L. Sessler, M. C. Hoehner, *Synlett* **1994**, 211.