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Synthetic access to 5,10-disubstituted porphyrins

Sabine Hatscher[a] and Mathias O. Senge[b,*]

[a]*Institut für Chemie, Organische Chemie, Freie Universität Berlin, Takustraße 3, D-14195 Berlin, Germany*
[b]*Institut für Chemie, Universität Potsdam, Karl-Liebknecht-Straße 24-25, D-14476 Golm, Germany*

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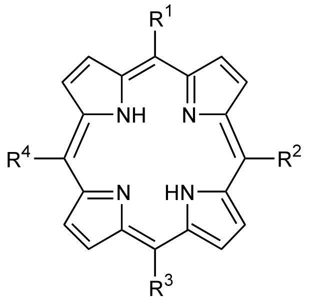
Abstract—A simple acid-catalyzed condensation of unsubstituted tripyrranes with pyrrole and various aldehydes affords 5,10-disubstituted-β-unsubstituted porphyrins by the '3+1' approach in low to moderate yields. A complementary synthesis of similar compounds involves reaction of unsubstituted porphyrin (porphine) with organolithium reagents in good yields. © 2002 Elsevier Science Ltd. All rights reserved.

meso-Substituted porphyrins bearing specific patterns of functional groups are valuable components in the synthesis of porphyrin-based biomimetic systems and crucial building blocks for applications in material chemistry. With regard to possible types of *meso*-substituted porphyrins, the most widely studied synthetic porphyrin group encompasses the symmetrical 5,10,15,20-tetraarylporphyrins like 5,10,15,20-tetraphenylporphyrin (TPP) (A_4-porphyrin **1**).[1] Additionally, symmetrical *trans*-substituted porphyrins (*trans*-A_2 **2** or *trans*-A_2B_2 porphyrins **4**) have recently found much use due to their simple synthesis. Less symmetrical representatives of the *meso* substituted porphyrin family have been studied only infrequently based on the absence (e.g. for *mono*-substituted porphyrins) or complexity (e.g. for ABCD-porphyrins) of the necessary syntheses.



1	$R^1 = R^2 = R^3 = R^4$	A_4-porphyrin
2	$R^1 = R^3,\ R^2 = R^4 = H$	*trans*-A_2-porphyrin
3	$R^1 = R^2,\ R^3 = R^4 = H$	*cis*-A_2-porphyrin
4	$R^1 = R^3,\ R^2 = R^4$	*trans*-A_2B_2-porphyrin
5	$R^1 = R^2 = R^3,\ R^4 = H$	A_3B-porphyrin
6	$R^1 = R^2,\ R^3 = R^4$	*cis*-A_2B_2-porphyrin
7	$R^1 = R^2 =$ phenyl, $R^3 = R^4 = H$	5,15-diphenylporphyrin

For porphyrins of the *trans*-AB_2C type we described a method involving treatment of a 5,15-disubstituted porphyrin **3** with an organolithium reagent, quenching with water, followed by addition of an alkyl iodide and oxidation[2] or by two sequential nucleophilic substitutions of 5,15-disubstituted porphyrin **3**.[3] Other rational routes, with dipyrromethane–dicarbinols have also been reported.[4] In contrast, the preparation of *cis*-A_2B_2 porphyrins **4** by non-statistical means was only successful in small amounts by the reaction of a substituted tripyrrane with a pyrrole–dicarbinol.[5] Both, **4** and *cis*-A_2BC, which have not been prepared by rational syntheses yet, are very interesting compounds, as they could combine features of electron-releasing and electron-withdrawing groups like the known push–pull-porphyrins in a new way. With our recent success in using nucleophilic substitution reactions for the modification of porphyrins[6,7] we envisage the possibility of synthesizing A_2B_2 porphyrins from *cis*-A_2 porphyrins via reaction with Li″B″. However, this requires access to *cis*-A_2 porphyrins, which have remained elusive.

In comparison to the large number of references for the synthesis of symmetrical *meso*-substituted, β-unsubstituted porphyrins, little is known about the preparation of 5,10-disubstituted, β-unsubstituted A_2 porphyrins. One *cis*-A_2 porphyrin, 5,10-diphenylporphyrin **7**, was recently described by Briñas and Brückner, who pre-

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* Corresponding author. Tel.: +0049-331-977-5187; fax: +0049-331-977-5059; e-mail: mosenge@chem.uni-potsdam.de

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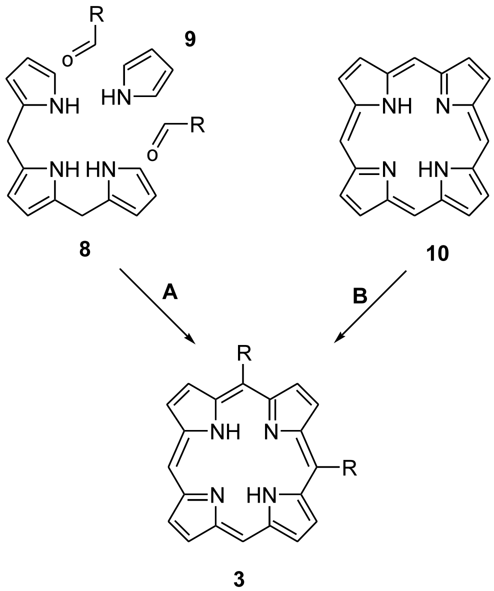
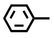
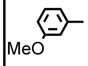
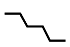
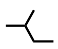
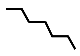
pared it by an elaborate synthesis involving the condensation of a substituted diacyldipyrromethane.[8] 5,10-bis(3,5-di-*tert*-butylphenyl)porphyrin has also been prepared in small amounts.[9] Syntheses for porphyrins with both 5,10- and β-substituents always utilized use of β-substituted tripyrranes.[10,11] As porphyrins with substituents solely at the 5,10-positions (**3**) present a fundamental class of tetrapyrroles, both in its own right as and as starting materials for more complex systems, we present here results on their preparation involving two different strategies as shown in Scheme 1: a 3+1 approach using tripyrrane **8** and pyrrole **9** with different aldehydes (route A) and the reaction of unsubstituted porphyrin **10**, prepared from tetra-*tert*-butylporphyrin,[12] with organolithium compounds (route B).

For route A the required tripyrrane **8** was prepared by condensation of pyrrole **9** with 2,5-bis(hydroxymethyl)pyrrole,[13] which itself was obtained in good yield from pyrrole **9** and formalin according to a modification of the literature methods.[14,15] As shown in Scheme 1, tripyrrane **8**, pyrrole **9** and the respective aldehyde were condensed (molar ration 1:1:2) in the presence of TFA as acid catalyst in dichloromethane to afford the desired 5,10-disubstituted porphyrins. Testing this method with a series of aliphatic and aromatic aldehydes resulted in yields of up to 11% (**12a**, Table 1). Both aromatic and aliphatic aldehydes may be used in this reaction, sterically demanding groups like *tert*-butyl lead to a preference for the *meso* monosubstituted product, which is observed as a second product in these reactions. Although the yields are still low, this method presents the first facile entry into this class of compounds and the *mono*-substituted derivative is easily separated by column chromatography and presents an interesting compound in its own right.[16,17]



Scheme 1. *Reaction conditions*: (A) TFA, CH_2Cl_2, rt; (B) THF, LiR (R = hexyl or *tert*-butyl), −78°C.

Table 1. Yields and product distribution according to the syntheses shown in Scheme 1

	R =	5,10-di-substitution **a**	5-mono-substitution **b**	route
11		6.3 %	2.0 %	A
		75.0 %	—	B
12		11.0 %	3.0 %	A
13		7.3 %	2.0 %	A
14		—	5.9 %	A
		—	4.0 %	B
15		4.0 %	5.0 %	A
16		6.8 %	1.0 %	A
17		5.0 %	—	A
18		61.0 %	—	B

Alternatively, route B offers a technically more involved procedure, however, this one results in higher yields. First, we prepared unsubstituted porphyrin **10** by the method of Neya and Funasaki[8] and subjected this to an addition–oxidation sequence[18] involving reaction with 3 equiv. of hexyllithium followed by treatment with DDQ. This gave the desired 5,10-dihexylated porphyrin **18a** in 61% yield as the sole product while the respective 5,10-diphenyl derivative **11a** was prepared in 75% yield.[19] For unencumbered substrates such as porphine both *mono*- and disubstitution can occur, depending on the reactivity, steric bulk and amount of organolithium reagent used.[7] Thus, when using standard reagents like hexyllithium or phenyllithium 3 equiv. are necessary to yield the desired disubstituted porphyrins. The formation of a single product was in both cases verified by several repetitions of the respective experiment. Similar, reaction of porphine with *tert*-butyllithium gave only 4% of *mono*-*tert*-butylated porphyrin **14b**. The substitution pattern of each porphyrin was clearly determined by 2-dimensional NMR spectroscopy. The ^1H NMR spectra reveal some interesting structure- and symmetry-dependent splitting patterns and trends, which could be used to confirm the identities of the compounds. In particular, the ^1H NMR couplings of the β-pyrrole hydrogens are very diagnostic of the substitution patterns of the *meso*-aryl groups on the porphyrin ring.

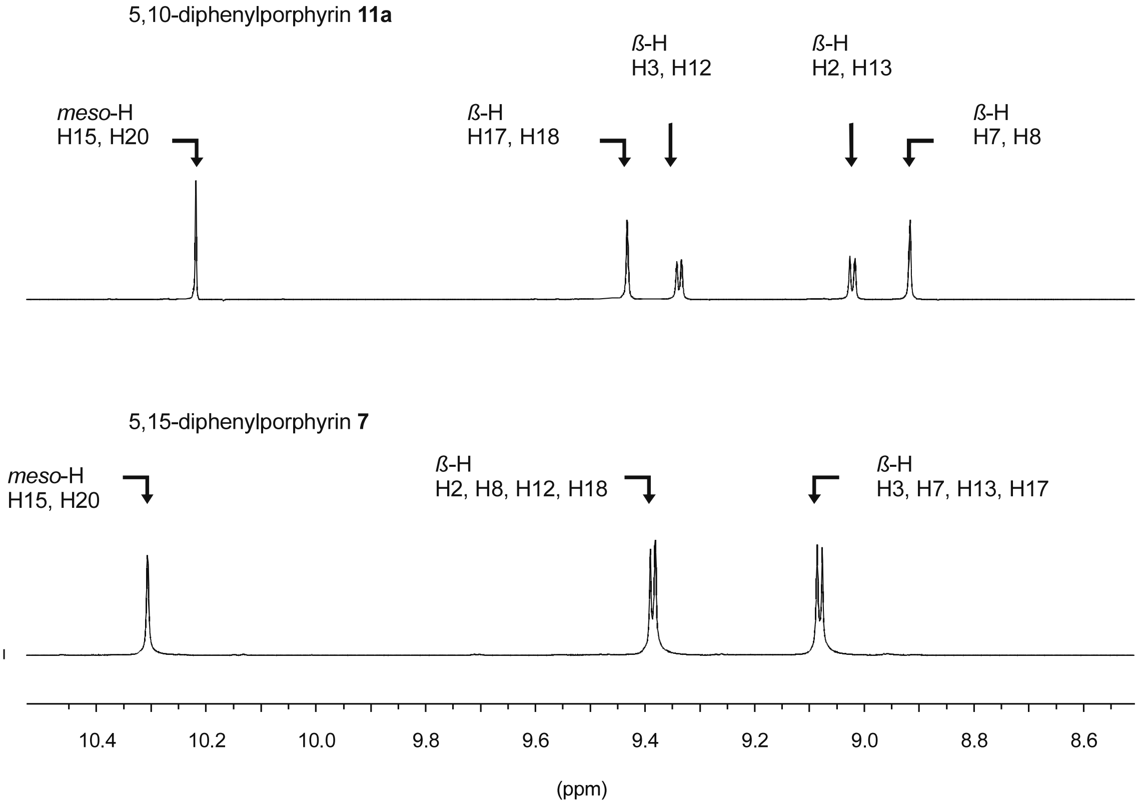


Figure 1. ^{1}H NMR spectra of porphyrins **7** and **11a** in $CDCl_3$ at rt; only low field section is shown.

For example, comparative spectra of 5,10-diphenylporhyrin **11a** and 5,15-diphenylporphyrin **7** are shown in Figure 1. Porphyrin **7** belongs to the D_2 point group and as the hydrogens on each pyrrole unit are non-equivalent, the signals appear as two doublets (9.39 and 9.09 ppm). Porphyrin **11a** has C_2 symmetry, where the C_2 axis is bisecting diagonally opposing pyrrole units. According to this, the ^{1}H NMR spectrum shows two β-pyrrolic singlets (9.43 and 8.92 ppm), enclosing two doublets (9.34 and 9.02 ppm, $^3J=4.55$ Hz).

In summary, different 5,10-disubstituted porphyrins can be prepared by simple methodologies using a practical 3+1 approach or the reaction of porphine with organolithium reagents. This presents the first practical pathway to β-unsubstituted *cis*-A_2-substituted porphyrins. Currently, we are expanding and optimizing the methodology described above.

Acknowledgements

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16. A typical procedure following route A: A solution of the tripyrrane **8** (1 equiv.), pyrrole **9** (1 equiv.) and tolylaldehyde (2 equiv.) in dichloromethane was stirred at rt under an argon atmosphere and shielded from ambient light for 30 min, then TFA (100 μl) was added. The mixture was stirred for 18 h, followed by treatment with 1.8 g (7.9

mmol) DDQ. Stirring was continued for 60 min, followed by addition of NEt_3 (1 ml) and concentration of the mixture in vacuo. The resulting residue was purified by column chromatography on silica gel using dichloromethane/*n*-hexane (1:2, v/v) as the eluent. Recrystallization from dichloromethane/methanol afforded 111 mg (0.23 mmol, 11.0%) of 5,10-ditolylporphyrin **12a** as purple crystals. Mp 270°C; ^{1}H NMR (270 MHz, $CDCl_3$, 320 K) $\delta = 10.19$ (s, 2H, 15,20-$C_{meso\text{-}\underline{H}}$), 9.41 (s, 2H, 17,18-$C_{\beta\text{-}\underline{H}}$), 9.32 (*AB*, 2H, 3,12-$C_{\beta\text{-}\underline{H}}$, $^3J=$ 4.55 Hz), 9.05 (*AB*, 2H, 2,13 $C_{\beta\text{-}\underline{H}}$, $^3J=4.55$ Hz), 8.95 (s, 2H, 7,8$C_{\beta\text{-}\underline{H}}$), 8.13 (d, 4H, $Ar_{o\text{-}\underline{H}}$, $^3J=8.20$ Hz), 7.78 (d, 46H, $Ar_{m\text{-}\underline{H}}$, $^3J=8.20$ Hz), 2.72 (s, 6H, $C\underline{H}_3$), −3.35 ppm (bs, 2H, $N\underline{H}$); ^{13}C NMR (126 MHz, $CDCl_3$, 320 K) $\delta = 139.20$ (2C, C21, C27), 137.37 (2C, C24, C30), 134.56 (4C, C22, C26, C28, C32), 131.04 (m, 8C, β-C) 127.39 (4C, C23, C25, C29, C31), 120.19 (2C, C5, C10), 103.98 (2C, C15, C20), 21.50 ppm (2C, C33, C34); MS (EI, 200°C, 80 eV), $m/z = 490$ (15.80%, $[M]^{\bullet+}$), 400 (25.0%$[M-C_6H_5]^+$); UV–vis (CH_2Cl_2): λ_{max} ($\log \varepsilon$) $= 405$ (5.48), 502 (4.33), 531 (3.66), 575 (3.84), 625 (3.32); HRMS (EI): $[C_{34}H_{26}N_4[M^+]]$: calcd 490.21575, found 490.21537.

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19. Route B: A solution of porphine **10** in dry THF (38.5 mg, 0.12 mmol) was degassed with argon and cooled to −78°C. After dropwise addition of 0.37 mmol hexyllithium, the mixture was stirred for 15 min at rt. After this time, a mixture of 1 ml water in 5 ml THF was added and stirring was continued for 5 min. For oxidation 109 mg DDQ were added. After filtration through a short silica column, eluting with dichloromethane, the solution was concentrated in vacuo and the residue purified by column chromatography using dichloromethane/*n*-hexane (1:1, v/v) as eluent. Recrystallization from dichloromethane/methanol afforded 35.0 mg (0.07 mmol, 61%) of 5,10-dihexylporphyrin **18a** as purple crystals. Mp 133°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.98$ (2H, s, 10,20-$C_{meso\text{-}H}$), 9.55 (4H, m, 3,7,8,12-$C_{\beta\text{-}H}$), 9.29 (4H, m, 2,13,17,18-$C_{\beta\text{-}H}$), 4.99 (4H, t, $^3J_{H25,H26}=8.2$ Hz, $^3J_{H31,H32}=8.2$ Hz, 5,10-$C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 2.55 (4H, m, 5,10-$CH_2C\underline{H}_2CH_2CH_2CH_2CH_3$), 1.83 (4H, m, 5,10-$CH_2CH_2C\underline{H}_2CH_2CH_2CH_3$), 1.53 (4H, m, 5,10-$CH_2CH_2CH_2C\underline{H}_2CH_2CH_3$), 1.43 (4H, m, 5,10-$CH_2CH_2CH_2CH_2C\underline{H}_2CH_3$), 0.96 (6H, t, $^3J_{H30,H29}=7.3$ Hz, $^3J_{H36,H35}=7.3$ Hz, 5,10-$CH_2CH_2CH_2CH_2CH_2C\underline{H}_3$), −3.37 ppm (2H, bs, $N\underline{H}$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 131$–127 (C2, C3, C7, C8, C12, C13, C17, C18), 119.76 (C5, C10), 102.83 (C15, C20), 38.96 (C26, C32), 35.62 (C25, C31), 31.90 (C28, C34), 30.32 (C27, C33), 22.76 (C29, C35), 14.19 ppm (C30, C36); MS (EI; 180°C, 80 eV): $m/z = 479$ (40%, $[M+1]^+$), 478 (100%, $[M]^{\bullet+}$), 407 (53%, $[M-C_5H_{11}]^+$), 336 (9%, $[M-C_{10}H_{22}]^{\bullet+}$), 239 (5% $[M]^{2+}$); UV–vis (CH_2Cl_2): λ_{max} ($\log \varepsilon$) $= 406$ (6.31), 504 (5.17), 535 (4.39), 579 (4.65), 634 (4.17); HRMS (EI) $[C_{32}H_{38}N_4[M^+]]$: calcd 478.3096, found 478.30734.