Chemistry of Pyrrocorphins: Synthesis of Isobacteriochlorins and Pyrrocorphins bearing a Methyl Group at the *meso* Position between Rings A and D

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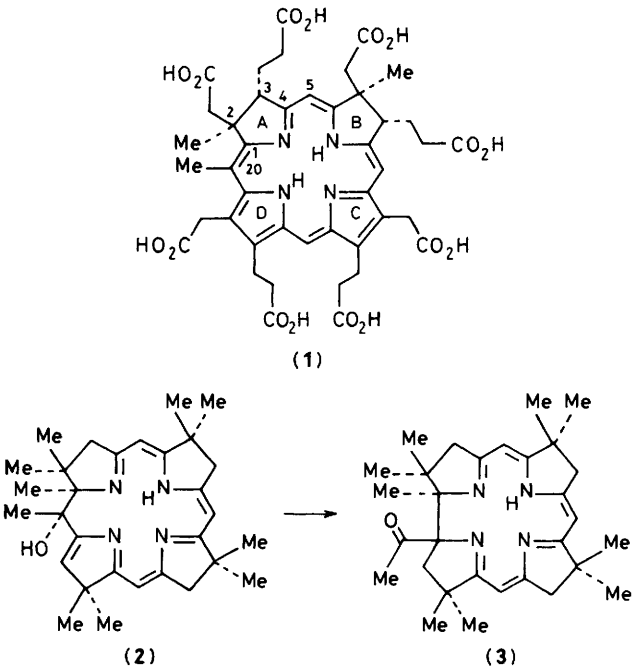
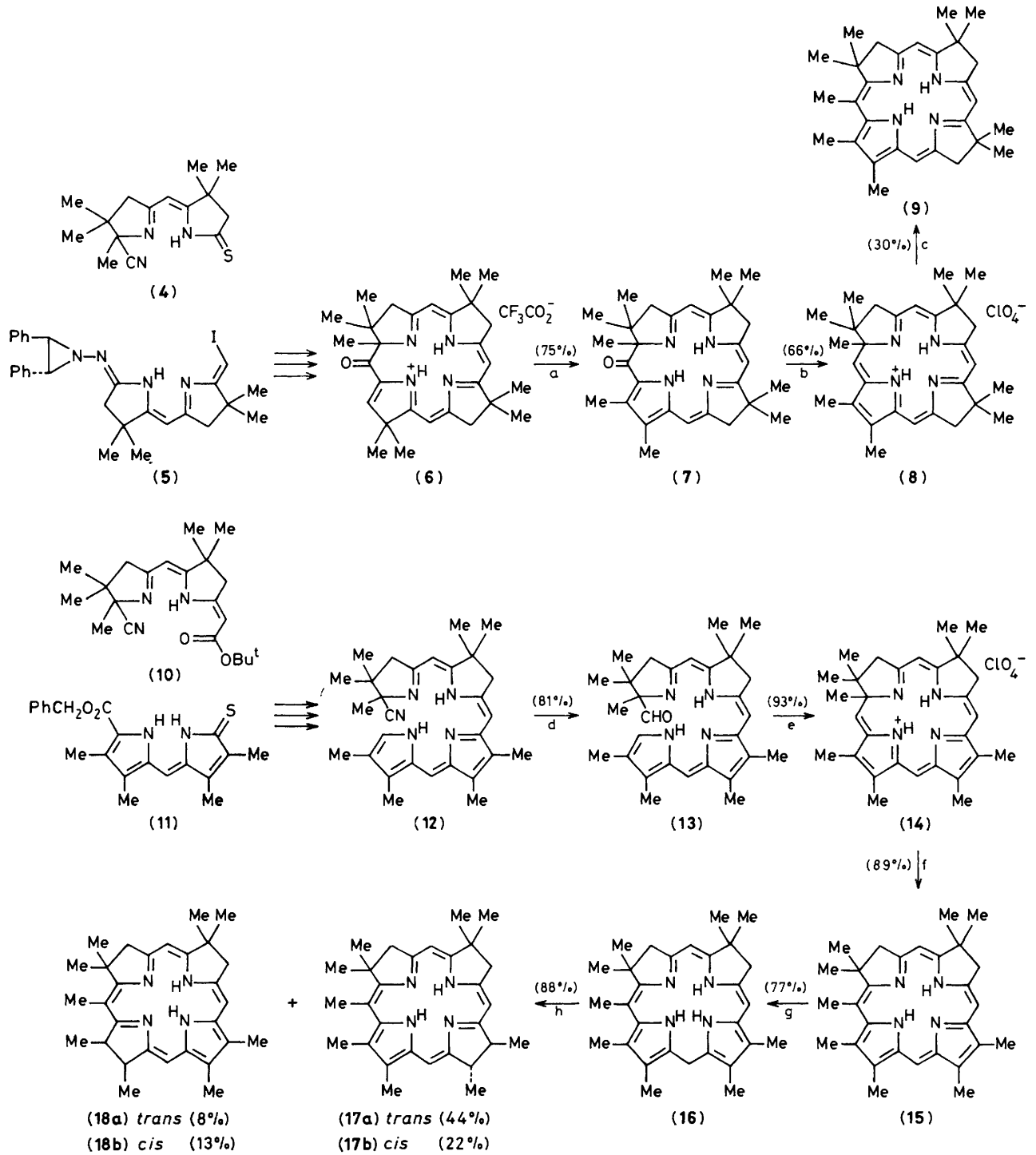
A sigmatropic methyl shift from the angular position C-1 in ring A to the *meso* position C-20 between rings A and D constitutes the crucial step in syntheses leading to a 20-methyl-isobacteriochlorin and to 20-methyl-pyrrocorphins which served as substrates in the investigation presented in the accompanying communication.

To date, the structurally most advanced compound that has been successfully fed into the biosynthetic pathway between uroporphyrinogen III and cobyrinic acid is the trimethylated isobacteriochlorin (**1**).[1] Its methionine-derived methyl group located at the *meso*-position C-20[1b] has become the focal point in the theoretical and experimental analysis of the intriguing chemistry involved in the generation of the corrin ring during the biosynthesis of vitamin B_{12}. Both Arigoni *et al.*[2] and Battersby *et al.*[3] have demonstrated that, at some unknown later stage of the biosynthesis, this *meso* methyl is extruded again together with carbon C-20 as an equivalent of acetic acid. In a synthetic model series, the dihydrocorphinol → corrin rearrangement (**2**) → (**3**) (Scheme 1)[4] has adumbrated how such an extrusion could constitute a crucial part of the biosynthetic ring contraction process. Extension of these chemical studies in model systems of potential biosynthetic intermediates[5] (see accompanying communication[6]) demanded the development of synthetic pathways to isobacteriochlorins[7] and pyrrocorphins[8] bearing a methyl group at C-20. Scheme 2 summarises two approaches by which this goal has been reached; in both approaches a sigmatropic methyl shift from the angular position C-1 to the *meso* position C-20 plays a central role.

A three-step synthesis of the ketone (**6**) from the building blocks (**4**) and (**5**) had previously served for the construction of the dihydrocorphinol (**2**).[4] The reaction sequence has now been extended to produce the pyrrocorphin (**9**). Treatment of (**6**)

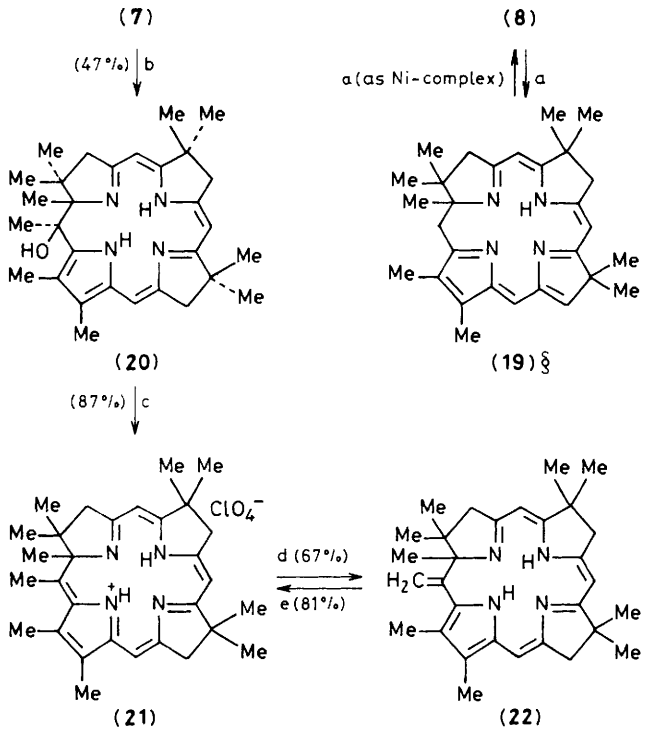


Scheme 1



Scheme 2. *Reaction conditions* (for details see refs. 13 and 14; c.c. = column chromatography): a, excess of $AlCl_3$ in CH_2Cl_2, 40 °C, 1 h; c.c. (SiO_2); b, 25 equiv. of Dibal, toluene, −78 °C, *ca.* 30 min; + MeOH + TFA, −78 °C → room temp. (dehydration); $NaClO_4$, H_2O; c.c. (SiO_2 + 1% $NaClO_4$); c, in degassed sulpholane (*c ca.* 2 × 10^{-3} M), 140 °C, 3 h; c.c. (SiO_2 60 G, t.l.c.-quality; benzene–hexane, 1:1); cryst. from benzene–methanol in glove-box (<5 p.p.m. O_2); d, 12 equiv. of Dibal in CH_2Cl_2, −78 °C, 40 min; + MeOH, −78 °C → room temp., + 1 M aqueous TFA, room temp. (imine hydrolysis), c.c. (Al_2O_3); e, 10 equiv. of $ZnCl_2$ in MeCN, 60 °C, 17 h, molecular sieves (5 Å), TFA–MeCN (1:2), room temp., 10 min (decomplexation), $NaClO_4$–H_2O; c.c. (SiO_2 + 2% $NaClO_4$); f, in degassed sulpholane (*c ca.* 2 × 10^{-3} M), 140 °C, 2 h; c.c. (SiO_2); g, in ethyl acetate (*c ca.* 10^{-3} M), 3.0 weight equiv. Pt/C (5%), H_2, room temp.; c.c. (SiO_2, benzene); cryst. from benzene–hexane, in glove-box (<5 p.p.m. O_2); h, 15 equiv. of 1,5,7-triazabicyclo[4.4.0]-dec-5-ene[8] + 5 equiv. of MeMgI (1.3 M ethereal solution) in xylene (*c* 9 × 10^{-3} M), 85 °C, 20 h, exclusion of O_2; decomplexation with $MeCO_2H$, *ca.* 5 min, room temp., work-up with benzene–water; chromatographic separation of (**17a, b**) and (**18a, b**) (SiO_2 60 G, t.l.c.-quality; benzene + 2% ether) followed by h.p.l.c. [SiO_2 Partisil 5, pentane–ether (2:1) + 1.5 vol-% Et_3N], cryst. from benzene–methanol in glove-box (<5 p.p.m. O_2).

with $AlCl_3$ in CH_2Cl_2 induced a sigmatropic methyl shift from C-17 to C-18 (not unexpected in view of the electrophilicity of the β carbon of the adjacent enone system) to give the mono-pyrrolic ketone (**7**) in 75% yield. Reduction of the carbonyl group of (**7**) with di-isobutylaluminium hydride (Dibal) and work-up with methanolic trifluoroacetic acid (TFA) led to



Scheme 3. a, 0.5 M Et_3N–$MeCO_2H$ (1 : 1) in benzene, 90 °C, 2 h; 0.1 M aqueous $NaClO_4$, CH_2Cl_2; c.c. [SiO_2, 1% $NaClO_4$; CH_2Cl_2–ether (10 : 1)], crystallised as perchlorate salt, from CH_2Cl_2–ether; prep. of Ni^{II} complex of (**19**):(**19**)-perchlorate + excess of $Ni(OAc)_2 \cdot H_2O$, MeCN, 70 °C, 30 min (86%); b, 130 equiv. of MeLi in ether (containing LiBr), room temp., 3 h; work-up with aqueous NaH_2PO_4, buffer; c.c. (Al_2O_3); c, 0.1 M TFA in CH_2Cl_2, room temp., 10 min; 0.1 M aqueous $NaClO_4$; d, satd. aqueous Na_2CO_3, CH_2Cl_2, a few min, room temp.; c.c. (Al_2O_3); e, 0.5 M TFA in CH_2Cl_2, room temp., 0.1 M aqueous $NaClO_4$.

(**8**); without TFA, the corresponding secondary alcohol could be isolated. The crucial sigmatropic methyl shift from the angular position C-1 to the *meso* position C-20 in (**8**) required an extensive search for reaction conditions; eventually, a modest 30% yield of crystalline pyrrocorphin (**9**) could be obtained reproducibly when a solution of (**8**) in degassed sulpholane was kept for 3 h at 140 °C, and the product isolated by (anaerobic) chromatography.† In contrast, the analogous methyl shift [(**14**) → (**15**)] in the synthesis of the isobacteriochlorin (**15**) was found to proceed under similar conditions in up to 90% yield. In both cases, the rearrangement is expected to occur as a consequence of the electrophilic (azafulvenic) character of the *meso* carbon C-20 in the (protonated) substrates (**8**) and (**14**). It is no surprise that the latter rearrangement is preparatively a better reaction, the isobacteriochlorins being more robust structures than the labile pyrrocorphins [*cf.* also the tautomerisation (**8**) → (**19**) referred to below].

For the synthesis of (**15**), both the bicyclic components (**10**) and (**11**), as well as their tetracyclic coupling product (**12**), were available from earlier investigations.[7d] Acid-catalysed cyclisation of the aldehyde (**13**), obtained from (**12**) by reduction with Dibal according to Montforts' method,[9] proceeded almost quantitatively *via* a procedure which included complexation of (**13**) with $ZnCl_2$ and subsequent decomplexation with TFA.‡

Oxygen-sensitive 'C,D-dipyrro-corphin' (**16**) was accessible by catalytic hydrogenation of (**15**) in ethyl acetate in the presence of non-catalytic amounts of platinum on carbon.[7b,10] Finally, using the reaction conditions of the porphyrinogen → pyrrocorphin-tautomerisation,[8a,8c,11] (**16**) was tautomerised almost quantitatively to a 3 : 1-mixture of isomeric pyrrocorphins (**17a,b**) and (**18a,b**). All four pyrrocorphins were isolated in crystalline form after h.p.l.c. separation. 20-Methyl-D-pyrrocorphins and 20-methyl-C-pyrrocorphins differ clearly in details of their u.v.–visible spectra.

Scheme 3 contains information concerning the position of tautomerisation equilibria among corphinoid ligand systems with an angular methyl group at C-1. Such equilibria can depend on the presence or absence of a *meso* methyl group at C-20. Heating the perchlorate (**8**) with $MeCO_2H$–Et_3N (1 : 1) in benzene tautomerises the C-20 double bond to C-13 in ring C to give (**19**).§ This tautomerisation reveals the position of the equilibrium between the chromophores of (**8**) and (**19**) in their neutral form; under identical conditions the nickel(II)-(perchlorate) complex of (**19**) reverts to the nickel(II) complex of (**8**). In the 20-methyl series, dehydration of the tertiary alcohol (**20**) gave (**21**), provided that the product was not brought into contact with base. Shaking a solution of (**21**) with saturated Na_2CO_3 solution suffices to convert it into the methylene isomer (**22**); reprotonation with TFA leads back to (**21**).

All compounds in Schemes 2 and 3 were obtained in crystalline and spectrally pure form. Their structural assignments, mostly based on mass spectral molecular weight determinations, u.v.–visible spectra, 300 MHz ^1H n.m.r. spectra, and ^1H n.m.r.-nuclear Overhauser effect correlations are straightforward.¶ For further experimental details see refs. 13 and 14.

† One of the side products of the reaction was the (neutral) pyrrolic 20,24-dihydro-derivative of (**8**), presumably formed by hydride transfer from an unidentified source. Thermolysis of (**8**) in sulpholane containing 0.8 M TFA (10 min; 180 °C) yielded 29% of (**9**), 14% of 20,24-dihydro-(**8**), and 7% of 2,3,7,7,12,12,-17,18,20-nonamethyl-isobacteriochlorin (rings A and D part of the pyrromethene system). Traces of the isomeric isobacteriochlorin (**15**) were also observed.

‡ Exploratory studies had shown that the nitrile group of (**12**) can also serve as a cyclising functionality. The nickel(II) complex of (**12**) cyclised with ease to the macrocyclic ketimine isomer; the latter was obtained in 91% yield on treatment of (**12**) with nickel(II) acetate in CH_2Cl_2–MeOH (1 : 1) at room temperature, and could be hydrolysed to the corresponding keto derivative with 2 M aqueous HCl at 130 °C (77%).

§ Isomer (**19**) was crystallised as the (unstable) perchlorate. The tautomerisation (**8**) → (**19**) did not occur at room temperature. The new double bond position in (**19**) is established by nuclear Overhauser effect correlation between the protons at C-13, C-15, and the (C-17)-methyl group. The (**8**) → (**19**) isomerisation is related to a previously observed acid-catalysed conversion of a C,D-dipyrrocorphin into an isomeric 1,20-dihydro-isobacteriochlorin.[7b] For the latter type of structure see also ref. 12.

¶ Selected spectral data (for complete data see refs. 13 and 14): u.v.–vis. (EtOH) in nm (log ε); ^1H n.m.r. ($CDCl_3$); (**7**): m.p. 191 °C; λ_{max} 274 (4.42), 337 (4.77), and 482 (3.82, br.); δ 2.03 and 2.39 (pyrrolic C-CH_3); (**8**): m.p. 172 °C; λ_{max} 279 (4.54), 323 (4.56), 340 (4.57), 405 (3.71), and 575 (4.31); δ 5.36, 5.75, 6.01, and 6.32 (4 × s, *meso* protons); (**9**): m.p. 264 °C; u.v.–vis. (hexane) similar to spectrum of (**17a**); δ 2.62, 2.70, and 2.82 [3 × s, C(sp^2)-CH_3]; 5.75, 5.85, and 7.10 (3 × s, *meso* protons) in C_6D_6; (**14**): m.p. 165 °C; λ_{max} 284 (4.62), 348 (4.71), and 635 (4.08); (**15**): m.p. 289 °C: λ_{max} 371 (5.09), 403 (4.91), 482 (3.86), 539 (4.00), 584 (4.16), and 632 (4.20) in CH_2Cl_2; δ 3.34 (s, CH_3 at C-20); (**16**): m.p. 294 °C; λ_{max} 284 (4.43) and 442 (4.03); (**17a**): m.p. 209 °C; λ_{max} 332 (4.67), 343 (4.68), 358 (4.63), 376 (4.54), 486 (3.95), 531 (3.98), and 574 (3.99) in hexane; δ 5.73, 5.81, and 7.01 (3 × s, *meso* protons) in C_6D_6; (**18b**): m.p. 262 °C; λ_{max} 350 (4.72), 360 (4.69), 379 (4.55), 503 (3.96), 549 (3.97), and 595 (4.01) in hexane [similar to spectrum of (**18a**)]; δ 2.31, 2.66, and 2.71 [3 × s, C(sp^2)-CH_3]; 5.93, 7.13, and 7.18 (3 × s, *meso* protons) in C_6D_6.

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