Syntheses relevant to Vitamin B_{12} Biosynthesis: Synthesis of (±)Faktor-I Octamethyl Ester

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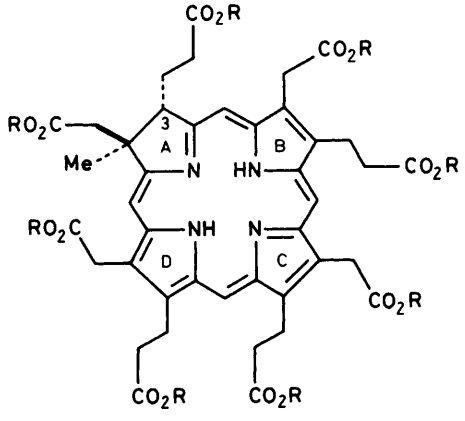
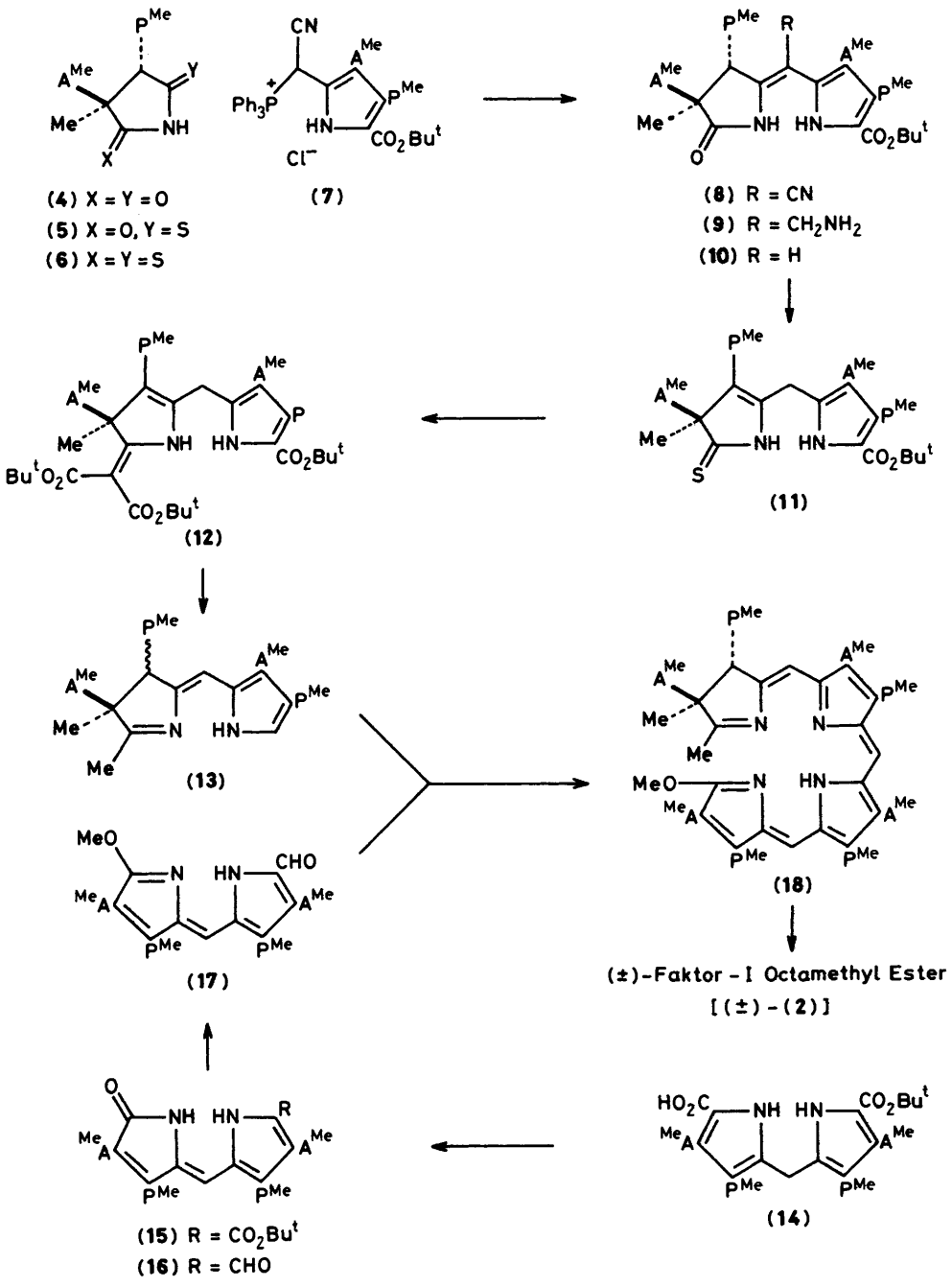
Faktor-I, the chlorin which arises by aromatisation of the mono-*C*-methylated intermediate on the biosynthetic pathway to vitamin B_{12}, has been synthesised in racemic form as its octamethyl ester by ring-closing the macrocycle photochemically.

The B_{12}-producer *Clostridium tetanomorphum* yields minute quantities of a *C*-methylated chlorin, called Faktor-I, shown[1] to have structure (**1**). This product results from air oxidation during work-up of the true mono-methylated biosynthetic intermediate which is almost certainly a tetrahydro-derivative of the aromatised chlorin (**1**). Chemical and biosynthetic studies on Faktor-I are severely limited by its scarcity so its synthesis was undertaken. The successful outcome is now outlined; the reported yields have not yet been optimised so significant future increases are expected.

The imide (**4**) is available in optically active form by degradation of vitamin B_{12}[2] and was prepared as a correlation substance in Eschenmoser's synthetic work on vitamin B_{12}.[3] The racemate has now been synthesised in quantity (>10 g batches) by a new route to be described in full elsewhere.[4] The (±)-imide [as (**4**)] was converted by Lawesson's reagent[5] into the monothioimide (**5**) together with a little of the separable dithioimide (**6**). Heating the monothioimide (**5**) and the Wittig salt[6] (**7**) with base in toluene gave the *E*-nitrile (**8**), 76%, accompanied by the *Z*-isomer (10.5%). The former was



(**1**) R = H
(**2**) R = Me
(**3**) C-3 epimer of (**2**)



smoothly reduced by W2 Raney nickel in methanol–water–acetic acid to give a mixture of the *Z*-amine (**9**) and its *E*-isomer (total 86%). These amines were not separated but were heated in anisole with *N,N'*-dimethyl-1,2-diaminoethane which trapped the product (CH_2=$\overset{+}{N}H_2$) of the desired reverse Mannich reaction to yield the unsaturated lactam (**10**), 47%. Lawesson's reagent converted this lactam into the thiolactam (**11**), 70%, resulting from the illustrated double-bond migration. The thiolactam (**11**) was then treated with di-t-butyl monobromomalonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the *S*-malonyl derivative which with triphenylphosphine and DBU in refluxing toluene was forced to undergo sulphur extrusion[7] so providing the ester (**12**), 40%. This product is the immediate precursor of the labile ring A–ring B building block (**13**) for Faktor-I octamethyl ester (**2**), see later.

Synthesis of the ring C–ring D building block started with the readily available pyrromethane[8] (**14**); this was oxidatively brominated and hydrolysed[9] to form the pyrromethenone (**15**), 43%. The related aldehyde (**16**), 86%, was prepared from (**15**) using trimethyl orthoformate and trifluoroacetic acid (TFA) and finally, treatment of (**16**) with trimethyloxonium tetrafluoroborate set up the required imino ether system (**17**), 55%.

The labile ring A–ring B component (**13**) was generated from its precursor (**12**) by TFA (3 decarboxylations); structure (**13**) is drawn as a conjugated system through it is conceivable that the double-bond migration occurs at a later stage. The α-free pyrrole (**13**) was immediately condensed with the ring C–ring D unit (**17**) to form the seco-system (**18**). This was ring-closed by irradiation[10] to form (±)-Faktor-I octamethyl ester (**2**), 26% over the four steps from the precursors (**12**) and (**17**); (±)-3-epi-Faktor-I (**3**) octamethyl ester[11] was also isolated, 8%. The former product was identical, apart from its racemic nature (t.l.c., h.p.l.c., u.v.–visible, 400 MHz n.m.r., and field desorption mass spectrometry), with authentic Faktor-I octamethyl ester isolated from *C. tetanomorphum*.[11]

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References

1 R. Deeg, H.-P. Kriemler, K.-H. Bergmann, and G. Muller, *Hoppe-Seyler's Z. Physiol. Chem.*, 1977, **358**, 339; M. Imfeld, D. Arigoni, R. Deeg, and G. Muller, in 'Vitamin B_{12},' eds. B. J. Zagalak and W. Friedrich, de Gruyter, Berlin, 1979, p. 315.
2 T. L. Bogard and A. Eschenmoser, unpublished work.
3 A. Eschenmoser, Special Lectures, 23rd IUPAC International Congress of Pure and Applied Chemistry, Butterworths, 1971, vol. 2, p. 69.
4 A. R. Battersby and S. W. Westwood, manuscript in preparation.
5 B. S. Pedersen and S.-O. Lawesson, *Tetrahedron*, 1979, **35**, 2433.
6 D. M. Arnott, A. R. Battersby, P. J. Harrison, G. B. Henderson, and Z.-C. Sheng, *J. Chem. Soc., Chem. Commun.*, 1984, 525.
7 M. Roth, P. Dubs, E. Gotschi, and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710.
8 A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald, and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2413.
9 K. M. Smith and D. Kishore, *J. Chem. Soc., Chem. Commun.*, 1982, 888.
10 A. R. Battersby, C. J. Dutton, C. J. R. Fookes and S. P. D. Turner, *J. Chem. Soc., Chem. Commun.*, 1983, 1235.
11 A. R. Battersby and S. Seo, *J. Chem. Soc., Perkin Trans. 1*, 1983, 3049.