Syntheses Relevant to Vitamin B_{12} Biosynthesis: the Glutamate Route to (−)-Ring-B Imide and Synthesis of the 2,7,12,20-Tetramethylisobacteriochlorin

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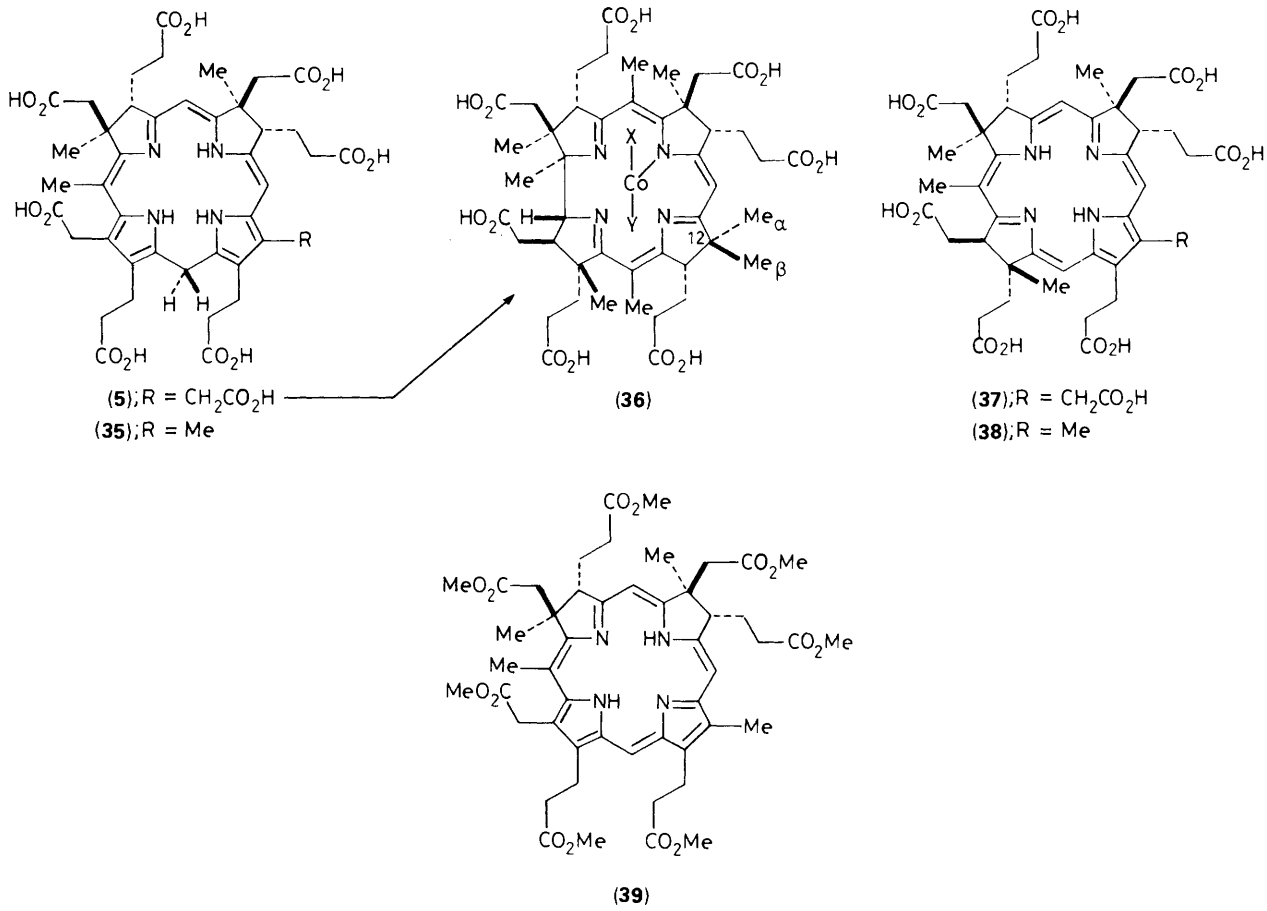
An enantioselective synthesis of (−)-ring-B imide (**19**) from inexpensive glutamic acid is described and the product is used for synthesis of the 2,7,12,20-tetramethylisobacteriochlorin (**39**) required for future transformation into later biosynthetic intermediates for vitamin B_{12}.

The 12-β-methyl group of cobyrinic acid (**36**), a late biosynthetic precursor of vitamin B_{12}, is formed by decarboxylation, at some as yet unknown point on the pathway, of the 12-acetate residue still present in the trimethylated precursor, precorrin-3 (**5**); note that the numbering of structures is continued from the preceding Communication. Recent experiments have indicated that enzymic decarboxylation of precorrin-3 (**5**) itself to form the 12-methyl analogue (**35**) does *not* occur.[1] This leads to the conclusion[1] that the 12-methyl group is probably generated at the tetramethylated[2] (pyrrocorphin) stage involving (**37**) → (**38**). The aromatised form of (**35**) as its ester (**39**) was prepared for the foregoing experiments by an enzymic procedure[1] and was obtained in sub-milligram amounts. Much larger quantities (*ca.* 100 mg) of (**39**) are required for work aimed at the synthesis of pyrrocorphin (**38**); accordingly, synthesis of (**39**) was undertaken.

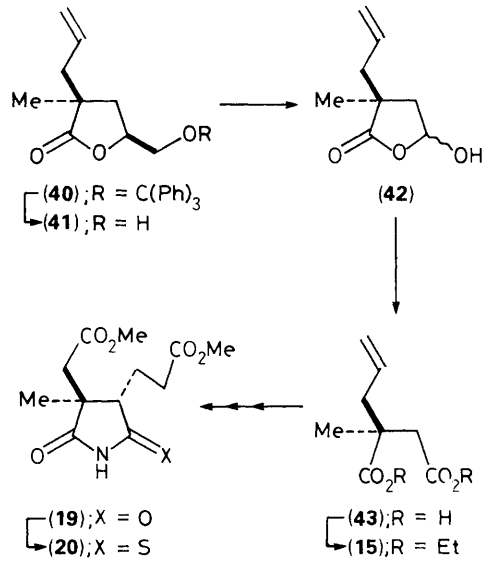
As in the preceding Communication, the (−)-ring B imide (**19**) is an essential building block for this work and an alternative (cheaper) route to it has been developed as in Scheme 1. The lactone (**40**) is readily available[3] on a large scale from inexpensive *S*-glutamic acid. Acidic cleavage of the trityl group gave the crystalline alcohol (**41**) and *X*-ray analysis[4] confirmed the configuration at the quaternary carbon relative to the known *S*-configuration at the other



centre. The lactone (**41**) was opened with alkali and the resultant sodium salt was cleaved with sodium periodate to yield the epimeric mixture of lactols (**42**). These were oxidised with Jones reagent and the diacid (**43**) so formed was converted into its ester (**15**) with EtOH–H_2SO_4. This product was identical with the material (**15**) synthesised in Scheme 1 of the preceding Communication[5] and the rest of the steps to crystalline (−)-ring-B imide (**19**) were as in that earlier route. The glutamic acid route will yield 5—10 g quantities of (−)-ring-B imide from one convenient run.

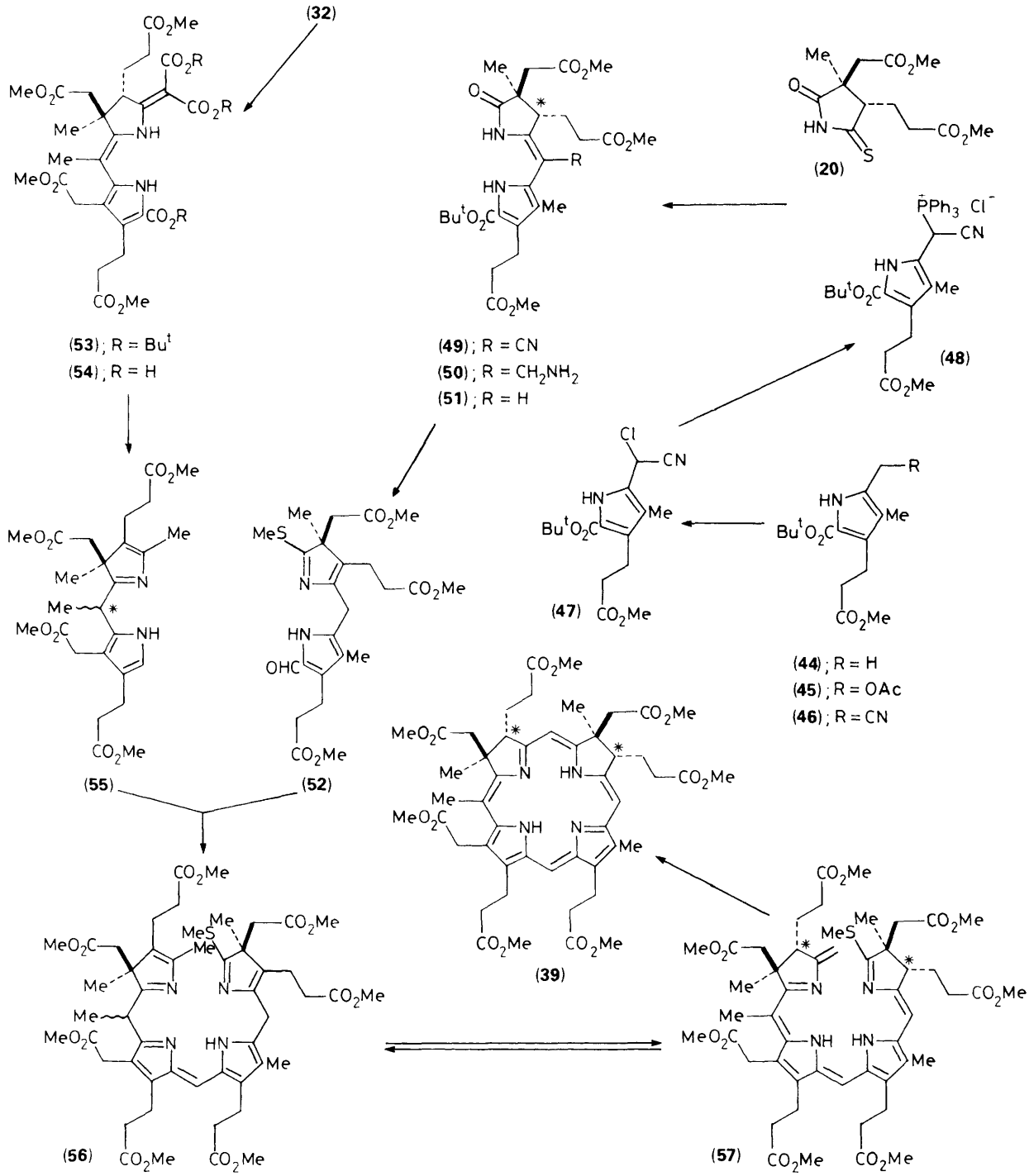
The precursor (**49**) of the eastern building block required for construction of (**39**) was synthesised from the monothioimide (**20**) and the phosphonium salt (**48**) by steps analogous to those used earlier.[5—7] The salt (**48**) was made by the sequence (**44**) → (**45**) → (**46**) → (**47**) → (**48**). Removal of the unwanted nitrile residue from (**49**) involved Co^{II}–borohydride reduction[8] of the nitrile to aminomethyl (**50**) followed by reverse-Mannich chemistry.[7] The product was mainly the *Z*-isomer (**51**) containing variable amounts (5—25%) of the corresponding *E*-isomer; these were separated for characterisation but preparatively were used together. The asterisk on (**51**) and on other structures indicates the presence of some epimer at that centre. Conversion of the lactams (**51**) by Lawesson's reagent into the thiolactams and treatment of these with trifluoroacetic acid (TFA) and trimethylorthoformate gave the material for the eastern half of (**39**) mainly as the thioiminoether (**52**) with the *endo* double bond (4 parts), together with 1 part of a *Z*/*E* mixture retaining the original double bond position.

A similar double-bond migration was also experienced in



Scheme 1

building the western block, starting from the thiolactam (**32**) synthesised in the preceding Communication.[5] This reacted with di-t-butyl 2-bromomalonate to yield the *S*-malonyl system, which by sulphur extrusion[9] using 1,8-diazabicyclo[5,4,0]undec-1-ene (DBU) and triphenylphosphine in hot



Scheme 2

toluene gave the tri-t-butyl ester (**53**). All three t-butyl groups were then cleaved by TFA but, unlike the analogous system lacking the methyl group on the methine bridge,[7] decarboxylation was incomplete in TFA. The tri-acid (**54**) required heating in toluene to remove all three carboxy groups and the product proved to have completely isomerised to the pyrrolenine (**55**) as a mixture of diastereoisomers (at the starred centre). This material was extremely sensitive to oxygen and was best handled in a glove box (<20 p.p.m. O_2).

Earlier experience in the chlorin series[6] indicated that under the acidic conditions used for reacting (**52**) with (**55**), presumably to form (**56**) initially, re-equilibration of the system would occur to allow formation of some of the tautomer (**57**) required for photochemical cyclisation, which would be siphoned off. The eastern (**52**) and western (**55**) blocks were therefore condensed together using MeOH–HCl and the product mixture was irradiated for 3.5 days in THF containing Hünig's base-TFA salt. Successful formation of the isobacteriochlorin macrocycle occurred and the product consisted of the 2,7,12,20-tetramethylisobacteriochlorin (**39**) together with the two epimers at one and the other starred centre. Such epimers can be isomerised to yield the more

stable *trans* arrangement of the ester side-chains[10] and so are not wasted products.

The pure material (**39**) was isolated and was shown to be identical with authentic material produced enzymically[1] (see above) by comparison using t.l.c., h.p.l.c., ^{1}H n.m.r. (400 MHz), u.v.–visible and field desorption mass spectroscopy. The synthetic route to this key macrocycle (**39**) is thus established. The yields from the outset up to the production of the eastern (**52**) and western blocks (**55**) are all at least acceptable (50—70%) and most are good (>70%). Production of the necessary quantities of (**39**) for further synthetic transformations depends on our current efforts to improve the yields for the final two steps from *ca.* 20% to preparative levels following the strategy outlined in the previous Communication.

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