Synthetic Studies Relevant to Biosynthetic Research on Vitamin B_{12}. Part 5.[1] Synthesis of (*RS*)-Ring-B Imide

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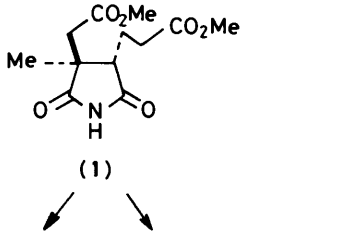
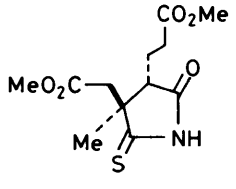
Future biosynthetic research on vitamin B_{12} depends on the synthesis of a family of isobacteriochlorin pigments. A key building block required for this work is 2-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-3-methylsuccinimide, usually called the ring-B imide. A practical synthesis of the racemic form of this substance is described which can yield multigramme quantities of product.

The preceding paper[1] emphasised the importance for future biosynthetic research on vitamin B_{12}, of producing workable quantities of the pigments (**4**) and (**5**) by synthesis. This formidable problem immediately presents two fundamental subsidiary ones, *viz.* (*a*) how to synthesize the parent isobacteriochlorin macrocycle of the pigments (**4**) and (**5**) by a method able to cope with the presence of acetic and propionic acid residues and (*b*) how to control the chirality of the four chiral centres at positions 2, 3, 7, and 8. Problem (*a*) was solved by development of the photochemical route to isobacteriochlorins.[1] Problem (*b*) is the topic of the present paper.

Our synthetic plan made use of the same precursor (**1**) to generate both ring-A and ring-B of the pigments (**4**) and (**5**). It was envisaged that this imide should be modifiable in some regiospecific way, *e.g.* by formation of the isomeric monothioimides (**2**) and (**3**), to allow ring-C and ring-D of the pigments (**4**) and (**5**) to be bonded to the correct sites. It is not necessary here to consider the entire plan; details will be given in future papers. Suffice to say that such a strategy requires the synthetic production of the succinimide (**1**) in large quantities. This is because the desired final products (**4**) and (**5**) are needed in amounts sufficient to sustain a major biological effort as part of the Cambridge biosynthetic research on vitamin B_{12}.



(**1**)



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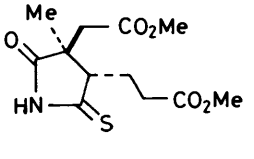

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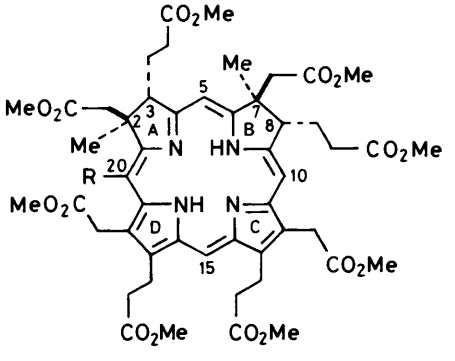
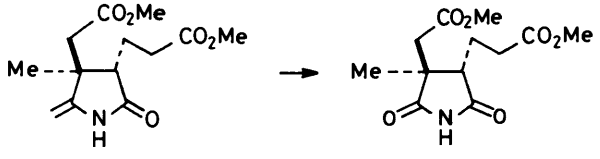


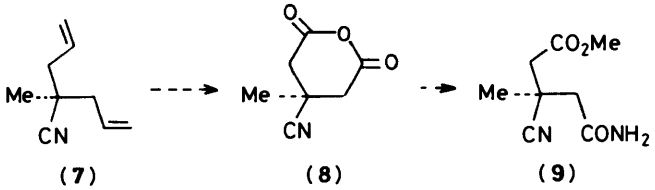
(**4**) R = H
(**5**) R = Me

The succinimide (**1**) can be obtained (very expensively!) by degradation[2] of vitamin B_{12} and since it arises from ring-B of the vitamin its common name is *ring-B imide*. It was also prepared on a small scale in optically active form[3] to confirm the absolute stereochemistry of the intermediate (**6**) required for the synthesis of vitamin B_{12}.[4] However, the real target in this latter study was the enamide (**6**) not the imide (**1**). So a practical route aimed directly at the ring-B imide (**1**) was needed.



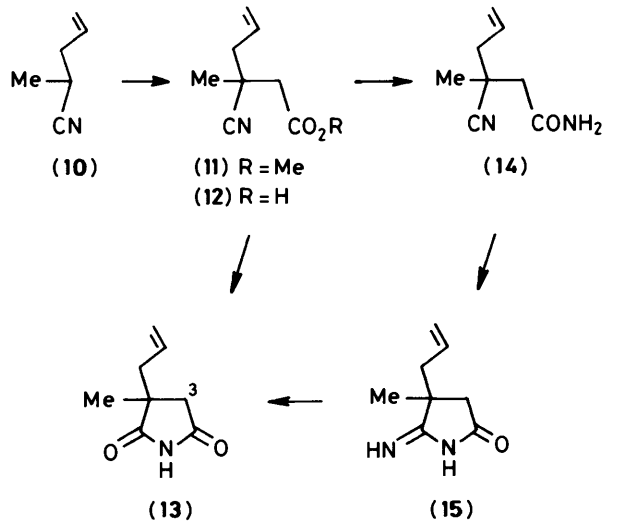
(**6**) (**1**)

A major concern was to ensure unambiguous formation of the correct succinimide ring for structure (**1**) rather than of alternative isomeric imides. So this ring was to be built relatively early in the sequence. Initially, the anhydride (**8**) seemed an attractive intermediate *en route* to the amide (**9**) but although the di-allyl system (**7**) was readily obtained, satisfactory conditions could not be found for its oxidative conversion into the glutaric acid corresponding to anhydride (**8**). This was not studied exhaustively because a more promising route had emerged from parallel work.



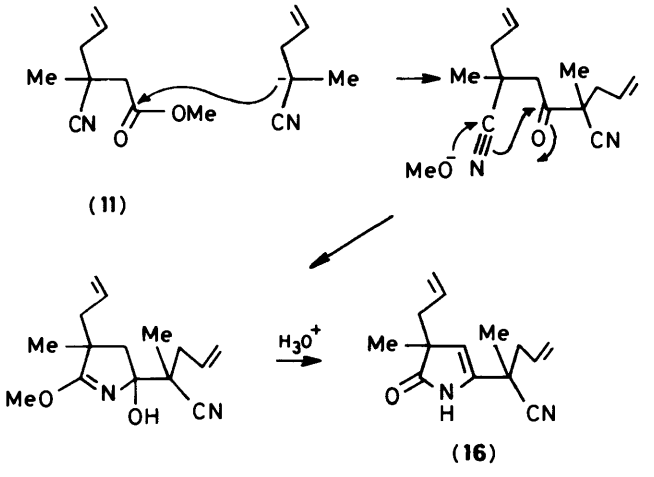
(**7**) (**8**) (**9**)

This alternative approach (Scheme 1) involved the alkylation of the nitrile[5] (**10**) followed by ring-closure of the nitrile ester (**11**) by treatment with alkali to form the imide (**13**). The acid (**12**), not surprisingly, was also formed and this too could be converted into the imide (**13**) by way of the amide (**14**) and amidine (**15**) using straightforward steps (Scheme 1). However, the yield in the alkylation stage (**10**) ⟶ (**11**) was modest



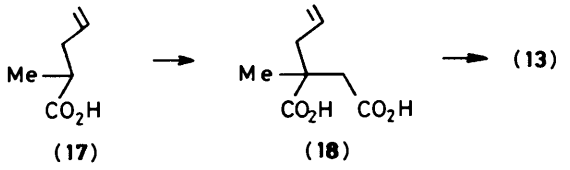
Scheme 1.

probably due to proton transfers among the various species. An interesting by-product, assigned structure (**16**), was isolated and its formation is rationalised as shown in Scheme 2.



Scheme 2.

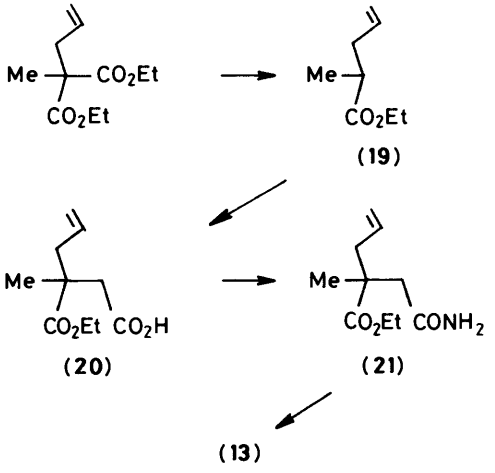
The foregoing experiments gave the first supplies of the imide (**13**) for further study but since the route was unsatisfactory, the acidities of the sites suspected to be the cause of low yields in Scheme 1 were reduced by working with a carboxylate bis-anion[6] as shown in Scheme 3. This change was a clear



Scheme 3.

improvement over Scheme 1 but there were drawbacks: (*a*) it proved impracticable to separate unchanged starting material (**17**) from the product (**18**) on any reasonable scale and (*b*) though the final step (**18**) ⟶ (**13**) worked well on < 1 mmol scale, the yield fell with larger amounts.

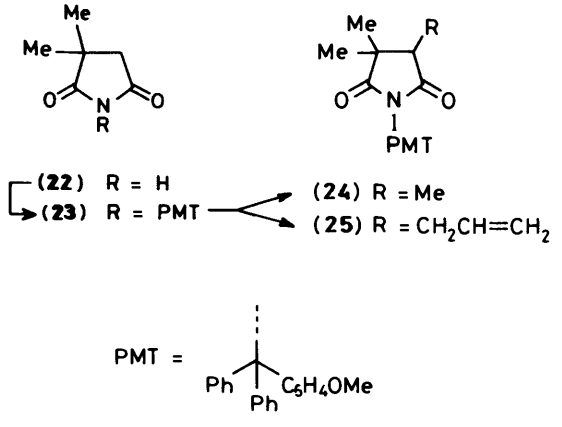
A small modification now led to a very satisfactory route shown in Scheme 4. Separation of unchanged starting material



Scheme 4.

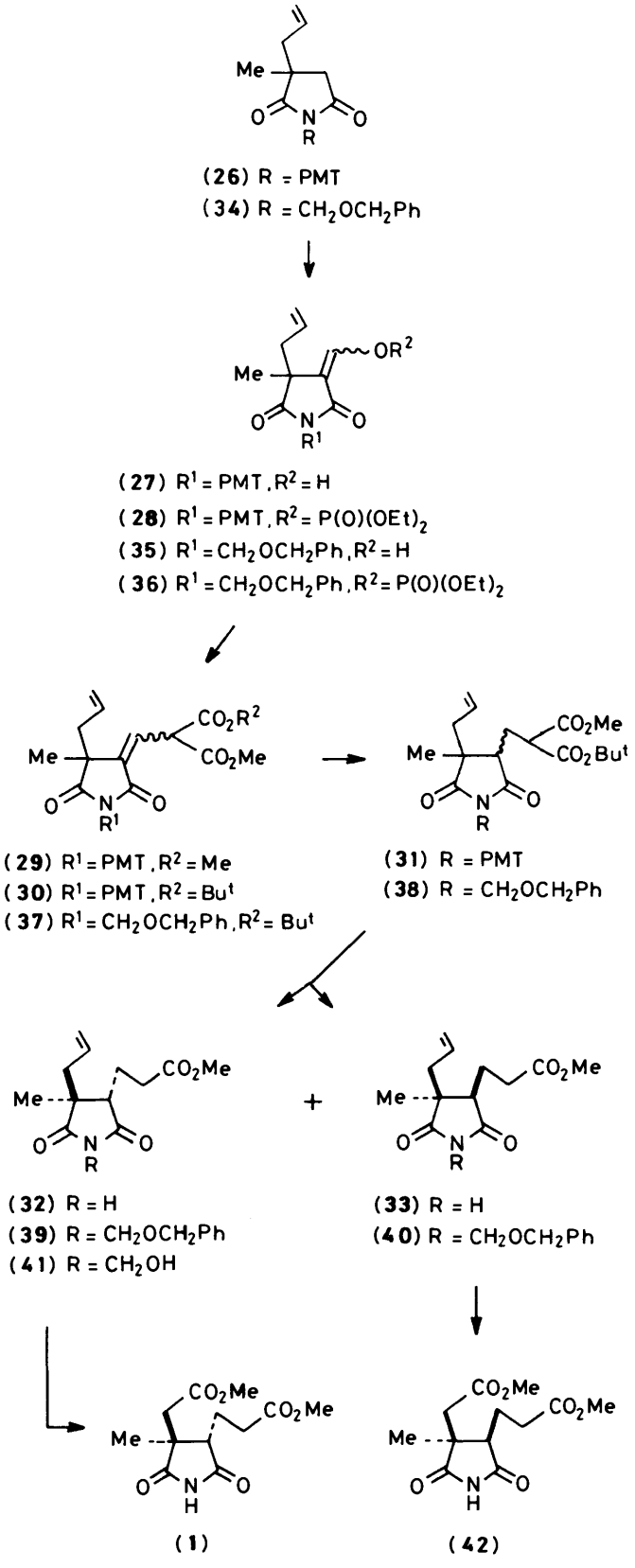
(**19**) from product (**20**) was now trivial and the remaining stages *via* the amide (**21**) to the imide (**13**) were all achieved in high yields. Using this route, batches of 50 g of the succinimide (**13**) have been routinely synthesized from diethyl malonate in 27% overall yield.

Introduction of the propionate residue (or a precursor of that function) at C-3 of the imide (**13**) necessitated protection of the nitrogen atom. Deutscher[7] had successfully used the *p*-methoxytrityl group to protect 'natural' ring-B imide (**1**) and, following that lead, we found that the protection–alkylation sequence (**22**) ⟶ (**23**) ⟶ (**24**) or (**25**) worked well in the illustrated model series (Scheme 5). Also the desired protected



Scheme 5.

imide (**26**) was readily prepared but conditions could not be found for alkylation of the C-3 anion from the imide (**26**) with synthetically useful reagents. However, this anion did react readily with ethyl formate to yield the hydroxymethylene derivative (**27**) (Scheme 6). Spectroscopic study showed that this product exists essentially completely in the enolic form (**27**) probably due to the relief of steric pressures which this tautomer affords.



Scheme 6.

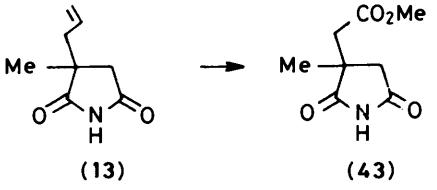
Advantage was taken of this preferred enol to allow chain extension *via* the enol phosphate[8] (**28**) which was produced in high yield. It was reasoned that the phosphate (**28**) should undergo addition–elimination using dimethyl sodiomalonate to form the imide (**29**) and so it proved; to our knowledge, there is no precedent in the literature for chain-extension by malonate in this way.

This approach was modified for the main synthesis by using t-butyl methyl malonate to form the imide (**30**). After selective reduction of the conjugated double-bond by dissolving magnesium,[9] the t-butoxycarbonyl and *p*-methoxytrityl groups were readily cleaved from the products (**31**) by trifluoroacetic acid to produce directly a 1:2 mixture of the *trans*- and *cis*-imides* (**32**) and (**33**), respectively, carrying the propionate group at C-3. That the *cis*-isomer (**33**) was the major one is surely the result of kinetic control of protonation because the *trans*-form (**32**) must be thermodynamically favoured as shown for a closely analogous system to be described later.

Experiments aimed at converting the *cis*- (**33**) into the *trans*-form (**32**) by base-catalysed equilibration were only partially successful but they indicated that it would be better to maintain *N*-protection until after the equilibration step. Accordingly, the imide (**13**) was converted into its *N*-benzyloxymethyl derivative (**34**) (Scheme 6). All the chemistry previously developed using the *p*-methoxytrityl protecting group worked at least as well in the *N*-benzyloxymethyl series. Indeed, by combining the early stages in a 'one pot' process, the malonate (**37**) was obtained in 70—80% overall yield from the imide (**34**). Similarly, the remaining steps gave an overall yield of 70—75% for the series (**37**) ⟶ (**38**) ⟶ (**39**) + (**40**).

Equilibration of the *cis*- and *trans*-isomers (**40**) and (**39**) using a suspension of sodium methoxide in methylene dichloride now proceeded smoothly to give a 2:1 mixture in favour of the *trans*-isomer (**39**). This could be separated chromatographically and the remaining material then re-equilibrated. In this way, the required *trans*-imide (**39**) was obtained in 65% yield from the initial mixture; 10% of the deprotected imide was also formed largely as the *trans*-form (**32**). The latter product presumably arises by direct nucleophilic attack of methoxide on the protecting group.

The benzyloxymethyl group was removed from the imide (**39**) by debenzylation with boron tribromide[10] to yield the *N*-hydroxymethyl derivative (**41**) which underwent quantitative thermal cleavage of formaldehyde. The product (**32**) was then oxidized with ruthenium tetraoxide[11] and esterified to afford the (*RS*)-ring-B imide (**1**) in crystalline form and 72% yield from the olefin (**32**). The conditions for the oxidative step had been developed by studying the simpler conversion of olefin (**13**) into ester (**43**).



The synthetic ring-B imide (**1**) was shown to be identical, apart from its racemic nature, with the optically active imide (**1**) obtained from degradation of vitamin B_{12} by ^1H and ^{13}C n.m.r., i.r., m.s., and chromatographic comparisons. In fact, the synthetic sample was of higher purity than the 'natural' one which invariably contains traces of the imides derived from rings C and D of the vitamin. The use of the synthetic ring-B imide (**1**) for experiments aimed at synthesis of the natural isobacteriochlorin esters (**4**) and (**5**) will be reported in detail in

* The terms *trans* and *cis* refer to the relative stereochemistry of the allyl and propionate groups and later, of the acetate and propionate groups for (**1**) and (**42**).

future papers but part of this work, which led to the synthesis of pigment (**4**) has already been outlined.[12] The synthesis of a natural chlorin related to vitamin B_{12} which depended upon the synthetic imide (1) has also been reported briefly.[13]

Experimental

For general directions, see ref. 14. ^{1}H N.m.r. spectra were recorded on Varian EM 360 (A), XL100 (B), and Bruker WM 250 (C) and WH 400 (D) spectrometers. For spectra run on spectrometer A, tetramethylsilane was the internal standard whereas for B, C, and D the residual proton signal from the solvent was used. Unless stated otherwise, solutions for n.m.r. were in $CDCl_3$ and shift values are quoted on the δ scale. ^{13}C N.m.r. spectra were recorded at 62.5 MHz on the Bruker WM 250 instrument in $CDCl_3$ with the carbon signal from the solvent as internal standard. The chemical shifts are quoted relative to tetramethylsilane as δ = 0.

(RS)-2-*Allyl*-2-*methylpent*-4-*enonitrile* (**7**).—To a solution of lithium di-isopropylamide (93 mmol) in tetrahydrofuran (THF) (40 ml) at 0 °C under nitrogen was added rapidly 2-allylpent-4-enonitrile[15] (6 g, 74 mmol) in THF (20 ml) and the solution was stirred at 0 °C for 10 min. Iodomethane (12.5 g, 88 mmol) was added (immediate discharge of colour) and after 3 h at 20 °C the solution was concentrated. The residue in ether (200 ml) was washed with aqueous hydrochloric acid (3M; 2 × 100 ml) and water (100 ml) and the residue from the organic phase was distilled to give the *nitrile* (**7**) as a liquid (7.4 g, 74%), b.p. 64—66 °C/9 mmHg (Found: C, 80.0; H, 9.7; N, 10.3. $C_9H_{13}N$ requires C, 80.0; H, 9.7; N, 10.4%); $\nu_{max.}$ (liq. film) 3 090, 2 245, and 1 645 cm^{-1}; δ(A) 1.24 (3 H, s, Me), 2.27 (4 H, br d, C=CCH_2), and 4.91—6.22 (6 H, m, C=CH); *m*/*z* 135 (M^+, 5%), 120 ($M^+ - CH_3$, 12), 108 (M^+ − HCN, 18), and 93 (100).

(RS)-*Methyl* 3-*Cyano*-3-*methylhex*-5-*enoate* (**11**).—2-Methylpent-4-enonitrile (**10**) (9 g, 95 mmol) in THF (25 ml) was added to lithium di-isopropylamide (96 mmol) in THF (50 ml) at −75 °C under nitrogen and the solution was stirred at −75 °C for a further 5 min. The resulting orange solution was rapidly added to methyl bromoacetate (16 g, 105 mmol) in THF (25 ml) at −75 °C. The mixture was held at −75 °C for 90 min after which it was allowed to warm to 18 °C, stirred for a further 90 min, and then concentrated. The residue was treated with 3M hydrochloric acid (250 ml) and extracted with ether (3 × 250 ml, 3 × 100 ml). The combined extracts were washed with 3M hydrochloric acid (200 ml) and brine (200 ml). The residue from the ether was chromatographed on silica (300 g) with 1:1 dichloromethane–hexane to give the starting nitrile (**10**) (2.3 g, 25%). Further elution with dichloromethane–hexane (2:1) gave a mixture of the products (**11**) and (**16**). Trituration with ethanol precipitated 3-*allyl*-5-(1-*cyano*-1-*methylbut*-3-*enyl*)-3-*methylpyrrol*-2(3H)-*one* (**16**) (350 mg, 9%), m.p. 138—141 °C from ethanol (Found: C, 73.3; H, 7.7; N, 12.4%; M^+, 230.1428. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%; *M*, 230.1420); $\nu_{max.}$ 3 200, 3 080, 2 250, 1 710, and 1 645 cm^{-1}; δ(A) 1.20 (3 H, s, Me), 1.60 (3 H, s, Me), 2.32 (2 H, br, d, C=CCH_2), 2.57 (2 H, br d, C=CCH_2CCN), 4.8—6.1 (7 H, m, C=CH), and 9.60 (1 H, br s, NH); *m*/*z* 230 (M^+, 9%) and 189 ($M^+ - C_3H_5$, 100). Concentration of the mother liquor from the initial trituration with ethanol gave the *cyano ester* (**11**) as an oil (5 g, 30%); $\nu_{max.}$ (liq. film) 3 080, 2 240, 1 745, and 1 645 cm^{-1}; δ(A) 1.48 (3 H, s, CH_3), 2.47 (2 H, br d, C=CCH_2), 2.52 (1 H, d, *J* 18 Hz, CH_AH$_B$$CO_2$Me), 2.71 (1 H, d, *J* 18 Hz, CH$_A$$H_B$$CO_2$Me), 3.77 (3 H, s, CO_2Me), and 5.0—6.2 (3 H, m, C=CH); *m*/*z* 152 ($M^+ - CH_3$, 5%), 140 (M^+ − HCN, 20), and 75 (100) (Found: M^+ − Me, 152.0711. $C_9H_{13}NO_2$ requires *M* − Me, 152.0711).

(RS)-2-*Allyl*-2-*methylsuccinimide* (**13**).—(*a*) Methyl 3-cyano-3-methylhex-5-enoate (**11**) (4.5 g, 27 mmol) was shaken at room temperature with 2M aqueous potassium hydroxide (60 ml) for 90 min and then extracted with ether (5 × 20 ml) which removed starting material (520 mg). The aqueous phase was acidified with concentrated hydrochloric acid and the product, isolated *via* ethyl acetate (5 × 50 ml) extraction, was dissolved in benzene (20 ml) and treated at 0 °C with thionyl chloride (10 ml) for 10 min; the mixture was then heated at 40 °C for 30 min. The solvent and excess of thionyl chloride were evaporated and the residue in THF (20 ml) was added to liquid ammonia (10 ml) in THF (50 ml) at −75 °C. After the solution had warmed to 18 °C, it was concentrated and the residue was extracted with hot acetone (5 × 10 ml); the solution was then filtered. The residue from evaporation was purified by flash chromatography, elution with ethyl acetate yielding first the *succinimide* (**13**) as an oil (1.5 g, 41%); $\nu_{max.}$ 3 410, 3 220, 3 080, 1 790, 1 720, and 1 645 cm^{-1}; δ(B) 1.33 (3 H, s, Me), 2.36 (2 H, br d, C=CCH_2), 2.40 (1 H, d, *J* 18 Hz, CH_AH$_B$CO), 2.75 (1 H, d, *J* 18 Hz, CH$_A$$H_B$CO), 4.9—5.8 (3 H, m, C=CH), and 8.5 (1 H, br s, NH); *m*/*z* 153 (M^+, 24%), 138 (M^+ − Me, 16) and 67 (100) (Found: M^+, 153.0795. $C_8H_{11}NO_2$ requires *M*, 153.0790). Further elution afforded 3-*cyano*-3-*methylhex*-5-*enamide* (**14**) which crystallized from ethyl acetate–ether (420 mg, 11%), m.p. 73—75 °C (Found: C, 62.9; H, 8.1; N, 18.1. $C_8H_{12}N_2O$ requires C, 63.1; H, 8.0; N, 18.4%); $\nu_{max.}$ 3 540, 3 420, 2 250, 1 695, and 1 645 cm^{-1}; δ(A) 1.48 (3 H, s, Me), 2.40 (2 H, br d, C=CCH_2), 2.51 (1 H, d, *J* 17 Hz, CH_AH$_B$CO), 2.87 (1 H, d, *J* 17 Hz, CH$_A$$H_B$CO), and 4.9—6.5 (5 H, m, C=CH + $CONH_2$); *m*/*z* 152 (M^+, 13%) and 59 (100).

(*b*) The foregoing cyanoamide (**14**) (0.4 g, 2.6 mmol) in dry ethanol (10 ml) was treated with a solution of sodium ethoxide in ethanol (2M; 10 ml). The mixture was stirred at 20 °C for 90 min after which it was concentrated and the residue chromatographed on silica. Elution with methanol–ethyl acetate (1:4) afforded 4-allyl-5-imino-4-methylpyrrolidin-2-one (**15**) (320 mg, 80%) (Found: M^+, 152.0946. $C_8H_{12}N_2O$ requires *M*, 152.0955). This was heated at reflux in 0.3M hydrochloric acid (5 ml) for 3 h after which the aqueous phase was extracted with ether (4 × 5 ml) and the combined extracts were concentrated to afford 2-allyl-2-methylsuccinimide (**13**) (250 mg, 66%) identical by t.l.c., ^{1}H n.m.r. and mass spectral analysis with the material from (*a*).

(*c*) Propionic acid (1.6 g, 22 mol) was added at −20 °C under nitrogen to a solution of lithium di-isopropylamide (48 mmol) in THF (30 ml) and stirred at 0 °C for 15 min. Hexamethylphosphoramide (5 ml) was added and the solution was heated at 45 °C for 30 min and then cooled to 18 °C. Allyl bromide (2.7 g, 22 mmol) was added and the solution was stirred at 18 °C for 1.5 h. After neutralization with 3M hydrochloric acid (75 ml), the mixture was extracted with hexane (3 × 50 ml) and the combined organic phases were washed successively with 3M hydrochloric acid (3 × 50 ml), water (50 ml), and brine (50 ml). The residue from the organic solution was distilled to give the acid (**17**) (1.4 g, 55%) as a liquid, b.p. 110 °C/24 mmHg (lit.,[16] 102—104 °C/20 mmHg); $\nu_{max.}$ 3 090, 3 400—2 700, 1 710, and 1 645 cm^{-1}; δ (A) 1.18 (3 H, d, *J* 6 Hz, CHCH_3), 1.84—2.79 (3 H, m, C=CCH_2 + C*H*Me), 4.81—6.17 (3 H, m, C=CH), and 11.2 (1 H, br s, exchangeable with D_2O, CO_2H).

This acid (570 mg, 5 mmol) was added dropwise to a solution of lithium di-isopropylamide (10 mmol) in THF at 0 °C under nitrogen and then stirred at 0 °C for 15 min. Hexamethylphosphoramide (1 ml) was added and the solution was heated at 45 °C for 90 min; a solution of lithium bromoacetate (5 mmol) in THF (5 ml) containing hexamethylphosphoramide (1 ml) was then added dropwise to the solution of the dianion at 0 °C. The mixture was heated at 35 °C for 2 h, then neutralized with 1M hydrochloric acid (15 ml) saturated with sodium chloride and the aqueous phase was extracted with ether (3 × 20 ml). The

combined extracts were washed with brine (15 ml) and the residue from the ether was chromatographed on silica (10 g). Elution with ether gave a 7:3 mixture of the succinic acid (**18**) and starting material; $\nu_{max.}$ 3 090, 3 400—2 700, 1 720, 1 710, and 1 645 cm^{-1}; δ(A) 1.32 (3 H, s, Me), 2.31 (1 H, d, *J* 12 Hz, $CH_AH_BCO_2H$), 2.35 (2 H, br d, C=CCH_2), 2.59 (1 H, d, *J* 12 Hz, $CH_AH_BCO_2H$), 4.8—6.1 (3 H, m, C=CH), and 10.6 (2 H, br s, exchangeable with D_2O, CO_2H) plus signals due to (17); *m/z* 154 ($M^+ - H_2O$, 10%) and 126 (110).

The foregoing impure succinic acid (**18**) (0.1 g) was dissolved in concentrated aqueous ammonia (1 ml) and the solution was evaporated. The resulting residue was heated to 160 °C for 1 h after which it was cooled and extracted with hot dichloromethane (3 × 5 ml). The residue therefrom was chromatographed on silica (3 g) with ether as eluant to afford 2-allyl-2-methylsuccinimide (**13**) (55 mg), identical with that from (*a*) and (*b*) (Found: M^+, 153.1780. $C_8H_{11}NO_2$ requires *M*, 153.1790).

The lithium bromoacetate used above was made by cooling a solution of bromoacetic acid in THF (quantities as stated) to 0 °C under argon. Lithium hydride (1.1 equiv.) was added to the stirred solution and when vigorous hydrogen evolution ceased, hexamethylphosphoramide (1 ml/5 mmol acid) was added and the solution was stirred for 10 min at 0 °C prior to use.

(RS)-*Ethyl 2-Methylpent-4-enoate* (**19**).—A solution of diethyl 2-allyl-2-methylmalonate[16] (35 g) in dimethyl sulphoxide (270 ml) containing water (2.9 ml) and lithium chloride[17] (13.6 g) was heated at reflux for 6 h. The cooled reaction mixture was diluted with water (200 ml) and the organic layer was separated; the aqueous phase was then extracted with ether (4 × 200 ml). The organic layer and extracts were combined, washed with water (3 × 100 ml) and brine (100 ml), and the residue therefrom was distilled to give ethyl 2-methylpent-4-enoate (**19**) (19.5 g, 85%), b.p. 65—67 °C/34 mmHg (lit.,[18] 153—155 °C/760 mmHg); $\nu_{max.}$ 3 090, 1 720, and 1 645 cm^{-1}; δ(A) 1.20 (3 H, s, Me), 1.25 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.68—2.72 (3 H, m, C=CCH_2 + $CHCH_3$), 4.12 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), and 4.79—6.05 (3 H, m, C=CH).

(RS)-3-*Ethoxycarbonyl*-3-*methylhex*-5-*enoic acid* (**20**).—To a stirred solution of lithium di-isopropylamide (0.75 mol) in THF (500 ml) at −75 °C under nitrogen was added the foregoing ester (**19**) (99 g, 0.7 mol) at a rate such that the reaction temperature remained below −60 °C. The solution was then stirred at −75 °C for 1 h. Separately, a solution of lithium bromoacetate (0.75 mol) in THF (500 ml) containing hexamethylphosphoramide (100 ml) was prepared and cooled to −75 °C. This was transferred through a wide-bore cannula into the above solution of the ester anion at a rate such that the reaction temperature remained below −55 °C. After the resulting mixture had been warmed to 18 °C and stirred for 12 h, it was neutralized with 3M hydrochloric acid (400 ml) and the phases were separated; the aqueous phase was extracted with dichloromethane (5 × 200 ml). The residue from evaporation of the combined organic phases was fractionated on silica (500 g) using ether which removed the phosphoramide. The later fractions were concentrated (*ca.* 500 ml) and washed with saturated aqueous sodium carbonate (3 × 200 ml). The organic layer yielded unchanged starting material (30.5 g). The basic extracts were acidified to pH 3 with concentrated hydrochloric acid, extracted with dichloromethane (2 × 200 ml, 3 × 100 ml), and the combined extracts were washed to remove traces of bromoacetic acid. The organic solution yielded the *acidic ester* (**20**) [82.8 g, 85% based on unrecovered (**19**)] further purified by short-path distillation, b.p. 90 °C/0.5 mmHg (Found: C, 59.7; H, 8.0. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.0%); $\nu_{max.}$ 3 400—2 700, 1 730, 1 710, and 1 645 cm^{-1}; δ (B) 1.24 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.28 (3 H, s, Me), 2.37 (2 H, br d, C=CCH_2), 2.46 (1 H, d, *J* 16 Hz, $CH_AH_BCO_2H$), 2.79 (1 H, d, *J* 16 Hz, $CH_AH_BCO_2H$), 4.14 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 4.8—5.8 (3 H, m, C=CH), and 6.6 (1 H, br s, exchangeable with D_2O, CO_2H); *m/z* 155 ($M^+ - CO_2H$, 20%) and 85 (100).

(RS)-3-*Ethoxycarbonyl*-3-*methylhex*-5-*enamide* (**21**).—Thionyl chloride (50 ml) was added to a solution of the acid (**20**) (75 g) in toluene (500 ml) at 0 °C and the mixture was stirred at 0 °C for 15 min; it was then heated at 70 °C for 45 min. After evaporation of the mixture, the residue in THF (500 ml) was slowly added to a solution of ammonia (20 ml) in THF (500 ml) at −75 °C and the mixture was stirred at 18 °C for 3 h. The residue from evaporation was treated with hot acetone (200 ml), filtered, and the filter cake was washed with acetone (3 × 100 ml). The crude product from evaporation of the combined filtrates was fractionated on silica (500 g), eluting with acetone–ether (1:3) to afford the *amido ester* (**21**) (61.5 g, 82%); $\nu_{max.}$ 3 500, 3 400, 1 720, 1 690, 1 645, and 1 585 cm^{-1}; δ(B) 1.18 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.22 (3 H, s, Me), 2.25 (1 H, d, *J* 15 Hz, $CH_AH_BCONH_2$), 2.32 (2 H, br d, C=CCH_2), 2.65 (1 H, d, *J* 15 Hz, $CH_AH_BCONH_2$), 4.14 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 4.8—5.8 (3 H, m, C=CH), and 6.0 (2 H, br s, $CONH_2$); *m/z* 199 (M^+, 11%), 155 ($M^+ - CONH_2$, 30), and 59 (100) (Found: M^+, 199.1218. $C_{10}H_{17}NO_3$ requires *M*, 199.1227).

(RS)-2-*Allyl*-2-*methylsuccinimide* (**13**).—The foregoing amide (60 g) in 50% aqueous methanol (500 ml) containing potassium hydroxide (25 g) was stirred at 18 °C for 3 h and then washed with ether (200 ml). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with dichloromethane (2 × 200 ml, 3 × 100 ml). The combined organic phases were dried and the residue therefrom in toluene (500 ml) was heated with acetyl chloride (50 ml) at 70 °C for 1 h and then cooled to 18 °C. The solution was washed with 10% aqueous sodium hydrogencarbonate until the aqueous washings were basic and the product from the organic phase was purified by flash chromatography. Elution with ether–hexane (1:1) gave 2-allyl-2-methylsuccinimide (**13**), identical with an authentic sample (43.6 g, 95%). It crystallized after short-path distillation, m.p. 44—45 °C (Found: C, 62.8; H, 7.4; N, 9.2. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.1%).

N-(p-*Methoxytrityl*)-2,2-*dimethylsuccinimide* (**23**).—To a stirred solution of 2,2-dimethylsuccinimide (**22**) (390 mg) in THF (9 ml) under argon was added potassium t-butoxide in t-butyl alcohol (1.08M; 3.6 mmol), followed by dimethylformamide (3 ml). The solution was stirred at 20 °C for 5 min and then *p*-methoxytrityl chloride (1.05 g) was added in one portion. Stirring was continued for a further 2.5 h. Most of the THF was evaporated, brine (50 ml) was added, and the aqueous phase was extracted with dichloromethane (4 × 20 ml). The residue from the combined extracts was purified by flash chromatography eluting with ether to give the protected *succinimide* (**23**) as an amorphous solid (640 mg, 52%); $\nu_{max.}$ 3 550, 1 785, and 1 710 cm^{-1}; δ(A) 1.21 (6 H, s, 2 × Me), 2.53 (2 H, s, CH_2CO), 3.72 (3 H, s, OMe), and 6.6—7.4 (14 H, m, ArH); *m/z* 399 (M^+, 46%) and 273 (100) (Found: M^+, 399.1865. $C_{26}H_{25}NO_3$ requires *M*, 399.1835).

(RS)-N-(p-*Methoxytrityl*)-2,2,3-*trimethylsuccinimide* (**24**).—The foregoing succinimide (**23**) (100 mg) in THF (3 ml) was added dropwise to a stirred solution of lithium di-isopropylamide (0.35 mmol) in THF (1 ml) at −75 °C. After 10 min, iodomethane (200 mg) was added and the solution was warmed to 18 °C and stirred overnight. The residue from evaporation of the mixture was treated with water (5 ml) and extracted with ether (3 × 5 ml) and the residue from the combined organic

extracts was purified by p.l.c. (1 × 1 mm plate, Et_2O as eluant) to give the amorphous *methylated succinimide* (**24**) (82 mg, 79%); $\nu_{max.}$ 3 550, 1 785, and 1 710 cm^{-1}; δ(A) 0.91 (3 H, s, Me), 1.08 (3 H, d, *J* 10 Hz, $CHCH_3$), 1.22 (3 H, s, Me), 2.50 (1 H, q, *J* 10 Hz, $CHCH_3$), 3.72 (3 H, s, OMe), and 6.6—7.4 (14 H, m, ArH); *m/z* 413 (M^+, 32%) and 273 (100) (Found: M^+, 413.1973. $C_{27}H_{27}NO_3$ requires *M*, 413.1991).

(RS)-2-*Allyl*-N-(p-*methoxytrityl*)-3,3-*dimethylsuccinimide* (**25**).—The above procedure was repeated using the succinimide (**23**) (120 mg) but with allyl bromide (290 mg) as the electrophile. Work-up as before afforded the *succinimide* (**25**) as an oil (93 mg, 73%); $\nu_{max.}$ 3 550, 3 060, 1 785, 1 710, and 1 645 cm^{-1}; δ(A) 1.04 (3 H, s, Me), 1.28 (3 H, s, Me), 2.10—2.95 (3 H, m, $C{=}CCCH_2$ + $CHCH_2$), 3.72 (3 H, s, OMe), 4.82—5.95 (3 H, m, C=CH), and 6.6—7.4 (14 H, m, ArH); *m/z* 439 (M^+, 30%) and 273 (100) (Found: M^+, 439.2155. $C_{29}H_{29}NO_3$ requires *M*, 439.2147).

(RS)-2-*Allyl*-N-(p-*methoxytrityl*)-2-*methylsuccinimide* (**26**).—A solution of succinimide (**13**) (0.7 g, 4.6 mmol) in THF (10 ml) under argon at 0 °C was treated first with potassium t-butoxide in t-butyl alcohol (1.2M, 5 mmol) and then dimethylformamide (4 ml). The solution was then stirred at 0 °C for 10 min after which *p*-methoxytrityl chloride (1.7 g, 5 mmol) was added in one portion. After 2 h at 0 °C the mixture was concentrated and the residue was treated with water (25 ml) and extracted with dichloromethane (3 × 25 ml), the combined organic extracts being washed with brine (25 ml), dried, and evaporated. The residue crystallized at −17 °C from ether–hexane to give the *protected succinimide* (**26**) (1.31 g, 66%), m.p. 118—120 °C (Found: C, 78.8; H, 6.6; N, 3.3%; M^+, 425.1997. $C_{28}H_{27}NO_3$ requires C, 79.0; H, 6.4; N, 3.3%; *M*, 425.1991); $\nu_{max.}$ 3 560, 3 080, 1 785, 1 710, and 1 645 cm^{-1}; δ(B) 1.27 (3 H, s, Me), 2.36 (1 H, d, *J* 18 Hz, CH_AH_BCO), 2.40 (2 H, br d, $C{=}CCH_2$), 2.71 (1 H, d, *J* 18 Hz, CH_AH_BCO), 3.78 (3 H, s, OMe), 4.81—5.93 (3 H, m, C=CH), and 6.83—7.50 (14 H, m, ArH); *m/z* 425 (M^+, 28%) and 273 (100).

E- *and* Z-*Isomers of* (RS)-2-*Allyl*-3-*hydroxymethylidene*-N-(p-*methoxytrityl*)-2-*methylsuccinimide* (**27**).—A 50% dispersion of sodium hydride in oil (0.5 g, 10 mmol) was washed with hexane (3 × 5 ml) and suspended in THF (10 ml) at 0 °C under nitrogen. To this was added a solution of the foregoing succinimide (**26**) (1.5 g, 3.5 mmol) in THF (15 ml) and the mixture was stirred at 0 °C for 1 h. Ethyl formate (0.5 g, 7 mmol) was then added and after the solution had been stirred at 0 °C for 1 h, further ethyl formate (0.5 g, 7 mmol) was added. After 2 h at 18 °C, the mixture was treated with saturated aqueous ammonium chloride (2 ml), water (10 ml), and extracted with ether (4 × 20 ml). The combined extracts were washed with brine (30 ml), dried, and evaporated. The residue was purified by flash chromatography, eluting with hexane–ether (1:3) to give initially starting material (220 mg) followed by the isomeric *hydroxymethylene derivatives* (**27**) as a foam (1.18 g, 86% based on unrecovered starting material); $\nu_{max.}$ 3 550, 3 600—2 900, 1 760, 1 710, 1 690, 1 640, and 1 610 cm^{-1}; δ(A) 1.30 (3 H, s, Me), 2.42 (2 H, br d, $C{=}CCH_2$), 3.78 (3 H, s, OMe), 4.8—5.9 (3 H, m, C=CH), and 6.8—7.6 (16 H, m, ArH + $C{=}CH{-}OH$); *m/z* 453 (M^+, 17%) and 273 (100) (Found: M^+, 453.1980. $C_{29}H_{27}NO_4$ requires *M*, 453.1940).

E- *and* Z-*Isomers of* (RS)-2-*Allyl*-N-(p-*methoxytrityl*)-3-(2,2-*bismethoxycarbonylethylidene*)-2-*methylsuccinimide* (**29**).—A 50% dispersion of sodium hydride in oil (190 mg, 3.9 mmol) was washed with hexane (3 × 10 ml) and suspended in THF (10 ml) at 0 °C under nitrogen. To this was added dropwise with stirring a solution of the foregoing succinimide (**27**) (1.18 g, 2.6 mmol) in THF (10 ml); after 30 min at 0 °C diethyl chlorophosphate (0.5 g, 2.9 mmol) was also added. The solution was stirred at 18 °C for 1 h. Separately dimethyl malonate (2.4 g, 18 mmol) was added to a suspension of hexane-washed sodium hydride (430 mg, 18 mmol) in THF (30 ml) and hexamethylphosphoramide (5 ml) and this solution was transferred through a cannula into the solution of the enol phosphate. After the mixture had been stirred for 16 h at 18 °C, it was treated with saturated aqueous ammonium chloride (20 ml) and then water (30 ml), filtered through Celite, and concentrated to remove the bulk of the THF. The aqueous residue was extracted with hexane (4 × 50 ml) and the combined organic phases were washed with brine, dried, and evaporated. The residue was purified by flash chromatography eluting with hexane–ether (1:3) to give the *succinimides* (**29**) as a foam (1.05 g, 75% based on unrecovered starting material); $\nu_{max.}$ 3 550, 1 740, 1 710, 1 680, and 1 605 cm^{-1}; δ(B) 1.30 (2.2 H, s, Me, *Z*-isomer), 1.38 (0.8 H, s, Me, *E*-isomer), 2.42 (2 H, br q, $C{=}CCH_2$), 3.72 (6 H, s, CO_2Me), 3.76 (3 H, s, OMe), 4.8—5.4 [3 H, m, C=CH (allyl group)], 5.54 [1 H, d, *J* 10 Hz, $CH(CO_2Me)_2$], 6.10 [1 H, d, *J* 10 Hz, $C{=}CHCH(CO_2Me)_2$], and 6.60—7.42 (14 H, m, ArH); *m/z* 567 (M^+, 8%) and 273 (100) (Found: M^+, 567.2272. $C_{34}H_{33}NO_7$ requires *M*, 567.2257). Further elution afforded unchanged enol phosphate (**28**) (220 mg).

E- *and* Z-*Isomers of* (RS)-2-*Allyl*-N-(p-*methoxytrityl*)-3-(2-*methoxycarbonyl*-2-*t*-*butoxycarbonylethylidene*)-2-*methylsuccinimide*.—The enol phosphate (**28**) was prepared from the hydroxymethylenesuccinimide (**27**) (7.1 g, 16 mmol) as above and was treated with a solution of methyl t-butyl sodiomalonate[19] (40 mmol) in THF (50 ml) and hexamethylphosphoramide (5 ml) prepared as before. After the mixture had been stirred for 16 h at 18 °C, saturated aqueous ammonium chloride (10 ml) was added and the THF was evaporated; water (100 ml) was added to the residue and the aqueous phase was extracted with hexane (4 × 100 ml). The residue from the combined organic phases was purified by flash chromatography, eluting with hexane–ether (1:3) to yield the *malonate esters* (**30**) as an oil (6.8 g, 70%); $\nu_{max.}$ 3 570, 1 750, 1 710, 1 680, and 1 605 cm^{-1}; δ(B) 1.25 (1 H, s, Me, *E*-isomer), 1.33 (2 H, s, Me, *Z*-isomer), 1.49 (9 H, s, Bu^t), 2.1—2.7 (2 H, m, $C{=}CCH_2$), 3.73 and 3.75 (each 3 H, s, OMe), 4.8—5.4 [3 H, m, C=CH (allyl group)], 5.42 [0.3 H, d, *J* 12 Hz, $CH(CO_2R)_2$, *E*-isomer], 5.48 [0.7 H, d, *J* 12 Hz, $CH(CO_2R)_2$, *Z*-isomer], 6.06 [1 H, d, *J* 12 Hz, $C{=}CHCH(CO_2R)_2$], and 6.6—7.5 (14 H, m, ArH); *m/z* 609 (M^+, 19%), 472 (25), and 273 (100) (Found: M^+, 609.2716. $C_{37}H_{39}NO_7$ requires *M*, 609.2726).

cis- *and* trans-*Isomers of Racemic*-2-*Allyl*-N-(p-*methoxytrityl*)-3-(2-*methoxycarbonyl*-2-*t*-*butoxycarbonylethyl*)-2-*methylsuccinimide* (**31**).—The foregoing product (**30**) (5 g) in methanol (150 ml) was stirred at 18 °C for 30 min with magnesium turnings (2.5 g) with ice cooling when vigorous hydrogen evolution commenced. After 3 h at 18 °C, the mixture was acidified with 50% aqueous acetic acid (120 ml), diluted with water (120 ml), and extracted with ether (200 ml, 4 × 100 ml). The combined extracts were washed with water (2 × 200 ml) and brine (200 ml), dried, and evaporated. The residue was chromatographed on silica, eluting with hexane–ether (1:3) to give the isomeric *succinimides* (**31**) as an oil (4. 8 g, 96%); $\nu_{max.}$ 3 560, 1 780, 1 750, 1 720, 1 640, and 1 605 cm^{-1}; δ(B) 1.28 (3 H, s, Me), 1.47 (9 H, s, Bu^t), 1.70—2.78 [5 H, m, $C{=}CCH_2$ + CHCON + $CH_2CH(CO_2R)_2$], 3.74 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.81 [1 H, m, $CH(CO_2R)_2$], 4.8—5.5 (3 H, m, C=CH), and 6.6—7.5 (14 H, m, ArH); *m/z* 611 (M^+, 43%) and 273 (100) (Found: M^+, 611.2882. $C_{37}H_{41}NO_7$ requires *M*, 611.2883).

cis- *and* trans-*Isomers of Racemic* 2-*Allyl*-3-(2-*methoxycarbonylethyl*)-2-*methylsuccinimide* (**33**) *and* (**32**).—The fore-

going succinimides (**31**) (3.95 g) in toluene (50 ml) and trifluoroacetic acid (20 ml) were stirred for 3 h at 18 °C and the solution was then evaporated. The residue was purified by flash chromatography, eluting initially with hexane–ether (1:1) to remove *p*-methoxytrityl alcohol. Elution with ether gave the crude acids as an oil (1.5 g) which was heated at 130—140 °C for 4 h. The product was purified by flash chromatography, eluting with hexane–ethyl acetate (1:1) to give a 2:1 mixture of the *cis*- and *trans*-imides (**33**) and (**32**); [δ(B) 1.17 (1 H, s, Me *trans*) and 1.27 (2 H, s, Me *cis*)] as an oil (1.17 g, 75%). They were separated by h.p.l.c. on silica (13:7 ethyl acetate–hexane eluant, flow rate = 2.0 ml/min); repeated passes were necessary. The faster running trans-*imide* (**32**) was an oil; $\nu_{max.}$ 3 690, 3 410, 1 780, 1 730, 1 715, and 1 640 cm^{-1}; δ(B) 1.17 (3 H, s, Me), 1.67—1.93 (2 H, m, $CH_2CH_2CO_2CH_3$), 2.19 (1 H, d, *J* 7 Hz, C=CCH_AH_B), 2.44 (1 H, d, *J* 7 Hz, C=CCH_AH_B), 2.53—2.77 (3 H, m, $CH_2CH_2CO_2Me$ + CHCONH), 3.62 (3 H, s, CO_2Me), 5.02—5.73 (3 H, m, C=CH), and 9.2 (1 H, br s, NH); *m/z* 239 (M^+, 22%), 224 (M^+ − Me, 13), 208 (M^+ − MeO, 47), 207 (M^+ − MeOH, 71), and 95 (100) (Found: M^+, 239.1153. $C_{12}H_{17}NO_4$ requires *M*, 239.1158).

The slower running cis-*imide* (**33**) was also an oil; $\nu_{max.}$ 3 590, 3 400, 1 785, 1 730, 1 710, and 1 640 cm^{-1}; δ(B) 1.27 (3 H, s, Me), 1.81—2.16 (2 H, m, $CH_2CH_2CO_2CH_3$), 2.27 (2 H, br d, C=CCH_2), 2.53—2.75 (3 H, m, $CH_2CH_2CO_2Me$ + CHCONH), 3.64 (3 H, s, CO_2Me), 4.95—5.75 (3 H, m, C=CH), and 8.9 (1 H, br s, NH); *m/z* 239 (M^+, 22%), 224 (M^+ − Me, 15), 208 (M^+ − MeO, 49), 207 (M^+ − MeOH, 80), and 166 (100) (Found: M^+, 239.1153. $C_{12}H_{17}NO_4$ requires *M*, 239.1158).

(RS)-2-*Allyl*-N-*benzyloxymethyl*-2-*methylsuccinimide* (**34**).—A solution of 2-allyl-2-methylsuccinimide (16.6 g) in dichloromethane (100 ml) at 0 °C was treated with di-isopropylethylamine (20 g) in dichloromethane (20 ml) and the mixture was stirred at 0 °C for 10 min. Benzyl chloromethyl ether (20.3 g) in dichloromethane (100 ml) was then added during 10 min and the solution was stirred for 16 h at 18 °C. It was washed with 3M hydrochloric acid (100 ml) and brine (100 ml) and the organic phase was dried and concentrated. The residue was chromatographed on silica (400 g) using ether–hexane (1:1) to give the *protected succinimide* (**34**) as an oil (19.5 g, 83% based on unrecovered starting material) followed by starting material (3.5 g). The product (**34**) was short-path distilled, b.p. 130 °C/0.25 mmHg (Found: C, 70.6; H, 7.1; N, 5.6%; M^+, 273.1372. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.3%; *M*, 273.1365); $\nu_{max.}$ 3 650, 3 480, 3 030, 1 785, 1 720, and 1 640 cm^{-1}; δ(B) 1.26 (3 H, s, Me), 2.27 (2 H, br d, C=CCH_2), 2.35 (1 H, d, *J* 18 Hz, CH_AH_BCO), 2.63 (1 H, d, *J* 18 Hz, CH_AH_B), 4.61 (2 H, s, $PhCH_2O$), 4.90—5.68 (3 H, m, C=CH), 5.00 (2 H, s, OCH_2N), and 7.3 (5 H, br s, ArH); *m/z* 273 (M^+, 6%) and 167 (100).

cis- *and* trans-*Isomers of Racemic* 2-*Allyl*-N-*benzyloxymethyl*-3-(2-*methoxycarbonyl*-2-*t*-*butoxycarbonylethylidene*)-2-*methylsuccinimide* (**37**).—A 50% dispersion of sodium hydride in oil (6.7 g) was washed under argon with hexane (3 × 20 ml) and then suspended in THF (250 ml); a solution of the foregoing succinimide (**34**) (19.1 g) and ethyl formate (30 ml) in THF (100 ml) was then added under argon to the stirred suspension. The mixture was periodically cooled in ice when the reaction became too vigorous. After 6 h at 18 °C when the hydroxymethylene derivative (**35**) had formed, the mixture was cooled in ice and diethyl chlorophosphate (30 g) was added to it; the mixture was then stirred for a further 45 min at 18 °C. Separately, a solution of methyl t-butyl malonate (24.4 g) in THF (120 ml) and hexamethylphosphoramide (40 ml) was added under argon to a suspension of hexane-washed sodium hydride (3.6 g) in THF (150 ml). The resulting solution of methyl t-butyl sodiomalonate at 0 °C was transferred through a cannula into the solution of enol phosphate (**36**) prepared above and stirred at 18 °C for 12 h. Saturated aqueous ammonium chloride (150 ml) was carefully added and after most of the THF had been evaporated, the residue was diluted with water (200 ml) and extracted with hexane (5 × 200 ml). The combined extracts were dried and the residue from evaporation was chromatographed on silica (2 × 20 g samples of the crude product on 500 g of silica). Elution with hexane–ether (2:1), then gradually increasing the solvent polarity to hexane–ether (1:2), gave initially unchanged methyl t-butyl malonate and then the two isomeric *succinimides* (**37**) as an oil (24 g, 75%); $\nu_{max.}$ 3 560, 1 780, 1 750, 1 720, 1 680, and 1 645 cm^{-1}; δ(C) 1.31 (1.4 H, s, Me, *E*-isomer), 1.32 (1.6 H, s, Me, *Z*-isomer), 1.45 (9 H, s, Bu^t), 2.27—2.72 (2 H, m, C=CCH_2), 3.75 (3 H, s, CO_2Me), 4.56 (2 H, s, $PhCH_2O$), 4.95—5.65 (3 H, m, C=CH), 5.01 (2 H, s, OCH_2N), 5.69 [0.45 H, d, *J* 10 Hz, $CH(CO_2R)_2$, *E*-isomer], 5.72 [0.55 H, d, *J* 10 Hz, $CH(CO_2R)_2$, *Z*-isomer], 6.28 [1 H, d, *J* 10 Hz, C=CHCH$(CO_2R)_2$], and 7.29 (5 H, br s, ArH); *m/z* 400 (M^+ − C_4H_9, 1%), 295 (55), and 91 (100) (Found: M^+ − C_4H_9, 400.1405. $C_{25}H_{31}NO_7$ requires *M* − C_4H_9, 400.1405).

cis- *and* trans-*Isomers of Racemic* 2-*Allyl*-N-*benzyloxymethyl*-3-(2-*methoxycarbonyl*-2-*t*-*butoxycarbonylethyl*)-2-*methylsuccinimide* (**38**).—A solution of the foregoing product (36.6 g) in methanol (400 ml) was stirred at 18 °C with magnesium turnings (15 g) until hydrogen evolution commenced and the rate of the reaction was controlled by cooling. After 4 h, the mixture was acidified with concentrated hydrochloric acid (150 ml), diluted with water (150 ml), and extracted with dichloromethane (3 × 200 ml). The combined extracts were dried and evaporated to give the two isomeric *reduced succinimides* (**38**) as an oil (35.7 g, 97%); $\nu_{max.}$ 3 560, 1 785, 1 750, 1 730, 1 720, and 1 645 cm^{-1}; δ(C) 1.13, 1.23, 1.25 (3 H, 3 × s, Me, isomers), 1.46 (9 H, s, Bu^t), 1.97—2.72 [5 H, m, C=CCH_2 + $CH_2CH(CO_2R)_2$ + CHCON], 3.74, 3.75, and 3.76 (3 H, 3 × s, CO_2Me, isomers), 3.88—4.12 [1 H, m, $CH_2CH(CO_2R)_2$], 4.58 (2 H, br s, $PhCH_2$), 4.92 (1 H, d, *J* 18 Hz, OCH_AH_BN), 4.95—5.70 (3 H, m, C=CH), 4.98 (1 H, d, *J* 18 Hz, OCH_AH_BN), and 7.31 (5 H, m, ArH); *m/z* 402 (M^+ − C_4H_9, 20%), 297 (55), and 91 (100) (Found: M^+ − C_4H_9, 402.1533. $C_{25}H_{33}NO_7$ requires *M* − C_4H_9, 402.1513).

cis- *and* trans-*Isomers of Racemic* 2-*Allyl*-N-*benzyloxymethyl*-3-(2-*methoxycarbonylethyl*-2-*methylsuccinimide* (**40**) and (**39**).—A solution of the foregoing succinimides (**38**) (35.5 g) in dichloromethane (300 ml) and trifluoroacetic acid (30 ml) was stirred under argon for 8 h at 18 °C. The solution was evaporated (finally at high vacuum) and the residue was heated under argon at 135—150 °C for 4 h. Complete esterification was ensured by treatment of the residue in dichloromethane (50 ml) with ethereal diazomethane to yield the crude mixture of *cis*- and *trans*-succinimides (**40**) and (**39**) (20.5 g, 75%) [δ(B) 1.11 (0.84 H, s, Me, *trans*), 1.22 (2.16 H, s, Me, *cis*)]. The stereochemical equilibration was carried out as follows.

Freshly cut sodium (1.15 g) was dissolved in methanol (10 ml) in a flame-dried flask and the methanol was evaporated finally at high-vacuum. The mixture of (**40**) and (**39**) (20 g) in dichloromethane (200 ml) was stirred under argon with the freshly prepared sodium methoxide at 18 °C for 72 h and was then acidified with 3M hydrochloric acid (50 ml). The organic layer was separated, the aqueous layer was extracted with dichloromethane (50 ml), and the combined organic phases were dried and evaporated. The residue [δ(B) 1.11 (2 H, s, Me, *trans*), 1.22 (1 H, s, Me, *cis*)] was divided into four 5-g portions and each was purified by flash chromatography on silica (200 g). Elution with hexane–ether (2:1) gave initially the trans-

succinimide (**39**) as an oil (8.8 g); $\nu_{max.}$ 3 550, 3 460, 3 030, 1 780, 1 730, 1 715, and 1 640; δ(C) 1.11 (3 H, s, Me), 1.74—1.85 (2 H, m, $CH_2CH_2CO_2Me$), 2.21 (1 H, dd, *J* 14, 8 Hz, C=CHCH_AH_B), 2.45 (1 H, dd, *J* 14, 7 Hz, C=CHCH$_A$$H_B$), 2.57—2.76 (3 H, m, CHCON + $CH_2CH_2CO_2Me$), 3.67 (3 H, s, CO_2Me), 4.57 (2 H, s, $PhCH_2O$), 4.92 (1 H, d, *J* 10 Hz, OCH_AH_BN), 4.96 (1 H, d, *J* 10 Hz, OCH$_A$$H_B$N), 5.05—5.68 (3 H, m, C=CH), and 7.32 (5 H, br s, ArH); *m/z* 328 ($M^+ - CH_3O$, 5%) and 91 (100) (Found: $M^+ - CH_3O$, 328.1555. $C_{20}H_{25}NO_5$ requires $M - CH_3O$, 328.1549). Following fractions containing the *trans*- and *cis*-products (6.6 g), the pure cis-*succinimide* (**40**) eluted as an oil (820 mg); $\nu_{max.}$ 3 600, 3 400, 3 030, 1 780, 1 730, 1 710, and 1 645 cm^{-1}; δ(C) 1.22 (3 H, s, CH_3), 1.78—1.92 (2 H, m, $CH_2CH_2CO_2Me$), 2.20—2.34 (2 H, m, C=CCH_2), 2.55—2.83 (3 H, m, CHCON + $CH_2CH_2CO_2Me$), 3.69 (3 H, s, CO_2CH_3), 4.59 (2 H, s, $PhCH_2O$), 4.89 (1 H, d, *J* 9 Hz, OCH_AH_BN), 4.97 (1 H, d, *J* 9 Hz, OCH$_A$$H_B$N), 5.02—5.67 (3 H, m, C=CH), and 7.32 (5 H, br s, ArH); *m/z* 328 ($M^+ - CH_3O$, 8%) and 91 (100) (Found: $M^+ - CH_3O$, 328.1544. $C_{20}H_{25}NO_5$ requires $M - CH_3O$, 328.1549). Further elution afforded a mixture of the *cis*- and *trans*-deprotected succinimides (**33**) and (**32**) (1.6 g).

The mixed isomers (**40**) and (**39**) (6.6 g) were re-treated using the equilibration–separation cycle twice and all the pure *trans*-succinimide (**39**) was combined (13.3 g, 65%). The mixture of deprotected succinimides (**33**) and (**32**) (total 2.4 g) was fractionated by flash chromatography on silica (100 g). Elution with hexane–ether (1:1) gave the pure *trans*-succinimide (**32**) (1 g) and a mixture of (**33**) and (**32**) (1.3 g), the latter by preparative h.p.l.c. (30% ethyl acetate–hexane as eluant) affording the deprotected succinimide (**32**) (total 1.4 g, 10%) identical with the earlier sample.

Racemic trans-2-*Allyl*-N-*hydroxymethyl*-3-(2-*methoxycarbonylethyl*)-2-*methylsuccinimide* (**41**).—Boron tribromide (5.3 g) was added dropwise to a vigorously stirred solution of the *trans*-succinimide (**39**) (5 g, 13 mmol) in dichloromethane (50 ml) at −75 °C under argon and was stirred for 3 h at −75 °C. The mixture was treated with ether (10 ml) and then allowed to warm to 20 °C when 3M hydrochloric acid (15 ml) was added. After the mixture had been stirred for a further 15 min at 20 °C, water (15 ml) was added, the organic phase was separated, and the aqueous phase was washed with dichloromethane (20 ml). The product from the combined organic phases was purified by flash chromatography using ether–hexane (2:1) to afford unchanged starting material (505 mg) followed by the N-*hydroxymethylsuccinimide* (**41**) as an oil (3.22 g, 95% based on unrecovered starting material); $\nu_{max.}$ 3 670, 3 580, 3 700—3 300, 3 080, 1 780, 1 730, 1 710, and 1 640 cm^{-1}; δ(C) 1.19 (3 H, s, Me), 1.79—1.98 (2 H, m, $CH_2CH_2CO_2Me$), 2.23 (1 H, dd, *J* 14, 9 Hz, C=CHCH_AH_B), 2.50 (1 H, dd, *J* 14, 6 Hz, C=CHCH$_A$$H_B$), 2.63—2.75 (3 H, m, CHCON + $CH_2CH_2CO_2Me$), 3.67 (3 H, s, CO_2Me), 4.97 (2 H, br s, CH_2OH), 5.10—5.80 (3 H, m, C=CH), and 8.3 (1 H, br s, CH_2OH); *m/z* 251 ($M^+ - H_2O$, 47%), 238 ($M^+ - CH_2OH$, 68), and 208 (100) (Found: $M^+ - H_2O$, 251.1158. $C_{13}H_{19}NO_5$ requires $M - H_2O$, 251.1158).

Racemic trans-2-*Allyl*-3-(2-*methoxycarbonylethyl*)-2-*methylsuccinimide* (**32**).—A solution of the foregoing *N*-hydroxymethylsuccinimide (**41**) (3.2 g) in xylene (40 ml) was heated at reflux under argon for 14 h and was then evaporated. The residue was purified by flash chromatography using ether–hexane (2:1) to give the deprotected succinimide (**32**) (2.76 g, 97%), spectroscopically identical with the earlier sample; it was short-path distilled, b.p. 130 °C/0.1 mmHg (Found: C, 60.4; H, 6.9; N, 6.3. $C_{12}H_{17}NO_4$ requires C, 60.2; H, 7.1; N, 6.0%).

(RS)-2-*Methoxycarbonylmethyl*-2-*methylsuccinimide* (**43**).—A solution of the succinimide (**13**) (540 mg) in carbon tetrachloride (6 ml) and acetonitrile (6 ml) at 0 °C was stirred vigorously with sodium periodate (3 g) and water (9 ml) while ruthenium(IV) oxide hydrate (10 mg) was added. The mixture was stirred at 0 °C for 1 h and for a further 1 h at 18 °C and was then mixed with dichloromethane (10 ml) and filtered. The separated aqueous phase was extracted with ethyl acetate (3 × 10 ml) and the combined organic phases were dried and evaporated. A solution of the residual acid (Found: M^+, 171.0532. $C_7H_9NO_4$ requires *M*, 171.0523) in dichloromethane (10 ml) was treated with an excess of ethereal diazomethane. The excess was then destroyed by the addition of formic acid (1 drop) and the residue from evaporation was purified by p.l.c. (2 × 1 mm plates, ether eluant) to give the *succinimide* (**43**) as an oil (0.5 g, 85%); $\nu_{max.}$ 3 670, 3 410, 1 780, 1 720, and 1 710 cm^{-1}; δ(B) 1.31 (3 H, s, Me), 2.46 (1 H, d, *J* 18 Hz, CH_AH_BCONH), 2.53 (1 H, d, *J* 17 Hz, C$H_AH_B$$CO_2Me$), 2.85 (1 H, d, *J* 18 Hz, CH$_A$$H_B$CONH), 2.88 (1 H, d, *J* 17 Hz, CH$_A$$H_B$$CO_2Me$), 3.63 (3 H, s, CO_2Me), and 8.9 (1 H, br s, NH); *m/z* 185 (M^+, 10%), 154 ($M^+ - CH_3O$, 26), 126 ($M^+ - CO_2CH_3$, 25), and 59 (100) (Found: M^+, 185.0680. $C_8H_{11}NO_4$ requires *M*, 185.0688).

(2RS,3RS)-2-(2-*Methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-3-*methylsuccinimide* (*The Ring*-B *Imide*) (**1**).—To a solution of the *trans*-succinimide (**32**) (2.39 g) in acetonitrile (20 ml) and carbon tetrachloride (20 ml), was added sodium periodate (8.8 g) in water (30 ml), followed at 0 °C with ruthenium(IV) oxide hydrate (25 mg). The mixture was stirred for 1 h at 0 °C, a further 2 h at 18 °C and was then diluted with dichloromethane (80 ml) and filtered; the filter pad was washed with acetonitrile–dichloromethane (1:9; 20 ml). The aqueous layer was extracted with acetonitrile–dichloromethane (1:9; 3 × 20 ml) and all the organic phases and washings were combined. A solution of the residue therefrom in dichloromethane (20 ml) was treated at 0 °C with an excess of ethereal diazomethane. Formic acid (1 drop) was then added and the solution was evaporated to give the racemic *ring*-B *imide* (**1**) which crystallized from ethyl acetate–hexane (1.9 g, 70%), m.p. 111.5—113.5 °C (Found: C, 53.2; H, 6.3; N, 5.1. $C_{12}H_{17}NO_6$ requires C, 53.1; H, 6.3; N, 5.2%); $\nu_{max.}$ 3 660, 3 400, 1 780, 1 730, and 1 715 cm^{-1}; δ(D) (C_6D_6) 0.73 (3 H, s, Me), 1.33—1.67 (2 H, m, $CH_2CH_2CO_2Me$), 2.18 (1 H, d, *J* 18 Hz, C$H_AH_B$$CO_2Me$), 2.39—2.48 (2 H, m, $CH_2CH_2CO_2Me$), 2.56 (1 H, d, *J* 18 Hz, CH$_A$$H_B$$CO_2Me$), 2.95 (1 H, dd, *J* 10, 5 Hz, C*H*CONH), 3.10 (3 H, s, CO_2Me), 3.26 (3 H, s, CO_2Me), and 8.30 (1 H, br s, NH); *m/z* 271 (M^+, 7%), 240 (M^+ − MeO, 78), and 166 (100) (Found: M^+, 271.1056. $C_{12}H_{17}NO_6$ requires *M*, 271.1056); δ_C 20.5, 20.8, 32.1, 39.4, 46.1, 47.0, 51.7, 52.0, 171.1, 173.2, 178.3, and 181.0 p.p.m. This product was shown to be identical (^{1}H n.m.r. and t.l.c.), apart from its racemic nature, with an authentic sample of ring-B imide from degradation of vitamin B_{12}.

(2SR,3RS)-2-(2-*Methoxycarbonylethyl*)-3-*methoxycarbonylmethyl*-3-*methylsuccinimide* (*epi-Ring*-B *imide*) (**42**).—The *cis*-allylsuccinimide (**33**) from the first synthetic route described earlier was oxidized as for the *trans*-series to give the *racemic epi-ring*-B *imide* (**42**) as a gum (7 mg, 32%); $\nu_{max.}$ 3 660, 3 410, 1 785, 1 720, and 1 715 cm^{-1}; δ(D) (C_6D_6) 1.05 (3 H, s, Me), 1.42—1.89 (2 H, m, $CH_2CH_2CO_2Me$), 2.23—2.62 (3 H, m, $CH_2CH_2CO_2Me$ + CHCON), 2.29 (1 H, d, *J* 17 Hz, C$H_AH_B$$CO_2Me$), 2.58 (1 H, d, *J* 17 Hz, CH$_A$$H_B$$CO_2Me$), 3.29 (3 H, s, CO_2Me), 3.39 (3 H, s, CO_2Me), and 9.3 (1 H, br s, NH); *m/z* 240 (M^+ − MeO, 42%), 239 (M^+ − MeOH, 39), and 59 (100) (Found: $M^+ - CH_3O$, 240.0881. $C_{12}H_{17}NO_6$ requires *M* − MeO, 240.0872).

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