Asymmetric synthesis of (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid and its methyl ester †

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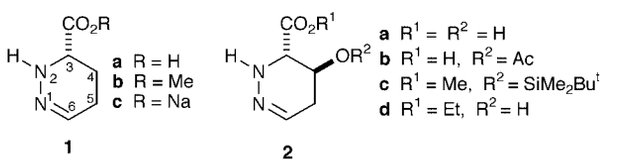
Methyl (2*E*,4*E*)-5-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)penta-2,4-dienoate **16a**, assembled by a Wittig condensation of tributyl(methoxycarbonylmethylene)phosphorane **19a** and (2*E*)-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)propenal **20**, displays excellent *Re*-face reactivity towards diethyl azodicarboxylate **15a**, bis(2,2,2-trichloroethyl) azodicarboxylate **15b**, dibenzyl azodicarboxylate **15c**, diisopropyl azodicarboxylate **15d** and di-*tert*-butyl azodicarboxylate **15e** in thermal hetero-Diels–Alder reactions to give the cycloadducts **17a**–**e**. When subjected to the action of hydrogen over palladium–carbon, the cycloadducts **17a, 17b, 17d** and **17e** undergo hydrogenation of their olefinic bonds to give the dihydro derivatives **18a, 18b, 18d** and **18e**; in the case of the cycloadduct **17c**, hydrogenolysis of the benzyloxycarbonyl group also occurs to give methyl (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate **1b** with an ee of 98% and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose **22**. Compound **1b**, with an ee of 98%, is also available from the dihydro derivative **18e** by the action of trifluoroacetic acid; however, under the acidic conditions, a condensation reaction between the aglycone **1b** and the glycone **22** competes to give methyl (3*S*)-2,3,4,5-tetrahydro-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)pyridazine-3-carboxylate **25**.

Sodium (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate **1c**, with an ee of 99%, is available from the ester **1b** by a saponification reaction. The trifluoroacetic acid salt **27**, with an ee of 95%, is obtained from benzyl (3*S*,6*S*)-1,2-bis(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate **17g** by a hydrogenation–trifluoroacetolysis sequence. A hetero-Diels–Alder reaction involving the benzyl pentadienoate **16c** and di-*tert*-butyl azodicarboxylate **15e** provides the cycloadduct **17g**.

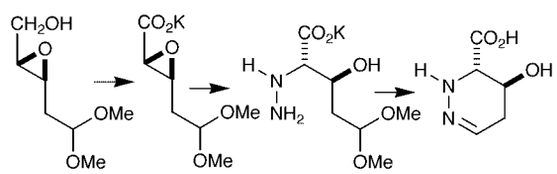
Introduction

2,3,4,5-Tetrahydropyridazine-3-carboxylic acids are an interesting class of cyclic α-hydrazono acids. The (3*S*)-isomer of the parent compound, *i.e.* **1a**, was first reported in 1981 as an alkaline hydrolysis product of antrimycin A[2] (a linear hexapeptide with antitubercular activity). Subsequently, the hydrazono acid **1a** was shown to be a constituent of several other antrimycins[3] and of aurantimycin B[4] (a cyclic hexadepsipeptide with antibacterial activity). Both compound **1a** and its enantiomer are present in L-365,209[5] (a semi-synthetic cyclic hexapeptide that acts as an oxytocin antagonist) and in aurantimycin C.[4] The (4*S*)-hydroxy and (4*S*)-acetoxy derivatives, *i.e.* **2a** and **2b**, are components of luzopeptins[6] (cyclic decadepsipeptides with antitumour properties). 4-Acetoxy and 4-(*trans*-2-methylcyclopropylcarbonyloxy) derivatives of 2,3,4,6-tetrahydropyridazine-3-carboxylic acid (of unreported absolute stereochemistry) are present in quinoxapeptins[7] (relatives of luzopeptins with HIV reverse transcriptase inhibitory properties).



1 **2**

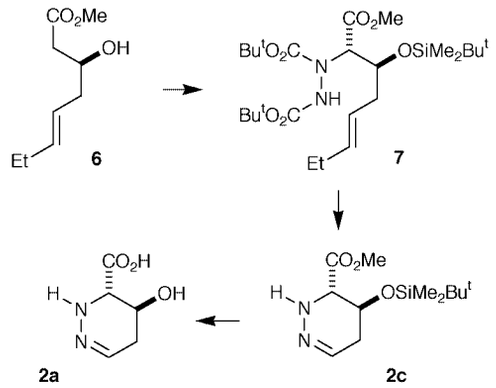
At the commencement of our studies, the only synthesis of a tetrahydropyridazinecarboxylic acid derivative was that of Hughes and Clardy,[8] who had prepared the hydroxy acid **2a** by the route outlined in Scheme 1. Thus, the epoxy alcohol **3** (prepared by a Sharpless asymmetric epoxidation) was transformed into the glycidic acid salt **4**, which underwent a highly regioselective hydrazinolysis to give compound **5**; an acid-induced cyclocondensation reaction then led to the target **2a**. Recently, a second synthesis of the hydroxy acid **2a** was described by Genêt's group[9] (Scheme 2). It also featured an acid-induced cyclocondensation reaction in which the product of ozonolysis of the alkene **7** was transformed into the tetrahydropyridazine **2c**; a highly *anti*-selective electrophilic amination with di-*tert*-butyl azodicarboxylate was used in the assembly of compound **7** from the hydroxy ester **6** (obtained by a Noyori-type asymmetric reduction of the corresponding keto ester). Ciufolini and Xi prepared the (±)-hydroxy ester **2d** using a similar approach.[10] The first synthesis of a derivative of the parent acid **1a** was reported by Nakamura and Shin,[11] who prepared the ester **1b** by an acid-induced cyclocondensation reaction. Thus, as shown in Scheme 3, the cyclisation precursor **10** was obtained by methanolysis of the imide **9**, assembled from compound **8** using Evans' electrophilic amination technology. A similar approach was adopted by Schmidt and Riedl[12] in their synthesis of the ester **1b**.



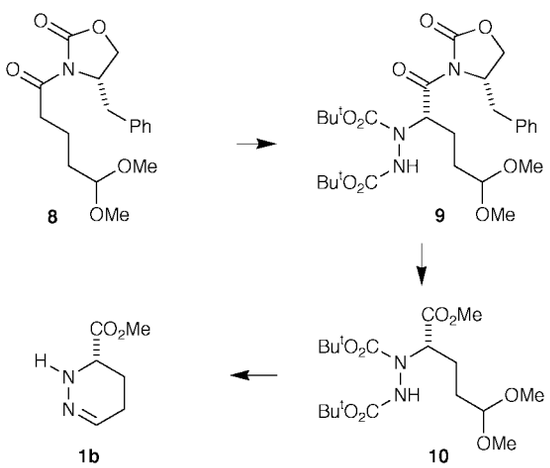
Scheme 1

In earlier work, we had shown that the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl unit conferred a useful level of *Re*-face reactivity on 1-oxybuta-1,3-dienes in Diels–Alder cycloadditions with cyclic electron-deficient dienophiles under thermal

† For preliminary communication, see ref. 1.

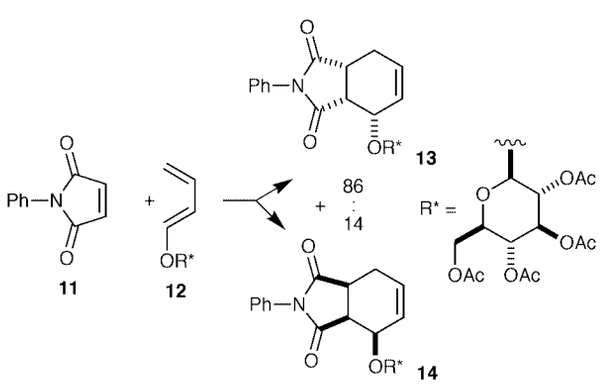


Scheme 2



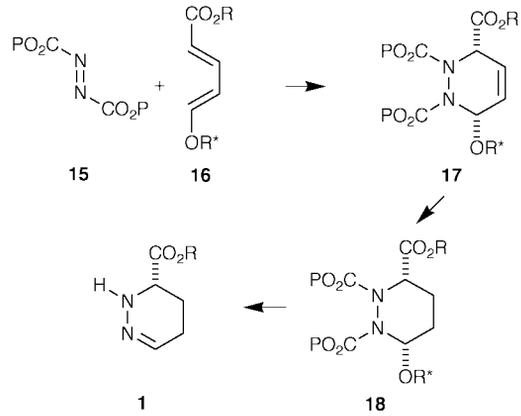
Scheme 3

conditions.[13–15] For example, the diene **12** reacted with *N*-phenylmaleimide **11** in benzene to give an 86 : 14 mixture of the *endo*-cycloadducts **13** and **14** (Scheme 4), from which the major



Scheme 4

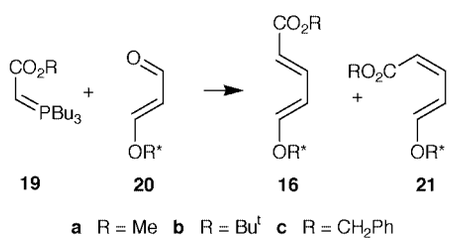
diastereomer **13** was isolated in 59% yield after crystallisation.[14] Based on such findings, we hoped that the sequence outlined in Scheme 5 would provide a new route to pyridazinecarboxylic acid derivatives of type **1**. Thus, the reaction of azodicarboxylates of type **15** with dienes of type **16** should give cycloadducts of type **17**; removal of the *N*-protecting groups from hydrogenation products of type **18** should then afford targets of type **1**. Clearly, the success of such a venture would require an efficient assembly of dienes of type **16**, an ability to isolate cycloadducts of type **17** (or their dihydro derivatives of type **18**) in a near-stereopure state, and a capacity to remove the *N*-protecting groups from compounds of type **18**. We now report the successful implementation of this plan.



Scheme 5 R* as defined in Scheme 4.

Results and discussion

Initially, the synthesis of the diene **16a** was undertaken. The route adopted, shown in Scheme 6, was based upon that used



Scheme 6 R* as defined in Scheme 4.

by Maddaluno and d'Angelo[16] to assemble achiral relatives of the diene **16a**. Thus, in dichloromethane, the phosphorane **19a** reacted with the propenal **20**[14,17] to give a 4 : 1 mixture of the dienes **16a** and **21a**; following chromatography and crystallisation, the diene **16a** was isolated in 61% yield.

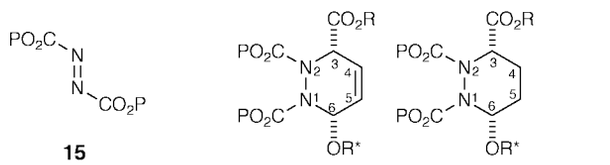
The diene **16a** was found to react slowly with diethyl azodicarboxylate **15a** (250 mol%) in hot ethyl acetate (*ca.* 70 °C; 3 days) to give an adduct in 82% yield after crystallisation. The 300 MHz ^{1}H NMR spectrum of the product (in $CDCl_3$) showed some broad signals at ambient temperature; however, at 55 °C, mainly sharp signals were observed. The latter spectrum left little doubt that the adduct was a cycloadduct, which was provisionally assigned the stereostructure **17a**. Presumably, the signal broadening is due to a high barrier to ring inversion caused by an interaction between the adjacent urethane groups; similar effects have been noted with simple 1,2-bisalkoxycarbonyl-1,2,3,6-tetrahydropyridazines.[18,19] By operating in hot toluene (*ca.* 100 °C), it was possible to effect the cycloaddition in 6 h using a stoichiometric quantity of the azodicarboxylate **15a**; the cycloadduct **17a** was then obtained in 66% yield after crystallisation.

The isolation of a single cycloadduct in good yield indicated that the hetero-Diels–Alder reaction displayed significant stereoselectivity. Indeed, when the crude product of the cycloaddition reaction (conducted in PhMe) was examined by ^{1}H NMR spectroscopy (at 55 °C), there was no evidence for the presence of a second cycloadduct.

The diene **16a** also reacted with bis-2,2,2-trichloroethyl azodicarboxylate **15b** (100 mol%) (PhMe; 100 °C; 7 h) to give the cycloadduct **17b** (75% yield after crystallisation), with dibenzyl azodicarboxylate **15c** (250 mol%) (PhMe; 90 °C; 18 h) to afford the cycloadduct **17c** (87% after chromatography), with diisopropyl azodicarboxylate **15d** (100 mol%) (PhMe; 100 °C; 7 h) to furnish the cycloadduct **17d** (57% yield after crystallisation), and with di-*tert*-butyl azodicarboxylate **15e** (300 mol%)

(CH_2Cl_2; reflux; 5 days)‡ to provide the cycloadduct **17e** (77% yield after chromatography). In all cases, the ^{1}H NMR spectra of the cycloadducts showed broad signals at ambient temperature; however, at 100 °C, mainly sharp signals were observed that were consistent with diastereomeric purity.

In the presence of hydrogen and palladium–carbon in ethyl acetate, the cycloadduct **17a** was readily transformed into the dihydro derivative **18a** (93% yield after crystallisation). Similarly, the cycloadduct **17b** afforded the dihydro derivative **18b** (84% yield after crystallisation), the cycloadduct **17d** gave rise to the dihydro derivative **18d** (82% yield after crystallisation) and the cycloadduct **17e** provided the dihydro derivative **18e** (84% yield). As in the case of their precursors, the dihydro derivatives showed broad signals in the ^{1}H NMR spectra at ambient temperature;§ however, at 90–100 °C, sharp signals were observed.



15

a P = Et
b P = CH_2CCl_3
c P = CH_2Ph
d P = Pr^i
e P = Bu^t

17

a R = Me, P = Et
b R = Me, P = CH_2CCl_3
c R = Me, P = CH_2Ph
d R = Me, P = Pr^i

18

e R = Me, P = Bu^t
f R = P = Bu^t
g R = CH_2Ph, P = Bu^t
h R = H, P = Bu^t

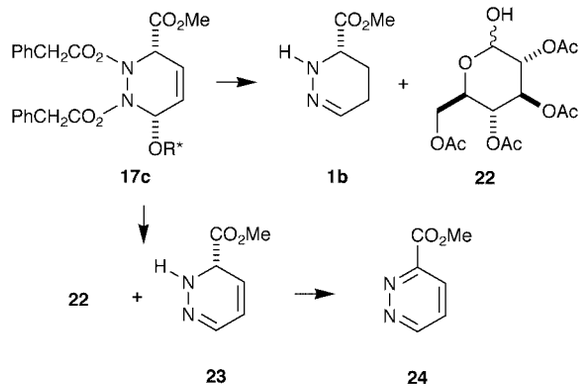
R* as defined in Scheme 4

It was hoped that, under the hydrogenation conditions, the cycloadduct **17c** would give rise to a 1:1 mixture of the target **1b** and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose **22** (Scheme 7). In the event, mainly a 5:3:1 mixture of materials was produced according to ^{1}H NMR spectroscopy. The two more prevalent components were considered to be the expected products, *i.e.* the glycone **22**[20] (as a 1:1 mixture of α- and β-anomer) and the target **1b**;[11] the third component was considered to be the pyridazine **24**.[21] Column chromatography led to the isolation of compound **22** (as a 2:1 mixture of the α- and β-anomers) in essentially quantitative yield, compound **1b** in 37% yield and compound **24** in a slightly impure state in *ca.* 13% yield. The specific rotation of compound **1b** {$[\alpha]_D$ +100 (MeOH)}¶ was the same in sign but smaller in magnitude to that published {$[\alpha]_D$ +139 (MeOH)},[11] corroborating the stereochemical assignments.

Presumably, under the hydrogenation conditions, compound **17c** undergoes two competing reactions. In the major pathway, hydrogenation of the olefinic bond to give the saturated-ring intermediate **18c** is followed by hydrogenolysis of the benzyl groups, decarboxylation and elimination to give the target **1b** and the glycone **22**. In the minor pathway, hydrogenolysis of the benzyl groups, decarboxylation and elimination affords the glycone **22** and the dihydropyridazine **23**; dehydrogenation of compound **23** then produces the pyridazine **24** (Scheme 7).

It was envisaged that the target ester **1b** would be accessible from the bis(*tert*-butoxycarbonyl) derivative **18e** under acidic conditions. Indeed, treatment of compound **18e** with trifluoroacetic acid (TFA) and subjection of the product to column chromatography resulted in the isolation of the glycone **22** (as a 3:1 mixture of α- and β-anomer) and the tetrahydropyridazine **1b**, $[\alpha]_D$ +124 (MeOH), as an oil in 57% yield. Although essentially pure by ^{1}H NMR spectroscopy, the sample failed to give an acceptable elemental analysis. In a repeat of the aforecited

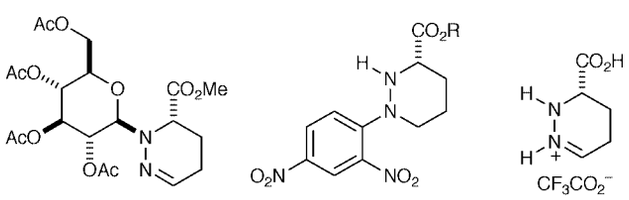
‡ Some decomposition occurred (as evidenced by the production of **22**) when the reaction was conducted in hot toluene (*ca.* 80 °C; 3 days).
§ Similar temperature-dependent effects have been noted with simple 1,2-bis(methoxycarbonyl)-1,2,3,4,5,6-hexahydropyridazines; see ref. 19.
¶ $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.



17c **1b** **22** **23** **24**

Scheme 7 R* as defined in Scheme 4.

reaction, performed under slightly different conditions (see Experimental section), three products were obtained after column chromatography. The first fraction (57% yield) was the tetraacetate **22** (as a 3:1 mixture of α- and β-anomer). The second fraction (31% yield) was identified as compound **25** on the basis of its spectral and analytical properties. In particular, the ^{1}H NMR spectrum showed the presence of a broad triplet (J 4 Hz) at δ 4.14, attributed to the 3-proton of the tetrahydropyridazine ring, a broad singlet at δ 6.68, ascribed to the 6-proton of the tetrahydropyridazine ring, and a doublet (J 9 Hz) at δ 4.69, assigned to the anomeric 1′-proton of the sugar unit. The third fraction (48% yield), $[\alpha]_D$ +108 (MeOH), was compound **1b**.



25 **26** **27**

a R = Me **b** R = H

Presumably, compound **25** arises from the tetrahydropyridazine **1b** and the tetraacetate **22** by a condensation reaction, induced by the acidic conditions.

Seeking to streamline the synthesis of compound **1b**, the diene **16a** was heated with the azodicarboxylate **15e** (300 mol%) and the crude product was subjected to the sequential actions of hydrogen over palladium–carbon, TFA, and methanol containing toluene-*p*-sulfonic acid (to convert **22** into D-glucose); a simple work-up (involving partitioning the product between CH_2Cl_2 and aq. $NaHCO_3$ and evaporation of the organic phase) gave the tetrahydropyridazine **1b**, $[\alpha]_D$ +86 (MeOH), in a reasonably pure state in *ca.* 20% overall yield (based on the diene **16a**).

Fears that the disparate optical rotations of samples of the tetrahydropyridazine **1b** reflected differing degrees of enantiomeric purity were dispelled by derivatisation and HPLC studies. Thus, samples of the tetrahydropyridazine **1b**, with $[\alpha]_D$ values of +124 and +86 (MeOH), were each converted into the 2,4-dinitrophenyl (DNP) derivative **26a**[11] [by sequential reactions with $Na(CN)BH_3$ in MeOH and 2,4-dinitrofluorobenzene in EtOH]; HPLC analyses[22] established that the samples possessed ees of 98%.

Clearly, the tetrahydropyridazine **1b** had been produced in states of high enantiomeric purity and the diene **16a** had displayed excellent *Re*-face selectivity in its hetero-Diels–Alder reactions with azodicarboxylates of type **15**.

Finally, efforts were made to prepare the parent acid **1a**. Saponification of the ester **1b** {$[\alpha]_D$ +124 (MeOH)} with sodium hydroxide in THF afforded mainly the sodium salt of

the desired product in high yield. Athough only characterised by ^{1}H NMR spectroscopy, the salt **1c** was converted into the DNP derivative **26a** [by sequential reactions with $Na(CN)BH_3$ in HOAc, 2,4-dinitrofluorobenzene and $NaHCO_3$ in aq. EtOH, and CH_2N_2 in $CHCl_3$], which was shown to possess an ee of 99%. Clearly, no racemisation accompanied the saponification reaction.

It was envisaged that the acid **1a**, or its trifluoroacetic acid salt **27**, would be available more efficiently from the hexahydropyridazine **18f**. The diene **16b** was readily synthesised (54% yield after crystallisation) from the reaction of the phosphorane **19b** with the propenal **20**. However, its reaction with the azodicarboxylate **15e** (320 mol%) in refluxing toluene (3 days) was sluggish and accompanied by significant decomposition (as evidenced by the production of **22**); following column chromatography, the cycloadduct **17f** was isolated in only 48% yield. Although the hydrogenation reaction was uneventful, producing compound **18f** in 86% yield, the trifluoroacetolysis reaction was not examined because of the relatively poor overall yield of compound **18f**.

A more satisfactory outcome resulted when the diene **16c** (prepared in 62% yield after chromatography and crystallisation from the reaction of the phosphorane **19c** and the propenal **20**) was allowed to react with the azodicarboxylate **15e** (340 mol%). In hot toluene (*ca.* 85 °C; 5 days), the cycloadduct **17g** was produced in 76% yield after chromatography. It was transformed into the acid **18h** (69% yield after crystallisation) by the action of hydrogen over 10% palladium–carbon. In the presence of TFA, compound **18h** afforded a 1:1 mixture of the tetraacetylglucose **22** (as a 3:1 mixture of α- and β-anomers) and the salt **27**; a simple work-up (in which the mixture was partitioned between CH_2Cl_2 and H_2O and the aqueous phase was concentrated) afforded the salt **27**, $[a]_D$ +62 (MeOH), in 98% yield. The sample was transformed into the DNP derivative **26a**, which possessed an ee of 95%.

The aforecited findings are of interest in a number of respects. First, although the reaction of dienes with azo dienophiles has been extensively studied,[23] there are few examples of such hetero-Diels–Alder reactions that involve dienes bearing detachable stereodirectors.[24] Secondly, the excellent *Re*-face selectivity displayed by the dienes **16a**–**c** in the cycloaddition reactions is notable, considering that acyclic dienophiles are involved (earlier, we found[14] that the diastereofacial reactivity of the diene **12** was poorer towards tetracyanoethylene than towards *N*-phenylmaleimide). Thirdly, it is worth pointing out that the absolute stereochemical outcome of the cycloaddition reactions is in accord with expectations based upon our previously proposed model.[13,14,25] Fourthly, the array of reactive functionality present in cycloadducts of type **17** offers opportunities for extensive synthetic manipulations. Finally, a reasonably practical route to compounds **1b** and **27** is available as a consequence of the work.

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: dichloromethane was distilled off calcium hydride; ethyl acetate was allowed to stand over 5 Å molecular sieves; toluene was distilled from sodium and benzophenone. Light petroleum refers to that fraction boiling in the range 35–60 °C. Diazomethane was generated from Diazald and potassium hydroxide.[26]

The progress of reactions was monitored by TLC, using Merck plastic or aluminium sheets coated with silica gel (60 F_{254}); chromatograms were initially examined under UV light (Mineralight UVG2-58 lamp) and visualised with a *p*-anisaldehyde stain [plates were sprayed with *p*-$MeOC_6H_4CHO$–conc. H_2SO_4–EtOH (1:4:95) and heated]. Column chromatography was effected, under positive pressure from a compressed air line, with Crossfield Sorbsil C60 flash silica. HPLC analyses were carried out using a Chiralcel OD column (25 × 0.46 cm), a Kontron 420 pump, a Rheodyne 7125 injector and a Kontron 742 UV detector; data were analysed with Kontron software.

Evaporations were conducted under reduced pressure (using a water-pump or an oil-pump) at ≤40 °C with a Buchi rotary evaporator (fitted with a water or Me_2CO–solid CO_2 condenser). Mps were determined with a Buchi 512 melting point apparatus and are uncorrected. Specific optical rotations, given in 10^{-1} deg cm^2 g^{-1}, were measured at *ca.* 20 °C using a Thorn Automation Type 243 or an Optical Activity 1000 polarimeter with a cell of path length 0.1 dm. Carbon, hydrogen and nitrogen contents were determined with a Carlo Erba Model 1108 analyser; chlorine content was measured by oxygen combustion followed by automatic argentometric titration on a Mettler DL25 titrator. A Perkin-Elmer Lambda 15 spectrometer was used to determine UV spectra; extinction coefficients (ε) are presented in cm^2 mmol^{-1}. IR Spectra were recorded using a Perkin-Elmer 783 spectrometer. NMR Spectra were measured using a Bruker AC 300 or a Bruker AM 400 [with distortionless enhancement by polarisation transfer (DEPT) editing for ^{13}C spectra]; *J*-values and separations are given in Hz. Proton assignments were supported by COSY 45° experiments. FAB Mass spectra (*m*-$NO_2C_6H_4CH_2OH$ as matrix) were measured using a Kratos MS 50 spectrometer; EI and CI (NH_3 as carrier gas) were determined on a VG 7070 instrument. High resolution mass spectra were recorded on a Kratos Concept IS spectrometer.

Diene syntheses

General procedure. A solution of tributylphosphine (15.0 cm^3, 60 mmol) and the requisite α-bromoacetic acid ester (60 mmol) in dry toluene (60 cm^3) was stirred for 18 h and then concentrated. The resultant phosphonium salt was dissolved in dichloromethane (75 cm^3) and the solution was washed with aq. sodium hydroxide (*ca.* 1 mol dm^{-3}; 2 × 60 cm^3) followed by water and dried ($MgSO_4$).

The aforecited solution was added to a solution of the propenal **20** (20.0 g, 50 mmol) in dichloromethane (100 cm^3) and the mixture was left for 18 h. Concentration gave a residue, which was washed with hexanes (3 × 20 cm^3) and then purified in the manner described.

Methyl (2*E*,4*E*)-5-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)penta-2,4-dienoate 16a. The residue, obtained from the reaction of the propenal **20** (20.0 g, 50 mmol) and the phosphorane **19a**, was shown to comprise an 80:20 mixture of the dienes **16a** and **21a** by ^{1}H NMR spectroscopy [the ratio was estimated from the integrals of the doublets at δ 4.87 and 4.94 (attributed to the 1′-H signals of **16a** and **21a**)]. The product was subjected to column chromatography [Et_2O–hexanes (2:1) as eluent] and the chromatographed material was crystallised from dichloromethane–diethyl ether–hexanes to furnish the *title diene* **16a** (13.9 g, 61%); mp 123–125 °C; $[a]_D$ −24 (*c* 0.7, CH_2Cl_2) (Found: C, 52.3; H, 6.0. $C_{20}H_{26}O_{12}$ requires C, 52.4; H, 5.7%); λ_{max} (EtOH)/nm 202 (ε 3900) and 273 (29 400); ν_{max} (KBr)/cm^{-1} 1750br (ester C=O), 1720 (vinylogous carbonate C=O) and 1650 and 1635 (C=C); δ_H (300 MHz; $CDCl_3$) 2.02, 2.04, 2.06 and 2.09 (each 3 H, s, 4 × $MeCO_2$), 3.73 (3 H, s, MeO_2C), 3.79–3.85 (1 H, m, 5′-H), 4.15 and 4.27 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.87 (1 H, d, *J* 7.5, 1′-H), 5.13 (2 H, t, *J* 9, 2′- and 4′-H), 5.25 (1 H, t, *J* 9, 3′-H), 5.80 (1 H, d, *J* 15, 2-H), 5.91 (1 H, t, *J* 12, 4-H), 6.82 (1 H, d, *J* 12, 5-H) and 7.22 (1 H, dd, *J* 12 and 15, 3-H); *m*/*z* (CI) 476 [$M(NH_4)^+$, 100%] and 331 ($C_{14}H_{19}O_9^+$, 80).

***tert*-Butyl (2*E*,4*E*)-5-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)penta-2,4-dienoate 16b.** (*With P. D. Wyatt.*) The residue, obtained from the reaction of the propenal **20** (1.40 g, 3.5 mmol) and the phosphorane **19b**, was crystallised from

diethyl ether–hexanes to give the *title diene* **16b** (0.950 g, 54%); mp 112–113 °C; $[\alpha]_D$ +19 (*c* 1, CH_2Cl_2) (Found: C, 55.2; H, 6.3. $C_{23}H_{32}O_{12}$ requires C, 55.2; H, 6.4%); λ_{max} (EtOH)/nm 270 (ε 30 700); ν_{max} (KBr)/cm^{-1} 1750br (ester C=O), 1705 (vinylogous carbonate C=O) and 1650 (C=C); δ_H (300 MHz; $CDCl_3$) 1.47 (9 H, s, Me_3C), 2.01, 2.03, 2.05 and 2.09 (each 3 H, s, 4 × $MeCO_2$), 3.80 (1 H, ddd, *J* 2.5, 5 and 10, 5′-H), 4.13 and 4.27 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.85 (1 H, d, *J* 7.5, 1′-H), 5.08–5.15 (2 H, m, 2′- and 4′-H), 5.23 (1 H, t, *J* 9.5, 3′-H), 5.71 (1 H, d, *J* 15, 2-H), 5.88 (1 H, t, *J* 12, 4-H), 6.77 (1 H, d, *J* 12, 5-H) and 7.09 (1 H, dd, *J* 12 and 15, 3-H); *m*/*z* (CI) 518 [$M(NH_4)^+$, 13%], 462 (21) and 366 (100).

Benzyl (2*E*,4*E*)-5-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)penta-2,4-dienoate 16c. The residue, obtained from the reaction of the propenal **20** (20.0 g, 50 mmol) and the phosphorane **19c**, was subjected to column chromatography [hexanes–Et_2O (1 : 2) as eluent]. Crystallisation of the chromatographed material from dichloromethane–diethyl ether–hexanes gave the *title diene* **16c** (16.8 g, 62%); mp 110–111 °C; $[\alpha]_D$ −18 (*c* 0.32, CH_2Cl_2) (Found: C, 58.7; H, 5.5. $C_{26}H_{30}O_{12}$ requires C, 58.4; H, 5.7%); λ_{max} (EtOH)/nm 204 (ε 12 800) and 274 (31 800); ν_{max} (KBr)/cm^{-1} 1750br (ester C=O), 1710 (vinylogous carbonate C=O) and 1650 (C=C); δ_H (300 MHz; $CDCl_3$) 2.02, 2.04, 2.05 and 2.09 (each 3 H, s, 4 × $MeCO_2$), 3.81 (1 H, ddd, *J* 2.5, 5 and 10, 5′-H), 4.14 and 4.27 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.86 (1 H, d, *J* 7.5, 1′-H), 5.09–5.16 (2 H, m, 2′- and 4′-H), 5.17 (2 H, s, OCH_2Ph), 5.24 (1 H, t, *J* 9.5, 3′-H), 5.84 (1 H, d, *J* 15, 2-H), 5.91 (1 H, t, *J* 12, 4-H), 6.82 (1 H, d, *J* 12, 5-H), 7.24 (1 H, dd, *J* 12 and 15, 3-H) and 7.30–7.38 (5 H, m, C_6H_5); *m*/*z* (FAB) 535 (MH^+, 4%), 331 ($C_{14}H_{19}O_9^+$, 60), 169 (100) and 91 ($C_7H_7^+$, 90).

Cycloaddition reactions

Methyl (3*S*,6*S*)-1,2-bis(ethoxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 17a. *Method (a).*—A solution of the diene **16a** (1.63 g, 3.6 mmol) and diethyl azodicarboxylate **15a** (1.54 g, 8.9 mmol) in dry ethyl acetate (20 cm^3) was heated at *ca.* 70 °C for 3 days. Evaporation of the solvent and crystallisation of the residue from diethyl ether–hexanes gave the *title compound* **17a** (1.84 g, 82%); mp 135–136 °C; $[\alpha]_D$ −60 (*c* 0.46, CH_2Cl_2) (Found: C, 49.3; H, 5.7; N, 4.4. $C_{26}H_{36}N_2O_{16}$ requires C, 49.4; H, 5.7; N, 4.4%); λ_{max} (EtOH)/nm 203 (ε 2700); ν_{max} (KBr)/cm^{-1} 1760, 1750 and 1740 (ester C=O), 1730 and 1720 (urethane C=O) and 1660 (C=C); δ_H (300 MHz; $CDCl_3$; 55 °C) 1.28 and 1.34 [each 3 H, t (*J* 7) and br t (*J* 7), 2 × *Me*CH_2], 1.996, 2.003, 2.02 and 2.10 (each 3 H, s, 4 × $MeCO_2$), 3.76 (3 H, s, MeO_2C), 3.78 (1 H, ddd, *J* 2.5, 5 and 10, 5′-H), 4.17–4.33 (6 H, m, 2 × OCH_2Me and 6′-H_2), 4.79 (1 H, br s, 3-H), 4.98 (1 H, br d, *J* 7.5, 1′-H), 5.06–5.14 (2 H, m, 2′- and 4′-H), 5.23 (1 H, t, *J* 9.5, 3′-H), 5.84 (1 H, dd, *J* 2 and 9.5, 4-H) and 6.02–6.11 (2 H, m, 5- and 6-H); δ_C (75 MHz; $CDCl_3$) 14.36 and 14.43 (2 × CH_3CH_2), 20.29, 20.54 and 20.66 (4 × CH_3CO), 52.79 (CH_3O), 57.47 (5′-CH), 61.67, 62.64 and 63.35 (2 × OCH_2Me and 6′-CH_2), 68.36, 70.13, 72.20 and 72.79 (2′-, 3′-, 4′- and 6-CH), 77.19 (3-CH), 95.88 (1′-CH), 125.6 and 126.1 (4- and 5-CH), 154.9 (2 × urethane CO) and 167.3, 169.4, 169.5, 170.2 and 170.7 (5 × ester CO); *m*/*z* (FAB) 655 [$M(Na)^+$, 3%], 632 (M^+, 1), 331 ($C_{14}H_{19}O_9^+$, 17) , 285 [$(M - C_{14}H_{19}O_{10})^+$, 51] and 213 (100); *m*/*z* (CI) 650 [$M(NH_4)^+$, 60%], 366 (100) and 302 (100).

Method (b).—A solution of the diene **16a** (0.917 g, 2.0 mmol) and diethyl azodicarboxylate **15a** (0.348 g, 2.0 mmol) in dry toluene (15 cm^3) was heated at *ca.* 100 °C for 6 h. Evaporation of the solvent and crystallisation of the residue from diethyl ether–hexanes gave the cycloadduct **17a** (0.832 g, 66%), mp 135–136 °C. The ^{1}H NMR spectrum of the sample matched that of the product obtained in method (*a*).

Methyl (3*S*,6*S*)-1,2-bis(2,2,2-trichloroethoxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 17b. A solution of the diene **16a** (0.917 g, 2.0 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate **15b** (0.762 g, 2.0 mmol) in dry toluene (20 cm^3) was heated at *ca.* 100 °C for 7 h. Evaporation of the solvent and crystallisation of the residue from dichloromethane–diethyl ether–hexanes gave the *title compound* **17b** (1.26 g, 75%); mp 161–162 °C; $[\alpha]_D$ −59 (*c* 0.73, CH_2Cl_2) (Found: C, 37.5; H, 3.7; N, 3.2. $C_{26}H_{30}Cl_6N_2O_{16}$ requires C, 37.2; H, 3.6; N, 3.3%); λ_{max} (EtOH)/nm 204 (ε 3600); ν_{max} (KBr)/cm^{-1} 1760br (ester and urethane C=O) and 1660 (C=C); δ_H (300 MHz; $C_6D_5CD_3$; 100 °C) 1.77, 1.80, 1.87 and 2.04 (each 3 H, s, 4 × $MeCO_2$), 3.52 (3 H, s, MeO_2C), 3.79–3.83 (1 H, m, 5′-H), 4.29 and 4.37 [each 1 H, dd (*J* 3 and 12.5) and dd (*J* 4.5 and 12.5), 6′-H_2], 4.47, 4.75 and 4.80 [1, 1 and 2 H, d (*J* 12), d (*J* 12) and AB q (*J* 12, separation of inner lines 8.5), 2 × OCH_2CCl_3], 4.96–5.00 (1 H, m, 3-H), 5.24–5.48 (4 H, m, 1′-, 2′-, 3′- and 4′-H), 5.52 (1 H, dd, *J* 2 and 10, 4-H), 5.70 (1 H, ddd, *J* 2, 4.5 and 10, 5-H) and 6.28 (1 H, dd, *J* 1.5 and 4.5, 6-H); *m*/*z* (FAB) 865, 863, 861 and 859 [$M(Na)^+$, 4% (for 861)], 783, 781, 779 and 777 [$(M - CO_2Me)^+$, 6 (for 779)], 495, 493, 491 and 489 [$(M - C_{14}H_{19}O_{10})^+$, 71 (for 491)], 331 ($C_{14}H_{19}O_9^+$, 51), 319, 317 and 315 [$C_9H_{10}Cl_3N_2O_4^+$, 74 (for 315)], 259, 257 and 255 [$C_7H_6Cl_3N_2O_3^+$, 69 (for 255)] and 169 (100).

Methyl (3*S*,6*S*)-1,2-bis(benzyloxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 17c. A solution of the diene **16a** (0.458 g, 1.0 mmol) and 90% dibenzyl azodicarboxylate **15c** (0.835 g, 2.5 mmol) in dry toluene (10 cm^3) was heated at *ca.* 90 °C for 18 h. Evaporation of the solvent and subjection of the residue to column chromatography gave two fractions. The first fraction [eluted with hexanes–Et_2O (1 : 1)] was the unchanged azodicarboxylate. The second fraction (eluted with Et_2O) was the *title compound* **17c** (0.658 g, 87%) as a foam. A sample, crystallised from diethyl ether–hexanes, showed mp 68–70 °C; $[\alpha]_D$ −33 (*c* 0.4, CH_2Cl_2) (Found: C, 57.0; H, 5.4; N, 3.7. $C_{36}H_{40}N_2O_{16}$ requires C, 57.1; H, 5.3; N, 3.7%); λ_{max} (EtOH)/nm 208 (ε 18 300), 247 (720), 251 (770), 257 (830), 262 (750) and 267 (600); ν_{max} (KBr)/cm^{-1} 1760br (ester C=O) and 1730sh (urethane C=O); δ_H (300 MHz; $C_6D_5CD_3$; 100 °C) 1.795, 1.804, 1.85 and 2.00 (each 3 H, s, 4 × $MeCO_2$), 3.33–3.40 (1 H, m, 5′-H), 3.48 (3 H, s, MeO_2C), 4.07 and 4.21 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.83–4.86 (1 H, m, 3-H), 4.91–5.35 (8 H, m, 2 × OCH_2Ph, 1′-, 2′-, 3′- and 4′-H), 5.47 (1 H, dd, *J* 2 and 10, 4-H), 5.64 (1 H, ddd, *J* 2, 4.5 and 10, 5-H) and 6.16–6.19 (1 H, m, 6-H) (the C_6H_5 signals were partly obscured by the solvent signals); *m*/*z* (FAB) 779 [$M(Na)^+$, 5%], 365 (56), 331 ($C_{14}H_{19}O_9^+$, 28) and 169 (100).

Methyl (3*S*,6*S*)-1,2-bis(isopropoxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 17d. A solution of the diene **16a** (0.917 g, 2.0 mmol) and diisopropyl azodicarboxylate **15d** (0.404 g, 2.0 mmol) in dry toluene (15 cm^3) was heated at *ca.* 100 °C for 7 h. Evaporation of the solvent and crystallisation of the residue from diethyl ether gave the *title cycloadduct* **17d** (0.748 g, 57%); mp 135–136 °C; $[\alpha]_D$ −72 (*c* 0.5, CH_2Cl_2) (Found: C, 50.9; H, 6.1; N, 4.1. $C_{28}H_{40}N_2O_{16}$ requires C, 50.9; H, 6.1; N, 4.2%); λ_{max} (EtOH)/nm 206 (ε 2400) and 273 (330); ν_{max} (KBr)/cm^{-1} 1755br and 1740 (ester C=O), 1720 (urethane C=O) and 1660 (C=C); δ_H (300 MHz; $C_6D_5CD_3$; 100 °C) 1.13, 1.15, 1.24 and 1.37 (each 3 H, d, *J* 6, 2 × Me_2CH), 1.78, 1.81, 1.90 and 2.08 (each 3 H, s, 4 × $MeCO_2$), 3.53 (3 H, s, MeO_2C), 3.69–3.75 (1 H, m 5′-H), 4.26 and 4.34 [each 1 H, dd (*J* 2.5 and 12) and dd (*J* 5 and 12), 6′-H_2], 4.81–4.83 (1 H, m, 3-H), 4.91 and 5.00 (each 1 H, septet, *J* 6, 2 × OC*H*Me_2), 5.23 (1 H, t, *J* 9, 4′-H), 5.26 (1 H, d, *J* 7.5, 1′-H), 5.37 (1 H, t, *J* 8.5, 2′-H), 5.44 (1 H, t, *J* 9, 3′-H), 5.50 (1 H, dd, *J* 1.5 and 9.5, 4-H), 5.70 (1 H, ddd,

J 2, 4.5 and 9.5, 5-H) and 6.16–6.20 (1 H, m, 6-H); *m*/*z* (FAB) 683 [M(Na)$^+$, 8%], 331 ($C_{14}H_{19}O_9^+$, 14), 227 (100) and 185 (86).

Methyl (3*S*,6*S*)-1,2-bis(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 17e. A solution of the diene **16a** (3.40 g, 7.4 mmol) and di-*tert*-butyl azodicarboxylate **15e** (5.10 g, 22.1 mmol) in dry dichloromethane (80 cm^3) was heated under reflux for 5 days. Evaporation of the solvent and subjection of the residue to column chromatography gave two fractions. The first fraction [eluted with hexanes–Et_2O (1:1)] was the unchanged azodicarboxylate. The second fraction (eluted with Et_2O) was the *title compound* **17e** (3.94 g, 77%) as a foam. A sample, crystallised from diethyl ether–hexanes, showed mp 88–90 °C; $[\alpha]_D$ −62 (*c* 0.28, CH_2Cl_2) (Found: C, 52.6; H, 6.4; N, 4.1. $C_{30}H_{44}N_2O_{16}$ requires C, 52.3; H, 6.4; N, 4.1%); λ_{max} (EtOH)/nm 208 (ε 2200); ν_{max} (KBr)/cm^{-1} 1760 and 1740 (ester C=O) and 1710 (urethane C=O); δ_H (300 MHz; CD_3SOCD_3; 100 °C) 1.56 (18 H, s, 2 × Me_3C), 2.06, 2.08, 2.10 and 2.13 (each 3 H, s, 4 × $MeCO_2$), 3.77 (3 H, s, MeO_2C), 3.95–4.00 (1 H, m, 5′-H), 4.20 and 4.36 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.73 (1 H, br d, separation 2, 3-H), 4.97–5.12 (3 H, m, 1′-, 2′- and 4′-H), 5.29 (1 H, t, *J* 9.5, 3′-H), 5.97 (1 H, dd, *J* 2 and 4.5, 6-H), 6.00 (1 H, dd, *J* 2 and 10, 4-H) and 6.20 (1 H, ddd, *J* 2, 4.5 and 10, 5-H); *m*/*z* (FAB) 711 [M(Na)$^+$, 1%], 331 ($C_{14}H_{19}O_9^+$, 29), 185 (100) and 169 (71).

***tert*-Butyl (3*S*,6*S*)-1,2-bis(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 17f.** A solution of the diene **16b** (0.546 g, 1.1 mmol) and di-*tert*-butyl azodicarboxylate **15e** (0.800 g, 3.5 mmol) in dry toluene (20 cm^3) was heated under reflux for 3 days. Evaporation of the solvent and subjection of the residue to column chromatography [light petroleum–Et_2O (1:1) as eluent] gave two fractions. The first fraction was the unchanged azodicarboxylate. The second fraction was the *title compound* **17f** (0.381 g, 48%) as an amorphous solid. A sample, crystallised from diethyl ether–light petroleum, showed mp 79–81 °C; $[\alpha]_D$ −72 (*c* 0.22, CH_2Cl_2) (Found: C, 54.5; H, 6.9; N, 4.1. $C_{33}H_{50}N_2O_{16}$ requires C, 54.2; H, 6.9; N, 3.8%); λ_{max} (EtOH)/nm 206 (ε 4400) and 307 (540); ν_{max} (KBr)/cm^{-1} 1760 (ester C=O) and 1720 (urethane C=O); δ_H (300 MHz; CD_3SOCD_3; 100 °C) 1.53, 1.56 and 1.58 (each 9 H, s, 3 × Me_3C), 2.05, 2.09, 2.10 and 2.14 (each 3 H, s, 4 × $MeCO_2$), 3.93–3.99 (1 H, m, 5′-H), 4.22 and 4.36 [each 1 H, dd (*J* 3 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.57 (1 H, br d, separation 2, 3-H), 4.98–5.14 (3 H, m, 1′-, 2′- and 4′-H), 5.28 (1 H, t, *J* 9.5, 3′-H), 5.97–6.06 (2 H, m, 4- and 6-H) and 6.18 (1 H, ddd, *J* 2, 5 and 9.5, 5-H); *m*/*z* (FAB) 731 (MH$^+$, 0.2%), 331 ($C_{14}H_{19}O_9^+$, 30) and 171 (100).

Benzyl (3*S*,6*S*)-1,2-bis(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 17g. A solution of the diene **16c** (1.00 g, 1.9 mmol) and di-*tert*-butyl azodicarboxylate **15e** (1.50 g, 6.5 mmol) in dry toluene (30 cm^3) was heated at *ca.* 85 °C for 5 days. Evaporation of the solvent and subjection of the residue to column chromatography [light petroleum–Et_2O (1:1→1:2) as eluent] gave two fractions. The first fraction was the unchanged azodicarboxylate. The second fraction (1.08 g, 76%), obtained as a foam, was the *title compound* **17g**. A sample, crystallised from diethyl ether–light petroleum, showed mp 131–133 °C; $[\alpha]_D$ −18 (*c* 0.22, CH_2Cl_2) (Found: C, 56.5; H, 6.1; N, 3.4. $C_{36}H_{48}N_2O_{16}$ requires C, 56.5; H, 6.3; N, 3.7%); λ_{max} (EtOH)/nm 205 (ε 12 300), 250 (900), 256 (800), 261 (700), 267 (550) and 290 (400); ν_{max} (KBr)/cm^{-1} 1750br (ester C=O) and 1720sh (urethane C=O); δ_H (300 MHz; $C_6D_5CD_3$; 80 °C) 1.39 and 1.56 (each 9 H, s and br s, 2 × Me_3C), 1.74, 1.77, 1.86 and 2.07 (each 3 H, s, 4 × $MeCO_2$), 3.70–3.80 (1 H, m, 5′-H), 4.25 and 4.34 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.82–4.86 (1 H, m, 3-H), 5.07 (2 H, s, OCH_2Ph), 5.20–5.50 (5 H, m, 1′-, 2′-, 3′-, 4′- and 4-H), 5.62 (1 H, ddd, *J* 2, 4 and 10, 5-H) and 6.13–6.18 (1 H, m, 6-H) (the C_6H_5 signals were partly obscured by the solvent signals); *m*/*z* (FAB) 765 (MH$^+$, 0.2%), 331 ($C_{14}H_{19}O_9^+$, 20), 261 (95) and 91 ($C_7H_7^+$, 100).

Hydrogenation reactions

General procedure. A mixture of the tetrahydropyridazine (0.6 mmol) and 10% palladium–carbon (0.100 g) in ethyl acetate (20 cm^3) was stirred under an atmosphere of hydrogen (contained in a balloon) for 18 h. The mixture was then filtered through a pad of Celite® and the filtrate was concentrated. The residue was processed in the manner described.

Methyl (3*S*,6*S*)-1,2-bis(ethoxycarbonyl)-1,2,3,4,5,6-hexahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 18a. The residue obtained from the reaction of the tetrahydropyridazine **17a** (0.442 g, 0.70 mmol) was crystallised from diethyl ether–hexanes to give the *title compound* **18a** (0.412 g, 93%); mp 127–128 °C; $[\alpha]_D$ −20 (*c* 0.5, CH_2Cl_2) (Found: C, 49.3; H, 6.1; N, 4.4. $C_{26}H_{38}N_2O_{16}$ requires C, 49.2; H, 6.0; N, 4.4%); λ_{max} (EtOH)/nm 202 (ε 1850); ν_{max} (KBr)/cm^{-1} 1760 and 1745 (ester C=O) and 1730 and 1715 (urethane C=O); δ_H (300 MHz; $CDCl_3$; 55 °C) 1.29 and 1.35 [each 3 H, t (*J* 7) and br t (*J* 6.5), 2 × *Me*CH_2], 1.51–1.65 (2 H, m, 4-H_2), 1.87–2.09 (2 H, m, 5-H_2), 2.00, 2.016, 2.019 and 2.10 (each 3 H, s, 4 × $MeCO_2$), 3.69–3.75 (1 H, m, 5′-H), 3.75 (3 H, s, MeO_2C), 4.12–4.32 (7 H, m, 2 × O*C*H_2Me, 3-H and 6′-H_2), 4.86 (1 H, br d, *J* 8, 1′-H), 5.04–5.32 (3 H, m, 2′-, 3′- and 4′-H) and 5.85 (1 H, br t, *J* 6.5, 6-H); δ_H (300 MHz; $C_6D_5CD_3$; 100 °C) 1.11 (3 H, t, *J* 7, *Me*CH_2), 1.19–1.33 (5 H, m, *Me*CH_2 and 4-H_2), 1.56–1.72 and 1.78–1.90 (each 1 H, m, 5-H_2), 1.78, 1.80, 1.90 and 2.03 (each 3 H, s, 4 × $MeCO_2$), 3.53 (3 H, s MeO_2C), 3.68–3.74 (1 H, m, 5′-H), 4.04–4.32 (7 H, m, 2 × O*C*H_2Me, 3-H and 6′-H_2), 5.13 (1 H, br d, *J* 7.5, 1′-H), 5.22 (1 H, t, *J* 9, 4′-H), 5.34 (1 H, t, *J* 9, 2′-H), 5.42 (1 H, t, *J* 9, 3′-H) and 5.96 (1 H, br t, *J* 6.5, 6-H); δ_C (75 MHz; $CDCl_3$) 14.32 and 14.38 (2 × *C*H_3CH_2), 20.29, 20.46, 20.50 and 20.62 (4 × *C*H_3CO_2), 21.86 and 23.68 (4- and 5-CH_2), 52.18 (CH_3O), 56.56 (5′-CH), 61.61, 62.47 and 63.07 (2 × O*C*H_2Me and 6′-CH_2), 68.43, 70.13, 72.15 and 72.56 (2′-, 3′-, 4′- and 6-CH), 81.03 (3-CH), 95.18 (1′-CH), 155.1 (2 × urethane CO) and 169.3, 169.48, 169.53, 170.2 and 170.7 (5 × ester CO); *m*/*z* (FAB) 673 [M(K)$^+$, 2%], 657 [M(Na)$^+$, 5], 634 (M$^+$, 2), 331 ($C_{14}H_{19}O_9^+$, 34), 287 [(M − $C_{14}H_{19}O_{10}$)$^+$, 66] and 215 (100).

Methyl (3*S*,6*S*)-1,2-bis(2,2,2-trichloroethoxycarbonyl)-1,2,3,4,5,6-hexahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 18b. The residue obtained from the reaction of the tetrahydropyridazine **17b** (0.504 g, 0.60 mmol) was crystallised from diethyl ether–hexanes to give the *title compound* **18b** as a hemi-diethyl ether addition compound (0.446 g, 84%); mp 123–124 °C; $[\alpha]_D$ −20 (*c* 0.5, CH_2Cl_2) (Found: C, 38.0; H, 4.4; Cl, 24.2; N, 3.3. $C_{26}H_{32}Cl_6N_2O_{16}\cdot 0.5C_4H_{10}O$ requires C, 38.3; H, 4.3; Cl, 24.2; N, 3.2%); λ_{max} (EtOH)/nm 202 (ε 2200); ν_{max} (KBr)/cm^{-1} 1760br (ester and urethane C=O); δ_H (300 MHz; $C_6D_5CD_3$; 100 °C) 1.29–1.49 and 1.59–1.89 (each 2 H, m, 4- and 5-H_2), 1.76, 1.79, 1.88 and 2.02 (each 3 H, s, 4 × $MeCO_2$), 3.52 (3 H, s, MeO_2C), 3.76–3.84 (1 H, m, 5′-H), 4.29 and 4.36 [each 1 H, dd (*J* 2.5 and 12) and dd (*J* 4.5 and 12), 6′-H_2], 4.37–4.45 (1 H, m, 3-H), 4.49, 4.73 and 4.84–5.00 [1, 1 and 2 H, br d (*J* 12.5), d (*J* 11.5) and br m, 2 × OCH_2CCl_3], 5.24 (1 H, d, *J* 8, 1′-H), 5.26 (1 H, t, *J* 9, 4′-H), 5.36 (1 H, t, *J* 8.5, 2′-H), 5.47 (1 H, t, *J* 9, 3′-H) and 6.06 (1 H, t, *J* 6.5, 6-H); *m*/*z* (FAB) 867, 865, 863 and 861 [M(Na)$^+$, 1% (for 863)], 497, 495, 493 and 491 [(M − $C_{14}H_{19}O_{10}$)$^+$, 40 (for 493)], 331 ($C_{14}H_{19}O_9^+$, 36), 321, 319 and 317 [$C_9H_{12}Cl_3N_2O_4^+$, 55 (for 317)], 261, 259 and 257 [$C_7H_8Cl_3N_2O_2^+$, 25 (for 257)], 169 (96) and 141 (100).

Reaction involving the tetrahydropyridazine 17c. The residue (0.348 g) obtained from the hydrogenation of the tetrahydropyridazine **17c** (0.490 g, 0.65 mmol) [using 5% Pd–C (0.200 g) for 1.5 h] comprised of mainly a 5 : 3 : 1 mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose **22** (as a 1 : 1 mixture of α- and β-anomers), methyl (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate **1b** and methyl pyridazine-3-carboxylate **24** by ^{1}H NMR spectroscopy [the proportions were estimated from the integrals of the triplet at δ 5.23 (attributed to the 3-H signal of the β-anomer of **22**), the triplet at δ 5.53 (ascribed to the 3-H signal of the α-anomer of **22**), the broad singlet at δ 6.73 (attributed to the 6-H signal of **1b**) and the double doublet at δ 7.67 (assigned to the 5-H signal of **24**)]. Subjection of the product to column chromatography gave three fractions.

The first fraction (0.232 g, *ca.* 100%) (eluted with Et_2O), isolated as a colourless foam, was mainly compound **22** (as a 2 : 1 mixture of α- and β-anomers) by ^{1}H NMR spectroscopy.

The second fraction (0.034 g, 37%) (eluted with Et_2O), isolated as a colourless syrup, was methyl (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate **1b** on the basis of its specific rotation {$[\alpha]_D$ +100 (*c* 0.25, MeOH) [lit.,[11] +139 (*c* 0.83, MeOH)]} and ^{1}H NMR spectrum (which matched that of the sample obtained from the reaction of **18e** with CF_3CO_2H).

The third fraction (0.012 g, *ca.* 13%) (eluted with EtOAc), isolated as a pale yellow solid, was mainly methyl pyridazine-3-carboxylate **24**; δ_H (300 MHz; $CDCl_3$) *inter alia* 4.09 (3 H, s, MeO_2C), 7.67 (1 H, dd, *J* 5 and 8.5, 5-H), 8.23 (1 H, dd, *J* 1.5 and 8.5, 4-H) and 9.37 (1 H, dd, *J* 1.5 and 5, 6-H);‖ *m/z* (CI) 156 [$M(NH_4)^+$, 7%], 140 (MH_2^+, 39) and 139 (MH^+, 100); *m/z* (FAB) 139 (MH^+, 100%).

Methyl (3*S*,6*S*)-1,2-bis(isopropoxycarbonyl)-1,2,3,4,5,6-hexahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylate 18d. The residue obtained from the reaction of the tetrahydropyridazine **17d** (0.462 g, 0.70 mmol) was crystallised from diethyl ether–hexanes to give the *title compound* **18d** (0.380 g, 82%); mp 109–110 °C; $[\alpha]_D$ −14 (*c* 0.5, CH_2Cl_2) (Found: C, 50.8; H, 6.5; N, 4.2. $C_{28}H_{42}N_2O_{16}$ requires C, 50.8; H, 6.4; N, 4.2%); λ_{max} (EtOH)/nm 202 (ε 1750); ν_{max} (KBr)/cm^{-1} 1765, 1755 and 1740 (ester C=O) and 1705 (urethane C=O); δ_H (300 MHz; $C_6D_5CD_3$; 90 °C) 1.15 and 1.18 (each 3 H, d, *J* 6.5, Me_2CH), 1.16–1.44 (8 H, m, Me_2CH and 4-H_2), 1.59–1.69 and 1.81–1.91 (each 1 H, m, 5-H_2), 1.78, 1.80, 1.91 and 2.08 (each 3 H, s, 4 × $MeCO_2$), 3.52 (3 H, s, MeO_2C), 3.72–3.80 (1 H, br m, 5′-H), 4.27–4.39 (3 H, m, 3-H and 6′-H_2), 4.90–5.00 (2 H, m, 2 × OC*H*Me_2), 5.15–5.27 (2 H, m, 1′- and 4′-H), 5.37 (1 H, t, *J* 8.5, 2′-H), 5.45 (1 H, t, *J* 9, 3′-H) and 5.97 (1 H, t, *J* 6.5, 6-H); *m/z* (FAB) 685 [$M(Na)^+$, 13%], 662 (M^+, 3), 331 ($C_{14}H_{19}O_9^+$, 26) and 229 (100).

Methyl (3*S*,6*S*)-1,2-bis(*tert*-butoxycarbonyl)-1,2,3,4,5,6-hexahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-pyridazine-3-carboxylate 18e. The residue obtained from the hydrogenation of the tetrahydropyridazine **17e** (4.00 g, 5.8 mmol) was the *title compound* **18e** (3.38 g, 84%) as a foam. A sample, crystallised from diethyl ether–hexanes, showed mp 96–98 °C; $[\alpha]_D$ −5 (*c* 0.2, CH_2Cl_2) (Found: C, 52.2; H, 7.0; N, 4.3. $C_{30}H_{46}N_2O_{16}$ requires C, 52.2; H, 6.7; N, 4.1%); λ_{max} (EtOH)/nm 203 (ε 1800); ν_{max} (KBr)/cm^{-1} 1760 and 1740 (ester C=O) and 1710 (urethane C=O); δ_H (300 MHz; $C_6D_5CD_3$; 100 °C) 1.18–1.30 (2 H, m, 4-H_2), 1.44 (18 H, br s, 2 × Me_3C), 1.52–1.62 and 1.74–1.86 (each 1 H, m, 5-H_2), 1.75, 1.77, 1.80 and 1.91 (each 3 H, s, 4 × $MeCO_2$), 3.49 (3 H, br s, MeO_2C), 3.80–3.86 (1 H, br m, 5′-H), 4.28–4.34 (3 H, m, 3-H and 6′-H_2), 5.16–5.24 (1 H, br m, 1′-H), 5.27 (1 H, t, *J* 9.5, 4′-H), 5.30–5.58 (2 H, br m, 2′- and 3′-H) and 5.93 (1 H, br t, *J* 6.5, 6-H); *m/z* (FAB) 713 [$M(Na)^+$, 5%], 490 (39), 331 ($C_{14}H_{19}O_9^+$, 36) and 187 (100).

***tert*-Butyl (3*S*,6*S*)-1,2-bis(*tert*-butoxycarbonyl)-1,2,3,4,5,6-hexahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-pyridazine-3-carboxylate 18f.** The residue obtained from the hydrogenation of the tetrahydropyridazine **17f** (0.300 g, 0.41 mmol) was the *title compound* **18f** (0.259 g, 86%) as an amorphous solid. A sample, crystallised from diethyl ether–light petroleum, showed mp 184–186 °C; $[\alpha]_D$ −13 (*c* 0.15, CH_2Cl_2) (Found: C, 54.4; H, 7.4; N, 3.9. $C_{33}H_{52}N_2O_{16}$ requires C, 54.1; H, 7.2; N, 3.8%); λ_{max} (EtOH)/nm 204 (ε 2000); ν_{max} (KBr)/cm^{-1} 1760, 1750 and 1730 (ester C=O) and 1705 (urethane C=O); δ_H (300 MHz; CD_3SOCD_3; 100 °C) 1.53 and 1.57 (9 and 18 H, each s, 3 × Me_3C), 1.61–1.87 (4 H, m, 4- and 5-H_2), 2.05, 2.10 and 2.13 (3, 6 and 3 H, each s, 4 × $MeCO_2$), 3.85–3.90 (1 H, br m, 5′-H), 4.07–4.17 (1 H, br m, 3-H), 4.20 and 4.32 [each 1 H, dd (*J* 3 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.95–5.10 (3 H, br m, 1′-, 2′- and 4′-H), 5.25–5.30 (1 H, br m, 3′-H) and 5.77 (1 H, t, *J* 7.5, 6-H); *m/z* (FAB) 733 (MH^+, 1), 532 (9) and 173 (100).

(3*S*,6*S*)-1,2-Bis(*tert*-butoxycarbonyl)-1,2,3,4,5,6-hexahydro-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyridazine-3-carboxylic acid 18h. The residue obtained from the hydrogenation of the tetrahydropyridazine **17g** (6.69 g, 8.7 mmol) was crystallised from diethyl ether–hexanes to give the *title compound* **18h** (4.09 g, 69%); mp 100–101 °C; $[\alpha]_D$ −5 (*c* 0.4, CH_2Cl_2) (Found: C, 51.8; H, 6.8; N, 4.1. $C_{29}H_{44}N_2O_{16}$ requires C, 51.5; H, 6.6; N, 4.1%); λ_{max} (EtOH)/nm 203 (ε 1900); ν_{max} (KBr)/cm^{-1} 1760 and 1745 (ester C=O), 1730 (acid C=O) and 1710 (urethane C=O); δ_H (300 MHz; CD_3SOCD_3; 100 °C) 1.56 and 1.58 (each 9 H, br s and s, 2 × Me_3C), 1.65–1.90 (4 H, m, 4- and 5-H_2), 2.05, 2.08, 2.10 and 2.13 (each 3 H, s, 4 × $MeCO_2$), 3.85–3.90 (1 H, br m, 5′-H), 4.17–4.23 (2 H, m, 3- and 6′-H), 4.32 (1 H, dd, *J* 5 and 12.5, 6′-H), 4.93–5.09 (3 H, m, 1′-, 2′- and 4′-H), 5.28 (1 H, t, *J* 9, 3′-H) and 5.76 (1 H, t, *J* 7.5, 6-H); *m/z* (FAB) 699 [$M(Na)^+$, 0.2%], 677 (MH^+, 0.3), 476 (95), 331 ($C_{14}H_{19}O_9^+$, 27) and 173 (100).

Trifluoroacetolysis studies

Reactions involving the tetrahydropyridazinecarboxylate 18e. *Method (a).*—A solution of compound **18e** (2.73 g, 4.0 mmol) in TFA (5 cm^3) was left for 10 min. Evaporation of the TFA and subjection of the residue to column chromatography [light petroleum–Et_2O (1 : 2) as eluent] gave two fractions.

The first fraction, isolated as a syrup, was identified as 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose **22** (as a 3 : 1 mixture of α- and β-anomers) by ^{1}H NMR spectroscopy.

The second fraction (0.319 g, 57%), obtained as a colourless oil, was methyl (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate **1b**; $[\alpha]_D$ +124 (*c* 1.6, MeOH) [lit.,[11] +139 (*c* 0.83, MeOH)]; ν_{max} (film)/cm^{-1} 3370 (N–H) and 1740 (ester C=O); δ_H (400 MHz; $CDCl_3$) 2.00–2.26 (4 H, m, 4- and 5-H_2), 3.76 (3 H, s, MeO_2C), 3.76–3.80 (1 H, m, 3-H), 6.0 (1 H, br s, NH) and 6.74 (1 H, br s, 6-H) (addition of D_2O caused the signal at δ 6.0 to disappear and that at δ 3.76–3.80 to sharpen); *m/z* (CI) 143 (MH^+, 51%), 83 (23) and 32 (100); *m/z* (EI) 142 (M^+, 19%) and 83 (100) (Found: M, 142.0742. $C_6H_{10}N_2O_2$ requires *m/z* 142.0742); *m/z* (FAB) 143 (MH^+, 100%).

Method (b).—A solution of compound **18e** (0.830 g, 1.2 mmol) in TFA (2.4 cm^3) was left for 15 min. Evaporation of the TFA and subjection of the residue to column chromatography (Et_2O as eluent) gave three fractions.

The first fraction (0.238 g, 57%), isolated as a syrup, was 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose **22** (as a 3 : 1 mixture of α- and β-anomers) by ^{1}H NMR spectroscopy.

The second fraction (0.174 g, 31%), isolated as a crystalline

‖ The NMR spectrum matched that of an authentic sample of compound **24** [obtained by the action of CH_2N_2 on pyridazine-3-carboxylic acid (prepared from pyridazine by the method of Letsinger and Lasco; see ref. 27)].

solid, was *methyl (3S)-2,3,4,5-tetrahydro-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)pyridazine-3-carboxylate* **25**; mp 129–130 °C; $[\alpha]_D$ −26 (*c* 0.25, CH_2Cl_2) (Found: C, 50.9; H, 6.3; N, 5.9. $C_{20}H_{28}N_2O_{11}$ requires C, 50.8; H, 6.0; N, 5.9%); λ_{max} (EtOH)/nm 222 (ε 6900); ν_{max} (KBr)/cm^{-1} 1740br (ester C=O) and 1615 (C=N); δ_H (400 MHz; $CDCl_3$) 1.85–2.20 (4 H, m, 4- and 5-H_2), 2.012, 2.015, 2.019 and 2.07 (each 3 H, s, 4 × $MeCO_2$), 3.66–3.72 (1 H, m, 5′-H), 3.69 (3 H, s, MeO_2C), 4.07 and 4.24 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 4.5 and 12.5), 6′-H_2], 4.14 (1 H, br t, *J* 4, 3-H), 4.69 (1 H, d, *J* 9, 1′-H), 5.06 (1 H, t, *J* 9.5, 4′-H), 5.28 (1 H, t, *J* 9.5, 3′-H), 5.40 (1 H, t, *J* 9.5, 2′-H) and 6.68 (1 H, br s, 6-H); *m/z* (FAB) 495 [M(Na)$^+$, 11%], 473 (MH^+, 80), 413 (42), 353 (53), 331 ($C_{14}H_{19}O_9^+$, 43) and 169 (100).

The third fraction (0.082 g, 48%), isolated as a colourless oil, was methyl (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate **1b** [the 300 MHz ^{1}H NMR spectrum matched that of the sample prepared by method (*a*)]; $[\alpha]_D$ +108 (*c* 0.25, MeOH) [lit.,[11] +139 (*c* 0.83, MeOH)]; δ_C (75 MHz; $CDCl_3$) 21.06 (4- and 5-CH_2), 52.18 (CH_3O), 53.27 (3-CH), 140.0 (6-CH) and 171.7 (ester CO).

Reaction involving the tetrahydropyridazinecarboxylic acid 18h. A solution of the acid **18h** (1.13 g, 1.7 mmol) in TFA (8 cm^3) was left for 20 min. Evaporation of the TFA left a residue, which was partitioned between dichloromethane and water. Evaporation of the dried ($MgSO_4$) organic phase left 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose **22** (0.534 g, 92%) (as a 3:1 mixture of α- and β-anomers) by ^{1}H NMR spectroscopy.

After having been washed twice with dichloromethane, the aqueous phase was concentrated and dried (*in vacuo*; P_2O_5) to give *(3S)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid trifluoroacetic acid salt* **27** (0.395 g, 98%) as a pale yellow oil; $[\alpha]_D$ +62 (*c* 0.3, MeOH); λ_{max} (EtOH)/nm 203 (ε 3900), 227 (4100) and 280 (1900); ν_{max} (film)/cm^{-1} 3300–2500br (O–H and N–H), 1730br (acid C=O) and 1670br (trifluoroacetate C=O); δ_H (400 MHz; D_2O) 2.03–2.29 and 2.42–2.65 (each 2 H, m, 4- and 5-H_2), 4.01 (1 H, dd, *J* 4 and 8, 3-H), 4.8 (HOD) and 7.56 (1 H, t, *J* 3, 6-H); δ_F (188 MHz; D_2O) 2.12 (s, $CF_3CO_2^-$); *m/z* (CI) 146 [M(NH_4)$^+$, 23%] and 129 (MH^+, 100) (Found: MH, 129.0666. $C_5H_9N_2O_2$ requires *m/z* 129.0664); *m/z* (EI) 128 (M^+, 4%) and 31 (100).

Chromatography-free preparation of methyl (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate 1b

A solution of the diene **16a** (0.917 g, 2.0 mmol) and the azodicarboxylate **15e** (1.38 g, 6.0 mmol) in dry dichloromethane (25 cm^3) was heated under reflux for 5 days. Evaporation of the solvent left a yellow foam, which was dissolved in ethyl acetate (40 cm^3) and stirred with 10% palladium–carbon (0.200 g) under a hydrogen atmosphere for 18 h. The mixture was filtered through a pad of Celite® and the filtrate was concentrated. The resultant foam was dissolved in TFA (4 cm^3) and, after 15 min, the solution was diluted with dichloromethane (25 cm^3) and washed sequentially with water (10 cm^3), saturated aq. sodium hydrogen carbonate (2 × 10 cm^3) and water (10 cm^3). Evaporation of the dried ($MgSO_4$) organic phase left an orange syrup, which was treated with methanol (10 cm^3) containing toluene-*p*-sulfonic acid (0.570 g, 3.0 mmol) for 18 h. The mixture was then diluted with water (50 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were washed with saturated aq. sodium hydrogen carbonate (2 × 50 cm^3) and water (25 cm^3), dried ($MgSO_4$) and concentrated to leave mainly the title compound **1b** (0.058 g, *ca.* 20% based on **16a**), $[\alpha]_D$ +86 (*c* 0.25, MeOH), as a yellow syrup (identified by ^{1}H NMR spectroscopy).

Sodium (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylate 1c

Sodium hydroxide (2 mol dm^{-3}; 0.70 cm^3, 1.4 mmol) was added to a stirred solution of the ester **1b** (0.144 g, 1.0 mmol) in THF (20 cm^3). After 5 h, the mixture was concentrated to leave an oil (0.150 g, *ca.* 100%) that was largely the title salt **1c**; δ_H (400 MHz; D_2O) 1.87–2.00 and 2.06–2.17 (each 1 H, m, 4-H_2), 2.18–2.34 (2 H, m, 5-H_2), 3.55 (1 H, dd, *J* 4 and 8, 3-H), 4.8 (HOD) and 6.90 (1 H, br t, *J* 2.5, 6-H).

Methyl (3*S*)-1-(2,4-dinitrophenyl)-1,2,3,4,5,6-hexahydropyridazine-3-carboxylate 26a

Method (a).—Sodium cyanoborohydride (0.030 g, 0.48 mmol) was added to a stirred solution of the tetrahydropyridazine **1b** (0.056 g, 0.4 mmol) {$[\alpha]_D$ +124 (*c* 1.6, MeOH)} in methanol (12 cm^3). Removal of the solvent after 18 h left a residue, which was dissolved in ethanol (10 cm^3) and treated with 2,4-dinitrofluorobenzene (0.2 cm^3, 1.6 mmol) for 5 h. Concentration, subjection of the residue to column chromatography [hexanes–Et_2O (1:1) as eluent] and crystallisation of the chromatographed material from ethyl acetate–hexanes gave the title compound **26a** (0.032 g, 26%) as a yellow solid; mp 94–95 °C (lit.,[11] 95–96 °C); $[\alpha]_D$ −294 (*c* 0.3, $CHCl_3$) [lit.,[11] −296.3 (*c* 0.3, $CHCl_3$); lit.,[22] *ent*-**26a** +299 (*c* 1, $CHCl_3$); lit.,[28] *ent*-**26a** +250 (*c* 0.3, $CHCl_3$)] (Found: C, 46.8; H, 4.4; N, 17.8. Calc. for $C_{12}H_{14}N_4O_6$: C, 46.4; H, 4.5; N, 18.0%); λ_{max} (EtOH)/nm 204 (ε 14 800), 224 (12 000) and 368 (14 200); ν_{max} (KBr)/cm^{-1} 3240 (N–H), 1755 (ester C=O), 1610 and 1590 (C=C) and 1540 and 1320 (NO_2); δ_H (300 MHz; $CDCl_3$) 1.52–1.64, 1.92–2.04 and 2.10–2.17 (1, 2 and 1 H, each m, 4- and 5-H_2), 3.06–3.16 (1 H, m, 6-H), 3.64–3.84 (3 H, m, NH, 3- and 6-H), 3.73 (3 H, s, MeO_2C), 7.00, 8.20 and 8.43 [each 1 H, d (*J* 9.5), dd (*J* 2.5 and 9.5) and d (*J* 2.5), C_6H_3]; *m/z* (FAB) 621 (M_2H^+, 3%) and 311 (MH^+, 100). By HPLC, the sample was shown to possess an ee of 98% [using hexanes–propan-2-ol (3:1) as eluent with a flow rate of 1 cm^3 min^{-1}; retention times: 28.6 min for **26a** and 60.2 min for *ent*-**26a**].

Method (b).—The aforecited reaction sequence was repeated using the tetrahydropyridazine **1b** (0.050 g, *ca.* 0.35 mmol) {$[\alpha]_D$ +86 (*c* 0.25, MeOH)}. Work-up and chromatography as before gave the title compound **26a** (0.028 g, 26%), $[\alpha]_D$ −243 (*c* 0.2, $CHCl_3$), as a yellow syrup. The ^{1}H NMR spectrum of the material matched that of the sample obtained by method (*a*). By HPLC, the material possessed an ee of 98%.

Method (c).—Sodium cyanoborohydride (0.103 g, 1.6 mmol) was added to a stirred solution of the salt **27** (0.329 g, 1.4 mmol) {$[\alpha]_D$ +62 (*c* 0.3, MeOH)} in acetic acid (10 cm^3). Removal of the solvent after 18 h left a residue, which [after treatment with H_2O and evaporation of the solution (3×)] was dissolved in a mixture of water (10 cm^3) and ethanol (4 cm^3). Sodium hydrogen carbonate (0.50 g) and 2,4-dinitrofluorobenzene (1.0 cm^3, 8.0 mmol) were added to the stirred solution, which, after 3 h, was washed with diethyl ether (3×). The aqueous layer was acidified with hydrochloric acid (*ca.* 6 mol dm^{-3}) and extracted with diethyl ether (3×). The organic extracts were combined, dried ($MgSO_4$) and concentrated. Crystallisation of the residue from ethyl acetate–hexanes gave *(3S)-1-(2,4-dinitrophenyl)-1,2,3,4,5,6-hexahydropyridazine-3-carboxylic acid* **26b** (0.179 g, 45%) as a yellow solid; mp 150–151 °C (for *ent*-**26b**: lit.,[22] 150.5–151.5 °C; lit.,[28] 153–155 °C; lit.,[29] 151.5–152 °C); $[\alpha]_D$ −321 (c 0.5, MeOH) [for *ent*-**26b**: lit.,[22] +341 (*c* 1, MeOH); lit.,[28] +307 (*c* 0.18, MeOH); lit.,[29] +324.6 (*c* 1, MeOH)] (Found: C, 44.4; H, 4.4; N, 18.6. $C_{11}H_{12}N_4O_6$ requires C, 44.6; H, 4.1; N, 18.9%); λ_{max} (EtOH)/nm 205 (ε 16 700), 224 (13 900) and 370 (16 500); ν_{max} (KBr)/cm^{-1} 3200–2500br (N–H and O–H), 1720 (acid C=O), 1610 (C=C) and 1540 and 1340 (NO_2); δ_H (300 MHz; CD_3COCD_3) 1.68–1.88 (1 H, m, 5-H), 3.43–3.52 and 3.73–3.82 (each 1 H, m, 6-H_2), 4.18 (1 H, dt, *J* 12.5 and 3.5, 3-H), 7.42, 8.40 and 8.50 [each 1 H, d (*J* 9.5), dd (*J* 2.5 and 9.5) and d (*J* 2.5), C_6H_3] (the other 5-H and the 4-H_2 signals were obscured by the solvent signals); *m/z* (FAB) 297 (MH^+, 100%), 296 (M^+, 90) and 154 (100).

A stream of argon containing diazomethane was bubbled into an ice-cooled solution of the aforecited acid **26b** (0.093 g, 0.3 mmol) in chloroform (20 cm^3). After having been washed with aq. sodium hydrogen carbonate and water, the solution was dried ($MgSO_4$) and concentrated. Crystallisation of the residue from ethyl acetate–hexanes gave the title compound **26a** (0.059 g, 61%) as a yellow solid; mp 96–97 °C; $[\alpha]_D$ −289 (*c* 0.75, $CHCl_3$). The ^1H NMR spectrum of the material matched that of the sample obtained by method (*a*). By HPLC, the material possessed an ee of 95%.

Method (d).—Sodium cyanoborohydride (0.127 g, 2.0 mmol) was added to a stirred solution of the tetrahydropyridazine **1c** (0.129 g, *ca.* 0.9 mmol) in acetic acid (15 cm^3). After 3 days, the mixture was concentrated and the product [obtained after treatment with H_2O and evaporation of the solution (3×)] was transformed, as described in method (*c*), into the title compound **26a** (0.033 g, *ca.* 13%); mp 95–97 °C; $[\alpha]_D$ −231 (*c* 0.75, $CHCl_3$). The ^1H NMR spectrum of the material matched that of the sample obtained by method (*a*). By HPLC, the material possessed an ee of 99%.

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