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Studies related to carba-pyranoses: synthesis of acetylated derivatives of 4-amino-2,4-dideoxy-3-*O*-(β-D-glucopyranosyl)-β-L-(and β-D-) altrocarba-pyranose from a D-glucose template†

Robin G. Pritchard,[a] Richard J. Stoodley[a] and Wai-Hung Yuen*[b]

[a] *Department of Chemistry, UMIST, PO Box 88, Manchester, UK M60 1QD*

[b] *Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong. E-mail: yuenwh@hkusua.hku.hk; Fax: (852) 2857-1586; Tel: (852) 2859-8965*

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Methyl (*E*)-3-nitroacrylate **15**, the X-ray analysis of which is reported here, is prepared from methyl acrylate by a new route involving sequential reactions with mercury(II) chloride–sodium nitrite, bromine and sodium acetate. The dienophile **15** reacts with Danishefsky's diene **17** to give, after acidic hydrolysis, a 67 : 33 mixture of the ketones *rac*-**18** and *rac*-**19**. With (*E*)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-3-(trimethylsiloxy)buta-1,3-diene **1**, it affords, after hydrolysis, a 42 : 18 : 28 : 12 mixture of the ketones **30**, **31**, **32** and **33**.
The alcohol **36**, obtained by sodium borohydride reduction of the ketone **30**, is converted into the monocarba-disaccharide **35** by the action of aluminium amalgam, lithium aluminium hydride and acetic anhydride. Similarly, the alcohol **41**, derived from the ketone **32**, is transformed into the monocarba-disaccharide **40**; the structure of the alcohol **41** is secured by an X-ray analysis. The isolation of a mixture of the acetoxyamino and acetylamino derivatives **38** and **39** from the reaction of the alcohol **36** with aluminium amalgam and acetic anhydride indicates that the nitro function is converted into the hydroxylamino and amino groups by the reducing agent.
The cyclohexane rings of the ketones *rac*-**18**, *rac*-**19**, **30**, **31** and **33** adopt the expected chair conformations. Thus, the methoxycarbonyl, nitro and oxy substituents are equatorially orientated in the ketones *rac*-**18** and **30**; in the ketones *rac*-**19**, **31** and **33**, the methoxycarbonyl and nitro groups occupy equatorial dispositions and the oxy substituent is axially orientated. The cyclohexane ring of the ketone **32** (which bears a diastereomeric relationship to that of the ketone **30**) displays unexpected conformational properties, that are attributed to a significant population of the chair conformer with axial arrangements of the methoxycarbonyl, nitro and oxy groups.

Introduction

Over the past few years, we have demonstrated that anomerically linked glycopyranose units can confer a useful degree of facial reactivity on 1-oxybuta-1,3-dienes in cycloaddition reactions.[1–13] For example, the diene **1** displays good *Re*-face‡ reactivity and undergoes highly *endo*-selective Diels–Alder reactions,[1,2,7] with cyclic dienophiles of type **2** to give predominantly cycloadducts of type **3**. As well as endeavouring to understand the basis of the stereoinduction, we have sought to employ such cycloaddition reactions in the assembly of compounds of biological importance. Within the latter context, asymmetric syntheses of anthracyclinones,[1,7,13,14] bostrycins,[8] dehydropiperazic acids,[9] dihydropyranone,[12] 5-arylpentopyranoses[15] and *epi*-shikimic acid[16] have been effected.

In the aforementioned syntheses, the glycopyranose moiety served as a 'chiral auxiliary' role, being removed from the pre-target structures by mild acidic hydrolysis. Mindful of the emerging importance of saccharides in medicinal chemistry,[17–19] we have also sought to prepare oligosaccharide-like compounds that retain the glycopyranose unit. Within this framework, monocarba-disaccharides that feature a pyranose entity glycosidically linked to a carba-pyranose§ moiety have attracted our attention. Such assemblies, which are found in some aminoglycoside antibiotics, *e.g.* validamycin A **4**,[21] have been the subject of relatively few synthetic endeavours. Typically, they are prepared by glycosidation methodology in which an appropriately protected carba-pyranose (often as racemate) serves as the glycosyl acceptor.[20]

We planned to use Diels–Alder reactions to construct such monocarba-disaccharides and initially decided to employ the readily available diene **1**.[1–3] In consequence, any targets would feature the β-D-glucopyranosyl unit. Noting that few acetal-linked (1→3)-monocarba-disaccharides had been synthesised[21] (examples include compounds **5** and **6**[22]), we decided to prepare further representatives of this class and have recently reported the syntheses of (1→3) linked monocarba-disaccharides **7**, **8**[23] and **9**.[24]

Earlier,[25] we showed that the cycloadduct **10** (obtained from the reaction of the diene **1** with maleic anhydride) could be readily converted into the monocarba-disaccharide **14** by way of the intermediates **11–13** as outlined in Scheme 1. It should be noted that the sequence, in which one new stereocentre had been developed, led to the generation of a 4-acetylamino-2,4-dideoxycarbahexopyranose unit¶ with the 'β-L-*galacto*' configuration.

In seeking to complement this technology and provide access to relatives of compounds **7**, **8** and **14** in which the 4-acetylamino-2,4-dideoxycarba-hexopyranose unit featured an *anti* arrangement of the 4- and 5-substituents (sugar numbering), we have undertaken a study of the reactivity of the diene **1** with methyl (*E*)-3-nitroacrylate **15**[28] and of the derived cycloadducts. We now report our findings.

† The work presented in this article was carried out at UMIST.

‡ The stereodescriptor refers to the carbon atom of the diene bearing the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy unit.

§ Carba-pyranoses—pyranoses in which the ring oxygen atom is replaced by a methylene group—are examples of carbasugars (also called *pseudo*-sugars); for review, see ref. 20.

¶ Although hexopyranoses with an amino or substituted amino group at position 4 feature in numerous compounds of biological relevance (ref. 26), only two such carba-hexopyranose representatives appear to have been synthesised (ref. 27).

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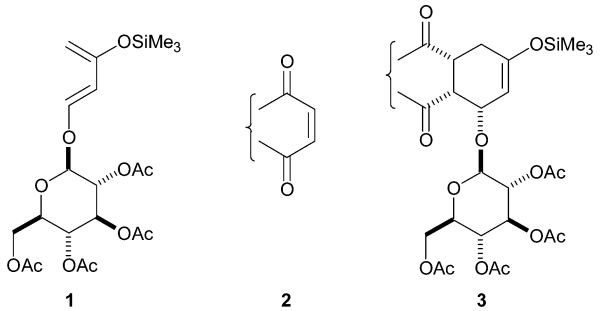
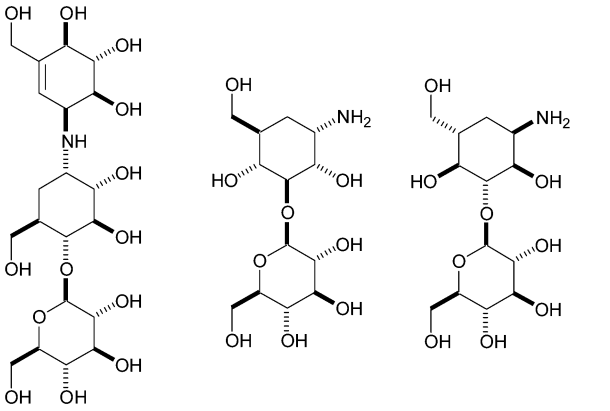
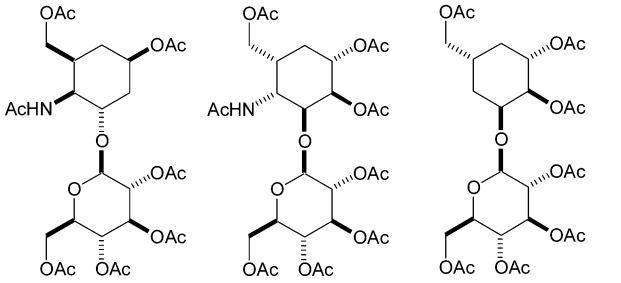


1 **2** **3**



4 **5** **6**



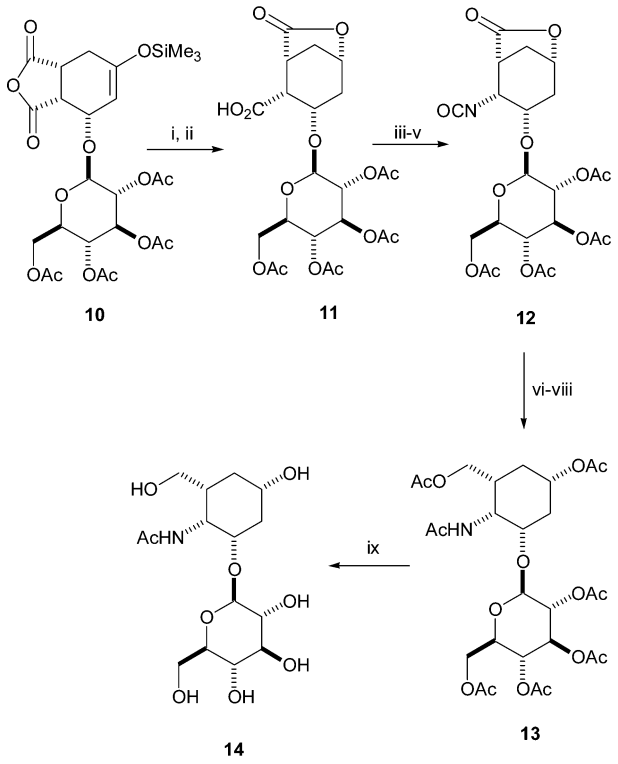
7 **8** **9**

Results and discussion

Previously, we had shown[2,3] that the *Re*-face : *Si*-face selectivity of the diene **1** was 86 : 14 towards *N*-phenylmaleimide and 67 : 33 towards tetracyanoethylene in benzene at ambient temperature. Furthermore, Danishefsky had reported[29] that the nitroacrylate **15** underwent reaction with the diene **17** under comparable conditions to give, after acidic work-up, the ketone *rac*-**18** as the major product and the ketone *rac*-**19** as the minor product.

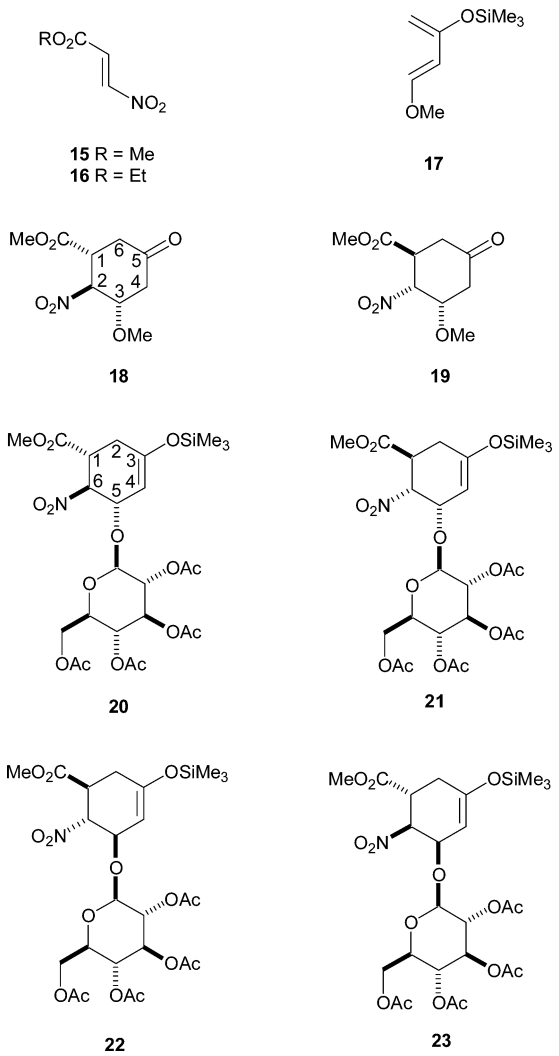
On the basis of the foregoing information, we envisaged that the Diels–Alder reaction of the diene **1** with the nitroacrylate **15** would display reasonable-to-moderate facial selectivity, high regioselectivity and reasonable *exo*-nitro group selectivity. Thus, the *Re*-face *exo*-nitro cycloadduct **20** and the *Re*-face *endo*-nitro cycloadduct **21** were expected to predominate over their *Si*-face counterparts **22** and **23**; furthermore, the total *exo*-nitro cycloadduct production was expected to exceed the total *endo*-nitro cycloadduct production (*i.e.* **20** + **22** > **21** + **23**).

The usual method for the preparation of β-nitroacrylates is that developed by Stevens and Emmons,[28] involving the formal addition of nitryl iodine to an acrylate ester using iodine and dinitrogen tetraoxide followed by dehydroiodination; the procedure is reported to give the nitroacrylate **15** in 70% overall yield[30] and the nitroacrylate **16** in 81% overall yield.[31] Shin prepared the latter nitroacylate in 45% overall yield using nitrosyl chloride in the first step.[32] The procedure we used, which is an adaptation of that developed by Corey[33] for the



10 **11** **12** **13** **14**

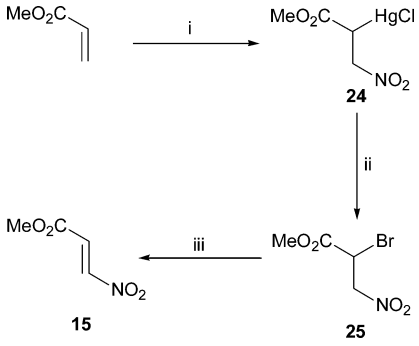
Scheme 1 Reagents: i, H^+, $CHCl_3$; ii, $Na(CN)BH_3$, HOAc; iii, $(COCl)_2$, DMF, CH_2Cl_2; iv, NaN_3, THF; v, Δ, PhH; vi, Et_3N, THF, H_2O; vii, Δ, $LiAlH_4$, THF; viii, Ac_2O, pyridine, DMAP; ix, IR-400 (OH^-), MeOH.



15 R = Me
16 R = Et

17 **18** **19** **20** **21** **22** **23**

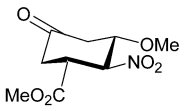
conversion of alkenes into nitroalkenes (but not hitherto used for the synthesis of β-nitroacrylates), is outlined in Scheme 2. Thus, methyl acrylate was converted into the nitromercuration product **24** and thence the bromide **25**; dehydrobromination of compound **25** provided the nitroacrylate **15** in 67% overall yield.



Scheme 2 Reagents: i, $HgCl_2$, $NaNO_2$, H_2O; ii, Br_2, H_2O, Et_2O; iii, NaOAc, Et_2O.

Initially, we decided to re-examine the reaction of Danishefsky's diene **17** with the nitroacrylate **15** in order to quantify the *exo*-nitro cycloadduct : *endo*-nitro cycloadduct stereoselectivity.[34] In dichloromethane at ambient temperature, the reaction led to mainly a 67 : 33 mixture of cycloadducts; following acidic hydrolysis, a 60 : 40 ratio of ketones resulted. As noted by Danishefsky,[29] it was possible to isolate the major ketone from the mixture simply by crystallization; we obtained the material in 34% yield (compared to 48% yield reported by the Pittsburgh group). Subjection of the mother liquor to preparative HPLC gave a pure sample of the minor ketone.

A comparison of the NMR spectroscopic properties of the aforecited ketones left little doubt that they were stereoisomers. On the basis of conformational considerations, the major ketone was considered to possess the stereostructure *rac*-**18** and the minor ketone the stereostructure *rac*-**19**, in accord with Danishefsky's assignments. Thus from the coupling constants presented in Table 1, it was clear that the major ketone adopted the chair conformation *rac*-**26** in which the 1-, 2- and 3-substituents were equatorially orientated. Similarly, the minor ketone existed in the chair geometry *rac*-**27**, with the 1- and 2-substituents equatorial and the 3-substituent axial.



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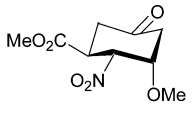

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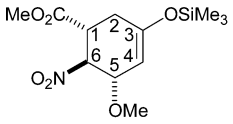

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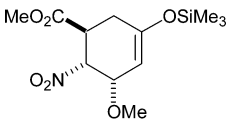

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In summary, the Diels–Alder reaction of the nitroacrylate **15** and the diene **17** in dichloromethane provides a 67 : 33 mixture of the *exo*-nitro cycloadduct *rac*-**28** and the *endo*-nitro cycloadduct *rac*-**29**.

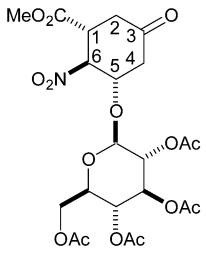
The reaction of the diene **1** with the nitroacrylate **15**, carried out in dichloromethane, afforded four cycloadducts in the ratio of 43 : 30 : 18 : 9 by NMR spectroscopic analysis. Acidic hydrolysis of the cycloadducts gave a 42 : 28 : 18 : 12 mixture of four ketones, designated **A–D** (in order of their decreasing abundance). Following fractionation of the mixture by column chromatography and crystallisation, ketone **A** was isolated in 24% yield and ketone **B** in 18% yield. The use of preparative HPLC led to the isolation of ketone **C** and a 75 : 25 mixture of ketones **D** and **C**.

Table 1 Selected coupling constants (Hz) of the cyclohexanone-ring protons of compounds *rac*-**18**, *rac*-**19** and **30–33** (in $CDCl_3$)

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4ax}$	$J_{3,4eq}$	$J_{1,6ax}$	$J_{1,6eq}$
rac-**18**	9.5	7.5	9	4.5	11.5	6
rac-**19**	11	3	3	3.5	13.5	5.5
30[a]	11.5	9.5	11.5	5.5	13.5	5
31[b]	11	3	3	3	13	5.5
32[c]	8	5.5	7	4.5[e]	←16[f]→	
33[d]	11.5	2.5	2.5	3	13	5.5

[a] Ketone **A**. [b] Ketone **C**. [c] Ketone **B**. [d] Ketone **D**. [e] License is implied in the use of the axial and equatorial descriptors in this instance. [f] Because of the deceptively simple nature of the spectrum, only the sum of these coupling constants could be deduced (see ref. 35).

A comparison of the NMR spectroscopic properties of ketones **A–D** left little doubt that they were stereoisomers and represented by the structures **30–33**. The coupling constants of the cyclohexane-ring protons of ketone **A**, summarised in Table 1, showed a good match to those of ketone *rac*-**18**, indicating that ketone **A** possessed the stereostructure **30** or **32**. Similarly, the cyclohexane-ring proton coupling constants of ketones **C** and **D** (Table 1) were very similar to those of ketone *rac*-**19**, revealing that ketones **C** and **D** possessed the stereostructures **31** and **33**. In view of the previously established *Re*-face selectivity of the diene **1**, ketone **A** was assigned the stereostructure **30**, ketone **C** the stereostructure **31** and ketone **D** the stereostructure **33**. By difference, ketone **B** was considered to possess the stereostructure **32**. As can be seen from Table 1, its



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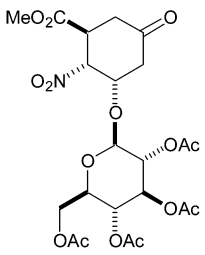

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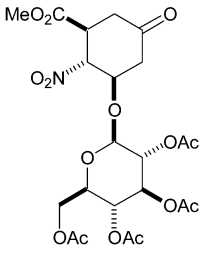

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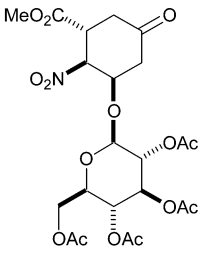

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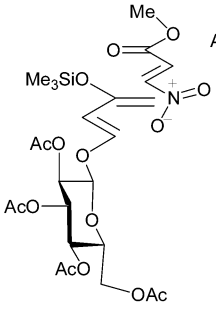

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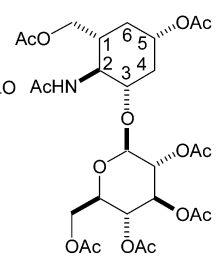

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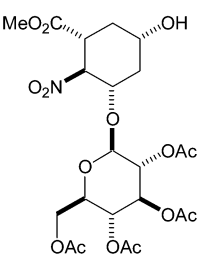


36

cyclohexane-ring coupling constants differed significantly from those of its relative **30**; this issue will be considered later.

In summary, the reaction of the diene **1** with the nitroacrylate **15** leads to a 43 : 18 : 30 : 9 mixture of the cycloadducts **20**, **21**, **22** and **23**, corresponding to a *Re*-face : *Si*-face selectivity of 61 : 39 and an *exo*-nitro : *endo*-nitro selectivity of 73 : 27. Clearly, the former selectivity is quite similar to that (67 : 33) seen in the cycloaddition of the diene **1** with tetracyanoethylene and the latter selectivity is comparable to that (67 : 33) observed in the cycloaddition of the diene **17** with the nitroacrylate **15**.

Having earlier defined the solid-state structure of the diene **1**,[3] we felt that a knowledge of the corresponding geometry of the nitroacrylate **15** would be a valuable input into transition-state modelling studies. Surprisingly, in spite of their wide application in synthesis, β-nitroacrylates are not represented in the Cambridge crystallographic data base. An X-ray analysis of the nitroacrylate **15**, depicted in Fig. 1 with its crystallographic labelling, revealed planarity of both the nitro and ester groups. Moreover, the ester carbonyl and olefinic unit bore a *syn* relationship. As an example, therefore, an arrangement such as **34** is possibly relevant to the development of the transition-state geometry leading to the *Re*-face *exo*-nitro cycloadduct **20**.

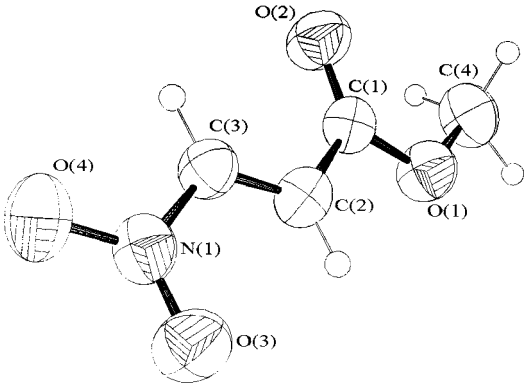


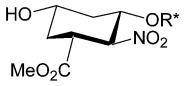
Fig. 1 Molecular structure of the nitroacrylate **15**.

Having shown that the ketone **30** was the major product from the hydrolysate of the reaction of the diene **1** with the nitroacrylate **15**, attention was turned to effecting its conversion into the monocarba-disaccharide **35**. The first task was to stereoselectively reduce the ketone function.

Treatment of the ketone **30** with sodium borohydride in methanol at −78 °C gave the alcohol **36** (74% yield after crystallisation), the stereostructure of which was established by NMR spectroscopy. The cyclohexane ring of compound **36** would be expected to adopt the chair geometry **37**, in which the 5-hydroxy group is equatorial. This was borne out by the coupling constants shown in Table 2; in particular, the axial 6-H, which resonated at δ 1.52 as a double triplet, displayed three large coupling constants (J 11, 13 and 13 Hz).

After screening a variety of reducing agents, aluminium amalgam[36] in aq. methanol was found to effect the nitro-group reduction[37] of compound **36**. Following acetylation of the product and column chromatographic fractionation, the hydroxylamine‖[38] and amine derivatives **38** and **39** were isolated in respective yields of 37 and 26%. That these reductions had occurred with retention of configuration at position 2 was demonstrated by the cyclohexane-ring proton coupling constants (Table 2), which were comparable to those of the nitro precursor **36**. When the product from the aluminium amalgam reduction was subjected to the action of lithium aluminium hydride in THF and acetic anhydride in pyridine, the target carba-disaccharide **35** was obtained (37% yield after chromatography). Again, the coupling constants of the cyclohexane-ring protons (Table 2) left little doubt that the ester-reduction step had occurred with retention of configuration.

To conclude the study, the conversion of the ketone **32** into the monocarba-disaccharide **40** was undertaken. Sodium borohydride reduction of the ketone **32** gave the alcohol **41** (73% yield after crystallisation). According to NMR spectroscopy, the cyclohexane ring of compound **41** adopted the chair conformation **42** (see Table 2). Subjection of compound **41** to the reductive acetylation sequence (Al·Hg/MeOH/H_2O; $LiAlH_4$/THF; Ac_2O/pyridine) gave the monocarba-disaccharide **40** (35% yield after chromatography). On the basis of NMR spectroscopy, its



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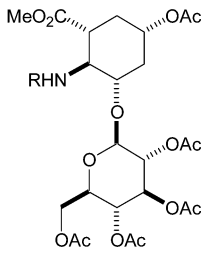
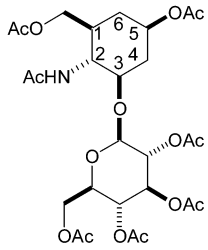


38 R = OAc
39 R = Ac



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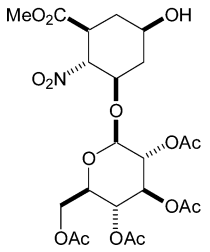

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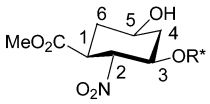

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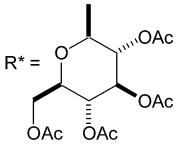


‖Hydroxylamines are the usual products of aluminium amalgam reductions of nitro compounds when the reactions are conducted in moist diethyl ether (ref. 38).

Table 2 Selected coupling constants (Hz) of the cyclohexane-ring protons of compounds **35**, **36** and **38**–**41** (in $CDCl_3$)

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4ax}$	$J_{3,4eq}$	$J_{4ax,5}$	$J_{4eq,5}$	$J_{5,6ax}$	$J_{5,6eq}$	$J_{1,6ax}$	$J_{1,6eq}$
35	10	11	11	4.5	12	4	12	4	12	—
36	11.5	10	11.5	4.5	12	—	11	—	13	4.5
38	11	11	12	—	12	4	12.5	4	13	4
39	11	10.5	12	—	12	4	12	4	13	3.5
40	10	10.5	11	4	11	4	11.5	4	12	—
41	11	10	11.5	—	11.5	—	11.5	—	13	4

Table 3 Calculated[a] coupling constants (Hz) of the cyclohexanone-ring protons of the chair conformers **43** and **44** of the ketone **32**

Conformer	$J_{1,2}$	$J_{2,3}$	$J_{3,4ax}$	$J_{3,4eq}$	$J_{1,6ax}$	$J_{1,6eq}$
43	12.9	10.3	11.2	5.1	12.3	3.7
44	1.8	3	3.8	2.2	2.2	4.5
43 : 44 (1 : 1)	7.4	6.7	7.5	3.7	7.3	4.1

[a] Using Macromodel Version 5.5 (see Experimental section).

cyclohexane ring adopted a chair conformation akin to that of its precursor (Table 2).

An X-ray crystallographic analysis of compound **41**, shown in Fig. 2 with its crystallographic labelling, established that the cyclohexane ring possessed the absolute stereochemistry that had been assigned to it. Clearly, the chair conformation **42** observed in deuteriochloroform solution was also present in the crystalline state.

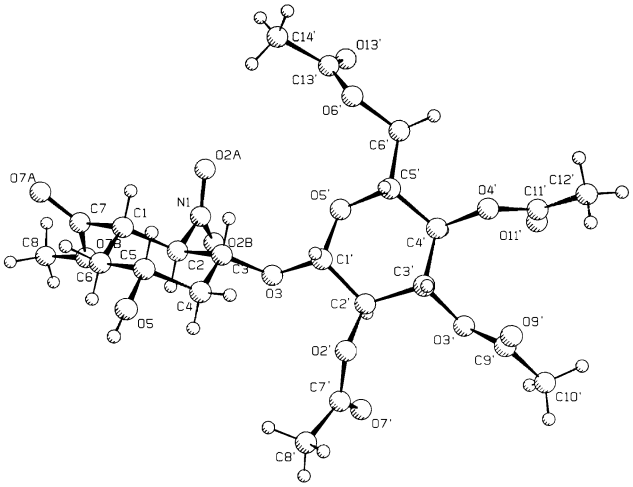


Fig. 2 Molecular structure of compound **41**.

The present work reveals that 3-*O*-β-D-glucopyranosyl derivatives of 4-acetylamino-2,4-dideoxycarbapyranoses with the 'β-L-*altro*' and 'β-D-*altro*' configurations can be assembled from the β-D-glucopyranosyl diene template **1**. The results complement previous findings[23,24] in which related monocarba-disaccharides with the 'β-L-*galacto*' and 'β-D-*galacto*' configurations were constructed from the same template.

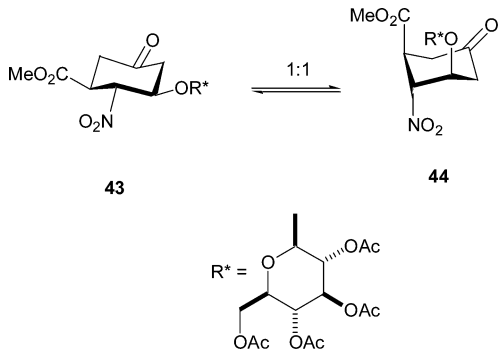
As mentioned earlier, the differing conformational properties of the ketones **30** and **32**, which feature cyclohexanone rings that bear the diastereomeric relationship, is noteworthy. Clearly, the sugar residue is responsible for the difference. In the case of the ketone **30**, the cyclohexanone ring adopted the expected chair conformation **43** (in which the 1-, 2- and 3-substituents were equatorially orientated) in deuteriochloroform on the basis of the observed coupling constants (Table 1), which were close to those calculated for an equivalent conformer (see **43**, Table 3). In the case of the ketone **32**, the cyclohexanone ring probably existed mainly as a *ca.* 50 : 50 mixture of the chair conformers **43** (in which the 1-, 2- and 3-substituents occupied equatorial positions) and **44** (in which the 1-, 2- and 3-substituents adopted axial locations) (Scheme 3); thus, the observed coupling constants (Table 1) were in moderate agreement with the calculated ones (Table 3). The NOE enhancements of the cyclohexanone-ring protons of the ketones **30** and **32** (Table 4) were consistent with the conformational situations proposed. In particular, on average, the 1- and 2-protons and the 3- and 4-protons were closer together in compound **32** than in compound **30**.

Seemingly, therefore, the sugar modifies the conformational behaviour of compound **32** by increasing the equilibrium concentration of the conformer **44** in which the 1-, 2- and 3-substituents are axially orientated. The unexpected conformational behaviour induced by the sugar residue was not observed after the reduction. Presumably, the steric and dipolar interactions between the methoxycarbonyl, nitro and oxy groups play an important role in the conformational properties of the alcohol **41**. As has already been noted, the cyclohexane ring of the reduction product **41** displayed normal conformational behaviour in deuteriochloroform; thus, it adopted the chair geometry **42** (comparable to the geometry **37** adopted by the reduction product **36**). Evidently, the cyclohexanone carbonyl group of compound **32** is also required for the anomalous conformational properties. A study of solvent effects on the coupling constants of the cyclohexanone-ring protons of compound **32**, shown in Table 5, revealed that the atypical conformational behaviour was most pronounced in deuteriochloroform and perdeuteriobenzene. In perdeuteriodimethyl sulfoxide, the cyclohexanone ring of compound **32** existed mainly as the chair conformer **43**;

Table 4 Enhancement of the cyclohexanone-ring protons of compounds **30** and **32** observed in NOE difference spectroscopic studies (in $CDCl_3$)[a]

Compound			
30	1 1-H ⇆ 2-H [b] —	4 1-H ⇆ 3-H 6	0 1-H ⇆ 6-H_{ax} 2
	3 1-H ⇆ 6-H_{eq} 4	[b] 2-H ⇆ 3-H 1	[b] 2-H ⇆ 4-H 2
	[b] 2-H ⇆ 6-H_{ax} 2	3 3-H ⇆ 4-H_{eq} 3	13 4-H_{ax} ⇆ 4-H_{eq} 11
	0 4-H_{eq} ⇆ 6-H_{eq} 2	13 6-H_{ax} ⇆ 6-H_{eq} 9	
32	4 1-H ⇆ 2-H 3	3 1-H ⇆ 3-H 4	3 1-H ⇆ 6-$H_{ax,eq}$ 9
	3 2-H ⇆ 3-H 5	1 2-H ⇆ 4-H_{ax}[c] 2	1 2-H ⇆ 6-$H_{ax,eq}$ 3
	3 3-H ⇆ 4-H_{eq}[c] 4	0 3-H ⇆ 4-H_{ax}[c] 1	0 3-H ⇆ 6-$H_{ax,eq}$ 1
	11 4-H_{ax} ⇆ 4-H_{eq}[c] 14	1 4-H_{ax} ⇆ 6-$H_{ax,eq}$ 5	

[a] The number associated with an arrow represents the % enhancement of the proton at the arrow head caused by irradiation of the proton at the arrow tail. [b] Not determined. [c] License is implied in the use of the axial and equatorial descriptors in this instance.



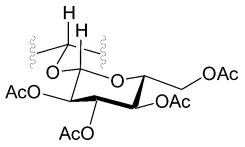
Scheme 3

Table 5 Effect of solvent on the coupling constants (Hz) of the cyclohexanone-ring protons of compounds *rac*-**18** and **32**

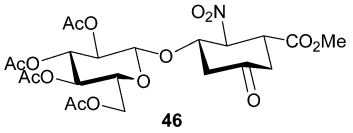
Compound	Solvent	$J_{1,2}$	$J_{2,3}$	$J_{3,4ax}$	$J_{3,4eq}$	$J_{1,6ax}$	$J_{1,6eq}$
rac-**18**	$CDCl_3$	9.5	7.5	9	4.5	11.5	6
	$(CD_3)_2SO$	11	9	10.5	5	13	5
	CCl_4	9.5	7	9	4.5	—	—
32	$CDCl_3$	8	5.5	7	4.5	←16→	
	C_6D_6	8	5.5	7	4.5	9.5	6.5
	CD_2Cl_2	9	6.5	9	4.5	11	6
	$(CD_3)_2SO$	10.5	9	10	5.5	12.5	5
	C_4D_8O	9.5	7	8.5	5	—	—

in perdeuteriochloromethane and perdeuteriotetrahydrofuran, an intermediary situation was in evidence.

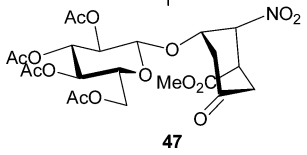
A knowledge of the global conformations of compounds **30** and **32** is relevant to the origins of the differing conformational properties of their cyclohexane rings. That the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy moieties adopted the expected $^4C_1$ conformations was secured from vicinal coupling constants values and NOE measurements (see Experimental section). Based on *exo*-anomeric effect[39] and torsional considerations,[40] the partial geometry **45** would be expected to make a significant contribution to the global conformations of both compounds **30** and **32**; this was borne out by the sizable NOE enhancements between the anomeric protons and the cyclohexanone 3-protons (8–9% for **30** and 6–7% for **32**). This partial geometry can be accommodated in the conformers **46** and **47** (Scheme 4) in the case of compound **30** and in the conformers **48** and **49** (Scheme 5) in the case of compound **32**.



45



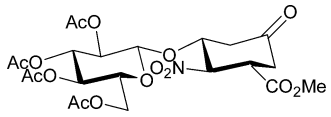
46



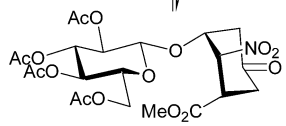
47

Scheme 4

For compound **30**, the conformer **46** is preferred because of the equatorial arrangement of the substituents of its cyclohexanone ring. In the case of compound **32**, conformers akin to **48** and **49** are considered to contribute significantly to the overall conformational situation. As represented, the conformer **48** would experience a severe destabilising interaction between the nitro group and the oxygen atom of the pyranose ring; relief of the interaction is achievable by enlargement of the O(5′)–C(1′)–O(3)–C(3) torsion angle, rotation about the O(3)–C(3) bond and expansion of the C(1′)–O(3)–C(3) bond angle.** In the conformer **49**, the aforecited intra-annular interaction is



48



49

Scheme 5

absent, although there is a penalty to be paid because of the axial arrangement of the cyclohexanone-ring substituents.

It may be noted that the coupling constants of the cyclohexanone-ring protons of compound **32** in perdeuteriodichloromethane and perdeuteriotetrahydrofuran were very similar to those of compound *rac*-**18** in deuteriochloroform, implying that the invertomer of the conformer *rac*-**26** makes a small contribution to the conformational situation in the case of compound *rac*-**18**. Accordingly, it was of interest to determine whether the conformational properties of compound *rac*-**18** could be influenced by solvent. From the results shown in Table 5, it is clear that they can. Thus, in perdeuteriodimethyl sulfoxide, it is evident that the conformer *rac*-**26** is the dominant species. Possibly, intramolecular dipolar interactions between the carbonyl carbon atom of the 1-methoxycarbonyl group and a lone pair of electrons on the oxygen atom of the 3-oxy substituent contribute to the stabilisation of the axial conformer in the non-polar solvents.

Experimental

Dry solvent, referred to in the ensuing experiments were prepared as follows: diethyl ether was distilled off sodium–benzophenone; dichloromethane was distilled off phosphorus(V) oxide; pyridine was distilled off sodium hydroxide pellets. Sodium acetate was dried in an oven at 110 °C for 5 h.

TLC was performed on Merck plastic or aluminium plates coated with silica gel (60 F_{254}); chromatograms were initially examined under UV light (Mineralight UVG-58 lamp) and visualised with either iodine vapour or a *p*-anisaldehyde stain [plates were sprayed with EtOH : conc. H_2SO_4 : *p*-$MeOC_6H_4CHO$ (95 : 4 : 1) and heated]. Column chromatography was effected, under positive pressure from a compressed-air line, employing Crossfield Sorbsil C60 flash silica. HPLC was carried out on Spherisorb S10 silica columns (25 × 0.46 cm for analytical and 25 × 0.8 cm for preparative work), using a Kontron 420 pump and Kontron 742 UV/ERC-7515A RI detectors.

Evaporations were conducted under reduced pressure (using a water-pump or an oil-pump) at ≤40 °C with a Büchi rotary

** It is worth nothing that for compound **41** in the crystal state, the O(5′)–C(1′)–O(3)–C(3) torsion angle was 92.3°, the H(1′) · · · H(3) interatomic distance was 2.257 Å and the C(1′)–O(3)–C(3) bond angle was 113.3°.

evaporator. Mps were determined with a Büchi 512 melting point apparatus. Optical rotations, given in 10^{-1} deg cm^2 g^{-1}, were measured at *ca.* 20 °C using a Thorn Automation Type 243 polarimeter. Elemental analyses were performed with a Carlo-Erba Model 1108 analyser. A Perkin-Elmer Lambda 15 spectrometer was used to measure UV spectra; extinction coefficients (ε) are presented in cm^2 mmol^{-1}. IR Spectra were recorded with a Perkin-Elmer 783 spectrometer. NMR Spectra were determined using a Bruker AC 300 or a Varian VXR600S spectrometer (with DEPT editing for ^{13}C NMR spectra); *J* values and separations are given in Hz. Proton assignments were supported by COSY 45° experiments. FAB Mass spectra (*m*-$O_2NC_6H_4CH_2OH$ as matrix) were recorded using a Kratos MS50TC spectrometer.

Methyl (*E*)-3-nitroacrylate 15

Methyl acrylate (20.4 g, 0.24 mol) was added in portions to a vigorously stirred solution of mercury(II) chloride (61.2 g, 0.23 mol) and sodium nitrite (31.2 g, 0.45 mol) in water (500 cm^3). After 16 h, the precipitated material was collected by filtration, washed with water followed by hexanes, and dried *in vacuo* to afford the nitromercurial chloride **24** (61.8 g, 74%) as a white solid.

Bromine (52.7 g, 0.33 mol) was added in portions to a vigorously stirred, ice-cooled mixture of the nitromercurial chloride **24** (61.8 g, 0.17 mol) in water (200 cm^3) and diethyl ether (500 cm^3). After the addition was complete, the mixture was allowed to warm to room temperature and stirred overnight. Sodium hydrogen carbonate was then added in portions until effervescence ceased. The organic phase was separated and the aqueous phase was extracted with diethyl ether. Evaporation of the combined, dried ($MgSO_4$) organic phases gave the nitro bromide **25** (33.7 g, 95%) as a yellow oil.

Dried sodium acetate (77.9 g, 0.95 mol) was added in portions to a stirred solution of nitro bromide **25** (33.7 g, 0.16 mmol) in dry diethyl ether (100 cm^3). After 3 days, the mixture was diluted with diethyl ether (50 cm^3) and filtered. The filtrate was washed with saturated aq. sodium hydrogen carbonate (3 ×) and water, dried ($MgSO_4$) and concentrated. Crystallisation of the oil from diethyl ether–hexanes at low temperature gave the *title compound* **15** (19.9 g, 95%); mp 34–35 °C (lit., 37–38 °C,[28] 33–35 °C)[30] (Found: C, 36.8; H, 4.0; N, 10.6. Calc. For $C_4H_5NO_4$: C, 36.6; H, 3.8; N, 10.7%); λ_{max} (EtOH)/nm 221 (ε 10 700); ν_{max} (KBr)/cm^{-1} 1740 (ester C=O), 1655 (C=C) and 1550 (NO_2); δ_H (300 MHz; $CDCl_3$) 3.88 (3 H, s, MeO_2C) and 7.10 and 7.69 (each 1 H, d, *J* 13.5, 2- and 3-H); δ_C (75 MHz; $CDCl_3$) 52.92 (CH_3O), 127.1 (2-CH), 149.0 (3-CH) and 163.0 (1-CO).

Crystal data for compound 15. $C_4H_5NO_4$, M = 131.1. Colourless plate, dimensions: 0.3 × 0.3 × 0.15 mm. Monoclinic, a = 5.356(2), b = 6.688(2), c = 16.787(7) Å, b = 96.99(3)°, V = 596.9(4) Å^3. Space group $P2_1/n$ (no. 14), Z = 4, D_c = 1.459 g cm^{-3}, $F(000)$ = 272, μ (Mo-Kα) = 1.33 cm^{-1}.

Data collection and processing. Intensity data were collected on a Enraf Nonius CAD-4 diffractometer with monochromated Mo–Kα radiation (λ = 0.71073 Å) using the $\omega/2\theta$ scanning technique to a maximum 2θ value of 50.0° with a scan rate of 10.0° min^{-1} and a scan width of (1.2 + 0.35 tan θ); a total of 987 reflections were measured of which 878 were unique (R_{int} = 0.0227). Corrections for Lorentz and polarization effects were applied; absorption was ignored.

Structure analysis and refinement. The structure was solved by direct methods (SHELXS-97[41]) and refined by full-matrix least squares based on F^2 (SHELXL-97[41]). All non-hydrogens were refined anisotropically and hydrogen atoms were constrained to chemically reasonable positions. The refinement converged to give final values of ωR^2 = 0.140 (R = 0.083) using all 878 reflections and 90 variable parameters. The molecule and its atomic labeling, drawn using the ORTEP-3 for Windows programme, is shown in Fig. 1.††

Cycloaddition–hydrolysis studies

General procedure. A solution of the diene (0.3 mmol) and the nitroacrylate **15** (0.039 g, 0.3 mmol) in dry dichloromethane (10 cm^3) was allowed to stand under argon for 4 h. Evaporation of the solvent left a residue which was analysed by NMR spectroscopy. The residue was treated with aq. acetic acid (50 vol%, 20 cm^3) and the solution was neutralised after 2 h with saturated aq. sodium hydrogen carbonate. The mixture was extracted twice with dichloromethane and the dried ($MgSO_4$) extracts were concentrated to leave a residue, which was analysed by NMR spectroscopy and then purified in the manner described.

Reaction of the diene 17

(*a*) The diene **17** (90% purity, 0.050 g, 0.26 mmol) gave rise to a yellow oil which comprised mainly a 67 : 33 mixture of the cycloadducts *rac*-**28** and *rac*-**29** [the ratio was estimated from the integrals of the double quartet (*J* 8 and 2.5) at δ 4.51 and of the double doublet (*J* 4 and 6) at δ 4.40, attributed to the 5-Hs of *rac*-**28** and *rac*-**29**]. After acidic hydrolysis, a 60 : 40 mixture of the ketones *rac*-**18** and *rac*-**19** (the ratio was estimated from the intensities of the singlets at δ 3.38 and 3.32, attributed to the methoxy groups of the ketones *rac*-**18** and *rac*-**19**) was isolated.

(*b*) The diene **17** (90% purity, 4.51 g, 24 mmol) gave rise, after hydrolysis, to a brown foam. Crystallisation of the material from dichloromethane–diethyl ether–hexanes afforded *methyl* (1R*,2S*,3S*)-3-*methoxy*-2-*nitro*-5-*oxocyclohexane*-1-*carboxylate rac*-**18** (1.88 g, 34%); mp 110–112 °C (lit.,[29] 110–112 °C) (Found: C, 47.1; H, 6.0; N, 6.2. Calc. For $C_9H_{13}NO_6$: C, 46.8; H, 5.7; N, 6.1%); λ_{max} (EtOH)/nm 207 (ε 3600); ν_{max} (KBr) 1740br (ester C=O), 1730 (ketone C=O) and 1560 (NO_2); δ (300 MHz; $CDCl_3$) 2.54 and 2.88 [each 1 H, ddd (*J* 1, 9 and 15) and ddd (*J* 1.5, 4.5 and 15), 4-H_{ax} and 4-H_{eq}], 2.67 and 2.76 [each 1 H, ddd, (*J* 1, 11.5 and 16) and ddd (*J* 1.5, 6 and 16), 6-H_{ax} and 6-H_{eq}], 3.38 (3 H, s, MeO), 3.49 (1 H, ddd, *J* 6, 9.5 and 11.5, 1-H), 3.75 (3 H, s, MeO_2C), 4.07 (1 H, ddd, *J* 4.5, 7.5 and 9, 3-H) and 5.08 (1 H, dd, *J* 7.5 and 9.5, 2-H); *m/z* (FAB) 254 (MNa^+, 24%), 232 (MH^+, 75) and 200 ($C_8H_{10}NO_5^+$, 100).

Evaporation of the filtrate obtained from the foregoing crystallisation gave a residue that contained a 50 : 50 mixture of the ketones *rac*-**18** and *rac*-**19**. A portion of the mixture (0.100 g) was fractionated by HPLC [hexanes–EtOAc (2 : 1) as eluent].

The first-eluted material (0.030 g), isolated as a crystalline solid, was identified as the ketone *rac*-**18** by NMR spectroscopy.

The second-eluted material (0.040 g) was *methyl* (1S*,2R*,3S*)-3-*methoxy*-2-*nitro*-5-*oxocyclohexane*-1-*carboxylate rac*-**19**; mp 88–90 °C (Found: C, 47.0; H, 5.4; N, 5.9. Calc. $C_9H_{13}NO_6$ requires C, 46.8; H, 5.7; N, 6.1%); λ_{max} (EtOH)/nm 206 (ε 4000); ν_{max} (KBr)/cm^{-1} 1740 (ester C=O), 1720 (ketone C=O) and 1550 (NO_2); δ (300 MHz; $CDCl_3$) 2.42 and 2.79 [each 1 H, dd, (*J* 13.5 and 15) and ddd (*J* 2.5, 5.5 and 15), 6-H_{ax} and 6-H_{eq}], 2.58 and 2.91 [each 1 H, dd (*J* 3 and 15.5) and ddd (*J* 2.5, 3.5 and 15.5), 4-H_{ax} and 4-H_{eq}], 3.32 (3 H, s, MeO), 3.77 (3 H, s, MeO_2C), 3.85 (1 H, ddd, *J* 5.5, 11 and 13.5, 1-H), 4.56 (1 H, br q, separation 3, 3-H) and 5.12 (1 H, dd, *J* 3 and 11, 2-H); *m/z* (FAB) 232 (MH^+, 92%) and 200 ($C_8H_{10}NO_5^+$, 100).

Reaction of the diene 1

(*a*) The diene **1** (0.200 g, 0.41 mmol) gave rise to a yellow oil which comprised mainly a 43 : 30 : 18 : 9 mixture of the cycloadducts **20**, **22**, **21**, and **23** [the ratio was estimated from the intensities of

†† CCDC reference numbers 245218 (**15**) and 245217 (**41**). See http://www.rsc.org/suppdata/ob/b4/b410556g/ for crystallographic data in .cif or other electronic format.

the doublets (J 8 Hz) at δ 4.50, 4.59, 4.46 and 4.65, attributed to the 1′-Hs of the cycloadducts]. After hydrolysis, a foam (0.200 g) was isolated which comprised mainly a 42 : 28 : 18 : 12 mixture of the ketones **30**, **32**, **31** and **33** [the ratio was determined from the intensities of the doublets (J 8 Hz) at δ 4.48, 4.58, 4.45 and 4.47, attributed to the 1′-Hs of the ketones]. Subjection of the mixture to column chromatography [hexanes–EtOAc (1 : 1) as eluent] gave rise to two fractions.

The first-eluted material (0.070 g) was mainly compound **30**. After crystallisation from dichloromethane–diethyl ether–hexanes, *methyl* (1R,2S,3S)-2-*nitro*-5-*oxo*-3-(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*) -*cyclohexane*-1-*carboxylate* **30** (0.054 g, 24%) was obtained as needles; mp 182–184 °C; $[\alpha]_D$ −13 (c 0.5, CH_2Cl_2) (Found: C, 48.3; H, 5.0; N, 2.8. $C_{22}H_{29}NO_{15}$ requires C, 48.3; H, 5.3; N, 2.6%); λ_{max} (EtOH)/nm 204 (ε 4200); ν_{max} (KBr)/cm^{-1} 1760 and 1740 (ester C=O), 1720 (ketone C=O) and 1565 (NO_2); δ (300 MHz; $CDCl_3$) 1.99, 2.02, 2.07 and 2.11 (each 3 H, s, 4 × $MeCO_2$), 2.60 and 2.75 [each 1 H, dd, (J 13.5 and 15) and ddd (J 2, 5 and 15), 6-H_{ax} and 6-H_{eq}], 2.67 and 3.07 (each 1 H, dd, (J 11 and 15) and ddd (J 2, 5 and 15), 4-H_{ax} and 4-H_{eq}], 3.32 (1 H, ddd, J 5, 11 and 13.5, 1-H), 3.69 (1 H, ddd, J 2.5, 5.5 and 10, 5′-H), 3.74 (3 H, s, MeO_2C), 4.11 and 4.23 [each 1 H, dd, (J 2.5 and 12.5) and dd (J 5.5 and 12.5), 6′-H_2], 4.30 (1 H, ddd, J 5, 10 and 11, 3-H), 4.48 (1 H, d, J 8, 1′-H), 4.95 (1 H, dd, J 8 and 9.5, 2′-H), 5.01 (2 H, br t, J 10, 4′- and 2-H) and 5.15 (1 H, t, J 9.5, 3′-H); δ (600 MHz; $CDCl_3$) 1.99, 2.02, 2.08 and 2.11 (each 3 H, s, 4 × $MeCO_2$), 2.61 and 2.75 [each 1 H, ddd, (J 0.5, 13.5 and 15.5) and ddd (J 2, 5 and 15.5), 6-H_{ax} and 6-H_{eq}], 2.68 and 3.06 (each 1 H, ddd (J 0.5, 11.5 and 15) and ddd (J 2, 5.5 and 15), 4-H_{ax} and 4-H_{eq}], 3.32 (1 H, ddd, 5, 11.5 and 13.5, 1-H), 3.69 (1 H, ddd, J 2.5, 5.5 and 10, 5′-H), 3.75 (3 H, s, MeO_2C), 4.12 and 4.23 [each 1 H, dd (J 2.5 and 12.5) and dd (J 5.5 and 12.5), 6′-H_2], 4.31 (1 H, ddd, J 5.5, 9.5 and 11.5, 3-H), 4.49 (1 H, d, J 8, 1′-H), 4.95 (1 H, dd, J 8 and 9.5, 2′-H), 5.01 [2 H, t (J 9.5) and dd (J 9.5 and 11.5), 4′- and 2-H] and 5.15 (1 H, t, J 9.5, 3′-H) [NOE difference: δ 2.61→2.75 (13%), 3.32 (2%) and 5.01 (2%); δ 2.68→3.06 (13%) and 5.01 (2%); δ 2.75→2.61 (9%), 3.06 (2%) and 3.32 (4%); δ 3.06→2.68 (11%) and 4.31 (3%); δ 3.32→2.75 (3%), 4.31 (4%) and 5.01 (1%); δ 3.69→4.12 (2%), 4.23 (2%), 4.49 (7%), 5.01 (1%) and 5.15 (5%); δ 4.12→3.69 (3%), 4.23 (11%) and 5.01 (1%); δ 4.23→4.12 (9%) and 5.01 (2%); δ 4.31→3.06 (3%), 3.32 (6%), 4.49 (8%) and 5.01 (1%); δ 4.49→3.69 (7%), 4.31 (9%), 4.95 (3%) and 5.15 (5%); δ 4.95→5.15 (2%); δ 5.15→3.69 (3%), 4.49 (3%) and 5.01 (2%)]; m/z (FAB) 570 (MNa^+, 15%), 548 (MH^+, 18) and 331 ($C_{14}H_{19}O_9^+$, 100).

The second-eluted material (0.051 g) was mainly a mixture of compounds **31** and **32**, containing the latter material as the major component. After crystallisation from diethyl ether–hexanes, *methyl* (1S,2R,3R)-2-*nitro*-5-*oxo*-3-(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)*cyclohexane*-1-*carboxylate* **32** (0.040 g, 18%) was obtained; mp 164–166 °C; $[\alpha]_D$ −26 (c 0.5, CH_2Cl_2) (Found: C, 48.5; H, 5.3; N, 2.4); λ_{max} (EtOH)/nm 204 (ε 2600); ν_{max} (KBr)/cm^{-1} 1750br (ester C=O), 1720sh (ketone C=O) and 1565 (NO_2); δ (300 MHz; $CDCl_3$) 1.99, 2.02, 2.03 and 2.11 (each 3 H, s, 4 × $MeCO_2$), 2.60 and 2.73 [each 1 H, dd (J 7 and 16) and dd (J 4 and 16), 4-H_{ax} and 4-H_{eq}], 2.70 (2 H, d, separation 8, 6-H_2), 3.58 (1 H, q, separation 8, 1-H), 3.69 (1 H, ddd, J 2.5, 5 and 10, 5′-H), 3.76 (3 H, s, MeO_2C), 4.13 and 4.23 [each 1 H, dd (J 2.5 and 12.5) and dd (J 5 and 12.5), 6′-H_2], 4.58 (1 H, d, J 8, 1′-H), 4.69 (1H, ddd, J 4.5, 5.5 and 7, 3-H), 4.89 (1 H, dd, J 8 and 9.5, 2′-H), 5.05 (1 H, t, J 9.5 Hz, 4′-H), 5.16 (1 H, t, J 9.5, 3′-H) and 5.30 (1 H, dd, J 5.5 and 8, 2-H); δ (600 MHz; $CDCl_3$) 2.00, 2.025, 2.031 and 2.11 (each 3 H, s, 4 × $MeCO_2$), 2.61 and 2.73 [each 1 H, dd, (J 7 and 16) and dd (J 4.5 and 16), 4-H_{ax} and 4-H_{eq}], 2.71 (2 H, d, separation 8, 6-H_2), 3.58 (1 H, q, separation 8, 1-H), 3.69 (1 H, ddd, J 2.5, 5 and 10, 5′-H), 3.76 (3 H, S, MeO_2C), 4.14 and 4.23 [each 1 H, dd (J 2.5 and 12.5) and dd (J 5 and 12.5), 6′-H_2], 4.59 (1 H, d, J 8, 1′-H), 4.69 (1 H, ddd, J 4.5, 5.5 and 7, 3-H), 4.89 (1 H, dd, J 8 and 9.5, 2′-H), 5.06 (1 H, t, J 9.5, 4′-H), 5.17 (1 H, t, J 9.5, 3′-H) and 5.30 (1 H, dd, J 5.5 and 8, 2-H) [NOE difference: δ 2.61→2.71 (1%), 2.73 (11%), 4.59 (1%), 4.69 (1%) and 5.30 (2%); δ 2.71→2.61 (5%), 3.58 (9%), 4.69 (1%) and 5.30 (3%); δ 2.73→2.61 (14%) and 4.69 (4%); δ 3.58→2.71 (3%), 4.69 (3%) and 5.30 (4%); δ 3.69→4.14 (2%), 4.23 (2%), 4.59 (7%), 5.06 (2%) and 5.17 (6%); δ 4.14→3.69 (4%) and 4.23 (8%); δ 4.23→3.69 (2%), 4.14 (8%) and 5.06 (3%); δ 4.59→3.69 (6%), 4.69 (6%) and 5.17 (5%); δ 4.69→2.73 (3%), 3.58 (4%), 4.59 (7%) and 5.30 (5%); δ 4.89→5.06 (5%) and 5.17 (4%); δ 5.06→3.69 (1%), 4.14 (1%), 4.23 (1%) and 4.89 (7%); δ 5.17→3.69 (4%), 4.59 (3%) and 4.89 (3%); δ 5.30→2.61 (1%), 2.71 (1%), 3.58 (3%) and 4.69 (3%)]; m/z (FAB) 570 (MNa^+, 100%), 548 (MH^+, 13) and 331 ($C_{14}H_{19}O_9^+$, 100).

(*b*) The aforecited experiment was repeated and the hydrolysate was subjected to fractionation by HPLC [CH_2Cl_2–EtOAc (7 : 3) as eluent].

The first-eluted material (0.060 g, 27%), isolated as a crystalline solid, was identified as the ketone **30** by NMR spectroscopy.

The second-eluted material (0.039 g, 17%), also isolated as a crystalline solid, was considered to be the ketone **32** by NMR spectroscopy.

The third-eluted material (0.025 g, 11%) was *methyl* (1S,2R,3S)-2-*nitro*-5-*oxo*-3-(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)*cyclohexane*-1-*carboxylate* **31**; mp 160–162 °C; $[\alpha]_D$ +20 (c 0.5, CH_2Cl_2) (Found: C, 48.1; H, 5.0; N, 2.5); λ_{max} (EtOH)/nm 204 (ε 3800); ν_{max} (KBr)/cm^{-1} 1760 (ester C=O), 1740 (ketone C=O) and 1570 and 1545 (NO_2); δ (300 MHz; $CDCl_3$) 1.98, 2.01, 2.03 and 2.11 (each 3 H, s, 4 × $MeCO_2$), 2.39 and 2.83 [each 1 H, dd, (J 13 and 15.5) and ddd (J 2.5, 5.5 and 15.5), 6-H_{ax} and 6-H_{eq}], 2.62 and 3.00 [each 1 H, dd (J 3 and 16) and dt (J 16 and 3), 4-H_{ax} and 4-H_{eq}], 3.62–3.74 (2 H, m, 1- and 5′-H), 3.77 (3 H, s, MeO_2C), 4.15 and 4.22 [each 1 H, dd (J 4.5 and 12.5) and dd (J 2.5 and 12.5), 6′-H_2], 4.45 (1 H, d, J 8, 1′-H), 4.90 (1 H, dd, J 8 and 9.5, 2′-H), 4.92 (1 H, q, separation 3, 3-H), 5.02 (1 H, t, J 9.5, 4′-H), 5.11 (1 H, dd, J 3 and 11, 2-H) and 5.13 (1 H, t, J 9.5, 3′-H); m/z (FAB) 570 (MNa^+, 100%) and 331 ($C_{14}H_{19}O_9^+$, 81).

The fourth-eluted material, isolated as a foam, was mainly a 50 : 50 mixture of the ketones **31** and **33** [the ratio was estimated from the heights of the doublets (J 8 Hz) at δ 4.45 and 4.47, attributed to the 1′-Hs of the ketones **31** and **33**]. It was resubjected to HPLC fractionation to give a 25 : 75 mixture of the ketones **31** and **33**; δ (300 MHz; $CDCl_3$) (for **33**) 1.99, 2.00, 2.07 and 2.11 (each 3 H, s, 4 × $MeCO_2$), 2.41 (1 H, dd, J 13 and 15, 6-H_{ax}), 2.64 (1 H, dd, J 2.5 and 15, 4-H_{ax}), 2.69–2.83 (2 H, m, 4- and 6-H_{eq}), 3.63 (1 H, ddd, J 2.5, 5 and 10, 5′-H), 3.77 (3 H, s, MeO_2C), 3.79 (1 H, ddd, J 5.5, 11.5 and 13, 1-H), 4.08 and 4.18 [each 1 H, dd (J 2.5 and 12.5) and dd (J 5 and 12.5), 6′-H_2], 4.47 (1 H, d, J 8, 1′-H), 4.87 (1 H, dd, J 8 and 9.5, 2′-H), 5.00 (1 H, q, separation 3, 3-H), 5.01 (1 H, t, J 9.5, 4′-H), 5.10 (1 H, dd, J 2.5 and 11.5, 2-H) and 5.16 (1 H, t, J 9.5, 3′-H).

Ketone reduction studies

General procedure. Sodium borohydride (0.005 g, 0.13 mmol) was added to a stirred solution of the ketone (0.050 g, 0.09 mmol) in methanol (10 cm^3), cooled in an acetone–solid carbon dioxide bath. After 6 h, the mixture was acidified with aq. hydrochloric acid (10 vol%) and extracted twice with dichloromethane. The extracts were washed with water, dried ($MgSO_4$) and concentrated to leave an oil which was examined by NMR spectroscopy and then purified as described.

Methyl (1*R*,2*S*,3*S*,5*S*)-5-hydroxy-2-nitro-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)cyclohexane-1-carboxylate 36

Reduction of the ketone **30** gave the alcohol **36**. Crystallisation of the material from diethyl ether–hexanes gave the *title compound* **36** (0.037 g, 74%); mp 180–182 °C; $[\alpha]_D$ −33 (c 0.5, CH_2Cl_2)

(Found: C, 48.2; H, 5.4; N, 2.8. $C_{22}H_{31}NO_{15}$ requires C, 48.1; H, 5.7; N, 2.5%), λ_{max} (EtOH)/nm 205 (ε 4200); ν_{max} (KBr)/cm^{-1} 3500 (OH), 1755 and 1735 (ester C=O) and 1560 (NO_2); δ (300 MHz; $CDCl_3$) 1.52 and 2.30–2.39 [each 1 H, dt (*J* 11 and 13) and m, 6-H_{ax} and 6-H_{eq}], 1.58 and 2.52–2.61 [each 1 H, q (separation 12) and m, 4-H_{ax} and 4-H_{eq}], 1.98, 2.02, 2.07 and 2.09 (each 3 H, s, 4 × $MeCO_2$), 3.04 (1 H, ddd, *J* 4.5, 11.5 and 13, 1-H), 3.63–3.69 (1 H, m, 5′-H), 3.70 (3 H, s, MeO_2C), 3.76–3.88 (1 H, m, 5-H), 4.01 (1 H, ddd, *J* 4.5, 10 and 11.5, 3-H), 4.19–4.21 (2 H, m, 6′-H_2), 4.44 (1 H, d, *J* 8, 1′-H), 4.63 (1 H, dd, *J* 10 and 11.5, 2-H), 4.94 (1 H, dd, *J* 8 and 9.5, 2′-H), 5.04 (1 H, t, *J* 9.5, 4′-H) and 5.14 (1 H, t, *J* 9.5, 3′-H); *m/z* (FAB) 572 (MNa^+, 63%), 550 (MH^+, 33) and 331 ($C_{14}H_{19}O_9^+$, 100).

Methyl (1*S*,2*R*,3*R*,5*R*)-5-hydroxy-2-nitro-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)cyclohexane-1-carboxylate 41

Reduction of the ketone **32** (0.100 g, 0.18 mmol) gave the alcohol **41**. Crystallisation of the material from diethyl ether–hexanes gave the *title compound* **41** (0.073 g, 73%); mp 172–174 °C; $[\alpha]_D$ −29 (*c* 0.25, CH_2Cl_2) (Found: C, 48.3; H, 5.9; N, 2.6. $C_{22}H_{31}NO_{15}$ requires C, 48.1; H, 5.7; N, 2.5%), λ_{max} (EtOH)/nm 204 (ε 4000); ν_{max} (KBr)/cm^{-1} 3460br (OH), 1760, 1740 and 1720 (ester C=O) and 1560 (NO_2); δ (300 MHz; $CDCl_3$) 1.49 (1 H, q, separation 11.5, 4-H_{ax}), 1.56 (1 H, q, separation 11.5, 6-H_{ax}), 1.99, 2.01, 2.04 and 2.10 (each 3 H, s, 4 × $MeCO_2$), 2.31–2.43 (2 H, m, 4- and 6-H_{eq}), 3.07 (3 H, 1 H, ddd, *J* 4, 11 and 13, 1-H), 3.63 (1 H, ddd, *J* 2.5, 4.5 and 10, 5′-H), 3.70 (3 H, s, MeO_2C), 3.78–3.90 (1 H, m, 5-H), 4.10 (1 H, dd, *J* 2.5 and 12, 6′-H), 4.14–4.22 (2 H, m, 6′- and 3-H), 4.56 (1 H, d, *J* 8, 1′-H), 4.68 (1 H, dd, *J* 10 and 11, 2-H), 4.92 (1 H, dd, *J* 8 and 9.5, 2′-H), 5.05 (1 H, t, *J* 9.5, 4′-H) and 5.16 (1 H, t, *J* 9.5, 3′-H); *m/z* (FAB) 572 (MNa^+, 3%), 550 (MH^+, 2), 331 ($C_{14}H_{19}O_9^+$, 44) and 169 (100).

Crystal data for compound 41. $C_{22}H_{31}NO_{15}$, M = 549.5. Colourless needle, dimensions: 0.30 × 0.20 × 0.20 mm. Monoclinic, a = 5.773(1), b = 22.641(3), c = 10.86(2) Å, β = 105.38(2)°, V = 1369(4) Å^3. Space group $P2_1$, Z = 2, D_c = 1.333 g cm^{-3}, $F(000)$ = 580, μ(Mo-Kα) = 1.14 cm^{-1}.

Data collection and processing. Intensity data were collected at 24 °C on an Enraf-Nonius CAD-4 diffractometer with monochromated Mo-Kα radiation (λ = 0.71069 Å) using the $\omega/2\theta$ scanning technique to a maximum 2θ value of 50.0° with a scan rate of 10.0° min^{-1} and a scan width of (0.8 + 0.35 tan θ); a total of 4176 reflections were measured of which 2451 were unique (R_{int} = 0.068). Corrections for Lorentz and polarization effects were applied; absorption was corrected by χ-scan.

Structure analysis and refinement. The structure was solved by direct methods (SHELXS-97[41]) and refined by full-matrix least squares (SHELXL-97[41]). All non-hydrogens were refined anisotropically and hydrogen atoms were constrained to chemically reasonable positions. The refinement converged to give final values of R = 0.062 and R_w = 0.084, using 1085 [$I > 2\sigma(I)$] observed reflections and 343 variable parameters. The molecule and its atomic labeling, drawn using the ORTEP-3 for Windows programme, is shown in Fig. 2.††

Reductive acetylation of the nitro alcohol 36

Aq. methanol (10 vol% H_2O, 1 cm^3) was added to a stirred mixture of the nitro alcohol **36** (0.100 g, 0.18 mmol) and aluminium amalgam [prepared from Al foil (2.0 g) by Corey's procedure[36]] in methanol (100 cm^3). After 4 h, Celite (5 g) was added and the mixture was filtered. Evaporation of the filtrate left a residue which was stirred with acetic anhydride (10 cm^3) and pyridine (10 cm^3) for 4 h. The mixture was diluted with dichloromethane and washed with water and dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic phase left a foamy residue (0.114 g), which was subjected to column chromatography [hexanes–EtOAc (1 : 2→neat EtOAc) as eluent] to give two fractions.

The first-eluted material (0.042, 37%), isolated as a crystalline solid, was *methyl* (1R,2S,3S,5S)-5-*acetoxy*-2-*acetoxyamino*-3-(2′,3′,4′,6′-*tetra*-*O*-*acetyl*-β-D-*glucopyranosyloxy*)*cyclohexane*-1-*carboxylate* **38**; mp 104–106 °C; $[\alpha]_D$ +13 (*c* 0.25, CH_2Cl_2) (Found: C, 50.4; H, 5.9; N, 2.6. $C_{26}H_{37}NO_{16}$ requires C, 50.4; H, 6.0; N, 2.3%), λ_{max} (EtOH)/nm 204 (ε 5100); ν_{max} (KBr)/cm^{-1} 1750 (ester C=O); δ (300 MHz; $CDCl_3$) 1.61 and 2.14–2.21 [each 1 H, q (separation 12.5) and m, 6-H_{ax} and 6-H_{eq}], 1.64 and 2.48–2.54 [each 1 H, q (separation 12) and m, 4-H_{ax} and 4-H_{eq}], 2.00, 2.02, 2.03, 2.05, 2.06 and 2.08 (each 3 H, s, 6 × $MeCO_2$), 2.60 (1 H, ddd, *J* 4, 11 and 13, 1-H), 3.17 (1 H, dt, *J* 2 and 11, 2-H), 3.60–3.73 (2 H, m, 3- and 5′-H), 3.71 (3 H, s, MeO_2C), 4.11 and 4.21 [each 1 H, dd (*J* 2.5 and 12.5) and dd (*J* 5.5 and 12.5), 6′-H_2], 4.62 (1 H, d, *J* 8, 1′-H), 4.72 (1 H, tt, *J* 4 and 11.5, 5-H), 4.99 (1 H, dd, *J* 8 and 9.5, 2′-H), 5.03 (1 H, t, *J* 9.5, 4′-H), 5.19 (1 H, t, *J* 9.5, 3′-H) and 7.76 (1 H, d, *J* 2, N*H*OAc); *m/z* (FAB) 642 (MNa^+, 13%), 620 (MH^+, 82) and 331 ($C_{14}H_{19}O_9^+$, 46 and 169 (100).

The second-eluted material (0.029 g, 26%), isolated as a crystalline solid, was *methyl* (1R,2S,3S,5S)-5-*acetoxy*-2-*acetylamino*-3-(2′,3′,4′,6′-*tetra*-*O*-*acetyl*-β-D-*glucopyranosyloxy*)*cyclohexane*-1-*carboxylate* **39**; mp 192–194 °C; $[\alpha]_D$ −17 (*c* 0.25, CH_2Cl_2) (Found: C, 51.8; H, 5.9; N, 2.6. $C_{26}H_{37}NO_{15}$ requires C, 51.7; H, 6.2; N, 2.3%), λ_{max} (EtOH)/nm 205 (ε 4700); ν_{max} (KBr)/cm^{-1} 1760 (ester C=O) and 1660br (amide C=O); δ (300 MHz; $CDCl_3$) 1.54 and 2.18–2.27 [each 1 H, q (separation 12) and m, 6-H_{ax} and 6-H_{eq}], 1.58 and 2.39–2.46 [each 1 H, q (separation 12) and m, 4-H_{ax} and 4-H_{eq}], 1.94, 1.99, 2.02, 2.03, 2.04 and 2.09 (each 3 H, s, 5 × $MeCO_2$ and MeCON), 3.03 (1 H, ddd, *J* 3.5, 11 and 13, 1-H), 3.47 (1 H, dt, *J* 7.5 and 10.5, 2-H), 3.67 (3 H, s, MeO_2C), 3.67–3.71 (1 H, m, 5′-H), 4.10 and 4.22 [each 1 H, d, (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.12–4.21 (1 H, m, 3-H), 4.60 (1 H, d, *J* 8, 1′-H), 4.79 (1 H, tt, *J* 4 and 11.5, 5-H), 4.94 (1 H, dd, *J* 8 and 9.5, 2′-H), 5.02 (1 H, t, *J* 9.5, 4′-H), 5.15 (1 H, t, *J* 9.5, 3′-H) and 5.58 (1 H, d, *J* 7.5, N*H*Ac); *m/z* (FAB) 626 (MNa^+, 46%), 604 (MH^+, 46), 331 ($C_{14}H_{19}O_9^+$, 79) and 169 (100).

Nitro ester reductions and acetylation studies

General procedure. Aq. methanol (10 vol%, 1 cm^3) was added to a stirred mixture of the nitro ester (0.100 g, 0.18 mmol) and aluminium amalgam [prepared from Al foil (2.0 g) by Corey's procedure[36]] in methanol (100 cm^3). After 4 h, Celite (5 g) was added and the mixture was filtered. Evaporation of the filtrate left a residue which was stirred at 0 °C with an ice-cold solution of lithium aluminium hydride in THF (1 mol dm^{-3}, 3 cm^3) for 1 h. Drops of ethyl acetate were then added to destroy the excess reducing agent and the mixture was evaporated. The residue was stirred with a mixture of acetic anhydride (10 cm^3) and dry pyridine (10 cm^3) for 4 h and then partitioned between dichloromethane and water. After having been washed with dilute hydrochloric acid and water, the organic phase was dried ($MgSO_4$) and concentrated. Subjection of the residue to column chromatography (EtOAc as eluent) led to the isolation of the product.

(1*R*,2*S*,3*S*,5*S*)-5-Acetoxy-1-acetoxymethyl-2-acetylamino-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)cyclohexane 35

Compound **36** gave rise to the *title compound* **35** (0.042 g, 37%) as a crystalline solid; mp 210–212 °C; $[\alpha]_D$ −16 (*c* 0.75, CH_2Cl_2) (Found: C, 52.2; H, 6.3; N, 2.4. $C_{27}H_{39}NO_{15}$ requires C, 52.5; H, 6.4; N, 2.3%), λ_{max} (EtOH)/nm 208 (ε 3900); ν_{max} (KBr)/cm^{-1} 3320br (NH), 1750 (ester C=O) and 1660 (amide C=O); δ (300 MHz; $CDCl_3$) 1.35 (1 H, q, separation 12, 6-H_{ax}), 1.58 and 2.40–2.43 [each 1 H, q (separation 12) and m, 4-H_{ax} and 4-H_{eq}], 1.991, 1.993, 2.02, 2.03, 2.056, 2.061 and 2.09 (each 3 H, s, 6 × $MeCO_2$ and MeCON), 3.37 (1 H, br q, separation 10,

2-H), 3.68 (1 H, ddd, *J* 2.5, 5 and 10, 5′-H), 3.88 (1 H, dt, *J* 4.5 and 11, 3-H), 4.02 and 4.08 [each 1 H, dd, (*J* 3 and 11) and dd (*J* 5 and 11), 1-CH_2OAc], 4.11 and 4.23 [each 1 H, dd, (*J* 2.5 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.61 (1 H, d, *J* 8, 1′-H), 4.77 (1 H, tt, *J* 4 and 11, 5-H), 4.94 (1 H, dd, *J* 8 and 9.5, 2′-H), 5.03 (1 H, t, *J* 9.5, 4′-H), 5.16 (1 H, t, *J* 9.5, 3′-H) and 5.42 (1 H, d, *J* 8.5, NH) (1-H and 6-H_{eq} were located at *ca.* δ 2.10 in a COSY 45° experiment); *m*/*z* (FAB) 640 (MNa^+, 9%), 618 (MH^+, 39) and 331 ($C_{14}H_{19}O_9^+$, 100).

(1*S*,2*R*,3*R*,5*R*)-5-Acetoxy-1-acetoxymethyl-2-acetylamino-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)cyclohexane 40

The nitro ester **41** gave rise to the *title compound* **40** (0.039 g, 35%) as a crystalline solid; mp 218–220 °C; $[\alpha]_D$ +5 (*c* 0.5, CH_2Cl_2) (Found: C, 52.8; H, 6.7; N, 2.3. $C_{27}H_{39}NO_{15}$ requires C, 52.5; H, 6.4; N, 2.3%), λ_{max} (EtOH)/nm 206 (ε 5000); ν_{max} (KBr)/cm^{-1} 3400br (NH), 1740 (ester C=O) and 1670 (amide C=O); δ (300 MHz; $CDCl_3$) 1.38 (1 H, q, separation 12, 6-H_{ax}), 1.43 and 2.28–2.35 [each 1 H, q (separation 11) and m, 4-H_{ax} and 4-H_{eq}], 1.96, 1.99, 2.02, 2.03, 2.05 and 2.10 (3, 3, 3, 3, 6 and 3 H, each s, 6 × $MeCO_2$ and MeCON), 3.37 (1 H, dt, *J* 8 and 10, 2-H), 3.67 (1 H, ddd, *J* 2, 5 and 9.5, 5′-H), 3.74 (1 H, dt, *J* 4 and 10.5, 3-H), 4.04 and 4.12 [each 1 H, dd (*J* 6 and 11) and dd (*J* 2.5 and 11), 1-CH_2OAc], 4.08 and 4.35 [each 1 H, dd (*J* 2 and 12.5) and dd (*J* 5 and 12.5), 6′-H_2], 4.51 (1 H, d, *J* 8, 1′-H), 4.74 (1 H, tt, *J* 4 and 11, 5-H), 4.88 (1 H, dd, *J* 8 and 9.5, 2′-H), 5.04 (1 H, t, *J* 9.5, 4′-H), 5.17 (1 H, t, *J* 9.5, 3′-H) and 5.63 (1 H, d, *J* 7.5, NH) (1-H and 6-H_{eq} were located at δ 2.06 in a COSY 45° experiment); *m*/*z* (FAB) 656 (MK^+, 79%), 618 (MH^+, 24) and 331 ($C_{14}H_{19}O_9^+$, 100).

Computational methods

The conformational searches of **43** and **44** were obtained by Monte Carlo searches in MacroModel version 5.5[42] on a Silicon Graphics IRIS workstations using the MM2 force field. The searches were performed with 2000 random structures generated per rotatable bond followed by energy minimization. The coupling constants (Hz) of the cyclohexanone-ring protons was calculated based on the two lowest energy conformations using the modified Karplus equation.[43]

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