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SYNTHESIS OF THE INDOLIZIDINE ALKALOID SWAINSONINE FROM D-GLUCOSE

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ABSTRACT

Since the stereochemistry of the alkaloid exactly matches that of 3-amino-3-deoxy-D-mannose, the latter compound is an ideal chiron for the synthesis of the former. Selective tosylation of methyl 3-benzyloxycarbonylamino-3-deoxy-α-D-mannopyranoside, followed by removal of the benzyloxycarbonyl group and cyclisation, afforded the 3,6-imine which was converted into its benzyloxycarbonyl derivative. Hydrolysis of the glycosidic group then afforded 3,6-benzyloxycarbonylimino-3,6-dideoxy-D-mannose. The attempted addition of a C_2 unit at C-1 by the Wittig or the Wadsworth–Emmons–Horner reaction either failed to give the required product or was followed by Michael addition of one of the hydroxyl groups to the newly formed double-bond. 2,4,5-Tri-*O*-acetyl-3,6-benzyloxycarbonylimino-3,6-dideoxy-*aldehydo*-D-mannose was prepared *via* the diethyl dithioacetal and condensed with ethoxycarbonylmethylenetriphenylphosphorane to give the Wittig adduct in good yield, which, on catalytic reduction, underwent hydrogenation of the double bond, loss of the benzyloxycarbonyl group, and attack of the released amino group on either the terminal ethoxycarbonyl group or the 2-*O*-acetyl group to give a mixture of the required cyclic lactam and the *N*-acetyl derivative. Reduction of the lactam with the borane–dimethyl sulphide complex afforded swainsonine triacetate, from which the parent alkaloid was obtained.

INTRODUCTION

Recently, several hydroxylated indolizidine alkaloids have been isolated from various plants and micro-organisms, which have created much interest because of their interesting biological activities[1–5]. For example, swainsonine (**1**), which has been isolated from the plants *Swainsona canescens* (Benth.)[1] and *Astralagus lentiginosus*[2], and from the fungus *Rhizoctonia leguminicola*[3], is a particularly potent inhibitor of α-D-mannosidase[6] and affects the processing of glycoproteins[7]. In some mammals, the alkaloid is a potent toxin inducing a condition similar to the genetic disease mannosidosis. As a result, the alkaloid may be used as a means of experimentally inducing this rare condition in animals, thereby permitting a study of this debilitating disease. The alkaloid has been shown to be (1*S*,2*R*,8*R*)-1,2,8-tri-

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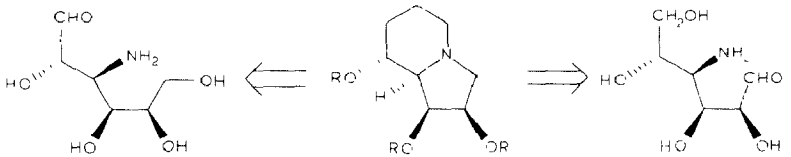
hydroxyoctahydroindolizine (**1**) by spectroscopic and X-ray methods[8]. One point of interest concerning the stereochemistry of the alkaloid, which has not previously been commented on, is that the 7,8-diacetate adopts a configuration at nitrogen, as indicated by the X-ray structure analysis[8], such that the five-membered ring is *trans*-fused to the six-membered ring, whereas *cis*-fusion in such circumstances is usually preferred with other fused-ring bicycles. There may be special factors which force the diacetate to adopt this form, but it cannot be assumed that swainsonine (**1**) adopts the same form since inversion at pyramidal nitrogen is not difficult under normal circumstances. Indeed, the rather large difference between the optical rotations[3] of **1** and **2** [−87° (methanol) and +7° (methanol), respectively] indicates that swainsonine may well differ from its acetylated derivatives in the stereochemistry at nitrogen.

RESULTS AND DISCUSSION

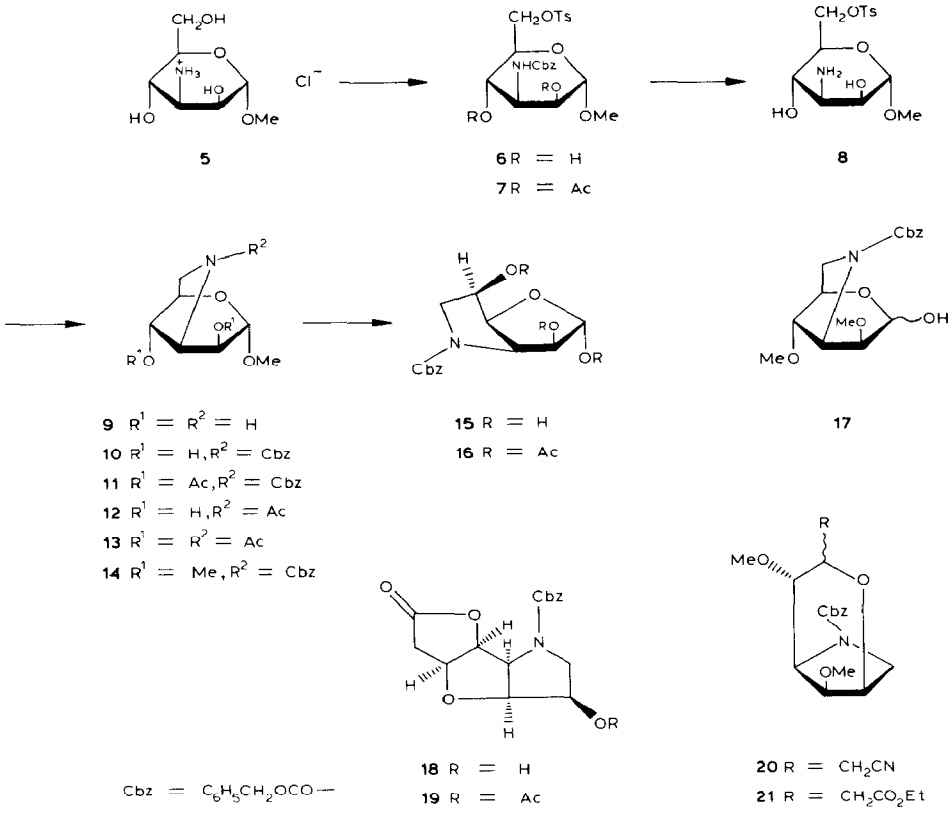
Retrosynthetic reasoning indicated that the appropriate chiral precursors of swainsonine (**1**) would be either 3-amino-3-deoxy-D-mannose (**3**) or 4-amino-4-deoxy-D-mannose (**4**) since there would be no need to change the existing chiral centres or create new ones. There would simply be a need to form the pyrrolidine ring by linking the 3-(or 4)-amino group to the appropriate terminal position of the hexose and then to introduce a $-CH_2CH_2-$ unit between the other terminal carbon atom and the nitrogen atom to give the correct skeletal and stereochemical arrangement in swainsonine. Since the publication of our preliminary communication[9], there have been at least three other syntheses reported of which two utilise the 4-amino-4-deoxy-D-mannose route[10,11] and one[12] employs the 3-amino-3-deoxy-D-mannose pathway, thus reflecting the interest in these and related alkaloids.



3 1 R = H 2 R = Ac 4

Methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (**5**) is readily available from methyl α-D-glucopyranoside in 20–25% yield *via* the dialdehyde–nitromethane procedure[13] and appeared to be the most readily available derivative of **3**. When **5** was treated with benzyloxycarbonyl chloride and the crude *N*-benzyloxycarbonyl derivative was immediately treated with an equimolar quantity of tosyl chloride, it gave the crystalline 6-tosylate **6** in 82% yield overall, which was also characterised as the 2,4-diacetate **7**. Removal of the benzyloxycarbonyl group from **6** was accomplished by catalytic hydrogenolysis, and the 3-aminopyranoside

8, without purification, was treated with boiling ethanolic sodium acetate to give the 3,6-imino derivative **9**, which was immediately converted into its syrupy *N*-benzyloxycarbonyl derivative **10** (73% from **6**). Similarly, *N*-acetylation of **9** afforded the crystalline *N*-acetyl derivative **12**, and *N,O*-acetylation gave the syrupy acetyl derivative **13**.



Hydrolysis of the iminomannoside **10** with mineral acid gave the crystalline sugar **15** (52%), which was characterised as the crystalline triacetate **16**. The ^{1}H-n.m.r. spectrum of **16** indicated that it was a single anomer, probably α, since the H-1 resonance was a singlet at δ 6.11. When **15** was condensed with ethoxycarbonylmethylenetriphenylphosphorane in boiling ethanol, the main product was syrupy **18** which was converted into the crystalline acetate **19** (55% from **15**). However, the product was not the desired adduct **33**, since the ^{1}H-n.m.r. spectrum indicated that it did not possess an ethoxycarbonyl group and that only one *O*-acetyl group was present. The i.r. spectrum was indicative of three distinctly different carbonyl groups with stretching frequencies of 1710, 1745, and 1785 cm^{-1}, and neither of these spectroscopic techniques indicated the presence of an olefinic group. The presence of only one acetyl group suggested that the other two hydroxyl

groups had been substituted, and the carbonyl-stretching frequency at 1785 cm^{-1} was characteristic of a five-membered lactone ring suggesting that HO-2 had attacked the ethoxycarbonyl group to form a lactone. The absence of an olefinic group suggested that the initial Wittig adduct had undergone a Michael addition with HO-4 to form the tricyclic lactone **18**. This suggestion was supported by the mass spectrum of **19** which contained a signal for $(M + 1)^+$ at *m/z* 362. It has been assumed that the ring junctions of **18** would need to be *cis* so that only one isomer would be formed. Michael additions of this type occur very commonly in Wittig adducts in which there is a suitably placed hydroxyl group[14].

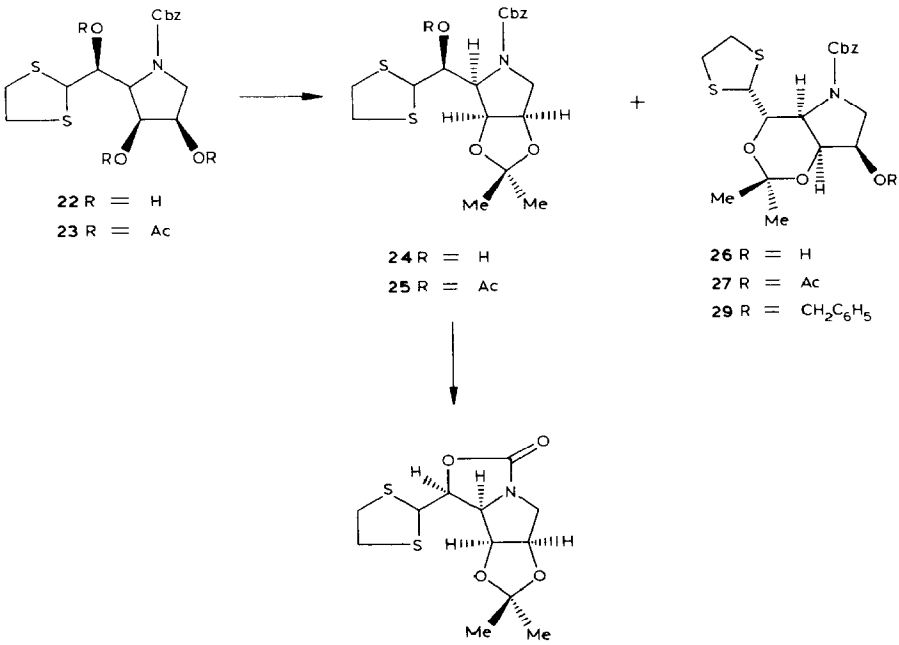
The tricyclic lactone **18** was of no further interest in the synthesis at hand, but indicated the desirability of protecting HO-2 and HO-4. Consequently, **10** was converted into the 2,4-dimethyl ether **14**, which was then hydrolysed with acid to give the syrupy free hexose **17** (31% from **10**). When **17** was condensed with ethoxycarbonylmethylenetriphenylphosphorane in ethanol, the ^{1}H-n.m.r. spectrum of the product (59%) indicated the absence of olefinic protons and the presence of an ethoxycarbonyl group, showing that the initial Wittig reaction had been followed by a Michael addition of HO-5 to give the bicyclic ester **21**. This conclusion was supported by the lack of i.r. absorption for hydroxyl and the presence of a signal for M^+ at *m/z* 393 in the mass spectrum. The product appeared to be homogeneous in t.l.c., but its ^{1}H-n.m.r. spectrum at elevated temperature indicated that it was a mixture of two isomers in the ratio ~2:1. Similarly, reaction of **17** with the anion derived from diethyl cyanomethylphosphonate afforded 39% of an analogous product **20**, which was also probably a mixture of isomers.

These results indicated the desirability of either protecting all three of the hydroxyl groups prior to the Wittig reaction or using a Wittig reagent which would give an adduct incapable of undergoing the Michael reaction. However, when **17** was condensed with the anion derived from the reaction of diethyl 2,2-diethoxyethylphosphonate with sodamide, no reaction took place. Variation of the solvent or the temperature and the use of a large excess of the reagent failed to promote reaction.

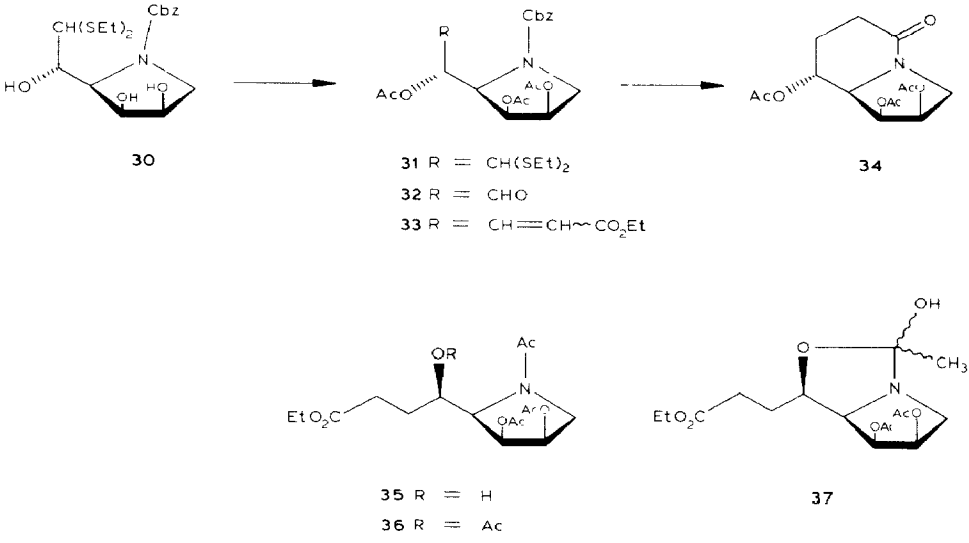
An alternative way of introducing the $-CH_2CH_2-$ group, namely, by alkylation[15] of a lithio derivative of the ethylene dithioacetal **22** with 2-bromo-1,1-dimethoxyethane, was then investigated. Accordingly, the iminohexose **15** was condensed with ethane-1,2-dithiol in the presence of acid to give the syrupy dithioacetal **22** (80%) as a syrup. Reaction of **22** with 2,2-dimethoxypropane in the presence of an acid catalyst afforded a mixture of the isopropylidene derivatives **24** and **26** which could not be separated by chromatography, except after acetylation. Unfortunately, the reaction of **22** with acetone in the presence of sulphuric acid also gave the same mixture of products in the same ratio. The two crystalline, acetylated isopropylidene derivatives **27** and **25** were obtained in yields of 26% and 51%, respectively, and shown to be the 2,4- and the 4,5-*O*-isopropylidene derivatives, respectively. The structures of the two compounds were based mainly on the ^{13}C-n.m.r. spectrum, in which the isopropylidene acetal carbon resonated at 100.5

p.p.m. in the 2,4-isomer and at 114.3 p.p.m. in the 4,5-isomer; these respective values are typical for a skewed six-membered acetal ring and for a five-membered isopropylidene ring fused to a five-membered ring[16]. The presence of such a large proportion of **27** was unexpected and made the proposed route to swainsonine less attractive. The route was finally abandoned when benzylation of the mixture of **24** and **26** with sodium hydride and benzyl bromide was investigated. The major component of the product mixture was a 2,3-*O*,*N*-carbonyl derivative **28**, which was formed from **24** by nucleophilic attack of the 2-alkoxide group on the carbonyl group of the benzyloxycarbonyl group. The carbamate **28** could be obtained directly from **25** by treatment with methanolic sodium methoxide, when it crystallised directly from the reaction mixture. In addition to the formation of **28** from the benzylation, there were a further two products, of which one could be isolated crystalline in a yield of ~20% and the ^{1}H- and ^{13}C-n.m.r. spectra of which suggested that the 2,4-*O*-isopropylidene derivative **26** had undergone *O*-benzylation to give the required product **29**. In addition, the mass spectrum contained an ($M^+ - Me_2CO$) ion at *m/z* 443. The other product, which was only obtained in small quantities, was unstable and could not be identified.

The above results coupled with other considerations, such as the difficulties associated with the removal of the dithioacetal group (see below), indicated that the dithiane route would not be fruitful, and it was therefore decided to convert the dithioacetal **22** into the triacetate **23** and remove the dithioacetal group to generate the *aldehydo*-hexose **32**. However, **23** proved to be difficult to convert into **32** with



the usual reagent (mercuric chloride and cadmium carbonate) even under forcing conditions. This behaviour has been encountered previously with ethylene dithioacetals, and it has been noted that the diethyl dithioacetals were much more readily cleaved by this reagent[17]. Consequently, the diethyl dithioacetal **30** was prepared by reaction of **15** with ethanethiol in the presence of hydrochloric acid, which gave the crystalline dithioacetal **30** (74%). The syrupy triacetate **31** of **30** was readily converted into the *aldehydo*-hexose **32** in good yield, although its ^{1}H-n.m.r. spectrum was complex and, even at 95° in pyridine-d_5, two rotamers were still present. Reaction of **32** with ethoxycarbonylmethylenetriphenylphosphorane in acetonitrile gave the Wittig adduct **33** which appeared to be homogeneous in t.l.c., but the exceedingly complex ^{1}H-n.m.r. spectrum indicated that it was composed of a 1:1 mixture of the *E* and *Z* isomers, each of which existed as a mixture of non-separable isomers due to the restricted rotation about the N-$CO_2CH_2C_6H_5$ bond. The spectra of a solution of the rotamers in pyridine at 100° did not coalesce.



The configuration about the double bond in **33** was of no consequence since the next stage was hydrogenation. When the mixture of olefins **33** was hydrogenated (Pd/C), the benzyloxycarbonyl group was also removed. The released amino group then attacked both the ethoxycarbonyl group and AcO-2 to give a ~1:1 mixture of the cyclic lactam **34** and the product **35** of *O* → *N* acetyl migration, each isolated in a yield of ~25%. The ^{1}H-n.m.r. spectrum of **34** was virtually first-order at 400 MHz and was without the complication of restricted rotation about the amide bond. The ^{1}H-n.m.r. spectrum of **35** revealed three acetyl groups, and the complexity of the spectrum indicated that the nitrogen was acylated and therefore existed as two inseparable rotamers. There was also i.r. absorption for hydroxyl, but the location of the hydroxyl group could not be determined because of the

TABLE I

FIRST-ORDER ^{1}H-N M R DATA AT 250 MHz[a]

Atom	**7**[b]	**11**[c]	**13**[d,f]	**16**[e]	**23**[d]	**25**[d]	**28**[d]	**29**[e]	**31**[e]	**32**[e]
H-1	4.88d	4.97d	4.73d 4.65d	6.11s		5.04d	5.29d		4.12d	9.69d
H-2	5.46dd		5.04dd	5.29m	5.55dd	5.35dd	4.59dd	5.84d	5.69dd	5.85dd
H-3	4.89td	4.96d	4.47dd 4.44dd	4.70dd	4.47dd	4.87dd	3.81dd	4.43dd	4.69dd	4.78dd
H-4	5.65dd	5.24d		4.85dd	5.29dd	4.61dd	5.27dd	4.29dd	5.50dd	5.69dd
H-5	4.23ddd	3.65m		4.70dd	5.43td	4.77td	4.81td		5.31td	5.60ddd
H-6a	4.41d	4.00d	3.75dd	4.05dd	3.94m	4.02dd	3.89d	3.55dd	4.04dd	4.00dd
H-6b			3.69dd	3.26dd	3.51d	3.21dd	3.11dd		3.41dd	3.63dd
$J_{1,2}$	1.2	6.4	7.2	0		9.8	10.6		7.2	1.0
$J_{2,3}$	3.1		1.9		8.2	7.8	7.1	1.8	6.8	6.9
$J_{3,4}$	10.2	2.6	0.7	6.0	7.3	7.3	3.3	4.8	6.5	7.0
$J_{4,5}$	10.4	6.0		4.8	5.8	4.1	5.2	7.7	5.1	5.2
$J_{5,6a}$				5.3	2.6	5.0	0.7		6.7	5.5
$J_{5,6b}$				5.3	7.5	7 2	5.2		5.2	3.4
$J_{6a,6b}$			3.3	10.9		11 3	13.4	10.1	12.1	12.2

[a]Chemical shifts, δ scale; J in Hz. Most of the spectra, particularly those measured at room temperature, contained resonances due to the other rotamers. Even those obtained at elevated temperature were not always completely coalesced. The parameters reported are for the major rotamer except in the case of **13**, for which the two rotamers were in about equal proportions. [b]In pyridine-d_5 at room temperature. [c]In pyridine-d_5 at 90°. [d]In $CDCl_3$ at room temperature. [e]In $CDCl_3$ at 55°. [f]Comprised two rotamers in approximately equal amounts.

complexity of the ^{1}H-n.m.r. spectrum. However, considerations of the cyclic intermediate **37** necessary for the migration of any of the *O*-acetyl groups suggested that migration of AcO-2 would be the most favoured kinetically, since migration of AcO-4 and AcO-5 would involve formation of less-favourable, bridged bicyclic intermediates. Acetylation of **35** afforded the fully acetylated derivative **36**.

The final stages of the synthesis involved reduction of the lactam **34** and *O*-deacetylation. Preliminary attempts using lithium aluminium hydride achieved both steps simultaneously, but isolation difficulties were encountered. However, the use of the borane–dimethyl sulphide complex[18] resulted in selective reduction of the amide linkage to give 94% of tri-*O*-acetylswainsonine (**2**). However, two products were present in the early stages of the reaction, each of which was more mobile in t.l.c. than **34**. The more mobile product was slowly transformed into the slower-moving component **2** during 15–20 h. When the reaction mixture was processed after only 8 h, ~20% of the faster-moving product was isolated in addition to 71% of **2**. The compound had a ^{1}H-n.m.r. spectrum which was different from, and more complex than, that of **2**. However when the n.m.r. solution was stored, the faster-moving isomer was completely transformed into **2**. Although we have not investigated this behaviour fully, it appears probable that the two products are isomers which differ only in the configuration at nitrogen and are formed under kinetic control, which is followed by a slow, thermodynamically controlled conversion of one into the other.

Zemplén *O*-deacetylation of **2** gave crystalline swainsonine (**1**) in quantitative yield, which was identical with the natural product.

Although swainsonine has been synthesised from methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (**5**) in 3.2% overall yield, none of the yields has been optimised and the number of stages could be lessened, for example by the formation of the diethyl dithioacetal **30** directly from the glycoside **10**.

EXPERIMENTAL

All evaporations were conducted under reduced pressure, and optical rotations were measured on solutions in chloroform at 18–22°. Column chromatography was performed on Silica gel G (Merck 7734). ^{1}H-N.m.r. spectra (250 MHz) were recorded with a Bruker WH-250 spectrometer and ^{13}C-n.m.r. spectra with a Bruker WP-60 instrument. All chemical shifts are relative to internal Me_4Si. Mass spectra (e.i., 70 eV) were measured on a Kratos MS-24 spectrometer; the signal at *m/z* 91 was the base peak unless otherwise stated.

Methyl 3-benzyloxycarbonylamino-3-deoxy-6-O-tosyl-α-D-mannopyranoside (**6**). — To a solution of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride[13] (**5**; 10 g, 43.5 mmol) in 50% aqueous ethanol (80 mL) was added sodium hydrogencarbonate (8 g). The clear solution was cooled (ice bath), benzyloxycarbonyl chloride (10 mL, 70 mmol) was added portionwise, and the solution was stirred at room temperature for 2 h when t.l.c. (chloroform–methanol, 4:1) indicated that all of **5** had been converted into a faster-moving product. The reaction mixture was concentrated to dryness, the residue was extracted with ethanol, the extract was concentrated to dryness, and dry toluene was thrice evaporated from the residue to remove traces of hydroxylic solvents. A solution of the residual syrup in dry pyridine (100 mL) was stirred and cooled (ice-bath), and then treated dropwise with a solution of tosyl chloride (8.2 g, 43 mmol) in dry pyridine (30 mL). The mixture was stored at room temperature for 36 h when t.l.c. (chloroform–ethyl acetate, 2:1) revealed one major product and several minor products. The mixture was treated with a little ice and concentrated to dryness, and the last traces of pyridine were removed from the syrup by distillation of toluene therefrom. The syrupy residue was then purified by column chromatography (chloroform–ethyl acetate, 5:1) to give the major component which, on recrystallisation from ethanol, afforded **6** (17.1 g, 82%), m.p. 114–116°, $[\alpha]_D$ +65° (*c* 2.2) (Found: C, 54.45; H, 5.60; N, 2.76. $C_{22}H_{27}NO_9S$ calc.: C, 54.88; H, 5.61; N, 2.91%).

Acetylation of **6**, in the usual way (acetic anhydride–pyridine), afforded the syrupy diacetate **7** (95%), $[\alpha]_D$ +25° (*c* 1.2) (Found: C, 55.28; H, 5.49; N, 2.20. $C_{26}H_{31}NO_{11}S$ calc.: C, 55.22; H, 5.49; N, 2.48%). Mass spectrum: *m/z* 566 [0.1%, $(M + 1)^+$] and 534 [0.9, $(M^+ - OMe)$].

Methyl 3,6-benzyloxycarbonylimino-3,6-dideoxy-α-D-mannopyranoside (**10**). — A mixture of **6** (15 g, 31.2 mmol) and 10% Pd/C (~1.5 g) in ethanol (100 mL) was hydrogenated at 60 p.s.i. for 18 h, and then filtered. T.l.c. (chloroform–ethyl

acetate, 2:1) revealed no **6** but a non-mobile compound. Sodium acetate (10 g) was then added, and the mixture was heated under reflux for 8 h, cooled to room temperature, filtered, and concentrated to dryness. The residue was extracted three times with boiling ethyl acetate, and the combined extracts were concentrated to dryness to give crude **9** as a syrup that was immediately dissolved in 50% aqueous ethanol (70 mL), and sodium hydrogencarbonate (6 g) was added. The stirred mixture was cooled (ice-bath) and treated with benzyloxycarbonyl chloride (6 mL). After 2 h, t.l.c. (chloroform–methanol, 8:1) indicated that the reaction was complete and that one major product had been formed. The mixture was then filtered and concentrated to dryness, and the residue was purified by column chromatography (ethyl acetate–light petroleum, 4:1 initially, then 6:1) to give **10** as a syrup (7.0 g, 73%), $[\alpha]_D$ −16° (*c* 1.4) (Found: C, 58.52; H, 6.26; N, 4.16. $C_{15}H_{19}NO_6$ calc.: C, 58.25; H, 6.15; N, 4.53%).

Acetylation of **10**, in the usual way (acetic anhydride–pyridine), afforded the syrupy 2,4-diacetate **11** (71% yield after column chromatography using ether–light petroleum, 2:1), $[\alpha]_D$ +3° (*c* 4.8) (Found: C, 58.91; H, 6.24; N, 3.66. $C_{19}H_{23}NO_8$ calc.: C, 58.02; H, 5.85; N, 3.56%). Mass spectrum: *m/z* 394 [10%, $(M + 1)^+$], 362 [36, $(M^+ - OMe)$], and 333 [5.6, $(M^+ - HOAc)$].

*Methyl 3,6-benzyloxycarbonylimino-3,6-dideoxy-2,4-di-*O*-methyl-α-*D*-mannopyranoside* (**14**). — An excess of sodium hydride (0.6 g) was added to a solution of **10** (1.1 g, 3.56 mmol) in *N,N*-dimethylformamide (15 mL), and the mixture was stirred at room temperature for 30 min. Methyl iodide (1 mL) was then added dropwise to the stirred solution, and the mixture was stored for 1 h at room temperature, when t.l.c. (ethyl acetate–light petroleum, 5:1) revealed a major product and two slower-moving minor components. A few drops of ethanol were added followed by ice–water, the mixture was extracted three times with ether, and the combined extracts were washed well with water, dried ($MgSO_4$), and concentrated to dryness. The major component (0.8 g, 67%), isolated by column chromatography (ethyl acetate–light petroleum, 2:1), failed to crystallise and had $[\alpha]_D$ +30° (*c* 2.6) (Found: C, 60.55; H, 6.85; N, 4.08. $C_{17}H_{23}NO_6$ calc.: C, 60.53; H, 6.82; N, 4.15%).

*Methyl 3,6-acetylimino-3,6-dideoxy-α-*D*-mannopyranoside* (**12**). — Crude **9** [prepared as above from **6** (10 g)] was dissolved in methanol (50 mL) and treated with acetic anhydride (8 mL). The solution was kept at room temperature for 1 h when t.l.c. (chloroform–methanol, 4:1) indicated that the reaction was complete and revealed a major and several minor products. The mixture was concentrated and the residue was subjected to chromatography on a dry-packed[19] column of silica gel using first ethyl acetate–acetone (1:1) and then ethyl acetate–methanol (5:1) to give the major component which was crystallised from ethanol to give **12** (2.7 g, 29%), m.p. 166–167°, $[\alpha]_D$ +25° (*c* 3.8) (Found: C, 49.98; H, 6.89; N, 6.3. $C_9H_{15}NO_5$ calc.: C, 49.77; H, 6.91; N, 6.45%).

The syrupy 2,4-diacetate **13**, prepared (69%) from **9** by conventional acetylation followed by column chromatography (ethyl acetate–acetone, 8:1), had $[\alpha]_D$

+23° (*c* 1.8) (Found: C, 51.75; H, 6.18; N, 4.60. $C_{13}H_{19}NO_7$ calc.: C, 51.83; H, 6.31; N, 4.65%). Mass spectrum: *m/z* 302 [60%, $(M + 1)^+$], 270 [11, $(M^+ - OMe)$], 241 [8.2, $(M^+ - HOAc)$], and 43 (100).

3,6-Benzyloxycarbonylimino-3,6-dideoxy-D-*mannofuranose* (**15**). — Compound **10** (1.4 g, 4.5 mmol) was heated at 95–100° with ~0.4M hydrochloric acid (25 mL) for 16 h, after which t.l.c. (ethyl acetate) indicated that the reaction was complete and that a slower-moving product had been formed. The mixture was neutralised by the addition of solid sodium hydrogencarbonate, filtered, and concentrated to dryness. The crude syrup so obtained was purified by column chromatography with ethyl acetate–acetone (4:1) to give **15** as a syrup which readily crystallised from ethanol (0.7 g, 52%); m.p. 138–139°, $[\alpha]_D$ −11° (*c* 0.25, methanol) (Found: C, 56.81; H, 5.73; N, 4.35. $C_{14}H_{17}NO_6$ calc.: C, 56.95; H, 5.76; N, 4.75%).

The imine **15** was acetylated in the usual way (acetic anhydride–pyridine) to give the triacetate **16** in 70% yield, m.p. 97–98° (from ethanol), $[\alpha]_D$ +33° (*c* 2) (Found: C, 56.92; H, 5.45; N, 3.37. $C_{20}H_{23}NO_9$ calc.: C, 57.0; H, 5.46; N, 3.33%). Mass spectrum: *m/z* 362 [9.7%, $(M^+ - OAc)$] and 361 [6, $(M^+ - HOAc)$].

*3,6-Benzyloxycarbonylimino-3,6-dideoxy-2,4-di-*O-*methyl*-D-*mannopyranose* (**17**). — To a solution of **14** (1.6 g, 4.75 mmol) in a little methanol was added 1:1 ethanol–water (50 mL) containing 4 mL of conc. hydrochloric acid. The stirred mixture was then heated under reflux for 16 h, when t.l.c. (ethyl acetate–light petroleum, 5:1) indicated the formation of a major slower-moving product together with two minor components. The mixture was neutralised with barium carbonate, filtered, and concentrated to dryness. The crude residue was extracted with 1:1 chloroform–methanol and, after filtration, the extracts were concentrated to dryness. The syrup was then purified by column chromatography (ethyl acetate–light petroleum, 2:1) to give **17** as a syrup (0.7 g, 46%), $[\alpha]_D$ +11.6 → −24° (*c* 2) (Found: C, 59.43; H, 6.84; N, 4.48. $C_{16}H_{21}NO_6$ calc.: C, 59.44; H, 6.5; N, 4.33%).

Acetylation in the usual way (acetic anhydride–pyridine) gave the monoacetate (88% yield after column chromatography with ether–light petroleum, 3:1), $[\alpha]_D$ +3.3° (*c* 2.4) (Found: C, 60.34; H, 6.29; N, 4.33. $C_{18}H_{23}NO_7$ calc.: C, 59.18; H, 6.30; N, 3.83%).

Reaction of the 3,6-iminohexose **15** *with ethoxycarbonylmethylenetriphenylphosphorane.* — A mixture of **15** (0.295 g, 1 mmol), ethoxycarbonylmethylenetriphenylphosphorane (0.765 g, 2.1 mmol), and ethanol (8 mL) was heated under reflux for 30 min, when t.l.c. (chloroform–methanol, 8:1) indicated the complete conversion of **15** into a single faster-moving product. Silica gel was added to the mixture, the solvent was evaporated, and the residue was placed on the top of a dry-packed column of silica gel. Elution with chloroform removed non-carbohydrate material and a minor faster-moving unindentified carbohydrate component, and ethyl acetate–acetone (8:1) then eluted the major component, 3,6-anhydro-5,8-benzyloxycarbonylimino-2,5,8-trideoxy-D-*glycero*-D-*galacto*-octono-1,4-lactone (**18**), isolated as a syrup (0.2 g). Acetylation of **18** and column chromatography (ethyl acetate–light petroleum, 3:1) of the product afforded the acetate **19** (0.2 g,

55%), m.p. 165–167° (from ethanol), $[\alpha]_D$ −116° (*c* 1) (Found: C, 59.68; H, 5.29; N, 3.79. $C_{18}H_{19}NO_7$ calc.: C, 59.83; H, 5.26; N, 3.88%). Mass spectrum: *m/z* 362.1242 [2.6%, calc. for $(M^+ + 1)$ 362.1240], 318 [2.4, $(M^+ - Ac)$], and 301 [6.8, $(M^+ - HOAc)$].

Reactions of the 2,4-dimethyl ether **17**. — (*a*) *With ethoxycarbonylmethylenetriphenylphosphorane.* A solution of **17** (0.7 g, 2.17 mmol) in ethanol (15 mL) was treated with ethoxycarbonylmethylenetriphenylphosphorane (1 g) and the solution was heated under reflux for 90 min, when t.l.c. (ethyl acetate–light petroleum, 5:1) indicated that the reaction was complete and that a faster-moving product had been formed. The mixture was concentrated to dryness and the residue was fractionated by column chromatography (ethyl acetate–light petroleum, 1:1) to give ethyl 3,7-anhydro-5,8-benzyloxycarbonylimino-2,5,8-trideoxy-4,6-di-*O*-methyl-D-*glycero*-D-*galacto* (and/or -*talo*)-octonate (**21**; 0.5 g, 59%), $[\alpha]_D$ +5° (*c* 1.5) (Found: C, 60.92; H, 6.96; N, 3.26. $C_{20}H_{27}NO_7$ calc.: C, 61.07; H, 6.87; N, 3.56%). Mass spectrum: *m/z* 394 [1.3%, $(M + 1)^+$] and 393 (2.2, M^+).

(*b*) *With diethyl cyanomethylphosphonate.* Diethyl cyanomethylphosphonate (0.33 g, 1.86 mmol) was added dropwise to a slurry of sodium hydride (0.0446 g, 1.86 mmol) in dry 1,2-dimethoxyethane (5 mL), and the mixture was stirred at room temperature until the evolution of hydrogen ceased (~20 min). A solution of **17** (0.6 g, 1.86 mmol) in dry 1,2-dimethoxyethane (3 mL) was then added in small portions and the mixture was stirred at room temperature for 1 h, after which t.l.c. (ethyl acetate–light petroleum, 5:1) revealed the formation of a faster-moving product. Water was added to the mixture, the product was extracted with ether in the usual way, and the syrupy product was purified by column chromatography (ethyl acetate–light petroleum, 2:1) to give syrupy 3,7-anhydro-5,8-benzyloxycarbonylimino-2,5,8-trideoxy-4,6-di-*O*-methyl-D-*glycero*-D-*galacto* (and/or -*talo*)-octono-nitrile (**20**; 0.25 g, 39%), $[\alpha]_D$ +27° (*c* 1.8) (Found: C, 62.59; H, 6.39; N, 8.25. $C_{18}H_{22}N_2O_5$ calc.: C, 62.43; H, 6.36; N, 8.09%). Mass spectrum: *m/z* 346 (3.2%, M^+).

*3,6-Benzyloxycarbonylimino-3,6-dideoxy-*D*-mannose ethylene dithioacetal* (**22**). — (*a*) To a suspension of **15** (0.5 g, 1.7 mmol) in ethane-1,2-dithiol (0.5 mL) was added conc. hydrochloric acid (0.2 mL), and the mixture was stirred vigorously. After ~15 min, the mixture became homogeneous and t.l.c. (chloroform–methanol, 8:1) indicated that the reaction was complete and that one major and at least three minor products had been formed. Ice–water was then added and the mixture was extracted three times with chloroform. The combined extracts were washed well with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated to dryness. The resulting syrup was purified by column chromatography (chloroform–ethyl acetate, 4:1) to give **22** as a syrup (0.5 g, 80%), $[\alpha]_D$ −23° (*c* 1.7) (Found: C, 50.97; H, 6.09; N, 3.35. $C_{16}H_{21}NO_5S_2$ calc.: C, 51.75; H, 5.66; N, 3.77%).

The triacetate **23** of **22**, after purification by column chromatography (ether–light petroleum, 3:2), was obtained as a syrup, $[\alpha]_D$ +11.5° (*c* 2.3) (Found: C,

53.20; H, 5.46; N, 2.45. $C_{22}H_{27}NO_8S_2$ calc.: C, 53.12; H, 5.43; N, 2.82%). Mass spectrum: *m/z* 498 [0.9%, $(M^+ + 1)$] and 437 [3.9, $(M^+ - HOAc)$].

(*b*) To a stirred suspension of **15** (0.1 g, 0.34 mmol) in chloroform (5 mL) was added ethane-1,2-dithiol (0.1 mL) followed immediately by boron trifluoride etherate (0.1 mL). The mixture was stirred at room temperature for 2 h when t.l.c. (chloroform–methanol, 8:1) indicated that the reaction was complete. The mixture was concentrated to dryness and the resulting syrup was purified by column chromatography (ethyl acetate–acetone, 4:1) to give **22** (0.1 g, 80%) identical with the product in (*a*).

Reaction of **22** *with 2,2-dimethoxypropane.* — To a solution of **22** (0.5 g, 1.35 mmol) in 2,2-dimethoxypropane (10 mL) was added toluene-*p*-sulphonic acid (10 mg), and the mixture was heated under reflux for 20 min when t.l.c. (chloroform–ethyl acetate, 7:1) indicated the formation of two products of similar mobilities. A small amount of silica gel was added to the mixture which was concentrated to dryness, and the residue was applied to the top of a dry-packed column. Elution with ether–light petroleum (1:1) furnished a mixture (0.55 g, 99%) of the two isopropylidene derivatives which was acetylated, and the products were subjected to column chromatography (ether–light petroleum, 1:2). The minor product was eluted first and crystallised from ethanol to give 5-*O*-acetyl-3,6-benzyloxycarbonylimino-3,6-dideoxy-2,4-*O*-isopropylidene-D-mannose ethylene dithioacetal (**27**; 0.17 g, 26%), m.p. 143–144°, $[\alpha]_D$ +21° (*c* 1.6) (Found: C, 55.45; H, 6.02; N, 2.76. $C_{21}H_{27}NO_6S_2$ calc.: C, 55.63; H, 5.96; N, 3.09%). Mass spectrum: *m/z* 454 [0.1%, $(M^+ + 1)$].

Eluted second was 2-*O*-acetyl-3,6-benzyloxycarbonylimino-3,6-dideoxy-4,5-*O*-isopropylidene-D-mannose ethylene dithioacetal (**25**; 0.34 g, 56%), m.p. 137–138°, $[\alpha]_D$ −23° (*c* 2.3) (Found: C, 55.48; H, 5.96; N, 3.11. $C_{21}H_{27}NO_6S_2$ calc.: C, 55.63; H, 5.96; N, 3.09%). Mass spectrum: *m/z* 438 [0.5%, $(M^+ - Me)$].

When **22** was stirred overnight at room temperature with acetone containing 1% of sulphuric acid, t.l.c. indicated that the same isopropylidene derivatives had been formed in a similar ratio.

Benzylation of the mixture of isopropylidene dithioacetals **24** *and* **26**. — A stirred mixture of the above mixture of isopropylidene derivatives (0.8 g) in dry *N,N*-dimethylformamide (15 mL) and benzyl bromide (2 mL) was cooled (ice-bath) and treated with sodium hydride (0.5 g) in small portions during ~5 min. The mixture was then kept at 0° for 15 min, when t.l.c. (ether–light petroleum, 2:1) indicated that all of the starting materials had reacted and formed a slower-moving major product together with two faster-moving products. Water was added, and the precipitated solid was collected and recrystallised from ethanol to give needles of 2,3-*O,N*-carbonyl-3,6-dideoxy-3,6-imino-4,5-*O*-isopropylidene-D-mannose ethylene dithioacetal (**28**, 0.3 g), m.p. 233–234°, $[\alpha]_D$ −24° (*c* 2.9) (Found: C, 47.61; H, 5.31; N, 4.57. $C_{12}H_{17}NO_4S_2$ calc.: C, 47.52; H, 5.61; N, 4.62%). Mass spectrum: *m/z* 304 [1.5%, $(M^+ + 1)$] and 303 (3.3, M^+).

The carbamate **28** could also be obtained (70%) by treatment of **25** with methanolic sodium methoxide.

The liquor obtained after the filtration of **28** contained the faster-moving components, which were extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated to dryness. The resulting syrup was subjected to column chromatography (light petroleum and then light petroleum–ether, 3:1). Eluted first was 5-*O*-benzyl-3,6-benzyloxycarbonylimino-3,6-dideoxy-2,4-*O*-isopropylidene-D-mannose ethylene dithioacetal (**29**, 0.2 g), m.p. 158–160° (from ethanol), $[\alpha]_D$ +1.3° (*c* 1.6) (Found: C, 62.01; H, 6.12; N, 2.72. $C_{26}H_{31}NO_5S_2$ calc.: C, 62.27; H, 6.19; N, 2.79%). Mass spectrum: *m/z* 443 [0.4%, ($M^+ - Me_2CO$)].

Eluted later was a small amount of another compound which was inadequately characterised because it was unstable.

3,6-Benzyloxycarbonylimino-3,6-dideoxy-D-*mannose diethyl dithioacetal* (**30**). — Conc. hydrochloric acid (3 mL) was added dropwise to a vigorously stirred suspension of **15** (0.5 g, 1.7 mmol) in ethanethiol (1 mL). After 15 min, the mixture was neutralised with ice-cold aqueous sodium hydrogencarbonate, and the solid so obtained was filtered off and was sufficiently pure for the next stage. The diethyl dithioacetal (0.5 g, 74%) obtained by elution from a short column of silica gel (ethyl acetate–light petroleum, 1:1) had m.p. 98–100° (from ether), $[\alpha]_D$ −61° (*c* 1) (Found: C, 53.71; H, 6.78; N, 3.52. $C_{18}H_{27}NO_5S_2$ calc.: C, 53.86; H, 6.73; N, 3.49%).

Conventional acetylation of the crude dithioacetal obtained from 1.0 g of **15** gave a syrupy product which was sufficiently pure for the next stage; purification by column chromatography (ether–light petroleum, 1:1) gave **31** as a colourless syrup (1.3 g, 73%), $[\alpha]_D$ +17° (*c* 1.6) (Found: C, 54.93; H, 6.28; N, 2.70. $C_{24}H_{33}NO_8S_2$ calc.: C, 54.65; H, 6.26; N, 2.66%). Mass spectrum: *m/z* 467 [1.8%, (M^+ − HOAc)].

*2,4,5-Tri-*O*-acetyl-3,6-benzyloxycarbonylimino-3,6-dideoxy*-aldehydo-D-*mannose* (**32**). — To a solution of **31** (0.55 g, 1.04 mmol) in 50% aqueous acetone (15 mL) was added mercuric chloride (0.8 g) and cadmium carbonate (0.8 g), and the stirred mixture was heated under reflux for 30 min when t.l.c. (ether–light petroleum, 4:1) indicated that some **31** remained. More (0.4 g) of each inorganic salt was added and the reaction was continued for a further 30 min when t.l.c. indicated that all of the **31** had reacted. The mixture was filtered through Hyflo Supercell and concentrated to dryness. The last traces of water were removed by distillation of toluene from the residue, since evaporation of ethanol therefrom led to the formation of the diethyl acetal. The residue was extracted with acetone–chloroform (1:1), and the extract was filtered and concentrated to dryness. The resulting syrup was purified by column chromatography (ether–light petroleum, 1:1 initially and then 3:1) which afforded **32** as a colourless syrup (0.5 g, 96%), $[\alpha]_D$ −3° (*c* 5.8) (Found: C, 57.00; H, 5.30; N, 3.17. $C_{20}H_{23}NO_9$ calc.: C, 57.00; H, 5.46; N, 3.33%). Mass spectrum: *m/z* 422 [0.2%, (M^+ + 1)].

*Ethyl 4,6,7-tri-*O*-acetyl-5,8-benzyloxycarbonylimino-2,3,5,8-tetradeoxy*-D-manno-*oct-2-enonate* (**33**). — A solution of **32** (0.7 g, 1.66 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (1.16 g, 3.32 mmol) in acetonitrile (12 mL)

was heated under reflux for 15 min. T.l.c. (ether) then indicated that the reaction was complete and that a faster-moving product had been formed. Silica gel was added to the mixture which was then concentrated to dryness, and the residue was applied to the top of a dry-packed column. Elution with ether–light petroleum (3:2) afforded the faster-moving minor products, and elution with a 2:1 solvent mixture then furnished the pure syrupy Wittig-adduct as an *E,Z*-mixture **33** (0.7 g, 86%) which could not be further fractionated by column chromatography and had $[\alpha]_D$ +26.5° (*c* 3.8) (Found: C, 58.36; H, 5.90; N, 2.59. $C_{24}H_{29}NO_{10}$ calc.: C, 58.66; H, 5.91; N, 2.85%). Mass spectrum: *m/z* 492 [0.1%, $(M^+ + 1)$].

Catalytic hydrogenation of **33**. — The above *E,Z*-mixture **33** (1 g, 2.04 mmol) was hydrogenated in ethanol (20 mL) containing glacial acetic acid (~0.2 mL) over 10% Pd/C (0.3 g) at 60 p.s.i. for 2 h. T.l.c. (ethyl acetate–acetone, 4:1) then indicated that **33** had been converted into two slower-moving products in the ratio ~1:1. The mixture was filtered and concentrated to dryness, and the residue was subjected to column chromatography (ethyl acetate–acetone, 5:1). Eluted first was 4,6,7-tri-*O*-acetyl-2,3,5,8-tetradeoxy-5,8-imino-D-*manno*-octono-1,5-lactam (**34**; 0.16 g, 25%), m.p. 143–145° (from ether), $[\alpha]_D$ −12° (*c* 0.5) (Found: C, 53.44; H, 6.06; N, 4.21. $C_{14}H_{19}NO_7$ calc.: C, 53.67; H, 6.07; N, 4.47%). Mass spectrum: *m/z* 314 [1%, $(M + 1)^+$] and 194 [15.2, $(M^+ - OAc - HOAc)$]. ^{1}H-N.m.r. data ($CDCl_3$, 400 MHz): δ 5.52 (dd, 1 H, $J_{5,6}$ 3, $J_{6,7}$ 3.7 Hz, H-6), 5.31 (ddd, 1 H, $J_{7,8a} = J_{7,8b} = 9$ Hz, H-7), 5.03 (ddd, 1 H, $J_{4,3a}$ 11.25 Hz, $J_{4,3e}$ 4.6, $J_{4,5}$ 9.1 Hz, H-4), 3.85 (dd, 1 H, $J_{8a,8b}$ 12 Hz, H-8a), 3.78 (dd, 1 H, H-5), 3.53 (dd, 1 H, H-8b), 2.58 (ddd, 1 H, $J_{2a,2e}$ 18.3 Hz, $J_{2e,3e}$ 3.0 Hz, $J_{2e,2a}$ 7 Hz, H-2*e*), 2.50 (ddd, 1 H, $J_{1a,2a}$ 11 Hz, $J_{1a,2e}$ 5.0 Hz, H-2*a*), 2.18 (cm, 1 H, H-3*e*), and 1.89 (cm, 1 H, H-3*a*).

Eluted subsequently was syrupy ethyl 6,7-di-*O*-acetyl-5,8-acetylimino-2,3,5,8-tetradeoxy-D-*manno*-octonate (**35**), $[\alpha]_D$ −32.5° (*c* 3.6) (Found: C, 53.11; H, 6.83; N, 4.04. $C_{16}H_{25}NO_8$ calc.: C, 53.48; H, 6.96; N, 3.90%).

The fully acetylated derivative **36** of **35**, obtained in quantitative yield after column chromatography (ethyl acetate–acetone, 5:1), had $[\alpha]_D$ +18° (*c* 0.8) (Found: C, 53.49; H, 6.59; N, 3.47. $C_{18}H_{27}NO_9$ calc.: C, 53.86; H, 6.73; N, 3.49%). Mass spectrum: *m/z* 402 [15%, $(M + 1)^+$] and 358 [29.3, $(M^+ - Ac)$].

*Tri-*O*-acetylswainsonine* (**2**). — Under an atmosphere of dry nitrogen, the borane–dimethyl sulphide complex (0.2 mL) was added to a stirred solution of **34** (0.1 g, 0.32 mmol) in anhydrous tetrahydrofuran (10 mL). The mixture was then stirred under nitrogen at room temperature and monitored by t.l.c. (ethyl acetate–acetone, 2:1). Initially, two products were formed but, on storage of the mixture, the faster-moving product was slowly converted into the other. After ~8 h when both products were still present, the mixture was diluted with water and extracted three times with chloroform, and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (light petroleum–ethyl acetate, 3:2) gave the faster-moving component (20 mg); the slower-moving component, swainsonine triacetate (**2**; 68 mg, 71%), eluted with a 1:1 solvent mixture, had $[\alpha]_D$ +6° (*c* 0.5) (Found: C, 56.30; H, 7.33; N, 4.51.

$C_{14}H_{21}NO_6$ calc.: C, 56.19; H, 7.02; N, 4.68%). Mass spectrum: *m/z* 300 [38%, $(M + 1)^+$], 299 (0.6, M^+), and 239 [46, $(M^+ - HOAc)$]. ^{1}H-N.m.r. data ($CDCl_3$, 250 MHz): δ 5.52 (dd, 1 H, $J_{1,2}$ 6.5, $J_{1,8a}$ 4.2 Hz, H-1), 5.21 (ddd, 1 H, $J_{2,3a}$ 1.7, $J_{2,3b}$ 7.3 Hz, H-2), 4.96 (ddd, 1 H, $J_{8,8a}$ 9.5, $J_{8,7a}$ 11.0, $J_{8,7e}$ 5.0 Hz, H-8), 3.17 (dd, 1 H, $J_{3a,3b}$ 11.2 Hz, H-3a), 3.06 (dt, 1 H, $J_{5e,5a}$ 10.5, $J_{5e,6e} = J_{5e,6a}$ 3 Hz, H-5*e*), 2.57 (dd, 1 H, H-3b), 2.15 (dd, 1 H, H-8a), 2.09, 2.05, 1.99 (3 s, each 3 H, 3 Ac), and 1.65–2.00 (m, 5 H, H-5*a*,6,6′,7,7′); lit.[3] $[\alpha]_D$ +7°.

When the reaction was repeated and the mixture left overnight at ~4°, the faster-moving component was completely converted into **2**, which was then obtained in improved yield (94%).

Swainsonine (**1**). — A solution of **2** (0.13 g, 0.43 mmol) in dry methanol (5 mL) was treated with a few drops of methanolic sodium methoxide. After 3 h, t.l.c. (acetone–chloroform–water–conc. ammonia, 75:12.5:10:2.5) showed that the reaction was complete and that a single compound had been formed with the mobility of swainsonine. The mixture was then passed through a pad of silica gel, which was washed with a little methanol. Concentration of the combined filtrate and washings afforded a quantitative yield of **1** (0.075 g). Sublimation *in vacuo* at 80–100° afforded pure **1**, m.p. 146°, $[\alpha]_D$ −84°; lit.[3] m.p. 144–145°, $[\alpha]_D$ −87.2° (*c* 0.5, methanol), which was identical (i.r., t.l.c., m.p. and mixture m.p., and biological activity) with an authentic specimen provided by Dr. B. G. Winchester. Mass spectrum: *m/z* 174 [39%, $(M^+ + 1)$], 173 (22.5, M^+), and 155 [32.5, $(M^+ - H_2O)$].

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