Synthesis of nitrogen-containing unsaturated carbohydrates *via* an allyl cyanate-to-isocyanate rearrangement

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A new method for the synthesis of 4-amino-D-hex-2-enopyranosides and 2-amino-D-hex-3-enopyranosides has been developed. The key feature in this method involves construction of the allylamine moiety in the pyranose framework by employing an allyl cyanate-to-isocyanate rearrangement.

Introduction

Over the last few years we have been concerned with the development of both the synthesis of allyl cyanate and the [3,3] sigmatropic rearrangement. This reaction offers an efficient transformation of allyl alcohols into allylamines in a highly stereospecific manner, as illustrated in Scheme 1.[1] Starting from the allyl alcohols **1**, dehydration of the allyl carbamates **2** provides the allyl cyanates **3**. These allyl cyanates **3** undergo a concerted [3,3] sigmatropic rearrangement below ambient temperature to furnish the allyl isocyanates **4**,[2] which are successively transformed into either the allylureas **5** or the *N*-allylacetamides **6**. As an application of this allyl cyanate-to-isocyanate rearrangement, we have initiated an investigation of the synthesis of nitrogen-containing unsaturated carbohydrates.

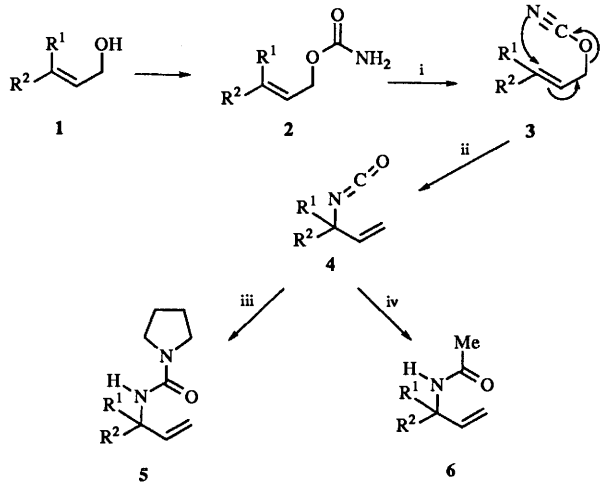
Several workers have reported the synthesis of nitrogen-containing unsaturated carbohydrates by using sigmatropic rearrangement; for example, the pioneer work of R. J. Ferrier in 1970 employed the [3,3] sigmatropic rearrangement of the allyl thiocyanate.[3] Similar strategies using the [3,3] sigmatropic rearrangement of allyl imidates has also appeared.[4]

In this report, we present a full description of an allyl cyanate-to-isocyanate rearrangement for the synthesis of nitrogen-containing unsaturated carbohydrates.[5]

Results and discussion

The starting unsaturated carbohydrates, hex-3- and hex-2-enopyranosides (**9**, **10**, **13**, **14**), were prepared as shown in Scheme 2. Synthesis of the hex-3-enopyranosides **9** and **10** began with the isopropyl glycoside **7**.[6] Treatment of compound **7** with lithium aluminium hydride and selective protection of the resulting diol **8** with *tert*-butyldimethylsilyl chloride (TBDMSCl) gave the hex-3-enopyranoside **9**. Inversion of the C-2 hydroxy group of compound **9** by the Mitsunobu reaction and hydrolysis of the resulting benzoate furnished the inverted hex-3-enopyranoside **10**.[7] The hex-2-enopyranoside **12** was prepared from tri-*o*-acetyl-D-glucal **11**[8] by employing Ferrier glycosidation. Selective protection of the diol **12** with TBDMSCl provided the hex-2-enopyranoside **13**, which was further converted into its epimer **14** by the Mitsunobu reaction and hydrolysis. With the four enopyranosides in hand, their allyl cyanate-to-isocyanate rearrangement was undertaken.

At the beginning of this study, we were most interested in the rearrangement of the hex-3-enopyranoside **9** to the 4-amino-3-enopyranoside, because the 4-amino-3-enopyranoside is a structural unit found among the naturally occurring antifungal

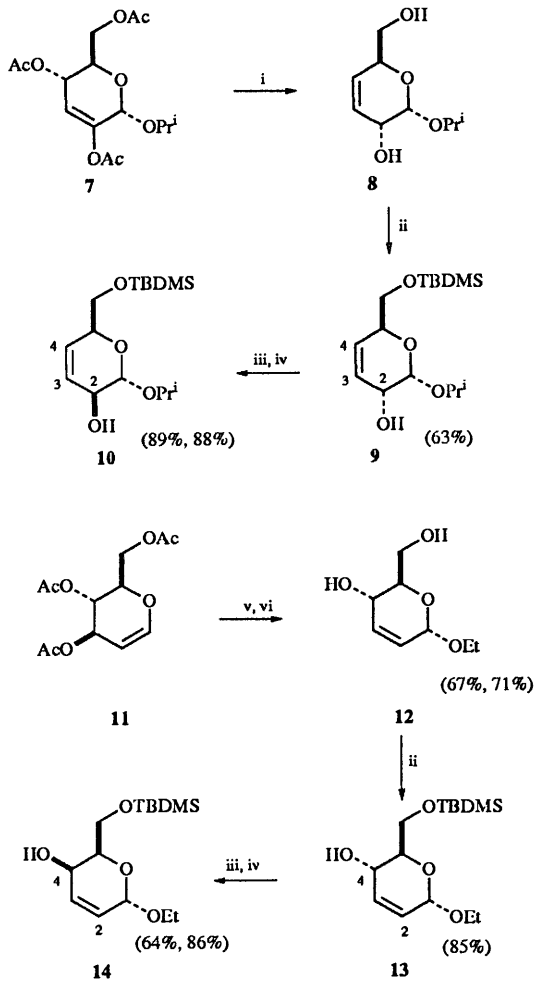


Scheme 1 *Reactions:* i, dehydration; ii, rearrangement. *Reagents:* iii, pyrrolidine; iv, $AlMe_3$.

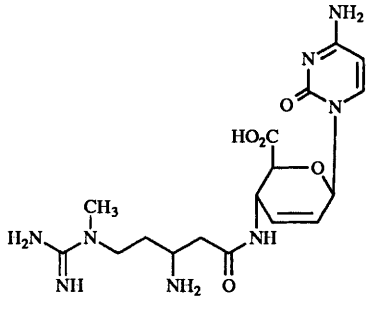
nucleoside antibiotics, such as blasticidin S **15**[9] and mildiomycin **16**.[10]

We expected that an allyl cyanate-to-isocyanate rearrangement of the hex-3-enopyranoside **9** would be difficult, because the C-2 hydroxy group of **9** adopts a pseudo-equatorial conformation. In fact, a literature search revealed that rearrangement of hex-3-enopyranoside **17**[4a] with a pseudo-equatorial hydroxy group proceeded in moderate yield to give compound **18** (Scheme 3). On the other hand, rearrangement of compound **19**[4a] with a pseudo-axial hydroxy group proceeded smoothly in good yield to give compound **20** (Scheme 4).

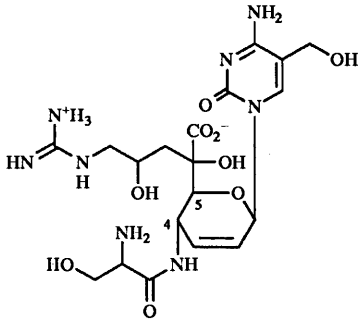
Scheme 5 illustrated an allyl cyanate-to-isocyanate rearrangement of compound **9**. Treatment of the alcohol **9** with trichloroacetyl isocyanate and hydrolysis with potassium carbonate in aq. methanol provided the carbamate **21**. Dehydration of the carbamate **21** with trifluoromethanesulfonic anhydride and diisopropylethylamine (DIPEA) at −78 °C for 2.5 h and successive treatment with pyrrolidine furnished no detectable rearrangement product.[1] After a substantial amount of experimentation, we realized that the reaction time and temperature after dehydration of the carbamate **21** was crucial for the rearrangement. Subsequently, dehydration of the carbamate **21** with triphenylphosphine, tetrabromomethane and DIPEA was complete after 150 min at −20 °C, and gave the allyl cyanate **22**. After dehydration, it was necessary for rearrangement to occur, so that the reaction mixture was stirred at room temperature for 60 min. The resulting reaction mixture was recooled to −78 °C, and then was treated with pyrrolidine.



Scheme 2 *Reagents and conditions:* i, $LiAlH_4$; ii, Bu^tMe_2SiCl, imidazole; iii, $PhCO_2H$, Ph_3P, DEAD; iv, KOH, MeOH; v, EtOH, $BF_3{\cdot}OEt_2$; vi, Et_3N, aq. MeOH



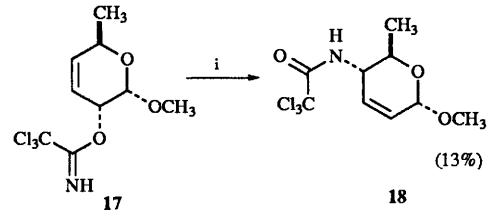
Blasticidin S **15**



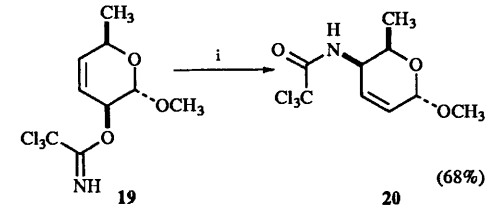
Mildiomycin **16**

The urea **24** was isolated in 68% overall yield from the hex-3-enopyranoside **9** after chromatographic purification.

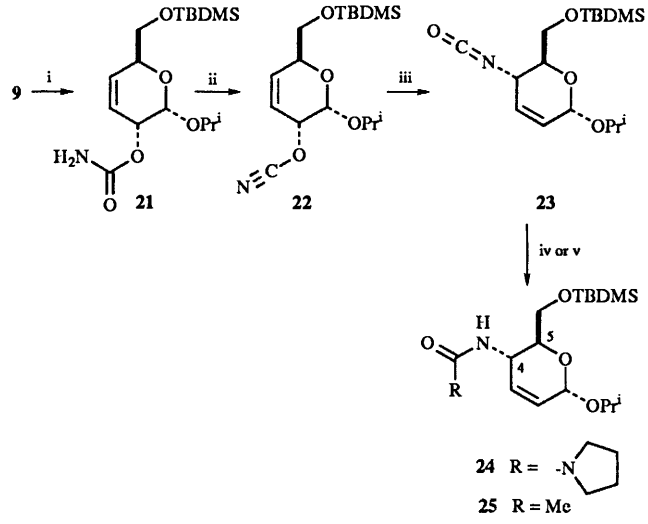
When trimethylaluminium was employed for the transformation of the allyl isocyanate **23**, the acetamide **25** was obtained in 59% overall yield from alcohol **9**. In this transformation, the reaction time (2.5 min) and temperature (0 °C) were both necessary to obtain the given yield. A prolonged reaction time as well as a low reaction temperature resulted in variable and often low yields (30–40%).



Scheme 3 *Reagents and conditions:* i, *o*-dichlorobenzene, 165 °C, 11 h



Scheme 4 *Reagents and conditions:* i, *o*-dichlorobenzene, 165 °C, 6 h



Scheme 5 *Reagents and conditions:* i, CCl_3CONCO; K_2CO_3, aq. MeOH; ii, Ph_3P, CBr_4, Pr^i_2NEt, −20 °C; iii, room temp., 60 min; iv, pyrrolidine; v, Me_3Al, 2.5 min, 0 °C

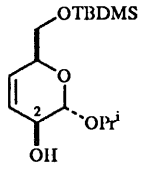
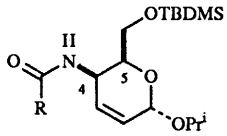
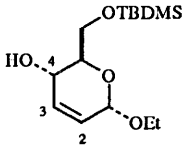
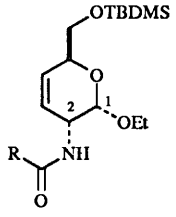
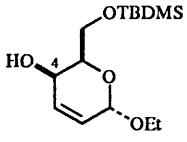
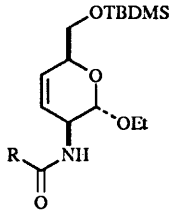
The stereochemistry of the acetamide **25** was determined by ^1H NMR spectroscopy. Thus, the large vicinal coupling constant of 9 Hz between 4-H and 5-H ($J_{4,5}$) of compound **25** indicated that these protons were *trans*. This $J_{4,5}$ value was consistent with that of mildiomycin **16** ($J_{4,5}$ 10 Hz).[10]

Other examples of the rearrangement are collected in Table 1 and the generality of this allyl cyanate-to-isocyanate rearrangement for the synthesis of nitrogen-containing unsaturated carbohydrates was evident from these results.

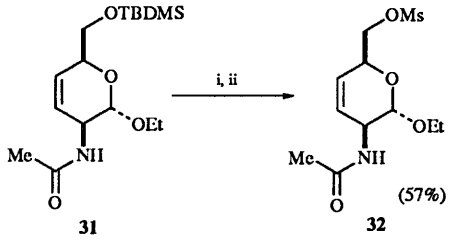
The stereochemistry of entries **A**, **B** and **C** was determined by ^1H NMR analysis. In case of entry **A**, the small $J_{4,5}$ value of 3 Hz found for compound **27** was consistent with the *cis*-relationship.

Ferrier reported an empirical relationship between 2-substituted hex-3-enopyranosides and the $J_{1,2}$ value in the ^1H NMR spectra.[8] The generalization was that 2α-isomers displayed a value for the coupling constant $J_{1,2}$ within the range 3–4 Hz, while the 2β-isomers had $J_{1,2} \approx 0$ Hz. This may be the result of the conformational difference between 2α- and 2β-substituted hex-3-enopyranosides which resulted in significantly different ^1H NMR spectra $J_{1,2}$ values. We confirmed the

Table 1 Synthesis of nitrogen-containing unsaturated carbohydrates from hexenopyranosides

Entry	Reactant		Product (yield, %)	
A		**10**		**26** R =  (66) **27** R = Me (63)
B		**13**		**28** R =  (47) **29** R = Me (47)
C		**14**		**30** R =  (78) **31** R = Me (58)

stereochemistry of entries **B** and **C** based on his empirical rule; that is, both compounds **28** and **29** had coupling-constant values of 4 Hz between 1-H and 2-H ($J_{1,2}$). These values were in good agreement with the stereochemistry of a 2α-substituent. In the case of compounds **30** and **31**, we observed $J_{1,2} \approx 0$ Hz, which was consistent with the 2β-stereochemistry. Further stereochemical confirmation was obtained by transforming the acetamide **31** into the known mesyl derivative **32** as shown in Scheme 6. Desilylation of compound **31** with tetrabutylammonium fluoride (TBAF) and mesylation with methanesulfonyl chloride in pyridine provided the methanesulfonate **32**. The spectroscopic data of our synthetic ester **32** was in good agreement with those reported by R. D. Guthrie.[11]



Scheme 6 *Reagents and conditions:* i, Bu_4NF; ii, MsCl, Py

Conclusions

The stereochemistry of the rearranged product was consistent with our expectations for such suprafacial allyl rearrangements that the asymmetry at the initial allylic centre was transmitted into the new centre as a nitrogenous substituent. The better yields of compounds **10** and **14** compared with those of **9** and **13** followed from the *quasi*-axial orientation of their C-2 and C-4 hydroxy substituents. This stereochemistry provided the consequent relative ease with which cyclic transition states involved in the allyl cyanate-to-isocyanate rearrangement could be formed.[2]

Further transformation of the nitrogen-containing unsaturated carbohydrates prepared in this study into naturally occurring amino sugars is now under study.

Experimental

Mps were determined on a hot-stage melting apparatus and were uncorrected. IR spectra were recorded using a JASCO FT/IR-7000S for KBr discs unless otherwise stated. ^{1}H NMR spectra were determined using a JEOL EX 270 spectrometer operating at 270 MHz unless otherwise stated. ^{13}C NMR spectra were determined using the JEOL EX 270 instrument, operating at 67.80 MHz unless otherwise stated. Dilute solutions in [^{2}H]chloroform were used as solvent throughout unless stated otherwise, with tetramethylsilane as the internal standard. All *J* values are in Hz. Optical rotations were measured on a JASCO DIP-0181 digital polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. All organic solutions from work-ups were dried by brief exposure to anhydrous sodium sulfate. Column chromatography was performed on silica gel supplied by Fuji Davison (BW-820MH). Preparative TLC was carried out on plates prepared with a 2 mm layer of silica gel PF_{254} obtained from E. Merck (Art #7747).

Isopropyl 6-*O*-(*tert*-butyldimethylsilyl)-3,4-dideoxy-α-D-*erythro*-hex-3-enopyranoside 9

To a solution of diol **8** (1.40 g, 7.50 mmol) and imidazole (1.54 g, 22.6 mmol) dissolved in a mixture of dichloromethane (33 cm^3) and *N*,*N*-dimethylformamide (DMF) (14 cm^3) was added TBDMSCl (1.36 g, 9.0 mmol) portionwise. After being stirred for 3.5 h at room temperature, the reaction mixture was poured into water. The separated aqueous layer was extracted with diethyl ether (three times). The combined extracts were washed successively with water and brine, dried, and concentrated under reduced pressure to afford the crude product, which was purified by silica gel chromatography (silica gel 40 g) with a mixture of diethyl ether–hexane (1 : 5, v/v) to provide the *silyl ether* **9** (1.42 g, 63%), $[\alpha]_D^{20}$ −11.0 (*c* 0.49, $CHCl_3$) (Found: C, 59.5; H, 10.2. $C_{15}H_{30}O_4Si$ requires C, 59.56; H, 10.00%); ν_{max}(film)/cm^{-1} 3427 (OH); δ_H(270 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.19 (3 H, d, *J* 6, $CHMe_2$), 1.25 (3 H, d, *J* 6, $CHMe_2$), 3.57 (1 H, dd, *J* 10 and 6, 6-H), 3.67 (1 H, dd, *J* 10 and 6, 6-H), 3.99 (1 H, sept, *J* 6, $CHMe_2$), 4.10–4.19 (2 H, 2- and 5-H), 5.06 (1 H, d, *J* 4, 1-H) and 5.68–5.84 (2 H, 3- and 4-H).

Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside 13

Starting from diol **12** (300 mg, 1.72 mmol), TBDMSCl (452 mg, 3.0 mmol), imidazole (532 mg, 7.7 mmol), dichloromethane (7 cm^3) and DMF (3 cm^3), the *silyl ether* **13** (420 mg) was isolated in 85% yield after chromatographic purification, $[\alpha]_D^{20}$ +22.6 (*c* 1.20, $CHCl_3$) (Found: C, 58.3; H, 9.8. $C_{14}H_{28}O_4Si$ requires C, 58.29; H, 9.78%); ν_{max}(film)/cm^{-1} 3442 (OH); δ_H(270 MHz; $CDCl_3$) 0.11 (6 H, s, $SiMe_2$), 0.91 (9 H, s, Bu^t), 1.23 (3 H, t, *J* 7, CH_3), 3.53 (1 H, dq, *J* 10 and 7, OCH_2CH_3), 3.68–3.94 (4 H), 4.16 (1 H, br d, *J* 8), 4.95 (1 H, br, 1-H), 5.73 (1 H, dt, *J* 10 and 2) and 5.93 (1 H, br d, *J* 10).

Isopropyl 6-*O*-(*tert*-butyldimethylsilyl)-3,4-dideoxy-α-D-*threo*-hex-3-enopyranoside 10

To a solution of *erythro*-isomer **9** (297 mg, 0.98 mmol), triphenylphosphine (1.16 g, 4.41 mmol) and benzoic acid (360 mg, 2.94 mmol) in tetrahydrofuran (THF) (7.5 cm^3) cooled to 0 °C was added diethyl azodicarboxylate (DEAD) (0.76 cm^3, 4.9 mmol) dropwise. After being stirred for 70 min at 0 °C, the reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with diethyl ether and washed successively with saturated aq. sodium hydrogen carbonate and brine. After being dried, evaporation of the solvent gave the crude product (1.6 g), which was purified by silica gel chromatography (50 g) with a mixture of diethyl ether–hexane (1:10, v/v) to provide the benzoate (357 mg, 89%).

A solution of the benzoate (870 mg, 2.14 mmol) in methanol (30 cm^3) was treated with sodium methoxide (4.1 mol dm^{-3} solution in methanol; 1.14 cm^3, 4.7 mmol) at 0 °C for 15 min. Cracked solid CO_2 was added, and the solution was concentrated under reduced pressure. The resulting residue was diluted with water, and the aqueous layer was extracted with diethyl ether. The combined extracts were dried, and then concentrated under reduced pressure. Purification of the resulting residue by silica gel chromatography (24 g) with a mixture of diethyl ether–hexane (1:2, v/v) furnished threo-*isomer* **10** (568 mg, 88%), $[\alpha]_D^{20}$ +66.5 (*c* 0.95, $CHCl_3$) (Found: C, 59.5; H, 10.0. $C_{15}H_{30}O_4Si$ requires C, 59.56; H, 10.00%); ν_{max}(film)/cm^{-1} 3447 (OH); δ_H(270 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 1.16 (3 H, d, *J* 6, $CHMe_2$), 1.21 (3 H, d, *J* 6, $CHMe_2$), 3.69–3.78 (3 H, 2-H and 6-H_2), 3.97 (1 H, sept, *J* 6, $CHMe_2$), 4.19–4.27 (1 H, m, 5-H), 4.95 (1 H, s, 1-H), 5.89 (1 H, dd, *J* 11 and 2, 4-H) and 6.07 (1 H, br d, *J* 11, 3-H).

Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside 14

The procedure described here was similar to that used for compound **10**. Thus, starting from *erythro*-compound **13** (300 mg, 1.04 mmol), DEAD (0.82 cm^3, 5.2 mmol), triphenylphosphine (1.23 g, 4.7 mmol), benzoic acid (381 mg, 3.12 mmol) and THF (7.5 cm^3), the benzoate (263 mg) was isolated in 64% yield.

Starting from the benzoate (1.56 g, 4.27 mmol), sodium methoxide (4.1 mol dm^{-3} solution in methanol; 0.93 cm^3, 3.8 mmol) and methanol (50 cm^3), the *alcohol* **14** (1.06 g) was obtained in 86% yield, $[\alpha]_D^{20}$ −28.9 (*c* 0.42, $CHCl_3$) (Found: C, 58.3; H, 9.8. $C_{14}H_{28}O_4Si$ requires C, 58.29; H, 9.78%); ν_{max}(film)/cm^{-1} 3448 (OH); δ_H(270 MHz; $CDCl_3$) 0.09 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 1.23 (3 H, t, *J* 7, CH_3), 2.03–2.17 (1 H, br d, OH), 3.53 (1 H, dq, *J* 9 and 7, OCH_2CH_3), 3.78–3.94 (4 H, OCH_2CH_3, 4-H and 6-H_2), 4.04 (1 H, td, *J* 6 and 2, 5-H), 5.02 (1 H, d, *J* 3, 1-H), 5.90 (1 H, dd, *J* 10 and 3, 2-H) and 6.15 (1 H, dd, *J* 10 and 5, 3-H).

General procedure for the synthesis of the urea derivative isopropyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-(4-pyrrolidine-1-carboxamido)-α-D-*erythro*-hex-2-enopyranoside 24

To a solution of compound **9** (500 mg, 1.66 mmol) in dichloromethane (17 cm^3) was added trichloroacetyl isocyanate (0.24 cm^3, 1.99 mmol) dropwise at 0 °C. After the mixture had been stirred for 15 min at 0 °C, solvent was removed by evaporation under reduced pressure. The resulting residue was dissolved in a mixture of methanol (7 cm^3) and water (5 cm^3). To this solution, cooled to 0 °C, was added potassium carbonate (705 mg, 4.98 mmol) portionwise. After the solution had been stirred for 60 min at 0 °C, the cooling bath was removed, and stirring was continued for a further 120 min at room temperature. Methanol was evaporated off and the resulting aqueous phase was extracted with dichloromethane (three times). The combined organic phases were dried, and then concentrated under reduced pressure to afford the carbamate **21** (552 mg, 97%), which was used for the next reaction without further purification.

To a solution of the carbamate **21** (149 mg, 0.43 mmol), triphenylphosphine (283 mg, 1.08 mmol) and DIPEA (0.18 cm^3, 1.1 mmol) in dichloromethane (4 cm^3) was added a solution of tetrabromomethane (398 mg, 1.21 mmol) in dichloromethane (1 cm^3) dropwise at −20 °C. After being stirred for 150 min at −20 °C, the cooling bath was removed, and the stirring was continued for 60 min at room temperature. The resulting solution was cooled to −78 °C and then treated with pyrrolidine (0.29 cm^3, 3.5 mmol). After being stirred for 30 min at −78 °C and for 30 min at −20 °C, the reaction mixture was poured into water, and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried, and concentrated under reduced pressure to provide a crude oil (0.96 g), which was purified by silica gel chromatography with diethyl ether to afford the *urea* **24** (121 mg, 68% overall yield from **9**), mp 93–96 °C (Found: C, 60.3; H, 9.5; N, 6.9. $C_{20}H_{38}N_2O_4Si$ requires C, 60.26; H, 9.61; N, 7.03%); $[\alpha]_D^{20}$ +96.4 (*c* 0.93, $CHCl_3$); ν_{max}(film)/cm^{-1} 3304 (NH) and 1633 (C=O); δ_H(270 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.85 (9 H, s, Bu^t), 1.17 (3 H, d, *J* 6, $CHMe_2$), 1.26 (3 H, d, *J* 6, $CHMe_2$), 1.86–1.94 (4 H, NCH_2CH_2), 3.22–3.37 (4 H, NCH_2CH_2), 3.66–3.80 (2 H, 5- and 6-H), 3.88 (1 H, d, *J* 11, 6-H), 4.06 (1 H, sept, *J* 6, $OCHMe_2$), 4.13 (1 H, br d, *J* 10, NH), 4.33 (1 H, br d, *J* 10, 4-H), 5.11 (1 H, d, *J* 2, 1-H) and 5.80–5.87 (2 H, 2- and 3-H).

General procedure for the synthesis of the acetamide isopropyl 4-acetamido-6-*O*-(*tert*-butyldimethylsilyl)- 2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside 25

To a solution of the carbamate **21** (148 mg, 0.43 mmol), triphenylphosphine (283 mg, 1.08 mmol) and DIPEA (0.18 cm^3, 1.1 mmol) in dichloromethane (4 cm^3) was added a solution of tetrabromomethane (398 mg, 1.21 mmol) in dichloromethane (1.0 cm^3) dropwise at −20 °C. After being stirred for 150 min at −20 °C and then for 60 min at room temperature, the solution was recooled to −20 °C. To this solution was added a solution of trimethylaluminium (1.3 mol dm^{-3} solution in hexane; 2.2 cm^3, 2.8 mmol). After the solution had been stirred for 2.5 min at −20 °C, methanol was added cautiously. The reaction mixture was poured into saturated aq. potassium sodium tartrate, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, and concentrated under reduced pressure. Purification of the resulting residue (0.75 g) with silica gel chromatography with diethyl ether furnished the *acetamide* **25** (90 mg, 59% overall from **9**), mp 99–100 °C (from diethyl ether–hexane) (Found: C, 59.4; H, 9.6; N, 4.0. $C_{17}H_{33}NO_4Si$ requires C, 59.44; H, 9.68; N, 4.08%); $[\alpha]_D^{20}$ +56.0 (*c* 0.26, $CHCl_3$); ν_{max}(film)/cm^{-1} 3259 (NH) and 1647 (C=O); δ_H(270 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 1.16 (3 H, d, *J* 6, $CHMe_2$), 1.24 (3 H, d, *J* 6, $CHMe_2$), 1.97 (3 H, s, Ac), 3.64–3.79 (3 H, 5-H and 6-H_2), 4.03 (1 H, sept, *J* 6, $CHMe_2$), 4.43 (1 H, t, *J* 9, 4-H), 5.09 (1 H, d, *J* 2, 1-H), 5.45 (1 H, br d, *J* 9, NH) and 5.72–5.83 (2 H, 2- and 3-H).

Isopropyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy- 4-(pyrrolidine-1-carboxamido)-α-D-*threo*-hex-2-enopyranoside 26

The procedure used here was similar to that used in the general procedure for the synthesis of the epimeric urea **24**. Starting from compound **10** (568 mg, 1.88 mmol), trichloroacetyl isocyanate (0.27 cm^3, 2.3 mmol), dichloromethane (19 cm^3), potassium carbonate (780 mg, 5.64 mmol), methanol (9 cm^3) and water (5 cm^3), the corresponding carbamate (627 mg) was obtained in 97% yield. A portion of this carbamate was used for the next reaction without further purification.

The carbamate (120 mg, 0.35 mmol) was transformed into the *urea* **26** (95 mg, 66% overall yield from substrate **10**) by employing tetrabromomethane (325 mg, 0.98 mmol), triphenylphosphine (230 mg, 0.88 mmol), DIPEA (0.15 cm^3, 0.88 mmol), dichloromethane (5 cm^3) and pyrrolidine (0.23 cm^3, 2.8 mmol), $[\alpha]_D^{20}$ −142 (*c* 0.42, $CHCl_3$); ν_{max}(film)/cm^{-1} 3272 (NH) and 1626 (C=O); δ_H(270 MHz; $CDCl_3$) 0.04 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 1.15 (3 H, d, *J* 6, $CHMe_2$), 1.24 (3 H, d, *J* 6, $CHMe_2$), 1.84–1.91 (4 H, m, NCH_2CH_2), 3.23–3.33 (4 H, NCH_2CH_2), 3.67 (1 H, dd, *J* 10 and 7, 6-H), 3.81 (1 H, dd, *J* 10 and 4, 6-H), 4.06 (1 H, sept, *J* 6, $OCHMe_2$), 4.14–4.22 (1 H, 5-H), 4.22–4.26 (2 H, 4-H and NH), 5.09 (1 H, d, *J* 3, 1-H), 5.77 (1 H, dd, *J* 10 and 3, 2-H) and 6.07 (1 H, br d, *J* 10, 3-H) (Found: M^+, 398.2587. $C_{20}H_{38}N_2O_4Si$ requires M, 398.2601).

Isopropyl 4-acetamido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside 27

The procedure used was similar to that used in the general procedure for the synthesis of the epimeric acetamide **25**. The carbamate (150 mg, 0.43 mmol) was transformed into the *acetamide* **27** (97 mg, 63% overall yield from substrate **10**) by using tetrabromomethane (398 mg, 1.20 mmol), triphenylphosphine (283 mg, 1.08 mmol), DIPEA (0.18 cm^3, 1.1 mmol), dichloromethane (5 cm^3) and trimethylaluminium (1.3 mol dm^{-3} solution in hexane; 2.15 cm^3, 2.8 mmol), mp 52–54 °C; $[\alpha]_D^{20}$ −96.8 (*c* 0.34, $CHCl_3$) (Found: C, 59.2; H, 9.7; N, 4.0. $C_{17}H_{33}NO_4Si$ requires C, 59.44; H, 9.69; N, 4.08%); ν_{max}(film)/cm^{-1} 3259 (NH) and 1647 (C=O); δ_H(270 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.16 (3 H, d, *J* 6, $CHMe_2$), 1.23 (3 H, d, *J* 6, $CHMe_2$), 1.96 (3 H, s, Ac), 3.63 (1 H, dd, *J* 11 and 7, 6-H), 3.75 (1 H, dd, *J* 11 and 4, 6-H), 4.03 (1 H, sept, *J* 6, Me_2CHO), 4.17 (1 H, ddd, *J* 7, 4 and 3, 5-H), 4.36 (1 H, ddd, *J* 9, 6 and 3, 4-H), 5.09 (1 H, d, *J* 3, 1-H), 5.70 (1 H, d, *J* 9, NH), 5.81 (1 H, dd, *J* 10 and 3, 2-H) and 6.02 (1 H, dd, *J* 10 and 6, 3-H).

Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-2-(pyrrolidine-1-carboxamido)-α-D-*erythro*-hex-3-enopyranoside 28

The procedure used was similar to that used in the general procedure for the synthesis of the ureas **24** and **26**. Starting from compound **13** (471 mg, 1.64 mmol), trichloroacetyl isocyanate (0.25 cm^3, 2.1 mmol), dichloromethane (17 cm^3), potassium carbonate (721 mg, 5.22 mmol), methanol (8 cm^3) and water (5 cm^3), the corresponding carbamate (550 mg) was obtained in 96% yield. The carbamate was used for the next reaction without further purification.

The carbamate (150 mg, 0.45 mmol) was transformed into the *urea* **28** (85 mg, 47% overall yield from alcohol **13**) by employing tetrabromomethane (418 mg, 1.26 mmol), triphenylphosphine (295 mg, 1.13 mmol), DIPEA (0.20 cm^3, 1.1 mmol), dichloromethane (5 cm^3) and pyrrolidine (0.30 cm^3, 3.6 mmol), $[\alpha]_D^{20}$ −40.7 (*c* 0.46, $CHCl_3$) (Found: C, 59.3; H, 9.5; N, 7.3. $C_{19}H_{36}N_2O_4Si$ requires C, 59.34; H, 9.44; N, 7.29%); ν_{max}(film)/cm^{-1} 3344 (NH) and 1652 (C=O); δ_H(270 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 1.22 (3 H, t, *J* 7, CH_2CH_3), 1.84–1.95 (4 H, NCH_2CH_2), 3.25–3.39 (4 H, NCH_2CH_2), 3.51–3.64 (2 H, CH_3CH_2O and 6-H), 3.71 (1 H, dd, *J* 10 and 6, 6-H), 3.83 (1 H, dq, *J* 10 and 7, CH_3CH_2O), 4.08–4.16 (1 H, br, 5-H), 4.56–4.69 (2 H, 2-H and NH), 4.94 (1 H, d, *J* 4, 1-H), 5.64 (1 H, br d, *J* 10, CH=C*H*) and 5.83 (1 H, br d, *J* 10, C*H*=CH).

Ethyl 2-acetamido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*erythro*-hex-3-enopyranoside 29

The procedure used was similar to that used in the general procedure for the synthesis of the acetamides **25** and **27**. The carbamate (150 mg, 0.45 mmol) was transformed into the *acetamide* **29** (74 mg, 47% overall yield from alcohol **13**) by using tetrabromomethane (418 mg, 1.26 mmol), triphenylphosphine (295 mg, 1.13 mmol), DIPEA (0.20 cm^3, 1.1 mmol), dichloromethane (5 cm^3) and trimethylaluminium (1.3 mol dm^{-3} solution in hexane; 2.3 cm^3, 2.9 mmol), mp 90–91 °C; $[\alpha]_D^{20}$ −18.1 (*c* 0.24, $CHCl_3$) (Found: C, 58.6; H, 9.5; N, 4.3. $C_{16}H_{31}NO_4Si$ requires C, 58.32; H, 9.48; N, 4.25%); ν_{max}(film)/cm^{-1} 3292 (NH) and 1652 (NHC=O); δ_H(270 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.24 (3 H, t, *J* 7, CH_3CH_2), 2.00 (3 H, s, Ac), 3.51–3.64 (2 H, CH_3CH_2O and 6-H), 3.71 (1 H, dd, *J* 10 and 6, 6-H), 3.76–3.90 (1 H, CH_3CH_2), 4.08–4.17 (1 H, m, 5-H), 4.67–4.77 (1 H, m, 2-H), 4.92 (1 H, d, *J* 4, 1-H), 5.57 (1 H, br d, *J* 10, CH=C*H*), 5.77–5.81 (1 H, NH) and 5.85 (1 H, dt, *J* 10 and 1, C*H*=CH).

Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-2-(pyrrolidine-1-carboxamido)-α-D-*threo*-*hex*-3-enopyranoside 30

The procedure used was similar to that used in the general procedure for the synthesis of the ureas. Starting from compound **14** (500 mg, 1.74 mmol), trichloroacetyl isocyanate (0.25 cm^3, 2.1 mmol), dichloromethane (17 cm^3), potassium carbonate (721 mg, 5.22 mmol), methanol (8 cm^3) and water (5 cm^3), the corresponding carbamate (551 mg) was obtained in 96% yield. The resulting carbamate was used for the next reaction without further purification.

The carbamate (127 mg, 0.38 mmol) was transformed into the *urea* **30** (113 mg, 78% overall yield from the alcohol **14**) by using tetrabromomethane (315 mg, 0.95 mmol), triphenylphosphine (252 mg, 0.96 mmol), triethylamine (0.18 cm^3, 0.96 mmol), dichloromethane (4 cm^3) and pyrrolidine (0.25 cm^3, 3.0 mmol), $[\alpha]_D^{20}$ +85.4 (*c* 0.74, $CHCl_3$) (Found: C, 59.3; H, 9.6; N, 7.1. $C_{19}H_{36}N_2O_4Si$ requires C, 59.34; H, 9.44; N, 7.29%); ν_{max}(film)/cm^{-1} 3313 (NH) and 1652 (C=O); δ_H(270 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 1.20 (3 H, t, *J* 7, CH_2CH_3), 1.79–1.92 (4 H, NCH_2CH_2), 3.17–3.36 (4 H, NCH_2CH_2), 3.48–3.84 (4 H, CH_3CH_2O and 6-H_2), 4.1–4.23 (3 H, 2- and 5-H, NH), 4.82 (1 H, s, 1-H) and 5.78–5.95 (2 H, 3- and 4-H).

Ethyl 2-acetamido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside 31

The procedure used was similar to that used in the general procedure for the synthesis of the acetamides. The carbamate (122 mg, 0.36 mmol) was transformed into the *acetamide* **31** (73 mg, 58% overall yield from the alcohol **14**) by using tetrabromomethane (334 mg, 1.01 mmol), triphenylphosphine (236 mg, 0.90 mmol), DIPEA (0.16 cm^3 0.90 mmol), dichloromethane (4 cm^3) and trimethylaluminium (1.3 mol dm^{-3} solution in hexane; 1.8 cm^3, 2.4 mmol), $[\alpha]_D^{20}$ +52.1 (*c* 0.13, $CHCl_3$); ν_{max}(film)/cm^{-1} 3281 (NH) and 1653 (C=O); δ_H(270 MHz; $CDCl_3$) 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 1.22 (3 H, t, *J* 7, CH_3CH_2), 1.96 (3 H, s, Ac), 3.51–3.85 (4 H, CH_3CH_2O and 6-H_2), 4.19 (1 H, br, 5-H), 4.33 (1 H, dd, *J* 9 and 6, 2-H), 4.78 (1 H, s, 1-H), 5.59 (1 H, br d, *J* 9, NH) and 5.79–5.98 (2 H, 3- and 4-H) (Found: M^+, 329.2014. $C_{16}H_{31}NO_4Si$ requires M, 329.2022).

Ethyl 2-acetamido-2,3,4-trideoxy-6-*O*-methylsulfonyl-α-D-*threo*-hex-3-enopyranoside 32

A solution of TBAF (1 mol dm^{-3} solution in THF; 0.14 cm^3, 0.14 mmol) was added to a solution of the silyl ether **31** (70 mg, 0.21 mmol) in acetonitrile (2.3 cm^3) at room temperature. The resulting reaction mixture was stirred for 90 min and then concentrated under reduced pressure. Purification of the resulting residue by silica gel chromatography (3 g) with ethyl acetate afforded the alcohol (38 mg). This alcohol (38 mg, 0.18

mmol) was dissolved in pyridine (2.7 cm^3), and then treated with methanesulfonyl chloride (0.15 cm^3, 2.0 mmol) at room temperature. After being stirred for 90 min, the reaction mixture was concentrated under reduced pressure to provide a residue (0.14 g), which was purified by silica gel chromatography (2 g) with ethyl acetate to furnish the mesyl derivative **32** (36 mg, 57% overall yield from substrate **31**), mp 92–93 °C (lit.,[11] 89–91 °C); $[\alpha]_D^{20}$ +121 (*c* 1.78, $CHCl_3$) [lit.,[11] +132 (*c* 2.0 in $CHCl_3$)] (Found: C, 44.9; H, 6.5; N, 4.8. Calc. for $C_{11}H_{19}NO_6S$: C, 45.04; H, 6.53; N, 4.77%); δ_H(270 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7, CH_2CH_3), 1.98 (3 H, s, Ac), 3.08 (3 H, s, CH_3SO_2), 3.60 (1 H, dq, *J* 10 and 7, OCH_2CH_3), 3.79 (1 H, dq, *J* 10 and 7, OCH_2CH_3), 4.28 (1 H, dd, *J* 11 and 4, 6-H), 4.32–4.46 (2 H), 4.54 (1 H, dd, *J* 11 and 3), 4.83 (1 H, s, 1-H), 5.82–6.04 (2 H, 3- and 4-H) and 6.19 (1 H, d, *J* 9, NH) [lit.,[11] τ_H 3.8–4.2 (3 H, m), 5.2 (1 H, s), 5.48–5.96 (4 H, m), 6.17–6.58 (2 H, m), 6.94 (3 H, s), 8.2 (3 H, s) and 8.76 (3 H, t)].

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