Stereoselective photochemical transformations of hexopyranosyl imides to highly functionalised heterocycles

Swantje Thiering,[a] Carsten E. Sowa[b] and Joachim Thiem[a]

[a] *Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany*
[b] *Bayer AG, GBCH Strategische Planung, D-51368 Leverkusen, Germany*

Received (in Cambridge, UK) 15th December 2000, Accepted 24th January 2001
First published as an Advance Article on the web 8th March 2001

Reaction of *O*-protected glycosylamines with succinic anhydride and subsequent acylation afford both anomers of *gluco*- and *manno*-configurated *N*-glycosylsuccinimides. Irradiation with UV light of 254 nm wavelength leads to abstraction of H-2 and H-5, respectively, by the excited carbonyl function. The stereoselective recombination of the resulting 1,4- and 1,5-diradicals gives the annelated azacyclobutanol and azacyclopentanol derivatives, respectively. Owing to the strained four-membered rings, the azacyclobutanol derivatives fragment by an aza-analogous retroaldol addition to give the hexopyranosyl-annelated azepanedione systems.

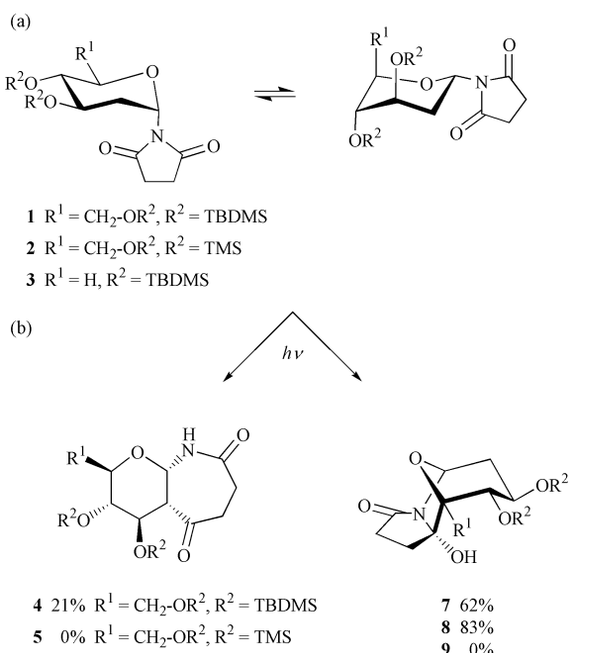
Introduction

The structural element of the azepanedione ring is widespread in physiologically active compounds, with slight structural changes inducing significantly diverse effects. Besides applications ranging from calcium antagonists in the treatment of cardiovascular disease,[1] as well as potent inhibitors of HIV-1 reverse transcriptase[2] and non-peptidic inhibitors of blood coagulation,[3] it is principally to be found in numerous well established psychopharmaceuticals.[4,5] These drugs affect the central nervous system in multifaceted ways and are currently being used in the treatment of various diseases or irregularities. This pharmaceutical potential attracted our interest in the synthesis of sugar-derived compounds containing an annelated azepanedione ring.

As previously reported,[6,7] *N*-2-deoxyglycosylsuccinimides such as **1**, **2** and **3** could be photochemically transformed into the corresponding bicyclic (**4**–**6**) and tricyclic (**7**–**9**) oxalactams, respectively. Irradiation of the imide derivatives results in abstraction of γ- or δ-hydrogen atom by means of a Norrish-Type II reaction. Subsequent intramolecular alkylation (Yang cyclisation) affords the tricyclic aminals or the azepinedione derivatives (Scheme 1).

The regiochemistry of this alkylation reaction is controlled by stereoelectronic as well as conformational factors, caused by both the nature of the individual monosaccharide (configurational aspects) and the applied protecting groups. With pentopyranoses such as **3**, the inverse anomeric effect of the succinimidyl substituent in the α-position at the anomeric centre, preferring an equatorial position, forces the pyranose chair to adopt the $^1C_4$(D) conformation. For this conformation, abstraction of only the γ-hydrogen atom, and thus *cis*-alkylation of the 2-position, could be observed. On the other hand, with hexopyranoses such as **1** or **2**, the inverse anomeric effect may be dominated by steric factors. Thus there is no such strong preference for the equatorial position and correspondingly of the $^1C_4$(D) conformation, as observed in the ^{1}H-coupling constants. For example, in solution the amount of the $^4C_1$(D) conformation of the hexopyranosylsuccinimide **1** in the ground state is about 95%. Starting from the $^1C_4$(D) conformation, the reaction of the 1,4-diradical with the γ-hydrogen atom is the only abstraction possible. In contrast, the $^4C_1$(D) conformation also allows the abstraction of the δ-hydrogen atom from C-5, leading to the tricyclic aminals **7** and **8**.

In order to investigate those factors controlling the regioselectivity of hydrogen abstraction more intensively, we were interested in studying the corresponding reaction with the 'normal' sugar derivatives. Thus, we synthesised the corresponding 2-hydroxy derivatives of *N*-glycosylsuccinimides such as **1**–**3**, and here we report some results of that work with *gluco*- and *manno*-configurated hexopyranoses.



1 $R^1 = CH_2\text{-}OR^2$, R^2 = TBDMS
2 $R^1 = CH_2\text{-}OR^2$, R^2 = TMS
3 R^1 = H, R^2 = TBDMS

4 21% $R^1 = CH_2\text{-}OR^2$, R^2 = TBDMS
5 0% $R^1 = CH_2\text{-}OR^2$, R^2 = TMS
6 50% R^1 = H, R^2 = TBDMS

7 62%
8 83%
9 0%

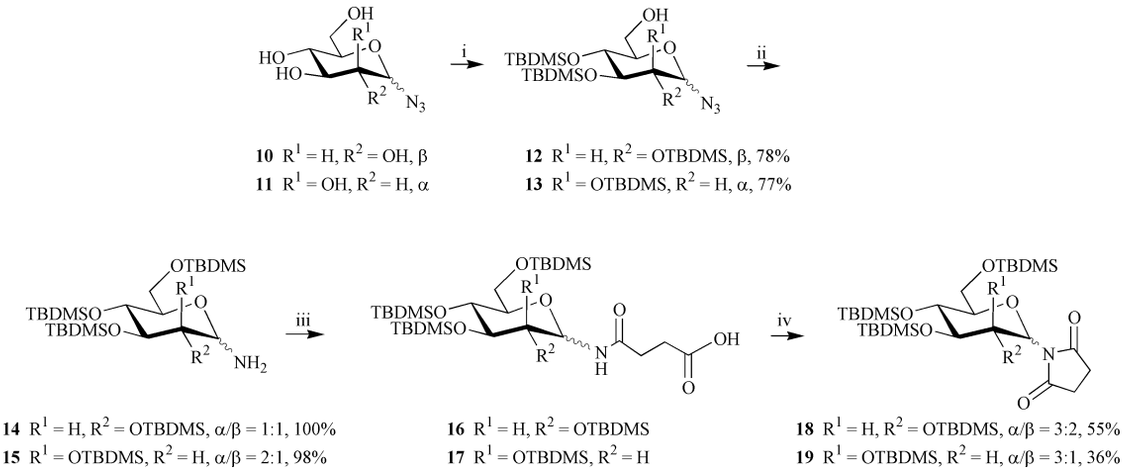
Scheme 1

Results and discussion

Preparation of *N*-glycosylsuccinimides

A simple and effective way of preparing *N*-2-deoxyglycosylsuccinimides involves the addition of *N*-iodosuccinimide to glycals and the subsequent reduction of the iodo function.[8] It would seem attractive to perform a nucleophilic substitution with a hydroxy function or any equivalent group at the site of the iodo function. However, to date no such transfer could be realised due to the special situation of the sugar 2-position.

DOI: 10.1039/b010020j



Scheme 2 *Reagents and conditions*: i: *tert*-butyldimethylsilyl trifluoromethanesulfonate, pyridine, 0 °C–RT, 48 h; ii: H_2, Pd/C, ethyl acetate–CH_3OH, RT, 48 h; iii: succinic anhydride, $NEtPr^i_2$, RT, 20 h; iv: pyridine, Ac_2O **18**: 60 °C, 3 days; **19**: 100 °C, 5 days.

Furthermore, the nucleophilicity of the succinimide anion is extremely low, so that nucleophilic substitution reactions of leaving groups such as tosyloxy and mesyloxy groups at other than primary positions[9] do not take place. Recently, a glycosylation reaction leading to *N*-glycosylsuccinimides has been reported by Krog-Jenson and Oscarson.[10] In a more versatile approach, *N*-glycosylimides of different kinds are accessible by reaction of the primary amine with the anhydride of a dicarbonic acid. Proceeding from the glycosylamines available by reduction of glycosyl azides, reaction with succinic anhydride leads to the corresponding *N*-glycosylsuccinamidic acids. Under acetylation conditions, a subsequent cyclisation reaction affords the *N*-glycosylsuccinimides.

The synthetic strategy used to access the target compounds for photoreactions is subject to some restrictions, because under the conditions of the photoreaction only photochemically inert hydroxy-protecting groups such as silyl or alkyl ethers could be applied, and thus some alternative routes are required.

The glycopyranosyl azides **10** and **11** were synthesised by reaction of the pentaacetylhexopyranoses with trimethylsilyl azide under catalysis of tin(IV) chloride as Lewis acid,[11,12] succeeded by deacetylation. Silylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate provides the fully protected glycopyranosyl azides **12** and **13** (Scheme 2).

Reduction of the glycosyl azides **12** and **13** by hydrogenolysis using palladium on activated charcoal afforded the glycosylamines **14** and **15** in mostly quantitative yield.

The *N*-glycosylamines **14** and **15** were treated with 10 equivalents of succinic anhydride in dichloromethane with *N*-ethyldiisopropylamine as auxiliary base. Without isolation the *N*-glycosylsuccinamidic acids **16** and **17** obtained were cyclised directly with acetic anhydride in pyridine.[13,14]

In this cyclisation, the applied protecting groups showed significant influences on both the required reaction conditions and the stereoselectivity. Using methyl or benzyl ethers with *gluco*-configuration, room temperature was sufficient, the reaction was stereoselective and proceeded to give the β-anomer in good yields.[15] With *tert*-butyldimethylsilyl (TBDMS) ethers, which are well suited for the photoreaction and subsequent transformations, high temperatures and longer reaction times were required. Thus, both anomers in the *gluco*- as well as the *manno*-configuration were obtained, which could be separated by column chromatography to give the *N*-glycosylsuccinimides **18**α/β and **19**α/β, respectively.

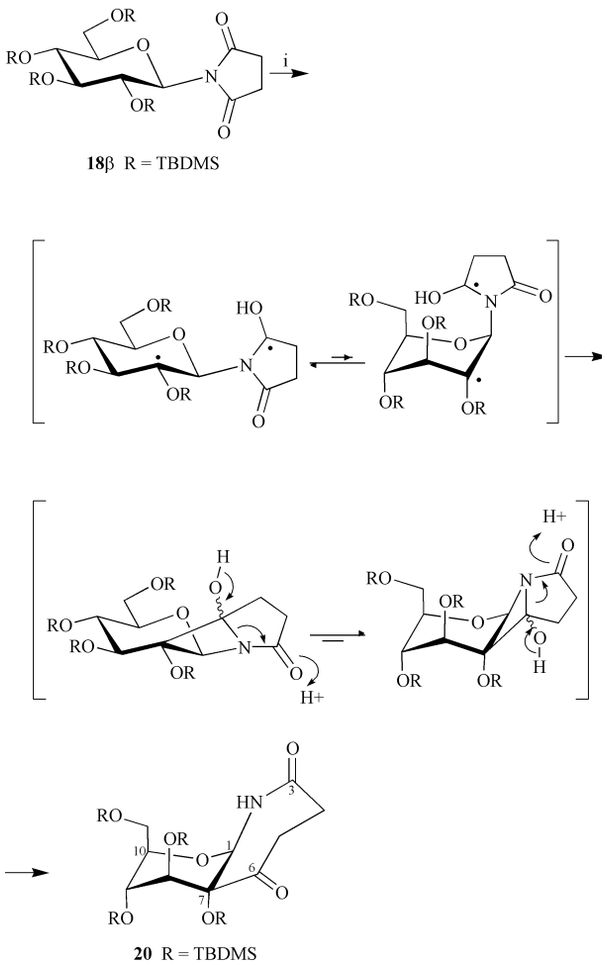
Irradiation of *N*-glycosylsuccinimides

By irradiation of an *N*-glycosylsuccinimide with UV light of 254 nm wavelength an excited state of the carbonyl group is generated, whose properties are comparable to those of a diradical. The approach of the excited carbonyl function to a hydrogen atom of the sugar ring at the correct distance results in the abstraction of this hydrogen generating a diradical. Steric aspects are the reason for a preference of the formation of a 1,4-diradical, because this γ-hydrogen abstraction proceeds *via* a six-membered transition state. However, electronic aspects such as the polarisation of a C–H bond by heteroatoms like sulfur and the absence of a hydrogen in the γ-position can cause the abstraction of remote hydrogen atoms, of which principally the δ-hydrogen abstraction is quite common. In the case of γ- and δ-hydrogen abstraction, recombination of the radical centres affords azacyclobutanol and azacyclopentanol derivatives, respectively, where the former are unstable and fragment by an aza-analogous retroaldol addition to give the azepanedione system. Owing to the tension of the resulting four- or five-membered rings, the Yang cyclisation of the diradicals proceeds stereoselectively to the *cis*-annelated products.[16]

Irradiation of the *gluco* component **18**β yielded the expected product of γ-hydrogen abstraction and *cis*-alkylation at the 2-position, the azepanedione derivative **20**, stereoselectively (Scheme 3). Some characteristic ^{13}C NMR data are the new quaternary centre C-7 at δ_C 83.45, the carbonyl functions NHC=O at δ_C 173.20 and C=O at δ_C 206.93, and the two secondary centres of the former succinimide ring C-5 at δ_C 35.35 and C-4 at δ_C 31.38. The ^1H NMR data show the NH-doublet at δ 6.35 and the splitting of the former succinimide methylene protons into an ABCD-spin system. Furthermore, the coupling constants $J_{8,9}$ 2.5 and $J_{9,10} \leq 1$ Hz indicate that the pyranose ring no longer adopts a $^4C_1$(D) conformation.

With similar selectivity, the photoreaction of the *gluco*-derivative **18**α afforded one product, which was identified as the heterotricyclic aminal **21** (Scheme 4), whose *exo*-configuration may be presumed on the basis of former investigations[6] and NOESY experiments. There is a strong nuclear Overhauser effect (NOE) between the new hydroxy group (δ 6.66) and H-9 and H-12b and a weaker NOE with H-8 and H-12a. However, no coupling of the methylene protons (ABCD-spin system) at C-4 (δ_C 34.00) and C-5 (δ_C 37.86) with the protons of the pyranose ring can be observed. Further decisive NMR data are the signals of the carbonyl function C=O at δ_C 184.39, the new chiral centre C-6 at δ_C 102.15, and the new quaternary centre C-7 at δ_C 85.17.

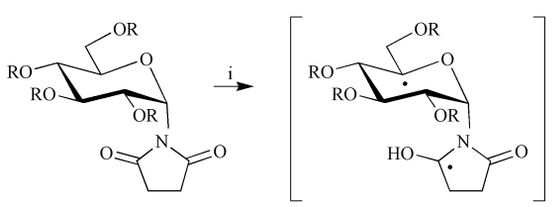
By irradiation of the *manno* compound **19**α two products were isolated in different amounts. The main product was identified as the heterotricycle **23** (OH δ 6.27, C=O δ_C 185.09, C-6 101.18, C-7 85.96, C-5 37.97, C-4 33.74) whereas the azepanedione derivative **22** (NH δ 6.36, C=O δ_C 208.69, NHC=O 174.16, C-7 82.13, C-5 37.73, C-4 31.27) was isolated



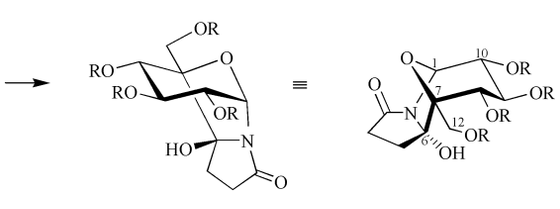
18β R = TBDMS

20 R = TBDMS

Scheme 3 *Reaction conditions*: i, *hv* 254 nm, CH_3CN, 18 °C, 3 h (69%).



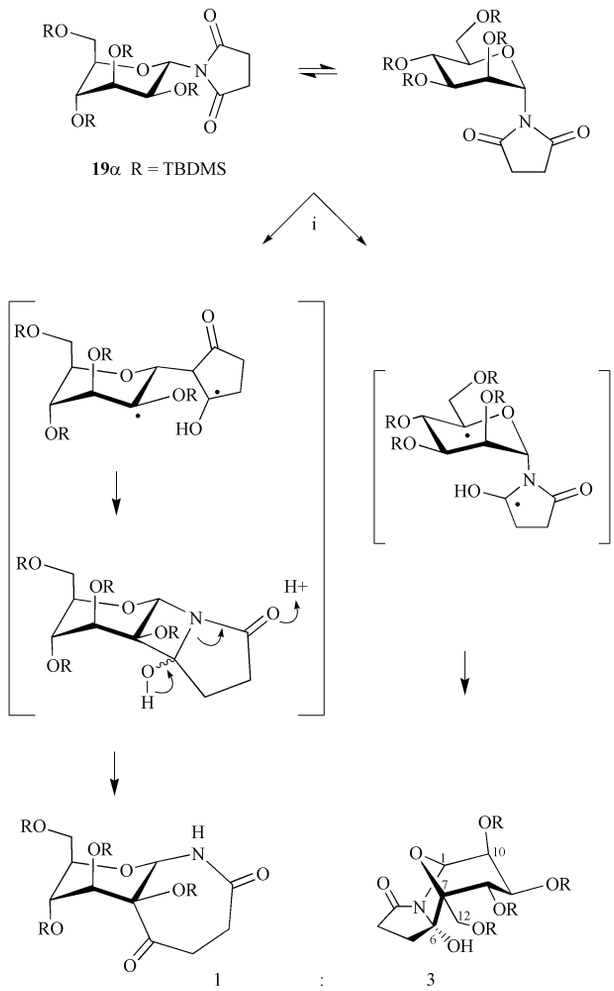
18α R = TBDMS



21 R = TBDMS

Scheme 4 *Reaction conditions*: i, *hv* 254 nm, CH_3CN, 18 °C, 2.5 h (83%).

as a side product (Scheme 5). This distribution of products corresponds to the results of the photoreaction of the analogous 2-deoxyglycosylsuccinimide **1**.[7] As with the *gluco*-configurated heterotricycle **21**, the supposed *exo*-configuration of **23** is supported by a NOESY experiment, showing again the lack of an NOE between the methylene protons at C-4 and C-5 with the protons of the pyranose ring. However, there is a strong coupling of the new hydroxy group with H-9 and weaker couplings with H^a-12, H^b-12 and H-8.

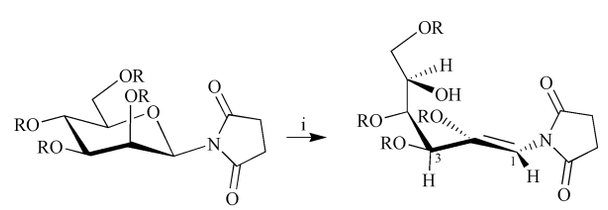


19α R = TBDMS

22 R = TBDMS, 20% **23** R = TBDMS, 62%

Scheme 5 *Reaction conditions*: i, *hv* 254 nm, CH_3CN, 18 °C, 3 h.

The photoreaction of the other *manno*-configurated compound **19**β turned out to be a special case. With no γ- or δ-hydrogen atom in a *cis*-position, a fragmentation reaction towards the 2-siloxyglycal and free succinimide was expected; instead, the acylated enamine **24** was isolated (OH δ 2.46, CH_2CH_2 δ 2.67 and δ_C 28.82, C-2 δ_C 153.02, C-1 102.6) (Scheme 6).



19β R = TBDMS **24** R = TBDMS

Scheme 6 *Reaction conditions*: i, *hv* 254 nm, CH_3CN, 18 °C, 7 h (55%).

This result indicates that the radical centre at C-2 generated by *trans*-hydrogen abstraction does not achieve the state of planarity, since in this case inversion at C-2 would be possible and should cause a transition from *manno*- to *gluco*-configuration to result in the azepanedione **20**. Since obviously there is no planarity at C-2, and because steric tension is likely to inhibit a cyclisation of the 1,4-diradical to the *trans*-annelated azetidinole, an alternative path must be considered. Through a mechanism yet unconfirmed, the bond between C-1

and the ring oxygen is homolytically cleaved and a double bond between C-1 and C-2 stereospecifically generated. The double bond is presumed to have the (*Z*)-configuration, since formation of the (*E*)-isomer would require rotation about the C-1–C-2 axis after cleavage of the bond between the ring oxygen and C-1. Since recombination of the radical centres to form the double bond is considered to be fast, rotation should not occur. This assumption was confirmed by a NOESY experiment, showing an NOE between the vinylic proton H-1 and H-3.

The photoreactions of the *N*-2-deoxyglycosylsuccinimides were accompanied by a significant amount of elimination to afford the glycal and free succinimide. The result of the irradiation of **19**β supports the hypothesis that in the case of the corresponding 2-hydroxy derivatives no such elimination is to be expected. The yields do not exceed 85% though, since the longer reaction times required for complete conversion of the starting materials are bound up with an increase in decomposition reactions, especially of the products.

The results of the photoreactions of these hexopyranosylsuccinimides confirm the observations we made with the corresponding 2-deoxy derivatives; however, advantageously, no elimination as a side reaction occurred. Furthermore, they underline the strong influence of conformational aspects on the regioselectivity of the hydrogen abstraction. Stronger control of the conformation, for example *via* fixation by using bridged sugar derivatives,[17] should lead to an even better predictability of the hydrogen abstraction. As a summary, these photoreactions of saccharide imides represent a gateway to interesting stuctures, whose chemical transformations offer versatile access to variably functionalised heterocycles and higher sugar derivatives.

Experimental

General

TLC was performed on silica gel 60-coated aluminium sheets (Merck) using the given eluent mixtures. Spots were visualised under UV light at 366 nm and by spraying with 10% sulfuric acid in ethanol and subsequent heating. Column chromatography was performed on silica gel 60 (230–240 mesh, grain size 0.040–0.063 nm, Merck). All irradiations were performed in commercial dry acetonitrile (Fluka), deoxygenated by degassing (30 min) with argon in an ultrasonic bath. A 60 W low-pressure mercury vapour lamp from the company Heraeus ($\lambda = 254$ nm) was used. The photoreactor was made of quartz glass and measured 35 cm in length and 4.5 cm in diameter and the temperature was maintained at 18 °C by water cooling. Mps were measured on an ST-apotec and are reported uncorrected. Optical rotations were measured on a Perkin-Elmer polarimeter 243, with $[\alpha]_D$-values given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the microanalytical laboratory of the Institute of Organic Chemistry of the University of Hamburg. IR absorptions were recorded on an ATI Matteson FTIR (Genesis Series). NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer. Chemical shifts are referred to the solvent used, and *J*-values are given in Hz. Petroleum spirit refers to the fraction with distillation range 50–70 °C.

2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl azide 12

A solution of β-D-glucopyranosyl azide (2.2 g, 10.7 mmol) in pyridine (50 cm^3) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (19.5 cm^3, 85.6 mmol). After two days of stirring at room temperature, the reaction was quenched by addition of methanol (10 cm^3) and the solvents were evaporated off under reduced pressure. The residue was co-distilled with toluene, taken up in dichloromethane, and washed successively with saturated aq. sodium bicarbonate and brine. Drying and evaporation of the solvent left a crude product. Purification by column chromatography using petroleum spirit–ethyl acetate (700 : 1) as eluent afforded the product **12** (5.5 g, 78%) as a colourless oil {$[\alpha]_D^{20}$ −16.8 (*c* 1.0 in $CHCl_3$); Found: C, 54.5; H, 10.25; N, 6.4. Calc. for $C_{30}H_{67}N_3O_5Si_4$: C, 54.4; H, 10.2; N, 6.3%}; ν_{max} (film)/cm^{-1} 2116 (N_3); δ_H (400 MHz; $CDCl_3$) 0.05, 0.06, 0.07, 0.075, 0.085, 0.09, 0.10, 0.105 (24 H, 8 s, CH_3Si), 0.875, 0.885, 0.889 [36 H, 3 s, $C(CH_3)_3Si$], 3.49 (1 H, dd, $J_{1,2}$ 6.6, $J_{2,3}$ 3.0, 2-H), 3.74–3.79 (3 H, m, $J_{6a,6b}$ 9.1, 4-H, 6-H_2), 3.88 (1 H, dt, $J_{4,5}$ 7.0, $J_{5,6a}$ 7.0, $J_{5,6b}$ 1.0, 5-H), 3.95 (1 H, dd, $J_{3,4}$ 1.5, 3-H), 4.89 (1 H, d, 1-H); δ_C (100.6 MHz; $CDCl_3$) −4.87, −4.37, −4.35, −4.27, −4.11, −4.03, −3.88, −3.17 (8 C, CH_3Si), 18.27, 18.34, 18.41, 18.75 (4 C, CSi), 26.05, 26.19, 26.20, 26.26, 26.33, 26.57 [12 C, $(CH_3)_3CSi$], 64.12 (C-6), 70.34 (C-3), 77.57 (C-2), 78.69 (C-4), 82.94 (C-5), 89.90 (C-1).

2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranosyl azide 13

α-D-Mannopyranosyl azide (3.2 g, 15.6 mmol) dissolved in pyridine (75 cm^3) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (28.44 cm^3, 124.8 mmol). After two days of stirring at room temperature, the reaction was quenched by addition of methanol (10 cm^3) and the solvents were evaporated off under vacuum. The residue was co-distilled with toluene, dissolved in dichloromethane, and washed successively with saturated aq. sodium bicarbonate and brine. Drying and evaporation of the solvent afforded a crude product, which was purified by column chromatography with petroleum spirit–ethyl acetate (750 : 1) as eluent to give **13** (7.89 g, 77%) as a colourless oil {$[\alpha]_D^{20}$ +70.3 (*c* 1.0 in $CHCl_3$); Found: C, 54.7; H, 10.4; N, 6.0. Calc. for $C_{30}H_{67}N_3O_5Si_4$: C, 54.4; H, 10.2; N, 6.3%}; ν_{max} (film)/cm^{-1} 2111 (N_3); δ_H (400 MHz; $CDCl_3$) 0.01, 0.05, 0.06, 0.07, 0.08, 0.09, 0.12 (24 H, 7 s, CH_3Si), 0.86, 0.88, 0.89, 0.91 [36 H, 4 s, $(CH_3)_3CSi$], [3.66 (1 H, dd), 3.71–3.79 (4 H, m), 3.84 (1 H, dd) (2-, 3-, 4-, 5-H, 6-H_2)], 5.00 (1 H, d, $J_{1,2}$ 7.1, 1-H).

2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-D-glucopyranosylamine 14

Compound **12** (5.5 g, 8.4 mmol) was dissolved in a mixture of dry ethyl acetate (25 cm^3) and dry methanol (25 cm^3) and hydrogenated using Pd/C (10%) (550 mg) by stirring at room temperature under one hydrogen atmosphere for two days. Removal of the catalyst by filtration through a short pad of Celite, and evaporation of the solvents yielded **14** (5.3 g, 100%) as a colourless oil (α : β ≈ 1 : 1), δ_H (400 MHz; C_6D_6) 0.11–0.26 (2 × 24 H, 12 s, CH_3Si), 0.97–1.07 [2 × 36 H, 5s, $C(CH_3)_3$) Si], 3.65 (1 H, dd, $J_{1\beta,2\beta}$ 5.6, 2-H), [3.88–4.00 (5 H, m), 4.02–4.06 (4 H, m) and 4.10 (1 H, dd), together 2-, 3-, 4-, 5-Hα, 6-H_2α, 3-, 4-Hβ, 6-H_2β], 4.15 (1 H, ddd, 5-Hβ), 4.50 (1 H, d, 1-Hβ), 4.80 (1 H, d, $J_{1\alpha,2\alpha}$ 3.0, 1-Hα); δ_C (100.6 MHz; C_6D_6) −4.77 to −3.41 (2 × 8 C, CH_3Si), 18.4–18.7 (2 × 4 C, CSi), 26.21–26.66 [2 × 12 C, $(CH_3)_3CSi$], 63.83, 64.94 (C-6α, -6β), 71.60, 72.02, 73.21, 76.00, 76.95, 77.90, 79.57, 79.64, 80.75, 85.58 (C-5αβ, -4αβ, -3αβ, -2αβ, -1αβ).

2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-D-mannopyranosylamine 15

To a solution of azide **13** (4.0 g, 6.0 mmol) in a mixture of dry ethyl acetate (25 cm^3) and dry methanol (25 cm^3) was added Pd/C (10%) (600 mg). After stirring at room temperature under one atmosphere of hydrogen for two days, the catalyst was removed by filtration through a short pad of Celite. Evaporation of the mixture afforded **15** (3.76 g, 98%) as a colourless oil (α : β ≈ 2 : 1). Anomer **15**α showed δ_H (400 MHz; C_6D_6) 0.07–0.28 (24 H, CH_3Si), 0.95–1.08 [36 H, $(CH_3)_3CSi$], 3.91 (1 H, dd, $J_{1,2}$

8.6, $J_{2,3}$ 2.5, 2-H), 3.99 (1 H, dd, $J_{5,6a}$ 5.6, $J_{6a,6b}$ 12.2, 6-H^a), 4.06 (2 H, m, 3-, 4-H), 4.12 (1 H, ddd, $J_{4,5}$ 2.5, $J_{5,6b}$ 2.5, 5-H), 4.18 (1 H, dd, 6-H^b), 4.60 (1 H, 1-H); δ_C (100.6 MHz; C_6D_6) −2.92–0.00 (8 C, CH_3Si), 20.00–21.39 (4 C, CSi), 28.01–29.19 [12 C, $(CH_3)_3CSi$], 65.33 (C-6), 73.88 (C-5), 74.63 (C-2), 78.60 (C-4), 81.60 (C-1), 85.91 (C-3).

N-[2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-D-glucopyranosyl]-succinimide 18

A suspension of **14** (2.5 g, 3.9 mmol), succinic anhydride (3.90 g, 39.0 mmol) and *N*-ethyldiisopropylamine (0.66 cm^3, 3.9 mmol) in dry dichloromethane (50 cm^3) was stirred overnight at room temperature. After addition of methanol (10 cm^3) the solvents were evaporated off under reduced pressure. The reaction mixture was dissolved in a mixture of dry pyridine (50 cm^3) and acetic anhydride (50 cm^3) and the solution was stirred for three days at 60 °C, poured into ice–water (500 cm^3), and acidified to pH 3 with 2 M hydrochloric acid. After extraction of the aqueous solution with dichloromethane the combined organic layers were neutralised with saturated aq. sodium bicarbonate and washed with brine. Drying and evaporation of the solvent afforded a crude product, which was purified by column chromatography using petroleum spirit–ethyl acetate (80 : 1) as eluent, to give the separated anomers **18**α (0.89 g, 32%) and **18**β (0.66 g, 23%) both as colourless crystals. Isomer **18**α showed mp 105 °C; $[\alpha]_D^{20}$ +21.7 (*c* 1 in $CHCl_3$) (Found: C, 57.1; H, 10.1; N, 1.9. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1781, 1705 (CO); δ_H (400 MHz; $CDCl_3$) −0.13, 0.00, 0.01, 0.06, 0.09, 0.10, 0.11, 0.14 (24 H, 8 s, CH_3Si), 0.84, 0.86, 0.87, 0.90 [36 H, 4 s, $(CH_3)_3CSi$], 2.53–2.67 (4 H, m, CH_2CH_2, imide), 3.75–3.86 (3 H, m, $J_{2,3}$ 7.6, 6-H$_2$, 3-H), 3.95 (1 H, ddd, $J_{1,2}$ 4.0, 2-H), 4.04 (1 H, d, 4-H), 4.39 (1 H, ddd, 5-H), 5.74 (1 H, d, 1-H); δ_C (100.6 MHz; $CDCl_3$) −4.99, −4.58, −4.41, −4.32, −4.18, −3.64, −3.53 (8 C, CH_3Si), 18.01, 18.24, 18.41, 18.74 (4 C, CSi), 26.04, 26.34, 27.33 [12 C, $(CH_3)_3CSi$], 28.88 (2 C, CH_2CH_2, imide), 61.97 (C-6), 71.10 (C-2), 72.32 (C-4), 76.50 (C-3), 77.01 (C-5), 81.33 (C-1), 176.36 (2 C, C=O).

Isomer **18**β showed mp 103 °C; $[\alpha]_D^{20}$ +2.5 (*c* 1 in $CHCl_3$) (Found: C, 56.9; H, 10.0; N, 2.0. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1785, 1721 (CO); δ_H (400 MHz; $CDCl_3$) −0.11, 0.01, 0.015, 0.04, 0.08, 0.10, 0.11, 0.14 (24 H, 8 s, CH_3Si), 0.79, 0.86, 0.90, 0.92 [36 H, 4 s, $(CH_3)_3CSi$], 2.64 (4 H, s, CH_2CH_2, imide), 3.66–3.78 (2 H, m, $J_{6a,6b}$ 11.2, 6-H$_2$), 3.86 (1 H, d, $J_{3,4}$ 3.0, 4-H), 3.94 (1 H, dd, $J_{5,6a}$ 5.6, $J_{5,6b}$ 9.1, 5-H), 4.03 (1 H, d, 3-H), 4.87 (1 H, d, $J_{1,2}$ 8.6, 2-H), 5.64 (1 H, d, 1-H); δ_C (100.6 MHz; $CDCl_3$) −4.88, −4.57, −4.54, −4.25, −4.11, −3.59, −3.38 (8 C, CH_3Si), 18.27, 18.33, 18.75 (4 C, CSi), 25.98, 26.19, 26.21, 26.35 [12 C, $(CH_3)_3CSi$], 28.41 (2 C, CH_2CH_2, imide), 64.19 (C-6), 70.14 (C-3), 72.02 (C-2), 79.19 (C-4), 79.40 (C-1), 84.01 (C-1), 176.87 (2 C, C=O).

N-[2,3,4,6-Tetra-*O*-*tert*-butyldimethylsilyl-D-mannopyranosyl]-succinimide 19

A solution of **15** (3.7 g, 5.8 mmol) in dry dichloromethane (50 cm^3) was treated with succinic anhydride (5.80 g, 58.0 mmol) and *N*-ethyldiisopropylamine (0.99 cm^3, 5.8 mmol) overnight at room temperature. The reaction was quenched by addition of methanol (20 cm^3). After evaporating off the solvents, the residue was dissolved in a mixture of dry pyridine (50 cm^3) and acetic anhydride (50 cm^3) and stirred for five days at 100 °C. The solution was poured into ice–water (500 cm^3) and acidified to pH 3 with 2 M hydrochloric acid. After extraction of the aqueous solution with dichloromethane, the combined organic layers were neutralised with saturated aq. sodium bicarbonate and washed with brine. Drying and evaporation of the solvent provided a crude product, which was purified by column chromatography using petroleum spirit–ethyl acetate (10 : 1) as eluent. Separation of the anomeric mixture was performed by a second column chromatography process using petroleum spirit–ethyl acetate (70 : 1) to afford anomers **19**α (1.14 g, 27%) and **19**β (381.7 mg, 9%), both as white crystalline solids.

Anomer **19**α had mp 109 °C; $[\alpha]_D^{20}$ +40.0 (*c* 1.0 in $CHCl_3$) (Found: C, 56.5; H, 10.10; N, 1.90. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1784, 1716 (CO); δ_H (400 MHz; C_6D_6) 0.07, 0.12, 0.14, 0.16, 0.19, 0.27, 0.32, 0.44 (24 H, 8 s, CH_3Si), 0.94, 1.01, 1.02, 1.10 [36 H, 4 s, $(CH_3)_3CSi$], 1.75–1.95 (4 H, br m, CH_2CH_2, imide), 4.01 (1 H, dd, $J_{5a,6}$ 6.1, $J_{6a,6b}$ 11.2, 6-H^a), 4.11–4.15 (2 H, m, 6-H^b, 4-H), 4.19 (1 H, dd, $J_{3,4}$ 3.0, $J_{2,3}$ 2.0, 3-H), 4.55 (1 H, ddd, $J_{5,6b}$ 4.6, 5-H), 5.30 (1 H, dd, $J_{1,2}$ 9.1, 2-H), 6.14 (1 H, d, 1-H); δ_C (100.6 MHz; C_6D_6) −4.84, −4.67, −4.61, −4.36, −4.00, −3.51, −3.08 (8 C, CH_3Si), 18.36, 18.43, 18.78, 18.89 (4 C, CSi), 26.18, 26.32, 26.44, 26.48 [12 C, $(CH_3)_3CSi$], 28.31 (2 C, CH_2CH_2, imide), 63.69 (C-6), 66.57 (C-2), 72.45 (C-3), 77.37, 77.43 (C-4, -1), 81.05 (C-5), 176.6 (2 C, C=O).

Anomer **19**β showed mp 79 °C; $[\alpha]_D^{20}$ +19.5 (*c* 1.0 in $CHCl_3$) (Found: C, 56.8; H, 9.7; N, 1.95. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1784, 1717 (CO); δ_H (400 MHz; $CDCl_3$) −0.09, 0.03, 0.07, 0.09, 0.11, 0.12, 0.15 (24 H, CH_3Si), 0.87, 0.89, 0.90, 0.95 [36 H, 4 s, $(CH_3)_3CSi$], 2.615 (4 H, s, CH_2CH_2, imide), 3.27 (1 H, ddd, $J_{4,5}$ 8.1, $J_{5,6a}$ 6.6, $J_{5,6b}$ 3.0, 5-H), 3.67–3.78 (2 H, m, 3-H, 6-H^a), 3.88 (1 H, dd, $J_{6a,6b}$ 10.7, 6-H^b), 3.98 (1 H, t, $J_{3,4}$ 8.6, 4-H), 4.11 (1 H, dd, $J_{1,2}$ 2.0, $J_{2,3}$ 7.1, 2-H), 5.27 (1 H, d, 1-H); δ_C (100.6 MHz; $CDCl_3$) −2.88, −2.86, −2.03, −1.84, −1.48, −1.31, −0.96, 0.00 (8 C, CH_3Si), 20.62, 20.65, 21.11, 21.72 (4 C, CSi), 28.40, 28.52, 28.81, 29.48 [12 C, $(CH_3)_3CSi$], 30.75 (2 C, CH_2CH_2, imide), 65.98 (C-6), 70.66 (C-2), 75.34 (C-4), 78.44 (C-3), 84.88 (C-5), 86.45 (C-1), 177.25 (2 C, C=O).

(1*R*,7*R*,8*S*,9*R*,10*R*)-7,8,9-Tri(*tert*-butyldimethylsiloxy)-10-*tert*-butyldimethylsiloxymethyl-11-oxa-2-azabicyclo[5.4.0]-undecane-3,6-dione 20

Compound **18**β (144 mg, 0.20 mmol) was dissolved in dry, deoxygenated acetonitrile (200 cm^3) and irradiated at 18 °C under an argon atmosphere for 3 hours. Purification by column chromatography with petroleum spirit–ethyl acetate (35 : 1 to 20 : 1) yielded recovered starting material **18**β (7.2 mg, 5%) and title bicycle **20** (99.0 mg, 69%) as white crystals, mp 174–179 °C (subl.); $[\alpha]_D^{20}$ +76.3 (*c* 1 in $CHCl_3$) (Found: C, 56.95; H, 10.0; N, 1.95. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1729 (CO), 1671 (N–CO); δ_H (400 MHz; $CDCl_3$) −0.09, 0.02, 0.06, 0.07, 0.08, 0.10, 0.12, 0.13 (24 H, 8 s, CH_3Si), 0.85, 0.88, 0.89, 0.90 [36 H, 4 s, $(CH_3)_3CSi$], 2.29 (1 H, ddd, $J_{4a,4b}$ 14.7, $J_{4a,5b}$ 6.6, $J_{4a,5b}$ 5.1, 4-H^a), 2.53 (1 H, ddd, $J_{5a,5b}$ 21.2, $J_{4b,5a}$ 7.1, 5-H^a), 2.73 (1 H, ddd, $J_{4b,5b}$ 4.5, 4-H^b), 3.74 (1 H, ddd, 5-H^b), 3.83 (2 H, m, $J_{12a,12b}$ 7.6, 12-H^a, 12-H^b), 4.00 (1 H, dd, $J_{8,9}$ 2.5, $J_{9,10}$ 1.0, 9-H), 4.06 (1 H, d, 8-H), 4.12 (1 H, dt, $J_{10,12a}$ 7.6, $J_{10,12b}$ 7.6, 10-H), 4.86 (1 H, d, $J_{1,NH}$ 7.6, 1-H), 6.35 (1 H, d, NH); δ_C (100.6 MHz; d$_6$-DMSO–$CDCl_3$) −5.67, −5.52, −5.50, −4.84, −4.26, −3.25, −2.90 (8 C, CH_3Si), 17.42, 17.58, 17.99, 18.35 (4 C, CSi), 25.50, 25.67, 25.72, 26.17 [12 C, $(CH_3)_3CSi$], 31.38 (C-4), 35.35 (C-5), 63.42 (C-12), 69.62 (C-8), 80.58 (C-1), 82.18 (C-9), 83.45 (C-7), 83.58 (C-10), 173.20 (C-3, NC=O), 206.93 (C-6, C=O).

(1*S*,6*S*,7*R*,8*S*,9*S*,10*R*)-8,9,10-Tri(*tert*-butyldimethylsiloxy)-7-*tert*-butyldimethylsiloxymethyl-6-hydroxy-11-oxa-2-azatricyclo[5.3.1.0^{2,6}]undecan-3-one 21

Irradiation of **18**α (195 mg, 0.27 mmol) in dry, deoxygenated acetonitrile (200 cm^3) was performed at 18 °C under an atmosphere of argon for 2.5 hours. Purification by column chromatography with petroleum spirit–ethyl acetate (25 : 1) afforded **21** (162 mg, 83%) as white crystals, mp 84 °C; $[\alpha]_D^{20}$ +3.0 (*c* 1 in $CHCl_3$) (Found: C, 56.95; H, 10.2; N, 1.9. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1729 (CO); δ_H (400 MHz; $CDCl_3$) 0.06, 0.07, 0.16, 0.19, 0.21, 0.25 (24 H, CH_3Si), 0.89, 0.90, 0.91, 0.92 [36 H, $(CH_3)_3CSi$], 2.01

(1 H, ddd, $J_{5a,5b}$ 14.7, $J_{4a,5a}$ 4.6, $J_{4b,5a}$ 7.6, 5-H^a), 2.09 (1 H, ddd, $J_{4a,4b}$ 12.7, $J_{4a,5b}$ 7.6, 4-H^a), 2.18 (1 H, ddd, $J_{4b,5b}$ 5.1, 5-H^b), 2.90 (1 H, ddd, 4-H^b), 3.74 (1 H, d, $J_{12a,12b}$ 11.7, 12-H^a), 3.94 (1 H, dd, $J_{1,10}$ 3.5, $J_{9,10}$ 7.1, 10-H), 4.01 (1 H, d, 12-H^b), 4.16 (1 H, t, $J_{8,9}$ 7.1, 9-H), 4.27 (1 H, d, 8-H), 5.28 (1 H, d, 1-H), 6.66 (1 H, s, OH); δ_C (100.6 MHz; $CDCl_3$) −2.72, −2.40, −1.79, −0.43, 0.00, 0.31, 0.81, 1.31 (8 C, CH_3Si), 20.89, 20.95, 21.11 (4 C, CSi), 28.47, 28.67, 28.82, 29.38 [12 C, $(CH_3)_3CSi$], 34.00 (C-4), 37.86 (C-5), 63.55 (C-12), 77.31 (C-10), 78.49 (C-8), 83.15 (C-9), 85.17 (C-7), 88.82 (C-1), 102.15 (C-6), 184.39 (C-3, C=O).

(1*S*,7*S*,8*S*,9*R*,10*R*)-7,8,9-Tri(*tert*-butyldimethylsiloxy)-10-*tert*-butyldimethylsiloxymethyl-11-oxa-2-azabicyclo[5.4.0]-undecane-3,6-dione 22 and (1*S*,6*S*,7*R*,8*S*,9*S*,10*S*)-8,9,10-tri(*tert*-butyldimethylsiloxy)-7-*tert*-butyldimethylsiloxymethyl-6-hydroxy-11-oxa-2-azatricyclo[5.3.1.0^{2,6}]undecan-3-one 23

A solution of **19**α (167 mg, 0.23 mmol) in dry, deoxygenated acetonitrile (200 cm^3) was irradiated at 18 °C under an atmosphere of argon for 3 hours. Purification and separation of the products were performed by column chromatography with petroleum spirit–ethyl acetate (25 : 1) as eluent. Besides unchanged **19**α (15 mg, 9% recovery), products **22** (33.9 mg, 20%) and **23** (103.7 mg, 62%) were also isolated.

Compound **22** was obtained as a colourless oil, $[\alpha]_D^{20}$ −22.9 (*c* 1 in $CHCl_3$) (Found: C, 57.2; H, 10.1; N, 1.9. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1713 (CO), 1667 (N–CO); δ_H (400 MHz; $CDCl_3$) −0.09, 0.05, 0.055, 0.06, 0.07, 0.14, 0.16, 0.21 (24 H, 8 s, CH_3Si), 0.84, 0.85, 0.89, 0.92 [36 H, 4 s, $(CH_3)_3CSi$], 2.42 (1 H, ddd, $J_{5a,5b}$ 14.2, $J_{4a,5a}$ 6.1, $J_{4b,5a}$ 4.1, 5-H^a), 2.62 (1 H, ddd, $J_{4a,4b}$ 18.3, $J_{4a,5b}$ 12.2, 4-H^a), 2.87 (1 H, ddd, $J_{4b,5b}$ 7.1, 5-H^b), 3.90–4.14 (5 H, m, 12-H_2, 8-, 9-, 10-H), 4.09 (1 H, ddd, 5-H^b), 4.68 (1 H, d, $J_{1,NH}$ 8.1, 1-H), 6.36 (1 H, d, NH); δ_C (100.6 MHz; d_6-DMSO–$CDCl_3$) −4.80, −4.56, −3.53, −2.49 (8 C, CH_3Si), 17.92, 18.23, 18.86 (4 C, CSi), 25.66, 25.92, 26.40, 26.60 [12 C, $(CH_3)_3CSi$], 31.27 (C-4), 37.73 (C-5), 61.59 (C-12), 70.27, 78.16, 82.12 (3 C, C-8, -9, -10), 76.66 (C-1), 82.13 (C-7), 174.16 (C-3, NC=O), 208.69 (C-6, C=O).

Compound **23** was found to be a white crystalline solid, mp 95 °C; $[\alpha]_D^{20}$ −25.0 (*c* 1 in $CHCl_3$) (Found: C, 56.8; H, 10.1; N, 1.95. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1728 (CO); δ_H (400 MHz; d_6-DMSO–$CDCl_3$) 0.18, 0.21, 0.22, 0.23, 0.26, 0.31 (24 H, CH_3Si), 1.01, 1.02, 1.02, 1.05 [36 H, $(CH_3)_3CSi$], 2.14 (1 H, dd, $J_{5a,5b}$ 12.2, $J_{4b,5a}$ 6.6, 5-H^a), 2.26 (1 H, dd, $J_{4a,4b}$ 15.2, $J_{4a,5b}$ 7.6, 4-H^a), 2.36 (1 H, ddd, $J_{4b,5b}$ 12.2, 5-H^b), 2.99 (1 H, ddd, 4-H^b), 3.92 (1 H, d, $J_{12a,12b}$ 12.2, 12-H^a), 4.04 (1 H, t, $J_{1,10}$ 3.5, $J_{9,10}$ 3.5, 10-H), 4.15 (1 H, d, 12-H^b), 4.31 (1 H, d, $J_{8,9}$ 9.1, 8-H), 4.64 (1 H, dd, 9-H), 5.21 (1 H, d, 1-H), 6.27 (1 H, s, OH); δ_C (100.6 MHz; d_6-DMSO–$CDCl_3$) −2.79, −2.46, −2.12, −1.87, −0.67, −0.63, −0.24, 0.00 (8 C, CH_3Si), 20.65, 20.69, 20.93 (4 C, CSi), 28.50, 28.58, 28.88, 29.51 [12 C, $(CH_3)_3CSi$], 33.74 (C-4), 37.97 (C-5), 62.95 (C-12), 74.49 (C-10), 74.90 (C-9), 75.31 (C-8), 85.96 (C-7), 89.15 (C-1), 101.18 (C-6), 185.09 (C-3, C=O).

N-[(*Z*)-(3*S*,4*R*,5*R*)-2,3,4,6-Tetra(*tert*-butyldimethylsiloxy)-5-hydroxyhex-1-enyl]succinimide 24

Compound **19**β (94.8 mg, 0.13 mmol) was dissolved in dry, deoxygenated acetonitrile (200 cm^3) and irradiated at 18 °C under an argon atmosphere for 7 hours. The crude product was purified by column chromatography with petroleum spirit–ethyl acetate (25 : 1) as eluent to afford **24** (52.2 mg, 55%) as a colourless oil, $[\alpha]_D^{20}$ +11 (*c* 1 in $CHCl_3$) (Found: C, 57.1; H, 10.0; N, 1.9. Calc. for $C_{34}H_{71}NO_7Si_4$: C, 56.85; H, 9.96; N, 1.95%); ν_{max} (film)/cm^{-1} 1784, 1720 (CO); δ_H (400 MHz; $CDCl_3$) 0.01, 0.07, 0.075, 0.09, 0.13, 0.14, 0.15, 0.21 (24 H, 8 s, CH_3Si), 0.86, 0.87, 0.88, 0.89 [36 H, 4 s, $(CH_3)_3CSi$], 2.46 (1 H, d, $J_{5,OH}$ 5.6, OH), 2.67 (4 H, s, CH_2CH_2, imide), 3.59 (1 H, m, $J_{4,5}$ 3.5, $J_{5,6a}$ 5.6, $J_{5,6b}$ 3.5, 5-H), 3.67 (1 H, dd, $J_{6a,6b}$ 10.2, 6-H^a), 3.82 (2 H, m, 6-H^b, 4-H), 4.41 (1 H, s, 3-H), 5.66 (1 H, s, 1-H); δ_C (100.6 MHz; $CDCl_3$) −4.96, −4.75, −4.71, −3.86, −3.81, −3.77, −3.60, −3.11 (8 C, CH_3Si), 18.41, 18.60, 18.67, 18.91 (4 C, CSi), 26.00, 26.05, 26.31, 26.66 [12 C, $(CH_3)_3CSi$], 28.82 (2 C, CH_2CH_2, imide), 64.89 (C-6), 71.51 (C-5), 72.12 (C-4), 72.15 (C-3), 102.58 (C-1), 153.02 (C-2), 175.66 (2 C, C=O).

Acknowledgements

Support of this study by the Fonds der Chemischen Industrie is gratefully acknowledged. This paper is dedicated to the memory of Prof. Göran Magnusson, an excellent colleague in chemistry and a very good friend.

References

1 D. J. Triggle, D. A. Langs and R. A. Janis, *Med. Res. Rev.*, 1989, **9**, 123.
2 V. J. Merluzzi, K. D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J. C. Wu, K.-C. Shih, K. Eckner, S. Hattox, J. Adams, A. S. Rosenthal, R. Faanes, R. J. Eckner, K. R. Koup and J. L. Sullivan, *Science*, 1990, **250**, 1411.
3 R. S. McDowell, K. B. Blackburn, T. R. Gadek, L. R. McGee, T. Rawson, M. E. Reynolds, K. D. Robarge, T. C. Somers, E. D. Thorsett, M. Tischler, R. R. Webb II and M. C. Venuti, *J. Am. Chem. Soc.*, 1994, **116**, 5077.
4 K.-H. Weber, in *Nutzen und Gefahren der Therapie mit Benzodiazepinen*, ed. U. Borchard and C. Haring, Steinkopff Verlag, Darmstadt, 1986, pp. 1–14.
5 K.-H. Weber, in *Sleep and Wakefulness*, ed. A. N. Nicholson and J. B. Welber, Boehringer, Ingelheim, 1985.
6 C. E. Sowa, J. Kopf and J. Thiem, *J. Chem. Soc., Chem. Commun.*, 1995, 211.
7 C. E. Sowa and J. Thiem, *Angew. Chem.*, 1994, **106**, 2041; C. E. Sowa and J. Thiem, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1979.
8 L. Laupichler, C. E. Sowa and J. Thiem, *Bioorg. Med. Chem.*, 1994, **2**, 1281.
9 C. E. Sowa, M. Stark, T. Heidelberg and J. Thiem, *Synlett*, 1996, 227.
10 C. Krog-Jensen and S. Oscarson, *J. Org. Chem.*, 1996, **61**, 1234.
11 L. Birkhofer and A. Ritter, *Angew. Chem.*, 1965, **77**, 414; L. Birkhofer and A. Ritter, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 417.
12 H. Paulsen, Z. Györgydeák and M. Friedmann, *Chem. Ber.*, 1974, **107**, 1568.
13 R. U. Lemieux, S. Z. Abbas, M. H. Burzynskas and R. M. Ratcliffe, *Can. J. Chem.*, 1982, **60**, 63.
14 R. R. Schmidt and G. Grundler, *Carbohydr. Res.*, 1985, **135**, 203.
15 S. Thiering, Diploma Thesis, Universität Hamburg, 1998.
16 A. Gilbert and J. Baggot, *Essentials of Molecular Photochemistry*, Blackwell, Oxford, 1991.
17 S. Thiering, C. Sund and J. Thiem, in preparation.