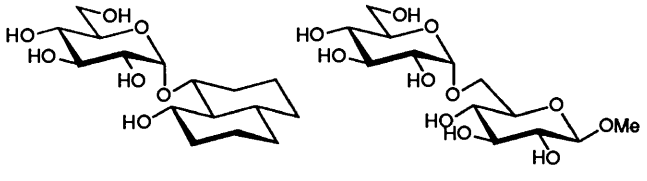
Synthesis of a Conformationally Rigid Isomaltose Analogue: Remarkable Example of Enantioselective Glycosylation

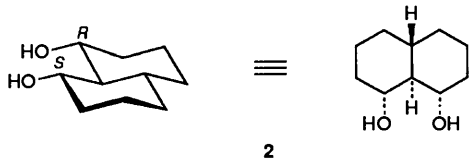
Klaus Bock* and Troels Skrydstrup
Department of Chemistry, Carlsberg Laboratory, Gamle Carlsberg Vej 10, DK-2500 Copenhagen Valby, Denmark

The synthesis of the dihydroxydecalin **2** has been accomplished based on intramolecular nitrile oxide cyclization using the nitro cyclohexene derivative **13** in 29% overall yield. Several glycosylation reagents and promoters using the diol **2** as aglycone and activated derivatives of tetra-*O*-benzyl-D-glucopyranose as glycosyl donors were investigated for the selective monoglucosylation of **2** (*i.e.*, enantioselective glycosylation) giving preferably the *R*-COH glycoside **1**, which represents a rigid analogue of isomaltose. Trimethylsilyl trifluoromethanesulphonate (TMSOTf) and tetra-*O*-benzylglucopyranose 1-acetate proved to be the best, and gave, under thermodynamic control, excellent regioselectivity and acceptable stereoselectivity.

In connection with work on the substrate specificity of the starch-degrading enzyme amyloglucosidase (E.C. 3.2.1.3),[1] a need arose for 8-hydroxydecahydro-1-naphthyl α-D-glucopyranoside **1**, an isomaltose model, in which the torsional angle defined by O^6–C^6–C^5–O^5 is 180° (*tg*-conformation). For the preparation of compound **1**, this in turn required preparation of the dihydroxydecalin **2**, a seemingly simple yet hitherto unknown compound. Closer examination of compound **2** reveals the presence of two enantiotopic hydroxy groups locked in a rigid bicyclic construction. We were therefore intrigued by the possibility of whether or not the intrinsic structural and reactive properties of various glucosyl donors could generate any selectivity upon the monoglucosylation of diol **2** (*e.g.*, enantioselective glycosylation) and in this particular case preferably on the (*R*)-C-OH. If this can be achieved, selective protection of the (*S*)-C-OH of diol **2** could be avoided. We now disclose our results along these lines for the preparation of glucoside **1**, as well as a short stereoselective synthesis of the diol **2**.



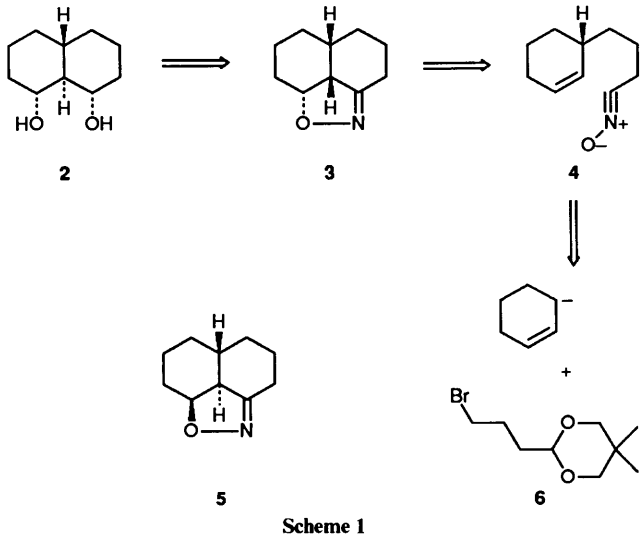
1 Isomaltose



2

Results and Discussion

Retrosynthetically, the construction of diol **2** was envisaged to proceed through the INOC protocol (*i*ntramolecular *n*itrile *o*xide *c*yclization) as described by Kozikowski for the construction of the decalin core of compactin (Scheme 1).[2] Thus, cyclization of nitrile oxide **4** would lead to the isoxazoline **3**, addressing two of the four stereogenic centres of the diol **2**, and allowing for the appropriate introduction of the remaining two. Of particular interest in this approach was the facial selectivity of compound **4** that would be obtained, affording the *cis*-fused decalin **3** and the *trans*-fused decalin **5** because compound **4** represents the simplest model for decalin synthesis by the INOC approach. Molecular mechanics calculations and computation-based modelling methods performed by Kozikowski's group indicated that a *ca.* 3 kcal mol^{-1} energy difference exists between the minimum energies of the isoxazolines **3** and **5** in favour of **3**, as well as between the corresponding transition states during cyclization.[2a] Hence, exclusive production of compound **3** would be predicted, although this has not been shown experimentally. Formation of nitrile oxide **4** is believed to take place by initial condensation of the cyclohexenyl anion with bromide **6** followed by further elaboration.

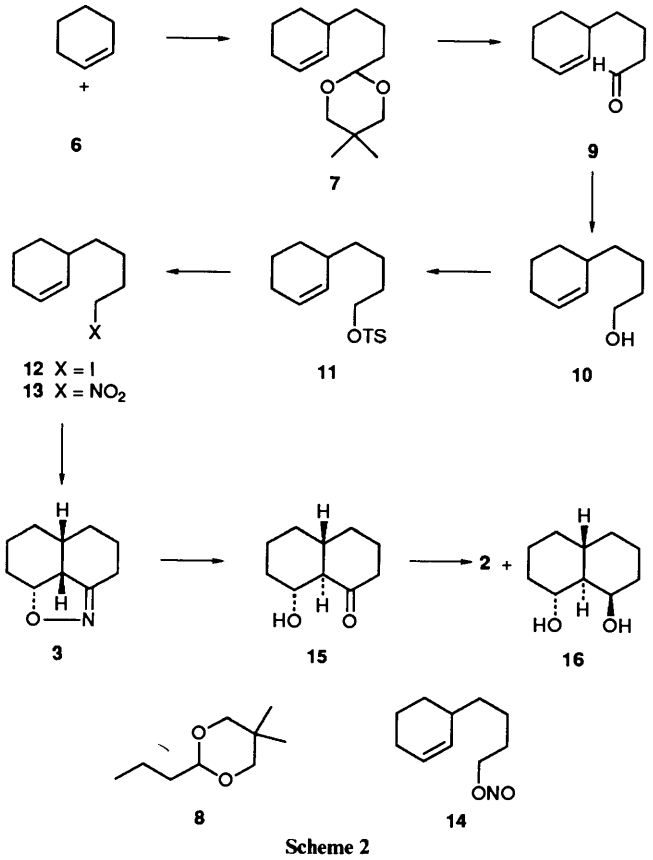


Scheme 1

Synthesis of Diol **2**.—Metallation of cyclohexene with butyllithium-potassium t-butoxide according to the procedure of Hartmann and Schlosser,[3] followed by treatment with 2-(3-bromopropyl)-5,5-dimethyl-1,3-dioxane **6** gave acetal **7** in 85% yield, plus a 13% yield of the reduced product **8**. Attempted coupling of the cyclohexenyl anion with the corresponding iodide, or halogen-metal exchange of compound **6** with Bu^tLi (2 mol equiv.) and subsequent addition of 3-bromocyclohexene, led only to reduced yields of compound **7** and increased yields of compound **8**. Efforts towards the direct hydrolysis of compound **7** proved futile. Hence, a two-step procedure was devised, consisting first of reacetalization to the corresponding

dimethyl acetal, followed by hydrolysis in the presence of acetone and *p*-TsOH to furnish aldehyde **9**. Without isolation, compound **9** was reduced in the presence of sodium borohydride to give primary alcohol **10**. Tosylation of alcohol **10**, and subsequent transformation of the ester **11** with NaI gave iodide **12**, which was converted into a mixture of nitro compound **13** and the nitrite ester **14** in the ratio of 1.5:1, upon treatment with $AgNO_2$.[4]

Dehydration of nitro compound **13** with phenyl isocyanate and cyclization led to a single isoxazoline isomer,[5] which was assigned as (±)-**3**, in analogy with observations by Kozikowski.[2a] Hydrogenation with Raney-nickel in the presence of AcOH gave the *trans*-fused hydroxydecalinone (±)-**15**, which upon the treatment with $NaBH_4$ furnished a mixture of diols **2** and (±)-**16** in the ratio 10:1, respectively, in 35% overall yield from nitro compound **13** (Scheme 2). The observed facially selective reduction of ketone (±)-**15** by $NaBH_4$, with preference for axial attack, is in agreement with stereochemical studies on the reduction of cyclohexanones by hydride reagents.[6]



Scheme 2

The assignment of all four stereogenic centres of the major diol obtained to stereostructure **2** was based on the following ^{13}C and ^1H NMR spectral observations. Since structure **2** belongs to point group C_s, only 6 carbon signals would be observed in the ^{13}C NMR spectrum, as is the case for the major diol, in contrast to compound **16**, where 10 signals would be expected, and are seen for the minor diol. The relative configurations can easily be determined by measurement of the coupling constants of the C-8a methine proton since, as for compound **2**, three large *trans*-axial coupling constants would be expected. Indeed, after acetylation of the major diol, the ^1H NMR spectrum revealed a double triplet for the C-8a proton at δ 1.54, with $J_{8a\text{-}H,1\text{-}H} = J_{8a\text{-}H,4a\text{-}H} = 10.2$ Hz. On the other hand, for compound **16** two large *trans*-axial and one *cis*-axial, equatorial couplings of the C-8a proton would be expected, and after acetylation of the minor diol, a double double doublet with $J_{8a\text{-}H,1\text{-}H} = J_{8a\text{-}H,4a\text{-}H} = 11.0$, $J_{8a\text{-}H,8\text{-}H} = 2.5$ Hz was observed. Hence the stereochemical outcome of the INOC reaction, epimerization of the C-8a proton during hydrogenation of (±)-**3**, as well as the assignment of the major diol as compound **2** after reduction, have been established.

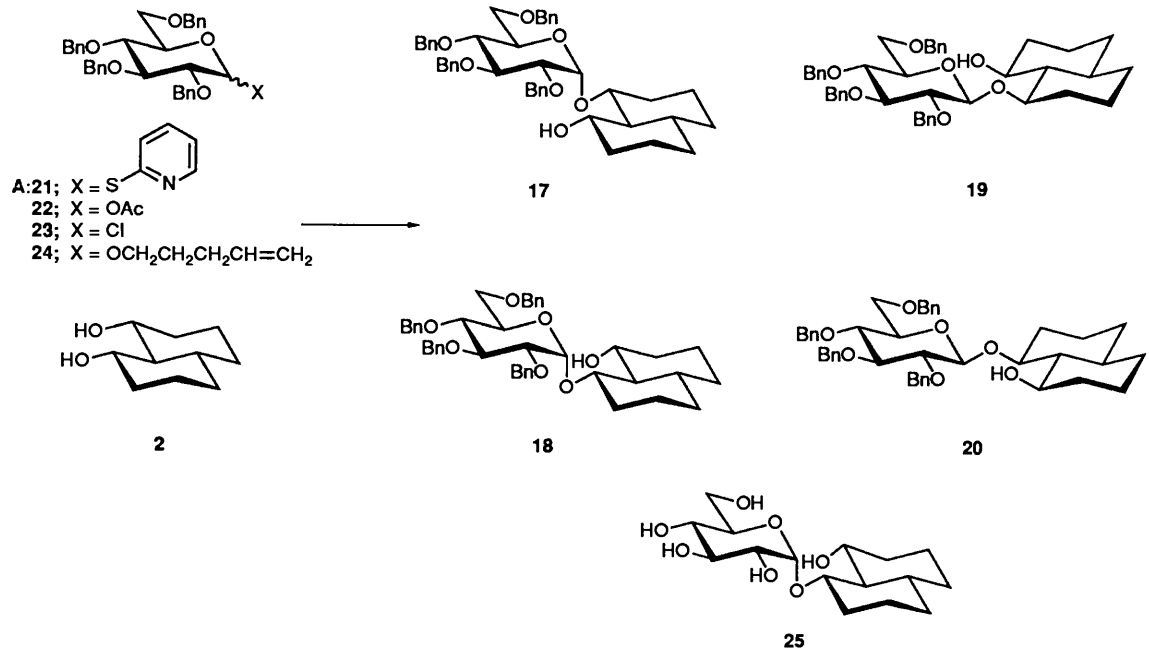
Glycosylation Studies of Diol **2**.—Several glucosylating reagents were allowed to react with the diol **2**, as shown in Table 1. We initially chose a recently published method by Mereyala and co-workers for the mild synthesis of α-linked disaccharides,[7] employing the 2-thiopyridyl glucoside **21** and MeI as a promoter. As can be seen, upon treatment of compound **2** with one mol equiv. of compound **21** in CH_2Cl_2 a 1.9:1 mixture of the tetrabenzyl-α-glucosides **17** and **18** was obtained, which was inseparable by chromatographic means; however, neither of the β-glucosides **19** and **20** was detected. Upon hydrogenation, glucosides **1** and **25** were obtained and could be separated by column chromatography. Assignment of the two glucosides was based on nuclear Overhauser effect (NOE) experiments, in comparison with those calculated for the minimum-energy conformations of compounds **1** and **25**, using the Hard Sphere Exo Anomeric (HSEA) program,[8] and those of 3-deoxymaltose, an analogue of compound **25**. These results suggest that the major glucoside, obtained in the above mentioned glycosylation, is compound **1**.[8] Although a modest selectivity was observed when using the 2-thioglucoside **21**, and some selectivity might possibly have been expected, due to the chiral nature of glucose, we were surprised to find that upon treatment of diol **2** with one mol equiv. of tetrabenzylglucosyl acetate **22**, in CH_2Cl_2 and in the presence of trimethylsilyl trifluoromethane sulphonate, *the selectivity was increased to* 16.6:1 *in favour of the* (R)-*COH group of compound* **2**, whereas the α:β selectivity was reduced to 7.3:1. On the other hand, exposure of diol **2** to either tetrabenzylglucosyl chloride **23** (1 equiv.) and silver triflate in CH_2Cl_2, or the pent-4-enyl tetrabenzylglucoside **24** (1 mol equiv.) and bis-(2,4,6-trimethylpyridyl)iodonium perchorate in CH_2Cl_2,[9] gave in both cases no enantioselective glycosylation and low α:β selectivity. In the latter case, however, the α:β selectivity could be increased substantially by employing the solvent system Et_2O–CH_2Cl_2 (5:1),[9] although the enantioselectivity remained the same.

In an attempt to explain the selectivities obtained we

Table 1 Glycosylation studies of diol **2**[a]

A	Promoter	Product: Overall yield (%)	**17**α	**18**α	**19** + **20**β	Ratio **17**:**18**	Ratio α/β
21 SPyr α:β 1:4	MeI	55	65	35	0	1.9:1	100:0
22 OAc α:β 5:1	TMSOTf	52	83	5	12	16.6:1	7.3:1
23 Cl α	AgOTf	90	29	29	42	1:1	1.3:1
24 *O*-Pent-4-enyl α:β 3:2	Bis-(1,4,6-trimethylpyridyl)$IClO_4^-$	80	31	30	39	1:1	1.5:1
24 *O*-Pent-4-enyl[b] α:β 3:2	Bis-(1,4,6-trimethylpyridyl)$IClO_4^-$	53	51	47	3	1.1:1	32:1

[a] Reactions carried out in CH_2Cl_2 unless otherwise stated. [b] Reaction carried out in Et_2O–CH_2Cl_2 (5:1).



assumed, for the silver triflate-promoted glycosylation of the glucosyl chloride **23**, and the iodonium ion-promoted glycosylation of the pentenyl glucoside **24**, that both reactions proceed through the highly reactive oxonium ion intermediate, which would probably not lead to any enantioselectivity, as is observed. As for the thioglucoside **21**, it is not apparent whether the reacting intermediate is a methyl sulphonium ion or a β-iodo glucoside. Nevertheless, the 2:1 enantioselectivity observed suggests that the oxonium ion intermediate is perhaps not involved. On the other hand, for the TMSOTf-promoted glycosylation with the 1-acetate **22**, it was also assumed that an oxonium ion intermediate would be involved but, unlike the former glycosylations, the reaction proceeds under acidic conditions. Hence, the kinetically produced glucosides are perhaps transformed into a thermodynamically more stable distribution, favouring compound **17**, and therefore accounting for the high enantioselectivity observed. In contrast, due to the nonacidic conditions of the other glycosylations, equilibration cannot take place, explaining their low selectivities. Thus the high enantioselective glycosylation observed upon using TMSOTf may not be a result of the initial glycosylation step, but in fact an equilibration after glycosylation under thermodynamic control. Indeed, when a mixture (~2:2:3:3) of the tetrabenzylated glucosides **19**:**20**:**17**:**18**, respectively, as obtained using the pentenyl tetrabenzylglucoside **24**, was subjected to an equimolar amount of TMSOTf under identical experimental conditions as those used with the 1-acetete **22**, a new distribution was obtained in the approximate proportions 0:2:7:1, respectively (enantioselectivity **17**:**18** ~ 7:1, α:β ~ 4:1). These results suggest that one of the β-products anomerizes to compound **17** (hence this β-anomer probably corresponds to compound **19** and was thus assigned this structure), whereas the other β-product (compound **20**) remained unchanged. In addition, 66% of compound **18** in the mixture had undergone transglucosylation to compound **17**. Further support for these observations was obtained by taking the individual β-anomers **19** and **20**, which unlike the α-anomers were separable by chromatography, and treating them with TMSOTf. This resulted in one of the β-anomers remaining unchanged as observed above, whereas 91% of the other was converted into compound **17**. Furthermore, treatment of the α-glucoside **17** with TMSOTf resulted in no change. The greater stability of compound **17** in comparison with compound **18** could be a direct result of the *exo*-anomeric effect whereby steric hindrance in compound **18** could prevent such an effect being optimal. In contrast, such a steric interaction would not be present in compound **17**. The close proximity of the free (*R*)-C-OH group in compound **18** to the glycosidic linkage therefore allows transglycosylation to occur under acidic conditions to afford the more favoured product **17**. The well known acid-catalysed β-to-α anomerization of the glucosides seems to account for the transformation of isomer **19** to compound **17**. Although the anomeric effect certainly plays a role in this isomerization, the *exo*-anomeric effect may also be contributing, as steric interactions could here, too, be preventing the *exo*-anomeric effect from being optimal, whereas for compound **20** the *exo*-anomeric effect would not give rise to this interaction, explaining its apparent stability towards treatment with TMSOTf.

In conclusion, a short stereoselective synthesis of compound **1** has been demonstrated, whereby selective glycosylation of the (*R*)-C-OH group of compound **2** has been achieved under thermodynamic control. The consequences of these results, as well as studies on the enzymatic hydrolysis of the glucosylated dihydroxydecalins by amyloglucosidase will be reported in due course.

Experimental

NMR spectra were recorded on a Bruker WH-90 and an AM-500 spectrometer with either $CDCl_3$ or D_2O as solvent. In the latter, acetone (δ 2.22) for ^1H NMR spectra and 1,4-dioxane (δ_C 67.4) for ^{13}C NMR spectra were used as internal references. *J*-values are given in Hz. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were determined at the LEO company, Ballerup, Denmark. Column chromatography was performed on Kieselgel 60H (TLC-grade) obtained from the Merck Co. M.p.s were measured on a Büchi melting point apparatus and are uncorrected.

(±)-2-[3-(*Cyclohex-2-enyl*)*propyl*]-5,5-*dimethyl*-1,3-*dimethyl*-1,3-*dioxane* **7**.—BuLi (1.6 mol dm^{-3} in pentane; 33 cm^3, 50 mmol) was added dropwise during 15 min to a stirred suspension of Bu^{t}OK (5.60 g, 50 mmol) in cyclohexene (50 cm^3)

at 0 °C, under argon, to give a bright yellow mixture. After being stirred for 22 h at 22 °C the mixture was recooled to 0 °C and 2-(3-bromopropyl)-5,5-dimethyl-1,3-dioxane (5.5 cm^3, 29 mmol) was injected. The mixture was stirred for an additional hour followed by quenching with water and extraction with CH_2Cl_2. Evaporation to dryness and column chromatography (hexane → toluene) gave compound **7** as an oil (5.90 g, 85%), $\delta_H(CDCl_3)$ 5.67 (1 H, ddd, *J* 10.5, *J'* 3.0, *J''* 3.0, C=C*H*CH_2), 5.59 (1 H, dd, *J* 10.5, *J'* 3.0, C=C*H*CH), 4.44 (1 H, t, *J* 4.54, OCHO), 3.63 (2 H, d, *J* 10.5, OCH_2), 3.46 (2 H, d, *J* 10.5, OCH_2), 2.07 (1 H, m), 1.98 (2 H, m), 1.80 (1 H, m), 1.73 (1 H, m), 1.63 (2 H, m), 1.50 (2 H, m), 1.43–1.17 (4 H, m), 1.22 (3 H, s, CH_2) and 0.74 (3 H, s, Me); $\delta_C(CDCl_3)$ 132.0, 126.5, 102.1, 77.1 (2 C), 36.1, 35.0 (2 C), 30.0, 28.8, 25.2, 22.8, 21.7, 21.3 and 21.2.

Further elution provided 5,5-dimethyl-2-propyl-1,3-dioxane **8** as an oil (0.60 g, 13%), $\delta_H(CDCl_3)$ 4.43 (1 H, *J* 4.5, OCHO), 3.63 (2 H, d, *J* 10.5, OCH_2), 3.47 (2 H, *J* 10.5, OCH_2), 1.61 (2 H, m, CH_2), 1.44 (2 H, m, CH_2), 1.20 (3 H, s, Me), 0.92 (3 H, t, *J* 7.9, Me) and 0.73 (3 H, s, Me).

(±)-4-(*Cyclohex-2-enyl*)*butan-1-ol* **10**.—A solution of acetal **7** (5.90 g, 24.6 mmol) and *p*-TsOH (300 mg) in MeOH (300 cm^3) was heated to near boiling for 1 h, and was then stirred at 22 °C for 2 days. Aq. $NaHCO_3$ (sat.) was added. Evaporation to dryness and column chromatography (toluene → CH_2Cl_2) afforded the dimethyl acetal (4.00 g, 99% based on recovered starting material) and the dioxane **7** (1.1 g).

The dimethyl acetal (4.00 g, 19.8 mmol) was redissolved in acetone (200 cm^3), followed by the addition of *p*-TsOH (200 mg). After being stirred overnight at 22 °C, the solution was neutralized with triethylamine, followed by evaporation to dryness. Some decomposition was noted (TLC; CH_2Cl_2). The oil obtained was dissolved in MeOH (100 cm^3), and $NaBH_4$ (3.7 g, 98 mmol) was added slowly to the stirred solution. After being stirred for 1 h, the solution was neutralized (pH paper) with AcOH and evaporated to dryness. The residue was partitioned between CH_2Cl_2 and water, and the aq. phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated to dryness. Column chromatography (CH_2Cl_2) afforded the alcohol **10** as an oil [1.50 g, 57% based on recovered starting material (0.6 g)], $\delta_H(CDCl_3)$ 5.70 (1 H, ddd, *J* 10.2, *J'* 2.6, *J''* 2.6, C=C*H*CH_2), 5.61 (1 H, dd, *J* 10.2, *J'* 2.3, C=C*H*CH), 3.68 (2 H, t, *J* 6.5, OCH_2), 2.10 (1 H, m), 2.01 (2 H, m), 1.83 (1 H, m), 1.76 (1 H, m) and 1.67–1.29 (7 H, m); $\delta_C(CDCl_3)$ 131.9, 126.6, 62.6, 36.0, 35.0, 32.8, 29.5, 28.7, 25.2, 22.9 and 21.3.

(±)-3-(4-*Nitrobutyl*)*cyclohexene* **13**.—A solution of the alcohol **10** (1.50 g, 9.62 mmol) and TsCl (2.76 g, 14.4 mmol) in CH_2Cl_2 (20 cm^3) was left overnight at 4 °C, followed by addition of water and extraction with diethyl ether. The combined organic phases were washed successively with 1 mol dm^{-3} AcOH (aq.) and saturated $NaHCO_3$ and then dried ($MgSO_4$) and evaporated to dryness. Column chromatography (toluene) gave the tosyl ester **11** (2.85 g, 95%) as a syrup. The tosyl ester was redissolved in acetone (250 cm^3) and sodium iodide (6.9 g, 46 mmol) was added. The solution was stirred overnight in the dark at 22 °C. The mixture obtained was evaporated to dryness and partitioned between water and hexane. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness to give the iodide **12**, which without isolation was dissolved in diethyl ether (8 cm^3) and cooled to 0 °C. $AgNO_2$ (2.1 g, 13.6 mmol) was added and the mixture was stirred in the dark at 0 °C for 24 h and then at 22 °C for 48 h. The mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness. Column chromatography (hexane) gave the nitrite ester **14** (644 mg, 38%), $\delta_H(CDCl_3)$ 5.72 (1 H, ddd, *J* 10.5, *J'* 3.0, *J''* 3.0, C=C*H*CH_2), 5.58 (1 H, dd, *J* 10.5, *J'* 3.0, C=C*H*CH), 4.48 (2 H, t, *J* 5.5, CH_2NO_2), 2.10 (1 H, m), 2.02 (2 H, m), 1.86–1.71 (4 H, m) and 1.62–1.18 (6 H, m).

Further elution with hexane–toluene (1:1) afforded the nitro compound **13** as an oil (995 mg, 59%), $\delta_H(CDCl_3)$ 5.70 (1 H, ddd, *J* 10.5, *J'* 10.5, *J''* 3.0, C=C*H*CH_2), 5.55 (1 H, dd, *J* 10.5, *J'* 3.0, C=C*H*CH), 4.41 (2 H, t, *J* 7.0, CH_2NO_2), 2.13–1.92 (5 H, m), 1.83–1.67 (2 H, m) and 1.59–1.17 (6 H, m).

(1α,4aβ,8α,8aα)-*Decahydronaphthalene-1,8-diol* **2**.—A solution of nitro alkene **13** (590 mg, 3.20 mmol), phenyl isocyanate (0.67 cm^3, 6.10 mmol), and triethylamine (4 drops, catalytic amount) in benzene (10 cm^3) was refluxed for 15 h, during which a colourless precipitate was formed. The mixture was filtered through a pad of Celite and the filtrate was evaporated to dryness. Column chromatography (CH_2Cl_2) afforded the crude isoxazoline (±)-**3** contaminated with *ca.* 10% of *N,N'*-diphenylurea, and was used without further purification in the subsequent step; $\delta_H(CDCl_3)$ 4.61 (1 H, ddd, *J* 11.2, *J'* 9.1, *J''* 7.1, OCH), 3.07 (1 H, br t, *J* 8.2, N=CCH_2), 2.76 (1 H, dd, *J* 14.8, *J'* 3.4, CH), 2.17 (1 H, m), 2.04 (1 H, m), 1.88 (1 H, m), 1.73 (1 H, m), 1.68 (1 H, m), 1.65–1.50 (3 H, m), 1.45 (1 H, m) and 1.37–1.00 (3 H, m); $\delta_C(CDCl_3)$ 158.7 (C=N), 77.4 (C–O), 48.7, 32.4, 29.3, 28.3, 26.6, 24.7, 19.7 and 19.1.

The ^1H NMR spectrum showed the presence of no other isomeric isoxazoline derivatives.

A mixture of the crude isoxazole (±)-**3**, acetic acid (0.7 cm^3) and Raney-nickel (a spatula tip) in MeOH–water (10:1; 77 cm^3) was stirred under hydrogen at 22 °C for 3 h. The mixture was filtered through a pad of Celite and the filtrate was neutralized (pH paper) with saturated aq. $NaHCO_3$ (~2 cm^3). The residue obtained after evaporation to dryness was partitioned between water and EtOAc and the aq. phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated to dryness to give the crude hydroxydecalinone (±)-**15**, $\delta_H(CDCl_3)$ 3.81 (1 H, ddd, *J* 9.8, *J'* 9.7, *J''* 4.4, OCH), 3.61 (1 H, br s, OH), 2.38 (1 H, dm, *J* 14.0), 2.31 (1 H, ddd, *J* 14.0, *J'* 14.0, *J''* 6.2), 2.06 (1 H, m), 2.01–1.94 (2 H, m), 1.84–1.59 (4 H, m), 1.49–1.42 (2 H, m) and 1.37–1.11 (3 H, m).

Crude (±)-**15** was redissolved in MeOH (10 cm^3) and the stirred solution was cooled to 0 °C. $NaBH_4$ (250 mg, 6.6 mmol) was added, and the mixture was stirred at 0 °C for 0.5 h, and then at 22 °C for 2 h. The solution was neutralized with AcOH and evaporated to dryness, and the residue was partitioned between diethyl ether and water. The aq. phase was extracted several times with diethyl ether and the combined etheral phases were dried ($MgSO_4$) and evaporated to dryness. Column chromatography (EtOAc–hexane, 1:1) afforded *diol* **2** (160 mg, 29% from **13**) as plates, m.p. 97–99 °C (from hexane) (Found: C, 70.15; H, 10.6. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66%); $\delta_H(CDCl_3)$ 4.10 (2 H, s, OH), 3.64 (2 H, ddd, *J* 10.5, *J'* 9.3, *J''* 4.5, HCO), 1.97 (2 H, m), 1.74 (2 H, m), 1.41–1.37 (4 H, m) and 1.10–1.00 (4 H, m); $\delta_C(CDCl_3)$ 76.3, 54.7, 39.4, 35.5, 32.8 and 23.7.

Upon acetylation of diol **2**, the ^1H NMR spectrum displayed the HCO signal at δ 4.75 (2 H, ddd, *J* 10.2, *J'* 10.2, *J''* 4.5) and the 8a-H signal at 1.54 (1 H, dt, *J* 10.2, *J'* 10.2).

Further elution from the column afforded diol (±)-**16** as a syrup (17 mg, 4% yield from **13**), $\delta_H(CDCl_3)$ 4.32 (1 H, ddd, *J* 2.5, *J'* 2.5, *J''* 2.5, *eq.*-OCH), 3.63 (1 H, ddd, *J* 10.2, *J'* 10.2, *J''* 4.4, *ax*-OCH), 2.26–1.95 (3 H, m), 1.91 (1 H, m), 1.77–1.68 (4 H, m), 1.56–1.27 (5 H, m) and 1.07–0.90 (3 H, m); $\delta_C(CDCl_3)$ 69.8, 64.4, 53.7, 35.8, 34.1, 33.6, 33.3, 33.2, 23.8 and 19.6.

Upon acetylation of diol (±)-**16**, the ^1H NMR spectrum showed, among others, signals at δ 5.19 (1 H, ddd, *J* 3.2, *J'* 3.2, *J''* 3.2, 8-H), 4.68 (1 H, ddd, *J* 11.7, *J'* 11.7, *J''* 4.5, 1-H) and 1.32 (1 H, ddd, *J* 11.0, *J'* 11.0, *J''* 2.5, 8a-H).

(1α,4aβ,8α,8aα)-*Decahydro*-8-*hydroxy*-1-*naphthyl* α-D-*Glucopyranoside* **1** *and* (1β,4aα,8β,8aβ)-*Decahydro*-8-*hydroxy*-1-*naphthyl* α-D-*Glucopyranoside* **25**.—A solution of diol **2** (76 mg, 0.45 mmol) and 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-D-glucopyranoside[7] (α:β 1:4; 291 mg, 0.46 mmol) in CH_2Cl_2 (6 cm^3) containing 6% MeI, and in the presence of 3Å molecular sieves (300 mg, crushed) was refluxed at 50 °C for 42 h. After filtration through Celite and evaporation, the residue was chromatographed (hexane–EtOAc, 5:1) to give an inseparable mixture of monoglucosylated products in the ratio 1.86:1, according to the ^{13}C NMR spectrum, as a semi-solid (171 mg, 55%).

The above mentioned mixture (165 mg, 0.24 mmol) was dissolved in MeOH–AcOH (6:1; 28 cm^3) and stirred under hydrogen in the presence of Pd/C (80 mg) for 5 h. The mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness. Column chromatography (CH_2Cl_2–MeOH, 7:1) afforded, first compound **25** as a syrup (21 mg), $\delta_H(D_2O)$ 5.26 (1 H, d, *J* 4.1, 1′-H), 3.86 (1 H, dd, *J* 12.4, *J′* 2.3, 6′-H), 3.81 (1 H, ddd, *J* 10.5, *J′* 10.0, *J″* 3.8, 8-H), 3.76 (1 H, dd, *J* 12.4, *J′* 5.2, 6′-H), 3.68 (1 H, ddd, *J* 10.0, *J′* 9.3, *J″* 4.7, 1-H), 3.64 (1 H, ddd, *J* 9.7, *J′* 5.2, *J″* 4.7, 5′-H), 3.59 (1 H, dd, *J* 9.7, *J′* 4.0, 2′-H), 3.48 (1 H, dd, *J* 9.7, *J′* 9.7, 3′-H), 3.43 (1 H, dd, *J* 9.7, *J′* 9.7, 4′-H), 2.22 (1 H, m), 1.91 (1 H, m), 1.77 (1 H, m), 1.68 (1 H, m), 1.62–1.53 (2 H, m), 1.34–1.21 (4 H, m), 1.28 (1 H, ddd, *J* 9.9, *J′* 9.9, *J″* 9.9, 8a-H) and 1.09–0.98 (2 H, m); $\delta_C(D_2O)$ 93.8, 81.2, 75.6, 74.2, 73.5, 71.5, 70.2, 61.3, 53.2, 40.1, 34.7, 33.3, 33.0, 29.9, 24.0 and 23.6.

Further elution from the column afforded compound **1** as a syrup (50 mg) after evaporation. Addition of a slight amount of water resulted in crystallization, suggesting that compound **1** crystallizes as a hydrate. However, recrystallization of compound **1** proved difficult and hence the product was characterized solely by ^1H and ^{13}C NMR spectroscopy; $\delta_H(D_2O)$ 5.10 (1 H, d, *J* 3.8, 1′-H), 3.81 (1 H, dd, *J* 11.5, *J′* 1.8, 6′-H), 3.78 (1 H, m, 5′-H), 3.74 (1 H, dd, *J* 11.5, *J′* 4.5, 6′-H), 3.68 (1 H, ddd, *J* 10.0, *J′* 9.2, *J″* 4.7 1-H), 3.63 (1 H, ddd, *J* 10.5, *J′* 10.0, *J″* 4.0, 8-H), 3.69 (1 H, dd, *J* 9.6, *J′* 8.9, 3′-H), 3.57 (1 H, dd, *J* 9.6, *J′* 3.8, 2′-H), 3.49 (1 H, dd, *J* 9.2, *J′* 8.9, 4′-H), 2.25 (1 H, m), 1.88 (1 H, m), 1.68 (2 H, m), 1.56 (1 H, m), 1.43 (1 H, m), 1.37–1.20 (3 H, m), 1.21 (1 H, ddd, *J* 10.0, *J′* 10.0, *J″* 10.0, 8a-H) and 1.13–0.95 (3 H, m); $\delta_C(D_2O)$ 101.2, 89.2, 75.6, 74.0, 72.9, 71.6, 70.2, 61.3, 53.8, 40.1, 34.7, 34.6, 33.3, 33.1, 24.1 and 23.9).

(1α,4aβ,8α,8aα)-*Decahydro*-8-*hydroxy*-1-*naphthyl* 2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranoside* **17** *from Tetrabenzylglucosyl Acetate* **22**.—A solution of diol **2** (30 mg, 0.18 mmol) and acetate **22** (a 5:1 α:β mixture; 111 mg, 0.19 mmol) in CH_2Cl_2 (2 cm^3) in the presence of 3 Å molecular sieves (300 mg, crushed) was stirred at 22 °C for 1 h, after which the mixture was cooled to −20 °C and TMSOTf (0.04 cm^3, 0.21 mmol) was injected. The mixture was slowly warmed to 22 °C during 1 h and then stirred for an additional 3 h. After filtration through a pad of Celite, the filtrate was washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness. Column chromatography (hexane–EtOAc, 5:1) gave the α-glucosylated decalins (57 mg, 16.6:1 mixture of compounds **17** and **18** respectively, according to ^{13}C NMR spectrum). Recrystallization from hexane afforded *compound* **17** as crystals, m.p. 133–134 °C (Found: C, 75.8; H, 7.45. $C_{44}H_{52}O_7$ requires C, 76.27; H, 7.56%); $[\alpha]_D$ +12.3° (*c* 1.1, $CHCl_3$); $\delta_H(CDCl_3)$ 7.41 (2 H, d, *J* 6.8), 7.37–7.23 (16 H, m), 7.15 (2 H, d, *J* 6.8), 5.15 (1 H, s, OH), 4.95 (1 H, d, *J* 10.8, C*H*Ph), 4.85 (1 H, d, *J* 10.8, C*H*Ph), 4.84 (1 H, d, *J* 12.0, C*H*Ph), 4.79 (1 H, d, *J* 10.8, C*H*Ph), 4.78 (1 H, d, *J* 3.8, 1′-H), 4.68 (1 H, d, *J* 12.0, C*H*Ph), 4.60 (1 H, d, *J* 12.0, C*H*Ph), 4.47 (1 H, d, *J* 10.8, C*H*Ph), 4.43 (1 H, d, *J* 12.0, C*H*Ph), 3.96 (1 H, dd, *J* 9.3, *J′* 9.3, 3′-H), 3.91 (1 H, m, 5′-H), 3.71 (1 H, dd, *J* 10.5, *J′* 2.3, 6′-H), 3.62 (1 H, dd, *J* 9.3, *J′* 9.3, 4′-H), 3.60 (1 H, m, 1-H), 3.59 (1 H, dd, *J* 10.5, *J′* 2.3, 6′-H), 3.51 (1 H, dd, *J* 9.3, *J* 3.8, 2′-H), 3.35 (1 H, ddd, *J* 10.0, *J′* 10.0, *J″* 4.3, 8-H), 2.32 (1 H, m), 2.05 (1 H, m), 1.74 (1 H, m), 1.66 (1 H, m), 1.57 (2 H, m), 1.43–1.19 (6 H, m) and 1.11–0.95 (2 H, m); $\delta_C(CDCl_3)$ 99.6, 88.9, 82.1, 79.2, 77.3, 75.8, 74.8, 74.3, 73.5, 73.4, 70.6, 68.4, 53.8, 39.8, 34.8, 34.0, 33.2, 32.9, 23.8 and 23.7 (aromatic carbon signals not included). Compound **18** displayed signals for 1′-H and C-1′ at δ 5.15 and δ_C 91.5, respectively.

Further elution of the column provided the β-glucosylated decalins (8 mg) to give a combined overall yield of 52%. The ^{13}C NMR spectra of the β-glucosylated decalins displayed signals for C-1′ at δ_C 102.4 and 100.9, respectively.

Glycosylation of Diol **2** *with Tetrabenzylglucosyl Chloride* **23**.—A solution of diol **2** (15 mg, 0.09 mmol), silver trifluoromethanesulphonate (30 mg, 0.12 mmol), and 2,4,6-trimethylpyridine (16 mm^3, 0.12 mmol) dissolved in CH_2Cl_2 (1 cm^3) in the presence of 3 Å molecular sieves (150 μg, crushed) was stirred at 22 °C for 1 h, after which the mixture was cooled to −60 °C and a solution of tetrabenzylglucosyl chloride **23** (67 mg, 0.12 mmol) in CH_2Cl_2 (0.5 cm^3) was added. The mixture was slowly warmed to 22 °C (2 h) and was then stirred for an additional 2 h. After filtration through a pad of Celite the solution was evaporated to dryness and chromatographed (hexane–EtOAc, 5:1), to give the glucosylated decalins (56 mg, 90%). Product distributions were obtained by measuring the integrals of the δ_C signals of the C-1′ carbon atoms.

Glycosylation of Diol **2** *with Pent*-4-*enyl Tetrabenzylglucopyranoside* **24**.—A solution of diol **2** (15 mg), 0.09 mmol) and the pentenyl glucoside **24** (a 3:2 α:β mixture; 60 mg, 0.09 mmol) in CH_2Cl_2 (1 cm^3) was stirred in the presence of 3 Å molecular sieves (150 mg, crushed) at 22 °C for 2 h. Freshly prepared bis-(2,4,6-trimethylpyridyl)iodonium perchlorate (70 mg, 0.15 mmol) was added in one portion and the solution was stirred for 14 h. Diethyl ether was added, and the mixture was filtered through a pad of Celite, after which the filtrate was washed successively with aq. $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ and was then dried ($MgSO_4$) and concentrated to dryness. Column chromatography (hexane–EtOAc, 1:5) afforded the glucosylated decalins (50 mg, 80%).

The reaction was repeated as above, but with the following modifications: (a) the reaction was run in Et_2O–CH_2Cl_2 (5:1; 1 cm^3); (b) 100 mg (0.21 mmol) of bis-(2,4,6-trimethylpyridyl)-iodonium perchlorate was employed; and (c) a reaction time of 48 h was allowed. This afforded, after column chromatography, the glucosylated decalins (32 mg, 53%). Product distributions were obtained by measurement of the integrals of the δ_C signals of the C-1′ carbon atoms.

Treatment of the Tetrabenzylglucosylated Dihydroxydecalins with TMSOTf.—A mixture of glucosides **17**, **18**, **19** and **20** (45 mg, 0.065 mmol) (as obtained from the glycosylation with the pentenyl glucoside **24**) and 3 Å molecular sieves (100 mg, crushed) in CH_2Cl_2 (1 cm^3) was stirred for 1 h at 22 °C. The mixture was cooled to −30 °C and TMSOTf (14 mm^3, 0.078 mmol) was injected, followed by slow warming of the mixture to 22 °C during 1 h. After being stirred for 2 h, the mixture was filtered and the filtrate was partitioned between diethyl ether and saturated aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated to dryness to give a syrup (43 mg). Product distributions were obtained by measurement of the integrals of the δ_C signals of the C-1′ carbon atoms.

Treatment of Compound **17** *and the* β-*Tetrabenzylglucosylated Dihydroxydecalins* **19** *and* **20** *with TMSOTf*.—The individual β-anomers **19** and **20** were easily obtained by chromatography of

the reaction mixtures of the previous glycosylations of the dihydroxydecalin **2**. The following procedure is representative for the three glucosides. A mixture of the glucoside (11 mg, 0.016 mmol) and 3 Å molecular sieves (70 mg, crushed) in CH_2Cl_2 (0.7 cm^3) was stirred for 1 h at 22 °C. The mixture was cooled to −30 °C and TMSOTf (6 mm^3, 0.033 nmol) was injected, followed by slow warming of the mixture to 22 °C during 1 h. After being stirred for 2 h the mixture was worked up as described above. This gave 10 mg of product. Product distributions were obtained by measurement of the integrals of the δ_C signals of the C-1′ carbon atoms. The β-glucoside with the C-1′ signal at δ_C 100.9 and the α-glucoside **17** remained unchanged after subjection to TMSOTf, whereas 91% of the β-glucoside with the C-1′ signal at δ_C 102.4 was transformed into the α-glucoside **17**.

Acknowledgements

This work was supported by a grant (T. S.) from The Danish Technical Science Research Council. The 500 MHz NMR facilities were provided by the Danish Natural Science Research Council and The Carlsberg Foundation.

References

1 K. Bock and S. Refn, *Acta Chem. Scand.*, 1989, **43**, 373; For a recent review see: K. Bock. *Pure Appl. Chem.*, 1987, **59**, 1447.
2 (*a*) A. P. Kozikowski and C. Li, *J. Org. Chem.*, 1987, **52**, 3541; (*b*) The use of the INOC procedure for the construction of natural products has been reviewed: A.P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410.
3 J. Hartmann and M. Schlosser, *Helv. Chim. Acta*, 1976, **59**, 453.
4 N. Kornblum and H. E. Ungnade, *Org. Synth.*, 1963; Coll. vol. IV, p. 724.
5 T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339.
6 D. C. Wigfield, *Tetrahedron*, 1979, **35**, 449.
7 G. V. Reddy, V. R. Kulkarni and H. B. Mereyala, *Tetrahedron Lett.*, 1989, **30**, 4283.
8 K. Bock, T. Skrydstrup and J. Ø. Duus, manuscript in preparation.
9 B. Fraser-Reid, P. Konradsson, D. R. Mootoo and U. Udodorg, *J. Chem. Soc., Chem. Commun.*, 1988, 823.

Paper 0/04041J
Received 5*th September* 1990
Accepted 12*th November* 1990