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A HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF DL-OLEANDROSE

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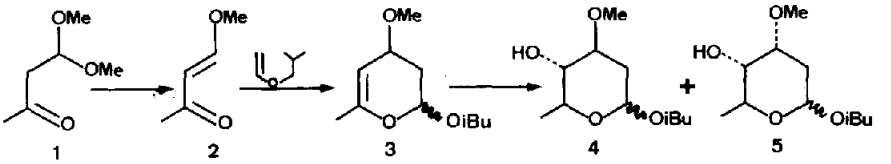
Abstract—Racemic oleandrose (2,6-dideoxy-3-O-methyl-*arabino*-hexose) has been obtained starting from the Diels–Alder adduct between 4-methoxy-3-buten-2-one and isobutyl vinyl ether, which was converted into a mixture of the isobutyl β- and α-oleandrosides through hydroboration-oxidation. The latter reaction is highly diastereoselective since attack by borane takes place exclusively anti to the OMe group: none of the diastereoisomeric cymarosides are formed. The only side-products are small amounts of the isobutyl β- and α-amicetosides formed by a demethoxylation occurring during the hydroboration step.

The four diastereoisomeric 2,6 - dideoxy - 3 - O - methylhexoses, oleandrose, sarmentose, cymarose and diginose are present as the D forms in cardioactive glycosides, and L-oleandrose and L-cymarose are components of antibiotics.[1] Several syntheses of the optically active forms of these deoxysugars have been reported starting from easily available carbohydrates[2] or amino-acids[3] but they usually involve many steps. The racemic forms of many deoxysugars can be obtained much more simply by syntheses involving as the first step hetero-cycloadditions of an α,β-unsaturated ketone and a vinyl ether, followed by hydroboration-oxidation of the adduct and by other reactions.[4] Yasuda and Matsumoto[5] have used such an approach to synthesise methyl α-DL-oleandroside and β-DL-cymaroside starting from the adduct between 3-buten-2-one and ethyl vinyl ether (6 - methoxy - 2 - methyl - 5,6 - dihydro - 4H - pyran), but several steps were required for the introduction of the OMe group. It occurred to us that a much simpler approach would be that shown in the Scheme 1,† starting from an unsaturated ketone already substituted with the methoxy group, that is from 4-methoxy-3-buten-2-one (**2**) easily prepared from the commercially available acetal **1**.[6]

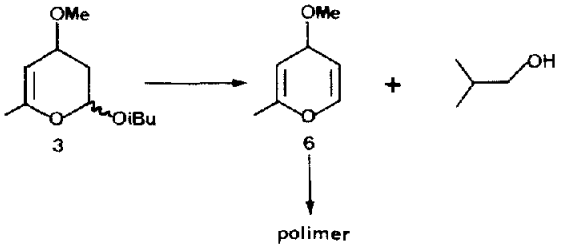
The only reference in the literature to a cycloaddition of a vinyl ether to a β-alkoxy α,β-unsaturated carbonyl compound is in a preliminary note[7] on the reaction between 3-methoxyacrolein and methyl vinyl ether at 240°, which reported the formation of the diastereoisomeric *cis* and *trans* adducts in an unstated ratio and in 60% yield. The reaction between **2** and isobutyl vinyl ether was found to be considerably slower than the corresponding one between the same vinyl ether and 3-buten-2-one.[4] A 2.5–3.1 molar excess of the vinyl ether was necessary in order to obtain acceptable yields. Small amounts of hydroquinone were added to avoid radical polymerizations of the reactants, but omission of this inhibitor did not affect yields substantially. The two diastereoisomers of **3** were formed in a 55:45 ratio, that changed little with changes of the reaction conditions, as ascertained by GLC on the crude reaction product, and were separated as a mixture by fractional distillation. The best conversion into the adducts **3** was achieved by heating between 190 and 210° for 24 h in a glass vial. Longer reaction times or higher temperatures reduced yields and gave larger amounts of side products. Even in the indicated ranges conversion into adducts **3** never exceeded 45% and a substantial amount of unreacted **2** was still present. Apparently an equilibrium between cycloaddition and retrocycloaddition is reached at the operating temperatures, which is not much displaced toward the adducts. At lower temperatures cycloaddition is too slow and side reactions take place, at higher temperatures retrocycloaddition predominates together with other reactions, such as elimination of isobutanol probably giving 4 - methoxy-2-methyl-4H-pyran (**6**), certainly a very unstable product that is expected to be converted into tars at the high reaction temperature. Formation of isobutyl alcohol was often directly observed by GLC and the isolation of variable amounts of 4-isobutoxy-3-buten-2-one (**7**) as a side product can be explained by the exchange reaction indicated in the Scheme 2.

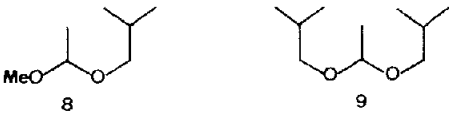
It was further found that when the cycloaddition reaction was conducted directly in a steel autoclave results

†All formulas in this paper represent, for the sake of simplicity, only one enantiomer, but all the corresponding compounds were racemic. Pyran numbering was used for the dihydropyran derivatives **3** and **17**, carbohydrate numbering for the tetrahydropyran derivatives.



SCHEME 1





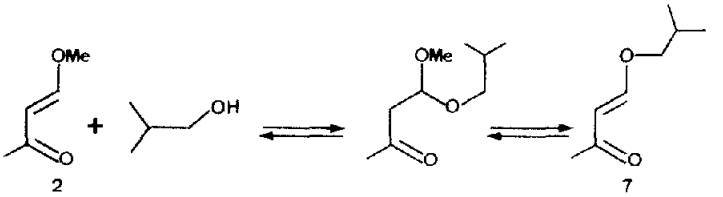
were rather irreproducible, ranging from a fair conversion into **3** to very low yields of these adducts and prevalent formation of **7** and of other side products, mainly acetaldehyde methyl isobutyl acetal (**8**) and diisobutylacetal (**9**), obviously formed by addition of methanol or isobutyl alcohol to isobutyl vinyl ether. The mode of formation of methanol is not yet clear. These variable results must be due to a catalytic effect of the steel surface, or of some impurity present in the manometer of the autoclave which is difficult to clean perfectly. Reactions were therefore carried out in sealed glass vials that were inserted into the autoclave, with toluene on the outside in order to equalize pressure; under these conditions the results were fully reproducible and only trace amounts of products **7–9** and of the other unidentified side products were formed.

The *cis* and *trans* forms of **3** were obtained pure as a mixture by fractional distillation through a spinning band column, which did however not lead to their separation. Also column adsorption chromatography on silica did not separate them. They are very stable under neutral conditions, but are rapidly decomposed by traces of acids. The proton NMR spectrum of mixture of *cis*- and *trans*-**3** confirmed their structures even if extensive overlap of diagnostic signals (anomeric and olefinic protons) did not permit separate assignments of those relative to the two diastereoisomers. Side-products **7–9** were identified through their NMR spectra and by direct comparison with authentic samples. **8** and **9** are known compounds, **7** was prepared by an exchange reaction between **2** and isobutyl alcohol.

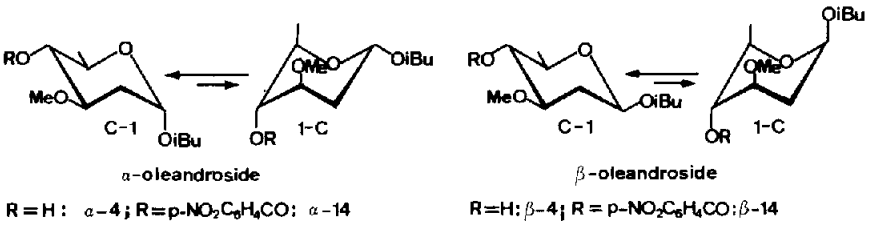
The subsequent step, hydroboration–oxidation, was first carried out on the pure mixture of anomers **3c** and **3t** as obtained by the high efficiency distillation. Since the long heating required for this distillation decreased yields, owing to partial decomposition in the distilling flask, a product obtained by short path distillation, containing about 10% impurities, was later used and found to be equally satisfactory, since after the hydroboration step the crude product had practically the same composition as that obtained from the pure adducts. The hydroboration products of the side-products were evidently hydrosoluble and eliminated during work-up. Borane-dimethyl sulfide (BMS) was used as the source of BH_3.[8] It is well known that attack by borane on vinyl ethers takes place predominantly, or exclusively at the β-carbon[9] and that the addition occurs entirely in a syn way. This has been repeatedly confirmed in the specific cases of 5,6-dihydro-4H-pyran derivatives.[4,10] It was to be expected that hydroboration–oxidation of **3c** and **3t** would give a mixture of two of the four possible pairs of enantiomers of 2,6-dideoxy-3-O-methylhexoses isobutyl glycosides, namely the isobutyl α- and β-oleandrosides (α- and β-**4**) and cymarosides (α- and β-**5**), while the corresponding diginosides and sarmentosides, in which there is a *cis* relationship between the Me group and the 4 OH group, should not be formed. It was therefore somewhat surprising to find by gas-chromatographic analysis of the hydroboration–oxidation crude mixture that only two major products were formed, later identified as the oleandrosides (α- and β-**4**), together with two minor ones which had the same retention times as the isobutyl β- and α-amicetosides (β- and α-**12**). The ratios of the GLC peak were 58:36:5:1. No appreciable amounts of the cymarosides α-**5** and β-**5** were formed.

Separation and identification of the products was made possible by conversion of the sugars of the crude hydroboration–oxidation mixture into the corresponding *p*-nitrobenzoates. These were easily separated by crystallization and column chromatography, and identified by their NMR spectra. The isobutyl β-amicetopyranoside *p*-nitrobenzoate (β-**13**-PNB) was compared with an authentic sample;[4] the α-anomer (α-**12** PNB) was present in too small amounts for isolation. The isobutyl α-oleandropyranoside *p*-nitrobenzoate (α-**14**) exists certainly entirely in the C-1 conformation with the i-BuO group axial and the other three substituents equatorial (Scheme 3). Its PMR spectrum is entirely consistent with this assumption because the anomeric proton signal at δ 4.82 is a narrow multiplet as expected for an equatorial hydrogen, and that for the 4-CH proton is a triplet at δ 5.00 with a J of 9 Hz, characteristic for an axial proton coupled with two vicinal axial protons. The latter signal clearly differentiates α-**14** from the *p*-nitrobenzoate of isobutyl α-cymaroside (α-**5**-PNB) in which the shape of the 4-CH proton signal would be definitely different, owing to the existence of only one axial–axial interaction.

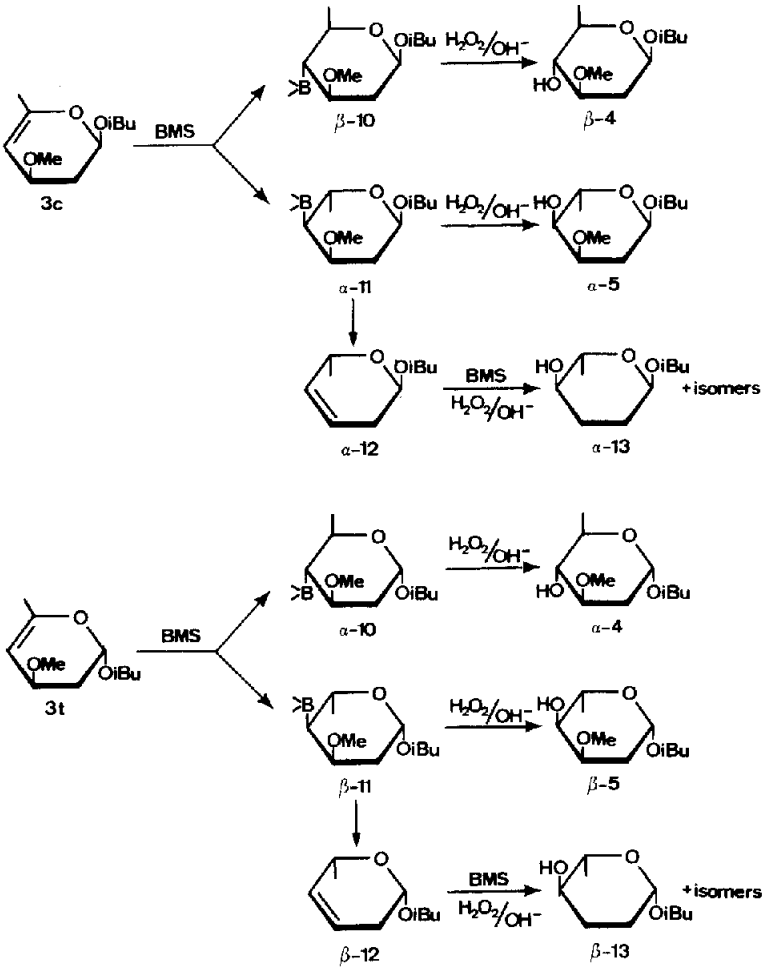
The isobutyl β-oleandropyranoside *p*-nitrobenzoate (β-**14**) must exist in the C-1 conformation too, since the unfavourable equatorial disposition of the anomeric substituent is more than compensated by the triequatorial situation of the remaining substituents. Its PMR spectrum is very similar to that of the α-anomer, except for the fact that the anomeric proton signal at δ 4.40 is a quartet with J 2.5 and 9.5 Hz in accordance with its axial



SCHEME 2



SCHEME 3



disposition. The values of chemical shift and J found for the anomeric protons of **α-14** and **β-14** agree with those reported for the corresponding methyl oleandrosides.[11] The ^{13}CMR spectra of **α-14** and **β-14** both have the expected 15 signals, and the fact that the anomeric C signal is found at higher field for the α than for the β anomer is in accordance with expectations.[12]

The anomeric relationship of the two isolated *p*-nitrobenzoates was also established by the fact that equilibration of **β-14** with isobutyl alcohol in the presence of Dowex 50W(H$^+$) resin gave rise to a mixture of **α-** and **β-14**. Saponification of the equilibrated mixture gave the isobutyl **α-** and **β-**oleandrosides in a 75:25 ratio, as exptected on the basis of the anomeric effect favouring the α anomer.

Saponification of the pure *p*-nitrobenzoates **α-14** and **β-14** gave the isobutyl oleandrosides **α-4** and **β-4**. Their anomeric relationship was further confirmed by the fact that both **α-4** and **β-4** gave oleandrose (**15**) on hydrolysis with 10% aqueous H_2SO_4. For the larger scale preparation of this sugar the crude hydroboration–oxidation product was subjected to chromatography on silica and the purified mixed glycosides fractions were hydrolyzed.

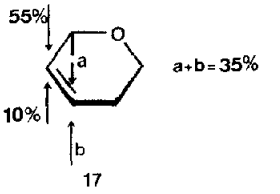
The PMR spectrum of distilled oleandrose is fully in accordance with its being essentially a mixture of the α- and β-pyranose forms, as shown by the presence of only two anomeric proton signals identical in shape with those present in **α-4** and in **β-4**. No appreciable amounts of furanose tautomers were detected. Integration of the anomeric proton signals indicated a ratio of α to β anomer of 60:40 in $CDCl_3$ and about 50:50 in D_2O. The ^{13}CMR spectrum also confirmed that the pyranose forms

were present in practically equal amounts in D_2O: couples of signals of similar intensity were present for each carbon, with the exception of the signals relative to the C–Me and OMe groups that had the same chemical shift in the α- and β-anomer. Assignments were made on the basis of comparison with known ^{13}C data for similar hexoses[12] and empirical additivity rules.[13]

Oleandrose was also characterized by its reaction with 2,4 - dinitrophenylhydrazine: a product with the reported[14] m.p. was obtained, but the absence of the OMe signal in its PMR spectrum showed that elimination of methanol occurred during the derivatization, to yield probably the 2,4 - dinitrophenylhydrazone of 4,5 - dihydroxy - 2 - hexenal (**16**). The presence of a double bond conjugated with the CH=N function was clearly confirmed by a maximum at 370 nm that shifted to 460 nm in alkaline solution.[15] A similar observation had been made with the structurally similar 2,6-dideoxyhexose chromose A in which the OMe and OH functions are inverted with respect to **15**. It therefore eliminates water to produce the 2,4-dinitrophenylhydrazone of 5 - hydroxy - 4 - methoxy - 2 - hexenal.[16]

The high preference for the formation of α- and β-oleandrosides and the practical absence of the cymarosides make the hydroboration of the mixture of adducts **3** a useful preparative method for (±) oleandrose, since it avoids a certainly difficult separation from the diastereoisomeric cymarosides. This unexpected diastereoselectivity can be explained if one considers the regio and stereoselectivity of the hydroboration of 2,3-dihydro-4H-pyran,[4,10] and the results obtained by Pasto and Hickmann in the hydroboration of 3-methoxycyclohexene.[17] They found in the latter reaction a high preference (90%) for attack by borane at position 2 and a high stereoselectivity (88%) favoring attack anti to the OMe group. They further observed the formation of 5% of cyclohexanol at short reaction times (20 min) and a slow increase of the latter compound (34.7% after 24 days) with a concomitant decrease of the *trans*-2-methoxycyclohexanol. This behaviour was explained by assuming a steric effect of the substituent favoring anti attack, and a rapid syn elimination reaction involving the *cis* borane adduct yielding cyclohexane, which on further hydroboration followed by oxidation gives cyclohexanol. A much slower reaction involves the *trans* adduct which, through a β transfer reaction, gives a cyclohexylmethoxyborane, converted after oxidation into cyclohexanol.

Our results agree in good part with this interpretation: the effect of the vinylic dihydropyran ring oxygen and of the allylic methoxy oxygen both strongly favor attack by borane at position 5 of **3c** and **3t**, which becomes thus the only site of reaction. The high preference for the formation of the oleandrosides is in accordance with the reported preference for anti attack in 3-methoxycyclohexene. This effect is further increased in **3c** since also the i-BuO group exerts a steric effect disfavoring attack syn to itself.[4,18] The conversion **3c** → β-**10** will be a highly favored path and therefore lead almost exclusively to the



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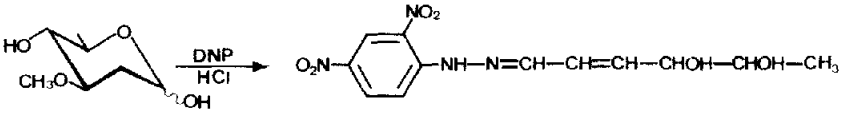
β-oleandroside (β-**4**). The hydroboration of **3t** is less straightforward, since the effects of the OMe and i-BuO group act in opposite directions; although the effect of the OMe group that is nearer to the reaction site should be predominant and lead to the formation of an excess of α-**10**, some formation of β-**11** could be expected. However, since in the products α-**11** and β-**11** boron and OMe group are *cis* to each other a rapid syn elimination can occur to give respectively the dihydropyrans α-**12** and β-**12** that can be further hydroborated with the possible formation of up to four isomeric trideoxyglycosides. A preference for attack at the position 3, anti to Me, in the hydroboration–oxidation of 2-methyl-5,6-dihydro-2H-pyran (**17**) has been observed;[19] this can explain the prevalent formation of β-**13** from β-**12**, as the main side product of the hydroboration of **3c** and **3t**.

EXPERIMENTAL

M.ps (uncorrected) were taken on a Kofler block. IR spectra, taken with a Perkin–Elmer 197 on neat liquids or paraffin oil mulls, were used for all comparisons. PMR spectra were recorded on *ca* 10% solns in the indicated solvents (TMS or sodium 3 - (trimethylsilyl) - propanesulfonate internal standard) on a Varian EM 360 spectrometer. ^{13}CMR spectra were recorded on *ca* 20% solns (TMS or sodium 3 - (trimethylsilyl) - propanesulfonate internal standard) on a Varian CFT-20 spectrometer. GLC analyses were carried out on a Carlo Erba Fractovap GV apparatus equipped with a flame ionization detector and a glass column (2 m × 2.5 mm) with 10% Carbowax 20M on 80–100 mesh silanized Chromosorb W under the following conditions: N_2 30 ml/min, programmed temp, low isotherm 80° (5 min), 5°/min, high isotherm 200°, injection block 210°. Relative retention times for the cycloaddition products **1**, **2**, **3c(3t)**, **3t(3c)** and **7**, 1.00:1.34:1.76:1.81:1.81; for the hydroboration–oxidation products α-**4**, β-**4**, α-**13**, β-**13**, 1.04:1.17:1.00:1.10. Since the peaks corresponding to **7** and one of the anomers of **3** overlapped, samples containing **7** were also analyzed on a 20-m glass capillary column coated with EGS that resolved well the two peaks. Petroleum ether refers to the fraction with b.p. 40–60°.

2 was prepared according to Lienhard *et al.*[6] in 85% yield from 4,4-dimethoxy-2-butanone (Aldrich).

cis- *and* trans - 2 - *isobutoxy* - 4 - *methoxy* - 6 - *methyl* - 2,3 - *dihydro* - 4H - *pyran* (**3c** *and* **3t**). A mixture of **2** (7.95 g, 79.5 mmole), isobutyl vinyl ether (21.4 g, 214.0 mmole) and hydroquinone (280 mg) was sealed in a glass vial and heated 24 h at 190° in an autoclave containing toluene in order to counterbalance the pressure inside the vial. The product was distilled. After a forerun containing the excess of the vinyl ether and unreacted **2** a mixture of **3c** and **3t** (6.2 g) in a ratio of *ca* 55:45 (GLC) distilled between 60 and 70° (1 mm). GLC and NMR analysis showed that it contained about 10% of side products. This product was used without further purification for the hydroboration–oxidation reaction.



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The same reaction was also carried out on a larger scale directly in a 150-ml steel autoclave with a mixture of 0.284 mole of **2**, 0.764 mole of isobutyl vinyl ether and 1 g of hydroquinone, which was heated 7.5 h at 200°. The product was first evaporated at 1 mm at room temp. The volatile product was collected in a dry-ice trap and fractionated at 760 mm. It contained, beside the excess isobutyl vinyl ether, b.p. 84–85°, **8**, b.p. 124–127° (lit.[20] b.p. 125–127°) identified by its NMR spectrum ($CDCl_3$): δ0.93 (6H, d, $J = 7$ Hz, $\underline{Me}_2CH$–), 1.27 (3H, d, $J = 5$ Hz, $\underline{MeCH}$–), 1.83 (1H, sept, $J = 7$ Hz, $Me_2\underline{CH}$), 3.0–3.5 (2H, dq, –$\underline{OCH}_2$–), 3.30 (3H, s, MeO–), 4.62 (1H, q, $J = 5$ Hz, $\underline{MeCH}$). The last fraction of the distillation contained beside **8** some **9**, as seen from the NMR spectrum, which differed from that of pure **8** by the fact that in the δ3.0–3.5 region the OMe singlet was much lower, the MeCH signals higher and the Me–C$\underline{H}$ signal was shifted to slightly lower field (δ4.66). These attributions were confirmed by comparison with the spectra of pure **8** and **9**, prepared by addition, respectively, of MeOH and of i-BuOH to isobutyl vinyl ether, according to Reppe.[21]

The product remaining after the evaporation at room temp was fractionated through a spinning band column. The first fraction, b.p. 78–80° (23 mm) contained unreacted **2** (14 g), the second fraction (3 g), b.p. 64–66° (5 mm) contained **7**, the third fraction (8.2 g), b.p. 80–82° (2 mm), was a mixture of the pure adducts **3c** and **3t** in a ratio of 55:45. Some tarry material remained as the residue.

NMR spectra. Compound **7** ($CDCl_3$): δ0.96 (6H, d, $J = 7$ Hz, $\underline{Me}_2CH$–), 1.75–2.16 (1H, m, $Me_2\underline{CH}$–), 2.13 (3H, s, $\underline{Me}$–CH=), 3.63 (2H, d, $J = 7$ Hz, –CH_2O), 5.60 (1H, d, $J = 13$ Hz, –$\underline{H}$C=CH–O–), 7.60 (1H, d, $J = 13$ Hz, C=C$\underline{H}$–O–). **3c** + **3t** ($CDCl_3$): δ0.94 (6H, d, $J = 7$ Hz, $\underline{Me}_2CH$), 1.80–2.30 (3H, m, $Me_2\underline{CH}$ + 3–CH_2), 1.81 (3H, bs, C=C–Me), 3.34 (3H, s, OMe), 3.12–4.06 (3H, m, –CH_2–O– + 4–CH), 4.65–5.12 (2H, m, 2–CH + C=CH). Extensive overlap of the signals for the two anomers did not allow individual assignments.

Similar runs conducted for longer times (24 and 40 h at 190°) directly in the autoclave gave much lower yields in adducts **3c** and **3t**, while the amounts of the products **7**, **8** and **9** increased considerably; much more tarry products were formed and in one instance were the sole product.

Equilibration between **2** *and isobutanol.* Compound **2** (0.5 ml) in 10 ml i-BuOH was refluxed 10 h. GLC analysis of the product showed that over 90% of **7** had formed; peaks corresponding to **2**, 4,4-dimethoxybutan-2-one (**1**) and possibly to 4-isobutoxy-4-methoxybutan-2-one were also present in a total amount of about 6%.

A soln of **2** (0.50 g), i-BuOH (0.50 g) and *p*-toluenesulphonic acid (10 mg) in toluene (25 ml) was kept at room temp for 3 hr, shaken with $NaHCO_3$ (1 g) for 30 min and analyzed by GLC: it showed peaks corresponding to **7**, **2**, **1** and possibly to 4-isobutoxy-4-methoxybutan-2-one in a ratio of 60:34:1:5.

Hydroboration–oxidation of **3c** + **3t**. A soln of the 55/45 mixture of **3c** + **3t** (5.94 g, 29.7 mmole) in hexane was cooled at 0° and treated under N_2 with magnetic stirring with BMS (2.8 ml, 28 mmole), shaken 2 h at 0° and left for 20 h at room temp, diluted with EtOH (35 ml) and treated with 3N NaOH aq (8 ml). The soln was cooled in ice, treated with 36% H_2O_2 (4.9 ml), refluxed 2 h, diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The extract was washed with H_2O (50 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The extract was washed with H_2O (100 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give 4.63 g (72%) of a syrup which was analyzed by GLC: it showed three main peaks corresponding respectively to the **α-4** and **β-4** and **β-13** in the ratio of 57:36:7. A small peak (*ca* 1%) with the same retention time as **α-13** was also present. Distillation of this product (b.p. 78–90°, 10 mm) did not change appreciably the composition of the mixture. Column chromatography on SiO_2 with 9:1 $CHCl_3$/AcOEt as the eluant allowed to separate the **β-13** in the head fraction and produced some fractionation but not a complete separation of **α-4** from **β-4**.

Separation of **α-4** *and* **β-4** *through the* **p-nitrobenzoates.** A mixture of the crude product from the hydroboration–oxidation (2.10 g, 9.17 mmole) and *p*-nitrobenzoyl chloride (2.50 g, 11.65 mmole) in anhyd pyridine (24 ml) was shaken 7 h at 80°, then treated with crushed ice (50 g) and concd HCl (25 ml), extracted with ether (9 × 50 ml). The ether soln was washed with H_2O (50 ml), satd $NaHCO_3$ aq (50 ml), H_2O (50 ml) and dried ($MgSO_4$), shaken with decolorizing coal, filtered and evaporated *in vacuo* to yield a viscous residue (3.11 g). One crystallization from petroleum ether gave the pure **β-14** m.p. 98–100°. A part of the product obtained from the mother liquor (1.65 g) was chromatographed on a 2 × 20-cm column of silica. A 60:35:5 mixture of CH_2Cl_2/petroleum ether/AcOEt eluted first 0.21 g of the product containing as the main component isobutyl β-amicetoside PNB, which, after crystallization from petroleum ether, had m.p. 60–62° and was identical (IR and NMR) with an authentic sample.[4] Further elution with the same solvent mixture gave a mixture of **α-** and **β-14** (0.45 g) and the pure **α-14** (0.63 g), m.p. 75° (from petroleum ether).

Isobutyl 2,6 - *dideoxy* - 3 - O - *methyl* - 4 - O - (*p-nitrobenzoyloxy*) - DL - *arabino* - *β* - *hexopyranoside* (*isobutyl* DL - *β* - *oleandroside* p - *nitrobenzoate*, ***β*-14**). Found : C, 59.13; H, 6.90; N, 3.84. $C_{18}H_{25}NO_7$ requires: C, 58.84; H, 6.86; N, 3.81. ^{1}HMR ($CDCl_3$): δ0.95 (6H, d, $J = 7$ Hz, $\underline{Me}_2CH$–), 1.30 (3H, d, $J = 7$ Hz, 6–Me), 1.5–2.6 (3H, m, 2–CH_2 + $Me_2\underline{CH}$–), 3.33 (3H, s, –OMe), 3.1–3.9 (4H, m, –OCH_2– + 3–CH + 5–CH), 4.60 (1H, q, $J = 9$, 2.5 Hz, 1–CH), 5.00 (1H, t, spl. 9 Hz, 4–CH), 8.45 (4H, m, –C_6H_4). ^{13}CMR ($CDCl_3$): δ17.59, 19.22, 28.39, 35.81 ($\underline{Me}_2C$, 6–Me, 2–CH_2, $\underline{C}Me_2$); 56.28 (OMe); 69.85, 76.16, 77.11, 77.96 (–CH_2O, 3–CH, 4–CH, 5–CH); 99.91 (1–CH); 123.46, 130.69, 135.34, 150.55 (aromatic); 163.84 (CO).

Isobutyl 2,6 - *dideoxy* - 3 - O - *methyl* - 4 - O - (p - *nitrobenzoyloxy*) - DL - *arabino* - *α* - *hexopyranoside* (*isobutyl* DL - *α* - *oleandroside* p - *nitrobenzoate*, ***α*-14**). Found: C, 59.44; H, 6.92; N, 3.54. $C_{18}H_{25}NO_7$ requires: C, 58.84; H, 6.86; N, 3.81. ^{1}HMR ($CDCl_3$): δ0.97 (6H, d, $J = 7$ Hz, $\underline{Me}_2CH$–), 1.21 (3H, d, $J = 7$ Hz, 6–Me), 1.4–2.6 (3H, m, 2–CH_2 + $Me_2\underline{CH}$–), 3.30 (3H, s, OMe), 2.9–4.1 (4H, m, –O–CH_2– + 3–CH + 5–CH), 4.92 (1H, m, $W_{1/2} = 6$ Hz, 1–CH), 4.93 (1H, t, spl. 9.0 Hz, 4–CH), 8.24 (4H, m, –C_6H_4). ^{13}CMR ($CDCl_3$): δ17.68, 19.39, 28.41, 35.01 ($\underline{Me}_2C$, 6–Me, 2–CH_2, $\underline{C}Me_2$); 65.72, 74.35, 74.92, 78.02 (–CH_2O–, 3–CH, 4–CH, 5–CH); 97.10 (1–CH); 123.58, 130.85, 135.59, 150.69 (aromatic); 164.05 (CO).

Equilibration of **β-14** *and* **α-14**. The *p*-nitrobenzoate **β-14** (380 mg) in i-BuOH (10 ml) was heated under stirring 3 h at 80° in the presence of Dowex 50W(H^+) resin (200 mg). After filtration the solvent was evaporated *in vacuo*. NMR analysis of the residue showed a diminution of the intensity of the quartet at δ4.60 for the anomeric proton of **β-14** and the appearance of the narrow multiplet at δ4.98 for the corresponding proton of **α-14**. After alkaline hydrolysis (see below) GLC analysis showed that the isobutyl glycosides **α-4** and **β-4** had formed in a ratio of 75:25.

Isobutyl DL - *α- and β-oleandrosides* (**α-4** *and* **β-4**). The ester **α-14** (423 mg) in MeOH (10 ml) was treated with 4N KOH aq (1 ml) and left 18 h at room temp. Solid $NaHCO_3$ (1 g) was added, the suspension was stirred 1 h, filtered and evaporated again to yield pure **α-4** (GLC) (0.14 g) as a colorless oil. ^{1}HMR ($CDCl_3$): δ0.90 (6H, d, $J = 7$ Hz, $\underline{Me}_2CH$), 1.26 (3H, d, $J = 7$ Hz, 6–Me), 1.4–2.5 (3H, m, $Me_2\underline{CH}$ + 2–CH_2), 3.37 (3H, s, –OMe), 2.9–3.8 (5H, m, –OCH_2– + 3–CH + 4–CH + 5–CH), 4.83 (1H, m, $W_{1/2} = 6$ Hz, 1–CH).

The ester **β-14** was similarly hydrolyzed to give **β-4**, m.p. 43–45°. ^{1}HMR ($CDCl_3$): δ0.90 (6H, d, $J = 7$ Hz, $\underline{Me}_2CH$), 1.33 (3H, d, $J = 7$ Hz, 6–Me), 1.4–2.5 (3H, m, $MeC\underline{H}$ + 2–CH_2), 3.37 (3H, s, –OMe), 2.7–3.8 (5H, m, –OCH_2– + 3–CH + 4–CH + 5–CH), 4.40 (1H, q, $J = 9.0$, 2.5 Hz, 1–CH).

2,6 - *dideoxy* - 3 - O - *methyl* - DL - *arabino* - *hexose* (DL - *oleandrose*, **15**). The mixture (1.3 g) of **α-4** and **β-4**, obtained after column chromatography of the crude hydroboration–oxidation product, in 2% H_2SO_4 (25 ml) was heated at 50° until it dissolved completely (1 h), then neutralized by stirring with an excess of $BaCO_3$, filtered and evaporated *in vacuo*. The residue was distilled in a Kugelrohr at 150° (external temp) and 0.5 mm to give **15** as a viscous colorless oil that resisted all attempts to crystallize it. (D-oleandrose is reported in the literature to crystallize with difficulty, m.p. 62–63°[22]). ^{1}HMR ($CDCl_3$): δ1.29 (3H, d, $J = 7$ Hz, 6–Me), 1.38–2.60 (2H, m, 2–CH_2), 2.93–3.70 (3H, m,

3-CH + 4-CH + 5-CH), 3.35 (3H, s, -OMe), 4.75 (0.4H, q, J = 10.0, 2.5 Hz, β-1-CH), 5.30 (0.6H, m, $W_{1/2}$ = 6 Hz, α-1-CH). In D_2O the spectrum was similar, but the ratio of the anomeric proton signals was different: δ4.96 (0.5H, q, J = 10.0, 2.5 Hz, β-1-CH), 5.32 (0.5H, m, $W_{1/2}$ = 6 Hz, α-1-CH). ^{13}CMR (D_2O): δ19.57 ($\alpha + \beta$-6-Me), 36.86 (α-2-CH_2), 39.01 (β-2-CH_2), 58.85 ($\alpha + \beta$-OMe), 70.56 (α-5-CH), 74.44 (β-5-CH), 77.38, 77.97 ($\alpha + \beta$-4-CH), 79.88 (α-3-CH), 82.07 (β-3-CH), 93.78 (α-1-CH), 95.87 (β-1-CH).

Oleandrose (0.13 g) was treated with a soln of 2,4-dinitrophenylhydrazine (0.2 g) in H_2O (5 ml) and conc H_2SO_4 (1 ml). The precipitate was crystallized from EtOH/water to yield crystals, m.p. 159–164° (lit.[17], m.p. 155–160°), probably **16**; λ_{max} (EtOH) 370 nm; λ_{max} (0.25N NaOH in EtOH) 460 nm. ^{1}HMR (DMSO) δ: 1.11 (3H, d, 6-Me), 3.0–4.2 (4H, m, 4-CH + 5-CH + 4-OH + 5-OH), 6.4 (2H, m, 3-CH + 4-CH), 7.8–8.4 (3H, m, 1-CH + 5'-CH + 6'-CH), 8.90 (1H, d, 3'-CH), 11.1 (1H, s, NH).

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