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Alternative Syntheses of L-(-)-Oleandrose from L-Rhamnose[1] Preparation of Glycals

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SYNTHETIC COMMUNICATIONS, 22(17), 2459-2477 (1992)

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ALTERNATIVE SYNTHESES OF L-(−)-OLEANDROSE FROM L-RHAMNOSE: PREPARATION OF GLYCALS

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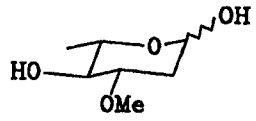
ABSTRACT: L-Rhamnal (2) is prepared from L-rhamnose (3) by use of an improved generalized Fischer-Zach reaction. L-Rhamnal (2) is then converted to L-(−)-oleandrose (1) by stannylene mediated selective methylation and effective hydration. Benzyl α-L-oleandrose (12) is prepared by selective methylation and deoxygenation of L-rhamnose (3).

The 2,6-dideoxy sugar L-(−)-oleandrose (1) occurs in the leaves of *Nerium oleander* (Apocynaceae).[2] L-(−)-Oleandrose (1) also occurs as a component of several antibiotics such as oleandomycin[3] and the avermectin series.[4] Several syntheses of DL-[5] and L-(−)-oleandrose (1)[6-8] have been reported as well as alkyl DL-[9] and L-(−)-oleandrosides.[10-12] As part of our interest in the efficient preparation and use of unsaturated sugar derivatives in the chiral synthesis of natural compounds,[13] we herein report a short synthesis of L-(−)-oleandrose (1) from L-rhamnal (2) which is prepared from L-rhamnose (3).



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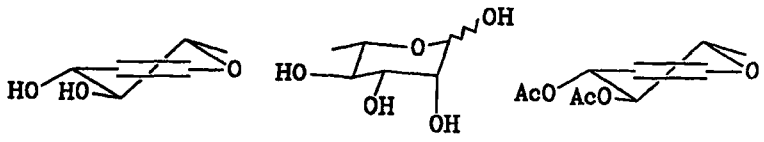
The use of zinc in acetic acid for the reductive debromoacetylation of peracetylated glycopyranosyl bromides is still the most widely used method for the preparation of pyranoid[14] glycals since its serendipitous origin in 1913.[15] A few modifications to the original method were introduced, e.g. reduction with zinc catalysed by silver on graphite[16] or by aluminium amalgam[17] of the peracetylated glycopyranosyl bromides. These methodologies are, however, technically difficult and expensive, and thus do not enjoy general application.

Despite its widespread use, the yields of the Fischer-Zach[15] preparation of glycals are usually moderate. The import of these compounds as chiral precursors have stimulated efforts to improve this preparation over several decades.[18] One of these improvements entailed reduction with *in situ* prepared zinc/copper couple in an aqueous acetic acid medium.[19] However, we found that the presence of the water in the reaction mixture led to competitive hydrolysis of the glycosyl bromide. Prior preparation of the zinc/copper couple followed by rigorous drying by washing with ethanol and THF and evacuating over P_2O_5 overnight made provision for an anhydrous Fischer-Zach reaction in 10% acetic acid in THF. Peracetylated (or perbenzoylated) D-glucal, D-galactal, D- and L-arabinal, D-xylal and L-rhamnal (**4**) were thus prepared in 80 – 90% yields in three steps from the corresponding sugars.[20]

The triethylamine catalyzed methanolysis of **4** furnished **2**[21] in quantitative yield. The conversion of **2** into L-oleandrose (**1**) requires selective *O*-methylation at position 3 and hydration of the double bond. Rhamnal (**2**) has been selectively 3-*O*-methylated either in several steps[22] or adroitly by diazome-



2 3 4

thane yielding at best a 7:1 mixture of 3- and 4-*O*-methylrhamnal in moderate yield.[7] Dibutylstannoxane mediated selective 3-*O*-acylation of rhamnal (2)[23] and 3-*O*-benzylation of 6-tributylsilylglucal[24] suggested analogous selectivity in the *O*-methylation of rhamnal (2). This selectivity is most likely induced sterically and electronically. In view of the reported[25] enhanced yields in tin mediated selective alkylation when caesium fluoride is added, a THF[26] solution of the dibutylstannoxane complex of rhamnal was treated with methyl iodide in the presence of caesium fluoride for 2.5 days yielding 73% of the desired 3-*O*-methyl-L-rhamnal[10] (oleandral 5) exclusively. The position of methylation was elucidated when the *in situ* treatment of an NMR sample of (5) with trichloroacetyl isocyanate caused significant deshielding (δ3.51 to 5.02) of the unmethylated proton at position 4.

Perusal of the available methodology[27] for the hydration of the enolic double bond of the glycal (5) suggested the recent contribution of Horton and coworkers[28] as the most promising possibility. Treatment of the 3-*O*-methylrhamnal (5) with *N*-iodosuccinimide in the presence of ^{t}BuOH[29] furnished the trans diaxial alkoxy iodide (6) in 86% yield. Facile reductive deiodination of 6 with tributylstannane and AIBN rendered *tert*-butyl α-L-oleandropyranoside (7) in 96% yield. Hydrolysis also proceeded smoothly with catalytic amounts of trifluoroacetic acid and rapid work up furnishing L-olean-

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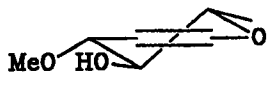
drose (1, 86%) with physical properties ($[\alpha]_D$ and ^1H and ^{13}C NMR) in good correlation with the published data.[8]

The remarkable selectivity in the stannylene mediated *O*-methylation of L-rhamnal (2) gave impetus to the possibility of an even shorter synthesis of L-oleandrose (1) from L-rhamnose (3).[11] Selective *O*-methylation of a suitable alkyl α-L-rhamnopyranoside should, by analogy to the selective benzoylation of methyl α-D-mannopyranoside,[30] furnish the 3-*O*-methyl derivative. A THF solution of the dibutylstannoxane complex of benzyl α-L-rhamnopyranoside (8) was treated with methyl iodide in the presence of caesium fluoride to furnish after 1 h the 3-*O*-methylated product (9) in 86% yield. Prolonged reaction (14 h) resulted in the further 2-*O*-methylation to give the 2,3-di-*O*-methylrhamnopyranoside (10) as the major product (58%). The position of methylation in 9 was again proven by the *in situ* administration of trichloroacetyl isocyanate during ^1H NMR spectroscopy. The positions of methylation in 10 are indicated with ^{13}C NMR spectroscopy by the upfield chemical shift experienced by C-2 when compared to the monomethyl analogue 9 (δ75.96 and 66.88 resp.) relative to the similar chemical shifts experienced by C-3 which is methylated in both instances (δ81.08 and 81.25 resp.) and C-4 which is not methylated in both instances (δ71.69 and 71.64 resp.).



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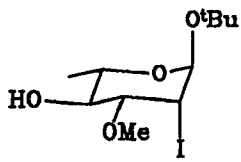

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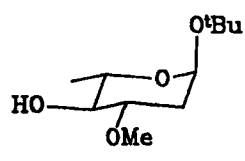

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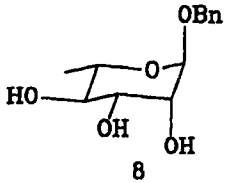

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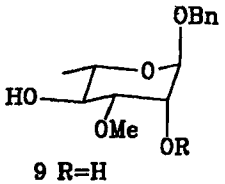
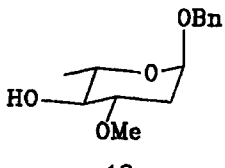


9 R=H
10 R=Me
11 R=CS_2Me



12

The next phase was the introduction of a group to the 2-*O*-position that would enable deoxygenation at that position. Tin mediated selective phenoxythiocarbonylation[31] of the 2-*O*-position seemed to be the designated methodology. Efforts to introduce a phenoxythiocarbonyl group at the 2-*O*-position by the addition of the thiocarbonyl chloride to the same pot in which benzyl rhamnopyranoside (8) had been 3-*O*-methylated whilst the chlorostannyl group still activated the 2-*O*-position failed. Phenoxythiocarbonylation of 9 after tributylstannyl activation also failed. As an alternative the 2-xanthate (11) was selectively formed by classical means, using only a slight molar excess of sodium hydride. This selectivity may be rationalized in terms of the greater acidity of the 2- relative to the 4-hydroxy group due to the former being juxtaposed to the electron withdrawing anomeric position. Deoxygenation of the 2-position was realized by homolytic removal of the xanthate by the drop wise addition of a mixture of 11, tributylstannane and AIBN in benzene to refluxing benzene furnishing benzyl α-L-oleandropyranoside (12).

Benzyl α-L-oleandropyranoside (12) is well disposed as a glycosyl acceptor and is easily converted into a glycosyl donor by acetylation and then debenzylation catalyzed by 20% $Pd(OH)_2/C$ under one atmosphere of hydrogen.[8]

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We are currently investigating the synthesis of other deoxy and dideoxy sugars *via* selective xanthate formation and selective tin mediated thiocarbonylation followed by homolytic deoxygenation.

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Experimental

All reagents excepting the Zn/Cu-couple (see below) and tetra-*O*-acetyl-L-rhamnopyranose[32] were commercially available and used without prior processing. The following AR solvents were also used without prior processing: Ac_2O, glacial AcOH, EtOH and $CHCl_3$. Benzene, toluene and THF were distilled off a sodium/potassium liquid alloy (1:5) after a trace of benzophenone in the pot had turned blue with refluxing. Pyridine was refluxed and distilled off BaO, Et_3N off Na, CH_2Cl_2 and acetonitrile off P_2O_5 and absolute MeOH off $Mg(OMe)_2$. EtOAc as solvent and eluting agent was distilled off K_2CO_3 and hexane as eluting agent distilled. For standard column chromatography Silica gel 60 (Merck, 63-200 μm) was used as stationary phase and for flash chromatography MN-Kieselgel 60 (Macherey Nagel, 40-63 μm) was used. Silica gel 60 F_{254} plates (Merck, 0.15 mm) was used for TLC. Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Varian VXR 200 spectrometer, with $CDCl_3$ serving as solvent and internal reference [converted to tetramethylsilane as reference, δ_H ($CHCl_3$) being 7.24 and δ_C ($CDCl_3$) being 77.00]. Mass spectra were recorded on a Varian Mat 8200 mass spectrometer. A Jasco DIP-370 spectropolarimeters was used for determining optical

rotations. IR spectra were recorded on a Perkin-Elmer 297/841 spectrophotometer in chloroform, except where specified otherwise.

In order to determine the position of free hydroxy groups (if any) in a compound in an NMR tube, 30 – 50 μl of trichloroacetyl isocyanate (Aldrich) were added *in situ*, and an NMR spectrum rerun. Severe downfield shift ($\Delta\delta_H > 1$ ppm) of protons geminal to an oxygen atom is indicative of the oxygen atom being a hydroxy group having been derivatized.

Preparation of the Zinc/Copper couple.– To a suspension of zinc (70 g) in a solution of $CuSO_4 \cdot 5H_2O$ (7 g) in water (50 ml) at 0°C was added a solution of sodium acetate (35 g) in a mixture of water (200 ml) and acetic acid (115 ml). The resulting suspension was stirred for 10 min at 0°C after which the supernatant liquid was decanted off the zinc/copper couple. The zinc/copper couple was then consecutively washed with 96% ethanol (3x350 ml) and THF (4x100 ml) by stirring and decantation and finally dried for 16 h in a vacuum desiccator over P_2O_5.

L-*Rhamnal (2).*– A solution of tetra-*O*-acetyl-L-rhamnopyranose[32] (40.1 g, 121 mmol) in acetic acid (20 ml) and acetic anhydride (5 ml) was treated with a solution of HBr in acetic acid (80 ml of 30%, 402 mmol) and stirred for 4 h at ambient temperature. The volatiles were removed *in vacuo* furnishing crude tri-*O*-acetyl-L-rhamnopyranosyl bromide; ^{1}H NMR[33] δ1.25 (d, 3H, $^3J_{Me,5} = 6.3$ Hz, CH_3), 1.97, 2.05 and 2.13 (3xs, 3x3H, 3xCH_3CO_2), 4.07 (dq, 1H, $^3J_{5,4} = 10.0$ and $^3J_{5,Me} = 6.4$ Hz, H-5), 5.12 (t, 1H, $^3J_{4,3} \approx {}^3J_{4,5} \approx 10.1$ Hz, H-4), 5.42 (d, 1H, $^3J_{2,3} = 3.6$ Hz, H-2), 5.64 (dd, 1H, $^3J_{3,4} = 10.2$

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and $^3J_{3,2}$ = 3.4 Hz, H-3) and 6.22 (s, 1H, H-1); ^{13}C NMR δ16.95 (q, CH_3), 20.61, 20.74 and 20.75 (3xq, 3xCH_3CO_2), 67.88, 70.26, 71.07 and 72.41 (4xd, C-2, C-3, C-4 and C-5), 83.66 (d, C-1) and 169.58, 169.72 and 169.81 (3xs, 3xCH_3CO_2).

Tri-*O*-acetyl-L-rhamnopyranosyl bromide and NaOAc (14 g) were dissolved in a mixture of THF (200 ml) and acetic acid (10 ml) and cooled down to 0°C. Zn/Cu couple (80 g) was then added and the mixture allowed to reach ambient temperature while stirring for 2 h. The mixture was then treated with Na_2CO_3 (7.5 g) and stirred for 30 min after which the solids were filtered off and the solvent removed from the filtrate *in vacuo*. The residue was dissolved in $CHCl_3$ (200 ml), saturated aq Na_2CO_3 (300 ml) added and vigorously stirred for 30 min. The phases were separated and the organic phase dried ($MgSO_4$), the solvent removed *in vacuo* and the residue distilled furnishing di-*O*-acetyl-L-rhamnal (4) (21.6 g, 83%); $[\alpha]_D^{30}$ +61.5° ±2.1 (*c* 1.00, $CHCl_3$) (lit.[34] $[\alpha]_D^{21}$ +66.9°, *c* 0.9, $CHCl_3$); ^{1}H[34] and ^{13}C[35] NMR spectra in agreement with published data.

Triethylamine (7.25 ml, 52.1 mmol) was added to a solution of di-O-acetyl-L-rhamnal (4) (5.00 g, 23.3 mmol) in MeOH (60 ml) and stirred at ambient temperature for 3 days. The solvents were removed *in vacuo* and the residue recrystalized from benzene furnishing L-rhamnal (2) (2.82 g, 93%) mp 71-74°C (lit.[21] 70-73°C, benzene); $[\alpha]_D^{23}$ -20.4° ±1.9 (*c* 1.00, $CHCl_3$) (lit.[36] $[\alpha]_D^{20}$ -21°, *c* 2, $CHCl_3$); ν_{max} ($CHCl_3$) 3432 cm^{-1} (H-bonded OH); ^{1}H NMR (acetone-d_6) δ1.28 (d, 3H, $^3J_{Me,5}$ = 6.3 Hz, CH_3), 3.25 (ddd, 1H, $^3J_{4,5}$ = 9.8, $^3J_{4,3}$ = 6.9 and $^3J_{4,4OH}$ = 4.8 Hz, H-4), 3.72 (dq, 1H, $^3J_{5,4}$ = 9.8 and $^3J_{5,Me}$ = 6.4 Hz, H-5), 4.02 (d, 1H, $^3J_{3OH,3}$ = 5.4 Hz, OH-3), 4.07 (tt, 1H, $^3J_{3,4} \approx {}^3J_{3,3OH} \approx$ 6.9 and $^3J_{3,2} \approx {}^4J_{3,1} \approx$ 1.7 Hz, H-3), 4.41 (d, 1H, $^3J_{4OH,4}$ =

5.1 Hz, OH-4), 4.62 (dd, 1H, $^3J_{2,1}$ = 6.1 and $^3J_{2,3}$ = 2.0 Hz, H-2) and 6.23 (dd, 1H, $^3J_{1,2}$ = 6.0 and $^4J_{1,3}$ = 1.7 Hz, H-1); ^{13}C NMR spectrum and assignment by HETCORR in agreement with published data;[35] *m/z* (EI, 70 eV) 130 (M^+-2OH, 13%) and 73 (100).

3-O-Methyl-L-rhamnal (5) (L-oleandral).– L-rhamnal (2) (1.00 g, 7.69 mmol) and dibutylstannoxane (1.92 g, 7.71 mmol) were suspended in toluene (50 ml) and brought to reflux for 2.5 h using a Dean and Stark separator. The solvent was removed by distillation, CsF (2.35 g, 15.5 mmol) added, and the last traces of solvent removed *in vacuo*. The residue was dissolved/suspended in THF (50 ml) and MeI (1.90 ml, 30.5 mmol) added. After 2.5 days of stirring at ambient temperature, imidazole (1.05 g, 15.4 mmol) was added,[37] stirred for 1 h and filtered through a short column of silica gel and the crude product, obtained on the removal of the solvent *in vacuo*, flash chromatographed (EtOAc/hexane-1:2) furnishing 3-*O*-methyl-L-rhamnal (5) (816 mg, 74%); ^{1}H NMR[10] δ1.36 (d, 3H, $^3J_{Me,5}$ = 6.4 Hz, CH_3), 2.58 (bs, 1H, OH), 3.38 (s, 3H, OCH_3), 3.51 (ddd, 1H, $^3J_{4,5}$ = 9.7, $^3J_{4,3}$ = 6.9 and $^3J_{4,OH}$ = 3.0 Hz, H-4, moved to δ5.02 on addition of trichloroacetyl isocyanate into NMR tube), 3.83 (dt, 1H, $^3J_{3,4}$ = 7.2 and $^3J_{3,2} \approx {}^4J_{3,1} \approx$ 2.0 Hz, H-3), 3.86 (dq, 1H, $^3J_{5,4}$ = 9.6 and $^3J_{5,Me}$ = 6.5 Hz, H-5), 4.80 (dd, 1H, $^3J_{2,1}$ = 6.2 and $^3J_{2,3}$ = 2.7 Hz, H-2) and 6.31 (dd, 1H, $^3J_{1,2}$ = 6.3 and $^4J_{1,3}$ = 1.5 Hz, H-1); ^{13}C NMR δ17.10 (q, CH_3), 55.75 (q, OCH_3), 72.39 (d, C-4, moved to δ73.15 or 74.55 on addition of trichloroacetyl isocyanate into NMR tube), 74.38 (d, C-5), 78.55 (d, C-3), 99.03 (d, C-2) and 144.99 (d, C-1); *m/z* (EI, 70 eV) 144 (M^+, 5.4%; found 144.0773, $C_7H_{12}O_3$ requires 144.0786), 143 (21), 129 (18), 113 (56) and 59 (100).

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Tert-*butyl 2-deoxy-2-iodo-3-O-methyl-α-L-rhamnopyranoside (6).*— To a solution of 3-*O*-methyl-L-rhamnal (5) (100 mg, 693 μmol) in acetonitrile (1 ml) and ^{t}BuOH (1 ml) at O°C was added *N*-iodosuccinimide (234 mg, 1.04 mmol). The reaction mixture was allowed to slowly warm to ambient temperature while stirring for 16 h. The volatiles were removed *in vacuo* and the residue flash chromatographed (EtOAc/hexane-1:3) furnishing tert-*butyl 2-deoxy-2-iodo-3-O-methyl-α-L-rhamnopyranoside* (6) (206 mg, 86%) mp 71-74°C; $[\alpha]_D^{23}$ -11.9° ±2.0 (*c* 1.00, $CHCl_3$); υ_{max} ($CHCl_3$) 2980 (CH) and 1241, 1108 and 1046 cm^{-1} (C–O); ^{1}H NMR δ1.22 [s, 9H, $C(CH_3)_3$], 1.27 (d, 3H, $^3J_{Me,5}$ = 6.3 Hz, CH_3), 2.78 (ddd, 1H, $^3J_{3,4}$ = 8.8, $^3J_{3,2}$ = 4.0 and $^4J_{3,5}$ = 0.7 Hz, H-3), 3.34 (s, 3H, OCH_3), 3.53 (t, 1H, $^3J_{4,5} \approx {}^3J_{4,3} \approx$ 9.2 Hz, H-4), 3.94 (dqd, 1H, $^3J_{5,4}$ = 9.3, $^3J_{5,Me}$ = 6.3 and $^4J_{5,3}$ = 0.6 Hz, H-5), 4.34 (dd, 1H, $^3J_{2,3}$ = 3.7 and $^3J_{2,1}$ = 0.6 Hz, H-2) and 5.35 (d, 1H, $^3J_{1,2}$ = 0.7 Hz, H-1); ^{13}C NMR δ17.66 (q, CH_3), 28.49 [q, $C(CH_3)_3$], 34.35 (d, C-2), 55.86 (q, OCH_3), 68.01 (d, C-5), 73.89 (d, C-4), 76.00 (s, [$C(CH_3)$], 77.97 (d, C-3) and 96.44 (d, C-1); *m/z* (EI, 70 eV) 344 (M^+, 1.6%), 271 (14), 270 (15) and 57 (100).

Tert-*butyl 2-deoxy-3-O-methyl-α-L-rhamnopyranoside (7).*— To a solution of *tert*-butyl 2-deoxy-2-iodo-3-*O*-methyl-α-L-rhamnopyranoside (6) (700 mg, 2.03 mmol) in benzene (50 ml) was added Bu_3SnH (546 μl, 2.03 mmol) and AIBN (20 mg, 122 μmol). The reaction mixture was refluxed for 1 h, further portions of Bu_3SnH (546 μl, 2.03 mmol) and AIBN (20 mg, 122 μmol) added and refluxing continued for a further 1 h. The volatiles were removed *in vacuo* and the residue flash chromatographed (EtOAc/hexane-1:9) furnishing tert-*butyl 2-deoxy-3-O-methyl-α-L-rhamnopyranoside* (7) (426 mg, 96%); $[\alpha]_D^{23}$

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-162.2° ±0.7 (*c* 1.00, $CHCl_3$); υ_{max} ($CHCl_3$) 3598 (OH), 2982 and 2975 (CH) and 1223, 1108, 1068 and 998 cm^{-1} (C–O); ^1H NMR δ1.20 [s, 9H, $C(CH_3)_3$], 1.21 (d, 3H, $^3J_{Me,5}$ = 5.8 Hz, CH_3), 1.47 (ddd, 1H, $^2J_{2,2}$ = 12.3, $^3J_{2ax,3}$ = 11.5 and $^3J_{2ax,1}$ = 3.7 Hz, H-2ax), 2.07 (ddd, 1H, $^2J_{2,2}$ = 12.3, $^3J_{2eq,3}$ = 4.8 and $^3J_{2eq,1}$ = 1.4 Hz, H-2eq), 2.51 (d, 1H, $^3J_{OH,4}$ = 2.0 Hz, OH), 3.10 (td, 1H, $^3J_{4,5} \approx {}^3J_{4,3} \approx$ 9.0 and $^3J_{4,OH}$ = 1.7 Hz, H-4), 3.36 (s, 3H, OCH_3), 3.53 (ddd, 1H, $^3J_{3,2ax}$ = 11.5, $^3J_{3,4}$ = 8.8 and $^3J_{3,2eq}$ = 4.9 Hz, H-3), 3.82 (dq, 1H, $^3J_{5,4}$ = 9.4 and $^3J_{5,Me}$ = 6.2 Hz, H-5) and 5.16 (dd, 1H, $^3J_{1,2eq}$ = 1.3 and $^3J_{1,2ax}$ = 3.8 Hz, H-1); ^{13}C NMR (assignments made by HETCORR) δ17.77 (q, CH_3), 28.58 [q, $C(CH_3)_3$], 35.49 (t, C-2), 56.33 (q, OCH_3), 66.90 (d, C-5), 74.41 (s, [$C(CH_3)$], 76.36 (d, C-4), 78.48 (d, C-3) and 91.83 (d, C-1); *m/z* (EI, 70 eV) 161 (M^{+}-^{t}Bu, 0.59%), 145 (19), 144 (2.0) and 74 (100).

2-Deoxy-3-O-methyl-L-rhamnose (1) (L-oleandrose).– *Tert*-butyl 2-deoxy-3-O-methyl-α-L-rhamnopyranoside (7) (50 mg, 229 μmol) was dissolved in CH_2Cl_2 (5 ml) and trifluoroacetic acid (50 μl, 649 μmol) and stirred for 1.5 h. The mixture was neutralized with $NaHCO_3$ and then filtered through silica gel (EtOAc), the volatiles removed from the filtrate *in vacuo*, and the residue flash chromatographed (EtOAc/hexane-1:1) furnishing 3-*O*-methyl-2-deoxy-L-rhamnose (1) (32 mg, 86%); $[\alpha]_D^{23}$ +11.2° ±1.4 (*c* 1.00, water) (lit.[8] $[\alpha]_D^{23}$ +10.3°, *c* 1.23, water); υ_{max}[8] (KBr) 3399 (H-bonded OH), 2932 (CH) and 1105 cm^{-1} (C–O); ^1H NMR[8] reveals an α:β anomeric mixture of 2.4:1 (α-anomer) δ1.26 (d, 3H, $^3J_{Me,5}$ = 6.3 Hz, CH_3), 1.47 (ddd, 1H, $^2J_{2,2}$ = 12.9, $^3J_{2ax,3}$ = 11.4 and $^3J_{2ax,1}$ = 3.6 Hz, H-2ax), 2.28 (ddd, 1H, $^2J_{2,2}$ = 12.9, $^3J_{2eq,3}$ = 4.8 and $^3J_{2eq,1}$ = 1.3 Hz, H-2eq), 3.14 (t, 1H, $^3J_{4,5} \approx {}^3J_{4,3} \approx$ 9.2 Hz, H-4), 3.38 (s, 3H, OCH_3), 3.56 (ddd, 1H, $^3J_{3,2ax}$ = 11.6, $^3J_{3,4}$ = 9.0 and

$^3J_{3,2eq}$ = 4.8 Hz, H-3), 3.91 (dq, 1H, $^3J_{5,4}$ = 9.4 and $^3J_{5,Me}$ = 6.3 Hz, H-5) and 5.34 (bd, 1H, $^3J_{1,2ax}$ = 2.9 Hz, H-1), (β-anomer) δ1.32 (d, 3H, $^3J_{Me,5}$ = 6.1 Hz, CH_3), 1.25-1.60 (m, 1H, H-2ax), 2.39 (ddd, 1H, $^2J_{2,2}$ = 12.3, $^3J_{2eq,3}$ = 4.2 and $^3J_{2eq,1}$ = 2.1 Hz, H-2eq), 3.00-3.50 (m, 3H, H-3 H-4 and H-5) 3.33 (s, 3H, OCH_3) and 4.79 (dd, 1H, $^3J_{1,2ax}$ = 9.7 and $^3J_{1,2eq}$ = 2.1 Hz, H-1); ^{13}C NMR (assignments made by HETCORR) (α-anomer) δ17.89 (q, CH_3), 33.90 (t, C-2), 56.45 (q, OCH_3), 67.67 (d, C-5), 76.17 (d, C-4), 77.85 (d, C-3) and 92.17 (d, C-1), (β-anomer) δ17.85 (q, CH_3), 35.51 (t, C-2), 56.33 (q, OCH_3), 71.80 (d, C-5), 75.27 (d, C-4), 80.53 (d, C-3) and 94.03 (d, C-1).

Benzyl α-L-rhamnopyranoside (8).— To benzyl alcohol (4.60 ml, 44.2 mmol) at -10°C acetyl chloride (1.60 ml, 22.4 mmol) was added dropwise. The mixture was allowed to reach ambient temperature and L-rhamnose (500 mg, 3.05 mmol) was added. After 5 h of stirring, the solution was evaporated *in vacuo* and the residue chromatographed (hexane then EtOAc/hexane-1:3) over silica gel to remove the excess benzyl alcohol. The fractions containing the product was flash chromatographed (EtOAc) over silica gel furnishing benzyl α-L-rhamnopyranoside (8); $[\alpha]_D^{23}$ -93.1° ±1.2 (*c* 1.00, MeOH); υ_{max} (KBr) 3547 (free OH), 3394 (H-bonded OH), 1091 and 1064 cm^{-1} (C–O); ^{1}H NMR (acetone-d_6) δ1.23 (d, 3H, $^3J_{Me,5}$ = 6.2 Hz, CH_3), 2.95 (bs, 2H, OH-3 and -4), 3.40 (t, 1H, $^3J_{4,3} \approx {}^3J_{4,5} \approx$ 9.3 Hz, H-4), 3.62 (dq, 1H, $^3J_{5,4}$ = 9.3 and $^3J_{5,Me}$ = 6.1 Hz, H-5), 3.66 (dd, 1H, $^3J_{3,4}$ = 9.4 and $^3J_{3,2}$ = 3.4 Hz, H-3), 3.84 (bs, 1H, H-2), 3.88-3.96 (bs, 1H, OH-2), 4.48 (d, 1H, $^2J_{H',H'}$ = 12.0 Hz, H'b), 4.70 (d, 1H, $^2J_{H',H'}$ = 12.0 Hz, H'a), 4.79 (d, 1H, $^3J_{1,2}$ = 1.3 Hz, H-1) and 7.10-7.35 (m, 5H, Ph); ^{13}C NMR (acetone-d_6, assignments made by HETCORR) δ18.10 (q, CH_3), 69.18 (d, C-5), 69.35 (t, C'), 71.88 (d, C-2),

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72.49 (d, C-3), 73.72 (d, C-4), 100.33 (d, C-1), 128.28 (d, *p*-Ph), 128.57 (d, *o*-Ph), 129.08 (d, *m*-Ph) and 139.09 (s, *ipso*-Ph); *m/z* (EI, 70 eV) 181 (M^+-$C_3H_5O_2$, 4.7%), 163 (11), 145 (4.9) and 91 (100).

Benzyl 3-O-methyl-α-L-rhamnopyranoside (9).— Benzyl α-L-rhamnopyranoside (8) (1.50 g, 5.90 mmol) and dibutylstannoxane (1.47 g, 5.91 mmol) were suspended in toluene (50 ml) and brought to reflux for 1 h using a Dean and Stark separator. The solvent was removed by distillation, CsF (1.80 g, 11.8 mmol) added, and the last traces of solvent removed *in vacuo*. The residue was dissolved/suspended in THF (50 ml) and MeI (1.50 ml, 24.1 mmol) added. After 2 h of stirring at ambient temperature, imidazole (800 mg, 11.8 mmol) was added,[37] stirred for 1 h and filtered through a short column of silica gel and the crude product, obtained on the removal of the solvent *in vacuo*, flash chromatographed (EtOAc/hexane-1:1) furnishing *benzyl 3-O-methyl-α-L-rhamnopyranoside* (9) (1.36 g, 86%); $[\alpha]_D^{23}$ -76.2° ±1.2 (*c* 1.00, water); υ_{max} 1231 cm^{-1} (C–O); ^1H NMR δ1.30 (d, 3H, $^3J_{Me,5}$ = 6.2 Hz, CH_3), 2.02 and 3.42 (2xbs, 2x1H, 2xOH), 3.41 (m, 1H, H-3), 3.45 (s, 3H, OCH_3), 3.54 (t, 1H, $^3J_{4,3} \approx {}^3J_{4,5} \approx$ 9.1 Hz, H-4, moved to δ4.94 on addition of trichloroacetyl isocyanate into NMR tube), 3.73 (dq, 1H, $^3J_{5,4}$ = 8.9 and $^3J_{5,Me}$ = 6.2 Hz, H-5), 4.09 (dd, 1H, $^3J_{2,3}$ = 3.1 and $^3J_{2,1}$ = 1.7 Hz, H-2), 4.46 (d, 1H, $^2J_{H',H'}$ = 11.8 Hz, H'b), 4.69 (d, 1H, $^2J_{H',H'}$ = 11.8 Hz, H'a), 4.91 (d, 1H, $^3J_{1,2}$ = 1.5 Hz, H-1) and 7.20-7.40 (m, 5H, Ph); ^{13}C NMR (assignments made by HETCORR) δ17.62 (q, CH_3), 56.96 (q, OCH_3), 66.88 (d, C-2), 67.80 (d, C-5), 69.13 (t, C'), 71.64 (d, C-4), 81.25 (d, C-3), 98.56 (d, C-1), 127.92 (d, *p*-Ph), 128.07 (d, *o*-Ph), 128.46 (d, *m*-Ph) and 137.19 (s, ipso-Ph); *m/z* (EI, 70 eV) 251 (M^+-OH, 12%; found 251.1255, $C_{14}H_{19}O_4$ requires 251.1283), 177 (6.7), 161 (28) and 91 (100).

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Benzyl 3-O-methyl-2-O-(thiomethoxythiocarbonyl)-α-L-rhamnopyranoside (11).– To a solution of benzyl 3-*O*-methyl-α-L-rhamnopyranoside (9) (820 mg, 3.06 mmol) in THF at 0°C was added NaH (80% suspension in oil, 105 mg, 3.07 mmol) and imidazole (20 mg, 290 μmol) and stirred for 45 min, while allowing to reach ambient temperature. CS_2 (480 μl, 7.98 mmol) was then added and after a further 10 min of stirring, MeI (400 μl, 6.43 mmol). After 20 min, the volatiles were removed *in vacuo* and the residue flash chromatographed (EtOAc/hexane-1:2 then 1:1) furnishing *benzyl 3-O-methyl-2-O-(thiomethoxythiocarbonyl)-α-L-rhamnopyranoside* (11) (928 mg, 85%); $[\alpha]_D^{27}$ -51.6° ±1.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ1.33 (d, 3H, $^3J_{Me,5}$ = 6.2 Hz, CH_3), 2.44 (bs, 1H, OH-4), 2.54 (s, 3H, SCH_3), 3.38 (s, 3H, OCH_3), 3.50-3.70 (m, 2H, H-3 and H-4), 3.79 (q_n, 1H, $^3J_{5,4} \approx {}^3J_{5,Me} \approx$ 6.2 Hz, H-5), 4.51 (d, 1H, $^2J_{H',H'}$ = 11.9 Hz, H'b), 4.71 (d, 1H, $^2J_{H',H'}$ = 11.9 Hz, H'a), 4.97 (d, 1H, $^3J_{1,2}$ = 1.7 Hz, H-1), 6.11 (dd, 1H, $^3J_{2,3}$ = 2.7 and $^3J_{2,1}$ = 1.8 Hz, H-2) and 7.20-7.40 (m, 5H, Ph); ^{13}C NMR (assignments made by HETCORR) δ17.73 (q, CH_3), 18.97 (q, SCH_3), 57.48 (q, OCH_3), 68.23 (d, C-5), 69.52 (t, C'), 72.21 (d, C-4), 75.70 (d, C-2), 79.44 (d, C-3), 99.25 (d, C-1), 127.99 (d, *p*- and *o*-Ph), 128.49 (d, *m*-Ph), 136.90 (s, *ipso*-Ph) and 215.81 (s, OCS_2); *m/z* (EI, 70 eV) 341 (M^+-OH, 0.72%), 250 (6.8), 219 (2.8) and 91 (100).

Benzyl 2-deoxy-3-O-methyl-α-L-rhamnopyranoside (benzyl α-L-oleandropyranoside) (12).– To a refluxing solution of benzyl 3-*O*-methyl-2-*O*-(thiomethoxythiocarbonyl)-α-L-rhamnopyranoside (11) (440 mg, 1.23 mmol) in benzene (15 ml) was added dropwise over 80 min a solution of Bu_3SnH (589 μl, 2.23 mmol) and AIBN (48 mg, 292 μmol) in benzene (10 ml). The reaction mixture was cooled down, the solvent removed *in vacuo* and the residue

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dissolved in $CHCl_3$ (10 ml), washed with sat. aq. $NaHCO_3$ (10 ml) and the aq. phase reextracted with $CHCl_3$ (10 ml). The solvent from the combined organic extracts was removed *in vacuo* and the residue flash chromatographed (EtOAc/hexane-1:2) furnishing benzyl 2-deoxy-3-*O*-methyl-α-L-rhamnopyranoside (**12**) (252 mg, 82%); $[\alpha]_D^{30}$ -104.2° ±2.3 (*c* 1.00, $CHCl_3$) (lit.[8] $[\alpha]_D^{24}$ -86.7°, *c* 3.97, $CHCl_3$); ^1H NMR[8] 1.29 (d, 3H, $^3J_{Me,5}$ = 6.2 Hz, CH_3), 1.51 (ddd, 1H, $^2J_{2,2}$ = 12.8, $^3J_{2ax,3}$ = 11.4 and $^3J_{2ax,1}$ = 3.7 Hz, H-2ax), 2.30 (ddd, 1H, $^2J_{2,2}$ = 12.8, $^3J_{2eq,3}$ = 4.9 and $^3J_{2eq,1}$ = 1.3 Hz, H-2eq), 2.59 (d, 1H, $^3J_{OH,4}$ = 2.3 Hz, OH), 3.16 (td, 1H, $^3J_{4,3} \approx {}^3J_{4,5} \approx$ 9.1 and $^3J_{4,OH}$ = 1.9 Hz, H-4), 3.37 (s, 3H, OCH_3), 3.55 (ddd, 1H, $^3J_{3,2ax}$ = 11.4, $^3J_{3,4}$ = 8.9 and $^3J_{3,2eq}$ = 4.9 Hz, H-3), 3.73 (dq, 1H, $^3J_{5,4}$ = 9.3 and $^3J_{5,Me}$ = 6.2 Hz, H-5), 4.43 (d, 1H, $^2J_{H',H'}$ = 11.8 Hz, H'b), 4.67 (d, 1H, $^2J_{H',H'}$ = 11.8 Hz, H'a), 4.97 (bd, 1H, $^3J_{1,2ax}$ = 3.7 Hz, H-1) and 7.25-7.40 (m, 5H, Ph); ^{13}C NMR (assignments made by HETCORR) δ17.84 (q, CH_3), 33.92 (t, C-2), 56.45 (q, OCH_3), 67.67 (d, C-5), 68.81 (t, C'), 76.17 (d, C-4), 78.29 (d, C-3), 96.63 (d, C-1), 127.70 (d, *p*-Ph), 127.91 (d, *o*-Ph), 128.40 (d, *m*-Ph) and 137.72 (s, ipso-Ph).

Notes and References:

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