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Preparation of an analogue of orbicuside A, an unusual cardiac glycoside

John T. Dixon,[a] Fanie R. van Heerden[b,*] and Cedric W. Holzapfel[a]

[a]*Department of Chemistry and Biochemistry, Rand Afrikaans University, PO Box 524, Auckland Park 2006, South Africa*
[b]*School of Chemistry, University of KwaZulu-Natal, Private Bag X01, Scottsville, 3209 Pietermaritzburg, South Africa*

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Abstract—A steroid containing a multi-linked glycoside, analogous to the bufadienolide orbicuside A, has been prepared. The key steps were (i) the preparation of a 2α-allyloxycarbonyloxy-3β-hydroxy steroid, (ii) a Ferrier reaction between the steroid and a rhamnal derivative, (iii) removal of protecting group and oxidation of the 2-hydroxy group, (iv) dihydroxylation of the pseudoglycal from the sterically more hindered side and finally (v) ring closure by acetal formation under acidic conditions.

1. Introduction

Several members of the Crassulaceae family are toxic to animals and an investigation of the active metabolites of some of these plants resulted in the isolation of a number of bufadienolide glycosides with unusual carbohydrate moieties,[1] for example, orbicuside A **1** from *Cotyledon orbiculata*[2] and tyledoside A **2** and tyledoside C **3** from *Tylecodon grandiflorus*[3] (Fig. 1). Cardiac glycosides are of the oldest drugs used by mankind[4] and digoxin, the most commonly prescribed cardiac glycoside, is still one of the most used prescription drugs. However, these drugs are extremely toxic and there is accordingly a demand for analogues with diminished toxicity, but with enhanced therapeutic activity. The unusual features of the Crassulaceae cardiac glycosides prompted us to attempt the syntheses of analogues in order to evaluate the effect of the carbohydrate arrangement on the biological activity of these compounds. The glycosides isolated from the *Cotyledon* and *Tylecodon* species, for example, **1**, **2** and **3** have neurotoxic side effects apart from the cardiac activity.[5] Furthermore, it is known that oxygen substituents on the aglycone (except for the essential 14β-hydroxy group) of cardiac glycosides are detrimental to the cardiac activity and that cardenolides are more reactive than bufadienolides.[1] Considering all these facts, we investigated the synthesis of cardiac glycosides containing only the essential substituents on the aglycone (i.e., a 14β-hydroxy group and a 17β-unsaturated lactone moiety), but with unusual carbohydrate features. We have already reported the preparation of the cardenolide aglycone,[6] and we describe herein the synthesis of a model steroid glycoside containing the carbohydrate moiety present in orbicuside A (Fig. 1).

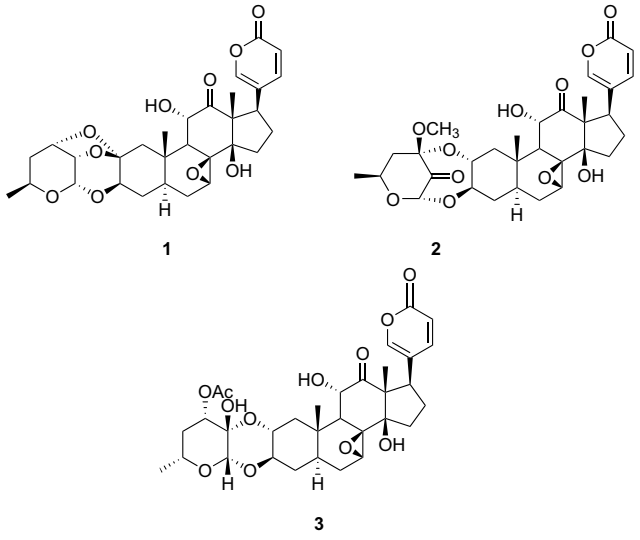

Figure 1.

* Corresponding author. Tel.: +27 33 2605326; fax: +27 33 2605009; e-mail: vanheerdenf@ukzn.ac.za

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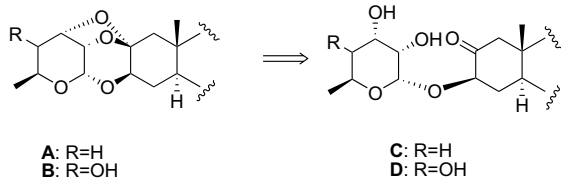
2. Results and discussion

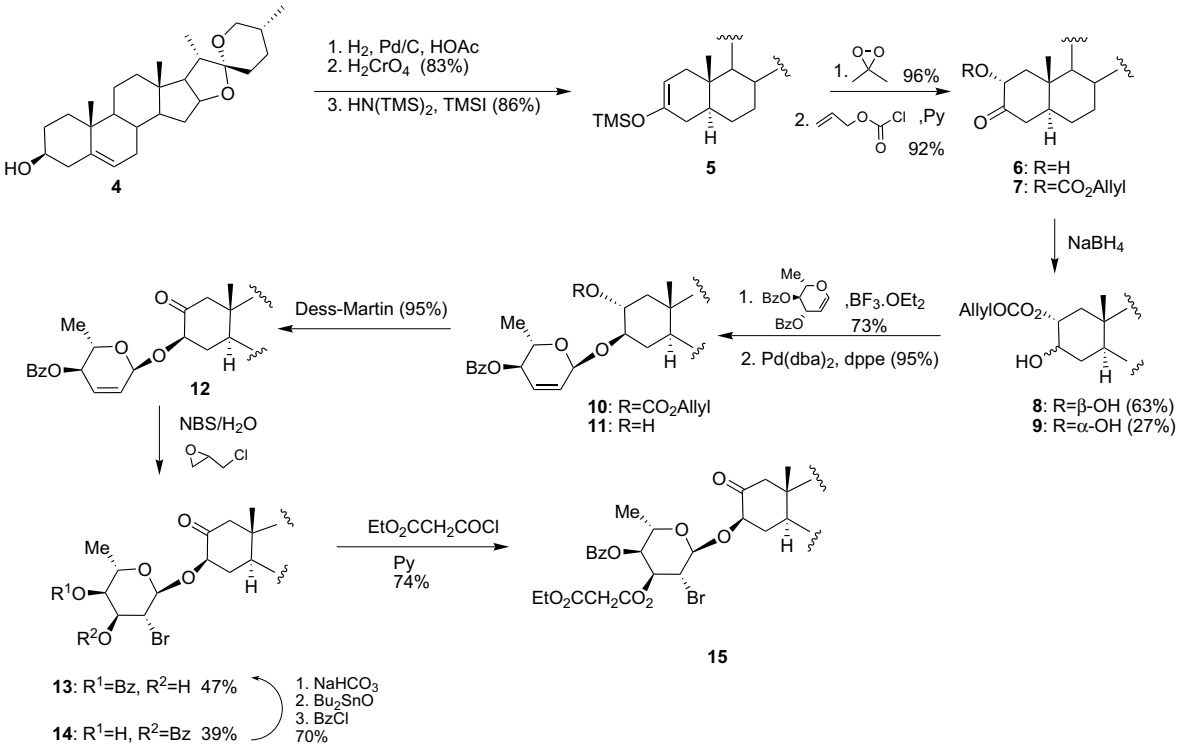
A retrosynthetic analysis of the target compound **A** (Scheme 1) yielded a 2-oxo-3-*O*-α-L-glycosyloxy steroid with a 1,2,3-*cis*,*cis* configuration of the carbohydrate, that is, a 4,6-dideoxyallopyranoside derivative **C**, as the logical precursor. Two approaches to the 4,6-dideoxyallopyranoside were envisaged, direct glycosylation with a suitable carbohydrate precursor or reaction of the steroid with a glycal derivative followed by dihydroxylation of the pseudoglycal. We have demonstrated that the second approach is successful for the preparation of 3-*O*-α-L-allopyranosyl steroids.[7] Therefore, the challenges of the synthesis were reduced to (i) the preparation of a 2,3-dioxygenated steroid, (ii) preparation of a suitable glycal and (iii) coupling of the steroidal and carbohydrate moieties via a Ferrier reaction[8] and subsequent transformations of the glycoside. Since the methodology for the deoxygenation of carbohydrate alcohols is well developed, the target of this synthesis was a multi-linked glycoside of type **B** (Scheme 1).



Scheme 1.

Diosgenin **4** was used as the aglycone, since the D/E/F ring system of this steroid can be transformed into a 16-dehydropregnane derivative[9] that can serve as a precursor to a 14β-hydroxy cardenolide.[10] The transformation of diosgenin into a suitable 2,3-dioxygenated steroid is illustrated in Scheme 2. Steroid **4** was transformed into the 3-oxo-5,6-dihydro-5α-analogue by standard methodology, and the oxygen functionality was introduced at C-2 by formation of the enol TMS ether and subsequent epoxidation with dimethyldioxirane. Huffman and Balke[11] observed that, under thermodynamic control, the 2,3-enol ether was formed from a 3-keto-5α-steroid, whereas kinetically controlled conditions yielded the 3,4-enol ether. By using TMSI in the presence of hexamethyldisilisane, enol ether **5** was obtained in a good yield and none of the 3,4-isomer was detected. Under the experimental conditions used for the epoxidation of **5**, an in situ rearrangement of the epoxide occurred and only the required 2α-hydroxy ketone **6** was isolated.

Having the α-hydroxy ketone **6** in hand, the choice of the protecting group for the hydroxy function was critical. Several criteria had to be fulfilled: the protection and deprotection steps need to be performed under mild conditions, the protected compound should be stable towards epimerization, the protecting group must not migrate to the C-3 hydroxy in the subsequent step (as was observed for acetate[12]) or cause steric hindrance detrimental to a future glycosidation step. Both the hydroxy derivative **6** and its acetate and benzoate derivatives were found to be prone to epimerization under conditions used for chromatography. Reaction of **6** with allyloxycarbonyl chloride yielded carbonate derivative **7**, which satisfied all the above-mentioned criteria. Reduction of the ketone with sodium borohydride yielded two



Scheme 2.

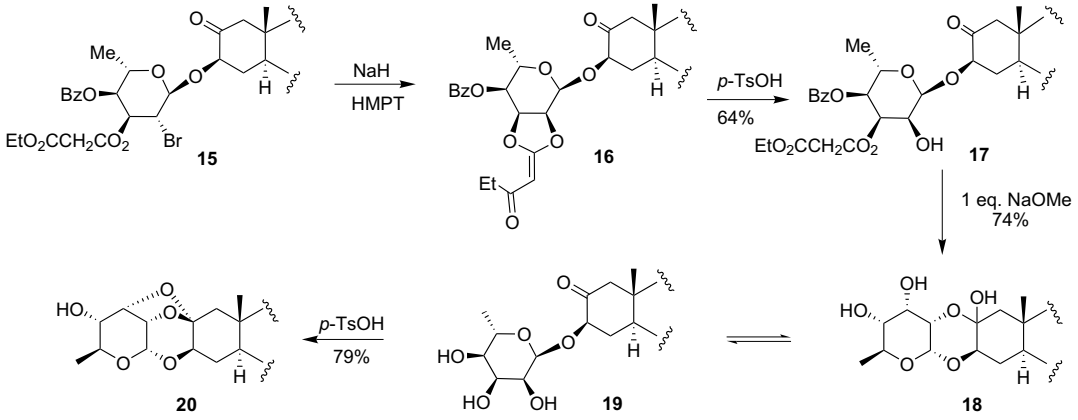
products in a 7:3 ratio with the required 3β-hydroxy derivative **8** as the major product. Efforts to increase the ratio of the required product by using solvents such as dioxane or isopropanol were unsuccessful.

Our initial approach involved a Ferrier reaction of a 4-deoxy glycal. Rhamnal was prepared by the method described by Bredenkamp et al.[13] and transformed to the 4-deoxyrhamnal derivative as described by Paquette and Oplinger.[14] However, this compound was extremely unstable and we were forced to postpone the deoxygenation of the 4-position of the carbohydrate to the last step. Using rhamnal acetate in this synthesis presented separation problems at a later stage,[7] and 3,4-di-*O*-benzoylrhamnal was used as substrate in the Ferrier reaction to furnish the pseudorhamnal **10** in a good yield (Scheme 3). The challenge now was to dihydroxylate the carbohydrate alkene from the sterically more hindered side. To prevent competition between the two alkene functionalities in **10**, the protecting group at C-3 was removed at this stage. Allyl carbonates are good substrates for Pd(0)-catalyzed reactions,[15] and the deprotection of the hydroxy group proceeded under neutral conditions. Initially $Pd(PPh_3)_4$ was used as catalyst, but it was observed that the reaction stopped after ca. 10% of the starting material was consumed. The lack of further reaction was attributed to coordination of the palladium to the 2′,3′-double bond of the carbohydrate. This problem was solved by using a catalyst containing the bidentate ligand 1,2-bis(diphenylphosphino)ethane, and the deprotected glycoside **11** was now obtained in almost quantitative yield. Oxidation with the Dess–Martin periodinane[16,17] yielded the ketone **12**.

In order to dihydroxylate the pseudoglycal **12** from the more hindered side, an indirect approach first described by Woodward and Brutscher[18] and Corey and Das[19] was followed in which a halohydrin is formed and the halogen is then subsequently replaced by an oxygen nucleophile. Initial attempts to form the bromohydrin **13** by treatment of **12** with NBS in dimethoxyethane/water resulted in the quantitative hydrolysis of the sugar and the formation of two isomeric vinylic α-ketols from the aglycone. It was clear that the formation of HBr in the reaction should be avoided, and, therefore, epichlorohydrin was added to the reaction as an acid scavenger. Although the reaction formed the required bromohydrin **13**, a side product **14**, resulting from the migration of the benzoyl protecting group was also formed. Fortunately, this unwanted product could be recycled into **13** by hydrolysis of the benzoyl ester followed by selective benzoylation of the equatorial 4-hydroxy group of the corresponding stannylene derivative.

Preparation of the allose derivative **19** from **13** was possible by using a variation[20] of the Corey method.[19,21] Bromohydrin **13** was transformed into the mixed malonate ester **15** (Scheme 2), which, upon treatment with sodium hydride in HMPA, yielded the ketene acetal **16**. Although NMR analysis of the crude product confirmed the ketene acetal structure of **16**, the compound was not stable and in subsequent reactions this compound was not isolated, but hydrolyzed in situ to **17** (Scheme 3). Saponification of the esters was accomplished by treatment of **17** with sodium methoxide. NMR analysis of the product in $CDCl_3$ revealed that it consists of a mixture of two isomeric compounds, of which the major one is the hemiacetal **18**. However, when D_2O was added to simplify the spectrum, the chemical shifts indicted that the equilibrium was reversed, and only the triol **19** was detected.

The final step entails the formation of the intramolecular acetal to form the multi-linked glycosidic moiety that is also present in orbicuside A **1**. It can be envisaged that in the treatment of **19** with acid two isomeric compounds can form resulting from acetalization of the 2-keto functionality with either the 2′,3′- or the 3′,4′-diol. However, reaction with the 3′,4′-diol will form a compound containing an unfavourable combination of five- and seven-membered rings, whereas reaction with the 2′,3′-diol will yield the more stable compound containing two six-membered rings, both in the chair conformation. As predicted, treatment of **19** with *p*-toluenesulfonic acid in the presence of anhydrous copper(II) sulfate resulted in the quantitative formation of **20**, the target compound of this synthesis. Although the NMR data were in agreement with structure **20**, further confirmation for the structure was obtained by adding trichloromethylisocyanate to the NMR tube. The



Scheme 3.

chemical shifts observed for the resultant trichloromethylcarbamate was in agreement with an acetal structure containing a free 4′-hydroxy group.

3. Conclusion

The presence of multi-linked steroid glycosides presented an interesting synthetic challenge. Herewith, it was proven that a viable approach to this problem involved the formation of the glycosidic bond by a Ferrier reaction between a steroid and a glycal, followed by indirect dihydroxylation of the resulting pseudoglycal and acid-catalyzed acetal formation to give the desired product.

4. Experimental

4.1. General

Mps were determined on a Kofler hotplate apparatus and are uncorrected. IR spectra were obtained as dilute solutions in spectroscopic grade $CHCl_3$ using a Perkin Elmer 881 instrument. ^1H (200 MHz) and ^{13}C (50 MHz) NMR data were recorded on a Varian VXR 200 NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. Mass spectra were recorded on a Finnigan-MAT 8200 spectrometer at an electron impact of 70 eV. Column chromatography was performed with silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM) and thin-layer chromatography with Whatman silica gel 60 A K6F.

4.2. (25*R*)-5α-Spirostan-3-one

Palladium (10%) on activated carbon (2.0 g) was added to a solution of diosgenin **4** (20.0 g, 48.2 mmol) in HOAc (1000 mL) and the resulting mixture was stirred under a hydrogen atmosphere (2 bar) for 24 h. The reaction mixture was filtered through Celite, cooled to 15 °C and then a chromic acid solution (24.2 mL, 2.0 M, 48.2 mmol) was added over a period of 45 min while the temperature was maintained between 15 and 20 °C. After the addition was completed, the reaction mixture was stirred for 90 min 15 °C. H_2O (750 mL) was then added to the reaction mixture and it was stirred for another 10 min. The mixture was extracted with $CHCl_3$ (2×750 mL), the combined organic extracts washed with a saturated solution of $NaHCO_3$ (2×500 mL) and H_2O (500 mL), the organic layer dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Chromatography of the residue (hexane–EtOAc, 10:1) gave the ketone (16.6 g, 83%) as white crystals, mp 200–203 °C; $[\alpha]_D^{22} = -34.1$ (*c* 1.06, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1711 (C=O); δ_H 2.16–2.30 (m, 2H, 2α-H and 4β-H), 2.32 (dt, 1H, *J* 6.2 and 13.0, 2b-H), 3.32 (t, 1H, *J* 10.5, 26β-H), 3.39–3.47 (m, 1H, 26α-H) and 4.36 (dt, 1H, *J* 6.6 and 7.2, 16H); δ_C 11.5 (C-19), 14.4 (C-21), 16.4 (C-18), 17.1 (C-27), 21.2 (C-11), 28.8 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 31.8 (C-7), 35.0 (C-8), 35.7 (C-10), 38.1 (C-2), 38.5 (C-1), 39.9 (C-12), 40.5 (C-13), 41.6 (C-20), 44.6 (C-4), 46.6 (C-5), 53.8 (C-9), 56.1 (C-14), 62.2 (C-17), 66.8 (C-26), 80.7 (C-16), 109.2 (C-22) and 211.8 (C-3); *m*/*z* 414 (M^+, 21%), 399 (2) and 384 (1).

4.3. (25*R*)-3-Trimethylsilyloxy-5α-spirost-2-ene 5

Hexamethyldisilazane (4.3 g, 20.4 mmol) and TMSI (2.8 mL, 20.4 mmol) was added consecutively to a solution of (25*R*)-5α-spirostan-3-one (7.7 g, 18.6 mmol) in CH_2Cl_2 (100 mL) at −30 °C under a N_2 atmosphere. The reaction mixture was stirred for 2 h at −30 °C and then stirred at room temperature for a further 24 h. It was washed with a saturated $NaHCO_3$ solution (2×30 mL) and H_2O (30 mL), the organic layer dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexane–EtOAc, 20:1) to give the trimethylsilyl enol ether **5** (7.8 g, 86%) as white crystals, mp 135–137 °C (hexane–CH_2Cl_2); $[\alpha]_D^{22} = -11.8$ (*c* 1.22, $CHCl_3$); (found: M^+, 486.355 $C_{30}H_{50}O_3Si$ requires *M*, 486.3529); ν_{max} ($CHCl_3$)/cm^{-1} 1684 (C=C); δ_H 0.15 [s, 9H, $(CH_3)_3SiO$], 3.39 (t, 1H, *J* 10.5, 26β-H), 3.41–3.48 (m, 1H, 26α-H), 4.36 (q, 1H, *J* 7.0, 16H) and 4.71 (d, 1H, *J* 5.5, 2H); δ_C 0.4 [$(CH_3)_3Si$], 11.6 (C-19), 14.5 (C-21), 16.4 (C-18), 17.1 (C-27), 21.0 (C-11), 28.5 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.8 (C-15), 31.9 (C-7), 34.6 (C-4), 34.6 (C-8), 35.2 (C-10), 38.5 (C-1), 40.1 (C-12), 40.5 (C-13), 41.6 (C-20), 42.0 (C-5), 53.8 (C-9), 56.3 (C-14), 62.2 (C-17), 66.8 (C-26), 80.8 (C-16), 102.9 (C-2), 109.2 (C-22) and 148.8 (C-3); *m*/*z* 486 (M^+, 40%), 471 (5) and 457 (1).

4.4. (25*R*)-2α-Hydroxy-5α-spirostan-3-one 6

A dimethyldioxirane–acetone solution[22] (187 mL, 0.85 M, 15.9 mmol) was added to a cold solution (0 °C) of (25*R*)-3-trimethylsilyloxy-5α-spirost-2-ene **5** (7.8 g, 15.9 mmol) in CH_2Cl_2 (80 mL) and the mixture was stirred for 50 min at 0 °C. The volatile components were removed under reduced pressure at room temperature to yield the crude α-ketol **6** (6.9 g, >98%) that was used directly to prepare the allyl carbonate. Purification of the crude product by crystallization from hexane–CH_2Cl_2 yielded pure (25*R*)-2α-hydroxy-5α-spirostan-3-one **6** as white crystals, mp 178–180 °C; $[\alpha]_D^{22} = -27.0$ (*c* 1.58, $CHCl_3$); (found: M^+, 430.3087. $C_{27}H_{42}O_4$ requires *M*, 430.3083); ν_{max} ($CHCl_3$)/cm^{-1} 1076 (C–O), 1719 (C=O) and 3529 (O–H); δ_H 2.19 (dd, 1H, *J* 3.8 and 13.4, 4a-H), 2.35 (t, 1H, *J* 12.6, 1β-H), 2.40 (dd, 1H, *J* 6.8 and 12.8, 1α-H), 3.29 (t, 1H, *J* 10.5, 26β-H), 3.36–3.42 (m, 1H, 26α-H), 4.16 (dd, 1H, *J* 7.3 and 12.2, 2H) and 4.33 (dt, 1H, *J* 6.2 and 7.4, 16H); δ_C 12.8 (C-19), 14.4 (C-21), 16.4 (C-18), 17.0 (C-27), 21.3 (C-11), 28.4 (C-6), 28.7 (C-24), 30.2 (C-25), 31.3 (C-23), 31.6 (C-7), 31.7 (C-15), 34.2 (C-8), 37.1 (C-10), 39.7 (C-12), 40.5 (C-13), 41.5 (C-20), 42.3 (C-4), 48.3 (C-5), 48.4 (C-1), 53.7 (C-9), 55.8 (C-14), 62.1 (C-17), 66.7 (C-26), 72.7 (C-2), 80.6 (C-16), 109.1 (C-22) and 210.8 (C-3); *m*/*z* 430 (M^+, 9%), 415 (3) and 400 (1).

4.5. (25*R*)-2α-Allyloxycarbonyloxy-5α-spirostan-3-one 7

Crude (25*R*)-2α-hydroxy-5α-spirostan-3-one **6** (6.9 g, ca. 15.9 mmol) was dissolved in CH_2Cl_2 (80 mL) and the

solution cooled to −40 °C. Pyridine (5.1 mL, 63.6 mmol) and allyl chloroformate (6.7 mL, 63.6 mmol) was added to the cold solution consecutively and the reaction mixture was allowed to warm up to 0 °C over a period of 2 h. It was then washed with a cold (0 °C) HCl solution (10%, 80 mL) and H_2O (2 × 50 mL), the organic layer dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Chromatography of the residue (hexane–EtOAc, 10:1) gave the allyl carbonate **7** as white crystals (7.5 g, 92% over two steps), mp 174–177 °C; $[\alpha]_D^{22} = -6.8$ (*c* 1.40, $CHCl_3$); (found: M^+, 514.3289. $C_{31}H_{46}O_6$ requires *M*, 514.3294); ν_{max} ($CHCl_3$)/cm^{-1} 1659 (C=C), 1729 (C=O, cyclic) and 1756 (C=O, allyl carbonate); δ_H 2.19 (dd, 1H, *J* 3.6 and 14.2, 4a-H), 2.31 (dd, 1H, *J* 6.6 and 12.4, 1α-H), 2.39 (t, 1H, *J* 12.9, 1β-H), 3.32 (t, 1H, *J* 10.8, 26β-H), 3.39–3.45 (m, 1H, 26α-H), 4.35 (q, 1H, *J* 6.6, 16H), 4.61 (d, 2H, *J* 5.7, OC*H*$_2$CH=CH$_2$), 5.08 (dd, 1H, *J* 6.3 and 12.7, 2H), 5.23 [d, 1H, *J* 10.5, OCH$_2$CH=C*H*$_2$ (*cis*)], 5.34 [d, 1H, *J* 17.3, OCH$_2$CH=C*H*$_2$ (*trans*)] and 5.89 (ddt, 1H, *J* 5.6, 10.0 and 17.1, OCH$_2$C*H*=CH$_2$); δ_C 12.7 (C-19), 14.4 (C-21), 16.4 (C-18), 17.0 (C-27), 21.4 (C-11), 28.2 (C-6), 28.7 (C-24), 30.2 (C-25), 31.3 (C-23), 31.7 (C-15), 31.7 (C-7), 34.3 (C-8), 37.3 (C-10), 39.7 (C-12), 40.5 (C-13), 41.6 (C-20), 43.3 (C-4), 44.6 (C-1), 47.6 (C-5), 53.7 (C-9), 55.8 (C-14), 62.1 (C-17), 66.8 (C-26), 68.7 (RO*C*H$_2$CH=CH$_2$), 77.4 (C-2), 80.6 (C-16), 109.1 (C-22), 118.8 (ROCH$_2$CH=*C*H$_2$), 131.3 (ROCH$_2$*C*H=CH$_2$), 154.2 [ROC(O)OR′] and 203.4 (C-3); *m*/*z* 514 (M^+, 9%), 499 (1) and 484 (1).

4.6. (25*R*)-2α-Allyloxycarbonyloxy-5α-spirostan-3β-ol 8

(25*R*)-2α-Allyloxycarbonyloxy-5α-spirostan-3-one **7** (7.4 mmol, 14.4 mmol) was dissolved in to a mixture of MeOH (80 mL) and THF (20 mL). $NaBH_4$ (544 mg, 14.4 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. CH_2Cl_2 (500 mL) was added and the mixture was washed with ice H_2O (2 × 250 mL), the organic layers dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Chromatography of the residue (hexane–EtOAc, 4:1) resulted in the isolation of **8** (4.7 g, 63%) and **9** (2.0 g, 27%). (25*R*)-2α-Allyloxycarbonyloxy-5α-spirostan-3β-ol **7** had mp 163–165 °C; $[\alpha]_D^{22} = -75.7$ (*c* 1.00, $CHCl_3$); (found: M^+, 516.3458. $C_{31}H_{48}O_6$ requires *M*, 516.3451); ν_{max} ($CHCl_3$)/cm^{-1} 1688 (C=C) and 1751 (C=O); δ_H 2.09 (dd, 1H, *J* 4.9 and *J* 12.3, 1β-H), 3.33 (t, 1H, *J* 10.7, 26β-H), 3.40–3.46 (m, 1H, 26α-H), 3.61 (ddd, 1H, *J* 5.6, *J* 9.5 and 11.0, 3H), 4.36 (dt, 1H, *J* 6.2 and 7.4, 16H), 4.59 (dt, 2H, *J* 1.3 and 5.8, OC*H*$_2$CH=CH$_2$), 4.62 (ddd, 1H, *J* 4.9, 9.5 and 11.7, 2H), 5.24 [ddd, 1H, *J* 1.1, 2.4 and 10.5, OCH$_2$CH=C*H*$_2$ (*cis*)], 5.33 [ddd, 1H, *J* 1.5, 2.9 and 17.3, OCH$_2$CH=C*H*$_2$ (*trans*)] and 5.91 (ddt, 1H, *J* 5.7, 10.3 and 17.2, OCH$_2$C*H*=CH$_2$); δ_C 13.1 (C-19), 14.4 (C-21), 16.4 (C-18), 17.1 (C-27), 21.2 (C-11), 27.6 (C-6), 28.8 (C-24), 30.2 (C-25), 31.3 (C-23), 31.7 (C-15), 31.9 (C-7), 34.3 (C-8), 35.6 (C-4), 37.5 (C-10), 39.8 (C-12), 40.5 (C-13), 41.6 (C-20), 41.9 (C-1), 44.4 (C-5), 54.1 (C-9), 56.1 (C-14), 62.1 (C-17), 66.8 (C-26), 68.5 (RO*C*H$_2$CH=CH$_2$), 73.1 (C-3), 80.6 (C-2), 80.7 (C-16), 109.2 (C-22), 119.0 (ROCH$_2$CH=*C*H$_2$), 131.5 (ROCH$_2$*C*H=CH$_2$) and 154.9 [ROC(O)OR′]; *m*/*z* 516 (M^+, 6%), 501 (1) and 486 (1). (25*R*)-2α-Allyloxycarbonyloxy-5α-spirostan-3α-ol **8** had mp 171–173 °C; $[\alpha]_D^{22} = -51.8$ (*c* 1.00, $CHCl_3$); (found: M^+, 516.3449. $C_{31}H_{48}O_6$ requires *M*, 516.3451); ν_{max} ($CHCl_3$)/cm^{-1} 1655 (C=C) and 1752 (C=O); δ_H 3.33 (t, 1H, *J* 10.8, 26β-H), 3.38–3.47 (m, 1H, 26α-H), 4.09 (br s, 1H, 3H), 4.36 (dt, 1H, *J* 6.4 and 7.8, 16H), 4.59 (dt, 2H, *J* 1.3 and 5.8, OC*H*$_2$CH=CH$_2$), 4.75 (ddd, 1H, *J* 3.0, 4.7 and 12.2, 2H), 5.25 [ddd, 1H, *J* 1.2, 2.5 and 10.4, OCH$_2$CH=C*H*$_2$ (*cis*)], 5.33 [ddd, 1H, *J* 1.5, 2.9 and 17.2, OCH$_2$CH=C*H*$_2$ (*trans*)] and 5.91 (ddt, 1H, *J* 5.8, 10.4 and 17.2, OCH$_2$C*H*=CH$_2$); δ_C 12.3 (C-19), 14.5 (C-21), 16.4 (C-18), 17.1 (C-27), 20.8 (C-11), 27.4 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 31.9 (C-7), 33.9 (C-4), 34.4 (C-8), 37.0 (C-1), 37.3 (C-10), 38.0 (C-5), 39.9 (C-12), 40.6 (C-13), 41.6 (C-20), 54.1 (C-9), 56.2 (C-14), 62.2 (C-17), 66.8 (C-26), 67.2 (C-3), 68.4 (RO*C*H$_2$CH=CH$_2$), 77.2 (C-2), 80.8 (C-16), 109.2 (C-22), 119.0 (ROCH$_2$CH=*C*H$_2$), 131.5 (ROCH$_2$*C*H=CH$_2$) and 154.2 [ROC(O)OR′]; *m*/*z* 516 (M^+, 6%), 458 (5) and 444 (4).

4.7. 3,4-Di-*O*-acetyl-L-rhamnal

L-Rhamnose monohydrate (10.0 g, 54.9 mmol) was dissolved in a mixture of pyridine (52.0 mL, 0.64 mol) and Ac_2O (64.0 mL, 0.68 mol) the reaction mixture stirred at 40 °C for three days. Evaporation of the solvents under reduced pressure yielded an anomeric mixture of crude tetra-*O*-acetyl-L-rhamnopyranose (18.1 g, ca. 99%) as a light yellow syrup. The crude tetra-*O*-acetyl-L-rhamnopyranose (18.1 g, ca. 54.4 mmol), CH_2Cl_2 (20.0 mL) and Ac_2O (1.0 mL) were treated under a N_2 atmosphere with a solution of 30% HBr in HOAc (16.3 mL, 81.7 mmol). The reaction mixture was stirred for 2 h at room temperature and the volatile components were removed under reduced pressure to give an anomeric mixture of crude tri-*O*-acetyl-L-rhamnopyranosyl bromide (18.2 g, ca. 95%) as a red syrup. Zinc powder (6.8 g, 103.4 mmol) was added under a N_2 atmosphere to a mixture of anhydrous $CuSO_4$ (675 mg, 10.3 mmol), NaOAc (3.8 g, 93.1 mmol), CH_3CN (10 mL), HOAc (3.0 mL, 103.4 mmol) and Ac_2O (3.4 mL, 72.4 mmol). The mixture was stirred at room temperature for 30 min, a solution of crude tri-*O*-acetyl-L-rhamnopyranosyl bromide (18.2 g, ca. 51.7 mmol) in CH_3CN (50 mL) was added and the mixture was stirred for a further 2 h. CH_2Cl_2 (200 mL) was added to the reaction mixture and all the solids removed by filtration through a short column. The filtrate was washed with saturated $NaHCO_3$ solution (2 × 100 mL), dried over anhydrous Na_2SO_4 and filtered through Celite and the solvent evaporated under reduced pressure. Chromatography of the residue (hexane–ethyl acetate, 7:1) gave di-*O*-acetyl-L-rhamnal (8.8 g, 79%) as a colourless oil; $[\alpha]_D^{22} = +55.2$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1236 (C–O) and 1732 (C=O); δ_H 1.29 (d, 3H, *J* 6.5, CH_3), 2.01 and 2.06 (2 × s, 2 × 3H, 2 × OCOC*H*$_3$), 4.08 (dq, 1H, *J* 6.6 and 8.5, 5H), 4.75 (dd, 1H, *J* 3.0 and 6.2, 2H), 5.00 (dd, 1H, *J* 6.1 and 8.2, 4H), 5.29–5.35 (m, 1H, 3H) and 6.40 (dd, 1H, *J* 1.4 and 6.2, 1H); δ_C 16.5 (C-6), 20.9 and 21.0 (2 × *C*H$_3$CO$_2$), 68.3 (C-3), 71.8

(C-4), 72.5 (C-5), 98.7 (C-2), 145.9 (C-1), 169.9 and 170.6 ($2\times CH_3CO_2$); *m/z* 214 (M^+, 1%), 112 (25) and 43 (100).

4.8. 3,4-Di-*O*-benzoylrhamnal

K_2CO_3 (18 mg, 0.1 mmol) was added to a solution of di-*O*-acetyl-L-rhamnal (2.79 g, 13.0 mmol) in MeOH (15 mL) and the mixture was stirred for 24 h at room temperature. The mixture was filtered through a short silica gel column, the solvent evaporated under reduced pressure and the residue purified by crystallization (hexane) to give pure L-rhamnal (1.64 g, 97%) as white crystals. Pyridine (2.24 mL, 27.8 mmol) and benzoyl chloride (3.22 mL, 27.8 mmol) were added successively to a solution of L-rhamnal (1.64 g, 12.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the mixture stirred for 24 h at room temperature. CH_2Cl_2 (40 mL) and H_2O (40 mL) were added, the mixture was shaken, the organic layer dried over anhydrous Na_2SO_4 and the removed under reduced pressure. Chromatography of the residue (hexane–ethyl acetate, 4:1) gave 3,4-di-*O*-benzoyl-L-rhamnal (3.57 g, 84%) as a colourless oil; $[\alpha]_D^{22} = +204.8$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1219 (C–O), 1529 (C=C), 1659 (C=C) and 1699 (C=O); δ_H 1.43 (d, 3H, *J* 6.6, CH_3), 4.34 (q, 1H, *J* 6.8, 5H), 4.99 (dd, 1H, *J* 2.9 and 6.1, 2H), 5.49 (dd, 1H, *J* 6.0 and 7.8, 4H), 5.68–5.73 (m, 1H, 3H), 6.52 (dd, 1H, *J* 1.4 and 6.1, 1H), 7.35–7.58 (m, 6H, $C_6H_5CO_2$) and 7.96–8.09 (m, 4H, $C_6H_5CO_2$); δ_C 16.7 (C-6), 68.8 (C-3), 72.1 (C-4), 72.7 (C-5), 98.8 (C-2), 128.3, 128.4, 129.7 and 129.8 (*ortho*- and *meta*-Ph), 129.5 and 129.9 (*ipso*-Ph), 133.1 and 133.3 (*para*-Ph), 146.1 (C-1), 165.4 and 166.0 ($2\times C_6H_5CO_2$); *m/z* 217 ($M^+-OCOC_6H_5$, 9%), 201 (4) and 105 (100).

4.9. (25*R*)-2α-Allyloxycarbonyloxy-3β-(4′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-α-L-rhamnopyranosyloxy)-5α-spirostan 10

A solution of 3,4-di-*O*-benzoyl-L-rhamnal (3.5 g, 10.3 mmol) and (25*R*)-2α-allyloxycarbonyloxy-5α-spirostan-3β-ol **8** (2.3 g, 4.5 mmol) in CH_2Cl_2 (30 mL) were cooled to 0 °C under a N_2 atmosphere and $BF_3{\cdot}OEt$ (138 μL, 1.1 mmol) was added. The reaction mixture was stirred at 0 °C for 35 min. A saturated $NaHCO_3$ solution (100 mL) and CH_2Cl_2 (250 mL) were added. After shaking the mixture thoroughly, the two layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and all the solvent removed in vacuo. Chromatography (hexane–EtOAc, 7:1) of the residue afforded the pseudoglycal **10** (2.4 g, 74%) as a colourless glass, mp 102–105 °C (CH_2Cl_2–hexane); $[\alpha]_D^{22} = -118.9$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1457 (C=C, aromatic), 1656 (C=C), 1725 (C=O) and 1750 (C=O); δ_H 2.12 (dd, 1H, *J* 4.5 and 12.4, 1β-H), 3.33 (t, 1H, *J* 10.3, 26β-H), 3.40–3.48 (m, 1H, 26α-H), 3.77 (dt, 1H, *J* 5.4 and 10.9, 3H), 4.10 (dq, 1H, *J* 5.9 and 9.1, 5′H), 4.36 (dt, 1H, *J* 6.2 and 7.4, 16H), 4.54 (ddt, 1H, *J* 1.3, 5.6 and 13.2, $OCH_2CH{=}CH_2$), 4.63 (ddt, 1H, *J* 1.3, 5.6 and 13.1, $OCH_2CH{=}CH_2$), 4.80 (ddd, 1H, *J* 4.9, 9.5 and 11.7, 2H), 5.08–5.31 (m, 4H, 1′H, 4′H and $OCH_2CH{=}CH_2$), 5.76 (dt, 1H, *J* 2.4 and 10.2, 2′H), 5.81–5.97 (m, 2H, 3′H and $OCH_2CH{=}CH_2$), 7.34–7.48 (m, 2H, *meta*-Ph), 7.50–7.59 (m, 1H, *para*-Ph) and 7.93–8.01 (m, 2H, *ortho*-Ph); δ_C 12.9 (C-19), 14.4 (C-21), 16.4 (C-18), 17.1 (C-27), 17.9 (C-6′), 21.2 (C-11), 27.8 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 32.0 (C-7), 32.8 (C-4), 34.4 (C-8), 37.2 (C-10), 39.8 (C-12), 40.5 (C-13), 41.6 (C-20), 42.4 (C-1), 44.2 (C-5), 54.2 (C-9), 56.1 (C-14), 62.3 (C-17), 65.1 (C-5′), 66.8 (C-26), 68.0 ($ROCH_2CH{=}CH_2$), 71.3 (C-4′), 76.9 (C-3), 77.3 (C-2), 80.7 (C-16), 91.4 (C-1′), 109.2 (C-22), 118.3 ($ROCH_2CH{=}CH_2$), 128.1 (C-2′), 128.6 and 129.6 (*ortho*- and *meta*-Ph), 129.9 (C-3′), 130.0 (*ipso*-Ph), 131.8 ($ROCH_2CH{=}CH_2$), 133.1 (*para*-Ph), 154.8 [ROC(O)OR′] and 165.9 [RC(O)OR′]; *m/z* 732 (M^+, 1%), 688 (16) and 673 (2).

4.10. (25*R*)-3β-(4′-*O*-Benzoyl-2′,3′-didehydro-2′,3′-dideoxy-α-L-rhamnopyranosyloxy)-5α-spirostan-2α-ol 11

Tris(dibenzylideneacetone)dipalladium(0)–$CHCl_3$ adduct (172 mg, 0.3 mmol) and 1,2-bis(diphenylphosphino)ethane (120 mg, 0.3 mmol) was added successively to a solution of (25*R*)-2α-allyloxycarbonyloxy-3β-(4′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-α-L-rhamnopyranosyloxy)-5α-spirostan **10** (2.2 g, 3.0 mmol) in THF (70 mL) under a N_2 atmosphere. The mixture was stirred for 6 h at 50 °C and then the solvent was removed under reduced pressure. Chromatography (hexane–EtOAc, 5:1) of the residue gave in addition to unreacted starting material (462 mg, 21%) the alcohol **11** (1.4 g, 73%) as a colourless glass, mp 176–178 °C (CH_2Cl_2–hexane); $[\alpha]_D^{22} = -114.9$ (*c* 1.00, $CHCl_3$); (found: M^+, 648.4032. $C_{40}H_{56}O_7$ requires *M*, 648.4026); ν_{max} ($CHCl_3$)/cm^{-1} 1457 (C=C, aromatic) and 1724 (C=O); δ_H 2.04 (dd, 1H, *J* 5.0 and 12.9, 1β-H), 3.33 (t, 1H, *J* 10.4, 26β-H), 3.25–3.57 (m, 2H, 3H and 26α-H), 3.66 (ddd, 1H, *J* 5.0, 9.0 and 11.6, 2H), 4.20 (dq, 1H, *J* 6.3 and 9.4, 5′H), 4.36 (q, 1H, *J* 7.3, 16H), 5.14 (s, 1H, 1′H), 5.29 (dd, 1H, *J* 1.4 and 9.2, 4′H), 5.79 (dt, 1H, *J* 2.5 and 10.3, 2′H), 5.97 (d, 1H, *J* 10.3, 3′H), 7.37–7.45 (m, 2H, *meta*-Ph), 7.51–7.59 (m, 1H, *para*-Ph) and 7.98–8.02 (m, 2H, *ortho*-Ph); δ_C 13.3 (C-19), 14.4 (C-21), 17.1 (C-27), 17.9 (C-6′), 17.9 (C-18), 21.1 (C-11), 27.9 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.8 (C-15), 32.1 (C-7), 33.5 (C-4), 34.5 (C-8), 36.8 (C-10), 40.0 (C-12), 40.6 (C-13), 41.6 (C-20), 44.6 (C-5), 44.7 (C-1), 54.3 (C-9), 56.2 (C-14), 62.3 (C-17), 65.7 (C-5′), 66.8 (C-26), 70.8 (C-2), 70.9 (C-4′), 80.8 (C-16), 85.1 (C-3), 93.8 (C-1′), 109.2 (C-22), 127.8 (C-2′), 128.4 and 129.7 (*ortho*- and *meta*-Ph), 129.8 (*ipso*-Ph), 129.8 (C-3′), 133.2 (*para*-Ph) and 165.9 [RC(O)OR′]; *m/z* 648 (M^+, 4%), 618 (1) and 604 (13).

4.11. (25*R*)-3β-(4′-*O*-Benzoyl-2′,3′-didehydro-2′,3′-dideoxy-α-L-rhamnopyranosyloxy)-5α-spirostan-2-one 12

Dess–Martin periodinane[16,17] (828 mg, 2.0 mmol) was added to a solution of (25*R*)-3β-(4′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-α-L-rhamnopyranosyloxy)-5α-spirostan-2α-ol **11** (1.1 g, 1.7 mmol) in CH_2Cl_2 (20 mL) under a N_2 atmosphere and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with Et_2O (150 mL) and extracted with a

saturated $NaHCO_3$ solution (150 mL) containing sodium thiosulfate (1.9 g, 11.9 mmol). The organic layer was washed with H_2O (2 × 50 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to give the ketone **12** (1.04 g, 95%) as a colourless glass, mp 185–187 °C (CH_2Cl_2–hexane); $[\alpha]_D^{22} = -102.7$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1456 (C=C, aromatic), 1656 (C=C) and 1727 (C=O); δ_H 2.45 (d, 1H, *J* 12.6, 1β-H), 3.34 (t, 1H, *J* 10.3, 26β-H), 3.41–3.48 (m, 1H, 26α-H), 4.36 (dd, 1H, *J* 4.5 and 8.4, 3H), 4.38 (q, 1H, *J* 7.9, 16H), 4.44 (dq, 1H, *J* 5.9 and 9.5, 5′H), 5.06 (s, 1H, 1′H), 5.29 (ddd, 1H, *J* 1.8, 3.2 and 9.5, 4′H), 5.84 (dt, 1H, *J* 2.5 and 10.2, 2′H), 5.99 (d, 1H, *J* 10.2, 3′H), 7.38–7.46 (m, 2H, *meta*-Ph), 7.50–7.59 (m, 1H, *para*-Ph) and 8.00–8.05 (m, 2H, *ortho*-Ph); δ_C 12.4 (C-19), 14.4 (C-21), 16.3 (C-18), 17.1 (C-27), 17.8 (C-6′), 21.1 (C-11), 27.6 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 31.8 (C-7), 34.5 (C-4), 36.6 (C-8), 39.7 (C-12), 40.5 (C-13), 41.4 (C-10), 41.6 (C-20), 44.7 (C-5), 52.9 (C-1), 54.0 (C-9), 56.0 (C-14), 62.2 (C-17), 65.5 (C-5′), 66.8 (C-26), 71.1 (C-4′), 80.7 (C-3), 80.8 (C-16), 93.7 (C-1′), 109.2 (C-22), 127.3 (C-2′), 128.4 and 129.7 (*ortho*- and *meta*-Ph), 129.9 (*ipso*-Ph), 130.6 (C-3′), 133.1 (*para*-Ph), 166.0 [RC(O)OR′] and 207.2 (C-2); *m*/*z* 646 (M^+, 1%), 602 (7) and 587 (1).

4.12. (25*R*)-3β-(4′-*O*-Benzoyl-2′-bromo-2′,6′-dideoxy-α-L-altropyranosyloxy)-5α-spirostan-2-one 13

H_2O (567 μL, 32 mmol), epichlorohydrin (617 μl, 8 mmol) and NBS (2.8 g, 16 mmol) were added successively to a solution of (25*R*)-3β-(4′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-α-L-rhamnopyranosyloxy)-5α-spirostan-2-one **12** (1.0 g, 1.6 mmol) in 1,2-dimethoxyethane (40 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and then for a further 2 h at room temperature. The reaction mixture was diluted with Et_2O (250 mL) and extracted with a saturated $NaHCO_3$ solution (150 mL) containing sodium thiosulfate (1.9 g, 11.9 mmol). The organic layer was washed with H_2O (2 × 50 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Chromatography (hexane–EtOAc, 7:1) of the residue yielded **13** (492 mg, 42%) and **14** (340 mg, 29%). (25*R*)-3β-(4′-*O*-benzoyl-2′-bromo-2′,6′-dideoxy-α-L-altropyranosyloxy)-5α-spirostan-2-one **13** had mp 109–112 °C (diethyl ether–hexane); $[\alpha]_D^{20} = -80.2$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1457 (C=C, aromatic) and 1729 (C=O); δ_H 2.52 (d, 1H, *J* 13.2, 1β-H), 3.34 (t, 1H, *J* 10.4, 26β-H), 3.42–3.49 (m, 1H, 26α-H), 4.20–4.44 (m, 5H, 2′H, 3′H, 5′H, 3H and 16H), 5.12 (s, 1H, 1′H), 5.38 (dd, 1H, *J* 2.7 and 10.3, 4′H), 7.36–7.48 (m, 2H, *meta*-Ph), 7.50–7.58 (m, 1H, *para*-Ph) and 8.03–8.10 (m, 2H, *ortho*-Ph); δ_C 12.7 (C-19), 14.4 (C-21), 16.3 (C-18), 17.1 (C-27), 17.6 (C-6′), 21.1 (C-11), 27.6 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 31.7 (C-7), 34.4 (C-4), 36.2 (C-8), 40.0 (C-12), 40.5 (C-13), 41.2 (C-10), 41.6 (C-20), 43.9 (C-5), 46.6 (C-2′), 52.7 (C-1), 53.8 (C-9), 56.0 (C-14), 62.2 (C-17), 62.7 (C-5′), 66.9 (C-26), 69.5 (C-3′), 70.9 (C-4′), 77.7 (C-3), 80.7 (C-16), 97.3 (C-1′), 109.2 (C-22), 128.3 and 129.9 (*ortho*- and *meta*-Ph), 129.8 (*ipso*-Ph), 133.2 (*para*-Ph), 165.7 [RC(O)OR′] and 206.7 (C-2); *m*/*z* 429 ($M^+ - C_{13}H_{14}O_4Br$, 1%), 356 (1) and 314 (3). (25*R*)-3β-(3′-*O*-Benzoyl-2′-bromo-2′,6′-dideoxy-α-L-altropyranosyloxy)-5α-spirostan-2-one **14** had mp 156–158 °C (diethyl ether–hexane); $[\alpha]_D^{20} = -51.4$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1458 (C=C, aromatic) and 1734 (C=O); δ_H 2.44 (d, 1H, *J* 12.7, 1β-H), 3.33 (t, 1H, *J* 10.4, 26β-H), 3.40–3.48 (m, 1H, 26α-H), 4.03 (dd, 1H, *J* 3.0 and 9.1, 4′H), 4.14 (dd, 1H, *J* 7.0 and 10.9, 3H), 4.33 (dd, 1H, *J* 1.0 and 3.7, 2′H), 4.37 (q, 1H, *J* 7.3, 16H), 4.58 (dq, 1H, J 6.3 and 9.0, 5′H), 4.99 (s, 1H, 1′H), 5.47 (t, 1H, *J* 3.3, 3′H), 7.36–7.62 (m, 3H, *meta*- and *para*-Ph) and 8.19–8.24 (m, 2H, *ortho*-Ph); δ_C 12.4 (C-19), 14.4 (C-21), 16.3 (C-18), 17.1 (C-27), 17.5 (C-6′), 21.1 (C-11), 27.5 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 31.7 (C-7), 34.4 (C-4), 36.2 (C-8), 39.7 (C-12), 40.5 (C-13), 41.2 (C-10), 41.6 (C-20), 44.4 (C-5), 45.9 (C-2′), 53.0 (C-1), 53.8 (C-9), 56.0 (C-14), 62.2 (C-17), 66.2 (C-5′), 66.9 (C-26), 68.0 (C-4′), 72.4 (C-3′), 80.7 (C-16), 80.8 (C-3), 98.7 (C-1′), 109.2 (C-22), 128.3 and 130.4 (*ortho*- and *meta*-Ph), 129.8 (*ipso*-Ph), 133.3 (*para*-Ph), 166.3 [RC(O)OR′] and 206.3 (C-2); *m*/*z* 430 ($M^+ - C_{13}H_{15}O_4Br$, 1%), 358 (1) and 316 (2).

4.13. (25*R*)-3β-(4′-*O*-Benzoyl-2′-bromo-2′,6′-dideoxy-3′-*O*-ethylmalonyl-α-L-altropyranosyloxy)-5α-spirostan-2-one 15

Pyridine (39 μL, 0.485 mmol) and ethyl (chloroformyl)acetate (62 μL, 0.485 mmol) was added to a solution of (25*R*)-3β-(4′-*O*-benzoyl-2′-bromo-2′,6′-dideoxy-α-L-altropyranosyloxy)-5α-spirostan-2-one **12** (301 mg, 0.404 mmol) in CH_2Cl_2 (5 mL) at 0 °C under a N_2 atmosphere and the mixture was stirred for 18 h at room temperature. CH_2Cl_2 (100 mL) was added and the solution washed successively with a cold 10% HCl solution (40 mL), H_2O (2 × 20 mL), the organic layer dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure at room temperature. Chromatography (hexane–EtOAc, 4:1) of the residue gave the mixed malonyl ester **15** (257 mg, 74%) as a colourless glass, $[\alpha]_D^{20} = -48.2$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1457 (C=C, aromatic), 1737 (C=O) and 1754 (C=O); δ_H 2.43 (d, 1H, *J* 12.9, 1β-H), 3.33 (t, 1H, *J* 10.2, 26β-H), 3.36–3.49 (m, 1H, 26α-H), 3.48 (d, 1H, *J* 16.1, ROCOCH_2COOR′), 3.57 (d, 1H, *J* 16.1, ROCOCH_2COOR′), 4.07 (dq, 2H, *J* 3.1 and 7.1, RCH_2COOCH_2CH$_3$), 4.18 (dd, 1H, *J* 7.1 and 11.0, 3H), 4.35 (dd, 1H, *J* 2.0 and 4.2, 2′H), 4.37 (q, 1H, *J* 7.4, 16H), 4.61 (dq, 1H, *J* 6.5 and 8.5, 5′H), 5.03 (d, 1H, *J* 1.9, 1′H), 5.39 (t, 1H, *J* 3.4, 3′H), 5.45 (dd, 1H, *J* 3.2 and 8.6, 4′H), 7.37–7.45 (m, 2H, *meta*-Ph), 7.51–7.59 (m, 1H, *para*-Ph) and 7.98–8.07 (m, 2H, *ortho*-Ph); δ_C 12.5 (C-19), 14.0 [RC(O)OCH$_2$*C*H$_3$], 14.4 (C-21), 16.4 (C-18), 17.1 (C-27), 17.3 (C-6′), 21.1 (C-11), 27.6 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.8 (C-15), 31.8 (C-7), 34.4 (C-4), 35.6 (C-8), 39.7 (C-12), 40.5 (C-13), 41.3 (C-10), 41.3 [RC(O)*C*H$_2$C(O)R′], 41.6 (C-20), 44.3 (C-5), 45.1 (C-2′), 53.0 (C-1), 53.9 (C-9), 56.0 (C-14), 61.4 [RC(O)O*C*H$_2$CH$_3$], 62.2 (C-17), 64.6 (C-5′), 66.9 (C-26), 69.5 (C-3′), 71.0 (C-4′), 79.9 (C-3), 80.7 (C-16),

98.0 (C-1′), 109.2 (C-22), 128.4 and 129.6 (*ortho*- and *meta*-Ph), 129.4 (*ipso*-Ph), 133.3 (*para*-Ph), 165.4 [RC(O)OR′], 166.0 [RC(O)OR′], 166.1 [RC(O)OR′] and 206.0 (C-2); *m/z* 663 ($M^+-OCOC_6H_5$ and $-COOCH_2CH_3$, 2%), 646 (3) and 429 (9).

4.14. (25*R*)-3β-(4′-*O*-Benzoyl-6′-deoxy-3′-*O*-ethylmalonyl-α-L-allopyranosyloxy)-5α-spirostan-2-one 17

NaH (5 mg, ~75% pure, ~0.151 mmol) was added under a N_2 atmosphere to a solution of (25*R*)-3β-(4′-*O*-benzoyl-3′-*O*-ethylmalonyl-2′-bromo-2′,6′-dideoxy-α-L-altropyranosyloxy)-5α-spirostan-2-one **15** (130 mg, 0.151 mmol) in HMPA (9 mL) at room temperature. The mixture was stirred for 5 min at room temperature and then for a further 6 h at 60 °C. Et_2O (50 mL) was added to the reaction mixture, and it was then extracted with H_2O (2 × 25 mL), the organic layer dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Chromatography (hexane–EtOAc, 1:1) of the residue gave a single product **16** (128 mg) as a colourless oil. The product (128 mg) was dissolved in benzene (10 mL) and H_2O (4 μL, 0.222 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.052 mmol) were added. After stirring the mixture for 20 min at room temperature, it was diluted with benzene (20 mL) and washed with H_2O (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and all volatile components removed under reduced pressure. Chromatography (hexane–EtOAc, 2:1) of the residue gave the alcohol **17** (77 mg, 64%) as a colourless glass, $[\alpha]_D^{20} = -98.4$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1459 (C=C, aromatic), 1734 (C=O) and 1759 (C=O); δ_H 2.43 (d, 1H, *J* 12.9, 1β-H), 3.34 (t, 1H, *J* 10.6, 26β-H), 3.39 (d, 1H, *J* 16.2, ROCOCH_2COOR′), 3.40–3.46 (m, 1H, 26α-H), 3.62 (d, 1H, *J* 16.2, ROCOCH_2COOR′), 3.86 (t, 1H, *J* 3.8, 2′H), 4.02–4.21 (m, 3H, $RCH_2COOCH_2CH_3$ and 3H), 4.38 (q, 1H, *J* 7.6, 16H), 4.58 (dq, 1H, *J* 6.3 and 10.1, 5′H), 4.86 (d, 1H, *J* 3.6, 1′H), 4.87 (dd, 1H, *J* 2.8 and 10.2, 4′H), 5.70 (t, 1H, *J* 2.9, 3′H), 7.36–7.49 (m, 2H, *meta*-Ph), 7.52–7.57 (m, 1H, *para*-Ph) and 7.92–7.97 (m, 2H, *ortho*-Ph); δ_C 12.5 (C-19), 14.0 [RC(O)OCH$_2$*C*H$_3$], 14.4 (C-21), 16.3 (C-18), 16.9 (C-6′), 17.1 (C-27), 21.1 (C-11), 27.5 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-7), 31.7 (C-15), 34.4 (C-4), 35.8 (C-8), 39.7 (C-12), 40.5 (C-13), 41.3 (C-10), 41.5 [RC(O)*C*H$_2$C(O)R′], 41.6 (C-20), 44.3 (C-5), 53.0 (C-1), 53.9 (C-9), 56.0 (C-14), 61.5 [RC(O)O*C*H$_2$CH$_3$], 61.7 (C-5′), 62.2 (C-17), 66.8 (C-26), 67.2 (C-2′), 71.0 (C-3′), 71.5 (C-4′), 80.6 (C-16), 81.1 (C-3), 96.8 (C-1′), 109.2 (C-22), 128.3 and 129.7 (*ortho*- and *meta*-Ph), 129.5 (*ipso*-Ph), 133.1 (*para*-Ph), 165.2 [RC(O)OR′], 166.0 [RC(O)OR′], 167.1 [RC(O)OR′] and 206.7 (C-2); *m/z* 776 (M^+-H_2O, 1%), 662 (2) and 644 (1).

4.15. (25*R*)-3β-(6′-Deoxy-α-L-allopyranosyloxy)-5α-spirostan-2-one 19

NaH (46 mg, ~75% pure, ~1.44 mmol) was dissolved in MeOH (25 mL) under a N_2 atmosphere. Twenty percent of this solution (5 mL) was added to a solution of (25*R*)-3β-(4′-*O*-benzoyl-3′-*O*-ethylmalonyl-6′-deoxy-α-L-allopyranosyloxy)-5α-spirostan-2-one **17** (115 mg, 0.144 mmol) in toluene (3 mL) at 0 °C. The reaction was stirred for 80 min at room temperature. CH_2Cl_2 (25 mL) was added and the mixture was extracted with H_2O (10 mL), the organic layer dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure at room temperature. Chromatography ($CHCl_3$–MeOH, 10:1) of the residue gave a mixture of the triol **19** and the corresponding hemiacetal **18** (62 mg, 74%) as white crystals, ν_{max} ($CHCl_3$, D_2O)/cm^{-1} 1723 (C=O); δ_H ($CDCl_3$+D_2O) 2.49 (d, 1H, *J* 13.4, 1β-H), 3.12 (dd, 1H, *J* 3.2 and 10.2, 4′H), 3.33 (t, 1H, *J* 10.5, 26β-H), 3.41–3.64 (m, 3H, 2′H, 5′H and 26α-H), 4.01 (t, 1H, *J* 2.7, 3′H), 4.25 (dd, 1H, *J* 6.9 and 11.2, 3H), 4.37 (q, 1H, *J* 7.3, 16H) and 4.93 (d, 1H, *J* 2.9, 1′H); δ_C (D_2O) 12.7 (C-19), 14.4 (C-21), 16.3 (C-18), 17.1 (C-27), 17.3 (C-6′), 21.1 (C-11), 27.5 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 31.7 (C-7), 34.4 (C-4), 34.9 (C-8), 39.7 (C-12), 40.5 (C-13), 41.3 (C-10), 41.6 (C-20), 43.9 (C-5), 52.6 (C-1), 53.8 (C-9), 56.0 (C-14), 62.2 (C-17), 64.2 (C-5′), 66.9 (C-26), 67.9 (C-4′), 71.9 (C-2′), 72.1 (C-3′), 77.3 (C-3), 80.7 (C-16), 96.2 (C-1′), 109.3 (C-22) and 207.3 (C-2).

4.16. (25*R*)-2α,2β,3β-[(2*S*,3*S*,4*S*,5*S*,6*S*)-Tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-4,3,2-trioxytriyl]-5α-spirostane 20

Anhydrous $CuSO_4$ (60 mg, 0.376 mmol) and *p*-toluenesulfonic acid monohydrate (8 mg, 0.042 mmol) was added sequentially to a solution of a mixture of the triol **19** and the corresponding hemiacetal **18** (37.0 mg, 0.064 mmol) in toluene (20 mL) under a N_2 atmosphere and the mixture was stirred for 45 min at 50 °C. The mixture was allowed to reach to room temperature, Et_3N (40 μL, 0.286 mmol) was added and the mixture was stirred for a further 10 min at room temperature. CH_2Cl_2 (50 mL) was added, the mixture was washed with H_2O (2 × 10 mL), the organic layer dried over anhydrous $CuSO_4$ and all the volatile components removed in vacuo at room temperature. Chromatography of the residue (hexane–EtOAc, 1:2) gave the acetal **20** (28.4 mg, 79%) as white crystals, mp 260–263 °C; $[\alpha]_D^{20} = -37.1$ (*c* 1.00, $CHCl_3$); (found: M^+, 558.3558. $C_{33}H_{50}O_7$ requires *M*, 558.3556); ν_{max} ($CHCl_3$)/cm^{-1} 1164 (C–O, acetal); δ_H 3.32 (dd, 1H, *J* 3.5 and 9.9, 4′H), 3.35 (t, 1H, *J* 10.9, 26β-H), 3.44–3.48 (m, 2H, 26α-H and OH), 3.78 (t, 1H, *J* 8.2, 3H), 3.92 (dq, 1H, *J* 6.2 and 9.7, 5′H), 4.16 (t, 1H, *J* 3.7, 3′H), 4.35 (t, 1H, *J* 4.4, 2′H), 4.38 (q, 1H, *J* 7.5, 16H) and 5.23 (d, 1H, *J* 5.4, 1′H); δ_C 12.6 (C-19), 14.4 (C-21), 16.4 (C-18), 17.1 (C-27), 17.3 (C-6′), 21.1 (C-11), 27.5 (C-6), 28.8 (C-24), 30.3 (C-25), 31.4 (C-23), 31.7 (C-15), 32.0 (C-7), 34.4 (C-4), 34.9 (C-8), 36.8 (C-10), 39.9 (C-12), 40.5 (C-13), 41.6 (C-20), 43.8 (C-5), 45.9 (C-1), 54.9 (C-9), 56.1 (C-14), 62.2 (C-17), 62.9 (C-5′), 66.8 (C-26), 71.5 (C-4′), 73.2 (C-3′), 73.4 (C-2′), 80.4 (C-3), 80.7 (C-16), 89.1 (C-1′), 106.8 (C-2) and 109.2 (C-22); *m/z* 558 (M^+, 10%), 541 (4) and 499 (5).

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