Synthesis of methyl secolonitoside

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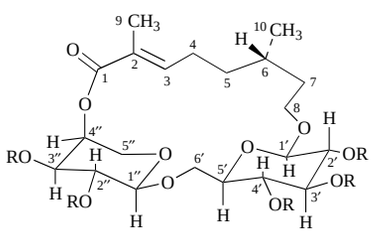
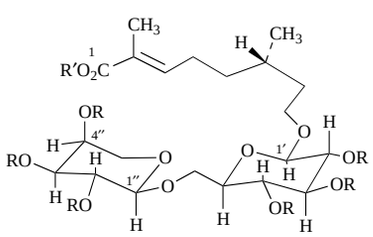
The monoterpene diglycoside macrolide, lonitoside 1, is assumed to be biosynthesized *via* the intermediate acid secolonitoside 3 which has also been isolated from *Lonicera nitida* E. H. Wilson. We have synthesized the methyl ester of acid 3 from D-glucose, L-arabinose and (−)-citronellol [*via* methyl (*E*,*S*)-8-hydroxy-2,6-dimethyloct-2-enoate], both as a formal proof of structure and as an approach to a total synthesis of the macrolide 1.

Introduction

Some time ago we reported the isolation of a novel monoterpene diglycoside macrolide, lonitoside **1**, from leaves of the honeysuckle *Lonicera nitida* E. H. Wilson, as the pentaacetate **2**, mp 200–202 °C, $[\alpha]_D$ $+10 \times 10^{-1}$ deg cm^2 g^{-1} (MeOH).[1] The structure was elucidated on the basis of spectroscopic data and chemical degradation to D-glucose, L-arabinose and methyl (*E*,*S*)-8-hydroxy-2,6-dimethyloct-2-enoate **6**. A small amount of an acidic compound was also isolated and shown to correspond to secolonitoside **3**, the product of hydrolysis of the lactone ring in lonitoside, by correlation *via* the methyl ester hexaformate **4**. It is reasonable to suppose that secolonitoside is a biosynthetic precursor of lonitoside by selective lactonisation of the C-1 acid with the 4″-hydroxy group. We thus proposed to synthesize the methyl secolonitoside derivative **4**, partly as a feasibility study for an eventual 'biomimetic' synthesis of lonitoside itself where lactonisation would be the final stage.



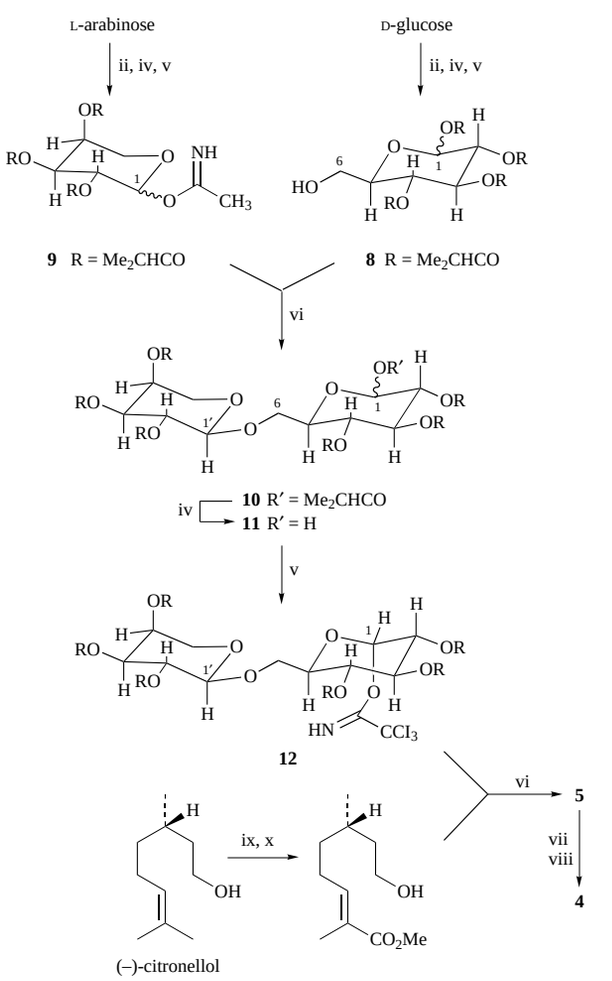
1 R = H
2 R = Ac



3 R = R′= H
4 R = CHO, R′= Me
5 R = Me_2CHO, R′= Me

Obvious disconnections at the C-1′ and C-1″ glycosidic bonds of the secolonitoside structure lead to the starting materials: D-glucose, L-arabinose and the monoterpene **6**, which can be prepared from (−)-citronellol **7**,[2] but there are two alternatives for assembly depending on which two components are linked first. We opted for synthesizing the protected disaccharide (vicianose) followed by linkage with the aglycone **6** (Scheme 1), using the glycosylation procedures that we have developed in our laboratory.[3] In particular, C-1 trichloroacetimidates with acid catalysis were used for coupling,[4] and the isobutyryl group was chosen for protection of the hydroxy groups in both the sugars since it combines minimal transacylation during glycosylation with β-stereoselectivity and ease of removal.

The first stage involved the selective protection of the primary alcohol of D-glucose as the *tert*-butyldiphenylsilyl[5] ether by treatment with *tert*-butylchlorodiphenylsilane (TBDPSCl) in pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Subsequent acylation with isobutyryl chloride in pyridine and removal of the silyl group with tetrabutylammonium fluoride (TBAF) gave a 28% yield of the desired 1,2,3,4-tetra-*O*-isobutyryl-D-glucose **8**, together



Scheme 1 *Reagents*: i, Bu^tPh_2SiCl–py–DMAP; ii, $Me_2CHCOCl$–py; iii, TBAF; iv, NH_3–CH_2Cl_2–MeOH; v, CCl_3CN–K_2CO_3; vi, BF_3–CH_2Cl_2; vii, NaOMe–MeOH; viii, AcOCHO–py; ix, SeO_2–EtOH; x, NaCN–MnO_2–Ac_2O–MeOH

with 22% of the unwanted 1,2,3,6-isomer, as mixtures of C-1 anomers. The products were characterised by appropriate IR, NMR and MS data, and in particular the C-6 methylene protons of compound **8** appeared at δ 3.5–3.7, showing that they were not acylated. A more traditional approach *via* a 6-trityl[6] derivative gave variable low yields of the desired product.

In the next stage, L-arabinose was treated with isobutyryl chloride in dichloromethane–pyridine to give a single anomer, tetraisobutyryl-α-L-arabinose, mp 49–50 °C, $[\alpha]_D$ +111 ($CHCl_3$) in 85% yield. Selective removal of the C-1 ester by treatment with ammonia in dichloromethane–methanol (9:1)[3] afforded the hemiacetal, which on subsequent reaction with trichloroacetonitrile and anhydrous potassium carbonate gave the required 2,3,4-triisobutyryl-L-arabinosyltrichloroacetimidate **9** in 63% yield. The product was a mixture of α/β anomers which were separated by chromatography and characterised by spectroscopic data, including the diagnostic imidate C=NH peaks at 1677 cm^{-1} in the IR and at δ 8.62/8.72, respectively, in the NMR spectrum.

Previously, vicianose has been synthesized as the heptaacetate by Helferich *et al.* employing the Koenigs–Knorr method.[7] We coupled the 2,3,4-triisobutyrylarabinose 1-imidate **9** to the free C-6 hydroxy group of 1,2,3,4-tetraisobutyrylglucose **8** in dichloromethane using BF_3–diethyl ether as catalyst to afford vicianose heptaisobutyrate **10**, $[\alpha]_D$ +70 ($CHCl_3$) in 55% yield. Its molecular composition was confirmed from an M + 18 ion in the CI mass spectrum at *m/z* 820.4315 which analysed for $C_{39}H_{62}O_{17} + NH_4$. The NMR spectrum showed that our product was, not unexpectedly, an epimeric mixture (~7:2, α:β) at C-1 of the glucose moiety, as indicated by H-1 signals at δ 6.36 (d, *J* 4 Hz) and 5.73 (d, *J* 8 Hz), respectively. Crucially, the glycosidic link from C-1′ of arabinose to C-6 of glucose was shown to have exclusively the required β orientation, since both epimers had a doublet for H-1′ (at δ 4.52/4.46) with a *trans*-diaxial coupling of 6 Hz. Selective removal of the C-1 ester group from the glucose moiety was achieved with ammonia in dichloromethane–methanol (3:1) to give the hemiacetal **11** in 46% yield as a 2:1 mixture of α and β epimers. The structure was confirmed *inter alia* by an M + 18 ion at *m/z* 750.3922 ($C_{35}H_{56}O_{16} + NH_4$) in the CI mass spectrum, a sharp OH peak in the IR spectrum at 3467 cm^{-1}, and the upfield shift compared with the starting material of ~1 ppm for the H-1 NMR signal.

Treatment of the hemiacetal mixture with trichloroacetonitrile and anhydrous potassium carbonate in dichloromethane gave only the α-epimer of the imidate **12**, $[\alpha]_D$ +36 ($CHCl_3$) in 90% yield. Its NMR spectrum showed the characteristic imidate NH as a singlet at δ 8.63 and the C-1 anomeric proton had shifted downfield to δ 6.55 (*J* 3.4 Hz) from δ 5.43 in precursor **11**. As expected, the NH stretch appeared at 3320 cm^{-1} in the IR spectrum, but no molecular ion could be detected in EI, CI or FAB mass spectra, although the last method did produce a fragment at *m/z* 715 corresponding to loss of the trichloroacetimidate group.

The required monoterpene methyl ester was obtained from (−)-citronellol **7** in two steps.[2] Allylic oxidation with selenium dioxide converted primary alcohol **7** into the 8-hydroxy aldehyde, as indicated by a one-proton singlet at δ 9.40 in the NMR spectrum, conjugated carbonyl IR bands at 1686 and 1645 cm^{-1} and a UV peak at 228 nm. Subsequent treatment of the aldehyde with manganese dioxide and sodium cyanide in methanol, following the procedure of Corey *et al.*,[8] produced in 16% yield methyl (*E*,*S*)-8-hydroxy-2,6-dimethyloct-2-enoate **6**, $[\alpha]_D$ −9 ($CHCl_3$), whose structure was confirmed from spectra. The Cl mass spectrum had an M + 18 ion at *m/z* 218.1757 corresponding to $C_{11}H_{20}O_3 + NH_4$. A hydroxy group was indicated by a peak at 3412 cm^{-1} in the IR spectrum, which also showed signals at 1712 and 1649 cm^{-1} for an α,β-unsaturated carbonyl, whereas the NMR spectrum clearly showed the loss of the aldehyde signal and a new methyl ester singlet at δ 3.73. All the spectroscopic data of both the aldehyde and the methyl ester were identical with those reported by Iwagawa and Haase.[2]

It now remained to couple the monoterpene alcohol **6** to the disaccharide. Thus vicianose imidate **12** was treated with an excess of the methyl ester **6** in the presence of boron trifluoride–diethyl ether to afford in 47% yield methyl secolonitoside hexaisobutyrate **5**, mp 78 °C (from ethanol); $[\alpha]_D$ −12 ($CHCl_3$). A molecular ion + NH_4 at *m/z* 932.5218 ($C_{46}H_{78}NO_{18}$) in the CI mass spectrum showed that both moieties were linked and this was corroborated by appropriate signals in the 500 MHz NMR spectrum. Importantly, the new glycosidic linkage to glucose was confirmed as β by the *trans*-diaxial coupling of 8 Hz for the H-1′ proton at δ 4.43. Zemplen deacylation gave methyl secolonitoside **3** and subsequent formylation with acetic formic anhydride in pyridine gave the corresponding hexaformate **4**, $[\alpha]_D$ −9 ($CHCl_3$), which was identical by spectroscopic and chromatographic criteria with that obtained from the natural product.

The above synthesis of methyl secolonitoside from D-glucose, L-arabinose and (−)-citronellol constitutes a formal confirmation of the structure of the secolonitoside isolated in small quantity from *Lonicera nitida* but, more importantly, has established the feasibility of a synthesis of the macrolide lonitoside itself. Selective lactonisation of the 4″-hydroxy group on the arabinose moiety is the major challenge, and our work in this area will be reported in due course.

Experimental

For analytical and preparative TLC, Polygram Sil G/UV_{254} silica plates and Merck silica plates precoated with Kieselgel 60 (F254) were used, respectively, and visualisation was effected by UV light and by spraying with a saturated solution of ammonium cerium(IV) sulfate in 10% sulfuric acid and warming. Solvents systems used for development are given in parentheses, and relative mobilities were recorded by the R_f conversion. Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh).

Mps were determined on a Kofler block and are uncorrected. Optical rotations $[\alpha]_D$ were determined on an Optical Activity AA-100 polarimeter, with concentration (g/100 ml) and the solvent used given in parentheses. UV absorption spectra (λ_{max}) were recorded on a Shimadzu UV-260 spectrometer, and IR spectra (ν_{max}) on a Perkin-Elmer 1710 FT-IR spectrometer. NMR spectra were recorded at 200 MHz on a Varian Gemini 200, at 300 MHz on a Bruker AC300 or a Varian XL 300, and at 500 MHz on a Varian Unity 500 instrument. Line positions or centres of multiplets are given on the δ-scale with respect to tetramethylsilane (TMS) as the internal standard, with the multiplicities, integrated areas and coupling constants in Hz indicated in parentheses. Mass spectra were run on Kratos Concept IS and Kratos MS 25 spectrometers using electron (EI) and chemical ionisation (CI), and fast atom bombardment (FAB). Molecular formulae were determined from accurate mass measurement and by combustion analysis.

Solvents and reagents were purified when necessary by standard methods as found in ref. 9.

6-*O*-(*tert*-Butyldiphenylsilyl)-1,2,3,4-tetra-*O*-isobutyryl-D-glucopyranose

A suspension of D-glucose (5.0 g, 27.8 mmol) in pyridine (20 ml) was heated on a steam-bath until the sugar had dissolved. The solution was placed under nitrogen, cooled to below 0 °C (ice–NaCl), then DMAP (344 mg) was added followed by TBDPSCl (7.8 ml, 8.2 g, 30 mmol) over a period of 10 min. The mixture was stirred overnight and allowed to warm to room temperature. The resulting yellow solution was diluted with dichloromethane (30 ml), cooled to −8 °C (ice/NaCl), and a solution of isobutyryl chloride (15 ml, 15.4 g, 0.144 mol) in

dichloromethane (15 ml) was added over a period of 2 h at a rate which kept the temperature below 10 °C. After the addition was complete, the mixture was diluted with dichloromethane (90 ml), washed successively with 2 M HCl, saturated aq. sodium hydrogen carbonate, then brine, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to afford the crude product (α/β, 1:1 by NMR) as an oil (20 g) which partially solidified on storage, R_f 0.74 [light petroleum 40–60 °C–EtOAc (2:1)]; ν_{max}(film)/cm^{-1} 3072, 2974, 2935, 2878, 2859, 1754, 1471, 1429 and 1247; λ_{max}(95% EtOH)/nm 269, 263, 259 and 218; δ_H(300 MHz; $CDCl_3$) 7.74–7.54 (4 H, m, 4 × SiPhH-*ortho*), 7.46–7.22 (6 H, m, 4 × SiPhH-*meta* and 2 × SiPhH-*para*), 6.42 (1 H, d, *J* 3.5, H-1α), 5.78 (1 H, d, *J* 8, H-1β), 5.54 (1 H, t, *J* 10, H-3α), 5.36–5.24 (3 H, m, H-3β, H-4α + -β), 5.20 (1 H, dd, *J* 10 + 8, H-2β), 5.13 (1 H, dd, *J* 10 + 3.5, H-2α), 4.01 (1 H, dt, *J* 10 + 3, H-5α), 3.78–3.64 (3 H, m, H-5β, H-6a and -6b), 2.74–2.34 [4 H, m, 4 × C*H*$(CH_3)_2$] and 1.26–1.01 [33 H, m, 4 × CH(C*H*$_3)_2$ and C$(CH_3)_3$]; *m/z* (EI) 641, 611, 269, 91 and 71; *m/z* (CI) 716 (M + 18), 641, 611 and 256 (Found: [M + NH_4], 716.3830. $C_{38}H_{58}NO_{10}Si$ requires *m/z*, 716.3799).

1,2,3,4-Tetra-*O*-isobutyryl-D-glucopyranose 8

To a solution of crude 6-(*tert*-butyldiphenylsilyl)-1,2,3,4-tetra-*O*-isobutyryl-D-glucopyranose (18 g, 25 mmol) in anhydrous THF (60 ml) was added TBAF (31 ml, 31 mmol) during 5 min. After 16 h the dark solution was filtered through a pad of silica, eluted with diethyl ether and the filtrate evaporated *in vacuo*. Chromatography of the residue on silica with light petroleum 40–60 °C–ethyl acetate afforded two products as gummy anomeric mixtures.

1,2,3,4-*Tetra*-O-*isobutyryl*-D-*glucopyranose* **8** (3.3 g, 28%); R_f 0.46 (light petroleum 40–60 °C–EtOAc, 2:1); ν_{max}(film)/cm^{-1} 3538 sharp, 2976, 2950, 2880, 1752, 1471, 1389 and 1248; δ_H(300 MHz; $CDCl_3$) 6.36 (1 H, d, *J* 3.5, H-1α), 5.75 (1 H, d, *J* 8, H-1β), 5.60 (1 H, t, *J* 9.5, H-3α), 5.39 (1 H, t, *J* 9.5, H-3β), 5.21–5.06 (4 H, m, H-2α + -β, H-4α + -β), 3.91 (1 H, ddd, *J* 10, 4.5 and 2, H-5α), 3.79–3.63 (2 H, m, H-6a, H-5β), 3.53 (1 H, dd, *J* 13 + 4.5, H-6b), 2.73–2.41 [4 H, m, 4 × C*H*$(CH_3)_2$] and 1.28–1.07 [24 H, m, 4 × CH(C*H*$_3)_2$]; *m/z* (EI) 373, 285, 213, 197 and 71; *m/z* (CI) 478 (M + 18), 373, 285 and 197 (Found: [M + NH_4], 478.2657. $C_{22}H_{40}NO_{10}$ requires *m/z*, 478.2652).

1,2,3,6-*Tetra*-O-*isobutyryl*-D-*glucopyranose* (2.6 g, 22%); R_f 0.53 (light petroleum 40–60 °C–EtOAc, 2:1); ν_{max}(film)/cm^{-1} 3492, 2976, 2930, 2870, 1749, 1471, 1389, 1347, 1251; δ_H(300 MHz; $CDCl_3$) 6.35 (1 H, d, *J* 3.5, H-1α), 5.75 (1 H, d, *J* 8, H-1β), 5.39 (1 H, t, *J* 10, H-3α), 5.20–5.11 (2 H, m, H-3β and -2β), 5.10 (1 H, dd, *J* 10 and 3.5, H-2α), 4.60–4.51 (2 H, m, H-6α + -6β), 4.37–4.29 (2 H, m, H-6α + -β), 3.99 (1 H, ddd, *J* 10, 4 and 2.5, H-5α), 3.71 (1 H, ddd, *J* 10, 4 and 2.5, H-5β), 3.60 (1 H, t, *J* 10, H-4α), 3.59 (1 H, t, *J* 10, H-4β), 2.76–2.42 [4 H, m, 4 × CH$(CH_3)_2$], 1.30–1.11 [24 H, m, 4 × CH(C*H*$_3)_2$]; *m/z* (EI) 443, 373, 285, 197 and 71; *m/z* (CI) 478 (M + 18), 443, 373, 285 and 71.

1,2,3,4-Tetra-*O*-isobutyryl-α-L-arabinopyranose

To a mechanically stirred suspension of L-arabinose (30.8 g, 0.2 mol) in dichloromethane (150 ml)–pyridine (80 ml) at −14 °C (ice–NaCl–MeOH) was added a solution of isobutyryl chloride (111 ml, 114 g, 1.07 mol) in dichloromethane (50 ml) over a period of 1.5 h at a rate which kept the temperature below 5 °C. After being stirred overnight at room temperature the mixture was diluted with dichloromethane (300 ml), washed with 3 M HCl (2 × 100 ml), and then treated with 0.880 aq. ammonia (100 ml) by stirring it as a two-phase mixture for 15 min. After separation, the organic phase was washed successively with water (3 × 100 ml) and brine (150 ml), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to afford the product as a gum. This crystallised when placed under a high vacuum to give an *off-white solid* (75.0 g, 85%), mp 49–50 °C; R_f 0.53 (light petroleum 40–60 °C–EtOAc, 3:1); $[\alpha]_D$ +111 (*c* 3.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 2977, 2940, 2880, 1745, 1471, 1388 and 1251; δ_H(300 MHz; $CDCl_3$) 6.38 (1 H, d, *J* 2.5, H-1), 5.49–5.38 (3 H, m, H-4, -3 and -2), 4.09 (1 H, d, *J* 13, H-5a), 3.83 (1 H, dd, *J* 13 + 1, H-5b), 2.75–2.59 [2 H, m, 2 × C*H*$(CH_3)_2$], 2.55–2.40 [2 H, m, 2 × CH$(CH_3)_2$], 1.27–1.20 [12 H, m, 2 × CH(C*H*$_3)_2$], 1.16–1.10 [12 H, m, 2 × CH(C*H*$_3)_2$]; *m/z* (EI) 429 (M − 1), 343, 255 and 226; *m/z* (CI) 448 (M + 18) and 343 (Found: [M + NH_4], 448.2535. $C_{21}H_{38}NO_9$ requires *m/z*, 448.2546) (Found: C, 58.6; H, 8.1. $C_{21}H_{34}O_9$ requires C, 58.6; H, 8.0%).

2,3,4-Tri-*O*-isobutyryl-L-arabinopyranose

Gaseous ammonia was bubbled into a mixture of dichloromethane (790 ml) and methanol (90 ml) at −63 °C (Cardice–Pr^{i}OH) over a period of 1 h while the temperature rose to −25 °C, a mixture of arabinose tetraisobutyrate (69.0 g, 0.16 mol) in dichloromethane (100 ml) was added, and the solution was allowed to warm to room temperature overnight. TLC (light petroleum 40–60 °C–EtOAc, 3:1) showed approximately 50% conversion into the product, so the solution was again cooled to −60 °C, gaseous ammonia bubbled in for 1 h, and the mixture was allowed to react at room temperature overnight. When TLC showed approximately 90% conversion into the product, the procedure was repeated yet again and then solution was evaporated *in vacuo* to leave a dark oil. This was dissolved in dichloromethane (1.2 l), and the solution was washed successively with 2 M HCl (250 ml) and brine (250 ml), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to leave the *desired product* as an orange–brown oil (33.9 g, 59%), R_f 0.22 (light petroleum 40–60 °C/EtOAc, 3:1); ν_{max}(film)/cm^{-1} 3357, 2975, 2940, 2880, 1741, 1664, 1472 and 1389; δ_H(300 MHz; $CDCl_3$) 5.48–5.10 (3 H, m, H-4, -3 and -2), 4.62 (1 H, br s, H-1α), 4.22 (1 H, dd, *J* 13 + 1.5, H-5a), 4.11 (1 H, d, *J* 7, H-1β), 3.67 (1 H, dd, *J* 13 + 3, H-5b), 2.70–2.38 [6 H, m, 3 × C*H*$(CH_3)_2$] and 1.28–1.10 [18 H, m, 3 × CH(C*H*$_3)_2$]; *m/z* (EI) 360 (M^+), 344 and 273; *m/z* (CI) 378 (M + 18), 361, 343, 290 and 273 (Found: [M^+], 360.1799. $C_{18}H_{28}O_8$ requires M, 360.1784).

2,3,4-Tri-*O*-isobutyryl-1-*O*-trichloroacetimidoyl-α-L-arabinopyranose 9

To a solution of the 2,3,4-tri-*O*-isobutyryl-L-arabinose (30.9 g, 0.086 mol) in anhydrous dichloromethane (340 ml) was added trichloroacetonitrile (17.2 ml, 24.8 g, 0.172 mol). After 10 min anhydrous potassium carbonate (41 g) was added and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then filtered through a pad of silica and eluted with diethyl ether (200 ml) followed by (3:1) light petroleum 40–60 °C–EtOAc (400 ml). Evaporation *in vacuo* afforded a mixture of the α and β imidates as a dark gum (26.6 g, 63%). The pure anomers were separated by chromatography of some of the product on silica, using light petroleum 40–60 °C–EtOAc (3:1) as eluent.

2,3,4-Tri-*O*-isobutyryl-1-*O*-trichloroacetimidoyl-α-L-arabinopyranose **9α**; R_f 0.62 (light petroleum 40–60 °C–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 3319, 2977, 2938, 2879, 1745, 1677, 1470, 1389 and 1252; δ_H(300 MHz; $CDCl_3$) 8.62 (1 H, s, NH), 6.56 (1 H, d, *J* 2.5, H-1), 5.50–5.44 (3 H, m, H-4, -3 and -2), 4.19 (1 H, br d, *J* 13, H-5a), 3.87 (1 H, dd, *J* 13 and 1.5, H-5b), 2.73–2.42 [3 H, m, 3 × C*H*$(CH_3)_2$] and 1.30–1.08 [18 H, m, 3 × CH(C*H*$_3)_2$]; *m/z* (EI) 343 (M − O·CNH·CCl_3) and 273.

2,3,4-*Tri*-O-*isobutyryl*-1-O-*trichloroacetimidoyl*-β-L-*arabinopyranose* **9β**; R_f 0.47 (light petroleum 40–60 °C–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 3343, 2976, 2936, 2878, 1744, 1678, 1470, 1389 and 1257; δ_H(300 MHz; $CDCl_3$) 8.72 (1 H, br s, NH), 5.96 (1 H, d, *J* 5, H-1), 5.37–5.25 (3 H, m, H-4, -3 and -2), 4.17–4.09 (1 H, m, H-5a), 3.83 (1 H, dd, *J* 13 and 3, H-5b), 2.67–2.54 [3 H, m, 3 × C*H*$(CH_3)_2$], 1.30–1.12 [18 H, m, 3 × CH$(CH_3)_2$]; *m/z* (EI) 343 and 273 (Found [M − O·CNH·CCl_3], 343.1752. $C_{17}H_{27}O_7$ requires *m/z*, 343.1757).

1,2,2′,3,3′,4,4′-Hepta-*O*-isobutyrylvicianose 10

To a stirred solution of 1,2,3,4-tetra-*O*-isobutyryl-D-glucopyranose **8** (1.7 g, 3.7 mmol) and the mixture of L-arabinose imidate anomers **9** (3.6 g, 7.3 mmol) in anhydrous dichloromethane (15 ml) containing activated 4 Å molecular sieves below 0 °C (ice–NaCl) under nitrogen, was added boron trifluoride–diethyl ether (0.92 ml, 7.3 mmol). The mixture was allowed to warm to room temperature overnight, and then was diluted with dichloromethane, washed successively with saturated aq. sodium hydrogen carbonate, water, and then brine, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was chromatographed on silica with light petroleum 40–60 °C–EtOAc (3:1) as eluent to afford vicianose heptaisobutyrate **10** (7:2 α/β mixture) as a gum (1.64 g, 55%), R_f 0.43 (light petroleum 40–60 °C–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 2976, 2937, 2880, 1747, 1470, 1389 and 1251; δ_H(300 MHz; $CDCl_3$) 6.36 (1 H, d, *J* 4, H-1α), 5.73 (1 H, d, *J* 8, H-1β), 5.56 (1 H, t, *J* 9.5, H-3β), 5.31–5.26 (1 H, m, H-4′), 5.21 (1 H, dd, *J* 9 and 6, H-2′α), 5.19 (1 H, dd, *J* 9 and 6, H-2′β), 5.14–5.06 (5 H, m, H-4α and -β, H-3′ and H-2α + -β), 4.52 (1 H, d, *J* 6, H-1′β), 4.46 (1 H, d, *J* 6, H-1′α), 4.18–4.11 (1 H, m, H-5), 4.02 (1 H, dd, *J* 13 and 3, H-5′), 3.90 (1 H, dd, *J* 11 and 2, H-6), 3.65 (1 H, dd, *J* 13 and 1.5, H-5′), 3.55 (1 H, dd, *J* 11 and 6, H-6), 2.75–2.42 [7 H, m, 7 × C*H*(CH_3)$_2$] and 1.29–1.09 [42 H, m, 7 × CH(C*H*$_3$)$_2$]; *m/z* 820 (M + 18), 7.15, 627, 498, 443 and 401 (Found: [M + NH_4], 820.4315. $C_{39}H_{66}NO_{17}$ requires *m/z*, 820.4330).

2,2′,3,3′,4,4′-Hexa-*O*-isobutyrylvicianose 11

Gaseous ammonia was bubbled into a mixture of dichloromethane (80 ml) and methanol (27 ml) at −5 °C (ice–NaCl) for 2.5 h while the temperature rose to 5 °C, when vicianose heptaisobutyrate **10** (1.63 g, 2.0 mmol) was added and ammonia was bubbled in for a further 1 h. The mixture was then allowed to react at room temperature for 22 h, when TLC (light petroleum 40–60 °C–EtOAc, 3:1) showed that no starting material remained. The solution was evaporated *in vacuo*, and the residue was redissolved in dichloromethane, the solution was washed with water and brine, dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo*. Chromatography on silica using light petroleum 40–60 °C–EtOAc (3:1) as eluent afforded the gummy hemiacetal **11** (684 mg, 46%) as a mixture of anomers (α:β, 2:1 by NMR), R_f 0.16 (light petroleum 40–60 °C–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 3467 (sharp), 2976, 2940, 2880, 1745, 1471, 1389 and 1253; δ_H(300 MHz; $CDCl_3$) 5.64 (1 H, t, *J* 10, H-3α), 5.43 (1 H, d, *J* 3.5, H-1α), 5.35 (1 H, t, *J* 9.5, H-3β), 5.33–5.27 (1 H, m, H-4′), 5.20 (1 H, dd, *J* 9 and 6.5, H-2′), 5.13 (1 H, dd, *J* 9 and 3.5, H-3′), 5.00 (1 H, t, *J* 9.5, H-4β), 4.99 (1 H, t, *J* 10, H-4α), 4.90 (1 H, dd, *J* 9.5 and 8, H-2β), 4.89 (1 H, dd, *J* 10 and 3.5, H-2α), 4.74 (1 H, d, *J* 8, H-1β), 4.58 (1 H, d, *J* 6.5, H-1′β), 4.55 (1 H, d, *J* 6.5, H-1′α), 4.35–4.26 (1 H, m, H-5), 2.73–2.42 [6 H, m, 6 × C*H*(CH_3)$_2$] and 1.35–1.08 [36 H, m, 6 × CH(C*H*$_3$)$_2$]; *m/z* (CI) 750 (M + 18), 715, 645, 557, 443, 401 and 343 (Found: [M + NH_4], 750.3922. $C_{35}H_{60}NO_{16}$ requires *m/z*, 750.3912).

2,2′,3,3′,4,4′-Hexa-*O*-isobutyryl-1α-*O*-(trichloroacetimidoyl)-vicianose 12

A solution of the hemiacetal **11** (600 mg, 0.82 mmol) and trichloroacetonitrile (0.25 ml, 2.5 mmol) in anhydrous dichloromethane (7.5 ml) was stirred at room temperature overnight with anhydrous potassium carbonate (0.4 g, 2.9 mmol). The reaction mixture was then filtered through a pad of silica, eluted with ethyl acetate–diethyl ether, and the eluate was evaporated *in vacuo* to give the imidate **12** as a pale yellow gum (645 mg, 90%); R_f 0.48 (light petroleum 40–60 °C–EtOAc, 2:1); [α]$_D$ +36 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3320, 2976, 2940, 2880, 1745, 1678, 1471, 1389 and 1252; δ_H(200 MHz; $CDCl_3$) 8.63 (1 H, s, NH), 6.55 (1 H, d, *J* 3.4, H-1), 5.63 (1 H, dd, *J* 10 and 9.5, H-3), 5.29–5.21 (1 H, m, H-4′), 5.21–5.02 (4 H, m, H-4, -3′, -2, -2′), 4.45 (1 H, d, *J* 6, H-1′), 4.26–4.15 (1 H, m, H-5), 3.99 (1 H, dd, *J* 13 and 3.5, H-5′), 3.87 (1 H, dd, *J* 11 and 2, H-6), 3.61 (1 H, dd, *J* 13 and 2, H-5′), 3.51 (1 H, dd, *J* 11 and 6, H-6), 2.67–2.34 [6 H, m, C*H*(CH_3)$_2$] and 1.30–1.02 [36 H, m, 6 × CH(C*H*$_3$)$_2$]; *m/z* (FAB) 715 (M − OCNHCCl_3), 645, 343, 273 and 255.

(*E*,*S*)-8-Hydroxy-2,6-dimethyloct-2-enal[2,10]

To a solution of (−)-β-citronellol **7** (5.0 g, 32 mmol) in absolute ethanol (50 ml) was added a mixture of selenium dioxide (5.6 g, 32 mmol) in ethanol (25 ml) and the mixture was stirred at 50–60 °C for 22 h, then at room temperature for a further 2 days. The resulting yellow solution was filtered from a black residue through a pad of silica and was then eluted with diethyl ether until the washings appeared colourless. The filtrate was evaporated *in vacuo* to give the aldehyde as a yellow oil (4.5 g), R_f 0.44 (Et_2O); [α]$_D$ −7 (*c* 4.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3369, 2960, 2928, 2880, 1686, 1645, 1459, 1379 and 1063; λ_{max}(95% EtOH)/nm 228; δ_H(300 MHz; $CDCl_3$) 9.40 (1 H, s, CHO), 6.51 (1 H, td, *J* 7 and 1, H-3), 3.73 (2 H, t, *J* 7, H-8), 2.44–2.25 (2 H, m, H-4), 1.76 (3 H, s, H_3-9), 0.96 (3 H, d, *J* 6, H-10); *m/z* (EI) 147, 133 and 121; *m/z* (CI) 188 (M + 18), 171, 155 and 138 (Found: [M + NH_4], 188.1655. $C_{10}H_{22}NO_2$ requires *m/z*, 188.1651).

Methyl (*E*,*S*)-8-hydroxy-2,6-dimethyloct-2-enoate 6[8]

To a solution of the above aldehyde (2.0 g, 11.7 mmol) in methanol (110 ml) at room temperature were added sodium cyanide (3.2 g, 6.5 mmol), activated manganese dioxide (21.7 g, 0.25 mmol), and acetic anhydride (1.25 ml). The mixture was stirred overnight, then was filtered through a pad of Celite and the filter cake was eluted with methanol until the filtrate appeared colourless. The filtrate was evaporated *in vacuo* to give an orange–brown oil which was then chromatographed on silica with diethyl ether as eluent to afford the methyl ester **6** as an orange oil (0.37 g, 16%), R_f 0.53 (Et_2O); [α]$_D$ −9 (*c* 3.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3412, 2950, 2927, 1715, 1649 and 1437; λ_{max}(95% EtOH)/nm 217; δ_H(300 MHz; $CDCl_3$) 6.76 (1 H, td, *J* 7 and 1, H-3), 3.73 (3 H, s, CO_2CH_3), 2.28–2.12 (2 H, m, H_2-4), 1.84 (3 H, s, H_3-9) and 0.93 (3 H, d, *J* 6.5, H_3-10); *m/z* (EI) 168, 153, 140, 127 and 43; *m/z* (CI) 218 (M + 18), 201, 186, 169 and 154 (Found: [M + NH_4], 218.1757. $C_{11}H_{24}NO_3$ requires *m/z* 218.1756).

Methyl secolonitoside hexaisobutyrate 5

To a solution of vicianose imidate **12** (670 mg, 0.77 mmol) and the methyl ester **6** (370 mg, 1.86 mmol) in anhydrous dichloromethane (5 ml) under nitrogen was added boron trifluoride–diethyl ether (150 μl, 170 mg, 1.2 mmol). After 18 h, the solution was diluted with dichloromethane, washed successively with saturated aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was chromatographed on silica, using light petroleum 40–60 °C–EtOAc (4:1 to 2:1) to afford the secolonitoside derivative **5** as a gum (326 mg, 47%) which solidified on storage. Recrystallisation from 95% ethanol gave *methyl secolonitoside hexaisobutyrate* **5**, mp 78 °C; R_f 0.20 (light petroleum 40–60 °C–EtOAc, 4:1); [α]$_D$ −12 (*c* 3.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 2975, 2940, 2880, 1745 and 1470; λ_{max}(95% EtOH)/nm 216; δ_H(500 MHz; $CDCl_3$) 6.70 (1 H, td, *J* 7 and 1, H-3), 5.23 (1 H, br s, H-4″), 5.22 (1 H, t, *J* 9.5, H-3′), 5.16 (1 H, dd, *J* 9 and 7, H-2″), 5.03 (1 H, dd, *J* 9 and 3, H-3″), 4.94 (1 H, t, *J* 9.5, H-4′), 4.92 (1 H, dd, *J* 9.5 and 8, H-2′), 4.49 (1 H, d, *J* 7, H-1″), 4.43 (1 H, d, *J* 8, H-1′), 3.96 (1 H, dd, *J* 13 and 3.5, H-5″), 3.76 (1 H, dd, *J* 11 and 1.5, H-6′), 3.70 (3 H, s, CO_2CH_3), 3.60 (1 H, dd, *J* 11 and 7, H-6′), 3.46–3.40 (2 H, m, H_2-8), 2.64–2.39 [6 H, m, C*H*(CH_3)$_2$], 2.19–2.05 (2 H, m, H_2-4), 1.80 (3 H, s, H_3-9), 1.20–1.01 [36 H, m, 6 × CH(C*H*$_3$)$_2$] and 0.85 (3 H, d, *J* 6, H_3-10); *m/z* (CI) 932 (M + 18), 343, 218 and 169 (Found: [M + NH_4], 932.5218. $C_{46}H_{78}NO_{18}$ requires *m/z*, 932.5208) (Found: C, 60.2; H, 7.9. $C_{46}H_{74}O_{18}$ requires C, 60.4; H, 8.2%).

Methyl secolonitoside hexaformate 4

To a solution of methyl secolonitoside hexaisobutyrate **5** (113 mg, 0.13 mmol) in dry methanol (4 ml) at room temperature was added 2 M methanolic sodium methoxide (1 ml). After storage overnight the mixture was treated with a lump of solid CO_2 and the solution was evaporated to dryness *in vacuo*. The residual solid was then taken up with stirred dichloromethane (1.5 ml)–pyridine (0.5 ml) followed by acetic formic anhydride[11] (0.1 ml) and the solution was left at room temperature overnight. It was then diluted with dichloromethane, washed successively with water, saturated aq. sodium hydrogen carbonate and brine, dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was chromatographed on silica with dichloromethane–diethyl ether (8:1) as eluent to give methyl secolonitoside hexaformate **4** as a glass (16 mg, 20%); R_f 0.30 (CH_2Cl_2–Et_2O, 8:1); $[\alpha]_D$ −9 (*c* 1.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 2975, 2954, 1732 and 1437; λ_{max}(95% EtOH)/nm 218; δ_H(300 MHz; $CDCl_3$) 8.16–8.04 (6 H, m, 6 × CHO), 6.76 (1 H, td, *J* 7 and 1, H-3), 5.48 (1 H, br s, H-4″), 5.46 (1 H, t, *J* 9.5, H-3′), 5.32 (1 H, dd, *J* 9 and 7, H-2″), 5.25 (1 H, dd, *J* 9 and 3, H-3″), 5.18 (1 H, t, *J* 9.5, H-4′), 5.06 (1 H, dd, *J* 9.5 and 8, H-2′), 4.57 (1 H, d, *J* 7, H-1″), 4.56 (1 H, d, *J* 8, H-1′), 4.14 (1 H, dd, *J* 13 and 3, H-5″), 4.01 (1 H, dd, *J* 11 and 1.5, H-6′), 3.77 (3 H, s, CO_2CH_3), 3.68 (1 H, dd, *J* 11 and 6.5, H-6′), 3.58–3.49 (2 H, m, H-8), 2.26–2.15 (2 H, m, H_2-4), 1.87 (3 H, s, H_3-9), 0.93 (3 H, d, *J* 6, H_3-10); *m/z* (FAB) 663 (M + 1), 462, 217, 184 (Found: [M + H], 663.2160. $C_{28}H_{39}O_{18}$ requires *m/z*, 663.2130).

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References

1 R. T. Brown, B. E. N. Dauda, M. Kandasamy and C. A. M. Santos, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1539.
2 T. Iwagawa and T. Haase, *Phytochemistry*, 1983, **22**, 255.
3 R. T. Brown, N. E. Carter, K. W. Lumbard and F. Scheinmann, *Tetrahedron Lett.*, 1995, **36**, 8661 and references cited therein.
4 R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 212.
5 A. J. Ratcliffe, P. Konradson and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1990, **112**, 5665.
6 D. D. Williams and W. L. Evans, *Org. Synth.*, 1955, **Coll. Vol. 3**, p. 432.
7 B. Helferich and H. Brederek, *Justus Liebigs Ann. Chem.*, 1928, 465, 166.
8 E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.*, 1968, **90**, 5616.
9 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1966.
10 K. C. Chan, R. A. Jewell, W. H. Nutting and H. Rapoport, *J. Org. Chem.*, 1968, **33**, 3382.
11 R. Schijf and W. Stevens, *Recl. Trav. Chim. Pays-Bas*, 1966, **85**, 627 (*Chem. Abstr.*, 1966, **65**, 8754c).

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