Synthesis of 3-(Glycosyloxymethyl)isocoumarins and (S)-3-(Glycosyloxy-methyl)-3,4-dihydroisocoumarins by Coupling of Propargyl Glycosides with 2-Iodobenzoic Acid Mediated by Palladium Complex and Zinc Chloride

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Received 13 January 2006; revised 3 May 2006

Abstract: Palladium-catalyzed coupling of propargyl glycosides with o-iodobenzoic acid leads to the selective syntheses of hitherto unknown, novel isocoumarin glycosides in 43–55% yields. We have observed that reduction of the keto acids to the corresponding alcohols was highly stereospecific due to the neighboring glycosyl substitution and leads to the formation of (S)-3-(glycosyloxymethyl)-3,4-dihydroisocoumarins in 21–37% overall yield.

Key words: palladium-catalyzed coupling, propargyl glycosides, 2-iodobenzoic acid, isocoumarin glycosides, (S)-3-(glycosyloxymethyl)-3,4-dihydroisocoumarins, antifungal

Isocoumarins and 3,4-dihydroisocoumarins are naturally occurring lactones that display a wide range of biological activities,1,2 such as antibacterial,3 anti-inflammatory,4 antiulcer,5 and anti-trail pheromonal effects.1,6 Notable among them are 3-hydroxymethylisocoumarin antibiotic cytogenin,5,9 several 3-alkylisocoumarin derivatives,6b and 3-hydroxylated amino acid side-chain substituted dihydroisocoumarin derivative AI-77-B,10 3-aminoalkyldihydroisocoumarin viz., amicoumacins and 3-aryldihydroisocoumarin viz., phyllodulcin.2a,11 Recently, the 3-aryl and -alkyl side-chain was shown to be a prerequisite for high antifungal activity against rice blast fungus Pyricularia grisea.7 As a part of our ongoing investigation, and considering the wealth of bioactivities found in isocoumarin derivatives, we decided to examine the synthesis and antifungal properties of hitherto-unknown isocoumarin and 3,4-dihydroisocoumarin glycoside scaffolds. Because of the mild reaction conditions typically required to build isocoumarin glycoside frame-work bearing labile O-glycosidic linkage and protecting groups, we considered palladium-catalyzed cross-coupling methodologies that have become increasingly important for carbon–carbon bond formation in organic synthesis.12 Of these, palladium-phosphine complex and zinc chloride system, as reported by Cheng and co-workers for coupling of 2-iodobenzoic acid and methyl 2-iodobenzoate with internal alkynes to prepare selectively isocoumarins rather than phthalides, was selected.13

As a starting point for this study, the propargyl glycoside derivatives 1a–e required for the coupling reaction were synthesized by literature-described methods and fully characterized.14 Compound 1a was prepared by reaction of b-D-glucose pentaacetate with propargyl alcohol/ BF3·OEt214a and compounds 1b–e by O-alkylation of the appropriate sugar alcohols with propargyl bromide/NaH.14b

With the required propargyl glycosides in hand, the coupling reaction of propargyl glucoside derivative 1a with 2-iodobenzoic acid (2) was studied. Thus, reaction of 1a and 2 in presence of Pd(PPh3)4 (5% mol), ZnCl2 (1 mol equiv) and Et3N (5 mol equiv) in DMF at 100 °C under nitrogen for eight hours gave 3-glucopyranosyloxymethylisocoumarin 3a (Table 1) in moderate yield (55%) (Scheme 1).13

The isocoumarin glycoside derivative 3a was characterized from 1H NMR spectrum by the appearance of H-4 at δ = 6.50 as a singlet and the anemic proton H-1’ at 4.44

Table 1 Isocoumarin Derivatives 3 Prepared

<table>
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<th>Entry</th>
<th>Propargyl glycoside</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>[α]D27</th>
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<tr>
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<td>3a</td>
<td>55</td>
<td>114–115</td>
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<td>3b</td>
<td>45</td>
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<tr>
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<td>3c</td>
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<tr>
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<td>1d</td>
<td>3d</td>
<td>43</td>
<td>136–138</td>
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</tr>
<tr>
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<td>1e</td>
<td>3e</td>
<td>45</td>
<td>134–136</td>
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SYNTHESIS 2006, No. 17, pp 2944–2950
Advanced online publication: 27.07.2006
DOI: 10.1055/s-2006-942504; Art ID: Z01506SS
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as a doublet \( (J_{1’,2} = 9.1 \text{ Hz}) \), and \(^{13}\text{C} \) NMR spectrum by the appearance of C-1 at \( \delta = 162.2 \), C-3 at 121.1, C-4 at 105.1, C-1’ at 100.5. Interestingly, the sensitive ester protecting groups of the sugar were tolerant of the reaction conditions.

After finding a suitable method for the synthesis of isocoumarin glycoside derivative 3a, we have explored the applicability of this methodology for general synthesis of several other isocoumarin glycosides. Thus, reaction of propargyl galactoside derivative 1b with 2-iodobenzoic acid (2) under the same conditions for eight hours afforded 3-galactosyloxymethylisocoumarin 3b (Table 1) in moderate yield (45%) (Scheme 1). The sensitive isopropylidene protecting groups were tolerant of the reaction conditions. The isocoumarin galactoside derivative 3b was characterized from \(^1\text{H} \) NMR spectrum by the appearance of H-4 at \( \delta = 6.63 \) as a singlet and the anomeric proton H-1’ at 5.51 as a doublet \( (J_{1’,2} = 3.8 \text{ Hz}) \), and \(^{13}\text{C} \) NMR spectrum by the appearance of carboxyl absorption at 1731 cm\(^{-1} \) characteristic of isocoumarin.

The scope of the reaction was further extended for coupling of propargyl glycoside derivatives 1c, 1d and 1e with 2. Thus, coupling of propargyl mannofuranoside derivative 1c with 2 under the same reaction conditions afforded the corresponding 3-mannofuranosyloxymethylisocoumarin derivative 3c in 44% yield (Table 1). Once again similar yields were obtained due to the presence of labile isopropylidene protecting groups present on the sugar. In an analogous manner, coupling of propargyl glucofuranose derivative 1d with 2 gave the corresponding 3-glucofuranosyloxymethylisocoumarin derivative 3d in 43% yield, and 1e with 2 gave 3-fructopyranosyloxymethylisocoumarin derivative 3e in 45% yield (Table 1). The lower yields are reflective of sensitive cyclohexylidene protecting groups of the sugar. The spectroscopic features of isocoumarin glycosyl derivatives 3c, 3d and 3e were analogous to products 3a and 3b and fully supported the assigned structures. The reaction conditions were tolerant of ester, isopropylidene and cyclohexylidene protecting groups present on the propargyl glycoside derivatives 1a–e.

Next, we turned our attention to transform isocoumarin glucosides 3a–e to the corresponding 3-glycosyloxymethyl-3,4-dihydroisocoumarin glycoside derivatives 6a–e by a sequence of alkaline hydrolysis, reduction and cyclization reactions. Thus, reaction of 3a–e in aqueous 5% potassium hydroxide in ethanol at reflux temperature for four hours gave the corresponding lactone ring-opened keto acids 4b–e, respectively, in good yields (63–83%).
Compound 4a could not be isolated under these reaction conditions probably due to hydrolysis of alkali labile ester groups of the sugar. The keto acid 4b was characterized from $^1$H NMR spectrum by the appearance of H-1 at $\delta = 5.48$ ($J_{1,2} = 3.7$ Hz) as a doublet, methylene protons adjacent to carboxyl group at 3.69 (1 H) and 3.55 (1 H) as AB-type doublets ($J_{\text{gem}} = 12.0$ Hz), benzyl protons (2 H) at 3.20 (1 H) and 3.17 (1 H) as AB-type doublets ($J_{\text{gem}} = 14.0$ Hz) and by the appearance of carboxyl absorptions at 1725 and 1693 cm$^{-1}$ in the IR spectrum. The keto acids 4c, 4d and 4e were fully characterized analogous to 4b.

The critical reduction step of keto acids 4b–e was carried out with sodium borohydride in aqueous 1% NaOH at room temperature for two hours to afford the corresponding alcohols 5b–e in good yields (69–85%).$^6$ The hydroxy acids 5b–e could not be characterized by NMR analysis due to rapid cyclization to the corresponding dihydroisocoumarin glycosides 6b–e during work-up. The hydroxy acids 5b–e were alternatively cyclized by heating to reflux in Ac$_2$O for two hours to isolate the corresponding 3-glycosyloxyethyl-3,4-dihydroisocoumarins 6b–e in good yields (78–82%). The dihydroisocoumarin derivatives 6b–e were found to be nearly single isomers by $^1$H NMR spectra and were purified by column chromatography. The 3,4-dihydroisocoumarin glycoside derivative 6b was characterized from $^1$H NMR spectrum from the appearance of H-1 at $\delta = 5.45$ (d, $J_{1,2} = 3.5$ Hz), H-3 as a multiplet and, and $^{13}$C NMR spectrum from the appearance of C-1 at $\delta = 164.9$, C-1' at 96.3, and from the lactone carboxyl absorption at 1724 cm$^{-1}$ in the IR spectrum. The 3,4-dihydroisocoumarin glycosides 6c–e were characterized in a similar way from the $^1$H NMR spectra.

The absolute configuration of the dihydroisocoumarin glycosides 6b–e was determined as S at C-3 by analysis of their CD spectra$^{15a}$ and by direct comparison with related compounds of known stereochemistry, such as (S)-3-(hydroxyethyl)-5,7-dimethoxydihydroisocoumarin.$^{15b}$ The compounds 6b–e showed the CD bands at 4.70–4.60, H-4 at 3.20–2.95 as a multiplet, $J_{\text{gem}} = 12.0$ Hz), benzyl protons (2 H) at 3.20 (1 H) and 3.17 (1 H) as AB-type doublets ($J_{\text{gem}} = 14.0$ Hz) and by the appearance of carboxyl absorptions at 1725 and 1693 cm$^{-1}$ in the IR spectrum. The keto acids 4c, 4d and 4e were fully characterized analogous to 4b.

In summary, a general synthesis of novel isocoumarin glycosides 3a–e and (S)-3-glycosyloxyethyl-3,4-dihydroisocoumarins 6b–e in moderate yields (21–37%) has been achieved by palladium/ZnCl$_2$ mediated coupling of various terminal acetylene glycosides with 2-iodobenzoic acid (2). It was established that the reaction conditions are selective to afford isocoumarins; they are also mild, and tolerant of sensitive isopropylidene, cyclohexylidene and acetate protecting groups of the glycosides. Isocoumarin glycosides 3a–e, upon alkaline hydrolysis, stereospecific reduction, and cyclization, give the corresponding (S)-3-glycosyloxyethyl-3,4-dihydroisocoumarins 6b–e in good yields, except the glycoside 6a which bears acetate protecting groups. This approach in principle is applicable to the synthesis of other chiral 3,4-dihydroisocoumarins. We have examined antifungal activity of all the new compounds against five pathogens, however none showed appreciable activity.

Melting points were determined by using Fisher John’s melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrometer. FAB Mass Spectra were recorded on an AUTO SPEC-M (Manchester, UK) mass spectrometer. $^1$H NMR spectra in CDCl$_3$ were recorded at 300 MHz on a Bruker Avance FT-NMR spectrometer. Optical rotations were measured with a JASCO DIP-370 instrument. All CD spectra were recorded on JASCO 810 spectrophotometer on methanolic solutions of products. For column chromatography, silica gel 60–120 mesh was used. For TLC, silica gel 60 F$_{254}$ (Merck) was used.

1,2,5,6-Di-O-cyclohexylened-3-O-(prop-2-ynyl)-a-D-glucopyranoside (1d) To a solution of 1,2,5,6-di-O-cyclohexylened-3-O-glucopyranosan (5.0 g, 14.7 mmol) in DMF (10 mL) at 5 °C was added NaH (0.9 g, 37.5 mmol) and the mixture was stirred for 15 min. The mixture was cooled to 0 °C and propargyl bromide (1.75 g, 14.7 mmol) was added dropwise. The mixture was brought to r.t. and stirred for 2 h. The reaction was quenched by the addition of MeOH (0.5 mL), diluted with H$_2$O (100 mL) and extracted with Et$_2$O (2 × 50 mL). The combined organic phases were washed with H$_2$O (2 × 50 mL), dried (Na$_2$SO$_4$) and evaporated on a rotary evaporator to obtain 1d; yield: 4.2 g (76%); colorless syrup; [a]$_D^{27}$+2.0 (c = 0.5, CH$_2$Cl$_2$).

IR (film): 3433, 2972, 2853, 1730, 1693, 1589, 1462, 1455, 1432, 1330, 1217, 1066, 1044, 1003, 905, 778, 745 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.15 (s, 2 H, 2,3-OCH$_2$), 4.76 (d, $J$ = 3.7 Hz, 1 H, H-1), 4.44 (d, $J$ = 1.7 Hz, 1 H, H-3), 4.27 (d, $J$ = 1.5 Hz, 1 H, H-2), 4.21 (d, $J$ = 1.2 Hz, 1 H, H-6), 4.02 (t, $J$ = 1.2 Hz, 2 H, C=CH$_2$), 3.79 (m, 1 H, H-4), 3.72 (m, 4 H, H-3,5,6,6'), 2.42 (t, $J$ = 1.2 Hz, 1 H, C=CH$_2$), 1.75–1.30 (m, 20 H, 20, H, cyclohexylidene).


1,2:4,5-Di-O-cyclohexylened-3-O-(prop-2-ynyl)-a-D-fructopyranoside (1e) To a solution of 1,2:4,5-di-O-cyclohexylened-3-O-fructopyranosan (5.1 g, 15.0 mmol) in DMF (12 mL) at 5 °C was added NaH (0.9 g, 37.5 mmol) and the mixture was stirred for 15 min. The mixture was cooled to 0 °C and propargyl bromide (1.75 g, 14.7 mmol) was added dropwise. The mixture was brought to r.t. and stirred for 2 h. The reaction was quenched by addition of MeOH (0.6 mL), diluted with H$_2$O (100 mL) and extracted with Et$_2$O (2 × 50 mL). The combined organic phases were washed with H$_2$O (2 × 50 mL), dried (Na$_2$SO$_4$) and evaporated on a rotary evaporator to obtain 1e; yield: 4.1 g (72%); colorless syrup; [a]$_D^{27}$-38.5 (c = 1.00, CH$_2$Cl$_2$).

IR (film): 3433, 2972, 2853, 1730, 1693, 1589, 1462, 1455, 1432, 1330, 1217, 1066, 1044, 1003, 905, 778, 745 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.41 (d, $J$ = 1.2 Hz, 2 H, OCH$_2$), 4.30–4.15 (m, 3 H, H-4,5,6), 4.08 (d, $J_{1,2}$ = 13.1 Hz, 1 H, H-1), 3.96 (d, $J$ = 13.1 Hz, 1 H, H-1'), 3.84 (d, $J_{2,3}$ = 8.7 Hz, 1 H, H-6'), 3.66 (d, $J_{3,4}$ = 7.3 Hz, 1 H, H-3), 2.37 (t, $J$ = 1.2 Hz, 1 H, C=CH$_2$), 1.80–1.25 (m, 20 H, cyclohexylidene).


Synthesis 2006, No. 17, 2944–2950 © Thieme Stuttgart · New York
3-[1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylmethyl)-β-D-galactopyranosyloxy]isocoumarin (3b)

To a solution of 2-iodobenzoic acid (2; 4.0 g, 16.1 mmol) in DMF (16 mL) was added 1.2:3:4:6-di-O-isopropylidene-6-O-(prop-2-ynyl)-α-D-galactopyranoside (1b; 4.8 g, 16.1 mmol), Et,N (8.0 g, 80 mmol), Pd(PPh₃)₄ (0.96 g, 0.8 mmol), and ZnCl₂ (2.18 g, 16 mmol) under N₂ and heated to 100 °C for 8 h. The mixture was chromatographed [SiO₂, EtOAc–hexane (1:3)] to isolate 3b; yield: 3.06 g (45%); colorless syrup; [α]₂³⁷

IR (KBr): 1728 cm⁻¹.

3-[1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylmethyl)-α-D-fructopyranosyloxy]isocoumarin (3e)

To a solution of 2-iodobenzoic acid (2; 4.0 g, 16.0 mmol) in DMF (16 mL) was added prop-2-ynyl 3-[2,3,4,6-di-O-isopropylidene-β-D-mannofuranosyl-1-(prop-2-ynyl)-α-D-glucopyranoside (1e; 4.77 g, 16.0 mmol), Et,N (8.90 g, 80 mmol), Pd(PPh₃)₄ (0.93 g, 0.8 mmol), and ZnCl₂ (2.18 g, 16 mmol) under N₂ and heated to 100 °C for 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was chromatographed [SiO₂, EtOAc–hexane (1:19)] to isolate 3e; yield: 2.96 g (44%); colorless solid; mp 93–94 °C; [α]₂³⁷

IR (KBr): 1732 cm⁻¹.

3-[1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylmethyl)-β-D-galactopyranosyl]isocoumarin (3a)

To a solution of 2-iodobenzoic acid (2; 3.7 g, 15.0 mmol) in DMF (5 mL) was added prop-2-ynyl 2,3,4,6-di-O-acetyl-β-D-glucopyranoside (1a; 7.68 g, 18.0 mmol), Et,N (7.59 g, 75.0 mmol), Pd(PPh₃)₄ (0.87 g, 0.75 mmol), and ZnCl₂ (2.04 g, 15.0 mmol) under N₂ and heated to 100 °C for 8 h. The mixture was column chromatographed [SiO₂, EtOAc–hexane (1:9)] to isolate 3a; yield: 4.2 g (55%); colorless solid; mp 114–115 °C; [α]₂³⁷

IR (KBr): 1760, 1720 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.25 (d, J = 7.7 Hz, 1 H, H-8), 7.65 (dd, J = 7.6 Hz, 1 H, H-7), 7.50 (dd, J = 7.6 Hz, 1 H, H-6), 7.38 (d, J = 7.7 Hz, 1 H, H-5), 6.50 (s, 1 H, H-4), 5.25–5.05 (m, 3 H, H-2′,3′,4′), 4.68–4.60 (m, 1 H, H-6′), 4.44 (d, J = 9.1 Hz, 1 H, H-1′), 4.35–4.25 (m, 1 H, H-1′), 4.15–4.05 (m, 2 H, CH₂O), 3.78–3.70 (m, 2 H, H-5), 2.10, 2.04, 1.96 (4 s, 12 H, OCH₃).

1H NMR (50 MHz, CDCl₃): δ = 170.9, 170.4, 169.7 × 2 (4 × COCH₃), 162.2 (C-1), 152.5 (C-1a), 135.3, 130.1, 128.7, 126.2 (arom), 121.1 (C-3), 105.1 (C-4), 100.5 (C-1′), 73.0, 72.4, 71.6, 68.7, 67.4 (2′-C,3′,4′,5′,6′), 62.2 (CH₂O), 20.9 × 2, 18.0 × 2 (4 × CH₃).

FAB MS: m/z = 507 [M + H]+.


3-[1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylmethyl)-α-D-galactopyranosyl]isocoumarin (3d)

To a solution of 2-iodobenzoic acid (2; 4.0 g, 16.1 mmol) in DMF (16 mL) was added 1.2:3:4:6-di-O-isopropylidene-3-O-(prop-2-ynyl)-α-D-galactopyranoside (1d; 6.1 g, 16.1 mmol), Et,N (8.09 g, 80 mmol), Pd(PPh₃)₄ (0.93 g, 0.8 mmol), and ZnCl₂ (2.18 g, 16.0 mmol) under N₂ and heated to 100 °C for 8 h. Progress of the reaction was monitored by TLC. After work-up, the residue obtained was column chromatographed [SiO₂, EtOAc–hexane (1:3)] to isolate 3d; yield: 3.47 g (43%); white solid; mp 136–138 °C; [α]₂³⁷

IR (KBr): 1728 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.28 (d, J = 7.7 Hz, 1 H, H-8), 7.72 (t, J = 7.7 Hz, 1 H, H-7), 7.52 (t, J = 7.7 Hz, 1 H, H-6), 7.40 (d, J = 7.7 Hz, 1 H, H-5), 6.62 (s, 1 H, H-4), 5.84 (d, J = 3.7 Hz, 1 H, H-1′), 4.92, 4.45 (AB-type doublet, J = 10.1 Hz, 2 H, OCH₂), 4.35–4.30 (m, 1 H, H-3′), 3.45–4.00 (m, 4 H, H-4′,5′,6′), 1.73–1.35 (m, 20 H, cyclohexylidene).

1C NMR (50 MHz, CDCl₃): δ = 161.8 (C-1), 152.8 (C-3a), 136.6 (C-4a), 134.8, 129.7, 128.5, 125.6 (arom), 120.8 (C-7), 112.8, 109.2 (2 × CO₂), 106.0 (C-1′), 104.6 (C-4′), 85.0, 80.8, 79.4, 73.0, 67.6, 65.1 (C-2′,3′,4′,5′,6′, CH₂O), 26.8, 25.8, 25.1, 24.5 [2 × (CH₂O)].

FAB MS: m/z = 498 [M + H]+.

Anal. Calc. for C₃₉H₄₀O₁₉: C, 76.79; H, 6.68. Found: C, 76.72; H, 6.73.

3-[1-(2,3,4,5,6-Pentakis-O-(2-cyclohexylidene-3-(prop-2-ynyl))-α-D-fructopyranosylmethyl)]isocoumarin (3e)

To a solution of 2-iodobenzoic acid (2; 3.0 g, 12.0 mmol) in DMF (12 mL) was added 1.2:4.5-di-O-(2-cyclohexylidene-3-(prop-2-ynyl))-α-D-fructopyranoside (1e; 4.5 g, 12.0 mmol), Et,N (6.00, 60.0 mmol), Pd(PPh₃)₄ (0.70 g, 0.6 mmol), and ZnCl₂ (1.60 g, 12 mmol) under N₂ and heated to 100 °C for 8 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was worked up and the residue obtained was column chromatographed [SiO₂, neat hexane] to isolate 3e; yield: 2.70 g (45%); colorless solid; mp 134–136 °C; [α]₂³⁷

IR (KBr): 1737 cm⁻¹.
1.391 (d, J_{1,2} = 7.95 Hz, 1 H, H-6'), 3.47 (d, J = 7.2 Hz, 1 H, H-3'), 1.80–1.20 (m, 20 H, cyclohexylidene).

1^1C NMR (50 MHz, CDCl$_3$): δ = 162.1 (C-1), 152.1 (C-8a), 136.7 (C-4a), 134.8, 129.7, 128.2, 125.6 (arom), 121.0 (C-3), 112.9, 109.9 (2 × CO$_2$), 104.7 (C-4), 103.7 (C-2'), 77.6, 77.0, 73.5, 71.5, 68.8, 60.4 (C-1',3',4',5',6'), CH$_2$O), 38.0, 36.5, 35.4, 24.9, 23.8, 23.6 (cyclohexylidene).

FAB MS: m/z = 531 [M + Na$^+$].

Anal. Calcd for C$_{29}$H$_{35}$O$_5$: C, 67.87; H, 7.24. Found: C, 67.87; H, 7.16.

2-[3-(1,2,3,4-Di-O-isopropylidene-α-D-galactopyranosyl)-2-oxopropyl]benzoic Acid (4b)

To a solution of 2b (3.24 g, 7.7 mmol) in EtOH (144 mL) was added aq 5% KOH (270 mL) and refluxed for 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to r.t., acidified with 10% aq HCl (176 mL), and extracted with CH$_2$Cl$_2$ (2 × 30 mL) and EtOAc (2 × 25 mL). The combined organic phases were washed with H$_2$O (2 × 50 mL), dried (Na$_2$SO$_4$) and evaporated on a rotary evaporator to obtain the title compound 4b; yield: 2.64 g (83%); colorless solid; mp 145–147 °C; [α]$_D^{27}$ = -16.0 (c = 0.25, CH$_2$Cl$_2$).

IR (film): 3418, 1726, 1695 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): δ = 8.05 (d, J$_{6,7}$ = 7.2 Hz, 1 H, H-6), 7.58 (dd, J$_{3,4} = 7.1$ Hz, 1 H, H-5), 7.42 (dd, J$_{6,7} = 7.2$ Hz, 1 H, H-4), 7.18 (d, J = 7.4 Hz, 1 H, H-3), 5.86 (2 d, J$_{1,2} = 3.8$ Hz, 1 H, H-1'), 4.64–3.50 (m, 8 H, H-2',3',4',5',6',6''), OCH$_2$CO), 3.20–2.90 (m, 2 H, PhCH$_2$O), 1.85–1.30 (m, 20 H, cyclohexylidene).

FAB MS: m/z = 539 [M + Na$^+$], 517 [M + H$^+$].

Anal. Calcd for C$_{28}$H$_{36}$O$_9$: C, 65.32; H, 7.09.

2-[3-(1,2,4,5-Di-O-cyclohexylidene-α-D-glucopyranosyl)-2-oxopropyl]benzoic Acid (4c)

To a solution of compound 4b (1.3 g, 3.0 mmol) in 1% aq NaOH (34 mL) was added NaBH$_4$ (0.3 g) at 0 °C. The mixture was stirred for 2 h at r.t. and acidified with 10% aq HCl (120 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with H$_2$O (2 × 15 mL), dried (Na$_2$SO$_4$) and evaporated on a rotary evaporator to obtain 4c; yield: 1.16 g (83%); colorless solid; mp 140–142 °C; [α]$_D^{27}$ = -32.4 (c = 0.25, CH$_2$Cl$_2$).

IR (KBr): 1727, 1695 cm$^{-1}$.

1H NMR (600 MHz, CDCl$_3$): δ = 5.89 (d, J$_{6,7}$ = 7.2 Hz, 1 H, H-6), 5.78 (dd, J$_{3,4} = 7.1$ Hz, 1 H, H-5), 7.42 (dd, J$_{6,7} = 7.2$ Hz, 1 H, H-4), 7.18 (d, J = 7.4 Hz, 1 H, H-3), 5.86 (2 d, J$_{1,2} = 3.8$ Hz, 1 H, H-1'), 4.64–3.50 (m, 8 H, H-2',3',4',5',6',6''), OCH$_2$CO), 3.20–2.90 (m, 2 H, PhCH$_2$O), 1.85–1.30 (m, 20 H, cyclohexylidene).

Anal. Calcd for C$_{28}$H$_{36}$O$_9$: C, 65.32; H, 7.09.

2-[3-(1,2,3,4,5,6-Di-O-cyclohexylidene-β-D-mannofuranosyl)-2-oxopropyl]benzoic Acid (4e)

To a solution of 3e (3.24 g, 7.7 mmol) in EtOH (144 mL) was added aq 5% KOH (270 mL) and the mixture was refluxed for 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to r.t., acidified with 10% aq HCl (120 mL), and extracted with CH$_2$Cl$_2$ (2 × 30 mL) and EtOAc (2 × 25 mL). The combined organic phases were washed with H$_2$O (2 × 50 mL), dried (Na$_2$SO$_4$) and evaporated on a rotary evaporator to obtain the title compound 4e; yield: 1.15 g (63%); colorless solid; mp 140–142 °C; [α]$_D^{27}$ = -32.4 (c = 0.25, CH$_2$Cl$_2$).

IR (KBr): 1727, 1695 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): δ = 8.06 (d, J$_{6,7}$ = 7.2 Hz, 1 H, H-6), 7.51 (dd, J$_{3,4} = 7.2$ Hz, 1 H, H-5), 7.42 (dd, J$_{6,7} = 7.2$ Hz, 1 H, H-4), 7.18 (d, J = 7.4 Hz, 1 H, H-3), 5.86 (2 d, J$_{1,2} = 3.8$ Hz, 1 H, H-1'), 4.64–3.50 (m, 9 H, H-2',3',4',5',6',6'', OCH$_2$CO), 3.20–2.90 (m, 2 H, PhCH$_2$O), 1.85–1.30 (m, 20 H, cyclohexylidene).

1C NMR (50 MHz, CDCl$_3$): δ = 204.7 (C=O), 164.1 (CO$_2$H), 136.3, 133.7, 130.0, 128.3, 127.4 × 2 (arom), 112.7, 112.0 (2 × CO$_2$), 105.1 (C-1'), 82.1 × 2, 81.4 × 2, 72.5, 67.3 (C-2',3',4',5',6'), OCH$_2$CO), 36.4, 36.2, 35.6, 34.3, 24.8, 24.7, 23.7 × 2 (cyclohexylidene, PhCH$_2$CO).

ESI MS: m/z = 539 [M + Na$^+$], 517 [M + H$^+$].

Anal. Calcd for C$_{28}$H$_{36}$O$_9$: C, 65.32; H, 7.09.
To a solution of (1.0 g, 2 mmol) in Ac₂O (1 mL) was refluxed for 2 h at r.t., acidified with 10% aq HCl (80 mL) and extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with H₂O (2 x 20 mL), dried (Na₂SO₄) and evaporated on a rotary evaporator to afford the title compound 6b; yield: 0.7 g (81%); colorless syrup; [α]_D^27 +46.0 (c = 0.25, CHCl₃).

IR (film): 1724 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.06 (d, J = 7.7 Hz, 1 H, H-8), 7.50 (dd, J = 7.8 Hz, 1 H, H-7), 7.37 (dd, J = 7.7 Hz, 1 H, H-6), 7.23 (d, J = 7.7 Hz, 1 H, H-5), 5.45 (d, J = 3.5 Hz, 1 H, H-1'), 4.65 (m, 1 H, H-3), 4.55 (dd, J = 2.8 Hz, 3.2 Hz, 1 H, H-4'), 4.23 (m, 1 H, CH₂O), 3.95–3.60 (m, 5 H, H-2',3',5',6',6''), 3.20–2.95 (m, 2 H, H-5), 1.52, 1.41, 1.31, 1.24 [4 s, 12 H, 2 × (CH₃)₂CO₂].

13C NMR (50 MHz, CDCl₃): δ = 164.9 (C-1), 138.9 (C-8a), 133.7, 130.2, 127.5 × 2 (arom), 125.0 (C-4a), 109.3, 108.5 (2 × Me₂CO₂), 96.3 (C-1'), 71.1, 70.6 × 2, 70.5 × 2, 67.0 (C-2',3',4',5',6', C-3, CH₂O), 36.7 (PhCH₂) 26.1, 25.9, 24.9, 24.4 [2 × (CH₃)₂CO₂].

CD (MeOH): λ_{max} (Δc) = 277.2 (–0.37), 226.3 (–1.25), 205.0 nm (-0.53).

FAB MS: m/z = 443 [M + Na]^+.


(S)-3-(1,2,5,6-Di-O-isopropylidene-β-D-mannofuranosyl-oxymethyl)-3,4-dihydroisocoumarin (6c)

To a solution of (0.8 g, 1.4 mmol) in Ac₂O (1 mL) was refluxed for 2 h at r.t., acidified with 10% aq HCl (80 mL) and extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with H₂O (2 x 20 mL), dried (Na₂SO₄) and evaporated on a rotary evaporator to afford the title compound 6c; yield: 0.4 g (83%); syrup; [α]_D^27 +49.0 (c = 0.75, CHCl₃).

IR (film): 1727 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.06 (d, J = 7.7 Hz, 1 H, H-8), 7.51 (dd, J = 7.8 Hz, 1 H, H-7), 7.38 (dd, J = 7.7 Hz, 1 H, H-6), 7.21 (d, J = 1.6 Hz), 5.81 (d, J = 3.2 Hz, 1 H, H-1'), 4.70–4.65 (m, 1 H, H-3), 4.53 (d, J = 3.2 Hz, 1 H, H-2'), 4.50–3.80 (m, 6 H, H₃'₄',5',6', C₃H₂O), 3.25 (dd, J = 14.2 Hz, J = 6.8 Hz, 1 H, H-4'), 2.95 (dd, J = 3.0 Hz, 1 H, H-4), 1.70–1.20 (m, 20 H, cyclohexyldiene).

13C NMR (50 MHz, CDCl₃): δ = 165.2 (C-1), 138.8 (C-8a), 133.7, 130.4, 127.7, 127.5 (arom), 124.7 (C-4a), 112.7, 109.7 (2 × CO₂), 104.9 (C-1'), 83.5, 83.3, 82.4, 81.4, 72.0, 71.6, 67.4 (C-2',3',4',5',6', C₃H₂O, C-3), 36.5 (PhCH₂), 29.9, 29.6, 24.9, 23.9, 23.6 (cyclohexyldiene).

CD (MeOH): λ_{max} (Δc) = 286.4 (–0.46), 243.4 (–0.61), 222.2 (–1.50), 204.0 nm (-5.23).

FAB MS: m/z = 523 [M + Na]^+.


(S)-3-(1,2,5,6-Di-O-cyclohexyldiene-α-D-fructofuranosyl-oxymethyl)-3,4-dihydroisocoumarin (6d)

To a solution of (0.7 g, 1.4 mmol) in 1% aq NaOH (30 mL) was added NaBH₄ (0.15 g) at 0 °C. The mixture was stirred for 2 h at r.t., acidified with 10% aq HCl (80 mL) and extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with H₂O (2 x 20 mL), dried (Na₂SO₄) and evaporated on a rotary evaporator to afford the title compound 6d; yield: 0.4 g (83%); solid; mp 119–120 °C; [α]_D^27 +58.0 (c = 0.25, CHCl₃).

IR (KBr): 1730 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.10 (d, J = 7.5 Hz, 1 H, H-8), 7.51 (dd, J = 7.7 Hz, 1 H, H-7), 7.35 (dd, J = 7.5 Hz, 1 H, H-6), 7.21 (d, J = 7.5 Hz, 1 H, H-5), 4.70–4.55 (m, 1 H, H-3), 4.30–3.60 (m, 8 H, H₃',1''₄',3',4',5',6',6'' OCH₂CO₂), 3.45 (dd, J = 13.0 Hz, J = 10.2 Hz, 1 H, OCH₃), 3.10–2.90 (m, 2 H, PhCH₂), 1.80–1.10 (m, 20 H, cyclohexyldiene).

13C NMR (50 MHz, CDCl₃): δ = 164.9 (C-1), 138.9 (C-8a), 133.8, 130.2, 127.4 × 2 (arom), 124.8 (C-4a), 112.7, 109.8 (2 × CO₂), 103.8 (C-2''), 76.9, 76.5, 73.5, 75.2, 71.4, 72.1 (C-1''₃',4',5',6''), C₃H₂O, C-3), 38.0 (PhCH₂), 36.4, 35.4, 30.1, 24.9, 23.9, 23.7 (cyclohexyldiene).

CD (MeOH): λ_{max} (Δc) = 296.2 (–1.90), 244.2 (–1.19), 227.0 nm (-0.67).

FAB MS: m/z = 523 [M + Na]^+.

Acknowledgment

GP thanks Director, IICT for financial assistance and support of this work.

References