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

Hari Babu Mereyala,* Gopal Pathuri

Organic Chemistry Division II, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)27193382; E-mail: mereyalahb@rediffmail.com

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] antifungal (plant pathogenic fungi),[6] sweetening[7] and anti-trail pheromonal effects.[1,2,8] 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*.[6] 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 β-D-glucose pentaacetate with propargyl alcohol/$BF_3{\cdot}OEt_2$[14a] and compounds **1b–e** by O-alkylation of the appropriate sugar alcohols with propargyl bromide/NaH.[14b]

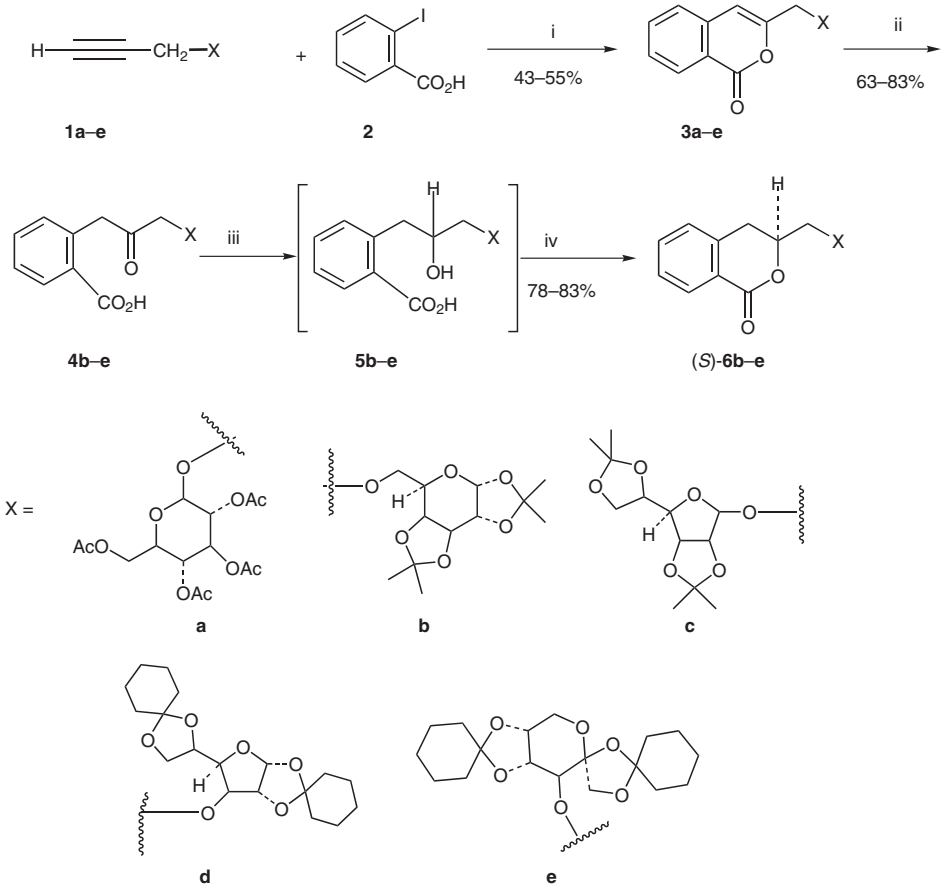
With the required propargyl glycosides in hand, the coupling reaction of propargyl glucoside derivative **1a** with 2-iodobenzoic acid (**2**) was studied. Thus, reaction of **1a** and **2** in presence of $Pd(PPh_3)_4$ (5% mol), $ZnCl_2$ (1 mol equiv) and Et_3N (5 mol equiv) in DMF at 100 °C under nitrogen 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 anomeric proton H-1′ at 4.44

Table 1 Isocoumarin Derivatives **3** Prepared

Entry	Propargyl glycoside	Product	Yield (%)	Mp (°C)	$[\alpha]_D^{27}$
1	**1a**	**3a**	55	114–115	–18.9 (*c* = 0.5, MeOH)
2	**1b**	**3b**	45	syrup	–30.3 (*c* = 0.1, CH_2Cl_2)
3	**1c**	**3c**	44	93–94	+51.2 (*c* = 0.05, CH_2Cl_2)
4	**1d**	**3d**	43	136–138	–28.0 (*c* = 0.1, CH_2Cl_2)
5	**1e**	**3e**	45	134–136	–55.8 (*c* = 1.0, CH_2Cl_2)

SYNTHESIS 2006, No. 17, pp 2944–2950
Advanced online publication: 27.07.2006
DOI: 10.1055/s-2006-942504; Art ID: Z01506SS



Scheme 1 *Reagents and conditions*: (i) $Pd(Ph_3P)_4$ (5 mol%), $ZnCl_2$ (1 equiv), Et_3N (5 equiv), DMF, 100 °C, 8 h; (ii) aq 5% KOH, EtOH, reflux, 4 h; (iii) $NaBH_4$, aq 1% NaOH, r.t., 2 h; (iv) Ac_2O, reflux, 2 h

as a doublet ($J_{1',2'}$ = 9.1 Hz), and ^{13}C NMR spectrum by the appearance of C-1 at δ = 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).[13] The sensitive isopropylidene protecting groups were tolerant of the reaction conditions. The isocoumarin galactoside derivative **3b** was characterized from ^1H NMR spectrum by the appearance of H-4 at δ = 6.63 as a singlet and the anomeric proton H-1′ at 5.51 as a doublet ($J_{1',2'}$ = 3.8 Hz), and ^{13}C NMR spectrum by the appearance of C-1 at δ = 162.2, C-3 at 122.7, C-4 at 103.9, C-1′ at 96.3, and also from IR spectrum by the appearance of carbonyl 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 δ = 5.48 ($J_{1',2'}$ = 3.7 Hz) as a doublet, methylene protons adjacent to carbonyl group at 3.69 (1 H) and 3.55 (1 H) as AB-type doublets (J_{gem} = 12.0 Hz), benzyl protons (2 H) at 3.20 (1 H) and 3.17 (1 H) as AB-type doublets (J_{gem} = 14.0 Hz) and by the appearance of carbonyl 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 twohours to afford the corresponding alcohols **5b–e** in good yields (69–85%).[6a] 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_2O for two hours to isolate the corresponding 3-glycosyloxymethyl-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 δ = 5.45 (d, $J_{1',2'}$ = 3.5 Hz), H-3 as a multiplet at 4.70–4.60, H-4 at 3.20–2.95 as a multiplet, and ^{13}C NMR spectrum from the appearance of C-1 at δ = 164.9, C-1′ at 96.3, and from the lactone carbonyl 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-(hydroxymethyl)-5,7-dimethoxydihydroisocoumarin.[15b] The compounds **6b–e** showed the CD bands at 296–286, 288–277, 244–237, 227–222 and 205–204 nm, with negative sign. The selectivity observed for stereospecific reduction of keto acids could be attributed to the neighboring glycosyl substitution and thus, this methodology has advantages over the existing methods.

In summary, a general synthesis of novel isocoumarin glycosides **3a–e** and (*S*)-3-glycosyloxymethyl-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-glycosyloxymethyl-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 and at 400 MHz on a Unity FT-NMR spectrometer with TMS as an internal standard (chemical shifts in δ, ppm). ^{13}C NMR spectra in $CDCl_3$ were recorded exclusively 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*-cyclohexylidene-3-*O*-(prop-2-ynyl)-α-D-glucofuranoside (1d)

To a solution of 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (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_2O (100 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (2 × 50 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain **1d**; yield: 4.2 g (76%); colorless syrup; $[\alpha]_D^{27}$ +2.0 (*c* = 0.5, CH_2Cl_2).

IR (film): 2118 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.81 (d, $J_{1,2}$ = 3.9 Hz, 1 H, H-1), 4.52 (d, *J* = 3.9 Hz, 1 H, H-2), 4.27 (d, *J* = 1.2 Hz, 2 H, OCH_2), 4.21 (m, 1 H, H-4), 4.15–3.90 (m, 4 H, H-3,5,6,6′), 2.42 (t, *J* = 1.2 Hz, 1 H, C≡CH), 1.75–1.30 (m, 20 H, cyclohexylidene).

ESI MS: *m*/*z* = 401 [M + Na]$^+$, 379 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.64; H, 7.98. Found: C, 66.82; H, 7.89.

1,2:4,5-Di-*O*-cyclohexylidene-3-*O*-(prop-2-ynyl)-α-D-fructopyranoside (1e)

To a solution of 1,2:4,5-di-*O*-cyclohexylidene-α-D-fructopyranose (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_2O (100 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (2 × 50 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain **1e**; yield: 4.1 g (72%); colorless syrup; $[\alpha]_D^{27}$ –38.5 (*c* = 1.00, $CHCl_3$).

IR (film): 2357 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $J_{1,1'}$ = 13.1 Hz, 1 H, H-1), 3.96 (d, *J* = 13.1 Hz, 1 H, H-1′), 3.84 (d, $J_{6,6'}$ = 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), 1.80–1.25 (m, 20 H, cyclohexylidene).

ESI MS: *m*/*z* = 401 [M + Na]$^+$, 379 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.64; H, 7.98. Found: C, 66.83; H, 7.82.

3-[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)]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-tetra-*O*-acetyl)-β-D-glucopyranoside (**1a**; 7.68 g, 18.0 mmol), Et_3N (7.59 g, 75.0 mmol), $Pd(PPh_3)_4$ (0.87 g, 0.75 mmol), and $ZnCl_2$ (2.04 g, 15.0 mmol) under N_2 and heated to 100 °C for 8 h. The mixture was column chromatographed [SiO_2, EtOAc–hexane (1:9)] to isolate **3a**; yield: 4.2 g (55%); colorless solid; mp 114–115 °C; $[\alpha]_D^{27}$ –18.2 (*c* = 0.5, MeOH).

IR (KBr): 1760, 1720 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, $J_{7,8}$ = 7.7 Hz, 1 H, H-8), 7.65 (dd, $J_{6,7}$ = 7.6 Hz, 1 H, H-7), 7.50 (dd, $J_{5,6}$ = 7.7 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, $J_{1',2'}$ = 9.1 Hz, 1 H, H-1′), 4.35–4.25 (m, 1 H, H-6″), 4.15–4.05 (m, 2 H, CH_2O), 3.78–3.70 (m, 1 H, H-5), 2.10, 2.04, 2.00, 1.96 (4 s, 12 H, $OCOCH_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.9, 170.4, 169.7 × 2 (4 × $OCOCH_3$), 162.2 (C-1), 152.5 (C-8a), 136.8 (C-4a), 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 (C-2′,3′,4′,5′,6′), 62.2 (CH_2O), 20.9 × 2, 20.8 × 2 (4 × CH_3).

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

Anal. Calcd for $C_{24}H_{26}O_{12}$: C, 56.92; H, 5.20. Found: C, 57.12; H, 5.11.

3-[6-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyloxymethyl)]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-di-*O*-isopropylidene-6-*O*-(prop-2-ynyl)-α-D-galactopyranoside (**1b**; 4.8 g, 16.1 mmol), Et_3N (8.0 g, 80 mmol), $Pd(PPh_3)_4$ (0.96 g, 0.8 mmol), and $ZnCl_2$ (2.18 g, 16 mmol) under N_2 and heated to 100 °C for 8 h. The mixture was chromatographed [SiO_2, EtOAc–hexane (1:3)] to isolate **3b**; yield: 3.06 g (45%); colorless syrup; $[\alpha]_D^{27}$ –30.3 (*c* = 0.1, CH_2Cl_2).

IR (film): 1731 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, $J_{7,8}$ = 7.5 Hz, 1 H, H-8), 7.67 (dd, $J_{6,7}$ = 7.7 Hz, 1 H, H-7), 7.47 (dd, $J_{5,6}$ = 7.6 Hz, 1 H, H-6), 7.38 (d, *J* = 7.6 Hz, 1 H, H-5), 6.63 (s, 1 H, H-4), 5.51 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H-1′), 4.61 (dd, $J_{3,4}$ = 3.4 Hz, $J_{2,3}$ = 8.5 Hz, 1 H, H-3′), 4.43, 4.35 (AB-type doublet, J_{gem} = 10.5 Hz, 2 H, OCH_2), 4.30–4.20 (m, 2 H, H-2′,4′), 3.97 (m, 1 H, H-5′), 3.85–3.60 (m, 2 H, H-6′,6″), 1.52, 1.41, 1.32, 1.21 [4 s, 12 H, 2 × $(CH_3)_2CO_2$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.2 (C-1), 153.6 (C-8a), 136.8 (C-4a), 134.7, 129.6, 128.1, 125.6 (arom), 122.7 (C-3), 109.3, 108.6 (2 × Me_2CO_2), 103.9 (C-4), 96.3 (C-1′), 71.1, 70.7, 70.5, 69.9, 69.3, 66.9 (C-2′,3′,4′,5′,6′ and CH_2O), 26.0, 25.9, 24.9, 24.4 [2 × $(CH_3)_2CO_2$].

FAB MS: *m*/*z* = 419 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.14; H, 6.26. Found: C, 63.28; H, 6.17.

3-(2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyloxymethyl)isocoumarin (3c)

To a solution of 2-iodobenzoic acid (**2**; 4.0 g, 16.0 mmol) in DMF (16 mL) was added prop-2-ynyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside (**1c**; 4.77 g, 16.0 mmol), Et_3N (8.09 g, 80.0 mmol), $Pd(PPh_3)_4$ (0.93 g, 0.8 mmol), and $ZnCl_2$ (2.18 g, 16.0 mmol) under N_2 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 [SiO_2, EtOAc–hexane (1:19)] to isolate **3c**; yield: 2.96 g (44%); colorless solid; mp 93–94 °C; $[\alpha]_D^{27}$ +51.2 (*c* = 0.5, CH_2Cl_2).

IR (KBr): 1732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, $J_{7,8}$ = 7.5 Hz, 1 H, H-8), 7.70 (t, $J_{7,8}$ = $J_{6,7}$ = 7.5 Hz, 1 H, H-7), 7.50 (t, $J_{6,7}$ = $J_{5,6}$ = 7.5 Hz, 1 H, H-6), 7.40 (d, *J* = 7.5 Hz, 1 H, H-5), 6.44 (s, 1 H, H-4), 5.08 (d, $J_{1',2'}$ = 3.1 Hz, 1 H, H-1′), 4.79 (dd, $J_{2',3'}$ = 3.3 Hz, 1 H, H-2′), 4.66 (dd, $J_{3',4'}$ = 5.5 Hz, 1 H, H-3′), 4.51 (m, 1 H, H-4′), 4.30 (AB-type doublet, J_{gem} = 10.3 Hz, 1 H, OCH_2), 4.10–3.95 (m, 3 H, H-5′,6′,6″), 1.46, 1.38, 1.34, 1.30 [4 s, 12 H, 2 × $(CH_3)_2CO_2$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.0 (C-1), 152.7 (C-8a), 136.5 (C-4a), 134.8, 129.7, 128.5, 125.6 (arom), 120.8 (C-3), 112.8, 109.2 (2 × Me_2CO_2), 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′, CH_2O), 26.8, 25.8, 25.1, 24.5 [2 × $(CH_3)_2CO_2$].

FAB MS: *m*/*z* = 419 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{26}O_8$: C, 62.84; H, 6.71. Found: C, 62.95; H, 6.79.

3-[3-(1,2:5,6-Di-*O*-cyclohexylidene-α-D-glucofuranosyloxymethyl)]isocoumarin (3d)

To a solution of 2-iodobenzoic acid (**2**; 4.0 g, 16.1 mmol) in DMF (16 mL) was added 1,2:5,6-di-*O*-cyclohexylidene-3-*O*-(prop-2-ynyl)-α-D-glucofuranoside (**1d**; 6.1 g, 16.1 mmol), Et_3N (8.09 g, 80 mmol), $Pd(PPh_3)_4$ (0.93 g, 0.8 mmol), and $ZnCl_2$ (2.18 g, 16.0 mmol) under N_2 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 [SiO_2, EtOAc–hexane (1:9)] to isolate **3d**; yield: 3.47 g (43%); white solid; mp 136–138 °C; $[\alpha]_D^{27}$ –28.0 (*c* = 0.1, CH_2Cl_2).

IR (KBr): 1728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, $J_{7,8}$ = 7.7 Hz, 1 H, H-8), 7.72 (t, $J_{7,8}$ = $J_{6,7}$ = 7.7 Hz, 1 H, H-7), 7.52 (t, $J_{6,7}$ = $J_{5,6}$ = 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, $J_{1',2'}$ = 3.7 Hz, 1 H, H-1′), 4.60 (d, *J* = 3.7 Hz, 1 H, H-2′), 4.52, 4.45 (AB-type doublet, J_{gem} = 10.1 Hz, 2 H, OCH_2), 4.35–4.30 (m, 1 H, H-3′), 4.15–4.00 (m, 4 H, H-4′,5′,6′,6″), 1.73–1.35 (m, 20 H, cyclohexylidene).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.9 (C-1), 152.9 (C-8a), 136.6 (C-4a), 134.7, 129.6, 128.3, 125.5 (arom), 120.7 (C-3), 112.6, 109.7 (2 × CO_2), 105.9 (C-1′), 103.4 (C-4), 82.3 × 2, 81.2, 71.8, 68.3, 67.2 (C-2′,3′,4′,5′,6′, CH_2O), 35.6, 34.7, 25.0, 23.4 (cyclohexylidene).

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

Anal. Calcd for $C_{28}H_{33}O_8$: C, 67.59; H, 6.68. Found: C, 67.72; H, 6.73.

3-[3-(1,2:4,5-Di-*O*-cyclohexylidene-α-D-fructopyranosyloxymethyl)]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*-cyclohexylidene-3-*O*-(prop-2-ynyl)-α-D-fructopyranoside (**1e**; 4.5 g, 12.0 mmol), Et_3N (6.00 g, 60.0 mmol), $Pd(PPh_3)_4$ (0.70 g, 0.6 mmol), and $ZnCl_2$ (1.60 g, 12 mmol) under N_2 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 [SiO_2, neat hexane] to isolate **3e**; yield: 2.70 g (45%); colorless solid; mp 134–136 °C; $[\alpha]_D^{27}$ –55.8 (*c* = 1.0, CH_2Cl_2).

IR (KBr): 1737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, $J_{7,8}$ = 7.7 Hz, 1 H, H-8), 7.65 (dd, $J_{6,7}$ = 7.6 Hz, 1 H, H-7), 7.47 (dd, $J_{5,6}$ = 7.8 Hz, 1 H, H-6), 7.35 (d, *J* = 7.8 Hz, 1 H, H-5), 6.52 (s, 1 H, H-4), 4.78, 4.50 (AB-type doublet, J_{gem} = 13.6 Hz, 2 H, OCH_2), 4.35 (dd, $J_{3',4'}$ = 7.2 Hz, $J_{4',5'}$ = 4.8 Hz, 1 H, H-4′), 4.20–4.05 (m, 2 H, H-5′,6′), 4.12 (d, $J_{1',1''}$ = 12.5 Hz, 1 H, H-1′, merged), 3.96 (d, $J_{6',6''}$ = 7.95 Hz, 1 H, H-

1″), 3.91 (d, $J_{6',6''}$ = 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).

^{13}C 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_2O), 38.0, 36.5, 35.4, 24.9, 23.8, 23.6 (cyclohexylidene).

FAB MS: m/z = 521 [M + Na].

Anal. Calcd for $C_{28}H_{33}O_8$: C, 67.18; H, 7.24. Found: C, 67.27; H, 7.16.

2[3-{6-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl)-2-oxopropyl)}]benzoic Acid (4b)

To a solution of **3b** (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 (90 mL), and extracted with CH_2Cl_2 (2 × 40 mL) and EtOAc (2 × 25 mL). The combined organic phases were washed with H_2O (2 × 20 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain the title compound **4b**; yield: 2.82 g (84%); colorless syrup; $[\alpha]_D^{27}$ –23.4 (c = 0.25, $CHCl_3$).

IR (KBr): 1725, 1693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, $J_{5,6}$ = 7.1 Hz, 1 H, H-6), 7.51 (dd, $J_{4,5}$ = 7.2 Hz, 1 H, H-5), 7.40 (dd, $J_{3,4}$ = 7.1 Hz, 1 H, H-4), 7.18 (d, J = 7.4 Hz, 1 H, H-3), 5.48 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, H-1′), 4.59 (m, 1 H, H-3′), 4.40–3.70 (m, 5 H, H-2′,4′,5′,6′,6″), 3.69, 3.55 (AB-type doublet, J_{gem} = 12.0 Hz, 2 H, OCH_2CO), 3.20, 3.17 (AB-type doublet, J_{gem} = 14.0 Hz, 2 H, $C_6H_5CH_2$), 1.56, 1.51, 1.48, 1.43 [4 s, 12 H, 2 × $(CH_3)_2CO_2$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.7 (C=O), 165.1 (CO_2H), 136.3, 133.6, 130.1, 129.0, 127.3, 127.2 (arom), 109.1, 108.2 (2 × Me_2CO_2), 96.1 (C-1′), 71.0, 70.7 × 2, 70.5, 70.3, 66.8 (C-2′,3′,4′,5′,6′, OCH_2CO), 36.2, 25.9, 25.8, 24.8, 24.3 [PhCH_2CO, × $(CH_3)_2CO_2$].

ESI MS: m/z = 459 [M + Na]$^+$, 437 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{21}O_9$: C, 60.54; H, 6.47. Found: C, 60.67; H, 6.38.

2[3-{1-(2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl)-2-oxopropyl)}]benzoic Acid (4c)

To a solution of **3c** (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 reaction, the mixture was cooled to r.t., acidified with 10% aq HCl (90 mL), and extracted with CH_2Cl_2 (2 × 40 mL) and EtOAc (2 × 25 mL). The combined organic phases were washed with H_2O (2 × 20 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain the title compound **4c**; yield: 2.52 g (75%); colorless syrup; $[\alpha]_D^{27}$ +12.0 (c = 0.25, CH_2Cl_2).

IR (film): 3416, 1739, 1688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, $J_{5,6}$ = 7.5 Hz, 1 H, H-6), 7.55–7.15 (m, 3 H, H-3,4,5), 5.10–5.04 (2 d, $J_{1',2'}$ = 3.8 Hz, 1 H, H-1′), 4.95–4.25 (m, 5 H, H-2′,3′,4′-OCH_2CO), 4.10–3.80 (m, 3 H, H-5′,6′,6″), 3.30–2.95 (m, 2 H, PhCH_2CO), 1.45 × 2, 1.34, 1.25 [4 s, 12 H, 2 × $(CH_3)_2CO_2$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.1 (C=O), 165.8 (CO_2H), 136.9, 130.6, 130.2, 127.4 × 2 (arom), 112.7, 109.2 (2 × Me_2CO_2), 106.3 (C-1′), 84.7, 80.3, 79.2, 73.0, 71.2, 66.4 (C-2′, 3′, 4′, 5′, 6′, OCH_2CO), 29.5, 26.6, 25.7, 25.0, 24.3 [PhCH_2CO, 2 × $(CH_3)_2CO_2$].

ESI MS: m/z = 459 [M + Na]$^+$, 437 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{28}O_9$: C, 60.54; H, 6.47. Found: C, 60.73; H, 6.55.

2[3-(1,2:5,6-Di-*O*-cyclohexylidene-α-D-glucofuranosyl)-2-oxopropyl]benzoic Acid (4d)

To a solution of **3d** (3.08 g, 6.2 mmol) in EtOH (132 mL) was added 5% aq KOH (220 mL) and the mixture was refluxed for 4 h. Progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled to r.t., acidified with 10% aq HCl (176 mL), and extracted with CH_2Cl_2 (2 × 30 mL) and EtOAc (2 × 25 mL). The combined organic phases were washed with H_2O (2 × 50 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain the title compound **4d**; yield: 2.64 g (83%); colorless solid; mp 145–147 °C; $[\alpha]_D^{27}$ –16.0 (c = 0.25, CH_2Cl_2).

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

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, $J_{5,6}$ = 7.2 Hz, 1 H, H-6), 7.58 (dd, $J_{4,5}$ = 7.1 Hz, 1 H, H-5), 7.42 (dd, $J_{3,4}$ = 7.2 Hz, 1 H, H-4), 7.18 (dd, J = 7.2 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_2CO), 3.20–2.90 (m, 2 H, PhCH_2), 1.85–1.30 (m, 20 H, cyclohexylidene).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.9 (C=O), 164.3 (CO_2H), 136.0, 133.8, 130.2, 129.9, 128.5, 127.4 (arom), 112.7, 110.2 (2 × CO_2), 105.1 (C-1′), 82.1 × 2, 81.4 × 2, 72.5, 67.3 (C-2′,3′,4′,5′,6′, OCH_2CO), 36.4, 36.2, 35.6, 34.3, 24.8, 24.7, 23.7 × 2 (cyclohexylidene, PhCH_2CO).

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

Anal. Calcd for $C_{28}H_{36}O_9$: C, 65.10; H, 7.02. Found: C, 65.32; H, 7.09.

2[3-(1,2:4,5-Di-*O*-cyclohexylidene-α-D-fructopyranosyl)-2-oxopropyl]benzoic Acid (4e)

To a solution of **3e** (2.30 g, 4.6 mmol) in EtOH (90 mL) was added 5% aq KOH (180 mL), and the mixture was refluxed for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled to r.t., acidified with 10% aq HCl (120 mL), and extracted with CH_2Cl_2 (2 × 25 mL) and EtOAc (2 × 25 mL). The combined organic phases were washed with H_2O (2 × 50 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain the title compound **4e**; yield: 1.51 g (63%); colorless solid; mp 140–142 °C, $[\alpha]_D^{27}$ –32.4 (c = 0.25, $CHCl_3$).

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

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, $J_{5,6}$ = 7.4 Hz, 1 H, H-6), 7.51 (dd, $J_{4,5}$ = 7.2 Hz, 1 H, H-5), 7.42 (dd, $J_{3,4}$ = 7.4 Hz, 1 H, H-4), 7.18 (d, 1 H, H-3), 4.50–3.50 (m, 9 H, H-1′,1″, 3′, 4′, 5′,6′,6″, OCH_2CO), 3.20–2.90 (m, 2 H, PhCH_2CO), 1.85–1.30 (m, 20 H, cyclohexylidene).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.7 (C=O), 164.1 (CO_2H), 136.3, 133.7, 130.0, 128.3, 127.4 × 2 (arom), 112.6, 110.0 (2 × CO_2), 103.6 (C-2′), 76.4, 75.9, 75.6, 73.2, 71.4, 60.6 (C-1′, 3′, 4′, 5′, 6′, OCH_2CO), 37.7, 35.2, 24.9, 24.8, 23.8, 23.6 (cyclohexylidene, PhCH_2CO).

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

Anal. Calcd for $C_{28}H_{36}O_9$: C, 65.10; H, 7.02. Found: C, 65.32; H, 7.09.

(*S*)-3-[6-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl-oxymethyl)]-3,4-dihydroisocoumarin (6b)

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_2O (2 × 15 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain **5b** (1.05 g, 80) as a syrup. A solution of

5b (0.9 g, 2 mmol) in Ac_2O (2 mL) was refluxed for 2 h. After completion of the reaction, the mixture was cooled, H_2O (10 mL) was added, stirred for 15 min, and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with H_2O, dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain the title compound **6b**; yield: 0.7 g (81%); colorless syrup; $[\alpha]_D^{27}$ –46.0 (*c* = 0.25, CH_2Cl_2).

IR (film): 1724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, $J_{7,8}$ = 7.7 Hz, 1 H, H-8), 7.50 (dd, $J_{6,7}$ = 7.8 Hz, 1 H, H-7), 7.37 (dd, $J_{5,6}$ = 7.7 Hz, 1 H, H-6), 7.23 (d, *J* = 7.7 Hz, 1 H, H-5), 5.45 (d, $J_{1',2'}$ = 3.5 Hz, 1 H, H-1′), 4.65 (m, 1 H, H-3), 4.55 (dd, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = 3.2 Hz, 1 H, H-4′), 4.23 (m, 1 H, CH_2O), 3.95–3.60 (m, 5 H, H-2′,3′,5′,6′,6″), 3.20–2.95 (m, 2 H, H-4), 1.52, 1.41, 1.31, 1.24 [4 s, 12 H, 2 × $(CH_3)_2CO_2$].

^{13}C NMR (50 MHz, $CDCl_3$): 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 × Me_2CO_2), 96.3 (C-1′), 71.1, 70.6 × 2, 70.5 × 2, 67.0 (C-2′,3′,4′,5′,6′, C-3, CH_2O), 36.7 (PhCH_2) 26.1, 25.9, 24.9, 24.4 [2 × (CH_3)$_2CO_2$].

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

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

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.89; H, 6.68.

(*S*)-3-[1-(2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyloxymethyl)]-3,4-dihydroisocoumarin (6c)

To a solution of **4c** (1.6 g, 3.7 mmol) in 1% aq NaOH (45 mL) was added $NaBH_4$ (0.4 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 × 30 mL). The combined organic phases were washed with H_2O (2 × 20 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to give **5c**; yield: 1.0 g (69%); colorless syrup. A solution of **5c** (0.8 g, 1.8 mmol) in Ac_2O (2 mL) was refluxed for 2 h. After completion of the reaction, the mixture was cooled to 15 °C, H_2O (10 mL) was added, stirred for 15 min, and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with H_2O (2 × 10 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to afford a residue (1.24 g) that was column chromatographed [SiO_2, EtOAc–hexane (1:4)] to isolate the title compound **6c**; yield: 0.6 g (78%); colorless syrup; $[\alpha]_D^{27}$ +23.5 (*c* = 1.0, $CHCl_3$).

IR (film): 1726 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, $J_{7,8}$ = 7.4 Hz, 1 H, H-8), 7.54 (dd, $J_{6,7}$ = 7.6 Hz, 1 H, H-7), 7.40 (dd, $J_{5,6}$ = 7.7 Hz, 1 H, H-6), 7.20 (d, *J* = 7.7 Hz, 1 H, H-5), 5.01 (d, $J_{1',2'}$ = 2.3 Hz, 1 H, H-1′), 4.78 (m, 1 H, H-2′), 4.68 (m, 1 H, H-3), 4.56–4.08 (m, 3 H, H-3′,4′,5′), 4.00–3.80 (m, 3 H, H-6′, CH_2O), 3.72 (m, 1 H, H-6″), 3.10–2.96 (m, 2 H, H-4), 1.45, 1.41, 1.37, 1.32 [4 s, 12 H, 2 × $(CH_3)_2CO_2$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.7 (C-1), 138.3 (C-8a), 133.8, 130.3, 127.7, 127.4 (arom), 124.5 (C-4a), 112.8, 109.2 (2 × Me_2CO_2), 106.8 (C-1′), 84.9, 80.9, 79.4, 76.5, 73.1, 68.2, 66.8 (C-2′,3′,4′,5′,6′, C-3, CH_2O), 35.8 (PhCH_2), 26.8, 25.9, 25.2, 24.5 [2 × (CH_3)$_2CO_2$].

CD (MeOH): λ_{max} (Δε) = 281.3 (–0.60), 237.5 (–1.25), 222.0 (–1.70), 205.2 nm (–3.10).

FAB MS: *m*/z = 443 $[M + Na]^+$, 421 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 63.04; H, 6.62.

(*S*)-3-[(1,2:5,6-Di-*O*-cyclohexylidene-α-D-glucofuranosyloxymethyl)]-3,4-dihydroisocoumarin (6d)

To a solution of **4d** (1.0 g, 2 mmol) in 1% aq NaOH (30 mL) was added $NaBH_4$ (0.2 g) at 0 °C. The mixture was stirred for 2 h at r.t. and acidified with 10% aq HCl (80 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with H_2O (2 × 20 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to give **5c** (0.8 g, 79.6%) as a syrup. A solution of **5d** (0.5 g, 1 mmol) in Ac_2O (1 mL) was refluxed for 2 h. After completion of the reaction, the mixture was cooled to r.t., H_2O (1 mL) was added, stirred for 15 min and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with H_2O (2 × 10 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain the crude compound (0.82 g). The crude compound **6d** was filtered on silica gel column to obtain the title compound **6d**; yield: 0.4 g (83%); syrup; $[\alpha]_D^{27}$ +4.9 (*c* = 0.75, $CHCl_3$).

IR (film): 1727 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, $J_{7,8}$ = 7.7 Hz, 1 H, H-8), 7.51 (dd, $J_{6,7}$ = 7.8 Hz, 1 H, H-7), 7.38 (dd, $J_{5,6}$ = 7.7 Hz, 1 H, H-6), 7.21 (d, 1 H, H-5), 5.81 (d, $J_{1',2'}$ = 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, H-3′,4′,5′,6′, CH_2O), 3.25 (dd, J_{gem} = 14.2 Hz, $J_{3,4}$ = 6.8 Hz, 1 H, H-4), 2.95 (dd, $J_{3,4'}$ = 3.0 Hz, 1 H, H-4), 1.70–1.20 (m, 20 H, cyclohexylidene).

^{13}C NMR (50 MHz, $CDCl_3$): 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 × CO_2), 104.9 (C-1′), 83.5, 83.3, 82.4, 81.4, 72.0, 71.6, 67.4 (C-2′,3′,4′,5′,6′, CH_2O, C-3), 36.5 (PhCH_2), 29.9, 29.6, 24.9, 23.9, 23.6 (cyclohexylidene).

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

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

Anal. Calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.24. Found: C, 67.38; H, 7.15.

(*S*)-3-[(1,2:4,5-Di-*O*-cyclohexylidene-α-D-fructopyranosyloxymethyl)]-3,4-dihydroisocoumarin (6e)

To a solution of **4e** (0.7 g, 1.4 mmol) in 1% aq NaOH (30 mL) was added $NaBH_4$ (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 × 30 mL). The combined organic phases were washed with H_2O (2 × 20 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to afford **5e** (0.6 g, 85%) as a syrup. A solution of **5e** (0.5 g, 1 mmol) in Ac_2O (1 mL) was refluxed for 2 h. After completion of the reaction, the mixture was cooled to r.t., H_2O (1 mL) was added, stirred for 15 min and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with H_2O (2 × 10 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to obtain the title compound **6e**; yield: 0.4 g (83%); solid; mp 119–120 °C; $[\alpha]_D^{27}$ –58.0 (*c* = 0.25, CH_2Cl_2).

IR (KBr): 1730 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, $J_{7,8}$ = 7.5 Hz, 1 H, H-8), 7.51 (dd, $J_{6,7}$ = 7.7 Hz, 1 H, H-7), 7.35 (dd, $J_{5,6}$ = 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, H-1′,1″,3′,4′,5′,6′,6″, OCH_2CO), 3.45 (dd, J_{gem} = 13.0 Hz, *J* = 10.2 Hz, 1 H, OCH_2), 3.10–2.90 (m, 2 H, PhCH_2), 1.80–1.10 (m, 20 H, cyclohexylidene).

^{13}C NMR (50 MHz, $CDCl_3$): 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 × CO_2), 103.8 (C-2′), 76.9, 76.5, 73.4, 72.5, 71.4, 72.1 (C-1′,3′,4′,5′,6′, CH_2O, C-3), 38.0 (PhCH_2), 36.4, 35.4, 30.1, 24.9, 23.9, 23.7 (cyclohexylidene).

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

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

Anal. Calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.24. Found: C, 67.38; H, 7.15.

Acknowledgment

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

References

(1) (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*, Vol. 1; Academic Press: New York, **1975**, 249. (b) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*, Vol. 1; Academic Press: New York, **1975**, 383. (c) Inubushi, Y.; Tsuda, Y.; Konita, T.; Matsumoto, S. *Chem. Pharm. Bull. Jpn.* **1964**, *12*, 749. (d) Inouye, H.; Okuda, T.; Hirata, Y.; Nagakura, N.; Yoshizaki, M. *Chem. Pharm. Bull. Jpn.* **1967**, *15*, 786. (e) Elander, M.; Leander, K.; Luning, B. *Acta Chem. Scand.* **1969**, *23*, 2177. (f) Pushan, W.; Xuanliang, G.; Yixiong, W.; Fukuyama, Y.; Miura, I.; Sugawara, M. *Phytochemistry* **1984**, *23*, 2033.

(2) (a) Hill, R. A. *Prog. Chem. Org. Nat. Prod.* **1986**, *49*, 1. (b) Mclnerney, B. V.; Taylor, W. C. *Studies in Natural Products Chemistry*, Vol. 15; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1995**, 381.

(3) (a) Barrero, A. F.; Oltra, J. E.; Herrador, M. M.; Sanchez, J. F.; Quilez, J. F.; Rojas, F. J.; Reyes, J. F. *Tetrahedron* **1993**, *49*, 141. (b) Abraham, W. R.; Arfmann, H. A. *Phytochemistry* **1988**, *27*, 3310.

(4) Itoh, J.; Omoto, S.; Nishizawa, N.; Kodma, Y.; Inouye, S. *Agric. Biol. Chem.* **1982**, *46*, 2659.

(5) Kumagai, H.; Masuda, T.; Osono, M.; Hattori, S.; Naganawa, H.; Sawa, T.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 1505.

(6) (a) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K. I.; Nakajima, S. *Chem. Pharm. Bull.* **1981**, *29*, 2491. (b) Engelmeier, D.; Hadacek, F.; Hofer, O.; Lutz-Kutschera, G.; Nagl, M.; Wurz, G.; Greger, H. *J. Nat. Prod.* **2004**, *67*, 19.

(7) (a) Asahina, Y.; Asano, J. *Yakugaku Zasshi* **1930**, *50*, 573; *Chem. Abstr.* **1930**, *24*, 3008. (b) Kaneko, H.; Fujimori, H.; Matsushita, H.; Noguchi, M. *Nippon Nogei-Kagaku Kaishi* **1973**, *47*, 605; *Chem. Abstr.* **1974**, *80*, 93153s. (c) Arakawa, H. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 200. (d) Yagi, A.; Washida, Y.; Takata, N.; Nishioka, I. *Chem. Pharm. Bull. Jpn.* **1972**, *20*, 1755.

(8) Bestmann, H. J.; Kern, F.; Schafer, D.; Witschel, M. C. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 795; *Angew. Chem.* **1992**, *104*, 757.

(9) (a) Takeo, Y.; Ryoichi, M.; Hiroshi, T.; Rokuro, O.; Hiroyuki, K.; Masaaki, I.; Tomio, T. Japan Kokai Tokkyo Koho JP 04112884, **1992**; *Chem. Abstr.* **1992**, *117*, 171087. (b) Shinichi, H.; Yutak, H.; Hiroshi, I.; Hiroshi, N.; Rokuro, O.; Hiroyuki, K.; Masaaki, I.; Tomio, T. Japan Kokai Tokkyo Koho JP 06183966, **1992**; *Chem. Abstr.* **1994**, *121*, 246307.

(10) (a) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M.; Iitaka, Y. *Tetrahedron Lett.* **1982**, *23*, 5435. (b) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Agric. Biol. Chem.* **1982**, *46*, 1823. (c) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Tetrahedron* **1984**, *40*, 2519.

(11) (a) Hashimito, T.; Tori, M.; Asakawa, Y. *Phytochemistry* **1987**, *12*, 3323. (b) Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *J. Org. Chem.* **1996**, *61*, 5371.

(12) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345. (c) Heck, R. F. *Chem. Soc. Rev.* **1979**, *12*, 146. (d) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (f) Bourisson, D.; Guerret, O.; Gabbai, F. P.; Betrand, G. *Chem. Rev.* **2000**, *100*, 39. (g) Tang, S.; Liang, Y.; Liu, W.-J.; Li, J.-H. *Chin. J. Org. Chem.* **2004**, *24*, 1133. (h) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711. (i) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86. (j) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

(13) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711.

(14) (a) Mereyala, H. B.; Gurrala, S. R. *Carbohydr. Res.* **1998**, *307*, 351. (b) Rochet, P.; Vatele, J.-M.; Gore, J. *Synthesis* **1994**, 795.

(15) (a) Sandor, A.; Gunther, S.; Iris, S. *Liebigs Ann. Chem.* **1983**, 2247. (b) Salvadori, P.; Superchi, S.; Minutolo, F. *J. Org. Chem.* **1996**, *61*, 4190.