# Exploiting enzymatic regioselectivity: a facile methodology for the synthesis of polyhydroxylated hybrid compounds†

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Polyhydroxylated hybrid molecules have been synthesized using a protocol based on the regioselective acylation of the target compounds with activated dicarboxylic acids catalyzed by Novozym-435. The procedure implies that the mixed ester derivatives prepared and isolated from the first esterification step act as acylating agents in the second esterification step.



## Introduction

In recent years different authors have explored the biological activity of hybrid compounds obtained by linking—*via* a suitable dicarboxylic acid—naturally occurring bioactive molecules. The rationale behind this approach is that these new hybrid molecules might have additive activities, as in the case of the so-called "dual-drug" strategy.[1] This can impart enhanced properties or efficacy relative to the equivalent physical combination and improve the therapeutic index (for instance, by linking podophyllotoxin and vinorelbine,[2] both acting on microtubules but with different mechanisms).[3] The same methodology can be applied to convey a drug to a given area of the body *via* conjugation with a molecule recognized by a specific receptor (*i.e.*, by linking the anticancer paclitaxel to 3,17-β-estradiol,[4] an estrogen that interacts with receptors on breast cancer cells). It has also been shown that the use of dicarboxylated linkers containing a disulfide bridge allows the synthesis of dynamic libraries of dimeric hybrids based on disulfide exchange reactions.[5] For instance, reduced glutathione in the cells could secure reduction of the disulfide bond, with subsequent release of the chemotherapeutic agents by nucleophilic attack of the thiol group (thiolate anion) at the ester function with formation of a thiolactone.[5b]

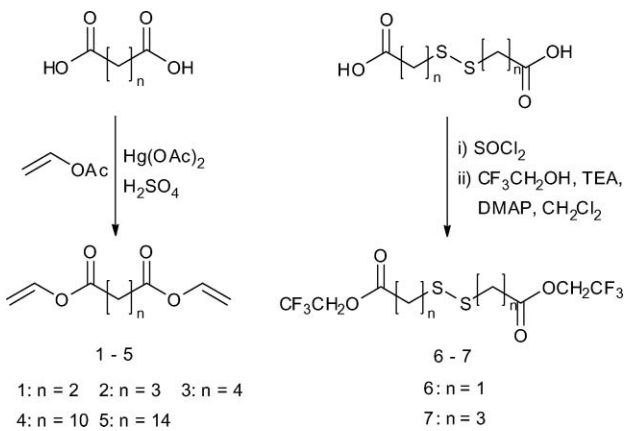
Moreover, in a completely different research area, it has been shown that polyhydroxylated molecules linked *via* a dicarboxylic chain (like the vitamin C-based bolaamphiphiles[6]) are capable of self-aggregation, giving origin to regular supramolecular structures.

All these compounds have been prepared using (sometimes troublesome) chemical protocols that require protection/deprotection steps and rigorous control of the reaction conditions. The structural complexity and inherent "fragility" of these molecules make them ideal substrates for a biocatalyzed approach, exploiting the regioselectivity of lipases and proteases suspended in organic solvents.[7] Different authors have shown that activated dicarboxylates (*i.e.*, divinyl adipate) are accepted by these enzymes as acyl donors. Specifically, in a pioneer work, Dordick and coworkers showed that divinyl adipate could be used to link paclitaxel and glucose in a two-step thermolisin-catalyzed acylation.[8] Similarly, Lin and coworkers allowed simple polyhydroxylated bioactive molecules or the nucleoside 5-fluorouridine to react with divinyl dicarboxylates.[9] The monovinyl esters obtained were then used either as co-monomers in AIBN-catalyzed polymerizations or as donors to acylate simple monosaccharides (galactose, glucose, or other sugars) in order to increase the solubility in water solutions.

Herein, we show that lipases' regioselectivity can be efficiently exploited to link together any kind of natural molecule carrying a nucleophilic group (obviously accessible by the enzyme active site) *via* diesters bridges of different lengths and nature. Specifically, for the first time, we show also that activated esters of dithio dicarboxylic acids are well-accepted acyl donors, thus offering a simple and efficient two-step synthetic approach to dynamic libraries of bioactive compounds.

## Results and discussion

As shown in Scheme 1, five different divinyl esters (**1–5**) and two different ditrifluoroethyl esters (**6–7**) were synthesized, following classical procedures.[10]




**Scheme 1** Synthesis of activated diesters.

Novozym®435 (the well-known immobilized preparation of the lipase B from *Candida antarctica*), one of the most popular enzymes among organic chemists, was the biocatalyst of choice for its well-known regioselectivity.[11]

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† Electronic supplementary information (ESI) available: Additional experimental details, spectroscopic data, $^{1}$H- and $^{13}$C NMR spectra of all new compounds are provided. See DOI: 10.1039/c0ob00304b

Phenyl β-D-glucopyranoside (**8**) and benzyl α-D-mannopyranoside (**9**, Fig. 1) were selected as model substrates and the corresponding conjugate compounds **25–29** (Fig. 3) were prepared using the general two-step protocol reported in Scheme 2 (where $R_1OH$ and $R_2OH$ take the place of the selected polyhydroxylated substrates).

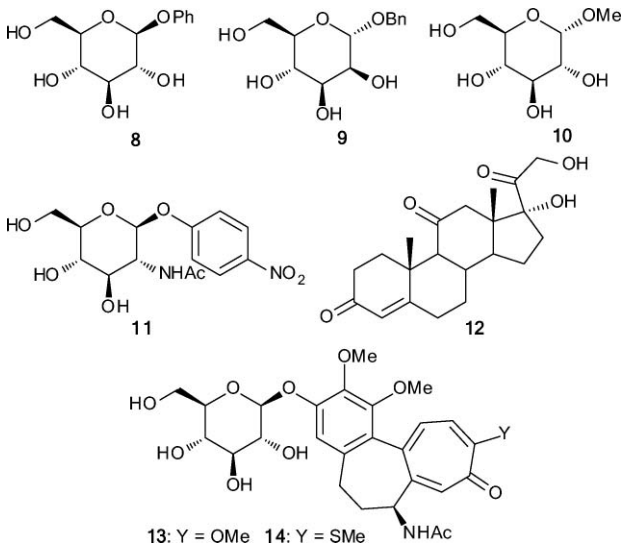
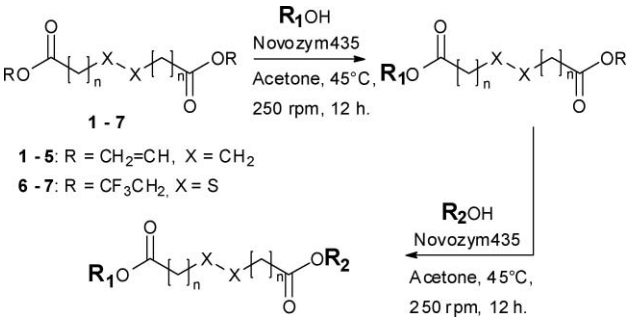



**Fig. 1** Polyhydroxylated substrates.

This procedure implies that the monoester intermediates (*i.e.*, **15–24**, Fig. 2) prepared and isolated from the first esterification step might act as acylating agents in the second esterification step, the lipase showing in both cases high regioselective control in the formation of the desired hybrid molecules. This was indeed the case, and, additionally, as expected, the isolated yield of the final




**Scheme 2** General two-steps synthetic protocol.

conjugated compounds **25–29** were not dependent on the choice of the first glycoside to be attached (**8** or **9**).

Compounds **25–34** were isolated in good to moderate yields as summarized in Table 1 (reactions were performed under similar conditions and not optimized for all the substrates) and fully characterized by mass spectrometry (thus confirming the formation of the hybrid molecules) and NMR analysis, which unambiguously showed the expected regioselective acylation at the primary OH's of the two sugar units (for details, see the ESI†).

In order to investigate the scope of the proposed procedure, other glycosides (methyl α-D-glucopyranoside, **10**; *p*-nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranoside, **11**) and some bioactive model compounds (cortisone, **12**; colchicoside, **13**; thiocolchicoside, **14**) were considered as substrates and subjected to the same reaction protocol shown in Scheme 2.

Fig. 3 summarizes the various conjugate products obtained. All the structures were deduced by $^{1}$H-, $^{13}$C-NMR and MS analysis, thus confirming the flexibility and simplicity of this two-steps enzymatic strategy. Specifically, the hybrid compounds **33** and **34**

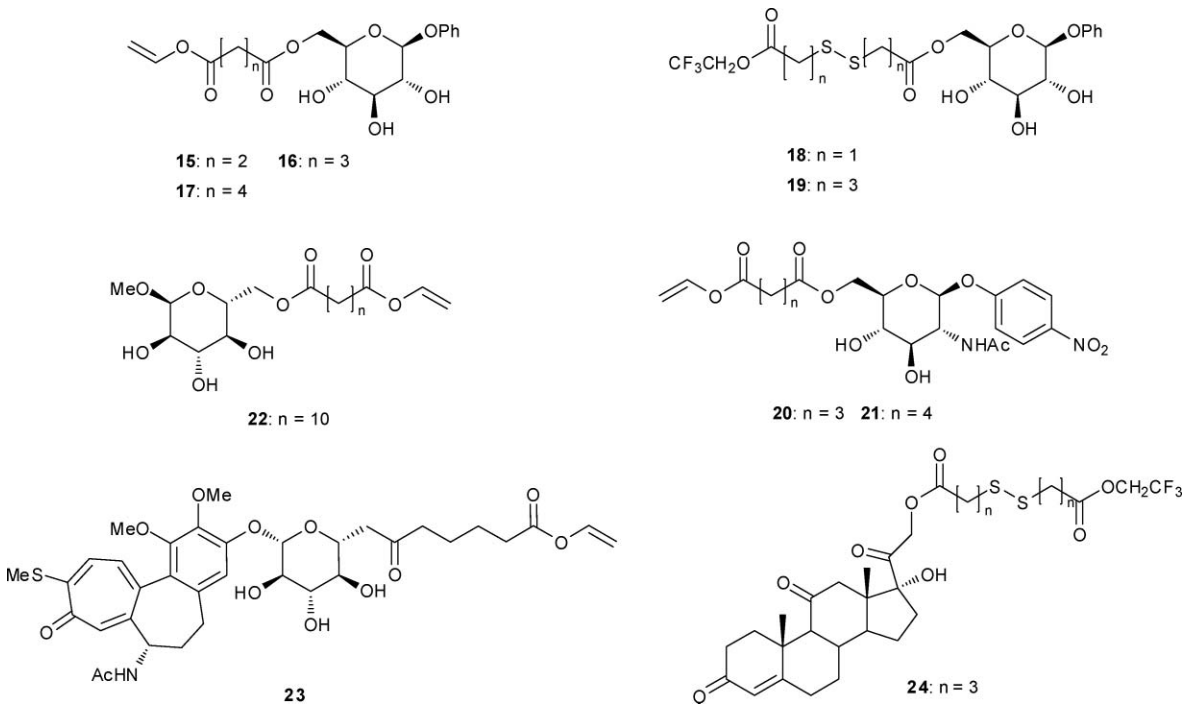



**Fig. 2** Intermediate activated monoesters obtained from the first esterification step.

**Table 1** Reaction yields for the hybrid compounds **25–34**

| Compound | Isolated yield (%): first step (**15–24**) | Isolated yield (%): second step |
|---|---|---|
| **25** | 33[a] | 61 |
| **26** | 68[a] | 48 |
| **27** | 72[a] | 70 |
| **28** | 47[a] | 42 |
| **29** | 37[a] | 63 |
| **30** | 96[b] | 35 |
| **31** | 83[b] | 57 |
| **32** | 89[c] | 32 |
| **33** | 72[d] | 63 |
| **34** | 54[e] | 31 |

[a] Relative to reaction with substrate **8**. [b] Relative to reaction with substrate **11**. [c] Relative to reaction with substrate **10**. [d] Relative to reaction with substrate **14**. [e] Relative to reaction with substrate **12**.

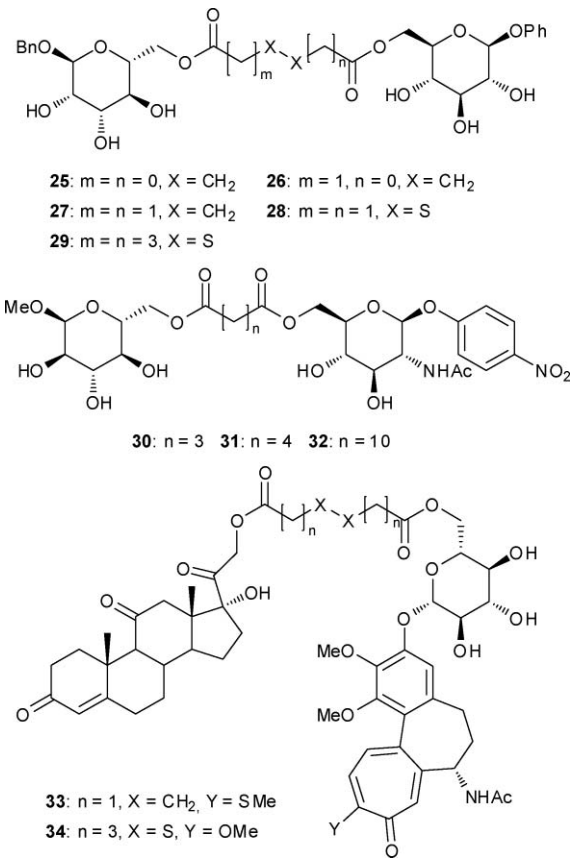



**Fig. 3** Novel hybrid compounds.

were designed to combine into a single structure two molecules associated with a potent anti-inflammatory activity.

Work is in progress to evaluate the self-aggregation properties of compounds **25–32** as well as the possibility of using them as substrates (acting both as donors and acceptors) for the glycosidases-catalyzed formation of intramolecular glycosidic bonds. Finally, the approach described here for the preparation of dynamic libraries of hybrid bioactive molecules (*i.e.*, **33–34**) is being applied to the design and synthesis of novel releasable compounds as potential anticancer and *anti*-angiogenesis agents. The results will be reported in due course.

## Conclusions

In summary, the present protocol describes a general and efficient two-step access to novel polyhydroxylated conjugated compounds based on enzymatic regioselective acylation of natural molecules with activated dicarboxylates, including activated esters of dithio dicarboxylic acids.

## Experimental

### General information

All chemicals were obtained from commercial sources (Aldrich) and used without further purification. All solvents were of reagent grade or HPLC grade. Novozym® 435 (immobilized lipase from *Candida antarctica*) was a gift from Novozymes Inc. Thin-Layer Chromatography (TLC) analysis were performed on precoated silica gel 60 $F_{254}$ plates (Merck) and treated with the molybdate reagent ($(NH_4)_6MoO_{24}\cdot 4H_2O$, 42 g; $Ce(SO_4)_2$, 2 g; $H_2SO_4$ concentrated 62 mL; made up to 1 L with deionized water) or $KMnO_4$ (0.5 g in 100 mL of NaOH 1M) or UV light (254 and 366 nm). Flash chromatography was performed using silica gel 60 (70–230 mesh, Merck). Molecular sieves (4 Å, beads, 8–12 mesh) were preactivated at *ca.* 150 °C for 3 days. The $^1H$ NMR and $^{13}C$ NMR spectra were recorded at the specified field strength and in the solvent indicated using standard pulse techniques on Bruker 300, 400, or 500 MHz and Varian Mercury 300 MHz spectrometers at ambient temperatures. Chemical shifts ($\delta$) were expressed in parts per million (ppm) and were referenced to TMS or the residual solvent peak. Coupling constants ($J$) are quoted to the nearest 0.1 Hertz (Hz). Assignments of signals were made using COSY, DEPT, APT, HMQC and HMBC experiments where necessary. EI and FAB mass spectra were recorded at an ionizing voltage of 6 keV on a VG 70–70 EQ instrument.

### General procedure for the synthesis of divinyl esters (1–5)[10]

A solution of the suitable dicarboxylic acid (0.1 mol) and $Hg(OAc)_2$ (0.8 g) in vinyl acetate (75 mL) was stirred under nitrogen flow at r.t. and fuming $H_2SO_4$ (50 μL) was carefully added dropwise. The reaction mixture was then heated under reflux for 4 h. After cooling to r.t., $NaOAc\cdot 3H_2O$ (0.3 g) was added portionwise and the mixture was then concentrated under reduced pressure. The crude product was purified by distillation or silica gel column chromatography.

### General procedure for the synthesis of ditrifluoroethyl esters (6–7)

A solution of the suitable dithiodicarboxylic acid (0.1 mol) in thionyl chloride (75 mL) was stirred under nitrogen at r.t for 20 h. After evaporation under reduced pressure, the residue was immediately added dropwise to a solution of TEA (0.22 mol), DMAP (75 mg) and 2,2,2-trifluoroethanol (0.24 mol) in $CH_2Cl_2$ (127 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then was kept at r.t. for 2.5 h. The precipitate was filtered off and the filtrate was washed with water (1 × 30 mL), $NaHCO_3$ sat. solution (1 × 30 mL), and water (1 × 30 mL). The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography.

**Ditrifluoroethyl dithiodiglycolate (6)**

Yellow oil (79% yield). $R_f$ 0.38 [PetEt/EtOAc (95 : 5)] (TLC detection by $KMnO_4$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 3.67 (4H, s, $CH_2S$) 4.76 (4H, q, $J$ = 8.5 Hz, $CH_2O$). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 41.38 ($CH_2S$) 61.95 (q, $J$ = 35.3 Hz, $CH_2O$) 124.56 (q, $J$ = 275.0 Hz, $CF_3$) 169.57 (C═O). EI$^+$-MS ($m/z$) 346 [M]$^+$.

**Ditrifluoroethyl dithiodibutyrate (7)**

Orange oil (84% yield). $R_f$ 0.41 [PetEt/EtOAc (95 : 5)] (TLC detection by $KMnO_4$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 2.04–2.08 (4H, m) 2.56 (4H, t, $J$ = 7.3 Hz) 2.72 (4H, $J$ = 7.0 Hz) 4.47 (4H, q, $J$ = 8.5 Hz, $CH_2O$). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 25.43 ($CH_2$) 32.98 ($CH_2$) 38.51 ($CH_2S$) 61.41 (q, $J$ = 35.3 Hz, $CH_2O$) 124.94 (q, $J$ = 276.7 Hz, $CF_3$) 173.10 (C═O). EI$^+$-MS ($m/z$) 402 [M]$^+$.

**General two-step procedure for the synthesis of compounds (15–34)**

To a solution of substrate $R_1OH$ (1 mmol) and activated diester (5 mmol) in pure acetone (20 mL), molecular sieves (beads, 4 Å, 8–12 mesh, 1 g) and Novozym®435 (150 mg) were added. The suspension was kept at 45 °C and shaken at 250 rpm for 12 h. The reaction was monitored by TLC and terminated by filtering off the enzyme. The filtrate was concentrated under reduced pressure and the product was isolated by silica gel column chromatography. The monoester and the second substrate $R_2OH$ were then subjected to the same reaction conditions (using a 1 : 1 molar ratio of the two reagents) to give the final product.

**6-*O*-(Phenyl β-D-glucopyranosyl) vinylsuccinate (15)**

The general procedure outlined above was followed, starting from phenyl β-D-glucopyranoside (196 mg, 0.764 mmol) and divinyl succinate **1** (650 mg, 3.82 mmol), obtaining pure **15** (95 mg) in 33% yield after purification by silica gel column chromatography (eluent: EtOAc). The TLC of the crude reaction showed a complete conversion of the starting material and the formation of a mixture of at least two byproducts that were not isolated. $R_f$ 0.62 [EtOAc–MeOH (95 : 5)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$: 2.67 (4H, s, $CH_2$) 3.38 (1H, m, CH) 3.45–3.48 (2H, m, CH) 3.61–3.67 (1H, m, CH) 4.20 (1H, dd, $J$ = 6.9, 11.8 Hz, $CH_2$) 4.44 (1H, dd, $J$ = 2.2, 11.8 Hz, $CH_2$) 4.57 (1H, dd, $J$ = 1.4, 6.3 Hz, $CH_2$vin) 4.88 (1H, dd, $J$ = 1.4, 14.0 Hz, $CH_2$vin) 4.90 (1H, d, $J$ = 6.4 Hz, CH) 6.90–7.10 (3H, m, ArH) 7.22–7.32 (3H, m, ArH, CHvin). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 28.41 ($CH_2$) 63.89 ($CH_2$) 70.48 (CH) 73.65 (CH) 74.13 (CH) 76.66 (CH) 97.01 ($CH_2$) 100.95 (CH) 116.64 (CH, Ar) 122.32 (CH, Ar) 129.25 (CH, Ar) 141.21 (CH) 157.79 (CH, Ar) 170.00 (C–O) 172.43 (C–O). FAB$^+$-MS ($m/z$): 405 [M+Na]$^+$.

**6-*O*-(Phenyl-β-D-glucopyranosyl)-6′-*O*-(benzyl-α-D-mannopyranosyl) succinate (25)**

The general procedure outlined above was followed, starting from 6-*O*-(phenyl β-D-glucopyranosyl)-vinyl succinate **15** (90 mg, 0.235 mmol) and benzyl α-D-mannopyranoside **9** (64 mg, 0.235 mmol), obtaining the pure compound **25** (205 mg) in 61% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. $R_f$ 0.25 [EtOAc–MeOH–$H_2O$ (95 : 5 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 2.66 (4H, s, $CH_2$) 3.35 (1H, m, CH) 3.46 (2H, m, CH) 3.59–3.67 (2H, m, CH) 3.69–3.76 (2H, m, CH) 3.82 (1H, dd, $J$ = 1.7, 3.0 Hz, CH) 4.19 (1H, dd, $J$ = 3.0, 6.3 Hz, $CH_2$) 4.22 (1H, dd, $J$ = 3.0, 6.3 Hz, $CH_2$) 4.40–4.51 (2H, m, $CH_2$) 4.46 (1H, d, $J$ = 11.8 Hz, $CH_2$Bn) 4.67 (1H, d, $J$ = 11.8 Hz, $CH_2$Bn) 4.79 (1H, d, $J$ = 1.4 Hz, CH) 4.87–4.92 (1H, m, CH) 6.97–7.07 (3H, m, ArH) 7.22–7.34 (7H, m, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 28.79, 63.81, 64.25, 67.53, 68.89, 70.45, 70.86, 71.16, 71.37, 73.65, 74.12, 76.64, 99.56, 100.91, 116.62, 122.34, 127.66, 127.99, 128.27, 129.27, 137.70, 157.78, 172.63, 172.85. FAB$^+$-MS ($m/z$): 631 [M+Na]$^+$.

**6-*O*-(Phenyl β-D-glucopyranosyl) vinylglutarate (16)**

The general procedure outlined above was followed, starting from phenyl β-D-glucopyranoside (1.00 g, 3.90 mmol) and divinyl glutarate **2** (3.59 g, 19.5 mmol), obtaining pure **16** (1.05 g) in 68% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (98 : 2)]. $R_f$ 0.51 [EtOAc–MeOH (95 : 5)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 1.97–2.00 (2H, m, $CH_2$) 2.45 (4H, t, $J$ = 7.3 Hz, $CH_2$) 3.52–3.56 (1H, m, CH) 3.61–3.65 (1H, m, CH) 3.69–3.71 (2H, m, CH) 4.37 (1H, dd, $J$ = 2.2, 12.1 Hz, $CH_2$) 4.44 (1H, dd, $J$ = 5.3, 12.1 Hz, $CH_2$) 4.57 (1H, dd, $J$ = 1.6, 6.3 Hz, $CH_2$vin) 4.88 (1H, dd, $J$ = 1.6, 14.0 Hz, $CH_2$vin) 4.90 (1H, d, $J$ = 6.4 Hz, CH) 7.04–7.08 (3H, m, ArH) 7.24 (1H, dd, $J$ = 6.3, 14.0 Hz, CHvin) 7.24–7.31 (2H, m, ArH). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$: 20.03 ($CH_2$) 33.16, 33.33 ($CH_2$) 63.57 ($CH_2$) 70.26 (CH) 73.77 (CH) 74.30 (CH) 76.36 (CH) 98.28 ($CH_2$) 101.10 (CH) 117.21 (CH, Ar) 123.43 (CH, Ar) 129.86 (CH, Ar) 141.36 (CH) 157.30 (CH, Ar) 170.52 (C–O) 173.58 (C–O). FAB$^+$-MS ($m/z$): 419 [M+Na]$^+$.

**6-*O*-(Phenyl-β-D-glucopyranosyl)-6′-*O*-(benzyl-α-D-mannopyranosyl) glutarate (26)**

The general procedure outlined above was followed, starting from **16** (250 mg, 0.630 mmol) and benzyl α-D-mannopyranoside **9** (170 mg, 0.630 mmol) obtaining pure **26** (190 mg) in 48% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. The moderate isolated yield was mainly due to the presence of minor byproducts possessing very similar chromatographic behaviour that could be separated from the desired product only by repeated purification steps. $R_f$ 0.25 [EtOAc–MeOH–$H_2O$ (95 : 5 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 1.88 (2H, t, $J$ = 7.1 Hz, $CH_2$) 2.40 (4H, t, $J$ = 7.1 Hz, $CH_2$) 3.35–3.38 (1H, m, CH) 3.42–3.47 (2H, m, CH) 3.59–3.66 (2H, m, CH) 3.69–3.79 (2H, m, CH) 3.82 (1H, dd, $J$ = 1.7, 3.3 Hz, CH) 4.18 (1H, dd, $J$ = 3.3, 6.5 Hz, $CH_2$) 4.22 (1H, dd, $J$ = 3.3, 6.5 Hz, $CH_2$) 4.39–4.49 (2H, m, $CH_2$) 4.46 (1H, d, $J$ = 11.8 Hz, $CH_2$Bn) 4.66 (1H, d, $J$ = 11.8 Hz, $CH_2$Bn) 4.79 (1H, d, $J$ = 1.4 Hz, CH) 4.87–4.89 (1H, m, CH) 6.94–7.08 (3H, m, ArH) 7.21–7.35 (7H, m, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 20.11, 32.86, 63.49, 63.91, 67.52, 68.87, 70.49, 70.84, 71.18, 71.38, 73.65, 74.12, 76.63, 99.56, 100.94, 116.65, 122.37, 127.68, 127.99, 128.28, 129.25, 137.66, 157.79, 173.28, 173.50. FAB$^+$-MS ($m/z$): 645 [M+Na]$^+$.

### 6-*O*-(Phenyl β-D-glucopyranosyl) vinyladipate (17)

The general procedure outlined above was followed, starting from phenyl β-D-glucopyranoside **8** (500 mg, 1.95 mmol) and divinyl adipate **3** (1.93 g, 9.76 mmol) obtaining pure **17** (575 mg) in 72% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (97 : 3)]. $R_f$ 0.62 [EtOAc–MeOH (95 : 5)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$: 1.63–1.67 (4H, m, $CH_2$) 2.34–2.40 (4H, m, $CH_2$) 3.35–3.39 (1H, m, CH) 3.44–3.49 (2H, m, CH) 3.65 (1H, ddd, $J$ = 2.3, 6.7, 9.2 Hz, CH) 4.25 (1H, dd, $J$ = 6.7, 11.8 Hz, $CH_2$) 4.45 (1H, dd, $J$ = 2.2, 11.8 Hz, $CH_2$) 4.58 (1H, dd, $J$ = 1.5, 6.3 Hz, $CH_2$vin) 4.87 (1H, dd, $J$ = 1.5, 14.0 Hz, $CH_2$vin) 4.88–4.93 (1H, m, CH) 7.02–7.10 (3H, m, ArH) 7.25–7.28 (3H, m, ArH, CHvin). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$: 27.57, 27.81, 36.69, 37.13, 67.27, 74.31, 77.42, 77.91, 80.44, 100.57, 104.77, 120.49, 126.11, 132.94, 145.17, 161.52, 174.51, 177.36. FAB$^+$-MS ($m/z$): 433 [M+Na]$^+$.

### 6-*O*-(Phenyl-β-D-glucopyranosyl)-6′-*O*-(benzyl-α-D-mannopyranosyl) adipate (27)

The general procedure outlined above was followed, starting from **17** (350 mg, 0.853 mmol) and benzyl α-D-mannopyranoside **9** (208 mg, 0.768 mmol) obtaining pure **27** (345 mg) in 70% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. $R_f$ 0.37 [EtOAc–MeOH–$H_2O$ (90 : 10 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 1.61–1.66 (4H, m, $CH_2$) 2.32–3.37 (4H, m, $CH_2$) 3.32–3.37 (1H, m, CH) 3.40–3.44 (2H, m, CH) 3.60–3.66 (2H, m, CH) 3.70–3.78 (2H, m, CH) 3.80–3.85 (1H, m, CH) 4.20 (2H, dd, $J$ = 6.3, 11.8 Hz, $CH_2O$) 4.36–4.41 (2H, m, $CH_2O$) 4.48 (1H, d, $J$ = 14.0 Hz, $CH_2$Bn) 4.67 (1H, d, $J$ = 14.0 Hz, $CH_2$Bn) 4.79 (1H, d, $J$ = 1.4 Hz, CH) 4.88–4.92 (1H, m, CH) 6.97–7.08 (3H, m, ArH) 7.23–7.35 (7H, m, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 24.19, 24.25, 33.42, 33.45, 63.46, 63.91, 67.54, 68.83, 70.49, 70.84, 71.21, 71.39, 73.65, 74.12, 76.64, 99.55, 100.92, 116.64, 122.37, 127.71, 127.98, 128.31, 129.24, 137.66, 157.79, 173.69, 173.89. FAB$^+$-MS ($m/z$): 659 [M+Na]$^+$.

### 6-*O*-(Phenyl-β-D-glucopyranosyl)-trifluoroethyl dithiodiglycolate (18)

The general procedure outlined above was followed, starting from phenyl β-D-glucopyranoside (250 mg, 0.975 mmol) and ditrifluoroethyl dithiodiglycolate **6** (1.35 g, 3.90 mmol) obtaining pure **18** (230 mg) in 47% yield after purification by silica gel column chromatography (eluent: EtOAc). The TLC of the crude reaction showed a complete conversion of the starting material and the formation of a mixture of unidentified byproducts that were not isolated. $R_f$ 0.65 [EtOAc–MeOH–$H_2O$ (95 : 5 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 3.34–3.40 (1H, m, CH) 3.46–3.49 (2H, m, CH) 3.65 (2H, s, $CH_2$) 3.67 (2H, s, $CH_2$) 3.75–3.77 (1H, m, CH) 4.23 (1H, dd, $J$ = 6.6, 11.8 Hz, $CH_2$) 4.52 (1H, dd, $J$ = 2.2, 11.8 Hz, $CH_2$) 4.57 (2H, q, $J$ = 8.8 Hz, $CH_2CF_3$) 4.91–4.93 (1H, m, CH) 6.95–7.10 (3H, m, ArH) 7.24–7.27 (2H, m, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 40.19, 40.99, 60.67 (q, $J$ = 36.0 Hz), 64.63, 70.37, 73.74, 74.08, 76.62, 100.97, 116.68, 122.35, 129.32, 157.80, 168.42, 169.80, 183.20. FAB$^+$-MS ($m/z$): 525 [M+Na]$^+$.

### 6-*O*-(Phenyl-β-D-glucopyranosyl)-6′-*O*-(benzyl-α-D-mannopyranosyl) dithiodiglycolate (28)

The general procedure outlined above was followed, starting from **18** (170 mg, 0.336 mmol) and benzyl α-D-mannopyranoside **9** (91 mg, 0.336 mmol) obtaining pure **28** (95 mg) in 42% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. The TLC of the crude reaction showed the presence both of unreacted starting material and of a mixture of unidentified byproducts that were not isolated. $R_f$ 0.35 [EtOAc–MeOH–$H_2O$ (95 : 5 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$: 3.39–3.42 (1H, m, CH) 3.48–3.50 (2H, m, CH) 3.60–3.61 (1H, m, CH) 3.66 (4H, s, $CH_2$) 3.67–3.76 (2H, m, CH) 3.78–3.85 (2H, m, CH) 4.24–4.33 (2H, m, $CH_2$) 4.47–4.55 (2H, m, $CH_2$) 4.50 (1H, d, $J$ = 11.8 Hz, $CH_2$Bn) 4.73 (1H, d, $J$ = 11.8 Hz, $CH_2$Bn) 4.82 (1H, d, $J$ = 1.7 Hz, CH) 4.89–4.91 (1H, m, CH) 6.99–7.08 (3H, m, ArH) 7.27–7.30 (3H, m, ArH) 7.32–7.37 (4H, m, ArH). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$: 41.06, 41.16, 64.71, 65.16, 67.67, 69.05, 70.52, 70.97, 71.23, 71.53, 73.77, 74.21, 76.76, 99.63, 101.17, 116.88, 122.49, 127.75, 128.11, 128.37, 129.41, 137.81, 157.90, 169.95, 170.09. FAB$^+$-MS ($m/z$): 695 [M+Na]$^+$.

### 6-*O*-(Phenyl-β-D-glucopyranosyl)-trifluoroethyl dithiodibutyrate (19)

The general procedure outlined above was followed, starting from phenyl β-D-glucopyranoside **8** (400 mg, 1.56 mmol) and ditrifluoroethyl dithiodibutyrate **7** (1.84 g, 6.24 mmol), obtaining pure **19** (320 mg) in 37% yield after purification by silica gel column chromatography (eluent: EtOAc). The TLC of the crude reaction showed a complete conversion of the starting material and the formation of a mixture of at least two byproducts that were not isolated. $R_f$ 0.60 [EtOAc (100%)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 1.95–2.04 (4H, m, $CH_2$) 2.40–2.49 (2H, m, $CH_2$) 2.50–2.58 (2H, m, $CH_2$) 2.69–2.73 (4H, m, $CH_2$) 3.35–3.40 (1H, m, CH) 3.46–3.48 (2H, m, CH) 3.64–3.65 (1H, m, CH) 4.22–4.27 (1H, dd, $J$ = 6.7, 11.8 Hz, $CH_2$) 4.45 (1H, d, $J$ = 11.6 Hz, $CH_2$) 4.57 (2H, q, $J$ = 8.7 Hz, $CH_2CF_3$) 4.87–4.89 (1H, m, CH) 6.99–7.10 (3H, m, ArH) 7.27–7.30 (2H, m, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 23.91, 24.16, 31.48, 32.20, 36.99, 37.38, 59.68, 63.58, 70.52, 73.66, 74.15, 76.64, 100.95, 116.62, 122.36, 125.18, 129.29, 157.80, 171.61, 173.29. FAB$^+$-MS ($m/z$): 581 [M+Na]$^+$.

### 6-*O*-(Phenyl-β-D-glucopyranosyl)-6′-*O*-(benzyl-α-D-mannopyranosyl) dithiodibutyrate (29)

The general procedure outlined above was followed, starting from **19** (250 mg, 0.449 mmol) and benzyl α-D-mannopyranoside **9** (121 mg, 0.449 mmol) obtaining pure **29** (204 mg) in 63% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (97 : 3)]. $R_f$ 0.75 [EtOAc–MeOH–$H_2O$ (90 : 10 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 1.92–2.04 (4H, m, $CH_2$) 2.38–2.53 (4H, m, $CH_2$) 2.66–2.73 (4H, m, $CH_2$) 3.39–3.41 (1H, m, CH) 3.46 (2H, m, CH) 3.58–3.61 (2H, m, CH) 3.64–3.66 (2H, m, CH) 3.71–3.80 (2H, m, CH) 3.82–3.84 (1H, m, CH) 4.21–4.26 (2H, dd, $J$ = 6.7, 11. Hz, $CH_2$) 4.43–4.47 (2H, m, $CH_2$) 4.50 (1H, d, $J$ = 11.8 Hz, $CH_2$) 4.70 (1H, d, $J$ = 11.8 Hz, $CH_2$) 4.82 (1H, bs, CH) 4.89 (1H,

m, CH) 7.00–7.03 (1H, m, ArH) 7.06–7.10 (2H, m, Ar) 7.26–7.28 (3H, m, ArH) 7.33–7.35 (4H, m, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 25.40, 33.46, 38.51, 62.57, 64.81, 65.28, 68.81, 70.10, 71.42, 71.75, 72.05, 72.40, 72.62, 74.88, 75.34, 77.87, 78.10, 100.76, 102.17, 117.86, 123.60, 128.91, 129.18, 129.51, 130.50, 138.83, 158.99, 174.51, 174.70. FAB$^+$-MS ($m/z$): 751 [M+Na]$^+$.

### 6-*O*-(*p*-Nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranosyl) vinylglutarate (20)

The general procedure outlined above was followed, starting from *p*-nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranoside **11** (500 mg, 1.46 mmol) and divinyl glutarate **2** (1.34 g, 7.30 mmol), obtaining pure **20** (675 mg) in 96% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (97 : 3)]. $R_f$ 0.38 [EtOAc–MeOH–$H_2O$ (95 : 5 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 1.90 (2H, quint, $J$ = 7.4 Hz, $CH_2$) 1.97 (3H, s, $CH_3$) 2.42–2.43 (4H, m, $CH_2$) 3.42 (1H, dd, $J$ = 8.8, 9.7 Hz, CH) 3.62 (1H, dd, $J$ = 8.8, 10.3 Hz, CH) 3.72 (1H, ddd, $J$ = 2.2, 6.6, 9.7 Hz, CH) 3.93 (1H, dd, $J$ = 8.4, 10.3 Hz, CH) 4.25 (1H, dd, $J$ = 6.6, 11.9 Hz, $CH_2$) 4.47 (1H, dd, $J$ = 2.2, 11.9 Hz, $CH_2$) 4.55 (1H, dd, $J$ = 1.6, 6.3 Hz, CH) 4.82 (1H, dd, $J$ = 1.6, 14.0 Hz, CH) 5.23 (1H, d, $J$ = 8.4 Hz, CH) 7.13 (2H, d, $J$ = 9.3 Hz, ArH) 7.23 (1H, dd, $J$ = 6.3, 14.0 Hz, CH) 8.19 (2H, d, $J$ = 9.3 Hz, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 21.21, 23.25, 33.76, 34.16, 57.38, 64.88, 72.24, 75.71, 75.93, 98.30, 99.94, 117.88, 127.00, 144.35, 163.75, 171.94, 174.25, 174.60. FAB$^+$-MS ($m/z$): 505 [M+Na]$^+$.

### 6-*O*-(*p*-Nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-6′-*O*-(methyl-α-D-glucopyranosyl) glutarate (30)

The general procedure outlined above was followed, starting from **20** (670 mg, 1.40 mmol) and methyl α-D-glucopyranoside **10** (272 mg, 1.40 mmol), obtaining pure **30** (290 mg) in 35% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. The TLC of the crude reaction showed the presence both of unreacted starting material and of a mixture of unidentified byproducts that were not isolated. $R_f$ 0.25 [EtOAc–MeOH–$H_2O$ (90 : 10 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 1.90–1.92 (2H, m, $CH_2$) 1.97 (3H, s, $CH_3$) 2.36–2.37 (4H, m, $CH_2$) 3.25 (1H, dd, $J$ = 8.9, 10.0 Hz, CH) 3.36 (3H, s, $CH_3$) 3.38–3.45 (2H, m, CH) 3.57–3.59 (2H, m, CH) 3.65–3.75 (2H, m, $CH_2$) 3.92 (1H, dd, $J$ = 8.4, 10.3 Hz, $CH_2$) 4.16 (1H, dd, $J$ = 6.0, 11.8 Hz, $CH_2$) 4.20 (1H, dd, $J$ = 6.5, 12.0 Hz, $CH_2$) 4.37 (1H, dd, $J$ = 2.2, 11.8 Hz, $CH_2$) 4.47 (1H, dd, $J$ = 2.2, 11.9 Hz, $CH_2$) 4.60 (1H, d, $J$ = 3.8 Hz, CH) 5.23 (1H, d, $J$ = 8.4 Hz, CH) 7.14 (2H, d, $J$ = 9.3 Hz, ArH) 8.20 (2H, d, $J$ = 9.3 Hz, ArH). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 21.62, 21.86, 23.25, 29.83, 34.27, 55.94, 56.35, 57.38, 64.83, 65.08, 71.30, 72.19, 73.73, 75.31, 75.71, 75.93, 99.96, 101.54, 117.93, 127.05, 144.38, 163.78, 174.25, 174.66, 174.84. FAB$^+$-MS ($m/z$): 655 [M+Na]$^+$.

### 6-*O*-(*p*-Nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranosyl) vinyladipate (21)

The general procedure outlined above was followed, starting from *p*-nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranoside **11** (500 mg, 1.46 mmol) and divinyl adipate **3** (1.44 g, 7.30 mmol), obtaining pure **21** (600 mg) in 83% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (97 : 3)]. $R_f$ 0.38 [EtOAc–MeOH (95 : 5)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 1.60–1.62 (4H, m, $CH_2$) 1.98 (3H, s, $CH_3$) 2.34–2.36 (4H, m, $CH_2$) 3.40 (1H, dd, $J$ = 8.8, 9.6 Hz, CH) 3.62 (1H, dd, $J$ = 8.8, 10.2 Hz, CH) 3.70–3.72 (1H, m, CH) 3.92 (1H, dd, $J$ = 8.5, 10.2 Hz, CH) 4.22 (1H, dd, $J$ = 6.3, 11.8 Hz, $CH_2$) 4.45 (1H, dd, $J$ = 2.2, 12.1 Hz, $CH_2$) 4.53 (1H, dd, $J$ = 1.6, 6.3 Hz, $CH_2$vin) 4.81 (1H, dd, $J$ = 1.6, 14.0 Hz, $CH_2$vin) 5.22 (1H, d, $J$ = 8.3 Hz, CH) 7.10 (2H, d, $J$ = 8.5 Hz, ArH) 7.19 (1H, dd, $J$ = 6.3, 14.0 Hz, CHvin) 8.16 (2H, d, $J$ = 8.5 Hz, ArH). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$: 22.23, 24.29, 24.56, 33.38, 33.84, 56.48, 63.82, 71.34, 74.72, 74.99, 97.29, 99.04, 116.99, 125.90, 141.67, 143.40, 162.76, 171.85, 173.17, 174.02. FAB$^+$-MS ($m/z$): 519 [M+Na]$^+$.

### 6-*O*-(*p*-Nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-6′-*O*-(methyl α-D-glucopyranosyl) adipate (31)

The general procedure outlined above was followed, starting from **21** (500 mg, 1.01 mmol) and methyl α-D-glucopyranoside **10** (214 mg, 1.01 mmol), obtaining pure **31** (350 mg) in 57% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (96 : 4)]. $R_f$ 0.25 [EtOAc–MeOH–$H_2O$ (95 : 5 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 1.62–1.64 (4H, m, $CH_2$) 1.97 (3H, s, $CH_3$) 2.34–2.36 (4H, m, $CH_2$) 3.26 (1H, dd, $J$ = 8.9, 10.0 Hz, CH) 3.37 (3H, s, $CH_3$) 3.38–3.43 (2H, m, CH) 3.56–3.58 (2H, m, CH) 3.65–3.67 (2H, m, $CH_2$) 3.93 (1H, dd, $J$ = 8.4, 10.3 Hz, $CH_2$) 4.16 (1H, dd, $J$ = 6.0, 11.8 Hz, $CH_2$) 4.24 (1H, dd, $J$ = 6.4, 12.0 Hz, $CH_2$) 4.35 (1H, dd, $J$ = 2.2, 11.8 Hz, $CH_2$) 4.45 (1H, dd, $J$ = 2.2, 11.9 Hz, $CH_2$) 4.61 (1H, d, $J$ = 3.7 Hz, CH) 5.23 (1H, d, $J$ = 8.4 Hz, CH) 7.14 (2H, d, $J$ = 9.3 Hz, ArH) 8.19 (2H, d, $J$ = 9.3 Hz, ArH).$^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 22.95, 25.38, 34.59, 55.64, 57.14, 64.48, 64.77, 71.03, 71.94, 73.46, 75.06, 75.43, 75.68, 99.69, 101.26, 117.68, 126.65, 144.08, 163.49, 173.93, 174.77, 174.92. FAB$^+$-MS ($m/z$): 669 [M+Na]$^+$.

### 6-*O*-(Methyl-α-D-glucopyranosyl)-vinyldodecanedioate (22)

The general procedure outlined above was followed, starting from methyl α-D-glucopyranoside **10** (300 mg, 1.54 mmol) and divinyl dodecanedioate **4** (2.18 g, 7.72 mmol), obtaining pure **22** (594 mg) in 89% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (97 : 3)]. $R_f$ 0.40 [EtOAc–MeOH (95 : 5)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 1.29–1.33 (12H, m, $CH_2$) 1.61–1.65 (4H, m, $CH_3$) 2.32–2.35 (4H, m, $CH_2$) 3.27–3.30 (2H, m, CH) 3.39 (3H, s, $CH_3$) 3.60 (1H, t, $J$ = 9.2 Hz, CH) 3.69–3.71 (1H, m, CH) 4.19 (1H, dd, $J$ = 6.0, 11.8 Hz, $CH_2$) 4.36 (1H, dd, $J$ = 1.8, 11.8 Hz, $CH_2$) 4.55 (1H, dd, $J$ = 1.4, 6.3 Hz, $CH_2$vin) 4.63 (1H, d, $J$ = 3.6 Hz, CH) 4.83 (1H, dd, $J$ = 1.6, 14.0 Hz, $CH_2$vin) 5.22 (1H, d, $J$ = 8.3 Hz, CH) 7.22 (1H, dd, $J$ = 6.3, 14.0 Hz, CHvin). FAB$^+$-MS ($m/z$): 455 [M+Na]$^+$.

### 6-*O*-(*p*-Nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)-6′-*O*-(methyl-α-D-glucopyranosyl) dodecanedioate (32)

The general procedure outlined above was followed, starting from **22** (189 mg, 0.438 mmol) and *p*-nitrophenyl-2-acetamido-2-deoxy-β-D-glucopyranoside **11** (150 mg, 0.438 mmol), obtaining pure

**32** (102 mg) in 32% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. The TLC of the crude reaction showed the presence both of unreacted starting material and of a mixture of unidentified byproducts that were not isolated. $R_f$ 0.25 [EtOAc–MeOH–$H_2O$ (95 : 5 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 1.20–1.28 (12H, m, $CH_2$) 1.56–1.60 (4H, m, $CH_2$) 1.97 (3H, s, $CH_3$) 2.32–2.34 (4H, m, $CH_2$) 3.25–3.27 (1H, m, CH) 3.37 (3H, s, $CH_3$) 3.38–3.43 (2H, m, CH) 3.59–3.61 (2H, m, CH) 3.70–3.72 (2H, m, $CH_2$) 3.93 (1H, dd, $J$ = 8.4, 10.2 Hz, $CH_2$) 4.16–4.26 (2H, m, $CH_2$) 4.36 (1H, dd, $J$ = 1.9, 11.8 Hz, $CH_2$) 4.44 (1H, dd, $J$ = 2.0, 11.8 Hz, $CH_2$) 4.64 (1H, d, $J$ = 3.6 Hz, CH) 5.23 (1H, d, $J$ = 8.4 Hz, CH) 7.15 (2H, d, $J$ = 9.2 Hz, ArH) 8.18 (2H, d, $J$ = 9.2 Hz, ArH).$^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$: 22.22, 25.30, 29.36, 29.43, 29.54, 29.69, 34.32, 54.87, 56.41, 63.82, 64.02, 70.37, 71.22, 71.38, 72.76, 74.34, 74.73, 74.95, 98.97, 100.53, 116.99, 125.89, 143.32, 162.80, 173.19, 174.50, 174.72. FAB$^+$-MS ($m/z$): 752 [M+Na]$^+$.

### 6-*O*-(Thiocolchicoside) vinyladipate (23)

The general procedure outlined above was followed, starting from thiocolchicoside **14** (400 mg, 0.710 mmol) and divinyl adipate **3** (563 mg, 2.84 mmol), obtaining pure **23** (365 mg) in 72% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. $R_f$ 0.55 [EtOAc–MeOH–$H_2O$ (90 : 10 : 1)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 1.62–1.66 (4H, m, $CH_2$) 1.90 (1H, m, $CH_2$) 1.98 (3H, s, $NHCOCH_3$) 2.12–2.22 (1H, m, $CH_2$) 2.34–2.40 (5H, m, $CH_2$) 2.47 (3H, s, $SCH_3$) 2.58–2.63 (1H, dd, $J$ = 6.3, 13.4 Hz, $CH_2$) 3.37–3.55 (3H, m, CH) 3.63 (3H, s, $OCH_3$) 3.64–3.67 (1H, m, CH) 3.94 (3H, s, $OCH_3$) 4.20–4.24 (1H, dd, $J$ = 6.3, 11.9 Hz, CH) 4.49–4.56 (3H, m, CH, $CH_2$vin) 4.82–4.86 (1H, d, $J$ = 14.0 Hz, $CH_2$vin) 4.98 (1H, d, $J$ = 7.4 Hz, CH) 6.87 (1H, s, ArH) 7.18 (1H, s, ArH) 7.21–7.26 (1H, dd, $J$ = 6.3, 14.0 Hz, CHvin) 7.34 (2H, s, ArH).$^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 15.39, 22.78, 25.32, 25.60, 30.87, 34.44, 34.86, 37.46, 53.92, 62.35, 62.53, 64.95, 71.81, 75.23, 75.85, 78.18, 98.29, 102.90, 113.76, 129.09, 136.12, 136.99, 140.05, 142.12, 143.51, 152.70, 153.02, 153.57, 160.55, 171.87, 172.96, 174.99, 184.07. FAB$^+$-MS ($m/z$): 718 [M+H]$^+$ 740 [M+Na]$^+$.

### 6-*O*-(Thiocolchicoside)-21′-*O*-(cortisone) adipate (33)

The general procedure outlined above was followed, starting from **23** (200 mg, 0.278 mmol) and cortisone **12** (100 mg, 0.278 mmol), obtaining pure **33** (180 mg) in 63% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (95 : 5)]. $R_f$ 0.15 [EtOAc–MeOH (95 : 5)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 0.70 (3H, s, $CH_3$) 1.25–2.73 (28H, m) 1.41 (3H, s, $CH_3$) 1.99 (3H, s, $NHCOCH_3$) 2.47 (3H, s, $SCH_3$) 2.94 (1H, d, $J$ = 12.2 Hz) 3.33–3.56 (3H, m) 3.63 (3H, s, $OCH_3$) 3.66–3.67 (1H, m) 3.95 (3H, s, $OCH_3$) 4.15–4.20 (1H, dd, $J$ = 7.0, 11.8 Hz) 4.49–4.56 (2H, m) 4.83 (1H, d, $J$ = 17.3 Hz) 4.92 (1H, d, $J$ = 17.3 Hz) 4.96 (1H, d, $J$ = 7.0 Hz) 5.71 (1H, s) 6.89 (1H, s) 7.18 (1H, s) 7.34 (2H, s). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$: 15.45, 16.17, 18.05, 22.89, 24.39, 25.65, 30.98, 33.77, 33.87, 34.50, 34.80, 34.97, 35.60, 35.96, 37.52, 38.11, 39.89, 51.27, 51.44, 52.76, 53.97, 62.39, 62.58, 63.79, 65.18, 69.73, 71.95, 75.23, 75.98, 78.24, 90.02, 103.00, 113.83, 125.09, 129.08, 129.25, 136.17, 136.97, 140.09, 144.04, 152.70, 153.09, 153.56, 160.50, 172.98, 173.16, 174.74, 175.06, 184.07, 202.73, 207.46, 212.37. FAB$^+$-MS ($m/z$): 1034 [M+H]$^+$ 1056 [M+Na]$^+$.

### 21-*O*-(Cortisone) trifluoroethyl dithiodibutyrate (24)

The general procedure outlined above was followed, starting from cortisone **12** (500 mg, 1.39 mmol) and ditrifluoroethyl dithiodibutyrate **7** (1.63 g, 5.55 mmol), obtaining pure **24** (501 mg) in 54% yield after purification by silica gel column chromatography [eluent: EtOAc/PetEt (7 : 3)]. The TLC of the crude reaction showed the presence of a mixture of unidentified byproducts that were not isolated. $R_f$ 0.35 [EtOAc/PetEt (7 : 3)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 0.68 (3H, s, $CH_3$) 1.26–1.28 (1H, m) 1.40 (3H, s, $CH_3$) 1.45–1.47 (1H, m) 1.64–1.66 (2H, m) 1.92–2.17 (8H, m) 2.26–2.58 (10H, m) 2.72–2.80 (6H, m) 2.86 (1H, d, $J$ = 12.4 Hz) 4.46 (2H, q, $J$ = 8.46 Hz, $CH_2CF_3$) 4.67 (1H, d, $J$ = 17.4 Hz, $CH_2O$) 5.08 (1H, d, $J$ = 17.4 Hz, $CH_2O$) 5.73 (1H, s, CH═C). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$: 15.72, 17.55, 23.54, 24.23, 24.52, 32.24, 32.49, 32.62, 33.99, 35.05, 35.17, 36.81, 37.77, 37.84, 37.91, 38.59, 50.12, 50.23, 51.56, 60.61 (q, $J$ = 36.3 Hz), 62.86, 68.02, 89.12, 123.23 (q, $J$ = 275.0 Hz), 124.75, 169.58, 171.66, 172.86, 200.45, 204.99, 209.35. FAB$^+$-MS ($m/z$): 663 [M+H]$^+$.

### 6-*O*-(Colchicoside)-21′-*O*-(cortisone) dithiodibutyrate (34)

The general procedure outlined above was followed, starting from **24** (230 mg, 0.347 mmol) and colchicoside **13** (190 mg, 0.347 mmol), obtaining pure **34** (119 mg) in 31% yield after purification by silica gel column chromatography [eluent: EtOAc–MeOH (85 : 15)]. The TLC of the crude reaction showed the presence of unreacted starting material. $R_f$ 0.20 [EtOAc–MeOH (85 : 15)] (TLC detection by UV light and molybdate reagent). $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$: 0.61 (3H, s, $CH_3$) 1.23 (1H, m) 1.42 (3H, s, $CH_3$) 1.43–2.77 (31H, m) 2.01 (3H, s, $NHCOCH_3$) 2.96 (1H, d, $J$ = 12.4 Hz) 3.39–3.57 (3H, m) 3.63 (3H, s, $OCH_3$) 3.66–3.68 (1H, m) 3.96 (3H, s, $OCH_3$) 4.01 (3H, s, $OCH_3$) 4.21 (1H, dd, $J$ = 6.7, 11.9 Hz) 4.51–4.53 (2H, m) 4.88 (2H, 2d, $J$ = 17.7 Hz) 4.97 (1H, m) 5.71 (1H, s, CH═) 6.90 (1H, s, ArH) 7.19 (1H, d, $J$ = 11.0 Hz, ArH) 7.39 (1H, s, ArH) 7.40 (1H, d, $J$ = 11.0 Hz, ArH). $^{13}$C NMR-DEPT (100 MHz, $CD_3OD$) $\delta_C$: 15.56, 17.50, 22.31, 23.85, 25.10, 25.23, 30.39, 32.85, 33.14, 33.20, 33.35, 34.23, 35.03, 35.45, 37.06, 37.61, 38.13, 38.30, 50.74, 50.90, 53.52, 56.83, 61.72, 62.01, 63.29, 64.60, 69.22, 71.38, 74.73, 75.37, 77.71, 102.66, 113.49, 114.75, 124.52, 130.97, 137.46. FAB$^+$-MS ($m/z$): 1110 [M+H]$^+$ 1122 [M+Na]$^+$.

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