Novel chemoenzymatic methodology for the regioselective glycine loading on polyhydroxy compounds†

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In the present work, we have developed a highly efficient temperature-dependent chemo-enzymatic methodology for the regioselective synthesis of novel esters of glycerol, G1 tri-glycerol dendrons and related esters for the first time using 4-nitrophenyl 2-(*tert*-butoxycarbonyl)acetate (Boc-gly-Ph-*p*NO_2) (**2**) as the acylating agent. This methodology offers efficient and controlled loading of amino acid (glycine) on polyhydroxy compounds.

Introduction

One of the major problems emphasized in the construction of complex polyfunctional molecules, *i.e.* mono- and oligosaccharides, nucleosides, and dendrimers is the presence of multiple functionalities of nearly identical reactivities which are difficult to protect and deprotect selectively.[1,2] Many classical chemical methods have been developed for the manipulation of hydroxyl groups using different protecting groups under mild conditions.[3,4] Furthermore, synthetic routes involving various protection and/or deprotection steps reduce the overall yields of the desired products and make the whole process tedious, time-consuming, and inefficient.[2,5] Attempts to exploit the same or similar tools as nature to perform comparable reactions have led to an extended use of biocatalysts, which have substantially enriched the arsenal of available protecting group techniques, offering viable alternatives to classical methods.[6,7]

Recent advances in enzyme-assisted organic synthesis have allowed the preparation of structurally well-defined molecules in high yields and greater selectivity. Among the different biocatalytic processes, lipase-catalyzed selective esterification/transesterification reactions represent an important class of enzymatic transformations in organic synthesis, which is mainly attributed to the low cost of lipases and their wide tolerance towards a variety of reaction conditions and substrates.[8,9] Due to their high versatility recognizing a broad range of substrates with high regio- and enantioselectivity, lipases could be an attractive alternative to obtain high specificity and regioselectivity.[10–13]

Dendritic polymeric architectures derived from polyglycerol (PG) have been extensively used in the design of scaffolds in several biomedical applications.[14] Due to their highly biocompatible nature, dendritic PGs show a broad range of potential applications in medicine and pharmacology, *e.g.* transport and stimuli-responsive delivery, as well as release of bioactive molecules in regenerative medicine in the form of non-fouling surfaces and matrix materials.

The presence of amine groups on the surface or focal point in polyglycerol (PG) architectures has been useful as an anchoring point in the preparation of protein resistant surfaces,[15,16] in the synthesis of macromolecular prodrugs,[17,18] and in the condensation of nucleic acid drugs.[19–23] The amount and localization of amine groups within the PG scaffold has shown to have an effect on several properties related to drug coupling efficiency, cellular uptake, gene transfection efficiency, toxicity, and unspecific interactions (*e.g.* to albumin).[24] To better tune these properties on polyglycerol amine compounds, it is relevant to develop a synthetic methodology which allows control of the loading and localization of the amine moieties. It is therefore interesting to explore the possibility of biocatalyzed regioselective esterification/transesterification of polyhydroxy compounds such as glycerol, dendritic generation analogues of glycerol and related compounds, which find potential applications in protein resistant surface coating materials, and drug, dye, and gene delivery.

Amino acids are naturally occuring building blocks and can be used as biodegradable linkers. We have chosen *N*-Boc-glycine 4-nitrophenyl ester (**2**) for the selective acylation of hydroxyl groups for biocatalytic transesterification reactions as this acylating agent allows the selective loading of glycine (the simplest amino acid), which ultimately allows the controlled loading of single primary amine functionality in the compound, after deprotection of the Boc-group. To the best of our knowledge, we are the first to use this protected amino acid for selectively protecting hydroxyl groups in biocatalytic transesterification reactions.

In the present study, we also show a highly efficient temperature dependent chemo-enzymatic route for the regioselective acylation of potentially useful polyhydroxy compounds as well as subsequent reactions leading to the synthesis of amino acid-based amphiphiles.

Results and discussion

Multiple approaches to design different PG architectures have been reported that offer a great variety in the degree of branching, size, surface topology, and chemical properties in general.[14] The use of PG dendrons as building blocks may allow a great

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diversity of polymeric architectures with potential for biomedical applications.[14]

We were interested in the selective/quantitative surface modifications of the [G1.0] glycerol dendrons in an endeavor to explore the effect of quantitative glycine amino acid loadings along with the hydroxyl groups of the dendrons. Consequently a number of terminal amine functionalities could also be controlled on the surface of the dendrimer. These assumptions prompted us to synthesize [G1.0] dendrons with selective glycine loadings *via* chemo-enzymatic pathways.

Based on our earlier experience of biocatalytic transacylation reactions on polyhydroxy compounds,[25–29] we chose to use the enzymes *Candida antarctica* lipase-B immobilized on polyacrylate (Lewatit), commonly known as Novozyme-435, *porcine pancreatic* lipase (PPL), *Candida rugosa* lipase (CRL), *Theremomyces lanuginosus* lipase immobilized on silica (Lipozyme® TL IM) and the *Candida antarctica* lipase-B immobilized on accurel [CAL B-L(A)] for selective transestrification reactions on glycerol, dendritic generation analogues of glycerol and related polyhydroxy compounds in different solvents at two different temperatures.

We first carried out regioselective transesterification reactions on glycerol (**1**) in the presence of the above-mentioned lipases using *N*-Boc-glycine 4-nitrophenyl ester (**2**) as the acylating reagent for the selective protection of hydroxyl groups at two different temperatures (50 and 70 °C) in different organic solvents. Lipozyme® TL IM in dioxane was found to be the most efficient biocatalyst for the regioselective transesterification on glycerol (**1**) to afford mono- and di-esterified products (Scheme 1). The other four lipases, *i.e.* Novozyme-435, PPL, CRL, and CAL B–L(A), did not accept the substrate. When transesterification was carried out at 50 °C for 30 h, only one primary hydroxyl group of glycerol was esterified to afford the compound **3** in 78% isolated yield (Scheme 1). When the compound **3** was further subjected to a transesterification reaction with *N*-Boc-glycine 4-nitrophenyl ester (**2**) for another 30 h at 50 °C in dioxane solvent, the second primary hydroxyl group was also esterified to afford the compound **4** in 75% yield. When the same transesterification reaction was carried out at 70 °C for 72 h, both the primary hydroxyl groups were simultaneously esterified in one step to afford the compound **4** in 65% yield (Scheme 1).

To ascertain whether the primary or secondary hydroxyl group of glycerol was esterified, we have compared the DEPT-NMR spectrum of compounds **1**, **3** and **4** (Fig. 1). In glycerol (**1**), peaks corresponding to methylene carbons C-1 and C-3 appeared at the same chemical shift value of δ 63.08 as a downward signal due to symmetry in the molecule, whereas the C-2 appeared at δ 72.58 as an upward signal. When the compound **1** was regioselectively esterified and converted to compound **3** using *N*-Boc-glycine 4-nitrophenyl ester (**2**), two peaks appeared as downward absorptions in the DEPT NMR spectrum of compound **3** at δ 62.63 and δ 65.82, corresponding to C-3′ and C-1′, respectively (Fig. 1). The peak for the C-2′ appeared at δ 69.70 while C-2 appeared at δ 41.75. These observations from the DEPT spectrum of compound **3** indicated that only one of the primary hydroxyl group of glycerol (**1**) was esterified. We would have expected only one peak as a downward absorption in the DEPT spectrum if the secondary hydroxyl group of glycerol (**1**) had been esterified. When compound **3** was further converted to compound **4**, the DEPT spectrum of the compound **4** revealed one peak at δ 65.30 as a downward absorption, corresponding to equivalent carbons, *i.e.* C-1 and C-3 carrying the ester moieties (due to symmetry in the molecule). The peak for C-2 appeared at

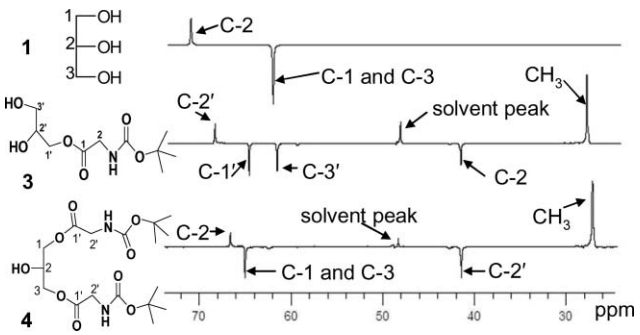
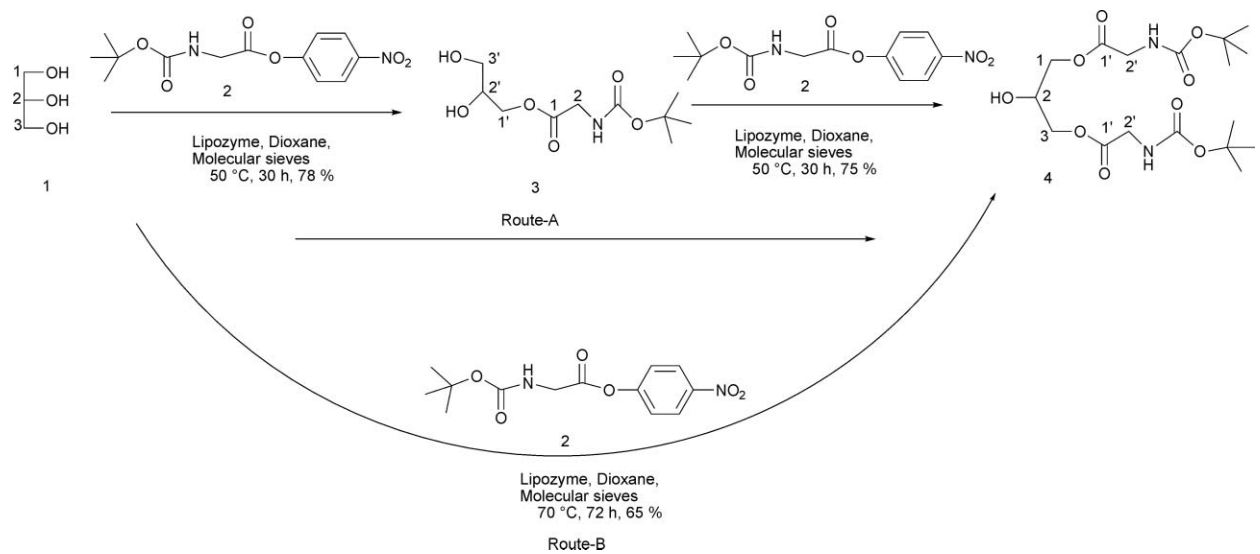


Fig. 1 Comparison of the DEPT-135 spectra of **1**, **3** and **4**.

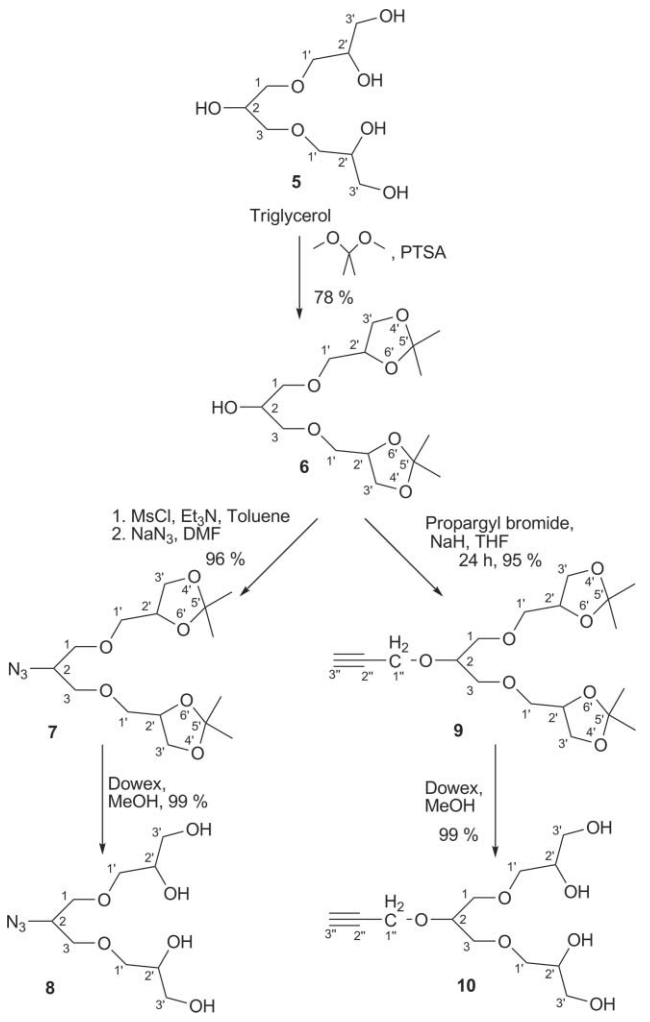


Scheme 1 Lipozyme-catalyzed transesterification of glycerol.

δ 66.89 as an upward signal and the C-2′ showed up at δ 41.70 as a downward absorption (Fig. 1). The peak corresponding to C-3′ at δ 62.63 in compound **3** disappeared in the DEPT-135 spectrum of compound **4** (Fig. 1). These observations led to the conclusion that esterification took place at both primary hydroxyl groups and not on secondary hydroxyl group.

To ascertain whether compound **3** is optically active we have recorded its optical rotation, but this compound did not show any optical rotation. Hence, no enantioselectivity was observed in case of compound **3**.

Prompted by the regioselectivity achieved in case of glycerol, we then extended this methodology on bifunctional G1 glycerol dendrons, *viz.* on compounds **8** and **10** bearing four hydroxyl groups (two primary and two secondary hydroxyl groups), which were prepared according to the synthetic pathway shown in Scheme 2. Compounds **6**, **7**, and **8** were previously reported by us.[30]

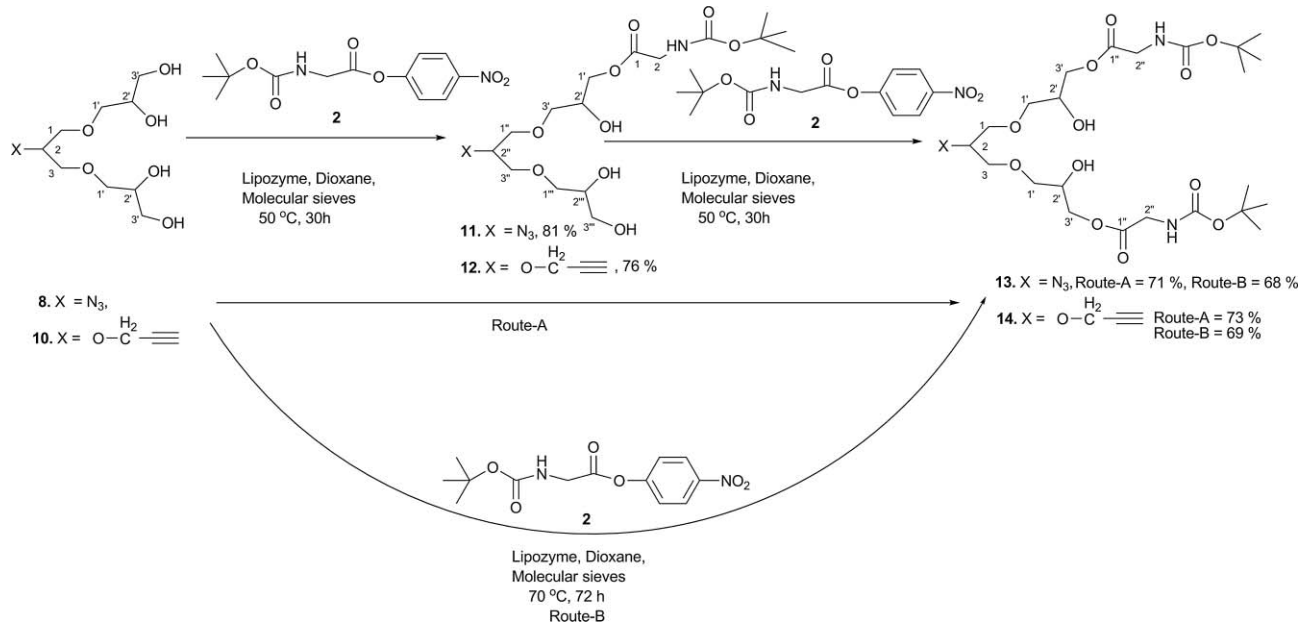


Scheme 2 Synthesis of bifunctional G1 glycerol dendrons **8** and **10**.

Lipozyme-catalyzed biocatalytic transesterification reactions on compounds **8** and **10** using *N*-Boc-glycine 4-nitrophenyl ester (**2**) at 50 °C for 30 h in dioxane afforded compounds **11** and **12** in 81 and 76% isolated yields, respectively, in which only one primary hydroxyl group in both the cases was esterified (Scheme 3). The mono-esterified compounds **11** and **12**, when further subjected to lipozyme-catalyzed transesterification reaction with *N*-Boc-glycine 4-nitrophenyl ester (**2**) for another 30 h at 50 °C in dioxane, afforded compounds **13** and **14** (with both the primary hydroxyl groups esterified) in 71 and 73% yields, respectively. The same transesterification reaction, when carried out on compounds **8** and **10** at 70 °C for 72 h, afforded the di-esterified products **13** and **14** in 68 and 69% yields, respectively, with both the primary hydroxyl groups esterified (Scheme 3).

To confirm whether primary or secondary hydroxyl groups were esterified during the biocatalytic transesterification reactions on compounds **8** and **10** shown in Scheme 3, we performed DEPT NMR studies on compounds **10**, **12**, and **14** (Fig. 2). The DEPT spectrum of compound **10** revealed the appearance of a peak at δ 63.14 for the two C-3′ carbons as a downward signal, while the two C-2′ carbons appeared at δ 70.89 as an upward signal, due to symmetry in the molecule (Fig. 2). When compound **10** was converted biocatalytically to compound **12**, the DEPT NMR spectrum of compound **12** showed the appearance of peaks at δ 63.09 and δ 65.86 for the C-3‴ and C-1′, respectively, as downward signals (Fig. 2). The appearance of a peak at δ 65.86 as a downward absorption indicated that the primary hydroxyl group was esterified. When compound **12** was further converted to compound **14**, the DEPT-135 NMR spectrum of compound **14** revealed the disappearance of the peak at δ 63.09 (present in compound **12** for C-3‴) and appearance of only one peak for equivalent carbons, *i.e.* C-3′ at δ 65.89 as a downward absorption due to symmetry in the molecule (Fig. 2). This confirmed that the primary hydroxyl group was again esterified when compound **12** was converted to compound **14**. In dendrons **8** and **10–14** different diastereoisomers did not give rise to more distinctly dispersed bunches of peaks in ^{13}C NMR for corresponding carbons rather than the single, albeit broadened lines, due to the polar and protic nature of the solvent (CD_3OD) in which we recorded our NMR spectra. Also, these compounds were insoluble in comparatively nonpolar solvents like $CDCl_3$, in which one might be able to see diastereoisomeric carbons. We had recorded the spectra in DMSO-d_6 as well but the spectra were not clear. Dendrons **12** and **14** could be modified by azido alkanethiols *via* click reaction to form SAMs on gold chips, and after Boc-deprotection their protein-resistant behavior could then be analyzed.

Impressed by the regioselectivity achieved in G1 glycerol dendrons **8** and **10**, we extended the application of this methodology to the synthesis of novel amino acid-based amphiphiles in an attempt to prepare hydrophobic dendrons as potential gene carriers. For this, we first prepared the octadecyl-propargyl ether with the help of a literature procedure[31] and then performed the click reaction on compound **8** with octadecyl-propargyl ether using copper triphenylphosphine bromide, diisopropylamine, and *N*,*N*-dimethylformamide as a solvent at 50 °C for 24 h to afford compound **15** in 83% yield (Scheme 4). Compound **15** was then transesterified using *N*-Boc-glycine 4-nitrophenyl ester (**2**) as the acylating agent in the presence of lipozyme at 50 and 70 °C in dioxane solvent to furnish compounds **16** and **17** in 77 and 69% isolated yields, respectively (Scheme 4). Compound **16**, when transesterified at 50 °C for 30 h using *N*-Boc-glycine 4-nitrophenyl ester (**2**) as the acylating agent in the presence of lipozyme in dioxane solvent, afforded compound **17** in 74% isolated yield (Scheme 4). Compounds **16** and **17** were then treated overnight



Scheme 3 Lipozyme-catalyzed transesterification of G1 generation dendrons **8** and **10**.

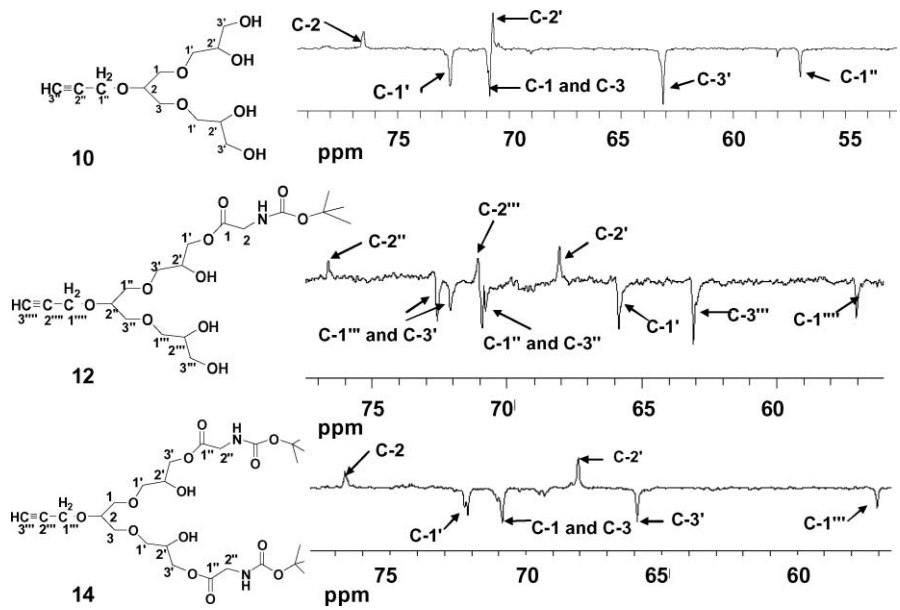
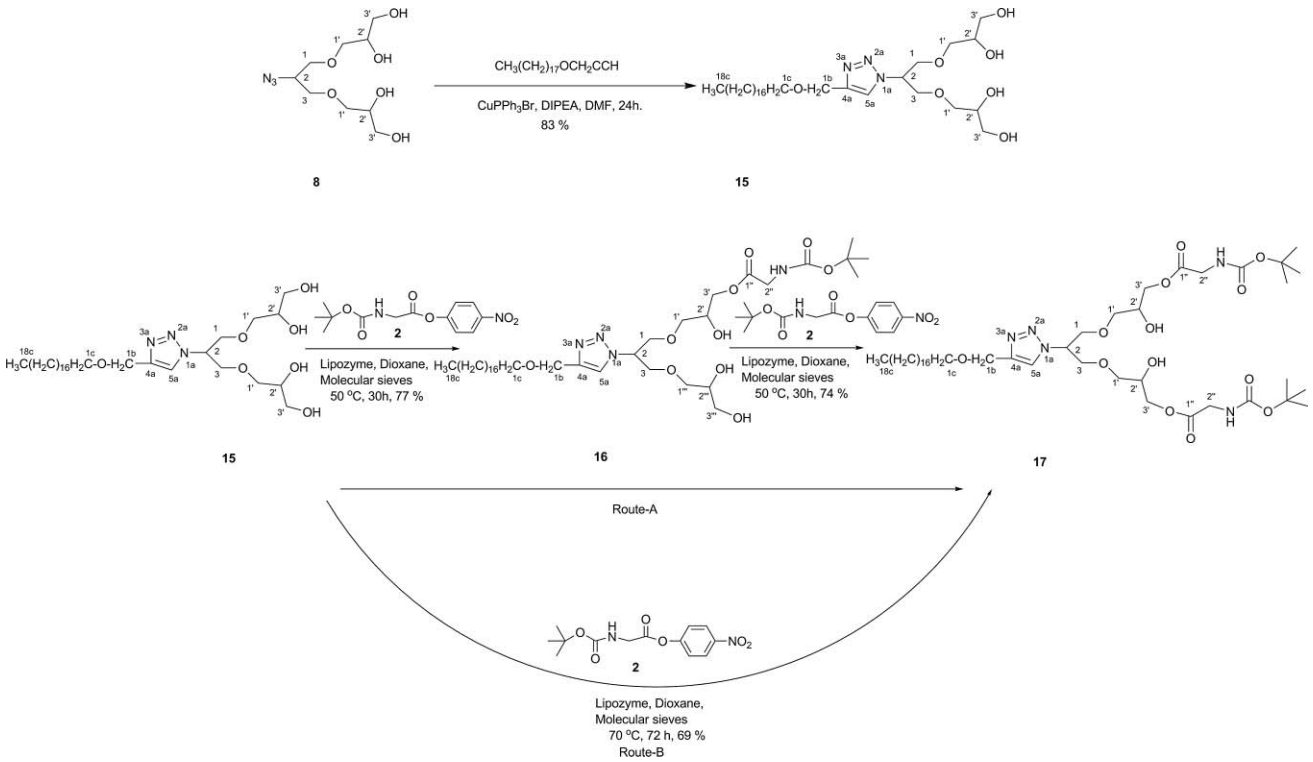


Fig. 2 Comparison of the DEPT-135 spectra of **10**, **12** and **14**.

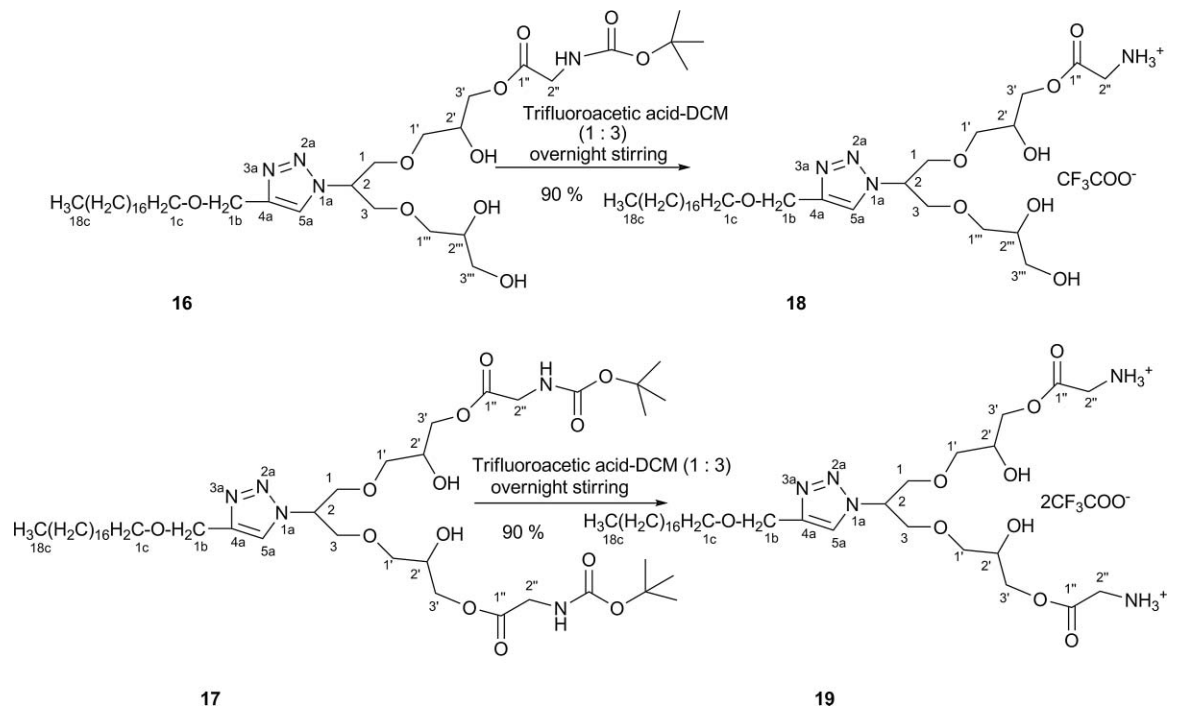
with a mixture of trifluoroacetic acid : dichloromethane (1 : 3) to afford monoamino and diamino dendrons **18** and **19**, respectively in 90% yields (Scheme 5). DNA complexation and binding studies on dendrons **18** and **19** are currently under way.

To ascertain the broader applicability of our above developed chemo-enzymatic methodology, we envisaged extending it to other polyhydroxy compounds, *viz.* **23** and **24** as well, which are the starting materials for the synthesis of functionalized dendritic aliphatic polyesters based on 2,2-bis(hydroxymethyl)propanoic acid (**20**).[32] We have carried out lipozyme-catalyzed transesterification using *N*-Boc-glycine 4-nitrophenyl ester (**2**) as the acylating reagent on compounds **23** and **24** (both having two primary hydroxyl groups) in dioxane at 50 °C for 72 h to afford regioselectively the mono-esterified compounds **25** and **26** in 71 and 74% yields, respectively (Scheme 6). The 2-methylpropanoate derivatives **23** and **24** were prepared in one step according to the literature reported procedure.[32]

Encouraged by the results on highly regioselective biocatalytic acylations on different compounds containing two primary hydroxyl groups, we attempted to apply this methodology to molecules containing three primary hydroxyl groups as well. Regioselective protection of commercially available 2-(hydroxymethyl)-2-nitropropane-1,3-diol (**27**) and 2-ethyl-2-(hydroxymethyl)propane-1,3-diol (**28**), both containing three primary hydroxyl groups, was also achieved by the lipozyme-catalyzed transesterification using *N*-Boc-glycine 4-nitrophenyl



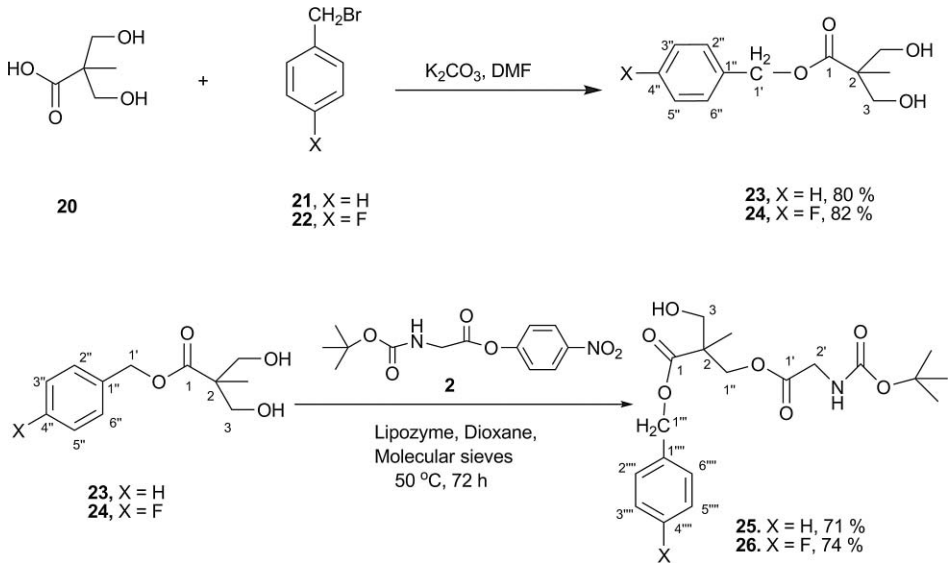
Scheme 4 Lipozyme catalyzed transesterification of G1 generation click dendron **15**.



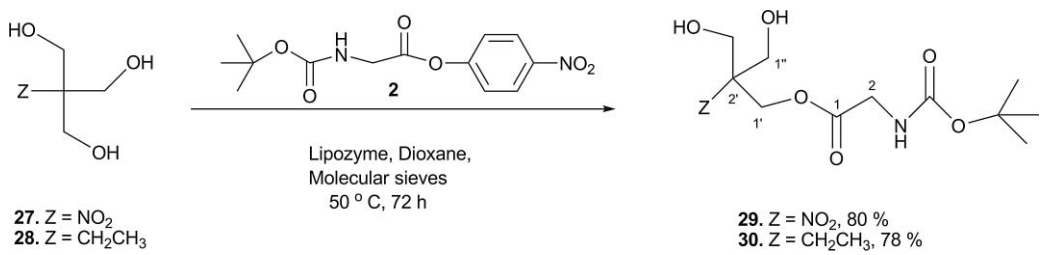
Scheme 5 Boc-deprotection of **16** and **17**.

ester (**2**) as the acylating reagent. At 50 °C, only one primary hydroxyl group was esterified in 72 h in both the compounds **27** and **28** to afford the compounds **29** and **30** in 80 and 78% yields, respectively (Scheme 7). Only one out of the three primary hydroxyl groups was regioselectively acylated using this methodology.

When mono-esterified compounds **29** and **30** were further subjected to biocatalytic transesterification with *N*-Boc-glycine 4-nitrophenyl ester (**2**) at 50 °C in dioxane solvent, the reaction mixture became very complex to be handled for work-up and purification of the reaction mass. Also, while performing the



Scheme 6 Lipozyme-catalyzed transesterification of **23** and **24**.



Scheme 7 Lipozyme-catalyzed transesterification of **27** and **28**.

same transesterification reaction on compounds **27** and **28** at 70 °C, the reaction mixture became too complex to be handled further.

The fourteen novel esters **3**, **4**, **11–14**, **16–19**, **25**, **26**, **29**, and **30** have been prepared for the first time *via* chemo-enzymatic routes and were unambiguously characterized using ^{1}H NMR, ^{13}C NMR, DEPT, FT-IR, and HRMS techniques.

Experimental

Reactions requiring dry conditions were carried out under argon. Dry and analytical-grade solvents and reagents were purchased from Sigma-Aldrich and Acros and used as received. *N*-Boc-glycine 4-nitrophenyl ester (**2**) was purchased from Fluka and lipozyme was a gift from Novozymes A/s, Copenhagen, Denmark. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer operating at 400 MHz and 100.5 MHz, respectively. Column chromatography was performed on silica gel 60 (230–400 mesh) with head pressure supplied by compressed air. Infrared spectra (IR) were recorded as thin films between KBr or CaF_2 plates on a Bruker IFS 66 FT-IR spectrophotometer. For ESI measurements, a TSQ 7000 (Finnigan Mat) instrument and for high-resolution mass spectra, a JEOL JMS-SX-102A spectrometer were used.

General procedure for the selective esterification of hydroxyl groups using Boc-Gly-Ph-*p*NO_2 (2)

The appropriate polyol compound (**1**, **8**, **10**, **15**, **23**, **24**, **27**, and **28**) and Boc-Gly-Ph-*p*NO_2 (4.0 mol equiv., **2**) were dissolved in dry dioxane (15 ml); lipozyme (50% by weight of the polyol compound) and activated molecular sieves were added to it. The reaction mixture was left for stirring at 50 °C for 30–72 h and monitored by TLC; after completion of reaction, lipozyme and molecular sieves were filtered off. The solvent was then removed under reduced pressure and the residue subjected to column chromatography. Elution with a mixture of 10% methanol : 90% chloroform gave the desired mono-esterified products (**3**, **11**, **12**, **16**, **25**, **26**, **29**, and **30**, respectively) in 70–80% isolated yields.

The di-esterified compounds **4**, **13**, **14**, and **17** were obtained in 71–75% yields when the same transesterification reaction was performed with lipozyme and the acylating agent **2** in dioxane at 50 °C for 30 h on compounds **3**, **11**, **12**, and **16**, respectively (**Route-A**).

The same di-esterified compounds **4**, **13**, **14**, and **17** were obtained in 60–70% yields when the biocatalytic transesterification reaction was performed with lipozyme and the glycine-derived acylating agent **2** at 70 °C for 72 h on compounds **1**, **8**, **10**, and **15**, respectively (**Route-B**).

2′,3′-Dihydroxypropyl 2-*N*-(*t*-butoxycarbonyl)aminoacetate (3)

Obtained as a light yellow viscous oil (1 g, 78% yield). R_f: 0.40 (1 : 5 methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 1.42 (9H, s, -OC(CH_3)$_3$), 3.53-3.54 (2H, m, C-3′H), 3.66 (1H, m, C-2′H), 3.80 (2H, s, C-2H), 4.08-4.12 and 4.17-4.21 (2H, 2 m, C-1′αH and C-1′βH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 27.44 (-OC(CH_3)$_3$), 41.75 (C-2), 62.63 (C-3′), 65.82 (C-1′), 69.70 (C-2′), 79.42 (-O*C*(CH_3)$_3$), 157.22 (NH*C*O), 170.81 (-CH_2O*C*O); IR data (film) ν_{max}: 3396 (NH and OH), 1746 (-COO-), 1694 (CONH), 1422, 1265 and 741 cm^{-1}; HRMS: *m*/*z* Calcd for $C_{10}H_{19}NO_6Na$ [M+Na]$^+$: 272.1110. Found: 272.1114.

1,3-Bis-{2′-*N*-(*t*-butoxycarbonyl)aminoacetoxy}propane-2-ol (4)

Obtained as a light yellow viscous oil (367 mg, 75% yield) from route-A and (1.4 g, 65% yield) from route-B. R_f: 0.54 (1 : 5 methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 1.42 (18H, s, -OC(CH_3)$_3$), 3.80 (4H, s, C-2′H), 4.01 (1H, *p*, *J* = 5.6 Hz, C-2H), 4.14-4.17 (4H, m, C-1H and C-3H); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 27.42 (2x -OC(CH_3)$_3$), 41.70 (2x C-2′), 65.30 (C-1 and C-3), 66.89 (C-2), 79.39 (2x -O*C*(CH_3)$_3$), 157.21 (2x NH*C*O), 170.60 (2x C-1′); IR data (film) ν_{max}: 3449 (NH and OH), 1751 (-COO-), 1711 (CONH), 1421, 1265, 895 and 738 cm^{-1}; HRMS: *m*/*z* Calcd for $C_{17}H_{30}N_2O_9Na$ [M+Na]$^+$: 429.1849. Found: 429.1859.

Procedure for the synthesis of compounds 6, 7 and 8

Compounds **6**, **7**, and **8** were synthesized according to a published procedure.[30]

Procedure for the synthesis of compound 9

Propargyl bromide (2.5 equiv.) was added to a solution of the compound **6** (20 g, 0.062 mol) and sodium hydride (2.5 equiv.) in dry tetrahydrofuran (70 ml) under argon. The reaction mixture was then stirred at 40–50 °C for 24 h. After completion of reaction, the reaction mixture was filtered and the solvent was evaporated under vacuum. The crude product was further purified by column chromatography on silica gel to give the product **9** as a yellow viscous oil (21.2 g, 95% yield). R_f: 0.45 (1 : 5 methanol–chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 & 1.31 (12H, 2 s, 4 x -CH_3), 2.36 (1H, m, C-3″H), 3.37-3.55, 3.62-3.66, 3.92-4.04 & 4.13-4.17 (15H, 4 m, C-1H, C-2H, C-3H, C-1′H, C-2′H and C-3′H), 4.21-4.22 (2H, m, C-1″H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 25.42 & 26.77 (4 x–CH_3), 57.69 (C-1″), 66.72 & 66.88 (2x C-3′), 71.42 (C-1 and C-3), 71.61 (2x C-2′), 72.44 (2x C-1′), 74.38 (C-3″), 74.63 (C-2″), 76.50 (C-2), 109.33 (2x C-5′); IR data (KBr) ν_{max}: 3054 (HC alkyne stretch), 1594, 1372, 1265, 1081 and 738 cm^{-1}; HRMS: *m*/*z* Calcd for $C_{18}H_{30}O_7Na$ [M+Na]$^+$: 381.1889. Found: 381.1902.

Procedure for the synthesis of compound 10

Ion-exchange resin Dowex® 50 W was added to a solution of the compound **9** (19.3 g, 55.88 mmol) in MeOH (100 ml), and the mixture was heated at reflux overnight. The resin was filtered off, and the residue was concentrated under vacuum to yield the compound **10** as a yellow viscous oil (14.81 g, 99% yield). R_f: 0.20 (1 : 5 methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 2.84 (1H, m, C-3″H), 3.46-3.48, 3.50-3.60 & 3.86-3.87 (15H, 3 m, C-1H, C-2H, C-3H, C-1′H, C-2′H and C-3′H), 4.31 (2H, d, *J* = 2.4 Hz, C-1″H); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 57.01 (C-1″), 63.14 (2x C-3′), 70.75 (C-1 and C-3), 70.89 (2x C-2′), 72.67 (2x C-1′), 74.56 (C-3″), 76.52 (C-2), 79.65 (C-2″); IR data (KBr) ν_{max}: 3377 (OH), 1593, 1457, 1384, 1047 and 662 cm^{-1}; HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_7Na$ [M+Na]$^+$: 301.1263. Found: 301.1270

Compound 11

Obtained as a light yellow viscous oil (386 mg, 81% yield). R_f: 0.35 (1 : 5 methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 1.42 (9H, s, -OC(CH_3)$_3$), 3.48-3.60, 3.69-3.73, 3.92-3.94 & 4.10-4.22 (15H, 4 m, C-1′H, C-2′H, C-3′H, C-1″H, C-2″H, C-3″H, C-1‴H, C-2‴H and C-3‴H), 3.80 (2H, s, C-2H); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 27.42 (-OC(CH_3)$_3$), 41.75 (C-2), 60.65 (C-2″), 62.94 (C-3‴), 65.80 (C-1′), 68.03 (C-2′), 70.75 (C-1″ and C-3″), 70.78 (C-2‴), 71.99 (C-1‴), 72.34 (C-3′), 79.41 (-O*C*(CH_3)$_3$), 157.19 (NH*C*O), 170.74 (C-1); IR data (KBr) ν_{max}: 3396 (NH and OH), 2130 (N_3 stretch), 1736 (-COO-), 1674 (CONH), 1520, 1367, 1162 and 1053 cm^{-1}; HRMS: *m*/*z* Calcd for $C_{16}H_{30}N_4O_9Na$ [M+Na]$^+$: 445.1910. Found: 445.1927.

Compound 12

Obtained as a light yellow viscous oil (356 mg, 76% yield). R_f: 0.31 (1 : 5 methanol–chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (9H, s, -OC(CH_3)$_3$), 2.45 (1H, t, *J* = 2.4 Hz, C-3⁗H), 2.87, 2.94 (3x–OH), 3.52-3.74, 3.85-3.87, 4.16-4.23 and 4.27-4.29 (17H, 4 m, C-1′H, C-2′H, C-3′H, C-1″H, C-2″H, C-3″H, C-1‴H, C-2‴H, C-3‴H and C-1⁗H), 3.92 (2H, d, *J* = 5.6 Hz, C-2H), 5.08 (1H, br s, NH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 27.40 (-OC(CH_3)$_3$), 41.72 (C-2), 57.05 (C-1⁗), 63.09 (C-3‴), 65.86 (C-1′), 68.06 (C-2′), 70.83 (C-1″ and C-3″), 70.84 (C-2‴), 72.11 (C-1‴), 72.59 (C-3′), 74.53 (C-3⁗), 76.65 (C-2″), 79.12 (C-2⁗), 79.39 (-O*C*(CH_3)$_3$), 157.22 (NH*C*O), 170.76 (C-1); IR data (KBr) ν_{max}: 3388 (NH and OH), 1746 (-COO-), 1705 (CONH), 1514, 1368, 1265, 1164 and 737 cm^{-1}; HRMS: *m*/*z* Calcd for $C_{19}H_{33}NO_{10}Na$ [M+Na]$^+$: 458.1997. Found: 458.1994.

Compound 13

Obtained as a light yellow viscous oil (194 mg, 71% yield) from route-A and (297 mg, 68% yield) from route-B. R_f: 0.49 (1 : 5, methanol–chloroform); ^{1}H NMR (400 MHz, methanol-d_4): δ 1.43 (18H, s, 2x -OC(CH_3)$_3$), 3.80 (4H, s, 2x C-2″H), 3.51-3.52, 3.55-3.68, 3.92-3.94, 4.10-4.14 and 4.18-4.22 (15H, 5 m, C-1H, C-2H, C-3H, 2x C-1′H, 2x C-2′H and 2x C-3′H); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 27.42 (2x -OC(CH_3)$_3$), 41.73 (2x C-2″), 60.57 (C-2), 65.80 (2x C-3′), 68.02 (2x C-2′), 70.76 (C-1 and C-3), 72.01 (2x C-1′), 79.37 (2x -O*C*(CH_3)$_3$, 157.20 (2x NH*C*O), 170.72 (2x C-1″); IR data (KBr) ν_{max}: 3398 (NH and OH), 2106 (N_3 stretch), 1750 (-COO-), 1697 (CONH), 1508, 1394, 1265, 1163, 1056 and 738 cm^{-1}; HRMS: *m*/*z* Calcd for $C_{23}H_{41}N_5O_{12}Na$ [M+Na]$^+$: 602.2644. Found: 602.2636.

Compound 14

Obtained as a light yellow viscous oil (300 mg, 73% yield) from route-A and (367 mg, 69% yield) from route-B. R_f: 0.45 (1 : 5,

methanol–chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (18H, s, -OC(CH_3)$_3$), 2.45 (1H, s, C-3‴H), 2.62 (2x–OH), 3.42 (4H, s, 2x C-2″H), 3.53-3.61, 3.89-3.99, 4.07-4.14 and 4.19-4.26 (17H, 4 m, C-1H, C-2H, C-3H, 2x C-1′H, 2x C-2′H, 2x C-3′H and C-1‴H), 5.28 (2H, br s, 2x CONH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 27.41 (2x -OC(CH_3)$_3$), 41.72 (2x C-2″), 57.05 (C-1‴), 65.89 (2x C-3′), 68.06 (2x C-2′), 70.85 (C-1 and C-3), 72.13 (2x C-1′), 74.54 (C-3‴), 76.65 (C-2), 79.35 (C-2‴), 79.75 (2x -OC(CH_3)$_3$, 157.18 (2x NHCO), 170.73 (2x C-1″); IR data (KBr) ν_{max}: 3379 (NH and OH), 1738 (-COO-), 1711 (CONH), 1519, 1367, 1251, 1165, 1055 and 735 cm^{-1}; HRMS: *m/z* Calcd for $C_{26}H_{44}N_2O_{13}Na$ [M+Na]$^+$: 615.2741. Found: 615.2767.

Compound 15

Compound **8** (500 mg, 0.0018 mol), octadecyl-propargyl ether[31] (1.5 mol eq.), *N*,*N*-diisopropyl ethylamine (1.5 mol eq.) and copper triphenylphosphine bromide (catalytic amount) were dissolved in dimethylformamide and the reaction mixture was left stirring at 50 °C for 24 h. The reaction mixture was monitored by TLC and after completion of reaction, the solvent was removed under reduced pressure and the residue subjected to column chromatography. Elution with 20% methanol–chloroform gave the desired product **15** (900 mg, 83% yield) as a light yellow viscous oil. R_f: 0.35 (1 : 5 methanol–chloroform); ^{1}H NMR (400 MHz, methanol-d_4): δ 0.87 (3H, t, J = 6.8 Hz, C-18‴″H), 1.26 (30H, brs, C-3cH to C-17cH), 1.56 (2H, brs, C-2cH), 3.43-3.53 (11H, m, C-1′H, C-2′H, C-3′H, C-2H), 3.71 (2H, brs, C-1cH), 3.92-3.98 (4H, m, C-1H and C-3H), 4.55 (2H, brs, C-1bH), 8.15 (1H, s, C-5aH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 13.16 (C-18c), 22.42, 25.91, 29.16, 29.32, 29.47, 31.76 (C-2c to C-17c), 61.11 (C-2), 62.84 (2x C-3′), 63.40 (C-1b), 70.01 (2x C-1′), 70.44 (C-1c), 70.63 (2x C-2′), 72.32 & 72.45 (C-1 and C-3), 123.71 (C-5a), 144.43 (C-4a); IR data (KBr) ν_{max}: 3365 (OH), 1661 (-C=C-), 1379, 1264, 1104, 1047 and 736 cm^{-1}; HRMS: *m/z* Calcd for $C_{30}H_{59}N_3O_7Na$ [M+Na]$^+$: 596.4251. Found: 596.4268.

Compound 16

Obtained as a yellow viscous oil (184 mg, 77% yield). R_f: 0.45 (1 : 5, methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 0.88 (3H, t, J = 6.8 Hz, C-18cH), 1.28 (26H, brs, C-4cH to C-16cH), 1.42 (13H, brs, -OC(CH_3)$_3$, C-3cH and C-17cH), 1.54-1.57 (2H, m, C-2cH), 3.43-3.50, 3.68-3.71 3.91-3.93 and 4.03-4.09 (17H, m, C-1H, C-2H, C-3H, C-1′H, C-2′H, C-3′H, C-1‴H, C-2‴H, C-3‴H and C-1cH), 3.78 (2H, s, C-2″H), 4.55 (2H, s, C-1bH), 8.06 (1H, s, C-5aH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 13.15 (C-18c), 22.42, 25.0, 29.16, 29.46, 30.38, 31.76 and 35.68 (C-2c to C-17c and -OC(CH_3)$_3$), 41.71(C-2″), 61.00 (C-2), 62.88 (C-3‴), 63.32 (C-1b), 65.57 (C-3′), 67.87 (C-2′), 69.92 & 70.02 (C-1‴ and C-1′), 70.38 (C-1c), 70.77 (C-2‴), 72.36 & 72.45 (C-1 and C-3), 79.32 (-OC(CH_3)$_3$), 123.71 (C-5a), 144.43 (C-4a), 157.18 (NHCO), 163.55 (C-1″); IR data (KBr) ν_{max}: 3388 (NH and OH), 1749 (-COO-), 1662 (CONH), 1515, 1378, 1165, 1056 and 737 cm^{-1}; HRMS: *m/z* Calcd for $C_{37}H_{70}N_4O_{10}Na$ [M+Na]$^+$: 753.4990. Found: 753.5011.

Compound 17

Obtained as a light yellow viscous oil (134 mg, 74% yield) from route-A and (213 mg, 69% yield) from route-B. R_f: 0.50 (1 : 5, methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 0.82 (3H, t, J = 6.8 Hz, C-18cH), 1.20 (28H, brs, C-3cH to C-16cH), 1.36 (22H, brs, 2x -OC(CH_3)$_3$, C-2cH and C-17cH), 3.39-3.43, 3.52-3.54, 3.63-3.64, 3.84-3.88 and 3.97-4.01 (15H, m, C-1H, C-2H, C-3H, C-1′H, C-2′H and C-3′H), 3.69 (2H, brs, C-1cH), 3.72 (4H, brs, C-2″H), 4.49 (2H, s, C-1bH), 7.99 (1H, s, C-5aH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 13.17 (C-18c), 22.44, 25.92, 27.43, 29.18, 29.48 and 31.77 (C-2c to C-17c and 2x -OC(CH_3)$_3$), 41.69 (2x C-2″), 60.93 (C-2), 63.32 (C-1b), 65.58 (2x C-3′), 67.90 (2x C-2′), 69.96 (C-1c), 70.46 (2x C-1′), 71.86 (C-1 and C-3), 79.32 (2x -OC(CH_3)$_3$), 123.76 (C-5a), 144.44 (C-4a), 157.19 (2xNHCO), 170.41 and 170.61 (2xC-1″); IR data (KBr) ν_{max}: 3365 (NH and OH), 1751 (-COO-), 1701 (CONH), 1515, 1379, 1165, 1056 and 737 cm^{-1}; HRMS: *m/z* Calcd for $C_{44}H_{81}N_5O_{13}Na$ [M+Na]$^+$: 910.5729. Found: 910.5765.

General procedure for the synthesis of compounds 18 and 19

Compounds **16** and **17** (100 mg) were treated overnight with a mixture of trifluoroacetic acid : dichloromethane (1 : 3). The reaction mixture was evaporated under reduced pressure to afford the mono and diamino aliphatic dendrons **18** and **19**, respectively, as viscous oils.

Compound 18

Obtained as a dark yellow viscous oil (76 mg, 90% yield). R_f: 0.45 (1 : 5, methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 0.88 (3H, t, J = 6.8 Hz, C-18cH), 1.26 (30H, brs, C-3cH to C-17cH), 1.54-156 (2H, m, C-2cH), 3.44-3.52 and 3.90-3.97 (17H, 2 m, C-1H, C-2H, C-3H, C-1′H, C-2′H, C-3′H, C-1‴H, C-2‴H, C-3‴H and C-1cH), 3.75 (2H, s, -NH$_2$), 3.85 (2H, s, C-2″H), 4.56 (2H, s, C-1bH), 7.95 (1H, s, C-5aH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 13.13 (C-18c), 22.40, 25.89, 29.14, 29.28, 29.45, 30.40, 31.74 and 35.70 (C-2c to C-17c), 39.74(C-2″), 61.01 (C-2′), 62.87 (C-3‴), 63.30 (C-1b), 66.59 (C-3′), 67.66 (C-2′), 69.93 & 69.99 (C-1′ and C-1‴), 70.45 (C-1c), 70.70 (C-2‴), 71.63 & 72.38 (C-1 and C-3), 123.74 (C-5a), 144.51 (C-4a), 163.63(C-1″); IR data (KBr) ν_{max}: 3398 (NH and OH), 1749 (-COO-), 1420, 1384, 1265, 895, 738 and 705 cm^{-1}; HRMS: *m/z* Calcd for $C_{32}H_{63}N_4O_8$ [M+H]$^+$: 631.4646. Found: 631.4659.

Compund 19

Obtained as a yellow viscous oil (70 mg, 90% yield). R_f: 0.50 (1 : 5, methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 0.87 (3H, t, J = 6.8 Hz, C-18cH), 1.26 (30H, brs, C-3cH to C-17cH), 1.54-156 (2H, m, C-2cH), 3.45-3.52, 3.88-396 and 4.09-4.16 (17H, 3 m, C-1H, C-2H, C-3H, C-1′H, C-2′H, C-3′H and C-1cH), 3.84 (4H, brs, C-2″H), 4.56 (2H, s, C-1bH), 8.07 (1H, s, C-5aH); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 13.14 (C-18c), 22.40, 25.89, 29.14, 29.45 and 31.74 (C-2c to C-17c), 39.71 (2x C-2″), 60.95 (C-2), 63.30 (C-1b), 66.64 (2x C-3′), 67.70 (2x C-2′), 69.99 (C-1c), 70.48 (2x C-1′), 71.66 (C-1 and C-3), 123.67 (C-5a), 144.45 (C-4a), 167.08 (2x C-1″); IR data (KBr) ν_{max}: 3395 (NH), 1747 (-COO-), 1384, 1203, 1128, 1050 and 722 cm^{-1}; HRMS: *m/z* Calcd for $C_{34}H_{66}N_5O_9$ [M+H]$^+$: 688.4861. Found: 688.4900.

General procedure for the synthesis of compounds 23 and 24

Compound **20** (400 mg, 0.0029 mol) was dissolved in DMF and potassium carbonate (1.5 mol eq.) was added. Benzyl bromide (**21**, 1.5 mol eq.) or 4-fluorobenzyl bromide (**22**, 1.5 mol eq.) was added dropwise under an ice bath for 1 h and the reaction mixture was left for stirring for 6 h. After completion of reaction, the reaction mixture was poured over crushed ice and extracted with ethyl acetate. The organic layer was then evaporated under reduced pressure and the crude product obtained was purified by column chromatography (60 : 40, ethyl acetate–hexane) to afford compound **23** as white solid[32] and compound **24** as viscous oil in 80 and 82% yields, respectively.

4-Fluorobenzyl 3-hydroxy-2-(hydroxymethyl)-2-methyl propanoate (24)

Obtained as a colorless viscous oil (592 mg, 82% yield). R_f: 0.45 (1 : 5, methanol–chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (3H, s, -CH_3), 2.97 (2 x OH), 3.82 (4H, dd, J = 11.4 Hz, J = 11.2 Hz, C-3H), 5.16 (2H, s, C-1′H), 7.02 -7.08 (2H, m, C-3″H and C-5″H), 7.31-7.36 (2H, m, C-2″H and C-6″H); ^{13}C NMR (75.5 MH_Z, $CDCl_3$): δ 17.08 (-CH_3), 49.25 (C-2) 65.97 (C-1′), 68.14 (2 x C-3), 115.44 (C-3″), 115.72 (C-5″), 129.84 (C-2″), 129.95 (C-6″), 131.52 (d, J = 3 Hz, C-1″), 162.66 (d, J = 246 Hz, C-4″), 175.65 (C-1); IR (KBr): 3234 (OH), 1729 (-COO), 1513, 1224, 1047 and 831 cm^{-1}; HRMS: m/z Calcd for $C_{12}H_{15}FO_4Na$ [M+Na]$^+$: 265.0847. Found: 265.0848.

Benzyl 2-{(2′-*N*-(*tert*-butoxycarbonylamino)acetoxymethyl}-3-hydroxy-2-methylpropanoate (25)

Obtained as a light yellow viscous oil (240 mg, 71% yield). R_f: 0.60 (1 : 5 methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 1.18 (3H, s, -CH_3), 1.42 (9H, s, -OC(CH_3)$_3$), 3.65-3.70 (2H, m, C-3H), 3.77 (2H, s, C-2′H), 4.32 (2H, s, C-1″H), 5.13 (2H, s, C-1‴H), 7.29-7.35 (5H, m, C-2⁗H, C-3⁗H, C-4⁗H, C-5⁗H and C-6⁗H); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 16.37 (-CH_3), 27.39 (-OC(CH_3)$_3$), 41.65 (C-2′), 62.46 (C-3), 64.04 (C-1″), 66.25 (C-1‴), 78.16 (C-2), 79.34 (-OC(CH_3)$_3$), 127.76 (C-2⁗ and C-6⁗), 127.88 (C-4⁗), 128.25 (C-3⁗ and C-5⁗), 136.185 (C-1⁗), 157.19 (NHCO), 170.64 (C-1′), 173.79 (C-1); IR data (KBr) ν_{max}: 3447 (NH and OH), 1751 (-COO-), 1712 (CONH), 1421, 1265, 1163, 895, 738 cm^{-1}; HRMS: m/z Calcd for $C_{19}H_{27}NO_7Na$ [M+Na]$^+$: 404.1685. Found: 404.1708.

4-Fluorobenzyl 2-{(2′-*N*-(*tert*-butoxycarbonylamino) acetoxymethyl}-3-hydroxy-2-methylpropanoate (26)

Obtained as a light yellow viscous oil (244 mg, 74% yield). R_f: 0.55 (1 : 5, methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 1.18 (3H, s, -CH_3), 1.42 (9H, s, -OC(CH_3)$_3$), 3.66 and 3.79 (2H, 2d, J = 8.4 Hz, C-3Hα and C-3Hβ), 3.72 (2H, s, C-2′H), 4.25-4.32 (2H, m, C-1″H), 5.11 (2H, s, C-1‴H), 7.04-7.08 (2H, m, C-3⁗H and C-5⁗H), 7.35-7.39 (2H, m, C-2⁗H and C-6⁗H); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 16.45 (-CH_3), 27.50 (-OC(CH_3)$_3$), 41.72 (C-2′), 64.08 (C-3), 65.05 (C-1″), 65.98 (C-1‴), 78.16 (C-2), 79.39 (-OC(CH_3)$_3$), 115.01 (d, J = 21.7 Hz, C-3⁗ and C-5⁗), 129.99 (d, J = 8.4 Hz, C-2⁗ and C-6⁗), 132.23 (d, J = 3.3 Hz, C-1⁗), 157.08 (NHCO), 162.67 (d, J = 245.2 Hz, C-4⁗), 170.52 (C-1′), 173.70 (C-1); IR data (KBr) ν_{max}: 3449 (NH), 1750 (-COO-), 1714 (CONH), 1421, 1265, 1164, 895 and 738 cm^{-1}; HRMS: m/z Calcd for $C_{19}H_{26}FNO_7Na$ [M+Na]$^+$: 422.1591. Found: 422.1586.

3′-Hydroxy-2′-hydroxymethyl-2′-nitropropyl 2-*N*-(*tert*-butoxycarbonylamino)acetate (29)

Obtained as a dark yellow viscous oil (326 mg, 80% yield). R_f: 0.45 (1 : 5, methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 1.43 (9H, s, -OC(CH_3)$_3$), 3.79 (2H, s, C-2H), 3.93 (4H, s, C-3′H and C-1″H), 4.58 (2H, s, C-1′H); ^{13}C NMR (100.5 MHz, methanol-d_4): δ 27.37 (-OC(CH_3)$_3$), 41.65 (C-2), 59.56 & 59.99 (C-3′ and C-1″), 60.46 (C-1′), 79.52 (-OC(CH_3)$_3$), 92.91 (C-2′), 157.24 (NHCO), 169.96 (C-1); IR data (KBr) ν_{max}: 3382 (NH and OH), 1748 (-COO-), 1693 (CONH), 1548, 1162 and 1054 cm^{-1}; HRMS: m/z Calcd for $C_{11}H_{20}N_2O_8Na$ [M+Na]$^+$: 331.1117. Found: 331.1126.

2′,2′-Bis(hydroxymethyl)butyl 2-*N*-(*tert*-butoxycarbonylamino)acetate (30)

Obtained as a light yellow viscous oil (338 mg, 78% yield). R_f: 0.55 (1 : 5, methanol–chloroform). ^{1}H NMR (400 MHz, methanol-d_4): δ 0.86 (3H, t, J = 7.6 Hz, C-4′H), 1.37 (2H, q, J = 7.2 Hz, C-3′H), 1.43 (9H, s, -OC(CH_3)$_3$), 3.45 (4H, s, C-1″H and C-1‴H), 3.77 (2H, s, C-2H), 4.02 (2H, s, C-1′H). ^{13}C NMR (100.5 MHz, methanol-d_4): δ 6.36 (C-4′), 21.53 (C-3′), 27.41 (-OC(CH_3)$_3$), 41.83 (C-2), 42.79 (C-2′), 61.70 (C-1″ and C-1‴), 64.69 (C-1′), 79.35 (-OC(CH_3)$_3$), 157.22 (NHCO), 170.92 (C-1); IR data (KBr) ν_{max}: 3447 (NH), 1742 (-COO-), 1713 (CONH), 1674, 1421, 1265, 895 and 738 cm^{-1}; HRMS: m/z Calcd for $C_{13}H_{25}NO_6Na$ [M+Na]$^+$: 314.1580. Found: 314.1584.

Conclusions

In the present work, we have achieved the chemo-enzymatic regioselective synthesis of fourteen novel esters of glycerol, triglycerol dendrons, and related esters, *i.e.* compounds **3**, **4**, **11–14**, **16–19**, **25**, **26**, **29**, and **30** for the first time by biocatalytic transesterification using 4-nitrophenyl 2-(*tert*-butoxycarbonyl)acetate (Boc-Gly-Ph-*p*NO_2) (**2**) as the acylating agent. Temperature-dependent lipozyme-catalyzed transesterification reactions of these polyhydroxy compounds were carried out in dioxane at 50 and 70 °C to afford mono- and di-esterified products in good yields, respectively. The protected amino acid, *N*-Boc-glycine 4-nitrophenyl ester (**2**) has been used for the first time for selectively protecting hydroxyl groups in biocatalytic transesterification reactions. This methodology offers efficient and controlled loading of amino acid (glycine) on polyhydroxy compounds and represents a platform for the selective amino acid attachment (decoration) to the PG scaffolds.

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