Tetrahedron Letters 51 (2010) 4411–4414

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Novel galactosyl donor with 2-naphthylmethyl (NAP) as the non-participating group at C-2 position: efficient synthesis of α-galactosyl ceramide

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ARTICLE INFO

Article history:
Received 12 April 2010
Revised 10 June 2010
Accepted 14 June 2010
Available online 19 June 2010

Keywords:
Glycans
α-Galactosyl ceramide
2-Naphthylmethyl (NAP)
Oligosaccharides

ABSTRACT

Predominant α-linked products can be generated in glycosylation involving galactosyl trichloroacetimidate donors with 2-naphthylmethyl (NAP) as the non-participating group at C-2 position. The above-mentioned donor was successfully utilized for the synthesis of α-galactosyl ceramide.

1. Introduction

Glycans, the vital endogenous biomolecules, found mostly in conjugation with lipids (to form glycolipids) and proteins (to form glycoproteins), are composed of various monosaccharide units linked together through O-glycosidic linkages. They are crucially engaged in various biochemical pathways and biological processes viz., cell-cell communication, cell adhesion, immune response, molecular recognition, tissue repair, and microbial and viral pathogenesis.[1] Therefore, practical and stereocontrolled synthesis of glycans occupies great importance in carbohydrate chemistry where a glycosylation reaction involving a donor and an acceptor can yield α- as well as β-isomers during the glycosidic bond formation.[2] Despite the enormous efforts put in by various groups for the development of efficient and stereoselective glycosylation methodologies, not all problems are completely answered.[3] In carbohydrate chemistry, generally it is believed that the glycosylation with glycosyl donors possessing an *O*-acyloxyl group at C-2 usually afford 1,2-*trans* glycoside with quite high stereoselectivity by virtue of its neighboring group participation.[2k,n,4] But, some reports revealed unusual 1,2-*cis*-glycosylation,[5] α-(1→3)-glycosylations,[6] and 1,2-*cis*-galactosylations[7] with glycosyl donors having a C-2 ester capable of neighboring group participation.

Stereoselective synthesis of 1,2-*cis* glycosides is usually a more difficult issue where no assistance by neighboring group participation is available.[2f] For instance, the stereoselective construction of certain 1,2-*cis* glycosyl linkages such as α-glucopyranosyl,[8] α-galactopyranosyl,[9] α-arabinofuranosyl,[10] α-sialyl linkages,[11] and β-mannopyranosyl[12] still presents significant challenge as each case requires a special strategy when applied to construct a complex carbohydrate structure.

In general, a non-assisting functionality at C-2 position of glycosyl donors in most cases is a benzyl, a substituted benzyl or allyl group for the introduction of 1,2-*cis*-glycosidic linkages. Invariably, the use of these glycosyl donors leads to the formation of mixtures of anomers.[2f] Time-consuming purification protocols are required for the separation of these anomers which also results in the loss of material. In order to find a better stereoselective glycosylation methodology, we became interested in checking the influence of 2-naphthylmethyl (NAP) group as a non-participating group in 1,2-*cis* α-galactosyl bond formation as it is endowed with versatile properties such as stability to variety of acidic and basic conditions, selective introduction, and chemoselective removal.[13] With the intention of studying the stereoselectivity–structure relationship, a variety of donors (with *O*-NAP group at C-2) and acceptors were used for coupling together (Table 1). Herein, we describe the results for the above-described coupling reactions and successful application of our findings to the synthesis of biologically important α-galactosyl ceramide **24**.[14] The synthesis of modified analogs of this molecule is the focus of attention in numerous laboratories.[14]

2. Results and discussion

Galactosyl imidates used for 1,2-*cis* galactosylations suffer from certain drawbacks. For example, 2,3,4,6-tetra-*O*-benzyl-galactosyl donor generates anomeric mixtures which are difficult to purify

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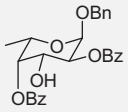
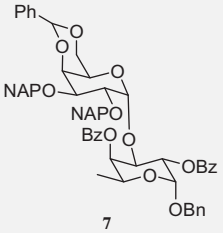
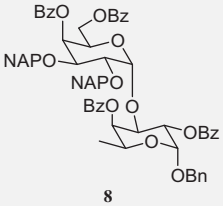
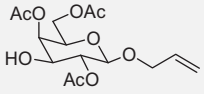
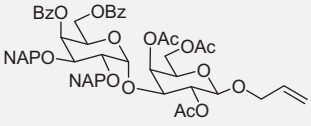
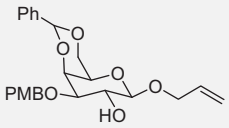
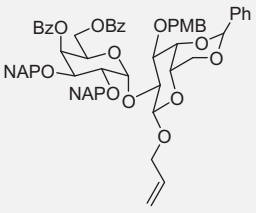
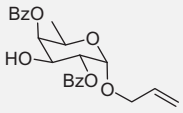
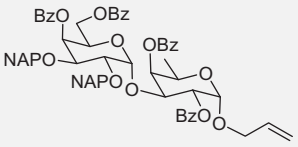
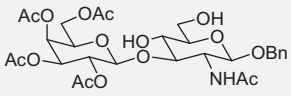
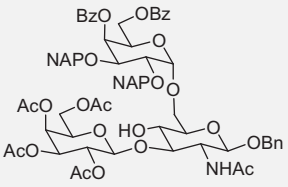
doi:10.1016/j.tetlet.2010.06.071

Table 1
Coupling results with different donors and acceptors[a]

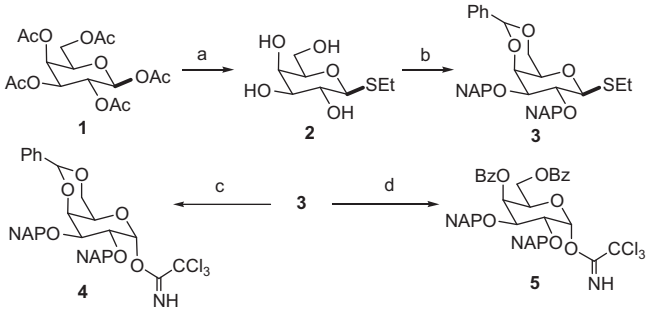
Entry	Donor (1.2 equiv)	Acceptor (1 equiv)	Product	Yield (%)	Ratio (α/β)
1	**4**	 **6**	 **7**	68	9:1
2	**5**	**6**	 **8**	88	Only α
3	**5**	 **9**	 **10**	82	Only α
4	**5**	 **11**	 **12**	68	6.2:1
5	**5**	 **13**	 **14**	78	Only α
6	**5**	 **15**	 **16**	74	Only α

[a] All the reactions were conducted using TMSOTf (0.2 equiv) in CH_2Cl_2 and at −15 °C. The reactions were completed within 3–4 h.

after glycosylation.[9c] Furthermore, its 4,6-benzylidene derivative is highly unstable and difficult to isolate and store.[9c] Inspired by the past success of NAP group in glycosylation, we became interested in exploring the applicability of NAP group being utilized as a non-participating group in α-glycosylations.[15]

We designed the synthesis of galactosyl donor **4** starting from D-galactose pentaacetate (**1**). Treatment of **1** with ethanethiol and BF_3–OEt_2 at 0 °C gave β-ethylthio galactoside,[16] which on Zemplén deacetylation[17] provided crystalline β-thioethyl galactoside **2** in 92% yield over two steps. Benzylidene protection of β-galactoside **2** with benzaldehyde dimethylacetal and PTSA followed by naphthylmethylation[13] of 2,3-hydroxyl groups provided compound **3** as a white solid in 78 % yield (for two steps). The removal of anomeric ethylthio group of **3** was accomplished using NBS,[18] followed by activation of the resultant hemiacetal with trichloroacetonitrile in the presence of DBU as a base,[9c] to afford the imidate **4** in 74% yield over two steps (Scheme 1).

We first examined the use of compound **4** as a galactosyl donor using benzyl 2,4-dibenzoyl-α-L-fucoside **6** as an acceptor, the reaction gave a moderate yield of dissacharide **7** with low α-selectivity (Table 1, entry 1). The ^1H NMR spectra of compound **7** showed a doublet at δ 5.63 for anomeric proton with $J_{1,2}$ = 3.7 Hz which confirm the α-stereochemistry in the dissacharide **7**. It was found (also reported for similar imidate in the literature) that the imidate **4** is very unstable and difficult to store.[9c] In order to increase the stability and α-selectivity of the donor **4**, the benzylidene protection was replaced with dibenzoyl ester protection. The dibenzoyl ester protection at C-4 and C-6 makes donor **5** less reactive than donor **4**

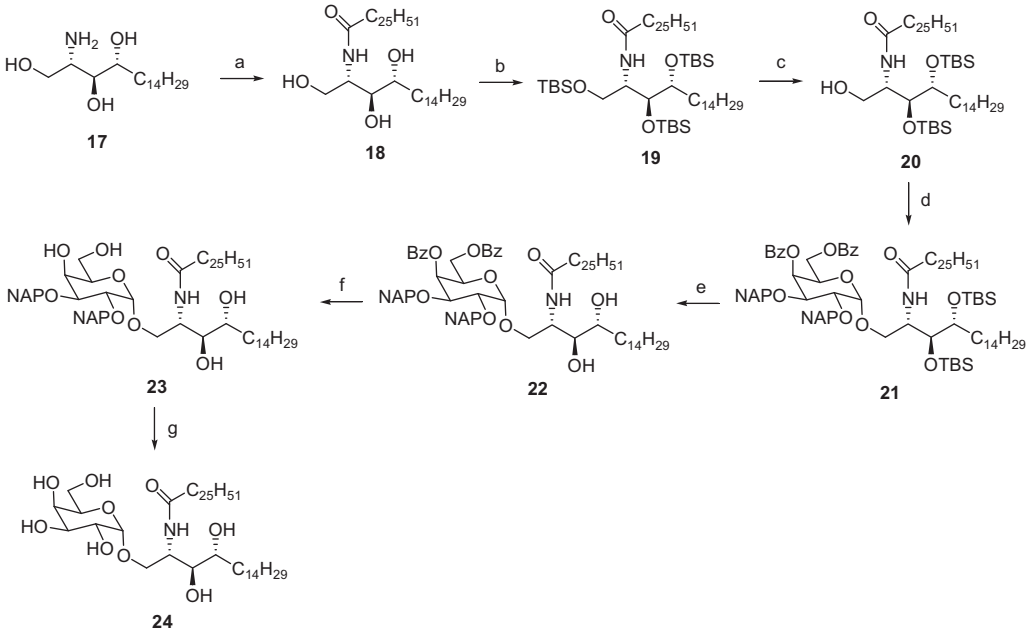


Scheme 1. Preparation of donor **4** and **5**. Reagents and conditions: (a) (i) DCM–ethanethiol (2.5 equiv), $BF_3{\cdot}Et_2O$ (1.5 equiv), 0 °C, 6 h, (ii) NaOMe (1 M), MeOH, rt, 20 h, 92% for two steps; (b) (i) $PhCH(OMe)_2$ (2 equiv), *p*-TsOH (0.1 equiv), rt, 6 h, (ii) NAP-Br (2.8 equiv), NaH (4 equiv), THF, rt, 6 h, 78% for two steps; (c) (i) NBS (1.4 equiv), acetone, 0 °C, 2 h, (ii) CCl_3CN (10 equiv), DBU (0.5 equiv), CH_2Cl_2, 0 °C, 30 min, 74% for two steps; (d) (i) 60% HOAc, 60 °C, 5 h, (ii) BzCl (3 equiv), py, rt, 6 h, (iii) NBS (1.4 equiv), acetone, 0 °C, 2 h, (iv) CCl_3CN (10 equiv), DBU (0.5 equiv), CH_2Cl_2, 0 °C, 30 min, 58%.

and hence, provides greater possibility of higher selectivity. Thus, removal of benzylidine ring of **3**, followed by conventional dibenzoylation, deprotection of anomeric ethylthio group, and finally treatment with trichloroacetonitrile and DBU afforded the desired galactosyl imidate **5** as a white crystalline solid in 58% yield over four steps (Scheme 1). As prerequisite, the galactosyl donor **5** was found to be very stable with a long shelf-life. It was found to be stable below 5 °C for over six months. Donor **5** was coupled initially with α-L-fucoside **6** in the presence of TMSOTf to give the disaccharide **8** in 88% yield with complete α-selectivity (Table 1, entry 2). The ^1H NMR spectra of compound **8** are indicative of the α-stereochemistry in the glycosylation reaction.

Encouraged by the initial results, we tested for the generality and efficiency of α-selectivity of donor **5** with other acceptors. A series of suitably protected mono- and disaccharide acceptors were glycosylated with donor **5** and the results are summarized in Table 1 (entries 2–6). It is evident from Table 1 that the donor **5** is a versatile alternative to donor **4**, furnishing the expected α-glycosides with remarkable stereoselectivities (entries 2, 3, 5, and 6). Presumably, the higher α-selectivity may be attributed to the low reactivity of donor **5** and non-participating nature of NAP group at C-2 position. Also, the effect of remote participation by 4- and 6-benzoyl group for the enhancement of α-selectivity could not be ruled out in this case. It is worth mentioning here that the similar glycosylation reaction when performed with imidate having benzyl group in the place of NAP gave a mixture of α:β products with very high β-selectivity.[19]

Having established the utility of novel galactosyl donor **5**, we initiated the synthesis of α-galactosy ceramide **24** (KRN7000), using this novel galactosyl donor (Scheme 2). Our synthetic route to galactosyl ceramide **24** started with the amidation reaction of hexacosanoic acid and commercially available phytosphingosine. Several attempts of N-acylation of sphingosine **17** with DCC and DIC were unsuccessful. Finally, sphingosine **17** was coupled with hexacosanoic acid using HOBT and EDC in DMF at 100 °C[20] to obtain the ceramide chain **18** in 92% yield. Compound **18** was silylated using TBSOTf and lutidine to yield the known TBS ether **19**[21] in 82% yield. The spectral data (^1H and ^{13}C NMR) of compound **19** obtained were identical with the literature values.[21] Chemoselective deprotection of **19**, to obtain free primary hydroxyl group, was carried out using 10% aq TFA in THF at −10 to 10 °C to provide compound **20** in 88% yield.[20,21] Glycosylation of **20** with **5** using TMSOTf in THF at −30 °C gave the desired product α-galactosyl ceramide **21** in 68 % yield. The stereoselectivity of the glycosylation was readily determined by ^1H and ^{13}C NMR spectral analysis of compound **21**. Complete deprotection of **21** was carried out in three steps. First, the removal of silyl groups of the ceramide chain of **21** was realized using TBAF in THF[20] to furnish **22** in 86% yield. Next, the treatment of **22** with NaOMe/MeOH resulted in the deprotection of benzoyl groups on galactose sugar affording **23** in quantitative yield. Finally, hydrogenolysis of NAP groups of **23** yielded the desired KRN7000 **24** in quantitative yield. The spectroscopic data for **24** were in accord with those previously reported in the literature.[21,22]



Scheme 2. Synthesis of α-galactosyl ceramide **24**. (a) hexacosanoic acid (1 equiv), EDC (2 equiv), HOBT (1.1 equiv), DMF, 100 °C, 6 h, 92%; (b) TBSOTf (5 equiv), 2,6-lutidine (15 equiv), CH_2Cl_2, 82%; (c) 10% aq TFA, −10 to 10 °C, 2 h, 88%; (d) **5** (1.2 equiv), TMSOTf (0.3 equiv), anhydrous THF, −30 °C, 4 h, 68%; (e) TBAF (4 equiv), THF, 3 h, 86%; (f) NaOMe (1 M), CH_3OH, rt, 6 h, 100%. (g) H_2, Pd–C (10 %), CH_3OH, 8 h, 100%.

3. Conclusions

In summary, the findings described above indicated that the α-linked glycosidic bond can be easily accessed using NAP as a non-participating group at C-2 position of the galactosyl donor **5**. As indicated by the results from glycosylation reactions, it appears that increased α-selectivity in the case of donor **5** is due to its lower reactivity coupled with the remote participation by 4- and 6-benzoyl groups. Moreover, the NAP-protecting group is found to be versatile in terms of introduction and removal. Glycosylation with this donor was successfully applied for the synthesis of KRN7000.

Acknowledgments

We acknowledge grant support from DOD (W81XWH-06-1-0013) and support, in part, by the NCI Cancer Center Support Grant to the Roswell Park Cancer Institute (5R21CA121294-02) and core P30 CA 016056.

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22. The selected analytical data of key compounds are listed: *Compound* **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.62 (s, 1H), 8.02 (d, J = 8.9 Hz, 2H), 7.98 (d, J = 6.9 Hz, 2H), 7.85–7.72 (m, 5H), 7.71–7.64 (m, 2H), 7.60–7.52 (m, 3H), 7.50–7.32 (m, 10H), 6.67 (d, J = 2.9 Hz, 1H), 6.04 (d, J = 1.9 Hz, 1H), 5.04 (d, J = 11.8 Hz, 1H), 4.96 (dd, J = 12.8 Hz, 17.7 Hz, 2H), 4.83 (d, J = 11.8 Hz, 1H), 4.59 (t, J = 5.9 Hz, 1H), 4.52–4.45 (m, 1H), 4.37 (dd, J = 5.9 Hz, 11.8 Hz, 1H), 4.25 (dt, J = 2.9 Hz, 9.8 Hz, 12.7 Hz, 2H). *Compound* **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99–8.12 (m, 6H), 7.88 (d, J = 8.1 Hz, 2H), 7.69 (dd, J = 8.1 Hz, 15.4 Hz, 2H), 7.28–7.62 (m, 20H), 7.14–7.26 (m, 9H), 5.93 (s, 1H), 5.58 (d, J = 3.7 Hz, 10.3 Hz, 1H, H-1), 5.47 (d, J = 2.93 Hz, 1H, H-1′), 5.54 (d, J = 2.9 Hz, 1H), 5.31 (d, J = 3.7 Hz, 1H), 4.87 (dd, J = 4.4 Hz, 7.3 Hz, 1H), 4.74–4.81 (m, 1H), 4.61–4.71 (m, 2H), 4.51–4.60 (m, 2H), 4.42–4.50 (m, 2H), 4.36 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.7 Hz, 1H), 3.98 (dd, J = 6.6 Hz, 13.2 Hz, 1H), 3.87–3.95 (m, 2H), 1.10 (d, J = 5.9 Hz, 3H). *Compound* **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.04 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 7.3 Hz, 2H), 7.81–7.66 (m, 6H), 7.61–7.51 (m, 4H), 7.49–7.38 (m, 8H), 7.30 (t, J = 8.1 Hz, 2H), 5.83–5.72 (m, 2H), 5.79 (d, J = 2.9 Hz, 1H), 5.52 (d, J = 2.9 Hz, 1H), 5.28 (d, J = 2.9 Hz, 1H), 5.25–5.21 (m, 1H), 5.20–5.18 (m, 1H), 5.17–5.12 (m, 1H), 4.95 (d, J = 10.9 Hz, 1H), 4.83 (d, J = 4.4 Hz, 1H), 4.80 (d, J = 10.9 Hz, 1H), 4.47 (dd, J = 4.4 Hz, 10.9 Hz, 1H), 4.38–4.26 (m, 2H), 4.10 (d, J = 6.6 Hz, 2H), 4.03 (dd, J = 3.6 Hz, 8.1 Hz, 2H), 3.97 (d, J = 8.1 Hz, 1H), 3.93–3.83 (m, 3H), 3.57 (t, J = 6.6 Hz, 1H), 2.08 (s, 3H), 1.86 (s, 3H), 1.84 (s, 3H). *Compound* **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.13–8.00 (m, 6H), 7.88 (d, J = 8.1 Hz, 2H), 7.70 (t, J = 8.8 Hz, 2H), 7.60–7.51 (m, 4H), 7.50–7.27 (m, 16H), 7.26–7.15 (m, 4H), 6.73 (d, J = 8.1 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.83–5.72 (m, 1H), 5.60 (dd, J = 3.7 Hz, 10.3 Hz, 1H), 5.55 (d, J = 2.9 Hz, 1H), 5.47 (d, J = 2.9 Hz, 1H), 5.29 (d, J = 3.6 Hz, 1H), 5.27–5.09 (m, 2H), 4.92–4.86 (dd, J = 4.4 Hz, 8.1 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 4.67 (dd, J = 2.9 Hz, 10.3 Hz, 1H), 4.62–4.55 (m, 1H), 4.49–4.42 (m, 2H), 4.32 (dd, J = 12.4 Hz, 24.8 Hz, 2H), 4.15–4.08 (m, 1H), 3.97 (dd, J = 5.8 Hz, 13.2 Hz, 2H), 3.92 (dd, J = 2.2 Hz, 7.3 Hz, 2H), 1.12 (d, J = 6.6 Hz, 3H). *Compound* **21**: ^{1}H NMR δ (ppm) = 8.04–7.98 (m, 4H), 7.68–7.83 (m, 7H), 7.65 (d, J = 7.96, 1H), 7.62 (d, J = 7.96, 1H), 7.52–7.58 (m, 2H), 7.33–7.51 (m, 9H), 5.98 (d, J = 2.7 Hz, 1H), 5.92 (d, J = 7.92 Hz, 1H), 5.04 (d, J = 11.5 Hz, 1H), 5.00 (d, J = 3.1 Hz, 1H), 4.96 (d, J = 11.9 Hz, 1H), 4.87 (d, J = 11.9 Hz, 1H), 4.76 (d, J = 11.5 Hz, 1H), 4.47 (dd, J = 5.8 Hz, 11.1 Hz, 1H), 4.39 (t, J = 6.6 Hz, 1H), 4.29 (dd, J = 7.1 Hz, 11.1 Hz, 1H), 4.20–4.26 (m, 1H), 4.17 (dd, J = 3.1 Hz, 9.7 Hz, 1H), 4.10–4.15 (m, 1H), 4.05 (dd, J = 3.5 Hz, 10.2 Hz, 1H), 3.91–3.95 (m, 1H), 3.76 (t, J = 8.8 Hz, 1H), 3.67 (m, 1H), 1.91–1.96 (m, 2H), 1.44–1.51 (m, 6H), 1.18–1.33 (m, 66H), 0.88–0.90 (m, 6H), 0.91 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 173.1, 135.6, 135.6, 133.3, 133.2, 133.1, 133.1, 133.0, 132.9, 129.9, 129.8, 129.7, 129.7, 128.4, 128.3, 128.2, 127.2, 127.7, 127.6, 127.0, 126.4, 126.1, 126.0, 125.9, 125.9, 125.8, 125.7, 99.8, 76.6, 76.0, 75.6, 75.1, 73.8, 72.0, 68.6, 68.4, 67.4, 62.5, 51.6, 36.8, 33.6, 31.9, 29.9, 29.7, 29.68, 29.64, 29.60, 29.5, 29.43, 29.38, 29.33, 26.1, 26.0, 25.6, 22.6, 18.5, 18.3, 18.1, 14.1, -3.7, -3.9, -4.6, -4.8. *Compound* **22**: ^{1}H NMR δ (ppm) = 8.04–7.95 (t, J = 8.7 Hz, 4H), 7.85–7.72 (m, 5H), 7.62–7.72 (m, 3H), 7.52–7.60 (m, 2H), 7.35–7.51 (m, 10H), 6.22 (d, J = 8.8 Hz, 1H), 5.95 (d, J = 2.9 Hz, 1H), 5.04 (m, 3H), 4.87 (d, J = 11.7 Hz, 1H), 4.77 (d, J = 10.9 Hz, 1H), 4.43–4.49 (m, 1H), 4.42–4.35 (m, 3H), 4.12–4.17 (m, 1H), 4.04 (dd, J = 3.7 Hz, 9.5 Hz, 1H), 3.98 (dd, J = 3.7 Hz, 10.3 Hz, 1H), 3.89 (dd, J = 2.9 Hz, 10.2 Hz, 1H), 3.45–3.56 (m, 2H), 2.27 (bs, H) 2.08 (t, J = 8.1 Hz, 2H), 1.53–1.62 (m, 6H), 1.06–1.37 (m, 66H), 0.88 (t, J = 7.3 Hz, 6H); ^{13}C NMR δ (ppm) = 172.9, 171.9, 133.6, 133.5, 130.2, 130.0, 128.8, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.6, 126.9, 126.5, 126.4, 126.3, 126.2, 126.1, 99.2, 77.7, 77.3, 76.7, 76.1, 74.9, 74.6, 73.5, 72.2, 69.9, 68.4, 67.8, 63.3, 49.7, 37.0, 33.7, 32.2, 30.0, 29.8, 29.7, 29.7, 29.6, 26.5, 26.0, 22.9, 14.4. *Compound* **23**: ^{1}H NMR δ (ppm) = 7.72–7.87 (m, 8H), 7.53–7.43 (m, 6H), 6.46 (d, J = 8.1 Hz, 1H), 4.99 (d, J = 3.7 Hz, 1H), 4.98 (d, J = 3.6 Hz, 1H), 4.90 (s, 2H), 4.86 (d, J = 11.7 Hz, 1H), 4.27 (d, J = 3.6 Hz, 1H), 4.11 (s, 1H), 3.91–4.00 (m, 3H), 3.81–3.91 (m, 3H), 3.70–3.78 (m, 2H), 3.48 (s, 2H), 2.08 (t, J = 7.3 Hz), 1.47–1.66 (m, 6H), 1.37–1.46 (m, H), 1.05–1.38 (m, 66H), 0.89 (t, J = 6.6 Hz, 6H); ^{13}C NMR δ (ppm) = 173.3, 134.94, 134.91, 133.0, 132.9, 128.23, 128.20, 127.8, 127.7, 127.55, 127.52, 126.7, 126.5, 126.1, 126.0, 125.99, 125.93, 125.6, 125.5, 98.4, 77.6, 76.1, 75.4, 74.0, 73.0, 72.4, 70.0, 68.9, 68.4, 62.7, 49.8, 36.8, 33.6, 32.0, 29.8, 29.7, 29.5, 29.4, 29.3, 25.9, 25.84, 22.80, 14.3.