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C-Glycosides of dodecanoic acid: new capping/reducing agents for glyconanoparticle synthesis

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ABSTRACT

A concise synthesis of 12-C-glycosylated dodecanoic acids employing an olefin cross-metathesis reaction is developed. Examination of these acids as capping agents for the synthesis of metal nanoparticles reveals that they do not cap the Co-metal nanoparticles synthesized in aqueous phase, but that two of them can reduce and cap the Ag nanoparticles in water without any aggregation.

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Over the last decade, the potential of noble metal nanoparticles has been explored in various fields such as optics, microelectronics, sensors, and catalysis, and so on.¹ The mutually advantageous conjugation of metal nanoparticles with biomolecules or biologically relevant ligands has gained much impetus because of their promising biomedicinal and bioanalytical applications, in addition to hydrophilic rendition to surfaces and biocompatiblity.² In this context, glyconanoparticles (GNPs), derived from the surface modification of metal nanoparticles by connecting with sugar residues through O-glycoside linkages, have been recognized as novel tools to investigate carbohydrate recognition processes.³ An important issue regarding the in vivo application of glyconanoparticles is their susceptibility to enzymatic degradation. A viable alternative in this regard is C-glycosides, which have served as potential carbohydrate analogs resistant to metabolic processes. C-Glycosides. which entail methylene substitution for the anomeric oxygen, are isosteric mimics of their O-glycoside counterparts, and offer a great deal of stability without substantial conformational amendment.⁴ Though the application of C-glycosylated long chain alkanes has been explored in liquid crystals and as surfactants,⁵ their use in glyconanoparticle synthesis has not yet been documented. Herein, we report our preliminary investigations on the synthesis of $12-\alpha$ -C-glycosyl long chain acids, and their use as capping/reducing agents for silver metal nanoparticles.

As shown in Figure 1, and considering the fact that simple monosaccharides in biological systems can exist either in furanose or in pyranose forms, three compounds 1-3 are selected as representatives of pentoaldofuranose (*D-ribo*), pentoaldopyranose (*D-ribo*), and hexoaldopyranose (*D-gluco*), respectively. The intended retrosynthetic strategy for the C-glycosyl acids 1-3 is based upon the cross-metathesis⁶ of the corresponding peracety-lated C-allyl glycosides **5–7** with 10-undecene-1-ol (**4**) followed by hydrogenation, oxidation, and deprotection.

The synthesis of differently protected α -C-allylribofuranosides⁷ and α -C-allylglucopyranosides⁸ is well established. As shown in Scheme 1, peracetylated allyl glucopyranoside **7** is prepared by adopting the reported procedure.⁸ As allylation of tetraacetyl ribofuranoside was documented to be nonspecific,^{7d} methyl 2,3,5-tri-*O*-acetyl- α -ribofuranoside (**8**)⁹ was subjected to allylation to afford a 11:1 anomeric mixture, α -anomer **5** being the major product.^{7d} Allylation of 2,3,4,5-tetra-*O*-acetyl- β -ribopyranoside (**10**)¹⁰ resulted in a mixture of anomers **6** and **11**.^{5b} The configurations of **6** and **11** were established with the help of NMR spectral analyses.¹¹ However, as the data of compound **6**^{11b} were found to match with those reported for the corresponding β -C-allylribofuranoside,^{7d} we carried out single crystal X-ray structural analysis of **6** (Fig. 2), which confirmed our assignments beyond doubt.¹²⁻¹⁴

Scheme 1 (step b) depicts the general strategy followed for the synthesis of $12-\alpha$ -C-glycosyl dodecanoic acids **1–3**, employing cross-metathesis of C-allyl derivatives **5–7** with 10-undecene-1-ol (**4**). The C-allyl sugar derivative underwent cross-metathesis with 10-undecene-1-ol using Grubbs' 2nd generation catalyst (5 mol %) to afford inseparable mixture of trans/cis olefins **12–14**,

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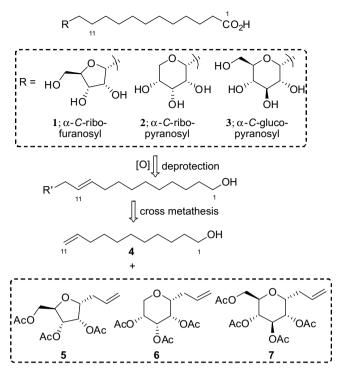
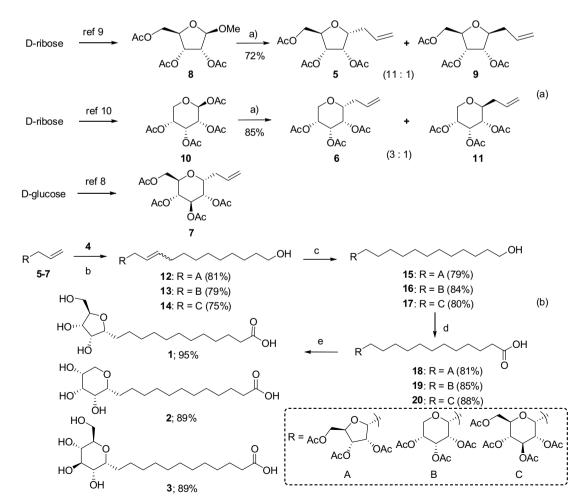


Figure 1. Selected 12-C glycosylated dodecanoic acid and the retrosynthetic strategy.

along with the 10-undecene-1-ol dimer. The olefin mixture was hydrogenated with 5% Pd/C in methanol:ethyl acetate (1:2) to yield saturated alcohols **15–17**. Oxidation of the hydroxyl group to acid with RuCl₃·H₂O and NalO₄¹⁵ followed by deacetylation completed the synthesis of 12-C- α -glycosyldodecanoic acids **1–3** in overall yields of 49%, 50%, and 47%, respectively.¹⁶

After synthesizing the requisite C-glycosyl acids 1-3, the next objective was to use them as capping agents for metal nanoparticles. Our initial experiments with Co-metal nanoparticle synthesis, employing 1-3 as the capping agents under established procedures,¹⁷ resulted in aggregation of the nanoparticles. This may be attributed to the lack of an olefinic moiety in these molecules, which seems to impart stability to metal nanoparticle systems such as Co and Ni.¹⁷ After a substantial optimization of the experimental parameters, a reductive synthesis of desired C-glycoside capped silver nanoparticles (Ag NPs) was concluded successfully by heating silver nitrate and C-glycoside 1 or 2 in dilute alkaline solution.^{18,19} The reduction was instantaneous and the Ag NPs could be isolated as stable powders by simple centrifugation. With C-glucoside **3**, aggregation of the initially formed Ag NPs occured. Figures A and C (Inset, Fig. 3) show UV-vis spectra and recorded from alkaline solutions of silver nitrate and acids 1 and 2, respectively. The strong absorption at ca. 410 nm clearly indicates the formation of Ag NPs. This absorption is due to excitation of the surface plasmons present in the nanoparticles. Transmission electron microscope (Fig. 3B and D) images of synthesized Ag NPs revealed the average particle size to be ~ 15 nm.



Scheme 1. Reagents and conditions: (a) allyltrimethyl silane, BF₃·Et₂O, CH₃CN, reflux, 8 h; (b) 2nd gen.Grubbs' catalyst, CH₂Cl₂, rt, 6 h; (c) H₂, 5% Pd/C, MeOH/EtOAc (2:1), 1 atm, rt, 2 h; (d) RuCl₃·H₂O, NalO₄, CCl₄-CH₃CN-H₂O (1:1:1.5), rt, 1 h; (e) K₂CO₃, methanol, rt, 2 h.

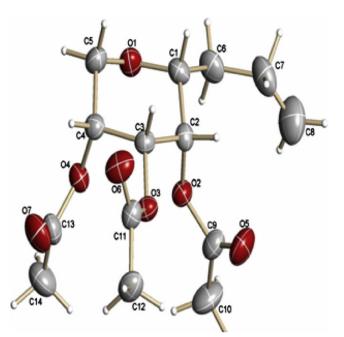


Figure 2. The molecular structure of compound 6. Displacement ellipsoids are drawn at the 40% probability level. H atoms are represented by circles of an arbitrary radius.

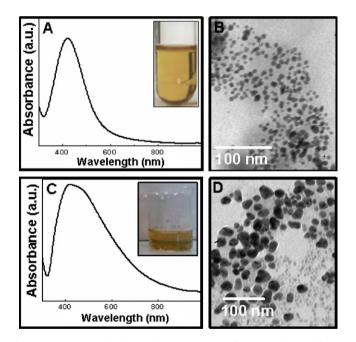


Figure 3. Figures A and C showing the UV-vis spectra of Ag NPs synthesized from 1 and 2, respectively. Figures B and D showing TEM image of AgNPs synthesized from 1 and 2, respectively. Insets (A) and (C) show the colors of the Ag NPs synthesized from 1 and 2, respectively.

To conclude, $12-\alpha$ -C-glycosyl dodecanoic acids containing either ribopentofuranose, ribopentopyranose, or glucohexopyranose motifs were synthesized, employing cross-metathesis as the key step. Further studies on the application of these acids as capping agents for the synthesis of metal nanoparticles reveal that they do not cap Co-metal nanoparticles synthesized in aqueous phase. However, C-glycosides 1 and 2 could reduce and cap the Ag NPs in water without any aggregation. Further studies to understand the mechanism of the reduction of AgNO₃ and also the relation between the sugar configuration and nanoparticle stabilizing ability are in progress. The biological activity/application of the synthesized Ag NPs will be published in due course.

Acknowledgments

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 (a) Spectral data of compound **6**: Mp 86.7 °C. [α]₂⁵⁵ +2.0 (c 1, CHCl₃). IR (CHCl₃): ν 3019, 1743, 1262, 1228, 668 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 2.00 (s, 3H). 2.16 (s, 3H), 2.17 (s, 3H), 2.21-2.26 (m, 1H), 2.42-2.48 (m, 1H), 3.55 (ddd, J = 1.2, 6.4, 7.6 Hz, 1H), 3.71 (dd, J = 1.5, 13.3 Hz, 1H), 4.13 (dd, J = 1.8, 13.3 Hz, 1H), 5.07–5.09 (m, 2H), 5.10–5.12 (m, 1H), 5.17–5.18 (m, 1H), 5.23 (dt, *J* = 1.2, 3.7 Hz, 1H), 5.73–5.81 (m, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 20.3 (q), 20.4 (q), 20.7 (q), 35.1 (t), 66.4 (d), 67.5 (d), 68.0 (d), 68.6 (t), 77.1 (d), 117.9 (t), 132.74 (d), 169.36 (s), 169.99 (s), 170.03(s) ppm. ESI-MS: m/z 323.4 (100%, [M+Na]⁺). Anal. Calcd for $C_{14}H_{20}$ (7; C, 55.99; H, 6.71. Found: C, 56.02; H, 6.74. (b) Spectral data of compound **11**: $[\alpha]_D^{25}$ –9.8 (c 1.5, CHCl₃). IR (CHCl₃): v 3079, 3022, 2981, 2882, 1747, 1372, 1222, 1108, 1038, 667 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 2.01 (s, 3H), 2.01 (s, 3H), 2.16 (s, 3H), 2.13-2.20 (m, 1H), 2.32-2.37 (m, 1H), 3.63 (t, J = 10.8 Hz, 1H), 3.73 (ddd, J = 3.5, 7.8, 10.8 Hz, 1H), 3.85 (ddd, J = 0.5,

5.3, 10.5 Hz, 1H), 4.73 (dd, *J* = 2.8, 10.0 Hz, 1H), 4.98 (ddd, *J* = 3.0, 5.5, 10.8 Hz, 1H), 5.06–5.11 (m, 2H), 5.63 (t, *J* = 2.5 Hz, 1H), 5.78–5.89 (m, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 20.4 (q, 2C), 20.5 (q), 35.5 (t), 63.2 (t), 66.5 (d), 67.8 (d), 69.5 (d), 72.7 (d), 117.3 (t), 133.2 (d), 169.1 (s), 169.2 (s), 169.8 (s) ppm. ESI-MS: *m/z* 323.6 (100%, [M+Na]⁺). Anal. Calcd for C₁₄H₂₀O₇: C, 55.99; H, 6.71. Found: C, 56.04; H, 6.73.

- 12. X-ray intensity data of compound **6** were collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo K α = 0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997)¹³ was used for structure solution and full-matrix least-squares refinement on F^2 . Hydrogen atoms were included in the refinement as per the riding model.
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- 16. Spectral data of compound 1: Mp 131–132 °C. $[α]_D^{25}$ +9.0 (*c* 1.0, MeOH). IR (Nujol): *ν* 3439, 3258, 2923, 2852, 1709, 1462, 1377 cm⁻¹. ¹H NMR (400 MHz, Methanol-*d*₄): δ 1.32 (s, 16H), 1.59–1.71 (m, 4H), 2.26 (*t*, *J* = 7.3 Hz, 2H), 3.58 (dd, *J* = 4.8, 11.8 Hz, 1H), 3.74 (dd, *J* = 2.8, 11.8 Hz, 1H), 3.77–3.81 (m, 1H), 3.91 (dt, *J* = 2.8, 6.8 Hz, 1H), 3.96 (dd, *J* = 3.0, 4.3 Hz, 1H), 4.11 (dd, *J* = 4.3, 7.8 Hz, 1H) pm. ¹³C NMR (100 MHz, Methanol-*d*₄): δ 26.4 (t), 27.0 (t), 30.4 (t), 30.5 (t), 30.6 (t), 30.7 (t), 30.8 (t), 31.0 (t), 35.8 (t), 63.5 (t), 73.8 (d), 74.0 (d), 82.6 (d), 82.9 (d), 178.8 (s) ppm. ESI-MS: *m*/2 355.15 (100%, [M+Na]⁺). Anal. Calcd for C₁₇H₃₂O₆: C, 61.42; H, 9.70. Found: C, 61.46; H, 9.73. Spectral data of compound **2**: Mp 115–116 °C $[α]_D^{25}$ 15.3 (*c* 0.5, MeOH). IR (Nujol): *ν* 3364, 3019, 2928, 2856, 1701, 1461, 1376, 1102, 722 cm⁻¹. ¹H NMR (200 MHz, Methanol-*d*₄): δ

1.31 (s, 18H), 1.57–1.69 (m, 2H), 2.20 (t, J = 7.3 Hz, 2H), 3.26 (dd, J = 5.3, 8.3 Hz, 1H), 3.60 (t, J = 3.3 Hz, 1H), 3.66 (br s, 1H), 3.79 (br s, 1H), 3.94 (dd, J = 2.0, 12.4 Hz, 1H). ¹³C NMR (50 MHz, Methanol-44): δ 26.4 (t), 26.7 (t), 30.8 (t), 30.8 (t), 32.4 (t), 70.5 (d), 71.3 (d), 72.3 (t), 73.2 (d), 80.8 (d) ppm. ESI-MS: m/z 355.42 (100%, [M+Na]⁺). Anal. Calcd for C₁₇H₃₂O₆: C, 61.42; H, 9.70. Found: C, 61.39; H, 9.66. Spectral data of compound **3**: $[\alpha]_{25}^{D}$ +46.5 (c 4.0, MeOH). IR (Nujol): v 3365, 2853, 1709, 1569, 1455, 1377, 1032, 721 cm⁻¹. ¹H NMR (400 MHz, Methanol- d_4): δ 1.30 (br s, 16H), 1.59–1.65 (m, 4H), 2.22 (t, J = 7.3 Hz, 1H), 3.25 (dd, J = 5.5, 9.5 Hz, 1H), 3.39 (ddd, J = 2.5, 3.8.0 Hz, 1H), 3.52 (t, J = 8.8 Hz, 1H), 3.60 (dt, J = 5.0, 10.0 Hz, 1H). ¹³C NMR (100 MHz, Methanol- d_4): δ 25.4 (t), 26.7 (t), 27.0 (t), 30.6 (t), 30.7 (t), 30.7 (t), 63.1 (t), 72.4 (d), 73.1 (d), 74.3 (d), 75.3 (d), 77.3 (d) ppm. ESI-MS: m/z 385.37 (100%, [M+Na]⁺). Anal. Calcd for C₁₈H₃₄O₇: C, 59.65; H, 9.45. Found: C, 59.69; H, 9.49. Kasture, M.; Singh, S; Patel, P.; Joy, P. A.; Prabhune, A. A.; Ramana, C. V.; Prasad,

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- 19. Typical experimental procedure for Ag NPs preparation: To a boiling solution of C-glycoside of dodecanoic acid 1 (33 mg, 100 μ mol) and silver nitrate (1.7 mg, 10 μ mol) in MilliQ H₂O (100 mL), 1 mL of 0.1 M KOH solution (pH ~10) was added and allowed to boil for 5 min. The colorless solution turned yellow, which indicated the formation of Ag NPs. The obtained Ag NPs were centrifuged at 8000 rpm for 20 min for removal of excess of C-glycoside of dodecanoic acid and KOH. The yellow pellet obtained was redispersed in MilliQ water (10 mL) and again centrifuged. The pellet was dried under ambient conditions. The purified sample was used for further characterizations. The dried pellet was found to be redispersible in water without any aggregation by mild sonication.