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Convenient synthesis of D- and L-xylo-1,2,3,4-alkane tetrols from a D-glucoconfigured common building block

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1. Introduction

Guggultetrol-18, 1 and guggultetrol-20, 2 are the major naturally occurring lipids isolated from the gum resin of the tree Commiphora mukul, known as Guggulu. It has been used in Ayurveda-the ancient Indian medicinal system for the treatment of inflammation, rheumatoid arthritis, obesity, and disorders of lipid metabolism besides several other ailments.¹ There are only few reports available in the literature for the synthesis of guggultetrols.² Baring the recently reported synthesis due to Sudalai,^{2a} which uses Sharpless asymmetric epoxidation of an allylic alcohol, the other synthetic routes banked on the starting material from the chiral pool. Prasad in 2007 had commenced their synthesis from L-(+)-tartaric acid derivative,^{2b} whereas the earlier approaches in 1981 due to Kjer^{2c} and later in 1986 due to Sukhdev^{2d} had made use of pentodialdo-1,4-furanosides and D-mannitol/D-xylose, respectively, as their starting material for their synthetic adventure. In a different perspective, long chain alkane-1,2,3,4-tetrols have also evinced great interests under carbohydrate based environmentally benign surfactants.³

Our new open chain D-gluco-configured building block, 2-O-benzyl-morpholine amide $\mathbf{3}^4$ easily amenable on multi-gram scale as crystalline solid from inexpensive and commercially available D-(+)- δ -gluconolactone, presented a unique potential to deliver synthesis of both D- and L-xylo-configured long chain polyol $\mathbf{4}$ with judicious interplay of sequence and mode of long carbon-chain addition.

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ABSTRACT

D-gluco-Configured building block derived from D-(+)-gluconolactone has served as a common chiral template for the synthesis of enantiopure D- and L-xylo-configured 1,2,3,4-alkane tetrols. This has enabled synthesis of medicinally important guggultetrols and their enantiomers from a common starting point. Wittig and Grignard reactions are the key steps used for the incorporation of lipophilic chain.

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In the building block **3**, the terminal isopropylidene protected diol and the amide functionality are orthogonal.

Tethering of alkyl chain on the left hand side through suitable functional group inter-conversions would furnish the *D-xylo*-1,2,3,4-alkane tetrol, whereas appending alkyl chain through the use of amide functionality on the right would enable synthesis of *L-xylo*-1,2,3,4-alkane tetrol. Hence syntheses of *D-xylo*-configured, natural guggultetrols, as well as their enantiomers, *L-xylo*-configured can be realized from the same building block **3** thereby illustrating the significance of our new building block **3**. (Fig. 1) The results presented herein constitute first report, wherein a common building block has enabled access to both natural guggultetrols and their enantiomers and paves the way for convenient access to any *D*- or *L-xylo* configured long chain 1,2,3,4-alkane tetrols **4**. This fully demonstrates the built-in versatility of our new building block.

2. Results and discussion

Syntheses of p-xylo-1,2,3,4-alkane tetrols were accomplished starting with the 2-O-benzyl-morpholine amide **3** as depicted in Scheme 1. The selective hydrolysis of the terminal isopropylidene protection in compound **3** was carried out with zinc nitrate hexahydrate in acetonitrile at 50 °C affording the diol **5** in 92% yield. The diol **5** was subjected to oxidative cleavage using sodium periodate in presence of sodium bicarbonate to furnish the aldehyde **6**. Wittig olefinations of the aldehyde **6** were carried out using different alkyl-triphenylphosphonium bromides $[CH_3(CH_2)_nCH_2P^+(Ph)_3Br^-]$ namely, butyltriphenylphosphonium bromide^{5a} (n = 2), octyltriphenylphosphonium



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Figure 1. Common building block 3 for D- and L-xylo-1,2,3,4-alkane tetrols.



[**a**: n = 2, **b**: n = 6, **c**: n = 11, **d**: n = 13]

Scheme 1. Synthesis of D-xylo-1,2,3,4-alkane tetrols. Reagents and conditions: (a) Zn(NO₃)₂·6H₂O, CH₃CN, 50 °C, 7 h, 92%; (b) CH₂Cl₂, aq NaHCO₃ soln, aq NalO₄ soln, 0 °C to rt, 2 h; (c) CH₃(CH₂)_nCH₂P⁺(Ph)₃Br⁻, BuLi, THF, 0 °C to rt, 6 h, 50% over two steps; (d) Pd/C, H₂, EtOH-AcOH (1:1), rt, 3 h, 75–90%; (e) NaBH₄, EtOH, 60 °C, 4 h, 80–90%; (f) Ac₂O, Et₃N, DMF, rt, 12 h, 80–90%; (g) CH₃COOH-H₂O, 80 °C, 6 h, 75–90%; (h) Ac₂O, Et₃N, DMF, rt, 12 h, 80–90%.

bromide^{5c} (n = 11), and pentadecyltriphenylphosphonium bromide^{5d} (n = 13). The alkyltriphenylphosphonium bromides were prepared by treating the corresponding alkyl bromides with triphenylphosphine in chlorobenzene at 125 °C except for butyltriphenylphosphonium bromide which was formed in toluene at 90 °C. Reacting alkyltriphenylphosphonium bromide with *n*-BuLi in THF as solvent and at 0 °C, produced the corresponding alkylidenetriphenylphosphorane [CH₃(CH₂)_nCH=PPh₃ where n = 2, 6, 11 or 13].

Addition of THF solution of the aldehyde 6 to the formed alkylidenetriphenylphosphorane at 0 °C and allowing the mixture to stir for six hours at room temperature furnished the Wittig olefination product **7a-d** in 50% yield over the two steps from diol **5**. Wittig chain extension afforded predominantly the Z-isomer. This inference was drawn from the H₆-olefinic proton appearing in the ¹H NMR spectra of **7b** and **7c** as doublet of triplets (*I* = 10.8, 7.2 Hz) in the range δ 5.66–5.71. The olefinated products **7a–d** were subjected to palladium catalyzed hydrogenation at atmospheric pressure and room temperature in ethanol-acetic acid mixture (1:1). These conditions facilitated reduction of the double bond and hydrogenolysis of the O-benzyl group and furnished the alkyl chain tethered α -hydroxymorpholine amide **8a–d**. Facile reduction of the morpholine amide in 8a-d with sodium borohydride afforded the partially protected D-xylo-configured 1,2,3,4-alkane tetrols, 9a-d, in 80-90% yield. Further confirmation of the obtained diol 9a-d, was achieved through the di-acetylated derivatives, 10a-d. The hydrolysis of the internal isopropylidene protection in diols **9a-d** with acetic acid and water at 80 °C afforded the targeted guggultetrols 1, 2 and the other analogues 11a,b. Thus syntheses of four Dxylo-1,2,3,4-alkane tetrols of varied chain lengths have been achieved. The tetrols 11a,b and guggultetrol 1, 2 were subjected to peracetylation to obtain the corresponding tetraacetates 12ad, respectively, for characterization and thereby confirmation of obtainment of the tetrols.

With successful synthesis of D-xylo-configured tetrols in the background, efforts toward the L-series started with the aldehyde **6**. Simple reduction of this aldehvde **6** in 90% yield and subsequent benzyl ether protection (60%) furnished the di-O-benzyl protected morpholine amide **14**. The addition of the alkyl carbon chain was now executed through the use of Grignard reaction on the amide functionality. Different alkylmagnesium bromides [CH₃(CH₂)_n CH₂MgBr] (Scheme 2), namely, pentadecylmagnesium bromide (n = 13), tridecylmagnesium bromide (n = 11), and octylmagnesium bromide (n = 6) were prepared by the standard procedure using the corresponding alkyl bromides. These alkylmagnesium bromides in THF solution were now added to the solution of morpholine amide 14 in THF at 10–15 °C. Allowing the reaction mixture to stir for 2.5–3 h at room temperature furnished the corresponding ketones 15a-c in excellent yields 80–82%. No trace of over-addition product was seen. The conversion of carbonyl group in ketones 15a-c to methylene group for the targeted synthesis was achieved through two-step protocol. Ketones 15a-c were reduced to alcohol 16a-c and subjected to Barton-McCombie deoxygenation⁶ through thionocarbonate derivatives.

The debenzylation in protected alkane-tetrols, **17a–c** was effected with $Pd/C/H_2$ in methanol–acetic acid (1:1) at room temperature. Hydrolysis of the internal isopropylidene protection was carried out by acetic acid–water (4:1) at 100 °C to obtain *ent-2*, *ent-1*, and **18**. These alkane tetrols were subjected to peracetylation to obtain the corresponding tetraacetates **19a–c** for complete characterization.

3. Conclusion

A versatile *D-gluco* configured building block, 2-O-benzylmorpholine amide is used as chiral template for synthesis of guggultetrols and their enantiomers. The long alkyl chain incorporation was achieved by Wittig olefination on the aldehyde and Grignard addition reaction on to the morpholine amide. The orthogonal protected building block enabled addition of alkyl chain. Hence guggultetrols, their enantiomers, other D- and L*xylo*-1,2,3,4-alkane tetrols are synthesized from common building block.

4. Experimental section

4.1. General

All reactions were carried out in oven dried glassware's. Dry DMF was prepared by stirring with Calcium hydride, downward distilled, and stored on 4 Å molecular sieves. Dry THF was prepared by distilling over Na wire. Solvents used for column chromatography were LR grade. Magnesium metal was cleaned using 20% HCl (thrice) followed by washing with distilled water and acetone, which was dried by keeping it in hot air oven for 12 h at 100 °C. Thin-layer chromatography was performed on aluminum plates coated with Silica Gel 60. Visualization was observed by UV light or by dipping into a solution of cerium (IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10% sulfuric acid (250 mL) followed by charring on a hot plate. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded in chloroform-d (CDCl₃) and tetramethylsilane (TMS) as reference. HRMS were recorded on a MICRO-Q TOF mass spectrometer by using the ESI technique at 10 eV. IR spectra were recorded on JASCO-FT/IR-4100 spectrometer. Optical rotations were recorded on Autopol IV polarimeter.

4.2. (*R*)-2-(Benzyloxy)-2-((45,5*R*)-5-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-morpholinoethanone (5)

Zinc nitrate hexahydrate (17.00 g, 57.0 mmol) was added to the solution of 2-O-benzyl-morpholine amide (3), (5.00 g, 17.5 mmol) in 60 mL of acetonitrile. Reaction mixture was heated at 50 °C for 7 h. After complete consumption of starting material, acetonitrile was evaporated at 40 °C on rotary evaporator. The residue was diluted by 100 mL of ethyl acetate. The ethyl acetate layer was washed with brine (100 mL). Then ethyl acetate layer was kept at 0 °C for 12 h. Ethyl acetate was evaporated and yellow colored gummy product was obtained. The crude compound was purified by column chromatography. Gummy liquid; yield: 92%; Rf 0.16 (ethyl acetate/hexane, 3:2); $[\alpha]_{D}^{23}$ = +17.71 (*c* 1.0, CHCl₃); IR (neat) v_{max} cm⁻¹ 3018, 1519, 1420, 1281, 764; ¹HNMR (CDCl₃/TMS, 500 MHz) δ 1.35, 1.36 (2 × s, 6H, 2 × CH₃); 2.56 (br s, 4H, D₂O exchangeable protons); 3.44-3.48 (m, 1H); 3.55-3.60 (m, 3H); 3.63-3.67 (m, 3H); 3.72-3.79 (m, 1H); 3.82-3.86 (m, 1H); 4.08 (t, 1H, J = 7.5 Hz; 4.29 (dd, 1H, $J_1 = 7.5 \text{ Hz}$, $J_2 = 5 \text{ Hz}$); 4.47 (d, 1H, J = 3.5 Hz; 4.50 (d, 1H, J = 11.5 Hz, PhCH_aH_bO); 4.69 (d, 1H, J = 11.5 Hz, PhCH_aH_bO); 7.26–7.37 (m, 5H, Aromatic); ¹³C NMR (CDCl₃/TMS, 125 MHz) δ 26.8, 27.2, 43.0, 46.1, 64.0, 66.8, 72.8, 73.0, 76.8, 76.87, 77.0, 79.0, 79.9, 109.8, 128.2, 128.3, 128.5, 136.5, 168.7; HRMS (ESI) *m*/z Calcd for C₂₀H₂₉NO₇Na [M+Na]⁺: 418.1842. Found: 418.1839.

4.3. Preparation of the aldehyde (6) and general procedure for Wittig olefination of the aldehyde

To a solution of the diol **5** (3.00 g, 7.59 mmol) in CH_2Cl_2 was added 5% sodium bicarbonate solution (16 mL) and the mixture was cooled to 0 °C; this was followed by addition of 13% solution of sodium periodate (2.44 g, 11.38 mmol) in water (19 mL). The reaction mixture was allowed to warm slowly to room temperature and was stirred for 2 h. Upon completion of the reaction as



Scheme 2. Synthesis of L-xylo-1,2,3,4-alkane tetrols. Reagents and conditions: (a) NaBH₄, methanol, 0 °C to rt, 30 min, 90%; (b) NaH, PhCH₂Br, DMF, 1 h, 0 °C to rt, 60%; (c) CH₃(CH₂)_nCH₂MgBr, THF.10–15 °C, 3 h, 80–82%; (d) NaBH₄, methanol, 0 °C to rt, 30 min, 97%; (e) 1,1'-thiocarbonyl diimidazole, toulene, 110 °C, 8–10 h, 75–85%; (f) Bu₃SnH, AlBN, toulene, 80 °C, 6–7 h, 55%; (g) H₂, Pd/C (10%), methanol–acetic acid (1:1), rt, 5–6 h; (h) acetic acid–H₂O (4:1), 100 °C, 12 h; (i) (AcO)₂O, Et₃N, DMAP, rt, 10–12 h, yield 60% (over three steps).

monitored by thin layer chromatography, the organic layer was separated and the aqueous layer was saturated with sodium chloride and then extracted with CH_2Cl_2 (20 mL \times 3). The combined organic extract was dried over Na_2SO_4 and evaporated under reduced pressure at room temperature to get crude compound. This was used in the next step without purification.

A solution of the alkyltriphenylphosphonium bromide (6.19 mmol) in anhydrous THF (20 mL) was cooled to 0 °C and *n*-BuLi (5.78 mmol) was added to it drop wise to obtain a dark red solution. The reaction mixture was allowed to stir at room temperature for 30 min and this was followed by drop wise addition of a solution of the aldehyde **6** (1.50 g, 4.13 mmol) in anhydrous THF (10 mL) at ice cold temperature. The reaction mixture was allowed to stir at room temperature for 6 h. Upon completion of the reaction as monitored by thin layer chromatography, the reaction mixture was treated with saturated solution of ammonium chloride and then extracted with ethyl acetate (30 mL × 3). The combined organic extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The resulting residue was subjected to silica gel column chromatography to furnish the olefinated products, **7a**–**7d** as syrup in 50–55% yield. These were directly subjected to hydrogenation.

4.4. General procedure for hydrogenation of compounds 7a-d

To a solution of the olefin (1.00 g) in 10 mL of ethanol, were added, 0.1 mL of acetic acid and 300 mg of 10% Pd/C and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 4 h. Upon completion of the reaction as monitored by thin layer chromatography, the Pd/C was filtered off over celite and washed with ethyl acetate (20 mL \times 3); the combined filtrate was evaporated under reduced pressure and any trace amount of acetic

acid remaining was removed by azeotropic distillation with toluene. The crude residue was subjected to silica gel column chromatography to obtain the pure products as syrup in 80–90% yield.

4.4.1. (*R*)-2-((4*R*,5*R*)-2,2-Dimethyl-5-pentyl-1,3-dioxolan-4-yl)-2-hydroxy-1-morpholinoethanone (8a)

Syrupy liquid; yield: 80%; $R_{\rm f}$ 0.16 (ethyl acetate/hexane, 3:7); [α]_D²⁵ = +9.99 (*c* 1.0, CHCl₃); IR (neat) $\nu_{\rm max}$ cm⁻¹ 3419, 1643, 1265, 1114; ¹HNMR (CDCl₃/TMS, 400 MHz) δ 0.78–0.88 (m, 3H, CH₃CH₂); 1.18–1.32 (m, 10H); 1.47–1.54 (m, 4H); 3.43–3.79 (m, 9H); 3.97–3.98 (m, 2H); 4.38–4.45 (m, 1H, CH₂CHCH); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 13.9 (CH₃CH₂); 22.4 (CH₃CH₂); 25.6 (CH₃CH₂CH₂); 26.6, 27.3 (C(CH₃)₂); 29.5, 31.7 (CH₂CH₂CH); 33.0 (CH₂CH₂CH); 42.9, 45.9 (CH₂NCH₂); 66.5 76.7, 77.0, 77.4, 80.8 (CHCHC=O); 108.9 (C(CH₃)₂); 170.0 (*C*=O); HRMS (ESI) *m*/z Calcd for C₁₆H₂₉NO₅-Na [M+Na]⁺: 338.1943. Found: 338.1953.

4.4.2. (*R*)-2-((4*R*,5*R*)-2,2-Dimethyl-5-nonyl-1,3-dioxolan-4-yl)-2-hydroxy-1-morpholinoethanone (8b)

Syrupy liquid; yield: 80%; R_f 0.32 (ethyl acetate/hexane, 3:7); [α]_D²⁵ = +10.59 (*c* 1.0, CHCl₃); IR (neat) v_{max} cm⁻¹ 3419, 1643, 1265, 1114; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.79–0.82 (m, 3H, CH₃CH₂); 1.14–1.28 (m, 10H, CH₃(CH₂)₅); 1.31, 1.32 (2s, 6H, C(CH₃)₂); 1.40–1.60 (m, 6H, (CH₂)₃CH); 3.38–3.69 (m, 8H, morpholinyl); 3.70–3.72 (m, 1H, CHC=O); 3.95–4.03 (m, 1H, CH₂CH); 4.38–4.42 (m, 1H, CHCHC=O); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.2 (CH₃CH₂); 22.7 (CH₃CH₂); 26.2 (CH₃CH₂CH₂); 26.7, 27.5 (C(CH₃)₂); 29.4, 29.6, 29.8, 31.9, 33.2 (CH₃CH₂CH₂(CH₂)₆CH); 43.1, 46.0 (H₂CNCH₂); 66.5 (CHC=O); 66.8, 76.8, 77.1, 77.2 (H₂COCH₂); 77.4 (CH₂CH); 80.9 (CHCHC=O); 109.1 (C(CH₃)₂); 170.2 (C=O); HRMS (ESI) *m*/z Calcd for C₂₀H₃₇NO₅Na [M+Na]⁺: 394.2569. Found: 394.2578.

4.4.3. (*R*)-2-((4*R*,5*R*)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-2-hydroxy-1-morpholinoethanone (8c)

Syrupy liquid; yield: 80%; R_f 0.12 (ethyl acetate/hexane, 2:8); $[\alpha]_D^{25} = +6.59$ (*c* 1.0, CHCl₃); IR (neat) v_{max} cm⁻¹ 3419, 1643, 1265, 1114; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.88 (t, 3H, *J* = 6.4 Hz, CH₃CH₂); 1.22–1.34 (m, 22H, CH₃(CH₂)₁₁); 1.38–1.39 (2s, 6H, C(CH₃)₂); 1.59–1.61 (m, 4H); 3.45–3.76 (m, 8H, morpholinyl); 3.73–3.77 (m, 1H, CH₂CH); 4.00–4.09 (m, 1H, CH₂CHCH); 4.47 (d, 1H, *J* = 1.6 Hz, CHC=O); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.1 (CH₃CH₂); 22.6, 26.1 (CH₃(CH₂)₂); 26.7, 27.4 (C(CH₃)₂); 29.3, 29.5, 29.60, 29.67, 29.68, 29.69, 29.72, 31.9, 33.1 (-(CH₂)₁₁–CH); 43.0, 45.9 (CH₂–N–CH₂); 66.35 (OCH₂); 76.7, 77.0, 77.1, 77.3, 80.8 (CHC=O); 109.1 (C(CH₃)₂); 170.1 (C=O); HRMS (ESI) *m*/z Calcd for C₂₅H₄₈NO₅ [M+H]⁺: 442.3532. Found: 442.3535.

4.5. General procedure for reduction of the α -hydroxy amides 8a-d to diols 9a-d and diacetylation of the diols 9a-d

4.5.1. Reduction of the α -hydroxymorpholine amides 8a-d

To a solution of the α -hydroxy amide **8a–d** (0.5 mmol) in 3 mL of ethanol, were added two equivalents of sodium borohydride (0.076 g, 2.0 mmol) and the reaction mixture was stirred at 60 °C for 4 h. Upon completion of the reaction as monitored by thin layer chromatography, ethanol was completely evaporated from the reaction mixture under reduced pressure and at room temperature. The resulting residue was diluted with 10 mL of water and neutralized using acetic acid and then extracted with ethyl acetate (15 mL × 3). The combined organic extract was concentrated under reduced pressure and the resulting crude material was subjected to silica gel column chromatography to obtain the pure product in 80–95% yield.

4.5.2. Diacetylation of the diols (9a-d)

To a solution of the diol (**9a–d**), (0.5 mmol) in 2 mL of anhydrous DMF, were added four equivalents of triethylamine (0.2 mL, 2.0 mmol) under inert atmosphere and the reaction mixture was cooled to 0 °C. This was followed by drop wise addition of three equivalents of acetic anhydride (0.15 mL, 1.50 mmol). The reaction mixture was allowed to stir at room temperature for 8 h. Upon completion of the reaction as monitored by thin layer chromatography, the reaction mixture was diluted with 15 mL of ethyl acetate and washed with saturated sodium bicarbonate solution (10 mL) and then with water (25 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated under reduced pressure to obtain the crude product which was subjected to silica gel column chromatography to obtain the pure product as colorless syrup in 80–90% yields.

4.5.3. (*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-pentyl-1,3-dioxolan-4-yl)ethane-1,2-diyl diacetate (10a)

Syrupy liquid; yield: 80%; R_f 0.47 (ethyl acetate/hexane, 2:8); $[\alpha]_D^{25} = -3.19(c \ 1.0, CHCl_3)$; IR (neat) $\nu_{max} \ cm^{-1}$ 1744, 1218, 1060; ¹H NMR (CDCl_3/TMS, 400 MHz) δ 0.84 (t, 3H, J = 6.8 Hz, CH_3CH_2); 1.32–1.37 (m, 6H, $CH_3(CH_2)_3$); 1.38, 1.39 (2s, 6H, $C(CH_3)_2$); 1.41– 1.59 (m, 2H, CH_2CH_2CH); 2.00, 2.12 (2s, 6H, $2 \times CH_3C=0$); 3.74– 3.82 (m, 2H, $CH-O-C(CH_3)_2-O-CH$); 4.11–4.16 (dd, 1H, $J_1 = 11.6$, $J_2 = 7.6$ Hz, $CH_aH_bOCOCH_3$); 4.28–4.32 (dd, 1H, J = 11.6 Hz, 3.6 Hz, $CH_aH_bOCOCH_3$); 5.13–5.15 (m, 1H, $CHOCOCH_3$); ¹³C NMR (CDCl₃/ TMS, 100 MHz) δ 14.0 (CH_3CH_2); 20.7, 20.8 (2 $\times CH_3C=0$); 22.5 (CH_3CH_2); 25.6 ($CH_3CH_2CH_2$); 26.5, 27.5 ($C(CH_3)_2$); 31.8 (CH_2CH_2 CH); 32.9 (CH_2CH_2CH); 63.5 (CH_2OCOCH_3); 69.2 (CH_2CH_2CH); 76.8, 76.83, 77.1, 77.4, 79.5, 109.1, 170.3, 170.6 (2 $\times C=0$); HRMS (ESI) m/z Calcd for $C_{16}H_{28}O_6Na$ [M+Na]⁺: 339.1784. Found: 339.1791.

4.5.4. (S)-1-((4S,5R)-2,2-Dimethyl-5-nonyl-1,3-dioxolan-4yl)ethane-1,2-diyl diacetate (10b)

Syrupy liquid; yield: 80%; $R_f 0.71$ (ethyl acetate/hexane, 3:7); $[\alpha]_D^{25} = +1.19$ (*c* 1.0, CHCl₃); IR (neat) v_{max} cm⁻¹ 1744, 1218, 1060; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.86 (t, 3H, *J* = 7.2 Hz, CH₃CH₂); 1.24–1.35 (m, 14H, CH₃(CH₂)₇); 1.37, 1.40 (2s, 6H, C(CH₃)₂); 1.51–1.59 (m, 2H, CH₂CH₂CH); 2.04, 2.11 (2s, 6H, 2 × CH₃C=O); 3.74–3.76 (m, 1H, CH₂CH₂CH); 4.14–4.19 (dd, 1H, *J*₁ = 12.0 Hz, *J*₂ = 8.0 Hz, CH_aH_bOCOCH₃); 4.31–4.35 (dd, 1H, *J*₁ = 12.0 Hz, *J*₂ = 4.0 Hz, CH_aH_bOCOCH₃); 5.15–5.18 (m, 1H, CHCH₂OCOCH₃); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.2 (CH₃CH₂); 20.8, 20.9 (2 × CH₃C=O); 22.7 (CH₃CH₂); 26.0 (CH₃CH₂CH₂); 26.6, 27.5 (C(CH₃)₂); 29.4, 29.5, 29.7, 29.8, 31.9, 33.0, 63.6 (CH₂OCOCH₃); 69.3 (CH₂CH₂CH); 76.8, 77.1, 77.4, 79.4 (CH₂CHCH); 109.2 (C(CH₃)₂); 170.4, 170.7 (2 × C=O); HRMS (ESI) *m*/z Calcd for C₂₀H₃G₆G₆Na [M+Na]⁺: 395.2410. Found: 395.2400.

4.5.5. (*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4yl)ethane-1,2-diyl diacetate (10c)

Syrupy liquid; yield: 80%; $R_{\rm f}$ 0.47 (ethyl acetate/hexane, 1:9); [α]_D²⁵ = -1.99 (*c* 1.0, CHCl₃); IR (neat) $\nu_{\rm max}$ cm⁻¹ 1744, 1218, 1060; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.88 (t, 3H, *J* = 6.8 Hz, *CH*₃); 1.25–1.33 (m, 24H, CH₃(*CH*₂)₁₂); 1.38, 1.40 (2s, 6H, C(*CH*₃)₂); 1.54–1.55 (m, 2H); 2.05, 2.12 (2s, 6H, 2 × *CH*₃C=O); 3.76–3.78 (m, 2H, C-3-H, C-4-H); 4.18–4.20 (dd, 1H, *J*₁ = 9.5 Hz, *J*₂ = 6.0 Hz, *CH*_aH_bOAc); 4.32–4.37 (dd, 1H, *J*₁ = 9.5 Hz, *J*₂ = 2.8 Hz, CH_aH_bOAc); 5.16–5.22 (m, 1H, CHCH₂OAc); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.1 (*C*H₃CH₂); 22.7, 26.15, 26.67, 27.42, 29.3, 29.5, 29.58, 29.65, 29.67, 29.69, 29.72, 31.9, 33.1, 43.0, 45.9, 66.3, 76.7, 77.0, 77.1, 77.3, 80.80, 109.1 (*C*(CH₃)₂); 170.11 (2 × *C*=O); HRMS (ESI) *m*/z Calcd for C₂₅H₄₆O₆Na [M+Na]⁺: 465.3192. Found: 465.3178.

4.5.6. (*S*)-1-((4*S*,5*R*)-5-Hexadecyl-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diyl diacetate (10d)

Syrupy liquid; yield: 80%; R_f 0.60 (ethyl acetate/hexane, 1:9); $[\alpha]_D^{25} = -0.99$ (*c* 1.0, CHCl₃); IR (neat) v_{max} cm⁻¹ 2924, 1749, 1220; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.81 (t, 3H, *J* = 6.4 Hz, CH₃CH₂); 1.17–1.27 (m, 28H, CH₃–(CH₂)₁₄); 1.31, 1.32 (2s, 6H, C(CH₃)₂); 1.44–1.54 (m, 2H, CH₂CH); 2.03, 2.10 (2s, 6H, 2 × CH₃C=O); 3.65–3.75 (m, 2H, H-3, H-4); 4.13–4.18 (dd, 1H, *J* = 7.6 Hz, CH_aH-_bOAc); 4.31–4.34 (dd, 1H, *J* = 4.0 Hz, CH_aH_bOAc); 5.14–5.18 (m, 1H, CHOAc); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.2 (CH₃CH₂); 20.8, 20.9 (2 × CH₃C=O); 22.8 (CH₃CH₂); 26.0, 26.6 (C(CH₃)₂); 27.5, 29.4, 29.6, 29.7, 29.77, 29.8, 29.88, 29.9, 32.04, 33.0, 63.6 (CH₂OAc); 69.2 (C-4); 76.8, 77.16, 77.4, 79.5, 109.2, 170.44, 170.74 (2 × C=O).

4.6. General procedure for preparation of tetraacetates (12a-d)

A mixture of the diol **9a–d** (0.50 mmol) and 3 mL of acetic acidwater (8:2) was stirred at 100 °C for 8 h and upon completion of the reaction as monitored by thin layer chromatography, the reaction mixture was concentrated under reduced pressure and any remaining acetic acid or water was removed by azeotropic distillation with toluene (5 mL \times 2). The resulting residue-the crude tetrol, was then dissolved in anhydrous DMF (3 mL) under inert atmosphere. To the solution was added 10 equiv of triethylamine (0.5 mL, 5 mmol) and the reaction mixture was cooled to 0 °C. This was followed by addition of 8 equiv of acetic anhydride (0.4 mL, 4 mmol) and the reaction mixture was allowed to stir at room temperature for 12 h. Upon completion of the reaction as monitored by thin layer chromatography, the reaction mixture was diluted with 15 mL ethyl acetate and washed with saturated sodium bicarbonate solution (10 mL) and then with water (30 mL). The organic layer was separated and concentrated under reduced pressure to obtain the crude product which was subjected to silica gel column chromatography to obtain the pure product as colorless syrup in 80–90% yields.

4.6.1. (2S,3S,4R)-Nonane-1,2,3,4-tetrayl tetraacetate (12a)

Syrupy liquid; yield: 80%; R_f 0.35 (ethyl acetate/hexane, 2:8); $[\alpha]_D^{25} = +1.19$ (*c* 1.0, CHCl₃); IR (neat) ν_{max} cm⁻¹ 1743, 1214, 733; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.86 (t, 3H, *J* = 6.8 Hz, CH₃CH₂); 1.20–1.34 (m, 6H, CH₃(CH₂)₃); 1.50–1.57 (m, 2H, CH₂CH); 2.04, 2.07, 2.08 (4s, 12H, 4 × CH₃C=O); 3.93–3.98 (dd, 1H, *J*₁ = 12.4 Hz, *J*₂ = 5.6 Hz, CH_aH_bOCOCH₃); 4.33–4.37 (dd, 1H, *J*₁ = 12.4 Hz, *J*₂ = 3.6 Hz, CH_aH_bOCOCH₃); 5.07–5.12 (m, 1H, CH₂CH₂CH); 5.23– 5.29 (m, 2H, CH₂CH₂CHCH); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 13.9 (CH₃CH₂); 20.6, 20.7, 20.8, 21.0 (4 × CH₃C=O); 22.4, 24.6, 30.5, 31.4 (CH₃(CH₂)₄); 62.1 (CH₂OCOCH₃); 69.6 (CH₂CH₂CH); 71.3, 71.4 (CHCHCH₂OCOCH₃); 76.8, 77.1, 77.4, 170.08, 170.12, 170.45, 170.50 (2 × C=O) HRMS (ESI) *m*/z Calcd for C₁₇H₂₈O₈Na [M+Na]⁺: 383.1682. Found: 383.1687.

4.6.2. (2S,3S,4R)-Tridecane-1,2,3,4-tetrayl tetraacetate (12b)

Syrupy liquid; yield: 70%; R_f 0.62 (ethyl acetate/hexane, 3:7); [α]_D²⁵ = -0.99 (*c* 1.0, CHCl₃); IR (neat) ν_{max} cm⁻¹ 1743, 1214, 733; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.86 (t, 3H, *J* = 6.8 Hz, CH₃CH₂); 1.17-1.40 (m, 14H, CH₃(CH₂)₈); 1.51 (m, 2H); 2.04, 2.06, 2.062, 2.09 (4s, 12H, 4 × CH₃C=O); 3.93-3.98 (dd, 1H, *J*₁ = 12.4 Hz, *J*₂ = 5.6 Hz, CH_aH_bOCOCH₃); 4.33-4.37 (dd, 1H, *J*₂ = 12.4 Hz, *J*₂ = 3.6 Hz, CH_aH_bOCOCH₃); 4.99-5.10 (m, 1H, CHCH₂OCOCH₃); 5.18-5.28 (m, 2H); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.0 (CH₃CH₂); 20.6, 20.7, 20.8, 21.0 (4 × CH₃C=O); 22.4, 22.7, 24.6, 24.9, 29.3, 29.4, 29.5, 30.5 (CH₃(CH₂)₈); 31.4, 31.9, 62.1, 69.6, 71.3, 71.4, 76.8, 77.1, 77.4, 170.08, 170.12, 170.45, 170.50 (4 × C=O); HRMS (ESI) *m*/z Calcd for C₂₁H₃₆O₈Na [M+Na]*: 439.2308. Found: 439.2306.

4.6.3. (2S,3S,4R)-Octadecane-1,2,3,4-tetrayl tetraacetate (12c)

Syrupy liquid; yield: 70%; R_f 0.20 (ethyl acetate/hexane, 1:9); $[\alpha]_D^{25} = +1.3(c \ 1.0, CHCl_3)$; IR (neat) $\nu_{max} \ cm^{-1} \ 1743, 1214, 733; {}^{1}H$ NMR (CDCl₃/TMS, 400 MHz) δ 0.86 (t, 3H, $J = 5.6 \ Hz, \ CH_3 \ CH_2)$; 1.24–1.30 (m, 24H, CH₃-(CH₂)₁₂); 1.30–1.90 (m, 2H), 2.04, 2.05, 2.081, 2.084 (4s, 12H, 4 × CH₃ CO); 3.95–4.01 (m, 1H, CH_aH_bOAc); 4.37–4.39 (m, 1H, CH₂CH₂CH); 5.06–5.12 (m, 1H, H-2); 5.25–5.26 (m, 2H); {}^{13}C \ NMR (CDCl_3/TMS, 100 \ MHz) \delta 14.2 (CH₃); 20.7, 20.8, 20.9, 21.0 (4 × CH₃C=O); 22.8, 25.0, 26.3, 29.4, 29.5, 29.6, 29.75, 29.79, 29.82, 30.7, 32.0, 62.1, 69.7, 71.3, 71.5, 76.8, 77.1, 77.4, 170.1, 170.2, 170.5, 170.6 (4 × C=O); HRMS (ESI) *m*/*z* Calcd for C₂₆H₄₆O₈ [M+Na]⁺: 509.3090. Found: 509.3104.

4.6.4. (2S,3S,4R)-Icosane-1,2,3,4-tetrayl tetraacetate (12d)

Syrupy liquid; yield: 70%; R_f 0.20 (ethyl acetate/hexane, 1:9); $[\alpha]_D^{25} = +0.99$ (*c* 1.0, CHCl₃); IR (neat) ν_{max} cm⁻¹ 1743, 1214, 733; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.86 (t, 3H, *J* = 6.0 Hz, CH₃CH₂); 1.20–1.31 (m, 28H, CH₃(CH₂)₁₄); 1.40–1.60 (m, 2H, CH₂); 2.04, 2.07, 2.09 (4s, 12H, 4 × CH₃C=O); 3.94–3.98 (dd, 1H, *J*₁ = 12.4 Hz, *J*₂ = 5.6 Hz, CH_aH_bOAc); 4.34–4.40 (dd, 1H, *J*₁ = 13.6 Hz, *J*₂ = 2.8 Hz, CH_aH_bOAc); 5.06–5.13 (m, 1H, H-4); 5.22–5.30 (m, 2H, H-2, H-3); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.2 (CH₃CH₂); 20.72, 20.79, 20.8, 21.05(4 × CH₃C=O); 22.8, 25.0, 29.3, 29.4, 29.6, 29.73, 29.77, 29.80, 30.6, 32.0 (CH₃(CH₂)₁₅); 62.1 (CH₂OAc); 69.7 (C-4); 71.3, 71.5 (C-2, C-3); 76.8, 77.1, 77.3, 77.4 170.1, 170.2, 170.5, 170.6 (4 × CH₃C=O); HRMS (ESI) *m*/z Calcd for C₂₈H₅₀O₈Na [M+Na]⁺: 537.3403. Found: 537.3416.

4.7. (*R*)-2-(Benzyloxy)-2-((4*S*,5*R*)-5-(hydroxymethyl)-2,2dimethyl-1,3-dioxolan-4-yl)-1-morpholinoethanone (13)

To a solution of aldehyde (6), (5.34 mmol) in 15 mL of methanol, sodium borohydride (0.22 g, 5.87 mmol) was added in fractions at 0 °C. Reaction mixture was stirred for 30 min. After complete consumption of starting material as monitored by thin layer chromatography, methanol was evaporated on rotary evaporator. To the reaction residue 10 mL saturated solution of ammonium chloride was added. Product was extracted by CH_2Cl_2 (20 mL \times 3) and dried over Na₂SO₄. Organic layer was evaporated to obtain crude product which was purified by column chromatography. Syrupy liquid; yield: 90%; $R_{\rm f}$ 0.20 (ethyl acetate/hexane, 2:3); $[\alpha]_{\rm D}^{23}$ = +31.72 (*c* 1.0 CHCl₃) IR (liquid film) v_{max} cm⁻¹ 3685, 3028, 1518, 1423, 1219, 928, 752; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 1.41, 1.43 (2 × s, 6H, $2 \times CH_3$; 2.55 (br s, 1H, OH); 3.49–3.87 (m, 10H); 4.23(br s, 2H); 4.35 (br s, 1H); 4.54 (d, 1H, J = 12 Hz, PhCH_aH_b); 4.73 (d, 1H, $I = 12 \text{ Hz}, \text{ PhCH}_{a}H_{b}$; 7.29–7.40 (m, 5H, Ar-H); ¹³C NMR (CDCl₃/ TMS, 100 MHz) δ 26.8, 27.1 (2 × CH₃); 42.8, 46.0 (2 × N–CH₂); 62.0, 66.9, 72.55, 76.7, 77.07, 77.3, 77.4, 77.5, 79.0, 109.5, 128.1, 128.2, 128.5, 136.6, (Aromatic); 167.9 (CO); HRMS (ESI) m/z Calcd for C₁₉H₂₈NO₆ [M+H]⁺: 366.1917. Found: 366.1907.

4.8. (*R*)-2-(Benzyloxy)-2-((4*S*,5*R*)-5-((benzyloxy)methyl)-2,2dimethyl-1,3-dioxolan-4-yl)-1-morpholinoethanone (14)

A solution of morpholine amide (13), (2.00 g, 5.47 mmol) in 3 mL of DMF was added to a solution of sodium hydride (0.144 g, 6.02 mmol) in 7 mL of DMF at 0 °C. After 10 min benzyl bromide (0.71 mL, 6.02 mmol) was added drop wise. Reaction mixture was stirred at 0 °C to room temperature for 1 h. After complete consumption of starting material as revealed by thin layer chromatography, reaction mixture was quenched by addition of 5 mL saturated solution of ammonium chloride. Product was extracted by 80 mL of ethyl acetate. The organic layer was washed by water and dried over Na₂SO₄. The organic layer was evaporated on rotary evaporator to furnish crude product. The product was purified by column chromatography. Syrupy liquid; yield: 70%; R_f 0.40 (ethyl acetate/hexane, 2:3); $[\alpha]_{D}^{23}$ = +19.12 (*c* 1.0, CHCl₃); IR (neat) v_{max} cm⁻¹ 3018, 2399, 1628, 1522, 1431, 1215, 768; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 1.31, 1.32 (2 \times s, 6H, 2 \times CH₃); 3.30–3.32 (m, 1H); 3.43–3.59 (m, 7H); 3.67 (d, 1H, / = 12.8 Hz); 3.84(d, 1H, / = 12.8 Hz); 4.09 (dd, 1H, $J_1 = 3.6 \text{ Hz}, J_2 = 8 \text{ Hz}$; 4.19 (d, 1H, J = 4 Hz); 4.22–4.26 (m, 1H); 4.39 (d, 1H, J = 11.6 Hz, PhCH_aH_b); 4.46 (s, 2H, PhCH₂); 4.58 (d, 1H, J = 11.6 Hz, PhCH_a H_b); 7.18–7.26 (m, 10H, Ar-H); ¹³C NMR (CDCl₃/ TMS, 100 MHz) δ 26.8, 27.1 (2 × CH₃); 42.9, 45.9 (2 × N-CH₂); 66.9 (CH₂OH); 70.22, 72.68, 73.5, 76.0, 76.8, 77.1, 77.4, 78.2, 80.0, 109.8 (CMe2); 127.6, 127.7, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 136.8, 137.9 (Aromatic); 168.1 (CO); HRMS (ESI) m/z Calcd for C₂₆H₃₄NO₆ [M+H]⁺: 456.2386. Found: 456.2385.

4.9. General procedure for the addition of Grignard reagents on to the morpholine amide 14

To a solution of morpholine amide (14), (1.960 g, 4.3 mmol) in 4 mL of dry THF, a solution of alkylmagnesium bromide (12.9 mmol) in dry THF (10 mL), was added under inert atmosphere at 10–15 °C and reaction mixture was stirred for 3 h at 15 °C to room temperature. Thin layer chromatography revealed the complete consumption of starting material. Subsequent hydrolysis was achieved by the cautious addition of saturated ammonium chloride solution. Aqueous layer was extracted with ethyl acetate (100 mL). Organic extract was washed with water, dried over Na₂SO₄, and evaporated to get crude product. This was purified by column chromatography to get the desired ketone.

4.9.1. (*R*)-1-(Benzyloxy)-1-((4*S*,5*R*)-5-((benzyloxy)methyl)-2,2dimethyl-1,3-dioxolan-4-yl) heptadecane-2-one (15a)

Gummy liquid; yield: 80%; R_f 0.60 (ethyl acetate/hexane, 2:3); $[\alpha]_D^{23} = +18.76$ (*c* 1.5, CHCl₃); IR(liquid film) v_{max} cm⁻¹ 2922, 2854, 1719, 1457, 1219; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.9 (t, 3H, J = 6.4 Hz, CH₂CH₃); 1.30 (m, 24H, CH₃(CH₂)₁₂); 1.41 (s, 3H, CCH₃); 1.46 (s, 3H, CCH₃); 1.52 (m, 2H, COCH₂CH₂); 2.60 (m, 2H, COCH₂); 3.56 (two dd, 2H, $J_1 = 10$ Hz, $J_2 = 5.2$ Hz, BnOCH₂); 3.38 (d, 1H, J = 3.2 Hz, BnOCH); 4.12 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 3.2$ Hz, C₂-H); 4.30 (ddd, 1H, $J_1 = 8$ Hz, $J_2 = 4.8$ Hz, $J_3 = 2.8$ Hz, C₃-H); 4.47 (d, 1H, J = 12 Hz, OCH₂Ph); 4.56 (s, 2H, OCH₂Ph); 4.70 (d, 1H, J = 12 Hz, OCH₂Ph); 7.35 (m, 10H); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.2, 22.8, 26.8, 27.2, 29.2, 29.4, 29.5, 29.6, 29.8, 32.0, 39.7, 70.3, 73.5, 73.6, 75.4, 76.8, 77.1, 77.4, 79.2, 83.3, 109.9, 127.8, 128.1, 128.6, 137.2, 138.0, 211.9; HRMS (ESI) *m*/z Calcd for C₃₇H₅₇O₅ [M+H]⁺: 581.4206. Found: 581.4185.

4.9.2. (*R*)-1-(Benzyloxy)-1-((4*S*,5*R*)-5-((benzyloxy)methyl)-2,2dimethyl-1,3-dioxolan-4-yl) pentadecane-2-one (15b)

Yellow colored gummy liquid; yield: 70%; $R_f 0.65$ (ethyl acetate/ hexane, 2:3); $[\alpha]_D^{23} = +30.14$ (*c* 1, CHCl₃); IR(liquid film) ν_{max} cm⁻¹ 2924, 2855, 2360, 1594, 1459, 1089; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.92 (t, 3H, *J* = 7.2 Hz, CH₂CH₃); 1.30 (br, 20H, CH₃(CH₂)₁₀); 1.41 (s, 3H, CH₃); 1.46 (s, 3H, CH₃); 1.57 (m, 2H, COCH₂CH₂); 2.6 (m, COCH₂); 3.55 (two dd, 2H, *J*₁ = 8 Hz, *J*₂ = 4 Hz, BnOCH₂); 3.86 (d, 1H, *J* = 2.8 Hz, BnOCH); 4.12 (dd, 1H, *J*₁ = 8 Hz, *J*₂ = 3.2 Hz); 4.28-4.35 (m, 1H, CH₂CHCH); 4.48 (d, 1H, *J* = 12 Hz, PhCH_aH_bO); 4.56 (s, 2H, PhCH₂O); 4.71 (d, 1H, *J* = 12 Hz, PhCH_aH_bO); 7.30-7.40 (m, 10H, ArH); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.1, 22.7, 22.8, 26.7, 27.1, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 39.6, 70.3, 73.4, 73.5, 75.3, 76.7, 77.0, 77.3, 79.1, 83.2, 109.0, 127.7, 128.0, 128.4, 128.5, 137.1, 137.9, 211.8; HRMS (ESI) *m*/z Calcd for C₃₅H₅₂O₅Na [M+Na]⁺ : 575.3712. Found: 575.3723.

4.9.3. (*R*)-1-(Benzyloxy)-1-((4*S*,5*R*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)decane-2-one (15c)

Yellow colored gummy liquid; yield: 82%; R_f 0.5 (ethyl acetate/ hexane, 2:3); $[\alpha]_D^{23} = +16.76$ (*c* 0.5, CHCl₃); IR (liquid film) v_{max} cm⁻¹ 2929, 2858, 1739, 1601, 1456, 1374, 1243, 1048, 851; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.80 (t, 3H, *J* = 6.8 Hz CH₂CH₃); 1.18 (br, 10H, CH₃(CH₂)₅); 1.29 (s, 3H, CH₃); 1.34 (s, 3H, CH₃); 1.45–1.49 (m, 2H, COCH₂CH₂); 2.4–2.5 (m, 2H, COCH₂); 3.41–3.48 (two dd, 2H, $J_1 = 10$ Hz, $J_2 = 4.8$ Hz, BnOCH₂); 3.76 (d, 1H, *J* = 3 Hz, BnOCH); 4.00 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 3.2$ Hz); 4.19 (ddd, 1H, $J_1 = 8$ Hz, $J_2 = 4.8$ Hz, $J_3 = 2$ Hz, CH₂CHCH); 4.36 (d, 1H, *J* = 12 Hz, PhCH_aH_bO); 4.44 (s, 2H, PhCH₂O); 4.58 (d, 1H, *J* = 12 Hz, PhCH_aH_b); 7.18–7.25 (m, 10H, ArH); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.2, 22.8, 22.9, 26.8, 27.2, 29.3, 29.5, 31.9, 39.8, 70.4, 73.5, 73.7, 75.4, 76.8, 77.1, 77.4, 79.3, 83.4, 109.9, 127.8, 128.1, 128.5, 128.6, 137.2, 138.0, 211.9; HRMS (ESI) *m*/z Calcd for C₃₀H₄₂O₅Na [M+Na]⁺: 505.2930. Found: 505.2923.

4.10. General procedure for deoxygenation of the alcohols 16a-c

To a solution of alcohol (**16a–c**), (0.70 mmol) in toluene (8 mL), 1,1'-thiocarbonyldiimidazole (1.26 mmol) was added. Reaction mixture was subjected to reflux at 110 °C for 6–7 h. After complete consumption of starting material, toluene was evaporated to obtain crude product. The product was purified by column chromatography.

To a solution of thionocarbonate (0.30 mmol) in toluene (5 mL), Bu_3SnH (0.13 mL, 0.45 mmol) was added. Then a pinch of AIBN was added to the reaction mixture. The reaction mixture was heated at 80 °C for 8–9 h. After completion of reaction toluene was

evaporated to obtain yellow colored gummy compound. Product was purified by column chromatography.

4.10.1. (4*R*,5*R*)-4-((*S*)-1-(Benzyloxy)heptadecyl-5-((benzyloxy) methyl)-2,2-dimethyl-1,3-dioxolane (17a)

Yellow colored gummy liquid; yield: 49% (over three steps); R_f 0.46 (ethyl acetate/hexane, 1:9); $[\alpha]_D^{23} = +2.39$ (*c* 1,CHCl₃); IR (liquid film) v_{max} cm⁻¹ 2924, 2851, 2797, 1719, 1593, 1458, 1088, 742; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.77–0.81 (m, 3H, CH₃); 1.18 (br, 28H, CH₃(CH₂)₁₄); 1.33 (s, 3H, CH₃); 1.35 (s, 3H, CH₃); 1.45–1.46 (m, 2H, BnOCHCH₂); 3.37–3.46 (two dd, 2H, $J_1 = 8$ Hz, $J_2 = 4$ Hz, BnOCH₂); 3.50 (dt, 1H, $J_1 = 12$ Hz, $J_2 = 4$ Hz, BnOCH); 3.88 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 4.4$ Hz, CHCHCH); 4.05–4.06 (m, 1H, CH₂COCH); 4.47 (s, 2H, PhCH₂); 4.51 (two d, 2H, J = 12 Hz, PhCH₂); 7.16–7.23 (m, 10H, ArH);¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.1, 22.7, 25.9, 27.14, 27.17, 29.4, 29.6, 29.72, 29.76, 30.6, 31.9, 71.0, 72.7, 73.5, 76.4, 77.1, 77.4, 78.4, 79.3, 109.0, 127.5, 127.6, 127.7, 128.0, 128.3, 138.1, 138.6; HRMS (ESI) *m*/z Calcd for C₃₇H₅₉O₄ [M+H]⁺: 567.4413. Found: 567.4423.

4.10.2. (4R,5R)-4-((Benzyloxy)methyl-5-((5)-1-benzyloxy) pentadecyl-2,2dimethyl-1,3dioxolane (17b)

Yellow colored gummy liquid; yield: 53% (over three steps); $R_{\rm f}$ 0.44 (ethyl acetate/hexane, 1:9); $[\alpha]_D^{23} = +1.59 (c \ 1, CHCl_3)$; IR (liquid film) v_{max} cm⁻¹ 2925, 2853, 1741, 1596, 1458, 1372, 1250, 1091, 741; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.80 (t, 3H, J = 5.2 Hz, CH₃); 1.18 (br, 24H, Ch₃(CH₂)₁₂); 1.34 (s, 3H, CH₃); 1.36 (s, 3H, CH₃); 1.45–1.46 (m, 2H, BnOCHCH₂); 3.38–3.43 (two dd, 2H, J₁ = 8 Hz, $J_2 = 4$ Hz, BnOCH₂); 3.48 (ddd, 1H, $J_1 = 16.4$ Hz, $J_2 = 10.4$ Hz, $J_3 = 5.6$ Hz, BnOCH); 3.89 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 4.4$ Hz, CHCHCH); 4.06-4.08 (m, 1H, BnOCH2COCH); 4.49 (s, 2H, PhCH2); 4.50 (d, 1H, J = 12.8 Hz, PhCH_aH_b); 4.54 (d, 1H, J = 12.4 Hz, PhH_aH_b); 7.18–7.25 (m, 10H, ArH); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.1, 22.7, 25.3, 25.9, 27.11, 27.14, 29.3, 29.61, 29.68, 29.7, 29.8, 30.6, 30.9, 31.9, 71.0, 71.70, 71.8, 72.7, 73.4, 73.5, 76.4, 76.7, 77.0, 77.3, 78.4, 79.3, 80.68, 109.1, 127.5, 127.63, 127.67, 127.7, 127.9, 128.0, 128.3, 128.4. 128.5. 137.9. 138.12. 138.5: HRMS (ESI) m/z Calcd for C₃₅H₅₅O₄ [M+H]⁺: 539.4100. Found: 539.4098.

4.10.3. (4R,5R)-4-((S)-1-(Benzyloxy)decyl-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolane (17c)

Yellow colored gummy liquid; yield: 54% (over three steps); R_f 0.38 (ethyl acetate/hexane, 1:1); $[\alpha]_D^{23} = +4.79$ (*c* 1, CHCl₃); IR (liquid film) $v_{\rm max}$ cm⁻¹ 2925, 2855, 1594, 1372, 1251, 1089, 739; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.81 (t, 3H, J = 6.8 Hz, CH₃); 1.17 (br, 14H, $CH_3(CH_2)_7$); 1.34 (s, 3H, CH_3); 1.36 (s, 3H, CH_3); 1.43–1.49 (m, 2H, BnOCHCH₂); 3.37–3.41 (two dd, 2H, J₁ = 7.2 Hz, $J_2 = 4.8$ Hz, BnOCH₂); 3.48 (ddd, 1H, $J_1 = 6$ Hz, $J_2 = 10.4$ Hz, *J*₃ = 14 Hz, BnOCH); 3.89 (dd, 1H, *J*₁ = 8 Hz, *J*₂ = 4.4 Hz, CHCHCH); 4.07 (ddd, 1H, $J_1 = 5.6$ Hz, $J_2 = J_3 = 3.6$ Hz, BnOCH₂COCH); 4.49 (s, 2H, PhCH₂); 4.51 (d, 1H, J = 12.8 Hz, PhCH_aH_b); 4.54 (d, 1H, J = 11.6 Hz, PhH_aH_b); 7.18–7.27 (m, 10H, ArH); ¹³C NMR (CDCl₃/ TMS, 100 MHz) & 14.2, 22.8, 26.0, 27.2, 29.4, 29.7, 29.8, 30.7, 32.0, 71.1, 72.8, 73.6, 76.5, 76.8, 77.1, 77.4, 77.6, 78.6, 79.4, 109.3, 127.6, 127.75, 127.79, 128.1, 128.42, 128.48, 138.2, 138.7; HRMS (ESI) *m*/z Calcd for C₃₀H₄₄O₄Na [M+Na]⁺: 491.3137. Found: 491.3135.

4.11. General procedure for debenzylation and isopropylidene deprotection of 17a–c

To a solution of 1,4-dibenzyloxy tetrol (**17a–c**), (0.159 mmol) in 4 mL methanol–acetic acid (1:1), 10% Pd/C (0.046 mmol) was added to the reaction mixture in H₂ gas atmosphere. Reaction mixture was stirred for 8 h. Thin layer chromatography revealed

complete consumption of starting material. Then Pd/C was filtered off over celite. The residue was washed with ethyl acetate. Combined organic layer was collected and evaporated to obtain yellow colored gummy product. Product used in next step without purification. Similar results were observed with palladium hydroxide.

A solution of 1,4-diol (0.129 mmol) in 2 mL acetic acid-water (4:1) was refluxed at 100 °C for 14 h. Thin layer chromatography showed complete consumption of starting material. Then acetic acid was evaporated by azeotropic distillation with toluene. Then saturated solution of sodium bicarbonate (2 mL) was added to the reaction residue and product was extracted in ethyl acetate. Crude compound was used in next step without purification.

4.12. General procedure for preparation of 1,2,3,4-tetraacetate 19a–c

To a solution of alkane-1,2,3,4-tetrol *ent-2*, *ent-1*, or **18** (0.201 mmol) in CH_2CI_2 (2 mL), acetic anhydride (0.15 mL, 1.612 mmol) was added. Then triethylamine (0.22 mL, 1.612 mmol) was added. A pinch of DMAP was added and reaction mixture was stirred at room temperature for 12 h. After consumption of starting material as revealed by thin layer chromatography, reaction mixture was quenched by adding 10 mL of water and product was extracted in CH_2CI_2 (10 mL \times 3). Yellow gummy product was obtained. Product was purified by column chromatography.

4.12.1. (2R,3R,4S)-Icosane-1,2,3,4tetrayl tetra acetate (19a)

Yellow colored gummy liquid; Yield 58% (over three steps); R_f 0.46 (ethyl acetate/hexane, 1:1); $[\alpha]_D^{23} = -1.39 (c 1, CHCl_3)$; IR (liquid film) ν_{max} cm⁻¹ 2923, 2853, 1745, 1371, 1223, 1025; ¹H NMR (CDCl_3/TMS, 400 MHz) δ 0.87 (t, 3H, J = 6 Hz, CH_3); 1.24 (br s, 28H, CH₃(CH₂)₁₄); 1.47–1.60 (m, 2H, ACOCHCH₂); 2.04 (s, 3H, OCOCH₃); 2.07 (two s merge, 6H, OCOCH₃); 2.09 (s, 3H, OCOCH₃); 3.96 (dd, 1H, $J_1 = 12.4$ Hz, $J_2 = 4.4$ Hz, ACOCH_aH_b); 4.35 (dd, 1H, $J_1 = 12.4$ Hz, $J_2 = 2.8$ Hz, ACOCH_aH_b); 5.07–5.08 (m, 1H, ACOCHCH₂); 5.23–5.25 (m, 2H, ACOCHCH); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.1, 20.6, 20.7, 20.9, 22.7, 23.3, 24.6, 24.9, 29.0, 29.2, 29.3, 29.5, 29.6, 29.7, 30.5, 31.9, 36.6, 62.0, 69.6, 71.2, 71.4, 76.7, 77.0, 77.3, 170.06, 170.1, 170.43, 170.49; HRMS (ESI) m/z Calcd for C₂₈H₅₀O₈Na [M+Na]⁺: 537.3403. Found: 537.3402.

4.12.2. (2R,3R,4S)-Octadeane-1,2,3,4tetrayl tetra acetate (19b)

Yellow colored liquid; Yield 56% (over three steps); R_f 0.58 (ethyl acetate/hexane, 1:1); $[\alpha]_2^{23} = -3.59$ (c 1, CHCl₃); IR(liquid film) v_{max} cm⁻¹ 2924, 2854, 1745, 1371, 1214, 1026; ¹H NMR (CDCl₃/TMS, 400 MHz) δ 0.81 (t, 3H, J = 7.2 Hz, CH₃); 1.17 (br s, 22H, CH₃(CH₂)₁₁); 1.34–1.60 (m, 4H); 1.95 (s, 3H, OCOCH₃); 1.962 (two s merge, 6H, OCOCH₃); 1.968 (s, 3H, OCOCH₃); 3.89 (dd, 1H, J_1 = 12 Hz, J_2 = 5.2 Hz, ACOCH_aH_b); 4.30 (dd, 1H, J_1 = 12 Hz, J_2 = 3.2 Hz, ACO-CH_aH_b); 5.00–5.02 (m, 1H, ACOCHCH₂); 5.16–5.21 (m, 2H, ACOCHCH); ¹³C NMR (CDCl₃/TMS, 100 MHz) δ 14.2, 20.7, 20.8,

20.9, 21.0, 22.8, 25.0, 29.4, 29.5, 29.6, 29.7, 30.7, 32.0, 62.1, 69.7, 71.3, 71.5, 76.8, 77.1, 77.4, 170.2, 170.5; HRMS (ESI) m/z Calcd for C₂₆H₄₆O₈Na [M+Na]⁺: 509.3090. Found: 509.3106.

4.12.3. (2R,3R,4S)-Trideane-1,2,3,4tetrayl tetra acetate (19c)

Yellow colored gummy liquid; Yield 60% (over three steps); $R_{\rm f}$ 0.56 (ethyl acetate/hexane, 1:1); $[\alpha]_D^{23} = -1.59$ (*c* 1, CHCl₃); IR(liquid film) $\nu_{\rm max}$ cm⁻¹ 2925, 2857, 1742, 1437, 1371, 1220, 1027, 953, 768; ¹H NMR(CDCl₃/TMS, 400 MHz) δ 0.86 (t, 3H, *J* = 6.4 Hz, CH₃); 1.17 (br s, 14H, CH₃(CH₂)₇); 1.48–1.51 (m, 2H, AcOCHCH₂); 2.02 (s, 3H, OCOCH₃); 2.05 (two s merge, 6H, OCOCH₃); 2.07 (s, 3H, OCOCH₃); 3.96 (dd, 1H, *J*₁ = 5.2 Hz, *J*₂ = 1.6 Hz, AcOCH₄H_b); 4.34 (dd, 1H, *J*₁ = 5.6 Hz, *J*₂ = 2.4 Hz, AcOCH₄H_b); 5.05–5.06 (m, 1H, AcOCHCH₂); 5.21–5.24 (m, 2H, AcOCHCH); ¹³C NMR (CDCl₃/TMS, 400 MHz) δ 14.1, 20.6, 20.7, 20.8, 20.9, 22.7, 24.7, 24.9, 29.3, 29.4, 29.5, 30.6, 31.9, 36.7, 62.1, 69.7, 71.3, 71.5, 76.8, 77.1, 77.4, 170.14, 170.17, 170.51, 170.57; HRMS (ESI) *m*/z Calcd for C₂₁H₃₆O₈Na [M+Na]⁺: 439.2308. Found: 439.2299.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012. 06.005.

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