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Preliminary communication

PRELIMINARY COMMUNICATION

Synthesis of a steroidal dendrimer core

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Abstract: Synthesis of a steroidal dendrimer core possessing various functional termini, such as ester, carboxy and hydroxy, is presented. The approach described enables further simple manipulations for the introduction of more complex functionalities.

Keywords: deoxycholic acid, trimesoyl trichloride, core, dendrimer.

INTRODUCTION

Dendrimers are well-defined macromolecules of uniform mass that contain a core, successive layers of branched repeat units and surface groups.¹ Over the last decade or more, the synthesis of novel dendrimers has been a very active area of research and one important aspect has been the incorporation of functional units such as crown ethers,² mesogenic groups³ and various redox-active substituents based on tetrathiafulvalene,⁴ anthraquinones,⁵ ferrocene,⁶ fullerenes,⁷ or transition metal complexes.⁸ An interesting consequence of placing a functional unit at the core of a dendrimer is its steric isolation which can prevent unwanted interference of the functionality.⁹

The three-dimensional globular morphology of dendrimer macromolecules¹ makes them attractive for higher level structural ordering in a manner resembling the folded structures of proteins.² Many of the potential applications envisaged for dendrimers (*e.g.*, enantioselective catalysts, chemical sensors, optical switches) can only be realized in materials expressing highly ordered and controllable conformations. However, the goal of inducing higher-order three-dimensional organization in chiral dendrimers³ has been severely hampered by the conformational flexibility of most commonly studied dendrimers.⁴

Recent results of our research in antimalarial peroxide chemistry¹⁰ prompted us to envisage steroidal-based dendrimers which would act as a carrier of the tetraoxane function-

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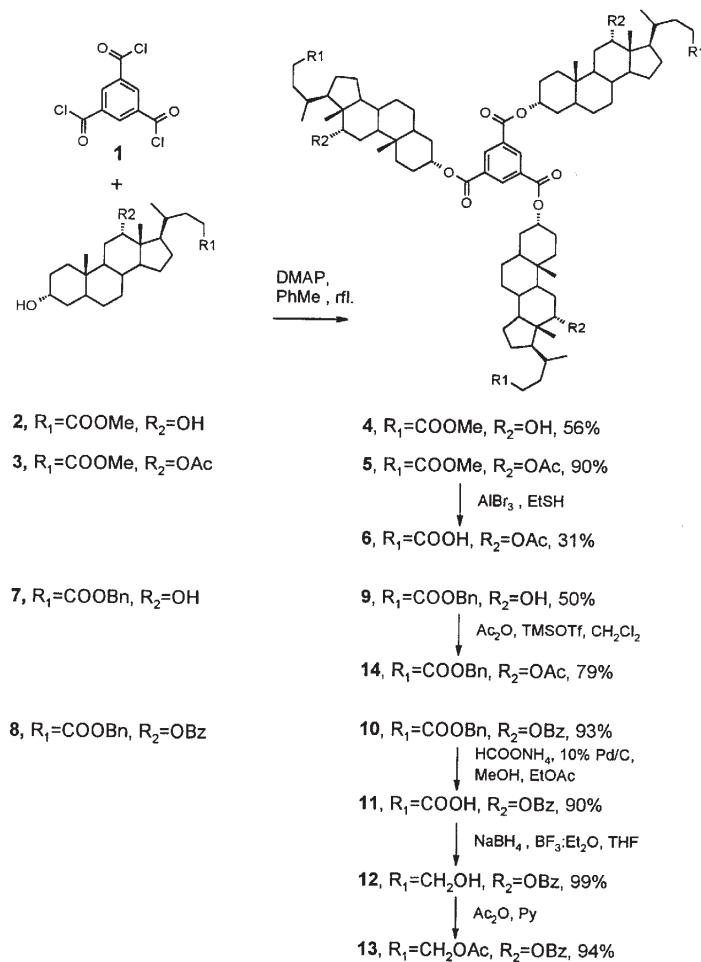
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ality. In this way, the delivery of a higher amount of the tetraoxane moiety, the actual pharmacophore, to the site of action of antimalarial peroxides, the infected erythrocyte,¹¹ could be realized.

Here, preliminary results on the synthesis of dendrimer cores based on steroidal branches are reported

SYNTHESIS

The first step in the synthesis is the coupling reaction of trimesoyl trichloride (**1**)¹² (an initial core) with the building block derived from deoxycholic acid. The direct esterification of trimesoyl trichloride by steroidal alcohols, methyl deoxycholate (**2**) and methyl deoxycholate 12 α -acetate (**3**)¹³, in dry toluene and in the presence of DMAP, afforded triester cores **4** and **5** in 56 % and 89 % yield, respectively (Scheme 1).¹⁴ The subsequent step, the selective hydrolysis of the ester at C(24) of the steroidal units using various reac-



Scheme 1.

tion conditions, NaOH/MeOH/H₂O, LiOH/MeOH/H₂O, KO^tBu/DMSO, NaCN/HMPT, NaCN/Py, gave unsatisfactory results. In addition, demethylation of the methyl ester **5** was effected using the system AlBr₃/EtSH,¹⁵ yielding the triacid core **6** in only 31 % yield. Hence, a new synthon had to be derived, which would be properly designed for the next coupling reaction and at the same time, affording a product suitably protected for further synthetic manipulations.

Because of their ease of preparation and mild deprotection route, it was decided to use benzyl esters in the further synthesis. Direct esterification of trimesoyl trichloride by the benzyl deoxycholate **7** and benzyl deoxycholate 12 α -benzoate (**8**)¹⁶ afforded the triester cores **9** and **10**, 79 % and 93 % yield, respectively. Heterogeneous hydrogenolysis of compound **10** under mild reaction conditions using the ammonium formate/methanol – Pd/C¹⁷ system, afforded the triacid core **11** in 90 % yield. Reduction of compound **11** by NaBH₄/BF₃·Et₂O gave the triol **12** in 99 % yield.¹⁸ For characterisation purposes, the triol core **12** was acylated to give the triacetate **13**. The 12 α -acetate **14** was prepared from core **9**, using TMSOTf catalysed acylation (79 % yield).

The introduction of the peroxide moiety as well as the results of biological screening will be published at a later time.

EXPERIMENTAL

General

Melting points were determined on a Boetius PMHK apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer Spectrophotometer FT-IR 1725X. ¹H-NMR and ¹³C-NMR spectra were recorded on Varian Gemini-200 spectrometer (at 200 and 50 MHz, respectively) in the indicated solvent using TMS as the internal standard. Chemical shifts are expressed in ppm (δ) values and coupling constants (J) in Hz. ESI MS spectra were recorded on an Autospec TOF instrument in the positive ion mode using CH₃CN/H₂O (1/1) with 1 % AcOH as the carrying solvent solution. The stock solutions of the samples were diluted in order to obtain 10 pmol/L solutions using the carrying solvent. The source temperature was 75 °C, and the cone voltage was set to 40 V. Abbreviations : Trm – trimesoyl; Bn – benzyl; Bz – benzoyl.

General procedure for the synthesis of the core. To a solution of steroidal alcohol (3.3 mmol) and DMAP (9.9 mmol) in dry toluene (60 mL), trimesoyl trichloride (1.00 mmol) was added and heated to reflux until the end of the reaction (TLC: toluene/ethyl acetate 9/1). The reaction mixture was allowed to cool to room temperature and purified by dry-flash chromatography, using the same solvent mixture as eluent.

1,3,5-Tris[(methyl 12 α -hydroxycholanoate)-3 α -oxycarbonyl]benzene (**4**)

Colourless, glassy substance, obtained according to the *General procedure* (56 % yield), mp. 163–173 °C (dichloromethane). IR (KBr): 3545 *m*, 3087 *w*, 2945 *s*, 1724 *s*, 1635 *w*, 1448 *m*, 1381 *m*, 1243 *s*, 1195 *m*, 1170 *m*, 986 *m* cm⁻¹. ¹H-NMR (200 MHz, CDCl₃): 8.79 (*s*, 3H–C_{Trm}), 5.03 (*m*, 3H–C(3)), 4.00 (*s*, 3H–C(12)), 3.67 (*s*, 9H, CH₃O₂C(24)), 0.97 (*s*, 9H, H₃C–C(10)), 0.70 (*s*, 9H, H₃C–C(13)). ¹³C-NMR-DEPT (50 MHz, CDCl₃): 174.72 (C(24)), 164.61 (Trm–COOSt), 134.26 (C_{Trm}–H), 131.71 (C_{Trm}–COOSt), 75.67 (CH–O–), 73.01 (CH–O–), 51.44 (CH₃O–), 48.23 (CH), 47.21 (CH), 46.41 (C_q), 41.82 (CH), 35.91 (CH), 35.03 (CH), 34.82 (CH₂), 34.10 (C_q), 33.60 (CH), 32.10 (CH₂), 30.97 (CH₂), 30.85 (CH₂), 28.68 (CH₂), 27.37 (CH₂), 26.88 (CH₂), 26.55 (CH₂), 25.93 (CH₂), 23.56 (CH₂), 23.04 (CH₃–C(10)), 17.25 (CH₃–C(20)), 12.69 (CH₃–C(13)).

1,3,5-Tris[(methyl 12 α -acetoxycholanoate)-3 α -oxycarbonyl]benzene (**5**)

Colourless, glassy substance, obtained according to the *General procedure* (89 % yield), mp. 164–170 °C. IR (KBr): 3451 *w*, 2951 *s*, 1738 *s*, 1450 *m*, 1379 *m*, 1244 *s* cm⁻¹. ¹H-NMR (200 MHz,

CDCl₃): 8.82 (s, 3H-C_{Tmm}), 5.10 (bs, 3H-C(12)), 5.01 (m, 3H-C(3)), 3.67 (s, CH₃O₂C(24)), 2.13 (s, CH₃COO⁻), 0.96 (s, 9H, H₃C-C(10)), 0.82 (d, *J* = 5.6 Hz, 9H, H₃C-C(20)), 0.75 (s, 9H, H₃C-C(13)). ¹³C-NMR-DEPT (50 MHz, CDCl₃): 174.60 (C(24)), 170.58 (CH₃COO⁻), 164.77 (Tmm-COOS_t), 134.30 (C_{Tmm}-H), 131.73 (C_{Tmm}-COOS_t), 75.80 (CH-O⁻), 51.44 (CH₃O⁻), 49.34 (CH), 47.50 (CH), 44.98 (C_q), 41.90 (CH), 35.65 (CH), 34.63 (CH), 34.47 (CH₂), 34.03 (CH), 32.27 (CH₂), 30.90 (CH₂), 30.76 (CH₂), 27.28 (CH₂), 26.90 (CH₂), 25.71 (CH₂), 23.34 (CH₂), 23.04 (CH₃COO⁻), 21.42 (CH₃-C(10)), 17.43 (CH₃-C(20)), 12.35 (CH₃-C(13)). MS-ESI (*m/z*): 1525 (100 %, M⁺+Na), 1541 (35 %, M⁺+K).

1,3,5-Tris[(12 α -acetoxycholanoic acid)-3 α -oxycarbonyl]benzene (6)

AlBr₃ (133 mg, 5.00 mmol) was carefully dissolved in EtSH (10 mL) (under argon) and **5** (500 mg, 0.33 mmol) was added, in one portion. The obtained mixture was stirred for 24 h at room temperature and then methanol (10 mL) was added until the precipitate dissolved. The reaction mixture was then treated with dilute HCl (3.6 %, 20 mL), extracted with CH₂Cl₂ (4 × 15 mL), dried over anhydrous Na₂SO₄, filtered and evaporated. Dry-flash chromatography on SiO₂ afforded 150.5 mg (31 %) of triacid **6**, as a colourless powder. IR (KBr): 3445 w, 2951 s, 2870 m, 1724 s, 1450 m, 1380 m, 1244 s, 1025 m, 987 m, 745 m cm⁻¹. ¹H-NMR (200 MHz, CDCl₃): 8.83 (s, 3H-C_{Tmm}), 5.11 (bs, 3H-C(12)), 5.01 (m, 3H-C(3)), 2.14 (s, 9H, CH₃COO⁻), 0.96 (s, 9H, H₃C-C(10)), 0.84 (d, *J* = 2 Hz, 9H, H₃C-C(20)), 0.75 (s, 9H, H₃C-C(13)). ¹³C-NMR (50 MHz, CDCl₃): 180.05, 170.69, 164.79, 131.71, 129.00, 75.89, 49.36, 47.54, 44.99, 41.88, 35.65, 34.62, 34.03, 32.27, 30.94, 30.54, 27.30, 26.90, 26.60, 25.73, 23.36, 23.05, 21.43, 17.43, 12.37.

1,3,5-Tris[(benzyl 12 α -hydroxycholanoate)-3 α -oxycarbonyl]benzene (9)

Colourless, glassy substance, obtained from diol **7** according to the *General procedure* (50 % yield), mp 110–123 °C. IR (KBr): 3529 m, 3034 w, 2942 s, 2868 s, 1725 s, 1451 m, 1381 m, 1242 s, 1158 m, 1094 w, 1024 w, 985 m, cm⁻¹. ¹H-NMR (200 MHz, CDCl₃): 8.79 (s, 3H-C_{Tmm}), 7.36–7.31 (5H-C_{Ph}), 5.12 (s, Ph-CH₂O⁻), 5.05 (m, 3H-C(3)), 3.98 (s, 3H-C(12)), 0.96 (s, 9H, H₃C-C(10)), 0.67 (s, 9H, H₃C-C(13)). ¹³C-NMR-DEPT (50 MHz; CDCl₃): 174.00 (C(24)), 164.54 (Tmm-COOS_t), 136.01 (C_{Ph}-CH₂O⁻), 134.18 (C_{Tmm}-H), 131.64 (C_{Tmm}-COOS_t), 128.47 (C_{Ph}-H), 128.16 (C_{Ph}-H), 75.62 (CH-O⁻), 72.94 (CH-O⁻), 66.00 (Ph-CH₂O⁻), 48.16 (CH), 47.16 (CH), 46.35 (C_q), 41.77 (CH), 35.84 (CH), 34.94 (CH), 34.94 (CH₂), 34.05 (C_q), 33.52 (CH), 32.05 (CH₂), 31.16 (CH₂), 30.77 (CH₂), 28.62 (CH₂), 27.33 (CH₂), 26.84 (CH₂), 26.50 (CH₂), 25.89 (CH₂), 23.53 (CH₂), 23.00 (CH₃-C(10)), 17.19 (CH₃-C(20)), 12.64 (CH₃-C(13)). MS-ESI (*m/z*): 1627 (100 %, M⁺+Na), 1643 (38 %, M⁺+K).

1,3,5-Tris[(benzyl 12 α -acetoxycholanoate)-3 α -oxycarbonyl]benzene (14)

To a solution of Ac₂O (0.050 mL) in CH₂Cl₂ (1 mL), cooled on ice, one drop of TMSOTf was added. Then, a solution of compound **9** (200 mg, 0.125 mmol) in CH₂Cl₂ (2 mL) was added dropwise. The reaction was completed in 10 min (TLC: PhMe/EtOAc 9/1). The reaction mixture was washed with sat. NaHCO₃ several times, dried over anhydrous Na₂SO₄, filtered and evaporated. After drying *in vacuo* 173.2 mg (79 %) of crude core **14** was obtained. Mp 116–125 °C. IR (KBr): 2947 s, 2868 m, 1732 s, 1244 s, 1158 m cm⁻¹. ¹H-NMR (200 MHz; CDCl₃): 8.83 (s, 3H-C_{Tmm}), 7.36 (m, 15H-C_{Ph}), 5.11 (bs, 3H-C(12)), 5.10–4.90 (m, 3H-C(3)), 2.11 (s, 9H, CH₃COO⁻), 0.96 (s, 9H, H₃C-C(10)), 0.80 (d, *J* = 5.6 Hz, 9H, H₃C-C(20)), 0.72 (s, 9H, H₃C-C(13)). ¹³C-NMR (50 MHz; CDCl₃): 173.97, 170.64, 164.79, 136.03, 134.33, 131.71, 128.52, 128.27, 128.20, 75.85, 75.80, 66.09, 49.33, 47.56, 44.98, 41.90, 35.65, 34.60, 34.47, 34.03, 32.27, 31.17, 30.74, 27.26, 26.91, 26.60, 25.71, 23.35, 21.45, 17.41, 12.35. MS-ESI (*m/z*): 1753 (100 %, M⁺+Na), 1769 (28 %, M⁺+K).

1,3,5-Tris[(benzyl 12 α -benzoyloxycholanoate)-3 α -oxycarbonyl]benzene (10)

Colourless, glassy substance, obtained from monoalcohol **8** according to the *General procedure* (93 % yield). Mp 119–129 °C. IR (KBr): 3550–3350 m, 2947 s, 2869 m, 1718 s, 1603 w, 1451 m, 1382 w, 1273 s, 1241 s, 1158 m, 1112 m, 1069 w, 1026 w, 986 m cm⁻¹. ¹H-NMR (200 MHz; CDCl₃): 8.60 (s, 3H-C_{Tmm}), 8.05 (d, *J* = 7 Hz, 6H-C_{Bz}), 7.4–7.2 (m, 24H), 5.38 (bs, 3H-C(12)), 5.07 (s, Ph-CH₂O⁻), 4.90

(*m*, 3H-C(3)), 0.98 (*s*, 9H, H₃C-C(10)), 0.84 (*bs*, 9H, H₃C-C(20)), 0.80 (*s*, 9H, H₃C-C(13)). ¹³C-NMR-DEPT (50 MHz; CDCl₃): 173.82 (C(24)), 165.90 (Ph-COO-), 164.52 (Trm-COOST), 135.95 (C_{Ph}-CH₂O-), 134.02 (C_{Trm}-H), 132.85 (C_{Bz}-H), 131.44 (C_{Trm}-COOST), 130.55 (C_{Bz}-COO-), 129.25 (C_{Bz}-H), 128.93 (C_{Bz}-H), 128.42 (C_{Ph}-H), 128.12 (C_{Ph}-H), 128.07 (C_{Ph}-H), 76.20 (CH-O-), 75.53 (CH-O-), 65.93 (Ph-CH₂O-), 50.07 (CH), 47.76 (CH), 45.36 (C_q), 41.75 (CH), 35.64 (CH), 34.63 (CH), 34.63 (CH₂), 33.91 (C_q), 32.12 (CH₂), 31.08 (CH₂), 30.61 (CH₂), 27.28 (CH₂), 26.75 (CH₂), 26.22 (CH₂), 25.79 (CH₂), 23.36 (CH₂), 22.95 (CH₃-C(10)), 17.32 (CH₃-C(20)), 12.46 (CH₃-C(13)). MS-ESI (*m/z*): 1939 (100 %, M⁺+Na), 1955 (26 %, M⁺+K).

1,3,5-Tris[(12 α -benzoyloxycholanoic acid)-3 α -oxycarbonyl]benzene (11)

To a suspension of **10** (117 mg, 0.061 mmol), HCOONH₄ (100 mg) and 10 % Pd/C (100 mg) in ethyl acetate (3 mL), at room temperature, methanol (3 mL) was added. The reaction mixture was stirred at room temperature under argon until the end of the reaction (1 h; TLC: PhMe/acetone 1/1). The mixture was filtered through celite and the filtrate was evaporated. The solid was suspended in CH₂Cl₂ and washed with brine. After drying over anhydrous Na₂SO₄, evaporating, pasting from benzene and drying *in vacuo* 90.0 mg (90 %) of triacid core **11** was isolated. Mp 201–210 °C (benzene). IR (KBr): 3600–3150 w, 2947 m, 2869 m, 1719 s, 1452 m, 1382 w, 1276 s, 1241 s, 1171 w, 1112 m, 986 w, 715 m cm⁻¹. ¹H-NMR (200 MHz; CDCl₃): 11.96 (*s*, HOOC(24)), 8.24 (*s*, 3H-C_{Trm}), 7.93 (*bs*, 6H-C_{Bz}), 7.32 (*bs*, 6H-C_{Bz}), 7.17 (*bs*, 3H-C_{Bz}), 5.29 (*bs*, 3H-C(12)), 4.83–4.78 (*m*, 3H-C(3)), 0.89 (*s*, 9H, H₃C-C(10)), 0.77 (*s*, 9H, H₃C-C(13)). ¹³C-NMR (50 MHz; CDCl₃): 174.92, 165.23, 163.56, 133.20, 132.97, 131.08, 130.50, 129.04, 128.77, 75.98, 75.30, 49.80, 47.88, 45.16, 35.35, 34.35, 33.71, 30.89, 25.79, 22.75, 17.49, 12.43. MS-ESI (*m/z*): 1669 (100 %, M⁺+Na), 1685 (42 %, M⁺+K).

1,3,5-Tris [(12 α -benzoyloxy-24-hydroxycholano)-3 α -oxycarbonyl]benzene (12)

To a solution of **11** (300 mg, 0.182 mmol) in THF (5 mL), NaBH₄ (300 mg) was added. After cessation of the reaction, 0.3 mL of BF₃·Et₂O was added dropwise and the reaction was completed in 30 min (TLC: toluene/acetone = 1/1). The reaction mixture was evaporated to dryness, the resulting solid suspended in CH₂Cl₂, and washed with 3.6 % HCl followed by sat. NaHCO₃ and brine. After evaporation of the solvent, drying and pasting from diethyl ether, 290 mg (99 %) of colourless, powdered core **12** was isolated.

IR (KBr): 3445 m, 2948 s, 2868 s, 1719 s, 1603 w, 1451 m, 1382 m, 1315 m, 1274 s, 1242 s, 1113 m cm⁻¹. ¹H-NMR (200 MHz; CDCl₃): 8.60 (*s*, 3H-C_{Trm}), 8.06 (*d*, *J* = 7.0, 6H-C_{Bz}), 7.46–7.27 (*m*, 9H-C_{Bz}), 5.40 (*bs*, 3H-C(12)), 4.94 (*m*, 3H-C(3)), 3.74 (*m*, 2H-C(24)), 0.98 (*s*, 9H, H₃C-C(10)), 0.83 (*s*, 9H, H₃C-C(13)). ¹³C-NMR-DEPT (50 MHz; CDCl₃): 166.01 (PhCOO-), 164.59 (Trm-COOST), 134.06 (C_{Trm}-H), 132.86 (C_{Bz}-H), 131.49 (C_{Trm}-COOST), 130.66 (C_{Bz}-COOST), 129.31 (C_{Bz}-H), 128.49 (C_{Bz}-H), 76.36 (CH-O-), 75.62 (CH-O-), 63.33 (C(24)), 50.13 (CH), 47.96 (CH), 45.39 (C_q), 41.84 (CH), 35.71 (CH), 35.00 (CH), 34.71 (CH), 34.71 (CH₂), 33.98 (C_q), 32.19 (CH₂), 31.58 (CH₂), 29.32 (CH₂), 27.44 (CH₂), 26.84 (CH₂), 26.28 (CH₂), 25.95 (CH₂), 23.44 (CH₂), 23.02 (CH₃-C(10)), 17.74 (CH₃-C(20)), 12.53 (CH₃-C(13)). MS-ESI (*m/z*): 1604 (37 %, M⁺), 1605 (38 %, M⁺+1), 1627 (100%, M⁺+Na), 1643 (12 %, M⁺+K).

1,3,5-Tris[(12 α -benzoyloxy-24-acetoxycholano)-3 α -oxycarbonyl]benzene (13)

To a solution of **11** (24.6 mg, 0.015 mmol) in THF (0.5 mL), NaBH₄ (20 mg) and BF₃·Et₂O (0.1 mL) was added and reduction was completed using the above procedure. Crude core **12** was dissolved in pyridine (2 mL) and Ac₂O (1 mL) and stirred at room temperature for 20 h. The reaction mixture was then poured into an ice-HCl mixture and extracted with chloroform (3 × 5 mL). After evaporating, drying and pasting from benzene, 25 mg (94 %) of **13** was isolated. Mp 70–80 °C. IR (KBr): 2924 s, 2855 s, 1718 s, 1603 w, 1453 m, 1370 w, 1315 w, 1274 s, 1242 s, 1175 m, 1112 m, 715 m cm⁻¹. ¹H-NMR (200 MHz; CDCl₃): 8.60 (*s*, 3H-C_{Ar}), 8.06 (*d*, *J* = 4.2 Hz, 6H-C_{Bz}), 7.5–7.3 (*m*, 9H-C_{Bz}), 5.4 (*bs*, 3H-C(12)), 5.0–4.85 (*m*, 3H-C(3)), 3.97 (*m*, 2H-C(24)), 2.01 (*s*, 9H, CH₃COO-), 0.99 (*s*, 9H, H₃C-C(10)), 0.83 (*s*, H₃C-C(13)). ¹³C-NMR (50 MHz; CDCl₃): 171.23, 166.01, 164.63, 134.11, 132.89, 131.53, 130.71, 129.36, 128.52, 76.36, 75.64, 64.89, 50.16,

47.98, 45.43, 41.88, 35.76, 34.89, 34.76, 34.75, 34.01, 32.32, 31.88, 31.70, 29.65, 29.32, 27.44, 26.86, 26.33, 25.99, 25.22, 23.47, 23.05, 22.65, 20.96, 17.68, 12.57.

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ИЗВОД

СИНТЕЗА ДЕНДРИМЕРСКОГ СТЕРОИДНОГ ЈЕЗГРА

ТАТЈАНА КОП¹, ГАБРИЈЕЛА ПОКСФАЛВИ² И БОГДАН А. ШОЛАЈА¹

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У овом раду приказана је синтеза дендримерског стероидног језгра са естарским карбоксилним и хидроксилним завршецима. Описани приступ синтези омогућава даљу, комплекснију функционализацију једноставним манипулацијама.

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