

First Total Synthesis of 3-Epi-calystegin B₂

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A straightforward chiral pool synthesis for a non-natural calystegin, 3-epi-B₂, is described. Key steps of this synthesis include an ultrasound-assisted Zn-mediated tandem ring opening reaction followed by a Grubbs' catalyst-mediated ring closure metathesis reaction. Compared to calystegin B₂, the target compound is no longer an inhibitor for a β -glycosidase hence proving that an equatorial hydroxyl group at position C-3 is necessary for a tight binding of calystegins into the active site of β -glycosidases.

Key words: Calystegin, Glucosidase Inhibitor, Ring Closure Metathesis

Introduction

Diabetes mellitus type-2 is characterized [1] by high blood glucose levels because of an impaired insulin action. This impaired insulin action ("insulin resistance") is a contributing factor [2–4] to hypertension, atherosclerosis and a risk factor for coronary heart diseases. Acarbose (Glucobay[®], Fig. 1) is an antidiabetic drug [5] to treat type-2 diabetes mellitus and prediabetes. It is a glucosidase inhibitor, and it acts by reducing the rate of digestion of complex carbohydrates into monosaccharides.

Calystegins [6] are polyhydroxylated bicyclic nortropane alkaloids which were first isolated from the roots of *Calystegia sepium* in 1988. They are lead substances [7–10] for chemotherapeutic drugs for the treatment of diabetes mellitus but also for viral infections, cancer and other metabolic disorders; they have

been suggested [11] as pharmacoperones to treat protein folding disorders.

Only a few non-natural calystegins have been synthesized [12,13] and screened for biological activity so far. Recently, we were able to show that a fluorine substitution at position C-3 in calystegine B₂ (Fig. 1) lowers its affinity to several glucosidases [14]. Based on these findings we became interested in the role of the hydroxyl group at position C-3 and therefore in the synthesis of a 3-epi-calystegin B₂ and the comparison of its activity as an inhibitor of a β -glucosidase.

Results and Discussion

Olefin metathesis is one of the most powerful tools in current organic synthesis. Routes to calystegins using ring closure metatheses [12,13,15] as key steps appear most promising and straightforward. Formally, calystegin B₂ is derived from D-glucose; to obtain an analog of inverted configuration at position C-3, a suitable allose derivative can serve as a starting material. Therefore, 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose **1** [16] was selected as a starting point for our synthesis of 3-epi-calystegin B₂ (**11**).

Hydrolysis of **1** with aqueous sulfuric acid (Scheme 1) resulted in the formation of a complex mixture of anomeric pyranoses and furanoses. Treatment of this mixture with methanol in the presence of dry HCl gave a mixture of the corresponding methyl glycosides whose *in situ* tritylation, benzylation, de-tritylation and chromatography gave the methyl α -D-

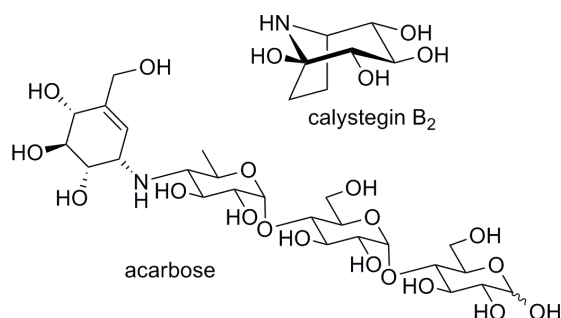
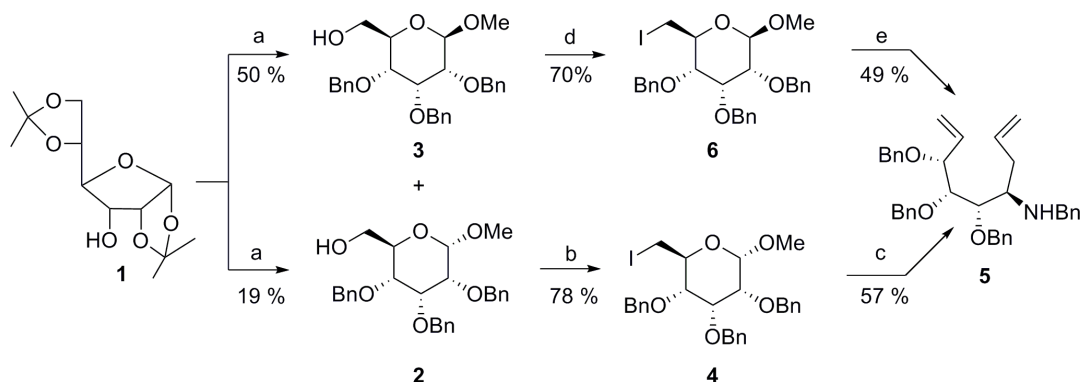
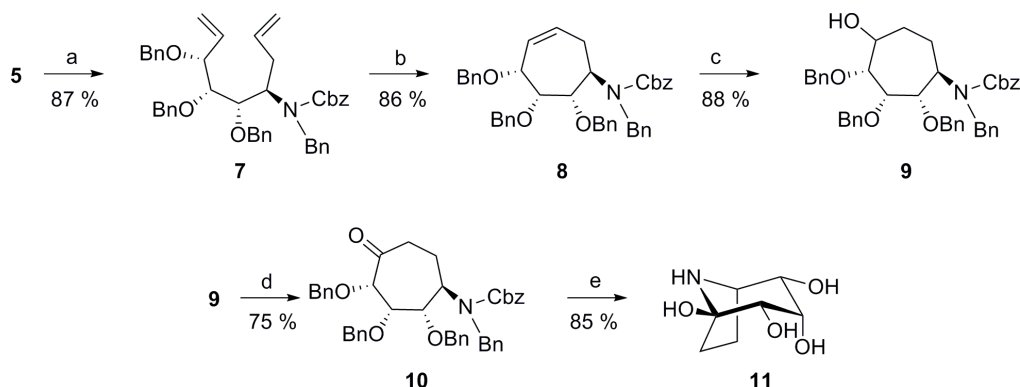


Fig. 1. Structure of glycosidase inhibitors acarbose and calystegin B₂.



Scheme 1. a) H_2SO_4 ; trityl chloride/pyridine/DMAP; DMF; BnBr/DMF ; *p*-TsOH; b) PPh_3 , imidazole, I_2 , toluene, 95 °C, 2 h; c) Zn , THF, 40 °C, ultrasound; BnNH_2 , 3 h, allyl bromide 4 h; d) PPh_3 , imidazole, I_2 , toluene, 95 °C, 2 h; e) Zn , THF, 40 °C, ultrasound; BnNH_2 , 3 h, allyl bromide 4 h.



Scheme 2. a) Benzyl chloroformate, NaHCO_3 , 25 °C, 2 h; b) Grubbs catalyst, 25 °C, 30 h; c) BH_3/THF , H_2O_2 , 25 °C, 5 h; d) PCC, CH_2Cl_2 , 25 °C, 24 h; e) Pd/C , H_2 , EtOAc/HOAc , 25 °C, 5 d.

allopyranoside **2** [17] and the benzylated methyl β -D-allopyranoside **3**. Compound **2** is characterized in its ^1H NMR spectra by the presence of a doublet at $\delta = 4.71$ ppm showing a $^3J_{1\text{-H},2\text{-H}} = 4.2$ Hz whereas for β -configured **3** [18] at $\delta = 4.81$ ppm a doublet with $^3J_{1\text{-H},2\text{-H}} = 7.9$ Hz is found, the latter being typical for a β -anomeric configuration.

Iodination of **2** using triphenylphosphane, iodine and imidazol [19] gave 6-deoxy-6-iodo-alloside **4** in 78% yield; iodination of **3** under similar conditions yielded **6** [20]. Ring opening [21, 22] of **4** gave 56% of the (*R*)-6-amino-diene **5**. The same product could also be obtained from the ring opening of **6** although in a lower yield.

Compound **5** was *N*-protected by carbobenzyloxilation (Scheme 2) to afford **7**, which was subjected to a RCM reaction using Grubbs' catalyst (2nd generation, $\text{Cl}_2\text{Ru}(\text{Imes})[\text{P}(\text{cyclohexyl})_3]=\text{CHPh}$) [21, 22], and the cycloheptene **8** was obtained. Regioselective oxidation

of **8** using the borane-THF complex followed by oxidative work-up [23] and PCC oxidation of **9** gave the cycloheptanone **10**. Compound **10** is characterized in its IR spectrum by a strong adsorption at $\nu = 1694\text{ cm}^{-1}$ for the carbonyl group of the ketone; this carbonyl group is also detected by a ^{13}C NMR signal at $\delta = 208.0$ ppm. Hydrogenation of **10** with Pd/C (10%) in ethyl acetate/acetic acid finally gave the target compound **11**.

Compared with naturally occurring calystegin B_2 , the signal of C-3 in 3-epi- B_2 is shifted to $\delta = 66.9$ ppm ($|\Delta\delta| = 8.3$ ppm, *cf.* C-3 in calystegin B_2 $\delta = 75.2$ ppm), and that of 3-H is shifted to $\delta = 3.67$ ppm ($|\Delta\delta| = 0.43$; *cf.* 3-H in calystegin B_2 $\delta = 3.24$ ppm). A proof for the D-allo-configuration is found in the coupling constants $^3J_{2\text{-H},3\text{-H}} = 3.9$ Hz (for calystegin B_2 $J = 8.5$ Hz was detected) and $^3J_{3\text{-H},4\text{-H}} = 4.2$ Hz.

Calystegin B_2 is a competitive inhibitor for the β -glucosidase from almonds. In a 4-nitro-phenolate as-

say [24] a $K_i = 5.9 \mu\text{M}$ was determined. A previously prepared 3-fluoro analog [14] gave a $K_i = 82 \mu\text{M}$. For compound **11**, however, no inhibition of the enzyme could be measured even at an inhibitor concentration of 10 mM. This might be explained by the axial position of the hydroxyl group at position C-3, therefore proving that an equatorial hydroxyl group at this position is necessary for a tight binding of the inhibitor into the active site of β -glycosidases.

Experimental Section

General methods

Melting points are uncorrected (Leica hot stage microscope). Optical rotations were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell, 20 °C). NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal SiMe_4 or internal CCl_3F), IR spectra (film or KBr pellet) on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. Mass spectra were taken on a Thermo Electron Finnigan LCQ instrument (electrospray, voltage 4.5 kV, sheath gas nitrogen). For elemental analysis, a Foss-Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10 % sulfuric acid, ammonium molybdate and cerium(IV) sulfate, followed by gentle heating). The solvents were dried according to usual procedures.

Methyl 2,3,4-tri-*O*-benzyl- α -D-allopyranoside (**2**) and methyl 2,3,4-tri-*O*-benzyl- β -D-allopyranoside (**3**)

A suspension of **1** (6.0 g, 23.1 mmol) in water (50 mL) and conc. sulfuric acid (98 %, 1 mL) was stirred at 25 °C for 24 h. The mixture was neutralized by the addition of NaHCO_3 (3.0 g), the solvents were removed and the residue was suspended in dry methanol (50 mL), the mixture was filtered and the filtrate was evaporated. The residue was dissolved in dry methanol (50 mL), and a 0 °C cold solution of methanol (5 mL) containing acetyl chloride (0.5 mL) was added. The mixture was heated under reflux for 8 h, neutralized (NaHCO_3), filtered and the solvents were removed from the filtrate. The residue was dissolved in dry pyridine (50 mL), trityl chloride (9.63 g, 34.6 mmol) and DMAP (0.4 g, 3.3 mmol) were added and stirring at 25 °C was continued for another 16 h. The solvent was removed, the residue re-dissolved in ether (100 mL), the solution was extracted with water (100 mL), the organic phase was dried (Na_2SO_4) and the solvents were removed. Purification by chromatography (silica gel, methanol/ethyl acetate 5 : 95) gave a mixture of the corresponding pyranosides [(56 g, 12.8 mmol; α : $R_f = 0.35$ (in ethyl acetate), β : $R_f = 0.49$ (in ethyl acetate))]. The mixture of the pyranosides (5.6 g, 12.8 mmol) was dissolved

in dry DMF (100 mL), and at 0 °C NaH (55 % in mineral oil, 2.79 g, 64 mmol) was added, stirring at 25 °C continued for 15 min, and benzyl bromide (9.84 g, 57.6 mmol) was added. After stirring for 5 h at 25 °C, methanol (30 mL) was slowly added to quench the reaction, and the solvents were removed under reduced pressure. The residue was re-dissolved in diethyl ether (150 mL), the solution washed with water ($3 \times 25 \text{ mL}$) and brine ($2 \times 25 \text{ mL}$) and dried (Na_2SO_4), and the solvents were removed. The residue was dissolved in a mixture of dichloromethane/methanol (100 mL, 2 : 1) containing catalytic amounts of *p*-toluenesulfonic acid and the solution stirred for 12 h at 25 °C. After neutralization with *N*-methylmorpholine and a usual aqueous work-up, the residue was purified by chromatography (silica gel, hexane/ethyl acetate 5 : 3) to afford **2** (2.04 g, 19.0 %) and **3** (5.32 g, 49.6 %).

Data for 2: colorless oil. – $[\alpha]_D = 77.6^\circ$ ($c = 0.7$, CHCl_3). – $R_f = 0.12$ (hexane/ethyl acetate 5 : 3). – IR (film): $\nu = 3261\text{m}$, 3088m, 3064m, 3030s, 2929s, 1952w, 1879w, 1808w, 1737w, 1669w, 1606w, 1497s, 1454m, 1396m, 1359m, 1322m, 1244m, 1210m, 1103m, 973m, 912w, 844w, 736s, 697s cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 7.43$ – 7.20 (m, 15 H, aryl), 4.95 (d, 1 H, $J = 12.5$ Hz, H-Bn), 4.85 (d, 1 H, $J = 12.5$ Hz, H-Bn), 4.71 (d, 1 H $^3J_{1,2} = 4.2$ Hz, 1-H), 4.59 (d, 1 H, $J = 12.5$ Hz, H-Bn), 4.54 (d, 1 H, $J = 12.5$ Hz, H-Bn), 4.50 (d, 1 H, $J = 11.7$ Hz, H-Bn), 4.35 (d, 1 H, $J = 11.7$ Hz, H-Bn), 4.16 (m, 2 H, 4-H and 5-H), 3.82 (dd, 1 H, $^2J_{6,6'} = 11.7$ Hz $^3J_{6,5} = 3.1$ Hz, 6-H), 3.77 (dd, 1 H, $^2J_{6',6} = 11.7$ Hz $^3J_{6',5} = 3.7$ Hz, 6-H'), 3.42 (s, 3 H, CH_3), 3.35 (m, 2 H, 2-H and 3-H). – ^{13}C NMR (100 MHz, CDCl_3): $\delta = 139.1$, 137.7, 137.65, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.83, 127.78, 127.74, 127.66, 127.6, 127.5, 127.0 (all C_{ar}), 98.3 (C-1), 76.2 (C3), 75.0 (C2), 73.5 (CH_2 -Ph), 71.9 (C4), 71.3 (CH_2Ph), 70.9 (CH_2 -Ph), 66.5 (C5), 62.2 (C-6), 56.0 (CH_3). – MS (ESI, $\text{MeOH} + \text{LiClO}_4$): m/z (%) = 471.2 (100) $[\text{M} + \text{Li}]^+$, 503.2 (10) $[\text{M} + \text{MeOH} + \text{Li}]^+$, 935.3 (17) $[\text{M}_2 + \text{Li}]^+$, 1041.3 (25) $[\text{M}_2\text{Li}_2\text{ClO}_4]^+$. – $\text{C}_{28}\text{H}_{32}\text{O}_6$ (464.55): calcd. C 72.39, H 6.94; found C 72.11, H 7.03.

Data for 3: colorless oil. – $[\alpha]_D = +11.2^\circ$ ($c = 0.9$, CHCl_3) (lit. [18]: $+17^\circ$). – $R_f = 0.28$ (hexane/ethyl acetate 5 : 3). – IR (film): $\nu = 3482\text{w}$, 3088w, 3063w, 3030m, 2888s, 1954w, 1734w, 1605w, 1497m, 1454s, 1387m, 1349w, 1307w, 1248w, 1206s, 1126s, 1091s, 1046s, 1028s, 914w, 819w, 736s, 698s cm^{-1} . – ^1H NMR (500 MHz, CDCl_3): $\delta = 7.40$ – 7.24 (m, 15 H, H-ar), 4.88 (d, 1 H, $J = 12.0$ Hz, H-Bn), 4.84 (d, 1 H $^3J_{1,2} = 7.9$ Hz, 1-H), 4.83 (d, 1 H, $J = 12.2$ Hz, H-Bn), 4.80 (d, 1 H, $J = 12.0$ Hz, H-Bn), 4.62 (d, 1 H, $J = 12.2$ Hz, H-Bn), 4.52 (d, 1 H, $J = 11.6$ Hz, H-Bn), 4.41 (d, 1 H, $J = 11.6$ Hz, H-Bn), 4.11 (dd, 1 H $^3J_{3,4} = 2.4$, $^3J_{3,2} = 2.6$ Hz, 3-H), 3.97 (ddd, 1 H $^3J_{5,6} = 3.1$, $^3J_{5,6'}^{\text{H}}$ = 4.1 $^3J_{5,4} = 9.7$ Hz, 5-H), 3.87 (dd, 1 H, $^2J_{6,6'} = 11.7$ Hz $^3J_{6,5} = 3.1$ Hz, 6-H), 3.73 (dd, 1 H, $^2J_{6',6} = 11.7$ Hz $^3J_{6',5} = 4.1$ Hz, 6-H'), 3.54 (s, 3 H, CH_3), 3.41 (dd, 1 H $^3J_{4,3} = 2.4$, $^3J_{4,5} = 9.7$ Hz, 4-H), 3.17 (dd, 1 H $^3J_{2,3} = 2.6$ $^3J_{2,1} = 7.9$ Hz, 2-H). – ^{13}C NMR

(100 MHz, CDCl_3): δ = 138.9, 138.6, 137.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.81, 127.78, 127.7, 127.5, 127.5, 127.3 (all C_{ar}), 102.1 (C1), 79.1 (C3), 75.7 (C2), 74.7 (C4), 74.4 ($\text{CH}_2\text{-Ph}$), 72.9 (CH_2Ph), 72.5 (C5), 71.6 (CH_2Ph), 62.3 (C-6), 57.0 (CH_3). – MS (ESI, $\text{MeOH}+\text{LiClO}_4$): m/z (%) = 471.6 (100) $[\text{M}+\text{Li}]^+$. – $\text{C}_{28}\text{H}_{32}\text{O}_6$ (464.55): calcd. C 72.39, H 6.94; found C 72.18, H 7.07.

Methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo- α -D-allopyranoside (4)

As described below for **6**, from **2** (1.02 g, 2.2 mmol), triphenylphosphane (1.26 g, 4.84 mmol), imidazole (0.67 g, 9.9 mmol), and iodine (1.11 g, 4.4 mmol), compound **4** (0.98 g, 78.0%) was obtained as a colorless oil. $[\alpha]_{\text{D}} = +41.2^\circ$ (c = 0.6, CHCl_3). – R_{f} = 0.30 (hexane/ethyl acetate 85:15). – IR (film): ν = 3650w, 3510w, 3088w, 3063m, 3030s, 3004w, 2890s, 2244w, 1953w, 1878w, 1813, 1723w, 1703w, 1605w, 1586w, 1496s, 1455s, 1360m, 1312m, 1243m, 1199s, 1170s, 1143s, 1097s, 981s, 911s, 735s, 697s cm^{-1} . – ^1H NMR (500 MHz, CDCl_3): δ = 7.41–7.17 (m, 15 H, H-ar), 4.93 (d, 1 H, 2J = 12.5 Hz, H-Bn), 4.82 (d, 1 H, J = 12.5 Hz, H-Bn), 4.75 (d, 1 H $^3J_{1,2}$ = 4.0 Hz, 1-H), 4.60 (d, 1 H, J = 12.5 Hz, H-Bn), 4.56 (d, 1 H, J = 12.5 Hz, H-Bn), 4.50 (d, 1 H, J = 11.3 Hz, H-Bn), 4.35 (d, 1 H, 2J = 11.3 Hz, H-Bn), 4.16 (dd, 1 H $^3J_{3,4}$ = 2.7 $^3J_{3,2}$ = 2.7 Hz, 3-H), 3.89 (ddd, 1 H $^3J_{5,6}$ = 2.6 $^3J_{5,6'}$ = 6.0 $^3J_{5,4}$ = 9.0 Hz, 5-H), 3.52 (dd, 1 H, $^2J_{6,6'}$ = 10.6 $^3J_{6,5}$ = 2.6 Hz, 6-H), 3.47 (s, 3 H, CH_3), 3.43 (dd, 1 H $^3J_{2,3}$ = 2.7 $^3J_{2,1}$ = 4.0 Hz, 2-H), 3.38 (dd, 1 H, $^2J_{6',6}$ = 10.6 $^3J_{6',5}$ = 6.0 Hz, 6-H'), 3.18 (dd, 1 H $^3J_{4,3}$ = 2.7 $^3J_{4,5}$ = 9.0 Hz, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 138.9, 137.7, 137.5, 134.3, 129.6, 128.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.84, 127.76, 127.65, 127.5, 127.2, 126.9 (all C_{ar}), 98.4 (C-1), 78.8 (C4), 76.5 (C2), 73.6 ($\text{CH}_2\text{-Ph}$), 71.5 (C3), 71.3 ($\text{CH}_2\text{-Ph}$), 71.1 ($\text{CH}_2\text{-Ph}$), 65.1 (C5), 56.3 ($-\text{CH}_3$), 9.2 (C6). – MS (ESI, $\text{MeOH}+\text{LiClO}_4$): m/z (%) = 581.7 (100) $[\text{M}+\text{Li}]^+$, 1260.9 (10) $[\text{M}_2\text{Li}_2\text{ClO}_4]^+$. – $\text{C}_{28}\text{H}_{31}\text{IO}_5$ (574.12): calcd. C 58.54, H 5.44; found C 58.31, H 5.57.

(3R, 4R, 5S, 6R)-6-[(N-Benzyl)amino]-3,4,5-tris-(benzyloxy)-1,8-nonadiene (5)

A suspension of **6** (1.52 g, 2.65 mmol) and activated zinc powder (1.73 g, 26.5 mmol) in abs. THF (50 mL) was heated in an ultrasound bath at 40 $^\circ\text{C}$, and within 30 min benzylamine (0.71 g, 6.62 mmol) was added. Sonification at 40 $^\circ\text{C}$ was continued for another 3 h. Allyl bromide (0.75 g, 6.62 g) was added and sonification continued for 4 h. The mixture was filtered through a small layer of silica gel, the silica gel was washed with ethyl acetate (500 mL), the solvents were removed, and the residue was subjected to chromatography (silica gel, hexane/ethyl acetate 85:15) to afford **5** (350 mg, 49.2%) as a colorless oil. In an analogous manner, com-

pound **5** (56.5%) was obtained from **4** as a colorless oil. $[\alpha]_{\text{D}} = -21.2^\circ$ (c = 0.7, CHCl_3). – R_{f} = 0.52 (hexane/ethyl acetate 85:15). – IR (film): ν = 3064m, 3030m, 2865m, 1699m, 1496s, 1454s, 1331w, 1208m, 1100s, 1070s, 1028s, 997m, 735s, 697s cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): δ = 7.35–7.19 (m, 20 H, H-ar), 5.99 (ddd, 1 H $^3J_{2,3}$ = 8.0 $^3J_{2,1}$ = 10.4 $^3J_{2,1'}$ = 17.4 Hz, 2-H), 5.70 (dddd, 1 H $^3J_{8,7}$ = 6.4 $^3J_{8,7'}$ = 8.0 $^3J_{8,9'}$ = 11.6, $^3J_{8,9}$ = 15.6 Hz, 8-H), 5.34 (dd, 1 H, $^2J_{1,1'}$ = 1.5 $^3J_{1,2}$ = 10.4 Hz, 1-H), 5.21 (dd, 1 H, $^2J_{1',1}$ = 1.5 $^3J_{1',2}$ = 17.4 Hz, 1'-H), 5.022 (d, 1 H $^3J_{9,8}$ = 15.6 Hz, 9-H), 5.017 (d, 1 H $^3J_{9',8}$ = 11.6 Hz, 9-H'), 4.87 (d, 1 H, J = 11.5 Hz, H-Bn), 4.80 (d, 1 H, J = 11.5 Hz, H-Bn), 4.66 (d, 1 H, J = 11.5 Hz, H-Bn), 4.62 (d, 1 H, J = 11.9 Hz, H-Bn), 4.60 (d, 1 H, J = 11.5 Hz, H-Bn), 4.37 (d, 1 H, J = 11.9 Hz, H-Bn), 4.24 (dd, 1 H $^3J_{3,4}$ = 3.4 $^3J_{3,2}$ = 8.0 Hz, 3-H), 3.92 (dd, 1 H $^3J_{4,3}$ = 3.4 $^3J_{4,5}$ = 6.9 Hz, 4-H), 3.78 (d, 1 H, J = 13.2 Hz, H-Bn-NHR), 3.69 (d, 1 H, J = 13.2 Hz, H-Bn-NHR), 3.63 (dd, 1 H $^3J_{5,6}$ = 3.5 $^3J_{5,4}$ = 6.9 Hz, 5-H), 3.04 (ddd, 1 H $^3J_{6,5}$ = 3.5 $^3J_{6,7}$ = 4.1 $^3J_{6,7'}$ = 7.6 Hz, 6-H), 2.37 (ddd, 1 H, $^2J_{7,7'}$ = 14.7 $^3J_{7,6}$ = 4.1 $^3J_{7,8}$ = 6.4 Hz, 7-H), 2.24 (ddd, 1 H, $^2J_{7',7}$ = 14.7 $^3J_{7',6}$ = 7.6 $^3J_{7',8}$ = 8.0 Hz, 7-H'). – ^{13}C NMR (100 MHz, CDCl_3): δ = 140.9, 138.9, 138.8, 136.5 (C-8), 135.5 (C2), 128.21, 128.19, 128.15, 128.12, 128.08, 128.0, 127.6, 127.33, 127.29, 127.2, 126.6 (all C_{ar}), 119.1 (C-1), 117.0 (C-9), 82.0 (C-3), 81.2 (C-4), 79.6 (C-5), 73.6 ($\text{CH}_2\text{-Ph}$), 73.4 ($\text{CH}_2\text{-Ph}$), 70.4 ($\text{CH}_2\text{-Ph}$), 57.5 (C-6), 52.0 ($\text{CH}_2\text{-Ph}$), 34.7 (C-7). – MS (ESI, MeOH): m/z (%) = 548.5 (100) $[\text{M}+\text{H}]^+$. – $\text{C}_{37}\text{H}_{41}\text{NO}_3$ (574.73): calcd. C 81.13, H 7.54; found C 81.00, H 5.68.

Methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo- β -D-allopyranoside (6)

To a solution of **3** (2.66 g, 5.7 mmol), triphenylphosphane (3.3 g, 12.54 mmol) and imidazole (1.75 g, 25.65 mmol) in dry toluene (50 mL), iodine (2.91 g, 11.46 mmol) was added in several portions at 95 $^\circ\text{C}$. Stirring was continued for 2 h, the hot solvent was decanted and the viscous residue rinsed with diethyl ether (3×25 mL). Purification of the residue by chromatography (silica gel, hexane/ethyl acetate 85:15) yielded **6** (2.3 g, 70%) as a colorless oil. $[\alpha]_{\text{D}} = +29.9^\circ$ (c = 0.6, CHCl_3) (lit. [20]: $+15.0^\circ$). – R_{f} = 0.48 (hexane/ethyl acetate 85:15). – IR (film): ν = 3063w, 3030m, 2895m, 1606s, 1496m, 1454s, 1346w, 1304w, 1210s, 1091s, 912w, 753s, 697s cm^{-1} . – ^1H NMR (500 MHz, CDCl_3): δ = 7.38–7.23 (m, 15 H, H-ar), 4.86 (d, 1 H, J = 11.8 Hz, H-Bn), 4.85 (d, 1 H, J = 12.1 Hz, H-Bn), 4.83 (d, 1 H, $^3J_{1,2}$ = 7.9 Hz, 1-H), 4.76 (d, 1 H, J = 11.8 Hz, H-Bn), 4.61 (d, 1 H, J = 12.1 Hz, H-Bn), 4.51 (d, 1 H, J = 11.5 Hz, H-Bn), 4.38 (d, 1 H, J = 11.5 Hz, H-Bn), 4.08 (dd, 1 H, $^3J_{3,4}$ = 2.4, $^3J_{3,2}$ = 2.6 Hz, 3-H), 3.71 (ddd, 1 H, $^3J_{5,6}$ = 2.5, $^3J_{5,6'}$ = 7.1, $^3J_{5,4}$ = 9.3 Hz, 5-H), 3.56 (s, 3 H, CH_3), 3.53 (dd, 1 H, $^2J_{6,6'}$ = 10.6, $^3J_{6,5}$ = 2.5 Hz, 6-H), 3.26 (dd, 1 H, $^2J_{6',6}$ = 10.6, $^3J_{6',5}$ = 7.1 Hz, 6-H'), 3.22 (dd, 1 H, $^3J_{2,3}$ = 2.6, $^3J_{2,1}$ = 7.9 Hz, 2-H),

3.18 (dd, 1 H, $^3J_{4,3} = 2.4$, $^3J_{4,5} = 9.3$ Hz, 4-H). – ^{13}C NMR (100 MHz, CDCl_3): $\delta = 138.7$ 138.6 137.4 133.8 133.6 132.0 128.7 128.51 128.47 128.43 128.37, 128.3, 128.2, 128.0, 127.9, 127.6, 127.51, 127.47 (all C_{ar}), 101.9 (C-1), 79.4 (C-4), 79.1 (C-2), 74.5 ($\text{CH}_2\text{-Ph}$), 74.2 (C-3), 73.0 ($\text{CH}_2\text{-Ph}$), 71.5 ($\text{CH}_2\text{-Ph}$), 71.1 (C-5), 56.9 (CH_3), 8.0 (C6). – MS (ESI, $\text{MeOH} + \text{LiClO}_4$): m/z (%) = 581.7 (100) $[\text{M} + \text{Li}]^+$, 1260.7 (25, $\text{M}_2\text{Li}_2\text{ClO}_4$) $^+$. – $\text{C}_{28}\text{H}_{31}\text{IO}_4$ (574.12): calcd. C 58.54, H 5.44; found C 58.39, H 5.51.

(3 *R*, 4 *R*, 5 *S*, 6 *R*) 6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (7)

To a solution of **5** (819 mg, 1.50 mmol) in dichloromethane/water (5 : 1, 50 mL), NaHCO_3 (1.26 g, 15.0 mmol) and benzyl chloroformate (766 mg, 4.5 mmol) in ethyl acetate (10 mL) were added. After stirring for 2 h at r.t., the phases were separated, the aqueous phase extracted with dichloromethane (3×25 mL). The organic phases were combined and the solvents removed. The residue was subjected to chromatography (silica gel, hexane/ethyl acetate 85 : 15) to yield **7** (890 mg, 87.0 %) as a colorless oil. $[\alpha]_{\text{D}} = +9.2^\circ$ ($c = 0.6$, CHCl_3). – $R_f = 0.55$ (hexane/ethyl acetate 85 : 15). – IR (film): $\nu = 3453\text{w}$, 3064w, 3031m, 2894w, 1748w, 1696s, 1642w, 1606w, 1496m, 1454s, 1233s, 1106s, 1028s, 993w, 914w, 735s, 698s, 599w cm^{-1} . – ^1H NMR (400 MHz, CDCl_3 , 27.0 $^\circ\text{C}$): $\delta = 7.41$ –6.87 (m, 25 H, H-ar), 5.82 (m, 1 H, 2-H), 5.39–5.26 (m, 3 H, 8-H, 1-H, 1'-H), 5.10 (m, 2 H, $\text{CH}_2\text{-Bn-Cbz}$), 4.79 (d, 1 H $^3J_{9,8} = 17.0$ Hz, 9-H), 4.70–3.96 (m, 12 H, 3-H, 4-H, 5-H, 9-H', $8 \times \text{CH}_2\text{-Bn}$), 3.60 (d, 1 H, $J = 7.2$ Hz, 6-H), 2.68–2.32 (m, 2 H, 7-H, 7-H'). – ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$, 120.0 $^\circ\text{C}$): $\delta = 7.37$ –7.08 (m, 25 H, H-ar), 5.94 (ddd, 1 H $^3J_{2,3} = 7.2$ $^3J_{2,1'} = 10.4$ $^3J_{2,1} = 17.5$ Hz, 2-H), 5.43 (ddd, 1 H $^3J_{8,7} = 7.4$ $^3J_{8,9'} = 10.2$ $^3J_{8,9} = 17.0$ Hz, 8-H), 5.27 (d, 1 H $^3J_{1,2} = 17.5$ Hz, 1-H), 5.25 (d, 1 H $^3J_{1',2} = 10.4$ Hz, 1'-H), 5.07 (s, 2 H, $\text{CH}_2\text{-Bn-Cbz}$), 4.74 (d, 1 H $^3J_{9,8} = 17.0$ Hz, 9-H), 4.71 (d, 1 H $^3J_{9',8} = 10.2$ Hz, 9-H'), 4.61 (d, 1 H, $^2J = 11.5$ Hz, H-Bn), 4.48 (d, 1 H, $^2J = 15.9$ Hz, H-Bn), 4.49 (d, 1H, $^2J = 11.1$, H-Bn), 4.45 (d, 1 H, $J = 11.7$ Hz, H-Bn), 4.35 (d, 1 H, $J = 11.5$ Hz, H-Bn), 4.33 (d $^3J_{3,2} = 7.2$ Hz, 3-H), 4.31 (d, 1 H, $J = 11.7$ Hz, H-Bn), 4.29 (d, 1 H, $J = 11.1$ Hz, H-Bn), 4.26 (d, 1 H, $J = 15.9$ Hz, H-Bn), 4.10 (d, 1 H $^3J_{4,5} = 7.1$ Hz, 4-H), 4.08 (d, 1 H $^3J_{5,4} = 7.1$ Hz, 5-H), 3.69 (dd, 1 H $^3J_{6,7} = 1.9$ $^3J_{6,7'} = 6.1$ Hz, 6-H), 2.54–2.40 (m, 2 H, 7-H, 7-H'). – ^{13}C NMR (125 MHz, $[\text{D}_6]\text{DMSO}$, 120.0 $^\circ\text{C}$): $\delta = 157.0$ (C=O, Cbz), 138.1, 137.9, 136.1 (all C_{ar}), 135.7 (C-8), 135.5 (C-2), 127.7, 127.5, 127.4, 127.3, 127.1 127.0, 126.9, 126.81, 126.80, 126.6, 126.0 (all C_{ar}), 117.2 (C-1), 115.0 (C-9), 81.2 (C-3), 80.9 (C-4), 79.9 (C-5), 72.2 ($\text{CH}_2\text{-Ph}$), 71.0 ($\text{CH}_2\text{-Ph}$), 69.8 ($\text{CH}_2\text{-Ph}$), 66.0 ($\text{CH}_2\text{-Ph}$), 58.2 (C-6), 49.0 ($\text{CH}_2\text{-Ph}$), 32.8 (C-7). – MS (ESI, $\text{MeOH} + \text{LiClO}_4$): m/z (%) = 688.8 (100) $[\text{M} + \text{Li}]^+$. – $\text{C}_{45}\text{H}_{47}\text{NO}_5$ (681.86): calcd. C 79.27, H 6.95; found C 79.02, H 7.13.

(3 *R*, 4 *R*, 5 *S'*, 6 *R*) 6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)-cycloheptene (8)

A solution of **7** (890 mg, 1.31 mmol) in dry dichloromethane (50 mL) containing Grubbs' catalyst (20 mg) was stirred at 25 $^\circ\text{C}$ for 30 h. The mixture was filtered, the filtrate evaporated and the residue purified by chromatography (silica gel, hexane/ethyl acetate 80 : 20) to yield **8** (735 mg, 86.1 %) as a colorless oil. $[\alpha]_{\text{D}} = -77.5^\circ$ ($c = 0.5$, CHCl_3). – $R_f = 0.35$ (hexane/ethyl acetate 85 : 15). – IR (film): $\nu = 3030\text{m}$, 2925s, 2854m, 1698s, 1496m, 1454s, 1412m, 1346m, 1259s, 1206s, 1095s, 1069s, 1028s, 735s, 697s cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 7.35$ –7.06 (m, 25 H, H-ar), 5.78–5.61 (m, 2 H, 1-H, 2-H), 5.08 (d, 1 H, $J = 12.5$ Hz, H-Bn-Cbz), 5.02 (d, 1 H, $J = 12.5$ Hz, H-Bn-Cbz), 4.78 (d, 1 H, $J = 11.6$ Hz, H-Bn), 4.72 (d, 1 H, $J = 13.1$ Hz, H-Bn), 4.63 (d, 1 H, $J = 11.8$ Hz, H-Bn), 4.60 (d, 1 H, $J = 11.6$ Hz, H-Bn), 4.54 (d, 1 H, $J = 11.8$ Hz, H-Bn), 4.55–4.38 (m, 3 H, Bn), 4.31 (m, 1 H, 3-H), 4.17 (dd, 1 H, $J = 3.5$, $J = 3.5$ Hz, 4-H), 4.06 (d, 1 H, $J = 3.5$ Hz, 5-H), 3.93 (m, 1 H, 6-H), 2.95 (dd, 1 H, $^2J_{7,7'} = 15.6$, $J = 7.2$ Hz, 7-H), 1.95 (dd, 1 H, $^2J_{7,7'} = 15.6$, $J = 7.3$ Hz, 7-H'). – ^{13}C NMR (100 MHz, CDCl_3): $\delta = 156.4$ (C=O, Cbz), 140.3, 138.8, 138.5, 136.5 (all C_{ar}), 130.2 (C-1), 129.1 (C-2), 128.1, 128.1, 128.0, 127.8, 127.5, 127.5, 127.35, 127.28, 127.1, 126.0, 125.8 (all C_{ar}), 78.9 (C-4), 78.8 (C-5), 77.8 (C-3), 72.6 ($\text{CH}_2\text{-Ph}$), 72.4 ($\text{CH}_2\text{-Ph}$), 71.8 ($\text{CH}_2\text{-Ph}$), 67.1 ($\text{CH}_2\text{-Cbz}$), 56.6 (C6), 48.6 ($\text{CH}_2\text{-Ph}$), 28.1 (C-7). – MS (ESI, $\text{MeOH} + \text{LiClO}_4$): m/z (%) = 660.9 (100) $[\text{M} + \text{Li}]^+$. – $\text{C}_{43}\text{H}_{43}\text{NO}_5$ (653.81): calcd. C 78.99, H 6.63; found C 78.74, H 6.84.

(1 *RS*, 2 *R*, 3 *S*, 4 *S*, 5 *R*) 5-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))amino]-2,3,4-tris(benzyloxy)-cycloheptanol (9)

To a solution of **8** (735 mg, 1.12 mmol) in abs. THF (60 mL) kept at -78°C a solution of $\text{BH}_3 \cdot \text{THF}$ (1 M, 3 mL) was added within 20 min. Stirring was continued at 25 $^\circ\text{C}$ for 12 h, aq. NaOH (2 N, 4.5 mL) and H_2O_2 (30 %, 0.9 mL) were added, and stirring was continued for another 5 h. The phases were separated, the aq. layer was extracted with diethyl ether (3×30 mL), the organic phases were combined, dried (Na_2SO_4), and the solvent was removed. The residue was subjected to chromatography (silica gel, hexane/ethyl acetate 8 : 2) to afford **9** (660 mg, 87.7 %) as a colorless oil. $[\alpha]_{\text{D}} = -10.0^\circ$ ($c = 0.5$, CHCl_3). – $R_f = 0.33$ (hexane/ethyl acetate 5 : 3). – IR (film): $\nu = 3441\text{w}$, 3088w, 3063w, 3031m, 2935m, 2872w, 1952w, 1809w, 1694s, 1606w, 1594w, 1496s, 1454s, 1417m, 1362m, 1324m, 1261s, 1212s, 1177w, 1112s, 1052s, 1028s, 911w, 813w, 734s, 697s, 598w cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 7.39$ –6.80 (m, 25 H, H-ar), 5.1 (d, 1 H, $J = 12.4$ Hz, H-Bn-Cbz), 5.0 (d, 1 H, $J = 12.4$ Hz, H-Bn-Cbz), 4.77–4.42 (m, 8 H, Bn), 4.05–3.90 (m, 4 H, 1-H, 2-H, 3-H, 4-H), 3.37 (dd, 1 H, $J =$

2.8, $J = 8.0$ Hz, 5-H), 2.32 (m, 1H, 7-H), 1.96–1.55 (m, 3 H, 6-H, 6-H', 7-H'). – ^{13}C NMR (100 MHz, CDCl_3): $\delta = 157.3$ (C=O, Cbz), 140.3, 138.6, 138.2, 138.1, 136.5, 129.5, 128.4, 128.3, 128.2, 128.11, 128.08, 128.0, 127.90, 127.86, 127.7, 127.6, 127.4, 127.3, 127.2, 126.3, 126.0, 125.9 (all C_{ar}), 86.3 (C-2), 80.6 (C-3), 80.5 (C-4), 74.0 (C-1), 73.9 ($\text{CH}_2\text{-Ph}$), 73.7 ($\text{CH}_2\text{-Ph}$), 73.1 ($\text{CH}_2\text{-Ph}$), 67.2 ($\text{CH}_2\text{-Cbz}$), 58.1 (C-5), 47.8 ($\text{CH}_2\text{-Ph}$), 29.5 (C-7), 25.9 (C-6). – MS (ESI, $\text{MeOH}+\text{LiClO}_4$): m/z (%) = 678.6 (100) $[\text{M}+\text{Li}]^+$. – $\text{C}_{43}\text{H}_{45}\text{NO}_6$ (671.82): calcd. C 76.87, H 6.75; found C 76.59, H 6.89.

(2*S*, 3*S*, 4*S*, 5*R*)-5-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-2,3,4-tris(benzyloxy)-cycloheptanone (**10**)

To a solution of **9** (660 mg, 0.98 mmol) in dry dichloromethane (100 mL), PCC (254 mg, 1.18 mmol) was added, and the mixture was stirred for 12 h at 25 °C. Additional PCC (254 mg, 1.18 mmol) was added and stirring continued for another 12 h. The solvent was partially removed (50 mL), ethyl acetate (100 mL) added, and the mixture was filtered through a layer (5 cm) of silica gel. The filtrate was evaporated and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 8:2) to yield **10** (490 mg, 74.5 %) as a colorless oil. $[\alpha]_{\text{D}} = -42.0^\circ$ ($c = 0.5$, CHCl_3). – $R_f = 0.40$ (hexane/ethyl acetate 5:3). – IR (film): $\nu = 3088\text{w}$, 3063w, 3031w, 2943w, 1954w, 1694s, 1604w, 1585w, 1497m, 1454s, 1416m, 1349m, 1254s, 1208s, 1102s, 1028s, 916w, 827w, 772w, 736s, 698s, 650w, 595w cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 7.31$ –6.96 (m, 25 H, H-ar), 5.09 (d, 1 H, $J = 12.5$ Hz, H-Bn-Cbz), 5.06 (d, 1 H, $J = 12.5$ Hz, H-Bn-Cbz), 4.98 (d, 1 H, $J = 11.4$ Hz, H-Bn), 4.89 (d, 1 H, $J = 11.4$ Hz, H-Bn), 4.63 (d, 1 H, $J = 11.6$ Hz, H-Bn), 4.56 (d, 1 H, $J = 11.6$ Hz, H-Bn), 4.54 (d, 1 H, $J = 11.3$ Hz, H-Bn), 4.49–4.13 (m, 6 H, 2-H, 3-H, 4-H, 3× H-Bn), 2.53 (m, 1 H, 5-H), 2.35 (m, 2 H, 7-H, 7-H'),

1.61 (m, 2 H, 6-H, 6-H'). – ^{13}C NMR (100 MHz, CDCl_3): $\delta = 208.0$ (C=O), 157.3 (C=O, Cbz), 139.8, 138.4, 137.8, 137.6, 128.3, 128.14, 128.10, 128.07, 127.9, 127.8, 127.6, 127.5, 127.2, 126.3, 125.8 (all C_{ar}), 83.6 (C-2), 82.0 (C-3), 81.1 (C-4), 74.0 ($\text{CH}_2\text{-Ph}$), 73.6 ($\text{CH}_2\text{-Ph}$), 72.1 ($\text{CH}_2\text{-Ph}$), 67.3 ($\text{CH}_2\text{-Cbz}$), 58.0 (C-5), 47.8 ($\text{CH}_2\text{-Ph}$), 38.6 (C-7), 24.3 (C-6). – MS (ESI, $\text{MeOH}+\text{LiClO}_4$): m/z (%) = 676.6 (100) $[\text{M}+\text{Li}]^+$. – $\text{C}_{43}\text{H}_{43}\text{NO}_6$ (669.80): calcd. C 77.11, H 6.47; found C 76.86, H 6.95.

(1*R*, 2*S*, 3*S*, 4*S*, 5*R*)-8-Azabicyclo[3.2.1]octane-1,2,3,4-tetraol [(+)-calystegin 3-epi-B₂] (**11**)

A solution of **10** (450 mg, 0.67 mmol) in ethyl acetate (20 mL) and acetic acid (66 %, 80 mL) was hydrogenated (35 psi) in the presence of Pd/C (10 %, 200 mg) for 5 d. The catalyst was filtered off, the solvent removed and the product purified by chromatography (silica gel, methanol/water/ammonia 95:5:1) to yield **11** (100 mg, 85.0 %) as a colorless semi-amorphous solid. $[\alpha]_{\text{D}} = +36.4^\circ$ ($c = 0.2$, MeOH). – $R_f = 0.05$ (methanol/ethyl acetate/ammonia 95:5:1). – IR (film): $\nu = 3453\text{w}$, 3064w, 3031m, 2894w, 1748w, 1696s, 1642w, 1606w, 1496m, 1454s, 1233s, 1106s, 1028s, 993w, 914w, 735s, 698s, 599w cm^{-1} . – ^1H NMR (400 MHz, CD_3OD): $\delta = 5$ 3.71 (d, 1 H $^3J_{2,3} = 3.9$ Hz, 2-H), 3.67 (dd, 1 H $^3J_{3,2} = 3.9$ $^3J_{3,4} = 4.2$ Hz, 3-H), 3.54 (dd, 1 H $^3J_{4,5} = 2.8$ $^3J_{4,3} = 4.2$ Hz, 4-H), 3.35 (dd, 1 H $^3J_{5,4} = 2.8$ $^3J_{5,6} = 7.7$ Hz, 5-H), 2.05 (ddd, 1 H, $^2J_{6,6'} = 14.0$ $^3J_{6,5} = 7.7$ $^3J_{6,7} = 10.7$ Hz, 6-H), 1.74–1.67 (m, 2 H, 7-H, 7-H'), 1.45 (ddd, 1 H, $^2J_{6,6'} = 14.0$ $^3J_{6',7} = 5.7$, $^3J_{6',7'} = 8.6$ Hz, 6-H'). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 91.1$ (C-1), 76.9 (C-2), 72.0 (C-4), 66.9 (C-3), 58.5 (C-5), 31.7 (C-7), 23.3 (C-6). – MS (ESI, MeOH): m/z (%) = 176.1 (100) $[\text{M}+\text{H}]^+$. – $\text{C}_7\text{H}_{13}\text{NO}_4$ (175.18): calcd. C 47.99, H 7.48; found C 47.80, H 7.63.

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