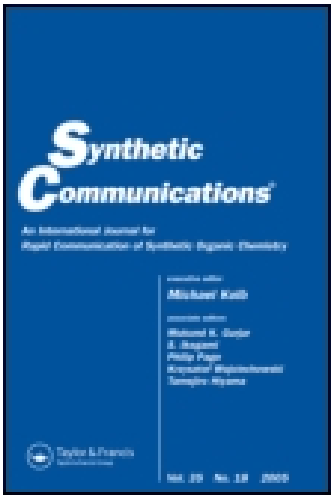

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Syntheses of Pantolactone and Pantothenic Acid Derivatives as Potential Lipid Regulating Agents

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Syntheses of Pantolactone and Pantothenic Acid Derivatives as Potential Lipid Regulating Agents

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Abstract: A series of pantolactone and pantothenic acid derivatives (**1**–**10**) were synthesized to be tested for their potential as lipid regulating agents that act as Coenzyme-A mimics. The syntheses were performed with moderate to high yields.

Keywords: Pantolactone, pantothenic acid, coenzyme-A, dyslipidemia, metabolic disorder

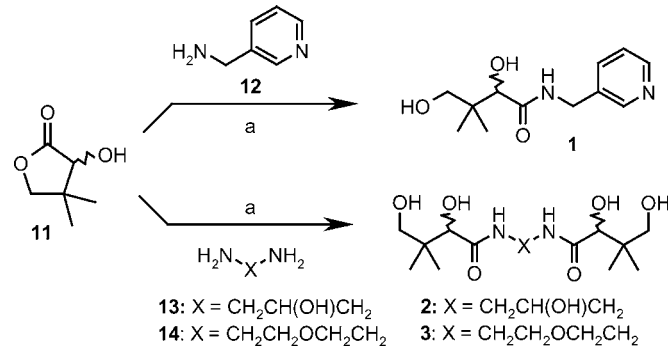
INTRODUCTION

Acyl Coenzymes-A (AcCoA) are key metabolic intermediates utilized for energy storage as well as energy production. For example, naturally occurring (endogenous) CoAs are utilized in triglyceride storage (such as the ones stored in adipose tissues) and to produce energy in muscle and liver via a β-oxidation pathway. Efforts have been made to mimic these agents to affect lipid metabolism and cardiovascular health.[1a–d] Pantosin, a dimer of pantothenic acid, has been demonstrated to be a lipid regulator in humans.[1e] AcCoA mimics that bind to and/or inhibit the activity of AcCoA-metabolizing or -binding proteins are considered to be essential in treating or preventing dyslipidemia and other metabolic disorders. The terminology of "AcCoA mimics" includes compounds that are CoA analogs as well as portions of CoA, such as the pantothenic acid portion, phosphorylated derivatives of pantothenic acid, and their analogs. Efforts in our groups have been directed toward obtaining AcCoA mimics that are not only selective but also nonsubstrate inhibitors of AcCoA ligases and metabolizing enzymes.[1f–g] Identification of such inhibitors is usually carried out using computer-assisted methods including docking procedures and pharmacophore models. We describe syntheses of various substituted pantamide derivatives that have been designed as pharmacophores to mimic AcCoA.

RESULTS AND DISCUSSION

A series of pantothenic acid mimics (**1**–**10**) was synthesized.[1f–g] Target compounds **1**, **2**, **3**, and **4** (***SS*** and ***RR***) were all prepared by treatment of pantolactone, either racemic (**11**), L-(+) (**11*S***), or D-(−) (**11*R***) with an appropriately functionalized amine (**12**, **13**, **14**, (prepared from the corresponding *bis*-HCl salt by *in situ* treatment with $NaHCO_3$) or **15**) in refluxing EtOH (Schemes 1 and 2). Diamine **14** was prepared from the corresponding *bis*-HCI salt by *in situ* treatment with $NaHCO_3$.

The synthesis of target compound **5** was planned via alkylation of the known amide **18**[2] (**18** was crystallized from EtOAc; mp 117.5–119.1°C). with ditosylate **17**, which was easily prepared from the known diol **16**[3] (Scheme 3). Treatment of **18** with NaH in THF at reflux and subsequent addition of **17** at room temperature gave, after stirring for 7 h at reflux, *bis*-amide **19** in moderate yield. Deprotection of **19** under acidic conditions

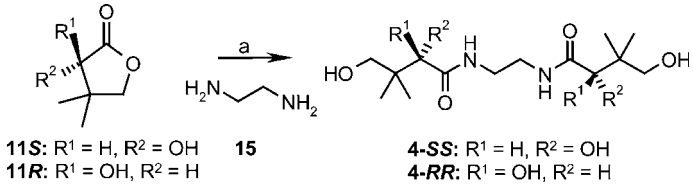


Scheme 1. (a) EtOH, Δ.

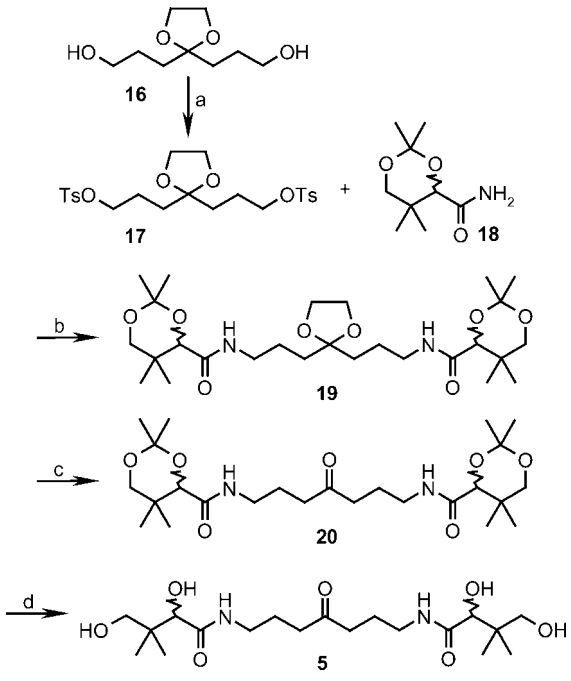
afforded target compound **5** as an inseparable mixture with ethylene glycol. To circumvent this purification problem, **19** was treated with acetone and TsOH to give the dioxolane deprotected analogue **20** and the isopropylidene acetal of ethylene glycol. The latter could easily be removed via evaporation. On acidic treatment of **20** in the presence of H_2O, target compound **5** was isolated in good yield.

The synthesis of pantothenic acid derivative **6** started with the reduction of chloro ester **21**[4] with $LiBH_4$ in MeOH[5] to chloro alcohol **22** (Scheme 4). Protection of the hydroxyl group in **22** gave THP ether **23**, which was subsequently transformed by Gabriel synthesis via phthalimide **24** to amine **25**. The sodium salt of D-pantothenic acid (**26**) was then activated with *N*-hydroxysuccinimide and *N*,*N*′-dicylohexylcarbodiimide (DCC) and coupled with amine **25** to afford THP ether **27**. Removal of the THP protection in **27** with pyridinium *p*-toluenesulfonate (PPTS) in EtOH at 55°C furnished compound **6**.

For the syntheses of target compounds **7** and **8**, it was planned to treat the sterically hindered anilines **31** and **37** with the known pantolactone derivative **32**[6] (Schemes 5 and 6). Because it was expected that stronger conditions were needed than in the syntheses of target compounds **1**–**4**, the rather acidic α-hydroxyl moiety present in pantolactone (**11**) was protected with ethyl vinyl ether. The anilines **31** and **37** were prepared via reductive



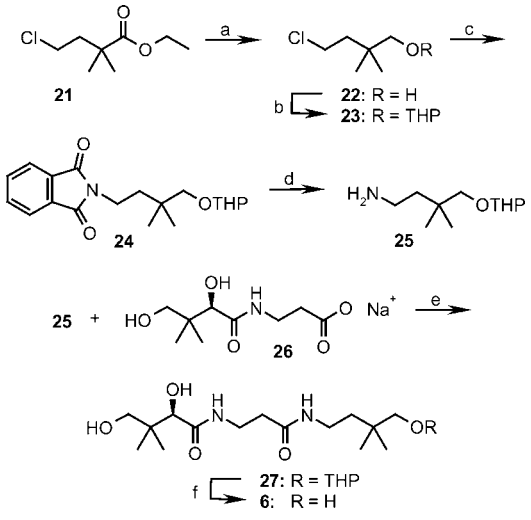
Scheme 2. (a) EtOH, Δ.



Scheme 3. (a) TsCl, Et_3N, 0–4°C; (b) NaH, THF, 75°C; (c) TsOH, acetone; (d) HOAc, H_2O.

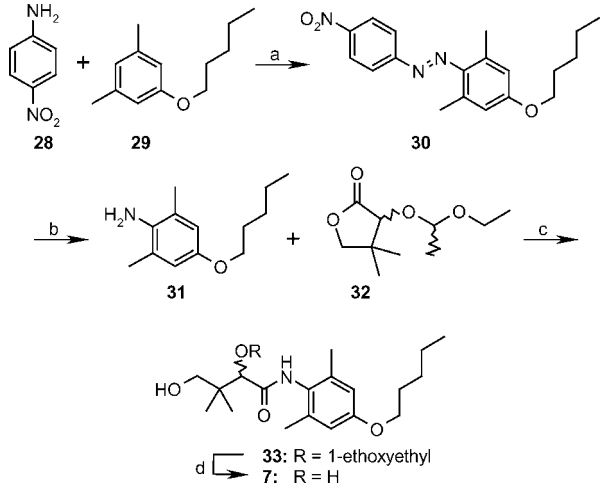
cleavage of the corresponding diazo-compounds **30** and **36** prepared respectively from phenolether **29**[7] via a diazonium coupling and alkylation of diazo-compound **34**[8] with bromide **35**.[9] Deprotonation of anilines **31** and **37** with NaH in DMF and subsequent treatment with **32** afforded, respectively, the amides **33** and **38** as mixtures of diastereomers in moderate yields. Acidic cleavage of the 1-ethoxyethyl-protected hydroxyl group present in **33** and **38** gave target compound **7** and ester **39**, respectively. Treatment of **39** with $LiAlH_4$ yielded target compound **8**.

With compound **39** in hand, saponification of the ester moiety was expected to give target compound **9**. However, on treatment of **39** with LiOH in refluxing $EtOH/H_2O$, the corresponding acid derivative of ester **37** was isolated as the main product, most probably formed via intramolecular attack of the primary hydroxyl on the amide moiety in **39**. To avoid this lactonization, the primary hydroxyl moiety had to be protected. For that purpose, it was chosen to prepare benzylidene acetal **40** (Scheme 7). Treatment of **39** with benzaldehyde dimethylacetal and TsOH in CH_2Cl_2 gave benzylidene acetal **40** in high yield. Subsequent saponification with LiOH gave **41** without any noticeable cleavage of the amide moiety. Reductive debenzylation of **41** provided target compound **9**.

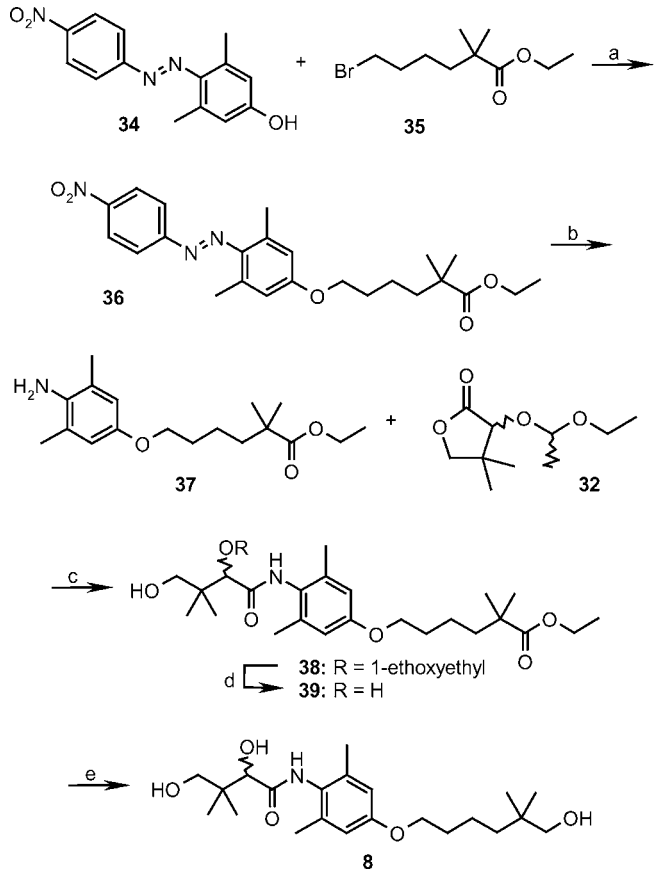


Scheme 4. (a) $LiBH_4$, MeOH, CH_2Cl_2, rt-Δ; (b) DHP, TsOH, CH_2Cl_2, 0°C; (c) potassium phthalimide, DMF, 90°C; (d) H_2NNH_2, EtOH, 70°C-Δ; (e) *N*-hydroxysuccinimide, DCC, DMF, CH_2Cl_2; (f) PPTS, EtOH, 55°C.

For the introduction of the α-D-xylosyl moiety in target compound **10**, a similar methodology as reported by Schmidt et al. for the synthesis of α-glycosides[10,11] was planned (Scheme 8). For that purpose the diprotected triol **47** and the known trichloroacetimidate **51** (isolation of **51** (∼50 mg) as a

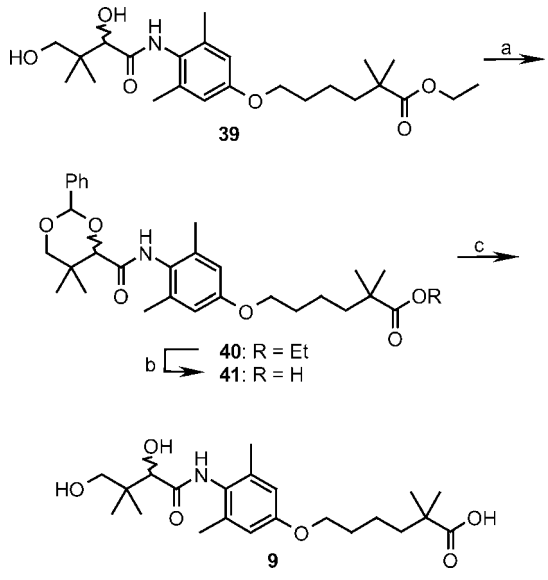


Scheme 5. (a) 1) **28**, HCl (concd.), $NaNO_2$, H_2O, 0–5°C; 2) **29**, AcOH, ∼10°C; (b) $Na_2S_2O_4$, H_2O/EtOH, Δ; (c) NaH, DMF; (d) HOAc, H_2O.



Scheme 6. (a) K_2CO_3, DMSO; (b) $Na_2S_2O_4$, H_2O/EtOH, Δ; (c) NaH, DMF; (d) HOAc, H_2O; (e) $LiAlH_4$, DME, 0°C.

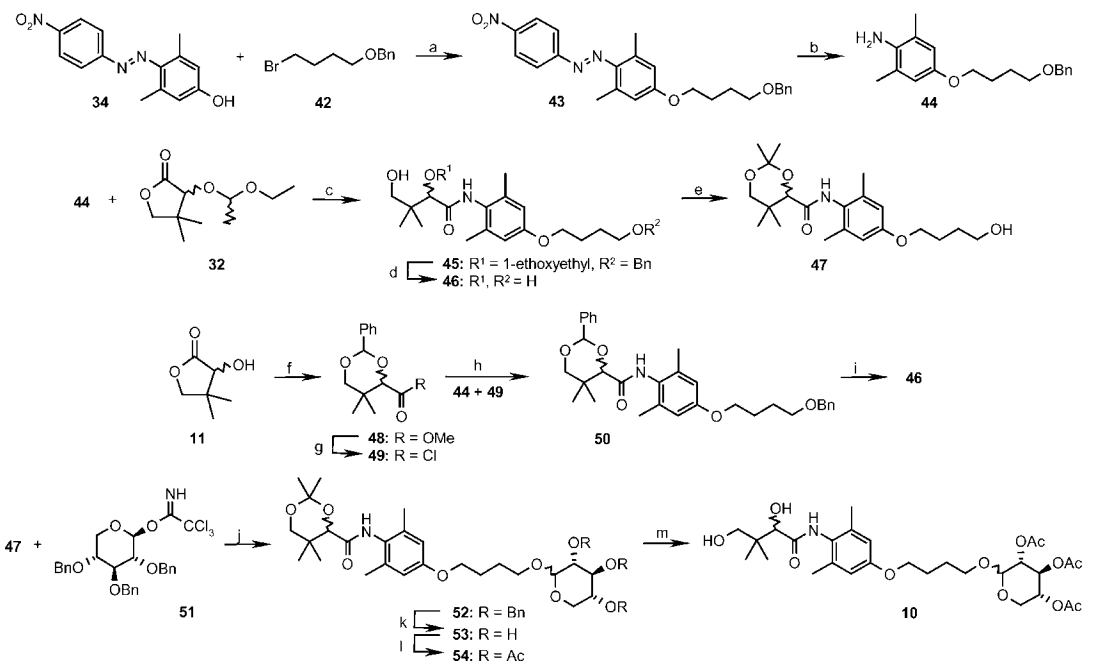
by-product, see Ref.[12]; preparation of **51** on a 24-g scale, see Experimental section) were desired. The synthesis of the aglycon part of target compound **10** was performed via a similar strategy as reported for the preparation of compounds **7** and **8**. Treatment of aniline **44**, prepared from the known diazo compound **34**,[8] with NaH and **32** gave amide **45** as a 2:1 mixture of diastereomers in moderate yield. A one-pot reductive debenzylation and acidic deprotection of the ethoxyethyl group in **45** provided triol **46**. Protection of the 1,3-diol moiety in **46** by treatment with 2,2-dimethoxypropane and TsOH gave compound **47**. An alternative preparation of **46**, via coupling of aniline **44** with acid chloride **49** and subsequent deprotection of **50**, was also developed (Scheme 8). (Starting from the isopropylidene acetal analogue of benzylidene acetal **48**, the desired isopropylidene acetal analogue of benzylidene acetal **50** could not be isolated). The novel acid



Scheme 7. (a) $PhCH(OMe)_2$, TsOH, CH_2Cl_2; (b) LiOH, $EtOH/H_2O$, Δ; (c) Pd/C, H_2, EtOH, 35°C.

chloride (**49**), prepared from pantolactone (**11**), is a convenient reagent for the synthesis of pantoic acid (2,4-dihydroxy-3,3-dimethylbutyric acid) or pantamide (2,4-dihydroxy-3,3-dimethylbutyramide) derivatives. Despite the vast amount of work published in this field no such reactive diprotected pantoic acid synthon is described. (For the synthesis of diprotected pantoic acid derivatives, see Ref.[13]) For the coupling of alcohol **47** with trichloroacetamide **51**, a method modified to the one developed by Schmidt et al.[10,11] was used. (Optimization experiments, performed in our laboratory for the synthesis of several α-xylopyranosyl alkylethers, revealed that the best α-selectivity was obtained when the Lewis acid catalyst TMSOTf was used in Et_2O at low temperature (-30 -78°C). However, at -78°C **51** was not soluble in Et_2O and 1,2-dichloroethane was needed as a cosolvent. As a result xyloside **52** was isolated as a mixture of anomers (**52**α:**52**$\beta \sim$ 2:1) in good yield. Debenzylation of **52** and subsequent acetylation of **53** provided compound **54** as a mixture of anomers, which could be partially separated by column chromatography (**54**α:**54**$\beta \sim$ 12:1). The target compound **10** (**10**α:**10**$\beta \sim$ 14:1) was obtained after treatment of **54** with acetic acid and column chromatography.

In conclusion, we have devised straightforward syntheses for ten different pantamide derivatives that are being evaluated for their lipid-lowering properties. In addition, the novel protected acid chloride **49** was developed, which should be of utility for the synthesis of related substituted pantoic esters and pantamides in the future.



Scheme 8. (a) K_2CO_3, DMSO; (b) $Na_2S_2O_4$, H_2O/EtOH, Δ; (c) NaH, DMF; (d) Pd/C, H_2, HOAc, H_2O; (e) 2,2-dimethoxypropane, 1,4-dioxane, TsOH; (f) $PhCH(OMe)_2$, TsOH, 1,4-dioxane; (g) 1) LiOH, H_2O, MeOH, 40°C; 2) $SOCl_2$, toluene; (h) pyridine, −40°C-rt; (i) Pd/C, 5 bar H_2, EtOH; (j) TMSOTf, −78°C, Et_2O, $(CH_2Cl)_2$; (k) Pd/C, $CaCO_3$, H_2, EtOH; (l) Ac_2O, pyridine, 0°C−rt; (m) HOAc, H_2O.

EXPERIMENTAL

General

All reagents and solvents were purchased from commercial suppliers and were used without prior treatment unless stated otherwise. All product solutions were dried over Na_2SO_4 or $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. Column chromatography was performed with silica gel (Fluka silica gel 60 with particle size 70–230 mesh or Acros silica gel with particle size 0.060–0.200 mm). Reactions were monitored by GC or TLC on Macherey-Nagel Polygram® SIL G/UV_{254} plastic sheets or on Whatman AL SIL G/UV aluminum sheets. Compounds on TLC were visualized by UV detection and/or dipping in *p*-anisaldehyde–H_2SO_4–EtOH = 1:1:19, basic $KMnO_4$, or ethanolic phosphomolybdic acid solution and subsequent heating. GC analysis was performed on a Hewlett Packard 5890A gas chromatograph with a flame ionization detector and an Alltech EC1 fused silica capillary column, internal diameter 30 m × 0.32 mm, film thickness 0.25 μm, and N_2 as carrier gas. GC peak areas were integrated electronically with a Hewlett Packard HP3396 series II integrator. LC/MS analysis was performed on a Shimadzu QP8000α with DAD (210–370 ηm)/MSD (100–600 D) detection and an Alltech Prefail C18, internal diameter 50 × 4.6 mm, film thickness 3 μm column with 10 mM of HCO_2H in CH_3CN/10 mM of HCO_2H in H_2O as elutes or a Agilent 1100-SL with ELSD/DAD (220–320 ηm)/MSD (100–800 D) detection and a Zorbax® SB-C18, internal diameter 150 mm × 4.6 mm, film thickness 3.5 μm column with CH_3CN/10 mM HCO_2H in H_2O as elutes or a Zorbax® Extend-C18, internal diameter 150 mm × 4.6 mm, film thickness 3.5 μm column with CH_3CN/10 mM NH_3 in H_2O as elutes, flow = 1 mL/min and column temperature = 35°C. ^1H and ^{13}C NMR spectra were recorded on either a Bruker AC-300 or a Varian Gemini 300 spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si for ^1H and relative to the solvent peak for ^{13}C data. HRMS data were obtained with a VG Micromass VG7070E, Finnigan MAT95Q, or Finnigan MAT900S spectrometer. Elemental analyses were carried out on a Carlo Erba Instruments CHNSO EA 1108 element analyser or were performed by Atlantic Microlab, Inc., Norcross, Georgia. Melting points were measured on a Büchi Melting Point B-540 or a Thomas Hoover capillary melting-point apparatus and are uncorrected. All prepared compounds were >95% pure unless otherwise stated.

2,4-Dihydroxy-3,3-dimethyl-*N*-pyridin-3-ylmethyl-butyramide (1). A solution of **12** (5.00 g, 4.72 mL, 43.7 mmol) and **11** (5.68 g, 43.7 mmol) in absolute EtOH (50 mL) was stirred under reflux for 5 d and then concentrated.

The residue was recrystallized from EtOH/iPr$_2$O to give **1** (9.26 g, 84%) as colorless crystals. Mp 120–122°C. ^{1}H NMR (DMSO-d_6): δ 8.50 (d, $J = 2.0$ Hz, 1H), 8.43 (dd, $J = 4.8$, 2.0 Hz, 1H), 8.36 (t, $J = 6.2$ Hz, 1H), 7.67 (d, $J = 7.7$ Hz, 1H), 7.32 (dd, $J = 7.7$, 4.8 Hz, 1H), 5.47 (d, $J = 5.5$ Hz, 1H), 4.47 (t, $J = 5.6$ Hz, 1H), 4.30 (m, 2H), 3.78 (d, 5.6 Hz, 1H), 3.31 (dd, $J = 10.4$, 5.8 Hz, 1H), 3.17 (dd, $J = 10.4$, 5.8 Hz, 1H), 0.80 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (CD_3OD): δ 176.4, 149.7, 148.8, 137.8, 137.0, 125.2, 77.5, 70.4, 41.2, 40.6, 21.5, 21.0. Anal. calcd. for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76; found: C, 60.41; H, 7.57; N, 11.70.

***N*-[3-(2,4-Dihydroxy-3,3-dimethylbutyrylamino)-2-hydroxypropyl]-2,4-dihydroxy-3,3-dimethylbutyramide (2).** A solution of **11** (5.2 g, 40 mmol) and **13** (1.8 g, 20 mmol) in absolute EtOH (50 mL) was heated to reflux for 3 d and evaporated. The residue was purified by column chromatography (silica, EtOAc) to obtain a foamy solid (6.0 g). Recrystallization from MeOH gave **2** (1.6 g, 23%) as a white solid. The mother liquor was purified by chromatography (silica, EtOAc) to obtain another portion of **2** (2.6 g, 37%). Mp 169–171°C (MeOH). ^{1}H NMR (CD_3OD): δ 4.90 (s, 7H), 3.92 (s, 2H), 3.80–3.65 (m, 1H), 3.46 (d, $J = 11.0$ Hz, 2H), 3.40 (d, $J = 11.0$ Hz, 2H), 3.30–3.18 (m, 4H), 0.94 (s, 12H). ^{13}C NMR (CD_3OD): δ 176.5 (2×), 77.4 (2×), 70.3 (3×), 43.3 (2×), 40.6 (2×), 21.6 (2×), 21.2 (2×). HRMS calcd. for $C_{15}H_{31}N_2O_7$ (MH^+): 351.2131; found: 351.2136.

***N*-{2-[2-(2,4-Dihydroxy-3,3-dimethylbutyrylamino)-ethoxy]-ethyl}-2,4-dihydroxy-3,3-dimethylbutyramide (3).** Under Ar atmosphere, a mixture of **11** (7.25 g, 55.1 mmol), the dihydrochloride of **14** (5.03 g, 27.6 mmol), and $NaHCO_3$ (4.78 g, 56.9 mmol) in EtOH (100 mL) was heated to reflux for 3 d. After cooling to rt, the solids were filtered and the filtrate was evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$ to $CHCl_3$–EtOH = 3:2) to give **3** (7.92 g, 79%) as a clear, colorless oil. ^{1}H NMR (CD_3OD): δ 3.91 (s, 2H), 3.6–3.3 (m, 14H), 0.93 (s, 12H). ^{13}C NMR (CD_3OD): δ 176.2 (2×), 77.4 (2×), 70.5 (2×), 70.4 (2×), 40.5 (2×), 39.8 (2×), 21.5 (2×), 21.0 (2×). HRMS calcd. for $C_{16}H_{33}N_2O_7$ (MH^+): 365.2288, found: 365.2284. Anal. calcd. for $C_{16}H_{32}N_2O_7$: C, 52.78; H, 8.85; N, 7.69; found: C, 52.42; H, 8.84; N, 7.27.

(*S*,*S*)-*N*-[2-(2,4-Dihydroxy-3,3-dimethylbutyrylamino)-ethyl]-2,4-dihydroxy-3,3-dimethylbutyramide (4-*SS*). A solution of **11*S*** (5.0 g, 38 mmol) and **15** (1.1 g, 18 mmol) in EtOH (25 mL) was heated to reflux for 3 d and evaporated. The residue was recrystallized from hot EtOAc (100 mL) containing just enough EtOH to fully dissolve the product to give **4-*SS*** (4.25 g, 70%) as sharp, rock-salt-like crystals. Mp 124.8–124.9°C. ^{1}H NMR (DMSO-d_6): δ 7.84 (s, 2H), 5.35 (d, $J = 5.0$ Hz, 2H), 4.49 (m, 2H), 3.71 (d, $J = 5.0$ Hz, 2H), 3.50–3.14 (m, 8H), 0.81 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 173.3 (2×), 75.1 (2×), 68.0 (2×), 39.0 (2×), 38.3 (2×), 21.1 (2×), 20.4

(2×). HRMS calcd. for $C_{14}H_{29}N_2O_6$ (MH^+): 321.2026; found: 321.2041. Anal. calcd. for $C_{14}H_{28}N_2O_6$: C, 52.48; H, 8.81; N, 8.74; found: C, 52.29; H, 8.82; N, 8.85. $[\alpha]_D^{25} = -69.2$ ($c = 1.09$, MeOH).

(*R*,*R*)-*N*-[2-(2,4-Dihydroxy-3,3-dimethylbutyrylamino)-ethyl]-2,4-dihydroxy-3,3-dimethylbutyramide (4-*RR*). A solution of **11*R*** (5.0 g, 38 mmol) and **15** (1.1 g, 18 mmol) in EtOH (25 mL) was heated to reflux for 3 d and evaporated. The residue was recrystallized from hot EtOAc (100 mL) containing just enough EtOH to fully dissolve the product to give **4-*RR*** (3.4 g, 56%) as sharp, rock-salt-like crystals. Mp 124.8–124.9°C. ^{1}H NMR (DMSO-d_6): δ 7.84 (s, 2H), 5.35 (d, $J = 5.0$ Hz, 2H), 4.49 (m, 2H), 3.71 (d, $J = 5.0$ Hz, 2H), 3.50–3.14 (m, 8H), 0.81 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 173.3 (2×), 75.1 (2×), 68.0 (2×), 39.0 (2×), 38.3 (2×), 21.1 (2×), 20.4 (2×). HRMS calcd. for $C_{14}H_{29}N_2O_6$ (MH^+): 321.2026; found: 321.2034. Anal. calcd. for $C_{14}H_{28}N_2O_6$: C, 52.48; H, 8.81; N, 8.74; found: C, 52.05; H, 8.82; N, 8.79. $[\alpha]_D^{25} = +67.6$ ($c = 1.06$, MeOH).

3-[2-(3-{[(4-Methylphenyl)sulfonyl]oxy}propyl)-1,3-dioxolan-2-yl]propyl 4-methyl-1-benzenesulfonate (17). (For another preparation of this compound, see Ref.[14]) At 0°C, TsCl (11.84 g, 62.1 mmol) was added to a solution of **16**[3] (4.72 g, 24.8 mmol) and Et_3N (10.5 mL, 74.7 mmol) in CH_2Cl_2 (100 mL), and the reaction mixture was placed in the refrigerator for 16 h. The resulting mixture was diluted with Et_2O (300 mL) and filtered. The residue was washed with Et_2O (100 mL). The combined organic layers were washed successively with aqueous HCl (1 M, 25 mL) and brine (3 × 25 mL) and evaporated. The remaining white solid was crystallized from a mixture of iPr$_2$O and EtOAc (10:1, ~240 mL) to give **17** (8.92 g, 72%) as white crystals. Mp 90–91°C. ^{1}H NMR: δ 7.78 (d, $J = 8.2$ Hz, 4H), 7.35 (d, $J = 8.2$ Hz, 4H), 4.02 (t, $J = 6.2$ Hz, 4H), 3.84 (s, 4H), 2.45 (s, 6H), 1.63–1.73 (m, 4H), 1.53–1.59 (m, 4H). ^{13}C NMR: δ 144.5 (2×), 132.9 (2×), 129.6 (4×), 127.6 (4×), 110.2, 70.5 (2×), 65.0 (2×), 33.0 (2×), 23.6 (2×), 21.8 (2×). Anal. calcd. for $C_{23}H_{30}O_8S_2$: C, 55.40; H, 6.06; found: C, 55.63; H, 5.96.

***N*-4-{3-[2-(3-{[(2,2,5,5-Tetramethyl-1,3-dioxan-4-yl)-carbonyl]-amino}-propyl)-1,3-dioxolan-2-yl]-propyl}-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide (19).** To a solution of **18**[2] (8.26 g, 44.2 mmol) in dry THF (200 mL) was added NaH (60 %w/w dispersion in mineral oil, 2.12 g, 53.0 mmol). After 10 min, the reaction mixture was stirred at 75°C for 30 min and cooled to rt with an H_2O bath. Then, **17** (9.95 g, 19.98 mmol) was added, and after 5 min, the reaction mixture was stirred at 75°C. After 7 h, the reaction mixture was allowed to gradually cool to rt and quenched with a mixture of brine and H_2O (2:1, 100 mL). The layers were separated and the H_2O layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (3 × 50 mL) and evaporated. The residue was purified by column chromatography (silica, EtOAc) to give **19**

(6.35 g containing ~7% w/w) EtOAc, 56%) as a colorless oil, which slowly crystallized on standing. An analytical sample of **19** for melting-point determination, ^{1}H NMR (containing ~1% w/w iPr$_2$O), ^{13}C NMR, elemental analysis, and LCMS was obtained via crystallization from iPr$_2$O as a white solid. Mp 109–125°C. ^{1}H NMR: δ 6.58 (br s, 2H), 4.07 (s, 2H), 3.93 (s, 4H), 3.68 (d, $J = 11.7$ Hz, 2H), 3.27 (d, $J = 11.4$ Hz, 2H), 3.16–3.35 (m, 4H), 1.56–1.67 (m, 8H), 1.46 (s, 6H), 1.43 (s, 6H), 1.05 (s, 6H), 0.99 (s, 6H). ^{13}C NMR: δ 169.2 (2×), 110.9, 98.9 (2×), 77.2 (2×), 71.5 (2×), 65.0 (2×), 38.7 (2×), 34.4 (2×), 33.1 (2×), 29.7 (2×), 24.2 (2×), 22.3 (2×), 19.1 (2×), 18.9 (2×). Anal. calcd. for $C_{27}H_{48}N_2O_8$: C, 61.34; H, 9.15; N, 5.30; found: C, 61.63; H, 9.43; N, 5.21.

***N*-1-{7-[(2,4-Dihydroxy-3,3-dimethylbutanoyl)-amino]-4-oxoheptyl}-2,4-dihydroxy-3,3-dimethylbutanamide (5).** To a solution of **19** (5.93 g, ~93% pure; containing ~7% EtOAc; 10.44 mmol) in acetone (250 mL) was added TsOH · H$_2$O (0.249 g, 1.31 mmol). After 18 h, the reaction mixture was concentrated at 30°C to ~50 mL, diluted with EtOAc (250 mL), washed with saturated aqueous NaHCO$_3$ (50 mL) and brine (3 × 50 mL), and evaporated. According to NMR analysis the residue still contained starting material. Therefore, this residue was taken up in acetone (100 mL), and TsOH · H$_2$O (0.250 g, 1.31 mmol) was added. After 19.5 h, the reaction mixture was concentrated at 30°C to ~50 mL, diluted with EtOAc (250 mL), washed with saturated aqueous NaHCO$_3$ (50 mL) and brine (3 × 50 mL), and evaporated. According to NMR analysis the residue still contained starting material. Therefore, this residue was taken up in acetone (100 mL), and TsOH · H$_2$O (0.253 g, 1.33 mmol) was added. After 3 d, the reaction mixture was concentrated at 30°C to ~50 mL, diluted with EtOAc (250 mL), washed with saturated aqueous NaHCO$_3$ (50 mL) and brine (3 × 50 mL), and evaporated to give crude **20** (5.26 g, containing ~7% w/w EtOAc) as a yellow oil. According to NMR analysis almost all starting material was converted. Compound **20** (4.97 g, ~ 9.86 mmol) was dissolved in HOAc (10 mL), and H$_2$O (20 mL) was added. After 22 h, the reaction mixture was evaporated and concentrated twice from toluene. The residue was purified by column chromatography (silica, CH$_2$Cl$_2$–MeOH = 4:1) to give **5** (2.94 g, 72%, containing ~3% w/w MeOH and ~0.5% w/w ethylene glycol) as a colorless oil. ^{1}H NMR (CD$_3$OD): δ 3.93 (s, 2H), 3.52 (d, $J = 11.1$ Hz, 2H), 3.43 (d, $J = 11.1$ Hz, 2H), 3.25 (t, $J = 6.9$ Hz, 2H), 3.25 (t, $J = 6.8$ Hz, 2H), 2.55 (t, $J = 7.2$ Hz, 4H), 1.81 (quintet, $J = 6.9$ Hz, 4H), 0.98 (s, 12H). ^{13}C NMR (CD$_3$OD): δ 212.0, 176.1 (2×), 77.8 (2×), 70.8 (2×), 41.0 (2×), 40.8 (2×), 39.7 (2×), 25.2 (2×), 22.0 (2×), 21.6 (2×). HRMS calcd. for $C_{19}H_{36}NaN_2O_7$ (MNa^+): 427.2420; found: 427.2384.

4-Chloro-2,2-dimethylbutan-1-ol (22). Under Ar atmosphere, CH$_2$Cl$_2$ (150 mL) was added to LiBH$_4$ (9.2 g, 0.42 mmol) followed by dropwise addition of anhydrous MeOH (17.2 mL, 0.42 mmol) over 1 h. After the H$_2$

effervescence had ceased, **21**[4] (50.5 g, 0.28 mmol) was added dropwise over 1 h. The reaction mixture was heated to reflux for 16 h, cooled to rt, and carefully hydrolyzed with saturated NH_4Cl solution (250 mL). The formed suspension was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with HCl (1M, 200 mL) and brine (100 mL), evaporated, and dried in high vacuo to furnish **22** (36.6 g, 96%) as a clear, colorless oil. ^{1}H NMR: δ 3.57 (m, 2H), 3.54–3.38 (m, 1H), 3.34 (s, 2H), 1.80 (m, 2H), 0.92 (s, 6H). ^{13}C NMR: δ 71.4, 42.0, 41.8, 35.7, 24.0 (2×).

2-(4-Chloro-2,2-dimethylbutyloxy)-tetrahydropyran (23). Under Ar atmosphere at 0°C, 3,4-dihydro-2*H*-pyran (DHP, 29.5 mL, 0.32 mmol) was added dropwise to a solution of **22** (35.3 g, 0.26 mmol) and $TsOH \cdot H_2O$ (260 mg, 1.4 mmol) in CH_2Cl_2 (200 mL) in 15 min. After 1 h, the reaction mixture was filtered through a bed of Al_2O_3 (activated, basic), concentrated, and dried in high vacuo to afford **23** (56.3 g, 98%) as a clear, colorless oil. A sample of 16.5 g was further purified by fractional distillation under reduced pressure to give **23** (13.6 g) as a clear, colorless oil. Bp 75–84°C (0.5 mmHg). ^{1}H NMR: δ 4.55 (t, $J = 2.9$ Hz, 1H), 3.81 (m, 1H), 3.57 (m, 2H), 3.50 (m, 1H), 3.48 (d, $J = 9.3$ Hz, 1H), 3.00 (d, $J = 9.3$ Hz, 1H), 1.84 (m, 2H), 1.80–1.46 (m, 6H), 0.95 (s, 3H), 0.94 (s, 3H). ^{13}C NMR: δ 98.1, 76.3, 62.0, 43.0, 41.6, 34.8, 30.7, 25.6, 24.7 (2×), 19.5. HRMS calcd. for $C_{11}H_{22}ClO_2$ (MH^+): 221.1308; found: 221.1346.

2-[3,3-Dimethyl-4-(tetrahydropyran-2-yloxy)-butyl]-isoindole-1,3-dione (24). To solution of **23** (13.5 g, 61.2 mmol) in anhydrous DMF (120 mL) was added potassium phthalimide (11.3 g, 61.2 mmol). The reaction mixture was heated to 90°C for 24 h and poured into ice-H_2O (200 mL). The resulting mixture was extracted with EtOAc (4 × 50 mL), and the combined organic layers were evaporated. The residue was purified by column chromatography (silica, hexane–EtOAc = 4:1) to furnish **24** (14.0 g, 69%) as a colorless oil. ^{1}H NMR: δ 7.90–7.80 (m, 2H), 7.80–7.60 (m, 2H), 4.59 (t, $J = 3.2$ Hz, 1H), 3.85 (m, 1H), 3.75 (t, $J = 8.3$ Hz, 2H), 3.53 (d, $J = 9.1$ Hz, 1H), 3.50 (m, 1H), 3.07 (d, $J = 9.1$ Hz, 1H), 1.90–1.40 (m, 8H), 1.03 (s, 3H), 1.01 (s, 3H). ^{13}C NMR: δ 168.2 (2×), 133.7 (2×), 132.2 (2×), 123.0 (2×), 99.0, 76.3, 61.8, 37.6, 34.4, 33.8, 30.5, 25.5, 24.6, 24.4, 19.3. HRMS calcd. for $C_{19}H_{26}NO_4$ (MH^+): 332.1861; found: 332.1860.

3,3-Dimethyl-4-(tetrahydropyran-2-yloxy)-butylamine (25). A mixture of **24** (14.0 g, 42.2 mmol) and absolute EtOH (85 mL) was heated to 70°C for 10 min until the starting material was completely dissolved. Hydrazine monohydrate (85%, 3.6 g, 71.9 mmol) was added and the reaction mixture was heated to reflux for 1 h. The formed solid was removed by filtration and the filtrate was concentrated. The residue was dissolved in $CHCl_3$ (100 mL) and washed with aqueous $NaHCO_3$ solution (10%, 100 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 60 mL). The combined organic layers were

washed with $NaHCO_3$ solution (10%, 100 mL), dried over $MgSO_4$, and concentrated to give **25** (6.7 g, 79%) as a light yellow oil. ^{1}H NMR: δ 4.55 (t, $J = 3.0$ Hz, 1H), 3.90–3.70 (m, 1H), 3.50 (m, 1H), 3.47 (d, $J = 9.0$ Hz, 1H), 2.98 (d, $J = 9.0$ Hz, 1H), 2.72 (m, 2H), 1.95–1.35 (m, 8H), 1.23 (m, 2H), 0.92 (s, 3H), 0.91 (s, 3H). ^{13}C NMR: δ 99.0, 76.6, 61.9, 43.7, 37.8, 33.8, 30.6, 25.5, 24.7 (2×), 19.4. HRMS calcd. for $C_{11}H_{24}NO_2$ (MH^+): 202.1807; found: 202.1806.

(2*R*)-*N*-{2-[3,3-Dimethyl-4-(tetrahydropyran-2-yloxy)-butylcarbamoyl]-ethyl}-2,4-dihydroxy-3,3-dimethyl-butyramide (27). To a solution of **26** (9.1 g, 37.6 mmol) in a mixture of DMF/CH_2Cl_2 (200 mL/135 mL) were added *N*-hydroxysuccinimide (4.4 g, 37.9 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 8.4 g, 40.7 mmol). After stirring for 3 h at room temperature, **25** (6.7 g, 33.3 mmol) was added, and stirring was continued overnight. The reaction mixture was concentrated. The residue was dissolved in EtOAc (300 mL), and the solution was washed with water (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica, EtOAc) to give **27** (7.5 g, 56%) as a colorless oil. ^{1}H NMR (acetone-d_6): δ 7.65 (br s, 1H), 7.28 (br s, 1H), 4.98 (d, $J = 5.2$ Hz, 1H), 4.53 (s, 1H), 4.32 (m, 1H), 3.92 (d, $J = 4.9$ Hz, 1H), 3.84–3.70 (m, 1H), 3.50–3.28 (m, 6H), 3.28–3.12 (m, 2H), 2.99 (d, $J = 9.0$ Hz, 1H), 2.38 (t, $J = 6.3$ Hz, 2H), 1.86–1.70 (m, 1H), 1.70–1.36 (m, 7H), 0.93 (s, 3H), 0.91 (s, 6H), 0.86 (s, 3H). ^{13}C NMR (acetone-d_6): δ 174.6, 171.9, 100.0, 77.8, 77.1, 71.1, 62.6, 40.5, 39.9, 36.7, 36.4 (2×), 34.7, 31.8, 26.7, 25.4 (2×), 22.3, 21.1, 20.6. HRMS calcd. for $C_{20}H_{38}N_2O_6Na$ (MNa^+): 425.2622; found: 425.2652.

(2*R*)-2,4-Dihydroxy-*N*-[2-(4-hydroxy-3,3-dimethyl-butylcarbamoyl)-ethyl]-3,3-dimethylbutyramide (6). A solution of **27** (7.3 g, 18.2 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 0.91 g, 3.63 mmol) in absolute EtOH (166 mL) was stirred at 55°C for 6 h and then evaporated. The residue was dissolved in water (20 mL), and solid Na_2CO_3 (1.0 g, 9.43 mmol) was added. The mixture was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica, $CHCl_3$–EtOH = 4:1) to give **6** (2.5 g, 43%) as a foam. ^{1}H NMR (CD_3OD): δ 3.88 (s, 1H), 3.52–3.30 (m, 4H), 3.25 (s, 2H), 3.45–3.18 (m, 2H), 2.40 (t, $J = 6.5$ Hz, 2H), 1.45 (t, $J = 8.5$ Hz, 2H), 0.91 (s, 6H), 0.89 (s, 6H). ^{13}C NMR (CD_3OD): δ 176.1, 173.5, 77.3, 71.8, 70.4, 40.5, 39.0, 36.7 (2×), 36.5, 35.6, 24.5 (2×), 21.5, 21.0. HRMS calcd. for $C_{15}H_{31}N_2O_5$ (MH^+): 319.2232, found: 319.2217. $[\alpha]_D^{22} = +24.5$ ($c = 0.96$, MeOH). Anal. calcd. for $C_{15}H_{30}N_2O_5$: C, 56.58; H, 9.50; N, 8.80, found: C, 56.16; H, 9.58; N, 8.58. (According to HPLC analysis this sample was 96.3% pure.)

(2,6-Dimethyl-4-pentyloxyphenyl)-(4-nitrophenyl)-diazene (30). A mixture of **28** (19.4 g, 0.141 mol), H_2O (50.5 mL), and concd. HCl (50.5 mL) was

heated until a clear solution was obtained. The mixture was cooled to 0°C using an ice-salt bath, and a solution of $NaNO_2$ (14.4 g, 0.209 mol) in H_2O (31 mL) was added dropwise at such a rate that the temperature remained below 5°C. The addition of the $NaNO_2$ solution was stopped when a positive reaction on KI/starch paper was observed. The obtained solution was kept cold (0°C) and added dropwise in 0.5 h to a solution of **29**[7] (27 g, 0.141 mol) in AcOH (500 mL). At the beginning of the addition, the solution of **29** was cooled to 15°C with an ice bath. During the addition the temperature dropped to 8°C. Then, AcOH (500 mL) was added to the reaction mixture under cooling in an ice bath (reaction mixture temperature was 10°C), until an almost homogeneous solution was obtained. H_2O (20 mL) was added, and the reaction mixture was set aside in the refrigerator. After 3 d, the mixture was filtered and the obtained crystalline material was washed with aqueous AcOH (50%, 3 × 130 mL). The filtrate and washings were combined and set aside in the refrigerator. The residue was washed with H_2O (3 × 100 mL) and air dried to give **30** (22.0 g, 46%) as a red-brown crystalline material. After 3 d, a second crop (6.1 g, 13%) was obtained, using the same procedure. A third crop (2.0 g, 4 %) was isolated after 3 d, and a fourth crop (2.1 g, 4 %) was isolated after standing for 5 d at rt. The third and fourth crops (sticky material) were combined and recrystallized from 2-propanol to give pure **30** (3.1 g, 6%). The combined yield of **30** amounted to 31.1 g (65%). Mp 98–99°C. ^{1}H NMR: δ 8.32 (d, $J = 9.0$ Hz, 2H), 7.89 (d, $J = 9.0$ Hz, 2H), 6.67 (s, 2H), 4.01 (t, $J = 6.6$ Hz, 2H), 2.55 (s, 6H), 1.81 (quintet, $J = 6.9$ Hz, 2H), 1.51–1.34 (m, 4H), 0.95 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR: δ 160.8, 156.5, 147.9, 143.6, 137.2 (2×), 124.6 (2×), 122.6 (2×), 115.3 (2×), 68.1, 28.9, 28.1, 22.4, 21.1, 14.0. Anal. calcd. for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31; found: C, 67.06; H, 6.56; N, 12.23.

2,6-Dimethyl-4-pentyloxyphenylamine (31). To a mixture of sodium dithionite (112 g, 0.644 mol) in EtOH (660 mL) and H_2O (660 mL) was added **30** (22.0 g, 0.0644 mol) portionwise in 10 min. The reaction mixture was stirred under reflux for 1 h, and then allowed to reach rt. The reaction mixture was concentrated to half its volume and extracted with Et_2O (1 × 600 mL, 2 × 100 mL). The combined organic layers were washed with brine (300 mL) and evaporated. The residue was purified by column chromatography (silica, heptane–EtOAc = 4:1) to give **31** (10.7 g, 80%) as a purple, thin oil. ^{1}H NMR: δ 6.55 (s, 2H), 3.86 (t, $J = 6.6$ Hz, 2H), 3.32 (br s, 2H) 2.15 (s, 6H), 1.73 (quintet, $J = 7.0$ Hz, 2H), 1.47-1.35 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR: δ 151.5, 136.2 (2×), 123.1, 114.7 (2×), 68.5, 29.1, 28.2, 22.4, 17.9 (2×), 14.0. HRMS calcd. for $C_{13}H_{21}NO$ (M^+): 207.1623; found: 207.1623.

***N*-(2,6-Dimethyl-4-pentyloxyphenyl)-2-(1-ethoxy-ethoxy)-4-hydroxy-3,3-dimethylbutyramide (33).** A solution of **31** (4.44 g, 21.4 mmol) in dry DMF (22 mL) was treated with NaH (60% w/w dispersion in mineral oil, 0.856 g, 21.4 mmol) and stirred for 5 min under an Ar atmosphere. Then, **32**[6]

(4.32 g, 21.4 mmol) was added to the mixture. The resultant mixture was stirred overnight, poured into a mixture of H_2O, ice (200 mL), and brine (50 mL), and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL) and evaporated. The residue was purified by column chromatography (silica, heptane–EtOAc = 4:1 to 2:1) to give recovered **31** (1.88 g, 42%) and **33** (two partly separated diastereomers, which were combined, 5.06 g, 58%). ^{1}H NMR (mixture of diastereomers), major diastereomer: $\delta = 7.68$ (s, 1H), 6.63 (s, 2H), 4.74 (q, $J = 5.1$ Hz, 1H), 4.19 (s, 1H), 3.91 (t, $J = 6.5$ Hz, 2H), 3.65–3.54 (m, 4H), 3.31 (dd, $J = 13.7$, 10.4 Hz, 1H), 2.20 (s, 6H), 1.76 (quintet, $J = 6.9$ Hz, 2H), 1.44–1.38 (m, 7H), 1.25 (t, $J = 7.1$, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.93 (t, $J = 7.1$ Hz, 3H), peaks not covered by major diastereomer: $\delta = 7.99$ (s), 6.59 (s), 4.63 (q, $J = 5.1$ Hz), 3.98 (s), 3.77 (m), 3.50–3.37 (m), 2.21 (s), 1.16 (t, $J = 7.1$ Hz), 0.97 (s). ^{13}C NMR (mixture of diastereomers), major diastereomer: $\delta = 170.7$, 157.9, 136.2 (2×), 125.7, 114.1 (2×), 100.6, 81.1, 70.1, 67.9, 62.5, 39.9, 28.8, 28.1, 22.3, 21.6, 20.7, 20.4, 19.3 (2×), 15.0, 13.9, peaks not covered by major diastereomer: $\delta = 171.5$, 157.7, 136.3, 125.9, 113.9, 103.8, 83.5, 70.3, 63.7, 40.8, 23.4, 20.6, 19.2, 19.1, 15.3. HRMS calcd. for $C_{23}H_{40}NO_5$ (MH^+): 410.2906; found: 410.2919.

***N*-(2,6-Dimethyl-4-pentyloxyphenyl)-2,4-dihydroxy-3,3-dimethylbutyramide (7).** Compound **33** (5.00 g, 12.2 mmol) was dissolved in a mixture of AcOH (40 mL) and H_2O (10 mL), set aside for 2 h and concentrated (10 Torr, 37°C). The resultant oil was concentrated from toluene (2 × 30 mL) and then crystallized from *i*Pr_2O (30 mL) to give **7** (3.56 g, 86%) as beige crystals. Mp 101–103°C. ^{1}H NMR: δ 7.99 (s, 1H), 6.62 (s, 2H), 4.23 (d, $J = 4.8$ Hz, 1H), 3.90 (t, $J = 6.6$ Hz, 2H), 3.70 (br s, 1H), 3.65 (dd, $J = 11.1$, 5.7 Hz, 1H), 3.56 (dd, $J = 11.1$, 5.7 Hz, 1H), 3.08 (br s, 1H), 2.20 (s, 1H), 1.75 (quintet, $J = 6.9$ Hz, 2H), 1.47–1.31 (m, 4H), 1.14 (3H), 1.04 (3H), 0.92 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR: δ 172.2, 157.9, 136.4 (2×), 125.8, 114.0 (2×), 78.2, 71.6, 68.0, 39.5, 28.9, 28.1, 22.4, 21.5, 20.3, 18.9 (2×), 14.0. HRMS calcd. for $C_{19}H_{32}NO_4$ (MH^+): 338.2331; found: 338.2337.

6-[3,5-Dimethyl-4-(4-nitrophenylazo)-phenoxy]-2,2-dimethylhexanoic acid ethyl ester (36). A solution of **34**[8] (10 g, 36.9 mmol) and **35**[9] (9.26 g, 36.9 mmol) in DMSO (50 mL) was treated with K_2CO_3 (5.09 g, 36.9 mmol). After 3 d, the reaction mixture was poured into a mixture of H_2O/ice (300 mL), and the resulting mixture was filtered, washed with H_2O (300 mL), and air dried. The residue was recrystallized from EtOH (100 mL) to give **36** (11.5 g, 71%) as dark red-brown needles. Mp 89–90°C. ^{1}H NMR: δ 8.34 (d, $J = 9.0$ Hz, 2H), 7.92 (d, $J = 9.0$ Hz, 2H), 6.67 (s, 2H), 4.13 (q, $J = 7.2$ Hz, 2H), 4.01 (t, $J = 6.5$ Hz, 2H), 2.56 (s, 6H), 1.79 (q, $J = 7.0$ Hz, 2H), 1.63–1.58 (m, 2H), 1.47–1.37 (m, 2H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.20 (s, 6H). ^{13}C NMR: δ 177.8, 160.7, 156.5, 147.9, 143.7, 137.2 (2×), 124.7 (2×), 122.6 (2×), 115.3 (2×), 67.8, 60.2, 42.1,

40.3, 29.6, 25.1 (2×), 21.5, 21.1 (2×), 14.2. Anal. calcd. for $C_{24}H_{31}N_3O_5$: C, 65.29; H, 7.08; N, 9.52; found: C, 65.62; H, 7.01; N, 9.71.

6-(4-Amino-3,5-dimethylphenoxy)-2,2-dimethyl-hexanoic acid ethyl ester (37). A mixture of **36** (10.75 g, 24.4 mmol) and sodium dithionite (44.9 g, 0.244 mol) in EtOH (250 mL) and H_2O (250 mL) was stirred under reflux for 1 h and concentrated to 200 mL. The mixture was extracted with Et_2O (1 × 300 mL, 2 × 100 mL), and the combined organic layers were washed with brine (150 mL) and evaporated. The residue was purified by column chromatography (silica, heptane–EtOAc = 2:1) to give **37** (6.74 g, 90%) as a brownish, thin oil, which solidified when kept at −20°C. A sample (0.727 g) was further purified by recrystallization from a mixture of EtOH and H_2O (1:1) to give **37** (0.583 g) as light red-brown crystals. Mp 32–34°C. ^{1}H NMR: δ 6.54 (s, 2H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.85 (t, $J = 6.5$ Hz, 2H), 3.23 (br s, 2H), 2.15 (s, 6H), 1.70 (quintet, $J = 6.9$ Hz, 2H), 1.60–1.54 (m, 2H), 1.43–1.32 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.67 (s, 6H). ^{13}C NMR: δ 177.8, 151.3, 136.3, 123.0 (2×), 114.7 (2×), 68.2, 60.1, 42.1, 40.3, 29.8, 25.0 (2×), 21.4, 17.8 (2×), 14.1. Anal. calcd. for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56; found: C, 70.50; H, 9.59; N, 4.31.

6-{4-[2-(1-Ethoxyethoxy)-4-hydroxy-3,3-dimethyl-butyrylamino]-3,5-dimethylphenoxy}-2,2-dimethyl-hexanoic acid ethyl ester (38). A solution of **37** (5.42 g, 17.7 mmol) in dry DMF (30 mL) was treated with NaH (60% w/w dispersion in mineral oil, 0.76 g, 19 mmol) and stirred for 30 min under N_2 atmosphere. Then, **32**[6] (3.57 g, 17.7 mmol) was added to the reaction mixture, and stirring was continued for another 6 h. The resultant mixture was poured into a mixture of ice (100 mL), H_2O (100 mL), and saturated aqueous $NaHCO_3$ (100 mL). After 1 h, the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (3 × 75 mL) and evaporated. The residue was purified by column chromatography (silica, heptane–EtOAc = 2:1) to give recovered **37** (1.59 g) and **38** (3.47 g, 39%) as a brown oil. ^{1}H NMR ($CDCl_3 + D_2O$) (mixture of diastereomers ∼ 2.5:1), major diastereomer: $\delta = 7.67$ (s, 1H), 6.62 (s, 2H), 4.74 (q, $J = 5.1$ Hz, 1H), 4.19 (s, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.91 (t, $J = 6.5$ Hz, 2H), 3.62 (q, $J = 7.0$ Hz, 2H), 3.57 (d, $J = 11.4$ Hz, 1H), 3.31 (d, $J = 11.4$ Hz, 1H), 2.20 (s, 6H), 1.73 (quintet, $J = 6.9$ Hz, 2H), 1.60–1.54 (m, 2H), 1.44 (d, $J = 5.1$ Hz, 3H), 1.42–1.37 (m, 2H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.17 (s, 6H), 1.09 (s, 3H), 1.07 (s, 3H), peaks not covered by major diastereomer: $\delta = 8.02$ (s), 6.60 (s), 4.65 (q, $J = 5.1$ Hz), 2.32 (s). ^{13}C NMR (mixture of diastereomers), major diastereomer: $\delta = 177.8$, 170.7, 157.8, 136.2 (2×), 125.8, 114.2 (2×), 100.6, 81.1, 70.1, 67.6, 62.6, 60.1, 42.0, 40.2, 39.9, 29.6, 25.0 (2×), 21.6, 21.4, 20.7, 20.4, 19.3 (2×), 15.0, 14.1, peaks not covered by major diastereomer: $\delta = 171.5$, 157.6, 136.4, 126.0, 114.0, 103.8, 83.6, 70.3, 63.7, 40.8, 23.5, 20.6, 19.1, 17.8, 15.3.

6-[4-(2,4-Dihydroxy-3,3-dimethylbutyrylamino)-3,5-dimethylphenoxy]-2,2-dimethylhexanoic acid ethyl ester (39). A solution of **38** (2.98 g, 5.86 mmol) in HOAc (28 mL) and H_2O (7 mL) was stirred for 4 h and then concentrated. The resultant oil was concentrated from toluene (2 × 20 mL) and purified by column chromatography (silica, heptane–EtOAc = 1:2) to give **39** (1.94 g, 76%) as a light brown oil. ^{1}H NMR ($CDCl_3 + D_2O$): δ 8.12 (s, 1H), 6.59 (s, 2H), 4.12 (s, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.88 (t, $J = 6.3$ Hz, 2H), 3.50 (d, $J = 11.4$ Hz, 1H), 3.47 (d, $J = 11.4$ Hz, 1H), 2.17 (s, 6H), 1.72 (quintet, $J = 7.0$ Hz, 2H), 1.60–1.54 (m, 2H), 1.42–1.34 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.17 (s, 6H), 1.07 (s, 3H), 1.00 (s, 3H). ^{13}C NMR: δ 178.1, 172.3, 157.8, 136.4 (2×), 125.9, 114.0 (2×), 78.1, 71.6, 67.6, 60.3, 42.1, 40.3, 39.5, 29.7, 25.1 (2×), 21.5, 21.4, 20.2, 18.9 (2×), 14.2. HRMS calcd. for $C_{24}H_{40}NO_6$ (MH^+): 438.2856; found: 438.2833.

2,4-Dihydroxy-*N*-[4-(6-hydroxy-5,5-dimethylhexyloxy)-2,6-dimethylphenyl]-3,3-dimethylbutyramide (8). Under N_2 atmosphere at 0° C, a solution of **39** (4.48 g, 10.25 mmol) in 1,2-dimethoxyethane (DME, 90 mL) was added dropwise to a suspension of $LiAlH_4$ (1.67 g, 43.8 mmol) in DME (450 mL) over a period of 30 min. After 1 h, H_2O (7 mL) was added dropwise in 30 min. The resultant mixture was treated with Na_2SO_4 (~40 g) and then filtered through a layer of Na_2SO_4 (1 cm) in a glass filter. The residue was washed with DME (5 × 100 mL), and the combined filtrates were concentrated. The residue was purified by column chromatography (silica, heptane–EtOAc = 3:1) to give **8** as an almost colorless foam (2.67 g, 67%). ^{1}H NMR ($CDCl_3 + D_2O$): δ 8.20 (s, 1H), 6.59 (s, 2H), 4.05 (s, 1H), 3.89 (t, $J = 6.5$ Hz, 2H), 3.44 (s, 2H), 3.25 (s, 2H), 2.14 (s, 6H), 1.71 (quintet, $J = 6.8$ Hz, 2H), 1.43–1.33 (m, 2H), 1.30–1.23 (m, 2H), 1.02 (s, 3H), 0.97 (s, 3H), 0.85 (s, 6H). ^{13}C NMR: δ 172.8, 157.7, 136.4 (2×), 125.9, 113.9 (2×), 77.7, 71.6, 71.3, 67.8, 39.4, 38.2, 35.0, 30.0, 23.8 (2×), 21.3, 20.3 (2×), 18.8 (2×). HRMS calcd. for $C_{22}H_{37}NO_5$ (M^+): 395.2664; found: 395.2671.

Ethyl 6-(4-[(5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)-carbonyl]-amino-3,5-dimethylphenoxy)-2,2-dimethylhexanoate (40). To a solution of **39** (1.29 g, 2.95 mmol) and benzaldehyde dimethylacetal (0.54 mL, 3.59 mmol) in CH_2Cl_2 (13 mL) was added $TsOH{\cdot}H_2O$ (10 mg, 0.053 mmol) under Ar atmosphere. The reaction mixture was stirred for 20 h, treated with $NaHCO_3$ (1 g), stirred for another 1 h, and filtered. The residue was washed with CH_2Cl_2 (5 × 5 mL), and the combined filtrate and washings were evaporated. The residue was purified by column chromatography (silica, heptane–EtOAc = 4:1) and concentrated from Et_2O (2 × 15 mL) to give **40** (1.47 g, 95%) as a slightly yellow oil. ^{1}H NMR: δ 7.71 (s, 1H), 7.53–7.50 (m, 2H), 7.42–7.37 (m, 3H), 6.56 (s, 2H), 5.59 (s, 1H), 4.30 (s, 1H), 4.09 (q, $J = 7.0$ Hz, 2H), 3.87 (t, $J = 6.5$ Hz, 2H), 3.78 (d, $J = 11.4$ Hz, 1H), 3.72 (d, $J = 11.4$ Hz, 1H), 2.18 (s, 6H), 1.72 (quintet, $J = 6.8$ Hz, 2H), 1.59–1.54 (m, 2H), 1.42–1.34 (m, 2H), 1.32 (s, 3H), 1.23 (t, $J = 7.0$ Hz,

3H), 1.17 (s, 3H), 1.16 (s, 6H). ^{13}C NMR: δ 177.5, 167.3, 157.4, 137.5, 136.1 (2×), 129.0, 128.2 (2×), 125.8 (2×), 125.6, 113.8 (2×), 101.4, 84.1, 78.7, 67.6, 60.2, 42.2, 40.4, 33.6, 29.8, 25.3 (2×), 22.1, 21.6, 19.8, 19.1 (2×), 14.4. HRMS calcd. for $C_{31}H_{43}NO_6$ (M^+): 525.3032; found: 525.3044.

6-(4-[(5,5-Dimethyl-2-phenyl-1,3-dioxan-4-yl)-carbonyl]-amino-3,5-dimethylphenoxy)-2,2-dimethylhexanoic acid (41). Compound **40** (11.05 g, 95% pure, 20.0 mmol) was dissolved in EtOH (300 mL) by heating and H_2O (100 mL) followed by $LiOH \cdot H_2O$ (3.716 g, 89 mmol) were added. The reaction mixture was refluxed for 38 h, allowed to cool to rt, and evaporated. The residue was dissolved in H_2O (200 mL) and CH_2Cl_2 (200 mL) and aqueous HCl (2M, 200 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 200 mL, 1 × 100 mL). The combined organic layers were washed with H_2O (200 mL) and saturated aqueous $NaHCO_3$ (200 mL), dried (Na_2SO_4, minimal amount), and concentrated, to give **41** (9.66 g, 97%) as a white foam. ^{1}H NMR: δ 7.72 (s, 1H), 7.53–7.49 (m, 2H), 7.42–7.35 (m, 3H), 6.57 (s, 2H), 5.60 (s, 1H), 4.31 (s, 1H), 3.89 (t, $J = 6.5$ Hz, 2H), 3.78 (d, $J = 11.1$ Hz, 1H), 3.72 (d, $J = 11.4$ Hz, 1H), 2.17 (s, 6H), 1.73 (quintet, $J = 6.8$ Hz, 2H), 1.61–1.36 (m, 4H), 1.32 (s, 3H), 1.19 (s, 6H), 1.17 (s, 3H). ^{13}C NMR: δ 183.4, 167.5, 157.5, 137.5, 136.2 (2×), 129.0, 128.2 (2×), 125.9 (2×), 125.6, 114.0 (2×), 101.4, 84.1, 78.7, 67.7, 42.2, 40.2, 33.7, 29.9, 25.1 (2×), 22.1, 21.6, 19.8, 19.1 (2×). HRMS calcd. for $C_{29}H_{29}NO_6Na$ (MNa^+): 520.2660; found: 520.2661.

6-{4-[(2,4-Dihydroxy-3,3-dimethylbutanoyl)-amino]-3,5-dimethylphenoxy}-2,2-dimethylhexanoic acid (9). Under N_2 atmosphere at 35°C, Pd on C (5% w/w, ~0.4 g) was added to a solution of **41** (8.96 g, 18.0 mmol) in EtOH (200 mL). The reaction mixture was stirred for 2 d under hydrogen atmosphere and filtered. The filtrate was concentrated to give **9** (7.14 g, 96%) as hard, white foam. An analytical sample was obtained by crystallization from iPr$_2$O (0.11 g from 0.21 g). Mp 130–132°C. ^{1}H NMR (CD_3OD): δ 6.63 (s, 2H), 4.09 (s, 1H), 3.92 (t, $J = 6.3$ Hz, 2H), 3.56 (d, $J = 11.0$ Hz, 1H), 3.47 (d, $J = 11.0$ Hz, 1H), 2.18 (s, 6H), 1.72 (quintet, $J = 6.8$ Hz, 2H), 1.61–1.38 (m, 4H), 1.17 (s, 6H), 1.06 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (CD_3OD): δ 182.0, 175.6, 159.4, 138.1 (2×), 128.1, 115.1 (2×), 77.9, 70.7, 68.9, 43.2, 41.7, 40.8, 31.0, 25.8 (2×), 22.9, 21.6, 21.3, 19.2 (2×). Anal. calcd. for $C_{22}H_{35}NO_6$: C, 64.52; H, 8.61; N, 3.42; found: C, 64.25; H, 8.99; N, 3.47. HRMS calcd. for $C_{22}H_{36}NO_6$ (MH^+): 410.2543; found: 410.2514.

[4-(4-Benzyloxybutoxy)-2,6-dimethylphenyl]-(4-nitrophenyl)-diazene (43). To a solution of **42** (18.3 g, 75.2 mmol) and **34**[8] (19.59 g, 72.3 mmol) in DMSO (100 mL) was added K_2CO_3 (10.4 g, 75.2 mmol). The mixture was stirred overnight and then poured into a mixture of ice and H_2O (300 mL). The amorphous solid material was filtered, washed with H_2O (4 × 75 mL),

and air dried (30.3 g). The residue (28.3 g) was purified by column chromatography (silica, heptane–EtOAc = 12:1) to give **43** (18.4 g, 63%) as a crystalline solid. An analytical sample of **43** (0.682 g, red-brown needles) was obtained after recrystallization of 0.757 g from *i*PrOH (50 mL). Mp 68–69.5°C. ^{1}H NMR: δ 8.34 (d with fine splitting, $J = 9$ Hz, 2H), 7.91 (d with fine splitting, $J = 9$ Hz, 2H), 7.36–7.25 (m, 5H), 6.67 (s, 2H), 4.53 (s, 2H), 4.05 (t, $J = 6.2$ Hz, 2H), 3.56 (t, $J = 6.0$ Hz, 2H), 2.56 (s, 6H), 1.97–1.88 (m, 2H), 1.86-1.76 (m, 2H). ^{13}C NMR: δ 160.7, 156.6, 148,0, 143.7, 138.5, 137.2 (2×), 128.4 (2×), 127.62 (2×), 127.56, 124.7 (2×), 122.7 (2×), 115.3 (2×), 72.9, 69.8, 67.8, 26.3, 26.1, 21.1 (2×). Anal. calcd. for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69; found: C, 69.29; H, 6.17; N, 9.59.

4-(4-Benzyloxybutoxy)-2,6-dimethylphenylamine (44). A mixture of **43** (18.35 g, 42.4 mmol) and sodium dithionite (73.7 g, 0.424 mol) in EtOH (460 mL) and H_2O (460 mL) was stirred under reflux for 1.5 h. An almost colorless mixture was obtained, which was allowed to cool to rt, concentrated to approximately 450-mL volume, and then extracted with Et_2O (1 × 300 mL, 2 × 100 mL). The combined organic layers were washed with brine (100 mL), and evaporated. The residue was purified by column chromatography (silica, heptane–EtOAc = 4:1) to give **44** (10.6 g, 84%) as a brown oil. ^{1}H NMR: δ 7.33–7.26 (m, 5H), 6.54 (s, 2H), 4.50 (s, 2H), 3.88 (t, $J = 5.9$ Hz, 2H), 3.52 (t, $J = 5.9$ Hz, 2H), 3.17 (br s, 2H), 2.15 (s, 6H), 1.84–1.77 (m, 4H). ^{13}C NMR: δ 151.4, 138.6, 136.3, 128.3 (2×), 127.6 (2×), 127.4, 123.1 (2×), 114.7 (2×), 72.8, 70.0, 68.2, 26.35, 26.27, 17.9 (2×). HRMS calcd. for $C_{19}H_{25}NO_2$ (M^+): 299.1885; found: 299.1881.

***N*-[4-(4-Benzyloxy-butoxy)-2,6-dimethyl-phenyl]-2-(1-ethoxy-ethoxy)-4-hydroxy-3,3-dimethyl-butyramide (45).** A solution of **44** (1.00 g, 3.34 mmol) in dry DMF (4 mL) was treated with NaH (60% w/w dispersion in mineral oil, 0.134 g, 3.35 mmol) under Ar atmosphere. Then, **32**[6] (0.676 g, 3.34 mmol) was added to the reaction mixture and stirring was continued for 16 h. The resultant mixture was poured into a mixture of H_2O and ice (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL) and evaporated. The residue was purified by column chromatography (silica, heptane–EtOAc = 2:1 to 1:1) to give recovered **44** (0.51 g) and **45** (0.742 g, 44%) as a light brown oil. ^{1}H NMR ($CDCl_3 + D_2O$) (mixture of diastereomers ~ 2:1), major diastereomer: $\delta = 7.66$ (br s, 1H), 7.30–7.20 (m, 5H), 6.59 (s, 2H), 4.71 (q, $J = 5.1$ Hz, 1H), 4.49 (s, 2H), 4.17 (s, 1H), 3.92 (t, $J = 6.2$ Hz, 2H), 3.60 (q, $J = 6.9$ Hz, 2H), 3.55 (d, $J = 11.4$ Hz, 1H), 3.51 (t, $J = 6.0$ Hz, 2H), 3.29 (d, $J = 11.4$ Hz, 1H), 2.18 (s, 6H), 1.90–1.71 (m, 4H), 1.42 (d, $J = 5.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.08 (s, 3H), 1.06 (s, 3H), peaks not covered by major diastereomer: $\delta = 7.98$ (br s), 6.57 (s), 4.62 (q, $J = 5.0$ Hz), 3.98 (s), 3.40 (d, $J = 11.7$ Hz), 2.21 (s), 1.40 (d, $J = 4.8$ Hz), 1.17 (t, $J = 7.1$ Hz), 0.98 (s). ^{13}C NMR (mixture of diastereomers ~ 2:1), major diastereomer: δ 170.4, 157.6, 138.3, 136.1

(2×), 128.2 (2×), 127.4 (2×), 127.3, 125.7, 114.1 (2×), 100.7, 81.3, 72.9, 70.3, 69.9, 67.71, 62.8, 40.2, 26.5, 26.3, 21.9, 21.0, 20.7, 19.6 (2×), 15.3, peaks not covered by major diastereomer: $\delta = 171.2$, 157.4, 136.3, 125.9, 113.9, 103.9, 83.7, 70.5, 67.67, 63.9, 41.1, 23.9, 19.4, 15.6.

2,4-Dihydroxy-*N*-[4-(4-hydroxybutoxy)-2,6-dimethyl-phenyl]-3,3-dimethylbutyramide (46). Under N_2 atmosphere, Pd on C (10% w/w, 0.070 g) was added to a solution of **45** (0.732 g, 1.46 mmol) in AcOH (8 mL) and H_2O (2 mL). The reaction mixture was stirred for 16 h under an H_2 atmosphere and filtered. The residue was washed with a mixture of HOAc and H_2O (1:1, 4 × 5 mL), and the combined filtrate and washings were evaporated. The residue was purified by column chromatography (silica, CH_2Cl_2–MeOH = 9:1) to give **46** (0.350 g, 71%) as a colorless oil. Crystallization from EtOAc/iPr$_2$O afforded **46** (0.312 g, 63%) as colorless crystals. Mp 101–102.5°C. ^{1}H NMR (DMSO-d_6): δ 8.89 (s, 1H), 6.62 (s, 2H), 5.60 (d, $J = 5.9$ Hz, 1H), 4.52 (t, $J = 5.5$ Hz, 1H), 4.43 (t, $J = 5.2$ Hz, 1H), 3.93 (s, 1H), 3.93 (t, $J = 5.7$ Hz, 2H), 3.48–3.37 (m, 3H), 3.26 (dd, $J = 10.4$, 5.2 Hz, 1H), 2.11 (s, 6H), 1.76–1.67 (m, 2H). 1.59–1.50 (m, 2H), 0.94 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (DMSO-*d6*): δ 171.5, 156.2, 136.0 (2×), 127.6, 113.0 (2×), 75.4, 68.0, 67.2, 60.3, 39.2, 29.0, 25.5, 21.3, 20.5, 18.8 (2×). Anal. calcd. for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13; found: C, 63.96; H, 8.68; N, 3.85.

5,5-Dimethyl-2-phenyl-[1,3]-dioxane-4-carboxylic acid methyl ester (48). To a solution of **11** (20.4 g, 156 mmol) and benzaldehyde dimethylacetal (40 mL, 265 mmol) in 1,4-dioxane (100 mL) was added TsOH·H_2O (0.606 g, 3.2 mmol). The reaction mixture was stirred for 2 d, treated with $NaHCO_3$ (5.1 g), and stirred for another 3 h. Et_2O (250 mL) was added, and the resulting mixture was washed successively with a mixture of saturated aquous $NaHCO_3$ solution (100 mL), H_2O (200 mL), and brine (100 mL). The organic layer was evaporated, and the residue was purified by column chromatography (silica, heptane–EtOAc = 7:1) to give a white solid (15.5 g). This solid was recrystallized from heptane (30 mL) to give **48** (14.0 g, 36%) as colorless crystals. Mp 86.5–88°C. ^{1}H NMR: δ 7.54–7.50 (m, 2H), 7.38–7.29 (m, 3H), 5.46 (s, 1H), 4.23 (s, 1H), 3.73 (s, 3H), 3.72 (d, $J = 11.4$ Hz, 1H), 3.64 (d, $J = 11.4$ Hz, 1H), 1.18 (s, 3H), 0.96 (s, 3H). ^{13}C NMR: δ 168.9, 137.5, 128.9, 128.1 (2×), 126.1 (2×), 101.4, 83.7, 78.1, 51.5, 32.7, 21.5, 19.4. Anal. calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; found: C, 67.18; H, 7.23.

5,5-Dimethyl-2-phenyl-[1,3]dioxane-4-carboxylic acid [4-(4-benzyloxybutoxy)-2,6-dimethylphenyl]-amide (50). A mixture of **48** (9.87 g, 39.5 mmol), $LiOH \cdot H_2O$ (1.99 g, 47.4 mmol), H_2O (6 mL), and MeOH (200 mL) was stirred at 40°C for 2 d. The reaction mixture was evaporated, and the residue was evaporated from toluene (2 × 100 mL). Toluene (300 mL) was

added, and the mixture was concentrated to ~200-mL volume. The resultant solution was treated with $SOCl_2$ (4.0 mL, 54 mmol) and stirred at rt for 1 h. Then, the mixture containing **49** was cooled to −40°C and treated with pyridine (40 mL). The cooling bath was removed, and immediately a solution of **44** (10.62 g, 35.5 mmol) in pyridine (40 ml) was added. The reaction mixture was stirred for 45 min and then poured into a H_2O/ice mixture (1 L). After 1 h, the obtained mixture was separated, and the H_2O layer was extracted with toluene (2 × 200 mL). The combined organic layers were washed with a mixture of aqueous HCl (4M, 350 mL) and ice (150 mL), brine (150 mL), and saturated aqueous $NaHCO_3$ solution (150 mL) and evaporated. The remaining oil (19.6 g) was purified by column chromatography (silica, heptane–EtOAc = 3:2) to give, after evaporation from Et_2O (100 mL), **50** (13.9 g, 76%) as a dark yellow oil. ^{1}H NMR: δ 7.70 (br s, 1H), 7.53–7.50 (m, 2H), 7.41–7.36 (m, 3H), 7.31–7.22 (m, 5H), 6.56 (s, 2H), 5.59 (s, 1H), 4.49 (s, 2H), 4.30 (s, 1H), 3.91 (t, $J = 6.0$ Hz, 2H), 3.79 (d, $J = 11.3$ Hz, 1H), 3.72 (d, $J = 11.3$ Hz, 1H), 3.51 (t, $J = 6.0$ Hz, 2H), 2.17 (s, 6H), 1.89–1.71 (m, 4H). 1.31 (s, 3H), 1.17 (s, 3H). ^{13}C NMR: δ 167.3, 157.4, 138.3, 137.6, 136.2 (2×), 129.0, 128.2 (2×), 128.1 (2×), 127.4 (2×), 127.3, 125.9 (2×), 125.7, 113.9 (2×), 101.4, 84.1 78.7, 72.9, 69.9, 67.7, 33.7, 26.5, 26.3, 22.1, 19.8, 19.1 (2×). HRMS calcd. for $C_{32}H_{39}NO_5$ (M^+): 517.2828; found: 517.2829.

2,4-Dihydroxy-*N*-[4-(4-hydroxybutoxy)-2,6-dimethyl-phenyl]-3,3-dimethyl-butyramide (46). Under N_2 atmosphere, Pd on C (10% w/w, 1.0 g) was added to a solution of **50** (13.5 g, 26.2 mmol) in EtOH (300 mL). (In some instances the reaction ceased. Most likely the catalyst became inactive because of the presence of small amounts of impurities. In those cases, the reaction mixture was filtered and treated again with fresh catalyst). The reaction mixture was stirred for 3 d under 5 bar H_2 atmosphere and filtered. The residue was washed with EtOH (4 × 50 mL), and the combined filtrate and washings were concentrated and concentrated from toluene (2 × 100 mL). The remaining oil was crystallized from a mixture of EtOAc and iPr$_2$O to give **46** (10.8 g, 84%) as yellowish crystals. Mp 101–103°C.

2,2,5,5-Tetramethyl-[1,3]dioxane-4-carboxylic acid [4-(4-hydroxybutoxy)-2,6-dimethylphenyl]-amide (47). A mixture of **46** (7.31 g, 21.6 mmol) in 2,2-dimethoxypropane (10 mL, 81 mmol) and 1,4-dioxane (100 mL) was treated with $TsOH \cdot H_2O$ (0.200 g, 1.05 mmol). After 1.5 h, $NaHCO_3$ (2.5 g) was added, and the resultant mixture was set aside over the weekend. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in EtOAc (100 mL) and filtered through a layer of silica in a glass filter. The residue was eluted with EtOAc (5 × 10 mL), and the filtrate and eluates were combined and concentrated to ~ 30 mL. Heptane was added to the resultant solution until spontaneous crystallization started. The obtained crystalline mass was filtered, washed with a mixture of heptane and EtOAc

(10:1, 3 × 20 mL), and air dried to give **47** (5.45 g, 67%) as colorless crystals. The mother liquor, which mainly consisted of less polar products, was concentrated and dissolved in a mixture of HOAc and H_2O (4:1, 10 mL). After 15 min, NaOAc (2.5 g) and H_2O (20 mL) were added, and after another 15 min, the formed crystalline material was filtered, washed with H_2O (3 × 10 mL), and air dried. The remaining solid was recrystallized from a mixture of *i*PrOH and H_2O to give another crop of **47** (2.09 g, 26%) as colorless crystals. Mp 127–128°C. ^{1}H NMR: δ 7.77 (s, 1H), 6.62 (s, 2H), 4.29 (s, 1H), 3.97 (t, $J = 6.0$ Hz, 2H), 3.76 (d, $J = 11.7$ Hz, 1H), 3.70 (t, $J = 6.1$ Hz, 2H), 3.35 (d, $J = 11.7$ Hz, 1H), 2.20 (s, 6H), 1.90–1.82 (m, 2H), 1.78–1.69 (m, 2H), 1.52 (s, 3H), 1.50 (s, 3H), 1.19 (s, 3H), 1.11 (s, 3H). ^{13}C NMR: δ 168.3, 157.5, 136.4 (2×), 126.2, 114.0 (2×), 99.3, 77.6, 71.7, 67.8, 62.4, 33.3, 29.51, 29.46, 25.8, 22.1, 19.4, 18.9 (2×), 18.8. Anal. calcd. for $C_{21}H_{33}NO_5$: C, 66.46; H, 8.76; N, 3.69; found: C, 66.42; H, 8.92; N, 3.65.

***O*-(2,3,4-Tri-*O*-benzyl-β-D-xylopyranosyl)-trichloroacetimidate (51).**[12] A mixture of 2,3,4-tri-*O*-benzyl-α-D-xylopyranose[15] (32.8 g, 78.1 mmol), trichloroacetonitrile (30 mL, 299 mmol), and powdered K_2CO_3 (32.8 g, 238 mmol) in CH_2Cl_2 (160 mL) was stirred for 6 h and then filtered through a layer of kieselguhr. The residue was washed with CH_2Cl_2 and the combined filtrate and washings were evaporated. The remaining oil was crystallized from *i*Pr_2O to give **51** (24.1 g, 55%) as colorless needles. Mp 81.5–83°C. ^{1}H NMR: δ 8.69 (s, 1H), 7.30 (m, 15H), 5.81 (m, 1H), 4.89 (d, $J = 11.0$ Hz, 1H), 4.85 (s, 2H), 4.75 (d, $J = 11.0$ Hz, 1H), 4.72 (d, $J = 11.7$ Hz, 1H), 4.43 (d, $J = 11.7$ Hz, 1H), 4.02 (m, 1H), 3.69 (m, 3H), 3.45 (m, 1H). ^{13}C NMR: δ 160.6, 138.0, 137.48, 137.45, 128.0 (2×), 127.92 (2×), 127.91 (2×), 127.49 (2×), 127.48, 127.43 (2×), 127.42 (2×), 127.3, 127.2, 98.5, 90.6, 82.7, 79.8, 76.4, 75.1, 74.6, 72.9, 64.3. Anal. calcd. for $C_{28}H_{38}Cl_3NO_5$: C, 59.54; H, 5.00; N, 2.48; found: C, 59.54; H, 5.00; N, 2.24. $[\alpha]_D^{20}$: +22.5 ($c = 1.02$, $CHCl_3$), $[\alpha]_{578}^{20}$: +23.0 ($c = 1.02$, $CHCl_3$).

2,2,5,5-Tetramethyl-[1,3]dioxane-4-carboxylic acid {4-[4-(2,3,4-tri-*O*-benzyl-D-xylopyranosyl)-butoxy]-2,6-dimethyl-phenyl}-amide (52). To a mixture of **51** (13.6 g, 24.0 mmol), and **47** (7.00 g, 18.5 mmol) in Et_2O (140 mL) and 1,2-dichloroethane (70 mL) was added TMSOTf (0.30 mL, 1.17 mmol) under N_2 atmosphere at −78°C. After 45 min, $NaHCO_3$ (5 g) was added, and the reaction mixture was allowed to reach rt. The reaction mixture was diluted with Et_2O (100 mL), washed with a mixture of brine (100 mL) and water (75 mL), and concentrated. The residue was purified by column chromatography (silica, heptane–EtOAc = 3:1) to give **52** (8.20 g, 57%, α:$\beta \sim$ 2:1) as a colorless oil. Continued elution gave another batch of **52** (7.26 g) contaminated with 2,2,2-trichloroacetamide, which was partly removed via crystallization from a mixture of CH_2Cl_2 and heptane. The mother liquor was evaporated and the residue was purified by column

chromatography (silica, heptane–EtOAc = 3:1) to give another crop of **52** (3.90 g, 27%, **52**α:**52**β ~ 2:1) as a colorless oil. **52α:** ^{1}H NMR: δ 7.76 (br s, 1H), 7.40–7.25 (m, 15H), 6.63 (s, 2H), 4.91 (d, J = 10.8 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.76 (d, J = 10.8 Hz, 1H), 4.72–4.57 (m, 4H), 4.27 (s, 1H), 3.94–3.86 (m, 3H), 3.73 (d, J = 11.7 Hz, 1H), 3.77–3.64 (m, 1H), 3.62–3.52 (m, 3H), 3.47–3.41 (m, 2H), 3.33 (d, J = 11.7 Hz, 1H) 2.18 (s, 6H), 1.89-1.76 (m, 4H) 1.51 (s, 3H), 1.49 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: δ 167.9, 157.3, 138.7, 138.1, 138.0, 136.1 (2×), 128.16 (2×), 128.14 (2×), 128.07 (2×), 127.74 (2×), 127.69 (2×), 127.56 (2×), 125.86, 113.8 (2×), 99.1, 96.9, 81.3, 79.8, 78.1, 77.5, 75.7, 73.5, 73.2, 71.7, 67.7, 67.6, 60.0, 33.5, 29.7, 26.32, 26.28, 22.3, 19.6, 19.1 (2×), 19.0. (Three tertiary aromatic signals of the α-anomer fell in the region δ 128.2–127.2. They could not be assigned because of the presence of aromatic signals of the β-isomer). **52**β: ^{1}H NMR: (visible signals) δ 6.60, 4.32 (d, J = 7.5 Hz), 3.22–3.15 (m). ^{13}C NMR: (visible signals) δ 157.25, 138.4, 138.2, 137.9, 104.0, 83.7, 81.9, 77.8, 75.5, 74.9, 73.3, 69.4, 67.4, 63.9, 26.6, 26.1. **52**α:**52**β ~ 2:1: HRMS calcd. for $C_{47}H_{59}NO_9$ (MNa^+): 804.4088; found 804.4084. $[\alpha]_D^{20}$: +26.9 (c = 0.88, CH_2Cl_2).

2,2,5,5-Tetramethyl-[1,3]dioxane-4-carboxylic acid {4-[4-(D-xylopyranosyl)-butoxy]-2,6-dimethylphenyl}-amide (53). Under N_2 atmosphere, Pd on C (10% w/w, 0.50 g, 0.47 mmol) and $CaCO_3$ (1.70 g, 17.0 mmol) were added to a solution of **52** (7.85 g, 10.1 mmol, **52**α:**52**β ~ 2:1) in EtOH (140 mL). The reaction flask was flushed with H_2, and the reaction mixture was stirred under a H_2 atmosphere for 4 h. (In some instances the reaction ceased. Most likely the catalyst became inactive because of the presence of small amounts of impurities. In those cases, the reaction mixture was filtered and treated again with fresh catalyst). The reaction mixture was treated with $NaHCO_3$ (1.00 g, 11.9 mmol), stirred for 0.5 h, and filtered. The residue was washed with EtOH (4 × 20 mL), and the combined filtrate and washings were evaporated. The residue was purified by column chromatography (silica, CH_2Cl_2–MeOH = 9:1) to give **53** (4.49 g, 87%, **53**α:**53**β ~ 2:1) as a foam. **53**α: ^{1}H NMR (DMSO-d_6 + D_2O): δ 8.66 (br s, 1H), 6.60 (s, 2H), 4.58 (d, J = 3.6 Hz, 1H), 4.18 (s, 1H), 3.92 (br q, J = 5.6 Hz, 2H), 3.80–3.44 (m, 3H), 3.41–3.15 (m, 6H), 2.05 (s, 6H), 1.84–1.61 (m, 4H), 1.41 (s, 3H), 1.40 (s, 3H), 1.06 (s, 3H), 0.94 (s, 3H). ^{13}C NMR: δ 168.5, 157.2, 136.3 (2×), 125.7, 113.9 (2×), 99.2, 98.4, 77.4, 74.5, 72.0, 71.6, 69.9, 68.0, 67.4, 61.7, 33.4, 29.6, 26.28, 26.0, 22.3, 19.5, 19.0 (2×), 18.9. (The presence of **53**α as a mixture of two diastereomers resulted in slightly different chemical shifts for the resonances of corresponding carbon atoms in the separate diastereomers). **53**β: ^{1}H NMR (DMSO-d_6 + D_2O): (visible signals) δ 4.08 (d, J = 7.5 Hz), 3.09 (t, J = 8.7 Hz), 3.02 (t, J = 10.8 Hz), 2.93 (dd, J = 8.2, 7.5 Hz). ^{13}C NMR: (visible signals) δ 168.2, 157.3, 136.1, 125.6, 102.8, 75.7, 72.7, 69.5, 69.2, 65.0, 26.33, 25.9.

53α:53β ~ 2:1: HRMS calcd. for $C_{26}H_{42}NO_9$ (MH^+): 512.2859; found 512.2842. $[\alpha]_D^{20}$: +33.7 ($c = 0.73$, EtOAc).

2,2,5,5-Tetramethyl-[1,3]dioxane-4-carboxylic acid {4-[4-(2,3,4-tri-*O*-acetyl-D-xylopyranosyl)-butoxy]-2,6-dimethylphenyl}-amide (54). To a solution of **53** (5.74 g, 11.2 mmol, **53**α:**53**β ~ 2:1) in pyridine (15 mL) was added Ac_2O (10 mL) at 0°C. After 30 min, the reaction mixture was allowed to warm to rt, and stirring was continued for 16 h. The reaction mixture was poured into a mixture of H_2O and ice (200 mL), and, after 2 h, extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with aqueous HCl (2M, 200 mL) and saturated aqueous $NaHCO_3$ (100 mL), and evaporated. The residue was purified by repeated column chromatography (silica, heptane–EtOAc = 1:1) to give **54** (4.10 g, 57%, **54**α:**54**β ~ 12:1), **54** (1.39 g, 20%, **54**α:**54**β ~ 1:1), and **54** (1.25 g, 17%, **54**α:**54**β ~ 1:8). **54**α: ^{1}H NMR: δ 7.74 (br s, 1H), 6.59 (s, 2H), 5.47 (t, $J = 9.8$ Hz, 1H), 4.99 (d, $J = 3.6$ Hz, 1H), 4.94 (ddd, $J = 10.5$, 9.5, 5.9 Hz, 1H), 4.79 (dd, $J = 10.2$, 3.6 Hz, 1H), 4.27 (s, 1H), 3.93 (t, $J = 6.0$ Hz, 2H), 3.80–3.72 (m, 3H), 3.61 (t, $J = 10.7$ Hz, 1H), 3.45 (dt, $J = 9.9$, 6.0 Hz, 1H), 3.33 (d, $J = 11.4$ Hz, 1H), 2.19 (s, 6H), 2.04 (s, 3H), 2.02 (s, 6H), 1.87–1.72 (m, 4H), 1.51 (s, 3H), 1.50 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: δ 169.9, 169.64, 169.59, 167.9, 157.2, 136.2 (2×), 126.0, 113.8 (2×), 99.2, 95.6, 77.6, 71.7, 71.1, 69.7, 69.4, 68.1, 67.5, 58.4, 33.5, 29.7, 26.26, 26.21, 22.3, 20.94, 20.89, 20.85, 19.6, 19.1 (2×), 19.0. **54**α:**54**β ~ 12:1: Anal. calcd. for $C_{32}H_{47}NO_{12}$: C, 60.27; H, 7.43; N, 2.20; found: C, 60.21; H, 7.57; N, 2.14. $[\alpha]_D^{20}$: +65 ($c = 0.73$, EtOAc). **54**β: ^{1}H NMR: δ 7.74 (br s, 1H), 6.58 (s, 2H), 5.14 (t, $J = 9.8$ Hz, 1H), 4.97–4.88 (m, 2H), 4.46 (d, $J = 6.6$ Hz, 1H), 4.27 (s, 1H), 4.10 (dd, $J = 11.7$, 5.1 Hz, 1H), 3.93–3.83 (m, 3H), 3.74 (d, $J = 11.7$ Hz, 1H), 3.56–3.46 (m, 1H), 3.35 (dd, $J = 11.7$, 9.2 Hz, 1H), 3.33 (d, $J = 11.4$ Hz, 1H) 2.19 (s, 6H), 2.04 (s, 6H), 2.03 (s, 3H), 1.84–1.70 (m, 4H), 1.51 (s, 3H), 1.50 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: δ 169.7, 169.4, 169.0, 167.9, 157.2, 136.1 (2×), 125.9, 113.8 (2×), 100.5, 99.1, 77.5, 71.7, 71.4, 70.8, 69.1, 68.9, 67.4, 62.0, 33.4, 29.7, 26.3, 25.9, 22.3, 20.88, 20.85 (2×), 19.6, 19.1 (2×), 19.0. **54**α:**54**β ~ 1:8: Anal. calcd. for $C_{32}H_{47}NO_{12}$: C, 60.27; H, 7.43; N, 2.20; found: C, 60.25; H, 7.59; N, 2.13. $[\alpha]_D^{20}$: −21 ($c = 1.10$, EtOAc).

2,4-Dihydroxy-*N*-{4-[4-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-butoxy]-2,6-dimethylphenyl}-3,3-dimethylbutyramide (10). A mixture of AcOH (32 mL) and H_2O (8 mL) was added to **54** (3.70 g, 5.76 mmol, **54**α:**54**β ~ 12:1). After 24 h, the reaction mixture was concentrated, and the resultant foam was concentrated from toluene (3 × 20 mL). The residue was purified by column chromatography (silica, CH_2Cl_2–MeOH = 19:1) to give **10** (3.26 g, 95%, **10**α:**10**β ~14:1) as a foam. **10**α: ^{1}H NMR ($CDCl_3 + D_2O$): δ 8.06 (br s, 1H), 6.60 (s, 2H), 5.46 (t, $J = 9.8$ Hz, 1H), 4.99 (d, $J = 3.6$ Hz, 1H), 4.94 (dt, $J = 9.9$, 5.9 Hz, 1H), 4.79 (dd, $J = 9.9$, 3.6 Hz, 1H), 4.15 (s, 1H),

3.93 (t, $J = 6.0$ Hz, 2H), 3.80–3.71 (m, 2H), 3.61 (t, $J = 10.4$ Hz, 1H), 3.56 (d, $J = 10.5$ Hz, 1H), 3.50 (d, $J = 10.5$ Hz, 1H), 3.44–341 (m, 1H), 2.18 (s, 6H), 2.04 (s, 3H), 2.03 (s, 6H), 1.86–1.75 (m, 4H), 1.10 (s, 3H), 1.02 (s, 3H). ^{13}C NMR: δ 171.6, 169.9, 169.7, 169.6, 157.4, 136.2 (2×), 125.9, 113.9 (2×), 95.6, 78.2, 71.6, 71.1, 69.7, 69.5, 68.1, 67.5, 58.3, 39.6, 26.3, 26.2, 21.8, 20.95, 20.90, 20.86, 20.4, 19.1 (2×). **10**α:**10**β ~14:1: Anal. calcd. for $C_{29}H_{43}NO_{12}$: C, 58.28; H, 7.25; N, 2.34; found: C, 58.22; H, 7.23; N, 2.40. $[\alpha]_D^{20}$: +64.9 ($c = 0.69$, EtOAc).

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