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Design and stereoselective synthesis of a *C*-aryl furanoside as a conformationally constrained CHIR-090 analogue

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ABSTRACT

The UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine deacetylase (LpxC) is a promising target for the development of novel antibiotic substances against multidrug-resistant Gram-negative bacteria.

The *C*-aryl glycoside **3** was designed as conformationally constrained analogue of the potent LpxC-inhibitor CHIR-090.

The chiral pool synthesis of **3** started with D-mannose. The *C*-aryl glycoside **8** was synthesized stereoselectively by nucleophilic attack of 4-iodine-substituted phenyllithium and subsequent reduction with Et_3SiH. The ester **10** was obtained in a one-pot diol cleavage, CrO_3 oxidation, and esterification. A Sonogashira reaction of the aryl iodide **11** led to the alkyne **17** which was transformed with H_2NOH into the hydroxamic acid **3**.

1. Introduction

Despite the large number of antibiotics being available today, there is an urgent need for novel antibiotic substances as an increasing number of bacterial pathogens develops resistance mechanisms against the major classes of commercial antibacterials.[1,2]

In order to combat infections caused by multiresistant Gram-negative bacteria, the inhibition of the biosynthesis of lipid A was identified as an attractive strategy which is so far unexploited by commercially available drugs.[3,4] Lipid A is a hexaacylated glucosamine disaccharide and represents the hydrophobic membrane anchor of lipopolysaccharide (LPS), constituting the main component of the outer leaflet of the outer membrane of Gram-negative bacteria.[5] While bacteria with a defective lipid A biosynthesis show an increased sensitivity to a range of anti-infective drugs as well as a decreased viability, the inhibition of the biosynthesis of lipid A is lethal to Gram-negative bacteria.[6–10]

LpxC is a Zn^{2+}-dependent enzyme catalyzing the irreversible deacetylation of UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**1**) which is the first committed step in the biosynthesis of lipid A (Fig. 1).[11,12] As the inhibition of LpxC is lethal to *Escherichia coli* and other Gram-negative bacteria, inhibitors of this key enzyme are promising new antibiotics.[13]

Some inhibitors of LpxC have been described in the literature: the hydroxamate-containing substrate-analogue TU-514,[14] the aryl oxazoline derivative L-161,240,[9] the sulfonamide BB-78485,[10] and the diphenylacetylene derivative CHIR-090 (Fig. 2).[15] These inhibitors share common structural features including a Zn^{2+}-coordinating hydroxamate group as well as a hydrophobic moiety which mimics the natural substrate's fatty acid chain and therefore occupies the enzyme's hydrophobic substrate binding tunnel.[16]

In disc diffusion assays, CHIR-090, which is one of the most extensively studied LpxC inhibitors, shows an antibacterial activity against *E. coli* and *Pseudomonas aeruginosa* comparable to that of ciprofloxacin.[15] Therefore, this substance was chosen as lead compound for the design of the C-glycosidic CHIR-090 analogue **3**. In this conformationally constrained derivative the pharmacophoric hydroxamate moiety and the diphenylacetylene side chain of CHIR-090 are fixed in a defined spatial orientation. The conformational restriction should lead to a reduced loss of degrees of freedom when binding to the enzyme, leading to a higher affinity. The central C-glycosidic scaffold was inspired by the sugar moiety of LpxC's natural substrate **1**. In compound **3**, the amide group of CHIR-090 and the hydroxyethyl moiety of its threonyl group are replaced by a 3,4-dihydroxytetrahydrofuran ring. Although the hydrogen-bond donating NH group of CHIR-090's amide moiety is exchanged by an ether oxygen, the affinity of oxazoline derivative L-161,240 toward the enzyme indicates that also a hydrogen-bond acceptor is tolerated in that position.

In this paper we wish to report the synthesis of C-glycoside **3** which will serve as starting point for the preparation of a new class of potential LpxC inhibitors.

2. Synthesis

In the first step of the chiral pool synthesis, the tetrahydrofuran scaffold of the designed LpxC inhibitors had to be established

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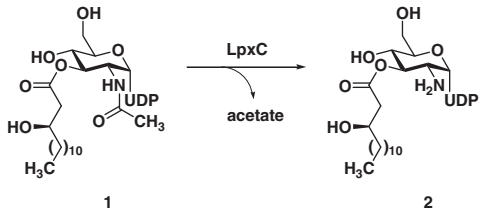


Figure 1. LpxC catalyzed deacetylation of UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**1**).

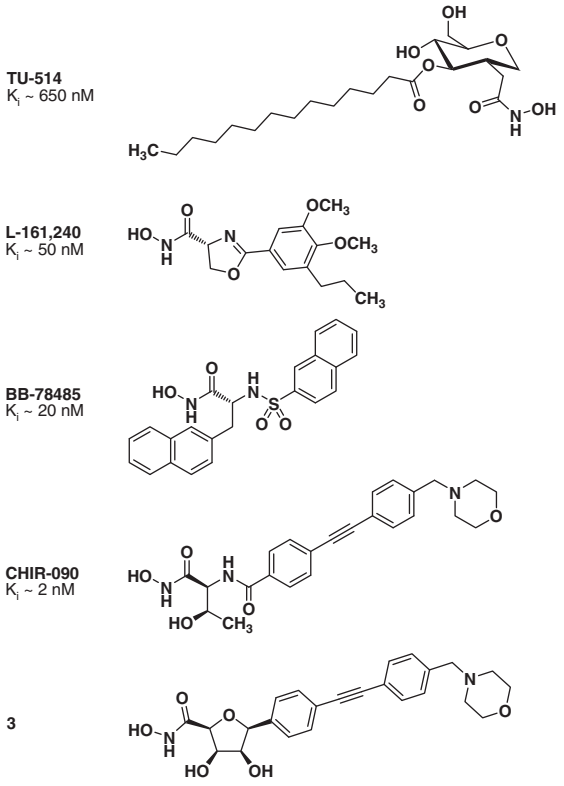


Figure 2. Structures and K_i values versus *E. coli* LpxC of several LpxC inhibitors[15] compared with the structure of the newly designed hydroxamic acid **3**.

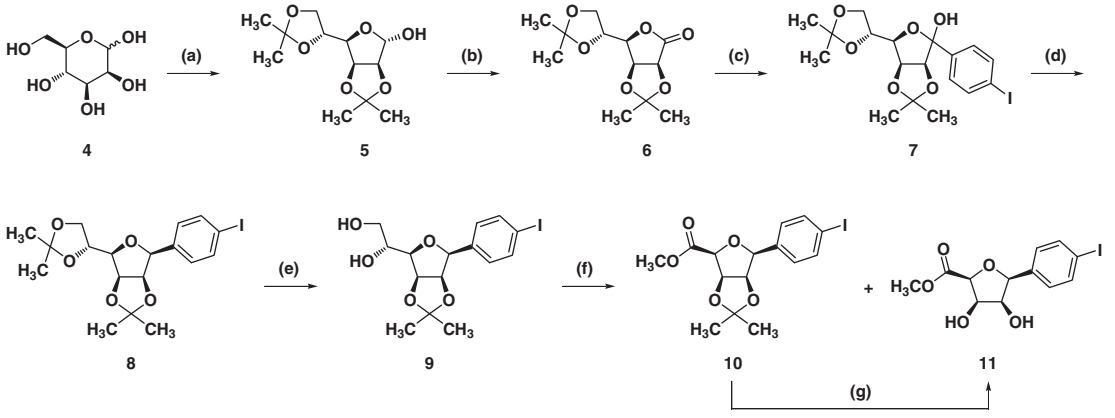
(Scheme 1). Therefore, D-mannose (**4**) was reacted with acetone using iodine as catalyst.[17] The reaction led to the thermodynamically most stable bisacetonide **5**, possessing the desired furanose system. Lactol **5** was transformed into lactone **6** by a Swern oxidation.[18]

In the next step of the synthesis an aromatic moiety bearing a good leaving group for a Sonogashira cross-coupling reaction should be introduced to the tetrahydrofuran scaffold. Therefore 4-iodine-substituted phenyllithium was generated by treating 1,4-diiodobenzene with *n*-butyllithium in THF at −78 °C. In order to avoid a double halogen-metal exchange, a fourfold excess of 1,4-diiodobenzene over *n*-butyllithium was employed. The nucleophilic attack of the generated aryllithium species to lactone **6** yielded hemiketal **7**.[19] In its ^{1}H NMR spectrum only one anomer could be observed.

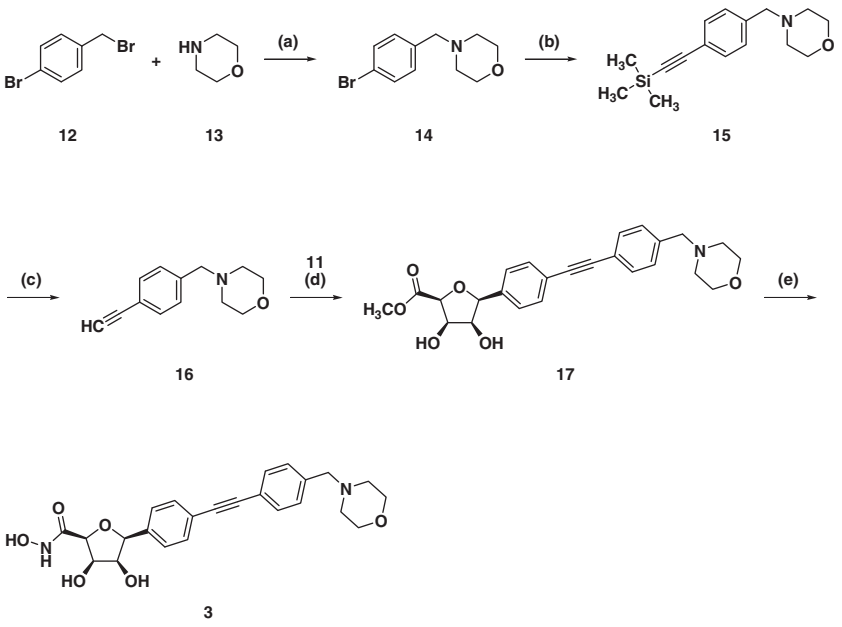
Subsequent reduction with Et_3SiH and $BF_3{\cdot}OEt_2$ led to the stereocontrolled transformation of hemiketal **7** into C-glycoside **8**. This S_N1 type reaction proceeded via an oxocarbenium ion generated by $BF_3{\cdot}OEt_2$. The hydride of triethylsilane was then transferred to this carbocation from the less hindered *Re*-face yielding the *C*-aryl β-D-mannofuranoside **8**. Due to the presence of the Lewis acid BF_3 a partial cleavage of the side chain acetonide occurred additionally. Therefore, the crude product of the reduction was dissolved in methanol and catalytic amounts of *p*-toluenesulfonic acid were added to completely convert the remaining bisacetonide **8** into the desired diol **9**. The stereochemistry of the tetrahydrofuran scaffold of **9** was confirmed by ^{1}H NMR spectroscopy. The doublet caused by the newly introduced proton in 5-position shows a coupling constant of 3.6 Hz indicating its *cis*-orientation relative to the proton in 4-position of the tetrahydrofuran ring. The obtained ^{1}H NMR data of **9** are in agreement with the already described *C*-phenyl β-D-mannofuranoside.[19]

In order to transform the 1,2-diol **9** into the ester **10**, an oxidant solution composed of periodic acid and catalytic amounts of CrO_3 in wet acetonitrile was used.[20] First, the periodic acid led to a glycol cleavage, then the CrO_3-mediated oxidation of the resulting aldehyde yielded the corresponding carboxylic acid. After work-up and extraction, the acid was transformed into methyl ester **10** by heating the crude product in methanol in the presence of *p*-toluenesulfonic acid. These acidic reaction conditions led to partial cleavage of the acetonide affording a mixture of acetonide **10** and diol **11**. Heating ester **10** in methanol containing catalytic amounts of *p*-toluenesulfonic acid led to the cleavage of the isopropylidene protecting group to give diol **11**.

The side chain of CHIR-090[21] was synthesized in three reaction steps (Scheme 2). First, 4-bromobenzyl bromide (**12**) was reacted with morpholine (**13**) affording the tertiary amine **14**. Subsequent Sonogashira coupling of **14** with trimethylsilylacetylene gave the silyl protected phenylacetylene **15**. Finally, the fluoride-mediated removal of the silyl protective group yielded the phenylacetylene **16**.



Scheme 1. Reagents and conditions: (a) acetone, I_2, rt, 2 h, 51%; (b) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 10 min, then **5**, 30 min, then NEt_3, rt, 91%; (c) 1,4-diiodobenzene, *n*-BuLi, THF, −78 °C, 15 min, then **6**, 30 min, 71%; (d) $BF_3{\cdot}OEt_2$, Et_3SiH, H_3CCN, −40 °C, 1 h; (e) *p*-TsOH, MeOH, rt, 16 h, 56% (over two steps); (f) (1) CrO_3/H_5IO_6, H_3CCN, rt, 3 h; (2) *p*-TsOH, MeOH, Δ, 16 h, 40% (**10**) and 37% (**11**); (g) *p*-TsOH, MeOH, Δ, 16 h, 39%.



Scheme 2. Reagents and conditions: (a) H_3CCN, Δ, 4 h, 98%; (b) $(H_3C)_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, NEt_3, Δ, 16 h, 71%; (c) Bu_4NF, THF, 0 °C, 30 min, 99%; (d) $Pd(PPh_3)_4$, CuI, NEt_3, H_3CCN, rt, 2 h, 26%; (e) $H_2NOH{\cdot}HCl$, NaOMe, MeOH, rt, 16 h, 29%.

The aromatic substituent of CHIR-090 was introduced into the C-glycosidic scaffold of **11** by a Sonogashira coupling.[22] Reaction of aryl iodide **11** with phenylacetylene **16** gave access to the diphenylacetylene **17**.

In the last step the hydroxamate group was established. Treatment of ester **17** with hydroxylamine hydrochloride and sodium methoxide in dry methanol yielded the desired hydroxamic acid **3**.[23]

3. Conclusion

A convergent synthesis was established giving access to the conformationally constrained CHIR-090 analogue **3**. This hydroxamic acid possesses a C-glycosidic scaffold, which replaces the threonine amide substructure of CHIR-090, and displays the first representative of a novel class of LpxC inhibitors.

4. Experimental section

4.1. Chemistry, general

Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (TLC): Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica Gel 60, 40–64 μm (Macherey-Nagel); parentheses include: diameter of the column, fraction size, eluent, R_f value. Melting point (mp): Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. Optical rotation α [°] was determined with a Polarimeter 341 (Perkin Elmer); path length 1 dm, wavelength 589 nm (sodium D line); the unit of the specific rotation $[\alpha]_D^{20}$ [° mL dm^{-1} g^{-1}] is omitted; the concentration of the sample *c* [mg mL^{-1}] and the solvent used are given in brackets. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury plus 400 spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. Where necessary, the assignment of the signals in the ^1H NMR and ^{13}C NMR spectra was performed using ^1H–^1H and ^1H–^{13}C COSEY NMR spectra as well as NOE (nuclear Overhauser effect) difference spectroscopy. IR: IR Prestige-21 (Shimadzu). MS: HRMS: MicrOTOF-QII (Bruker); ESI: LCQ Finnigan MAT mass spectrometer (Thermo Finnigan), peaks are given in *m/z* (% of basis peak). HPLC methods for the determination of product purity: Method 1: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm); LiCroCART® 250-4 mm cartridge; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm for 30 min; solvents: A: water with 0.05% (V/V) trifluoroacetic acid; B: acetonitrile with 0.05% (V/V) trifluoroacetic acid: gradient elution: (A%): 0–4 min: 90% , 4–29 min: gradient from 90% to 0%, 29–31 min: 0%, 31–31.5 min: gradient from 0% to 90%, 31.5–40 min: 90%. Method 2: Merck Hitachi Equipment; UV detector: L-7400; pump: L-6200A; column: phenomenex Gemini® 5 μm C6-Phenyl 110 Å; LC Column 250 × 4.6 mm; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection at λ = 254 nm for 20 min; solvents: A: acetonitrile:10 mM ammonium formate = 10:90 with 0.1% formic acid; B: acetonitrile:10 mM ammonium formate = 90:10 with 0.1% formic acid; gradient elution: (A%): 0–5 min: 100%, 5–15 min: gradient from 100% to 0%, 15–20 min: 0%, 20–22 min: gradient from 0% to 100%, 22–30 min: 100%.

4.2. Synthetic procedures

4.2.1. (3a*S*,4*S*,6*R*,6a*S*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (5)

Iodine (1.42 g, 5.6 mmol) was added to a suspension of D-mannose (5.0 g, 27.8 mmol) in acetone (250 mL) and the mixture was stirred for 2 h at ambient temperature. Then the reaction mixture was cooled down to 0 °C quenched with aqueous sodium bicarbonate and sodium thiosulfate. The mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The crude product was crystallized from an acetone/*n*-hexane mixture to give **5** as colorless solid (3.66 g, 14.1 mmol, 51%). Mp: 125 °C; $[\alpha]_D^{20}$ +16.1 (8.1; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ (ppm) = 1.32 (s, 3H, C*H*$_3$), 1.38 (s, 3H, C*H*$_3$), 1.45 (s, 3H, C*H*$_3$), 1.46 (s, 3H, C*H*$_3$), 2.92 (d, *J* = 2.4 Hz, O*H*), 4.02–4.11 (m, 2H, OCHC*H*$_2$O), 4.18 (dd, *J* = 7.2/3.7 Hz, 1H, 6-H), 4.37–4.43 (m, 1H, OC*H*CH$_2$O), 4.62 (d, *J* = 5.9 Hz, 1H, 3a-H), 4.81 (dd, *J* = 5.9/3.7 Hz, 1H, 6a-H), 5.38 (d, *J* = 2.4 Hz, 4-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 24.5 (1C, C(*C*H$_3$)$_2$), 25.3 (1C, C(*C*H$_3$)$_2$), 25.9 (1C, C(*C*H$_3$)$_2$), 27.1 (1C, C(*C*H$_3$)$_2$), 66.7 (1C, OCH*C*H$_2$O), 73.4 (1C, OCH-CH$_2$O), 79.7 (1C, C-6a), 80.3 (1C, C-6), 85.5 (1C, C-3a), 101.3 (1C,

C-4), 109.2 (1C, $C(CH_3)_2$), 112.8 (1C, $C(CH_3)_2$); IR (neat): ν (cm^{-1}) = 3436, 2978, 2948, 2899, 1372, 1201, 1060, 975, 838; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{20}O_6Na$, 283.1152; found, 283.1152.

4.2.2. (3a*S*,6*R*,6a*S*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6,6a-dihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (6)

Under N_2 atmosphere a solution of oxalyl chloride (1.75 mL, 2.34 g, 18.4 mmol) in CH_2Cl_2 (50 mL) was cooled down to −78 °C. Then a solution of DMSO (2.91 mL, 3.2 g, 41.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the mixture was stirred for 10 min at −78 °C. Then a solution of **5** (4.42 g, 17.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise and the solution was stirred for another 30 min at −78 °C. Afterward, triethylamine (12 mL, 8.7 g, 86.3 mmol) was added and the mixture was allowed to warm to ambient temperature. Then *n*-hexane was added, the mixture was filtered, and the precipitate was washed with Et_2O. The organic layer was concentrated in vacuo and the residue was purified by flash column chromatography (8 cm, 60 mL, *n*-hexane/ethyl acetate = 8/2, R_f = 0.19) to give **6** as colorless solid (4.0 g, 15.5 mmol, 91%). Mp: 126 °C; $[\alpha]_D^{20}$ +56.5 (4.6; CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 4.07 (dd, *J* = 9.3/3.7 Hz, 1 H, OCHCH_2O), 4.15 (dd, *J* = 9.2/5.8 Hz, 1H, OCHCH_2O), 4.37 (dd, *J* = 8.2/3.3 Hz, 1H, 6-H), 4.43 (ddd, *J* = 8.2/5.9/3.7 Hz, 1H, OC*H*CH$_2$O), 4.84 (d, *J* = 5.3 Hz, 1H, 3a-H), 4.88 (dd, *J* = 5.3/3.4 Hz, 1H, 6a-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 25.2 (1C, C(*C*H$_3$)$_2$), 26.1 (1C, C(*C*H$_3$)$_2$), 26.9 (1C, C(*C*H$_3$)$_2$), 27.1 (1C, C(*C*H$_3$)$_2$), 66.6 (1C, OCHCH$_2$O), 72.7 (1C, OCHCH$_2$O), 75.9 (1C, C-6a), 76.2 (1C, C-3a), 78.2 (1C, C-6), 110.0 (1C, *C*(CH$_3$)$_2$), 114.7 (1C, *C*(CH$_3$)$_2$), 173.6 (1C, C-4); IR (neat): ν (cm^{-1}) = 2987, 2891, 1769, 1381, 1194, 1082, 1039, 976, 851; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{18}O_6Na$, 281.0996; found, 281.0993.

4.2.3. (3a*S*,6*R*,6a*S*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-(4-iodophenyl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (7)

Under N_2 atmosphere a 1.6 M solution of *n*-butyllithium in hexanes (2.0 mL, 3.2 mmol) was added to a solution of 1,4-diiodobenzene (2.97 g, 9 mmol) in THF (40 mL). After stirring at −78 °C for 15 min, a solution of **6** (775 mg, 3 mmol) in THF (20 mL) was added dropwise and the mixture was stirred for additional 30 min at −78 °C. Then the mixture was allowed to warm to room temperature and a saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3×), the combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (4 cm, 30 mL, *n*-hexane/ethyl acetate = 8/2, R_f = 0.25) to give **7** as colorless solid (990 mg, 2.14 mmol, 71%). Mp: 80 °C; $[\alpha]_D^{20}$ +66.7 (0.6; CH_2Cl_2); ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.15 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.96 (dd, *J* = 8.3/6.0 Hz, 1H, OCHCH_2O), 4.05 (dd, *J* = 8.3/6.5 Hz, 1H, OCHCH_2O), 4.21 (dd, *J* = 5.8/3.9 Hz, 1H, 6-H), 4.38 (q, *J* = 6.1 Hz, 1H, OC*H*CH$_2$O), 4.45 (d, *J* = 5.8 Hz, 1H, 3a-H), 4.85 (dd, *J* = 5.8/3.9 Hz, 1H, 6a-H), 6.75 (s, 1H, O*H*), 7.20–7.25 (m, 2H, 2′-H$_{4\text{-iodophenyl}}$, 6′-H$_{4\text{-iodophenyl}}$), 7.66–7.72 (m, 2H, 3′-H$_{4\text{-iodophenyl}}$, 5′-H$_{4\text{-iodophenyl}}$); ^{13}C NMR (DMSO-d_6): δ (ppm) = 24.0 (1C, C(*C*H$_3$)$_2$), 25.3 (1C, C(*C*H$_3$)$_2$), 25.4 (1C, C(*C*H$_3$)$_2$), 26.6 (1C, C(*C*H$_3$)$_2$), 65.7 (1C, OCHCH$_2$O), 73.1 (1C, OCHCH$_2$O), 78.0 (1C, C-6), 79.9 (1C, C-6a), 86.1 (1C, C-3a), 94.3 (1C, C-4′$_{4\text{-iodophenyl}}$), 104.9 (1C, C-4), 107.8 (1C, *C*(CH$_3$)$_2$), 111.5 (1C, *C*(CH$_3$)$_2$), 129.4 (2C, C-2′$_{4\text{-iodophenyl}}$, C-6′$_{4\text{-iodophenyl}}$), 136.0 (2C, C-3′$_{4\text{-iodophenyl}}$, C-5′$_{4\text{-iodophenyl}}$), 140.2 (1C, C-1′$_{4\text{-iodophenyl}}$); IR (neat): ν (cm^{-1}) = 3374, 2985, 2937, 1372, 1208, 1039, 1002, 821; MS (ESI): *m/z* = 485 (M+Na$^+$, 100); HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{23}IO_6Na$, 485.0432; found, 485.0422; HPLC (method 1): t_R = 20.4 min, purity 97.4%.

4.2.4. (*R*)-1-[(3a*S*,4*R*,6*S*,6a*R*)-6-(4-Iodophenyl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]ethane-1,2-diol (9)

Under N_2 atmosphere Et_3SiH (0.63 mL, 452 mg, 3.9 mmol) was added to a solution of **7** (1.5 g, 3.2 mmol) and $BF_3{\cdot}Et_2O$ (0.41 mL, 460 mg, 3.2 mmol) in acetonitrile (30 mL) at −40 °C. The mixture was stirred at −40 °C for 1 h, then a saturated aqueous solution of K_2CO_3 (3 mL) was added and the mixture was stirred for 1 h at ambient temperature. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was dissolved in methanol (30 mL) and *p*-toluenesulfonic acid monohydrate (123 mg, 0.65 mmol) was added. The mixture was stirred at ambient temperature for 16 h. Then a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (4 cm, 30 mL, *n*-hexane/ethyl acetate = 1/1, R_f = 0.11) to give **9** as colorless solid (744 mg, 1.8 mmol, 56%). Mp: 181 °C; $[\alpha]_D^{20}$ +66.1 (1.6; CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.29 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.71 (dd, *J* = 7.8/3.8 Hz, 1H, H-4), 3.80 (dd, *J* = 11.6/5.6 Hz, 1H, HOCHCH_2OH), 3.93 (dd, *J* = 11.6/3.4 Hz, 1H, HOCHCH_2OH), 4.12–4.20 (m, 1H, HOC*H*CH$_2$OH), 4.57 (d, *J* = 3.6 Hz, 1H, 6-H), 4.80 (dd, *J* = 5.9/3.6 Hz, 1H, 6a-H), 4.93 (dd, *J* = 5.9/3.8 Hz, 1H, 3a-H), 7.09–7.14 (m, 2H, 2′-H$_{4\text{-iodophenyl}}$, 6′-H$_{4\text{-iodophenyl}}$), 7.65–7.70 (m, 2H, 3′-H$_{4\text{-iodophenyl}}$, 5′-H$_{4\text{-iodophenyl}}$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 24.5 (1C, C(*C*H$_3$)$_2$), 25.8 (1C, C(*C*H$_3$)$_2$), 64.8 (1C, HOCHCH_2OH), 70.4 (1C, HOCHCH$_2$OH), 81.0 (1C, C-4), 81.5 (1C, C-3a), 82.1 (1C, C-6a), 83.2 (1C, C-6), 93.9 (1C, C-4′$_{4\text{-iodophenyl}}$), 112.9 (1C, *C*(CH$_3$)$_2$), 129.4 (2C, C-2′$_{4\text{-iodophenyl}}$, C-6′$_{4\text{-iodophenyl}}$), 135.2 (1C, C-1′$_{4\text{-iodophenyl}}$), 137.2 (2C, C-3′$_{4\text{-iodophenyl}}$, C-5′$_{4\text{-iodophenyl}}$); IR (neat): ν (cm^{-1}) = 3456, 2978, 2919, 2862, 1482, 1381, 1207, 1161, 1009, 857, 745; MS (ESI): *m/z* = 429 (M+Na$^+$, 100); HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{19}IO_5Na$, 429.0169; found, 429.0173; HPLC (method 1): t_R = 17.3 min, purity 97.3%.

4.2.5. Methyl (3a*R*,4*S*,6*S*,6a*R*)-6-(4-iodophenyl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxylate (10) and methyl (2*S*,3*R*,4*S*,5*S*)-3,4-dihydroxy-5-(4-iodophenyl)-2,3,4,5-tetrahydrofuran-2-carboxylate (11)

An oxidant solution (17 mL), which was prepared by dissolving H_5IO_6 (11.4 g, 50 mmol) and CrO_3 (23 mg, 0.23 mmol) in wet acetonitrile (114 mL, 0.75% water V/V), was added to a solution of **9** (1.23 g, 3.0 mmol) in acetonitrile (20 mL). The mixture was stirred at ambient temperature for 3 h. The reaction was quenched by the addition of ethylene glycol. Then hydrochloric acid (1 M) was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was dissolved in methanol (30 mL) and *p*-toluenesulfonic acid monohydrate (57 mg, 0.30 mmol) was added. The mixture was heated to reflux for 16 h. Then the solvent was removed in vacuo and the residue was purified by flash column chromatography (4 cm, 30 mL, *n*-hexane/ethyl acetate = 8/2→1/1) to give **10** (*n*-hexane/ethyl acetate = 8/2, R_f = 0.13) as colorless solid (490 mg, 1.2 mmol, 40%) and **11** (*n*-hexane/ethyl acetate = 1/1, R_f = 0.20) as colorless solid (400 mg, 1.1 mmol, 37%).

Analytical data of **10**: mp: 167.6 °C; TLC (*n*-hexane/ethyl acetate, 8:2 V/V): R_F = 0.13; $[\alpha]_D^{20}$ +34.4 (1.9; CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.26 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.39 (d, *J* = 4.6 Hz, 1H, 4-H), 4.62 (d, *J* = 3.5 Hz, 1H, 6-H), 4.80 (dd, *J* = 5.9/3.5 Hz, 1H, 6a-H), 5.08 (dd, *J* = 5.9/4.6 Hz, 1H, 3a-H), 7.19–7.24 (m, 2H, 2′-H$_{4\text{-iodophenyl}}$, 6′-H$_{4\text{-iodophenyl}}$), 7.67–7.72 (m, 2H, 3′-H$_{4\text{-iodophenyl}}$, 5′-H$_{4\text{-iodophenyl}}$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 25.0 (1C, C(*C*H$_3$)$_2$), 25.8 (1C, C(*C*H$_3$)$_2$), 52.3 (1C, OCH$_3$), 80.8 (1C, C-4), 81.7 (1C, C-6a), 82.0 (1C, C-3a), 83.0 (1C, C-6),

94.1 (1C, C-4′$_{4\text{-iodophenyl}}$), 113.6 (1C, $C(CH_3)_2$), 129.5 (2C, C-2′$_{4\text{-iodophenyl}}$, C-6′$_{4\text{-iodophenyl}}$), 134.6 (1C, C-1′$_{4\text{-iodophenyl}}$), 137.2 (2C, C-3′$_{4\text{-iodophenyl}}$, C-5′$_{4\text{-iodophenyl}}$), 167.7 (1C, C=O); IR (neat): ν (cm^{-1}) = 2984, 2934, 1752, 1486, 1436, 1382, 1207, 1099, 1038, 815, 742; MS (ESI): m/z = 427 ($M+Na^+$, 100); HRMS (m/z): $[M+Na]^+$ calcd for $C_{15}H_{17}IO_5Na$, 427.0013; found, 427.0018; HPLC (method 1): t_R = 19.8 min, purity 98.5%.

4.2.6. Methyl (2*S*,3*R*,4*S*,5*S*)-3,4-dihydroxy-5-(4-iodophenyl)-2,3,4,5-tetrahydrofuran-2-carboxylate (11)

p-Toluenesulfonic acid monohydrate (43 mg, 0.23 mmol) was added to a solution of **10** (460 mg, 1.14 mmol) in methanol (30 mL). The mixture was heated to reflux for 16 h. Then the solvent was removed in vacuo and the residue was purified by flash column chromatography (3 cm, 20 mL, *n*-hexane/ethyl acetate = 1/1, R_f = 0.20) to give **11** as colorless solid (162 mg, 0.44 mmol, 39%). Mp: 125 °C; $[\alpha]_D^{20}$ +55.5 (1.3; CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.89 (s br, 1H, O*H*), 3.19 (s br, 1H, O*H*), 3.84 (s, 3H, OCH_3), 4.21–4.25 (m, 1H, 4-H), 4.68–4.74 (m, 2H, 2-H, 3-H), 5.07 (d, J = 4.6 Hz, 1H, 5-H), 7.20–7.24 (m, 2H, 2′-H$_{4\text{-iodophenyl}}$, 6′-H$_{4\text{-iodophenyl}}$), 7.70–7.74 (m, 2H, 3′-H$_{4\text{-iodophenyl}}$, 5′-H$_{4\text{-iodophenyl}}$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 52.8 (1C, OCH_3), 73.7 (1C, C-4), 74.1 (1C, C-3), 78.9 (1C, C-2), 83.2 (1C, C-5), 93.9 (1C, C-4′$_{4\text{-iodophenyl}}$), 128.9 (2C, C-2′$_{4\text{-iodophenyl}}$, C-6′$_{4\text{-iodophenyl}}$), 135.8 (1C, C-1′$_{4\text{-iodophenyl}}$), 137.6 (2C, C-3′$_{4\text{-iodophenyl}}$, C-5′$_{4\text{-iodophenyl}}$), 172.6 (1C, C=O); IR (neat): ν (cm^{-1}) = 3453, 3386, 2943, 2876, 1738, 1480, 1402, 1222, 1122, 1084, 1005, 976, 809, 743; MS (ESI): m/z = 387 ($M+Na^+$, 100); HRMS (m/z): $[M+Na]^+$ calcd for $C_{12}H_{13}IO_5Na$, 386.9700; found, 386.9705; HPLC (method 1): t_R = 15.4 min, purity 97.7%.

4.2.7. 4-(4-Bromobenzyl)morpholine (14)

Morpholine (**13**, 1.4 mL, 1.39 g, 16 mmol) was added to a solution of 4-bromobenzyl bromide (**12**, 1.0 g, 4 mmol) in acetonitrile (50 mL) and the mixture was heated to reflux for 4 h. Then water was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (6 cm, 50 mL, *n*-hexane/ethyl acetate = 8/2, R_f = 0.19) to give **14** as colorless solid (1.0 g, 3.9 mmol, 98%). Mp: 85 °C; ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.41–2.45 (m, 4H, NC$H_2$$CH_2O$), 3.45 (s, 2H, NC$H_2$Ar), 3.69–3.72 (m, 4H, NCH_2CH_2O), 7.19–7.23 (m, 2H, 2′-H$_{4\text{-bromophenyl}}$, 6′-H$_{4\text{-bromophenyl}}$), 7.42–7.46 (m, 2H, 3′-H$_{4\text{-bromophenyl}}$, 5′-H$_{4\text{-bromophenyl}}$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 53.7 (2C, NCH_2CH_2O), 62.8 (1C, NCH_2Ar), 67.1 (2C, NCH_2CH_2O), 121.1 (1C, C-4′$_{4\text{-bromophenyl}}$), 131.0 (2C, C-2′$_{4\text{-bromophenyl}}$, C-6′$_{4\text{-bromophenyl}}$), 131.5 (2C, C-3′$_{4\text{-bromophenyl}}$, C-5′$_{4\text{-bromophenyl}}$), 136.7 (1C, C-1′$_{4\text{-bromophenyl}}$); IR (neat): ν (cm^{-1}) = 2966, 2927, 2862, 2815, 1487, 1449, 1351, 1110, 1065, 1007, 910, 863, 848, 789; MS (ESI): m/z = 256 ($M(^{79}Br)+H^+$, 100), 258 ($M(^{81}Br)+Na^+$, 94); HRMS (m/z): $[M+H]^+$ calcd for $C_{11}H_{14}BrNOH$, 256.0332; found, 256.0327; HPLC (method 1): t_R = 11.4 min, purity 99.9%.

4.2.8. 4-[4-(2-(Trimethylsilyl)ethynyl)benzyl]morpholine (15)

Under N_2 atmosphere copper(I) iodide (65 mg, 0.34 mmol), tetrakis(triphenylphosphine)palladium(0) (197 mg, 0.17 mmol), and trimethylsilylacetylene (2.4 mL, 1.66 g, 16.9 mmol) were added to a solution of **14** (2.93 g, 11.4 mmol) in triethylamine (70 mL). The mixture was heated to reflux for 16 h. After evaporation of the solvent the residue was purified by flash column chromatography (6 cm, 50 mL, *n*-hexane/ethyl acetate = 8/2, R_f = 0.21) to give **15** as colorless solid (2.2 g, 8.0 mmol, 71%). Mp: 62 °C; ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.24 (s, 9H, Si(CH_3)$_3$), 2.41–2.45 (m, 4H, NC$H_2$$CH_2O$), 3.49 (s, 2H, NC$H_2$Ar), 3.69–3.72 (m, 4H, NCH_2CH_2O), 7.25–7.29 (m, 2H, 2′-H$_{4\text{-ethynylphenyl}}$, 6′-H$_{4\text{-ethynylphenyl}}$), 7.40–7.43 (m, 2H, 3′-H$_{4\text{-ethynylphenyl}}$, 5′-H$_{4\text{-ethynylphenyl}}$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.13 (3C, Si(CH_3)$_3$), 53.7 (2C, NCH_2CH_2O), 63.2 (1C, NCH_2Ar), 67.0 (2C, NCH_2CH_2O), 94.2 (1C, $C{\equiv}CSi(CH_3)_3$), 105.1 (1C, $C{\equiv}CSi(CH_3)_3$), 122.1 (1C, C-4′$_{4\text{-ethynylphenyl}}$), 129.2 (2C, C-2′$_{4\text{-ethynylphenyl}}$, C-6′$_{4\text{-ethynylphenyl}}$), 132.0 (2C, C-3′$_{4\text{-ethynylphenyl}}$, C-5′$_{4\text{-ethynylphenyl}}$), 138.3 (1C, C-1′$_{4\text{-ethynylphenyl}}$); IR (neat): ν (cm^{-1}) = 2959, 2851, 2811, 2156, 1507, 1245, 1114, 1005, 851, 766; MS (ESI): m/z = 274 ($M+H^+$, 100); HRMS (m/z): $[M+H]^+$ calcd for $C_{16}H_{23}NOSiH$, 274.1622; found, 274.1614; HPLC (method 1): t_R = 18.5 min, purity 97.5%.

4.2.9. 4-(4-Ethynylbenzyl)morpholine (16)

A 1.0 M solution of tetrabutylammonium fluoride in THF (2.35 mL, 2.35 mmol) was added dropwise to an ice-cooled solution of **15** (547 mg, 2.0 mmol) in THF (10 mL). The mixture was stirred at 0 °C for 30 min. Then a saturated solution of ammonium chloride (15 mL) was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (4 cm, 30 mL, *n*-hexane/ethyl acetate = 2/1, R_f = 0.29) to give **16** as colorless solid (397 mg, 1.97 mmol, 99%). Mp: 65 °C; ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.41–2.45 (m, 4H, NC$H_2$$CH_2O$), 3.49 (s, 2H, NC$H_2$Ar), 3.69–3.72 (m, 4H, , NCH_2CH_2O), 7.27–7.31 (m, 2H, 2′-H$_{4\text{-ethynylphenyl}}$, 6′-H$_{4\text{-ethynylphenyl}}$), 7.43–7.46 (m, 2H, 3′-H$_{4\text{-ethynylphenyl}}$, 5′-H$_{4\text{-ethynylphenyl}}$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 53.7 (2C, NCH_2CH_2O), 63.2 (1C, NCH_2Ar), 67.1 (2C, NCH_2CH_2O), 77.2 (1C, C≡CH), 83.7 (1C, *C*≡CH), 121.0 (1C, C-4′$_{4\text{-ethynylphenyl}}$), 129.2 (2C, C-2′$_{4\text{-ethynylphenyl}}$, C-6′$_{4\text{-ethynylphenyl}}$), 132.2 (2C, C-3′$_{4\text{-ethynylphenyl}}$, C-5′$_{4\text{-ethynylphenyl}}$), 138.5 (1C, C-1′$_{4\text{-ethynylphenyl}}$); IR (neat): ν (cm^{-1}) = 3223, 2926, 2824, 2036, 1454, 1351, 1110, 1004, 855, 684; MS (ESI): m/z = 202 ($M+H^+$, 100); HRMS (m/z): $[M+H]^+$ calcd for $C_{13}H_{15}NOH$, 202.1226; found, 202.1240; HPLC (method 1): t_R = 9.8 min, purity 97.5%.

4.2.10. Methyl (2*S*,3*R*,4*S*,5*S*)-3,4-dihydroxy-5-(4-{2-[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-2,3,4,5-tetrahydrofuran-2-carboxylate (17)

Under N_2 atmosphere triethylamine (0.21 mL, 1.54 mmol), copper(I) iodide (8.4 mg, 0.044 mmol), and tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.022 mmol) were added to a solution of **11** (80 mg, 0.22 mmol) in acetonitrile (5 mL). Then a solution of **16** (358 mg, 1.76 mmol) in acetonitrile (3 mL) was added dropwise over a period of 2 h. After evaporation of the solvent the residue was purified by flash column chromatography (2 cm, 10 mL, ethyl acetate, R_f = 0.14) to give **17** as colorless solid (25 mg, 0.06 mmol, 26%). Mp: 165 °C; $[\alpha]_D^{20}$ +60.0 (0.7; CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.43–2.48 (m, 4H, NC$H_2$$CH_2O$), 3.51 (s, 2H, NC$H_2$Ar), 3.69–3.73 (m, 4H, NCH_2CH_2O), 3.85 (s, 3H, OCH_3), 4.25–4.28 (m, 1H, 4-H), 4.70–4.75 (m, 2H, 2-H, 3-H), 5.14 (d, J = 3.9 Hz, 1H, 5-H), 7.30–7.34 (m, 2H, H$_{arom.}$), 7.45–7.50 (m, 4H, H$_{arom.}$), 7.53–7.57 (m, 2H, H$_{arom.}$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 52.8 (1C, OCH_3), 53.7 (2C, NCH_2CH_2O), 63.2 (1C, NCH_2Ar), 67.0 (2C, NCH_2CH_2O), 73.8 (1C, C-4), 74.1 (1C, C-2), 79.0 (1C, C-3), 83.4 (1C, C-5), 89.3 (1C, *C*≡C), 89.6 (1C, C≡*C*), 122.2 (1C, C$_{arom.}$), 123.2 (1C, C$_{arom.}$), 127.0 (2C, C$_{arom.}$), 129.3 (2C, C$_{arom.}$), 131.6 (2C, C$_{arom.}$), 131.7 (2C, C$_{arom.}$), 136.2 (1C, C$_{arom.}$), 138.1 (1C, C$_{arom.}$), 172.5 (1C, C=O); IR (neat): ν (cm^{-1}) = 3368, 2952, 2852, 2805, 1712, 1519, 1231, 1113, 1086, 1007, 865, 781; HRMS (m/z): $[M+H]^+$ calcd for $C_{25}H_{28}NO_6$, 438.1911; found, 438.1912; HPLC (method 1): t_R = 14.8 min, purity 95.4%.

4.2.11. (2*S*,3*R*,4*S*,5*S*)-*N*,3,4-Trihydroxy-5-(4-(2-(4-(morpholinomethyl)phenyl)ethynyl)phenyl)-tetrahydrofuran-2-carboxamide (3)

A 2.0 M solution of sodium methoxide in methanol (0.55 mL, 1.1 mmol) was added to a solution of **17** (200 mg, 0.46 mmol)

and hydroxylamine hydrochloride (69 mg, 1.0 mmol) in methanol (30 mL) and the mixture was stirred at ambient temperature for 16 h. Then the solvent was evaporated. Then water was added and the mixture was extracted with ethyl acetate (3×). Then the aqueous phase was extracted with CH_2Cl_2/methanol (8:2, 3×). The combined CH_2Cl_2 phases were dried (Na_2SO_4), filtered, and evaporated to give **3** as colorless solid (58 mg, 0.13 mmol, 29%). Mp: 155 °C; TLC (CH_2Cl_2/methanol, 9:1 V/V): R_f = 0.31; $[\alpha]_D^{20}$ +68.4 (1.9; methanol); ^{1}H NMR (D_3COD): δ (ppm) = 2.45–2.51 (m, 4H, NCH_2CH$_2$O), 3.55 (s, 2H, NCH_2Ar), 3.68–3.72 (m, 4H, NCH$_2$CH_2O), 4.21 (t, J = 4.4 Hz, 1H,4-H), 4.48 (d, J = 7.1 Hz, 1H, 2-H), 4.71 (dd, J = 7.1/4.8 Hz, 1H, 3-H), 5.06 (d, J = 4.1 Hz, 1H, 5-H), 7.35–7.39 (m, 2H, $H_{arom.}$), 7.45–7.51 (m, 6H, $H_{arom.}$); ^{13}C NMR (D_3COD): δ (ppm) = 54.6 (2C, NCH$_2$CH$_2$O), 63.9 (1C, NCH$_2$Ar), 67.7 (2C, NCH$_2$CH$_2$O), 7.43 (1C, C-3), 74.8 (1C, C-4), 80.2 (1C, C-2), 85.2 (1C, C-5), 89.8 (1C, C≡C), 90.3 (1C, C≡C), 123.6 (1C, $C_{arom.}$), 123.8 (1C, $C_{arom.}$), 128.8 (2C, $C_{arom.}$), 130.8 (2C, $C_{arom.}$), 132.0 (2C, $C_{arom.}$), 132.5 (2C, $C_{arom.}$), 138.7 (1C, $C_{arom.}$), 139.2 (1C, $C_{arom.}$), 169.3 (1C, C=O); IR (neat): ν (cm^{-1}) = 3175, 2920, 1655, 1516, 1454, 1296, 1107, 1026, 856, 833, 779; HRMS (m/z): $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_6$, 439.1864; found, 439.1870; HPLC (method 2): t_R = 10.8 min, purity 96.2%.

References

1. Boucher, H. W.; Talbot, G. H.; Bradley, J. S.; Edwards, J. E.; Gilbert, D.; Rice, L. B.; Scheld, M.; Spellberg, B.; Bartlett, J. *Clin. Infect. Dis.* **2009**, *48*, 1–12.
2. Cooper, M. A.; Shlaes, D. *Nature (London, UK)* **2011**, *472*, 32.
3. Raetz, C. R. H. *Prog. Clin. Biol. Res.* **1998**, *397*, 1–14.
4. Raetz, C. R. H.; Reynolds, C. M.; Trent, M. S.; Bishop, R. E. *Annu. Rev. Biochem.* **2007**, *76*, 295–329.
5. Raetz, C. R. H.; Whitfield, C. *Annu. Rev. Biochem.* **2002**, *71*, 635–700.
6. Vaara, M. *Antimicrob. Agents Chemother.* **1993**, *37*, 354–356.
7. Vuorio, R.; Vaara, M. *Antimicrob. Agents Chemother.* **1992**, *36*, 826–829.
8. Ritter, T. K.; Wong, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508–3533.
9. Onishi, H. R.; Pelak, B. A.; Gerckens, L. S.; Silver, L. L.; Kahan, F. M.; Chen, M. H.; Patchett, A. A.; Galloway, S. M.; Hyland, S. A.; Anderson, M. S.; Raetz, C. R. *Science* **1996**, *274*, 980–982.
10. Clements, J. M.; Coignard, F.; Johnson, I.; Chandler, S.; Palan, S.; Waller, A.; Wijkmans, J.; Hunter, M. G. *Antimicrob. Agents Chemother.* **2002**, *46*, 1793–1799.
11. Young, K.; Silver, L. L.; Bramhill, D.; Cameron, P.; Eveland, S. S.; Raetz, C. R. H.; Hyland, S. A.; Anderson, M. S. *J. Biol. Chem.* **1995**, *270*, 30384–30391.
12. Barb, A. W.; Zhou, P. *Curr. Pharm. Biotechnol.* **2008**, *9*, 9–15.
13. Jackman, J. E.; Fierke, C. A.; Tumey, L. N.; Pirrung, M.; Uchiyama, T.; Tahir, S. H.; Hindsgaul, O.; Raetz, C. R. H. *J. Biol. Chem.* **2000**, *275*, 11002–11009.
14. Li, X.; Uchiyama, T.; Raetz, C. R. H.; Hindsgaul, O. *Org. Lett.* **2003**, *5*, 539–541.
15. McClerren, A. L.; Endsley, S.; Bowman, J. L.; Andersen, N. H.; Guan, Z.; Rudolph, J.; Raetz, C. R. H. *Biochemistry* **2005**, *44*, 16574–16583.
16. Barb, A. W.; Jiang, L.; Raetz, C. R. H.; Zhou, P. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 18433–18438. S18433/1–S18433/6.
17. Kartha, K. P. R. *Tetrahedron Lett.* **1986**, *27*, 3415–3416.
18. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
19. Shing, T. K. M.; Gillhouley, J. G. *Tetrahedron* **1994**, *50*, 8685–8698.
20. Ferlin, N.; Grassi, D.; Ojeda, C.; Castro, M. J. L.; Grand, E.; Cirelli, A. F.; Kovensky, J. *Carbohydr. Res.* **2008**, *343*, 839–847.
21. Moser, H.; Lu, Q.; Patten, P. A.; Wang, D.; Kasar, R.; Kaldor, S.; Patterson, B. D. *Preparation of Antibacterial Agents*; Achaogen, Inc.: USA, 2008. p 510.
22. Chinchilla, R.; Najera, C. *Chem. Rev. (Washington, DC, US)* **2007**, *107*, 874–922.
23. Remiszewski, S. W.; Sambucetti, L. C.; Atadja, P.; Bair, K. W.; Cornell, W. D.; Green, M. A.; Howell, K. L.; Jung, M.; Kwon, P.; Trogani, N.; Walker, H. *J. Med. Chem.* **2002**, *45*, 753–757.