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C-Triazolyl β-D-furanosides as LpxC inhibitors: stereoselective synthesis and biological evaluation

Sunit Kumar Jana [a,b], Marius Löppenberg [a], Constantin G. Daniliuc [c], Ralph Holl [a,*]

[a] Institut für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität Münster, Corrensstr. 48, D-48149 Münster, Germany
[b] NRW Graduate School of Chemistry, Münster, Germany
[c] Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstr. 40, D-48149 Münster, Germany

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ABSTRACT

C-Triazolyl β-D-furanosides **10a**–**f** were synthesized in a stereocontrolled way, starting from D-mannose. In the key steps of the synthesis a diastereoselective reduction of hemiketal **14** and a Cu(I) catalyzed [3+2]-cycloaddition of central building block **18** with various azides were performed. The synthesized hydroxamic acids were tested for their inhibitory activity against LpxC, a Zn^{2+}-dependent deacetylase playing an important role in the biosynthesis of lipid A and therefore representing an interesting target for the development of novel antibiotics against Gram-negative bacteria. The C-triazolyl glycosides **10a**–**f** did not exhibit antibiotic activity. However, the described synthesis is a versatile way to access C-triazolyl β-D-furanosides bearing all of their substituents at the same side of the tetrahydrofuran ring.

1. Introduction

The 1,2,3-triazole moiety is a prominent structural element in medicinal chemistry. It possesses desirable properties like metabolic stability and the capability of forming hydrogen bonds.[1] The 1,2,3-triazole moiety is often used as mimetic of the peptide bond,[2] but it has also been reported to bioisosterically replace *trans*-olefinic moieties,[3] adenine[4] and pyrazole rings.[5] 1,2,3-Triazoles can be easily accessed by a copper(I)-catalyzed [3+2]-cycloaddition between azides and terminal alkynes, a reaction, which exhibits high selectivity and functional group tolerance.[6] Using combinatorial synthesis, this reaction allows the generation of vast libraries of compounds for high-throughput screening in the search for new pharmacologically active compounds.[7] In fragment-based drug discovery triazoles are used for fragment linkage.[8]

Various biologically active compounds containing a 1,2,3-triazole moiety have been described in the literature, amongst them, the β-lactam antibiotic cefatrizine (**1**), the β-lactamase inhibitor tazobactam (**2**) and sugar-based 1,2,3-triazoles such as the FimH antagonist **3** and the antitumour agent **4** (Fig. 1).[9,10]

Recently we have reported the stereoselective synthesis of hydroxamic acids **7** possessing a C-triazolyl α-furanosidic scaffold, which should serve as LpxC inhibitors (Fig. 3).[11] LpxC is a Zn^{2+}-dependent enzyme, which catalyzes the deacetylation of UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**5**) representing the first irreversible step in the biosynthesis of lipid A (Fig. 2), the membrane anchor of lipopolysaccharide (LPS).[12] LPS is the main component of the outer layer of the outer membrane of Gram-negative bacteria shielding the bacteria from detergents and certain antibiotics. As the inhibition of lipid A biosynthesis is lethal to these bacteria, LpxC inhibitors represent a class of novel antibacterial agents.[13] These inhibitors have the potential to cure even infections caused by multiresistant Gram-negative bacteria, as they exhibit their antibacterial activity via a mechanism of action, which

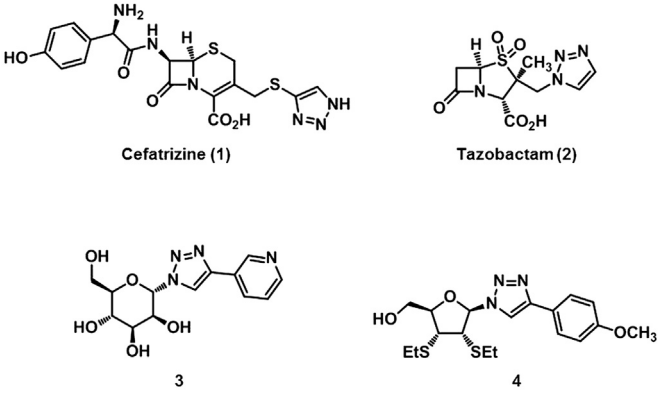

Fig. 1. 1,2,3-Triazole-containing bioactive compounds.

* Corresponding author. Tel.: +49 251 8333372; fax: +49 251 8332144; e-mail address: hollr@uni-muenster.de (R. Holl).

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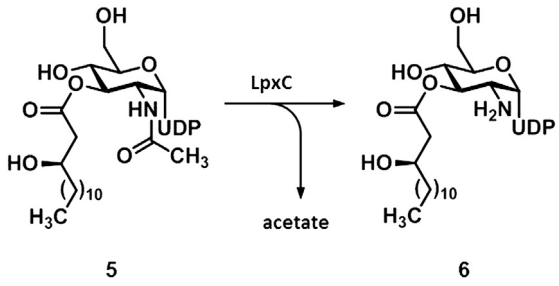


Fig. 2. LpxC catalyzed deacetylation of UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetyl-glucosamine (**5**).

not exhibit any antibiotic activity at all. As two properties were changed at the same time, it is hard to say whether the altered stereochemistry or the replacement of the proximal phenyl ring of **9** by a triazole moiety abolished the antibiotic activity of triazoles **7**. Therefore, in order to solely determine the influence of the introduction of a triazole-containing lipophilic side chain, *C*-triazolyl β-furanosides **10** having the same configuration as **9** should be synthesized.

In this paper we wish to report the synthesis of *C*-triazolyl β-D-furanosides **10** and their biological evaluation as LpxC inhibitors. With the all-*cis* orientation of their substituents at the furanose ring, these compounds represent a class of *C*-triazolyl glycosides, which has not been described in the literature before.

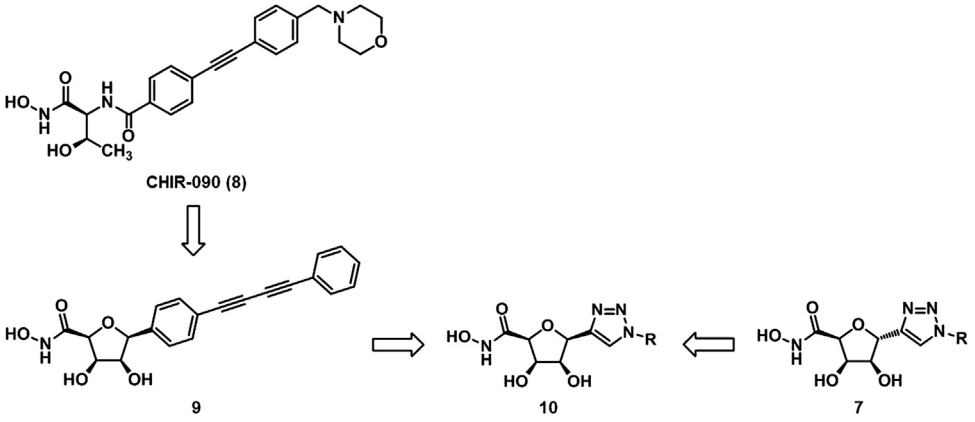
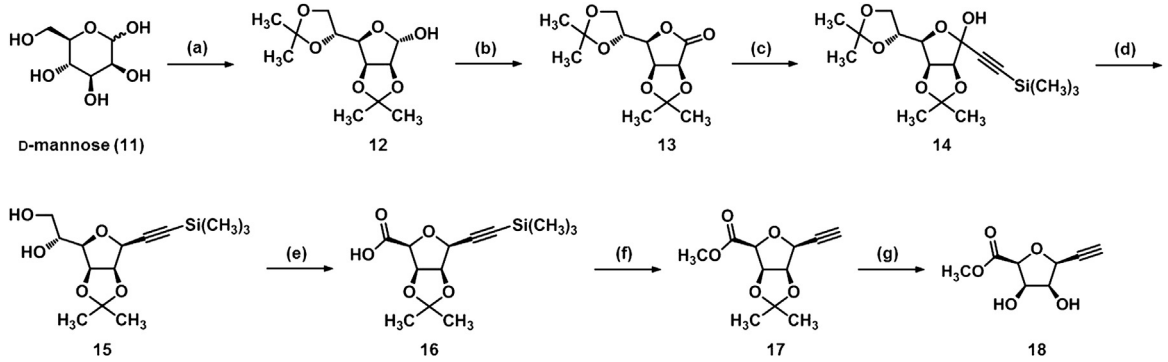


Fig. 3. Chemical structures of reported and planned LpxC inhibitors.

has not been exploited in antibiotic therapy so far. Some LpxC inhibitors have already been described in the literature, like the diphenylacetylene derivative CHIR-090 (**8**, Fig. 3).[14,15] Derived from this hydroxamic acid, which exhibits antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* being comparable to that of ciprofloxacin, we developed *C*-glycosidic compounds such as **9**, which shows weak inhibitory activity against LpxC.[16] In this compound, the amide group of CHIR-090 and the hydroxyethyl moiety of its threonyl group are replaced by a *C*-furanosidic scaffold. The central dihydroxytetrahydrofuran moiety causes conformational restriction of the compound, leading to a defined relative orientation of the hydroxamate moiety, which should complex the Zn^{2+}-ion in the active site, and the lipophilic side chain, which is supposed to bind to the hydrophobic substrate binding tunnel of LpxC. In order to find the optimal spatial orientation of these pharmacophoric groups and thereby improve the biological activity of the compounds, we began to vary the stereochemistry of the *C*-glycosides. However, the synthesized *C*-triazolyl α-furanosides **7** did

2. Synthesis

In order to get access to the designed triazole derivatives, at first, *C*-ethynyl furanoside **18** should be prepared, which represents the key intermediate of the synthesis (Scheme 1). As we have already successfully accomplished the synthesis of the corresponding *C*-aryl β-D-furanosides, our previously reported protocol for the preparation of these *C*-glycosides should also be applied for the synthesis of **18**.[17] Therefore, γ-lactone **13** was prepared in a chiral pool synthesis by reacting D-mannose with acetone in the presence of catalytic amounts of iodine,[18] followed by a Swern oxidation of the resulting lactol **12**. A subsequent nucleophilic attack of the acetylide, formed by deprotonation of trimethylsilyl acetylene with *n*-butyllithium, to lactone **13** gave hemiketal **14**. In the ^{1}H NMR spectrum of **14** in $CDCl_3$ two sets of signals can be observed in a ratio of 3:2, indicating that in solution an equilibrium exists between the two possible anomers. However, the X-ray crystal structure of **14** shows that the compound crystallizes solely as the



Scheme 1. Reagents and conditions: (a) acetone, I_2, rt, 51%; (b) oxalyl chloride, DMSO, −78 °C, then NEt_3, rt, 91%; (c) trimethylsilyl acetylene, *n*-BuLi, THF, −78 °C, 98%; (d) 1. $BF_3{\cdot}OEt_2$, Et_3SiH, H_3CCN, −40 °C, 2. *p*-TsOH, MeOH, rt, 43%; (e) 1. $NaIO_4$, MeOH, rt, 2. $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, *t*-BuOH/H_2O (5:2), rt, 82%; (f) MeI, K_2CO_3, DMF, rt, 76%; (g) $Er(OTf)_3$, MeOH, microwave irradiation, 42%.

(*S*)-configured hemiketal (Fig. 4). The Flack parameter for compound **14** was refined to the value −0.1(1) and confirms the expected configuration of this compound. Hemiketal **14** contains three heterocyclic rings: one furan ring and two dioxolane rings. The tetrahydrofuran ring (O1/C2/C3/C4/C5 atoms) adopts an envelope conformation, with O1 atom lying well out of the plane (by 0.598 Å). The puckering parameters[19] for this tetrahydrofuran derivative ring calculated with PLATON[20] are Q=0.406(2) Å and φ=357.3(1)°. The dioxolane ring (O3/C3/C4/O4/C11 atoms) attached to the furan ring adopts a similar envelope conformation, with C11 atom lying well out of the plane (by 0.411 Å). The puckering parameters are Q=0.269(8) Å and φ=132.0(2)°. The second dioxolane ring is best described as having the twisted conformation about the O6–C15 bond (with Q=0.331(8) Å and φ=349.5(2)°). The absolute configurations at atoms C2, C3, C4, C5 and C14 are *S*, *S*, *S*, *R* and *R*, respectively.

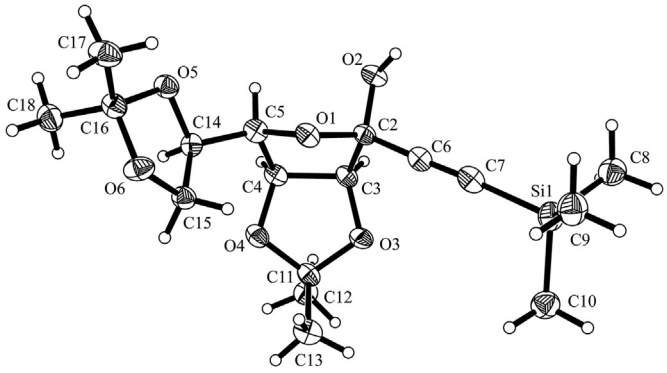


Fig. 4. Crystal structure of hemiketal **14**.

In order to transform hemiketal **14** into a *C*-ethynyl glycoside, the compound was treated with triethylsilane and boron trifluoride etherate. This reduction proceeded in a diastereoselective manner, yielding the corresponding *C*-ethynyl β-D-mannofuranoside, as the hydride of triethylsilane was transferred to the less hindered *Re*-face of the intermediately formed oxocarbenium ion. However, due to the presence of the Lewis acid boron trifluoride etherate, additionally, a partial cleavage of the monocyclic acetonide occurred during the reaction. Therefore, in order to transform the remaining bisacetonide into diol **15**, the crude product of the reduction was treated with catalytic amounts of *p*-toluenesulfonic acid in methanol, giving diol **15** in 43% yield over the two reaction steps.

The desired *C*-ethynyl furanoside **18** should finally be obtained by transforming the glycol moiety of **15** into an ester group. At first, the method, which successfully yielded the epimeric *C*-ethynyl α-furanoside **19** was employed.[11] This method includes a glycol cleavage to obtain an intermediate aldehyde, a subsequent Jones oxidation to yield the corresponding acid and a final esterification using methyl iodide in the presence of K_2CO_3. However, in case of the *C*-ethynyl β-furanoside **15** only very poor yields of ester **17** were obtained. Investigation of the three steps identified the oxidation of the aldehyde as the crucial step. Therefore, instead of using CrO_3 in acidic medium, other methods like the Ag^+-mediated Tollens oxidation, which was performed under basic conditions, were tested. However, these attempts were unsuccessful as well. A possible explanation for the failure of these metal-mediated oxidations might be the formation of a complex between the metal ion and the tetrahydrofuran derivative, which bears all of its substituents at the same side of the tetrahydrofuran ring. Thus, to obtain the desired carboxylic acid **16** an oxidation method, which is not metal-mediated should be employed. The Pinnick oxidation with $NaClO_2$ in the presence of 2-methylbut-2-ene proved to be applicable.[21] So starting with the $NaIO_4$-mediated glycol cleavage of diol **15**, the intermediately formed aldehyde was successfully subjected to a Pinnick oxidation to give carboxylic acid **16**, which was obtained in 82% yield over two reaction steps. Treatment of **16** with iodomethane in the presence of potassium carbonate led to the esterification of the carboxylic acid moiety. As additionally the trimethylsilyl protective group was cleaved in the course of the reaction, the transformation yielded terminal alkyne **17**. The key intermediate **18** could finally be obtained by cleaving the remaining acetonide of **17** with $Er(OTf)_3$ under microwave irradiation. In comparison to its anomer **19**, whose stereochemistry was confirmed by X-ray crystallography,[11] the ^{1}H NMR spectrum of **18** shows clear differences (Fig. 5). Whilst the chemical shift of 2-H is

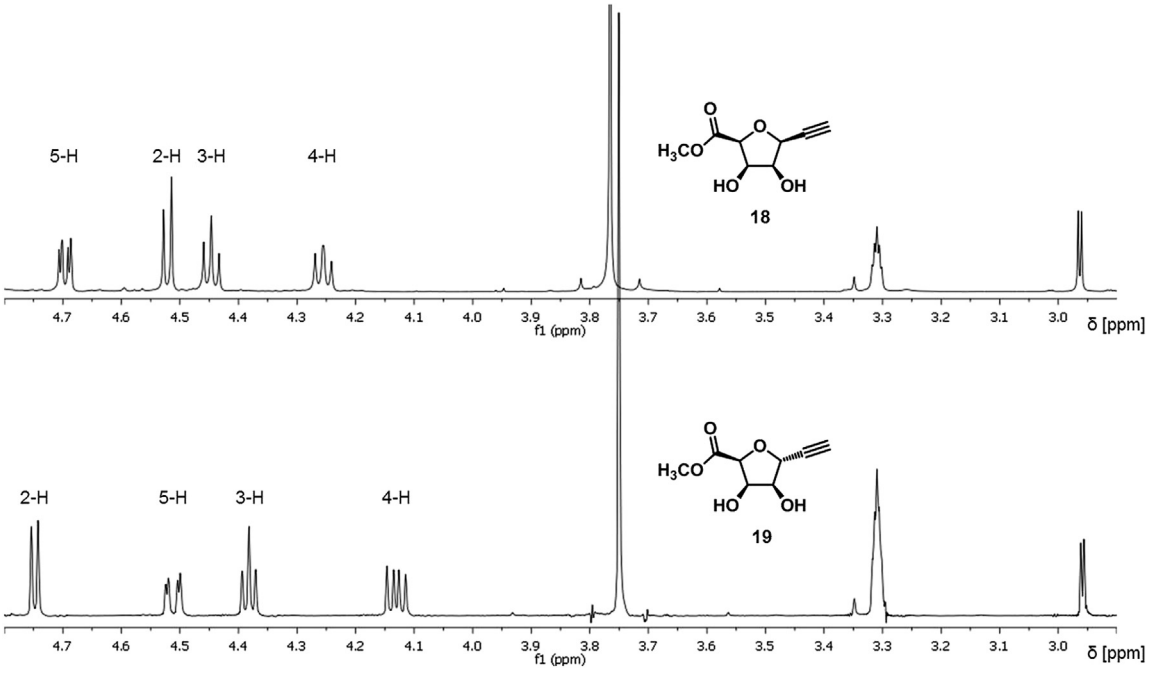


Fig. 5. Comparison of the ^{1}H NMR spectra of the anomers **18** and **19**.

decreased in the spectrum of **18**, the signal of 5-H is shifted downfield due to the altered location of the two protons within the magnetic anisotropy shielding/deshielding cones of the ethynyl group and the carboxyl moiety, respectively.

[3+2]-Cycloadditions of terminal alkyne **18** with several azides (**20a**–**f**) were carried out in the presence of copper(II) sulfate and sodium ascorbate in a 1:1 mixture of water and *tert*-butanol to give a set of triazole derivatives (**21a**–**f**) (Scheme 2).[6] The benzyl derivative **21b** was crystallized from methanol, yielding crystals suitable for X-ray crystal structure analysis. The obtained crystal structure confirmed the (*S*)-configuration at the anomeric center as well as the substitution pattern of the triazole ring (Fig. 6). The tetrahydrofuran ring adopts an envelope conformation, with C4 atom lying well out of the plane (by 0.581 Å). The puckering parameters calculated with PLATON program are Q=0.375(2) Å and φ=278.0(3) for the tetrahydrofuran derivative ring O1/C2/C3/C4/C5. The absolute configurations at atoms C2, C3, C4 and C5 of the five membered ring are *S*, *S*, *R* and *S*, respectively.

In the disc diffusion assays, *E. coli* BL21 (DE3) and the defective *E. coli* D22 strain were grown on agar plates in the presence of filter paper plates containing hydroxamic acids **10a**–**f** as well as CHIR-090 and DMSO serving as positive and negative control, respectively. Neither against *E. coli* BL21 (DE3) nor against *E. coli* D22, being more sensitive towards LpxC inhibition, the triazole derivatives **10a**–**f** showed inhibition of bacterial growth beyond the 6 mm filter discs.

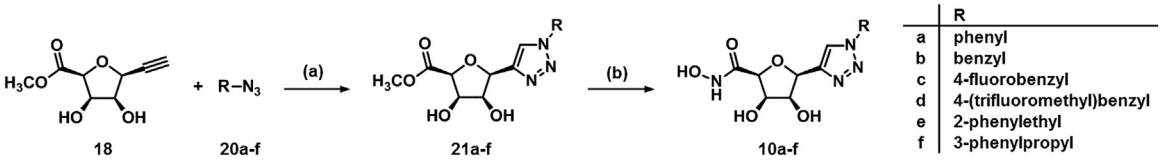
The outcome of the disc diffusion assays matches the results of the LpxC enzyme assay, as none of the *C*-triazolyl β-furanosides **10a**–**f** was able to inhibit the LpxC catalyzed deacetylation of the enzyme's natural substrate **5** even at concentrations up to 200 μM.

4. Conclusion

In a chiral pool synthesis starting from D-mannose, *C*-triazolyl β-D-furanosides **10a**–**f** were synthesized in a stereocontrolled manner. The β-configuration at the anomeric position could be established by a stereoselective reduction of hemiketal **14** with triethylsilane and boron trifluoride etherate. Triazole rings with different substituents were built up by performing [3+2]-cycloadditions of key intermediate **18** with several azides.

The synthesized hydroxamic acids **10a**–**f** did not inhibit the growth of *E. coli* in disc diffusion assays and inhibitory activity against LpxC could not be observed. Apparently, the replacement of the proximal phenyl ring of **9** by a triazole moiety is detrimental for the antibacterial activity of the *C*-glycosides. Compared to the *para*-substituted phenyl ring of **9**, the polar nature of the heterocycle and the slightly bent alignment of its substituents might not be optimal for the binding of the side chains of hydroxamates **10a**–**f** to the hydrophobic tunnel of LpxC.

However, the described reactions offer a convenient route to access diverse *C*-triazolyl β-D-furanosides **10a**–**f** bearing four *cis*-oriented substituents at their tetrahydrofuran ring.



Scheme 2. Reagents and conditions: (a) sodium ascorbate, $CuSO_4 \cdot 5H_2O$, *t*-BuOH/H_2O=1:1, rt, **21a** 78%, **21b** 64%, **21c** 66%, **21d** 60%, **21e** 69%, **21f** 61%; (b) $H_2NOH \cdot HCl$, NaOMe, MeOH, rt, **10a** 44%, **10b** 41%, **10c** 58%, **10d** 70%, **10e** 53%, **10f** 40%.

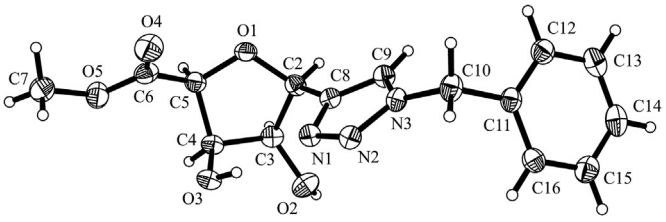


Fig. 6. Crystal structure of triazole derivative **21b**.

The obtained *C*-triazolyl β-furanosides **21a**–**f** were reacted with hydroxylamine hydrochloride and sodium methanolate in methanol. This final aminolysis yielded the desired hydroxamic acids **10a**–**f**.

3. Biological evaluation

In order to characterize the biological activities of *C*-triazolyl β-furanosides **10a**–**f**, an LpxC inhibition assay and disc diffusion assays were performed (Table 1).

Table 1
Results of the agar diffusion clearance assay and the LpxC assay

Compound	R	Zone of inhibition [mm]		Enzyme assay	
		E. coli BL21 (DE3)	*E. coli* D22	IC_{50} [μM]	K_i [μM]
CHIR-090		24.5	30	0.06	0.008
9	*p*-Phenylbutadiynyl	<6	9	32	4.4
10a	Phenyl	<6	<6	>200	—
10b	Benzyl	<6	<6	>200	—
10c	4-Fluorobenzyl	<6	<6	>200	—
10d	4-(Trifluoromethyl) benzyl	<6	<6	>200	—
10e	2-Phenylethyl	<6	<6	>200	—
10f	3-Phenylpropyl	<6	<6	>200	—

5. Experimental section

5.1. Chemistry, general

Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Macherey–Nagel); parentheses include: diameter of the column, length of the column, fraction size, eluent, R_f value. Melting point (mp): Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. Optical rotation α [deg] was determined with a Polarimeter 341 (Perkin–Elmer); path length 1 dm, wavelength 589 nm (sodium D line); the unit of the specific rotation $[\alpha]_D^{20}$ [deg 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 parts per million (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

COSY NMR spectra as well as NOE (nuclear Overhauser effect) difference spectroscopy. IR: IR Prestige-21 (Shimadzu). HRMS: MicrOTOF-QII (Bruker). 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%. X-ray crystal structure analyses: Datasets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (R. W. W. Hooft, Bruker AXS, 2008, Delft, The Netherlands); data reduction Denzo-SMN;[22] absorption correction, Denzo;[23] structure solution SHELXS-97;[24] structure refinement SHELXL-97[25] and graphics, XP (BrukerAXS, 2000). Thermals ellipsoids are shown with 15% probability for compound **14** and with 30% probability for compound **21b**, *R*-values are given for observed reflections, and wR^2 values are given for all reflections. *Exceptions and special features*: In compound **14** one $SiMe_3$ group and one cyclohexane solvent molecule were found disordered over two positions. Several restraints (SADI, SAME, ISOR and SIMU) were used in order to improve refinement stability. CCDC 1001429 (for **14**) and CCDC 1001430 (for **21b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5.2. Synthetic procedures

*5.2.1. (3aS,6R,6aS)-6-[(R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4-[(trimethylsilyl)ethynyl]tetrahydrofuro[3,4-d][1,3]dioxol-4-ol (**14**).* Under nitrogen atmosphere a 2.5 M solution of *n*-BuLi (9.7 mL, 24 mmol) in toluene was added to a solution of trimethylsilyl acetylene (3.1 mL, 22 mmol) in dry THF (20 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. Then a solution of **13** (5.2 g, 20 mmol) in dry THF (20 mL) was added slowly over a period of 30 min. The reaction mixture was stirred at −78 °C for additional 20 min and then quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with water and extracted with ethyl acetate (3×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (4 cm, 15 cm, 30 mL, cyclohexane/ethyl acetate=10:1, R_f=0.23) to give **14** as colourless crystalline solid (7.0 g, 19.6 mmol, 98% yield). Mp=122 °C; $[\alpha]_D^{20}$ +68.3 (*c* 2.4, MeOH); ^{1}H NMR ($CDCl_3$): δ [ppm]=0.20 (s, 9H, $Si(CH_3)_3$), 1.36–1.37 (m, 6×0.4H, CH_3^{Minor}), 1.38 (s, 3×0.6H, CH_3^{Major}), 1.39 (s, 3×0.6H, CH_3^{Major}), 1.45 (s, 3×0.4H, CH_3^{Minor}), 1.46 (s, 3×0.6H, CH_3^{Major}), 1.51 (s, 3×0.4H, CH_3^{Minor}), 1.54 (s, 3×0.6H, CH_3^{Major}), 3.69 (dd, *J*=8.4/3.3 Hz, 0.6H, 6-H^{Major}), 4.01–4.07 (m, 0.4H+1H, 6-H^{Minor}, $OCHCH_2O$ (1H)), 4.10 (dd, *J*=8.8/6.1 Hz, 1H, $OCHCH_2O$), 4.38 (ddd, *J*=8.4/6.0/4.3 Hz, 0.6H, $OCHCH_2O^{Major}$), 4.43 (ddd, *J*=8.4/6.1/4.2 Hz, 0.4H, $OCHCH_2O^{Minor}$), 4.58 (d, *J*=5.7 Hz, 0.4H, 3a-H^{Minor}), 4.60 (d, *J*=5.8 Hz, 0.6H, 3a-H^{Major}), 4.82–4.85 (m, 1H, 6a-H), ratio of anomers: 3 (Major): 2 (Minor); ^{13}C NMR ($CDCl_3$): δ [ppm]=−0.20 (3×0.4C, $Si(CH_3)_3^{Minor}$), −0.18 (3×0.6C, $Si(CH_3)_3^{Major}$), 25.1 (0.6C, CH_3^{Major}), 25.3 (0.6C, CH_3^{Major}), 25.4 (0.4C, CH_3^{Minor}), 25.6 (0.4C, CH_3^{Minor}), 26.0 (0.6C, CH_3^{Major}), 26.4 (0.4C, CH_3^{Minor}), 27.1 (0.6C, CH_3^{Major}), 27.2 (0.4C, CH_3^{Minor}), 67.2 (0.4C, $OCHCH_2O$), 67.4 (0.6C, $OCHCH_2O$), 72.8 (0.6C, $OCHCH_2O$), 73.1 (0.4C, $OCHCH_2O$), 77.4 (0.6C, C-6^{Major}), 79.6 (0.6C, C-$6a^{Major}$), 79.8 (0.4C, C-6^{Minor}), 80.4 (0.4C, C-$6a^{Minor}$), 84.0 (0.6C, C-$3a^{Major}$), 86.9 (0.4C, C-$3a^{Minor}$), 92.1 (0.6C, $C{\equiv}CSi^{Major}$), 92.2 (0.4C, $C{\equiv}CSi^{Minor}$), 97.1 (0.6C, C-4^{Major}), 99.8 (0.4C, C-4^{Minor}), 99.9 (0.4C, $C{\equiv}CSi^{Minor}$), 100.8 (0.6C, $C{\equiv}CSi^{Major}$), 109.5 (0.4C, $C(CH_3)_2^{Minor}$), 109.6 (0.6C, $C(CH_3)_2^{Major}$), 113.8 (0.4C, $C(CH_3)_2^{Minor}$), 113.9 (0.6C, $C(CH_3)_2^{Major}$), ratio of anomers: 3 (Major) : 2 (Minor); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3321, 1369, 1246, 1211, 1165, 1111, 1076, 1042, 1026, 841, 802, 760; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{29}O_6Si$, 357.1728; found, 357.1681; X-ray crystal structure analysis: recrystallization of **14** from cyclohexane gave crystals, which were suitable for X-ray crystal structure analysis. Formula $C_{17}H_{28}O_6Si\cdot C_6H_{12}$, *M*=440.64, colourless crystal, 0.15×0.12×0.02 mm, *a*=6.1119(6), *b*=11.6007(11), *c*=18.6748(15) Å, β=92.469(7)°, *V*=1322.9(2) $Å^3$, ρ_{calcd}=1.106 g cm^{-3}, μ=1.041 mm^{-1}, empirical absorption correction (0.859≤*T*≤0.979), *Z*=2, monoclinic, space group $P2_1$ (No. 4), λ=1.54178 Å, *T*=223(2) K, ω and φ scans, 9048 reflections collected (±*h*, ±*k*, ±*l*), [(sin θ)/λ]=0.60 $Å^{-1}$, 3674 independent (R_{int}=0.122) and 2137 observed reflections [$I>2\sigma(I)$], 359 refined parameters, *R*=0.104, wR^2=0.312, max. (min.) residual electron density 0.33 (−0.25) e $Å^{-3}$, the hydrogen atoms were calculated and refined as riding atoms. Flack parameter: −0.1(1).

*5.2.2. (R)-1-{(3aS,4R,6S,6aR)-2,2-Dimethyl-6-[(trimethylsilyl)ethynyl]tetrahydrofuro[3,4-d][1,3]dioxol-4-yl}ethane-1,2-diol (**15**).* Under N_2 atmosphere triethylsilane (2.1 mL, 13 mmol) and $BF_3\cdot OEt_2$ (1.5 mL, 12 mmol) were added to a solution of **14** (3.6 g, 10 mmol) in dry acetonitrile (50 mL) at −40 °C and the reaction mixture was stirred at this temperature for 1 h. Then a saturated aqueous solution of K_2CO_3 (5 mL) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was dissolved in methanol (100 mL) and *p*-toluenesulfonic acid monohydrate (380 mg, 2.0 mmol) was added. The reaction mixture was stirred at room temperature overnight. Then a saturated aqueous solution of $NaHCO_3$ (15 mL) was added and mixture was extracted with ethyl acetate (3×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (4 cm, 15 cm, 30 mL, cyclohexane/ethyl acetate=1:1, R_f=0.26) to give **15** as colourless crystalline solid (1.3 g, 4.3 mmol, 43% yield). Mp=106 °C; $[\alpha]_D^{20}$ +85.0 (*c* 2.6, MeOH); ^{1}H NMR ($CDCl_3$): δ [ppm]=0.18 (s, 9H, $Si(CH_3)_3$), 1.37 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.36 (br s, 1H, CH_2OH), 2.98 (br d, *J*=4.9 Hz, 1H, CHO*H*), 3.50 (dd, *J*=8.2/3.6 Hz, 1H, 4-H), 3.73 (dd, *J*=11.4/5.3 Hz, 1H, $OCHCH_2O$), 3.87 (dd, *J*=11.4/2.5 Hz, 1H, $OCHCH_2O$), 4.03–4.10 (m, 1H, $OCHCH_2O$), 4.24 (d, *J*=4.1 Hz, 1H, 6-H), 4.71 (dd, *J*=6.0/4.1 Hz, 1H, 6a-H), 4.81 (dd, *J*=6.0/3.6 Hz, 1H, 3a-H); ^{13}C NMR ($CDCl_3$): δ [ppm]=−0.1 (3C, $Si(CH_3)_3$), 25.5(1C, CH_3), 26.2 (1C, CH_3), 64.4 (1C, $OCHCH_2O$), 69.9 (1C, $OCHCH_2O$), 73.3 (1C, C-6), 80.8 (1C, C-4), 81.2 (1C, C-3a), 81.6 (1C, C-6a), 93.8 (1C, C≡*C*Si), 98.1 (1C, *C*≡CSi), 113.4 (1C, $C(CH_3)_2$); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3375, 2955, 1416, 1373, 1250, 1211, 1080, 1015, 841, 760; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{25}O_5Si$, 301.1466; found, 301.1491; HPLC (method 1): t_R=16.2 min, purity 99.9%.

*5.2.3. (3aR,4S,6S,6aR)-2,2-Dimethyl-6-[(trimethylsilyl)ethynyl]tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (**16**).* Under N_2 atmosphere $NaIO_4$ (710 mg, 3.3 mmol) was added to a solution of **15** (450 mg, 1.5 mmol) in methanol (15 mL) and stirred for 4 h until TLC showed complete conversion. Then the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3×). The combined organic phases were dried with Na_2SO_4,

filtered and the solvent was removed in vacuo. The crude aldehyde was dissolved in a mixture of *tert*-butanol and water (5:2, 10 mL). To this solution NaH_2PO_4 (900 mg, 7.5 mmol), 2-methylbut-2-ene (0.80 mL, 7.5 mmol) and sodium chlorite 80% (680 mg, 6.0 mmol) were added. The reaction mixture was stirred at room temperature for 30 min and then the reaction was quenched by the addition of a saturated aqueous solution of Na_2SO_3 (2 mL). Then the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed in vacuo to give **16** as colourless crystalline solid (350 mg, 1.2 mmol, 82% yield). Mp=136 °C; $[\alpha]_D^{20}$ +25.0 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$): δ [ppm]=0.20 (s, 9H, Si(C*H*$_3$)$_3$), 1.36 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 4.25 (d, *J*=4.0 Hz, 1H, 4-H), 4.38 (d, *J*=4.2 Hz, 1H, 6-H), 4.77 (dd, *J*=5.9/4.2 Hz, 1H, 6a-H), 5.00 (dd, *J*=5.9/4.0 Hz, 1H, 3a-H); ^{13}C NMR ($CDCl_3$): δ [ppm]=−0.2 (3C, Si(CH_3)$_3$), 25.6 (1C, CH_3), 26.2 (1C, CH_3), 73.6 (1C, C-6), 80.1 (1C, C-4), 81.2 (1C, C-6a), 81.4 (1C, C-3a), 95.1 (1C, C≡*C*Si(CH_3)$_3$), 96.9 (1C, *C*≡CSi(CH_3)$_3$) 114.3 (1C, *C*(CH_3)$_2$), 169.0 (1C, CO_2H); IR (neat): $\tilde{\nu}$ [cm^{-1}]=2955, 1728, 1381, 1246, 1211, 1115, 1080, 1030, 841, 760; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{21}O_5Si$, 285.1153; found, 285.1164.

*5.2.4. (3aR,4S,6S,6aR)-Methyl 6-ethynyl-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**17**).* Under N_2 atmosphere K_2CO_3 (690 mg, 5.0 mmol) and methyl iodide (0.31 mL, 5.0 mmol) were added to a solution of **16** (280 mg, 1.0 mmol) in dry DMF (10 mL), and the mixture was stirred overnight. Then the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (2 cm, 15 cm, 10 mL, cyclohexane/ethyl acetate=2:1, R_f=0.33) to give **17** as colourless crystalline solid (170 mg, 0.76 mmol, 76% yield). Mp=87 °C; $[\alpha]_D^{20}$ +19.0 (*c* 1.2, MeOH); ^{1}H NMR ($CDCl_3$): δ [ppm]=1.36 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.64 (d, *J*=2.3 Hz, 1H, C≡C*H*), 3.82 (s, 3H, CO_2CH_3), 4.21 (d, *J*=4.2 Hz, 1H, 4-H), 4.30 (dd, *J*=3.8/2.3 Hz, 1H, 6-H), 4.78 (dd, *J*=5.9/3.8 Hz, 1H, 6a-H), 4.99 (dd, *J*=5.9/4.2 Hz, 1H, 3a-H); ^{13}C NMR ($CDCl_3$): δ [ppm]=25.7 (1C, CH_3), 26.1 (1C, CH_3), 52.5 (1C, CO_2CH_3), 72.4 (1C, C-6), 76.3 (1C, *C*≡CH), 77.0 (1C, C≡*C*H), 80.8 (1C, C-4), 81.2 (1C, C-6a), 81.6 (1C, C-3a), 114.2 (1C, *C*(CH_3)$_2$), 167.0 (1C, *C*O_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3233, 2974, 1748, 1443, 1377, 1269, 1227, 1200, 1107, 1076, 1042, 976, 903, 853, 737; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{15}O_5$, 227.0914; found, 227.0920.

*5.2.5. (2S,3R,4S,5S)-Methyl 5-ethynyl-3,4-dihydroxytetrahydrofuran-2-carboxylate (**18**).* $Er(OTf)_3$ (18 mg, 0.03 mmol) was added to a solution of **17** (110 mg, 0.5 mmol) in methanol (2 mL) in a 10 mL microwave reaction vessel. The reaction mixture was stirred at 110 °C for 60 min at 200 psi and 100 W. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (2 cm, 15 cm, 10 mL, dichloromethane/methanol=30:1, R_f=0.25) to give **18** as colourless oil (39 mg, 0.21 mmol, 42% yield). $[\alpha]_D^{20}$ +4.4 (*c* 1.7, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=2.96 (d, *J*=2.3 Hz, 1H, C≡C*H*), 3.77 (s, 3H, CO_2CH_3), 4.25 (dd, *J*=6.0/5.2 Hz, 1H, 4-H), 4.45 (t, *J*=5.3 Hz, 1H, 3-H), 4.52 (d, *J*=5.4 Hz, 1H, 2-H), 4.70 (dd, *J*=6.0/2.3 Hz, 1H, 5-H); ^{13}C NMR (CD_3OD): δ [ppm]=52.5 (1C, CO_2CH_3), 73.1 (1C, C-5), 73.2 (1C, C-4), 73.4 (1C, C-3), 78.1 (1C, C≡*C*H), 79.8 (1C, *C*≡CH), 81.4 (1C, C-2), 171.6 (1C, *C*O_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3437, 3271, 1740, 1439, 1219, 1123, 1057, 741, 660; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_8H_{11}O_5$, 187.0601; found, 187.0606.

*5.2.6. (2S,3R,4S,5S)-Methyl 3,4-dihydroxy-5-(1-phenyl-1H-1,2,3-triazol-4-yl)tetrahydrofuran-2-carboxylate (**21a**).* 1-Azidobenzene (110 mg, 0.96 mmol) was added to a solution of **18** (90 mg, 0.48 mmol) in a 1:1 mixture of *t*-BuOH and H_2O (15 mL), followed by sodium ascorbate (19 mg, 0.096 mmol) and copper sulfate pentahydrate (12 mg, 0.048 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (2 cm, 15 cm, 10 mL, dichloromethane/methanol=20:1, R_f=0.34) to give **21a** as colourless solid (120 mg, 0.38 mmol, 78% yield). Mp=142 °C; $[\alpha]_D^{20}$ −31.0 (*c* 1.4, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=3.80 (s, 3H, CO_2CH_3), 4.53 (dd, *J*=6.1/5.0 Hz, 1H, 4-H), 4.59–4.62 (m, 1H, 3-H), 4.69 (d, *J*=5.5 Hz, 1H, 2-H), 5.30 (d, *J*=6.1 Hz, 1H, 5-H), 7.46–7.51 (m, 1H, 4″-H_{phenyl}), 7.55–7.60 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.81–7.85 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 8.56 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=52.5 (1C, CO_2CH_3), 73.3 (1C, C-4), 74.3 (1C, C-3), 78.0 (1C, C-5), 81.4 (1C, C-2), 121.6 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 124.8 (1C, C-5′$_{triazol}$), 130.0 (1C, C-4″$_{phenyl}$), 130.9 (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 138.5 (1C, C-1″$_{phenyl}$), 147.2 (1C, C-4′$_{triazol}$), 172.1 (1C, *C*O_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3402, 1751, 1597, 1501, 1439, 1215, 1080, 1042, 760, 691; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{16}N_3O_5$, 306.1084; found, 306.1103; HPLC (method 1): t_R=10.4 min, purity 98.2%.

*5.2.7. (2S,3R,4S,5S)-Methyl 5-(1-benzyl-1H-1,2,3-triazol-4-yl)-3,4-dihydroxytetrahydrofuran-2-carboxylate (**21b**).* (Azidomethyl)benzene (220 mg, 1.7 mmol) was added to a solution of **18** (150 mg, 0.81 mmol) in a 1:1 mixture of *t*-BuOH and H_2O (20 mL), followed by sodium ascorbate (34 mg, 0.17 mmol) and copper sulfate pentahydrate (21 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (2 cm, 15 cm, 10 mL, dichloromethane/methanol=30:1, R_f=0.22) to give **21b** as colourless solid (160 mg, 0.51 mmol, 64% yield). Mp=141 °C; $[\alpha]_D^{20}$ −28.7 (*c* 1.4, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=3.75 (s, 3H, CO_2CH_3), 4.41 (dd, *J*=5.9/5.0 Hz, 1H, 4-H), 4.56 (dd, *J*=5.6/5.0 Hz, 1H, 3-H), 4.62 (d, *J*=5.6 Hz, 1H, 2-H), 5.18 (d, *J*=5.9 Hz, 1H, 5-H), 5.56 (d, *J*=14.9 Hz, 1H, CH_2Ph), 5.61 (d, *J*=14.9 Hz, 1H, CH_2Ph), 7.29–7.41 (m, 5H, H_{phenyl}), 8.06 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=52.4 (1C, CO_2CH_3), 55.0 (1C, CH_2Ph), 73.1 (1C, C-4), 74.2 (1C, C-3), 78.1 (1C, C-5), 81.3 (1C, C-2), 126.8 (1C, C-5′$_{triazol}$), 129.2 (2C, C_{phenyl}), 129.5 (1C, C_{phenyl}), 130.0 (2C, C_{phenyl}), 136.8 (1C, C_{phenyl}), 146.4 (1C, C-4′$_{triazol}$), 172.1 (1C, *C*O_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3468, 3267, 1732, 1435, 1250, 1107, 1030, 964, 841, 729; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{18}N_3O_5$ 320.1241; found, 320.1248; HPLC (method 1): t_R=11.0 min, purity 96.6%; X-ray crystal structure analysis: recrystallization of **21b** from methanol gave crystals, which were suitable for X-ray crystal structure analysis. Formula $C_{15}H_{17}N_3O_5$, *M*=319.32, colourless crystal, 0.22×0.16×0.13 mm, *a*=5.7872(3), *b*=11.5403(6), *c*=22.5145(11) Å, *V*=1503.6(1) Å^3, ρ_{calcd}=1.411 g cm^{-3}, μ=0.904 mm^{-1}, empirical absorption correction ($0.825 \le T \le 0.891$), *Z*=4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ=1.54178 Å, *T*=223(2) K, ω and φ scans, 5205 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ)/λ]=0.60 Å^{-1}, 2478 independent (R_{int}=0.030) and 2414 observed reflections [$I>2\sigma(I)$], 217 refined parameters, *R*=0.030, wR^2=0.079, max. (min.) residual electron density 0.11 (−0.10) e Å^{-3}, the hydrogen atoms at O2 and O3 were refined freely, but with O–H distance restraints; others were calculated and refined as riding atoms. Flack parameter: −0.1(2).

*5.2.8. (2S,3R,4S,5S)-Methyl 5-[1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylate (**21c**).* 1-(Azidomethyl)-4-fluorobenzene (180 mg, 1.2 mmol) was added to

a solution of **18** (110 mg, 0.59 mmol) in a 1:1 mixture of *t*-BuOH and H_2O (15 mL), followed by sodium ascorbate (23 mg, 0.12 mmol) and copper sulfate pentahydrate (15 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (2 cm, 15 cm, 10 mL, dichloromethane/methanol=20:1, R_f=0.35) to give **21c** as colourless solid (130 mg, 0.39 mmol, 66% yield). Mp=132 °C; $[\alpha]_D^{20}$ −20.7 (*c* 1.6, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=3.76 (s, 3H, CO_2CH_3), 4.42 (dd, *J*=5.9/5.1 Hz, 1H, 4-H), 4.54–4.58 (m, 1H, 3-H), 4.62 (d, *J*=5.6 Hz, 1H, 2-H), 5.19 (d, *J*=6.0 Hz, 1H, 5-H), 5.58 (s, 2H, CH_2Ph), 7.07–7.13 (m, 2H, 3″-$H_{4\text{-fluorophenyl}}$, 5″-$H_{4\text{-fluorophenyl}}$), 7.37–7.42 (m, 2H, 2″-$H_{4\text{-fluorophenyl}}$, 6″-$H_{4\text{-fluorophenyl}}$), 8.07 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR ($CD_3OD$): δ [ppm]=52.4 (1C, CO_2CH_3), 54.1 (1C, CH_2Ph), 73.1 (1C, C-4), 74.2 (1C, C-3), 78.1 (1C, C-5), 81.3 (1C, C-2), 116.7 (d, *J*=22.0 Hz, 2C, C-3″$_{4\text{-fluorophenyl}}$, C-5″$_{4\text{-fluorophenyl}}$), 126.7 (1C, C-5′$_{triazol}$), 131.4 (d, *J*=8.4 Hz, 2C, C-2″$_{4\text{-fluorophenyl}}$, C-6″$_{4\text{-fluorophenyl}}$), 132.9 (d, *J*=3.2 Hz, 1C, C-1″$_{4\text{-fluorophenyl}}$), 146.5 (1C, C-4′$_{triazol}$), 164.2 (d, *J*=246 Hz, 1C, C-4″$_{4\text{-fluorophenyl}}$), 172.1 (1C, CO_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3471, 2970, 1732, 1512, 1435, 1288, 1227, 1107, 1061, 1042, 968, 837, 772; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{17}FN_3O_5$, 338.1147; found, 338.1107; HPLC (method 1): t_R=11.7 min, purity 97.3%.

*5.2.9. (2S,3R,4S,5S)-Methyl 3,4-dihydroxy-5{1-[4-(trifluoromethyl) benzyl]-1H-1,2,3-triazol-4-yl}tetrahydrofuran-2-carboxylate (**21d**).* 1-(Azidomethyl)-4-(trifluoromethyl)benzene (220 mg, 1.1 mmol) was added to a solution of **18** (100 mg, 0.54 mmol) in a 1:1 mixture of *t*-BuOH and H_2O (15 mL), followed by sodium ascorbate (21 mg, 0.11 mmol) and copper sulfate pentahydrate (14 mg, 0.054 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (2 cm, 15 cm, 10 mL, dichloromethane/methanol=20:1, R_f=0.34) to give **21d** as colourless solid (130 mg, 0.32 mmol, 60% yield). Mp=159 °C; $[\alpha]_D^{20}$ −20.8 (*c* 2.1, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=3.76 (s, 3H, CO_2CH_3), 4.44 (dd, *J*=6.0/5.0 Hz, 1H, 4-H), 4.56 (dd, *J*=5.6/5.0 Hz, 1H, 3-H), 4.64 (d, *J*=5.6 Hz, 1H, 2-H), 5.21 (d, *J*=6.0 Hz, 1H, 5-H), 5.71 (s, 2H, CH_2Ph), 7.49–7.52 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 7.66–7.69 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 8.13 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=52.4 (1C, CO_2CH_3), 54.2 (1C, CH_2Ph), 73.2 (1C, C-4), 74.2 (1C, C-3), 78.1 (1C, C-5), 81.3 (1C, C-2), 125.5 (q, *J*=271 Hz, 1C, CF_3), 126.8 (q, *J*=3.8 Hz, 2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 127.1 (1C, C-5′$_{triazol}$), 129.7 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 131.5 (q, *J*=32.1 Hz, 1C, C-4″$_{phenyl}$), 141.3 (1C, C-1″$_{phenyl}$), 146.7 (1C, C-4′$_{triazol}$), 172.1 (1C, CO_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3302, 2959, 2901, 1759, 1439, 1327, 1219, 1107, 1065, 1018, 964, 926, 826, 748; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{17}F_3N_3O_5$, 388.1115; found, 388.1131; HPLC (method 1): t_R=15.1 min, purity 97.4%.

*5.2.10. (2S,3R,4S,5S)-Methyl 3,4-dihydroxy-5-(1-phenethyl-1H-1,2,3-triazol-4-yl)tetrahydrofuran-2-carboxylate (**21e**).* (2-Azidoethyl) benzene (170 mg, 1.2 mmol) was added to a solution of **18** (110 mg, 0.59 mmol) in a 1:1 mixture of *t*-BuOH and H_2O (15 mL), followed by sodium ascorbate (23 mg, 0.12 mmol) and copper sulfate pentahydrate (15 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (Ø=2 cm, *h*=15 cm, *V*=10 mL, dichloromethane/methanol=20:1, R_f=0.38) to give **21e** as colourless solid (140 mg, 0.41 mmol, 69% yield). Mp=117 °C; $[\alpha]_D^{20}$ −14.9 (*c* 1.8, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=3.17–3.25 (m, 2H, CH_2CH_2Ph), 3.77 (s, 3H, CO_2CH_3), 4.42 (dd, *J*=6.0/5.0 Hz, 1H, 4-H), 4.55–4.57 (m, 1H, 3-H), 4.61–4.64 (m, 3H, CH_2CH_2Ph, 2-H), 5.17 (d, *J*=6.0 Hz, 1H, 5-H), 7.16–7.18 (m, 2H, 2″-H_{phenyl}, 5″-H_{phenyl}), 7.19–7.22 (m, 1H, 4″-H_{phenyl}), 7.25–7.28 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.93 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=37.5 (1C, CH_2CH_2Ph), 52.5 (1C, CO_2CH_3), 52.7 (1C, CH_2CH_2Ph), 73.2 (1C, C-4), 74.2 (1C, C-3), 78.1 (1C, C-5), 81.2 (1C, C-2), 126.7 (1C, C-5′$_{triazol}$), 127.9 (1C, C-4″$_{phenyl}$), 129.7 (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 129.9 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 138.7 (1C, C-1″$_{phenyl}$), 146.0 (1C, C-4′$_{triazol}$), 172.1 (1C, CO_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3441, 1751, 1439, 1404, 1219, 1146, 1115, 1057, 964, 922, 856, 733, 694; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{20}N_3O_5$, 334.1397; found, 334.1413; HPLC (method 1): t_R=12.3 min, purity 96.6%.

*5.2.11. (2S,3R,4S,5S)-Methyl 3,4-dihydroxy-5-[1-(3-phenylpropyl)-1H-1,2,3-triazol-4-yl]tetrahydrofuran-2-carboxylate (**21f**).* (3-Azidopropyl)benzene (190 mg, 1.2 mmol) was added to a solution of **18** (110 mg, 0.59 mmol) in a 1:1 mixture of *t*-BuOH and H_2O (15 mL), followed by sodium ascorbate (23 mg, 0.12 mmol) and copper sulfate pentahydrate (157 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (2 cm, 15 cm, 10 mL, dichloromethane/methanol=20:1, R_f=0.38) to give **21f** as colourless oil (130 mg, 0.36 mmol, 61% yield). $[\alpha]_D^{20}$ −10.6 (*c* 2.2, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=2.20–2.26 (m, 2H, $CH_2CH_2CH_2Ph$), 2.63–2.66 (m, 2H, $CH_2CH_2CH_2Ph$), 3.78 (s, 3H, CO_2CH_3), 4.39 (t, *J*=7.1 Hz, 2H, $CH_2CH_2CH_2Ph$), 4.45 (dd, *J*=5.9/5.1 Hz, 1H, 4-H), 4.58 (t, *J*=5.3 Hz, 1H, 3-H), 4.65 (d, *J*=5.6 Hz, 1H, 2-H), 5.21 (d, *J*=6.1 Hz, 1H, 5-H), 7.16–7.20 (m, 1H, H_{phenyl}), 7.21–7.23 (m, 2H, H_{phenyl}), 7.26–7.30 (m, 2H, H_{phenyl}), 8.07 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=33.0 (1C, $CH_2CH_2CH_2Ph$), 33.4 (1C, $CH_2CH_2CH_2Ph$), 50.7 (1C, $CH_2CH_2CH_2Ph$), 52.5 (1C, CO_2CH_3), 73.2 (1C, C-4), 74.2 (1C, C-3), 78.1 (1C, C-5), 81.3 (1C, C-2), 126.7 (1C, C-5′$_{triazol}$), 127.2 (1C, C_{phenyl}), 129.5 (4C, C_{phenyl}), 142.0 (1C, C_{phenyl}), 146.1 (1C, C-4′$_{triazol}$), 172.1 (1C, CO_2CH_3); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3406, 2951, 1755, 1497, 1439, 1215, 1119, 1080, 745, 702; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{22}N_3O_5$ 348.1554; found, 348.1563; HPLC (method 1): t_R=14.0 min, purity 95.6%.

*5.2.12. (2S,3R,4S,5S)-N,3,4-Trihydroxy-5-(1-phenyl-1H-1,2,3-triazol-4-yl)tetrahydrofuran-2-carboxamide (**10a**).* Hydroxylamine hydrochloride (120 mg, 1.8 mmol) and a 2.0 M solution of sodium methoxide in methanol (0.88 mL, 1.8 mmol) were added to a solution of **21a** (110 mg, 0.35 mmol) in dry methanol (5 mL). The reaction mixture was stirred at ambient temperature for 20 h until TLC showed complete conversion of the ester. The reaction mixture was acidified with 1.0 M HCl to pH 5–6. Then the mixture was extracted with ethyl acetate (3×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was dried in vacuo. The crude mixture was purified by flash column chromatography (1 cm, 15 cm, 5 mL, dichloromethane/methanol=9:1, R_f=0.29) to give **10a** as colourless crystalline solid (47 mg, 0.15 mmol, 44%). Mp=56 °C; $[\alpha]_D^{20}$ −16.9 (*c* 1.1, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=4.45 (dd, *J*=5.6/4.8 Hz, 1H, 4-H), 4.53 (d, *J*=5.8 Hz, 1H, 2-H), 4.63 (dd, *J*=5.8/4.8 Hz, 1H, 3-H), 5.30 (d, *J*=5.6 Hz, 1H, 5-H), 7.47–7.52 (m, 1H, 4″-H_{phenyl}), 7.56–7.61 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.83–7.87 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 8.55 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=73.6 (1C, C-4), 74.2 (1C, C-3), 78.2 (1C, C-5), 81.1 (1C, C-2), 121.6 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 124.2 (1C, C-5′$_{triazol}$), 130.1 (1C, C-4″$_{phenyl}$), 130.9 (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 138.5 (1C, C-1″$_{phenyl}$), 146.9 (1C, C-4′$_{triazol}$), 168.9 (1C,

CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3206, 2986, 2901, 1663, 1501, 1238, 1134, 1053, 756, 691; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{15}N_4O_5$, 307.1037; found, 307.1067; HPLC (method 2): t_R=12.6 min, purity 96.4%.

*5.2.13. (2S,3R,4S,5S)-5-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N,3,4-trihydroxytetrahydrofuran-2-carboxamide (**10b**).* Hydroxylamine hydrochloride (87 mg, 1.3 mmol) and a 2.0 M solution of sodium methoxide in methanol (0.63 mL, 1.3 mmol) were added to a solution of **21b** (80 mg, 0.25 mmol) in dry methanol (10 mL). The reaction mixture was stirred at ambient temperature for 16 h until TLC showed complete conversion of the ester. The reaction mixture was evaporated and purified by flash column chromatography (1 cm, 15 cm, 5 mL, dichloromethane/methanol=9:1, R_f=0.26) to give **10b** as colourless solid (33 mg, 0.10 mmol, 41% yield). Mp=50 °C; $[\alpha]_D^{20}$ −6.2 (*c* 1.3, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=4.33 (t, *J*=5.0 Hz, 1H, 4-H), 4.46 (d, *J*=6.1 Hz, 1H, 2-H), 4.60 (dd, *J*=6.0/4.8 Hz, 1H, 3-H), 5.19 (d, *J*=5.3 Hz, 1H, 5-H), 5.59 (s, 2H, CH_2Ph), 7.32−7.39 (m, 5H, H_{phenyl}), 8.03 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=55.0 (1C, CH_2Ph), 73.5 (1C, C-4), 74.1 (1C, C-3), 78.3 (1C, C-5), 80.8 (1C, C-2), 126.0 (1C, C-5′$_{triazol}$), 129.2 (2C, C_{phenyl}), 129.5 (1C, C_{phenyl}), 130.0 (2C, C_{phenyl}), 136.7 (1C, C_{phenyl}), 146.1 (1C, C-4′$_{triazol}$), 168.9 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3202, 1659, 1454, 1323, 1227, 1123, 1057, 1026, 718; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{17}N_4O_5$ 321.1193; found, 321.1200; HPLC (method 2): t_R=12.6 min, purity 95.4%.

*5.2.14. (2S,3R,4S,5S)-5-[1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl]-N,3,4-trihydroxytetrahydrofuran-2-carboxamide (**10c**).* Hydroxylamine hydrochloride (100 mg, 1.5 mmol) and a 2.0 M solution of sodium methoxide in methanol (0.74 mL, 1.5 mmol) were added to a solution of **21c** (100 mg, 0.30 mmol) in dry methanol (10 mL). The reaction mixture was stirred at ambient temperature for 16 h until TLC showed complete conversion of the ester. The reaction mixture was evaporated and purified by flash column chromatography (1 cm, 15 cm, 5 mL, dichloromethane/methanol=9:1, R_f=0.26) to give **10c** as colourless solid (58 mg, 0.17 mmol, 58% yield). Mp=77 °C (decomposition); $[\alpha]_D^{20}$ −10.2 (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=4.33 (t, *J*=5.0 Hz, 1H, 4-H), 4.46 (d, *J*=6.1 Hz, 1H, 2-H), 4.60 (dd, *J*=6.0/4.7 Hz 1H, 3-H), 5.19 (d, *J*=5.3 Hz, 1H, 5-H), 5.58 (s, 2H, CH_2Ph), 7.07−7.14 (m, 2H, 3″-$H_{4\text{-fluorophenyl}}$, 5″-$H_{4\text{-fluorophenyl}}$), 7.37−7.42 (m, 2H, 2″-$H_{4\text{-fluorophenyl}}$, 6″-$H_{4\text{-fluorophenyl}}$), 8.04 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR ($CD_3OD$): δ [ppm]=54.2 (1C, CH_2Ph), 73.5 (1C, C-4), 74.1 (1C, C-3), 78.2 (1C, C-5), 80.8 (1C, C-2), 116.7 (d, *J*=22.0 Hz, 2C, C-3″$_{4\text{-fluorophenyl}}$, C-5″$_{4\text{-fluorophenyl}}$), 126.0 (1C, C-5′$_{triazol}$), 131.4 (d, *J*=8.4 Hz, 2C, C-2″$_{4\text{-fluorophenyl}}$, C-6″$_{4\text{-fluorophenyl}}$), 132.9 (d, *J*=3.2 Hz, 1C, C-1″$_{4\text{-fluorophenyl}}$), 146.2 (1C, C-4′$_{triazol}$), 164.2 (d, *J*=246 Hz, 1C, C-4″$_{4\text{-fluorophenyl}}$), 168.9 (1C, CO_2NHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3213, 1655, 1508, 1223, 1126, 1057, 1018, 822, 772; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{16}FN_4O_5$, 339.1099; found, 339.1127; HPLC (method 2): t_R=13.1 min, purity 96.4%.

*5.2.15. (2S,3R,4S,5S)-N,3,4-Trihydroxy-5-{1-[4-(trifluoromethyl)benzyl]-1H-1,2,3-triazol-4-yl}tetrahydrofuran-2-carboxamide (**10d**).* Hydroxylamine hydrochloride (90 mg, 1.3 mmol) and a 2.0 M solution of sodium methoxide in methanol (0.63 mL, 1.3 mmol) were added to a solution of **21d** (100 mg, 0.26 mmol) in dry methanol (4 mL). The reaction mixture was stirred at ambient temperature for 16 h until TLC showed complete conversion of the ester. The reaction mixture was evaporated and purified by flash column chromatography (1 cm, 15 cm, 5 mL, dichloromethane/methanol=9:1, R_f=0.26) to give **10d** as colourless solid (70 mg, 0.18 mmol, 70% yield). Mp=88 °C; $[\alpha]_D^{20}$ −12.2 (*c* 1.3, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=4.35 (t, *J*=5.0 Hz, 1H, 4-H), 4.47 (d, *J*=6.0 Hz, 1H, 2-H), 4.60 (dd, *J*=6.0/4.8 Hz, 1H, 3-H), 5.21 (d, *J*=5.3 Hz, 1H, 5-H), 5.71 (s, 2H, CH_2Ph), 7.49−7.53 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 7.66−7.70 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 8.10 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=54.2 (1C, CH_2Ph), 73.6 (1C, C-4), 74.1 (1C, C-3), 78.2 (1C, C-5), 80.9 (1C, C-2), 125.5 (q, *J*=271 Hz, 1C, CF_3), 126.4 (1C, C-5′$_{triazol}$), 126.9 (q, *J*=3.9 Hz, 2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 129.7 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 131.6 (q, *J*=32.2 Hz, 1C, C-4″$_{phenyl}$), 141.2 (1C, C-1″$_{phenyl}$),146.4 (1C, C-4′$_{triazol}$), 168.9 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3217, 1663, 1420, 1323, 1165, 1119, 1065, 1018, 822; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{16}F_3N_4O_5$, 389.1067; found, 389.1093; HPLC (method 2): t_R=14.5 min, purity 97.1%.

*5.2.16. (2S,3R,4S,5S)-N,3,4-Trihydroxy-5-(1-phenethyl-1H-1,2,3-triazol-4-yl)tetrahydrofuran-2-carboxamide (**10e**).* Hydroxylamine hydrochloride (94 mg, 1.4 mmol) and a 2.0 M solution of sodium methoxide in methanol (0.68 mL, 1.4 mmol) were added to a solution of **21e** (90 mg, 0.27 mmol) in dry methanol (10 mL). The reaction mixture was stirred at ambient temperature for 16 h until TLC showed complete conversion of the ester. The reaction mixture was evaporated and purified by flash column chromatography (1 cm, 15 cm, 5 mL, dichloromethane/methanol=9:1, R_f=0.30) to give **10e** as colourless solid (48 mg, 0.14 mmol, 53% yield). Mp=51 °C; $[\alpha]_D^{20}$ −4.7 (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=3.21 (t, *J*=7.3 Hz, 2H, CH_2CH_2Ph), 4.33 (t, *J*=5.0 Hz, 4-H), 4.46 (d, *J*=6.0 Hz, 1H, 2-H), 4.58 (dd, *J*=6.0/4.8 Hz, 3-H), 4.63 (t, *J*=7.3 Hz, 2H, CH_2CH_2Ph), 5.16 (d, *J*=5.4 Hz, 1H, 5-H), 7.15−7.17 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 7.20−7.22 (m, 1H, 4″-H_{phenyl}), 7.26−7.28 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.88 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=37.5 (1C, CH_2CH_2Ph), 52.8 (1C, CH_2CH_2Ph), 73.6 (1C, C-4), 74.1 (1C, C-3), 78.2 (1C, C-5), 80.9 (1C, C-2), 126.1 (1C, C-5′$_{triazol}$), 127.9 (1C, C-4″$_{phenyl}$), 129.7 (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 129.8 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 138.7 (1C, C-1″$_{phenyl}$), 145.7 (1C, C-4′$_{triazol}$), 169.0 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3198, 2901, 1659, 1454, 1227, 1123, 1057, 1026, 748, 698; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{19}N_4O_5$, 335.1350; found, 335.1380; HPLC (method 2): t_R=13.2 min, purity 95.5%.

*5.2.17. (2S,3R,4S,5S)-N,3,4-Trihydroxy-5-[1-(3-phenylpropyl)-1H-1,2,3-triazol-4-yl]tetrahydrofuran-2-carboxamide (**10f**).* Hydroxylamine hydrochloride (110 mg, 1.6 mmol) and a 2.0 M solution of sodium methoxide in methanol (0.79 mL, 1.6 mmol) were added to a solution of **21f** (110 mg, 0.32 mmol) in dry methanol (10 mL). The reaction mixture was stirred at ambient temperature for 16 h until TLC showed complete conversion of the ester. The reaction mixture was evaporated and purified by flash column chromatography (1 cm, 15 cm, 5 mL, dichloromethane/methanol=9:1, R_f=0.30) to give **10f** as colourless solid (44 mg, 0.13 mmol, 40% yield). Mp=49 °C; $[\alpha]_D^{20}$ −1.8 (*c* 1.6, MeOH); ^{1}H NMR (CD_3OD): δ [ppm]=2.20−2.28 (m, 2H, $CH_2CH_2CH_2Ph$), 2.63−2.67 (m, 2H, $CH_2CH_2CH_2Ph$), 4.36 (t, *J*=5.0 Hz, 1H, 4-H), 4.40 (t, *J*=7.0 Hz, 2H, $CH_2CH_2CH_2Ph$), 4.48 (d, *J*=6.0 Hz, 1H, 2-H), 4.61 (dd, *J*=6.0/4.7 Hz, 1H, 3-H), 5.21 (d, *J*=5.3 Hz, 1H, 5-H), 7.17−7.23 (m, 3H, H_{phenyl}), 7.25−7.30 (m, 2H, H_{phenyl}), 8.03 (s, 1H, 5′-$H_{triazol}$); ^{13}C NMR (CD_3OD): δ [ppm]=32.9 (1C, $CH_2CH_2CH_2Ph$), 33.4 (1C, $CH_2CH_2CH_2Ph$), 50.8 (1C, $CH_2CH_2CH_2Ph$), 73.6 (1C, C-4), 74.2 (1C, C-3), 78.3 (1C, C-5), 80.9 (1C, C-2), 126.0 (1C, C-5′$_{triazol}$), 127.2 (1C, C_{phenyl}), 129.5 (2C, C_{phenyl}), 129.6 (2C, C_{phenyl}), 142.0 (1C, C_{phenyl}), 145.9 (1C, C-4′$_{triazol}$), 169.0 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}]=3210, 2920, 1659, 1497, 1454, 1126, 1061, 1026, 745, 698; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{21}N_4O_5$ 349.1506; found, 349.1539; HPLC (method 2): t_R=13.8 min, purity 95.5%.

5.3. Biological evaluation

5.3.1. Agar diffusion clearance assay. The antibiotic activity of the synthesized inhibitors was determined by agar disc diffusion clearance assays. Liquid cultures of *E. coli* BL21 (DE3) and the antibiotic resistant strain *E. coli* D22[26] were grown overnight in LB

broth[27] at 37 °C, 200 rpm. Overnight cell suspension (150 μL) was spread evenly onto LB agar Petri dishes. Each compound (15 μL) (10 mM in DMSO) was applied onto circular filter paper (Ø 6 mm, thickness 0.75 mm, Carl Roth). Pure DMSO, serving as a negative and CHIR-090,[15] serving as a positive control were also spotted. The Petri dishes were incubated overnight at 37 °C and the diameter of the zone of growth inhibition was measured for each compound.

5.3.2. Protein purification and LpxC assay. Purification of LpxC and the LpxC enzyme assay were performed as previously described.[11]

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