European Journal of Medicinal Chemistry 110 (2016) 340–375

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Chiral pool synthesis and biological evaluation of *C*-furanosidic and acyclic LpxC inhibitors

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ARTICLE INFO

Article history:
Received 9 November 2015
Received in revised form
13 January 2016
Accepted 14 January 2016
Available online 20 January 2016

Keywords:
LpxC inhibitors
Structure-activity relationships
Chiral pool synthesis
C-glycosides
Benzyloxyacetohydroxamic acids

ABSTRACT

Inhibitors of the bacterial deacetylase LpxC have emerged as a promising new class of Gram-negative selective antibacterials. In order to find novel LpxC inhibitors, in chiral-pool syntheses starting from D-mannose, *C*-furanosides with altered configuration in positions 2 and/or 5 of the tetrahydrofuran ring were prepared in stereochemically pure form. Additionally, the substitution pattern in positions 3 and 4 of the tetrahydrofuran ring as well as the structure of the lipophilic side chain in position 2 were varied. Finally, all stereoisomers of the respective open chain diols were obtained via glycol cleavages of properly protected *C*-glycosides.

The biological evaluation of the synthesized hydroxamic acids revealed that in case of the *C*-glycosides, 2,5-*trans*-configuration generally leads to superior inhibitory and antibacterial activities. The relief of the conformational strain leading to the respective open chain derivatives generally caused an increase in the inhibitory and antibacterial activities of the benzyloxyacetohydroxamic acids. With K_i-values of 0.35 μM and 0.23 μM, the (*S*,*S*)-configured open-chain derivatives **8b** and **8c** were found to be the most potent LpxC inhibitors of these series of compounds.

1. Introduction

Nowadays many bacteria have developed resistance to various classes of antibiotics [1]. Especially among Gram-negative bacteria, some pandrug-resistant strains, being resistant towards all available antibiotics, have already been found [2]. For the successful treatment of infections caused by these bacteria, novel antibiotics, possessing a so far unexploited mode of action, are urgently required.

The inhibition of lipid A biosynthesis is a promising strategy to combat Gram-negative bacteria. Lipid A is the lipophilic part of lipopolysaccharides (LPS), anchoring the molecules in the outer monolayer of the outer membrane of Gram-negative bacteria, and, when being released, elicits an activation of the mammalian innate immune system, which can evoke septic shock [3]. In *Escherichia coli*, lipid A-Kdo_2 is synthesized via nine consecutive steps of which the second one, the deacetylation of UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**1**) representing the first irreversible reaction of this biosynthetic pathway, is catalyzed by the Zn^{2+}-dependent deacetylase LpxC (Fig. 1) [4]. As inhibition of lipid A biosynthesis is lethal to Gram-negative bacteria and due to the fact that LpxC is highly conserved among these bacteria but shows no homology with mammalian proteins, this deacetylase seems to be a suitable target for the development of antibiotics, being able to cure infections caused by Gram-negative bacteria [4,5].

In the literature, several structurally diverse LpxC inhibitors have been described, like for example the substrate analog TU-514 (**3**) [6], the sulfonamide BB-78485 (**4**) [7], the aryloxazoline L-161,240 (**5**) [5] and the *N*-aroyl-L-threonine derivative CHIR-090 (**6**) [8] (Fig. 2). Most of the described LpxC inhibitors possess a Zn^{2+}-chelating hydroxamate moiety and a lipophilic side chain, mimicking the fatty acyl moiety of the natural substrate of LpxC.

Based on the structure of CHIR-090 (**6**), a series of benzyloxyacetohydroxamic acids was developed, like *C*-glycosides **7a**–**c**, open-chain diols **8a** and **8b** as well as ethylene glycol derivatives **9a** and **9b** lacking the hydroxymethyl group in α-position of the hydroxamate moiety (Fig. 3) [9–11].

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http://dx.doi.org/10.1016/j.ejmech.2016.01.032
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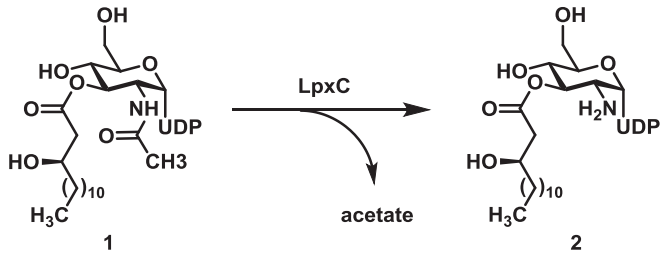


Fig. 1. LpxC catalyzed deacetylation of UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetyl-glucosamine (**1**).

Although docking of *C*-glycoside **7b** had given a favorable docking score, the compound exhibited only weak antibacterial activities and was unable to inhibit the enzymatic activity of LpxC at concentrations up to 200 μM [10]. An inspection of the docking pose revealed that one of the hydroxy groups of the *C*-glycoside is located in close proximity to an unpolar region of the active site of the enzyme [10]. Therefore, compounds **10** in which the hydroxy groups are transformed into less polar functional groups by etherification or acetalization were envisaged. Additionally, as in case of the open-chain derivatives the removal of the hydroxymethyl group in α-position of the hydroxamate moieties of **8a** and **8b** giving hydroxamic acids **9a** and **9b** led to an increase in inhibitory as well as antibacterial activity, a *C*-glycoside lacking the hydroxy group in position 3 of the tetrahydrofuran ring should be synthesized.

In case of *C*-glycosides **7a** and **7b** the central sugar ring causes a conformational restriction, keeping the hydroxamate moiety and the diphenylacetylene side chain in a defined relative orientation. In order to find the optimal spatial position of these two pharmacophoric elements, stereoisomeric *C*-glycosides **11** should be synthesized. Especially the configuration in α-position of the hydroxamate moiety as well as in benzylic position should be varied. As the structure of the lipophilic side chain had been shown to influence the biological activity of the LpxC inhibitors, besides the diphenylacetylene derivatives additionally the diphenyldiacetylene derivatives should be established.

Finally, in order to investigate the influence of the conformational restriction on the biological activity of the *C*-glycosides, the respective open-chain derivatives **12** should be synthesized.

2. Results and discussion

2.1. Chemistry

For the synthesis of the envisaged (2*S*,5*S*)-, (2*R*,5*S*)- and (2*S*,5*R*)-configured *C*-glycosides as well as the hydroxamic acids with a modified substitution pattern at the tetrahydrofuran ring, esters **18** and **19** were prepared as central building blocks (Scheme 1). In the described synthesis of 4-iodophenyl derivative **19**, at first, lactone **13**, which can be easily obtained from D-mannose, was reacted with 4-iodophenyllithium [11]. The organolithium compound was generated *in situ* by adding *n*-butyllithium to a solution of 1,4-diiodobenzene. In order to prevent a double halogen-metal exchange, an excess of 1,4-diiodobenzene was used, leading to the loss of huge amounts of the reagent. Therefore, as an alternative, 4-(benzyloxy)bromobenzene was employed as starting material for the halogen-metal exchange reaction. As this compound possesses only one halogen atom, which can be exchanged, the reagent could be used in a nearly equimolar amount. Additionally, the benzyl-protected phenol moiety of the compound allows the generation of aryltriflates at subsequent reaction steps, which can undergo Sonogashira coupling reactions like the iodophenyl derivatives. For the synthesis of 4-(benzyloxy)phenyl derivative **18**, after the addition of 4-(benzyloxy)phenyllithium to lactone **13**, the resulting hemiketal **14** was diastereoselectively reduced to the corresponding β-configured *C*-aryl furanoside with triethylsilane in the presence of the Lewis acid boron trifluoride diethyl etherate [11,12]. A subsequent selective cleavage of the more labile monocyclic acetonide gave diol **16**. Diol **16** was then transformed into methyl ester **18**. To access this compound, at first, the glycol moiety of **16** was cleaved with sodium metaperiodate. Then an oxidation with silver nitrate under basic conditions and a final esterification with methyl iodide and potassium carbonate in DMF were performed [13].

In order to obtain isopropylidene ketal **21**, aryl iodide **19** was at first reacted with 4-(morpholinomethyl)phenylacetylene under Sonogashira conditions to give the diphenylacetylene derivative **20**, which was then transformed into hydroxamic acid **21** by performing an aminolysis with hydroxylamine (Scheme 2).

For the synthesis of methyl ethers **27** and **28**, after deprotection of the acetonide moiety of ester **19**, the resulting diol **22** was alkylated using an excess of methyl iodide in the presence of LiHMDS in DMF at ambient temperature. The reaction gave regioisomers **23** and **24** in 44% and 21% yield, respectively, whereas the formation of the corresponding dimethylated compound was not observed. The fact that **23** and **24** were formed in a ratio of about two thirds (**23**) to one third (**24**) indicates, that an alkylation of the hydroxy group in position 4 of the tetrahydrofuran ring is sterically more hindered due to the adjacent phenyl ring. After separation of the regioisomers, the compounds were coupled with 4-(morpholinomethyl)phenylacetylene to yield the respective diphenylacetylene derivatives **25** and **26**. Finally, after an aminolysis with hydroxylamine, hydroxamic acids **27** and **28** were obtained.

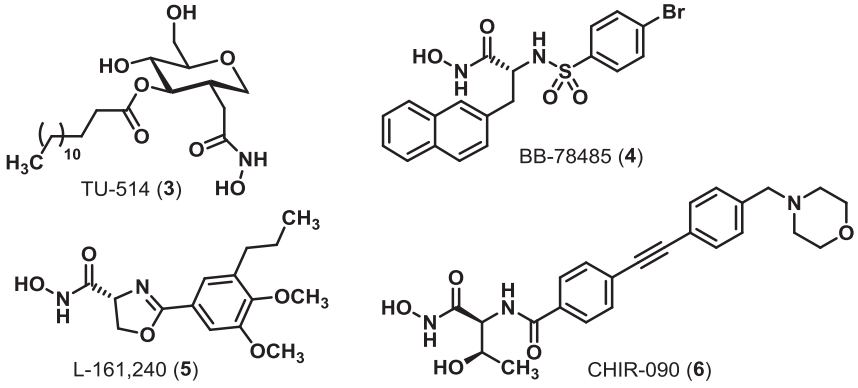


Fig. 2. Representative inhibitors of LpxC.

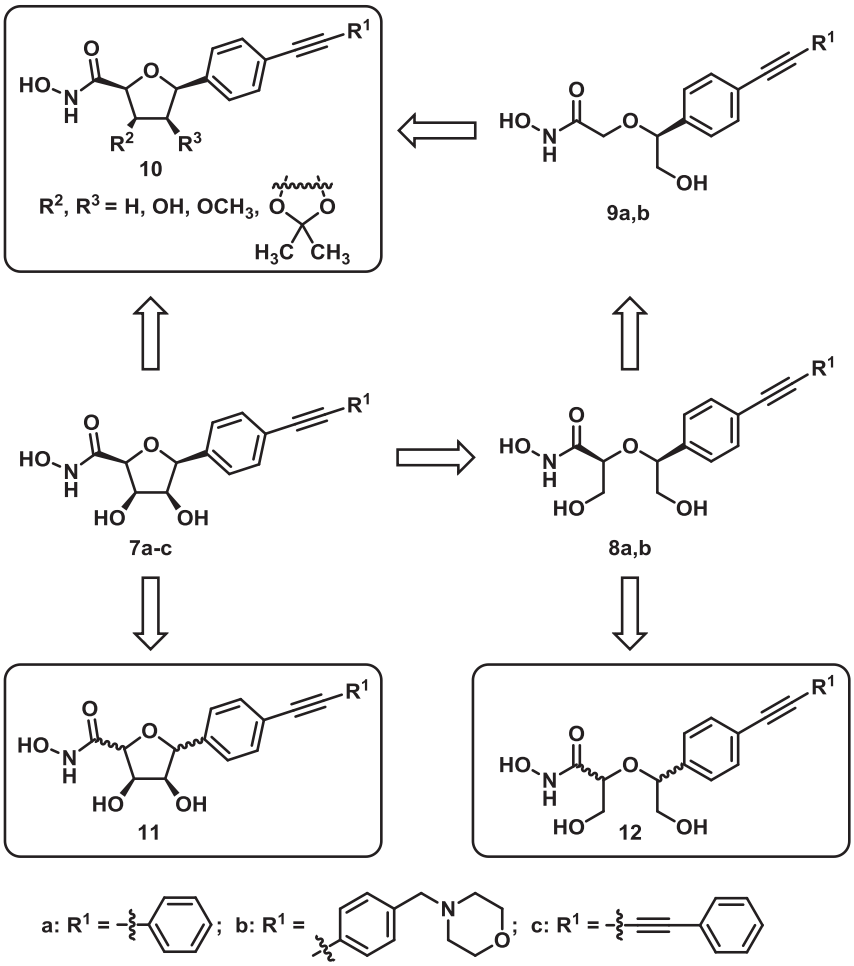
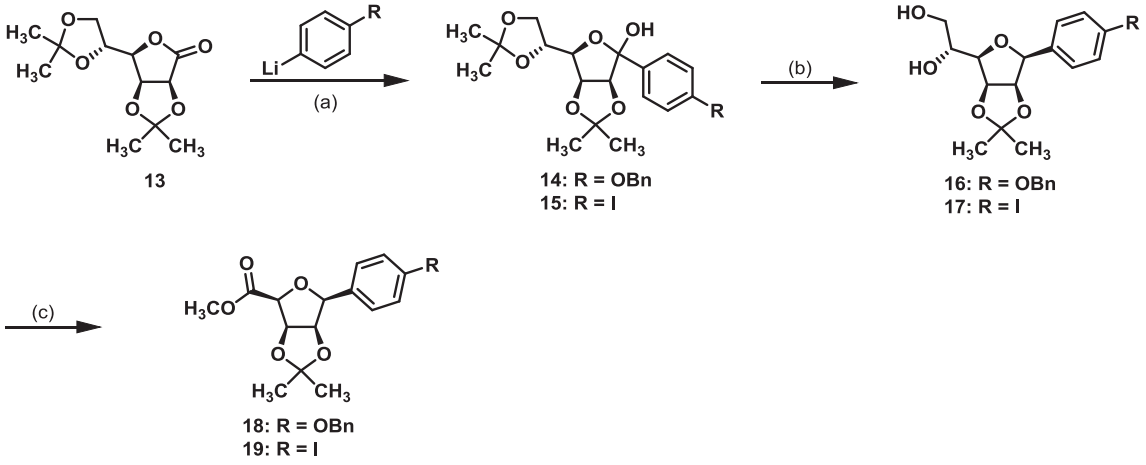
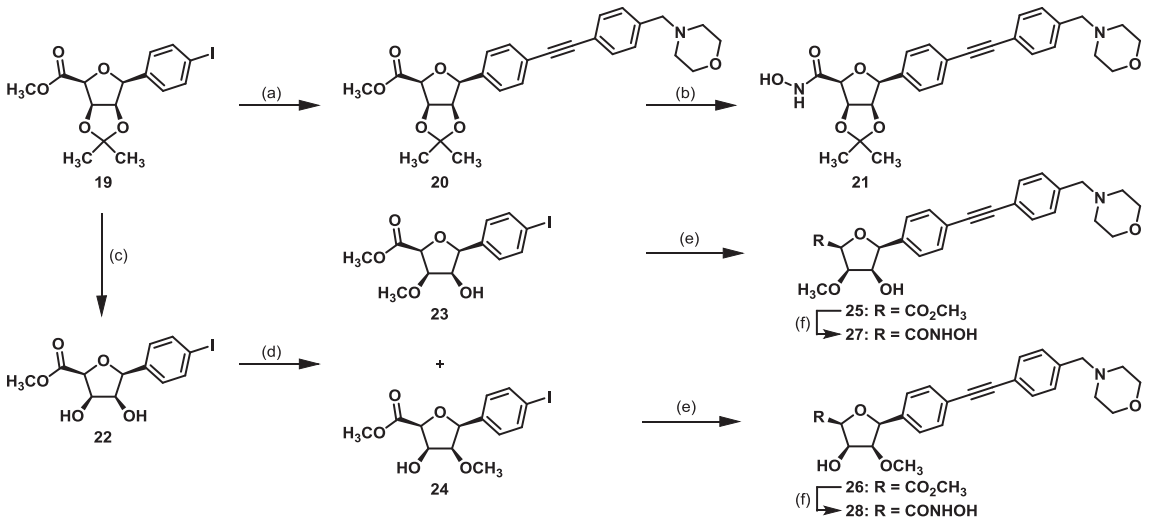


Fig. 3. Structures of described and envisaged LpxC inhibitors.

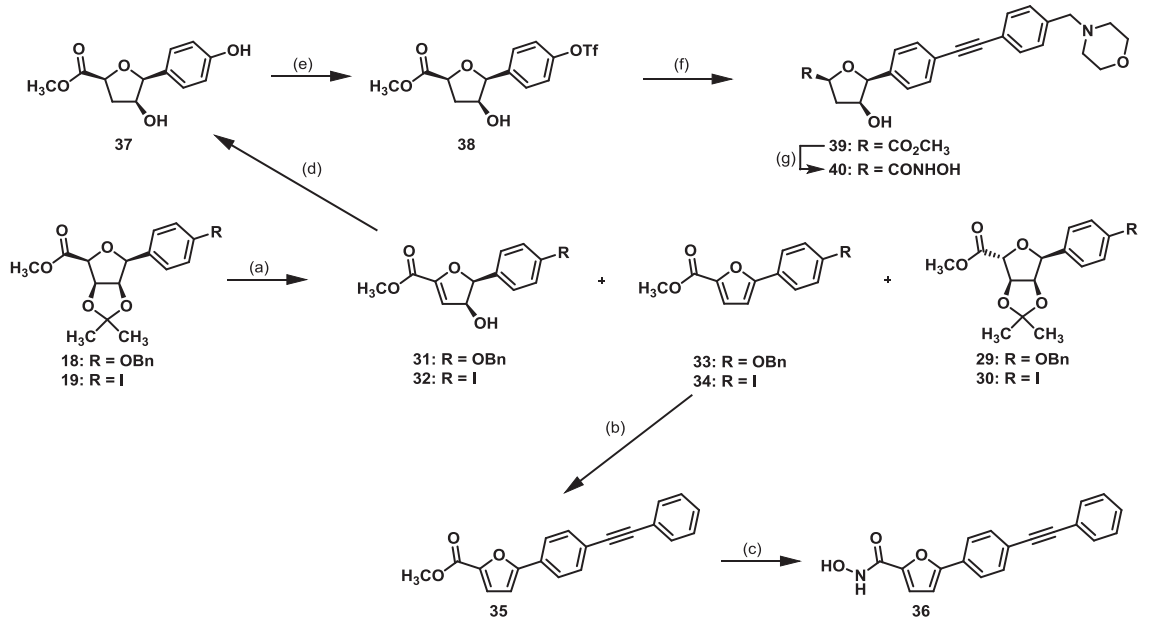


Scheme 1. Reagents and conditions: (a) THF, −78 °C, **14** 74%, **15** 83%; (b) 1. $BF_3 \cdot OEt_2$, Et_3SiH, ACN, −40 °C, 2. *p*-TsOH, MeOH, rt, **16** 61%, **17** 72% (2 steps each); (c) 1. $NaIO_4$, MeOH, rt, 2. $AgNO_3$, KOH, THF/H_2O, rt, 3. CH_3I, K_2CO_3, DMF, rt, **18** 80%, **19** 76% (3 steps each).

When esters **18** and **19** were reacted with sodium methoxide in methanol under refluxing conditions, the formation of several products was observed (Scheme 3). On the one hand, due to the increased CH-acidity in α-position of the ester moiety an epimerization occurred at this position, leading to the formation of (4*R*,6*S*)-configured esters **29** and **30**, respectively. The inversion of configuration at C-4 could be confirmed by ^{1}H NMR spectroscopy. Whereas the signals for 4-H of esters **18** and **19** appear as doublets (J = 4.6 Hz), the corresponding protons of the (4*R*)-configured epimers give singlet signals, suggesting *trans*-orientation of 4-H and 3a-H. These compounds were used for the synthesis of the (*R*,*S*)-configured hydroxamic acids (see below). On the other hand,



Scheme 2. Reagents and conditions: (a) 4-(morpholinomethyl)phenylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, ACN, rt, 66%; (b) $NH_2OH \cdot HCl$, NaOMe, DCM/MeOH, rt, 23%; (c) *p*-TsOH, MeOH, reflux, 33%; (d) LiHMDS, CH_3I, DMF, rt, **23** 44%, **24** 21%; (e) 4-(morpholinomethyl)phenylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, ACN, rt, **25** 66%, **26** 44%; (f) $NH_2OH \cdot HCl$, NaOMe, MeOH, rt, **27** 53%, **28** 33%.



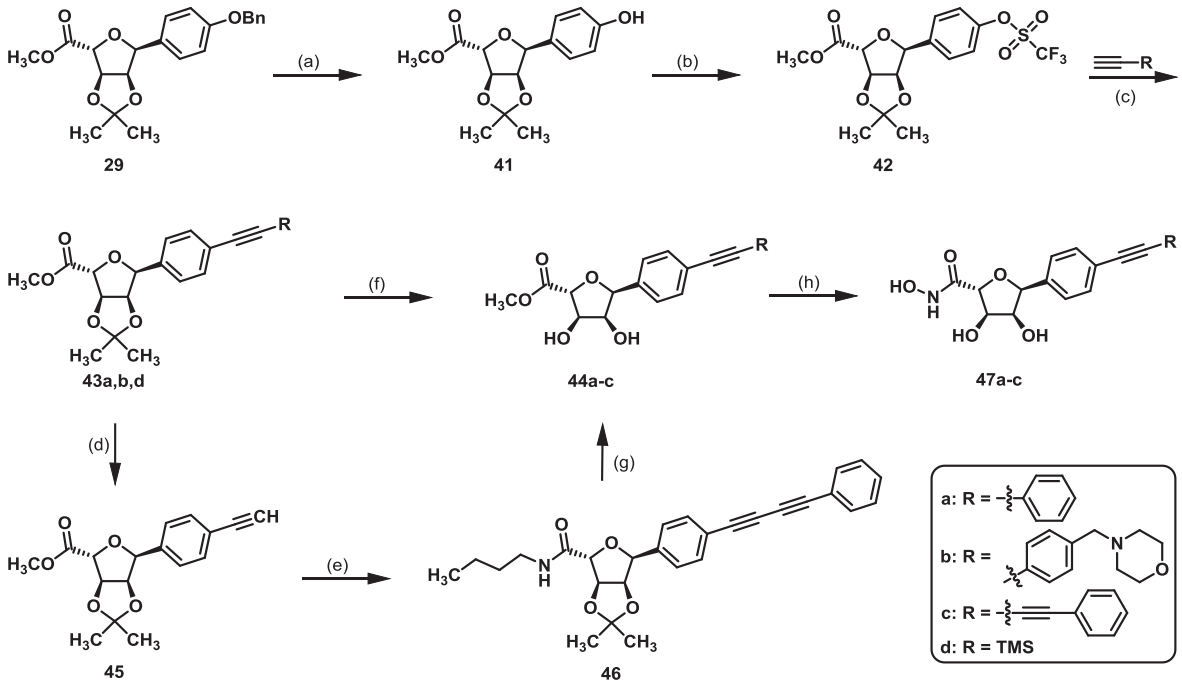
Scheme 3. Reagents and conditions: (a) NaOMe, MeOH, reflux, **29** 33%, **30** 18%; (b) phenylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, ACN, rt, 9% (2 steps from **19**); (c) $NH_2OH \cdot HCl$, NaOMe, MeOH/THF (1/1), rt, 49%; (d) H_2, Pd/C, MeOH, rt, 21% (2 steps from **18**); (e) Tf_2O, Et_3N, DCM, −20 °C, 82%; (f) 4-(morpholinomethyl)phenylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, ACN, reflux, 56%; (g) $NH_2OH \cdot HCl$, NaOMe, MeOH, rt, 32%.

an E1cB-elimination of the acetonide moiety was observed, yielding dihydrofuran derivatives **31** and **32** and subsequently furans **33** and **34**. These latter compounds gave access to the achiral, planar hydroxamic acid **36** as well as hydroxamic acid **40**, lacking the hydroxy group in position 3 of the tetrahydrofuran ring.

In order to synthesize furan derivative **36**, aryl iodide **34** was reacted with phenylacetylene under Sonogashira conditions to give **35** and a subsequent aminolysis of the ester moiety with hydroxylamine led to hydroxamic acid **36**.

As α,β-unsaturated esters **31** and **32** readily aromatize to the respective furan derivatives, the crude product obtained by heating ester **18** with sodium methoxide in methanol was directly hydrogenated to yield 4-hydroxytetrahydrofuran derivative **37**. In this reaction, besides the hydrogenolytic cleavage of the benzyl ether moiety, a hydrogenation of the double bond of α,β-unsaturated ester **31** occurred. Due to the directing effects of the substituents in positions 4 and 5 of the dihydrofuran ring, hydrogen was transferred to the double bond from the *Re*-face of C-2. Therefore, only the (2*S*)-configured 4-hydroxytetrahydrofuran derivative **37** was obtained. Its configuration in position 2 was confirmed by NOE experiments. Subsequently, phenol **37** was transformed into triflate **38** [14]. Coupling of triflate **38** with 4-(morpholinomethyl)phenylacetylene under Sonogashira conditions giving alkyne **39** and a final transformation of the ester moiety into a hydroxamate group yielded hydroxamic acid **40**.

In order to synthesize the *C*-glycosidic, (2*R*,5*S*)-configured hydroxamic acids **47a**–**c**, the 4-(benzyloxy)phenyl-substituted ester **29** was used (Scheme 4). At first, its benzyl protective group



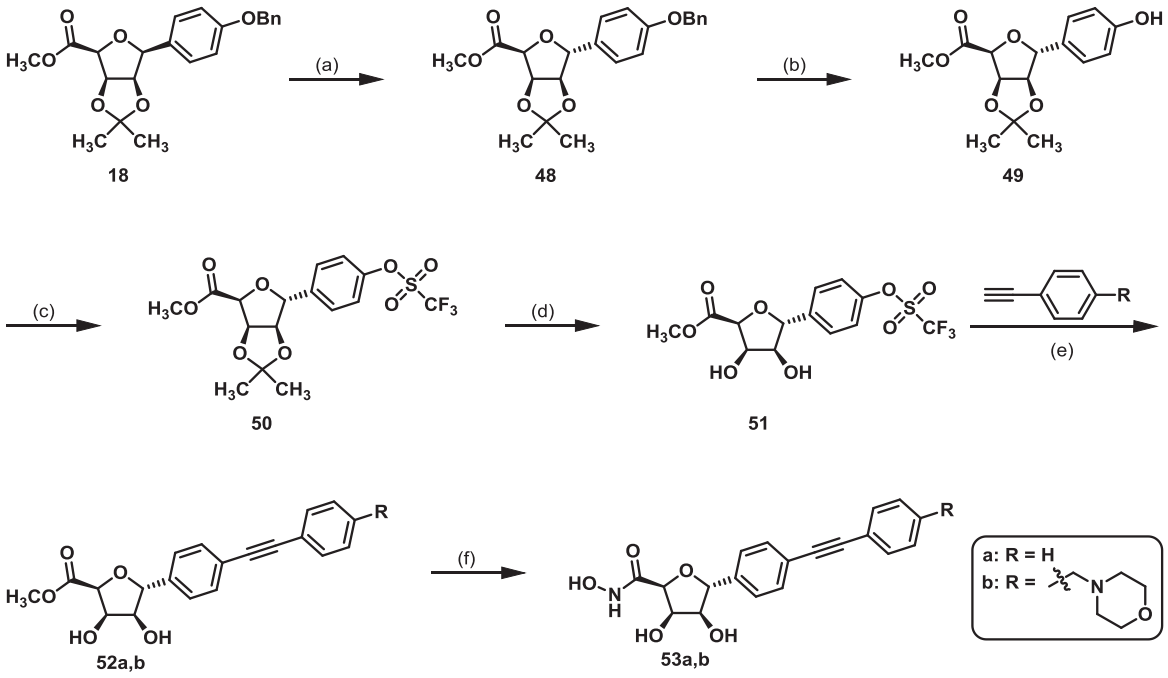
Scheme 4. Reagents and conditions: (a) H_2 (4 bar), Pd/C, MeOH/EtOAc (1/1), rt, 82%; (b) Tf_2O, Et_3N, DCM, −20 °C, 73%; (c) $Pd(PPh_3)_4$, CuI, Et_3N, ACN, reflux, **43a** 75%, **43b** 89%, **43d** 89%; (d) $AgNO_3$, H_2O, acetone, rt, 81%; (e) (bromoethynyl)benzene, CuCl, $NH_2OH{\cdot}HCl$, aq. *n*-$BuNH_2$ (30%), rt, 48%; (f) *p*-TsOH, MeOH, reflux, **44a** 64%, **44b** 64%; (g) *p*-TsOH, MeOH, microwave irradiation, 42%; (h) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, **47a** 56%, **47b** 30%, **47c** 57%.

was hydrogenolytically cleaved to yield phenol **41**. Triflate **42** was subsequently obtained by treating phenol **41** with trifluoromethanesulfonic anhydride in dichloromethane at −20 °C [14]. With this building block Sonogashira reactions with various alkynes were performed yielding coupling products **43a**, **43b** and **43d**. In case of acetonides **43a** and **43b**, the compounds were transformed into the desired diols **44a** and **44b** via an acid-catalyzed acetal cleavage. In order to obtain butadiyne **44c**, the trimethylsilyl protective group of alkyne **43d** was cleaved with silver nitrate as catalyst in water-containing acetone [15]. The resulting terminal alkyne **45** was then reacted with (bromoethynyl) benzene in an aqueous solution of *n*-butylamine (30% V/V), running an asymmetric Cadiot-Chodkiewicz C–C coupling reaction. This procedure followed a published protocol, that had already been successfully applied for the synthesis of a related compound [16]. In this case, however, in addition to the desired C–C coupling reaction, an aminolysis of the ester moiety occurred, leading to the formation of amide **46**. The amide was subsequently transferred into the desired methyl ester **44c** by reacting the compound in methanol in the presence of catalytic amounts of *p*-toluenesulfonic acid under microwave irradiation. Finally, the (2*R*,5*S*)-configured hydroxamic acids **47a**–**c** were obtained by reacting esters **44a**–**c** with hydroxylamine hydrochloride and sodium methoxide in methanol.

The crucial step of the synthesis of (2*S*,5*R*)-configured hydroxamic acids **53a** and **53b** was the inversion of configuration of the carbon atom in benzylic position (Scheme 5). Starting from benzyl-protected phenol derivative **18**, which represents a phenylogous acetal, an epimerization was performed using erbium trifluoromethanesulfonate as Lewis acid catalyst in acetonitrile under microwave irradiation. As C-6 of **18** is in conjugation with the benzyl-protected phenol oxygen atom, via a stabilized acyclic carbenium ion a mixture of epimeric esters **18** and **48** was obtained, from which the (4*S*,6*R*)-configured *C*-glycoside **48** could be isolated in 44% yield. The configuration of the stereocenters in positions 4 and 6 of the tetrahydrofuro[3,4-d][1,3]dioxole scaffold of **48** was confirmed by NOE experiments. Whereas irradiation with the resonance frequency of 4-H (4.66 ppm) led to a reinforcement of the signals for 3a-H (5.05–5.09 ppm), 6a-H (4.95 ppm) and the protons in 2′- and 6′-position of the proximal phenyl ring (7.23–7.27 ppm), the irradiation with the resonance frequency of 6-H (5.19 ppm) only reinforced the signals of 6a-H (4.95 ppm) and the aromatic protons in 2′- and 6′-position (7.23–7.27 ppm). These observations prove the spatial proximity of 4-H and 6a-H, which is consistent with (4*S*)-configuration, and *trans*-orientation of 4-H and 6-H, thereby confirming the desired (*R*)-configuration in position 6.

In the next reaction step, the benzyl group of **48** was hydrogenolytically cleaved to yield phenol **49**, which was subsequently transformed into triflate **50**. This triflate served as key building block for the synthesis of all (*S*,*R*)-configured hydroxamic acids. For the synthesis of the *C*-glycosidic hydroxamates **53a** and **53b**, at first, the acetonide protective group was removed by treating acetal **50** with catalytic amounts of *p*-toluenesulfonic acid in methanol under microwave irradiation to give diol **51**. In subsequent Sonogashira reactions, triflate **51** was coupled with phenylacetylene and 4-(morpholinomethyl)phenylacetylene, yielding alkynes **52a** and **52b**, respectively. Finally esters **52a** and **52b** were transformed into the corresponding hydroxamic acids **53a** and **53b** by performing aminolyses with hydroxylamine.

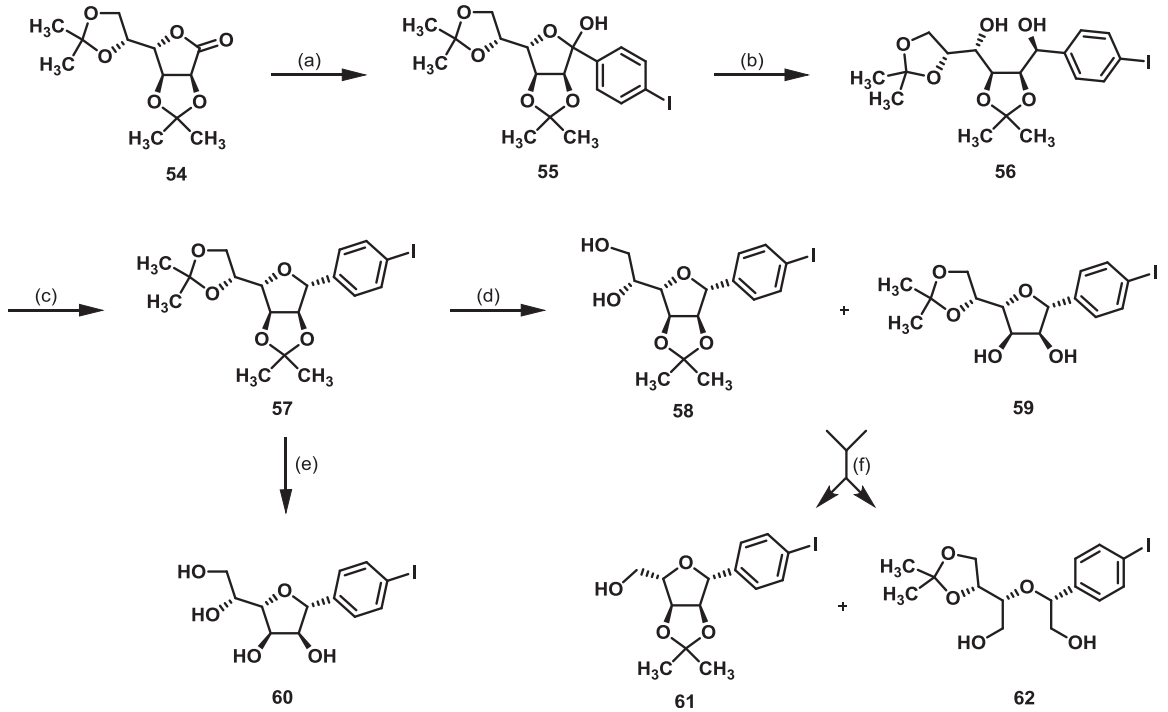
In order to obtain the (*R*,*R*)-configured hydroxamic acids **67a**–**c** and **74a**–**c**, L-talonic acid derivative **54** was used as starting material, which could be accessed from D-mannose according to literature procedures [17,18]. At first, L-talono-1,4-lactone **54** was reacted with (4-iodophenyl)lithium (Scheme 6). The nucleophilic attack yielded hemiketal **55**, which was stereoselectively reduced with L-selectride to give diol **56**. To form central building block **57**, diol **56** was subjected to an intramolecular Mitsunobu cycloetherification, leading to an inversion of configuration at the carbon atom in benzylic position [19–21]. These reaction steps were conducted according to the procedures described for the synthesis of the



Scheme 5. Reagents and conditions: (a) $Er(OTf)_3$, ACN, microwave irradiation, 44%; (b) H_2 (4 bar), Pd/C, MeOH/EtOAc (2/1), rt, 96%; (c) Tf_2O, Et_3N, DCM, −20 °C, 91%; (d) *p*-TsOH, MeOH, microwave irradiation, 85%; (e) $Pd(PPh_3)_4$, CuI, Et_3N, ACN, reflux, **52a** 79%, **52b** 78%; (f) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, **53a** 49%, **53b** 45%.

respective phenyl derivatives and the analytical data of the obtained iodine-substituted compounds were in agreement with the ones of their unsubstituted analogs [18].

For the next reaction step, the selective cleavage of the monocyclic acetonide moiety was envisaged. However, in contrast to the (4*R*,6*S*)-configured diastereomer of **57**, which had been published before [11], a selective acetonide cleavage could not be achieved in case of (4*S*,6*R*)-configured bisacetonide **57**. When *p*-toluenesulfonic acid in methanol was used at ambient temperature, a mixture of regioisomeric monoacetonides **58** and **59** was obtained, which was not separable by flash column chromatography. Harsher reaction conditions for the cleavage of bisacetonide **57** employing



Scheme 6. Reagents and conditions: (a) 1,4-diiodobenzene, *n*-butyllithium, THF, −78 °C, 69%; (b) L-selectride, THF, −78 °C, then rt, 94%; (c) PPh_3, DIAD, THF, reflux, 62%; (d) *p*-TsOH, MeOH, rt, **58** + **59** 46%; (e) aq. HCl/THF (1/1), microwave irradiation, 80%; (f) 1. $NaIO_4$, MeOH, rt, 2. $NaBH_4$, MeOH, rt, **61** 55% + **62** 27% (2 steps).

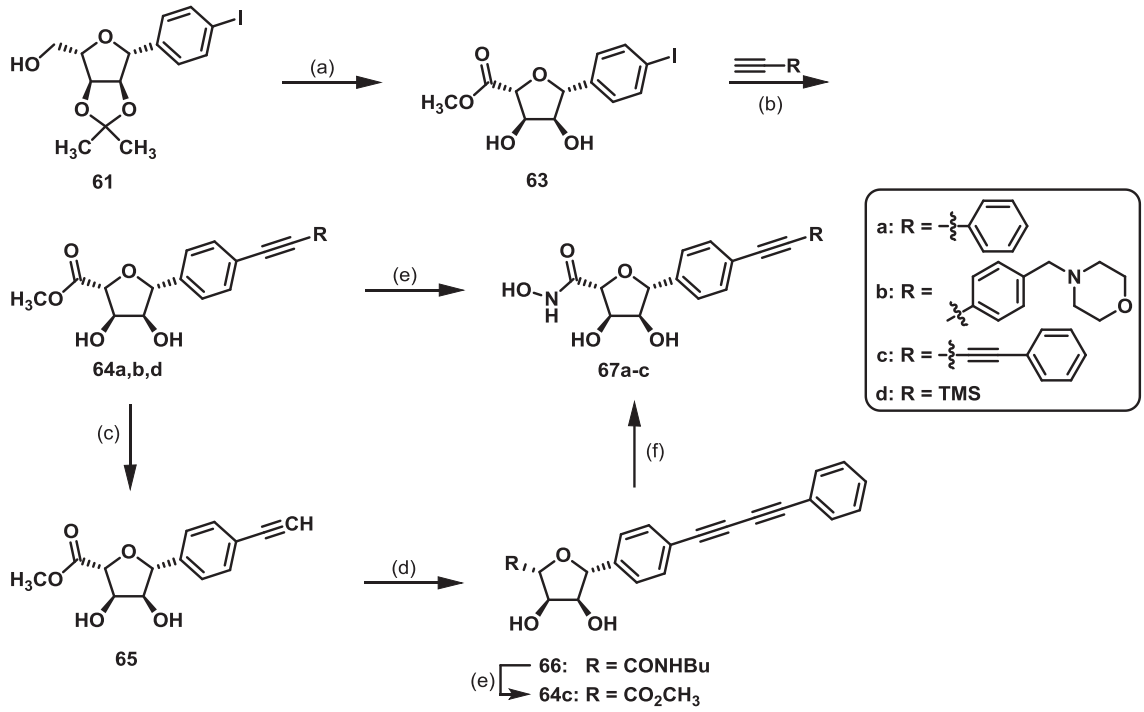
hydrochloric acid in THF under microwave irradiation led to the hydrolysis of both acetal moieties giving tetrol **60** in 80% yield. However, all three cleaved products could be used for subsequent reaction steps.

The treatment of the inseparable mixture of regioisomers **58** and **59** with sodium metaperiodate led to the cleavage of the respective glycol moieties of the compounds. A subsequent reduction of the resulting aldehydes with sodium borohydride yielded a mixture of *C*-glycosidic alcohol **61** and open chain diol **62**, which could be easily separated by flash column chromatography.

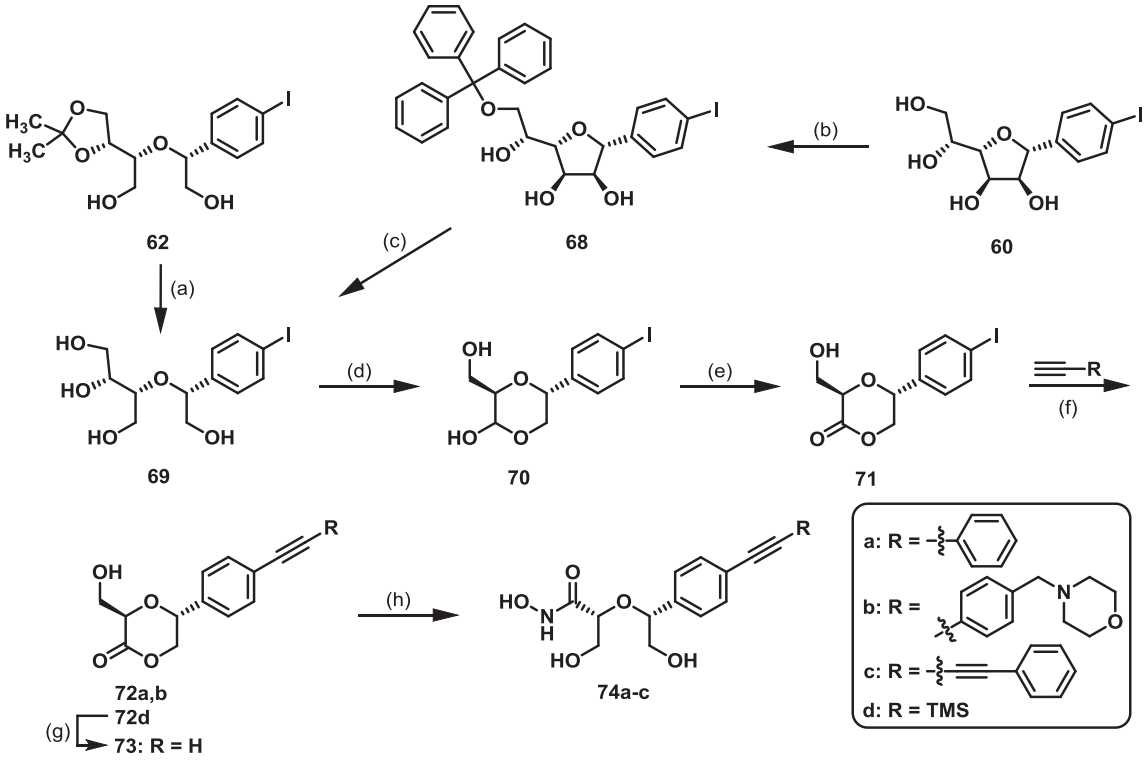
To synthesize the (2*R*,5*R*)-configured *C*-glycosidic hydroxamic acids **67a**–**c**, at first, alcohol **61** was oxidized to the respective carboxylic acid with TEMPO as catalyst and bis(acetoxy)iodobenzene as stoichiometric oxidant (Scheme 7) [22]. The intermediately formed carboxylic acid was then reacted with *p*-toluenesulfonic acid in methanol under microwave irradiation. Under these conditions, besides the esterification of the carboxylate moiety, the cleavage of the remaining acetonide occurred, leading to methyl ester **63**. The iodine-substituted aromat of this compound allowed the performance of C–C coupling reactions with various alkynes under Sonogashira conditions to give acetylenes **64a**, **64b** and **64d** in high yields. As described for the synthesis of diacetylene derivative **44c**, butadiyne **64c** was obtained from trimethylsilyl-protected alkyne **64d** via TMS-cleavage, a Cadiot-Chodkiewicz coupling and a final reaction with methanol in the presence of *p*-toluenesulfonic acid. In the last reaction step, esters **64a**–**c** were reacted with hydroxylamine hydrochloride and sodium methoxide in methanol to give hydroxamic acids **67a**–**c**.

To access the (*R*,*R*)-configured open-chain derivatives **74a**–**c**, the previously synthesized alcohols **60** and **62** were used (Scheme 8). After the selective trityl protection of the primary alcohol of tetrol **60**, yielding triol **68** [23], the glycol moiety of the compound was cleaved with sodium metaperiodate and the resulting dialdehyde was subsequently reduced with sodium borohydride. The acidic work-up of the reaction caused the cleavage of the trityl protective group leading to the formation of open chain tetrol **69**. Alternatively, this compound could be accessed via the deprotection of acetonide **62**. Glycol **69** was then treated with sodium metaperiodate to give lactol **70**, which was subsequently oxidized with bromine in a 9/1 mixture of methanol and water [9,24]. Due to partial solvolysis of the resulting lactone, to some extent the respective methyl ester was formed, which was retransformed into lactone **71** by treating the crude reaction mixture with *p*-toluenesulfonic acid in acetonitrile. Then Sonogashira reactions were performed to couple the 4-iodophenyl moiety of lactone **71** with several terminal alkynes, yielding acetylene derivatives **72a**, **72b** and **72d**. Aminolyses of lactones **72a** and **72b** with hydroxylamine hydrochloride and sodium methoxide in methanol gave (*R*,*R*)-configured hydroxamic acids **74a** and **74b**. For the synthesis of open-chain derivative **74c**, the trimethylsilyl protective group of lactone **72d** was cleaved, an aminolysis with hydroxylamine was performed and the intermediately obtained terminal alkyne was finally coupled with (bromoethynyl)benzene.

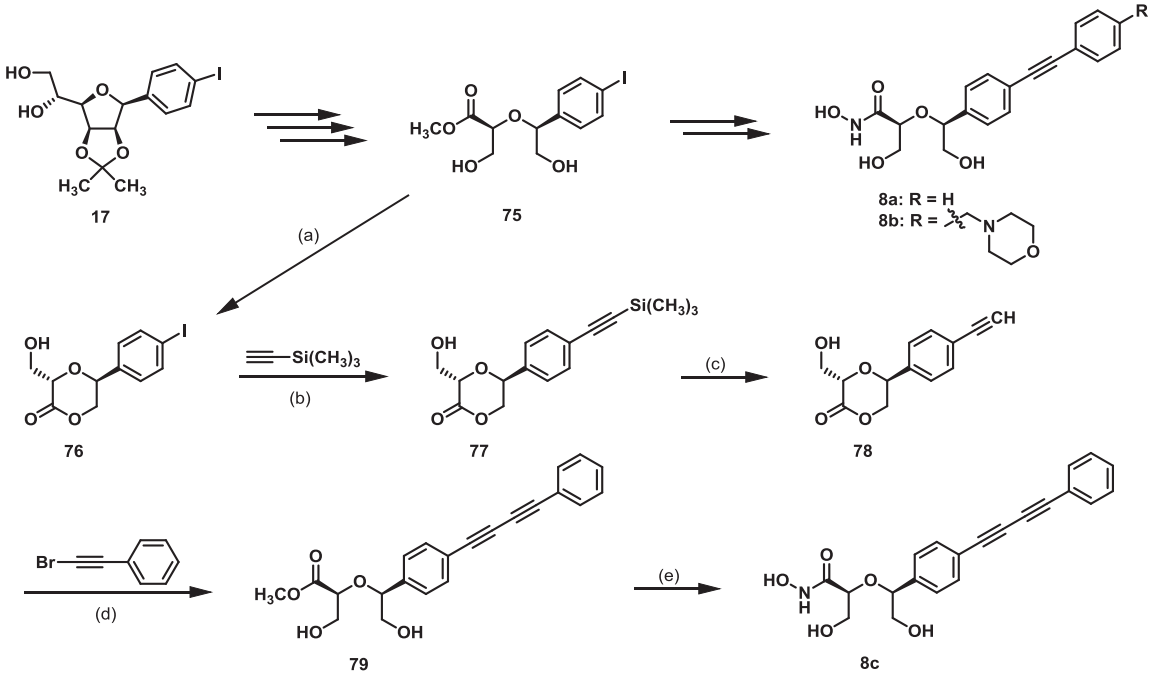
The synthesis of the acyclic, (*S*,*S*)-configured hydroxamic acids **8a** and **8b** has already been described in the literature [9]. In addition, phenylbutadiynyl-substituted hydroxamic acid **8c** was synthesized from ester **75** (Scheme 9). At first, diol **75** was converted into the corresponding lactone **76** by refluxing the compound in acetonitrile under acidic conditions. This cyclization was performed, as in solution the acyclic esters showed the tendency to partially form the corresponding lactones, which were always observed as side products in the subsequent steps of the synthesis. Additionally, lactone **76** allowed the performance of NOE experiments in order to confirm the configuration of the stereocenters. Irradiation with the resonance frequency of 3-H (4.61 ppm) of the dioxane ring led to a reinforcement of the signals for the methylene protons of the CH_2OH-group (4.00 and 4.13 ppm) and for the aromatic protons in 2'- and 6'-position (7.12–7.18 ppm). However, no



Scheme 7. Reagents and conditions: (a) 1. TEMPO, BAIB, ACN/aq. $NaHCO_3$ (1/1), rt, 2. *p*-TsOH, MeOH, microwave irradiation, 60% (2 steps); (b) $Pd(PPh_3)_4$, CuI, Et_3N, ACN, rt, **64a** 100%, **64b** 93%, **64d** 100%; (c) $AgNO_3$, H_2O, acetone, rt, 82%; (d) (bromoethynyl)benzene, CuCl, $NH_2OH{\cdot}HCl$, aq. *n*-$BuNH_2$ (30%), rt, 41%; (e) *p*-TsOH, MeOH, microwave irradiation, 34%; (f) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, **67a** 90%, **67b** 64%, **67c** 68%.



Scheme 8. Reagents and conditions: (a) *p*-TsOH, MeOH, reflux, 82%; (b) TrCl, DMAP, pyridine, DMF, 70 °C, 40%; (c) 1. $NaIO_4$, MeOH, rt, 2. $NaBH_4$, MeOH, rt, then HCl, rt, 66% (2 steps); (d) $NaIO_4$, MeOH, rt, 77%; (e) 1. Br_2, $NaHCO_3$, MeOH/H_2O (9/1), rt, 2. *p*-TsOH, ACN, reflux, 81% (2 steps); (f) $Pd(PPh_3)_4$, CuI, Et_3N, ACN, rt, **72a** 92%, **72b** 56%, **72d** 83%; (g) $AgNO_3$, H_2O, acetone, rt, 77%; (h) **72a** and **72b**: $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, **74a** 69%, **74b** 74%; **73**: 1. $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, 2. (bromoethynyl)benzene, CuCl, $NH_2OH{\cdot}HCl$, aq. *n*-$BuNH_2$ (30%), rt, **74c** 38% (2 steps).



Scheme 9. Reagents and conditions: (a) *p*-TsOH, ACN, reflux, 71%; (b) $Pd(PPh_3)_4$, CuI, Et_3N, ACN, rt, 79%; (c) $AgNO_3$, H_2O, acetone, rt, 72%; (d) CuI, $NH_2OH{\cdot}HCl$, Et_3N, MeOH, 40 °C, 19%; (e) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, 66%.

reinforcement of the signal for 5-H (5.18 ppm) was detectable, proving that in lactone **76** protons 3-H and 5-H are *trans*-configured and that the configuration of C-4 and C-6 of *C*-glycoside **17** was retained in the subsequent steps of the synthesis.

4-Iodophenyl derivative **76** was coupled with trimethylsilylacetylene under Sonogashira-conditions to give trimethylsilyl-

protected alkyne **77**, which was subsequently deprotected with silver nitrate to yield terminal alkyne **78**. In order to avoid the formation of the *N*-butylamide, which had been observed in the synthesis of butadiynes **64c** and **44c**, the Cadiot-Chodkiewicz coupling of terminal alkyne **78** with (bromoethynyl)benzene was performed in the presence of the base triethylamine [25]. However, the coupling gave butadiyne **79** in only 19% yield. Finally, the aminolysis of ester **79** with hydroxylamine yielded hydroxamic acid **8c**.

For the synthesis of the (*R*,*S*)-configured acyclic hydroxamic acid **84**, ester **30** was reduced with DIBAL-H in dichloromethane at −78 °C (Scheme 10). The resulting aldehyde was directly transformed into the corresponding dimethyl acetal by heating the compound to reflux in methanol in the presence of *p*-toluenesulfonic acid. As under these conditions the remaining acetonide was additionally cleaved, diol **80** was obtained. A cleavage of the glycol moiety of dimethyl acetal **80** with sodium metaperiodate, followed by a reduction with sodium borohydride yielded acyclic diol **81**. The ester moiety was reestablished by heating diol **81** in a 1/1 mixture of 1 M HCl and THF, which led to the hydrolysis of the dimethyl acetal, and a subsequent oxidation of the obtained aldehyde yielding methyl ester **82**. Then a Sonogashira reaction was performed to couple the 4-iodophenyl moiety of diol **82** with 4-(morpholinomethyl)phenylacetylene. The resulting diphenylacetylene derivative was then subjected to a final aminolysis with hydroxylamine to transform the ester into a hydroxamate moiety, yielding (*R*,*S*)-configured hydroxamic acid **84**.

In order to obtain the acyclic (*S*,*R*)-configured hydroxamic acids **90a**–**90c** (Scheme 11), methyl ester **50** was transformed into dimethyl acetal **85**. Reduction of the ester moiety of **50**, dimethyl acetal formation and acetonide cleavage were performed as described for the synthesis of diol **80**. In the next step, the dihydroxytetrahydrofuran ring of **85** was cleaved with sodium periodate and a subsequent reduction with $NaBH_4$ yielded acyclic diol **86**. Then the dimethyl acetal moiety of **86** was hydrolyzed leading to the formation of hemiacetal **87**. The oxidation of hemiacetal **87** with bromine in a mixture of methanol and water (9/1) gave access to lactone **88**. In order to transform the respective methyl ester, which was formed as a side product due to partial solvolysis of the lactone, into lactone **88**, the crude product of the oxidation was heated in acetonitrile under acidic conditions. In the next step, triflate **88** was reacted with phenylacetylene and 4-(morpholinomethyl)phenylacetylene under Sonogashira conditions to give alkynes **89a** and **89b**, respectively. Finally, lactones **89a** and **89b** were subjected to an aminolysis with hydroxylamine to yield the (*S*,*R*)-configured hydroxamic acids **90a** and **90b**.

For the synthesis of butadiyne derivative **90c**, at first, triflate **88** was subjected to a Sonogashira coupling with trimethylsilylacetylene. The trimethylsilyl protective group was subsequently cleaved to give the corresponding terminal alkyne. In order to build up the desired diacetylene moiety, the terminal alkyne should be coupled with (bromoethynyl)benzene under Cadiot-Chodkiewicz conditions. As the Cadiot-Chodkiewicz reaction of alkyne **78** using triethylamine as base had given only low yields (Scheme 9), *n*-butylamine (30% aq.) was chosen again as solvent for this coupling reaction. However, in order to avoid the formation of the undesired *N*-butylamide, at first, the previously obtained lactone was transformed into the corresponding hydroxamic acid **91** by performing an aminolysis with hydroxylamine. Finally, in the last step of the synthesis, the coupling of terminal alkyne **91** with (bromoethynyl)benzene yielded the desired (*S*,*R*)-configured hydroxamic acid **90c**.

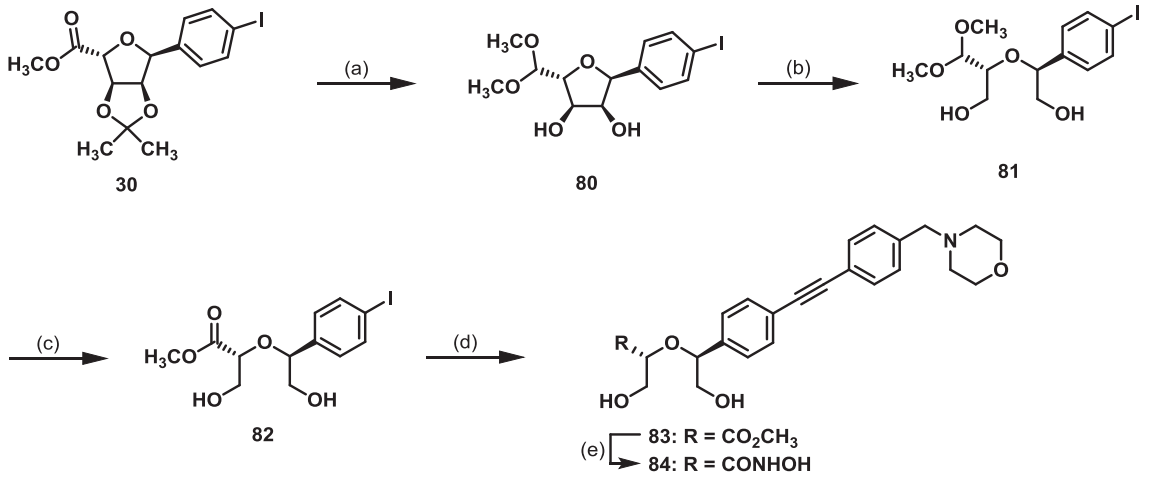
2.2. Biological evaluation

To evaluate the biological activity of the synthesized hydroxamic acids, they were assayed in disc diffusion tests to examine their antibacterial properties and in an enzyme assay to test their inhibitory activity against LpxC.

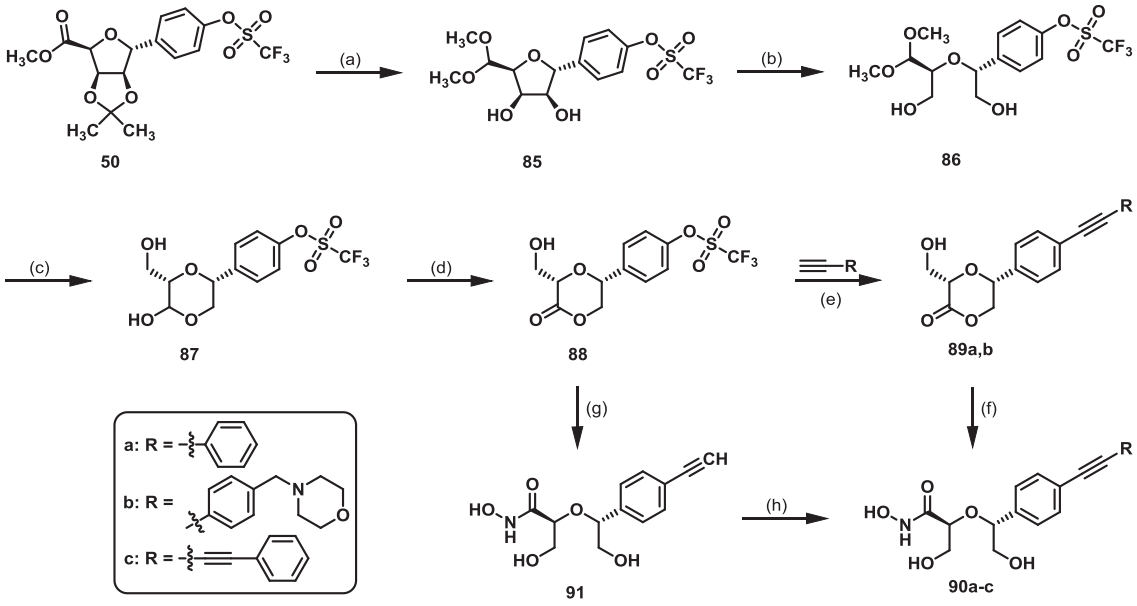
The disc diffusion tests were conducted with *E. coli* BL21 (DE3) and the defective *E. coli* strain D22 [26], which is more sensitive towards LpxC inhibition. Suspensions of these strains were spread onto agar plates. Afterwards filter discs containing solutions of the inhibitors were placed onto the surface of the agar. After incubation overnight at 37 °C the diameter of the zone of growth inhibition of each inhibitor was measured.

In the enzyme assay, the inhibition of the LpxC-catalyzed deacetylation of the enzyme's natural substrate **1** caused by varying concentrations of the tested inhibitor, ranging from 0.2 nM to 200 μM, was determined. After incubation, the amount of the formed primary amine **2** was measured by transforming the compound into a fluorescent isoindole [7].

At first, the (*S*,*S*)-configured *C*-glycosides with a modified substitution pattern at the tetrahydrofuran ring were investigated (Table 1). Whereas methylation of one of the hydroxy groups of **7b** did not lower the IC_{50}-value of the resultant ethers **27** and **28** below



Scheme 10. Reagents and conditions: (a) 1. DIBAL-H, DCM, −78 °C, 2. *p*-TsOH, MeOH, reflux, 49% (2 steps); (b) 1. $NaIO_4$, MeOH, rt, 2. $NaBH_4$, MeOH, rt, 46% (2 steps); (c) 1. aq. HCl/THF (1/1), reflux, 2. Br_2, $NaHCO_3$, MeOH/H_2O (9/1), rt, 67% (2 steps); (d) 4-(morpholinomethyl)phenylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, ACN, rt, 51%; (e) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, 19%.



Scheme 11. Reagents and conditions: (a) 1. DIBAL-H, DCM, −78 °C, 2. *p*-TsOH, MeOH, reflux, 75% (2 steps); (b) 1. $NaIO_4$, MeOH, rt, 2. $NaBH_4$, MeOH, rt, 83% (2 steps); (c) aq. HCl/THF (1/1), reflux, 64%; (d) 1. Br_2, $NaHCO_3$, MeOH/H_2O (9/1), rt, 2. *p*-TsOH, ACN, reflux, 63% (2 steps); (e) $Pd(PPh_3)_4$, CuI, Et_3N, ACN, reflux, **89a** 73%, **89b** 24%; (f) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, **90a** 62%, **90b** 32%; (g) 1. trimethylsilylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, ACN, reflux, 2. $AgNO_3$, H_2O, acetone, rt, 3. $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, 39% (3 steps); (h) (bromoethynyl)benzene, CuCl, $NH_2OH{\cdot}HCl$, aq. *n*-$BuNH_2$ (30%), rt, 18%.

200 μM, both compounds showed antibacterial activities against the defective *E. coli* D22 strain, with the activity of 4-*O*-methylated hydroxamic acid **28** exceeding the one of its regioisomer **27** as well as of diol **7b**. Also isopropylidene acetal **21** exhibited a higher antibacterial activity than diol **7b**. The modified hydroxamic acid **40** (K_i = 12 μM), lacking the hydroxy group in position 3, showed a considerably higher inhibitory activity towards LpxC than diol **7b** and also an increased antibacterial activity.

The planar furan derivative **36** could not be tested in the enzyme assay as the compound was fluorescent itself. In the disc diffusion assay against *E. coli* D22, the compound was only slightly more potent than diol **7a**.

When comparing the results of the biological evaluation of the dihydroxytetrahydrofuran derivatives, a strong influence of the structure of the lipophilic side chain as well as of the configuration in positions 2 and 5 of the tetrahydrofuran ring on the biological activity of these *C*-glycosides can be observed (Table 2).

In case of the unsubstituted diphenylacetylene derivatives **7a**, **47a**, **53a** and **67a**, the 2,5-*trans*-configured hydroxamic acids **47a** and **53a** were found to be more potent LpxC inhibitors than their 2,5-*cis*-configured diastereomers. With a K_i-value of 3.3 μM the (2*R*,5*S*)-configured stereoisomer **47a** is the most potent inhibitor of this series of stereoisomers. These observations are in general agreement with the antibacterial activities observed in the disc diffusion assay against *E. coli* D22, with **47a** causing the largest zone of inhibition. Although being a less potent LpxC inhibitor than **47a**, the (2*S*,5*R*)-configured hydroxamic acid **53a** was the only stereoisomer of this series of compounds, which exhibited antibacterial activity against *E. coli* BL21.

Similar results were obtained for the morpholinomethyl-substituted hydroxamic acids **7b**, **47b**, **53b** and **67b**. Also in this series of *C*-glycosides, the 2,5-*cis*-configured stereoisomers are less potent LpxC inhibitors than the 2,5-*trans*-configured hydroxamic acids **47b** and **53b**. With the exception of (2*R*,5*R*)-configured hydroxamic acid **67b**, morpholinomethyl-substitution leads to a pronounced increase in the antibacterial activity of the compounds in the disc diffusion assays.

The inhibitory activities of the butadiyne derivatives **7c**, **47c** and **67c** were found to be generally superior to the ones of their respective diphenylacetylene analogs. Strikingly, with a K_i-value of 0.69 μM the (2*R*,5*R*)-configured butadiyne derivative is the most potent LpxC inhibitor of the synthesized *C*-glycosides. For this reason, this compound is the only 2,5-*cis*-configured *C*-glycoside, which is more active than its respective (2*R*,5*S*)-configured diastereomer. The inhibitory activity of **67c** correlates well with its antibacterial activity against *E. coli* BL21.

The results of the biological evaluation of the acyclic hydroxamic acids revealed that diphenylacetylene derivatives **8a**, **90a** and **74a** exhibit the weakest inhibitory activity of the synthesized open-chain derivatives (Table 3). Whereas morpholinomethyl-substitution leads to a pronounced increase in inhibitory activity

Table 1
Results of the biological evaluation of the synthesized inhibitors with varied sugar scaffold. n.d.: not determinable.

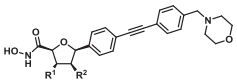
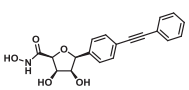
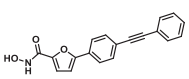
Cmpd.			Zone of inhibition [mm]		Enzyme assay	
	R^1	R^2	*E. coli* BL21 (DE3)	*E. coli* D22	IC_{50} [μM]	K_i [μM]
7b[9]	**OH**	**OH**	<6	13.2	>200	>27.6
40	**H**	**OH**	<6	15.3 ± 0.6	87 ± 31	12 ± 4
27	**OCH_3**	**OH**	<6	11.7 ± 1.5	>200	>27.6
28	**OH**	**OCH_3**	<6	20.5 ± 1.3	>200	>27.6
21			<6	14.7 ± 0.6	>200	>27.6
7a[9]			<6	6.5	>200	>27.6
36			<6	8.0	n. d.	n. d.

Table 2
Results of the biological evaluation of the synthesized *C*-glycosidic inhibitors.

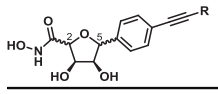
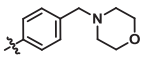
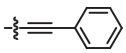
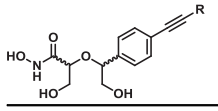
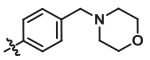
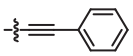
Cmpd.			Zone of inhibition [mm]		Enzyme assay	
	Config.	R	*E. coli* BL21 (DE3)	*E. coli* D22	IC_{50} [μM]	K_i [μM]
7a[9]	(2*S*,5*S*)		<6	6.5	>200	>27.6
47a	(2*R*,5*S*)		<6	18.0 ± 1.0	24 ± 32	3.3 ± 4.4
53a	(2*S*,5*R*)		6.8 ± 1.0	13.6 ± 2.0	43 ± 9	5.9 ± 1.2
67a	(2*R*,5*R*)		<6	16.3 ± 2.5	>200	>27.6
7b[9]	(2*S*,5*S*)		<6	13.2	>200	>27.6
47b	(2*R*,5*S*)		<6	22.1 ± 1.8	10 ± 1	1.4 ± 0.2
53b	(2*S*,5*R*)		9.8 ± 0.5	20.2 ± 2.1	34 ± 10	4.7 ± 1.4
67b	(2*R*,5*R*)		<6	<6	42 ± 4	5.8 ± 0.6
7c[9]	(2*S*,5*S*)		<6	9.0	32	4.4
47c	(2*R*,5*S*)		<6	15.7 ± 0.6	15 ± 3	2.1 ± 0.4
67c	(2*R*,5*R*)		10.7 ± 1.5	14.5 ± 1.3	5.0 ± 2.2	0.69 ± 0.30

Table 3
Results of the biological evaluation of the synthesized acyclic inhibitors.

Cmpd.			Zone of inhibition [mm]		Enzyme assay	
	Config.	R	*E. coli* BL21 (DE3)	*E. coli* D22	IC_{50} [μM]	K_i [μM]
8a[9]	(*S*,*S*)		<6	16.2	>200	>27.6
90a	(*S*,*R*)		6.8 ± 1.0	21.3 ± 0.6	150 ± 10	21 ± 2
74a	(*R*,*R*)		<6	9.3 ± 1.5	>200	>27.6
8b[9]	(*S*,*S*)		9.6	20.4	2.6	0.35
84	(*R*,*S*)		16.0 ± 0.8	26.1 ± 2.5	8.0 ± 0.6	1.1 ± 0.1
90b	(*S*,*R*)		14.3 ± 1.3	27.9 ± 1.1	21 ± 3	2.9 ± 0.4
74b	(*R*,*R*)		<6	20.3 ± 2.1	180 ± 4	25 ± 1
8c	(*S*,*S*)		13.7 ± 0.6	21.3 ± 2.5	1.7 ± 0.4	0.23 ± 0.05
90c	(*S*,*R*)		9.0 ± 1.0	18.0 ± 1.0	4.4 ± 0.6	0.60 ± 0.09
74c	(*R*,*R*)		7.1 ± 0.3	10.5 ± 1.0	20 ± 7.2	2.7 ± 1.0

in comparison with the equally configured diphenylacetylene derivatives, the respective butadiyne derivatives were found to be the most potent LpxC inhibitors. With a K_i-value of 0.60 μM, the inhibitory activity of the (*S*,*R*)-configured diphenyldiacetylene derivative **90c** is 35-fold higher than the one of its diphenylacetylene derivative **90a** and 5-fold higher than the one of the respective morpholinomethyl-substituted compound **90b**. In contrast to the results of the enzyme assay, especially in the disc diffusion assays against *E. coli* D22, the morpholinomethyl-substituted diphenylacetylene derivatives exhibited superior antibacterial activities, with all four compounds causing halos of inhibition with diameters exceeding 20 mm. These observations are in general agreement with the observations made in case of the *C*-glycosidic hydroxamic acids.

A comparison of the biological activities of the four stereoisomers of the morpholinomethyl-substituted acyclic hydroxamic acids revealed, that (*S*,*S*)-configured compound **8b** possesses a higher inhibitory activity than its (*R*,*S*)- and (*S*,*R*)-configured diastereomers and especially than its (*R*,*R*)-configured enantiomer **74b**. The same trend was observed for the diphenyldiacetylene derivatives. With K_i-values of 0.35 μM and 0.23 μM, (*S*,*S*)-configured open-chain derivatives **8b** and **8c** represent the most potent LpxC inhibitors in the described series of hydroxamic acids. However, this is in contrast to the results for unsubstituted diphenylacetylene derivative **8a**, for which no detectable inhibitory activity was observed.

When comparing the activities of the *C*-glycosidic hydroxamic acids with the ones of the respective acyclic derivatives, it can be observed that the relief of the conformational strain generally leads to an increase in inhibitory and antibacterial activity. Only in case of the (*R*,*R*)-configured compounds an opposite trend was found. E.g. the (*S*,*S*)-configured hydroxamic acids **8b** (K_i = 0.35 μM) and **8c** (K_i = 0.23 μM) showed higher inhibitory activities than their *C*-glycosidic derivatives **7b** (K_i > 27.6 μM) and **7c** (K_i = 4.4 μM). Also in the disc diffusion assays the acyclic compounds generally exhibited higher antibacterial activities than the corresponding *C*-glycosides, with the majority of the synthesized open-chain derivatives being active against *E. coli* BL21.

3. Conclusions

In chiral-pool syntheses starting from D-mannose, the stereoisomers of the previously described *C*-glycosides **7a**-**c** with altered configuration in positions 2 and/or 5 of the tetrahydrofuran ring as well as all stereoisomers of open chain LpxC inhibitor **8a** were synthesized. The (2*S*,5*R*)-configured *C*-glycosides **53a** and **53b** and the (2*R*,5*S*)-configured hydroxamic acids **47a**–**c** could be obtained via acid- and base-catalyzed epimerization reactions of ester **18**, respectively. The (2*R*,5*R*)-configured compounds **67a**–**c** were synthesized from L-talono-1,4-lactone **54**. From this compound hemiketal **55** was obtained, which was diastereoselectively reduced. The resultant diol **56** was subjected to an intramolecular Mitsunobu

cycloetherification, yielding *C*-glycoside **57** possessing the proper configuration.

The respective open chain derivatives were obtained by performing glycol cleavages of properly protected dihydroxytetrahydrofuran derivatives and a subsequent reduction of the resultant dialdehydes with sodium borohydride in the key steps of the synthesis.

Additionally, by employing Sonogashira couplings with different alkynes as well as Cadiot-Chodkiewicz reactions, the lipophilic side chain of the compounds was varied.

When comparing the biological activities of the hydroxamic acids with different lipophilic side chains, it becomes evident that the unsubstituted diphenylacetylene derivatives are the weakest LpxC inhibitors. Possibly, the lipophilic side chain of these compounds is too short to fully occupy the hydrophobic tunnel of the enzyme, which lowers their affinity. This is supported by the observation that the elongation of the side chain by another acetylene moiety, yielding the diphenyldiacetylene derivatives, distinctly increased the inhibitory activity of the LpxC inhibitors. Although the morpholinomethyl-substituted diphenylacetylene derivatives possess slightly weaker inhibitory activities than the respective diphenyldiacetylene derivatives, these compounds generally exhibit the highest antibacterial activities in the disc diffusion assays.

With the exception of the (2*R*,5*R*)-configured hydroxamic acid **67c**, the 2,5-*trans*-configured *C*-glycosides generally show superior inhibitory and antibacterial activities than their respective *cis*-configured stereoisomers, with the (2*R*,5*S*)-configured hydroxamic acids being the most potent LpxC inhibitors.

The biological activities of the acyclic diols showed, that flexibility of the central ether core is advantageous for the inhibitory and antibacterial properties of the compounds. The highest inhibitory activities against LpxC were observed for (*S*,*S*)-configured open-chain derivatives **8b** and **8c**. The relief of the conformational strain generally caused improved biological activities, with only the (*R*,*R*)-configured open-chain diols being slightly weaker LpxC inhibitors than the respective *C*-glycosides. As the conformational restriction of the bioactive conformation of a flexible ligand should lead to a pronounced increase in affinity, apparently, in case of the synthesized *C*-glycosides the optimally configured stereoisomer has not yet been synthesized. Therefore, additionally, the configuration in positions 3 and/or 4 of the tetrahydrofuran ring should be varied in the future.

In case of (2*S*,5*S*)-configured *C*-glycoside **7b** it was observed, that the removal of the hydroxy group in position 3 of the tetrahydrofuran ring (**40**) as well as methylation of the hydroxy group in position 4 (**28**) and the formation of the isopropylidene acetal (**21**) led to an increase in the antibacterial activities against *E. coli* D22. Also these results indicate that further variations of the substituents in positions 3 and 4 of the tetrahydrofuran ring might lead to superior biological activities, especially in case of the stereoisomeric *C*-glycosides.

4. Experimental section

4.1. Chemistry, general

Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Microwave assisted synthesis: adjustable parameters are given in brackets: irradiation power, maximum pressure, temperature, hold time. Microwave 1: CEM Discover LabMate (CEM Corp., NC); glass vessel (capacity 10 mL), sealed with Teflon septa; stirring: on; ramp time: 5 min; piezo-electric pressure sensor; external infrared temperature sensor. Microwave 2: MARS 240/50 (CEM Corp., NC); Teflon vessels (capacity 100 mL), sealed with Teflon cap; stirring: on; ramp time: 5 min; continuous mode turntable system; cavity exhaust fan; pressure and temperature control. Thin layer chromatography (TLC): Silica gel 60 F_{254} plates (Merck). Reversed phase thin layer chromatography (RP-TLC): Silica gel 60 RP-18 $F_{254}S$ plates (Merck). Flash chromatography (FC): Silica gel 60, 40–64 μm (Macherey-Nagel); brackets include: eluent, diameter of the column, fraction size, R_f value. Automatic flash column chromatography: Isolera™ One (Biotage®); brackets include: eluent, cartridge-type. Melting point: 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. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Agilent DD2 400 MHz spectrometer; δ in ppm related to tetramethylsilane. IR: IR Prestige-21 (Shimadzu). APCI/LC-MS: 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%. Method 3: Merck Hitachi Equipment; UV detector: L-7400; pump: L-7150; autosampler: L-7200; interface: D-7000; column: Agilent prep C18 10 μm, 250 × 21.2 mm; flow rate: 20.00 mL/min; injection volume: 400.0 μL; detection at λ = 254 nm; stop time: 20.0 min; solvent: acetonitrile: 10 mM ammonium formate = 40: 60 with 0.1% (V/V) formic acid.

4.2. Synthetic procedures

4.2.1. (3aS,6R,6aS)-4-[4-(Benzyloxy)phenyl]-6-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (**14**)

A 1.6 M solution of *n*-butyllithium in *n*-hexane (3.63 mL, 5.81 mmol) was added, under nitrogen atmosphere, to a solution of 4-benzyloxybromobenzene (1.73 g, 6.58 mmol) in dry THF (25 mL). The reaction was stirred for 15 min at −78 °C. Then a solution of **13** (1.00 g, 3.87 mmol) in dry THF (10 mL) was added. The reaction was stirred for 1 h and then warmed to ambient temperature. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1, Ø = 5 cm, h = 15 cm, V = 50 mL, R_f = 0.31) to give **14** as colorless oil (1.28 g, 2.88 mmol, 74% yield). Specific rotation: $[\alpha]_D^{20}$ = +49.2 (c = 5.0; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.26 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 4.10–4.17 (m, 2H, OCHCH_2O), 4.32 (dd, *J* = 7.1/4.0 Hz, 1H, 6-H), 4.49–4.54 (m, 1H, OC*H*CH$_2$O), 4.64 (d, *J* = 5.8 Hz, 1H, 3a-H), 4.93 (dd, *J* = 5.8/4.0 Hz,

1H, 6a-H), 5.06 (s, 2H, OCH_2Ph), 6.95–6.98 (m, 2H, H_{phenyl}), 7.30–7.49 (m, 7H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.3 (1C, C(CH_3)$_2$), 25.5 (1C, C(CH_3)$_2$), 25.8 (1C, C(CH_3)$_2$), 27.0 (1C, C(CH_3)$_2$), 66.9 (1C, OCHCH_2O), 70.1 (1C, OCH_2Ph), 73.6 (1C, OCHCH_2O), 79.0 (1C, C-6), 80.4 (1C, C-6a), 86.3 (1C, C-3a), 106.2 (1C, C-4), 109.2 (1C, C(CH_3)$_2$), 112.9 (1C, C(CH_3)$_2$), 114.2 (2C, C_{phenyl}), 127.7 (2C, C_{phenyl}), 128.1 (1C, C_{phenyl}), 128.3 (2C, C_{phenyl}), 128.7 (2C, C_{phenyl}), 131.8 (1C, C_{phenyl}), 137.0 (1C, C_{phenyl}), 159.2 (1C, C_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3379, 2936, 1612, 1512, 1454, 1373, 1065, 829, 733, 698; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{31}O_7$: 443.2064, found: 443.2111; HPLC (method 1): t_R = 20.8 min, purity 97.5%.

4.2.2. (R)-1-{(3aS,4R,6S,6aR)-6-[4-(Benzyloxy)phenyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}ethane-1,2-diol (**16**)

Under nitrogen atmosphere, triethylsilane (1.2 mL, 7.3 mmol) and boron trifluoride diethyl etherate (0.75 mL, 6.1 mmol) were added to a solution of **14** (2.7 g, 6.1 mmol) in dry acetonitrile (20 mL). The reaction was conducted simultaneously four times. The mixtures were stirred for 1 h at −40 °C. Afterwards, a saturated aqueous solution of potassium carbonate (20 mL) was added to each flask. The mixtures were then warmed to ambient temperature, stirred for 1 h, combined and extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol (30 mL) and *p*-TsOH (926 mg, 4.87 mmol) was added. The reaction was stirred for 16 h. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. Then the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 6 cm, h = 15 cm, V = 65 mL, R_f = 0.26) to give **16** as colorless solid (5.70 g, 14.8 mmol, 61% yield). Melting point: 154 °C; Specific rotation: $[\alpha]_D^{20}$ = +60.7 (c = 2.5; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.30 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.10–2.20 (m, 1H, OH), 2.79 (d, *J* = 5.1 Hz, 1H, OH), 3.69 (dd, *J* = 7.9/4.1 Hz, 1H, 4-H), 3.77–3.84 (m, 1H, HOCHCH_2OH), 3.88–3.95 (m, 1H, HOCHCH_2OH), 4.13–4.19 (m, 1H, HOCHCH$_2$OH), 4.56 (d, *J* = 3.6 Hz, 1H, 6-H), 4.76 (dd, *J* = 6.1/3.6 Hz, 1H, 6a-H), 4.92 (dd, *J* = 6.1/4.1 Hz, 1H, 3a-H), 5.06 (s, 2H, OCH_2Ph), 6.94–6.98 (m, 2H, H_{phenyl}), 7.29–7.44 (m, 7H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.5 (1C, C(CH_3)$_2$), 25.8 (1C, C(CH_3)$_2$), 64.9 (1C, HOCHCH_2OH), 70.1 (1C, OCH_2Ph), 70.5 (1C, HOCHCH$_2$OH), 81.0 (1C, C-4), 81.5 (1C, C-3a), 82.2 (1C, C-6a), 83.4 (1C, C-6), 112.7 (1C, C(CH_3)$_2$), 114.5 (2C, C_{phenyl}), 127.6 (1C, C_{phenyl}), 127.7 (2C, C_{phenyl}), 128.1 (1C, C_{phenyl}), 128.7 (2C, C_{phenyl}), 129.0 (2C, C_{phenyl}), 137.1 (1C, C_{phenyl}), 158.8 (1C, C_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3472, 3329, 2920, 2862, 1612, 1516, 1254, 1169, 826, 737; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{27}O_6$: 387.1802, found: 387.1771; HPLC (method 1): t_R = 18.5 min, purity 95.6%.

4.2.3. Methyl (3aR,4S,6S,6aR)-6-[4-(benzyloxy)phenyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**18**)

4.2.3.1. Method A. A solution of sodium metaperiodate (0.33 g, 1.55 mmol) in water (10 mL) was added to a solution of **16** (0.5 g, 1.29 mmol) in methanol (10 mL). The reaction was stirred for 2 h. The mixture was then extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo.

The residue was dissolved in acetonitrile/water (10/1, 20 mL), chromium(VI) oxide (0.13 g, 1.29 mmol) and concentrated sulfuric acid (12 drops) were added. The reaction was stirred for 3 h. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo.

Then the crude product was dissolved in DMF. Potassium carbonate (0.71 g, 5.16 mmol) and iodomethane (0.09 mL, 1.45 mmol) were added and the mixture was stirred for 4 h at ambient temperature. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo.

The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.21) to give **18** as colorless solid (0.29 g, 0.76 mmol, 59% yield).

4.2.3.2. Method B. Sodium metaperiodate (5.33 g, 24.91 mmol) was added to a solution of **16** (3.21 g, 8.30 mmol) in methanol (100 mL). The reaction was stirred for 2 h. Then water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo.

The residue was dissolved in THF (30 mL) and silver nitrate (3.24 g, 19.1 mmol) dissolved in water (30 mL) was added. A 0.91 M aqueous solution of KOH (42.0 mL, 38.2 mmol) was added dropwise over a period of 5 min. The reaction was stirred for 30 min. Afterwards, the mixture was filtered. The precipitate was washed twice with an aqueous solution of KOH (0.91 M, 10 mL). The filtrate was acidified to pH 2 with conc. hydrochloric acid. Then the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo.

The residue was dissolved in DMF. Potassium carbonate (4.59 g, 33.2 mmol) and iodomethane (0.57 mL, 9.13 mmol) were added and the mixture was stirred overnight at ambient temperature. Afterwards, water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo.

The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1, Ø = 6 cm, h = 15 cm, V = 65 mL, R_f = 0.21) to give **18** as colorless solid (2.55 g, 6.64 mmol, 80% yield). Melting point: 129 °C; Specific rotation: $[\alpha]_D^{20}$ = +50.6 (c = 3.8; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.28 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.85 (s, 3H, COOCH_3), 4.37 (d, *J* = 4.6 Hz, 1H, 4-H), 4.61 (d, *J* = 3.4 Hz, 1H, 6-H), 4.77 (dd, *J* = 5.9/3.4 Hz, 1H, 6a-H), 5.06 (s, 2H, OCH_2Ph), 5.07 (dd, *J* = 5.9/4.6 Hz, 1H, 3a-H), 6.95–7.00 (m, 2H, H_{phenyl}), 7.32–7.45 (m, 7H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 25.0 (1C, C(CH_3)$_2$), 25.8 (1C, C(CH_3)$_2$), 52.3 (1C, COOCH_3), 70.1 (1C, OCH_2Ph), 80.7 (1C, C-4), 81.8 (1C, C-6a), 82.0 (1C, C-3a), 83.3 (1C, C-6), 113.4 (1C, C(CH_3)$_2$), 114.5 (2C, C_{phenyl}), 127.0 (1C, C_{phenyl}), 127.7 (2C, C_{phenyl}), 128.1 (1C, C_{phenyl}), 128.7 (2C, C_{phenyl}), 129.2 (2C, C_{phenyl}), 137.2 (1C, C_{phenyl}), 158.9 (1C, C_{phenyl}), 167.9 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2986, 2928, 1751, 1612, 1512, 1242, 1211, 1099, 822, 733; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{25}O_6$: 385.1646, found: 385.1667; HPLC (method 1): t_R = 20.6 min, purity 97.9%.

4.2.4. Methyl (3aR,4S,6S,6aR)-6-(4-iodophenyl)-2,2-dimethyltetrahydrofuro [3,4-d][1,3]dioxole-4-carboxylate (**19**)

Sodium metaperiodate (2.83 g, 13.2 mmol) was added to a solution of **17** (2.69 g, 6.61 mmol) in methanol (40 mL) and the reaction was stirred for 2 h at ambient temperature. Then water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in THF (20 mL) and a solution of silver nitrate (2.58 g, 15.2 mmol) in water (20 mL) was added. Then a 0.91 M aqueous solution of KOH (33 mL, 30 mmol) was added dropwise over a period of 5 min. The reaction was stirred for 30 min. Afterwards, the mixture was

filtered. The precipitate was washed twice with an aqueous solution of KOH (0.91 M, 5 mL). The filtrate was acidified to pH 2 with conc. hydrochloric acid. Then the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was dissolved in DMF (20 mL). Potassium carbonate (3.65 g, 26.4 mmol) and iodomethane (0.45 mL, 7.3 mmol) were added and the mixture was stirred overnight at ambient temperature. Afterwards, water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (*n*-hexane/ethyl acetate = 8/2, Ø = 4 cm, h = 15 cm, V = 30 mL, R_f = 0.13) to give **19** as colorless solid (2.02 g, 4.99 mmol, 76% yield). HPLC (method 1): t_R = 19.8 min, purity 98.5%. The analytical data of the isolated compound were in agreement with published data [11].

4.2.5. Methyl (3aR,4S,6S,6aR)-2,2-dimethyl-6-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydrofuro [3,4-d][1,3]dioxole-4-carboxylate (**20**)

Under N_2 atmosphere copper(I) iodide (11 mg, 0.06 mmol), tetrakis(triphenylphosphine)palladium (34 mg, 0.03 mmol) and triethylamine (0.33 mL, 0.24 g, 2.4 mmol) were added to a solution of **19** (120 mg, 0.30 mmol) in acetonitrile (150 mL). Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (90 mg, 0.45 mmol) in acetonitrile (80 mL) was added dropwise over a period of 2 h. The reaction mixture was stirred at ambient temperature for 16 h. After evaporation of the solvent, the residue was purified by flash column chromatography (dichloromethane/methanol = 99/1, Ø = 2 cm, h = 15 cm, V = 10 mL), to give **20** as colorless solid (94 mg, 0.20 mmol, 66% yield). Melting point: 162 °C; TLC (ethyl acetate): R_f = 0.34; Specific rotation: $[\alpha]_D^{20}$ = +44.6 (4.0, methanol); ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.27 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.45–2.62 (m, 4H, NCH_2CH$_2$O), 3.60 (s br, 2H, NCH_2Ar), 3.71–3.83 (m, 4H, NCH$_2$CH_2O), 3.85 (s, 3H, COOCH_3), 4.40 (d, *J* = 4.5 Hz, 1H, 4-H), 4.69 (d, *J* = 3.6 Hz, 1H, 6-H), 4.84 (dd, *J* = 5.8/3.6 Hz, 1H, 6a-H), 5.07–5.11 (m, 1H, 3a-H), 7.33–7.38 (m, 2H, $H_{arom.}$), 7.43–7.55 (m, 6H, $H_{arom.}$); ^{13}C NMR ($CDCl_3$): δ [ppm] = 25.1 (1C, C(*C*H$_3$)$_2$), 25.8 (1C, C(*C*H$_3$)$_2$), 52.3 (1C, COO*C*H$_3$), 53.5 (2C, N*C*H$_2$CH$_2$O), 63.0 (1C, N*C*H$_2$Ar), 66.7 (2C, NCH$_2$*C*H$_2$O), 80.8 (1C, C-4), 81.8 (1C, C-6a), 82.0 (1C, C-3a), 83.3 (1C, C-6), 89.4 (1C, *C*≡C), 89.8 (1C, *C*≡C), 113.6 (1C, *C*(CH$_3$)$_2$), 123.1 (2C, $C_{arom.}$), 127.6 (2C, $C_{arom.}$), 129.6 (2C, $C_{arom.}$), 131.4 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 135.2 (2C, $C_{arom.}$), 167.7 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2982, 1767, 1670, 1520, 1454, 1381, 1204, 1111, 1092, 1007, 910, 864, 826, 795, 748; APCI (*m*/*z*): [M+H]$^+$ calcd for $C_{28}H_{32}NO_6$, 478.2224; found, 478.2322; HPLC (method 1): t_R = 18.3 min, purity 94.4%.

4.2.6. (3aR,4S,6S,6aR)-N-Hydroxy-2,2-dimethyl-6-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydrofuro [3,4-d][1,3]dioxole-4-carboxamide (**21**)

A 5.4 M solution of sodium methoxide in methanol (0.15 mL, 0.79 mmol) was added to a solution of **20** (94 mg, 0.20 mmol) in dichloromethane. Methanol was added until the developing precipitate was entirely dissolved. Then hydroxylamine hydrochloride (54 mg, 0.79 mmol) in methanol (50 mL) was added and the mixture was stirred at ambient temperature for 16 h. 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 purified by flash column chromatography (dichloromethane/methanol = 19/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.32) to give **21** as yellowish oil (22 mg, 0.05 mmol, 23% yield). Specific rotation: $[\alpha]_D^{20}$ = +25.8 (2.4, methanol); ^{1}H NMR (CD_3OD): δ [ppm] = 1.25 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.46–2.51 (m, 4H, NCH_2CH$_2$O), 3.56 (s, 2H, NCH_2Ar), 3.68–3.72 (m, 4H, NCH$_2$CH_2O), 4.34 (d, *J* = 4.1 Hz, 1H, 4-H), 4.77 (d, *J* = 3.6 Hz, 1H, 6-H), 4.88 (dd, *J* = 5.8/3.6 Hz, 1H, 6a-H), 5.06–5.09 (m, 1H, 3a-H), 7.35–7.39 (m, 2H, $H_{arom.}$), 7.47–7.54 (m, 6H, $H_{arom.}$); ^{13}C NMR (CD_3OD): δ [ppm] = 24.7 (1C, C(*C*H$_3$)$_2$), 26.0 (1C, C(*C*H$_3$)$_2$), 54.6 (2C, NCH$_2$CH$_2$O), 63.9 (1C, NCH$_2$Ar), 67.7 (2C, NCH$_2$CH$_2$O), 82.2 (1C, C-4), 82.8 (1C, C-6a), 83.0 (1C, C-3a), 84.6 (1C, C-6), 90.0 (1C, *C*≡C), 90.2 (1C, *C*≡C), 113.7 (1C, *C*(CH$_3$)$_2$), 123.7 (1C, $C_{arom.}$), 123.8 (1C, $C_{arom.}$), 128.7 (2C, $C_{arom.}$), 130.8 (2C, $C_{arom.}$), 131.9 (2C, $C_{arom.}$), 132.5 (2C, $C_{arom.}$), 137.2 (1C, $C_{arom.}$), 138.8 (1C, $C_{arom.}$), 166.7 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3240, 2920, 2855, 1674, 1520, 1454, 1373, 1265, 1207, 1111, 1007, 864, 826, 752; APCI (*m*/*z*): [M+H]$^+$ calcd for $C_{27}H_{31}N_2O_6$, 479.2177; found, 479.2182; HPLC (method 2): t_R = 13.1 min, purity 98.3%.

4.2.7. Methyl (2S,3R,4R,5S)-4-hydroxy-5-(4-iodophenyl)-3-methoxytetrahydrofuran-2-carboxylate (**23**) and Methyl (2S,3R,4S,5S)-3-hydroxy-5-(4-iodophenyl)-4-methoxytetrahydrofuran-2-carboxylate (**24**)

Under N_2 atmosphere a 1 M solution of LiHMDS in THF (0.27 mL, 0.27 mmol) and methyl iodide (0.03 mL, 58 mg, 0.41 mmol) were added to a solution of **22** (100 mg, 0.27 mmol) in DMF (100 mL) at 0 °C. Then the mixture was stirred at room temperature for 4 h. Afterwards, 1 M HCl (0.5 mL) and a saturated aqueous solution of $NaHCO_3$ were added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solved was removed in vacuo. The residue was purified by flash column chromatography (*n*-hexane/ethyl acetate = 8/2, Ø = 2 cm, h = 15 cm, V = 10 mL) to give **23** (*n*-hexane/ethyl acetate = 2/3, R_f = 0.58) as colorless solid (44 mg, 0.12 mmol, 44% yield) and **24** (*n*-hexane/ethyl acetate = 2/3, R_f = 0.63) as colorless oil (21 mg, 0.06 mmol, 21% yield). Analytical data of **23**: Melting point: 113 °C; Specific rotation: $[\alpha]_D^{20}$ = +22.6 (9.2, methanol); ^{1}H NMR (CD_3OD): δ [ppm] = 3.43 (s, 3H, OCH_3), 3.80 (s, 3H, COOCH_3), 4.34–4.38 (m, 2H, 3-H, 4-H), 4.74 (d, *J* = 7.0 Hz, 1H, 2-H), 4.98 (d, *J* = 3.8 Hz, 1H, 5-H), 7.26–7.30 (m, 2H, 2′-H$_{4\text{-iodophenyl}}$, 6′-H$_{4\text{-iodophenyl}}$), 7.66–7.70 (m, 2H, 3′-H$_{4\text{-iodophenyl}}$, 5′-H$_{4\text{-iodophenyl}}$); ^{13}C NMR (CD_3OD): δ [ppm] = 52.6 (1C, COOCH$_3$), 59.6 (1C, OCH$_3$), 73.3 (1C, C-4), 79.1 (1C, C-2), 84.1 (1C, C-3), 84.8 (1C, C-5), 93.6 (1C, C-4′$_{4\text{-iodophenyl}}$), 130.8 (2C, C-2′$_{4\text{-iodophenyl}}$, C-6′$_{4\text{-iodophenyl}}$), 137.9 (2C, C-3′$_{4\text{-iodophenyl}}$, C-5′$_{4\text{-iodophenyl}}$), 138.5 (1C, C-1′$_{4\text{-iodophenyl}}$), 173.1 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3460, 2951, 2882, 1724, 1439, 1377, 1227, 1126, 1084, 1007, 864, 810, 779, 725; APCI (*m*/*z*): [M+H]$^+$ calcd for $C_{13}H_{16}IO_5$, 379.0037; found, 379.0009; HPLC (method 1): t_R = 17.0 min, purity 88.0%. Analytical data of **24**: Specific rotation: $[\alpha]_D^{20}$ = +78.2 (3.3, methanol); ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.13 (s, 3H, OCH_3), 3.85 (s, 3H, COOCH_3), 3.97 (t, *J* = 5.4 Hz, 1H, 4-H), 4.56 (d, *J* = 5.7 Hz, 1H, 2-H), 4.66 (t, *J* = 5.4 Hz, 1H, 3-H), 4.98 (d, *J* = 5.7 Hz, 1H, 5-H), 7.27–7.29 (m, 2H, 2′-H$_{4\text{-iodophenyl}}$, 6′-H$_{4\text{-iodophenyl}}$), 7.66–7.69 (m, 2H, 3′-H$_{4\text{-iodophenyl}}$, 5′-H$_{4\text{-iodophenyl}}$); ^{13}C NMR ($CDCl_3$): δ [ppm] = 52.4 (1C, COOCH$_3$), 59.9 (1C, OCH$_3$), 72.6 (1C, C-3), 79.7 (1C, C-2), 82.1 (1C, C-5), 82.2 (1C, C-4), 93.7 (1C, C-4′$_{4\text{-iodophenyl}}$), 129.6 (2C, C-2′$_{4\text{-iodophenyl}}$, C-6′$_{4\text{-iodophenyl}}$), 136.4 (1C, C-1′$_{4\text{-iodophenyl}}$), 137.2 (2C, C-3′$_{4\text{-iodophenyl}}$, C-5′$_{4\text{-iodophenyl}}$), 169.7 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3487, 2932, 1755, 1439, 1366, 1211, 1123, 1088, 1007, 806, 741; APCI (*m*/*z*): [M+H]$^+$ calcd for $C_{13}H_{16}IO_5$, 379.0037; found, 379.0022; HPLC (method 1): t_R = 18.2 min, purity 91.4%.

4.2.8. Methyl (2S,3R,4R,5S)-4-hydroxy-3-methoxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydrofuran-2-carboxylate (**25**)

Under N_2 atmosphere copper(I) iodide (8.2 mg, 0.04 mmol), tetrakis(triphenylphosphine)palladium (24.8 mg, 0.02 mmol) and

triethylamine (0.24 mL, 0.17 g, 1.71 mmol) were added to a solution of **23** (81 mg, 0.21 mmol) in acetonitrile (100 mL). Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (65 mg, 0.32 mmol) in acetonitrile (50 mL) was added dropwise over a period of 2 h. The reaction was stirred at ambient temperature for 16 h. After evaporation of the solvent, the residue was purified by flash column chromatography (dichloromethane/methanol = 99/1, Ø = 2 cm, h = 15 cm, V = 10 mL), to give **25** as colorless solid (64 mg, 0.14 mmol, 66% yield). Melting point: 135 °C; TLC (ethyl acetate): $R_f = 0.31$; Specific rotation: $[\alpha]_D^{20} = +19.6$ (5.2, methanol); ^{1}H NMR (CD_3OD): δ [ppm] = 2.44–2.49 (m, 4H, NCH_2CH_2O), 3.45 (s, 3H, OCH_3), 3.54 (s, 2H, NCH_2Ar), 3.68–3.71 (m, 4H, NCH$_2$CH_2O), 3.81 (s, 3H, COOCH_3), 4.36–4.41 (m, 2H, 3-H, 4-H), 4.76 (d, J = 7.1 Hz, 1H, 2-H), 5.05 (d, J = 3.9 Hz, 1H, 5-H), 7.34–7.39 (m, 2H, H$_{arom.}$), 7.45–7.55 (m, 6H, H$_{arom.}$); ^{13}C NMR (CD_3OD): δ [ppm] = 52.7 (1C, COOCH_3), 54.7 (2C, NCH$_2$CH$_2$O), 59.6 (1C, OCH$_3$), 64.0 (1C, NCH$_2$Ar), 67.8 (2C, NCH$_2$CH$_2$O), 73.5 (1C, C-4), 79.1 (1C, C-2), 84.1 (1C, C-3), 85.0 (1C, C-5), 89.9 (1C, C≡C), 90.3 (1C, C≡C), 123.6 (1C, C$_{arom.}$), 123.7 (1C, C$_{arom.}$), 128.9 (2C, C$_{arom.}$), 130.7 (2C, C$_{arom.}$), 131.9 (2C, C$_{arom.}$), 132.5 (2C, C$_{arom.}$), 138.9 (1C, C$_{arom.}$), 139.0 (1C, C$_{arom.}$), 173.2 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3460, 2943, 2855, 2805, 1721, 1520, 1439, 1377, 1227, 1115, 1092, 1007, 868, 779; APCI (m/z): $[M+H]^+$ calcd for $C_{26}H_{30}NO_6$, 452.2068; found, 452.2059; HPLC (method 1): t_R = 16.4 min, purity 96.2%.

4.2.9. (2S,3R,4R,5S)-N,4-Dihydroxy-3-methoxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydrofuran-2-carboxamide (**27**)

A 5.4 M solution of sodium methoxide in methanol (0.10 mL, 0.56 mmol) was added to a solution of **25** (64 mg, 0.14 mmol) and hydroxylamine hydrochloride (38 mg, 0.56 mmol) in methanol (20 mL) and the mixture was stirred at ambient temperature for 16 h. Then water was added, the solution was neutralized with 1 M HCl 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 (dichloromethane/methanol = 10/1, Ø = 2 cm, h = 15 cm, V = 10 mL, $R_f = 0.54$) to give **27** as colorless solid (34 mg, 0.08 mmol, 53% yield). Melting point: 190 °C (decomposition); Specific rotation: $[\alpha]_D^{20} = +34.1$ (5.3, methanol); ^{1}H NMR (CD_3OD): δ [ppm] = 2.70–2.82 (m, 4H, NCH_2CH_2O), 3.46 (s, 3H, OCH_3), 3.74–3.80 (m, 4H, NCH$_2$CH_2O), 3.84 (s br, 2H, NCH_2Ar), 4.32 (t, J = 3.9 Hz, 1H, 4-H), 4.42–4.46 (m, 1H, 3-H), 4.57 (d, J = 7.7 Hz, 1H, 2-H), 5.09 (d, J = 3.0 Hz, 1H, 5-H), 7.42–7.45 (m, 2H, H$_{arom.}$), 7.46–7.48 (m, 2H, H$_{arom.}$), 7.49–7.51 (m, 2H, H$_{arom.}$), 7.52–7.55 (m, 2H, H$_{arom.}$); ^{13}C NMR (CD_3OD): δ [ppm] = 54.1 (2C, NCH$_2$CH$_2$O), 58.9 (1C, OCH$_3$), 63.1 (1C, NCH$_2$Ar), 66.8 (2C, NCH$_2$CH$_2$O), 73.1 (1C, C-4), 78.5 (1C, C-2), 83.6 (1C, C-3), 85.6 (1C, C-5), 89.6 (1C, C≡C), 90.9 (1C, C≡C), 123.4 (1C, C$_{arom.}$), 124.7 (1C, C$_{arom.}$), 128.7 (2C, C$_{arom.}$), 131.4 (2C, C$_{arom.}$), 132.0 (2C, C$_{arom.}$), 132.7 (2C, C$_{arom.}$), 139.3 (2C, C$_{arom.}$), 169.3 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3136, 2924, 1655, 1520, 1454, 1385, 1261, 1215, 1126, 1057, 1003, 864, 779, 667; LC-MS (m/z): $[M+H]^+$ calcd for $C_{25}H_{29}N_2O_6$, 453.2020; found, 453.2046; HPLC (method 2): t_R = 12.0 min, purity 97.0%.

4.2.10. Methyl (2S,3R,4S,5S)-3-hydroxy-4-methoxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydrofuran-2-carboxylate (**26**)

Under N_2 atmosphere copper(I) iodide (7.0 mg, 0.04 mmol) tetrakis(triphenylphosphine)palladium (21 mg, 0.02 mmol) and triethylamine (0.21 mL, 0.15 g, 1.5 mmol) were added to a solution of **24** (70 mg, 0.19 mmol) in acetonitrile (100 mL). Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (56 mg, 0.28 mmol) in acetonitrile (50 mL) was added dropwise over a period of 2 h. The reaction was stirred at ambient temperature for 16 h. After evaporation of the solvent, the residue was purified by flash column chromatography (dichloromethane/methanol = 99/1, Ø = 2 cm, h = 15 cm, V = 10 mL), to give **26** as a yellowish solid (37 mg, 0.08 mmol, 44% yield). Melting point: 129 °C; TLC (ethyl acetate): $R_f = 0.26$; Specific rotation: $[\alpha]_D^{20} = +16.9$ (5.0, methanol); ^{1}H NMR (CD_3OD): δ [ppm] = 2.46–2.53 (m, 4H, NCH_2CH_2O), 3.15 (s, 3H, OCH_3) 3.57 (s, 2H, NCH_2Ar), 3.68–3.72 (m, 4H, NCH$_2$CH_2O), 3.82 (s, 3H, COOCH_3), 4.10 (dd, J = 6.4/4.8 Hz, 1H, 4-H), 4.61 (d, J = 5.2 Hz, 1H, 2-H), 4.66 (t, J = 5.0 Hz, 1H, 3-H), 5.10 (d, J = 6.4 Hz, 1H, 5-H), 7.35–7.39 (m, 2H, H$_{arom.}$), 7.43–7.51 (m, 4H, H$_{arom.}$), 7.56–7.60 (m, 2H, H$_{arom.}$); ^{13}C NMR (CD_3OD): δ [ppm] = 52.4 (1C, COOCH$_3$), 54.6 (2C, NCH$_2$CH$_2$O), 59.5 (1C, OCH$_3$), 63.9 (1C, NCH$_2$Ar), 67.7 (2C, NCH$_2$CH$_2$O), 73.3 (1C, C-3), 81.1 (1C, C-2), 83.4 (1C, C-5), 83.9 (1C, C-4), 89.8 (1C, C≡C), 90.4 (1C, C≡C), 123.6 (1C, C$_{arom.}$), 123.9 (1C, C$_{arom.}$), 129.4 (2C, C$_{arom.}$), 130.8 (2C, C$_{arom.}$), 131.7 (2C, C$_{arom.}$), 132.5 (2C, C$_{arom.}$), 138.6 (1C, C$_{arom.}$), 139.5 (1C, C$_{arom.}$), 171.5 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3657, 3441, 2978, 2164, 1748, 1516, 1439, 1381, 1204, 1092, 1007, 961, 864, 783, 721; APCI (m/z): $[M+H]^+$ calcd for $C_{26}H_{30}NO_6$, 452.2068; found, 452.2113; HPLC (method 2): t_R = 13.4 min, purity 95.1%.

4.2.11. (2S,3R,4S,5S)-N,3-Dihydroxy-4-methoxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydrofuran-2-carboxamide (**28**)

A 5.4 M solution of sodium methoxide in methanol (0.09 mL, 0.46 mmol) was added to a solution of **26** (52 mg, 0.12 mmol) and hydroxylamine hydrochloride (32 mg, 0.46 mmol) in methanol (20 mL) and the mixture was stirred at ambient temperature for 16 h. Then water was added, the solution was neutralized with 1 M HCl 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 (dichloromethane/methanol = 10/1, Ø = 2 cm, h = 15 cm, V = 10 mL, $R_f = 0.71$) to give **28** as yellowish solid (17 mg, 0.04 mmol, 33% yield). Melting point: 88 °C; Specific rotation: $[\alpha]_D^{20} = -0.044$ (4.5, methanol); ^{1}H NMR (CD_3OD): δ [ppm] = 2.46–2.50 (m, 4H, NCH_2CH_2O), 3.18 (s, 3H, OCH_3), 3.55 (s, 2H, NCH_2Ar), 3.68–3.72 (m, 4H, NCH$_2$CH_2O), 4.13 (dd, J = 6.4/4.8 Hz, 1H, 4-H), 4.44 (d, J = 4.8 Hz, 1H, 2-H), 4.65 (t, J = 4.8 Hz, 1H, 3-H), 5.07 (d, J = 6.4 Hz, 1H, 5-H), 7.35–7.39 (m, 2H, H$_{arom.}$), 7.45–7.54 (m, 6H, H$_{arom.}$); ^{13}C NMR (CD_3OD): δ [ppm] = 54.6 (2C, NCH$_2$CH$_2$O), 59.6 (1C, OCH$_3$), 63.9 (1C, NCH$_2$Ar), 67.7 (2C, NCH$_2$CH$_2$O), 73.0 (1C, C-3), 81.6 (1C, C-2), 83.6 (1C, C-5), 84.0 (1C, C-4), 89.9 (1C, C≡C), 90.3 (1C, C≡C), 123.7 (2C, C$_{arom.}$), 129.4 (2C, C$_{arom.}$), 130.7 (2C, C$_{arom.}$), 131.8 (2C, C$_{arom.}$), 132.5 (2C, C$_{arom.}$), 138.9 (1C, C$_{arom.}$), 139.0 (1C, C$_{arom.}$), 168.4 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3221, 2924, 1667, 1516, 1454, 1292, 1111, 1069, 1007, 914, 864, 837, 752; LC-MS (m/z): $[M+H]^+$ calcd for $C_{25}H_{29}N_2O_6$, 453.2020; found, 453.2061; HPLC (method 2): t_R = 12.0 min, purity 95.0%.

4.2.12. Methyl (3aR,4R,6S,6aR)-6-[4-(benzyloxy)phenyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**29**)

Under nitrogen atmosphere, a 5.4 M solution of sodium methoxide in methanol (0.75 mL, 4.1 mmol) was added to a solution of **18** (1.3 g, 3.38 mmol) in dry methanol (20 mL) and the mixture was heated to reflux for 30 min. After cooling the solution to ambient temperature, a 1 M solution of hydrochloric acid (6 mL) was added. The mixture was then extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 4/1, Ø = 3 cm, h = 15 cm, V = 20 mL, $R_f = 0.26$) to give **29** as colorless solid

(444 mg, 1.16 mmol, 34% yield). Melting point: 97 °C; Specific rotation: $[\alpha]_D^{20}$ +62.1 (c = 4.3; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.29 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.79 (s, 3H, COOCH_3), 4.71 (s, 1H, 4-H), 4.77 (dd, J = 5.6/3.9 Hz, 1H, 6a-H), 5.02–5.09 (m, 4H, 3a-H, 6-H, OCH_2Ph), 6.94–6.99 (m, 2H, H_{phenyl}), 7.29–7.45 (m, 7H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.8 (1C, C(CH_3)$_2$), 26.3 (1C, C(CH_3)$_2$), 52.5 (1C, COOCH_3), 70.1 (1C, OCH_2Ph), 82.2 (1C, C-6a), 82.4 (1C, C-4), 83.9 (1C, C-6), 84.4 (1C, C-3a), 113.3 (1C, C(CH_3)$_2$), 114.5 (2C, C_{phenyl}), 127.4 (1C, C_{phenyl}), 127.6 (2C, C_{phenyl}), 128.1 (1C, C_{phenyl}), 128.7 (2C, C_{phenyl}), 129.1 (2C, C_{phenyl}), 137.2 (1C, C_{phenyl}), 158.8 (1C, C_{phenyl}), 171.1 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2974, 2936, 1759, 1612, 1516, 1254, 1211, 1092, 814, 745; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{22}H_{25}O_6$: 385.1646, found: 385.1682; HPLC (method 1): t_R = 21.0 min, purity 98.1%.

4.2.13. Methyl (3aR,4R,6S,6aR)-6-(4-iodophenyl)-2,2-dimethyltetrahydrofuro [3,4-d] [1,3]dioxole-4-carboxylate (**30**)

Under nitrogen atmosphere, a 2 M solution of sodium methoxide in methanol (4.65 mL, 9.30 mmol) was added to a solution of **19** (3.13 g, 7.75 mmol) in dry methanol (30 mL). After heating the mixture to reflux for 1 h, first hydrochloric acid (1 M, 12 mL) and then a saturated aqueous solution of sodium bicarbonate were added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 8/2, Ø = 6 cm, h = 15 cm, V = 65 mL, R_f = 0.28) to give **30** as colorless solid (558 mg, 1.38 mmol, 18% yield). Melting point: 86 °C; Specific rotation: $[\alpha]_D^{20}$ = +64.0 (c = 3.3; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.28 (s, 3H, C(CH_3)$_2$), 1.46 (s, 3H, C(CH_3)$_2$), 3.80 (s, 3H, COOCH_3), 4.73 (s, 1H, 4-H), 4.80 (dd, J = 5.8/3.8 Hz, 1H, 6a-H), 5.05–5.09 (m, 2H, 3a-H, 6-H), 7.13–7.17 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.67–7.70 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.9 (1C, C(CH_3)$_2$), 26.2 (1C, C(CH_3)$_2$), 52.5 (1C, COOCH_3), 82.1 (1C, C-6a), 82.6 (1C, C-4), 83.7 (1C, C-6), 84.4 (1C, C-3a), 93.9 (1C, C-4$_{phenyl}$), 113.5 (1C, C(CH_3)$_2$), 129.4 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 135.1 (1C, C-1$_{phenyl}$), 137.2 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 170.9 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2974, 2928, 1744, 1485, 1373, 1211, 1092, 1065, 1003, 810, 741; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{15}H_{18}IO_5$: 405.0193, found: 405.0219; HPLC (method 1): t_R = 20.4 min, purity 93.7%.

4.2.14. Methyl 5-(4-iodophenyl)furan-2-carboxylate (**34**)

Under nitrogen atmosphere, a 5.4 M solution of sodium methoxide in methanol (0.44 mL, 2.35 mmol) was added to a solution of **19** (793 mg, 1.96 mmol) in dry methanol (20 mL). After heating the mixture to reflux for 1 h, first hydrochloric acid (1 M, 3 mL) and then a saturated aqueous solution of sodium bicarbonate were added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 9/1, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.35) to give **34** as colorless solid (66 mg, 0.20 mmol, 10% yield). Melting point: 123 °C; ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.92 (s, 3H, COOCH_3), 6.75 (d, J = 3.6 Hz, 1H, 4-H_{furan}), 7.24 (d, J = 3.6 Hz, 1H, 3-H_{furan}), 7.49–7.53 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.74–7.77 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 52.1 (1C, COOCH_3), 94.8 (1C, C-4$_{phenyl}$), 107.6 (1C, C-4$_{furan}$), 120.1 (1C, C-3$_{furan}$), 126.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 129.1 (1C, C-1$_{phenyl}$), 138.1 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 144.1 (1C, C-2$_{furan}$), 156.6 (1C, C-5$_{furan}$), 159.2 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3132, 2978, 2947, 1697, 1470, 1435, 1300, 1277, 1134, 980, 918, 802, 756, 671; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{12}H_{10}IO_3$: 328.9669, found: 328.9679; HPLC (method 1): t_R = 21.1 min, purity 99.3%.

4.2.15. Methyl 5-[4-(phenylethynyl)phenyl]furan-2-carboxylate (**35**)

Under nitrogen atmosphere, copper(I) iodide (7 mg, 0.04 mmol), tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) and triethylamine (0.18 mL, 1.32 mmol) were added to a solution of **34** (62 mg, 0.19 mmol) in dry acetonitrile (10 mL) at ambient temperature. Then a solution of phenylacetylene (0.10 mL, 0.94 mmol) in dry acetonitrile (3 mL) was added dropwise over a period of 3 h. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (cyclohexane/ethyl acetate = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.27) to give **35** as yellowish solid (49 mg, 0.16 mmol, 86% yield). Melting point: 170 °C (decomposition); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.93 (s, 3H, COOCH_3), 6.77–6.78 (m, 1H, 4-H_{furan}), 7.25–7.27 (m, 1H, 3-H_{furan}), 7.34–7.38 (m, 3H, H_{phenyl}), 7.53–7.60 (m, 4H, H_{phenyl}), 7.75–7.79 (m, 2H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 52.1 (1C, COOCH_3), 89.2 (1C, PhC≡CPh), 91.3 (1C, PhC≡CPh), 107.7 (1C, C-4$_{furan}$), 120.2 (1C, C-3$_{furan}$), 123.2 (1C, C_{phenyl}), 123.9 (1C, C_{phenyl}), 124.8 (2C, C_{phenyl}), 125.5 (2C, C_{phenyl}), 128.6 (1C, C_{phenyl}), 129.2 (1C, C_{phenyl}), 131.8 (2C, C_{phenyl}), 132.2 (2C, C_{phenyl}), 144.0 (1C, C-2$_{furan}$), 157.0 (1C, C-5$_{furan}$), 159.3 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3121, 2951, 1701, 1474, 1296, 1273, 1130, 922, 810, 752, 687; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{20}H_{15}O_3$: 303.1016, found: 303.1047; HPLC (method 1): t_R = 25.5 min, purity 98.2%.

4.2.16. N-Hydroxy-5-[4-(phenylethynyl)phenyl]furan-2-carboxamide (**36**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (94 mg, 1.36 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.25 mL, 1.36 mmol) were added to a solution of **35** (41 mg, 0.14 mmol) in dry methanol/THF (1/1, 10 mL) and the mixture was stirred at ambient temperature for 60 h. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 98/2, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.15) to give **36** as colorless solid (20 mg, 0.07 mmol, 49% yield). Melting point: 153 °C (decomposition); ^{1}H NMR: (CD_3OD): δ [ppm] = 6.99 (d, J = 3.6 Hz, 1H, 4-H_{furan}), 7.18–7.21 (m, 1H, 3-H_{furan}), 7.35–7.41 (m, 3H, H_{phenyl}), 7.51–7.55 (m, 2H, H_{phenyl}), 7.57–7.60 (m, 2H, H_{phenyl}), 7.86–7.89 (m, 2H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 89.8 (1C, PhC≡CPh), 91.7 (1C, PhC≡CPh), 108.8 (1C, C-4$_{furan}$), 117.6 (1C, C-3$_{furan}$), 124.4 (1C, C_{phenyl}), 124.7 (1C, C_{phenyl}), 125.6 (2C, C_{phenyl}), 129.6 (2C, C_{phenyl}), 129.7 (1C, C_{phenyl}), 130.7 (1C, C_{phenyl}), 132.6 (2C, C_{phenyl}), 133.0 (2C, C_{phenyl}), 146.6 (1C, C-2$_{furan}$), 156.7 (1C, C-5$_{furan}$), 165.6 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3341, 2978, 2924, 1643, 1616, 1381, 1153, 1072, 957, 841, 799, 752, 691; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{19}H_{14}NO_3$: 304.0968, found: 304.0995; HPLC (method 2): t_R = 17.0 min, purity 98.3%.

4.2.17. Methyl (2S,4S,5S)-4-hydroxy-5-(4-hydroxyphenyl) tetrahydrofuran-2-carboxylate (**37**)

Under nitrogen atmosphere, a 5.4 M solution of sodium methoxide in methanol (0.05 mL, 0.27 mmol) was added to a solution of **18** (521 mg, 1.36 mmol) in dry methanol (15 mL) and the mixture was heated to reflux overnight. After cooling the solution to ambient temperature, an aqueous solution of sodium dihydrogen phosphate (1 M, 10 mL) was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography

(cyclohexane/ethyl acetate = 3/1, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.17) to give a colorless solid (119 mg). The colorless solid was dissolved in methanol (10 mL) and palladium on activated charcoal (10% Pd, 12 mg) was added. The mixture was stirred for 19 h under hydrogen (balloon) at ambient temperature. Afterwards, the mixture was filtered through Celite® 545. Then the solvent was removed in vacuo and the product was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.21) to give **37** as colorless oil (69 mg, 0.29 mmol, 21% yield over two steps). Specific rotation: $[\alpha]_D^{20}$ = +61.3 (c = 2.5; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 2.35 (ddd, J = 13.6/3.3/1.5 Hz, 1H, 3-H), 2.64 (ddd, J = 13.6/9.8/4.8 Hz, 1H, 3-H), 3.78 (s, 3H, COOCH_3), 4.23 (ddd, J = 4.8/3.4/1.5 Hz, 1H, 4-H), 4.61 (dd, J = 9.8/3.3 Hz, 1H, 2-H), 4.88 (d, J = 3.4 Hz, 1H, 5-H), 6.76–6.78 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.34–6.37 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 40.1 (1C, C-3), 52.5 (1C, COOCH_3), 73.4 (1C, C-4), 76.6 (1C, C-2), 88.1 (1C, C-5), 115.6 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 128.9 (1C, C-1$_{phenyl}$), 130.2 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 158.1 (1C, C-4$_{phenyl}$), 175.3 (1C, COOCH$_3$); NOE: Irradiation at 4.61 ppm (2-H): δ [ppm] = 2.35 (3-H), 2.64 (3-H), 3.78 (COOCH_3), 4.88 (5-H); Irradiation at 4.88 ppm (5-H): δ [ppm] = 2.64 (3-H), 4.23 (4-H), 4.61 (2-H), 7.34–6.37 (2-H_{phenyl}, 6-H_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3375, 2955, 1728, 1516, 1439, 1223, 1092, 1065, 814, 787; HRMS (m/z): [M+H]$^+$ calcd for $C_{12}H_{15}O_5$: 239.0914, found: 239.0918; HPLC (method 1): t_R = 8.2 min, purity 99.7%.

4.2.18. Methyl (2S,4S,5S)-4-hydroxy-5-(4-{[(trifluoromethyl) sulfonyl]oxy}phenyl)tetrahydrofuran-2-carboxylate (**38**)

Triethylamine (0.04 mL, 0.39 mmol) was added to a solution of **37** (62 mg, 0.26 mmol) in dichloromethane (10 mL) at −20 °C. Then a 10% (V/V) solution of trifluoromethanesulfonic anhydride (0.44 mL, 0.26 mmol) in dichloromethane was added slowly. The reaction was stirred for 30 min at −20 °C. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.33) to give **38** as colorless solid (79 mg, 0.21 mmol, 82% yield). Melting point: 95 °C; Specific rotation: $[\alpha]_D^{20}$ = +38.1 (c = 2.1; methanol); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 2.25 (ddd, J = 13.1/2.8/1.6 Hz, 1H, 3-H), 2.54 (ddd, J = 13.1/9.6/4.4 Hz, 1H, 3-H), 3.68 (s, 3H, COOCH_3), 4.26–4.29 (m, 1H, 4-H), 4.65 (dd, J = 9.6/2.8 Hz, 1H, 2-H), 4.73 (d, J = 4.0 Hz, 1H, OH), 4.97 (d, J = 3.5 Hz, 1H, 5-H), 7.42–7.45 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.65-6.68 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}); ^{13}C NMR: (DMSO-d_6): δ [ppm] = 39.5 (1C, C-3), 51.6 (1C, COOCH_3), 70.9 (1C, C-4), 75.2 (1C, C-2), 84.9 (1C, C-5), 118.3 (q, J = 321 Hz, 1C, CF$_3$), 120.3 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.9 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 139.5 (1C, C-1$_{phenyl}$), 148.2 (1C, C-4$_{phenyl}$), 173.0 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3491, 2959, 1732, 1504, 1416, 1200, 1138, 1084, 887, 783, 737; HRMS (m/z): [M+H]$^+$ calcd for $C_{13}H_{14}F_3O_7S$: 371.0407, found: 371.0427; HPLC (method 1): t_R = 19.6 min, purity 98.9%.

4.2.19. Methyl (2S,4S,5S)-4-hydroxy-5-(4-{[4-(morpholinomethyl) phenyl]ethynyl}phenyl)-tetrahydrofuran-2-carboxylate (**39**)

Under nitrogen atmosphere, copper(I) iodide (4 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.01 mmol) and triethylamine (0.10 mL, 0.74 mmol) were added to a solution of **38** (39 mg, 0.11 mmol) in dry acetonitrile (10 mL) at ambient temperature. Then the mixture was heated to reflux and a solution of 4-(morpholinomethyl)phenylacetylene [11] (32 mg, 0.16 mmol) in dry acetonitrile (1 mL) was added over a period of 1 h. The mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified by automatic flash column chromatography (ethyl acetate/methanol, 1% methanol → 10% methanol, Biotage® SNAP 25 g) to give **39** as yellowish oil (25 mg, 0.06 mmol, 56% yield). TLC (dichloromethane/methanol = 19/1): R_f = 0.44; Specific rotation: $[\alpha]_D^{20}$ = +27.6 (c = 1.5; dichloromethane); ^{1}H NMR: (CD_3OD): δ [ppm] = 2.38 (ddd, J = 13.5/3.2/1.5 Hz, 1H, 3-H), 2.47–2.52 (m, 4H, N(CH_2CH_2)$_2$), 2.67 (ddd, J = 13.5/9.8/4.7 Hz, 1H, 3-H), 3.56 (s, 2H, PhCH_2N), 3.69–3.71 (m, 4H, N(CH_2CH_2)$_2$), 3.79 (s, 3H, COOCH_3), 4.34–4.36 (m, 1H, 4-H), 4.67 (dd, J = 9.8/3.2 Hz, 1H, 2-H), 5.00 (d, J = 3.4 Hz, 1H, 5-H), 7.36–7.38 (m, 2H, 3′-H$_{4\text{-(morpholinomethyl)phenyl}}$, 5′-H$_{4\text{-(morpholinomethyl)phenyl}}$), 7.47–7.50 (m, 4H, 3-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, 5-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, 2′-H$_{4\text{-(morpholinomethyl)phenyl}}$, 6′-H$_{4\text{-(morpholinomethyl)phenyl}}$), 7.54–7.58 (m, 2H, 2-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, 6-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$); ^{13}C NMR: ($CD_3OD$): δ [ppm] = 40.3 (1C, C-3), 52.6 (1C, COOCH_3), 54.6 (2C, N(CH_2CH_2)$_2$), 63.9 (1C, PhCH_2N), 67.7 (2C, N(CH_2CH_2)$_2$), 73.4 (1C, C-4), 77.0 (1C, C-2), 87.9 (1C, C-5), 89.8 (1C, PhC≡CPh'), 90.4 (1C, PhC≡CPh'), 123.6 (1C, C-4$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 123.8 (1C, C-1′$_{4\text{-(morpholinomethyl)phenyl}}$), 129.0 (2C, C-2$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, C-6$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 130.8 (2C, C-3′$_{4\text{-(morpholinomethyl)phenyl}}$, C-5′$_{4\text{-(morpholinomethyl)phenyl}}$), 132.0 (2C, C-3$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, C-5$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 132.5 (2C, C-2′$_{4\text{-(morpholinomethyl)phenyl}}$, C-6′$_{4\text{-(morpholinomethyl)phenyl}}$), 138.7 (1C, C-4′$_{4\text{-(morpholinomethyl)phenyl}}$), 139.2 (1C, C-1$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 175.2 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2951, 2824, 1751, 1435, 1265, 1107, 1092, 1034, 1003, 864, 791, 721, 694; HRMS (m/z): [M+H]$^+$ calcd for $C_{25}H_{28}NO_5$: 422.1962, found: 422.1936.

4.2.20. (2S,4S,5S)-N,4-Dihydroxy-5-(4-{[4-(morpholinomethyl) phenyl]ethynyl}phenyl)tetrahydrofuran-2-carboxamide (**40**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (12 mg, 0.18 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.03 mL, 0.18 mmol) were added to a solution of **39** (25 mg, 0.06 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 70 h. Afterwards, the solvent was removed in vacuo and the residue was purified by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) to give **40** as colorless solid (8 mg, 0.02 mmol, 32% yield). RP-TLC (H_2O/ACN = 1/1): R_f = 0.20; Specific rotation: $[\alpha]_D^{20}$ = +92.8 (c = 1.3; DMF); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 1.91–1.96 (m, 1H, 3-H), 2.34–2.38 (m, 4H, N(CH_2CH_2)$_2$), 2.42–2.48 (m, 1H, 3-H), 3.49 (s, 2H, PhCH_2N), 3.56–3.59 (m, 4H, N(CH_2CH_2)$_2$), 4.10–4.13 (m, 1H, 4-H), 4.35 (dd, J = 9.5/1.9 Hz, 1H, 2-H), 4.81 (d, J = 3.0 Hz, 1H, 5-H), 7.34–7.37 (m, 2H, 3′-H$_{4\text{-(morpholinomethyl)phenyl}}$, 5′-H$_{4\text{-(morpholinomethyl)phenyl}}$), 7.40–7.48 (m, 4H, 2-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, 3-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, 5-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, 6-H$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 7.49–7.53 (m, 2H, 2′-H$_{4\text{-(morpholinomethyl)phenyl}}$, 6′-H$_{4\text{-(morpholinomethyl)phenyl}}$); ^{13}C NMR: (DMSO-$d_6$): δ [ppm] = 38.8 (1C, C-3), 53.2 (2C, N(CH_2CH_2)$_2$), 62.0 (1C, PhCH_2N), 66.2 (2C, N(CH_2CH_2)$_2$), 72.6 (1C, C-4), 76.7 (1C, C-2), 85.8 (1C, C-5), 88.7 (1C, PhC≡CPh'), 89.5 (1C, PhC≡CPh'), 120.5 (1C, C-4$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 121.0 (1C, C-1′$_{4\text{-(morpholinomethyl)phenyl}}$), 127.8 (2C, C-2$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, C-6$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 129.1 (2C, C-3′$_{4\text{-(morpholinomethyl)phenyl}}$, C-5′$_{4\text{-(morpholinomethyl)phenyl}}$), 130.3 (2C, C-3$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$, C-5$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 131.2 (2C, C-2′$_{4\text{-(morpholinomethyl)phenyl}}$, C-6′$_{4\text{-}}$

(morpholinomethyl)phenyl), 138.7 (1C, C-4′$_{4\text{-(morpholinomethyl)phenyl}}$), 140.0 (1C, C-1$_{4\text{-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}}$), 167.7 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3152, 2947, 2847, 1651, 1350, 1107, 1045, 1003, 845, 787, 694; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{24}H_{27}N_2O_5$: 423.1914, found: 423.1909; HPLC (method 2): t_R = 12.3 min, purity 95.5%.

4.2.21. Methyl (3aR,4R,6S,6aR)-6-(4-hydroxyphenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**41**)

Palladium on activated charcoal (10% Pd, 18 mg) was added to a solution of **29** (179 mg, 0.47 mmol) in a mixture of methanol and ethyl acetate (1/1, 20 mL). The mixture was stirred overnight at ambient temperature under hydrogen atmosphere at 4 bar pressure. Afterwards, the mixture was filtered through Celite® 545. Then the solvents were removed in vacuo and the crude product was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.16) to give **41** as colorless solid (112 mg, 0.38 mmol, 82% yield). Melting point: 138 °C; Specific rotation: $[\alpha]_D^{20}$ = +72.4 (c = 3.8; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.30 (s, 3H, C*H*$_3$), 1.51 (s, 3H, C*H*$_3$), 3.79 (s, 3H, COOC*H*$_3$), 4.72 (s, 1H, 4-H), 4.76 (dd, *J* = 5.7/3.7 Hz, 1H, 6a-H), 5.04 (d, *J* = 3.5 Hz, 1H, 6-H), 5.05–5.10 (m, 1H, 3a-H), 6.75–6.82 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.25–7.31 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.8 (1C, C(*C*H$_3$)$_2$), 26.2 (1C, C(*C*H$_3$)$_2$), 52.5 (1C, COO*C*H$_3$), 82.1 (1C, C-6a), 82.4 (1C, C-4), 83.9 (1C, C-6), 84.4 (1C, C-3a), 113.4 (1C, *C*(CH$_3$)$_2$), 115.1 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 127.2 (1C, C-1$_{phenyl}$), 129.2 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 155.6 (1C, C-4$_{phenyl}$), 171.2 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3402, 2994, 2951, 1748, 1520, 1200, 1092, 1049, 980, 748; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{15}H_{19}O_6$: 295.1176, found: 295.1179; HPLC (method 1): t_R = 14.5 min, purity 96.0%.

4.2.22. Methyl (3aR,4R,6S,6aR)-2,2-dimethyl-6-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylate (**42**)

Triethylamine (0.14 mL, 0.99 mmol) was added to a solution of **41** (97 mg, 0.33 mmol) in dichloromethane (20 mL) at −20 °C. Then a solution of trifluoromethanesulfonic anhydride (0.08 mL, 0.49 mmol) in dichloromethane (5 mL) was added slowly. The reaction was stirred for 30 min at −20 °C. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 8/2, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.22) to give **42** as colorless oil (102 mg, 0.24 mmol, 73% yield). Specific rotation: $[\alpha]_D^{20}$ = +39.2 (c = 1.8; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.29 (s, 3H, C*H*$_3$), 1.45 (s, 3H, C*H*$_3$), 3.80 (s, 3H, COOC*H*$_3$), 4.75 (s, 1H, 4-H), 4.84 (dd, *J* = 5.7/3.8 Hz, 1H, 6a-H), 5.07–5.11 (m, 1H, 3a-H), 5.15 (d, *J* = 3.7 Hz, 1H, 6-H), 7.24–7.30 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.46–7.53 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.8 (1C, C(*C*H$_3$)$_2$), 26.2 (1C, C(*C*H$_3$)$_2$), 52.6 (1C, COO*C*H$_3$), 81.9 (1C, C-6a), 82.6 (1C, C-4), 83.2 (1C, C-6), 84.5 (1C, C-3a), 113.6 (1C, *C*(CH$_3$)$_2$), 118.9 (q, *J* = 321 Hz, 1C, *C*F$_3$), 121.0 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 136.0 (1C, C-1$_{phenyl}$), 149.3 (1C, C-4$_{phenyl}$), 170.8 (1C, *C*OOCH$_3$); ^{19}F NMR: ($CDCl_3$): δ [ppm] = −73.4 (3F, C*F*$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2990, 2955, 1748, 1504, 1420, 1204, 1138, 1099, 883, 606; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{16}H_{18}F_3O_8S$: 427.0669, found: 427.0711; HPLC (method 1): t_R = 21.0 min, purity 99.3%.

4.2.23. Methyl (3aR,4R,6S,6aR)-2,2-dimethyl-6-[4-(phenylethynyl)phenyl]tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**43a**)

Under nitrogen atmosphere, copper(I) iodide (18 mg, 0.09 mmol), tetrakis(triphenylphosphine)palladium(0) (109 mg, 0.09 mmol) and triethylamine (1.18 mL, 8.53 mmol) were added to a solution of **42** (404 mg, 0.95 mmol) in dry acetonitrile (20 mL) at ambient temperature. Then a solution of phenylacetylene (0.16 mL, 1.42 mmol) in dry acetonitrile (5 mL) was added dropwise over a period of 1 h. The reaction mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (cyclohexane/ethyl acetate = 8/2, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.28) to give **43a** as yellowish solid (270 mg, 0.71 mmol, 75% yield). Melting point: 115 °C; Specific rotation: $[\alpha]_D^{20}$ = +103.9 (c = 2.9; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.29 (s, 3H, C(C*H*$_3$)$_2$), 1.47 (s, 3H, C(C*H*$_3$)$_2$), 3.81 (s, 3H, COOC*H*$_3$), 4.75–4.76 (m, 1H, 4-H), 4.84 (dd, *J* = 5.8/3.9 Hz, 1H, 6a-H), 5.09 (dd, *J* = 5.8/1.0 Hz, 1H, 3a-H), 5.14 (d, *J* = 3.9 Hz, 1H, 6-H), 7.31–7.36 (m, 3H, H$_{phenyl}$), 7.38–7.41 (m, 2H, H$_{phenyl}$), 7.51–7.54 (m, 4H, H$_{phenyl}$); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.9 (1C, C(*C*H$_3$)$_2$), 26.2 (1C, C(*C*H$_3$)$_2$), 52.5 (1C, COO*C*H$_3$), 82.2 (1C, C-6a), 82.6 (1C, C-4), 83.9 (1C, C-6), 84.5 (1C, C-3a), 89.5 (1C, PhC≡*C*Ph), 89.6 (1C, Ph*C*≡CPh), 113.5 (1C, *C*(CH$_3$)$_2$), 123.0 (1C, C$_{phenyl}$), 123.5 (1C, C$_{phenyl}$), 127.5 (2C, C$_{phenyl}$), 128.3 (1C, C$_{phenyl}$), 128.5 (2C, C$_{phenyl}$), 131.4 (2C, C$_{phenyl}$), 131.7 (2C, C$_{phenyl}$), 135.6 (1C, C$_{phenyl}$), 171.0 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2974, 2940, 1759, 1377, 1211, 1092, 1061, 980, 764, 694; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{23}H_{23}O_5$: 379.1540, found: 379.1562; HPLC (method 1): t_R = 22.0 min, purity 99.5%.

4.2.24. Methyl (3aR,4R,6S,6aR)-2,2-dimethyl-6-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**43b**)

Under nitrogen atmosphere, copper(I) iodide (28 mg, 0.15 mmol), tetrakis(triphenylphosphine)palladium(0) (85 mg, 0.07 mmol) and triethylamine (0.72 mL, 5.17 mmol) were added to a solution of **42** (315 mg, 0.74 mmol) in dry acetonitrile (20 mL) at ambient temperature. Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (1.19 g, 5.91 mmol) in dry acetonitrile (5 mL) was added dropwise over a period of 1 h. The reaction mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 49/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.26) to give **43b** as yellowish solid (313 mg, 0.66 mmol, 89% yield). Melting point: 112 °C; Specific rotation: $[\alpha]_D^{20}$ = +76.0 (c = 8.6; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.29 (s, 3H, C(C*H*$_3$)$_2$), 1.47 (s, 3H, C(C*H*$_3$)$_2$), 2.42–2.47 (m, 4H, N(*CH*$_2$CH$_2$)$_2$), 3.50 (s, 2H, PhC*H*$_2$N), 3.70–3.73 (m, 4H, N(CH$_2$*CH*$_2$)$_2$), 3.80 (s, 3H, COOC*H*$_3$), 4.75–4.76 (m, 1H, 4-H), 4.84 (dd, *J* = 5.8/3.9 Hz, 1H, 6a-H), 5.07–5.09 (m, 1H, 3a-H), 5.14 (d, *J* = 3.9 Hz, 1H, 6-H), 7.29–7.33 (m, 2H, H$_{phenyl}$), 7.37–7.41 (m, 2H, H$_{phenyl}$), 7.46–7.49 (m, 2H, H$_{phenyl}$), 7.50–7.53 (m, 2H, H$_{phenyl}$); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.9 (1C, C(*C*H$_3$)$_2$), 26.2 (1C, C(*C*H$_3$)$_2$), 52.5 (1C, COO*C*H$_3$), 53.8 (2C, N(*C*H$_2$CH$_2$)$_2$), 63.3 (1C, PhCH$_2$N), 67.1 (2C, N(CH$_2$*C*H$_2$)$_2$), 82.2 (1C, C-6a), 82.6 (1C, C-4), 83.9 (1C, C-6), 84.5 (1C, C-3a), 89.4 (1C, PhC≡*C*Ph), 89.5 (1C, Ph*C*≡CPh), 113.5 (1C, *C*(CH$_3$)$_2$), 122.2 (1C, C$_{phenyl}$), 123.0 (1C, C$_{phenyl}$), 127.5 (2C, C$_{phenyl}$), 129.2 (2C, C$_{phenyl}$), 131.3 (2C, C$_{phenyl}$), 131.7 (2C, C$_{phenyl}$), 135.6 (1C, C$_{phenyl}$), 138.3 (1C, C$_{phenyl}$), 171.0 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2951, 2808, 1736, 1520, 1373, 1207, 1111, 1007, 864, 748; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{28}H_{32}NO_6$: 478.2224, found: 478.2227; HPLC (method 1): t_R = 18.1 min, purity 99.5%.

*4.2.25. Methyl (3aR,4R,6S,6aR)-2,2-dimethyl-6-{4-[(trimethylsilyl) ethynyl]phenyl}tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**43d**)*

Under nitrogen atmosphere, copper(I) iodide (20 mg, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (123 mg, 0.11 mmol) and triethylamine (1.33 mL, 9.60 mmol) were added to a solution of **42** (455 mg, 1.07 mmol) in dry acetonitrile (20 mL) at ambient temperature. Then a solution of trimethylsilylacetylene (0.22 mL, 1.60 mmol) in dry acetonitrile (5 mL) was added dropwise over a period of 1 h. The reaction mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 9/1, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.18) to give **43d** as colorless solid (357 mg, 0.95 mmol, 89% yield). Melting point: 123 °C; Specific rotation: $[\alpha]_D^{20}$ = +89.5 (c = 3.5; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 0.24 (s, 9H, Si(CH_3)$_3$), 1.27 (s, 3H, C(CH_3)$_2$), 1.43 (s, 3H, C(CH_3)$_2$), 3.79 (s, 3H, COOCH_3), 4.73–4.75 (m, 1H, 4-H), 4.81 (dd, *J* = 5.7/4.0 Hz, 1H, 6a-H), 5.06–5.08 (m, 1H, 3a-H), 5.12 (d, *J* = 3.8 Hz, 1H, 6-H), 7.32–7.35 (m, 2H, H_{phenyl}), 7.44–7.47 (m, 2H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 0.12 (3C, Si(CH_3)$_3$), 24.9 (1C, C(CH_3)$_2$), 26.2 (1C, C(CH_3)$_2$), 52.5 (1C, COOCH_3), 82.2 (1C, C-6a), 82.6 (1C, C-4), 83.9 (1C, C-6), 84.4 (1C, C-3a), 94.3 (1C, PhC≡CSi(CH_3)$_3$), 105.3 (1C, PhC≡CSi(CH_3)$_3$), 113.5 (1C, C(CH_3)$_2$), 122.8 (1C, C-4$_{phenyl}$), 127.3 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.7 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 135.9 (1C, C-1$_{phenyl}$), 171.0 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2955, 2156, 1759, 1373, 1246, 1207, 1103, 976, 837, 752; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{20}H_{27}O_5Si$: 375.1622, found: 375.1632; HPLC (method 1): t_R = 22.7 min, purity 97.4%.

*4.2.26. Methyl (2R,3R,4S,5S)-3,4-dihydroxy-5-[4-(phenylethynyl) phenyl]tetrahydrofuran-2-carboxylate (**44a**)*

p-TsOH (21 mg, 0.11 mmol) was added to a solution of **43a** (211 mg, 0.56 mmol) in methanol (30 mL). The mixture was heated to reflux for 40 h. Then a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.24) to give **44a** as colorless solid (121 mg, 0.36 mmol, 64% yield). Melting point: 181 °C; Specific rotation: $[\alpha]_D^{20}$ = +81.3 (c = 2.9; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.81 (s, 3H, COOCH_3), 4.20–4.22 (m, 1H, 4-H), 4.50 (d, *J* = 7.5 Hz, 1H, 2-H), 4.52 (dd, *J* = 7.5/4.0 Hz, 1H, 3-H), 5.20 (d, *J* = 2.9 Hz, 1H, 5-H), 7.33–7.38 (m, 3H, H_{phenyl}), 7.39–7.42 (m, 2H, H_{phenyl}), 7.48–7.52 (m, 4H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 52.7 (1C, COOCH_3), 75.0 (1C, C-4), 78.1 (1C, C-3), 82.0 (1C, C-2), 85.1 (1C, C-5), 90.0 (1C, PhC≡CPh), 90.2 (1C, PhC≡CPh), 123.6 (1C, C$_{phenyl}$), 124.6 (1C, C$_{phenyl}$), 128.6 (2C, C$_{phenyl}$), 129.4 (1C, C$_{phenyl}$), 129.5 (2C, C$_{phenyl}$), 132.0 (2C, C$_{phenyl}$), 132.5 (2C, C$_{phenyl}$), 139.1 (1C, C$_{phenyl}$), 174.8 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3449, 2951, 1732, 1512, 1439, 1227, 1092, 972, 756, 694; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{20}H_{19}O_5$: 339.1227, found: 339.1252; HPLC (method 1): t_R = 18.0 min, purity 99.7%.

*4.2.27. Methyl (2R,3R,4S,5S)-3,4-dihydroxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydrofuran-2-carboxylate (**44b**)*

p-TsOH (240 mg, 1.26 mmol) was added to a solution of **43b** (274 mg, 0.57 mmol) in methanol (20 mL). The mixture was heated to reflux for 72 h. Then a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 19/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.30) to give **44b** as colorless solid (160 mg, 0.37 mmol, 64% yield). Melting point: 102 °C; Specific rotation: $[\alpha]_D^{20}$ = +60.8 (c = 2.1; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 2.40–2.45 (m, 4H, N(CH_2CH_2)$_2$), 3.49 (s, 2H, PhCH_2N), 3.67–3.70 (m, 4H, N(CH_2CH_2)$_2$), 3.83 (s, 3H, COOCH_3), 4.28–4.32 (m, 1H, 4-H), 4.56–4.58 (m, 2H, 2-H, 3-H), 5.28 (d, *J* = 3.2 Hz, 1H, 5-H), 7.29–7.32 (m, 2H, H_{phenyl}), 7.35–7.38 (m, 2H, H_{phenyl}), 7.46–7.49 (m, 2H, H_{phenyl}), 7.52–7.55 (m, 2H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 52.7 (1C, COOCH_3), 53.7 (2C, N(CH_2CH_2)$_2$), 63.3 (1C, PhCH_2N), 67.1 (2C, N(CH_2CH_2)$_2$), 73.4 (1C, C-4), 76.8 (1C, C-3), 81.6 (1C, C-2), 83.7 (1C, C-5), 89.1 (1C, PhC≡CPh), 89.9 (1C, PhC≡CPh), 122.1 (1C, C$_{phenyl}$), 123.4 (1C, C$_{phenyl}$), 127.1 (2C, C$_{phenyl}$), 129.3 (2C, C$_{phenyl}$), 131.7 (2C, C$_{phenyl}$), 131.8 (2C, C$_{phenyl}$), 136.0 (1C, C$_{phenyl}$), 138.3 (1C, C$_{phenyl}$), 172.5 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3372, 2951, 1736, 1516, 1292, 1204, 1111, 1003, 860, 795; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{25}H_{28}NO_6$: 438.1911, found: 438.1918; HPLC (method 1): t_R = 13.6 min, purity 99.7%.

*4.2.28. Methyl (3aR,4R,6S,6aR)-6-(4-ethynylphenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**45**)*

Silver nitrate (14 mg, 0.08 mmol) and water (1.50 mL, 83.3 mmol) were added to a solution of **43d** (312 mg, 0.83 mmol) in acetone (20 mL). The mixture was stirred for 24 h at ambient temperature in the dark. Afterwards, water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 8/2, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.32) to give **45** as colorless solid (205 mg, 0.68 mmol, 81% yield). Melting point: 115 °C; Specific rotation: $[\alpha]_D^{20}$ = +97.3 (c = 2.9; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.28 (s, 3H, C(CH_3)$_2$), 1.45 (s, 3H, C(CH_3)$_2$), 3.06 (s, 1H, PhC≡C*H*), 3.80 (s, 3H, COOCH_3), 4.74–4.75 (m, 1H, 4-H), 4.83 (dd, *J* = 5.7/4.0 Hz, 1H, 6a-H), 5.07–5.09 (m, 1H, 3a-H), 5.13 (d, *J* = 3.8 Hz, 1H, 6-H), 7.35–7.38 (m, 2H, H_{phenyl}), 7.47–7.50 (m, 2H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 24.9 (1C, C(CH_3)$_2$), 26.2 (1C, C(CH_3)$_2$), 52.5 (1C, COOCH_3), 77.3 (1C, PhC≡CH), 82.2 (1C, C-6a), 82.6 (1C, C-4), 83.8 (1C, PhC≡CH), 83.9 (1C, C-6), 84.4 (1C, C-3a), 113.5 (1C, C(CH_3)$_2$), 121.8 (1C, C-4$_{phenyl}$), 127.4 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.9 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 136.2 (1C, C-1$_{phenyl}$), 170.9 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3256, 2959, 1740, 1277, 1207, 1084, 980, 814, 706, 664; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{17}H_{19}O_5$: 303.1227, found: 303.1207; HPLC (method 1): t_R = 19.1 min, purity 96.7%.

*4.2.29. (3aR,4R,6S,6aR)-N-Butyl-2,2-dimethyl-6-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide (**46**)*

Copper(I) chloride (3 mg, 0.03 mmol) was added to an aqueous solution of *n*-butylamine (30% (V/V), 10 mL) at ambient temperature. The resulting blue color was discharged by adding a few crystals of hydroxylamine hydrochloride. Addition of **45** (178 mg, 0.59 mmol) at ambient temperature led to a yellow acetylide suspension that was immediately cooled by a water-ice bath. Afterwards (bromoethynyl)benzene (0.08 mL, 0.71 mmol) was added at once. Then the water-ice bath was removed and Et_2O (5 mL) was added. The reaction was stirred for 30 min. During this time hydroxylamine hydrochloride was added when the mixture turned green or blue. Afterwards, water was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried over sodium sulfate, filtered and the

solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.22) to give **46** as colorless solid (125 mg, 0.28 mmol, 48% yield). Melting point: 132 °C; Specific rotation: $[\alpha]_D^{20}$ = +145.9 (c = 1.3; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 0.92 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.28 (s, 3H, $C(CH_3)_2$), 1.33 (sext, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.45 (s, 3H, $C(CH_3)_2$), 1.49 (quint, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2CH_3$), 3.21–3.28 (m, 1H, $CH_2CH_2CH_2CH_3$), 3.28–3.35 (m, 1H, $CH_2CH_2CH_2CH_3$), 4.62 (s, 1H), 4.76–4.78 (m, 2H), 5.33–5.35 (m, 1H), 6.62 (t, *J* = 5.4 Hz, 1H, NH), 7.32–7.40 (m, 5H, H_{phenyl}), 7.51–7.56 (m, 4H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 13.8 (1C, $CH_2CH_2CH_2CH_3$), 20.2 (1C, $CH_2CH_2CH_2CH_3$), 23.8 (1C, $C(CH_3)_2$), 26.2 (1C, $C(CH_3)_2$), 31.8 (1C, $CH_2CH_2CH_2CH_3$), 39.1 (1C, $CH_2CH_2CH_2CH_3$), 74.0 (1C, PhC≡CC≡CPh), 74.4 (1C, PhC≡CC≡CPh), 81.5 (1C, PhC≡CC≡CPh), 81.9 (1C, PhC≡CC≡CPh), 82.0 (1C), 83.6 (1C), 83.7 (1C), 84.0 (1C), 113.1 (1C, $C(CH_3)_2$), 121.8 (1C, C_{phenyl}), 121.9 (1C, C_{phenyl}), 127.6 (2C, C_{phenyl}), 128.6 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 132.4 (2C, C_{phenyl}), 132.6 (2C, C_{phenyl}), 136.5 (1C, C_{phenyl}), 169.0 (1C, CONH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3298, 2928, 2851, 1651, 1531, 1369, 1207, 1088, 1065, 822, 752, 687; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}NO_4$: 444.2169, found: 444.2212; HPLC (method 1): t_R = 23.4 min, purity 99.4%.

4.2.30. Methyl (2R,3R,4S,5S)-3,4-dihydroxy-5-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]tetrahydrofuran-2-carboxylate (**44c**)

p-TsOH (730 mg, 3.84 mmol) was added to a solution of **46** (116 mg, 0.26 mmol) in methanol (10 mL). The mixture was heated under microwave irradiation for 1 h at 115 °C, 20 bar and 50 W. Then a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.20) to give **44c** as colorless solid (40 mg, 0.11 mmol, 42% yield). Melting point: 160 °C; Specific rotation: $[\alpha]_D^{20}$ = +77.9 (c = 0.9; methanol); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.84 (s, 3H, $COOCH_3$), 4.33 (t, *J* = 3.4 Hz, 1H, 4-H), 4.56–4.60 (m, 2H, 2-H, 3-H), 5.29 (d, *J* = 3.2 Hz, 1H, 5-H), 7.32–7.39 (m, 5H, H_{phenyl}), 7.51–7.56 (m, 4H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 52.7 (1C, $COOCH_3$), 73.5 (1C, C-4), 74.0 (1C, PhC≡CC≡CPh), 74.5 (1C, PhC≡CC≡CPh), 76.8 (1C, C-3), 81.3 (1C, PhC≡CC≡CPh), 81.6 (1C, C-2), 82.0 (1C, PhC≡CC≡CPh), 83.6 (1C, C-5), 121.8 (1C, C_{phenyl}), 121.9 (1C, C_{phenyl}), 127.1 (2C, C_{phenyl}), 128.6 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 132.6 (2C, C_{phenyl}), 132.7 (2C, C_{phenyl}), 137.1 (1C, C_{phenyl}), 172.4 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3453, 2951, 1728, 1438, 1204, 1084, 1049, 972, 772, 687; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{19}O_5$: 363.1227, found: 363.1223; HPLC (method 1): t_R = 19.5 min, purity 99.3%.

4.2.31. (2R,3R,4S,5S)-N,3,4-Trihydroxy-5-[4-(phenylethynyl)phenyl]tetrahydrofuran-2-carboxamide (**47a**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (59 mg, 0.84 mmol) and a 2 M solution of sodium methoxide in methanol (0.42 mL, 0.84 mmol) were added to a solution of **44a** (114 mg, 0.34 mmol) in dry methanol (20 mL) and the mixture was stirred at ambient temperature for 48 h. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.39) to give **47a** as colorless solid (64 mg, 0.19 mmol, 56% yield). Melting point: 143 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = +80.5 (c = 5.5; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 4.20–4.23 (m, 1H, 4-H), 4.35 (d, *J* = 7.6 Hz, 1H, 2-H), 4.52 (dd, *J* = 7.6/4.3 Hz, 1H, 3-H), 5.22 (d, *J* = 2.9 Hz, 1H, 5-H), 7.33–7.39 (m, 3H, H_{phenyl}), 7.39–7.43 (m, 2H, H_{phenyl}), 7.47–7.52 (m, 4H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 75.1 (1C, C-4), 77.8 (1C, C-3), 81.5 (1C, C-2), 85.0 (1C, C-5), 90.0 (1C, PhC≡CPh), 90.2 (1C, PhC≡CPh), 123.5 (1C, C_{phenyl}), 124.6 (1C, C_{phenyl}), 128.5 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 129.5 (2C, C_{phenyl}), 132.0 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 139.4 (1C, C_{phenyl}), 171.1 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3217, 2909, 1655, 1512, 1439, 1408, 1300, 1207, 1130, 1072, 1018, 779, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{18}NO_5$: 340.1179, found: 340.1215; HPLC (method 2): t_R = 16.3 min, purity 98.0%.

4.2.32. (2R,3R,4S,5S)-N,3,4-Trihydroxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydro-furan-2-carboxamide (**47b**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (125 mg, 1.80 mmol) and a 2 M solution of sodium methoxide in methanol (0.90 mL, 1.80 mmol) were added to a solution of **44b** (131 mg, 0.30 mmol) in dry methanol (15 mL) and the mixture was stirred at ambient temperature for 72 h. Then water and ethyl acetate were added. After separation of the layers, the solvent of the organic phase was removed in vacuo. The residue was washed with water and ethyl acetate and then dried in vacuo to obtain **47b** (dichloromethane/methanol = 9/1, R_f = 0.25) as colorless solid (40 mg, 0.09 mmol, 30% yield). Melting point: 143 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = +82.5 (c = 1.8; H_2O/acetonitrile = 9/1); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 2.32–2.38 (m, 4H, $N(CH_2CH_2)_2$), 3.49 (s, 2H, $PhCH_2N$), 3.56–3.60 (m, 4H, $N(CH_2CH_2)_2$), 4.08–4.11 (m, 1H, 4-H), 4.12 (d, *J* = 7.4 Hz, 1H, 2-H), 4.40 (dd, *J* = 7.4/4.3 Hz, 1H, 3-H), 4.79 (s br, 1H, 4-OH), 5.12 (d, *J* = 2.9 Hz, 1H, 5-H), 5.20 (s br, 1H, 3-OH), 7.34–7.38 (m, 4H, H_{phenyl}), 7.47–7.52 (m, 4H, H_{phenyl}), 8.93 (s br, 1H, NHOH), 10.76 (s br, 1H, NHOH); ^{13}C NMR: (DMSO-d_6): δ [ppm] = 53.1 (2C, $N(CH_2CH_2)_2$), 62.0 (1C, $PhCH_2N$), 66.2 (2C, $N(CH_2CH_2)_2$), 73.2 (1C, C-4), 75.8 (1C, C-3), 79.6 (1C, C-2), 82.8 (1C, C-5), 88.9 (1C, PhC≡CPh), 89.3 (1C, PhC≡CPh), 120.7 (1C, C_{phenyl}), 121.0 (1C, C_{phenyl}), 127.6 (2C, C_{phenyl}), 129.2 (2C, C_{phenyl}), 130.5 (2C, C_{phenyl}), 131.2 (2C, C_{phenyl}), 138.7 (1C, C_{phenyl}), 139.4 (1C, C_{phenyl}), 167.5 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3213, 2920, 2816, 1639, 1516, 1404, 1400, 1346, 1292, 1111, 1072, 1003, 860, 795; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_6$: 439.1864, found: 439.1837; HPLC (method 2): t_R = 11.4 min, purity 97.1%.

4.2.33. (2R,3R,4S,5S)-N,3,4-Trihydroxy-5-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]tetrahydrofuran-2-carboxamide (**47c**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (43 mg, 0.61 mmol) and a 2 M solution of sodium methoxide in methanol (0.31 mL, 0.61 mmol) were added to a solution of **44c** (37 mg, 0.10 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 72 h. Then water and ethyl acetate were added. After separation of the layers, the solvent of the organic phase was removed in vacuo. The residue was washed with water and ethyl acetate and then dried in vacuo to obtain **47c** (dichloromethane/methanol = 9/1, R_f = 0.26) as yellowish solid (21 mg, 0.06 mmol, 57% yield). Melting point: 152 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = +44.0 (c = 1.1; DMSO); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 4.08–4.14 (m, 2H, 4-H, 2-H), 4.37–4.42 (m, 1H, 3-H), 4.79 (s br, 1H, 4-OH), 5.10–5.15 m, 1H, 5-H), 5.17 (s br, 1H, 3-OH), 7.35–7.39 (m, 2H, H_{phenyl}), 7.42–7.51 (m, 3H, H_{phenyl}), 7.53–7.57 (m, 2H, H_{phenyl}), 7.59–7.63 (m, 2H, H_{phenyl}), 8.94 (s br, 1H, NHOH), 10.78 (s br, 1H, NHOH); ^{13}C

NMR: (DMSO-d_6): δ [ppm] = 73.1 (1C, PhC≡*C*C≡CPh), 73.2 (1C, C-4), 73.6 (1C, PhC≡C*C*≡CPh), 75.7 (1C, C-3), 79.7 (1C, C-2), 81.6 (1C, Ph*C*≡CC≡CPh), 82.2 (1C, Ph*C*≡CC≡CPh), 82.7 (1C, C-5), 118.7 (1C, C_{phenyl}), 120.5 (1C, C_{phenyl}), 127.7 (2C, C_{phenyl}), 128.9 (2C, C_{phenyl}), 129.9 (1C, C_{phenyl}), 131.6 (2C, C_{phenyl}), 132.4 (2C, C_{phenyl}), 141.0 (1C, C_{phenyl}), 170.3 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3252, 3055, 2978, 2905, 1628, 1508, 1489, 1439, 1408, 1373, 1273, 1072, 779, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{18}NO_5$: 364.1179, found: 364.1209; HPLC (method 2): t_R = 16.2 min, purity 95.2%.

4.2.34. Methyl (3aR,4S,6R,6aR)-6-[4-(benzyloxy)phenyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**48**)

Erbium(III) trifluoromethanesulfonate (127 mg, 0.21 mmol) was added to a solution of **18** (1.59 g, 4.13 mmol) in dry acetonitrile (10 mL). The mixture was heated under microwave irradiation for 30 min at 120 °C and 200 W. Then a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 8/2, Ø = 4 cm, h = 15 cm, V = 30 mL, R_f = 0.32) to give **48** as colorless solid (694 mg, 1.81 mmol, 44% yield). Melting point: 106 °C; Specific rotation: $[\alpha]_D^{20}$ = 0.0 (c = 2.9; dichloromethane); ^{1}H NMR: (CD_3OD): δ [ppm] = 1.33 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 3.77 (s, 3H, COOC*H*$_3$), 4.66 (d, *J* = 5.0 Hz, 1H, 4-H), 4.95 (dd, *J* = 6.0/1.9 Hz, 1H, 6a-H), 5.05–5.09 (m, 3H, 3a-H, OC*H*$_2$Ph), 5.19–5.20 (m, 1H, 6-H), 6.98–7.01 (m, 2H, 3′-H$_{4\text{-benzyloxyphenyl}}$, 5′-H$_{4\text{-benzyloxyphenyl}}$), 7.23–7.27 (m, 2H, 2′-H$_{4\text{-benzyloxyphenyl}}$, 6′-H$_{4\text{-benzyloxyphenyl}}$), 7.28–7.31 (m, 1H, 4-H$_{phenyl}$), 7.34–7.38 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.40–7.43 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$); ^{13}C NMR: ($CD_3OD$): δ [ppm] = 25.3 (1C, C(*C*H$_3$)$_2$), 26.6 (1C, C(C*H*$_3$)$_2$), 52.4 (1C, COO*C*H$_3$), 71.0 (1C, O*C*H$_2$Ph), 81.1 (1C, C-4), 83.1 (1C, C-3a), 86.5 (1C, C-6), 87.4 (1C, C-6a), 114.8 (1C, *C*(CH$_3$)$_2$), 116.2 (2C, C-3′$_{4\text{-benzyloxyphenyl}}$, C-5′$_{4\text{-benzyloxyphenyl}}$), 128.3 (2C, C-2′$_{4\text{-benzyloxyphenyl}}$, C-6′$_{4\text{-benzyloxyphenyl}}$), 128.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 128.9 (1C, C-4$_{phenyl}$), 129.5 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 131.3 (1C, C-1′$_{4\text{-benzyloxyphenyl}}$), 138.6 (1C, C-1$_{phenyl}$), 160.0 (1C, C-4′$_{4\text{-benzyloxyphenyl}}$), 170.6 (1C, *C*OOCH$_3$); NOE: Irradiation at 4.66 ppm (4-H): δ [ppm] = 3.77 (COOC*H*$_3$), 4.95 (6a-H), 5.05–5.09 (3a-H), 7.23–7.27 (2′-H$_{4\text{-benzyloxyphenyl}}$, 6′-H$_{4\text{-benzyloxyphenyl}}$); Irradiation at 5.19 ppm (6-H): δ [ppm] = 4.95 (6a-H), 7.23–7.27 (2′-H$_{4\text{-benzyloxyphenyl}}$, 6′-H$_{4\text{-benzyloxyphenyl}}$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2982, 2951, 1763, 1728, 1612, 1512, 1246, 1207, 1107, 1092, 1065, 1015, 860, 737, 694; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{25}O_6$: 385.1646, found: 385.1666; HPLC (method 1): t_R = 22.5 min, purity 98.8%.

4.2.35. Methyl (3aR,4S,6R,6aR)-6-(4-hydroxyphenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**49**)

Palladium on activated charcoal (10% Pd, 51 mg) was added to a solution of **48** (254 mg, 0.66 mmol) in a mixture of methanol and ethyl acetate (2/1, 15 mL). The mixture was stirred for 4 h under hydrogen atmosphere at 4 bar pressure. Afterwards, the mixture was filtered through Celite® 545. Then the solvent was removed in vacuo and the crude product was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.24) to give **49** as colorless solid (186 mg, 0.63 mmol, 96% yield). Melting point: 170 °C; Specific rotation: $[\alpha]_D^{20}$ = +10.6 (c = 4.2; methanol); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.35 (s, 3H, C*H*$_3$), 1.53 (s, 3H, C*H*$_3$), 3.82 (s, 3H, COOC*H*$_3$), 4.61 (d, *J* = 4.9 Hz, 1H, 4-H), 4.93 (dd, *J* = 6.0/1.3 Hz, 1H, 6a-H), 5.00–5.02 (m, 1H, 3a-H), 5.32–5.34 (m, 1H, 6-H), 6.81–6.84 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.16–7.19 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 25.3 (1C, C(*C*H$_3$)$_2$), 26.4 (1C, C(C*H*$_3$)$_2$), 52.4 (1C, COO*C*H$_3$), 80.2 (1C, C-4), 82.0 (1C, C-3a), 85.1 (1C, C-6), 86.1 (1C, C-6a), 114.0 (1C, *C*(CH$_3$)$_2$), 115.7 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 127.3 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 129.5 (1C, C-1$_{phenyl}$), 155.6 (1C, C-4$_{phenyl}$), 168.2 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3379, 2974, 2947, 1748, 1612, 1520, 1443, 1373, 1231, 1107, 1072, 1045, 922, 853, 837, 783, 752; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{19}O_6$: 295.1176, found: 295.1185; HPLC (method 1): t_R = 15.5 min, purity 99.6%.

4.2.36. Methyl (3aR,4S,6R,6aR)-2,2-dimethyl-6-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (**50**)

Triethylamine (0.88 mL, 6.29 mmol) was added to a solution of **49** (617 mg, 2.10 mmol) in dichloromethane (20 mL) at −20 °C. Then a solution of trifluoromethanesulfonic anhydride (0.53 mL, 3.14 mmol) in dichloromethane (5 mL) was added slowly. The reaction was stirred for 30 min at −20 °C. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 8/2, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.24) to give **50** as yellowish oil (811 mg, 1.90 mmol, 91% yield). Specific rotation: $[\alpha]_D^{20}$ = +1.5 (c = 5.2; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 1.36 (s, 3H, C*H*$_3$), 1.55 (s, 3H, C*H*$_3$), 3.84 (s, 3H, COOC*H*$_3$), 4.67 (d, *J* = 5.1 Hz, 1H, 4-H), 4.85 (dd, *J* = 6.1/2.4 Hz, 1H, 6a-H), 5.01–5.04 (m, 1H, 3a-H), 5.37–5.39 (m, 1H, 6-H), 7.26–7.30 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.43–7.47 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 25.4 (1C, C(*C*H$_3$)$_2$), 26.5 (1C, C(*C*H$_3$)$_2$), 52.4 (1C, COO*C*H$_3$), 80.4 (1C, C-4), 81.8 (1C, C-3a), 84.7 (1C, C-6), 86.6 (1C, C-6a), 114.8 (1C, *C*(CH$_3$)$_2$), 118.9 (q, *J* = 321 Hz, 1C, *C*F$_3$), 121.8 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 127.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 138.7 (1C, C-1$_{phenyl}$), 149.1 (1C, C-4$_{phenyl}$), 168.4 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2990, 2955, 1763, 1423, 1207, 1138, 1103, 883; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{18}F_3O_8S$: 427.0669, found: 427.0697; HPLC (method 1): t_R = 22.3 min, purity 99.1%.

4.2.37. Methyl (2S,3R,4S,5R)-3,4-dihydroxy-5-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)tetrahydro-furan-2-carboxylate (**51**)

p-TsOH (16 mg, 0.09 mmol) was added to a solution of **50** (363 mg, 0.85 mmol) in methanol (5 mL). The mixture was heated under microwave irradiation for 30 min at 115 °C, 20 bar and 50 W. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/3, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.21) to give **51** as colorless oil (279 mg, 0.72 mmol, 85% yield). Melting point: 114 °C; Specific rotation: $[\alpha]_D^{20}$ = +6.9 (c = 11.3; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.79 (s, 3H, COOC*H*$_3$), 3.91 (dd, *J* = 9.0/4.5 Hz, 1H, 4-H), 4.46 (t, *J* = 4.5 Hz, 1H, 3-H), 4.91 (d, *J* = 9.0 Hz, 1H, 5-H), 4.97 (d, *J* = 4.5 Hz, 1H, 2-H), 7.34–7.38 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.58–7.62 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$); ^{13}C NMR: (CD_3OD): δ [ppm] = 52.4 (1C, COO*C*H$_3$), 73.7 (1C, C-3), 80.0 (1C, C-4), 81.9 (1C, C-2), 83.0 (1C, C-5), 120.2 (q, *J* = 320 Hz, 1C, *C*F$_3$), 122.3 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.2 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 142.7 (1C, C-1$_{phenyl}$), 150.5 (1C, C-4$_{phenyl}$), 172.3 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3414, 2959, 1744, 1501, 1420, 1204, 1134, 1061, 1015, 880, 837; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{14}F_3O_8S$: 387.0356, found: 387.0378; HPLC (method 1): t_R = 18.0 min, purity 98.7%.

*4.2.38. Methyl (2S,3R,4S,5R)-3,4-dihydroxy-5-[4-(phenylethynyl) phenyl]tetrahydrofuran-2-carboxylate (**52a**)*

Under nitrogen atmosphere, copper(I) iodide (5 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium(0) (28 mg, 0.02 mmol) and triethylamine (0.31 mL, 2.21 mmol) were added to a solution of **51** (95 mg, 0.25 mmol) in dry acetonitrile (10 mL). Then a solution of phenylacetylene (0.13 mL, 1.23 mmol) in dry acetonitrile (2 mL) was added dropwise over a period of 1 h at ambient temperature and the reaction mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (cyclohexane/ethyl acetate = 2/3, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.25) to give **52a** as colorless solid (66 mg, 0.20 mmol, 79% yield). Melting point: 155 °C; Specific rotation: $[\alpha]_D^{20}$ = −9.8 (c = 1.9; ethyl acetate); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.79 (s, 3H, $COOCH_3$), 3.93 (dd, *J* = 9.0/4.5 Hz, 1H, 4-H), 4.46 (t, *J* = 4.5 Hz, 1H, 3-H), 4.88 (d, *J* = 9.0 Hz, 1H, 5-H), 4.96 (d, *J* = 4.5 Hz, 1H, 2-H), 7.34–7.39 (m, 3H, H_{phenyl}), 7.43–7.47 (m, 2H, H_{phenyl}), 7.48–7.53 (m, 4H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 52.4 (1C, $COOCH_3$), 73.7 (1C, C-3), 80.0 (1C, C-4), 81.9 (1C, C-2), 83.7 (1C, C-5), 90.0 (1C, PhC≡CPh), 90.2 (1C, PhC≡CPh), 124.0 (1C, C_{phenyl}), 124.6 (1C, C_{phenyl}), 127.4 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 129.5 (2C, C_{phenyl}), 132.4 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 142.1 (1C, C_{phenyl}), 172.4 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3429, 2978, 2951, 2905, 1744, 1439, 1362, 1315, 1134, 1053, 980, 818, 752; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{19}O_5$: 339.1227, found: 339.1242; HPLC (method 1): t_R = 19.5 min, purity 97.4%.

*4.2.39. Methyl (2S,3R,4S,5R)-3,4-dihydroxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-tetrahydrofuran-2-carboxylate (**52b**)*

Under nitrogen atmosphere, copper(I) iodide (6 mg, 0.03 mmol), tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.02 mmol) and triethylamine (0.16 mL, 1.14 mmol) were added to a solution of **51** (63 mg, 0.16 mmol) in dry acetonitrile (10 mL). Then a solution of 4-(morpholinomethyl)phenylacetylene (49 mg, 0.24 mmol) in dry acetonitrile (2 mL) was added dropwise over a period of 1 h at ambient temperature and the reaction mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 19/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.35) to give **52b** as colorless solid (56 mg, 0.13 mmol, 78% yield). Melting point: 184 °C; Specific rotation: $[\alpha]_D^{20}$ = −0.6 (c = 1.9; ethyl acetate); ^{1}H NMR: (CD_3OD): δ [ppm] = 2.44–2.48 (m, 4H, $N(CH_2CH_2)_2$), 3.53 (s, 2H, $PhCH_2N$), 3.67–3.70 (m, 4H, $N(CH_2CH_2)_2$), 3.79 (s, 3H, $COOCH_3$), 3.93 (dd, *J* = 9.0/4.5 Hz, 1H, 4-H), 4.46 (t, *J* = 4.5 Hz, 1H, 3-H), 4.88 (d, *J* = 9.0 Hz, 1H, 5-H), 4.96 (d, *J* = 4.5 Hz, 1H, 2-H), 7.34–7.37 (m, 2H, H_{phenyl}), 7.42–7.52 (m, 6H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 52.4 (1C, $COOCH_3$), 54.6 (2C, $N(CH_2CH_2)_2$), 64.0 (1C, $PhCH_2N$), 67.8 (2C, $N(CH_2CH_2)_2$), 73.7 (1C, C-3), 80.0 (1C, C-4), 81.9 (1C, C-2), 83.7 (1C, C-5), 90.0 (1C, PhC≡CPh), 90.1 (1C, PhC≡CPh), 123.6 (1C, C_{phenyl}), 124.0 (1C, C_{phenyl}), 127.4 (2C, C_{phenyl}), 130.7 (2C, C_{phenyl}), 132.5 (4C, C_{phenyl}), 139.0 (1C, C_{phenyl}), 142.1 (1C, C_{phenyl}), 172.4 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3348, 2932, 2870, 2812, 1751, 1516, 1435, 1292, 1204, 1107, 1057, 1007, 864, 829, 822; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{28}NO_6$: 438.1911, found: 438.1893; HPLC (method 1): t_R = 14.1 min, purity 98.5%.

*4.2.40. (2S,3R,4S,5R)-N,3,4-Trihydroxy-5-[4-(phenylethynyl) phenyl]tetrahydrofuran-2-carboxamide (**53a**)*

Under nitrogen atmosphere, hydroxylamine hydrochloride (48 mg, 0.70 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.13 mL, 0.70 mmol) were added to a solution of **52a** (59 mg, 0.17 mmol) in dry methanol (5 mL) and the mixture was stirred at ambient temperature for 4 days. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.27) to give **53a** as colorless solid (29 mg, 0.09 mmol, 49% yield). Melting point: 160 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −20.3 (c = 5.6; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 4.00 (dd, *J* = 8.7/4.0 Hz, 1H, 4-H), 4.41–4.45 (m, 1H, 3-H), 4.81 (d, *J* = 3.5 Hz, 1H, 2-H), 4.93 (d, *J* = 8.7 Hz, 1H, 5-H), 7.34–7.40 (m, 3H, H_{phenyl}), 7.43–7.54 (m, 6H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 74.0 (1C, C-3), 80.4 (1C, C-4), 82.6 (1C, C-2), 84.0 (1C, C-5), 90.0 (1C, PhC≡CPh), 90.1 (1C, PhC≡CPh), 123.9 (1C, C_{phenyl}), 124.6 (1C, C_{phenyl}), 127.3 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 129.5 (2C, C_{phenyl}), 132.4 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 142.6 (1C, C_{phenyl}), 168.8 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3240, 2920, 1655, 1508, 1111, 1045, 822, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{18}NO_5$: 340.1179, found: 340.1176; HPLC (method 2): t_R = 15.3 min, purity 99.1%.

*4.2.41. (2S,3R,4S,5R)-N,3,4-Trihydroxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)tetrahydro-furan-2-carboxamide (**53b**)*

Under nitrogen atmosphere, hydroxylamine hydrochloride (45 mg, 0.64 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.12 mL, 0.64 mmol) were added to a solution of **52b** (47 mg, 0.11 mmol) in dry methanol (5 mL) and the mixture was stirred at ambient temperature for 6 days. Afterwards, the mixture was acidified to pH 3 with 1 M hydrochloric acid. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.36) to give **53b** as colorless solid (21 mg, 0.05 mmol, 45% yield). Melting point: 150 °C; Specific rotation: $[\alpha]_D^{20}$ = −10.6 (c = 2.3; dichloromethane/methanol = 9/1); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 2.33–2.37 (m, 4H, $N(CH_2CH_2)_2$), 3.49 (s, 2H, $PhCH_2N$), 3.56–3.59 (m, 4H, $N(CH_2CH_2)_2$), 3.80–3.87 (m, 1H, 4-H), 4.20–4.24 (m, 1H, 3-H), 4.68 (d, *J* = 3.9 Hz, 1H, 2-H), 4.80 (d, *J* = 8.7 Hz, 1H, 5-H), 5.21 (d, *J* = 8.3 Hz, 1H, 4-OH), 5.29 (d, *J* = 4.4 Hz, 1H, 3-OH), 7.34–7.37 (m, 2H, 3′-$H_{4\text{-(morpholinomethyl)phenyl}}$, 5′-$H_{4\text{-(morpholinomethyl)phenyl}}$), 7.40–7.44 (m, 2H, 2-$H_{phenyl}$, 6-$H_{phenyl}$), 7.49–7.54 (m, 4H, 3-$H_{phenyl}$, 5-$H_{phenyl}$, 2′-$H_{4\text{-(morpholinomethyl)phenyl}}$, 6′-$H_{4\text{-(morpholinomethyl)phenyl}}$), 8.71 (s, 1H, NHOH), 10.43 (s br, 1H, NHOH); ^{13}C NMR: (DMSO-d_6): δ [ppm] = 53.2 (2C, $N(CH_2CH_2)_2$), 62.0 (1C, $PhCH_2N$), 66.2 (2C, $N(CH_2CH_2)_2$), 72.1 (1C, C-3), 78.7 (1C, C-4), 81.1 (1C, C-2), 81.9 (1C, C-5), 89.2 (2C, PhC≡CPh), 120.9 (1C, C-1′$_{4\text{-(morpholinomethyl)phenyl}}$), 121.2 (1C, C-4$_{phenyl}$), 126.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 129.2 (2C, C-3′$_{4\text{-(morpholinomethyl)phenyl}}$, C-5′$_{4\text{-(morpholinomethyl)phenyl}}$), 131.1 (2C, $C_{arom.}$), 131.2 (2C, $C_{arom.}$), 138.8 (1C, C-4′$_{4\text{-(morpholinomethyl)phenyl}}$), 142.2 (1C, C-1$_{phenyl}$), 165.6 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3225, 2920, 2855, 1655, 1516, 1454, 1292, 1111, 1045, 910, 864, 826; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_6$: 439.1864, found: 439.1875; HPLC (method 2): t_R = 11.6 min, purity 98.7%.

*4.2.42. (3aS,4RS,6S,6aS)-6-[(R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-(4-iodophenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (**55**)*

Under nitrogen atmosphere at −78 °C, a 2.5 M solution of *n*-butyllithium in *n*-hexane (2.9 mL, 7.1 mmol) was added to a solution of 1,4-diiodobenzene (4.3 g, 13 mmol) in dry THF (40 mL). The reaction was stirred for 15 min at −78 °C. Then a solution of **54**

(1.7 g, 6.5 mmol) in dry THF (10 mL) was added. The reaction was stirred for 1 h and then warmed to ambient temperature. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1, Ø = 6 cm, h = 15 cm, V = 65 mL, R_f = 0.35) to give **55** as colorless solid (2.1 g, 4.5 mmol, 69% yield). Specific rotation: $[\alpha]_D^{20}$ = +34.5 (c = 7.3; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 1.23 (s, 3 × 0.8H, $(H_3C)_2COCHCPh^{E1}$), 1.34–1.36 (m, 6 × 0.8H + 3 × 0.2H, $(H_3C)_2COCHCPh^{E1+E2}$, $(H_3C)_2COCH_2^{E1}$), 1.37 (s, 3 × 0.2H, $(H_3C)_2CO-CH_2^{E2}$), 1.40 (s, 3 × 0.2H, $(H_3C)_2COCH_2^{E2}$), 1.43 (s, 3 × 0.8H, $(H_3C)_2COCH_2^{E1}$), 1.64 (s, 3 × 0.2H, $(H_3C)_2COCHCPh^{E2}$), 3.83 (dd, *J* = 8.5/6.8 Hz, 0.8H, CH_2CH^{E1}), 3.91 (dd, *J* = 8.4/6.6 Hz, 0.2H, CH_2CH^{E2}), 4.11–4.17 (m, 1H, CH_2CH^{E1+E2}), 4.21–4.26 (m, 1H, 6-H^{E1+E2}), 4.36 (td, *J* = 6.7/5.1 Hz, 0.2H, CH_2CH^{E2}), 4.45 (td, *J* = 7.4/6.8 Hz, 0.8H, CH_2CH^{E1}), 4.54 (d, *J* = 7.4 Hz, 0.2H, 3a-H^{E2}), 4.58 (d, *J* = 5.7 Hz, 0.8H, 3a-H^{E1}), 4.74 (dd, *J* = 7.4/4.6 Hz, 0.2H, 6a-H^{E2}), 4.78 (dd, *J* = 5.7/2.1 Hz, 0.8H, 6a-H^{E1}), 7.31–7.36 (m, 2H, 2-H_{phenyl}^{E1+E2}, 6-H_{phenyl}^{E1+E2}), 7.66–7.72 (m, 2H, 3-H_{phenyl}^{E1+E2}, 5-H_{phenyl}^{E1+E2}); ratio of epimers 80(E1):20(E2); ^{13}C NMR: (CD_3OD): δ [ppm] = 25.2 (0.8C, $(H_3C)_2COCHCPh^{E1}$), 25.5 (0.2C, $(H_3C)_2COCH_2^{E2}$), 25.5 (0.8C, $(H_3C)_2COCHCPh^{E1}$), 25.7 (0.2C, $(H_3C)_2COCHCPh^{E2}$), 26.6 (0.2C, $(H_3C)_2COCHCPh^{E2}$), 26.8 (0.2C, $(H_3C)_2COCH_2^{E2}$), 26.9 (0.8C, $(H_3C)_2COCH_2^{E1}$), 27.0 (0.8C, $(H_3C)_2COCH_2^{E1}$), 66.4 (0.2C, CH_2CH^{E2}), 67.0 (0.8C, CH_2CH^{E1}), 77.1 (0.2C, CH_2CH^{E2}), 78.9 (0.8C, CH_2CH^{E1}), 82.2 (0.2C, C-6a^{E2}), 82.8 (0.2C, C-6^{E2}), 83.4 (0.8C, C-6a^{E1}), 87.6 (0.2C, C-3a^{E2}), 88.5 (0.8C, C-3a^{E1}), 89.2 (0.8C, C-6^{E1}), 94.5 (0.2C, C-4_{phenyl}^{E2}), 94.6 (0.8C, C-4_{phenyl}^{E1}), 103.3 (0.2C, C-4^{E2}), 108.5 (0.8C, C-4^{E1}), 110.9 (0.8C, $(H_3C)_2COCH_2^{E1}$), 111.0 (0.2C, $(H_3C)_2COCH_2^{E2}$), 114.1 (0.8C, $(H_3C)_2COCHCPh^{E1}$), 117.7 (0.2C, $(H_3C)_2COCHCPh^{E2}$), 128.9 (2 × 0.2C, C-2_{phenyl}^{E2}, C-6_{phenyl}^{E2}), 130.5 (2 × 0.8C, C-2_{phenyl}^{E1}, C-6_{phenyl}^{E1}), 137.6 (2 × 0.8C, C-3_{phenyl}^{E1}, C-5_{phenyl}^{E1}), 138.3 (2 × 0.2C, C-3_{phenyl}^{E2}, C-5_{phenyl}^{E2}), 141.6 (0.8C, C-1_{phenyl}^{E1}), 144.1 (0.2C, C-1_{phenyl}^{E2}); ratio of epimers 80(E1):20(E2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3337, 2982, 1377, 1207, 1157, 1057, 1038, 995, 856, 822; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{24}IO_6$: 463.0612, found: 463.0622; HPLC (method 1): t_R = 21.7 min, purity 96.1%.

4.2.43. (S)-[(R)-2,2-Dimethyl-1,3-dioxolan-4-yl]{(4S,5R)-5-[(S)-hydroxy(4-iodophenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl} methanol (**56**)

Under nitrogen atmosphere at −78 °C, a 1.0 M solution of lithium tri-*sec*-butylborohydride in THF (36.6 mL, 36.6 mmol) was added over a period of 30 min to a solution of **55** (5.63 g, 12.2 mmol) in dry THF (100 mL) at −78 °C. The reaction was stirred for 60 min and then warmed to ambient temperature. The reaction was stirred overnight. Afterwards, methanol (9 mL), water (4.5 mL) and a 6 M solution of sodium hydroxide in water (4.5 mL) were added. Then a solution of hydrogen peroxide in water (30% (m/m), 4.5 mL) was added carefully to the reaction mixture. The mixture was extracted with dichloromethane (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1, Ø = 6 cm, h = 15 cm, V = 65 mL, R_f = 0.17) to give **56** as colorless solid (5.33 g, 11.5 mmol, 94% yield). Specific rotation: $[\alpha]_D^{20}$ = +62.8 (c = 2.0; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 1.30 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.88–3.93 (m, 1H, OCH_2CHCH), 4.03–4.08 (m, 1H, OCH_2CHCH), 4.09–4.13 (m, 1H, OCH_2CHCH), 4.22 (dd, *J* = 8.9/6.6 Hz, 1H, PhCHCHCH), 4.26–4.31 (m, 2H, OCH_2CHCH, PhCHCHCH), 5.08–5.10 (m, 1H, PhCHCHCH), 7.19–7.23 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.64–7.68 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 25.2 (1C, $C(CH_3)_2$), 25.7 (1C, $C(CH_3)_2$), 26.6 (1C, $C(CH_3)_2$), 26.8 (1C, $C(CH_3)_2$), 67.0 (1C, OCH_2CHCH), 70.3 (1C, OCH_2CHCH), 71.8 (1C, PhCHCHCH), 78.4 (1C, OCH_2CHCH), 78.6 (1C, PhCHCHCH), 81.9 (1C, PhCHCHCH), 93.0 (1C, C-4_{phenyl}), 109.9 (1C, $C(CH_3)_2$), 110.2 (1C, $C(CH_3)_2$), 130.1 (2C, C-2_{phenyl}, C-6_{phenyl}), 138.1 (2C, C-3_{phenyl}, C-5_{phenyl}), 144.5 (1C, C-1_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3441, 2982, 2932, 1485, 1373, 1211, 1057, 1007, 845; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{26}IO_6$: 465.0769, found: 465.0760; HPLC (method 1): t_R = 20.1 min, purity 92.9%.

4.2.44. (3aS,4S,6R,6aR)-4-[(R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-(4-iodophenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole (**57**)

Under nitrogen atmosphere, triphenylphosphine (6.02 g, 22.9 mmol) was added to a solution of **56** (5.33 g, 11.5 mmol) in dry THF (100 mL) at 0 °C. Then DIAD (4.50 mL, 22.9 mmol) was added dropwise and the reaction mixture was heated to reflux for 2 h. Afterwards, the mixture was cooled to ambient temperature and triphenylphosphine (6.02 g, 22.9 mmol) and DIAD (4.50 mL, 22.9 mmol) were added to the mixture. The reaction mixture was heated to reflux overnight and then cooled to ambient temperature. Then the solvent was removed in vacuo and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 9/1, Ø = 6 cm, h = 15 cm, V = 65 mL, R_f = 0.16) to give **57** as colorless oil (3.18 g, 7.12 mmol, 62% yield). Specific rotation: $[\alpha]_D^{20}$ = +22.5 (c = 13.4; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 1.34 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 3.90 (dd, *J* = 8.3/6.6 Hz, 1H, $OCHCH_2O$), 4.03–4.05 (m, 1H, 4-H), 4.11 (dd, *J* = 8.3/6.9 Hz, 1H, $OCHCH_2O$), 4.30–4.34 (m, 1H, $OCHCH_2O$), 4.47 (dd, *J* = 6.8/5.5 Hz, 1H, 6a-H), 4.70 (dd, *J* = 6.8/4.4 Hz, 1H, 3a-H), 4.78 (d, *J* = 5.5 Hz, 1H, 6-H), 7.17–7.20 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.69–7.72 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 25.5 (1C, $C(CH_3)_2$), 25.7 (1C, $C(CH_3)_2$), 26.8 (1C, $C(CH_3)_2$), 27.8 (1C, $C(CH_3)_2$), 66.3 (1C, $OCHCH_2O$), 77.2 (1C, $OCH-CH_2O$), 83.0 (1C, C-3a), 85.4 (1C, C-4), 86.5 (1C, C-6), 87.9 (1C, C-6a), 93.8 (1C, C-4_{phenyl}), 110.9 (1C, $C(CH_3)_2$), 116.3 (1C, $C(CH_3)_2$), 129.0 (2C, C-2_{phenyl}, C-6_{phenyl}), 138.6 (2C, C-3_{phenyl}, C-5_{phenyl}), 141.0 (1C, C-1_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2982, 2936, 2886, 1485, 1369, 1211, 1072, 1007, 853, 810; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{24}IO_5$: 447.0663, found: 447.0643; HPLC (method 1): t_R = 23.8 min, purity 95.0%.

4.2.45. (R)-1-[(3aS,4S,6R,6aR)-6-(4-Iodophenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]ethane-1,2-diol (**58**) and (2R,3R,4S,5R)-2-[(R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5-(4-iodophenyl)tetrahydrofuran-3,4-diol (**59**)

p-TsOH (284 mg, 1.49 mmol) was added to a solution of **57** (3.33 g, 7.47 mmol) in methanol (40 mL). The mixture was stirred at ambient temperature for 20 h. Then a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 6 cm, h = 15 cm, V = 65 mL, R_f = 0.18) to give an inseparable mixture of regioisomers **58** and **59** as colorless oil (1.38 g, 3.40 mmol, 46% yield). Analytical data for the mixture of **58** and **59**: ^{1}H NMR: (CD_3OD): δ [ppm] = 1.34 (s, 3 × 0.75H, CH_3^{58}), 1.36 (s, 3 × 0.25H, CH_3^{59}), 1.40 (s, 3 × 0.25H, CH_3^{59}), 1.58 (s, 3 × 0.75H, CH_3^{58}), 3.64 (dd, *J* = 11.1/6.8 Hz, 0.75H, $HOCHCH_2OH^{58}$), 3.71 (dd, *J* = 11.1/5.5 Hz, 0.75H, $HOCHCH_2OH^{58}$), 3.79 (ddd, *J* = 6.8/5.5/3.7 Hz, 0.75H, $HOCHCH_2OH^{58}$), 3.83 (dd, *J* = 6.6/5.5 Hz, 0.25H, 4-H^{59}), 3.92–3.98 (m, 2 × 0.25H, 2-H^{59}, $OCHCH_2O^{59}$), 4.03–4.13 (m, 2 × 0.25H + 1 × 0.75H, 3-H^{59}, $OCHCH_2O^{59}$, 4-H^{58}), 4.31 (m, 0.25H, $OCHCH_2O^{59}$), 4.43 (dd, *J* = 6.8/5.7 Hz, 0.75H, 6a-H^{58}), 4.68 (d,

J = 6.6 Hz, 0.25H, 5-H^{59}), 4.73 (d, J = 5.7 Hz, 0.75H, 6-H^{58}), 4.83 (dd, J = 6.8/4.2 Hz, 0.75H, 3a-H^{58}), 7.20–7.24 (m, 2 × 0.75H, 2-H$^{58}_{phenyl}$, 6-H$^{58}_{phenyl}$), 7.24–7.27 (m, 2 × 0.25H, 2-H$^{59}_{phenyl}$, 6-H$^{59}_{phenyl}$), 7.66–7.71 (m, 2H, 3-H$^{58+59}_{phenyl}$, 5-H$^{58+59}_{phenyl}$); ratio of regioisomers 75(**58**):25(**59**); ^{13}C NMR: (CD_3OD): δ [ppm] = 25.6 (0.25C, CH_3^{59}), 25.8 (0.75C, CH_3^{58}), 26.8 (0.25C, CH_3^{59}), 27.9 (0.75C, CH_3^{58}), 64.1 (0.75C, HOCHCH_2OH^{58}), 66.4 (0.25C, OCHCH_2O^{59}), 73.2 (0.75C, HOCHCH$_2$OH^{58}), 73.5 (0.25C, C-3^{59}), 77.7 (0.25C, OCHCH$_2$O^{59}), 78.9 (0.25C, C-4^{59}), 83.2 (0.75C, C-3a^{58}), 84.7 (2 × 0.25C, C-2^{59}, C-5^{59}), 85.4 (0.75C, C-4^{58}), 86.6 (0.75C, C-6^{58}), 88.0 (0.75C, C-6a^{58}), 93.5 (0.25C, C-4$^{59}_{phenyl}$), 93.8 (0.75C, C-4$^{58}_{phenyl}$), 110.6 (0.25C, $C(CH_3)_2^{59}$), 116.1 (0.75C, $C(CH_3)_2^{58}$), 129.2 (2 × 0.75C, C-2$^{58}_{phenyl}$, C-6$^{58}_{phenyl}$), 129.3 (2 × 0.25C, C-2$^{59}_{phenyl}$, C-6$^{59}_{phenyl}$), 138.4 (2 × 0.25C, C-3$^{59}_{phenyl}$, C-5$^{59}_{phenyl}$), 138.6 (2 × 0.75C, C-3$^{58}_{phenyl}$, C-5$^{58}_{phenyl}$), 141.2 (0.75C, C-1$^{58}_{phenyl}$), 141.9 (0.25C, C-1$^{59}_{phenyl}$); ratio of regioisomers 75(**58**):25(**59**); LC-MS (m/z): $[M+H]^+$ calcd for $C_{15}H_{20}IO_5$: 407.0350, found: **59** (t_R = 5.3 min): 407.0364, **58** (t_R = 5.4 min): 407.0370; HPLC (method 1): t_R(**59**) = 18.5 min (25.1%), t_R(**58**) = 18.8 min (74.9%).

4.2.46. (2S,3R,4S,5R)-2-[(R)-1,2-Dihydroxyethyl]-5-(4-iodophenyl) tetrahydrofuran-3,4-diol (**60**)

A solution of **57** (345 mg, 0.77 mmol) in a mixture of 1 M hydrochloric acid (3 mL) and THF (3 mL) was heated under microwave irradiation for 45 min at 115 °C, 20 bar and 75 W. Then a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/methanol = 10/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.37) to give **60** as colorless solid (226 mg, 0.62 mmol, 80% yield). Melting point: 145 °C; Specific rotation: $[\alpha]_D^{20}$ = +3.5 (c = 4.3; methanol); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 3.38–3.51 (m, 2H, HOCHCH_2OH), 3.55–3.60 (m, 1H, HOCHCH$_2$OH), 3.67 (td, J = 7.2/5.4 Hz, 1H, 4-H), 3.88–3.90 (m, 1H, 2-H), 3.97 (td, J = 5.0/3.3 Hz, 1H, 3-H), 4.48 (d, J = 7.3 Hz, 1H, 5-H), 4.56 (dd, J = 5.9/5.3 Hz, 1H, HOCHCH$_2$OH), 4.74 (d, J = 5.3 Hz, 1H, HOCHCH$_2$OH), 4.85 (d, J = 4.7 Hz, 1H, C_3–OH), 4.91 (d, J = 7.2 Hz, 1H, C_4–OH), 7.24–7.27 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.65–7.69 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$); ^{13}C NMR: (DMSO-d_6): δ [ppm] = 62.5 (1C, HOCHCH$_2$OH), 71.4 (1C, HOCHCH$_2$OH), 71.9 (1C, C-3), 77.9 (1C, C-4), 82.1 (1C, C-5), 84.4 (1C, C-2), 93.0 (1C, C-4$_{phenyl}$), 128.6 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 136.6 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 141.7 (1C, C-1$_{phenyl}$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3333, 2932, 2889, 1485, 1296, 1111, 1057, 1038, 1003, 818, 694, 652; HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{16}IO_5$: 367.0037, found: 367.0076; HPLC (method 1): t_R = 13.4 min, purity 97.8%.

4.2.47. [(3aS,4S,6R,6aR)-6-(4-Iodophenyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]methanol (**61**) and (R)-2-[(R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-[(R)-2-hydroxy-1-(4-iodophenyl)ethoxy]ethan-1-ol (**62**)

The inseparable mixture of regioisomers **58** and **59** (1.14 g, 2.80 mmol) which had been obtained in the previous reaction step was dissolved in methanol (50 mL). Sodium metaperiodate (1.80 g, 8.40 mmol) was added and the reaction was stirred at ambient temperature for 1 h. Afterwards, water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol (30 mL) and sodium borohydride (318 mg, 8.40 mmol) was added. The reaction was stirred at ambient temperature for 15 min. Then a saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 3/1 → 1/2, Ø = 4 cm, h = 15 cm, V = 30 mL) to give **61** (cyclohexane/ethyl acetate = 3/1, R_f = 0.18) as colorless solid (579 mg, 1.54 mmol, 55% yield) and **62** (cyclohexane/ethyl acetate = 1/2, R_f = 0.15) as colorless oil (307 mg, 0.75 mmol, 27% yield). Analytical data for **61**: Melting point: 55 °C; Specific rotation: $[\alpha]_D^{20}$ = +47.8 (c = 5.4; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 1.34 (s, 3H, C(CH_3)$_2$), 1.58 (s, 3H, C(CH_3)$_2$), 3.71 (dd, J = 11.9/5.0 Hz, 1H, CH_2OH), 3.76 (dd, J = 11.9/4.2 Hz, 1H, CH_2OH), 4.06–4.10 (m, 1H, 4-H), 4.46 (dd, J = 6.8/5.6 Hz, 1H, 6a-H), 4.70 (dd, J = 6.8/4.0 Hz, 1H, 3a-H), 4.76 (d, J = 5.6 Hz, 1H, 6-H), 7.18–7.21 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.68–7.71 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$); ^{13}C NMR: (CD_3OD): δ [ppm] = 25.7 (1C, C(CH_3)$_2$), 27.8 (1C, C(CH_3)$_2$), 63.2 (1C, CH_2OH), 83.2 (1C, C-3a), 86.1 (1C, C-4), 86.6 (1C, C-6), 88.1 (1C, C-6a), 93.8 (1C, C-4$_{phenyl}$), 116.1 (1C, $C(CH_3)_2$), 129.0 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 138.6 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 141.2 (1C, C-1$_{phenyl}$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3356, 2928, 2886, 1485, 1373, 1211, 1076, 1053, 1003, 853, 810; LC-MS (m/z): $[M+H]^+$ calcd for $C_{14}H_{18}IO_4$: 377.0244, found: 377.0242; HPLC (method 1): t_R = 20.5 min, purity 97.4%. Analytical data for **62**: Specific rotation: $[\alpha]_D^{20}$ = −45.9 (c = 11.3; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 1.26 (s, 6H, C(CH_3)$_2$), 3.45 (ddd, J = 6.3/5.3/3.9 Hz, 1H, (OCH$_2$CHCHCH$_2$OH), 3.58 (dd, J = 11.7/3.8 Hz, 1H, PhCHCH_2OH), 3.60–3.69 (m, 3H, PhCHCH_2OH, OCH_2CHCHCH_2OH (2H)), 3.76 (dd, J = 12.0/3.9 Hz, 1H, OCH$_2$CHCHCH_2OH), 3.92 (dd, J = 8.4/6.6 Hz, 1H, OCH_2CHCHCH$_2$OH), 4.12–4.17 (m, 1H, OCH$_2$CHCHCH$_2$OH), 4.64 (dd, J = 7.9/3.8 Hz, 1H, PhCHCH$_2$OH), 7.19–7.23 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.67–7.70 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$); ^{13}C NMR: (CD_3OD): δ [ppm] = 25.6 (1C, C(CH_3)$_2$), 26.6 (1C, C(CH_3)$_2$), 62.2 (1C, OCH$_2$CHCHCH_2OH), 66.6 (1C, OCH_2CHCHCH$_2$OH), 67.8 (1C, PhCHCH_2OH), 77.4 (1C, OCH$_2$CHCHCH$_2$OH), 81.3 (1C, OCH$_2$CHCH-CH$_2$OH), 83.4 (1C, PhCHCH$_2$OH), 93.9 (1C, C-4$_{phenyl}$), 110.2 (1C, $C(CH_3)_2$), 130.6 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 138.4 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 140.7 (1C, C-1$_{phenyl}$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3364, 2982, 2932, 2882, 1481, 1369, 1211, 1049, 1007, 849, 818; HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_{22}IO_5$: 409.0506, found: 409.0472; HPLC (method 1): t_R = 18.6 min, purity 97.4%.

4.2.48. Methyl (2R,3R,4S,5R)-3,4-dihydroxy-5-(4-iodophenyl) tetrahydrofuran-2-carboxylate (**63**)

61 (574 mg, 1.53 mmol), TEMPO (48 mg, 0.31 mmol) and BAIB (1.08 g, 3.36 mmol) were dissolved in a mixture of acetonitrile and a saturated aqueous solution of sodium bicarbonate (1/1, 20 mL) at 0 °C. The reaction was stirred at ambient temperature for 68 h. Then a spatula tip of sodium thiosulfate was added and the mixture was acidified with 1 M hydrochloric acid. The mixture was extracted with dichloromethane (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol (5 mL) and *p*-TsOH (58 mg, 0.31 mmol) was added. The reaction mixture was heated under microwave irradiation for 1 h at 115 °C, 20 bar and 50 W. Afterwards a saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.21) to give **63** as colorless solid (332 mg, 0.91 mmol, 60% yield). Melting point: 106 °C; Specific rotation: $[\alpha]_D^{20}$ = +34.2 (c = 3.8; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.80 (s, 3H, COOCH_3), 3.86 (dd, J = 7.5/4.8 Hz, 1H, 4-H), 4.22 (dd, J = 4.8/2.7 Hz, 1H, 3-H), 4.49 (d, J = 2.7 Hz, 1H, 2-H), 4.78 (d, J = 7.5 Hz, 1H, 5-H), 7.34–7.37 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.68–7.72 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$); ^{13}C NMR: (CD_3OD):

δ [ppm] = 52.7 (1C, $COOCH_3$), 75.8 (1C, C-3), 79.2 (1C, C-4), 84.0 (1C, C-2), 84.9 (1C, C-5), 93.8 (1C, C-4_{phenyl}), 129.6 (2C, C-2_{phenyl}, C-6_{phenyl}), 138.5 (2C, C-3_{phenyl}, C-5_{phenyl}), 141.5 (1C, C-1_{phenyl}); 173.1 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3464, 2951, 1732, 1439, 1396, 1234, 1099, 1076, 1053, 1003, 806; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{14}IO_5$: 364.9880, found: 364.9880; HPLC (method 1): t_R = 17.0 min, purity 94.2%.

4.2.49. Methyl (2R,3R,4S,5R)-3,4-dihydroxy-5-[4-(phenylethynyl) phenyl]tetrahydrofuran-2-carboxylate (**64a**)

Under nitrogen atmosphere, copper(I) iodide (8 mg, 0.04 mmol), tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.02 mmol) and triethylamine (0.20 mL, 1.44 mmol) were added to a solution of **63** (75 mg, 0.21 mmol) in dry acetonitrile (10 mL) at ambient temperature. Then a solution of phenylacetylene (0.11 mL, 1.03 mmol) in dry acetonitrile (1 mL) was added dropwise over a period of 2 h. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.23) to give **64a** as colorless solid (70 mg, 0.21 mmol, 100% yield). Melting point: 138 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = +56.8 (c = 4.8; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.81 (s, 3H, $COOCH_3$), 3.91 (dd, *J* = 7.5/4.8 Hz, 1H, 4-H), 4.25 (dd, *J* = 4.8/2.8 Hz, 1H, 3-H), 4.52 (d, *J* = 2.8 Hz, 1H, 2-H), 4.86 (d, *J* = 7.5 Hz, 1H, 5-H), 7.32–7.40 (m, 3H, H_{phenyl}), 7.48–7.54 (m, 4H, H_{phenyl}), 7.57–7.61 (m, 2H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 52.7 (1C, $COOCH_3$), 75.8 (1C, C-3), 79.2 (1C, C-4), 83.9 (1C, C-2), 85.2 (1C, C-5), 90.1 (1C, PhC≡CPh), 90.2 (1C, PhC≡CPh), 123.9 (1C, C_{phenyl}), 124.6 (1C, C_{phenyl}), 127.7 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 129.5 (2C, C_{phenyl}), 132.4 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 142.0 (1C, C_{phenyl}), 173.2 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3460, 2951, 2916, 1736, 1512, 1439, 1219, 1103, 1061, 995, 829, 760, 691; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{19}O_5$: 339.1227, found: 339.1246; HPLC (method 1): t_R = 20.3 min, purity 97.6%.

4.2.50. Methyl (2R,3R,4S,5R)-3,4-dihydroxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-tetrahydrofuran-2-carboxylate (**64b**)

Under nitrogen atmosphere, copper(I) iodide (7 mg, 0.04 mmol), tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) and triethylamine (0.19 mL, 1.35 mmol) were added to a solution of **63** (70 mg, 0.19 mmol) in dry acetonitrile (10 mL). Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (77 mg, 0.38 mmol) in dry acetonitrile (1 mL) was added dropwise over a period of 2 h at ambient temperature. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 19/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.28) to give **64b** as yellowish oil (78 mg, 0.18 mmol, 93% yield). Specific rotation: $[\alpha]_D^{20}$ = +49.0 (c = 3.0; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 2.48–2.53 (m, 4H, N(CH_2CH_2)$_2$), 3.58 (s, 2H, PhCH_2N), 3.68–3.72 (m, 4H, N(CH_2CH_2)$_2$), 3.81 (s, 3H, $COOCH_3$), 3.91 (dd, *J* = 7.5/4.8 Hz, 1H, 4-H), 4.25 (dd, *J* = 4.8/2.8 Hz, 1H, 3-H), 4.51 (d, *J* = 2.8 Hz, 1H, 2-H), 4.85 (d, *J* = 7.5 Hz, 1H, 5-H), 7.35–7.39 (m, 2H, H_{phenyl}), 7.47–7.53 (m, 4H, H_{phenyl}), 7.57–7.61 (m, 2H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 52.8 (1C, $COOCH_3$), 54.5 (2C, N(CH_2CH_2)$_2$), 63.8 (1C, PhCH_2N), 67.6 (2C, N(CH_2CH_2)$_2$), 75.8 (1C, C-3), 79.2 (1C, C-4), 83.9 (1C, C-2), 85.2 (1C, C-5), 90.0 (1C, PhC≡CPh), 90.3 (1C, PhC≡CPh), 123.8 (1C, C_{phenyl}), 123.9 (1C, C_{phenyl}), 127.8 (2C, C_{phenyl}), 130.9 (2C, C_{phenyl}), 132.4 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 142.0 (1C, C_{phenyl}), 173.2 (1C, $COOCH_3$), 138.3 (1C, C_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3360, 2924, 1744, 1516, 1207, 1107, 1061, 1007, 864, 829; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{28}NO_6$: 438.1911, found: 438.1891; HPLC (method 1): t_R = 14.7 min, purity 95.8%.

4.2.51. Methyl (2R,3R,4S,5R)-3,4-dihydroxy-5-{4-[(trimethylsilyl) ethynyl]phenyl}tetrahydrofuran-2-carboxylate (**64d**)

Under nitrogen atmosphere, copper(I) iodide (22 mg, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (65 mg, 0.06 mmol) and triethylamine (0.55 mL, 3.96 mmol) were added to a solution of **63** (206 mg, 0.57 mmol) in dry acetonitrile (20 mL). Afterwards, trimethylsilylacetylene (0.40 mL, 2.83 mmol) in dry acetonitrile (2 mL) was added dropwise over a period of 2 h at ambient temperature. Then the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.29) to give **64d** as colorless solid (190 mg, 0.57 mmol, 100% yield). Melting point: 103 °C; Specific rotation: $[\alpha]_D^{20}$ = +47.0 (c = 4.4; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 0.23 (s, 9H, Si(CH_3)$_3$), 3.80 (s, 3H, $COOCH_3$), 3.88 (dd, *J* = 7.4/4.8 Hz, 1H, 4-H), 4.23 (dd, *J* = 4.8/2.8 Hz, 1H, 3-H), 4.50 (d, *J* = 2.8 Hz, 1H, 2-H), 4.83 (d, *J* = 7.4 Hz, 1H, 5-H), 7.40–7.45 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.52–7.57 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 0.01 (3C, Si(CH_3)$_3$), 52.7 (1C, $COOCH_3$), 75.8 (1C, C-3), 79.2 (1C, C-4), 83.9 (1C, C-2), 85.2 (1C, C-5), 94.3 (1C, PhC≡CSi(CH_3)$_3$), 106.2 (1C, PhC≡CSi(CH_3)$_3$), 123.8 (1C, C-4_{phenyl}), 127.6 (2C, C-2_{phenyl}, C-6_{phenyl}), 132.7 (2C, C-3_{phenyl}, C-5_{phenyl}), 142.3 (1C, C-1_{phenyl}), 173.1 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3507, 2955, 2153, 1751, 1408, 1219, 1123, 1053, 837, 826, 752; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{23}O_5Si$: 335.1309, found: 335.1353; HPLC (method 1): t_R = 21.6 min, purity 95.5%.

4.2.52. Methyl (2R,3R,4S,5R)-5-(4-ethynylphenyl)-3,4-dihydroxytetrahydrofuran-2-carboxylate (**65**)

Silver nitrate (9 mg, 0.05 mmol) and water (0.96 mL, 53 mmol) were added to a solution of **64d** (178 mg, 0.53 mmol) in acetone (10 mL). The mixture was stirred for 60 h at ambient temperature in the dark. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.24) to give **65** as colorless solid (114 mg, 0.43 mmol, 82% yield). Melting point: 109 °C; Specific rotation: $[\alpha]_D^{20}$ = +50.9 (c = 6.6; methanol); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.09 (s, 1H, PhC≡C*H*), 3.80 (s, 3H, $COOCH_3$), 3.96 (dd, *J* = 6.5/5.2 Hz, 1H, 4-H), 4.27 (dd, *J* = 5.2/3.9 Hz, 1H, 3-H), 4.52 (d, *J* = 3.9 Hz, 1H, 2-H), 4.83 (d, *J* = 6.5 Hz, 1H, 5-H), 7.40–7.44 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.45–7.49 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 52.8 (1C, $COOCH_3$), 74.2 (1C, C-3), 77.5 (1C, C-4), 77.7 (1C, PhC≡*C*H), 82.1 (1C, C-2), 83.5 (1C, Ph*C*≡CH), 84.5 (1C, C-5), 122.0 (1C, C-4_{phenyl}), 126.2 (2C, C-2_{phenyl}, C-6_{phenyl}), 132.4 (2C, C-3_{phenyl}, C-5_{phenyl}), 139.8 (1C, C-1_{phenyl}), 171.5 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3422, 3279, 2951, 2106, 1736, 1211, 1103, 1057, 829; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{15}O_5$: 263.0914, found: 263.0923; HPLC (method 1): t_R = 15.8 min, purity 93.3%.

4.2.53. (2R,3R,4S,5R)-N-Butyl-3,4-dihydroxy-5-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]tetrahydrofuran-2-carboxamide (**66**)

Copper(I) chloride (2 mg, 0.02 mmol) was added to an aqueous solution of *n*-butylamine (30% (V/V), 5 mL) at ambient temperature. The resulting blue color was discharged by adding a few crystals of hydroxylamine hydrochloride. Addition of **65** (107 mg, 0.41 mmol) at ambient temperature led to a yellow acetylide suspension that was immediately cooled by a water-ice bath. Afterwards (bromoethynyl)benzene (0.10 mL, 0.82 mmol) was added at once. Then the water-ice bath was removed and Et_2O (3 mL) was added. The reaction was stirred for 30 min.

During this time hydroxylamine hydrochloride was added when the mixture turned green or blue. Afterwards, water was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.16) to give **66** as yellowish solid (68 mg, 0.17 mmol, 41% yield). Melting point: 124 °C; Specific rotation: $[\alpha]_D^{20}$ = +72.2 (c = 5.6; dichloromethane); ^{1}H NMR: (CD_3OD): δ [ppm] = 0.95 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.33 (sext, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.49–1.55 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.22 (dt, *J* = 13.3/7.1 Hz, 1H, $CH_2CH_2CH_2CH_3$), 3.30 (dt, *J* = 13.3/7.2 Hz, 1H, $CH_2CH_2CH_2CH_3$), 3.90 (dd, *J* = 7.7/5.2 Hz, 1H, 4-H), 4.24 (dd, *J* = 5.2/3.1 Hz, 1H, 3-H), 4.35 (d, *J* = 3.1 Hz, 1H, 2-H), 4.83 (d, *J* = 7.7 Hz, 1H, 5-H), 7.36–7.43 (m, 3H, H_{phenyl}), 7.52–7.55 (m, 6H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 14.1 (1C, $CH_2CH_2CH_2CH_3$), 21.1 (1C, $CH_2CH_2CH_2CH_3$), 32.6 (1C, $CH_2CH_2CH_2CH_3$), 39.9 (1C, $CH_2CH_2CH_2CH_3$), 74.4 (1C, PhC≡CC≡CPh), 74.6 (1C, PhC≡CC≡CPh), 75.5 (1C, C-3), 78.5 (1C, C-4), 82.1 (1C, PhC≡CC≡CPh), 82.3 (1C, PhC≡CC≡CPh), 84.8 (1C, C-5), 85.4 (1C, C-2), 122.4 (1C, C_{phenyl}), 122.9 (1C, C_{phenyl}), 127.9 (2C, C_{phenyl}), 129.7 (2C, C_{phenyl}), 130.5 (1C, C_{phenyl}), 133.4 (2C, C_{phenyl}), 133.5 (2C, C_{phenyl}), 142.8 (1C, C_{phenyl}), 172.7 (1C, CONH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3410, 3264, 2955, 2928, 2870, 1659, 1531, 1103, 1049, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{26}NO_4$: 404.1856, found: 404.1880; HPLC (method 1): t_R = 23.1 min, purity 98.4%.

4.2.54. Methyl (2R,3R,4S,5R)-3,4-dihydroxy-5-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]tetrahydrofuran-2-carboxylate (**64c**)

p-TsOH (59 mg, 0.31 mmol) was added to a solution of **66** (63 mg, 0.16 mmol) in methanol (5 mL). The mixture was heated under microwave irradiation for 30 min at 115 °C, 20 bar and 50 W. Then again *p*-TsOH (59 mg, 0.31 mmol) was added and the mixture was heated under microwave irradiation for 90 min at 115 °C, 20 bar and 50 W. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.23) to give **64c** as colorless solid (19 mg, 0.05 mmol, 34% yield). Melting point: 149 °C; Specific rotation: $[\alpha]_D^{20}$ = +54.7 (c = 3.6; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.85 (s, 3H, $COOCH_3$), 4.05–4.08 (m, 1H, 4-H), 4.34–4.37 (m, 1H, 3-H), 4.59 (d, *J* = 3.8 Hz, 1H, 2-H), 4.90 (d, *J* = 6.4 Hz, 1H, 5-H), 7.32–7.39 (m, 3H, H_{phenyl}), 7.48–7.51 (m, 2H, H_{phenyl}), 7.52–7.55 (m, 4H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ pm] = 52.7 (1C, $COOCH_3$), 74.0 (1C, PhC≡CC≡CPh), 74.3 (1C, PhC≡CC≡CPh), 74.3 (1C, C-3), 77.6 (1C, C-4), 81.5 (1C, PhC≡CC≡CPh), 81.9 (1C, PhC≡CC≡CPh), 82.2 (1C, C-2), 84.6 (1C, C-5), 121.7 (1C, C_{phenyl}), 121.9 (1C, C_{phenyl}), 126.3 (2C, C_{phenyl}), 128.6 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 132.7 (2C, C_{phenyl}), 132.9 (2C, C_{phenyl}), 140.5 (1C, C_{phenyl}), 171.3 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3395, 2940, 2145, 1709, 1423, 1331, 1130, 1096, 1084, 1057, 818, 752, 683; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{19}O_5$: 363.1227, found: 363.1241; HPLC (method 1): t_R = 21.8 min, purity 99.2%.

4.2.55. (2R,3R,4S,5R)-N,3,4-Trihydroxy-5-[4-(phenylethynyl) phenyl]tetrahydrofuran-2-carboxamide (**67a**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (64 mg, 0.92 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.17 mL, 0.92 mmol) were added to a solution of **64a** (52 mg, 0.15 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 15 h. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.22) to give **67a** as colorless solid (47 mg, 0.14 mmol, 90% yield). Melting point: 103 °C; Specific rotation: $[\alpha]_D^{20}$ = +36.1 (c = 3.5; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 4.01 (dd, *J* = 7.2/5.2 Hz, 1H, 4-H), 4.28 (dd, *J* = 5.2/3.3 Hz, 1H, 3-H), 4.33 (d, *J* = 3.3 Hz, 1H, 2-H), 4.81 (d, *J* = 7.2 Hz, 1H, 5-H), 7.34–7.39 (m, 3H, H_{phenyl}), 7.48–7.56 (m, 6H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 75.2 (1C, C-3), 78.9 (1C, C-4), 83.8 (1C, C-2), 85.5 (1C, C-5), 90.0 (1C, PhC≡CPh), 90.2 (1C, PhC≡CPh), 124.0 (1C, C_{phenyl}), 124.6 (1C, C_{phenyl}), 127.9 (2C, C_{phenyl}), 129.4 (1C, C_{phenyl}), 129.5 (2C, C_{phenyl}), 132.4 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 141.6 (1C, C_{phenyl}), 169.6 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3240, 2920, 1663, 1512, 1092, 1049, 822, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{18}NO_5$: 340.1179, found: 340.1186; HPLC (method 2): t_R = 15.4 min, purity 98.5%.

4.2.56. (2R,3R,4S,5R)-N,3,4-Trihydroxy-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-tetrahydro-furan-2-carboxamide (**67b**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (27 mg, 0.38 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.07 mL, 0.38 mmol) were added to a solution of **64b** (56 mg, 0.13 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 16 h. Then hydroxylamine hydrochloride (27 mg, 0.38 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.07 mL, 0.38 mmol) were added and the mixture was stirred for 24 h. Afterwards, the solvent was removed in vacuo and the residue was purified by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) to give **67b** as colorless solid (36 mg, 0.08 mmol, 64% yield). RP-TLC (H_2O/ACN = 3/2): R_f = 0.26; Melting point: 203 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = +49.3 (c = 2.9; methanol); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 2.34–2.37 (m, 4H, $N(CH_2CH_2)_2$), 3.49 (s, 2H, $PhCH_2N$), 3.56–3.59 (m, 4H, $N(CH_2CH_2)_2$), 3.74 (dd, *J* = 8.3/4.4 Hz, 1H, 4-H), 3.99 (dd, *J* = 4.4/1.3 Hz, 1H, 3-H), 4.01 (d, *J* = 1.3 Hz, 1H, 2-H), 4.59 (d, *J* = 8.3 Hz, 1H, 5-H), 4.96 (s br, 1H, OH), 5.11 (s br, 1H, OH), 7.34–7.37 (m, 2H, 3′-$H_{4\text{-(morpholinomethyl)phenyl}}$, 5′-$H_{4\text{-(morpholinomethyl)phenyl}}$), 7.44–7.47 (m, 2H, 3-$H_{phenyl}$, 5-$H_{phenyl}$), 7.49–7.52 (m, 2H, 2′-$H_{4\text{-(morpholinomethyl)phenyl}}$, 6′-$H_{4\text{-(morpholinomethyl)phenyl}}$), 7.78–7.80 (m, 2H, 2-$H_{phenyl}$, 6-$H_{phenyl}$); ^{13}C NMR: (DMSO-$d_6$): δ [ppm] = 53.2 (2C, $N(CH_2CH_2)_2$), 62.0 (1C, $PhCH_2N$), 66.2 (2C, $N(CH_2CH_2)_2$), 75.4 (1C, C-3), 78.6 (1C, C-4), 82.4 (1C, C-5), 86.3 (1C, C-2), 88.8 (1C, PhC≡CPh'), 89.6 (1C, PhC≡CPh'), 120.7 (1C, C-4_{phenyl}), 121.1 (1C, C-1′$_{4\text{-(morpholinomethyl)phenyl}}$), 127.6 (2C, C-$2_{phenyl}$, C-$6_{phenyl}$), 129.1 (2C, C-3′$_{4\text{-(morpholinomethyl)phenyl}}$, C-5′$_{4\text{-(morpholinomethyl)phenyl}}$), 130.6 (2C, C-$3_{phenyl}$, C-$5_{phenyl}$), 131.2 (2C, C-2′$_{4\text{-(morpholinomethyl)phenyl}}$, C-6′$_{4\text{-(morpholinomethyl)phenyl}}$), 138.6 (1C, C-4′$_{4\text{-(morpholinomethyl)phenyl}}$), 144.0 (1C, C-$1_{phenyl}$), 174.3 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3294, 2970, 2916, 1597, 1412, 1292, 1107, 1065, 829, 795; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_6$: 439.1864, found: 439.1863; HPLC (method 2): t_R = 12.2 min, purity 97.5%.

4.2.57. (2R,3R,4S,5R)-N,3,4-Trihydroxy-5-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]tetrahydrofuran-2-carboxamide (**67c**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (7 mg, 0.10 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.02 mL, 0.10 mmol) were added to a solution of **64c** (19 mg, 0.05 mmol) in dry methanol (5 mL) and the mixture was stirred at ambient temperature for 17 h. Afterwards, the solvent was removed in vacuo and the residue was purified by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) to give **67c** as colorless solid (13 mg,

0.04 mmol, 68% yield). RP-TLC (H_2O/ACN = 1/1): $R_f = 0.32$; Melting point: 158 °C (decomposition); Specific rotation: $[\alpha]_D^{20} = +17.9$ (c = 3.9; MeOH); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.99 (dd, J = 7.3/5.2 Hz, 1H, 4-H), 4.27 (dd, J = 5.2/3.3 Hz, 1H, 3-H), 4.31 (d, J = 3.3 Hz, 1H, 2-H), 4.80 (d, J = 7.3 Hz, 1H, 5-H), 7.36–7.44 (m, 3H, H_{phenyl}), 7.50–7.57 (m, 6H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 74.4 (1C, PhC≡*C*C≡CPh), 74.4 (1C, PhC≡*C*C≡CPh), 75.2 (1C, C-3), 79.0 (1C, C-4), 82.2 (1C, Ph*C*≡CC≡CPh), 82.3 (1C, Ph*C*≡CC≡CPh), 83.9 (1C, C-2), 85.3 (1C, C-5), 122.3 (1C, C_{phenyl}), 122.9 (1C, C_{phenyl}), 127.9 (2C, C_{phenyl}), 129.7 (2C, C_{phenyl}), 130.5 (1C, C_{phenyl}), 133.4 (2C, C_{phenyl}), 133.4 (2C, C_{phenyl}), 143.0 (1C, C_{phenyl}), 169.5 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3240, 2920, 1655, 1269, 1099, 1061, 1015, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{18}NO_5$: 364.1179, found: 364.1195; HPLC (method 2): t_R = 16.3 min, purity 96.4%.

4.2.58. (2S,3R,4S,5R)-2-[(R)-1-Hydroxy-2-(trityloxy)ethyl]-5-(4-iodophenyl)tetrahydrofuran-3,4-diol (**68**)

Under nitrogen atmosphere, DMAP (52 mg, 0.42 mmol), pyridine (0.34 mL, 4.24 mmol) and trityl chloride (710 mg, 2.55 mmol) were added to a solution of **60** (777 mg, 2.12 mmol) in DMF (10 mL) at 0 °C. The mixture was stirred for 24 h at ambient temperature. Then pyridine (0.34 mL, 4.24 mmol) and trityl chloride (710 mg, 2.55 mmol) were added and the mixture was stirred for 60 h. Then the mixture was heated to 70 °C for 24 h. Afterwards, the solvent was removed in vacuo and an aqueous solution of acetic acid (3% (V/V), 10 mL) was added. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 4 cm, h = 15 cm, V = 30 mL, $R_f = 0.31$) to give **68** as colorless solid (515 mg, 0.85 mmol, 40% yield). Melting point: 138 °C; Specific rotation: $[\alpha]_D^{20} = -21.7$ (c = 8.2; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.25 (dd, J = 9.1/6.7 Hz, 1H, Ph_3COCH_2*C*H), 3.33 (dd, J = 9.1/6.3 Hz, 1H, Ph_3COCH_2*C*H), 3.78 (dd, J = 7.3/5.2 Hz, 1H, 4-H), 3.88–3.93 (m, 1H, Ph_3COCH_2CH), 4.12–4.17 (m, 2H, 2-H, 3-H), 4.60 (d, J = 7.3 Hz, 1H, 5-H), 7.15–7.31 (m, 11H, H_{aryl}), 7.46–7.51 (m, 6H, H_{aryl}), 7.60–7.63 (m, 2H, 3-$H_{iodophenyl}$, 5-$H_{iodophenyl}$); ^{13}C NMR: (CD_3OD): δ [ppm] = 65.9 (1C, Ph_3COCH_2*C*H), 71.5 (1C, Ph_3COCH_2*C*H), 73.4 (1C, C-3), 79.1 (1C, C-4), 84.1 (1C, C-5), 86.4 (1C, C-2), 88.1 (1C, Ph_3COCH_2CH), 93.4 (1C, C-$4_{iodophenyl}$), 128.0 (3C, C-4'$_{trityl}$), 128.7 (6C, C-3'$_{trityl}$, C-5'$_{trityl}$), 129.5 (2C, C-$2_{iodophenyl}$, C-$6_{iodophenyl}$), 130.0 (6C, C-2'$_{trityl}$, C-6'$_{trityl}$), 138.3 (2C, C-$3_{iodophenyl}$, C-$5_{iodophenyl}$), 142.0 (1C, C-$1_{iodophenyl}$), 145.5 (3C, C-1'$_{trityl}$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3375, 2978, 2886, 1485, 1447, 1393, 1072, 1003, 745, 702; HRMS (*m/z*): $[M\text{-}OCPh_3]^+$ calcd for $C_{12}H_{14}IO_4$: 348.9931, found: 348.9893; HPLC (method 1): t_R = 24.5 min, purity 98.6%.

4.2.59. (2R,3R)-3-[(R)-2-Hydroxy-1-(4-iodophenyl)ethoxy]butane-1,2,4-triol (**69**)

4.2.59.1. Method A. *p*-TsOH (14 mg, 0.07 mmol) was added to a solution of **62** (297 mg, 0.73 mmol) in methanol (10 mL). The mixture was stirred for 69 h at ambient temperature. Then the mixture was heated to reflux for 20 h. Afterwards the solvent was removed in vacuo. The residue was purified by flash column chromatography (ethyl acetate/methanol = 10/1, Ø = 2 cm, h = 15 cm, V = 10 mL, $R_f = 0.22$) to give an **69** as colorless oil (220 mg, 0.60 mmol, 82% yield).

4.2.59.2. Method B. Sodium metaperiodate (970 mg, 4.54 mmol) was added to a solution of **68** (920 mg, 1.51 mmol) in methanol (20 mL). The reaction was stirred for 3 h at ambient temperature. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol (20 mL) and sodium borohydride (171 mg, 4.54 mmol) was added. The reaction was stirred at ambient temperature for 30 min. Then concentrated hydrochloric acid (1.5 mL) was added and the reaction was stirred for 1 h. Afterwards, a saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (ethyl acetate/methanol = 10/1, Ø = 3 cm, h = 15 cm, V = 20 mL, $R_f = 0.22$) to give **69** as colorless oil (367 mg, 1.00 mmol, 66% yield). Specific rotation: $[\alpha]_D^{20} = -66.1$ (c = 8.4; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.44–3.54 (m, 3H, 1-H (2H), 3-H), 3.56 (dd, J = 11.7/3.7 Hz, 1H, PhCHC*H*$_2$OH), 3.63–3.69 (m, 2H, PhCHC*H*$_2$OH, 2-H), 3.77 (dd, J = 11.7/5.4 Hz, 1H, 4-H), 3.81 (dd, J = 11.7/4.7 Hz, 1H, 4-H), 4.65 (dd, J = 8.0/3.7 Hz, 1H, PhC*H*CH$_2$OH), 7.16–7.20 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.68–7.72 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 62.1 (1C, C-4), 64.2 (1C, C-1), 67.9 (1C, PhCH*C*H$_2$OH), 73.4 (1C, C-2), 80.3 (1C, C-3), 83.1 (1C, Ph*C*HCH$_2$OH), 94.1 (1C, C-4_{phenyl}), 130.5 (2C, C-2_{phenyl}, C-6_{phenyl}), 138.6 (2C, C-3_{phenyl}, C-5_{phenyl}), 140.6 (1C, C-1_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3329, 2924, 2882, 1481, 1400, 1096, 1038, 1003, 818; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{18}IO_5$: 369.0193, found: 369.0198; HPLC (method 1): t_R = 13.9 min, purity 98.0%.

4.2.60. (2RS,3R,5R)-3-(Hydroxymethyl)-5-(4-iodophenyl)-1,4-dioxan-2-ol (**70**)

Under nitrogen atmosphere, sodium metaperiodate (1.18 g, 5.52 mmol) was added to a solution of **69** (677 mg, 1.84 mmol) in dry methanol (20 mL). The mixture was stirred for 19 h at ambient temperature. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 3 cm, h = 15 cm, V = 20 mL, $R_f = 0.24$) to give **70** as colorless solid (474 mg, 1.41 mmol, 77% yield). Melting point: 118 °C; Specific rotation: $[\alpha]_D^{20} = +11.5$ (c = 6.0; dichloromethane); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 3.39–3.44 (m, 0.7H, 3-H^{E1}), 3.52–3.70 (m, 3 × 0.7H + 4 × 0.3H, C*H*$_2$OH^{E1+E2} (2H), 3-H^{E2} (0.3H), 6-H^{E1+E2} (1H)), 3.97 (dd, J = 11.8/7.3 Hz, 0.7H, 6-H^{E1}), 4.12 (dd, J = 11.8/3.3 Hz, 0.3H, 6-H^{E2}), 4.44–4.48 (m, 0.3H, CH$_2$O*H*^{E2}), 4.69–4.77 (m, 3 × 0.7H + 1 × 0.3H, 5-H^{E1+E2} (1H), CH$_2$O*H*^{E1} (0.7H), 2-H^{E1} (0.7H)), 4.83 (dd, J = 5.2/2.2 Hz, 0.3H, 2-H^{E2}), 6.54 (d, J = 5.9 Hz, 0.7H, OCHO*H*^{E1}), 6.68 (d, J = 5.2 Hz, 0.3H, OCHO*H*^{E2}), 7.21–7.29 (m, 2H, 2-H_{phenyl}^{E1+E2}, 6-H_{phenyl}^{E1+E2}), 7.70–7.74 (m, 2H, 3-H_{phenyl}^{E1+E2}, 5-H_{phenyl}^{E1+E2}); ratio of epimers 70(E1):30(E2); ^{13}C NMR: (DMSO-d_6): δ [ppm] = 57.6 (0.3C, *C*H$_2$OH^{E2}), 59.6 (0.7C, *C*H$_2$OH^{E1}), 63.0 (0.7C, C-6^{E1}), 64.1 (0.3C, C-6^{E2}), 69.3 (0.3C, C-5^{E2}), 70.0 (0.7C, C-5^{E1}), 73.8 (0.3C, C-3^{E2}), 75.1 (0.7C, C-3^{E1}), 89.7 (0.7C, C-2^{E1}), 90.9 (0.3C, C-2^{E2}), 93.4 (1C, C-4_{phenyl}^{E1+E2}), 129.0 (2 × 0.7C, C-2_{phenyl}^{E1}, C-6_{phenyl}^{E1}), 129.3 (2 × 0.3C, C-2_{phenyl}^{E2}, C-6_{phenyl}^{E2}), 136.9 (2 × 0.3C, C-3_{phenyl}^{E2}, C-5_{phenyl}^{E2}), 137.0 (2 × 0.7C, C-3_{phenyl}^{E1}, C-5_{phenyl}^{E1}), 138.5 (0.3C, C-1_{phenyl}^{E2}), 139.1 (0.7C, C-1_{phenyl}^{E1}); ratio of epimers 70(E1):30(E2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3291, 2967, 2889, 1485, 1312, 1138, 999, 972, 876, 814; LC-MS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{13}INaO_4$: 358.9751, found: 358.9749; HPLC (method 1): t_R = 15.7 min, purity 98.7%.

4.2.61. (3R,5R)-3-(Hydroxymethyl)-5-(4-iodophenyl)-1,4-dioxan-2-one (**71**)

Sodium bicarbonate (2.24 g, 26.7 mmol) was added to a solution of **70** (449 mg, 1.34 mmol) in methanol/water (9/1, 20 mL). Then a 1 M solution of bromine in methanol/water (9/1, 2.67 mL, 2.67 mmol) was added. The reaction was stirred for 2 h at

ambient temperature. Afterwards, a saturated solution of sodium thiosulfate in water was added until the mixture decolorized. Then the mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in dry acetonitrile (20 mL) and *p*-TsOH (51 mg, 0.27 mmol) was added. The reaction was heated to reflux overnight. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. Then the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.24) to give **71** as colorless solid (363 mg, 1.09 mmol, 81% yield). Melting point: 146 °C; Specific rotation: $[\alpha]_D^{20}$ = +3.2 (c = 10.0; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 4.00 (dd, *J* = 11.8/4.0 Hz, 1H, CH_2OH), 4.13 (dd, *J* = 11.8/4.7 Hz, 1H, CH_2OH), 4.46 (dd, *J* = 11.8/9.0 Hz, 1H, 6-H), 4.51 (dd, *J* = 11.8/3.2 Hz, 1H, 6-H), 4.61 (t, *J* = 4.3 Hz, 1H, 3-H), 5.18 (dd, *J* = 9.0/3.2 Hz, 1H, 5-H), 7.13–7.16 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.73–7.76 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 63.9 (1C, CH_2OH), 72.1 (1C, C-5), 72.2 (1C, C-6), 74.6 (1C, C-3), 94.9 (1C, C-4_{phenyl}), 128.3 (2C, C-2_{phenyl}, C-6_{phenyl}), 135.2 (1C, C-1_{phenyl}), 138.2 (2C, C-3_{phenyl}, C-5_{phenyl}), 168.3 (1C, C-2); NOE: Irradiation at 4.61 ppm (3-H): δ [ppm] = 4.00 (CH_2OH), 4.13 (CH_2OH), 4.46 (6-H), 7.13–7.16 (2-H_{phenyl}, 6-H_{phenyl}); Irradiation at 5.18 ppm (5-H): δ [ppm] = 4.46 (6-H), 4.51 (6-H), 7.13–7.16 (2-H_{phenyl}, 6-H_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3499, 2959, 2924, 2882, 1709, 1697, 1319, 1254, 1123, 1057, 814; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{12}IO_4$: 334.9775, found: 334.9775; HPLC (method 1): t_R = 17.9 min, purity 98.2%.

4.2.62. (3R,5R)-3-(Hydroxymethyl)-5-[4-(phenylethynyl)phenyl]-1,4-dioxan-2-one (**72a**)

Under nitrogen atmosphere, copper(I) iodide (7 mg, 0.04 mmol), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.09 mmol) and triethylamine (0.18 mL, 1.28 mmol) were added to a solution of **71** (61 mg, 0.18 mmol) in dry acetonitrile (10 mL). Then a solution of phenylacetylene (0.10 mL, 0.91 mmol) in dry acetonitrile (1 mL) was added dropwise over a period of 4 h. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.20) to give **72a** as colorless solid (52 mg, 0.17 mmol, 92% yield). Melting point: 143 °C; Specific rotation: $[\alpha]_D^{20}$ = −6.0 (c = 2.6; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 4.02 (dd, *J* = 11.9/4.2 Hz, 1H, CH_2OH), 4.14 (dd, *J* = 11.9/4.8 Hz, 1H, CH_2OH), 4.50 (dd, *J* = 11.8/8.9 Hz, 1H, 6-H), 4.54 (dd, *J* = 11.8/3.4 Hz, 1H, 6-H), 4.64 (t, *J* = 4.5 Hz, 1H, 3-H), 5.23 (dd, *J* = 8.9/3.4 Hz, 1H, 5-H), 7.34–7.37 (m, 3H, H_{phenyl}), 7.38–7.40 (m, 2H, H_{phenyl}), 7.53–7.55 (m, 2H, H_{phenyl}), 7.56–7.58 (m, 2H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 63.8 (1C, CH_2OH), 72.2 (1C, C-6), 72.3 (1C, C-5), 74.5 (1C, C-3), 88.7 (1C, PhC≡CPh), 90.5 (1C, PhC≡CPh), 123.0 (1C, C_{phenyl}), 124.3 (1C, C_{phenyl}), 126.5 (2C, C_{phenyl}), 128.5 (2C, C_{phenyl}), 128.7 (1C, C_{phenyl}), 131.8 (2C, C_{phenyl}), 132.2 (2C, C_{phenyl}), 135.4 (1C, C_{phenyl}), 168.4 (1C, C-2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3453, 2955, 2924, 1724, 1416, 1323, 1250, 1138, 1030, 988, 837, 764, 691; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{17}O_4$: 309.1121, found: 309.1131; HPLC (method 1): t_R = 21.1 min, purity 98.5%.

4.2.63. (3R,5R)-3-(Hydroxymethyl)-5-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1,4-dioxan-2-one (**72b**)

Under nitrogen atmosphere, copper(I) iodide (6 mg, 0.03 mmol), tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.02 mmol) and triethylamine (0.16 mL, 1.13 mmol) were added to a solution of **71** (54 mg, 0.16 mmol) in dry acetonitrile (10 mL). Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (65 mg, 0.32 mmol) in dry acetonitrile (1 mL) was added dropwise over a period of 2 h at ambient temperature. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.15) to give **72b** as colorless solid (37 mg, 0.09 mmol, 56% yield). Melting point: 159 °C; Specific rotation: $[\alpha]_D^{20}$ = −7.2 (c = 4.4; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 2.44–2.58 (m br, 4H, N(CH_2CH_2)$_2$), 3.53–3.62 (m br, 2H, PhCH_2N), 3.72–3.79 (m br, 4H, N(CH_2CH_2)$_2$), 4.02 (dd, *J* = 11.8/4.1 Hz, 1H, CH_2OH), 4.14 (dd, *J* = 11.8/4.7 Hz, 1H, CH_2OH), 4.50 (dd, *J* = 11.8/8.6 Hz, 1H, 6-H), 4.55 (dd, *J* = 11.8/3.7 Hz, 1H, 6-H), 4.64 (t, *J* = 4.4 Hz, 1H, 3-H), 5.24 (dd, *J* = 8.6/3.7 Hz, 1H, 5-H), 7.34–7.41 (m, 4H, H_{phenyl}), 7.48–7.52 (m, 2H, H_{phenyl}), 7.54–7.58 (m, 2H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 53.5 (2C, N(CH_2CH_2)$_2$), 63.0 (1C, PhCH_2N), 63.8 (1C, CH_2OH), 66.7 (2C, N(CH_2CH_2)$_2$), 72.3 (1C, C-6), 72.3 (1C, C-5), 74.6 (1C, C-3), 88.9 (1C, PhC≡CPh), 90.3 (1C, PhC≡CPh), 124.2 (1C, C_{phenyl}), 126.5 (2C, C_{phenyl}), 129.6 (2C, C_{phenyl}), 131.8 (2C, C_{phenyl}), 132.2 (2C, C_{phenyl}), 135.4 (1C, C_{phenyl}), 168.4 (1C, C-2), the signals for two C_{phenyl} cannot be observed in the spectrum; IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2959, 2920, 2874, 2828, 1748, 1208, 1115, 1003, 864, 833, 795; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{26}NO_5$: 408.1805, found: 408.1838; HPLC (method 1): t_R = 15.3 min, purity 97.6%.

4.2.64. (3R,5R)-3-(Hydroxymethyl)-5-{4-[(trimethylsilyl)ethynyl]phenyl}-1,4-dioxan-2-one (**72d**)

Under nitrogen atmosphere, copper(I) iodide (27 mg, 0.14 mmol), tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.07 mmol) and triethylamine (0.69 mL, 5.0 mmol) were added to a solution of **71** (238 mg, 0.71 mmol) in dry acetonitrile (20 mL) at ambient temperature. Then a solution of trimethylsilylacetylene (0.51 mL, 3.6 mmol) in dry acetonitrile (2 mL) was added dropwise over a period of 2 h. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.29) to give **72d** as colorless solid (181 mg, 0.59 mmol, 83% yield). Melting point: 118 °C; Specific rotation: $[\alpha]_D^{20}$ = −1.1 (c = 4.2; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 0.25 (s, 9H, Si(CH_3)$_3$), 4.01 (dd, *J* = 11.8/4.2 Hz, 1H, CH_2OH), 4.13 (dd, *J* = 11.8/4.8 Hz, 1H, CH_2OH), 4.46 (dd, *J* = 11.8/8.7 Hz, 1H, 6-H), 4.52 (dd, *J* = 11.8/3.6 Hz, 1H, 6-H), 4.62 (t, *J* = 4.5 Hz, 1H, 3-H), 5.20 (dd, *J* = 8.7/3.6 Hz, 1H, 5-H), 7.31–7.35 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.47–7.51 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 0.05 (3C, Si(CH_3)$_3$), 63.8 (1C, CH_2OH), 72.2 (1C, C-6), 72.3 (1C, C-5), 74.5 (1C, C-3), 95.6 (1C, PhC≡CSi(CH_3)$_3$), 104.3 (1C, PhC≡CSi(CH_3)$_3$), 124.1 (1C, C-4_{phenyl}), 126.4 (2C, C-2_{phenyl}, C-6_{phenyl}), 132.6 (2C, C-3_{phenyl}, C-5_{phenyl}), 135.6 (1C, C-1_{phenyl}), 168.4 (1C, C-2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3437, 2951, 2924, 2164, 1721, 1331, 1250, 1219, 1134, 864, 837, 760; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{21}O_4Si$: 305.1204, found: 305.1237; HPLC (method 1): t_R = 21.8 min, purity 99.4%.

4.2.65. (3R,5R)-5-(4-Ethynylphenyl)-3-(hydroxymethyl)-1,4-dioxan-2-one (**73**)

Silver nitrate (10 mg, 0.06 mmol) and water (1.1 mL, 59 mmol) were added to a solution of **72d** (181 mg, 0.59 mmol) in acetone (15 mL). The mixture was stirred for 60 h at ambient temperature in the dark. Then silver nitrate (10 mg, 0.06 mmol) was added and the mixture stirred for 24 h at ambient temperature in the dark. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed

in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.22) to give **73** as colorless solid (106 mg, 0.46 mmol, 77% yield). Melting point: 111 °C; Specific rotation: $[\alpha]_D^{20}$ = +2.5 (c = 2.8; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.11 (s, 1H, PhC≡C*H*), 4.01 (dd, *J* = 11.8/4.1 Hz, 1H, C*H*$_2$OH), 4.13 (dd, *J* = 11.8/4.7 Hz, 1H, C*H*$_2$OH), 4.47 (dd, *J* = 11.8/8.8 Hz, 1H, 6-H), 4.53 (dd, *J* = 11.8/3.4 Hz, 1H, 6-H), 4.62 (t, *J* = 4.4 Hz, 1H, 3-H), 5.22 (dd, *J* = 8.8/3.4 Hz, 1H, 5-H), 7.34–7.38 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.51–7.55 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 63.9 (1C, *C*H$_2$OH), 72.2 (2C, C-5, C-6), 74.6 (1C, C-3), 78.3 (1C, PhC≡CH), 83.0 (1C, Ph*C*≡CH), 123.1 (1C, C-4$_{phenyl}$), 126.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 132.7 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 136.1 (1C, C-1$_{phenyl}$), 168.4 (1C, C-2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3449, 3252, 2928, 2106, 1724, 1346, 1227, 1107, 1030, 1003, 837, 826, 714; APCI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{13}O_4$: 233.0808, found: 233.0834; HPLC (method 1): t_R = 16.2 min, purity 97.6%.

4.2.66. (R)-N,3-Dihydroxy-2-{(R)-2-hydroxy-1-[4-(phenylethynyl) phenyl]ethoxy}propanamide (**74a**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (26 mg, 0.38 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.07 mL, 0.38 mmol) were added to a solution of **72a** (39 mg, 0.13 mmol) in dry methanol (5 mL) and the mixture was stirred at ambient temperature for 16 h. Afterwards, the solvent was removed in vacuo and the residue was purified by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) to give **74a** as colorless solid (30 mg, 0.09 mmol, 69% yield). RP-TLC (H_2O/ACN = 1/1): R_f = 0.30; Melting point: 132 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −32.1 (c = 2.8; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.69 (dd, *J* = 11.9/3.5 Hz, 1H, PhCHC*H*$_2$OH), 3.76 (dd, J = 11.9/7.1 Hz, 1H, PhCHC*H*$_2$OH), 3.79–3.93 (m, 3H, HOHNOCC*HCH*$_2$OH), 4.73 (dd, *J* = 7.1/3.5 Hz, 1H, PhC*H*CH$_2$OH), 7.34–7.39 (m, 3H, 3′-H$_{phenyl}$, 4′-H$_{phenyl}$, 5′-H$_{phenyl}$), 7.39–7.44 (m, 2H, 2-H$_{(phenylethynyl)phenyl}$, 6-H$_{(phenylethynyl)phenyl}$), 7.48–7.53 (m, 4H, 3-H$_{(phenylethynyl)phenyl}$, 5-H$_{(phenylethynyl)phenyl}$, 2′-H$_{phenyl}$, 6′-H$_{phenyl}$); ^{13}C NMR: (CD_3OD): δ [ppm] = 63.0 (1C, HOHNOCCH*C*H$_2$OH), 67.3 (1C, PhCH*C*H$_2$OH), 79.9 (1C, HOHNOC*C*HCH$_2$OH), 83.6 (1C, Ph*C*HCH$_2$OH), 89.8 (1C, PhC≡*C*Ph), 90.4 (1C, Ph*C*≡CPh), 124.4 (1C, C-4$_{(phenylethynyl)phenyl}$), 124.5 (1C, C-1'$_{phenyl}$), 128.6 (2C, C-2$_{(phenylethynyl)phenyl}$, C-6$_{(phenylethynyl)phenyl}$), 129.5 (1C, C-4'$_{phenyl}$), 129.5 (2C, C-3'$_{phenyl}$, C-5'$_{phenyl}$), 132.5 (2C, C-2'$_{phenyl}$, C-6'$_{phenyl}$), 132.6 (2C, C-3$_{(phenylethynyl)phenyl}$, C-5$_{(phenylethynyl)phenyl}$), 140.1 (1C, C-1$_{(phenylethynyl)phenyl}$), 170.3 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3233, 2928, 2866, 1655, 1597, 1508, 1049, 752, 691; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{20}NO_5$: 342.1336, found: 342.1337; HPLC (method 2): t_R = 15.1 min, purity 96.1%.

4.2.67. (R)-N,3-Dihydroxy-2-[(R)-2-hydroxy-1-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-ethoxy]propanamide (**74b**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (18 mg, 0.26 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.05 mL, 0.26 mmol) were added to a solution of **72b** (35 mg, 0.09 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 64 h. Afterwards, the solvent was removed in vacuo and the residue was purified by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) to give **74b** as colorless solid (28 mg, 0.06 mmol, 74% yield). RP-TLC (H_2O/ACN = 1/1): R_f = 0.34; Melting point: 126 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −42.9 (c = 3.7; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 2.43–2.49 (m, 4H, N(C*H*$_2$CH$_2$)$_2$), 3.53 (s, 2H, PhC*H*$_2$N), 3.67–3.70 (m, 5H, PhCHC*H*$_2$OH (1H), N(CH$_2$C*H*$_2$)$_2$), 3.76 (dd, *J* = 11.9/7.3 Hz, 1H, PhCHC*H*$_2$OH), 3.82 (dd, *J* = 11.5/4.6 Hz, 1H, HOHNOCCHC*H*$_2$OH), 3.86 (dd, *J* = 4.6/2.9 Hz, 1H, HOHNOCC*H*-CH$_2$OH), 3.90 (dd, *J* = 11.5/2.9 Hz, 1H, HOHNOCCHC*H*$_2$OH), 4.73 (dd, *J* = 7.3/3.5 Hz, 1H, PhC*H*CH$_2$OH), 7.35–7.37 (m, 2H, 3′-H$_{4-(morpholinomethyl)phenyl}$, 5′-H$_{4-(morpholinomethyl)phenyl}$), 7.40–7.42 (m, 2H, 2-H$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$, 6-H$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$), 7.46–7.48 (m, 2H, 2′-H$_{4-(morpholinomethyl)phenyl}$, 6′-H$_{4-(morpholinomethyl)phenyl}$), 7.49–7.51 (m, 2H, 3-H$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$, 5-H$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$); ^{13}C NMR: ($CD_3OD$): δ [ppm] = 54.7 (2C, N(CH$_2$CH$_2$)$_2$), 63.0 (1C, HOHNOCCH*C*H$_2$OH), 64.0 (1C, PhCH$_2$N), 67.3 (1C, PhCH*C*H$_2$OH), 67.8 (2C, N(CH$_2$*C*H$_2$)$_2$), 79.9 (1C, HOHNOC*C*HCH$_2$OH), 83.6 (1C, Ph*C*HCH$_2$OH), 89.9 (1C, Ph*C*≡CPh'), 90.3 (1C, PhC≡*C*Ph'), 123.5 (1C, C-1′$_{4-(morpholinomethyl)phenyl}$), 124.5 (1C, C-4$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$), 128.6 (2C, C-2$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$, C-6$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$), 130.7 (2C, C-3′$_{4-(morpholinomethyl)phenyl}$, C-5′$_{4-(morpholinomethyl)phenyl}$), 132.5 (2C, C-2′$_{4-(morpholinomethyl)phenyl}$), C-6′$_{4-(morpholinomethyl)phenyl}$), 132.6 (2C, C-3$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$, C-5$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$), 139.1 (1C, C-4′$_{4-(morpholinomethyl)phenyl}$), 140.1 (1C, C-1$_{4-\{2-[4-(morpholinomethyl)phenyl]ethynyl\}phenyl}$), 168.4 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3248, 2862, 2812, 1655, 1516, 1111, 1053, 864, 833, 795; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{29}N_2O_6$: 441.2020, found: 441.2028; HPLC (method 2): t_R = 11.8 min, purity 97.7%.

4.2.68. (R)-N,3-Dihydroxy-2-{(R)-2-hydroxy-1-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]ethoxy}-propanamide (**74c**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (90 mg, 1.29 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.24 mL, 1.29 mmol) were added to a solution of **73** (50 mg, 0.22 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 90 min. Then the solvent was removed in vacuo to obtain the corresponding crude hydroxamic acid. Copper(I) chloride (1 mg, 0.01 mmol) was added to an aqueous solution of *n*-butylamine (30% (V/V), 10 mL) at ambient temperature. The resulting blue color was discharged by adding a few crystals of hydroxylamine hydrochloride. Addition of the previously obtained crude hydroxamic acid at ambient temperature led to a yellow acetylide suspension that was immediately cooled by a water-ice bath. Afterwards (bromoethynyl)benzene (0.05 mL, 0.43 mmol) was added at once. Then the water-ice bath was removed and Et_2O (3 mL) was added. The reaction was stirred for 30 min. During this time hydroxylamine hydrochloride was added when the mixture turned green or blue. Afterwards, water was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified twice by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) and once by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL) to give **74c** as colorless solid (30 mg, 0.08 mmol, 38% yield). RP-TLC (H_2O/ACN = 1/1): R_f = 0.29; Melting point: 139 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −34.3 (c = 1.0; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.69 (dd, *J* = 11.9/3.5 Hz, 1H, PhCHC*H*$_2$OH), 3.76 (dd, *J* = 11.9/7.2 Hz, 1H, PhCHC*H*$_2$OH), 3.81 (dd, *J* = 11.6/4.5 Hz, 1H, HOHNOCCHC*H*$_2$OH), 3.85 (dd, *J* = 4.5/3.0 Hz, 1H, HOHNOCC*H*CH$_2$OH), 3.91 (dd, *J* = 11.6/3.0 Hz, 1H, HOHNOCCHC*H*$_2$OH), 4.73 (dd, *J* = 7.2/3.5 Hz, 1H, PhC*H*CH$_2$OH), 7.36–7.40 (m, 2H, 3′-H$_{phenyl}$, 5′-H$_{phenyl}$), 7.40–7.44 (m, 3H, 2-H$_{4-(4-phenylbuta-1,3-diynyl)phenyl}$, 6-H$_{4-(4-phenylbuta-1,3-diynyl)phenyl}$, 4′-H$_{phenyl}$), 7.51–7.54 (m, 4H, 3-H$_{4-(4-phenylbuta-1,3-diynyl)phenyl}$, 5-H$_{4-(4-phenylbuta-}$

1,3-diynyl)phenyl, 2′-H_{phenyl}, 6′-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 62.7 (1C, HOHNOCCHCH_2OH), 67.2 (1C, PhCHCH_2OH), 74.3 (1C, PhC≡CC≡CPh), 74.7 (1C, PhC≡CC≡CPh), 79.8 (1C, HOHNOCCHCH_2OH), 81.9 (1C, PhC≡CC≡CPh), 82.4 (1C, PhC≡CC≡CPh), 83.6 (1C, PhCHCH_2OH), 122.8 (1C, $C_{arom.}$), 122.9 (1C, $C_{arom.}$), 128.8 (2C, C-2$_{4\text{-}(4\text{-phenylbuta-1,3-diynyl})phenyl}$, C-6$_{4\text{-}(4\text{-phenylbuta-1,3-diynyl})phenyl}$), 129.7 (2C, C-3′$_{phenyl}$, C-5′$_{phenyl}$), 130.6 (1C, C-4′$_{phenyl}$), 133.4 (2C, C-3$_{4\text{-}(4\text{-phenylbuta-1,3-diynyl})phenyl}$, C-5$_{4\text{-}(4\text{-phenylbuta-1,3-diynyl})phenyl}$), 133.6 (2C, C-2′$_{phenyl}$, C-6′$_{phenyl}$), 141.2 (1C, C-1$_{4\text{-}(4\text{-phenylbuta-1,3-diynyl})phenyl}$), 169.2 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3460, 3345, 3233, 2924, 1647, 1115, 1084, 1049, 756, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{20}NO_5$: 366.1336, found: 366.1333; HPLC (method 2): t_R = 15.6 min, purity 95.4%.

4.2.69. (3S,5S)-3-(Hydroxymethyl)-5-(4-iodophenyl)-1,4-dioxan-2-one (**76**)

p-TsOH (8 mg, 0.04 mmol) was added to a solution of **75** (77 mg, 0.21 mmol) in dry acetonitrile (10 mL). The reaction was heated to reflux overnight. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. Then the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.24) to give **76** as colorless solid (50 mg, 0.15 mmol, 71% yield). Melting point: 144 °C; Specific rotation: $[\alpha]_D^{20}$ = −4.7 (c = 4.4; dichloromethane); ^1H NMR: ($CDCl_3$): δ [ppm] = 4.00 (dd, *J* = 11.8/4.0 Hz, 1H, CH_2OH), 4.13 (dd, *J* = 11.8/4.6 Hz, 1H, CH_2OH), 4.45 (dd, *J* = 11.8/8.7 Hz, 1H, 6-H), 4.51 (dd, *J* = 11.8/3.3 Hz, 1H, 6-H), 4.61 (t, *J* = 4.3 Hz, 1H, 3-H), 5.18 (dd, *J* = 8.7/3.1 Hz, 1H, 5-H), 7.12–7.18 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.71–7.77 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 63.9 (1C, CH_2OH), 72.1 (1C, C-5), 72.2 (1C, C-6), 74.6 (1C, C-3), 94.9 (1C, C-4$_{phenyl}$), 128.3 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 135.1 (1C, C-1$_{phenyl}$), 138.2 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 168.3 (1C, C-2); NOE: Irradiation at 4.61 ppm (3-H): δ [ppm] = 4.00 (CH_2OH), 4.13 (CH_2OH), 7.12–7.18 (2-H_{phenyl}, 6-H_{phenyl}); Irradiation at 5.18 ppm (5-H): δ [ppm] = 4.00 (CH_2OH), 4.13 (CH_2OH), 4.45 (6-H), 7.12–7.18 (2-H_{phenyl}, 6-H_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3499, 2959, 2882, 1713, 1697, 1254, 1061, 934, 818, 706; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{12}IO_4$: 334.9775, found: 334.9778; HPLC (method 1): t_R = 16.1 min, purity 97.9%.

4.2.70. (3S,5S)-3-(Hydroxymethyl)-5-{4-[(trimethylsilyl)ethynyl]phenyl}-1,4-dioxan-2-one (**77**)

Under nitrogen atmosphere, copper(I) iodide (26 mg, 0.14 mmol), tetrakis(triphenylphosphine)palladium(0) (78 mg, 0.07 mmol) and triethylamine (0.66 mL, 4.74 mmol) were added to a solution of **76** (226 mg, 0.68 mmol) in dry acetonitrile (20 mL) at ambient temperature. Then a solution of trimethylsilylacetylene (0.47 mL, 3.38 mmol) in dry acetonitrile (5 mL) was added dropwise over a period of 3 h. Afterwards, the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.29) to give **77** as yellowish solid (163 mg, 0.54 mmol, 79% yield). Melting point: 117 °C; Specific rotation: $[\alpha]_D^{20}$ = +1.0 (c = 2.5; dichloromethane); ^1H NMR: ($CDCl_3$): δ [ppm] = 0.25 (s, 9H, Si(CH_3)$_3$), 4.01 (dd, *J* = 11.8/4.1 Hz, 1H, CH_2OH), 4.13 (dd, *J* = 11.8/4.8 Hz, 1H, CH_2OH), 4.47 (dd, *J* = 11.8/8.7 Hz, 1H, 6-H), 4.52 (dd, *J* = 11.8/3.6 Hz, 1H, 6-H), 4.62 (t, *J* = 4.5 Hz, 1H, 3-H), 5.20 (dd, *J* = 8.7/3.6 Hz, 1H, 5-H), 7.31–7.36 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.47–7.52 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 0.06 (3C, Si(CH_3)$_3$), 63.8 (1C, CH_2OH), 72.2 (1C, C-6), 72.3 (1C, C-5), 74.5 (1C, C-3), 95.6 (1C, PhC≡CSi(CH_3)$_3$), 104.3 (1C, PhC≡CSi(CH_3)$_3$), 124.1 (1C, C-4$_{phenyl}$), 126.4 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 132.6 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 135.6 (1C, C-1$_{phenyl}$), 168.4 (1C, C-2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3445, 2951, 2924, 2164, 1721, 1331, 1250, 1215, 1134, 1026, 864, 833, 760; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{21}O_4Si$: 305.1204, found: 305.1229; HPLC (method 1): t_R = 20.0 min, purity 95.7%.

4.2.71. (3S,5S)-5-(4-Ethynylphenyl)-3-(hydroxymethyl)-1,4-dioxan-2-one (**78**)

Silver nitrate (8 mg, 0.04 mmol) and water (0.81 mL, 44.9 mmol) were added to a solution of **77** (150 mg, 0.45 mmol) in acetone (20 mL). The mixture was stirred for 24 h at ambient temperature in the dark. Afterwards, water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 2/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.22) to give **78** as colorless solid (75 mg, 0.32 mmol, 72% yield). Melting point: 111 °C; Specific rotation: $[\alpha]_D^{20}$ −3.2 (c = 1.7; dichloromethane); ^1H NMR: ($CDCl_3$): δ [ppm] = 3.12 (s, 1H, PhC≡C*H*), 4.01 (dd, *J* = 11.8/4.1 Hz, 1H, CH_2OH), 4.14 (dd, *J* = 11.8/4.7 Hz, 1H, CH_2OH), 4.48 (dd, *J* = 11.8/9.0 Hz, 1H, 6-H), 4.53 (dd, *J* = 11.8/3.3 Hz, 1H, 6-H), 4.63 (t, *J* = 4.4 Hz, 1H, 3-H), 5.22 (dd, *J* = 9.0/3.3 Hz, 1H, 5-H), 7.35–7.38 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.52–7.54 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 63.9 (1C, CH_2OH), 72.2 (2C, C-5, C-6), 74.6 (1C, C-3), 78.3 (1C, PhC≡CH), 83.0 (1C, PhC≡CH), 123.1 (1C, C-4$_{phenyl}$), 126.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 132.7 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 136.1 (1C, C-1$_{phenyl}$), 168.4 (1C, C-2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3449, 3248, 2928, 2106, 1721, 1346, 1227, 1107, 1030, 1003, 837, 826, 714; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{13}O_4$: 233.0808, found: 233.0831; HPLC (method 1): t_R = 14.4 min, purity 99.1%.

4.2.72. Methyl (S)-3-hydroxy-2-{(S)-2-hydroxy-1-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]ethoxy}-propanoate (**79**)

Under nitrogen atmosphere, a solution of **78** (72 mg, 0.31 mmol) in dry methanol (2 mL) was added to a solution of copper(I) iodide (3 mg, 0.02 mmol), hydroxylamine hydrochloride (7 mg, 0.09 mmol) and triethylamine (0.13 mL, 0.93 mmol) in dry methanol. The mixture was heated to 40 °C. Then a solution of (bromoethynyl)benzene (84 mg, 0.47 mmol) in dry methanol was added dropwise and the mixture was stirred for 4 h. Afterwards, brine was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.11) to give **79** as yellowish oil (20 mg, 0.06 mmol, 19% yield). Specific rotation: $[\alpha]_D^{20}$ = +44.2 (c = 1.4; dichloromethane); ^1H NMR: (CD_3OD): δ [ppm] = 3.57 (s, 3H, COOCH_3), 3.63 (dd, *J* = 11.9/3.7 Hz, 1H, PhCHCH_2OH), 3.74 (dd, *J* = 11.9/7.7 Hz, 1H, PhCHCH_2OH), 3.81 (dd, *J* = 11.8/5.3 Hz, 1H, H_3COOCCHCH_2OH), 3.89 (dd, *J* = 11.8/3.8 Hz, 1H, H_3COOCCHCH_2OH), 4.08–4.11 (m, 1H, H_3COOCC*H*CH_2OH), 4.63 (dd, *J* = 7.7/3.7 Hz, 1H, PhC*H*CH_2OH), 7.34–7.45 (m, 5H, H_{phenyl}), 7.48–7.54 (m, 4H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 52.3 (1C, COOCH_3), 63.4 (1C, H_3COOCCHCH_2OH), 67.3 (1C, PhCHCH_2OH), 74.3 (1C, C≡C), 74.6 (1C, C≡C), 80.7 (1C, H_3COOCCHCH_2OH), 82.0 (1C, C≡C), 82.4 (1C, C≡C), 84.7 (1C, PhCHCH_2OH), 122.6 (1C, C_{phenyl}), 122.9 (1C, C_{phenyl}), 128.7 (2C, C_{phenyl}), 129.7 (2C, C_{phenyl}), 130.6 (1C, C_{phenyl}), 133.3 (2C, C_{phenyl}), 133.4 (2C, C_{phenyl}), 141.7 (1C, C_{phenyl}), 172.7 (1C, $COOCH_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3294, 2951, 2928, 2496, 1736, 1439, 1207, 1119, 1045, 833, 756, 687; LC-MS (*m/z*): $[M + NH_4]^+$ calcd for $C_{22}H_{24}NO_5$: 382.1649, found: 382.1695; HPLC (method 1): t_R = 20.1 min, purity 95.2%.

*4.2.73. (S)-N,3-Dihydroxy-2-{(S)-2-hydroxy-1-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]ethoxy}propanamide (**8c**)*

Under nitrogen atmosphere, hydroxylamine hydrochloride (10 mg, 0.15 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.03 mL, 0.15 mmol) were added to a solution of **79** (18 mg, 0.05 mmol) in dry methanol (5 mL) and the mixture was stirred at ambient temperature overnight. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 19/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.11) to give **8c** as yellowish solid (12 mg, 0.03 mmol, 66% yield). Melting point: 136 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = +38.0 (c = 3.0; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.66–3.94 (m, 5H, HOHNOCC*H*CH_2OH, PhCH*C*H_2OH), 4.70–4.76 (m, 1H, PhC*H*CH_2OH), 7.32–7.45 (m, 5H, H_{phenyl}), 7.35–7.58 (m, 4H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 62.7 (1C, HOHNOCCH*C*H_2OH), 67.2 (1C, PhCH*C*H_2OH), 74.3 (1C, PhC≡*C*C≡CPh), 74.7 (1C, PhC≡C*C*≡CPh), 79.9 (1C, HOHNOC*C*HCH_2OH), 81.9 (1C, PhC≡CC≡*C*Ph), 82.4 (1C, Ph*C*≡CC≡CPh), 83.6 (1C, Ph*C*HCH_2OH), 122.8 (1C, C_{phenyl}), 122.9 (1C, C_{phenyl}), 128.8 (2C, C_{phenyl}), 129.7 (2C, C_{phenyl}), 130.6 (1C, C_{phenyl}), 133.4 (2C, C_{phenyl}), 133.6 (2C, C_{phenyl}), 141.2 (1C, C_{phenyl}), 169.3 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3240, 2924, 2855, 1659, 1111, 1049, 829, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{20}NO_5$: 366.1336, found: 366.1341; HPLC (method 2): t_R = 16.1 min, purity 97.3%.

*4.2.74. (2R,3R,4S,5S)-2-(Dimethoxymethyl)-5-(4-iodophenyl) tetrahydrofuran-3,4-diol (**80**)*

Under nitrogen atmosphere, a 1.2 M solution of diisobutylaluminium hydride in toluene (2.83 mL, 3.39 mmol) was slowly added over a period of 60 min to a solution of **30** (457 mg, 1.13 mmol) in dry dichloromethane (20 mL) at −78 °C. The reaction was stirred for another 60 min at −78 °C. Afterwards, methanol (3 mL) was added and the solution was warmed to ambient temperature. Then hydrochloric acid (1 M, 5 mL) was added and the mixture was stirred for 5 min. Afterwards, water (20 mL) was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was dissolved in methanol (20 mL) and *p*-TsOH (43 mg, 0.23 mmol) was added. The reaction was heated to reflux overnight. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.29) **80** as colorless oil (209 mg, 0.55 mmol, 49% yield). Specific rotation: $[\alpha]_D^{20}$ = +50.6 (c = 3.4; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.50 (s, 3H, OC*H*$_3$), 3.53 (s, 3H, OC*H*$_3$), 4.14 (dd, *J* = 7.2/4.7 Hz, 1H, 2-H), 4.28 (dd, *J* = 4.4/3.3 Hz, 1H, 4-H), 4.49 (dd, *J* = 7.2/4.4 Hz, 1H, 3-H), 4.51 (d, *J* = 4.7 Hz, 1H, $(H_3CO)_2$C*H*), 5.08 (d, *J* = 3.3 Hz, 1H, 5-H), 7.11–7.15 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.67–7.71 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 55.1 (1C, O*C*H$_3$), 56.6 (1C, O*C*H$_3$), 73.7 (1C, C-4), 73.9 (1C, C-3), 81.9 (1C, C-2), 82.7 (1C, C-5), 93.5 (1C, C-4_{phenyl}), 105.6 (1C, $(H_3CO)_2$*C*H), 129.0 (2C, C-2_{phenyl}, C-6_{phenyl}), 136.8 (1C, C-1_{phenyl}), 137.4 (1C, C-3_{phenyl}, C-5_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3391, 2932, 2832, 1485, 1396, 1192, 1072, 1042, 791, 733; LC-MS (*m/z*): $[M + NH_4]^+$ calcd for $C_{13}H_{21}INO_5$: 398.0459, found: 398.0492.

*4.2.75. (R)-2-[(S)-2-Hydroxy-1-(4-iodophenyl)ethoxy]-3,3-dimethoxypropan-1-ol (**81**)*

Sodium metaperiodate (297 mg, 1.39 mmol) was added to a solution of **80** (176 mg, 0.46 mmol) in methanol (20 mL). The reaction was stirred at ambient temperature for 4 h. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol (20 mL) and sodium borohydride (87 mg, 2.31 mmol) was added. The reaction was stirred at ambient temperature for 30 min. Then hydrochloric acid (1 M) was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.18) to give **81** as colorless oil (135 mg, 0.35 mmol, 76% yield). Specific rotation: $[\alpha]_D^{20}$ = +88.8 (c = 7.1; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.34–3.38 (m, 1H, $(H_3CO)_2$CHC*H*CH_2OH), 3.42 (s, 3H, OC*H*$_3$), 3.49 (s, 3H, OC*H*$_3$), 3.53–3.56 (m, 2H, $(H_3CO)_2$CHCH-C*H*$_2$OH), 3.57 (dd, *J* = 11.6/4.3 Hz, 1H, PhCHC*H*$_2$OH), 3.66 (dd, *J* = 11.6/7.1 Hz, 1H, (PhCHC*H*$_2$OH), 4.49 (d, *J* = 5.6 Hz, 1H, $(H_3CO)_2$C*H*CHCH$_2$OH), 4.77 (dd, *J* = 7.1/4.3 Hz, 1H, PhC*H*CH$_2$OH), 7.17–7.21 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.67–7.71 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 56.0 (1C, O*C*H$_3$), 56.4 (1C, O*C*H$_3$), 62.7 (1C, $(H_3CO)_2$CHCHCH$_2$OH), 67.7 (1C, PhCHCH$_2$OH), 79.5 (1C, $(H_3CO)_2$CHCHCH$_2$OH), 83.5 (1C, PhCHCH$_2$OH), 94.0 (1C, C-4_{phenyl}), 106.7 (1C, $(H_3CO)_2$CHCH-CH$_2$OH), 130.7 (2C, C-2_{phenyl}, C-6_{phenyl}), 138.5 (2C, C-3_{phenyl}, C-5_{phenyl}), 140.9 (1C, C-1_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3387, 2932, 2832, 1585, 1477, 1400, 1192, 1061, 1007, 818; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{20}IO_5$: 383.0350, found: 383.0330.

*4.2.76. Methyl (R)-3-hydroxy-2-[(S)-2-hydroxy-1-(4-iodophenyl) ethoxy]propanoate (**82**)*

A solution of **81** (126 mg, 0.33 mmol) in a mixture of 1 M hydrochloric acid (10 mL) and THF (10 mL) was heated to reflux overnight. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. Then the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol/water (9/1, 20 mL) and sodium bicarbonate (554 mg, 6.60 mmol) was added. Then a 2 M solution of bromine in methanol/water (9/1, 0.66 mL, 1.32 mmol) was added. The reaction was stirred at ambient temperature overnight. Afterwards, a solution of sodium thiosulfate in water was added until the mixture decolorized and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.25) to give **82** as colorless oil (81 mg, 0.22 mmol, 67% yield). Specific rotation: $[\alpha]_D^{20}$ = +122.8 (c = 1.7; methanol); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 3.62 (dd, *J* = 11.6/4.2 Hz, 1H, PhCHC*H*$_2$OH), 3.73 (dd, *J* = 11.6/7.1 Hz, 1H, PhCHC*H*$_2$OH), 3.75–3.77 (m, 5H, H_3COOCCHC*H*$_2$OH, COOC*H*$_3$), 3.92 (t, *J* = 4.3 Hz, 1H, H_3COOCC*H*CH$_2$OH), 4.55 (dd, *J* = 7.1/4.2 Hz, 1H, PhC*H*CH$_2$OH), 7.14–7.18 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.69–7.74 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 52.5 (1C, COO*C*H$_3$), 64.3 (1C, H_3COOCCHCH$_2$OH), 67.5 (1C, PhCHCH$_2$OH), 78.9 (1C, H_3COOCCHCH$_2$OH), 83.2 (1C, Ph*C*HCH$_2$OH), 94.4 (1C, C-4_{phenyl}), 130.6 (2C, C-2_{phenyl}, C-6_{phenyl}), 138.7 (2C, C-3_{phenyl}, C-5_{phenyl}), 139.6 (1C, C-1_{phenyl}), 173.0 (1C, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3364, 2947, 2878, 1736, 1589, 1435, 1207, 1126, 1061, 1007, 818; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{16}IO_5$: 367.0037, found: 367.0014; HPLC

(method 1): t_R = 15.3 min, purity 95.2%.

4.2.77. Methyl (R)-3-hydroxy-2-[(S)-2-hydroxy-1-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-ethoxy]propanoate (**83**)

Under nitrogen atmosphere, copper(I) iodide (8 mg, 0.04 mmol), tetrakis(triphenylphosphine)palladium(0) (26 mg, 0.02 mmol) and triethylamine (0.21 mL, 1.55 mmol) were added to a solution of **82** (81 mg, 0.22 mmol) in dry acetonitrile (10 mL) at ambient temperature. Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (134 mg, 0.66 mmol) in dry acetonitrile (3 mL) was added dropwise over a period of 2 h. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (dichloromethane/methanol = 19/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.31) to give **83** as yellowish oil (50 mg, 0.11 mmol, 51% yield). Specific rotation: $[\alpha]_D^{20}$ = +122.1 (c = 0.7; methanol); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 2.44–2.50 (m, 4H, N(CH_2CH_2)$_2$), 3.54 (s, 2H, PhCH_2N), 3.65 (dd, J = 11.6/4.1 Hz, 1H, PhCHCH_2OH), 3.67–3.71 (m, 4H, N(CH_2CH_2)$_2$), 3.73–3.80 (m, 6H, PhCHCH_2OH (1H), COOCH_3, H_3COOCCHCH_2OH), 3.94 (t, J = 4.3 Hz, 1H, H_3COOCCHCH_2OH), 4.62 (dd, J = 7.1/4.1 Hz, 1H, PhCHCH_2OH), 7.35–7.41 (m, 4H, H_{phenyl}), 7.46–7.54 (m, 4H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 52.5 (1C, COOCH_3), 54.6 (2C, N(CH_2CH_2)$_2$), 63.9 (1C, PhCH_2N), 64.3 (1C, H_3COOCCHCH_2OH), 67.6 (1C, PhCHCH_2OH), 67.8 (2C, N(CH_2CH_2)$_2$), 78.9 (1C, H_3COOCCH-CH_2OH), 83.4 (1C, PhCHCH_2OH), 89.9 (1C, PhC≡CPh), 90.3 (1C, PhC≡CPh), 123.5 (1C, C_{phenyl}), 124.5 (1C, C_{phenyl}), 128.7 (2C, C_{phenyl}), 130.7 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 132.6 (2C, C_{phenyl}), 139.1 (1C, C_{phenyl}), 140.1 (1C, C_{phenyl}), 173.1 (1C, COOCH$_3$); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3379, 2928, 2859, 2812, 1736, 1516, 1439, 1207, 1115, 1065, 864, 833, 795; HRMS (m/z): $[M+H]^+$ calcd for $C_{25}H_{30}NO_6$: 440.2068, found: 440.2097; HPLC (method 1): t_R = 14.3 min, purity 93.5%.

4.2.78. (R)-N,3-Dihydroxy-2-[(S)-2-hydroxy-1-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-ethoxy]propanamide (**84**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (66 mg, 0.96 mmol) and a 2 M solution of sodium methoxide in methanol (0.48 mL, 0.96 mmol) were added to a solution of **83** (42 mg, 0.10 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 5 h. Then water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.22) to give **84** as colorless solid (8 mg, 0.02 mmol, 19% yield). Melting point: 136 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = +106.3 (c = 0.8; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 2.46–2.51 (m, 4H, N(CH_2CH_2)$_2$), 3.56 (s, 2H, PhCH_2N), 3.63 (dd, J = 11.7/3.2 Hz, 1H, PhCHCH_2OH), 3.68–3.77 (m, 7H, PhCHCH_2OH (1H), HOHNOCCH-CH_2OH, N(CH_2CH_2)$_2$), 3.82 (dd, J = 5.3/3.6 Hz, 1H, HOHNOCCH-CH_2OH), 4.53 (dd, J = 8.7/3.2 Hz, 1H, PhCHCH_2OH), 7.35–7.40 (m, 2H, H_{phenyl}), 7.42–7.46 (m, 2H, H_{phenyl}), 7.46–7.50 (m, 2H, H_{phenyl}), 7.50–7.54 (m, 2H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 54.6 (2C, N(CH_2CH_2)$_2$), 63.9 (1C, PhCH_2N), 64.3 (1C, HOHNOCCHCH_2OH), 67.4 (1C, PhCHCH_2OH), 67.7 (2C, N(CH_2CH_2)$_2$), 80.6 (1C, HOH-NOCCHCH_2OH), 84.5 (1C, PhCHCH_2OH), 89.9 (1C, PhC≡CPh), 90.4 (1C, PhC≡CPh), 123.6 (1C, C_{phenyl}), 124.6 (1C, C_{phenyl}), 128.5 (2C, C_{phenyl}), 130.8 (2C, C_{phenyl}), 132.5 (2C, C_{phenyl}), 132.7 (2C, C_{phenyl}), 138.9 (1C, C_{phenyl}), 139.7 (1C, C_{phenyl}), 169.6 (1C, CONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3387, 3217, 3036, 2920, 2855, 1655, 1516, 1126, 1111, 1065, 856, 802, 741; LC-MS (m/z): $[M+H]^+$ calcd for $C_{24}H_{29}N_2O_6$: 441.2020, found: 441.2020; HPLC (method 2): t_R = 11.3 min, purity 98.4%.

4.2.79. 4-[(2R,3S,4R,5S)-5-(Dimethoxymethyl)-3,4-dihydroxytetrahydrofuran-2-yl]phenyl trifluoromethanesulfonate (**85**)

Under nitrogen atmosphere, a 1 M solution of diisobutylaluminium hydride in dichloromethane (1.42 mL, 1.42 mmol) was added slowly over a period of 60 min to a solution of **50** (302 mg, 0.71 mmol) in dry dichloromethane (20 mL) at −78 °C. Afterwards, methanol (5 mL) was added and the solution was warmed to ambient temperature. Then hydrochloric acid (1 M, 2 mL) was added and the mixture was stirred for 5 min. Afterwards, water (20 mL) was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was dissolved in methanol (20 mL) and *p*-TsOH (13 mg, 0.07 mmol) was added. The reaction was heated to reflux overnight. Then a saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.27) to give **85** as colorless solid (215 mg, 0.53 mmol, 75% yield). Melting point: 96 °C; Specific rotation: $[\alpha]_D^{20}$ = −0.3 (c = 5.6; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.45 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.96 (dd, J = 8.8/4.0 Hz, 1H, 3-H), 4.18–4.20 (m, 1H, 4-H), 4.21 (dd, J = 7.7/3.2 Hz, 1H, 5-H), 4.69 (d, J = 7.7 Hz, 1H, (H_3CO)$_2$CH), 4.82 (d, J = 8.8 Hz, 1H, 2-H), 7.33–7.36 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.56–7.59 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 53.7 (1C, OCH_3), 55.9 (1C, OCH_3), 73.5 (1C, C-4), 80.9 (1C, C-3), 81.3 (1C, C-5), 82.8 (1C, C-2), 104.3 (1C, (H_3CO)$_2$CH), 120.2 (q, J = 320 Hz, 1C, CF_3), 122.3 (2C, C-2_{phenyl}, C-6_{phenyl}), 129.0 (1C, C-3_{phenyl}, C-5_{phenyl}), 144.0 (1C, C-4_{phenyl}), 150.4 (1C, C-1_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3418, 2940, 1501, 1420, 1207, 1134, 1065, 883, 833, 748; LC-MS (m/z): $[M+H]^+$ calcd for $C_{14}H_{18}F_3O_8S$: 403.0669, found: 403.06612; HPLC (method 1): t_R = 18.6 min, purity 98.9%.

4.2.80. 4-((R)-2-Hydroxy-1-{[(S)-3-hydroxy-1,1-dimethoxypropan-2-yl]oxy}ethyl)phenyl trifluoro-methanesulfonate (**86**)

Sodium metaperiodate (1.06 g, 4.96 mmol) was added to a solution of **85** (1.00 g, 2.48 mmol) in methanol (30 mL). The reaction was stirred at ambient temperature overnight. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol (20 mL) and sodium borohydride (281 mg, 7.44 mmol) was added. The reaction was stirred at ambient temperature for 15 min. Then hydrochloric acid (1 M) was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 4 cm, h = 15 cm, V = 30 mL, R_f = 0.18) to give **86** as colorless oil (832 mg, 2.06 mmol, 83% yield). Specific rotation: $[\alpha]_D^{20}$ = −67.1 (c = 4.7; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.37–3.40 (m, 1H, (H_3CO)$_2$CHCHCH_2OH), 3.43 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.57 (d, J = 4.5 Hz, 2H, (H_3CO)$_2$CHCHCH_2OH), 3.62 (dd, J = 11.6/4.4 Hz, 1H, PhCHCH_2OH), 3.69 (dd, J = 11.6/6.8 Hz, 1H, (PhCHCH_2OH), 4.49 (d, J = 5.5 Hz, 1H, (H_3CO)$_2$CHCHCH$_2$OH), 4.88 (dd, J = 6.8/4.4 Hz, 1H, PhCHCH_2OH), 7.33–7.36 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.57–7.60 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 56.0 (1C,

OCH_3), 56.4 (1C, OCH_3), 62.6 (1C, $(H_3CO)_2CHCHCH_2OH$), 67.6 (1C, $PhCHCH_2OH$), 79.8 (1C, $(H_3CO)_2CHCHCH_2OH$), 83.0 (1C, $PhCHCH_2OH$), 106.7 (1C, $(H_3CO)_2CHCHCH_2OH$), 120.2 (q, $J = 320$ Hz, 1C, CF_3), 122.2 (2C, C-2_{phenyl}, C-6_{phenyl}), 130.7 (2C, C-3_{phenyl}, C-5_{phenyl}), 142.2 (1C, C-4_{phenyl}), 150.6 (1C, C-1_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3399, 2936, 1501, 1420, 1207, 1138, 1065, 883, 841, 606; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{20}F_3O_8S$: 405.0825, found: 405.0827; HPLC (method 1): t_R = 18.6 min, purity 95.3%.

4.2.81. 4-[(2R,6S)-5-Hydroxy-6-(hydroxymethyl)-1,4-dioxan-2-yl] phenyl trifluoromethanesulfonate (**87**)

A solution of **86** (832 mg, 2.06 mmol) in a mixture of 1 M hydrochloric acid (15 mL) and THF (15 mL) was heated to reflux for 2 h. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. Then the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/2, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.25) to give **87** as colorless solid (474 mg, 1.32 mmol, 64% yield). Melting point: 105 °C; Specific rotation: $[\alpha]_D^{20}$ = −51.7 (c = 3.2; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.44 (ddd, J = 8.0/5.4/2.7 Hz, 0.66H, 6-H^{E1}), 3.55 (dd, J = 11.8/10.3 Hz, 0.66H, 3-H^{E1}), 3.59 (dd, J = 11.6/3.0 Hz, 0.34H, 3-H^{E2}), 3.68 (d, J = 5.9 Hz, 2 × 0.34H, CH_2OH^{E2}), 3.77 (dd, J = 12.0/5.4 Hz, 0.66H, CH_2OH^{E1}), 3.83 (dd, J = 12.0/2.7 Hz, 0.66H, CH_2OH^{E1}), 3.88 (dt, J = 5.9/1.9 Hz, 0.34H, 6-H^{E2}), 3.93 (t, J = 11.2 Hz, 0.34H, 3-H^{E2}), 3.98 (dd, J = 11.8/2.8 Hz, 0.66H, 3-H^{E1}), 4.72 (d, J = 8.0 Hz, 0.66H, 5-H^{E1}), 4.74 (dd, J = 10.3/2.8 Hz, 0.66H, 2-H^{E1}), 4.79 (dd, J = 10.7/3.0 Hz, 0.34H, 2-H^{E2}), 4.97 (d, J = 1.9 Hz, 0.34H, 5-H^{E2}), 7.32–7.37 (m, 2H, 2-H_{phenyl}^{E1+E2}, 6-H_{phenyl}^{E1+E2}), 7.59–7.64 (m, 2H, 3-H_{phenyl}^{E1+E2}, 5-H_{phenyl}^{E1+E2}); ratio of epimers 66(E1):34(E2); ^{13}C NMR: (CD_3OD): δ [ppm] = 62.4 (0.66C, CH_2OH^{E1}), 62.7 (0.34C, CH_2OH^{E2}), 64.3 (0.34C, C-3^{E2}), 71.8 (0.66C, C-3^{E1}), 77.4 (0.66C, C-2^{E1}), 78.3 (0.34C, C-2^{E2}), 80.1 (0.34C, C-6^{E2}), 81.7 (0.66C, C-6^{E1}), 89.6 (0.34C, C-5^{E2}), 93.8 (0.66C, C-5^{E1}), 120.2 (q, J = 320 Hz, 1C, CF_3^{E1+E2}), 122.3 (2C, C-2_{phenyl}^{E1+E2}, C-6_{phenyl}^{E1+E2}), 129.6 (2 × 0.66C, C-3_{phenyl}^{E1}, C-5_{phenyl}^{E1}), 129.7 (2 × 0.34C, C-3_{phenyl}^{E2}, C-5_{phenyl}^{E2}), 140.2 (0.66C, C-4_{phenyl}^{E1}), 140.7 (0.34C, C-4_{phenyl}^{E2}), 150.6 (1C, C-1_{phenyl}^{E1+E2}); ratio of epimers 66(E1):34(E2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3402, 2928, 2886, 1504, 1400, 1211, 1134, 1092, 1045, 1011, 880, 833, 644; LC-MS (*m/z*): $[M + NH_4]^+$ calcd for $C_{12}H_{17}F_3NO_7S$: 376.0672, found: 376.0681; HPLC (method 1): t_R = 18.0 min, purity 97.5%.

4.2.82. 4-[(2R,6S)-6-(Hydroxymethyl)-5-oxo-1,4-dioxan-2-yl] phenyl trifluoromethanesulfonate (**88**)

Sodium bicarbonate (2.74 g, 32.7 mmol) was added to a solution of **87** (585 mg, 1.63 mmol) in methanol/water (9/1, 20 mL). Then a 1 M solution of bromine in methanol/water (9/1, 3.27 mL, 3.27 mmol) was added. The reaction was stirred at ambient temperature for 1 h. Afterwards, a solution of sodium thiosulfate in water was added until the mixture decolorized and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in dry acetonitrile (20 mL) and *p*-TsOH (31 mg, 0.16 mmol) was added. The reaction was heated to reflux overnight. Afterwards, a saturated aqueous solution of sodium bicarbonate was added. Then the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 3 cm, h = 15 cm, V = 20 mL, R_f = 0.32) to give **88** as colorless solid (366 mg, 1.03 mmol, 63% yield). Melting point: 116 °C; Specific rotation: $[\alpha]_D^{20}$ = −47.1 (c = 3.3; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 4.07 (dd, J = 11.9/3.8 Hz, 1H, CH_2OH), 4.15 (dd, J = 11.9/4.1 Hz, 1H, CH_2OH), 4.43 (dd, J = 11.5/10.3 Hz, 1H, 3-H), 4.50 (dd, J = 11.5/3.1 Hz, 1H, 3-H), 4.59 (t, J = 3.9 Hz, 1H, 6-H), 5.02 (dd, J = 10.3/3.1 Hz, 1H, 2-H), 7.31–7.35 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.49–7.54 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 63.3 (1C, CH_2OH), 73.0 (1C, C-3), 73.5 (1C, C-2), 77.7 (1C, C-6), 118.8 (q, J = 321 Hz, 1C, CF_3), 122.1 (2C, C-2_{phenyl}, C-6_{phenyl}), 128.4 (2C, C-3_{phenyl}, C-5_{phenyl}), 135.7 (1C, C-4_{phenyl}), 149.9 (1C, C-1_{phenyl}), 167.3 (1C, C-5); NOE: Irradiation at 4.59 ppm (6-H): δ [ppm] = 4.07 (CH_2OH), 4.15 (CH_2OH), 5.02 (2-H); Irradiation at 5.02 ppm (2-H): δ [ppm] = 4.50 (3-H), 4.59 (6-H), 7.50–7.53 (3-H_{phenyl}, 5-H_{phenyl}); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3584, 3456, 3071, 2959, 1732, 1423, 1408, 1200, 1134, 1034, 880, 752; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{12}F_3O_7S$: 357.0250, found: 357.0242; HPLC (method 1): t_R = 19.4 min, purity 97.7%.

4.2.83. (3S,5R)-3-(Hydroxymethyl)-5-[4-(phenylethynyl)phenyl]-1,4-dioxan-2-one (**89a**)

Under nitrogen atmosphere, copper(I) iodide (11 mg, 0.06 mmol), tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.03 mmol) and triethylamine (0.35 mL, 2.53 mmol) were added to a solution of **88** (100 mg, 0.28 mmol) in dry acetonitrile (20 mL). Then a solution of phenylacetylene (0.08 mL, 0.70 mmol) in dry acetonitrile (1 mL) was added and the mixture was heated to reflux. Then again a solution of phenylacetylene (0.08 mL, 0.70 mmol) in dry acetonitrile (1 mL) was added and the mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (cyclohexane/ethyl acetate = 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.41) to give **89a** as colorless solid (63 mg, 0.20 mmol, 73% yield). Melting point: 153 °C; Specific rotation: $[\alpha]_D^{20}$ = −57.0 (c = 3.5; dichloromethane); ^{1}H NMR: ($CDCl_3$): δ [ppm] = 4.08 (dd, J = 11.9/4.0 Hz, 1H, CH_2OH), 4.14 (dd, J = 11.9/4.1 Hz, 1H, CH_2OH), 4.44 (dd, J = 11.5/9.9 Hz, 1H, 6-H), 4.50 (dd, J = 11.5/3.5 Hz, 1H, 6-H), 4.58 (t, J = 4.0 Hz, 1H, 3-H), 4.98 (dd, J = 9.9/3.5 Hz, 1H, 5-H), 7.34–7.40 (m, 5H, H_{phenyl}), 7.52–7.59 (m, 4H, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): δ [ppm] = 63.3 (1C, CH_2OH), 73.2 (1C, C-6), 74.2 (1C, C-5), 77.7 (1C, C-3), 88.7 (1C, PhC≡CPh), 90.6 (1C, PhC≡CPh), 123.0 (1C, C_{phenyl}), 124.4 (1C, C_{phenyl}), 126.3 (2C, C_{phenyl}), 128.5 (2C, C_{phenyl}), 128.7 (1C, C_{phenyl}), 131.8 (2C, C_{phenyl}), 132.2 (2C, C_{phenyl}), 134.9 (1C, C_{phenyl}), 167.6 (1C, C-2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3530, 2955, 2882, 1736, 1404, 1315, 1211, 1126, 1069, 1034, 826, 760, 694; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{17}O_4$: 309.1121, found: 309.1137; HPLC (method 1): t_R = 20.9 min, purity 98.4%.

4.2.84. (3S,5R)-3-(Hydroxymethyl)-5-(4-{[4-(morpholinomethyl) phenyl]ethynyl}phenyl)-1,4-dioxan-2-one (**89b**)

Under nitrogen atmosphere, copper(I) iodide (11 mg, 0.06 mmol), tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.03 mmol) and triethylamine (0.35 mL, 2.53 mmol) were added to a solution of **88** (100 mg, 0.28 mmol) in dry acetonitrile (20 mL). Then a solution of 4-(morpholinomethyl)phenylacetylene [11] (42 mg, 0.21 mmol) in dry acetonitrile (1 mL) was added and the mixture was heated to reflux. Then again a solution of 4-(morpholinomethyl)phenylacetylene [11] (42 mg, 0.21 mmol) in dry acetonitrile (1 mL) was added and the mixture was heated to reflux overnight. Afterwards, the solvent was removed in vacuo. The residue was purified twice by flash column chromatography (dichloromethane/methanol = 19/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f = 0.30) to give **89b** as colorless oil (28 mg, 0.07 mmol, 24% yield). Specific rotation: $[\alpha]_D^{20}$ = −37.0 (c = 2.3; methanol); ^{1}H NMR: (CD_3OD): δ [ppm] = 2.45–2.49 (m, 4H, $N(CH_2CH_2)_2$), 3.54 (s, 2H, $PhCH_2N$), 3.65 (dd, J = 11.6/4.2 Hz, 1H, 6-H), 3.68–3.71 (m, 4H, $N(CH_2CH_2)_2$), 3.76 (dd, J = 11.6/7.2 Hz, 1H, 6-H), 3.77–3.79 (m, 2H,

C*H*$_2$OH), 3.94 (t, J = 4.2 Hz, 1H, 3-H), 4.62 (dd, J = 7.2/4.2 Hz, 1H, 5-H), 7.35–7.41 (m, 4H, H$_{phenyl}$), 7.46–7.54 (m, 4H, H$_{phenyl}$); ^{13}C NMR: (CD$_3$OD): δ [ppm] = 54.7 (2C, N(*C*H$_2$CH$_2$)$_2$), 64.0 (1C, PhCH$_2$N), 64.3 (1C, *C*H$_2$OH), 67.6 (1C, C-6), 67.8 (2C, N(CH$_2$*C*H$_2$)$_2$), 78.9 (1C, C-3), 83.4 (1C, C-5), 89.9 (1C, Ph*C*≡CPh), 90.3 (1C, Ph*C*≡CPh), 123.5 (1C, C$_{phenyl}$), 124.5 (1C, C$_{phenyl}$), 128.7 (2C, C$_{phenyl}$), 130.7 (2C, C$_{phenyl}$), 132.5 (2C, C$_{phenyl}$), 132.6 (2C, C$_{phenyl}$), 139.1 (1C, C$_{phenyl}$), 140.1 (1C, C$_{phenyl}$), 173.1 (1C, C-2); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3406, 2924, 2855, 2812, 1740, 1454, 1315, 1204, 1115, 1034, 864, 829; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{24}H_{26}NO_5$: 408.1805, found: 408.1838; HPLC (method 2): t_R = 13.3 min, purity 94.6%.

4.2.85. (S)-N,3-Dihydroxy-2-{(R)-2-hydroxy-1-[4-(phenylethynyl) phenyl]ethoxy}propanamide (**90a**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (85 mg, 1.23 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.23 mL, 1.23 mmol) were added to a solution of **89a** (63 mg, 0.20 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 3 h. Then a 0.1 M solution of hydrochloric acid (15 mL) was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.35) to give **90a** as colorless solid (43 mg, 0.13 mmol, 62% yield). Melting point: 147 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −167.6 (c = 3.7; methanol); ^{1}H NMR: (DMSO-d_6): δ [ppm] = 3.45–3.59 (m, 4H, HOHNOCCHC*H*$_2$OH, PhCHC*H*$_2$OH), 3.65 (t, J = 4.9 Hz, 1H, HOHNOCC*H*CH$_2$OH), 4.45 (dd, J = 7.9/3.9 Hz, 1H, PhC*H*CH$_2$OH), 4.85 (s br, 1H, O*H*), 7.40–7.48 (m, 5H, H$_{phenyl}$), 7.50–7.57 (m, 4H, H$_{phenyl}$), 8.93 (s br, 1H, N*H*OH), 10.51 (s br, 1H, N*H*OH), the signal for one O*H* cannot be observed in the spectrum; ^{13}C NMR: (DMSO-d_6): δ [ppm] = 62.3 (1C, HOHNOCCH*C*H$_2$OH), 65.6 (1C, PhCH*C*H$_2$OH), 79.6 (1C, HOHNOC*C*HCH$_2$OH), 82.1 (1C, PhCHCH$_2$OH), 89.2 (1C, Ph*C*≡CPh), 89.3 (1C, Ph*C*≡CPh), 121.6 (1C, C$_{phenyl}$), 122.3 (1C, C$_{phenyl}$), 127.4 (2C, C$_{phenyl}$), 128.8 (3C, C$_{phenyl}$), 131.1 (2C, C$_{phenyl}$), 131.4 (2C, C$_{phenyl}$), 139.7 (1C, C$_{phenyl}$), 166.6 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3229, 2978, 2889, 1643, 1107, 1092, 1053, 887, 833, 756, 691; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{19}H_{20}NO_5$: 342.1336, found: 342.1329; HPLC (method 2): t_R = 15.4 min, purity 96.1%.

4.2.86. (S)-N,3-Dihydroxy-2-[(R)-2-hydroxy-1-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-ethoxy]propanamide (**90b**)

Under nitrogen atmosphere, hydroxylamine hydrochloride (18 mg, 0.26 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.05 mL, 0.26 mmol) were added to a solution of **89b** (26 mg, 0.06 mmol) in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 16 h. Then a solution of sodium dihydrogen phosphate monohydrate (138 mg, 1.0 mmol) and disodium hydrogen phosphate dihydrate (712 mg, 4.0 mmol) in water (20 mL) was added and the mixture was extracted with ethyl acetate (5 ×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol = 9/1, Ø = 1 cm, h = 15 cm, V = 5 mL, R_f = 0.27) to give **90b** as colorless solid (9 mg, 0.02 mmol, 32% yield). Melting point: 142 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −96.0 (c = 1.0; methanol); ^{1}H NMR: (CD$_3$OD): δ [ppm] = 2.45–2.48 (m, 4H, N(C*H*$_2$CH$_2$)$_2$), 3.54 (s, 2H, PhC*H*$_2$N), 3.62 (dd, J = 11.7/3.4 Hz, 1H, PhCHC*H*$_2$OH), 3.67–3.75 (m, 7H, PhCHC*H*$_2$OH (1H), HOHNOCCH-C*H*$_2$OH, N(CH$_2$C*H*$_2$)$_2$), 3.82 (dd, J = 5.5/3.6 Hz, 1H, HOHNOCC*H*-CH$_2$OH), 4.54 (dd, J = 8.6/3.4 Hz, 1H, PhC*H*CH$_2$OH), 7.35–7.39 (m, 2H, H$_{phenyl}$), 7.42–7.46 (m, 2H, H$_{phenyl}$), 7.46–7.50 (m, 2H, H$_{phenyl}$), 7.50–7.53 (m, 2H, H$_{phenyl}$); ^{13}C NMR: (CD$_3$OD): δ [ppm] = 54.7 (2C, N(*C*H$_2$CH$_2$)$_2$), 64.0 (1C, PhCH$_2$N), 64.3 (1C, HOHNOCCH*C*H$_2$OH), 67.5 (1C, PhCH*C*H$_2$OH), 67.8 (2C, N(CH$_2$*C*H$_2$)$_2$), 80.6 (1C, HOHNOC*C*H-CH$_2$OH), 84.4 (1C, Ph*C*HCH$_2$OH), 89.8 (1C, Ph*C*≡CPh), 90.3 (1C, Ph*C*≡CPh), 123.5 (1C, C$_{phenyl}$), 124.6 (1C, C$_{phenyl}$), 128.5 (2C, C$_{phenyl}$), 130.7 (2C, C$_{phenyl}$), 132.5 (2C, C$_{phenyl}$), 132.6 (2C, C$_{phenyl}$), 139.2 (1C, C$_{phenyl}$), 139.7 (1C, C$_{phenyl}$), 169.4 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3237, 2978, 2886, 1659, 1416, 1211, 1111, 1049, 864, 833, 795; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{24}H_{29}N_2O_6$: 441.2020, found: 441.2048; HPLC (method 2): t_R = 11.9 min, purity 97.2%.

4.2.87. (S)-2-[(R)-1-(4-Ethynylphenyl)-2-hydroxyethoxy]-N,3-dihydroxypropanamide (**91**)

Under nitrogen atmosphere, copper(I) iodide (24 mg, 0.12 mmol), tetrakis(triphenylphosphine)palladium(0) (71 mg, 0.06 mmol) and triethylamine (0.43 mL, 3.1 mmol) were added to a solution of **88** (220 mg, 0.62 mmol) in dry acetonitrile (10 mL). Then a solution of trimethylsilylacetylene (0.49 mL, 3.1 mmol) in dry acetonitrile (1 mL) was added over 1 h. The mixture was heated to reflux overnight. Afterwards, water was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate 8/2 → 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f (cyclohexane/ethyl acetate = 1/1) = 0.41). The purified product was dissolved in acetone (20 mL). Then silver nitrate (8 mg, 0.05 mmol) and water (0.88 mL, 0.88 mmol) were added and the mixture was stirred for 4 d at ambient temperature in the dark. Afterwards, a spatula tip of sodium chloride was added and the solvent was removed in vacuo. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate 8/2 → 1/1, Ø = 2 cm, h = 15 cm, V = 10 mL, R_f (cyclohexane/ethyl acetate = 1/1) = 0.33). Under nitrogen atmosphere, hydroxylamine hydrochloride (72 mg, 1.03 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.19 mL, 1.03 mmol) were added to a solution of the previously obtained product in dry methanol (10 mL) and the mixture was stirred at ambient temperature for 6 h. Afterwards, the solvent was removed in vacuo and the residue was purified by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) to give **91** as colorless solid (64 mg, 0.24 mmol, 39% yield over 3 steps). RP-TLC (H_2O/ACN = 2/1): R_f = 0.23; Melting point: 70 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −163.9 (c = 3.3; methanol); ^{1}H NMR: (CD$_3$OD): δ [ppm] = 3.47 (s, 1H, PhC≡C*H*), 3.59 (dd, J = 11.6/3.4 Hz, 1H, PhCHC*H*$_2$OH), 3.64–3.83 (m, 4H, PhCHC*H*$_2$OH (1H), HOHNOCC*H*C*H*$_2$OH (3H), 4.50 (dd, J = 8.6/3.4 Hz, 1H, PhC*H*CH$_2$OH), 7.35–7.47 (m, 4H, H$_{phenyl}$); ^{13}C NMR: (CD$_3$OD): δ [ppm] = 64.3 (1C, HOHNOCCH*C*H$_2$OH), 67.4 (1C, PhCH*C*H$_2$OH), 79.0 (1C, PhC≡*C*H), 80.6 (1C, HOHNOC*C*HCH$_2$OH), 84.0 (1C, Ph*C*≡CH), 84.4 (1C, Ph*C*HCH$_2$OH), 123.8 (1C, C-4$_{phenyl}$), 128.4 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 133.2 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 140.0 (1C, C-1$_{phenyl}$), 169.6 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3275, 2970, 2928, 2882, 1655, 1111, 1045, 833, 656; LC-MS (*m/z*): [M+H]$^+$ calcd for $C_{13}H_{16}NO_5$: 266.1023, found: 266.1029; HPLC (method 2): t_R = 12.5 min, purity 66.9%; the compound was contaminated with its (*R*,*R*)-configured epimer (29%).

4.2.88. (S)-N,3-Dihydroxy-2-{(R)-2-hydroxy-1-[4-(phenylbuta-1,3-diyn-1-yl)phenyl]ethoxy}-propanamide (**90c**)

Copper(I) chloride (1 mg, 0.01 mmol) was added to an aqueous solution of *n*-butylamine (30% (V/V), 5 mL) at ambient temperature. The resulting blue color was discharged by adding a few crystals of

hydroxylamine hydrochloride. Addition of **91** (37 mg, 0.14 mmol) at ambient temperature led to a yellow acetylide suspension that was immediately cooled by a water-ice bath. Afterwards, (bromoethynyl)benzene (0.03 mL, 0.28 mmol) was added at once. Then the water-ice bath was removed and Et_2O (3 mL) was added. The reaction was stirred for 30 min. During this time hydroxylamine hydrochloride was added when the mixture turned green or blue. When the color of the suspension turned rusty, the reaction was terminated. Afterwards, hydrochloric acid (0.1 M, 5 mL) was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The residue was first purified twice by automatic flash column chromatography (100% H_2O → 100% ACN, Biotage® SNAP KP-C18-HS 12 g) and then by preparative HPLC (method 3, t_R = 16.3 min) to give **90c** as colorless solid (10 mg, 0.02 mmol, 18% yield). RP-TLC (H_2O/ACN = 1/1): R_f = 0.25; Melting point: 143 °C (decomposition); Specific rotation: $[\alpha]_D^{20}$ = −125.3 (c = 1.0; DMSO); ^{1}H NMR: (CD_3OD): δ [ppm] = 3.62 (dd, *J* = 11.5/3.1 Hz, 1H, PhCHC*H*$_2$OH), 3.66–3.83 (m, 4H, PhCHC*H*$_2$OH, HOHNOCC*H*C*H*$_2$OH), 4.54 (dd, *J* = 8.3/3.1 Hz, 1H, PhC*H*CH$_2$OH), 7.36–7.47 (m, 5H, H_{phenyl}), 7.51–7.55 (m, 4H, H_{phenyl}); ^{13}C NMR: (CD_3OD): δ [ppm] = 64.3 (1C, HOHNOCCHCH_2OH), 67.3 (1C, PhCHCH_2OH), 74.3 (1C, PhC≡*C*C≡CPh), 74.7 (1C, PhC≡*C*C≡CPh), 80.7 (1C, HOHNOCCHCH$_2$OH), 81.9 (1C, Ph*C*≡CC≡CPh), 82.4 (1C, PhC≡CC≡CPh), 84.4 (1C, Ph*C*HCH$_2$OH), 122.8 (1C, C_{phenyl}), 122.9 (1C, C_{phenyl}), 128.6 (2C, C_{phenyl}), 129.7 (2C, C_{phenyl}), 130.6 (1C, C_{phenyl}), 133.4 (2C, C_{phenyl}), 133.6 (2C, C_{phenyl}), 141.0 (1C, C_{phenyl}), 169.5 (1C, *C*ONHOH); IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3321, 2924, 2874, 1674, 1111, 1042, 829, 752, 687; LC-MS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{20}NO_5$: 366.1336, found: 366.1342; HPLC (method 2): t_R = 16.4 min, purity 98.8%.

4.3. Biological evaluation

4.3.1. 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 defective strain *E. coli* D22 [26] were grown overnight in LB broth [27] at 37 °C, 200 rpm. 150 μL of an overnight cell suspension were spread evenly onto LB agar petri dishes. 15 μL of each compound (10 mM in DMSO) were applied onto circular filter paper (Ø = 6 mm, Whatman™, GE Healthcare). Pure DMSO, serving as a negative and CHIR-090, 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.

4.3.2. LpxC assay

4.3.2.1. Protein purification. The plasmid for the expression of LpxCC63A (pET11EcLpxCC63A) was kindly provided by Carol Fierke [28]. The C63A mutation lowers the undesired influence of Zn^{2+}-concentration on enzymatic activity. The purification of LpxC was performed essentially as previously described [29]. Weak anion exchange was performed with a column containing 30 mL diethylaminoethylcellulose (DEAE)-Sepharose fast flow media (GE Healthcare). Eluted fractions containing the desired enzyme were concentrated and desalted with molecular weight cut-off (MWCO) spin columns (10 kDa, PALL Corporation). Strong anion exchange was then performed with a column containing 20 mL of quaternary ammonium-sepharose (Q-Sepharose) fast flow media (GE Healthcare). The fractions containing LpxC (peak elution at 18.6 mS × cm^{-1}) were concentrated and desalted as above using MWCO columns. The final step of protein purification was performed with a pre-packed size exclusion chromatography column containing 120 mL of Superdex 200 (HiLoad 16/600) (GE Healthcare). LpxCC63A emerged in a peak after 80 mL of elution buffer. The purified LpxC was concentrated with MWCO columns and stored in 50 μL aliquots at −80 °C in Bis/Tris buffer 50 mM, pH 6.0, containing 150 mM NaCl. The presence of the enzyme during the purification progress was confirmed by sodium dodecyl sulfate-polyacrylamide gelelectrophoresis (SDS-PAGE) with Coomassie brilliant blue staining. The purified LpxC had a purity above 95% according to SDS PAGE, and was quantified by use of an Implen NanoPhotometer showing a concentration of 500 μg*mL^{-1}.

4.3.2.2. Enzyme inhibition assay. A fluorescence-based microplate assay for LpxC activity was performed as described by Clements et al. [7] The wells in a black, non-binding, 96 wells fluorescence microplate (Greiner Bio One, Frickenhausen) were filled with 93 μL of a 40 mM sodium morpholinoethanesulfonic acid buffer (pH 6.0) containing 26.9 μM UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine, 80 μM dithiothreitol and 0.02% Brij 35. Inhibitors were dissolved in DMSO and assayed over a range starting from 0.2 nM up to 200 μM. After addition of 250 ng purified LpxC, the microplate was incubated for 30 min at 37 °C in a plate shaker. Then the biochemical reaction was stopped by adding 40 μL of 0.625 M sodium hydroxide. The reaction mixture was further incubated for 10 min and neutralized by adding 40 μL of 0.625 M acetic acid. The deacetylated product UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]glucosamine was converted into a fluorescing isoindole by adding 120 μL of 250 nmol *o*-phthaldialdehyde-2-mercaptoethanol in 0.1 M borax [30] and detected by a Mithras plate reader (Berthold, Bad Wildbad) at 340 nm excitation and 460 nm emission wavelengths. The calculation of the IC_{50} values was performed with the aid of the software GraphPadPrism, which were then converted into K_i values using the Cheng-Prusoff equation. The K_M value was calculated from the Lineweaver-Burk plot. To validate the test system, the IC_{50} value of CHIR-090 was measured and was found to be comparable to the one in the literature [7].

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (HO 5220/2-1), which is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.01.032.

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