**Phenylethylene glycol-derived LpxC inhibitors with diverse $Zn^{2+}$-binding groups**

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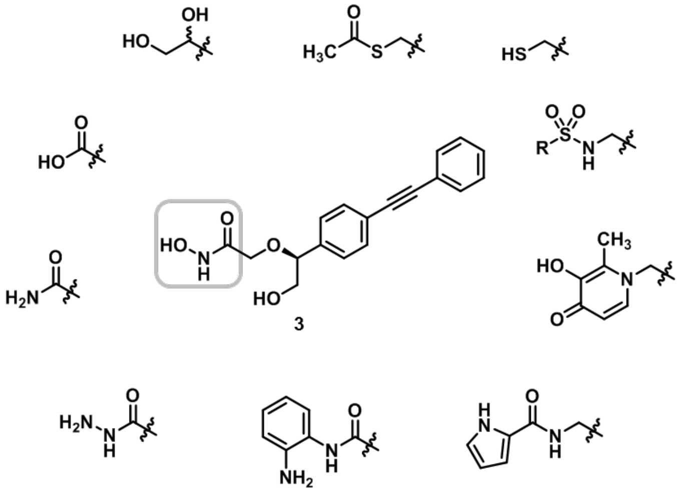
## Graphical abstract



## Key words

Antibacterials; LpxC inhibitors; hydroxamic acids; metabolic stability; $Zn^{2+}$-chelating groups

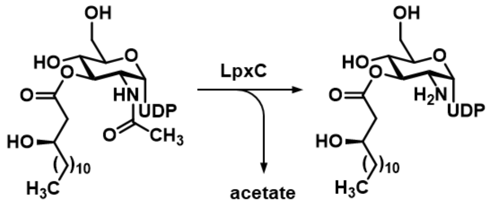
## Abstract

The $Zn^{2+}$-dependent bacterial deacetylase LpxC is a promising target for the development of novel antibiotics. Most of the known LpxC inhibitors carry a hydroxamate moiety as $Zn^{2+}$-binding group. However, hydroxamic acids generally exhibit poor pharmacokinetic properties. (*S*)-*N*-Hydroxy-2-{2-hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}acetamide (**3**) is a known phenylethylene glycol derivative potently inhibiting LpxC with a $K_i$ of 66 nM. *In vitro* experiments have confirmed *in silico* predictions that the hydroxamate moiety of **3** is indeed metabolically labile. In this study, several strategies were explored to replace the hydroxamate moiety by other $Zn^{2+}$-binding groups while maintaining target activity. In total, 15 phenylethylene glycol derivatives with diverse $Zn^{2+}$-binding groups like carboxylate, hydrazide, carboxamide, sulfonamide, vicinal diol, thiol, thioester, and hydroxypyridinone moieties were prepared in divergent syntheses. However, their biological evaluation revealed that the replacement of the hydroxamate moiety of **3** by any of the investigated $Zn^{2+}$-binding groups is detrimental for LpxC inhibitory and antibacterial activity.

## 1. Introduction

After iron, zinc is the second most abundant transition metal in all living organisms, including animals, plants, and microorganisms, with $Zn^{2+}$-containing enzymes constituting the largest category of metalloproteins.[1] Many of these enzymes are involved in biological processes also associated with the propagation of various diseases, like cancer, arthritis, hypertension, and bacterial infections, thus making them attractive targets for drug therapy.[2] In the design and development of inhibitors of these enzymes, their metal ion cofactor has frequently been targeted by chelating groups.[3-4]

The $Zn^{2+}$-dependent bacterial deacetylase LpxC represents a promising target for the development of antibiotics, selectively combating Gram-negative bacteria.[5] The enzyme, which is highly conserved among Gram-negative bacteria, is involved in the biosynthesis of lipid A. Lipid A is essential for growth and viability of Gram-negative bacteria as it constitutes the hydrophobic membrane anchor of lipopolysaccharides, representing the main component of the outer monolayer of the outer membrane of these germs.[6] LpxC plays a central role in lipid A biosynthesis, catalyzing its first irreversible step, which in *E. coli* is the deacetylation of UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**1**, Scheme 1).[7-8] The enzyme's catalytic $Zn^{2+}$-ion is located at the bottom of the ~20 Å deep, conical active site cleft, where it is coordinated by one aspartate and two histidine residues. From this active site, an approximately 15 Å long, hydrophobic tunnel leads outwards, which encloses the 3-*O*-[(*R*)-3-hydroxymyristoyl] substituent of the enzyme's natural substrate during catalysis.[9-10]




1 2

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

Various structural classes of LpxC inhibitors have been described in the patent and non-patent literature.[5, 11] Most of the described inhibitors share common structural features like a $Zn^{2+}$-binding group as well as a structural element addressing the enzyme's hydrophobic tunnel.[5, 11-12] The vast majority of the reported LpxC inhibitors uses a hydroxamate moiety as the $Zn^{2+}$-binding group.

Although a hydroxamate moiety is found in some approved drugs, like the histone deacetylase inhibitors vorinostat, panobinostat, and belinostat, the clinical effectiveness of hydroxamic acids is generally limited by their inadequate selectivity for $Zn^{2+}$-ions and poor pharmacokinetics.[13-18] The unfavorable pharmacokinetic properties of hydroxamic acids result from poor oral bioavailability as well as high clearance due to rapid metabolism *via* conjugate formation (glucuronidation and sulfation), reduction, and hydrolytic cleavage, the latter leading to the release of toxic hydroxylamine.[19-26]

In case of numerous $Zn^{2+}$-containing target enzymes, inhibitors have been developed which exhibit alternative $Zn^{2+}$-binding groups with more favorable pharmacological and pharmacokinetic properties.[13, 19, 24, 27-28] However, in the case of LpxC inhibitors, only a few inhibitors that do not contain the $Zn^{2+}$-chelating hydroxamate moiety have been reported so far.[29-37]

Recently, we have reported on a series of benzyloxyacetohydroxamic acids as inhibitors of LpxC, with the most potent compound, **3** (Figure 1), exhibiting promising activities in the enzyme assay ($IC_{50}$ = 0.48 µM, $K_i$ = 66 nM) as well as in the performed disc diffusion assays (Table 1).[38] Therefore, the compound should be further investigated. In this work, the results of *in silico* and *in vitro* experiments on the metabolism of hydroxamic acid **3** are reported. In addition, a systematic study of alternative metal binding groups is described, in which the hydroxamate moiety of **3** was replaced by various other $Zn^{2+}$-binding groups that are part of effective inhibitors of other $Zn^{2+}$-dependent enzymes.[24, 39-45] Thus a carboxylic acid, a hydrazide, several amides and sulfonamides, vicinal diols, a thiol, a thioester, and hydroxypyridinone derivatives were synthesized and tested for antibacterial activity.

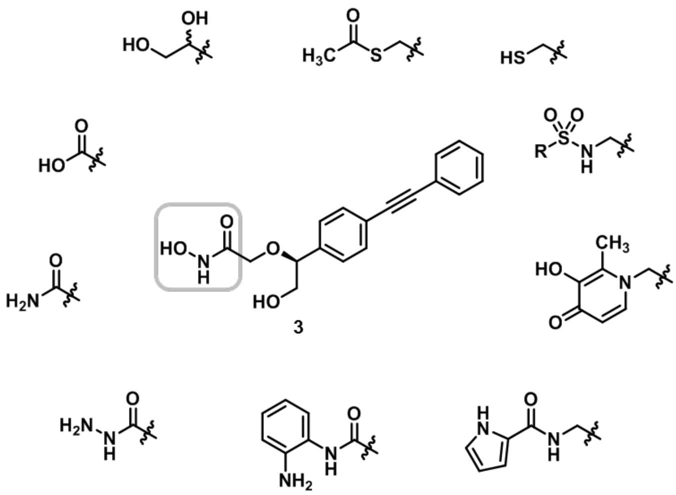


**Figure 1**: Structure of hydroxamic acid **3** and alternative $Zn^{2+}$-binding groups.

## 2. Results and Discussion

### 2.1. Prediction of the metabolism of 3

The susceptibility of **3** toward human cytochrome P450 (CYP)-mediated metabolism was investigated with FAME 2, a random forest-based predictor of sites of metabolism.[46] FAME 2 assigned a moderate likelihood of metabolism (0.602; values ranging from 0 to 1, with higher values indicating higher probabilities of atoms being sites of metabolism) to the *para*-position of the terminal phenyl moiety (Figure 2). This is interpreted as a moderate likelihood for a hydroxylation to happen at this atom position. All other atom positions were predicted as stable in the context of CYP metabolism.

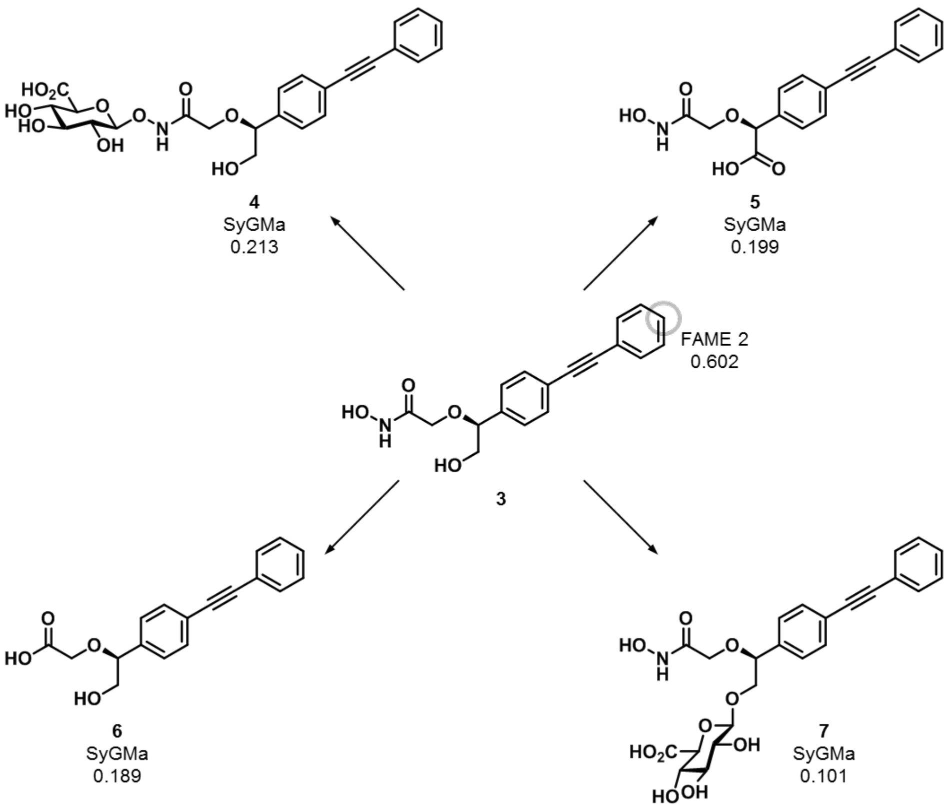



**Figure 2**: Predictions of sites of metabolism with FAME 2 and of metabolites with SyGMa. The circle in the center compound (parent) indicates the most likely labile atom position related to CYP-mediated metabolism. The numbers report the scores

(probabilities) assigned by FAME 2 or SyGMa. Note that scores from FAME 2 and SyGMa are not directly comparable. In the case of SyGMa they should primarily be considered as a means for ranking metabolites.

The most likely human metabolites of **3** resulting from phase I and phase II metabolism were predicted with SyGMa.[47] SyGMa assigns to all predicted metabolites an empirical probability score, which represents the proportion of correctly predicted metabolites of the training set. For **3**, SyGMa predicts four metabolites with a score greater than 0.09 (Figure 2): two glucuronic acid conjugates (**4**, **7**) and two carboxylic acid metabolites (**5**, **6**).

## 2.2. *In vitro* metabolism using rat liver microsomes

To identify the metabolically labile positions of hydroxamic acid **3** *in vitro*, the compound was incubated with NADPH (for CYP-mediated phase I metabolism) and UDPGA (for UGT-mediated phase II metabolism) in the presence of a suspension of rat liver microsomes (Figure 3).

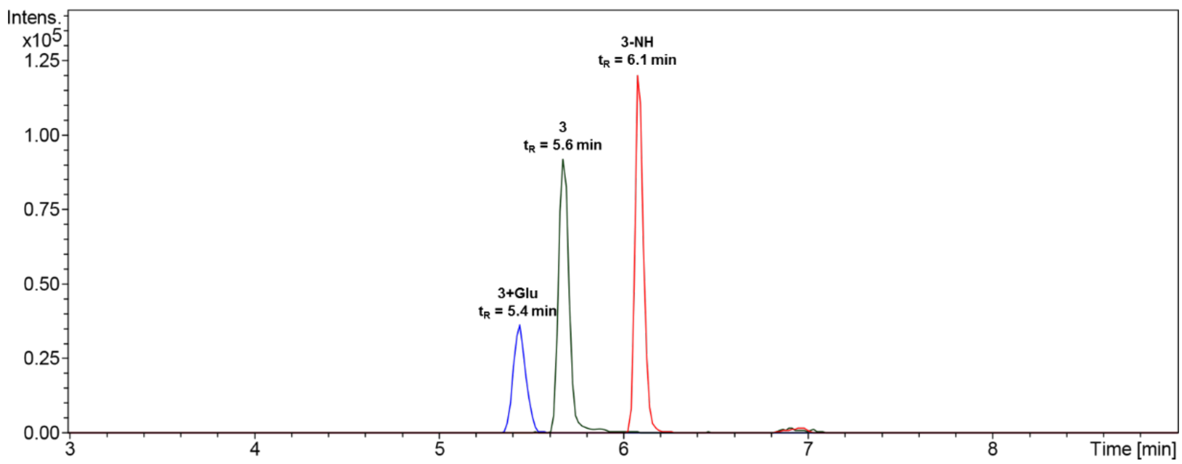



**Figure 3**: HPLC chromatogram of the incubation of **3** with a rat liver microsome suspension, NADPH/$H^+$ and UDPGA. EICs: **blue** (m/z 486.1414±0.05), **green**

(310.1091±0.05), **red** (295.0991±0.05), gradient elution (HPLC method 3), MS-detection in negative ion polarity.

Furthermore, experiments with **3** and the rat liver microsome suspension alone as well as with the addition of only one of the cofactors have been performed. All samples were analyzed by LC-MS. Suggestions on the chemical structure of the formed metabolites were made based on their exact masses and retention times (Figure 4).

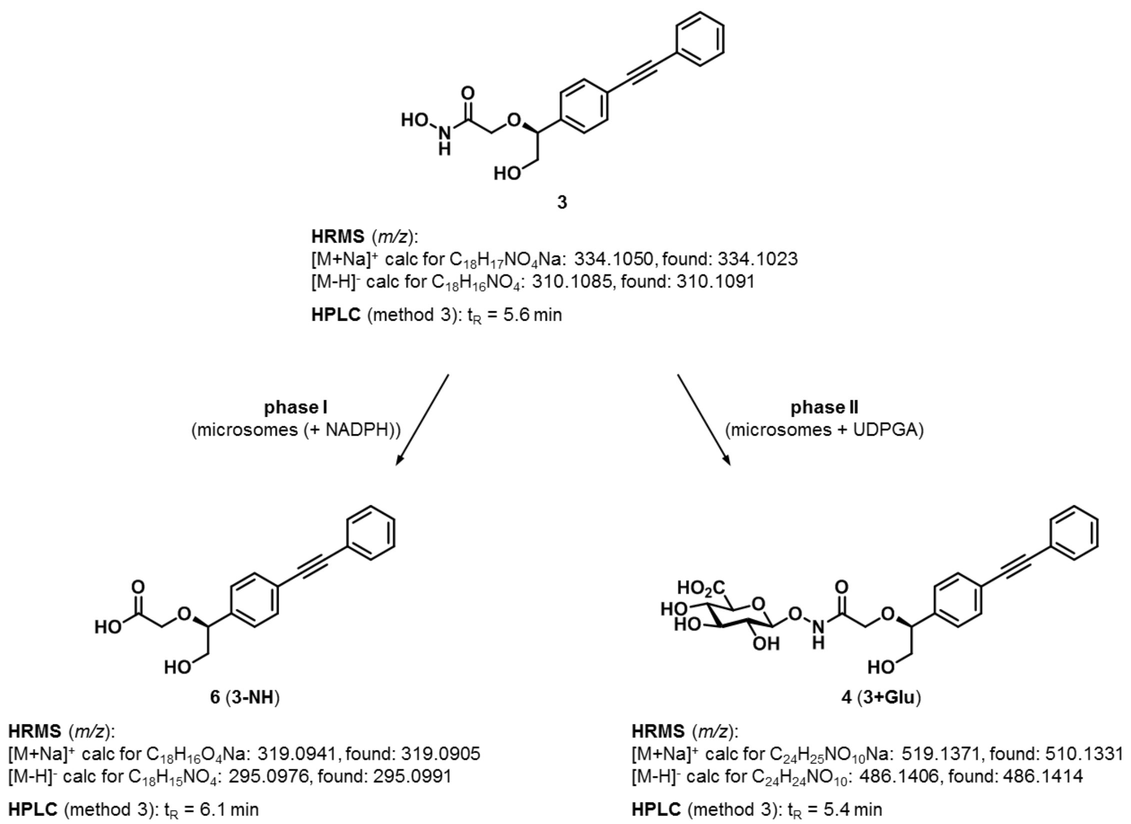



**Figure 4**: Suggested structures of the observed phase I- and phase II-metabolites of hydroxamic acid **3**.

When investigating the phase I metabolism of **3**, the formation of carboxylic acid **6** (**3-NH**) was observed. Whereas only traces of carboxylic acid **6** were found upon incubation of **3** in PBS buffer pH 7.4 for 120 min, the addition of the rat liver microsome suspension caused a hydrolytic cleavage of the hydroxamate moiety, irrespective of the absence or presence of the cofactor NADPH.

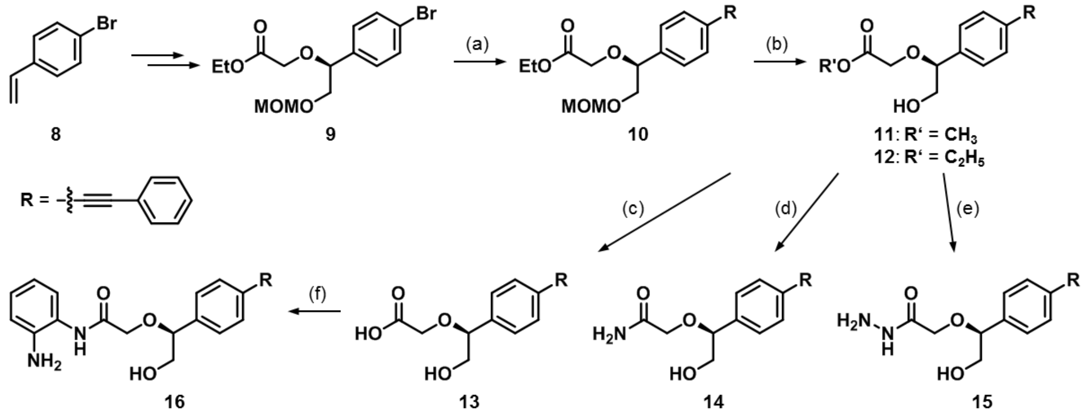
In the performed phase II metabolism study of **3**, conjugate formation yielded glucuronide **3+Glu**, which is most probably compound **4**, exhibiting a glucuronidated hydroxamate moiety.

The formation of monooxygenated products or metabolites arising from combined phase I and phase II biotransformation reactions could not be observed. Although these experiments were performed with rat liver microsomes rather than with human materials, the observations are in good agreement with the *in silico* predictions. Both the carboxylic acid metabolite **6** and the glucuronic acid metabolite **4** were predicted with SyGMa as two out of four metabolites. The transformation of the *para*-position of the terminal phenyl moiety, predicted by FAME 2 with a moderate likelihood, could not be experimentally confirmed. However, it is plausible that such a metabolite is formed in humans.

### 2.3. Chemistry

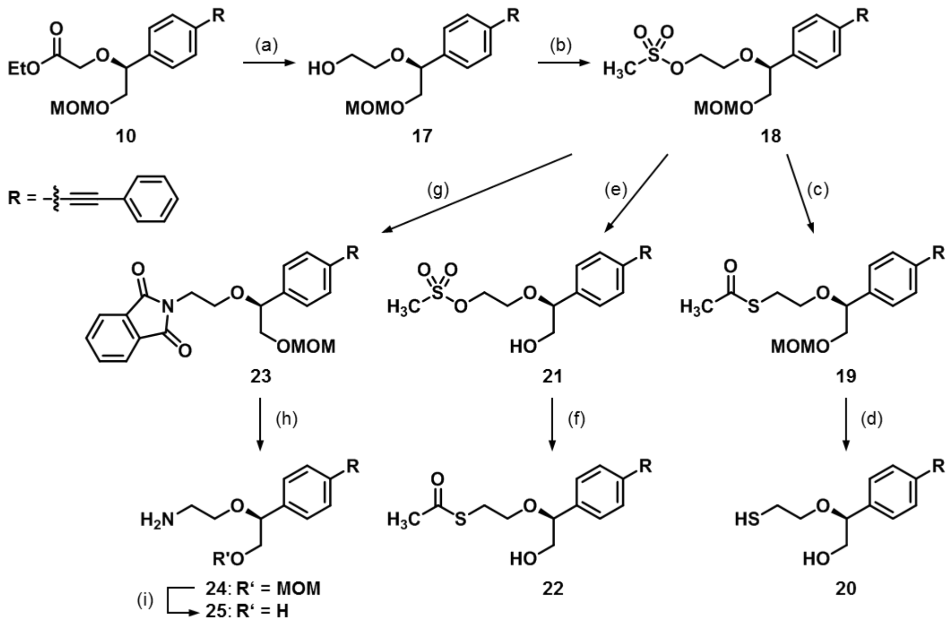
The envisaged carboxylic acid derivatives **13**, **14**, **15** and **16** were synthesized from ester **9** (Scheme 2), which can be accessed in enantiomerically pure form *via* a described procedure starting from 4-bromostyrene (**8**).[38] In order to establish the lipophilic side chain of the compounds, a Sonogashira coupling of aryl bromide **9** with phenylacetylene was performed to yield diphenylacetylene derivative **10**. Subsequently, the MOM protective group of ester **10** was cleaved under acidic conditions. When performing the reaction in ethanol, ethyl ester **12** was obtained. The use of methanol as solvent led to an additional transesterification, yielding methyl ester **11**. Whereas the saponification of ester **12** gave carboxylic acid **13**, the aminolyses of esters **11** and **12** with ammonia and hydrazine yielded primary amide **14** and hydrazide

**15**, respectively.[48-49] Finally, amide **16** was obtained by coupling carboxylic acid **13** with 1,2-phenylenediamine in the presence of the carboxyl activating agent EDCI hydrochloride and *N*-hydroxysuccinimide.[19, 50-51]




**Scheme 2**: Reagents and conditions: (a) phenylacetylene, $Pd(PPh_3)_4$, CuI, $NEt_3$, Δ, 16 h, 99 %; (b) HCl, MeOH or EtOH, rt, 16 h, **11** 86 %, **12** 84 %; (c) NaOH, THF, rt, 16 h, 82 %; (d) aq. $NH_3$, rt, 16 h, 75 %; (e) $H_2NNH_2$, EtOH, 37 %; (f) EDCI hydrochloride, *N*-hydroxysuccinimide, 1,2-phenylenediamine, $CH_2Cl_2$, rt, 16 h, 29 %.

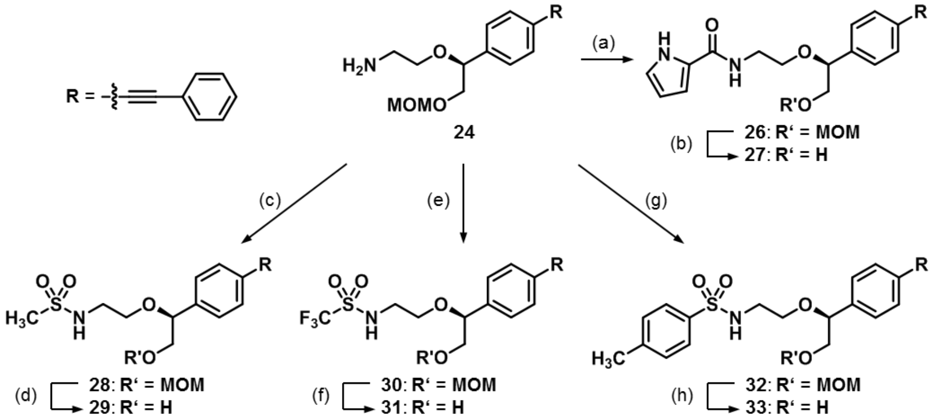
In order to access thiol derivatives **20** and **22**, ester **10** was reduced with DIBAL to yield primary alcohol **17** (Scheme 3).[52] Subsequently, the alcohol was mesylated and the resulting methanesulfonic acid ester **18** was subjected to a nucleophilic substitution with thioacetic acid to obtain thioester **19**.[53-54] The removal of the MOM protective group of thioester **19** under acidic conditions also led to the cleavage of the compound's thioester moiety, thus yielding thiol **20**. In order to obtain thioester **22**, at first, the MOM protective group of mesylate **21** was cleaved and thereafter a nucleophilic substitution with thioacetic acid was performed.




**Scheme 3**: Reagents and conditions: (a) DIBAL, $CH_2Cl_2$, rt, 30 min, 77 %; (b) mesyl chloride, $NEt_3$, DMAP, $CH_2Cl_2$, rt, 2.5 h, 69 %; (c) thioacetic acid, $NEt_3$, DMF, rt, 16 h, 67 %; (d) HCl, MeOH, rt, 16 h, 53 %; (e) HCl, MeOH, rt, 16 h, 87 %; (f) thioacetic acid, $NEt_3$, DMF, rt, 16 h, 72 %; (g) potassium phthalimide, DMF, 80 °C, 3 h, 84 %; (h) $H_2NCH_3$, EtOH, 70 °C, 16 h, 82 %; (i) HCl, EtOH, rt, 16 h, 41 %.

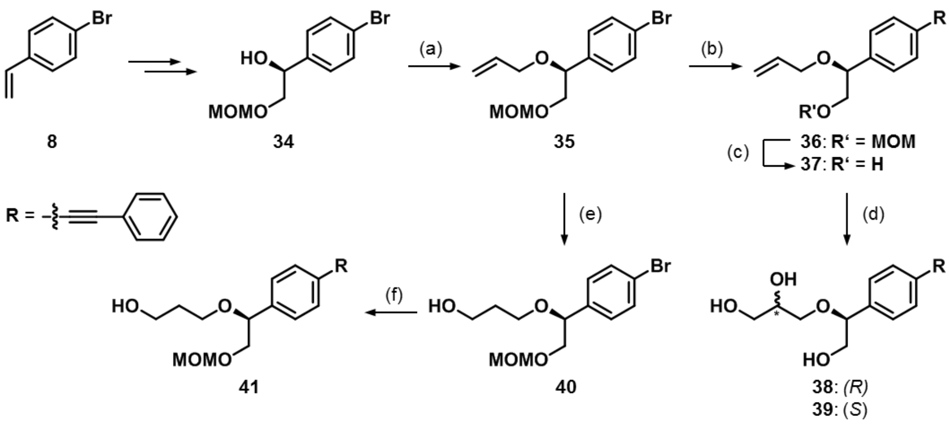
The primary amine **24** (Scheme 3) represents an important intermediate in the synthesis of the envisaged carboxamide and sulfonamide derivatives. The compound could be accessed *via* a Gabriel synthesis. Thus, mesylate **18** was subjected to a nucleophilic substitution with potassium phthalimide, yielding *N*-alkylphthalimide **23**, which was subsequently cleaved with methylamine to give primary amine **24**.[55] Additionally, the MOM protective group of compound **24** was removed under acidic conditions yielding amine **25**, which was also tested for antibacterial and LpxC inhibitory activity.

Subsequently, primary amine **24** was coupled with pyrrole-2-carboxylic acid to give carboxamide **26** and reacted with mesyl chloride, triflyl chloride, and tosyl chloride to yield sulfonamides **28**, **30**, and **32**, respectively (Scheme 4).[56] These compounds were finally deprotected under acidic conditions, giving access to alcohols **27**, **29**, **31**, and **33**.




**Scheme 4**: Reagents and conditions: (a) pyrrole-2-carboxylic acid, EDCI hydrochloride, HOBt, $NEt_3$, $CH_2Cl_2$, rt, 16 h, 87 %; (b) $H^+$, MeOH, rt, 82 %; (c) mesyl chloride, $NEt_3$, $CH_2Cl_2$, rt, 16 h, 79 %; (d) HCl, MeOH, rt, 16 h, 85 %; (e) triflyl chloride, $NEt_3$, $CH_2Cl_2$, rt, 16 h, 45 %; (f) HCl, MeOH, rt, 16 h, 63 %; (g) *p*TsCl, $NEt_3$, $CH_2Cl_2$, rt, 16 h, 85 %; (h) HCl, MeOH, rt, 16 h, 89 %.

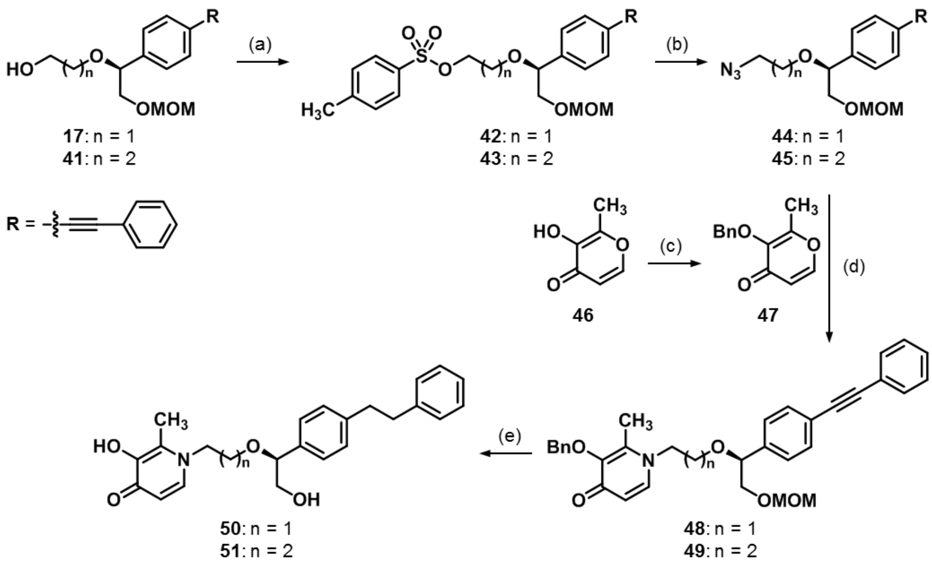
In order to obtain vicinal diols **38** and **39**, secondary alcohol **34**, which is another intermediate of the described synthesis of hydroxamic acid **3** and which is also accessible from 4-bromostyrene (**8**),[38] was reacted with allyl bromide to give allyl ether **35** (Scheme 5). The latter was subjected to a Sonogashira coupling with phenylacetylene, yielding diphenylacetylene derivative **36**. After cleavage of the MOM protective group, Sharpless asymmetric dihydroxylations were performed with the resulting alcohol **37**.[57] When AD-mix-α was used, allyl ether **37** should be transformed into the (*R*)-configured vicinal diol **38**, whereas the use of AD-mix-β should lead to the formation of the respective (*S*)-configured vicinal diol **39**. However, the diastereoselectivities of the performed asymmetric dihydroxylations of allyl ether **37** were relatively low. Whereas the reported Sharpless asymmetric dihydroxylations of 4-bromostyrene (**8**) had yielded the respective diols with high enantioselectivities (*ee* > 97 %),[38] the diastereomeric excess of vicinal diols **38** (*de* = 60 %) and **39** (*de* = 20 %) was rather poor.




**Scheme 5**: Reagents and conditions: (a) allyl bromide, LiHMDS, $NBu_4I$, THF, Δ, 16 h, 64 %; (b) phenylacetylene, $Pd(PPh_3)_4$, CuI, $NEt_3$, Δ, 16 h, 86 %; (c) HCl, MeOH, rt, 16 h, 91 %; (d) AD-mix-α, *t*BuOH/$H_2O$ (1:1), 0 °C, 16 h, **38** 93 %, *de* = 60 % or AD-mix-β, *t*BuOH/$H_2O$ (1:1), 0 °C, 16 h, **39** 90 %, *de* = 20 %; (e) 1. 9-BBN, THF, rt, 17.5 h, 2. MeOH, aq. NaOH, aq. $H_2O_2$, -25 °C → 40 °C, 99 %; (f) phenylacetylene, $Pd(PPh_3)_4$, CuI, $NEt_3$, Δ, 16 h, 78 %.

Primary alcohol **41** was obtained from ether **35** *via* the hydroboration of its allyl substituent with 9-borabicyclononane (9-BBN) followed by an oxidative workup with NaOH/$H_2O_2$, yielding propanol derivative **40**, and a subsequent Sonogashira coupling with phenylacetylene (Scheme 5).[58-59]

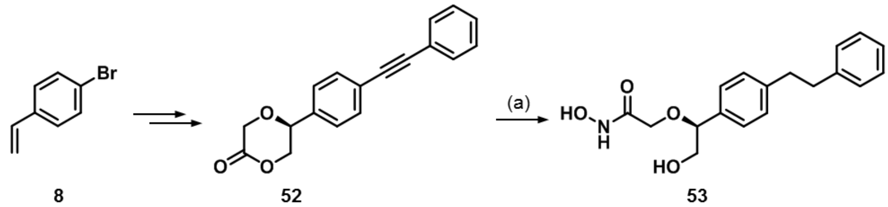
Primary alcohols **17** and **41** were used as stating materials for the synthesis of hydroxypyridinone derivatives (Scheme 6). Thus, the compounds were transformed into azides **44** and **45** *via* a tosylation and a subsequent substitution with sodium azide. The obtained azides **44** and **45** were subjected to a Staudinger reduction and the intermediately formed primary amines were reacted with benzyl-protected maltol (**47**) to yield pyridinone derivatives **48** and **49**, respectively.[60] Subsequently, both protective groups should be cleaved under acidic conditions. According to the literature, the benzyl protective group of the pyridinone derivatives should be removable under strongly acidic conditions.[60] However, these conditions also led to the cleavage of the second benzyl ether moiety within the molecules and consequently to a degradation of the compounds. Thus, after the acid-catalyzed cleavage of the MOM protective groups of pyridinone derivatives **48** and **49**, their benzyl groups were hydrogenolytically removed. However, under the latter reaction conditions, the triple bonds of the compounds were additionally hydrogenated, leading to the formation 1,2-diphenylethane derivatives **50** and **51**.




**Scheme 6**: Reagents and conditions: (a) pTsCl, DMAP, $NEt_3$, $CH_2Cl_2$, rt, **42** 86 %, **43** 82 %; (b) $NaN_3$, DMSO, Δ, 16 h, **44** 92 %, **45** 90 %; (c) BnBr, $K_2CO_3$, ACN, Δ, 16 h, 95

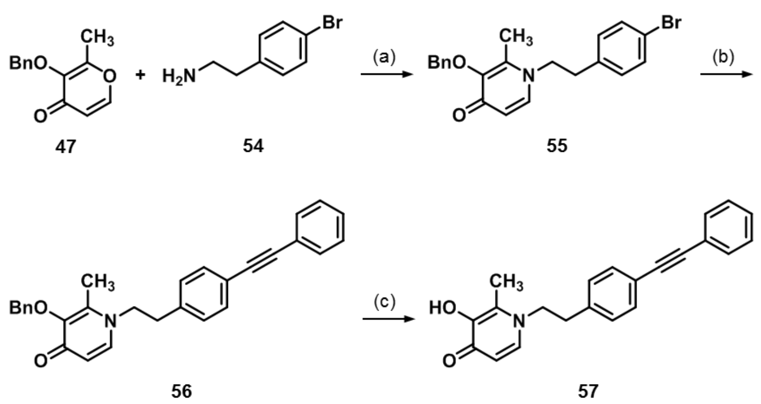
%; (d) 1. polymer-bound $PPh_3$, THF, $H_2O$, 2. **47**, $H_2O$, 140 °C, 7 d, **48** 19 %, **49** 14 %; (e) 1. HCl, MeOH, rt, 16 h, 2. $H_2$, Pd/C, MeOH, rt, 16 h, **50** 27 %, **51** 26 %.

For a better comparability, when elucidating the effect of the replacement of the hydroxamate group by a hydroxypyridinone moiety, two additional compounds were synthesized. On the one hand, the 1,2-diphenylethane-derived hydroxamic acid **53** was prepared (Scheme 7). Staring from the described lactone **52**,[38] at first, the hydrogenation of its acetylene moiety was performed, followed by an aminolysis with hydroxylamine, yielding hydroxamic acid **53**.




**Scheme 7**: Reagents and conditions: (a) 1. $H_2$, Pd/C, MeOH, rt, 16 h, 2. $H_2NOH \cdot HCl$, NaOMe, MeOH, rt, 16 h, 52 %.

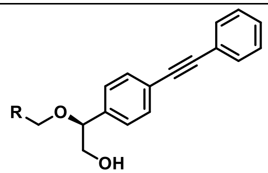
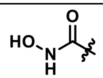
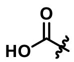
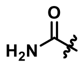
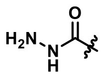
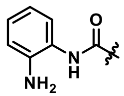
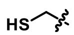
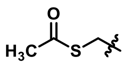
On the other hand, diphenylacetylene derivative **57** was synthesized (Scheme 8), which can be considered as a hydroxypyridinone-derived analogue of the described benzyloxyacetohydroxamic acid **58**.[38] The reaction of 2-(4-bromophenyl)ethylamine (**54**) with maltol derivative **47** yielded pyridinone derivative **55**. After a Sonogashira coupling with phenylacetylene, the benzyl protective group was removed by heating pyridinone derivative **56** under strongly acidic conditions to yield hydroxypyridinone derivative **57**.

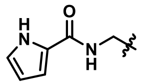
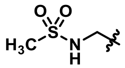
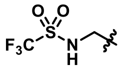
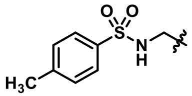
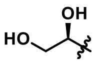
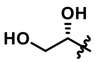
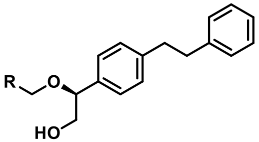
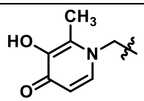
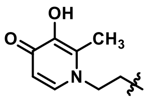
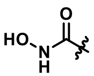
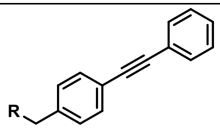


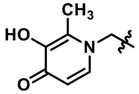
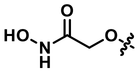
**Scheme 8**: Reagents and conditions: (a) $H_2O$, 140 °C, 10 d, 60 %; (b) phenylacetylene, $Pd(PPh_3)_4$, CuI, $NEt_3$, ACN, Δ, 16 h, 67 %; (c) aq. HCl, MeOH, Δ, 4 h, 60 %.

### 2.4. Biological evaluation

**Table 1**: Results of the biological evaluation of the synthesized inhibitors with various $Zn^{2+}$-binding groups. n. d.: not determinable. *: not soluble in the assay buffer at a concentration of 200 µM.

| **compound** |  | **zone of inhibition [mm]** | | **MIC [µg/mL]** | | **enzyme assay** | |
|---|---|---|---|---|---|---|---|
| | **R =** | ***E. coli* BL21** | ***E. coli* D22** | ***E. coli* BL21** | ***E. coli* D22** | **$IC_{50}$ [µM]** | **$K_i$ [µM]** |
| **3**[38] |  | 9.5 ± 0.4 | 20.5 ± 0.2 | 64 | 4 | 0.48 ± 0.23 | 0.066 ± 0.032 |
| **13** |  | <6 | <6 | >64 | >64 | >200 | - |
| **14** |  | <6 | <6 | >64 | >64 | >200 | - |
| **15** |  | 7.3 ± 1.2 | 9.8 ± 1.0 | >64 | >64 | >200 | - |
| **16** |  | <6 | 7.7 ± 1.5 | >64 | >64 | >20* | - |
| **20** |  | <6 | <6 | >64 | >64 | >200 | - |
| **22** |  | <6 | <6 | >64 | >64 | >200 | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **25** |  | 12.0 ± 2.0 | 13.8 ± 1.4 | >64 | 64 | n.d. | - |
| **27** |  | <6 | <6 | >64 | >64 | >20* | - |
| **29** |  | <6 | 8.7 ± 0.6 | >64 | >64 | >200 | - |
| **31** |  | 7.0 ± 1.0 | 7.7 ± 0.6 | >64 | >64 | >20* | - |
| **33** |  | <6 | <6 | >64 | >64 | >200 | - |
| **38** (*de* = 60 %) |  | 7.8 ± 1.6 | 8.7 ± 1.5 | >64 | >64 | >200 | - |
| **39** (*de* = 20 %) |  | 8.0 ± 1.7 | 8.5 ± 0.9 | >64 | >64 | >200 | - |
| **compound** |  | **zone of inhibition [mm]** | | **MIC [µg/mL]** | | **enzyme assay** | |
| | **R =** | ***E. coli* BL21** | ***E. coli* D22** | ***E. coli* BL21** | ***E. coli* D22** | **$IC_{50}$ [µM]** | **$K_i$ [µM]** |
| **50** |  | <6 | <6 | >64 | >64 | >200 | - |
| **51** |  | <6 | <6 | >64 | >64 | >200 | - |
| **53** |  | <6 | <6 | >64 | >64 | >200 | - |
| **compound** |  | **zone of inhibition [mm]** | | **MIC [µg/mL]** | | **enzyme assay** | |

| | R = | *E. coli* BL21 | *E. coli* D22 | *E. coli* BL21 | *E. coli* D22 | $IC_{50}$ [µM] | $K_i$ [µM] |
|---|---|---|---|---|---|---|---|
| **57** |  | <6 | <6 | >64 | >64 | >200 | - |
| **58**[38] |  | 10.6 ± 0.4 | 13.2 ± 1.6 | 32 | 2 | >200 | - |

In order to evaluate the antibacterial activities of the synthesized compounds, disc diffusion tests with *E. coli* BL21 (DE3) and the defective *E. coli* strain D22,[61] which is more sensitive towards LpxC inhibition, were performed and the MIC (minimal inhibitory concentration) values of the potential LpxC inhibitors were determined (Table 1). Additionally, a fluorescence-based LpxC enzyme assay was performed to test the inhibitory activity of the synthesized compounds against the isolated enzyme.[62] In the LpxC enzyme assay, purified *E. coli* LpxCC63A was employed, as the C63A mutation lowers the undesired influence of $Zn^{2+}$-concentration on enzymatic activity.[5, 63] The inhibition of the deacetylation of the enzyme's natural substrate **1** (Scheme 1) caused by a certain concentration of the putative inhibitors (ranging from 0.2 nM to 200 µM) was determined by transforming the resulting deacetylated primary amine **2** into a fluorescent isoindole with phthalaldehyde and 2-mercaptoethanol.

As under the conditions of the enzyme assay primary amine **25** gave a fluorescent product itself, an $IC_{50}$ value could not be determined for this compounds. For all the other phenylethylene glycol derivatives the results of the enzyme assay clearly showed that the replacement of the hydroxamate moiety of compound **3** by any other of the investigated functional groups is detrimental for the inhibitory activity toward LpxC. None of the assayed compounds was able to inhibit the enzymatic activity of LpxC by more than half at the highest concentrations tested. These data are in general agreement with the observed antibacterial activities.

Whereas carboxylic acid **13**, amide **14**, thiol **20** and thioester **22** did not show any antibacterial activity, neither in the disc diffusion nor in the MIC assays, hydrazide **15** was found to be able to inhibit the growth of both *E. coli* strains in the performed disc diffusion assays. However, the diameters of the observed halos of inhibition caused by this compound, which should be able to chelate the catalytic $Zn^{2+}$-ion of LpxC in a similar fashion as hydroxamic acid **3**, are considerably smaller compared to the ones caused by the latter compound. Also 1,2-phenylenediamine derivative **16** as well as vicinal diols **38** and **39** caused observable halos of inhibition, particularly against the sensitive *E. coli* D22 strain. Whereas pyrrole-2-carboxamide **27** was found to exhibit no antibacterial activity, among the investigated sulfonamides **29**, **31**, and **33**, noticeable halos of inhibition were found for mesylamide **29** and triflylamide **31**. In contrast, no inhibition of bacterial growth was observed for sulfonamide **33**.

Surprisingly, primary amine **25** caused quite large halos of inhibition, which however did not translate into low MIC values. Due to its primary amino group, the inhibitory activity of compound **25** could not be determined using the fluorescence-based LpxC enzyme assay. Thus, it still needs to be elucidated, whether the observed antibacterial activity in the disc diffusion assays is due to inhibitory activity of the compound toward LpxC or due to unspecific cytotoxicity, the latter being indicated by halos of inhibition of approximately the same size when being assayed against *E. coli* BL21 and the sensitive *E. coli* strain D22.

The hydroxypyridinone derivatives **50** and **51** also exhibit no antibacterial activity. However, their inactivity in the performed assays could be attributed to their flexible side chain, as the hydrogenation of the triple bond of the diphenylacetylene moiety also led to the complete inactivity of hydroxamic acid **53**. This finding is in agreement with previous observations that in case of the benzyloxyacetohydroxamic acids a long, linear, and rigid lipophilic side chain is required for potent LpxC inhibitory activity.[38, 64]

Additional evidence that the replacement of the hydroxamate group by a hydroxypyridinone is unfavorable for the biological activity of the compounds is given by hydroxypyridinone derivative **57**, which, in contrast to benzyloxyacetohydroxamic acid **58**, exhibits no antibacterial activity at the concentrations tested.

## 3. Conclusions

In divergent syntheses, phenylethylene glycol derivatives exhibiting various $Zn^{2+}$-binding groups, like e.g. carboxylate, hydrazide, amide, sulfonamide, and thiol moieties, were obtained. The biological evaluation of the synthesized compounds revealed that the replacement of the hydroxamate moiety of compound **3** by other $Zn^{2+}$-binding groups is detrimental for the LpxC inhibitory and antibacterial activity of the phenylethylene glycol derivatives. For this reason, the metabolic stability of none of the newly synthesized compounds exhibiting an alternative $Zn^{2+}$-binding group was investigated. Thus, hydroxamic acid **3**, whose hydroxamate moiety was shown by *in silico* predictions as well as by *in vitro* experiments to be the major metabolically labile position of the compound, still represents the most potent LpxC inhibitor of the presented phenylethylene glycol derivatives. In consequence, further efforts need to be undertaken to find suitable $Zn^{2+}$-binding groups that can replace the hydroxamate moiety without causing a loss of LpxC inhibitory and antibacterial activity.

## 4. Experimental Section

### 4.1. Chemistry, general

Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (TLC): Silica gel 60 $F_{254}$ 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: diameter of the column, fraction size, eluent. 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); LiChroCART® 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 x 4.6 mm; flow rate: 1.00 mL/min; injection volume: 5.0 µL; detection at λ = 254 nm for 20 min; solvents: A:

acetonitrile : 10 mM ammonium formate = 10 : 90 with 0.1 % formic acid; B: acetonitrile : 10 mM ammonium formate = 90 : 10 with 0.1 % formic acid; gradient elution: (A %): 0 – 5 min: 100 % , 5 – 15 min: gradient from 100 % to 0 %, 15 – 20 min: 0 %, 20 – 22 min: gradient from 0 % to 100 %, 22 – 30 min: 100 %.

## 4.2. Synthetic procedures

### 4.2.1. Ethyl (*S*)-2-{2-(methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}acetate (10)

Under $N_2$ atmosphere, copper(I) iodide (50 mg, 0.26 mmol), tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.18 mmol) and phenylacetylene (0.27 mL, 250 mg, 2.5 mmol) were added to a solution of **9** (610 mg, 1.8 mmol) in triethylamine (40 mL). The mixture was heated to reflux and additional phenylacetylene (0.27 mL, 250 mg, 2.5 mmol) was added. After stirring the mixture under reflux conditions for 16 h, the solvent was evaporated and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2, V = 20 mL) to give **10** as yellowish oil (650 mg, 1.8 mmol, 99 % yield). $R_f$ = 0.68 (cyclohexane/ethyl acetate = 2:1); specific rotation: $[\alpha]_D^{20}$ = +91.4 (3.5; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 1.26 (t, $J$ = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 3.29 (s, 3H, $OCH_2OCH_3$), 3.71 (dd, $J$ = 10.8/4.3 Hz, 1H, $OCHCH_2O$), 3.84 (dd, $J$ = 10.8/7.2 Hz, 1H, $OCHCH_2O$), 3.99 (d, $J$ = 16.3 Hz, 1H, $OCH_2CO_2Et$), 4.11 (d, $J$ = 16.3 Hz, 1H, $OCH_2CO_2Et$), 4.15-4.23 (m, 2H, $CO_2CH_2CH_3$), 4.64 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.67 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.69 (dd, $J$ = 7.2/4.3 Hz, 1H, $OCHCH_2O$), 7.31-7.39 (m, 5H, $H_{arom.}$), 7.49-7.56 (m, 4H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 14.3 (1C,

$CO_2CH_2CH_3$), 55.5 (1C, $OCH_2OCH_3$), 61.0 (1C, $CO_2CH_2CH_3$), 66.5 (1C, $OCH_2CO_2Et$), 71.3 (1C, $OCHCH_2O$), 81.4 (1C, $OCHCH_2O$), 89.1 (1C, *C*≡C), 89.9 (1C, *C*≡C), 96.7 (1C, $OCH_2OCH_3$), 123.3 (1C, $C_{arom.}$), 123.5 (1C, $C_{arom.}$), 127.4 (2C, $C_{arom.}$), 128.49 (1C, $C_{arom.}$), 128.50 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 131.9 (2C, $C_{arom.}$), 138.5 (1C, $C_{arom.}$), 170.3 (1C, $CO_2Et$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2928, 1751, 1508, 1443, 1381, 1277, 1200, 1111, 1034, 918, 837, 756, 691; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{25}O_5$: 369.1697, found: 369.1664; HPLC (method 1): $t_R$ = 22.0 min, purity 97.5 %.

### 4.2.2. Methyl (*S*)-2-{2-hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}acetate (11)

**10** (100 mg, 0.28 mmol) was dissolved in HCl-saturated methanol (5 mL). The reaction mixture was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water, 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 (Ø = 2 cm, h = 17 cm, cyclohexane/ethyl acetate = 8:2 → 2:1, V = 10 mL) to give **11** as colorless oil (73 mg, 0.24 mmol, 86 % yield). $R_f$ = 0.21 (cyclohexane/ethyl acetate = 2:1); specific rotation: $[\alpha]_D^{20}$ = +175.9 (3.4; $CH_2Cl_2$); $^1H$ NMR: ($CD_3OD$): $\delta$ [ppm] = 3.63 (dd, $J$ = 11.8/4.0 Hz, 1H, $OCHCH_2OH$), 3.72 (s, 3H, $OCH_2CO_2CH_3$), 3.74 (dd, $J$ = 11.8/7.4 Hz, 1H, $OCHCH_2OH$), 4.04 (d, $J$ = 16.3 Hz, 1H, $OCH_2CO_2CH_3$), 4.11 (d, $J$ = 16.3 Hz, 1H, $OCH_2CO_2CH_3$), 4.54 (dd, $J$ = 7.4/4.0 Hz, 1H, $OCHCH_2OH$), 7.34-7.40 (m, 5H, 2'-$H_{4-(phenylethynyl)phenyl}$, 6'-$H_{4-(phenylethynyl)phenyl}$, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.47-7.55 (m, 4H, 3'-$H_{4-(phenylethynyl)phenyl}$, 5'-$H_{4-(phenylethynyl)phenyl}$, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$); $^{13}C$ NMR ($CD_3OD$): $\delta$ [ppm] = 52.4 (1C, $CO_2CH_3$), 67.2 (1C, $OCH_2CO_2CH_3$), 67.4 (1C, $OCHCH_2OH$), 84.7 (1C, $OCHCH_2OH$), 89.8 (1C, *C*≡C), 90.4 (1C, *C*≡C), 124.46 (1C, $C_{arom.}$), 124.48 (1C, $C_{arom.}$), 128.4 (2C, C-2'$_{4-(phenylethynyl)phenyl}$, C-

6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.5 (1C, C-4"$_{\text{phenyl}}$), 129.6 (2C, C-3"$_{\text{phenyl}}$, C-5"$_{\text{phenyl}}$), 132.5 (2C, $C_{\text{arom.}}$), 132.7 (2C, $C_{\text{arom.}}$), 140.0 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 172.8 (1C, $\mathit{C}O_2CH_3$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3456, 2951, 1740, 1508, 1439, 1408, 1377, 1215, 1126, 1053, 833, 756, 691; LCMS (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{18}NaO_4$: 333.1097, found: 333.1097; HPLC (method 1): $t_R$ = 21.1 min, purity 95.7 %.

### 4.2.3. Ethyl (*S*)-2-{2-hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}acetate (12)

**10** (120 mg, 0.31 mmol) was dissolved in HCl-saturated ethanol (4 mL). The reaction was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water 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 (Ø = 2 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2 → 2:1, V = 10 mL) to give **12** as yellowish oil (84 mg, 0.26 mmol, 84 % yield). $R_f$ = 0.14 (cyclohexane/ethyl acetate = 3:1); specific rotation: $[\alpha]_D^{20}$ = +156.2 (2.6; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 1.29 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H}_3$), 3.65 (dd, *J* = 11.8/3.2 Hz, 1H, $OCHC\mathit{H}_2OH$), 3.76 (dd, *J* = 11.8/8.8 Hz, 1H, $OCHC\mathit{H}_2OH$), 3.94 (d, *J* = 16.8 Hz, 1H, $OC\mathit{H}_2CO_2Et$), 4.20 (d, *J* = 16.8 Hz, 1H, $OC\mathit{H}_2CO_2Et$), 4.21-4.28 (m, 2H, $CO_2C\mathit{H}_2CH_3$), 4.52 (dd, *J* = 8.8/3.2 Hz, 1H, $OC\mathit{H}CH_2OH$), 7.29-7.39 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3"-$H_{\text{phenyl}}$, 5"-$H_{\text{phenyl}}$, 4"-$H_{\text{phenyl}}$), 7.50-7.56 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{\text{phenyl}}$, 6"-$H_{\text{phenyl}}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 14.3 (1C, $CO_2CH_2\mathit{C}H_3$), 61.5 (1C, $CO_2\mathit{C}H_2CH_3$), 66.5 (1C, $O\mathit{C}H_2CO_2Et$), 67.3 (1C, $OCH\mathit{C}H_2OH$), 84.6 (1C, $O\mathit{C}HCH_2OH$), 89.0 (1C, *C*≡C), 90.0 (1C, *C*≡C), 123.2 (1C, C-1"$_{\text{phenyl}}$), 123.6 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 126.9 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.51 (2C, C-3"$_{\text{phenyl}}$, C-5"$_{\text{phenyl}}$), 128.53 (1C, C-4"$_{phenyl}$), 131.8 (2C, C-2"$_{phenyl}$, C-6"$_{phenyl}$), 132.0 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 137.9 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 171.3 (1C, *C*$O_2$Et); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3437, 2970, 1736, 1508, 1443, 1381, 1215, 1126, 949, 837, 756, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{21}O_4$: 325.1434, found: 325.1469; HPLC (method 1): $t_R$ = 22.1 min, purity 97.7 %.

#### 4.2.4. (*S*)-2-{2-Hydroxy-1-[4-(phenylethynly)phenyl]ethoxy}acetic acid (13)

**12** (310 mg, 0.95 mmol) was dissolved in THF (3 mL) and a 1 M aqueous solution of NaOH (10 mL) was added. The reaction was stirred at ambient temperature for 16 h. Then the mixture was acidified with a 1 M aqueous solution of HCl and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered, and the solvent was removed *in vacuo* to give **13** as a colorless solid (230 mg, 0.78 mmol, 82 % yield). $R_f$ = 0.41 (dichloromethane/methanol = 9:1); melting point: 122 °C; specific rotation: $[\alpha]_D^{20}$ = +87.3 (2.2; $CH_2Cl_2$); $^1H$ NMR ($CD_3OD$): $\delta$ [ppm] = 3.63 (dd, $J$ = 11.8/3.9 Hz, 1H, OCHC$H_2$OH), 3.74 (dd, $J$ = 11.8/7.5 Hz, 1H, OCHC$H_2$OH), 3.99 (d, $J$ = 16.5 Hz, 1H, OC$H_2$$CO_2$H), 4.08 (d, $J$ = 16.5 Hz, 1H, OC$H_2$$CO_2$H), 4.54 (dd, $J$ = 7.5/3.9 Hz, 1H, OC*H*$CH_2$OH), 7.30-7.41 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.45-7.59 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl,}$); $^{13}C$ NMR ($CD_3OD$): $\delta$ [ppm] =67.1 (1C, O*C*$H_2$$CO_2$H), 67.4 (1C, OCH*C*$H_2$OH), 84.7 (1C, O*C*H$CH_2$OH), 89.8 (1C, *C*≡C), 90.4 (1C, *C*≡C), 124.47 (1C, $C_{arom.}$), 124.49 (1C, $C_{arom.}$), 128.4 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.5 (1C, C-4"$_{phenyl}$), 129.6 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 132.5 (2C, $C_{arom.}$), 132.7 (2C, $C_{arom.}$), 140.0 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 174.2 (1C, O$CH_2$*C*$O_2$H); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2978, 2889, 1739, 1597, 1508, 1385, 1242, 1126, 1072, 1053, 953, 833, 752, 687; LCMS (*m/z*): $[M+NH_4]^+$ calcd for $C_{18}H_{20}NO_4$: 314.1387, found: 314.1416; HPLC (method 2): $t_R$ = 17.0 min, purity 98.0 %.

### 4.2.5. (*S*)-2-{2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}acetamide (14)

An emulsion of **11** (55 mg, 0.18 mmol) in ammonia solution (ca. 25 % $NH_3$, 4 mL) was stirred at ambient temperature overnight. The formed precipitate was filtered off, washed with water (3×) and dried in a desiccator for 7 d to give **14** as colorless solid (40 mg, 0.14 mmol, 75 % yield). $R_f$ = 0.34 (dichloromethane/methanol = 9:1); melting point: 139 °C; specific rotation: $[\alpha]_D^{20}$ = +127.1 (2.9; $CH_3OH$); $^1H$ NMR: ($CD_3OD$): $\delta$ [ppm] = 3.64 (dd, $J$ = 11.9/3.5 Hz, 1H, OCHC*H*$_2$OH), 3.71 (dd, $J$ = 11.9/8.0 Hz, 1H, OCHC*H*$_2$OH), 3.81 (d, $J$ = 15.7 Hz, 1H, OC*H*$_2$CONH$_2$), 3.93 (d, $J$ = 15.7 Hz, 1H, OC*H*$_2$CONH$_2$), 4.51 (dd, $J$ = 8.0/3.5 Hz, 1H, OC*H*CH$_2$OH), 7.33-7.41 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.48-7.56 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$); $^{13}C$ NMR: ($CD_3OD$): $\delta$ [ppm] = 67.4 (1C, OCH*C*H$_2$OH), 69.0 (1C, O*C*H$_2$CONH$_2$), 85.3 (1C, O*C*HCH$_2$OH), 89.7 (1C, *C*≡C), 90.5 (1C, *C*≡C), 124.5 (1C, $C_{arom.}$), 124.6 (1C, $C_{arom.}$), 128.2 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.5 (1C, C-4''$_{phenyl}$), 129.6 (2C, C-3''$_{phenyl}$, C-5''$_{phenyl}$), 132.5 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.8 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 139.7 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 175.6 (1C, *C*ONH$_2$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3348, 3194, 2978, 2913, 1686, 1655, 1597, 1504, 1412, 1331, 1238, 1107, 1076, 1049, 833, 756, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{18}NO_3$: 296.1281, found: 296.1289; HPLC (method 2): $t_R$ = 16.2 min, purity 97.2 %.

### 4.2.6. (*S*)-2-{2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}acetohydrazide (15)

After heating a solution of hydrazine monohydrate (98%, 0.20 mL, 210 mg, 4.1 mmol) in ethanol (6 mL) to reflux for 5 min, a solution of **12** (170 mg, 0.54 mmol) in ethanol (6 mL) was added and the mixture was heated to reflux for 75 min and then stirred at ambient temperature overnight. After removing the solvent *in vacuo*, the residue was purified by flash column chromatography (1. Ø = 2 cm, h = 15 cm, ethyl acetate/methanol = 100:0 → 10:1, V = 10 mL; 2. Ø = 2 cm, h = 15 cm, dichloromethane/ methanol = 98:2 → 95:5, V = 10 mL) to give **15** as colorless solid (61 mg, 0.20 mmol, 37 % yield). $R_f$ = 0.23 (ethyl acetate/methanol = 10:1); melting point: 104 °C; specific rotation: $[\alpha]_D^{20}$ = +106.5 (3.0; $CH_3OH$); $^1H$ NMR (DMSO-$d_6$): $\delta$ [ppm] = 3.41-3.64 (m, 2H, OCHC$H_2$OH), 3.78 (d, $J$ = 14.8 Hz, 1H, OC$H_2$CONH), 3.85 (d, $J$ = 14.8 Hz, 1H, OC$H_2$CONH), 4.20-4.55 (m, 2H, CONHN$H_2$), 4.45 (dd, $J$ = 7.3/3.4 Hz, 1H, OC*H*$CH_2$OH), 5.21-5.34 (m, 1H, OCH$CH_2$O*H*), 7.32-7.49 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.49-7.63 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$), 9.19 (s, 1H, CON*H*$NH_2$); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ [ppm] = 65.5 (1C, OCH*C*$H_2$OH), 67.7 (1C, O*C*$H_2$CONH), 83.2 (1C, O*C*H$CH_2$OH), 89.2 (1C, *C*≡C), 89.3 (1C, *C*≡C), 121.7 (1C, C-$4'_{4\text{-(phenylethynyl)phenyl}}$), 122.2 (1C, C-$1"_{phenyl}$), 127.3 (2C, C-$2'_{4\text{-(phenylethynyl)phenyl}}$, C-$6'_{4\text{-(phenylethynyl)phenyl}}$), 128.76 (2C, C-$3"_{phenyl}$, C-$5"_{phenyl}$), 128.80 (1C, C-$4"_{phenyl}$), 131.3 (2C, $C_{arom.}$), 131.4 (2C, $C_{arom.}$), 139.5 (1C, C-$1'_{4\text{-(phenylethynyl)phenyl}}$), 168.0 (1C, *C*ONHN$H_2$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3294, 2909, 1651, 1632, 1535, 1508, 1443, 1335, 1119, 1049, 833, 756, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_3$: 311.1390, found: 311.1384; HPLC (method 1): $t_R$ = 17.4 min, purity 95.7 %.

### 4.2.7. (*S*)-*N*-(2-Aminophenyl)-2-{2-hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}acetamide (16)

Under $N_2$ atmosphere, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) hydrochloride (65 mg, 0.34 mmol), *N*-hydroxysuccinimide (39 mg, 0.34 mmol) and 1,2-phenylenediamine (37 mg, 0.34 mmol) were added to a solution of **13** (100 mg, 0.34 mmol) in dry dichloromethane (15 mL). The reaction mixture was stirred under $N_2$ atmosphere (balloon) at ambient temperature for 16 h. Then 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 (Ø = 2 cm, h = 20 cm, dichloromethane/methanol = 100:0 → 9:1, V = 20 mL) to give **16** as yellowish solid (38 mg, 0.10 mmol, 29 % yield). $R_f$ = 0.23 (cyclohexane/ethyl acetate = 1:2); melting point: 134 °C; specific rotation: $[\alpha]_D^{20}$ = +115.2 (2.5; $CH_2Cl_2$); $^1H$ NMR ($CD_3OD$): $\delta$ [ppm] = 3.70 (dd, $J$ = 11.9/3.2 Hz, 1H, OCHC$H_2$OH), 3.76 (dd, $J$ = 11.9/8.5 Hz, 1H, OCHC$H_2$OH), 4.00 (d, $J$ = 15.8 Hz, 1H, OC$H_2$CONH), 4.17 (d, $J$ = 15.8 Hz, 1H, OC$H_2$CONH), 4.65 (dd, $J$ = 8.5/3.2 Hz, 1H, OC$H$C$H_2$OH), 6.74 (td, $J$ = 7.6/1.4 Hz, 1H, 5'''-$H_{2\text{-aminophenyl}}$), 6.88 (dd, $J$ = 8.0/1.4 Hz, 1H, 3'''-$H_{2\text{-aminophenyl}}$), 7.05 (ddd, $J$ = 8.0/7.4/1.5 Hz, 1H, 4'''-$H_{2\text{-aminophenyl}}$), 7.24 (dd, $J$ = 7.8/1.5 Hz, 1H, 6'''-$H_{2\text{-aminophenyl}}$), 7.34-7.40 (m, 3H, 3''-$H_{\text{phenyl}}$, 5''-$H_{\text{phenyl}}$, 4''-$H_{\text{phenyl}}$), 7.42-7.46 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.49-7.54 (m, 2H, 2''-$H_{\text{phenyl}}$, 6''-$H_{\text{phenyl}}$), 7.54-7.58 (m, 2H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$); $^{13}C$ NMR ($CD_3OD$): $\delta$ [ppm] = 67.3 (1C, OCH$C$H$_2$OH), 69.6 (1C, O$C$H$_2$CONH), 85.7 (1C, O$C$HCH$_2$OH), 89.7 (1C, $C$≡C), 90.6 (1C, $C$≡C), 118.5 (1C, 3'''-$C_{2\text{-aminophenyl}}$), 119.5 (1C, 5'''-$C_{2\text{-aminophenyl}}$), 124.2 (1C, 1'''-$C_{2\text{-aminophenyl}}$), 124.5 (1C, C-1''$_{\text{phenyl}}$), 124.7 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 127.1 (1C, 6'''-$C_{2\text{-aminophenyl}}$), 128.3 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.5 (1C, 4'''-$C_{2\text{-aminophenyl}}$), 129.5 (1C, C-4''$_{\text{phenyl}}$), 129.6 (2C, C-3''$_{\text{phenyl}}$, C-5''$_{\text{phenyl}}$), 132.5 (2C, C-2''$_{\text{phenyl}}$, C-6''$_{\text{phenyl}}$), 132.8 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 139.6 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 143.2 (2'''-$C_{2\text{-aminophenyl}}$), 171.4

(1C, *C*ONH); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3472, 3383, 3310, 2924, 2866, 1663, 1616, 1531, 1504, 1458, 1335, 1312, 1269, 1111, 1057, 833, 748, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3$: 387.1703, found: 387.1719; HPLC (method 2): $t_R$ = 17.4 min, purity 97.7 %.

#### 4.2.8. (*S*)-2-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethan-1-ol (17)

Under $N_2$ atmosphere, a 1.2 M solution of diisobutylaluminium hydride in toluene (14 mL, 17 mmol) was added to a solution of **10** (2.8 g, 7.6 mmol) in dry dichloromethane (100 mL). The mixture was stirred at ambient temperature. After 30 min the reaction was terminated by adding a saturated aqueous solution of Rochelle salt (50 mL). Then diethyl ether (100 mL) was added and the mixture was vigorously stirred until two clear layers appeared. The aqueous layer 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 (Ø = 6 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2 → 100% ethyl acetate, V = 50 mL) to give **17** as colorless oil (1.9 g, 5.9 mmol, 77 % yield). $R_f$ = 0.41 (cyclohexane/ethyl acetate = 1:1); specific rotation: $[\alpha]_D^{20}$ = +56.8 (3.1; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 3.34 (s, 3H, $OCH_2OCH_3$), 3.51 (ddd, $J$ = 10.7/6.0/3.8 Hz, 1H, $HOCH_2CH_2O$), 3.63 (ddd, $J$ = 10.7/5.4/3.3 Hz, 1H, $HOCH_2CH_2O$), 3.66 (dd, $J$ = 10.9/3.7 Hz, 1H, $OCHCH_2O$), 3.71-3.78 (m, 3H, $HOCH_2CH_2O$, $OCHCH_2O$ (1H)), 4.58 (dd, $J$ = 8.0/3.7 Hz, 1H, $OCHCH_2O$), 4.67 (s, 2H, $OCH_2OCH_3$), 7.31-7.37 (m, 5H, $H_{arom.}$), 7.51-7.55 (m, 4H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 55.5 (1C, $OCH_2OCH_3$), 62.0 (1C, $HOCH_2CH_2O$), 70.9 (1C, $HOCH_2CH_2O$), 72.1 (1C, $OCHCH_2O$), 81.8 (1C, $OCHCH_2O$), 89.1 (1C, *C*≡C), 89.8 (1C, *C*≡C), 96.9 (1C, $OCH_2OCH_3$), 123.2 (1C, $C_{arom.}$), 123.3 (1C,

$C_{arom.}$), 127.0 (2C, $C_{arom.}$), 128.47 (1C, $C_{arom.}$), 128.49 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 131.9 (2C, $C_{arom.}$), 139.3 (1C, $C_{arom.}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3429, 2927, 2882, 1597, 1508, 1443, 1408, 1343, 1211, 1150, 1107, 1030, 918, 833, 756, 691; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{23}O_4$: 327.1591, found: 327.1563; HPLC (method 1): $t_R$ = 21.4 min, purity 99.3 %.

### 4.2.9. (*S*)-2-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl methanesulfonate (18)

Under $N_2$ atmosphere, triethylamine (1.6 mL, 1.2 g, 12 mmol), DMAP (140 mg, 1.2 mmol) and methanesulfonyl chloride (0.9 mL, 1.3 g, 12 mmol) were added to a solution of **17** (1.9 g, 5.9 mmol) in dry dichloromethane (100 mL). The reaction was stirred for 2.5 h at ambient temperature. Then water and a saturated aqueous solution of sodium bicarbonate were added and the mixture was extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate, filtered, and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2→ 2:1, V = 50 mL) to give **18** as colorless solid (1.7 g, 4.1 mmol, 69 % yield). $R_f$ = 0.22 (cyclohexane/ethyl acetate = 2:1); melting point: 59 °C; specific rotation: $[\alpha]_D^{20}$ = +27.4 (2.4; $CH_2Cl_2$); $^1H$ NMR ($CD_2Cl_2$): $\delta$ [ppm] = 3.05 (s, 3H, $OSO_2CH_3$), 3.28 (s, 3H, $OCH_2OCH_3$), 3.63 (dd, $J$ = 10.9/4.1 Hz, 1H, $OCHCH_2O$), 3.65-3.71 (m, 2H, $OCH_2CH_2OS$) 3.74 (dd, $J$ = 10.9/7.4 Hz, 1H, $OCHCH_2O$), 4.32-4.37 (m, 2H, $OCH_2CH_2OS$), 4.56 (dd, $J$ = 7.4/4.1 Hz, 1H, $OCHCH_2O$), 4.60 (d, $J$ = 6.5 Hz, 1H, $OCH_2OCH_3$), 4.62 (d, $J$ = 6.5 Hz, 1H, $OCH_2OCH_3$), 7.32-7.40 (m, 5H, 2'-$H_{4-(phenylethynyl)phenyl}$, 6'-$H_{4-(phenylethynyl)phenyl}$, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.50-7.57 (m, 4H, 3'-$H_{4-(phenylethynyl)phenyl}$, 5'-$H_{4-(phenylethynyl)phenyl}$, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$); $^{13}C$ NMR ($CD_2Cl_2$):

$\delta$ [ppm] = 38.1 (1C, $OSO_2CH_3$), 55.6 (1C, $OCH_2OCH_3$), 67.7 (1C, $OCH_2CH_2OS$), 70.2 (1C, $OCH_2CH_2OS$), 72.0 (1C, $OCHCH_2O$), 82.3 (1C, OCHCH$_2$O), 89.5 (1C, *C*≡C), 90.1 (1C, *C*≡C), 97.2 (1C, $OCH_2OCH_3$), 123.6 (1C, $C_{arom.}$), 123.7 (1C, $C_{arom.}$), 127.7 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.98 (1C, C-4"$_{phenyl}$), 128.99 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 132.1 (2C, $C_{arom.}$), 132.2 (2C, $C_{arom.}$), 139.6 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2932, 1508, 1443, 1350, 1173, 1107, 1034, 1018, 968, 914, 833, 799, 756, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{25}O_6S$: 405.1366, found: 405.1365; HPLC (method 1): $t_R$ = 22.9 min, purity 99.7 %.

**4.2.10. (*S*)-*S*-{2-[2-(Methoxymethoxy)-1-(4-[phenylethynyl]phenyl)ethoxy]ethyl} ethanethioate (19)**

Triethylamine (40 µL, 26 mg, 0.26 mmol) was added to a solution of **18** (97 mg, 0.24 mmol) in DMF (10 mL). Then thioacetic acid (20 µL, 19 mg, 0.25 mmol) was added dropwise to the mixture. The reaction was stirred at ambient temperature for 16 h. After the addition of water, 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 (Ø = 2 cm, h = 15 cm, cyclohexane/ ethyl acetate = 10:1 → 8:2, V = 10 mL) to give **19** as reddish oil (61 mg, 0.16 mmol, 67 % yield). $R_f$ = 0.38 (cyclohexane/ethyl acetate = 8:2); specific rotation: $[\alpha]_D^{20}$ = +81.7 (2.6; $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$): $\delta$ [ppm] = 2.31 (s, 3H, $SCOCH_3$), 3.01-3.14 (m, 2H, $OCH_2CH_2S$), 3.27 (s, 3H, $OCH_2OCH_3$), 3.44-3.57 (m, 2H, $OCH_2CH_2S$), 3.60 (dd, *J* = 10.8/4.3 Hz, 1H, $OCHCH_2O$), 3.71 (dd, *J* = 10.8/7.2 Hz, 1H, $OCHCH_2O$), 4.51 (dd, *J* = 7.2/4.3 Hz, 1H, $OCHCH_2O$), 4.59 (d, *J* = 6.5 Hz, 1H, $OCH_2OCH_3$), 4.62 (d, *J* = 6.5 Hz, 1H, $OCH_2OCH_3$), 7.32-7.40 (m, 5H, 2'-H$_{4\text{-(phenylethynyl)phenyl}}$, 6'-H$_{4\text{-(phenylethynyl)phenyl}}$, 3"-H$_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.50-7.57 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); $^{13}$C NMR ($CD_2Cl_2$): $\delta$ [ppm] = 29.6 (1C, $OCH_2\mathit{C}H_2S$), 30.9 (1C, $SCO\mathit{C}H_3$), 55.6 (1C, $OCH_2O\mathit{C}H_3$), 68.5 (1C, $O\mathit{C}H_2CH_2S$), 71.9 (1C, $OCH\mathit{C}H_2O$), 81.9 (1C, $O\mathit{C}HCH_2O$), 89.6 (1C, *C*≡C), 89.9 (1C, *C*≡C), 97.2 (1C, $O\mathit{C}H_2OCH_3$), 123.3 (1C, $C_{arom.}$), 123.7 (1C, $C_{arom.}$), 127.7 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.9 (1C, C-4"$_{phenyl}$), 129.0 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 132.1 (4C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$, C-2"$_{phenyl}$, C-6"$_{phenyl}$), 140.3 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 195.7 (1C, $S\mathit{C}OCH_3$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2928, 1690, 1508, 1443, 1354, 1103, 1034, 953, 918, 837, 756, 691, 625; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{25}O_4S$: 385.1468, found: 385.1456; HPLC (method 1): $t_R$ = 24.7 min, purity 98.1 %.

#### 4.2.11. (*S*)-2-(2-Mercaptoethoxy)-2-[4-(phenylethynyl)phenyl]ethan-1-ol (20)

**19** (58 mg, 0.15 mmol) was dissolved in HCl-saturated methanol (7.5 mL). The reaction was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water 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 automatic flash column chromatography (100% $H_20$→ 100% ACN, Biotage® SNAP KP-C18-HS 12 g, V = 20 mL) to give **20** as colorless oil (25 mg, 0.08 mmol, 53 % yield). $R_f$ = 0.21 (cyclohexane/ethyl acetate = 3:1); specific rotation: $[\alpha]_D^{20}$ = +99.0 (1.7; $CH_3OH$); $^1$H NMR ($CD_3OD$): $\delta$ [ppm] = 2.64-2.72 (m, 2H, $OCH_2C\mathit{H_2}SH$), 3.53 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H_2}CH_2SH$), 3.59 (dd, *J* = 11.7/4.1 Hz, 1H, $OCHC\mathit{H_2}O$), 3.67 (dd, *J* = 11.7/7.5 Hz, 1H, $OCHC\mathit{H_2}O$), 4.44 (dd, *J* = 7.5/4.1 Hz, 1H, $OC\mathit{H}CH_2O$), 7.34-7.41 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.48–7.54 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); $^{13}$C NMR

($CD_3OD$): $\delta$ [ppm] =24.9 (1C, $OCH_2CH_2SH$), 67.6 (1C, $OCHCH_2OH$), 72.4 (1C, $OCH_2CH_2SH$), 84.4 (1C, $OCHCH_2OH$), 89.9 (1C, *C*≡C), 90.2 (1C, *C*≡C), 97.2 (1C, $OCH_2OCH_3$), 124.2 (1C, $C_{arom.}$), 124.6 (1C, $C_{arom.}$), 128.3 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.46 (1C, C-4"$_{phenyl}$), 129.54 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 132.5 (2C, $C_{arom.}$), 132.6 (2C, $C_{arom.}$), 141.2 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3402, 2866, 2558, 1682, 1504, 1443, 1393, 1339, 1177, 1096, 1034, 833, 752, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{19}O_2S$: 299.1100, found: 299.1131; HPLC (method 1): $t_R$ = 22.4 min, purity 95.8 %.

### 4.2.12. (*S*)-2-{2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl methanesulfonate (21)

**18** (190 mg, 0.46 mmol) was dissolved in HCl-saturated methanol (5 mL). The reaction was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water, 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 (Ø = 2 cm, h = 15 cm, cyclohexane/ethyl acetate = 3:1 → 1:2, V = 10 mL) to give **21** as colorless oil (150 mg, 0.40 mmol, 87 % yield). $R_f$ = 0.21 (cyclohexane/ethyl acetate = 1:1); specific rotation: $[\alpha]_D^{20}$ = +91.2 (5.5; $CH_2Cl_2$); $^1H$ NMR ($CD_2Cl_2$): $\delta$ [ppm] = 2.40-2.48 (m, 1H, $OCHCH_2OH$), 3.05 (s, 3H, $OSO_2CH_3$), 3.59-3.74 (m, 4H, $OCH_2CH_2OS$, $OCHCH_2OH$), 4.34-4.41 (m, 2H, $OCH_2CH_2OS$), 4.49 (dd, *J* = 8.2/3.6 Hz, 1H, $OCHCH_2O$), 7.32-7.35 (m, 2H, 2'-H$_{4\text{-(phenylethynyl)phenyl}}$, 6'-H$_{4\text{-(phenylethynyl)phenyl}}$), 7.35-7.39 (m, 3H, 3"-H$_{phenyl}$, 5"-H$_{phenyl}$, 4"-H$_{phenyl}$), 7.52-7.56 (m, 4H, 3'-H$_{4\text{-(phenylethynyl)phenyl}}$, 5'-H$_{4\text{-(phenylethynyl)phenyl}}$, 2"-H$_{phenyl}$, 6"-H$_{phenyl}$); $^{13}C$ NMR ($CD_2Cl_2$): $\delta$ [ppm] = 38.2 (1C, $OSO_2CH_3$), 67.56 (1C, $OCHCH_2O$), 67.63 (1C, $OCH_2CH_2OS$),

69.7 (1C, $OCH_2CH_2OS$), 84.2 (1C, OCHCH$_2$O), 89.4 (1C, *C*≡C), 90.1 (1C, *C*≡C), 123.6 (1C, C-1''$_{phenyl}$), 123.7 (1C, C-4'$_{4-(phenylethynyl)phenyl}$), 127.6 (2C, C-2'$_{4-(phenylethynyl)phenyl}$, C-6'$_{4-(phenylethynyl)phenyl}$), 129.0 (3C, C-3''$_{phenyl}$, C-5''$_{phenyl}$, C-4''$_{phenyl}$), 132.1 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.3 (2C, C-3'$_{4-(phenylethynyl)phenyl}$, C-5'$_{4-(phenylethynyl)phenyl}$), 139.0 (1C, C-1'$_{4-(phenylethynyl)phenyl}$); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3522, 2924, 1508, 1443, 1346, 1173, 1115, 1015, 972, 918, 833, 802, 756; LCMS (*m/z*): [M+H]$^+$ calcd for $C_{19}H_{21}O_5S$: 361.1104, found: 361.1126; HPLC (method 1): $t_R$ = 21.3 min, purity 99.7 %.

### 4.2.13. (*S*)-*S*-(2-{2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl) ethanethioate (22)

Triethylamine (90 µL, 65 mg, 0.64 mmol) and thioacetic acid (46 µL, 49 mg, 0.64 mmol) were added to a solution of **21** (120 mg, 0.32 mmol) in DMF (10 mL). The reaction 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 (Ø = 2 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2, V = 10 mL) to give **22** as reddish oil (78 mg, 0.23 mmol, 72 % yield). $R_f$ = 0.33 (cyclohexane/ethyl acetate = 3:1); specific rotation: $[\alpha]_D^{20}$ = +109.5 (9.0; $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$): *δ* [ppm] = 2.32 (s, 3H, SCOC*H*$_3$), 3.05-3.16 (m, 2H, OCH$_2$C*H*$_2$S), 3.46-3.66 (m, 4H, OC*H*$_2$CH$_2$S, OCHC*H*$_2$O), 4.44 (dd, *J* = 7.7/4.2 Hz, 1H, OC*H*CH$_2$O), 7.30-7.40 (m, 5H, H$_{arom.}$), 7.50–7.57 (m, 4H, H$_{arom.}$); $^{13}$C NMR ($CD_2Cl_2$): *δ* [ppm] = 29.7 (1C, OCH$_2$*C*H$_2$S), 31.0 (1C, SCO*C*H$_3$), 67.5 (1C, OCH*C*H$_2$O), 68.4 (1C, O*C*H$_2$CH$_2$S), 83.6 (1C, O*C*HCH$_2$O), 89.5 (1C, *C*≡C), 90.0 (1C, *C*≡C), 123.5 (1C, C$_{arom.}$), 123.7 (1C, C$_{arom.}$), 127.5 (2C, C$_{arom.}$), 128.96 (1C, C$_{arom.}$), 128.98 (2C, C$_{arom.}$), 132.1 (2C, C$_{arom.}$), 132.2 (2C, C$_{arom.}$), 139.5 (1C, C$_{arom.}$), 195.8 (1C, S*C*OCH$_3$); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3429, 2866, 1686, 1508, 1393, 1350, 1099, 1042, 953, 833, 756, 691, 625; LCMS (*m/z*): [M+H]$^+$ calcd for $C_{20}H_{21}O_3S$: 341.1206, found: 341.1218; HPLC (method 1): $t_R$ = 22.7 min, purity 97.2 %.

### 4.2.14. (*S*)-2-(2-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)isoindoline-1,3-dione (23)

Potassium phthalimide (840 mg, 4.5 mmol) was added to a solution of **18** (1.7 g, 4.1 mmol) in DMF (55 mL). The mixture was stirred at 80 °C for 3 h. After cooling the reaction mixture to ambient temperature, 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 evaporated *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2 → 2:1, V = 50 mL) to give **23** as colorless oil (1.6 g, 3.4 mmol, 84 % yield). $R_f$ = 0.26 (cyclohexane/ethyl acetate = 3:1); specific rotation: $[\alpha]_D^{20}$ = +7.6 (1.6; $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$): $\delta$ [ppm] = 3.18 (s, 3H, OCH$_2$OC*H*$_3$), 3.53 (dd, *J* = 10.8/4.3 Hz, 1H, OCHC*H*$_2$O), 3.62-3.70 (m, 3H, OCHC*H*$_2$O (1H), NCH$_2$C*H*$_2$O), 3.81 (dt, *J* = 14.1/5.4 Hz, 1H, NC*H*$_2$CH$_2$O), 3.90 (ddd, *J* = 14.1/7.0/5.2 Hz, 1H, NC*H*$_2$CH$_2$O), 4.45-4.49 (m, 2H, OC*H*CH$_2$O, OC*H*$_2$OCH$_3$ (1H)), 4.50 (d, *J* = 6.5 Hz, 1H, OC*H*$_2$OCH$_3$), 7.22-7.26 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.33–7.41 (m, 5H, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.50-7.55 (m, 2H, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$), 7.72-7.76 (m, 2H, 5'''-$H_{isoindoline}$, 6'''-$H_{isoindoline}$), 7.80-7.86 (m, 2H, 4'''-$H_{isoindoline}$, 7'''-$H_{isoindoline}$); $^{13}$C NMR ($CD_2Cl_2$): $\delta$ [ppm] = 38.3 (1C, N*C*H$_2$CH$_2$O), 55.4 (1C, OCH$_2$O*C*H$_3$), 66.5 (1C, NCH$_2$*C*H$_2$O), 71.7 (1C, OCH*C*H$_2$O), 81.9 (1C, O*C*HCH$_2$O), 89.6 (1C, *C*≡C), 89.9 (1C, *C*≡C), 97.1 (1C, O*C*H$_2$OCH$_3$), 123.3 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 123.6 (2C, C-4'''$_{isoindoline}$, C-7'''$_{isoindoline}$), 123.7 (1C, C-1''$_{phenyl}$), 127.6

(2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.9 (1C, C-4''$_{\text{phenyl}}$), 129.0 (2C, C-3''$_{\text{phenyl}}$, C-5''$_{\text{phenyl}}$), 132.0 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 132.1 (2C, C-2''$_{\text{phenyl}}$, C-6''$_{\text{phenyl}}$), 132.7 (2C, C-3a'''$_{\text{isoindoline}}$, C-7a'''$_{\text{isoindoline}}$), 134.5 (2C, C-5'$_{\text{isoindoline}}$, C-6'$_{\text{isoindoline}}$), 140.2 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 168.6 (2C, C-1'''$_{\text{isoindoline}}$, C-3'''$_{\text{isoindoline}}$); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 2882, 1775, 1709, 1393, 1107, 1030, 918, 837, 756, 718, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}NO_5$: 456.1805, found: 456.1784; HPLC (method 1): $t_R$ = 24.8 min, purity 98.8 %.

### 4.2.15. (*S*)-2-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethan-1-amine (24)

An aqueous solution of methylamine (40 % wt., 0.89 mL, 10 mmol) was added to a solution of **23** (1.6 g, 3.4 mmol) in absolute ethanol (60 mL). The mixture was heated to 70 °C for 16 h. Then water (60 mL) was added, the mixture was acidified (pH < 2) with a 1 N aqueous solution of sulfuric acid and extracted with ethyl acetate. Afterwards, the water layer was basified (pH > 10) with a 0.5 M aqueous solution of sodium hydroxide and 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 (Ø = 4 cm, h = 15 cm, dichloromethane/methanol = 20:1 → 5:1, V = 30 mL) to give **24** as yellowish solid (910 mg, 2.8 mmol, 82 % yield).$R_f$ (RP-TLC) = 0.33 (acetonitrile/water = 2:1); melting point: 97 °C; specific rotation: $[\alpha]_D^{20}$ = +62.1 (3.3; $CH_2Cl_2$); $^1$H NMR ($CD_3OD$): *δ* [ppm] = 3.06-3.14 (m, 1H, $H_2NCH_2CH_2O$), 3.14-3.21 (m, 1H, $H_2NC\mathit{H}_2CH_2O$), 3.30 (s, 3H, $OCH_2OC\mathit{H}_3$), 3.59-3.66 (m, 2H, $H_2NCH_2C\mathit{H}_2O$), 3.68 (dd, *J* = 10.8/4.2 Hz, 1H, $OCHC\mathit{H}_2O$), 3.79 (dd, *J* = 10.8/7.4 Hz, 1H, $OCHC\mathit{H}_2O$), 4.63 (dd, *J* = 7.4/4.2 Hz , 1H, $OC\mathit{H}CH_2O$), 4.65 (s, 2H, $OC\mathit{H}_2OCH_3$), 7.34-7.45 (m, 5H, 2'-H$_{4\text{-(phenylethynyl)phenyl}}$, 6'-H$_{4\text{-}}$

$_{(phenylethynyl)phenyl}$, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.48-7.57 (m, 4H, C-3'$_{4-(phenylethynyl)phenyl}$, C-5'$_{4-(phenylethynyl)phenyl}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); $^{13}$C NMR ($CD_3OD$): $\delta$ [ppm] = 40.8 (1C, $H_2NCH_2CH_2O$), 55.7 (1C, $OCH_2OCH_3$), 66.4 (1C, $H_2NCH_2CH_2O$), 72.6 (1C, $OCHCH_2O$), 82.8 (1C, $OCHCH_2O$), 89.7 (1C, *C*≡C), 90.6 (1C, *C*≡C), 97.8 (1C, $OCH_2OCH_3$), 124.4 (1C, C-1"$_{phenyl}$), 124.6 (1C, C-4'$_{4-(phenylethynyl)phenyl}$), 128.4 (2C, C-2'$_{4-(phenylethynyl)phenyl}$, C-6'$_{4-(phenylethynyl)phenyl}$), 129.6 (3C, C-3"$_{phenyl}$, C-5"$_{phenyl}$, C-4"$_{phenyl}$), 132.5 (2C, C-2"$_{phenyl}$, C-6"$_{phenyl}$), 132.8 (2C, C-3'$_{4-(phenylethynyl)phenyl}$, C-5'$_{4-(phenylethynyl)phenyl}$), 140.1 (1C, C-1'$_{4-(phenylethynyl)phenyl}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2874, 1597, 1508, 1485, 1150, 1099, 1022, 914, 829, 752, 687; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{24}NO_3$: 326.1751, found: 326.1779; HPLC (method 2): $t_R$ = 13.7 min, purity 97.6 %.

#### 4.2.16. (*S*)-2-(2-Aminoethoxy)-2-[4-(phenylethynyl)phenyl]ethan-1-ol (25)

**24** (560 mg, 1.7 mmol) was dissolved in a mixture of HCl-saturated ethanol (6 mL) and pure ethanol (9 mL). The reaction mixture was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water, 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 (Ø = 3 cm, h = 9 cm, dichloromethane/methanol/triethylamine = 9:1:0 → 5:1:0.05, V = 5 mL) to give **25** as yellowish solid (200 mg, 0.70 mmol, 41 % yield). $R_f$ (RP-TLC) = 0.20 (acetonitrile/water = 1:1); melting point: 72 °C; specific rotation: : $[\alpha]_D^{20}$ = +66.9 (1.5; $CH_3OH$); $^1$H NMR: ($CD_3OD$): $\delta$ [ppm] = 2.80 (ddd, *J* = 13.2/6.9/4.0 Hz, 1H, $H_2NCH_2CH_2O$), 2.85 (ddd, *J* = 13.2/6.0/3.9 Hz, 1H, $H_2NCH_2CH_2O$), 3.41 (ddd, *J* = 9.8/6.9/3.9 Hz, 1H, $H_2NCH_2CH_2O$), 3.48 (ddd, *J* = 9.8/6.0/4.0 Hz, 1H, $H_2NCH_2CH_2O$), 3.59 (dd, *J* = 11.8/3.7 Hz, 1H, $OCHCH_2OH$), 3.67 (dd, *J* = 11.8/7.9 Hz, 1H, OCHC$H_2$OH), 4.42 (dd, $J$ = 7.9/3.7 Hz , 1H, OC$H$C$H_2$OH), 7.33 − 7.39 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.48 − 7.54 (m, 4H, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$); $^{13}C$ NMR ($CD_3OD$): $\delta$ [ppm] = 42.3 (1C, $H_2NCH_2CH_2O$), 67.7 (1C, OCHC$H_2$OH), 71.4 (1C, $H_2NCH_2CH_2O$), 84.6 (1C, OCHC$H_2$OH), 89.9 (1C, C≡C), 90.3 (1C, C≡C), 124.2 (1C, $C_{arom.}$), 124.5 (1C, $C_{arom.}$), 128.2 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.5 (1C, C-4''$_{phenyl}$), 129.6 (2C, C-3''$_{phenyl}$, C-5''$_{phenyl}$), 132.5 (2C, $C_{arom.}$), 132.6 (2C, $C_{arom.}$), 141.1 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3453, 3352, 3287, 3040, 2913, 2851, 1605, 1504, 1443, 1335, 1192, 1177, 1099, 1049, 1015, 964, 910, 887, 860, 829, 752, 687; LC-MS ($m/z$): $[M+H]^+$ calcd for $C_{18}H_{20}NO_2$: 282.1489, found: 282.1514; HPLC (method 1): $t_R$ = 17.2 min, purity 97.4 %.

#### 4.2.17. (*S*)-*N*-(2-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)-1*H*-pyrrole-2-carboxamide (26)

Under $N_2$ atmosphere, triethylamine (0.13 mL, 93 mg, 0.92 mmol) and EDCI·HCl (88 mg, 0.46 mmol) were added to a suspension of pyrrole-2-carboxylic acid (26 mg, 0.23 mmol) and HOBt (47 mg, 0.35 mmol) in dry dichloromethane (2 mL). After stirring the reaction mixture for 1 h at ambient temperature, a solution of **24** (150 mg, 0.46 mmol) in dry dichloromethane (1 mL) was added at 0 °C (ice bath). Afterwards, the ice bath was removed and the mixture was stirred at ambient temperature overnight. Then a saturated aqueous solution of ammonium chloride and water were 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 (Ø = 2 cm, h = 17 cm, cyclohexane/ethyl acetate= 1:2, V = 10 mL) to give **26** as colorless oil

(85 mg, 0.20 mmol, 87 % yield). $R_f$ = 0.28 (cyclohexane/ethyl acetate = 1:2); specific rotation: $[\alpha]_D^{20}$ = +35.3 (2.6; $CH_2Cl_2$); $^1$H NMR ($CDCl_3$): $\delta$ [ppm] = 3.33 (s, 3H, $OCH_2OCH_3$), 3.50-3.61 (m, 2H, $HNCH_2CH_2O$ (1H), $HNCH_2CH_2O$ (1H)), 3.62-3.72 (m, 3H, $HNCH_2CH_2O$ (1H), $HNCH_2CH_2O$ (1H), $OCHCH_2O$ (1H)), 3.75 (dd, $J$ = 10.9/8.0 Hz, 1H, $OCHCH_2O$), 4.55 (dd, $J$ = 8.0/3.6 Hz, 1H, $OCHCH_2O$), 4.68 (d, $J$ = 6.9 Hz 1H, $OCH_2OCH_3$), 4.70 (d, $J$ = 6.9 Hz 1H, $OCH_2OCH_3$), 6.23-6.27 (m, 1H, 4'-$H_{pyrrole}$), 6.53-6.66 (m, 2H, 3'-$H_{pyrrole}$, CON*H*), 6.91-6.94 (m, 1H, 5'-$H_{pyrrole}$), 7.29-7.39 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.48-7.56 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$), 9.53 (s br, 1H, 1'-$H_{pyrrole}$); $^{13}$C NMR ($CDCl_3$): $\delta$ [ppm] = 39.3 (1C, $HNCH_2CH_2O$), 55.5 (1C, $OCH_2OCH_3$), 68.4 (1C, $HNCH_2CH_2O$), 72.0 (1C, $OCHCH_2O$), 81.8 (1C, $OCHCH_2O$), 89.1 (1C, *C*≡C), 89.9 (1C, *C*≡C), 96.9 (1C, $OCH_2OCH_3$), 109.1 (1C, 3'-$C_{pyrrole}$), 110.0 (1C, 4'-$C_{pyrrole}$), 121.5 (1C, 5'-$C_{pyrrole}$), 123.3 (1C, $C_{arom.}$), 123.4 (1C, $C_{arom.}$), 126.1 (1C, 2'-$C_{pyrrole}$), 126.9 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.49 (1C, C-4"$_{phenyl}$), 128.50 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 131.8 (2C, C-2"$_{phenyl}$, C-6"$_{phenyl}$), 132.0 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 139.0 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 161.2 (1C, *C*ONH); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3248, 2928, 1632, 1732, 1558, 1512, 1408, 1312, 1107, 1034, 833, 752, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_4$: 419.1965, found: 419.2006; HPLC (method 1): $t_R$ = 22.4 min, purity 99.3 %.

### 4.2.18. (*S*)-*N*-(2-{2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)-1*H*-pyrrole-2-carboxamide (27)

*p*-Toluenesulfonic acid monohydrate (16 mg, 0.09 mmol) was added to a solution of **26** (71 mg, 0.17 mmol) in methanol (2 mL) and the mixture was stirred at ambient temperature overnight. Then HCl-saturated methanol (0.5 mL) was added and the reaction mixture was stirred until TLC control indicated completion of the reaction. Then a saturated aqueous solution of sodium bicarbonate and water 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 (Ø =2 cm, h = 15 cm, ethyl acetate = 100%, V = 10 mL) to give **27** as colorless solid (52 mg, 0.14 mmol, 82 % yield). $R_f$ = 0.25 (ethyl acetate); melting point: 124 °C; specific rotation: $[\alpha]_D^{20}$ = +48.9 (3.0; $CH_2Cl_2$); $^1$H NMR: ($CDCl_3$): *δ* [ppm] = 3.48-3.60 (m, 2H, HNC*H*$_2$CH$_2$O (1H), HNCH$_2$C*H*$_2$O (1H)), 3.60-3.78 (m, 4H, HNC*H*$_2$CH$_2$O (1H), HNCH$_2$C*H*$_2$O (1H), OCHC*H*$_2$OH), 4.48 (dd, *J* = 8.2/3.7 Hz, 1H, OC*H*CH$_2$OH), 6.21-6.27 (m, 1H, 4'''-$H_{pyrrole}$), 6.55-6.72 (m, 2H, CON*H*, 3'''-$H_{pyrrole}$), 6.90-6.96 (m, 1H, 5'''-$H_{pyrrole}$), 7.25-7.31 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.31-7.40 (m, 3H, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.46-7.57 (m, 4H, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$), 9.70 (s, 1H, 1'''-$H_{pyrrole}$); $^{13}$C NMR ($CDCl_3$): *δ* [ppm] = 39.5 (1C, HN*C*H$_2$CH$_2$O), 67.3 (1C, OCH*C*H$_2$OH), 68.6 (1C, HNCH$_2$*C*H$_2$O), 83.5 (1C, O*C*HCH$_2$OH), 89.0 (1C, *C*≡C), 90.0 (1C, *C*≡C), 109.7 (1C, 3'''-$C_{pyrrole}$), 110.1 (1C, 4'''-$C_{pyrrole}$), 121.9 (1C, 5'''-$C_{pyrrole}$), 123.3 (1C, C-1''$_{phenyl}$), 123.5 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 125.8 (1C, 2'''-$C_{pyrrole}$), 126.9 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.5 (3C, C-3''$_{phenyl}$, C-5''$_{phenyl}$, C-4''$_{phenyl}$), 131.8 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.0 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 138.6 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 161.6 (1C, *C*ONH); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3657, 3291, 2978, 2886, 1620, 1562, 1516, 1393, 1319, 1250, 1099, 1069, 953, 833, 752, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{23}N_2O_3$: 375.1703, found: 375.1697; HPLC (method 2): $t_R$ = 17.2 min, purity 99.5 %.

**4.2.19. (*S*)-*N*-(2-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)methanesulfonamide (28)**

Under $N_2$ atmosphere, triethylamine (40 µL, 28 mg, 0.28 mmol) and methanesulfonyl chloride (20 µL, 32 mg, 0.28 mmol) were added to a solution of **24** (45 mg, 0.14 mmol) in dry dichloromethane (3 mL). After stirring the reaction mixture at ambient temperature for 16 h, 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 (Ø = 1 cm, h = 20 cm, dichloromethane/methanol = 98:2, V = 2.5 mL) to give **28** as colorless oil (44 mg, 0.11 mmol, 79 % yield). $R_f$ = 0.24 (dichloromethane/methanol = 99:1); specific rotation: $[\alpha]_D^{20}$ = +40.0 (4.5; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): *δ* [ppm] = 2.97 (s, 3H, $SO_2CH_3$), 3.26-3.39 (m, 2H, $HNCH_2CH_2O$), 3.35 (s, 3H, $OCH_2OCH_3$), 3.52 (ddd, *J* = 10.2/7.1/3.5 Hz, 1H, $HNCH_2CH_2O$), 3.62-3.68 (m, 2H, $HNCH_2CH_2O$ (1H), $OCHCH_2O$ (1H)), 3.72 (dd, *J* = 11.0/8.0 Hz, 1H, $OCHCH_2O$), 4.53 (dd, *J* = 8.0/3.6 Hz, 1H, $OCHCH_2O$), 4.67 (s, 2H, $OCH_2OCH_3$), 7.28-7.33 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.33-7.38 (m, 3H, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.50-7.56 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); $^{13}C$ NMR ($CDCl_3$): *δ* [ppm] = 40.5 (1C, $SO_2CH_3$), 43.3 (1C, $HNCH_2CH_2O$), 55.6 (1C, $OCH_2OCH_3$), 68.3 (1C, $HNCH_2CH_2O$), 72.1 (1C, $OCHCH_2O$), 82.0 (1C, $OCHCH_2O$), 89.0 (1C, *C*≡C), 90.0 (1C, *C*≡C), 96.9 (1C, $OCH_2OCH_3$), 123.2 (1C, C-1"$_{phenyl}$), 123.5 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 126.9 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.51 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 128.53 (1C, C-4"$_{phenyl}$), 131.8 (2C, C-2"$_{phenyl}$, C-6"$_{phenyl}$), 132.0 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 138.6 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3283, 2978, 2882, 1508, 1439, 1404, 1315, 1150, 1107, 1072, 1030, 976, 837, 756, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{26}NO_5S$: 404.1526, found: 404.1524; HPLC (method 1): $t_R$ = 21.7 min, purity 99.2 %.

### 4.2.19. (*S*)-*N*-(2-{2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)methanesulfonamide (29)

**28** (52 mg, 0.13 mmol) was dissolved in HCl-saturated methanol (5 mL). The reaction was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water, 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 (Ø = 1 cm, h = 15 cm, cyclohexane/ethyl acetate = 2:1 → 0:1, V = 5 mL) to give **29** as colorless oil (39 mg, 0.11 mmol, 85 % yield). $R_f$ = 0.35 (dichloromethane/methanol = 20:1); specific rotation: $[\alpha]_D^{20}$ = +51.8 (7.0; $CH_2Cl_2$); $^1H$ NMR ($CD_3OD$): *δ* [ppm] = 2.97 (s, 3H, $SO_2CH_3$), 3.23-3.32 (m, 2H, $HNCH_2CH_2O$), 3.47 (ddd, *J* = 10.0/6.7/4.2 Hz, 1H, $HNCH_2CH_2O$), 3.53 (ddd, *J* = 10.0/5.9/4.4 Hz, 1H, $HNCH_2CH_2O$), 3.60 (dd, *J* = 11.8/3.8 Hz, 1H, $OCHCH_2O$), 3.67 (dd, *J* = 11.8/7.9 Hz, 1H, $OCHCH_2O$), 4.45 (dd, *J* = 7.9/3.8 Hz, 1H, $OCHCH_2O$), 7.33-7.40 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.48-7.54 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); $^{13}C$ NMR ($CD_3OD$): *δ* [ppm] = 40.2 (1C, $SO_2CH_3$), 44.2 (1C, $HNCH_2CH_2O$), 67.6 (1C, $OCHCH_2O$), 69.5 (1C, $HNCH_2CH_2O$), 84.7 (1C, $OCHCH_2O$), 89.9 (1C, *C*≡C), 90.3 (1C, *C*≡C), 124.3 (1C, $C_{arom.}$), 124.5 (1C, $C_{arom.}$), 128.3 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.5 (1C, C-4"$_{phenyl}$), 129.6 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 132.5 (2C, $C_{arom.}$), 132.7 (2C, $C_{arom.}$), 140.7 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3480, 3287, 2928, 2870, 1732, 1508, 1439, 1408, 1312, 1150, 1103, 1065, 980, 833, 756, 691; LCMS (*m/z*):

$[M+H]^+$ calcd for $C_{19}H_{22}NO_4S$: 360.1264, found: 360.1268; HPLC (method 1): $t_R$ = 19.9 min, purity 99.4 %.

### 4.2.21. (*S*)-1,1,1-Trifluoro-*N*-(2-{2-(methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)methanesulfonamide (30)

Under $N_2$ atmosphere, triethylamine (60 µL, 44 mg, 0.43 mmol) and trifluoromethanesulfonyl chloride (46 µL, 73 mg, 0.43 mmol) were added to a solution of **24** (70 mg, 0.22 mmol) in dry dichloromethane (7 mL). After stirring the reaction mixture at ambient temperature for 16 h, the solvent was removed *in vacuo*. 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 (Ø = 1 cm, h = 20 cm, dichloromethane/ methanol = 98:2, V = 2.5 mL) to give **30** as colorless oil (44 mg, 0.10 mmol, 45 % yield). $R_f$ = 0.30 (cyclohexane/ethyl acetate = 3:1); specific rotation: $[\alpha]_D^{20}$ = +53.8 (3.5; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): *δ* [ppm] = 3.41 (s, 3H, $OCH_2OCH_3$), 3.44-3.54 (m, 3H, $HNCH_2CH_2O$, $HNCH_2CH_2O$ (1H)), 3.65-3.81 (m, 3H, $OCHCH_2O$, $HNCH_2CH_2O$ (1H)), 4.55 (dd, *J* = 7.8/4.0 Hz, 1H, $OCHCH_2O$), 4.70 (d, *J* = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.73 (d, *J* = 6.6 Hz, 1H, $OCH_2OCH_3$), 6.90 (s br, 1H, $SO_2NH$), 7.27-7.32 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.32-7.39 (m, 3H, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.50-7.57 (m, 4H, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$); $^{13}C$ NMR ($CDCl_3$): *δ* [ppm] = 44.4 (1C, $HNCH_2CH_2O$), 55.8 (1C, $OCH_2OCH_3$), 68.6 (1C, $HNCH_2CH_2O$), 73.0 (1C, $OCHCH_2O$), 82.8 (1C, $OCHCH_2O$), 88.9 (1C, *C*≡C), 90.1 (1C, *C*≡C), 97.3 (1C, $OCH_2OCH_3$), 120.0 (q, *J* = 321 Hz, 1C, $CF_3$), 123.2 (1C, C-1''$_{phenyl}$), 123.7 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 126.7 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.5 (2C, C-3''$_{phenyl}$, C-5''$_{phenyl}$), 128.6

(1C, C-4''$_{phenyl}$), 131.8 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.1 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 138.1 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3144, 2978, 2886, 1508, 1443, 1373, 1231, 1188, 1150, 1107, 1030, 968, 833, 756, 691; LCMS (*m/z*): $[M+NH_4]^+$ calcd for $C_{21}H_{26}F_3N_2O_5S$: 475.1509, found: 475.1513; HPLC (method 1): $t_R$ = 25.0 min, purity 94.7 %.

### 4.2.22. (*S*)-1,1,1-Trifluoro-*N*-(2-{2-hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)methanesulfonamide (31)

**30** (58 mg, 0.13mmol) was dissolved in a mixture of HCl-saturated methanol (0.5 mL) and pure methanol (1.5 mL). The reaction mixture was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water, 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 (Ø = 1 cm, h = 21 cm, cyclohexane/ethyl acetate = 2:1, V = 5 mL) to give **31** as colorless oil (33 mg, 0.08 mmol, 63 % yield). $R_f$ = 0.22 (cyclohexane/ethyl acetate = 2:1); specific rotation: $[\alpha]_D^{20}$ = +44.0 (1.4; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 3.40-3.57 (m, 3H, $HNCH_2CH_2O$, $HNCH_2CH_2O$ (1H)), 3.59-3.68 (m, 1H, $HNCH_2CH_2O$), 3.72 (dd, *J* = 11.8/4.0 Hz, 1H, $OCHCH_2OH$), 3.77 (dd, *J* = 11.8/7.8 Hz, 1H, $OCHCH_2OH$), 4.51 (dd, *J* = 7.8/4.0 Hz, 1H, $OCHCH_2OH$), 6.86-6.97 (m, 1H, $SO_2NH$), 7.26-7.31 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.32-7.39 (m, 3H, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.50-7.58 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 44.4 (1C, $HNCH_2CH_2O$), 67.3 (1C, $OCHCH_2OH$), 68.1 (1C, $HNCH_2CH_2O$), 83.4 (1C, $OCHCH_2OH$), 88.9 (1C, *C*≡C), 90.2 (1C, *C*≡C), 119.9 (q, *J* = 321 Hz, 1C, $CF_3$), 123.2 (1C, C-1''$_{phenyl}$), 123.9 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 126.9 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.5 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 128.6 (1C, C-4"$_{phenyl}$), 131.8 (2C, C-2"$_{phenyl}$, C-6"$_{phenyl}$), 132.2 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 137.6 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3661, 3314, 2978, 2886, 1508, 1443, 1373, 1227, 1184, 1150, 1111, 1065, 976, 833, 756, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{19}F_3NO_4S$: 414.0981, found: 414.0975; HPLC (method 2): $t_R$ = 18.3 min, purity 99.7 %.

### 4.2.23. (*S*)-*N*-(2-{2-[Methoxymethoxy]-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)-4-methylbenzenesulfonamide (32)

Under $N_2$ atmosphere, triethylamine (40 µL, 26 mg, 0.26 mmol) and *p*-toluenesulfonyl chloride (50 mg, 0.26 mmol) were added to a solution of **24** (43 mg, 0.13 mmol) in dry dichloromethane (5 mL). After stirring the reaction mixture at ambient temperature for 16 h, 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 (Ø = 1 cm, h = 15 cm, dichloromethane/methanol = 100:0 → 98:2, V = 2.5 mL) to give **32** as colorless oil (53 mg, 0.11 mmol, 85 % yield). $R_f$ = 0.28 (dichloromethane/methanol = 98:2); specific rotation: $[\alpha]_D^{20}$ = +22.3 (1.7; $CH_2Cl_2$); $^1H$ NMR ($CD_2Cl_2$): $\delta$ [ppm] = 2.44 (s, 3H, $SO_2PhCH_3$), 3.02-3.11 (m, 1H, $HNCH_2CH_2O$), 3.11-3.20 (m, 1H, $HNCH_2CH_2O$), 3.31 (s, 3H, $OCH_2OCH_3$), 3.37 (ddd, *J* = 10.2/7.3/3.6 Hz, 1H, $HNCH_2CH_2O$), 3.49 (ddd, *J* = 10.2/5.9/3.8 Hz, 1H, $HNCH_2CH_2O$), 3.58 (dd, *J* = 10.9/3.9 Hz, 1H, $OCHCH_2O$), 3.65 (dd, *J* = 10.9/7.8 Hz, 1H, $OCHCH_2O$), 4.40 (dd, *J* = 7.8/3.9 Hz, 1H, $OCHCH_2O$), 4.63 (s, 2H, $OCH_2OCH_3$), 5.36 (t, *J* = 5.9 Hz, 1H, $SO_2NH$), 7.22-7.28 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.31-7.41 (m, 5H, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$, 3'''-$H_{4\text{-}}$

methylbenzenesulfonamide, 5'''-$H_{4\text{-methylbenzenesulfonamide}}$), 7.48-7.57 (m, 4H, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.68-7.74 (m, 2H, 2'''-$H_{4\text{-methylbenzenesulfonamide}}$, 6'''-$H_{4\text{-methylbenzenesulfonamide}}$); $^{13}$C NMR ($CD_2Cl_2$): $\delta$ [ppm] = 21.8 (1C $SO_2PhCH_3$), 43.8 (1C, HN*C*$H_2CH_2O$), 55.8 (1C, $OCH_2OCH_3$), 68.2 (1C, $HNCH_2CH_2O$), 72.4 (1C, OCH*C*$H_2$O), 82.2 (1C, O*C*H$CH_2$O), 89.4 (1C, *C*≡C), 90.1 (1C, *C*≡C), 97.3 (1C, O*C*$H_2OCH_3$), 123.6 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 123.7 (1C, C-1''$_{phenyl}$), 127.4 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 127.5 (2C, C-2'''$_{4\text{-methylbenzenesulfonamide}}$, C-6'''$_{4\text{-methylbenzenesulfonamide}}$), 128.99 (1C, C-4''$_{phenyl}$), 129.00 (2C, C-3''$_{phenyl}$, C-5''$_{phenyl}$), 130.3 (2C, C-3'''$_{4\text{-methylbenzenesulfonamide}}$, C-5'''$_{4\text{-methylbenzenesulfonamide}}$), 132.1 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.2 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 137.7 (1C, C-1'''$_{4\text{-methylbenzenesulfonamide}}$), 139.6 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 144.1 (1C, C-4'''$_{4\text{-methylbenzenesulfonamide}}$); IR (neat): $\tilde{v}$ [$cm^{-1}$] = 3256, 2928, 2878, 1597, 1508, 1443, 1404, 1327, 1153, 1092, 1030, 961, 814, 756, 691, 660; LCMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{30}NO_5S$: 480.1839, found: 480.1846; HPLC (method 1): $t_R$ = 24.4 min, purity 96.3 %.

### 4.2.24. (*S*)-*N*-(2-{2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)-4-methylbenzenesulfonamide (33)

**32** (42 mg, 0.09 mmol) was dissolved in HCl-saturated methanol (4 mL). The reaction was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water, 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 (Ø = 2 cm, h = 10.5 cm, cyclohexane/ethyl acetate = 2:1→ 1:1, V = 10 mL) to give **33** as colorless oil (34 mg, 0.08 mmol, 89 % yield). $R_f$ = 0.17

(cyclohexane/ethyl acetate = 2:1); specific rotation: $[\alpha]_D^{20}$ = +52.1 (1.5; $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$): $\delta$ [ppm] = 2.26-2.31 (m, 1H, $OCHCH_2O\textit{H}$), 2.44 (s, 3H, $SO_2PhC\textit{H}_3$), 3.07-3.13 (m, 1H, $HNC\textit{H}_2CH_2O$), 3.17 (dtd, *J* = 13.4/6.3/3.6 Hz, 1H, $HNC\textit{H}_2CH_2O$), 3.39 (ddd, *J* = 10.2/6.8/3.6 Hz, 1H, $HNCH_2C\textit{H}_2O$), 3.44 (ddd, *J* = 10.1/6.3/3.8 Hz, 1H, $HNCH_2C\textit{H}_2O$), 3.56-3.65 (m, 2H, $OCHC\textit{H}_2OH$), 4.35 (dd, *J* = 7.9/3.9 Hz, 1H, $OC\textit{H}CH_2OH$), 5.13 (t, *J* = 6.1 Hz, 1H, $SO_2N\textit{H}$), 7.21-7.25 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.32-7.35 (m, 2H, 3'''-$H_{4\text{-methylbenzenesulfonamide}}$, 5'''-$H_{4\text{-methylbenzenesulfonamide}}$), 7.35-7.40 (m, 3H, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.49-7.52 (m, 2H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.52-7.56 (m, 2H, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$), 7.70-7.73 (m, 2H, 2'''-$H_{4\text{-methylbenzenesulfonamide}}$, 6'''-$H_{4\text{-methylbenzenesulfonamide}}$); $^{13}$C NMR ($CD_2Cl_2$): $\delta$ [ppm] = 21.8 (1C $SO_2Ph\textit{C}H_3$), 43.8 (1C, $HN\textit{C}H_2CH_2O$), 67.5 (1C, $OCH\textit{C}H_2OH$), 68.2 (1C, $HNCH_2\textit{C}H_2O$), 83.8 (1C, $O\textit{C}HCH_2O$), 89.4 (1C, *C*≡C), 90.2 (1C, *C*≡C), 123.6 (1C, C-1''$_{phenyl}$), 123.7 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 127.47 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 127.53 (2C, C-2'''$_{4\text{-methylbenzenesulfonamide}}$, C-6'''$_{4\text{-methylbenzenesulfonamide}}$), 129.0 (3C, C-3''$_{phenyl}$, C-5''$_{phenyl}$, C-4''$_{phenyl}$), 130.3 (2C, C-3'''$_{4\text{-methylbenzenesulfonamide}}$, C-5'''$_{4\text{-methylbenzenesulfonamide}}$), 132.1 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.3 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 137.6 (1C, C-1'''$_{4\text{-methylbenzenesulfonamide}}$), 139.2 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 144.3 (1C, C-4'''$_{4\text{-methylbenzenesulfonamide}}$); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3487, 3287, 2924, 2870, 1597, 1504, 1443, 1400, 1323, 1157, 1092, 961, 814, 756, 691, 660; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{26}NO_4S$: 436.1577, found: 436.1572; HPLC (method 1): $t_R$ = 22.8 min, purity 98.3 %.

### 4.2.25. (*S*)-1-[1-(Allyloxy)-2-(methoxymethoxy)ethyl]-4-bromobenzene (35)

Under $N_2$ atmosphere, a 1 M solution of LiHMDS in THF (4.8 mL, 4.8 mmol) and tetrabutylammonium iodide (150 mg, 0.40 mmol) were added to a solution of **34** (1.0 g, 4.0 mmol) in THF (50 mL). Then allyl bromide (0.69 mL, 960 mg, 8.0 mmol) was added and the mixture was heated to reflux for 16 h. After cooling the mixture to ambient temperature, 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 (Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2, V = 30 mL) to give **35** as colorless oil (760 g, 2.5 mmol, 64 % yield). $R_f$ = 0.17 (cyclohexane/ethyl acetate = 20:1); specific rotation: $[\alpha]_D^{20}$ = +58.9 (2.0; $CH_2Cl_2$); $^1$H NMR ($CDCl_3$): *δ* [ppm] = 3.29 (s, 3H, $OCH_2OCH_3$), 3.60 (dd, *J* = 10.8/4.3 Hz, 1H, $OCHCH_2O$), 3.73 (dd, *J* = 10.8/7.3 Hz, 1H, $OCHCH_2O$), 3.87 (ddt, *J* = 12.8/6.0/1.3 Hz, 1H, $OCH_2CH{=}CH_2$), 3.98 (ddt, *J* = 12.8/5.2/1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 4.51 (dd, *J* = 7.3/4.3 Hz, 1H, $OCHCH_2O$), 4.61 (d, *J* = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.64 (d, *J* = 6.6 Hz, 1H, $OCH_2OCH_3$), 5.16 (dq, *J* = 10.4/1.4 Hz, 1H, $OCH_2CH{=}CH_2$), 5.24 (dq, *J* = 17.2/1.6 Hz, 1H, $OCH_2CH{=}CH_2$), 5.86-5.93 (m, 1H, $OCH_2CH{=}CH_2$), 7.21-7.25 (m, 2H, 2'-$H_{4\text{-bromophenyl}}$, 6'-$H_{4\text{-bromophenyl}}$), 7.46-7.50 (m, 2H, 3'-$H_{4\text{-bromophenyl}}$, 5'-$H_{4\text{-bromophenyl}}$); $^{13}$C NMR ($CDCl_3$): *δ* [ppm] = 55.4 (1C, $OCH_2OCH_3$), 70.1 (1C, $OCH_2CH{=}CH_2$), 71.6 (1C, $OCHCH_2O$), 79.9 (1C, $OCHCH_2O$), 96.8 (1C, $OCH_2OCH_3$), 117.3 (1C, $OCH_2CH{=}CH_2$), 122.0 (1C, C-4'$_{4\text{-bromophenyl}}$), 128.9 (2C, C-2'$_{4\text{-bromophenyl}}$, C-6'$_{4\text{-bromophenyl}}$), 131.7 (2C, C-3'$_{4\text{-bromophenyl}}$, C-5'$_{4\text{-bromophenyl}}$), 134.6 (1C, $OCH_2CH{=}CH_2$), 138.5 (1C, C-1'$_{4\text{-bromophenyl}}$); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 2928, 2882, 1593, 1485, 1404, 1339, 1211, 1150, 1107, 1069, 1038, 1011, 918, 822; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{18}{}^{79}BrO_3$: 301.0434, found: 301.0412; HPLC (method 1): $t_R$ = 20.2 min, purity 99.5 %.

### 4.2.26. (*S*)-1-[1-(Allyloxy)-2-(methoxymethoxy)ethyl]-4-(phenylethynyl)benzene (36)

Under $N_2$ atmosphere, copper(I) iodide (67 mg, 0.35 mmol), tetrakis(triphenylphosphine)palladium(0) (280 mg, 0.24 mmol) and phenylacetylene (0.36 mL, 340 mg, 3.3 mmol) were added to a solution of **35** (710 mg, 2.4 mmol) in triethylamine (15 mL). The mixture was heated to reflux and additional phenylacetylene (0.36 mL, 340 mg, 3.3 mmol) was added. After heating the reaction mixture to reflux for 16 h, the solvent was evaporated and the residue was purified twice by flash column chromatography (1. Ø = 6 cm, h = 15 cm, cyclohexane/ethyl acetate = 20:1, V = 30 mL, 2. Ø = 5 cm, h = 15 cm, cyclohexane/ethyl acetate = 100:0 → 20:1, V = 30 mL) to give **36** as yellowish oil (650 mg, 2.0 mmol, 86 % yield). $R_f$ = 0.16 (cyclohexane/ethyl acetate = 20:1); specific rotation: $[\alpha]_D^{20}$ = +52.8 (1.6; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 3.29 (s, 3H, $OCH_2OCH_3$), 3.64 (dd, $J$ = 10.8/4.2 Hz, 1H, $OCHCH_2O$), 3.76 (dd, $J$ = 10.8/7.3 Hz, 1H, $OCHCH_2O$), 3.89 (ddt, $J$ = 12.8/6.0/1.3 Hz, 1H, $OCH_2CH=CH_2$), 4.01 (ddt, $J$ = 12.8/5.1/1.5 Hz, 1H, $OCH_2CH=CH_2$), 4.57 (dd, $J$ = 7.3/4.2 Hz, 1H, $OCHCH_2O$), 4.63 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.66 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 5.17 (dq, $J$ = 10.4/1.5 Hz, 1H, $OCH_2CH=CH_2$), 5.26 (dq, $J$ = 17.2/1.7 Hz, 1H, $OCH_2CH=CH_2$), 5.87-5.97 (m, 1H, $OCH_2CH=CH_2$), 7.32-7.44 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$), 7.50-7.57 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 55.4 (1C, $OCH_2OCH_3$), 70.1 (1C, $OCH_2CH=CH_2$), 71.7 (1C, $OCHCH_2O$), 80.3 (1C, $OCHCH_2O$), 89.3 (1C, $C\equiv C$), 89.7 (1C, $C\equiv C$), 96.8 (1C, $OCH_2OCH_3$), 117.2 (1C, $OCH_2CH=CH_2$), 123.1 (1C, $C_{arom.}$), 123.4 (1C, $C_{arom.}$), 127.3 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.4 (1C, C-4"$_{phenyl}$), 128.5 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 131.76 (2C, $C_{arom.}$), 131.82 (2C, $C_{arom.}$), 134.8 (1C, $OCH_2CH=CH_2$), 139.7 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2924, 2882, 1597, 1508, 1485, 1439, 1339, 1211, 1150, 1111, 1038, 918, 833, 756, 691; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{23}O_3$: 323.1642, found: 323.1613; HPLC (method 1): $t_R$ = 25.2 min, purity 71.9 %.

### 4.2.27. (*S*)-2-(Allyloxy)-2-[4-(phenylethynyl)phenyl]ethan-1-ol (37)

**36** (620 mg, 1.9 mmol) was suspended in a mixture of HCl-saturated methanol (4 mL) and pure methanol (6 mL). The reaction mixture was stirred at ambient temperature for 16 h. After addition of a saturated aqueous solution of sodium bicarbonate and water, 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 (Ø = 3 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2, V = 20 mL) to give **37** as yellow oil (490 mg, 1.8 mmol, 91 % yield). $R_f$ = 0.25 (cyclohexane/ethyl acetate = 8:2); specific rotation: $[\alpha]_D^{20}$ = +102.7 (2.7; $CH_2Cl_2$); $^1$H NMR ($CDCl_3$): $\delta$ [ppm] = 3.64 (dd, *J* = 11.7/3.8 Hz, 1H, OCHC*H*$_2$OH), 3.70 (dd, *J* = 11.7/8.4 Hz, 1H, OCHC*H*$_2$OH), 3.85-3.90 (m, 1H, OC*H*$_2$CH=CH$_2$), 4.00-4.05 (m, 1H, OC*H*$_2$CH=CH$_2$), 4.50 (dd, *J* = 8.4/3.8 Hz, 1H, OC*H*CH$_2$OH), 5.19-5.21 (m, 1H, OCH$_2$CH=C*H*$_2$), 5.25-5.29 (m, 1H, OCH$_2$CH=C*H*$_2$), 5.89-5.96 (m, 1H, OCH$_2$C*H*=CH$_2$), 7.29-7.33 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.33-7.38 (m, 3H, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.51-7.56 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$); $^{13}$C NMR ($CDCl_3$): $\delta$ [ppm] = 67.3 (1C, OCH*C*H$_2$OH), 70.1 (1C, O*C*H$_2$CH=CH$_2$), 82.0 (1C, O*C*HCH$_2$OH), 89.1 (1C, *C*≡C), 89.8 (1C, *C*≡C), 117.6 (1C, OCH$_2$CH=*C*H$_2$), 123.29 (1C, $C_{arom.}$), 123.30 (1C, $C_{arom.}$), 127.1 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 128.48 (1C, C-4''$_{phenyl}$), 128.50 (2C, C-3''$_{phenyl}$, C-5''$_{phenyl}$), 131.8 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.0 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 134.5 (1C, OCH$_2$*C*H=CH$_2$), 138.9 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3426, 2866, 1597, 1508, 1408, 1339, 1219, 1096, 1042, 922, 833, 756, 691; HPLC (method 1): $t_R$ = 22.7 min, purity 97.9 %.

### 4.2.28. (*R*)-3-{(*S*)-2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}propane-1,2-diol (38)

AD-mix-α (410 mg) was added to a mixture of *tert*-butyl alcohol (1.5 mL) and water (1.5 mL). The mixture was cooled to 0 °C, a solution of **37** (82 mg, 0.29 mmol) in a mixture of *tert*-butyl alcohol (1 mL) and water (1 mL) was added and the reaction mixture was stirred at 0 °C for 16 h. Then sodium sulfite (440 mg) was added, the mixture was warmed to ambient temperature and stirred for 1 h. Then ethyl acetate was added to the reaction mixture and after separation of the layers, the aqueous phase was again extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (Ø = 2 cm, h = 10 cm, ethyl acetate/methanol = 10:1, V = 10 mL) to give an inseparable mixture of diastereomers **38** and **39** (8:2) as colorless solid (84 mg, 0.27 mmol, 93 % yield). $R_f$ = 0.36 (ethyl acetate/methanol = 10:1); melting point: 111 °C; specific rotation: $[\alpha]_D^{20}$ = +89.6 (2.6; $CH_3OH$); $^1H$ NMR ($CD_3OD$): $\delta$ [ppm] = 3.35 (dd, $J$ = 9.8/6.8 Hz, 0.9H, $OCH_2CHCH_2OH^{38}$), 3.44-3.46 (m, 0.2H, $OCH_2CHCH_2OH^{39}$), 3.49-3.53 (m, 1.8H, $OCH_2CHCH_2OH^{38}$ (0.9H), $OCH_2CHCH_2OH^{38}$ (0.9H)), 3.56-3.60 (m, 2.1H, $OCH_2CHCH_2OH^{38}$ (0.9H), $OCHCH_2OH^{38}$ (0.9H), $OCHCH_2OH^{39}$ (0.1H), $OCH_2CHCH_2OH^{39}$), 3.66 (dd, $J$ = 11.7/7.9 Hz, 0.1H, $OCHCH_2OH^{39}$), 3.67 (dd, $J$ = 11.7/8.0 Hz, 0.9H, $OCHCH_2OH^{38}$), 3.77-3.84 (m, 1H, $OCH_2CHCH_2OH$), 4.44 (dd, $J$ = 7.9/3.7 Hz, 1H, $OCHCH_2OH$), 7.34-7.39 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.49-7.53 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4-(phenylethynyl)phenyl}$, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); ratio of the daistereomers: **38** : **39** = 8 : 2; $^{13}C$ NMR ($CD_3OD$): $\delta$ [ppm] = 64.3 (0.9C, $OCH_2CHCH_2OH^{38}$), 64.4 (0.1C, $OCH_2CHOHCH_2OH^{39}$), 67.7 (1C, OCH*C*$H_2$OH), 71.7 (0.1C, $OCH_2CHCH_2OH^{39}$), 72.1 (0.9C, $OCH_2CHCH_2OH^{38}$), 72.3 (0.1C, $OCH_2CHCH_2OH^{39}$), 72.6 (0.9C, $OCH_2CHCH_2OH^{38}$), 84.8 (0.1C, $OCHCH_2OH^{39}$), 85.1 (0.9C, $OCHCH_2OH^{38}$), 89.9 (1C, *C*≡C), 90.2 (1C, *C*≡C), 124.1 (0.1C, $C_{arom.}^{39}$), 124.2 (0.9C, $C_{arom.}^{38}$), 124.5 (1C, $C_{arom.}$), 128.3 (2C, C-2'$_{4-(phenylethynyl)phenyl}$, C-6'$_{4-(phenylethynyl)phenyl}$), 129.5 (1C, C-4"$_{phenyl}$), 129.6 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 132.5 (2C, $C_{arom.}$), 132.6 (2C, $C_{arom.}$), 140.9 (0.9C, C-1'$_{4-(phenylethynyl)phenyl}^{38}$), 141.0 (0.1C, C-1'$_{4-(phenylethynyl)phenyl}^{39}$); ratio of the daistereomers: **38** : **39** = 8 : 2; IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3456, 3271, 2905, 2862, 1504, 1443, 1404, 1296, 1219, 1107, 1038, 1022, 930, 829, 752, 691; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{21}O_4$: 313.1434, found: 313.1399; HPLC (method 2): $t_R$ = 15.2 min, purity 97.8 %.

### 4.2.29. (*S*)-3-{(*S*)-2-Hydroxy-1-[4-(phenylethynyl)phenyl]ethoxy}propane-1,2-diol (39)

AD-mix-β (410 mg) was added to a mixture of *tert*-butyl alcohol (1.5 mL) and water (1.5 mL). The mixture was cooled to 0 °C, a solution of **37** (82 mg, 0.29 mmol) in a mixture of *tert*-butyl alcohol (1 mL) and water (1 mL) was added and the reaction mixture was stirred at 0 °C for 16 h. Then sodium sulfite (440 mg) was added, the mixture was warmed to ambient temperature and stirred for 1 h. Then ethyl acetate was added to the reaction mixture and after separation of the layers, the aqueous phase was again extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (Ø = 2 cm, h = 10 cm, ethyl acetate/methanol = 10:1, V = 10 mL) to give an inseparable mixture of diastereomers

**39** and **38** (6:4) as colorless solid (81 mg, 0.26 mmol, 90 % yield). $R_f$ = 0.35 (ethyl acetate/methanol = 10:1); melting point: 106 °C; specific rotation: $[\alpha]_D^{20}$ = +83.1 (3.8; $CH_3OH$); $^1H$ NMR ($CD_3OD$): $\delta$ [ppm] = 3.35 (dd, $J$ = 9.8/6.8 Hz, 0.4H, $OCH_2CHCH_2OH^{38}$), 3.43-3.47 (m, 1.2H, $OCH_2CHCH_2OH^{39}$), 3.49-3.53 (m, 0.8H, $OCH_2CHCH_2OH^{38}$ (0.4H), $OCH_2CHCH_2OH^{38}$ (0.4H)), 3.56-3.62 (m, 2.6H, $OCH_2CHCH_2OH^{38}$ (0.4H), $OCHCH_2OH^{38}$ (0.4H), $OCHCH_2OH^{39}$ (0.6H), $OCH_2CHCH_2OH^{39}$), 3.66 (dd, $J$ = 11.7/7.9 Hz, 0.6H, $OCHCH_2OH^{39}$), 3.67 (dd, $J$ = 11.7/8.0 Hz, 0.4H, $OCHCH_2OH^{38}$), 3.79 (qi, $J$ = 5.3 Hz, 0.6H, $OCH_2CHCH_2OH^{39}$), 3.79-3.84 (m, 0.4H, $OCH_2CHCH_2OH^{38}$), 4.44 (dd, $J$ = 7.9/3.7 Hz, 1H, $OCHCH_2OH$), 7.34-7.39 (m, 5H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$, 3''-$H_{phenyl}$, 5''-$H_{phenyl}$, 4''-$H_{phenyl}$), 7.49-7.53 (m, 4H, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$, 2''-$H_{phenyl}$, 6''-$H_{phenyl}$); ratio of the daistereomers: **39** : **38** = 6 : 4; $^{13}C$ NMR ($CD_3OD$): $\delta$ [ppm] = 64.3 (0.4C, $OCH_2CHCH_2OH^{38}$), 64.4 (0.6C, $OCH_2CHOHCH_2OH^{39}$), 67.7 (1C, $OCHCH_2OH$), 71.7 (0.6C, $OCH_2CHCH_2OH^{39}$), 72.1 (0.4C, $OCH_2CHCH_2OH^{38}$), 72.3 (0.6C, $OCH_2CHCH_2OH^{39}$), 72.6 (0.4C, $OCH_2CHCH_2OH^{38}$), 84.8 (0.6C, $OCHCH_2OH^{39}$), 85.1 (0.4C, $OCHCH_2OH^{38}$), 89.9 (1C, $C$≡C), 90.2 (1C, $C$≡C), 124.1 (0.6C, $C_{arom.}^{39}$), 124.2 (0.4C, $C_{arom.}^{38}$), 124.5 (1C, $C_{arom.}$), 128.3 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.5 (1C, C-4''$_{phenyl}$), 129.6 (2C, C-3''$_{phenyl}$, C-5''$_{phenyl}$), 132.5 (2C, $C_{arom.}$), 132.6 (2C, $C_{arom.}$), 140.9 (0.4C, C-1'$_{4\text{-(phenylethynyl)phenyl}}^{38}$), 141.0 (0.6C, C-1'$_{4\text{-(phenylethynyl)phenyl}}^{39}$); ratio of the daistereomers: **39** : **36** = 6 : 4; IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3653, 3318, 2978, 2866, 1597, 1443, 1393, 1238, 1111, 1038, 833, 752, 687; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{21}O_4$: 313.1434, found: 313.1415; HPLC (method 2): $t_R$ = 15.2 min, purity 96.9 %.

#### 4.2.30. (*S*)-3-[1-(4-Bromophenyl)-2-(methoxymethoxy)ethoxy]propan-1-ol (40)

Under $N_2$ atmosphere, a 0.5 M solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (13.2 mL, 6.6 mmol) was added to a solution of **35** (1.0 g, 3.3 mmol) in THF (50 mL) and the mixture was stirred at ambient temperature overnight. Then again a 0.5 M solution of 9-BBN in THF (6.6 mL, 3.3 mmol) was added. After 1.5 h, the reaction mixture was cooled to -25 °C and methanol (1 mL) was added. After 15 min, 1 M NaOH (13.2 mL, 13.2 mmol) was added, whereupon after 15 min $H_2O_2$ (30 % in $H_2O$) (3.3 mL, ~33 mmol) was added. Then the mixture was stirred for 1 h at -25˚C, 1 h at ambient temperature and finally heated to 40 °C. After the gas formation had finished, the mixture was cooled to ambient temperature, 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 (Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate 8/2 → 1/2, V = 20 mL) to give **40** as colorless oil (1.1 g, 3.3 mmol, 99 % yield). $R_f$ = 0.49 (cyclohexane/ethyl acetate = 1:1); specific rotation: $[\alpha]_D^{20}$ = +37.7 (3.6; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): *δ* [ppm] = 1.83 (quin, *J* = 5.6 Hz, 2H, $OCH_2CH_2CH_2OH$), 3.32 (s, 3H, $OCH_2OCH_3$), 3.49 – 3.64 (m, 3H, $OCH_2CH_2CH_2OH$, $OCHCH_2O$ (1H)), 3.67 (dd, *J* = 10.7/8.1 Hz 1H, $OCHCH_2O$), 3.79 (m, 2H, $OCH_2CH_2CH_2OH$), 4.47 (dd, *J* = 7.9/3.9 Hz, 1H, $OCHCH_2O$), 4.63 (s, 2H, $OCH_2OCH_3$), 7.19 – 7.24 (m, 2H, 2'-$H_{4\text{-bromophenyl}}$, 6'-$H_{4\text{-bromophenyl}}$), 7.47 – 7.51 (m, 2H, 3'-$H_{4\text{-bromophenyl}}$, 5'-$H_{4\text{-bromophenyl}}$); $^{13}C$ NMR ($CDCl_3$): *δ* [ppm] = 32.1 (1C, $OCH_2CH_2CH_2OH$), 55.5 (1C, $OCH_2OCH_3$), 62.2 (1C, $OCH_2CH_2CH_2OH$), 68.9 (1C, $OCH_2CH_2CH_2OH$), 71.7 (1C, $OCHCH_2O$), 81.3 (1C, $OCHCH_2O$), 96.8 (1C, $OCH_2OCH_3$), 122.2 (1C, C-4'$_{4\text{-bromophenyl}}$), 128.8 (2C, C-2'$_{4\text{-bromophenyl}}$, C-6'$_{4\text{-bromophenyl}}$), 131.8 (2C, C-3'$_{4\text{-bromophenyl}}$, C-5'$_{4\text{-bromophenyl}}$), 138.1 (1C, C-1'$_{4\text{-bromophenyl}}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3433, 2924, 2874, 1589, 1485, 1404, 1339, 1300, 1211, 1150, 1107, 1069, 1034, 1011, 964, 918, 822; HRMS (*m/z*): $[M+H]^+$ calc for

$C_{13}H_{20}{}^{79}BrO_4$: 319.0562, found: 319.0539; HPLC (method 1): $t_R$ = 16.6 min, purity 99.5%.

**4.2.31. (*S*)-3-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}propan-1-ol (41)**

Under $N_2$ atmosphere, copper(I) iodide (240 mg, 1.3 mmol), tetrakis(triphenylphosphine)palladium(0) (420 mg, 0.4 mmol) and phenylacetylene (0.8 mL, 740 mg, 7.2 mmol) were added to a solution of **40** (1.1 g, 3.6 mmol) in triethylamine (50 mL). The mixture was heated to reflux and another portion of phenylacetylene (0.8 mL, 740 mg, 7.2 mmol) was added. After heating the mixture to reflux for 16 h, the solvent was evaporated and the residue was purified twice by flash column chromatography (1. Ø = 4 cm, h = 15 cm, dichloromethane/methanol 98/2 → 90/10, V = 20 mL, 2. Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate 8/2 → 1/2, V = 20 mL) to give **41** as yellowish oil (950 mg, 2.8 mmol, 78 % yield). $R_f$ = 0.49 (cyclohexane/ethyl acetate = 1:1); specific rotation: $[\alpha]_D^{20}$ = +57.2 (3.0; $CH_2Cl_2$); $^1H$ NMR: ($CDCl_3$): $\delta$ [ppm] = 1.83 (quin, $J$ = 5.6 Hz, 2H, $OCH_2CH_2CH_2OH$ with italic $H_2$ on C2), 3.33 (s, 3H, $OCH_2OC\mathit{H}_3$), 3.51 – 3.68 (m, 3H, $OC\mathit{H}_2CH_2CH_2OH$, $OCHC\mathit{H}_2O$ (1H)), 3.70 (dd, $J$ = 10.8/8.1 Hz, 1H, $OCHC\mathit{H}_2O$), 3.77 – 3.85 (m, 2H, $OCH_2CH_2C\mathit{H}_2OH$), 4.53 (dd, $J$ = 8.0/3.8 Hz, 1H, $OC\mathit{H}CH_2O$), 4.65 (s, 2H, $OC\mathit{H}_2OCH_3$), 7.29 – 7.38 (m, 5H, $H_{arom.}$), 7.51 – 7.55 (m, 4H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 32.1 (1C, $OCH_2\mathit{C}H_2CH_2OH$), 55.5 (1C, $OCH_2O\mathit{C}H_3$), 62.3 (1C, $OCH_2CH_2\mathit{C}H_2OH$), 69.0 (1C, $O\mathit{C}H_2CH_2CH_2OH$), 71.8 (1C, $OCH\mathit{C}H_2O$), 81.6 (1C, $O\mathit{C}HCH_2O$), 89.1 (1C, $\mathit{C}$≡C), 89.8 (1C, $\mathit{C}$≡C), 96.8 (1C, $O\mathit{C}H_2OCH_3$), 123.27 (1C, $C_{arom.}$), 123.28 (1C, $C_{arom.}$), 127.1 (2C, $C_{arom.}$), 128.48 (1C, $C_{arom.}$), 128.50 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 131.9 (2C, $C_{arom.}$), 139.2 (1C, $C_{arom.}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3441, 2928, 2882, 1597, 1508, 1443, 1400, 1342, 1211, 1150, 1107, 1034, 964, 918, 833, 756, 691; HRMS (*m/z*): $[M+H]^+$ calc for $C_{21}H_{25}O_4$: 341.1747, found: 341.1742; HPLC (method 1): $t_R$ = 20.0 min, purity 94.6%.

### 4.2.32. (*S*)-2-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl 4-methylbenzenesulfonate (42)

Under $N_2$ atmosphere, triethylamine (0.65 mL, 0.48 g, 4.7 mmol) and 4-dimethylaminopyridine (60 mg, 0.50 mmol) were added to a solution of **17** (770 mg, 2.3 mmol) in dry DCM (50 mL). Then 4-toluenesulfonyl chloride (900 mg, 4.7 mmol) was added and the reaction was stirred for 24 h at room temperature. Afterwards, the mixture was extracted with EtOAc (3×), the organic phase dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate 8/2 → 1/2, V = 10 mL) to give **42** as colorless oil (970 mg, 2.0 mmol, 86 % yield). $R_f$ = 0.76 (cyclohexane/ethyl acetate = 2:1); specific rotation: $[\alpha]_D^{20}$ = +15.3 (3.2; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 2.45 (s, 3H, $SO_3C_6H_4CH_3$), 3.27 (s, 3H, $OCH_2OCH_3$), 3.55 – 3.65 (m, 3H, $OCH_2CH_2OS$, $OCHCH_2O$ (1H)), 3.67 (dd, $J$ = 10.8/7.5 Hz, 1H, $OCHCH_2O$), 4.13 – 4.21 (m, 2H, $OCH_2CH_2OS$), 4.47 (dd, $J$ = 7.4/4.1 Hz, 1H, $OCHCH_2O$), 4.58 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.61 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 7.23 – 7.26 (m, 2H, $H_{arom.}$), 7.31 – 7.38 (m, 5H, $H_{arom.}$), 7.47 – 7.50 (m, 2H, $H_{arom.}$), 7.52 – 7.55 (m, 2H, $H_{arom.}$), 7.75 – 7.79 (m, 2H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 21.8 (1C, $SO_3C_6H_4CH_3$), 55.4 (1C, $OCH_2OCH_3$), 66.8 (1C, $OCH_2CH_2OS$), 69.3 (1C, $OCH_2CH_2OS$), 71.5 (1C, $OCHCH_2O$), 81.8 (1C, $OCHCH_2O$), 89.1 (1C, $C{\equiv}C$), 89.9 (1C, $C{\equiv}C$), 96.7 (1C, $OCH_2OCH_3$), 123.27 (1C, $C_{arom.}$), 123.28 (1C, $C_{arom.}$), 127.1 (2C, $C_{arom.}$), 128.1 (2C, $C_{arom.}$), 128.49 (1C, $C_{arom.}$), 128.51 (2C, $C_{arom.}$), 129.9 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 131.9 (2C, $C_{arom.}$), 133.2 (1C, $C_{arom.}$), 138.9 (1C, $C_{arom.}$), 144.9 (1C,

$C_{arom.}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2924, 2882, 1597, 1508, 1443, 1400, 1358, 1177, 1107, 1018, 918, 814, 756, 691, 664; HRMS (*m/z*): $[M+H]^+$ calc for $C_{27}H_{29}O_6S$: 481.1679, found: 481.1646; HPLC (method 1): $t_R$ = 23.0 min, purity 98.2%.

**4.2.33. (*S*)-3-{2-(Methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}propyl 4-methylbenzenesulfonate (43)**

Under $N_2$ atmosphere, triethylamine (0.75 mL, 0.55 g, 5.4 mmol) and 4-dimethylaminopyridine (66 mg, 0.54 mmol) were added to a solution of **41** (920 mg, 2.7 mmol) in dry DCM (50 mL). Then 4-toluenesulfonyl chloride (1.0 g, 5.4 mmol) was added and the reaction was stirred for 16 h at room temperature. Afterwards, the mixture was extracted with EtOAc (3×), the organic phase dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate 8/2 → 1/2, V = 10 mL) to give **43** as yellowish oil (1.1 g, 2.2 mmol, 82 % yield). $R_f$ = 0.62 (cyclohexane/ethyl acetate = 2:1); specific rotation: $[\alpha]_D^{20}$ = +26.0 (2.2; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 1.87 – 1.98 (m, 2H, $OCH_2CH_2CH_2O$), 2.45 (s, 3H, $SO_3C_6H_4CH_3$), 3.26 (s, 3H, $OCH_2OCH_3$), 3.42 (t, *J* = 6.0 Hz, 2H, $OCH_2CH_2CH_2O$), 3.57 (dd, 1H, *J* = 10.8/4.2 Hz, $OCHCH_2O$), 3.66 (dd, *J* = 10.8/7.3 Hz, 1H, $OCHCH_2O$), 4.12 – 4.22 (m, 2H, $OCH_2CH_2CH_2O$), 4.40 (dd, *J* = 7.3/4.2 Hz, 1H, $OCHCH_2O$), 4.58 (d, *J* = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.60 (d, *J* = 6.6 Hz, 1H, $OCH_2OCH_3$), 7.24 – 7.27 (m, 2H, $H_{arom.}$), 7.32 – 7.38 (m, 5H, $H_{arom.}$), 7.48 – 7.51 (m, 2H, $H_{arom.}$), 7.52 – 7.55 (m, 2H, $H_{arom.}$), 7.75 – 7.78 (m, 2H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 21.8 (1C, $SO_3C_6H_4CH_3$), 29.6 (1C, $OCH_2CH_2CH_2O$), 55.4 (1C, $OCH_2OCH_3$), 64.9 (1C, $OCH_2CH_2CH_2O$), 67.7 (1C, $OCH_2CH_2CH_2O$), 71.5 (1C, $OCHCH_2O$), 81.5 (1C, $OCHCH_2O$), 89.2 (1C, $C{\equiv}C$), 89.8 (1C, $C{\equiv}C$), 96.7 (1C, $OCH_2OCH_3$), 123.1 (1C,

$C_{arom.}$), 123.3 (1C, $C_{arom.}$), 127.0 (2C, $C_{arom.}$), 128.0 (2C, $C_{arom.}$), 128.46 (1C, $C_{arom.}$), 128.50 (2C, $C_{arom.}$), 130.0 (2C, $C_{arom.}$), 131.7 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 133.3 (1C, $C_{arom.}$), 139.5 (1C, $C_{arom.}$), 144.8 (1C, $C_{arom.}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2924, 2878, 1597, 1508, 1443, 1358, 1177, 1107, 1034, 941, 833, 814, 756, 691, 664; HRMS (*m/z*): $[M+H]^+$ calc for $C_{28}H_{31}O_6S$: 495.1836, found: 495.1891; HPLC (method 1): $t_R$ = 25.7 min, purity 92.8%.

### 4.2.34. (*S*)-1-[1-(2-Azidoethoxy)-2-(methoxymethoxy)ethyl]-4-(phenylethynyl)benzene (44)

Sodium azide (880 mg, 14 mmol) was added to a solution of **42** (1.1 g, 2.4 mmol) in DMSO (80 mL). The mixture was heated to reflux for 16 h. After cooling the mixture to ambient temperature, 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 (Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate 8/2 → 1/2, V = 20 mL) to give **44** as yellowish oil (770 mg, 2.2 mmol, 92 % yield). $R_f$ = 0.77 (cyclohexane/ethyl acetate = 2:1); specific rotation: $[\alpha]_D^{20}$ = +1.9 (2.5; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 3.30 (s, 3H, $OCH_2OCH_3$), 3.36 (dt, $J$ = 13.2/5.1 Hz, 1H, $OCH_2CH_2N_3$), 3.42 (dt, $J$ = 13.2/5.1 Hz, 1H, $OCH_2CH_2N_3$), 3.59 (t, $J$ = 5.1 Hz, 2H, $OCH_2CH_2N_3$), 3.65 (dd, $J$ = 10.8/4.2 Hz, 1H, $OCHCH_2O$), 3.78 (dd, $J$ = 10.8/7.4 Hz, 1H, $OCHCH_2O$), 4.54 (dd, $J$ = 7.4/4.2 Hz, 1H, $OCHCH_2O$), 4.63 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 4.66 (d, $J$ = 6.6 Hz, 1H, $OCH_2OCH_3$), 7.32 – 7.37 (m, 5H, $H_{arom.}$), 7.51 – 7.56 (m, 4H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 51.0 (1C, $OCH_2CH_2N_3$), 55.4 (1C, $OCH_2OCH_3$), 68.3 (1C, $OCH_2CH_2N_3$), 71.7 (1C, $OCHCH_2O$), 81.9 (1C, $OCHCH_2O$), 89.2 (1C, $C\equiv C$), 89.8 (1C, $C\equiv C$), 96.8 (1C, $OCH_2OCH_3$), 123.30 (1C, $C_{arom.}$), 123.32

(1C, $C_{arom.}$), 127.2 (2C, $C_{arom.}$), 128.48 (1C, $C_{arom.}$), 128.50 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 131.9 (2C, $C_{arom.}$), 139.1 (1C, $C_{arom.}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2928, 2882, 2102, 1597, 1508, 1443, 1342, 1285, 1211, 1150, 1107, 1034, 964, 918, 833, 756, 691; HRMS (*m/z*): $[M+H]^+$ calc for $C_{20}H_{22}N_3O_3$: 352.1656, found: 352.1656; HPLC (method 1): $t_R$ = 22.3 min, purity 97.8%.

### 4.2.35. (*S*)-1-[1-(3-Azidopropoxy)-2-(methoxymethoxy)ethyl]-4-(phenylethynyl)benzene (45)

Sodium azide (800 mg, 12 mmol) was added to a solution of **43** (1.1 g, 2.2 mmol) in DMSO (80 mL). The mixture was heated to reflux for 16 h. After cooling the mixture to ambient temperature, 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 (Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate 8/2 → 1/2, V = 20 mL) to give **45** as yellowish oil (730 mg, 2.0 mmol, 90 % yield). $R_f$ = 0.66 (cyclohexane/ethyl acetate = 8:2); specific rotation: $[\alpha]_D^{20}$ = +38.6 (1.9; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 1.77 – 1.94 (m, 2H, $OCH_2CH_2CH_2N_3$), 3.30 (s, 3H, $OCH_2OCH_3$), 3.35 – 3.48 (m, 2H, $OCH_2CH_2CH_2N_3$), 3.47 (t, *J* = 6.1 Hz, 2H, $OCH_2CH_2CH_2N_3$), 3.62 (dd, *J* = 10.8/4.1 Hz, 1H, $OCHCH_2O$), 3.74 (dd, *J* = 10.8/7.4 Hz, 1H, $OCHCH_2O$), 4.48 (dd, *J* = 7.5/4.1 Hz, 1H, $OCHCH_2O$), 4.62 (d, *J* = 6.5 Hz, 1H, $OCH_2OCH_3$), 4.65 (d, *J* = 6.5 Hz, 1H, $OCH_2OCH_3$), 7.29 – 7.38 (m, 5H, $H_{arom.}$), 7.50 – 7.56 (m, 4H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 29.4 (1C, $OCH_2CH_2CH_2N_3$), 48.6 (1C, $OCH_2CH_2CH_2N_3$), 55.4 (1C, $OCH_2OCH_3$), 66.1 (1C, $OCH_2CH_2CH_2N_3$), 71.7 (1C, $OCHCH_2O$), 81.6 (1C, $OCHCH_2O$), 89.2 (1C, *C*≡C), 89.7 (1C, *C*≡C), 96.7 (1C, $OCH_2OCH_3$), 123.1 (1C, $C_{arom.}$), 123.3 (1C, $C_{arom.}$), 127.1 (2C, $C_{arom.}$), 128.4 (1C,

$C_{arom.}$), 128.5 (2C, $C_{arom.}$), 131.7 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 139.6 (1C, $C_{arom.}$); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2928, 2874, 2095, 1597, 1508, 1443, 1400, 1342, 1300, 1261, 1211, 1150, 1107, 1034, 972, 918, 837, 756, 691; HRMS (*m/z*): $[M+H]^+$ calc for $C_{21}H_{24}N_3O_3$: 366.1812, found: 366.1819; HPLC (method 1): $t_R$ = 25.1 min, purity 97.3%.

### 4.2.36. 3-(Benzyloxy)-2-methyl-4*H*-pyran-4-one (47)

**47** was synthesized according to the literature:[65]

Potassium carbonate (4.8 g, 35 mmol) and benzyl bromide (1.3 mL, 1.9 g, 11 mmol) were added to a solution of 3-hydroxy-2-methyl-4*H*-pyran-4-one (1.1 g, 8.7 mmol) in dry acetonitrile (50 mL). After heating the mixture to reflux for 16 h, 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 (Ø = 4 cm, h = 15 cm, cyclohexane/ethyl acetate = 8:2→ 2:1, V = 30 mL) to give **47** as yellowish oil (1.8 g, 8.3 mmol, 95 % yield). $R_f$ = 0.49 (cyclohexane/ethyl acetate = 1:1); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 2.11 (s, 3H, $CH_3$), 5.16 (s, 2H, $OCH_2Ph$), 6.50 (d, $J$ = 5.6 Hz, 1H, OCH=C*H*CO), 7.30-7.36 (m, 3H, 3'-$H_{phenyl}$, 4'-$H_{phenyl}$, 5'-$H_{phenyl}$), 7.37-7.40 (m, 2H, 2'-$H_{phenyl}$, 6'-$H_{phenyl}$), 7.64 (d, $J$ = 5.6 Hz, 1H, OC*H*=CHCO); $^{13}C$ NMR ($CDCl_3$) $\delta$ [ppm] = 15.0 (1C, $CH_3$), 73.8 (1C, $OCH_2Ph$), 117.0 (1C, OCH=*C*HCO), 128.5 (1C, C-4'$_{phenyl}$), 128.6 (2C, C-3'$_{phenyl}$, C-5'$_{phenyl}$), 129.2 (2C, C-2'$_{phenyl}$, C-6'$_{phenyl}$), 136.9 (1C, C-1'$_{phenyl}$), 143.8 (1C, O*C*=$CCH_3$), 153.8 (1C, O*C*H=CHCO), 160.6 (1C, OC=$CCH_3$) 175.3 (1C, OCH=CH*C*O); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 3063, 3028, 2959, 2882, 1643, 1574, 1497, 1427, 1389, 1354, 1250, 1173, 1080, 1026, 972, 914, 829, 748, 702; LCMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{13}O_3$: 217.0859, found: 217.0875; HPLC (method 1): $t_R$ = 17.2 min, purity 97.9 %.

**4.2.37. (*S*)-3-(Benzyloxy)-1-(2-{2-(methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}ethyl)-2-methylpyridin-4(1*H*)-one (48)**

Under $N_2$ atmosphere, polymer-bound triphenylphosphine (1.6 mmol/g, 2.0 g, 3.2 mmol) was added to a solution of **44** (570 mg, 1.6 mmol) in dry THF (50 mL) and the reaction was stirred for 72 h at room temperature. Then water (0.5 mL) was added and the mixture was filtered through Celite via a Nutsch-type filter. The organic solvent was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* (obtained crude product: 407 mg). A portion of the crude product (180 mg) was dissolved in water (50 mL) and **47** (130 mg, 0.58 mmol) was added. The reaction mixture was stirred for 7 d at 140 °C and then quenched with a saturated aqueous solution of $NH_4Cl$. After cooling the mixture to ambient temperature, it 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 (Ø = 1 cm, h = 15 cm, dichloromethane/methanol 98/2 → 90/10, V = 5 mL) to give **48** as brown solid (71 mg, 0.14 mmol, 19 % yield). $R_f$ = 0.67 (dichloromethane/methanol = 9:1); melting point: 127 °C; specific rotation: $[\alpha]_D^{20}$ = +2.8 (c = 1.5; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 2.12 (s, 3H, OC=CC$H_3$), 3.28 (s, 3H, $OCH_2OCH_3$), 3.50 – 3.55 (m, 2H, OCHC$H_2$O (1H), OC$H_2$CH$_2$N (1H)), 3.60 – 3.67 (m, 2H, OCHC$H_2$O (1H), OC$H_2$CH$_2$N (1H)), 3.93 – 4.00 (m, 1H, OCH$_2$C$H_2$N), 4.06 (ddd, *J* = 14.9/7.6/3.8 Hz, 1H, OCH$_2$C$H_2$N), 4.42 (dd, *J* = 7.8/3.9 Hz, 1H, OC*H*CH$_2$O), 4.58 (d, *J* = 6.6 Hz, 1H, OC$H_2$OCH$_3$), 4.59 (d, *J* = 6.6 Hz, 1H, OC$H_2$OCH$_3$), 5.17 (d, *J* = 11.4 Hz, 1H, OC$H_2$C$_6$H$_5$), 5.29 (d, *J* = 11.4 Hz, 1H, OC$H_2$C$_6$H$_5$), 6.58 – 6.66 (m, 1H, NCH=C*H*CO), 7.06 – 7.09 (m, 2H, $H_{arom.}$), 7.26 – 7.31

(m, 3H, $H_{arom.}$), 7.32 – 7.37 (m, 4H, NC*H*=CHCO, $H_{arom.}$), 7.40 – 7.43 (m, 2H, $H_{arom.}$), 7.46 – 7.48 (m, 2H, $H_{arom.}$), 7.49 – 7.52 (m, 2H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 12.9 (1C, OC=C*C*$H_3$), 53.5 (1C, $OCH_2$*C*$H_2N$), 55.4 (1C, $OCH_2O$*C*$H_3$), 67.7 (1C, O*C*$H_2CH_2N$), 71.6 (1C, OCH*C*$H_2O$), 73.4 (1C, O*C*$H_2C_6H_5$), 82.0 (1C, O*C*H$CH_2O$), 88.9 (1C, *C*≡C), 90.2 (1C, *C*≡C), 96.8 (1C, O*C*$H_2OCH_3$), 116.9 (1C, NCH=*C*HCO), 123.1 (1C, $C_{arom.}$), 123.7 (1C, $C_{arom.}$), 126.9 (2C, $C_{arom.}$), 128.2 (1C, $C_{arom.}$), 128.4 (2C, $C_{arom.}$), 128.5 (2C, $C_{arom.}$), 128.6 (1C, $C_{arom.}$), 129.2 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 132.1 (2C, $C_{arom.}$), 137.6 (1C, $C_{arom.}$), 138.1 (1C, $C_{arom.}$), 139.3 (1C, N*C*H=CHCO), 141.9 (1C, OC=*C*$CH_3$), 145.9 (1C, O*C*=C$CH_3$), 172.9 (1C, NCH=CH*C*O); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2928, 2882, 1624, 1566, 1508, 1443, 1250, 1215, 1150, 1107, 1030, 968, 918, 833, 756, 691; HRMS (*m/z*): $[M+H]^+$ calc for $C_{33}H_{34}NO_5$: 524.2431, found: 524.2455; HPLC (method 2): $t_R$ = 18.5 min, purity 96.5%.

### 4.2.38. (*S*)-3-(Benzyloxy)-1-(3-{2-(methoxymethoxy)-1-[4-(phenylethynyl)phenyl]ethoxy}propyl)-2-methylpyridin-4(1*H*)-one (49)

Under $N_2$ atmosphere, polymer-bound triphenylphosphine (1.6 mmol/g, 2.2 g, 3.6 mmol) was added to a solution of **45** (650 mg, 1.8 mmol) in dry THF (50 mL) and the reaction was stirred for 72 h at room temperature. Then water (0.5 mL) was added and the mixture was filtered through Celite via a Nutsch-type filter. The organic solvent was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* (obtained crude product: 330 mg). A portion of the crude product (180 mg) was dissolved in water (50 mL) and **47** (120 mg, 0.53 mmol) was added. The reaction mixture was stirred for 7 d at 140 °C. Then a saturated aqueous solution of $NH_4Cl$ was added. After cooling the mixture to ambient temperature, it 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 (Ø = 1 cm, h = 15 cm, dichloromethane/methanol 98/2 → 90/10, V = 5 mL) to give **49** as yellowish oil (71 mg, 0.13 mmol, 14 % yield). $R_f$ = 0.69 (dichloromethane/methanol = 9:1); specific rotation: $[\alpha]_D^{20}$ = +17.0 (1.6; $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ [ppm] = 1.81 – 1.96 (m, 2H, $OCH_2CH_2CH_2N$), 2.17 (s, 3H, $OC{=}CCH_3$), 3.17 – 3.26 (m, 1H, $OCH_2CH_2CH_2N$), 3.33 (s, 3H, $OCH_2OCH_3$), 3.35 – 3.43 (m, 1H, $OCH_2CH_2CH_2N$), 3.61 (dd, *J* = 10.7/3.6 Hz, 1H, $OCHCH_2O$), 3.72 (dd, *J* = 10.7/8.1 Hz, 1H, $OCHCH_2O$), 3.94 – 4.15 (m, 2H, $OCH_2CH_2CH_2N$), 4.42 (dd, *J* = 8.1/3.6 Hz, 1H, $OCHCH_2O$), 4.64 (d, *J* = 6.3 Hz, 1H, $OCH_2OCH_3$), 4.66 (d, *J* = 6.3 Hz, 1H, $OCH_2OCH_3$), 5.24 (s, 2H, $OCH_2C_6H_5$), 6.81 – 7.00 (m, 1H, NCH=C*H*CO), 7.26 – 7.41 (m, 11H, NC*H*=CHCO, $H_{arom.}$), 7.49 – 7.58 (m, 4H, $H_{arom.}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ [ppm] = 12.7 (1C, $OC{=}CCH_3$), 30.4 (1C, $OCH_2CH_2CH_2N$), 51.3 (1C, $OCH_2CH_2CH_2N$), 55.6 (1C, $OCH_2OCH_3$), 64.3 (1C, $OCH_2CH_2CH_2N$), 71.7 (1C, $OCHCH_2O$), 73.6 (1C, $OCH_2C_6H_5$), 81.8 (1C, $OCHCH_2O$), 88.9 (1C, *C*≡C), 90.1 (1C, *C*≡C), 96.8 (1C, $OCH_2OCH_3$), 116.5 (1C, NCH=*C*HCO), 123.2 (1C, $C_{arom.}$), 123.6 (1C, $C_{arom.}$), 127.0 (2C, $C_{arom.}$), 128.4 (1C, $C_{arom.}$), 128.48 (2C, $C_{arom.}$), 128.53 (2C, $C_{arom.}$), 128.6 (1C, $C_{arom.}$), 129.3 (2C, $C_{arom.}$), 131.8 (2C, $C_{arom.}$), 132.0 (2C, $C_{arom.}$), 138.7 (1C, $C_{arom.}$), 139.6 (1C, N*C*H=CHCO); the signals for 1$C_{arom.}$, $OC{=}CCH_3$, $OC{=}CCH_3$, NCH=CH*C*O could not be observed in the spectrum; IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2928, 2882, 1624, 1566, 1497, 1250, 1215, 1150, 1107, 1034, 972, 918, 833, 756, 694; HRMS (*m/z*): $[M+H]^+$ calc for $C_{34}H_{36}NO_5$: 538.2588, found: 538.2627; HPLC (method 2): $t_R$ = 18.9 min, purity 96.4%.

### 4.2.39. (*S*)-3-Hydroxy-1-{2-[2-hydroxy-1-(4-phenethylphenyl)ethoxy]ethyl}-2-methylpyridin-4(1*H*)-one (50)

**48** (60 mg, 0.11 mmol) was dissolved in dry methanol (5 mL) and a saturated solution of hydrochloric acid in methanol (1 mL) was added. After stirring the mixture at room temperature overnight, the mixture was extracted with EtOAc (3×), the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved in dry methanol (10 mL) and Pd/C (10 %, 10 mg) was added. The mixture was stirred under $H_2$ atmosphere (4 bar) at room temperature for 16 h. The catalyst was filtered off (Celite) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 1 cm, h = 15 cm, dichloromethane/methanol 98/2 → 90/10, V = 5 mL) to give **50** as red solid (12 mg, 0.03 mmol, 27 % yield). $R_f$ = 0.47 (dichloromethane/methanol = 9:1); melting point: 255 °C (decomposition); specific rotation: $[\alpha]_D^{20}$ = +0.5 (1.2; $CH_2Cl_2$); $^1$H NMR ($CD_3OD$): $\delta$ [ppm] = 2.34 (s, 3H, HOC=C$CH_3$), 2.83 – 2.89 (m, 4H, Ph$CH_2CH_2$Ph), 3.40 – 3.65 (m, 3H, OCH$CH_2$O, O$CH_2$CH$_2$N (1H)), 3.68 – 3.74 (m, 1H, O$CH_2$CH$_2$N), 4.14 – 4.34 (m, 3H, O$CH$CH$_2$O, OCH$_2$$CH_2$N), 6.36 – 6.41 (m, 1H, NCH=C$H$CO), 6.89 – 6.94 (m, 2H, $H_{arom.}$), 7.03 – 7.07 (m, 2H, $H_{arom.}$), 7.11 – 7.17 (m, 3H, $H_{arom.}$), 7.19 – 7.25 (m, 2H, $H_{arom.}$), 7.56 – 7.64 (m, 1H, NC$H$=CHCO); $^{13}$C NMR ($CD_3OD$): $\delta$ [ppm] = 12.2 (1C, HOC=C$CH_3$), 38.7 (1C, Ph$CH_2$CH$_2$Ph), 39.0 (1C, PhCH$_2$$CH_2$Ph), 54.8 (1C, OCH$_2$$CH_2$N), 67.6 (1C, OCH$CH_2$OH), 68.4 (1C, O$CH_2$CH$_2$N), 84.8 (1C, O$CH$CH$_2$O), 112.3 (1C, NCH=$C$HCO), 126.9 (1C, $C_{arom.}$), 127.9 (2C, $C_{arom.}$), 129.3 (2C, $C_{arom.}$), 129.5 (2C, $C_{arom.}$), 129.7 (2C, $C_{arom.}$), 133.3 (1C, HOC=$C$CH$_3$), 137.3 (1C, $C_{arom.}$), 139.9 (1C, N$C$H=CHCO), 142.9 (1C, $C_{arom.}$), 143.2 (1C, $C_{arom.}$), 147.0 (1C, HO$C$=CCH$_3$), 170.8 (1C, NCH=CH$C$O); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3267, 2978, 2920, 1624, 1562, 1504, 1454, 1346, 1250, 1107, 1072, 822, 748, 698; HRMS (*m/z*): $[M+H]^+$ calc for $C_{24}H_{28}NO_4$: 394.2013, found: 394.2073; HPLC (method 2): $t_R$ = 15.5 min, purity 98.0%.

**4.2.40. (*S*)-3-Hydroxy-1-{3-[2-hydroxy-1-(4-phenethylphenyl)ethoxy]propyl}-2-methylpyridin-4(1*H*)-one (51)**

**49** (60 mg, 0.11 mmol) was dissolved in dry methanol (5 mL) and a saturated solution of hydrochloric acid in methanol (1 mL) was added. After stirring the mixture at room temperature overnight, the mixture was extracted with EtOAc (3×). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved in dry methanol (10 mL) and Pd/C (10 %, 10 mg) was added. The mixture was stirred under $H_2$ atmosphere (4 bar) at room temperature for 16 h. The catalyst was filtered off (Celite) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 1 cm, h = 15 cm, dichloromethane/methanol 98/2 → 90/10, V = 5 mL) to give **51** as red solid (12 mg, 0.03 mmol, 26 % yield). $R_f$ = 0.49 (dichloromethane/methanol = 9:1); specific rotation: $[\alpha]_D^{20}$ = +29.3 (1.8; $CH_2Cl_2$); $^1$H NMR ($CD_3OD$): $\delta$ [ppm] = 1.90 – 2.06 (m, 2H, $OCH_2CH_2CH_2N$), 2.43 (s, 3H, HOC=C$CH_3$), 2.84 – 2.94 (m, 4H, Ph$CH_2CH_2$Ph), 3.32 – 3.35 (m, 1H, O$CH_2$$CH_2CH_2N$), 3.36 – 3.41 (m, 1H, O$CH_2$$CH_2CH_2N$), 3.56 (dd, *J* = 11.7/3.5 Hz, 1H, OCH$CH_2$OH), 3.69 (dd, *J* = 11.7/8.2 Hz, 1H, OCH$CH_2$OH), 4.12 – 4.25 (m, 2H, $OCH_2CH_2$$CH_2$N), 4.31 (dd, *J* = 8.2/3.5 Hz, 1H, OC*H*$CH_2$OH), 6.34 (d, *J* = 7.0 Hz, 1H, NCH=C*H*CO), 7.12 – 7.20 (m, 5H, $H_{arom.}$), 7.20 – 7.24 (m, 4H, $H_{arom.}$), 7.59 (d, *J* = 7.0 Hz, 1H, NC*H*=CHCO); $^{13}$C NMR ($CD_3OD$): $\delta$ [ppm] = 11.9 (1C, HOC=C$CH_3$), 31.6 (1C, $OCH_2CH_2CH_2N$), 38.8 (1C, Ph$CH_2CH_2$Ph), 39.0 (1C, Ph$CH_2CH_2$Ph), 52.3 (1C, $OCH_2CH_2CH_2N$), 65.9 (1C, $OCH_2CH_2CH_2N$), 67.7 (1C, OCH$CH_2$OH), 84.9 (1C, O*C*H$CH_2$OH), 112.5 (1C, NCH=*C*HCO), 126.9 (1C, $C_{arom.}$), 128.1 (2C, $C_{arom.}$), 129.3 (2C, $C_{arom.}$), 129.5 (2C, $C_{arom.}$), 129.8 (2C, $C_{arom.}$), 132.9 (1C, OC=*C*$CH_3$), 137.9 (1C, $C_{arom.}$), 139.2 (1C, N*C*H=CHCO), 143.0 (1C, $C_{arom.}$), 143.1 (1C, $C_{arom.}$), 147.3 (1C, HO*C*=C$CH_3$), 170.5 (1C, NCH=CH*C*O); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3275, 2924, 2859, 1624, 1562, 1508, 1346, 1246, 1103, 1038, 822, 748, 698; HRMS (*m/z*): $[M+H]^+$ calc for $C_{25}H_{30}NO_4$: 408.2169, found: 408.2268; HPLC (method 2): $t_R$ = 16.0 min, purity 97.8%.

**4.2.41. (*S*)-*N*-Hydroxy-2-[2-hydroxy-1-(4-phenethylphenyl)ethoxy]acetamide (53)**

**52** (53 mg, 0.19 mmol) was dissolved in dry methanol (10 mL) and Pd/C (10 %, 10 mg) was added. The mixture was stirred under $H_2$ atmosphere (balloon) at ambient temperature for 16 h. Then, the catalyst was filtered off (Celite) and the solvent was removed *in vacuo*. The crude product (50 mg) was dissolved in dry methanol (5 mL) and hydroxylamine hydrochloride (38 mg, 0.54 mmol) and a 5.4 M solution of sodium methoxide in methanol (0.1 mL, 0.54 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h until TLC showed complete conversion. Then the reaction mixture was acidified with 1.0 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 (Ø = 1 cm, h = 15 cm, dichloromethane/methanol = 98/2 → 90/10, V = 5 mL) to give **53** as brown oil (33 mg, 0.10 mmol, 55 % yield). $R_f$ = 0.61 (dichloromethane/methanol = 9:1); specific rotation: $[\alpha]_D^{20}$ = +66.4 (3.0; $CH_2Cl_2$); $^1H$ NMR ($CD_3OD$): $\delta$ [ppm] = 2.84 – 2.95 (m, 4H, PhC$H_2$C$H_2$Ph), 3.58 (dd, $J$ = 11.9/3.2 Hz, 1H, OCHC$H_2$OH), 3.69 (dd, $J$ = 11.9/8.4 Hz, 1H, OCHC$H_2$OH), 3.84 (d, $J$ = 14.9 Hz, 1H, OC$H_2$CONHOH), 3.92 (d, $J$ = 14.9 Hz, 1H, OC$H_2$CONHOH), 4.41 (dd, $J$ = 8.4/3.2 Hz, 1H, OC*H*CH$_2$OH), 7.11 – 7.25 (m, 9H, $H_{arom.}$); $^{13}C$ NMR ($CD_3OD$): $\delta$ [ppm] = 38.7 (1C, Ph*C*H$_2$CH$_2$Ph), 39.0 (1C, PhCH$_2$*C*H$_2$Ph), 67.5 (1C, OCH*C*H$_2$OH), 68.3 (1C, O*C*H$_2$CONHOH), 85.6 (1C, O*C*HCH$_2$OH), 126.9 (1C, $C_{arom.}$), 128.0 (2C, $C_{arom.}$), 129.3 (2C, $C_{arom.}$), 129.5 (2C, $C_{arom.}$), 129.9 (2C, $C_{arom.}$), 136.4 (1C, $C_{arom.}$), 142.9 (1C, $C_{arom.}$), 143.5 (1C, $C_{arom.}$), 169.1 (1C, OCH$_2$*C*ONHOH); IR (neat): $\tilde{\nu}$ [$cm^{-1}$] = 2978, 1728, 1670, 1431, 1192, 1130, 1053, 1030, 818, 721, 698; HRMS (*m/z*): $[M+H]^+$ calc for $C_{18}H_{22}NO_4$: 316.1543, found: 316.1548; HPLC (method 2): $t_R$ = 15.8 min, purity 96.3%.

### 4.2.42. 3-(Benzyloxy)-1-(4-bromophenethyl)-2-methylpyridin-4(1*H*)-one (55)

2-(4-Bromophenyl)ethylamine (210 mg, 1.0 mmol) was added to an emulsion of **47** (230 mg, 1.0 mmol) in water (5 mL). The reaction mixture was stirred at 140 °C for 10 d. Afterwards, ethyl acetate was added and after separation of the layers, the aqueous phase was extracted with ethyl acetate (2×). 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 (Ø = 3 cm, h = 15 cm, dichloromethane/methanol = 97:3, V = 20 mL) to give **55** as brownish oil (250 mg, 0.62 mmol, 60 % yield). $R_f$ = 0.29 (dichloromethane/methanol = 10:1); $^1$H NMR ($CDCl_3$): *δ* [ppm] = 2.03 (s, 3H, OC=CC*H*$_3$), 2.84 (t, *J* = 6.8 Hz, 2H, NCH$_2$C*H*$_2$Ph), 3.95 (t, *J* = 6.8 Hz, 2H, NC*H*$_2$CH$_2$Ph), 5.22 (s, 2H, OC*H*$_2$Ph), 6.34 (d, *J* = 7.3 Hz, 1H, NCH=C*H*CO), 6.80 – 6.85 (m, 2H, 2'-$H_{4\text{-bromophenyl}}$, 6'-$H_{4\text{-bromophenyl}}$), 6.90 (d, *J* = 7.3 Hz, 1H, NC*H*=CHCO), 7.28 – 7.35 (m, 3H, 3''-$H_{benzyloxy}$, 4''-$H_{benzyloxy}$, 5''-$H_{benzyloxy}$), 7.37 – 7.42 (m, 4H, 2''-$H_{benzyloxy}$, 6''-$H_{benzyloxy}$, 3'-$H_{4\text{-bromophenyl}}$, 5'-$H_{4\text{-bromophenyl}}$); $^{13}$C NMR ($CDCl_3$): *δ* [ppm] = 12.6 (1C, OC=C*C*H$_3$), 36.6 (1C, NCH$_2$*C*H$_2$Ph), 54.9 (1C, N*C*H$_2$CH$_2$Ph), 73.1 (1C, O*C*H$_2$Ph), 117.3 (1C, NCH=*C*HCO), 121.5 (1C, C-4'$_{4\text{-bromophenyl}}$), 128.2 (1C, C-4''$_{benzyloxy}$), 128.4 (2C, C-3''$_{benzyloxy}$, C-5''$_{benzyloxy}$), 129.4 (2C, C-2''$_{benzyloxy}$, C-6''$_{benzyloxy}$), 130.6 (2C, C-2'$_{4\text{-bromophenyl}}$, C-6'$_{4\text{-bromophenyl}}$), 132.3 (2C, C-3'$_{4\text{-bromophenyl}}$, C-5'$_{4\text{-bromophenyl}}$), 135.3 (1C, C-1'$_{4\text{-bromophenyl}}$), 137.6 (1C, C-1''$_{benzyloxy}$), 138.3 (1C, N*C*H=CHCO), 140.6 (1C, OC=*C*CH$_3$), 146.2 (1C, O*C*=CCH$_3$), 173.5 (1C, NCH=CH*C*O); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 2978, 1701, 1624, 1566, 1524, 1489, 1454, 1400, 1362, 1246, 1215, 1150, 1069, 1011, 972, 818, 737, 702; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{21}{}^{79}BrNO_2$: 398.0750, found: 398.0761; HPLC (method 1): $t_R$ = 20.3 min, purity 97.4 %.

### 4.2.43. 3-(Benzyloxy)-2-methyl-1-[4-(phenylethynyl)phenethyl]pyridin-4(1*H*)-one (56)

Under $N_2$ atmosphere, copper(I) iodide (10 mg, 0.05 mmol), tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol) and phenylacetylene (54 µL, 50 mg, 0.49 mmol) were added to a solution of **55** (140 mg, 0.35 mmol) in a mixture of triethylamine (5 mL) and acetonitrile (2 mL). The mixture was heated to reflux and additional phenylacetylene (54 µL, 50 mg, 0.49 mmol) was added. After stirring the mixture under reflux conditions for 16 h, the solvent was evaporated and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, ethyl acetate/methanol = 10:1, V = 20 mL) to give **56** as brown oil (99 mg, 0.24 mmol, 67 % yield). $R_f$ = 0.29 (dichloromethane/methanol = 10:1); $^1$H NMR ($CDCl_3$): $\delta$ [ppm] = 2.04 (s, 3H, OC=CC$H_3$), 2.90 (t, $J$ = 7.0 Hz, 2H, $NCH_2CH_2$Ph), 3.98 (t, $J$ = 7.0 Hz, 2H, N$CH_2$$CH_2$Ph), 5.24 (s, 2H, OC$H_2$Ph), 6.37 (d, $J$ = 7.5 Hz, 1H, NCH=C*H*CO), 6.92 (d, $J$ = 7.5 Hz, 1H, NC*H*=CHCO), 6.93 – 6.96 (m, 2H, 2'-$H_{4\text{-(phenylethynyl)phenyl}}$, 6'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.28 – 7.38 (m, 6H, 3"-$H_{phenyl}$, 5"-$H_{phenyl}$, 4"-$H_{phenyl}$, 3'''-$H_{benzyloxy}$, 5'''-$H_{benzyloxy}$, 4'''-$H_{benzyloxy}$), 7.40 – 7.46 (m, 4H, 2'''-$H_{benzyloxy}$, 6'''-$H_{benzyloxy}$, 3'-$H_{4\text{-(phenylethynyl)phenyl}}$, 5'-$H_{4\text{-(phenylethynyl)phenyl}}$), 7.50 – 7.55 (m, 2H, 2"-$H_{phenyl}$, 6"-$H_{phenyl}$); $^{13}$C NMR ($CDCl_3$): $\delta$ [ppm] = 12.6 (1C, OC=C$CH_3$), 37.1 (1C, $NCH_2CH_2$Ph), 55.0 (1C, N$CH_2CH_2$Ph), 73.2 (1C, O$CH_2$Ph), 88.8 (1C, *C*=C), 90.2 (1C, *C*=C), 117.3 (1C, NCH=*C*HCO), 122.6 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 123.2 (1C, C-1"$_{phenyl}$), 128.2 (1C, C-4'''$_{benzyloxy}$), 128.4 (2C, C-3'''$_{benzyloxy}$, C-5'''$_{benzyloxy}$), 128.5 (2C, C-3"$_{phenyl}$, C-5"$_{phenyl}$), 128.6 (1C, C-4"$_{phenyl}$), 129.0 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$), 129.4

(2C, C-2'''$_{benzyloxy}$, C-6'''$_{benzyloxy}$), 131.7 (2C, C-2''$_{phenyl}$, C-6''$_{phenyl}$), 132.3 (2C, C-3'$_{4-(phenylethynyl)phenyl}$, C-5'$_{4-(phenylethynyl)phenyl}$), 136.5 (1C, C-1'$_{4-(phenylethynyl)phenyl}$), 137.6 (1C, C-1'''$_{benzyloxy}$), 138.4 (1C, N*C*H=CHCO), 140.7 (1C, OC=*C*CH$_3$), 146.2 (1C, O*C*=CCH$_3$), 173.5 (1C, NCH=CH*C*O); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 2978, 2886, 1732, 1624, 1562, 1508, 1497, 1454, 1369, 1242, 1215, 1153, 1069, 968, 826, 752, 691; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{29}H_{26}NO_2$: 420.1958, found: 420.1961; HPLC (method 1): $t_R$ = 22.8 min, purity 97.9 %.

**4.2.44. 3-Hydroxy-2-methyl-1-[4-(phenylethynyl)phenethyl]pyridin-4(1*H*)-one (57)**

An emulsion of **56** (87 mg, 0.21 mmol) in a 6 M aqueous solution of hydrochloric acid (7.5 mL) and methanol (2 mL) was heated to reflux for 4 h. Then the reaction mixture was cooled to ambient temperature, a saturated aqueous solution of potassium carbonate was added, and the mixture was extracted with ethyl acetate (3×). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 1 cm, h = 15 cm, cyclohexane/ ethyl acetate = 1:2 → 0:1 → ethyl acetate/methanol = 10:1 → 10:1 + 0.1 % triethylamine, V = 5 mL) to give **57** as yellowish solid (43 mg, 0.13 mmol, 60 % yield). $R_f$ = 0.21 (ethyl acetate/methanol = 10:1); melting point = 212 °C (decomposition); $^1$H NMR (DMSO-d$_6$): $\delta$ [ppm] = 2.27 (s, 3H, OC=CC*H*$_3$), 3.00 (t, *J* = 7.3 Hz, 2H, NCH$_2$C*H*$_2$Ph), 4.17 (t, *J* = 7.3 Hz, 2H, NC*H*$_2$CH$_2$Ph), 6.04 (d, *J* = 7.3 Hz, 1H, NCH=C*H*CO), 7.24 – 7.29 (m, 2H, 2'-H$_{4-(phenylethynyl)phenyl}$, 6'-H$_{4-(phenylethynyl)phenyl}$), 7.40 – 7.45 (m, 4H, NC*H*=CHCO, 3''-H$_{phenyl}$, 5''-H$_{phenyl}$, 4''-H$_{phenyl}$), 7.46 – 7.51 (m, 2H, 3'-H$_{4-(phenylethynyl)phenyl}$, 5'-H$_{4-(phenylethynyl)phenyl}$), 7.52 – 7.57 (m, 2H, 2''-H$_{phenyl}$, 6''-H$_{phenyl}$); $^{13}$C NMR (DMSO-d$_6$): $\delta$ [ppm] = 11.3 (1C, OC=C*C*H$_3$), 36.1 (1C, NCH$_2$*C*H$_2$Ph), 53.5 (1C, N*C*H$_2$CH$_2$Ph), 89.2 (2C, *C*=*C*), 110.4 (1C, NCH=*C*HCO), 120.5 (1C, C-4'$_{4\text{-(phenylethynyl)phenyl}}$), 122.3 (1C, C-1''$_{\text{phenyl}}$), 128.4 (1C, OC=*C*CH$_3$), 128.71 (1C, C-4''$_{\text{phenyl}}$), 128.73 (2C, C-3''$_{\text{phenyl}}$, C-5''$_{\text{phenyl}}$), 129.5 (2C, C-2'$_{4\text{-(phenylethynyl)phenyl}}$, C-6'$_{4\text{-(phenylethynyl)phenyl}}$) 131.3 (2C, C-2''$_{\text{phenyl}}$, C-6''$_{\text{phenyl}}$), 131.4 (2C, C-3'$_{4\text{-(phenylethynyl)phenyl}}$, C-5'$_{4\text{-(phenylethynyl)phenyl}}$), 137.5 (1C, N*C*H=CHCO), 138.4 (1C, C-1'$_{4\text{-(phenylethynyl)phenyl}}$), 145.4 (1C, HO*C*=CCH$_3$), 168.9 (1C, NCH=CH*C*O); IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3653, 3136, 2978, 2889, 1624, 1574, 1531, 1508, 1443, 1381, 1346, 1265, 1223, 1184, 1157, 1061, 1042, 953, 818, 756, 691; HRMS (*m/z*): [M+H]$^+$ calcd for $C_{22}H_{20}NO_2$: 330.1489, found: 330.1502; HPLC (method 1): $t_R$ = 27.0 min, purity 99.5 % (tailing).

### 4.3. Metabolism studies

#### 4.3.1. *In silico* prediction of metabolism

Sites of metabolism were predicted with FAME 2[46] with default settings. SyGMa was executed via a KNIME[66] node available within the 3D-e-Chem virtual machine.[67-68] The number of phase 1 and phase 2 cycles were each set to “1”.

#### 4.3.2. *In vitro* metabolism studies with rat liver microsome suspensions

##### 4.3.2.1. Chemicals and materials

Double distilled water for HPLC and for the preparation of buffer solutions was generated by a Milli-Q Advantage Ultrapure Water System, Millipore (Billerica, MA, USA). Magnesium chloride hexahydrate was purchased from Honeywell Riedel-de Haën (Seelze, Germany). Acetonirtrile in LC-MS grade was obtained from Thermo Fischer Scientific (Schwerte, Germany). NADPH tetra sodium salt was purchased from Carl Roth (Karlsruhe, Germany). Formic acid p.a. was obtained from Acros Organics

(Thermo Fischer Scientific). Phosphate buffer saline tablets, uridine 5´-diphospoglucoronic acid trisodium salt (UDGPA), Coomassive Brilliant Blue G® and methanol in LC-MS grade were purchased from Sigma-Aldrich (Munich, Germany).

#### 4.3.2.2. Preparation of rat liver microsomes

Deep frozen livers of rats were obtained from the working group of Prof. Dr. M. Düfer, Institute of Pharmaceutical and Medicinal Chemistry, Münster, Germany.

Livers (20 g) were thawed in 1.15 % (m/V) potassium chloride solution at 4 °C. Livers were cut in slices and homogenized in an Elvehjem-Potter (10 strokes, 3 sec.) with 20 mL of cold phosphate buffer (pH 7.4, 0.1 M) containing sodium EDTA (0.5 mM). 60 mL of cold sodium phosphate buffer (pH 7.4, 0.1 M) was added and the resulting suspension centrifuged for 20 min at 4 °C at 9,000 g. The supernatant was centrifuged at 45,000 g for 90 min. The resulting microsome pallet was resolved in sodium phosphate buffer (pH 7.4, 0.1 M). Aliquots were stored at -80 °C prior to use.

#### 4.3.2.3. Determination of protein concentration[69]

Bradford solution:

5 mg Coomassie® Brilliant Blue G 250 was dissolved in 2.5 mL abs. ethanol. 10 mL dist. water and 5 mL of phosphoric acid were added. The solution was diluted with dist. water to 50 mL. The resulting solution was stored in the dark and at 4 °C overnight. Before the experiment, the solution was filtered twice through paper filters.

A stock solution of BSA in dist. water (1.25 mg/mL) was prepared. A multi-point calibration curve (19.5 µg, 39 µg, 78 µg, 156µg, 312 µg, 615 µg, 1000 µg all of them per mL) was created by dilution of the stock solution with dist. water. The samples where diluted 20-fold (50 µL microsome solution, 200 µL 1 M NaOH, 750 µL dist. water) and 50-fold (20 µL microsome solution, 200 µL 1 M NaOH, 780 µL dist. water). The measurements were performed in a 96-well plate. To 10 µL of a diluted sample and each of the calibration solutions, 190 µL Bradford solution were added, respectively. The plate was shaken for 5 min and the absorption at 595 nm was recorded. Samples and calibration were prepared in triplicate.

#### 4.3.2.4. Incubation of 3 with rat liver microsomes and cofactors

A stock solution of hydroxamic acid **3** in DMSO (1.0 µL, 10 mM) was added to a solution that contained PBS (pH 7.4, 23 µL, 0.1 M), $MgCl_2$ solution (50 µL, 50 mM), NADPH solution (50 µL, 2 mg/mL in PBS), UDPGA solution (50 µL, 2 mg/mL in PBS), and rat liver microsome suspension (26 µL, 7.8 mg protein/mL). The experiments were performed in duplicate. In case of the incubation without UDPGA or NADPH, 50 µL PBS was added instead of the solution of the respective cofactor. The resulting suspensions were mixed vigorously and shaken for 120 min at 37 °C (900 rpm). The incubation was stopped by the addition of ice-cold acetonitrile/methanol (1:1, 400 µL). The Eppendorf cups were cooled to 0 °C for 10 min using a water/ice bath. The precipitated proteins were separated via centrifugation (15 min, 16000 rpm, 4 °C) and the supernatant was analyzed by the LC-MS method described below in positive and negative ion polarity. With the same procedure, the empty value (without stock solution), the blank value (without cofactors) were prepared. To detect possible impurities in the stock solution, a positive control (599 µL solvent and 1 µL DMSO stock solution) was prepared and analyzed by the LC-MS method immediately.

#### 4.3.2.5. HPLC-ESI-MS with micrOTOF-Q II (HPLC method 3)

For the determination of exact masses, an Ultimate 3000 RS LC system from Dionex (Dionex Softron, Bremen, Germany) was coupled with a microOTOF-Q II (Bruker Daltonics, Bremen, Germany). The MS was operated with the standard ESI-source. The LC system consisted of a solvent rack (SRD 3600), a pump (DGP-3600RS), an autosampler (WPS-3000RS), a column oven (TCC-3000RS) and a DAD-dectector (DAD-3000RS) operating at 230 and 250 nm. Control of the system and data handling were carried out using the software Hystar and DataAnalysis from Bruker Daltonics (Bremen, Germany). The calibration of the TOF spectra was achieved by injection of 10 mM lithium formiate (isopropyl alcohol/bidist. water = 1:1) via a 20 µL sample loop within each LC run at 1 min. Precolumn: Security GuardTM Cartidge C18 (4.0 x 2.0 mm, 4 µm particle size); main column: Phenomenex Synergi Hydro RP (50 x 2.10 mm, 2.6 µm particle size); solvents: A: bidist. water/acetonitrile = 90:10 with 0.1% formic acid (V/V), B: bidist. water/acetonitrile = 10:90 with 0.1% formic acid (V/V); gradient elution: (A %): 0 – 5 min: gradient from 100 % to 0 %, 5 – 6.5 min: 0 %, 6.5 – 7 min: gradient from 0 % to 100 %, 7 – 10 min: 100 %; flow: 0.4 mL; temperature: 25 °C.

#### 4.3.2.6. Metabolite identification

**3**: HRMS (*m/z*): $[M+Na]^+$ calc for $C_{18}H_{17}NO_4Na$: 334.1050, found: 334.1023; $[M-H]^-$ calc for $C_{18}H_{16}NO_4$: 310.1085, found: 310.1091; HPLC (method 3): $t_R$ = 5.6 min.

**3+Glu**: HRMS (*m/z*): $[M+Na]^+$ calc for $C_{24}H_{25}NO_{10}Na$: 519.1371, found: 510.1331; $[M-H]^-$ calc for $C_{24}H_{24}NO_{10}$: 486.1406, found: 486.1414; HPLC (method 3): $t_R$ = 5.4 min.

**3-NH**: HRMS (*m/z*): $[M+Na]^+$ calc for $C_{18}H_{16}O_4Na$: 319.0941, found: 319.0905; $[M-H]^-$ calc for $C_{18}H_{15}NO_4$: 295.0976, found: 295.0991; HPLC (method 3): $t_R$ = 6.1 min.

## 4.4. Biological evaluation

### 4.4.1. 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* strain D22[61] were grown overnight in LB broth[70] 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, thickness 0.75 mm, Carl Roth). Pure DMSO, serving as a negative and CHIR-090,[71] 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.

### 4.4.2. Minimum Inhibitory Concentration (MIC) determination

The MIC values of the compounds were determined by means of the microdilution method using a 96-well plate and LB medium in the presence of 5% DMSO as previously reported by Tangherlini *et al*.[72] *E. coli* BL21 (DE3) and *E. coli* D22 were grown overnight in LB medium at 37 °C and 200 rpm. The overnight suspension was diluted 1:100 in fresh LB broth and 190 µL of the inoculated medium were dispensed to each well of a 96-well plate. 10 µL of a twofold dilution series of the compounds in DMSO (ranging from 1.28 mg/mL to 1.25 µg/mL) was added to the inoculated medium resulting in a final concentration range between 64 µg/mL to 62.5 ng/mL. Then the plates were incubated for 20 h at 37 °C and 200 rpm. The lowest concentrations at which no visible growth of bacteria could be observed were taken as the MIC values.[72]

#### 4.4.3. LpxC assay

The expression and purification of *E. coli* LpxCC63A was performed as previously described.[72] A fluorescence-based microplate assay for LpxC activity was performed as described by Clements *et al*.[62] 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 nM *o*-phthaldialdehyde-2-mercaptoethanol in 0.1 M borax[73] 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 $K_i$ and $IC_{50}$

values are given as mean value ± SD from three independent experiments. The $K_M$ value was calculated from the Lineweaver-Burk plot.

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