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Synthesis of orthogonally protected 2-deoxystreptamine stereoisomers

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Abstract—Enantiomerically pure 4,6-diaminocyclohexenols are obtained from carbohydrate derived 1,7-dienes by ring-closing metathesis and palladium catalyzed allylic amination using *o*-nitrobenzenesulfonylamides as nucleophiles. In the latter reaction the use of a cyclic carbonate as a leaving group proved to be essential to facilitate a smooth substitution. The obtained compounds were converted into orthogonally protected diaminocyclitols, which are stereoisomers of the naturally occurring 2-deoxystreptamine, a constituent of aminoglycoside antibiotics.

1. Introduction

RNA is involved in several important biological processes including protein synthesis and regulation of transcription and translation. Small molecules that are able to modulate RNA functions are interesting compounds for the development of drugs.[1] For example, aminoglycoside antibiotics, such as neomycin B and kanamycin B (Fig. 1), form a major lead in RNA targeting drug research. The current clinical use of aminoglycoside antibiotics is based on the binding to the A-site of 16S rRNA[2] and its ability to induce misreading of the genetic code.[3] In the last decade aminoglycosides have been shown to target a variety of other RNA structures including hepatitis delta virus ribozyme,[4] HIV *trans*-activating region (TAR),[5] and HIV rev responsive element (RRE).[6] It may be expected that the development of aminoglycosides that can selectively target RNA structures will broaden the application of aminoglycoside antibiotics.

The preparation of aminoglycoside analogs has attracted the

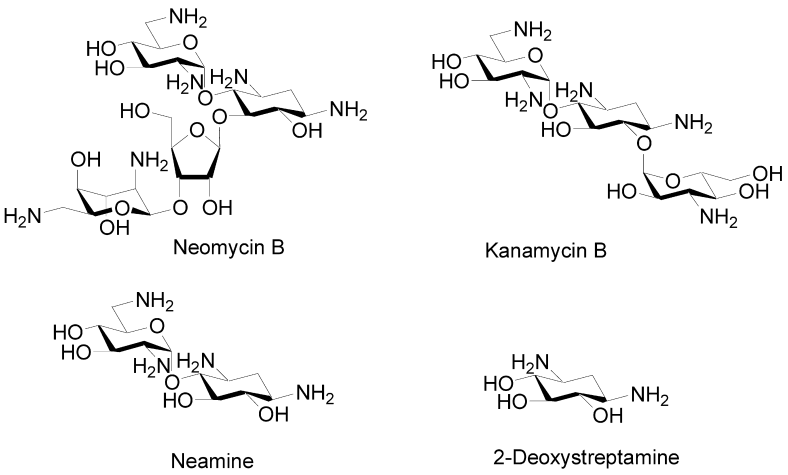

Figure 1. Examples of aminoglycoside antibiotics.

Keywords: Aminoglycoside antibiotics; 2-Deoxystreptamine; Cyclitols; Allylic substitution.
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attention of synthetic chemists. Most recent studies are based on the derivatization of natural aminoglycosides or substructures thereof, such as neamine and 2-deoxystreptamine (2-DOS; Fig. 1). For example, 2-DOS has been functionalized with polyamines[7] and aryl substituents.[8] Another promising approach towards the construction of aminoglycoside analogs is based on the glycosylation of cyclitol building blocks. The naturally occurring 2-DOS can be effectively obtained in its *meso* form by hydrolysis of neomycin B,[9] while protected and enantiomerically pure 2-DOS can be prepared by chemical transformation of neamine[10] or enzymatic desymmetrization of 2-DOS.[11] Both 2-DOS and its 2,5-dideoxy congener[12] have recently been used in glycosylations to obtain analogs of aminoglycoside antibiotics that closely resemble the natural products.[11,13,14]

The functionalization of synthetic, unnatural diaminocyclitols represents an attractive alternative strategy towards selective RNA binding molecules. The stereochemically more diverse aminoglycosides resulting from this approach can be an important extension of the aminoglycoside antibiotic research, since the three-dimensional positioning of the amino groups in the aminoglycoside core may well be decisive for selective interaction with the negatively charged binding pockets in RNA.[15]

We here report the synthesis, starting from carbohydrate derivatives, of chiral diaminocyclohexene derivatives **A** (Fig. 2) and their conversion into orthogonally protected stereoisomers of 2-deoxystreptamine (**B**), which are valuable compounds in the design of novel aminoglycoside antibiotics having unnatural stereochemistry.

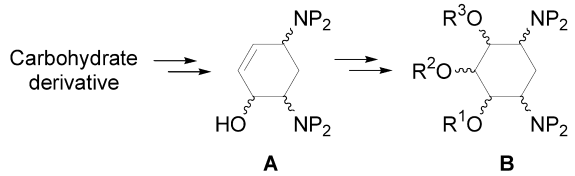
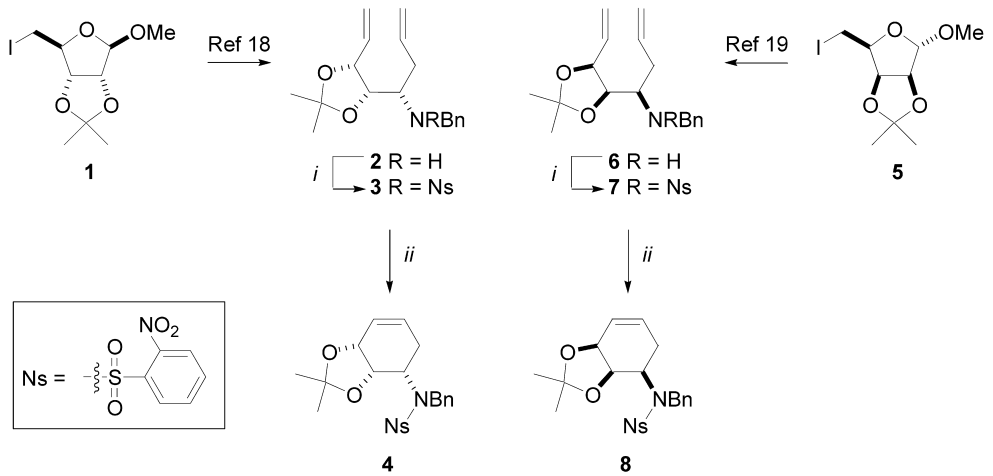


Figure 2. Strategy towards stereoisomers of 2-DOS.

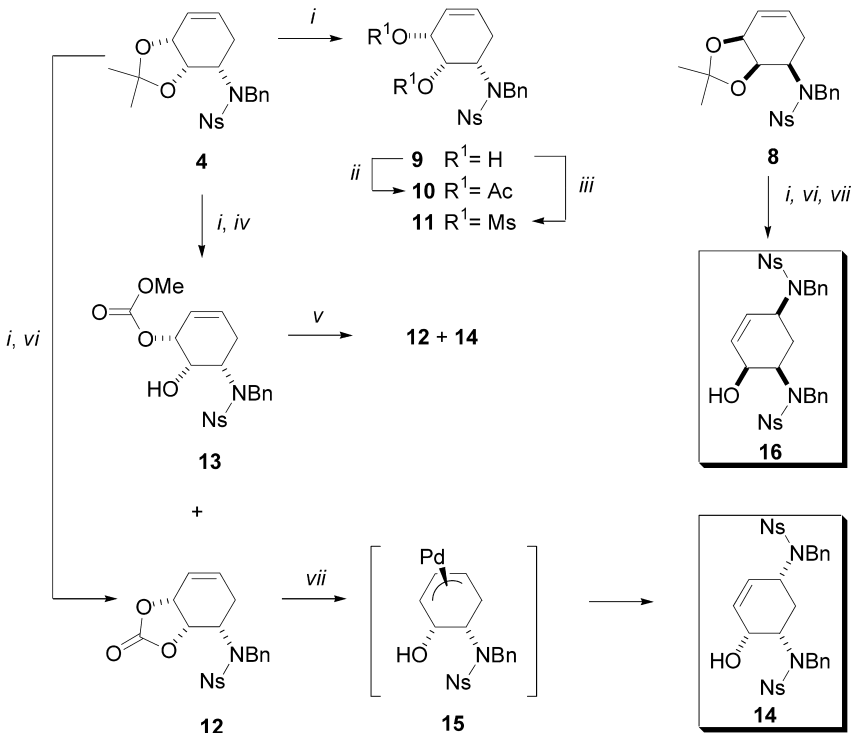
2. Results and discussion

The first objective in our approach comprises the transformation of a carbohydrate derivative into a six-membered carbocycle. A revolution in the synthesis of carbocycles was caused by the development of powerful metathesis catalysts.[16] Specifically, cyclization of 1,7-dienes by ring-closing metathesis proved to be an attractive method to synthesize cyclitols.[17,18] In the first instance, we used 1,7-dienes, prepared by the Vasella–Barbier reaction[18] of easily accessible 5-iodopentafuranosides, in the synthesis of diaminocyclohexenols **14** and **16**.[19] 1,7-Diene **2** was synthesized from methyl 5-deoxy-5-iodo-2,3-isopropylidene-β-D-ribofuranoside **1** in a one-pot process including Vasella fragmentation, entrapment of the intermediate aldehyde by an amine and subsequent Barbier type imine allylation (Scheme 1).[18] Similarly, the enantiomeric 1,7-diene **6** was obtained starting from methyl 5-deoxy-5-iodo-2,3-isopropylidene-β-D-lyxofuranoside (**5**).[19] The secondary amino functions in compounds **2** and **6** were protected with the *o*-nitrobenzenesulfonyl[20] (nosyl, Ns) group to give **3** and **7** in 92 and 89% yield, respectively. Both protected dienes smoothly underwent ring-closing metathesis using 0.5 mol% Grubbs' catalyst ($Cl_2(PPh_3)_2Ru{=}CHPh$)[16a] to give the fully protected cyclohexene derivatives **4** and **8**.

It was envisaged that a palladium catalyzed allylic amination using nitrobenzenesulfonamides as nucleophiles[21] could be employed to introduce the second amine functionality on the carbocyclic ring. In order to enable substitution, the protected allylic hydroxyl in compounds **4** and **8** had to be converted into a suitable leaving group. To this end, several leaving groups were installed on ribose-derived scaffold **4**. 1,2-Diacetate **10** and 1,2-dimesylate **11**, were obtained by cleavage of the isopropylidene and subsequent acetylation or mesylation of diol **9** (Scheme 2). Unfortunately, both compounds were unreactive, which is rather surprising, taken into consideration that especially allylic acetates are often used in Pd(0)-catalyzed allylic substitutions. It was expected that productive Pd(0) catalyzed allylic substitution could be effected when the hydroxyl functions of diol **9** were converted into methylcarbonates. This functionality has been described in the literature to be favorable compared with acetates, as CO_2 is



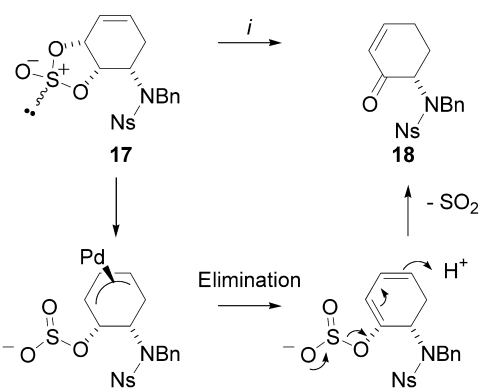
Scheme 1. Reagents and conditions: (i) *o*-Nitrobenzenesulfonylchloride (NsCl), DCM/sat. Na_2CO_3, **3**: 92%, **7**:89%. *(ii)* Grubbs' catalyst (0.5 mol%), quant.



Scheme 2. Reagents and conditions: (i) AcOH/H_2O 8:2, reflux. (ii) Ac_2O, pyridine, 94% (2 streps from **4**). (iii) MsCl (5 equiv.), pyridine, 69% (2 steps from **4**). (iv) Methyl chloroformate (5 equiv.), pyridine (6 equiv.), DCM. (v) NsNHBn (2.2 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF. (vi) Phosgene (1.1 equiv.), pyridine, DCM, **12**: 98%. (vii) NsNHBn (1.3 equiv.), $Pd_2(dba)_3{-}CHCl_3$ (0.25 mol%), PPh_3 (2.5 mol%), Et_3N (3 equiv.), THF, **14**: 87%. **16**: 76% (three steps).

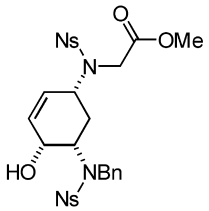
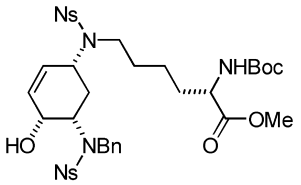
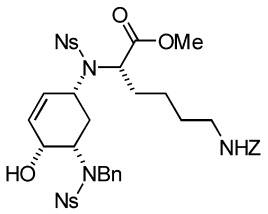
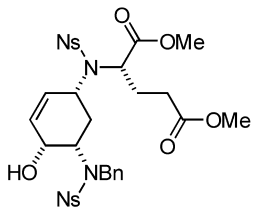
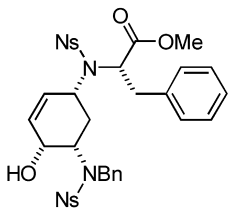
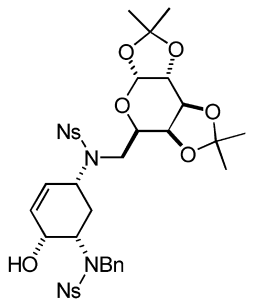
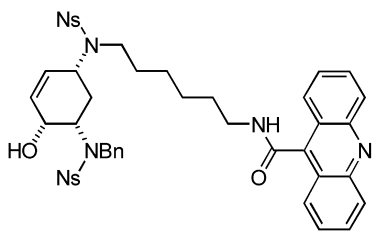
liberated upon substitution, leading to a favorable entropic contribution.[22] However, the installation of methylcarbonate functionalities on the hydroxyls of compound **9** did not proceed efficiently. Reaction of **9** with an excess of methylchloroformate led to the formation of a mixture of cyclic carbonate **12** and monosubstituted compound **13**. Subjection of **13** to the Pd(0)-catalyzed allylic amination using *N*-benzyl-nosylamide as a nucleophile, led to the sluggish formation of cyclic carbonate **12**, presumably via intramolecular attack of the free hydroxyl group on the carbonyl function (Scheme 2). Apart from this, a small amount of target molecule **14** was detected, probably originating from substitution of the in situ formed cyclic carbonate **12**. The latter reaction did not go to completion due to degradation of the palladium catalyst, as judged by the color of the reaction mixture, which turned from bright yellow to dark brown. However, cyclic carbonate **12** could be prepared on a large scale by hydrolysis of acetonide **4** under standard conditions and subsequent reaction of the diol with a slight excess of phosgene (98%; Scheme 2). Pd(0) catalyzed allylic amination of **12** gave the diaminocyclohexene derivative **14** in 87% yield. The regio- and stereoselectivity of this reaction originates from the formation of the π-allyl complex **15** and subsequent attack of the nucleophile at the less hindered carbon atom. Subjection of the enantiomeric carbocycle **8** to the same reaction conditions gave the diaminocyclohexene derivative **16**, which was isolated in 76% yield over 3 steps (Scheme 2).

The observation that cyclic carbonate **12**, but not its acyclic counterpart **13**, was a useful substrate indicates that the release of carbon dioxide and possibly the relief of strain in the five-six fused ring system of compound **12** upon formation of the π-allyl complex provides a favorable energetic contribution resulting in a smooth and high yielding reaction. We expected that cyclic sulfite **17**, accessible after reaction of diol **9** with thionylchloride, would follow a similar course to give compound **14**. However, subjection of **17** to the paladium catalyzed allylic amination gave the unexpected cyclohexenone derivative **18** in a non-optimized yield of 30%. The formation of **18** may be explained by the mechanism proposed in Scheme 3. Instead of substitution of the π-allyl complex by the nitrosulfonamide nucleophile, elimination of palladium takes place followed by liberation of sulfur dioxide to form the α,β-unsaturated ketone **18**. The observation that performing the reaction in the absence of catalyst did not result in the formation of **18** illustrates that the Pd(0) species plays a crucial role.[23]



Scheme 3. Reagents and conditions: (i) NsNHBn (2.2 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF.

Table 1. Transformation of **5** into 4,6-diaminocyclohexene derivatives[a]

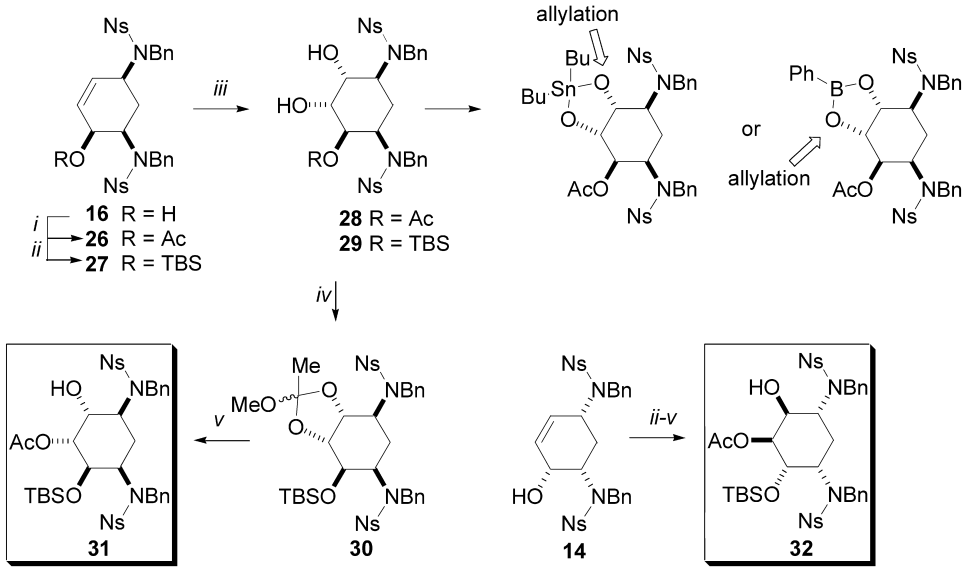
Entry	Product		Yield (%)
1		**19**	85
2		**20**	71
3		**21**	36
4		**22**	37
5		**23**	44 (51)[b]
6		**24**	80
7		**25**	58

[a] General conditions: NsNHR (1.5 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF.
[b] 10% Pd(0) catalyst was used.

The scope of the allylic amination of cyclic carbonate **12** was broadened by the use of other nosylamides as nucleophiles, leading to highly functionalized diaminocyclohexene derivatives (Table 1). Application of Ns-glycine methyl ester and ε-Ns-α-Boc-L-lysine methyl ester as nucleophiles led to the formation of peptide derivatives **19** and **20** in 85 and 71%, respectively. Lysine, glutamic acid and phenylalanine derivatives **21**–**23** were synthesized using the respective amino acids with a Ns-group at the α-amino functions. However, yields were lower compared to those in entry 1 and 2, probably due to steric hindrance around the nucleophilic center. A double amount of palladium catalyst only led to a slight increase in yield (see entry 5). In an attempt to improve the yield of the substitution by α-amino acids, several additional experiments were conducted using phenylalanine derivatives. However, the use of the less sterically demanding *p*-nitrobenzenesulfonyl group and the more electron withdrawing di-nitrobenzenesulfonyl group did not have a beneficial effect on the outcome of the reaction.

Besides nosyl-protected amino acids, acridine and galactose derivatives featuring a terminal nosylated amine were reacted with cyclic carbonate **12** to give compounds **24** and **25** in satisfactory yields (entry 6 and 7). The latter two compounds are of particular interest in the synthesis of aminoglycoside analogs. Acridine conjugate **24** can combine the RNA binding properties of positively charged amino functions on the aminocyclitol with the intercalating properties of acridine. Compound **25** illustrates that the cyclitol moiety can be easily appended to carbohydrates via an amine bond instead of a more difficult to introduce glycosidic linkage.

At this stage, we focused our attention on the conversion (Scheme 4) of the 4,6-diaminocyclohexene derivatives **14** and **16** into orthogonally protected 2-deoxystreptamine stereoisomers **31** and **32**. The first step entails protection of the allylic alcohol function in **16**. It was anticipated that the difference in reactivity of the equatorial and axial hydroxyl function, resulting from dihydroxylation of the double bond, could be utilized for selective introduction of a protective group. For example, the use of organotin derivatives in alkylations is a well-established method to discriminate between equatorial and axial hydroxyl functions.[24] With the purpose to regioselectively introduce an allyl protecting group, we first acetylated the alcohol function in compound **16**. Dihydroxylation of **26** using *N*-methylmorpholine-*N*-oxide (NMO) and a catalytic amount of osmium tetroxide yielded **28** in 92% yield (Scheme 4). Several attempts to allylate the equatorial hydroxyl in **28** via the tin-ketal procedure were abortive. Exploration of a recently reported regioselective alkylation of cyclic phenylboronate derivatives[25] on our substrates was also not successful. It may therefore be concluded that the hydroxyl functions in **28** are not reactive enough due to the electron withdrawing protecting groups on the nitrogen and oxygen functionalities. On the other hand, it is well documented that the opening of an orthoester of pyranose derivatives proceeds to give the axial acetate. Therefore, we decided to use this method in our route. The synthesis of the required orthoester **31** was accomplished by the following steps. The free hydroxyl in compound **16** was protected with a TBS group



Scheme 4. Reagents and conditions: (i) Ac_2O, pyridine, quant. (ii) TBSCl (3 equiv.), imidazole (4 equiv.), DMF, 59% or TBSOTf (1.2 equiv.), pyridine (5 equiv.), DCM, 89%. (iii) NMO (2.2 equiv.), $K_2OsO_4{\cdot}2H_2O$ (1 mol%); **28**: 92%, **29**: 94%. (iv) $(MeO)_3CHMe$, *p*-TsOH, DCM; (v) AcOH/H_2O (v/v); **31**: 95%. **32** 71% (4 steps).

under standard conditions (TBSCl, imidazole, DMF) to give compound **27** in a yield of 59%. The more reactive silylating agent TBS triflate yielded **27** in 89%. Dihydroxylation of **27** using a catalytic amount of osmium tetroxide and NMO as a co-oxidant provided 2-DOS stereoisomer **29** in 94% yield. Treatment of *cis*-diol **29** with trimethyl orthoacetate and subsequent acid mediated cleavage of the resulting orthoester yielded the desired orthogonally protected derivative **31** in 95%. Similarly, enantiomer **14** gave the second 2-deoxystreptamine stereoisomer **32** in 71% yield over the four last steps.

3. Conclusion

In this paper, we presented a route towards chiral, 4,6-diaminocyclohexene derivatives starting from carbohydrate derived 1,7-dienes. The versatility of our approach was demonstrated by the use of structurally diverse nucleophiles including amino acid, carbohydrate and intercalator derived nosyl amides. Two of the thus obtained diaminocyclohexene derivatives were converted into orthogonally protected diaminocyclitols via a four-step procedure. The use of 2-deoxystreptamine stereoisomers **31** and **32** in the construction of novel, stereochemically diverse aminoglycoside antibiotics, is currently under investigation.

4. Experimental

4.1. General methods and materials

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker AC-200 (200 MHz, 50.1 MHz, respectively), a Bruker DPX-300 (300 MHz, 75.1 MHz respectively), a Bruker AV-400 (400 MHz, 100 MHz respectively) or a DMX-600 (600 MHz, 150 MHz respectively). ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to tetramethyl silane (0.0) or $CDCl_3$ (77.0) as internal standards. Mass spectra were recorded on a Perkin–Elmer Sciex API 165 equipped with a custom made electrospray interface (ESI). Column chromatography was performed on silica gel 60 (230–400 mesh, Fluka). TLC-analysis was conducted on TLC-plastic sheets 60 F_{254} (Merck) with detection by UV absorption (254 nm) where applicable and/or by spraying with 20% H_2SO_4 in EtOH or a solution of molybdate (ammonium molybdate 25 g/L) and ceric ammonium sulfate (10 g/L in 10% aq. H_2SO_4) followed by charring at ~150 °C. Olefins were visualized by spraying with a permanganate solution (2% $KMnO_4$ and 1% K_2CO_3 in water).

4.2. Experimental procedures

Before performing reactions that require anhydrous conditions, traces of water were removed from the starting material by coevaporation with 1,2-dichloroethane, 1,4-dioxane or toluene. Reactions were run at ambient temperature unless stated otherwise.

4.3. General procedure for the Pd(0) catalyzed allylic aminations

THF was freshly distilled from $LiAlH_4$ under argon. Triethylamine was distilled from $LiAlH_4$ and stored on KOH. To a solution of the carbocycle and the appropriate nosylamide (1.5 equiv.) in THF (final concentration of carbocycle: 0.1 M) under argon was added 3 equiv. of Et_3N, 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 25 mol% of triphenylphosphine. The red mixture turned into a bright yellow solution within 1 min. After TLC analysis indicated no change in the composition of the reaction mixture, the solvent was evaporated and the reaction mixture was purified by column chromatography. Reactions were performed on a 50–100 mg scale. Note that on a large scale (see compounds **14** and **16**) the amount of catalyst was reduced to 0.25 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 2.5 mol% PPh_3.

4.4. *o*-Nitrobenzenesulfonyl-*N*-benzylamine

Benzylamine (8.7 mL, 80 mmol) was added to a mixture of $NaHCO_3$ (13.44 g, 160 mmol), dioxane (200 mL) and water (200 mL). To the white suspension, NsCl (19.5 g, 88 mmol, 1.1 equiv.) was added in portions. The reaction mixture was stirred for 2 h followed by evaporation of the solvents. The light yellow residue was dissolved in water (150 mL) and extracted EtOAc (4×150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The solid material was recrystallized from toluene/PE, affording the title compound (21.93 g, 75 mmol, 94%) as white crystals, mp 97 °C. ν_{max} (neat): 3294, 1541, 1367, 1340, 1171 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ_H 8.03–7.98 (m, 1H, H_{arom}), 7.85–7.81 (m, 1H, H_{arom}), 7.72–7.60 (m, 2H, H_{arom}), 7.22 (s, 5H, H_{arom}), 5.72 (m, 1H, NH), 4.32 (d, 2H, CH_2 Bn, J=6.6 Hz). ESI-MS: *m/z*: 315.0 $[M+Na]^+$, 607.2 $[2M+Na]^+$. HRMS: MNH_4^+, found 310.0849, $C_{13}H_{16}N_3O_4S$ requires 310.0862.

4.4.1. (3*R*,4*S*,5*S*)-3,4-*O*-Isopropylidene-5-(*N*-benzyl)-*o*-nitro-benzenesulfon-amino-octa-1,7-dien-3,4-diol (3). Aminodiene **2** (16.2 g, 56.5 mmol) was dissolved in DCM/sat Na_2CO_3 (1:1 v/v, 250 mL) and NsCl (18.8 g, 84.8 mmol, 1.5 equiv.) was added. The reaction mixture was stirred vigorously overnight. Pyridine was added to destroy the excess of NsCl and, after stirring for 15 min, the solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Silicagel column chromatography (elution 10%→20% EtOAc in light petroleum) yielded **3** (24.7 g, 52.2 mmol, 92%) as a white, crystalline solid, mp 90–91 °C. $[\alpha]_D^{20}$=+86 (c=0.50, $CHCl_3$). ν_{max} (neat): 1541, 1371, 1340, 1159, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ_H 7.54–7.15 (m, 9H, H_{arom}), 6.07–5.89 (m, 1H, H2 or H7), 5.73–5.65 (m, 1H, H2 or H7), 5.54–5.35 (m, 4H, H1, H8), 5.00–4.79 (m, 2H, H3, H4), 4.75 (d, 1H, C*H*H Bn, J=15.4 Hz), 4.56 (d, 1H, CH*H* Bn, J=15.4 Hz), 4.21–4.07 (m, 1H, H5), 2.47–2.34 (m, 1H, C*H*H H6), 2.22–2.11 (m, 1H, CH*H* H6), 1.47 (s, 3H, Me isoprop), 1.26 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 147.0, 136.7, 134.1 ($C_{q,\ arom}$), 134.3, 132.9, 131.1, 130.9, 128.8, 127.9, 127.1, 123.5 (CH_{arom}, H2, H7), 118.3, 117.0 (C1, C8), 108.3 (C_q isoprop), 81.1, 78.2 (C3, C4), 59.0 (C5), 48.5 (CH_2 Bn), 32.1 (C6), 26.1, 24.1 (Me isoprop). HRMS: MNH_4^+, found 490.2058, $C_{24}H_{32}N_3O_6S$ requires 490.2012.

4.4.2. (1*S*,2*R*,6*S*)-3-(*N*-Benzyl)-*o*-nitrobenzenesulfon-amino-1,2-*O*-isopropylidene-cyclohex-3-en-1,2-diol (4). Oxygen was removed from a solution of compound **3** (24.7 g, 52.2 mmol) in DCM (500 mL) by purging with argon for 15 min. Grubbs' catalyst $Cl_2(PPh_3)_2Ru$=CHPh (210 mg, 0.5 mol%) was added and the solution was stirred overnight under argon. The solvent was evaporated under reduced pressure affording crude **4** as a light brown foam. Crude RCM-product was applied in the next step without purification. A small purified sample was used for characterization. $[\alpha]_D^{20}$=−50.0 (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ_H 7.60–7.12 (m, 9H, H_{arom}), 5.75–5.68 (m, 1H, H_{olef}), 5.56–5.50 (m, 1H, H_{olef}), 4.94 (d, 1H, C*H*H Bn, J=16.1 Hz), 4.77–4.69, 4.49–4.39 (2m, 4H, CH*H* Bn, H1, H2, H6), 2.55–2.40 (m, 1H, C*H*H H5), 2.19–2.04 (m, 1H, CH*H* H5), 1.33 (s, 3H, Me isoprop), 1.26 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 147.0, 137.3, 134.0 ($C_{q,\ arom}$), 133.0, 131.2, 130.5, 127.8, 127.7, 126.9, 126.7, 125.9, 123.6 (CH_{arom}, C3, C4), 109.7 (C_q isoprop), 76.1, 74.8 (C1, C2), 55.1 (C6), 49.0 (CH_2 Bn), 27.5, 26.5 (Me isoprop), 25.1 (C5). ESI-MS: *m/z* 467.2 $[M+Na]^+$, 911.4 $[2M+Na]^+$.

4.4.3. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfonamino-cyclohex-3-ene-1,2-diol (9). Crude product **4** was refluxed in AcOH/H_2O (8:2, v/v, 0.2 M final concentration) for 2 h. After TLC analysis had showed complete conversion to a lower running product, the mixture was concentrated with coevaporation from toluene to remove traces of water and acetic acid. The crude diol was immediately used for protection of the hydroxyl functions.

4.4.4. (1*S*,2*R*,6*S*)-1,2-Di-*O*-acetyl-6-(*N*-benzyl)-*o*-nitrobenzenesulfonamino-cyclohex-3-ene-1,2-diol (10). A solution of compound **9** (888 mg, 2.0 mmol, 0.2 M in pyridine/Ac_2O) and dimethylaminopyridine (cat.) was stirred overnight. Solvents were removed under reduced pressure. 1 M HCl was added and the mixture was extracted two times with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ and brine. Water phases were backextracted. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography yielded title compound **10** (914 mg, 1.87 mmol, 94%) as a white solid, mp 132 °C. $[\alpha]_D^{20}$=−55 (c=0.50, $CHCl_3$). ν_{max} (neat): 1740, 1539, 1373, 1219, 1165, 1034, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.16 (m, 9H, H_{arom}), 5.86–5.81 (m, 1H, H_{olef}), 5.65–5.58 (m, 2H, H1, H2), 5.42–5.39 (m, 1H, H_{olef}), 4.75 (d, 1H, C*H*H Bn, J=16.6 Hz), 4.59 (d, 1H, CH*H* Bn, J=16.6 Hz), 4.51 (dd, 1H, H6, J=5.6, 11.2 Hz), 2.65–2.56 (m, 1H, C*H*H H5), 2.26 (dt, 1H, CH*H* H5, J=5.4, 17.0 Hz), 1.94 (s, 3H, Me Ac), 1.90 (s, 3H, Me Ac). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 169.7 (CO), 137.0, 134.0 ($C_{q,\ arom}$), 133.5, 131.7, 131.2, 128.5, 127.4, 127.2, 124.3, 124.0 (C3, C4, CH_{arom}), 70.6, 69.6 (C1, C2), 53.8 (C6), 49.0 (CH_2Bn), 26.8 (C5), 20.9, 20.7 (Me Ac). ESI-MS: *m/z*=511.2 $[M+Na]^+$, 977.4 $[M+M+H]^+$, 999.3 $[M+M+Na]^+$. HRMS: MNH_4^+, found 506.1605, $C_{23}H_{28}N_3O_8S$ requires 506.1597.

4.4.5. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfon-amino-1,2-di-*O*-methanesulfonyl-cyclohex-3-ene-1,2-diol (11). Methanesulfonylchloride (131 μL, 1.69 mmol, 10 equiv.) was added to a solution of compound **9** (150 mg, 0.338 mmol) in pyridine (3 mL). The solution was stirred overnight and concentrated under reduced pressure. EtOAc was added and the solution was washed with 1 M HCl, sat. $NaHCO_3$ and brine. Water phases were separately back-extracted with EtOAc and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography yielded compound **11** (131 mg, 0.234 mmol, 69%) as a yellowish oil. ν_{max} (neat): 1539, 1340, 1159 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ_H 7.59–7.13 (m, 9H, H_{arom}), 5.99–5.89, 5.63–5.36 (m, 4H, H1, H2, H3, H4), 5.02 (d, 1H, C*H*H Bn, J=16.8 Hz), 4.75 (d, 1H, CH*H* Bn, J=16.8 Hz), 4.69–4.61 (m, 1H, H6), 3.17 (s, 3H, Ms), 3.12 (s, 3H, Ms), 2.61–2.26 (m, 2H, H5). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 147.0, 136.4, 133.8 ($C_{q,\ arom}$),

133.8, 133.5, 131.9, 131.1, 130.0, 128.2, 127.6, 127.4, 123.8, 122.3 (C3, C4, CH_{arom}), 79.9, 76.2 (C1, C2), 53.7 (C6), 48.9 (CH_2 Bn), 39.5, 38.0 (2× Ms), 26.7 (C5).

4.4.6. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfonamino-1,2-*O*-carbonyl-cyclo-hex-3-ene-1,2-diol (12). Compound **9** (52.2 mmol) was dissolved in pyridine (19 mL) and DCM (40 mL), placed under argon and cooled to 0 °C. Next, phosgene (30 mL, 1.93 M in toluene, 58 mmol, 1.1 equiv.) was carefully added over a period of approximately 2 min. The reaction mixture was stirred for 2 h, after which the excess phosgene was quenched with water. The resulting mixture was poured into 1 M HCl. After separation of the organic layer, the water layer was extracted twice with DCM. Combined organic layers were washed with diluted $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silicagel column chromatography (elution 0%→16% EtOAc in toluene) furnished **12** (21.99 g, 51.1 mmol, 98%) as a white foam. $[\alpha]_D^{20}=-76.4$ (c=1.0, $CHCl_3$). ν_{max} (neat): 1798, 1539, 1369, 1344, 1153, 1126, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ_H 7.52–7.47 (m, 2H, H_{arom}), 7.40–7.39 (d, 1H, H_{arom}, J=8.0, 1.4 Hz), 7.27–7.24 (m, 1H, H_{arom}), 7.19–7.13 (m, 2H, H_{arom}), 7.07–7.04 (m, 3H, H_{arom}), 6.04 (ddd, 1H, H_{olef}, J=10.2, 6.2, 1.9 Hz), 5.64–5.61 (m, 1H, H_{olef}), 5.25–5.22 (m, 1H, H2), 5.09–5.07 (m, 1H, H1), 4.80 (d, 1H, C*H*H Bn, J=15.9 Hz), 4.55–4.52 (m, 2H, H6, CH*H* Bn), 2.47–2.42 (m, 1H, C*H*H H5), 2.32–2.28 (m, 1H, CH*H* H5). ^{13}C NMR ($CDCl_3$, 150 MHz): δ_C 154.1 (CO), 147.0, 135.7, 134.2 ($C_{q,\ arom}$), 133.4, 132.7, 131.7, 131.2, 128.3, 128.1, 127.7, 124.0, 121.1 (C1, C2, CH_{arom}), 79.0, 75.1 (C1, C2), 54.4 (C6), 49.3 (CH_2 Bn), 25.2 (C5). ESI-MS: m/z=431.2 $(M+H)^+$. HRMS: MNa^+, found 453.0672, $C_{20}H_{18}N_2O_7SNa$ requires 453.0732.

4.4.7. (1*R*,4*R*,6*S*)-4,6-Bis[(*N*-benzyl)-*o*-nitrobenzenesulfon-amino]-cyclohex-2-enol (14). To a solution of cyclic carbonate **12** (14.63 g, 34 mmol) and *o*-nitrobenzenesulfonyl-*N*-benzylamine (12.9 g, 44.2 mmol, 1.3 equiv.) in THF under argon, was added Et_3N (14.2 mL, 102 mmol, 3 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (87 mg, 0.25 mol%) and triphenylphosphine (223 mg, 2.5 mol%). The initial dark red solution turned bright yellow, and the solution was stirred for 3 h, followed by concentration under reduced pressure. Silica column chromatography (elution 0%→12.5% EtOAc in toluene) yielded the title compound (20.10 g, 29.6 mmol, 87%) as a white foam. $[\alpha]_D^{20}=-17.8$ (c=1.0, $CHCl_3$). ν_{max} (neat): 1539, 1340, 1157 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ_H 7.79–7.70 (m, 1H, H_{arom}), 7.56–7.51 (m, 5H, H_{arom}), 7.43–7.40 (m, 1H, H_{arom}), 7.39–7.36 (m, 1H, H_{arom}), 7.19–7.04 (m, 10H, H_{arom}), 5.80 (ddd, 1H, H_{olef}, J=10.0, 5.7, 2.6 Hz), 5.56–5.54 (m, 1H, H_{olef}), 4.69–4.65 (m, 1H, H4), 4.58 (d, 1H, C*H*H Bn, J=16.4 Hz), 4.50 (d, 1H, C*H*H Bn, J=15.8 Hz), 4.41 (d, 1H, CH*H* Bn, J=16.4 Hz), 4.27 (d, 1H, CH*H* Bn, J=15.8 Hz), 4.14 (bs, 1H, H1), 3.96 (dt, 1H, H6, J=13.1, 2.9 Hz), 2.04–1.97 (m, 1H, C*H*H H5), 1.80–1.74 (m, 1H, CH*H* H5), 1.53 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ_C 147.49, 147.46, 137.28, 133.84 ($C_{q,\ arom}$), 133.78, 133.52, 133.39, 131.68, 131.65, 131.37, 131.32, 130.95, 130.92, 128.51, 128.38, 127.73, 127.68, 127.45, 124.12, 124.08 (C2, C3, CH_{arom}), 66.72 (C1), 56.97, 56.75 (C4, C6), 49.29, 48.79 (CH_2 Bn), 27.44 (C5). ESI-MS: m/z=701.4 $[M+Na]^+$.

4.4.8. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfonamino-1,2-*O*-sulfonyl-cyclohex-3-ene-1,2-diol (17). A solution of pyridine (170 μL, 2.1 mmol, 2.1 equiv.) in EtOAc (1 mL) was added to a solution of compound **9** (444 mg, 1.0 mmol) and $SOCl_2$ (77 μL, 1.05 mmol) in EtOAc (4 mL) cooled in the waterbath. After TLC analysis indicated complete conversion to a higher running product (±1 h), the reaction was diluted with 1 M HCl and extracted twice with EtOAc. Organic phase was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (elution 0%→12.5% EtOAc in toluene) afforded cyclic sulfite **17** (350 mg, 0.77 mmol, 77%) as a white foam, being a mixture of two diastereoisomers of the sulfur ylide. ν_{max} (neat): 1541, 1369, 1346, 1209, 1161, 1124 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.59–7.10 (m, 9H, H_{arom}), 5.97–5.81, 5.60–5.56, 5.40–5.37 (3× m, 4H, H1, H2, H3, H4), 5.02–4.89 (m, 1H, benzylic H), 4.80–4.63 (m, 2H, H6, benzylic H), 2.69–2.61, 2.48–2.22 (2× m, 2H, H5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 136.1, 136.0 ($C_{q,\ arom}$), 133.4, 133.2, 131.7, 131.6, 131.3, 131.5, 129.9, 129.8, 128.4, 128.3, 128.2, 127.7, 127.5, 124.1, 124.0, 123.7, 122.4 (C3, C4, CH_{arom}), 85.0, 81.3, 80.2, 79.0 (C1, C2), 55.2, 53.8 (C6), 49.4, 49.3 (CH_2 Bn), 25.6, 25.2 (C5). ESI-MS: m/z=450.9 $[M+H]^+$, 468.2 $[M+NH_4]^+$, 473.0 $[M+Na]^+$. HRMS: MNH_4^+, found 468.0889, $C_{19}H_{22}N_3O_7S_2$ requires 468.0899.

4.4.9. (6*S*)-6-[(*N*-Benyzl)-*o*-nitrobenzenesulfonamino]-cyclo-hex-2-enone (18). Pd(0) catalyzed allylic amination on cyclic sulfite **17** was performed according to the general procedure. After column chromatography (elution 0%→15% EtOAc in toluene) compound **18** was isolated as a light brown oil in an unoptimized yield of 13 mg (30%). ν_{max} (neat): 1688, 1539, 1346, 1159, 1122 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99–7.17 (m, 9H, H_{arom}), 6.97–6.91 (m, 1H, H3), 6.04 (dd, 1H, H2, J=2.5, 10.0 Hz), 4.96–4.86 (m, 2H, H6, C*H*H Bn), 4.14 (d, 1H, CH*H* Bn, J=16.1 Hz), 2.67–2.55 (m, 1H, C*H*H H4), 2.48–2.35 (m, 1H, CH*H* H4), 2.26–2.18 (m, 1H, C*H*H H5), 1.95–1.81 (m, 1H, CH*H* H5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ195.0 (CO), 150.4 (C3), 137.0, 133.0 ($C_{q,\ arom}$), 132.7, 131.4, 130.9, 129.4, 128.7, 128.4, 128.2, 127.8, 127.6, 123.9 (CH_{arom}, C2), 64.1 (C6), 50.0 (CH_2 Bn), 30.4, 26.9 (C4, C5). ESI-MS: m/z 387.0 $[M+H]^+$, 409.1 $[M+Na]^+$, 795.2 $[M+M+Na]^+$. HRMS: MNH_4^+, found 404.1297, $C_{19}H_{22}N_3O_5S$ requires 404.1280.

4.4.10. *N*-*o*-Nitrobenzenesulfonyl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzene-sulfonamino-cyclohex-2-enol-4-yl]-glycine methyl ester (19). The title compound was isolated as an off-white foam (67 mg, 85%). $[\alpha]_D^{20}=-56$ (c=1.0, $CHCl_3$). ν_{max} (neat): 1749, 1541, 1346, 1159, 1124 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.18–8.15 (m, 1H, H_{arom}), 7.72–7.56 (m, 6H, H_{arom}), 7.45–7.39 (m, 1H, H_{arom}), 7.26–7.12, m, 5H, H_{arom}), 5.93 (ddd, 1H, H_{olef}, J=2.4, 5.7, 9.9 Hz), 5.63 (bd, 1H, H_{olef}, J=10.1 Hz), 4.79 (d, 1H, C*H*H Bn, J=16.5 Hz), 4.73–4.67 (m, 1H, H4), 4.61 (d, 1H, CH*H* Bn, J=16.5 Hz), 4.26 (bs, 1H, H1), 4.10–4.01 (m, 3H, H6, 2Hα), 3.62 (s, 3H, OMe), 2.13–2.03 (m, 1H, C*H*H H5), 1.95–1.93 (m, 1H, CH*H* H5). ^{13}C NMR (50.1 MHz): δ_C 170.1 (CO), 147.7, 147.3, 137.1 ($C_{q,\ arom}$), 133.9 (CH_{arom}), 133.4 ($C_{q,\ arom}$), 133.1 (CH_{arom}), 132.6 ($C_{q,\ arom}$), 132.0, 131.6, 131.4, 130.9, 129.8, 128.5, 127.7, 127.5, 124.3, 124.0 (C2, C3, CH_{arom}), 66.7 (C1), 56.6, 56.5 (C4,

C6), 52.3 (OMe), 49.4, 45.0 (Cα, CH2 Bn), 26.9 (C5). ESI-MS: *m/z* 683.3 $[M+Na]^+$. HRMS: MNH_4^+, found 678.1587, $C_{28}H_{32}N_5O_{11}S_2$ requires 678.1540.

4.4.11. N^{α}-*t*-Butyloxycarbonyl-N^{ε}-*o*-nitrobenzenesulfonyl-N^{ε}-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzenesulfon-amino-cyclohex-2-enol-4-yl]-L-lysine methyl ester (20). The title compound was isolated as an off-white foam (68 mg, 71%). $[\alpha]_D^{20}=-40$ (*c*=1.0, $CHCl_3$). ν_{max} (neat): 2972, 2901, 1740, 1699, 1541, 1369, 1344, 1159, 1057 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.09–8.00 (m, 1H, H_{arom}), 7.74–7.09 (m, 12H, H_{arom}), 5.99–5.94 (m, 1H, H_{olef}), 5.72 (d, 1H, H_{olef}, *J*=10.0 Hz), 5.10 (d, 1H, NH, *J*=8.7 Hz), 4.82 (d, 1H, C*H*H Bn, *J*=16.6 Hz), 4.76 (d, 1H, CH*H* Bn, *J*=16.6 Hz), 6.64 (bs, 1H, H4), 4.29–4.22 (m, 2H, H1, Hα), 4.19–4.08 (m, 1H, H6), 3.72 (s, 3H, OMe), 3.33–3.24 (m, 1H, *CH*H, Hε), 3.19–3.09 (m, 1H, CH*H* Hε), 2.07–2.00 (m, 1H, C*H*H H5), 1.79–1.678 (m, 3H, CH*H* H5, C*H*H Hδ, C*H*H Hβ), 1.63–1.51 (m, 2H, CH*H* Hβ, CH*H* Hδ), 1.38 (s, 9H, Boc), 1.33–1.16 (m, 2H, Hγ). ^{13}C NMR (50.1 MHz): δ_C 173.0 (CO ester), 155.5 (CO carbamate), 147.8, 147.5, 137.1, 133.6 ($C_{q,\ arom}$), 133.1 (CH_{arom}), 131.9 ($C_{q,\ arom}$), 131.5, 131.1, 130.9, 128.3, 127.9, 127.3, 124.2, 123.9 (CH_{arom}, C2, C3), 80.0 (C_q Boc), 67.0 (C1), 56.7, 56.3 (C4, C6), 52.3 (OMe+Cα), 49.7, 44.7 (CH_2 Bn, Cε), 32.3, 29.9, 27.0, 22.0 (C5, Cβ, Cγ, Cδ), 28.1 (Me Boc). ESI-MS: *m/z* 732.4 $[M\text{-Boc}+H]^+$ 854.3 $[M+Na]^+$. HRMS: MNH_4^+, found 849.2762, $C_{37}H_{49}N_6O_{13}S_2$ requires 849.2799.

4.4.12. N^{ε}-Benzyloxycarbonyl-N^{α}-*o*-nitrobenzenesulfonyl-N^{α}-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzenesulfon-amino-cyclohex-2-enol-4-yl]-L-lysine methyl ester (21). The title compound was isolated as an off-white foam (37 mg, 36%). $[\alpha]_D^{20}=-72$ (*c*=0.5, $CHCl_3$). ν_{max} (neat): 1740, 1705, 1541, 1369, 1344, 1157, 1124 cm^{-1}. ^1H NMR (300 MHz): δ_H 7.96–7.93 (m, 1H, H_{arom}), 7.72–7.12 (m, 17H, H_{arom}), 5.95–5.89 (m, 1H, H_{olef}), 5.67 (bd, 1H, H_{olef}, *J*=10.2 Hz), 5.07 (s, 2H, CH_2 Z), 4.91–4.82 (m, 2H, C*H*H Bn, NH Z), 4.75 (d, 1H, CH*H* bn, *J*=16.6 Hz), 4.59 (bs, 1H, H4), 4.25 (bs, 1H, H1), 4.18–4.07 (m, 2H, H6, Hα), 3.70 (s, 3H, OMe), 3.11 (q, 2H, Hε, *J*=6.4 Hz), 2.56–2.44 (m, 1H, C*H*H H5), 2.37 (bs, 1H, OH), 2.18–2.04 (m, 1H, CH*H* H5), 1.76–1.64 (m, 2H, Hβ), 1.50–1.28 (m, 4H, Hγ, Hδ).^{13}C NMR (50.1 MHz): δ_C 171.0 (CO ester), 156.5 (CO carbamate), 148.3, 147.5, 137.6, 131.2, 133.8 ($C_{q,\ arom}$), 133.3, 131.7, 131.0, 130.8, 130.6, 128.5, 128.4, 128.1, 127.7, 127.3, 124.1, 124.0 (C2, C3, CH_{arom}), 66.9 (C1), 66.6 (CH_2 Z), 59.3, 57.3, 56.8, 52.5 (C4, C6, Cα, OMe), 49.4 (CH_2 Bn), 40.5, 31.0, 29.3, 28.0, 23.8 (C5, Cβ, Cγ, Cδ, Cε). ESI-MS: *m/z* 866.6 $[M+H]^+$ 888.3 $[M+Na]^+$.

4.4.13. *N*-*o*-Nitrobenzenesulfonyl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitro-benzenesulfonamino-cyclohex-2-enol-4-yl]-L-glutamic acid methyl ester (22). The title compound was isolated as an slightly yellow foam (31 mg, 37%). $[\alpha]_D^{20}=-66$ (*c*=0.5, $CHCl_3$). ν_{max} (neat): 2957, 2901, 1736, 1541, 1371, 1346, 1161, 1124, 1065 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.01 (d, 1H, H_{arom}, *J*=1.4 Hz), 7.69–7.10 (m, 12H, H_{arom}), 5.96 (ddd, 1H, H_{olef}, *J*=2.5, 5.8, 9.8 Hz), 5.70 (bd, 1H, H_{olef}, *J*=10.0 Hz), 4.89 (d, 1H, C*H*H Bn, *J*=16.6 Hz), 4.77 (d, 1H, CH*H* Bn, *J*=16.6 Hz), 4.61–4.59 (m, 1H, H4), 4.35–4.27 (m, 2H, H1, Hα), 4.11–4.07 (m, 1H, H6), 3.65 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.55–2.37 (m, 4H, C*H*H H5, C*H*H Hβ, 2Hγ), 2.10–1.98 (m, 2H, CH*H* H5, CH*H* Hβ). ^{13}C NMR (50.1 MHz): δ_C 173.0, 170.5 (2 CO), 147.5, 137.6 ($C_{q,\ arom}$), 133.9 (CH_{arom}), 133.7 ($C_{q,\ arom}$), 133.3, 132.1, 132.0, 131.7, 131.6, 131.1, 130.8, 130.5, 128.6, 128.4, 127.9, 127.8, 127.3, 124.1, 124.0 (CH_{arom}), 66.8 (C1), 58.0, 57.3, 56.7 (C4, C6, Cα), 52.6, 51.8 (2 OMe), 49.4 (CH_2 Bn), 30.8, 27.8, 26.9 (C5, Cβ, Cγ). ESI-MS: *m/z* 769.3 $[M+Na]^+$. HRMS: MNH_4^+, found 764.1862, $C_{32}H_{38}N_4O_{13}S_2$ requires 764.1908.

4.4.14. *N*-*o*-Nitrobenzenesulfonyl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenz-enesulfonamino-cyclohex-2-enol-4-yl]-L-phenylalanine methyl ester (23). The title compound was isolated as a slightly yellow foam (38 mg, 44%). $[\alpha]_D^{20}=-35$ (*c*=0.5, $CHCl_3$). ν_{max} (neat): 1742, 1541, 1369, 1344, 1159, 1124, 1061 cm^{-1}. ^1H NMR (300 MHz): δ_H 7.86–7.11 (m, 18H, H_{arom}), 5.88 (ddd, 1H, H_{olef}, *J*=2.5, 5.8, 9.9 Hz), 5.35 (bd, 1H, H_{olef}, *J*=10.7 Hz), 4.90 (d, 1H, CH*H* Bn, *J*=16.5 Hz), 4.74 (d, 1H, CH*H* Bn, *J*=16.5 Hz), 4.69–4.34 (m, 1H, H4), 4.45 (dd, 1H, Hα, *J*=5.9, 8.6 Hz), 4.23 (bs, 1H, H1), 4.15–4.05 (m, 1H, H6), 3.55 (s, 3H, OMe), 3.42 (dd, 1H, C*H*H Hβ, *J*=8.8, 13.9 Hz), 3.04 (dd, 1H, CH*H* Hβ, *J*=5.9, 13.9 Hz), 2.50 (q, 1H, C*H*H H5, *J*=12.0 Hz), 2.09–2.03 (m, 1H, CH*H* H5). ^{13}C NMR (50.1 MHz): δ_C 170.5 (CO), 148.6, 147.3, 137.7, 136.7, 133.9 ($C_{q,\ arom}$), 133.3 (CH_{arom}), 131.7 ($C_{q,\ arom}$), 130.9, 130.7, 129.5, 128.5, 127.7, 127.4, 127.0, 124.1 (C2, C3, CH_{arom}), 66.9 (C1), 60.9, 57.1, 56.8 (C4, C5, Cα), 52.5 (OMe), 49.4 (CH2 Bn), 38.0 (Cβ), 28.0 (C5). ESI-MS: *m/z* 773.3 $[M+Na]^+$. HRMS: MNH_4^+, found 768.1989, $C_{35}H_{38}N_5O_{11}S_2$ requires 768.2009.

4.4.15. Acridine-9-carboxylic acid-(6-{*N*-*o*-nitrobenzenesulfon-yl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzenesulfon-amino-cyclohex-2-enol-4-yl]}-aminohexyl) amide (24). The title compound was isolated as a yellow foam (60 mg, 58%). ν_{max} (neat): 2928, 1639, 1541, 1439, 1369, 1342, 1159, 1121 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.03–7.96 (m, 2H, H_{arom}), 7.86–7.83 (m, 1H, H_{arom}), 7.69–7.03 (m, 18H, H_{arom}), 5.79–5.74 (m, 1H, H2′), 5.54 (bd, 1H, H3′, *J*=10.3 Hz), 4.73 (d, 1H, C*H*H Bn, *J*=16.3 Hz), 4.64–4.59 (m, 2H, H4′, CH*H* Bn), 4.18 (bs, 1H, H1′), 4.04–4.00 (m, 1H, H6′), 3.58 (q, 2H, H1, *J*=6.5 Hz), 3.22 (t, 2H, H6, *J*=7.8 Hz), 2.30–2.19 (m, 1H, C*H*H H5′), 1.82–1.79 (m, 1H, CH*H* H5), 1.67–1.60 (m, 4H, H2, H5), 1.42–1.22 (m, 4H, H3, H4). ^{13}C NMR (50.1 MHz): δ_C 166.9 (CO), 147.72, 147.66, 147.1, 141.4, 137.1, 134.1, 133.6 ($C_{q,\ arom}$), 133.3 (CH_{arom}), 133.1 ($C_{q,\ arom}$), 132.0, 131.8, 131.6, 131.4, 131.0, 130.8, 130.5, 128.7, 128.6, 128.3, 128.2, 127.8, 127.2, 126.6, 125.1, 124.1 123.8 (C2, C3, CH_{arom}), 121.9 ($C_{q,\ arom}$), 66.6 (C1), 56.5 (br; C4, C6) 53.4, 49.9, 44.9, 39.8, 30.5, 29.0, 27.5, 25.8 (CH_2 Bn, C5, CH_2 hexyl) ESI-MS: *m/z* 893.4 $[M+H]^+$, 915.2 $[M+Na]^+$.

4.4.16. 1,2,3,4-Di-*O*-isopropylidene-6-*N*-*o*-nitrobenzenesulfonyl-6-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitro-benzenesulfonamino-cyclohex-2-enol-4-yl]-amino-D-galactose (25). The title compound was isolated as a white foam (77 mg, 80%). $[\alpha]_D^{20}=-94$ (*c*=1.0, $CHCl_3$). ν_{max} (neat): 1541, 1371, 1342, 1211, 1161, 1065 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.05–8.02 (m, 1H, H_{arom}), 7.76–7.05 (m, 12H, H_{arom}), 6.18–6.12 (ddd, 1H, H2, *J*=2.4, 6.1, 9.8 Hz), 5.51 (dd, 1H, H3, *J*=2.2, 10.0 Hz), 5.41 (d, 1H, H1′,

J=5.0 Hz), 5.02 (d, 1H, C*H*H Bn, *J*=16.4 Hz), 4.82 (d, 1H, CH*H* Bn, *J*=16.4 Hz), 4.76–4.70 (m, 1H, H4), 4.54 (dd, 1H, H3′), *J*=2.5, 7.8 Hz), 4.32–4.29 (m, 2H, H1, H4′), 4.23–4.08 (m, 3H, H2′, H5′, H6), 3.61 (d, 1H, C*H*H H6′, *J*=16.4 Hz), 3.25 (dd, 1H, CH*H* H6′, *J*=7.5, 16.4 Hz), 2.92–2.80 (m, 1H, C*H*H H5), 2.35–2.22 (m, 1H, CH*H* H5), 1.38 (s, 3H, Me isoprop), 1.30 (s, 3H, Me isoprop), 1.22 (s, 3H, Me isoprop), 1.03 (s, 3H, Me isoprop). ^{13}C NMR (50.1 MHz): δ_C 148.2, 127.1, 137.4, 134.7 ($C_{q,\ arom}$), 133.8, 133.0, 132.8, 132.0, 131.1, 130.9, 129.4, 128.0, 127.0, 124.3, 123.7 (C2, C3, CH_{arom}), 109.4, 109.3 (C_q isoprop), 96.4 (C1′), 72.3, 70.5, 70.1 (br), 67.8 (1, 2′, 3′, 4′, 5′), 56.6, 56.5 (C4, C6), 49.5, 46.5 (C6′, CH_2 Bn), 29.1 (C6), 25.9, 25.5, 24.7, 24.3 (Me isoprop). ESI-MS: *m*/*z* 845.5 $[M+NH_4]^+$. HRMS: MNH_4^+, found 848.2440, $C_{37}H_{46}N_5O_{14}S_2$ requires 848.2483.

4.4.17. (1*S*,4*S*,6*R*)-4,6-bis[(*N*-benzyl)-*o*-nitrobenzenesulfon-amino]-1-*O*-(*tert*-butyldimethylsilyl)-cyclohex-2-enol (27). Pyridine (0.20 mL, 2.5 mmol, 5 equiv.) and *tert*-butyldimethylsilyl triflate (0.138 mL, 0.6 mmol, 1.2 equiv.) were added to a solution of compound **16** (339 mg, 0.5 mmol) in DCM (2 mL). After stirring for 2.5 h sat. $NaHCO_3$ was added and the mixture was extracted three times with EtOAc. Combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure. Silica column chromatography (elution 0%→20% EtOAc in toluene) afforded the title compound (353 mg, 0.446 mmol, 89%) as a white foam. $[\alpha]_D^{20}$=+60.8 (*c*=0.50, $CHCl_3$). ν_{max} (neat): 1541, 1367, 1344, 1157, 1124, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.96 (d, 1H, H_{arom}, *J*=8.3 Hz), 7.67–6.97 (m, 15H, H_{arom}), 6.87 (d, 2H, H_{arom}, *J*=7.3 Hz), 5.86 (ddd, 1H, H_{olef}, *J*=2.3, 5.5, 9.9 Hz), 5.52 (d, 1H, H_{olef}, *J*=10.1 Hz), 4.91–4.84 (m, 1H, H4), 4.70–4.65 (m, 2H, 2× C*H*H benzyl), 4.45 (d, 1H, CH*H* benzyl, *J*=16.2 Hz), 4.39–4.33 (m, 2H, H1, CH*H* benzyl), 4.03 (bd, 1H, H6, *J*=12.9 Hz), 2.24–2.15 (m, 1H, C*H*H H5), 1.99–1.91 (m, 1H, CH*H* H5), 0.91 (s, 9H, *t*-Bu), 0.19 (s, 3H, Me), 0.11 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 147.7, 147.3, 137.7, 136.2, 135.2, 134.0 ($C_{q,\ arom}$), 133.4, 132.8, 132.6, 131.8, 131.7, 131.1, 130.7, 129.8, 127.5, 127.3, 124.2, 123.7 (CH_{arom}, C2, C3), 68.9 (C1), 57.3, 57.1 (C4, C6), 50.1, 48.7 (CH_2 Bn), 28.3 (C5), 25.9 (Me *t*-Bu), 17.9 (C_q *t*-Bu), −4.0, −4.6 (2× Me TBS). ESI-MS: *m*/*z*=815.5 $[M+Na]^+$. HRMS: MNH_4^+, found 810.2603, $C_{38}H_{48}N_5O_9S_2Si$ requires 810.2663.

4.4.18. 1L-(1,4,6/2,3)-4,6-Bis[(*N*-benzyl)-nitrobenzenesulfon-amino]-1-*O*-(*tert*-butyldimethylsilyl)-cyclohexane-1, 2, 3-triol (29).[26] *N*-Methyl-morpholine-*N*-oxide (107 mg, 0.91 mmol, 2.2 equiv.) and $K_2Os_2O_4{\cdot}2H_2O$ (1.2 mg, 0.75 mol%) were added to a solution of alkene **27** (328 mg, 0.414 mmol) in acetone/water (2 mL, 3:1 v/v). After 72 h the reaction was quenched with aqueous $NaHSO_3$ and extracted three times with EtOAc. Combined organic layers were dried on $MgSO_4$ and evaporated under reduced pressure. Column chromatography (elution 10%→50% EtOAc in toluene) yielded compound **29** (314 mg, 0.38 mmol, 92%) as a slightly yellow foam. $[\alpha]_D^{20}$=+72.4 (*c*=0.50, $CHCl_3$). ν_{max} (neat): 1541, 1340, 1159, 1123, 1087, 1059, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.14–8.11 (m, 1H, H_{arom}), 7.73–7.01 (m, 15H, H_{arom}), 6.88–6.86 (m, 1H, H_{arom}), 4.68 (d, 1H, C*H*H benzyl, *J*=16.5 Hz), 4.56 (d, 1H, C*H*H benzyl, *J*=16.1 Hz), 4.48 (d, 1H, CH*H* benzyl, *J*=16.1 Hz), 4.41–4.36 (m, 2H, H6, CH*H* benzyl), 4.21–4.14 (m, 1H, H4), 4.00 (bs, 1H, H1), 3.77 (bs, 1H, H2), 3.73–3.68 (m, 1H, H3), 2.76 (d, 1H, OH, *J*=1.9 Hz), 2.61 (d, 1H, OH, *J*=5.4 Hz), 1.91–1.81 (m, 1H, C*H*H H5), 1.68–1.63 (m, 1H, CH*H* H5), 0.87 (s, 9H, *t*-Bu), 0.13 (s, 3H, Me), 0.03 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 147.5, 147.2, 137.5, 136.6, 134.6 ($C_{q,\ arom}$), 133.8. 132.9 (CH_{arom}), 132.8 ($C_{q,\ arom}$), 132.2, 131.7, 131.4, 130.9, 128.7, 128.1, 137.9, 127.8, 127.2, 124.3, 123.8 (CH_{arom}), 75.4, 72.4, 66.9 (C1, C2, C3), 57.1, 54.7 (C4, C6), 49.6, 48.2 (CH_2 Bn), 29.0 (C5), 25.9 (Me *t*-Bu), 17.7 (C_q *t*-Bu), −4.6, −5.0 (2× Me TBS). ESI-MS: *m*/*z*=827.3 $[M+H]^+$, 849.3 $[M+Na]^+$. HRMS: MNH_4^+, found 844.2657, $C_{38}H_{50}N_5O_{11}S_2Si$ requires 844.2718.

4.4.19. 1L-(1,4,6/2,3)-4,6-Bis[(*N*-benzyl)-nitrobenzenesulfon-amino]-2-*O*-acetyl-1-*O*-(*tert*-butyldimethylsilyl)-cyclo-hexane-1, 2, 3-triol (31). A solution of diol **29** (165 mg, 0.20 mmol), trimethylorthoacetate (0.25 mL, 2 mmol, 10 equiv.) and *p*-TsOH (4 mg, 0.1 equiv.) in DCM (1 mL) was stirred for 1 h. TLC analysis (eluens: toluene/EtOAc 2:1) indicated complete conversion to two higher running products, being the two stereoisomers of orthoester **30**. The reaction was neutralized with triethylamine and the solvents were removed under reduced pressure. Sat. $NaHCO_3$ was added and the mixture was extracted three times with EtOAc. Combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Crude orthoester **30** (ESI-MS: *m*/*z*=905.5 $[M+Na]^+$) was immediately used in the next step. It was dissolved in AcOH/H_2O (4:1 v/v) and stirred for 2 h, when TLC analysis indicated complete disappearance of the orthoester. The reaction mixture was diluted with toluene and concentrated under reduced pressure. During evaporation of the solvents, toluene was added several times to remove acetic acid traces. Silica column chromatography (elution 10%→40% EtOAc in toluene) provided orthogonally protected 2-deoxystreptamine epimer **31** (165 mg, 0.190 mmol, 95%) as a white foam. $[\alpha]_D^{20}$=+88.4 (*c*=1.0, $CHCl_3$). ν_{max} (neat): 1747, 1541, 1369, 1348, 1226, 1161, 1124, 1090, 1059, 1045, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.10–8.07 (m, 1H, H_{arom}), 7.72–7.02 (m, 15H, H_{arom}), 6.81 (d, 2H, H_{arom}, *J*=7.1 Hz), 4.94 (t, 1H, H2, *J*=4.6 Hz), 4.76 (d, 1H, C*H*H Bn, *J*=16.0 Hz), 4.60 (d, 1H, C*H*H Bn, *J*=16.3 Hz), 4.37–4.21 (m, 4H, H4, H6, 2× CH*H* Bn), 4.11–4.09 (m, 1H, H1), 3.99–3.94 (m, 1H, H3), 2.42 (d, 1H, OH, *J*=7.8 Hz), 2.15 (s, 3H, Me Ac), 1.83–1.71 (m, 2H, H5), 0.89 (s, 9H, Me *t*-Bu), 0.18 (s, 3H, Me TBS), 0.15 (s, 3H, Me TBS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.1 (CO), 147.6, 147.3, 137.1, 136.0, 134.5 ($C_{q,\ arom}$), 133.6 (CH_{arom}), 133.1 ($C_{q,\ arom}$), 132.9, 131.7, 131.5, 131.1, 130.5, 128.7, 128.09, 128.05, 128.0, 127.3, 124.2, 123.6 (CH_{arom}), 73.9 (C2), 73.3 (C1), 65.4 (C3), 57.6, 55.0 (C4, C6), 49.5, 48.0 (CH_2 Bn), 30.0 (C5), 25.9 (Me *t*-Bu), 20.7 (Me Ac), 17.7 (C_q *t*-Bu), −4.6, −5.2 (Me TBS). ESI-MS: *m*/*z*=869.5 $[M+H]^+$, 891.4 $[M+Na]^+$. HRMS: MNH_4^+, found 886.2781, $C_{40}H_{52}N_5O_{12}S_2Si$ requires 886.2823.

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