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Synthesis of $\alpha^{2,2},\beta^3$-Diamino Acids by Double Stereodifferentiation Aldol Addition of Oxazolidinone Enolates to *N*-(*tert*-Butylsulfinyl) Imines

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A novel application of Seebach's "SRS" synthetic principle works efficiently when conformationally restrained trisubstituted chiral $\alpha^{2,2},\beta^3$-diamino acids are synthesized by double stereoinduction reactions of chiral oxazolidinone enolates with *N*-sulfinyl aldimines. Two stereoisomers were isolated in a form of 1′-(sulfinylamino)oxazolidinones and bicyclic 1*H*,3*H*-imidazo[1,5-*c*]oxazole-1,5(6*H*)-diones, from which the $\alpha^{2,2},\beta^3$-diamino acids are obtained by selective deprotection methodologies. Among a variety of highly functionalized diamino acids, this highly diastereoselective protocol provides a synthetic route for yet unreported *C*-glycosyl and α-nucleoside diamino acids.

Introduction

α,β-Diamino acids are key structural units of many natural products that are involved in a variety of biological functions.[1] In particular, they are employed as building blocks for peptidomimetic syntheses to improve their stability toward peptidases[2] and to induce, in some cases, specific conformations in peptide segments.[3] Their metal complexing abilities have also been documented.[4] Among the several procedures described for the enantioselective synthesis of α,β-diamino acids,[5] the addition of glycine synthons to imines is one of the most important. For example, Staudinger's cycloaddition reactions of glycinyl chlorides to aldimines afford 3-amino-β-lactams, which are synthetic precursors of α,β-diamino acids.[6] However, enantioselective Mannich-type additions of glycine enolates to aldimines[7] are key methodologies that have been developed for several asymmetric syntheses of disubstituted 1,2-diamino acids. In the reaction between glycine enolates and electrophilically activated *N*-sulfinyl imines,[8] the proper choice of the *tert*-butylsulfinyl substituent stereochemistry serves as a chiral directing group,[9] even though the synthesis of the corresponding chiral diamino acid occurs with different degrees of selectivity[9b–9d] and more often requires hardly reproducible reaction conditions.[9a,9c]

Trisubstituted homochiral 1,2-diamino acids are not readily accessible. Even so, these highly substituted compounds might find application in the preparation of β-peptides with a restricted conformational flexibility and an increased lipophilicity.[10] To date, only a few disubstituted $\alpha^{2,2}$-diamino acids[11] and trisubstituted $\alpha^{2,2},\beta^3$-diamino acids[9g,12] with a quaternary chiral center at the α position have been synthesized.

We reasoned that, on the basis of Seebach's "self-regeneration of stereocenters" (SRS) synthetic principle,[13] the enolates of *N*-acyloxazolidinones could serve as directing chiral partners in the reaction with electrophilically activated imines for the synthesis of trisubstituted α,β-diamino acids. Apart from operational simplicity, this approach shows a number of other favorable features, including the use of easily attainable reagents such as natural α-amino acids and aldimines. Moreover, the use of a rigid cyclic enolate, unlike the corresponding alicyclic systems, could provide an additional element that could be used to control the stereochemical outcome. The present work proposes a general methodology for the preparation of a wide range of important molecular frameworks, including the synthesis of the first glycosyl- and nucleoside-1,2-diamino acid conjugates connected through a carbon–carbon bond.

Results and Discussion

According to a modified version of Seebach's methodology,[14] enantiomeric lithium enolates (*S*)-**8** and (*R*)-**8** of (2*S*,4*S*)-*cis*-4-methyl-1,3-oxazolidin-5-one (*cis*-**7**) and its (2*R*,4*S*)-*trans*-diastereomer (*trans*-**7**), respectively, (Figure 1) were treated with a variety of electrophilically activated aldimines **1**–**6** to prove the broad applicability of our protocol.

In our first attempt, performed with achiral *N*-(*tert*-butoxycarbonyl)benzenemethanimine, we were discouraged by the low reaction selectivity.[15] Therefore, we sought to im-

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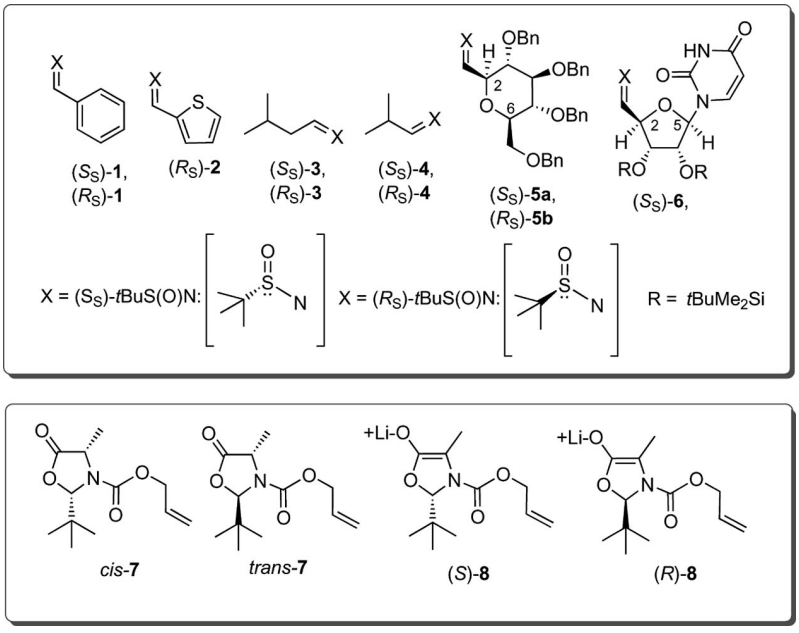


Figure 1. Oxazolidinones *cis*-**7**, *trans*-**7** and their corresponding lithium enolates (*S*)-**8**, (*R*)-**8**, and (S_S)- and (S_R)-(*N*-*tert*-butylsulfinyl) aldimines **1**–**6**.

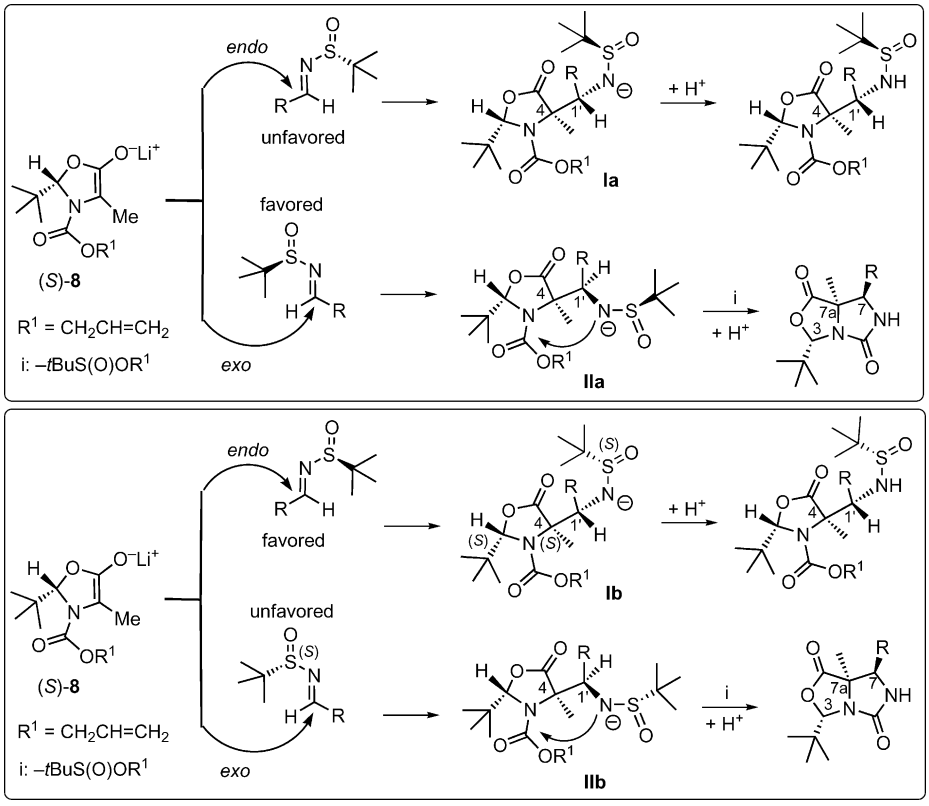
prove the efficiency of the method by using chiral *N*-(*tert*-butylsulfinyl) imines, as the *tert*-butylsulfinyl substituent affords an additional element of kinetic selectivity with respect to the achiral *tert*-butoxycarbonyl group.

In this respect, we recently reported the synthesis of chiral α-hydroxy-β-amino acids by asymmetric Mannich-type additions of homochiral 1,3-dioxolanon-4-one enolates to homochiral *N*-(*tert*-butylsulfinyl) aldimines and ketimines.[16] This methodology proved to be particularly useful for the synthesis of trisubstituted *C*-glycosyl isoserines.[16a] Instead, to the best of our knowledge, no report has been published concerning the synthesis of isosteric *C*-glycosyl-α,β-diamino acids and their corresponding *C*-glycopeptides, in which the diamino acid side chain is connected to the sugar moiety through a carbon–carbon bond. These compounds are expected to be more stable toward glycosidases relative to their N- and O-linked analogs.[17] Thus, we exploited the above-mentioned approach to obtain these valuable building blocks. In particular, we considered the "matching" and "mismatching" effects in the reactions involving enantiomeric pairs of aromatic, aliphatic, and sugar aldimines.[18] Modification to Seebach's protocol relies on the use of an orthogonal allyloxycarbonyl (Alloc) protecting group to the oxazolidinone nitrogen atom.[18,19] Treatment of *cis*-**7** (or *trans*-**7**) with lithium bis(trimethylsilyl)amide (LHMDS) affords nonracemic lithium enolates (2*S*)-**8** or (2*R*)-**8**, which can then be treated with aldimines at –78/–90 °C in THF/HMPA (85:15). An excess amount of enolate (3.5–5.5 equiv.) and a very slow addition rate of the imine were found to be crucial to minimize the competitive self-condensation of the *N*-sulfinyl imine under the basic reaction conditions,[20] and to ensure its complete consumption.

Scheme 1 reports the stereochemistry of the addition of an (*S*)- or (*R*)-configured sulfinamide to enolate (*S*)-**8**. Two structurally different compounds, that is, the 1′-(sulfinylamino)oxazolidinone or the bicyclic oxazoledione, were obtained. Regardless of the nature of the stereogenic centers of the reagents, the enolate attacks the aldimine from the opposite side of the bulky *tert*-butyl group with 1,3-induction. In particular, the addition of (*S*)-**8** to the (*R*)-configured *N*-sulfinyl imine affords, in principle, diastereomeric lithiated intermediates **Ia** and **IIa**, whereas the addition to the (*S*)-configured *N*-sulfinyl imine affords intermediates **Ib** and **IIb**. Intermediates **IIa** and **IIb**, which only differ in the stereochemistry at the sulfur atom, are derived from an *exo* approach of the imine to the enolate ring. In these intermediates, the *N*-sulfinyl amide substituents at the (1′*R*)-position are *syn* to the carbamate group; thus, they undergo cyclization with concomitant elimination of allyl 2-methylpropane-2-sulfinate to afford bicyclic oxazole derivatives. For intermediates **Ia** and **Ib**, which are derived from an *endo* approach of the imine to the enolate ring, the sulfinamide substituent of the (1′*S*)-position lays *anti* to the carbamate residue; thus, they afford the 1′-(sulfinylamino)-3-(allyloxycarbonyl)oxazolidinones upon treatment with 0.2 N HCl.

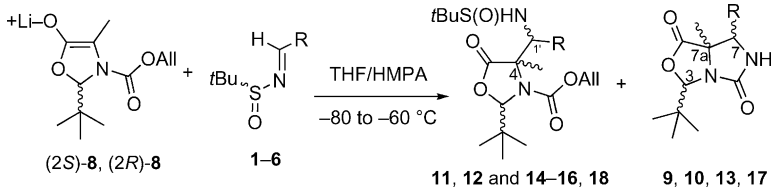
For aromatic and heteroaromatic aldimines we observed that the pairs (2*S*)-**8**/(R_S)-**1**, (2*R*)-**8**/(S_S)-**1**, and (2*S*)-**8**/(R_S)-**2** were highly diasterocontrolled and afforded bicyclic imidazo[1,5-*c*]oxazole derivatives **9**, *ent*-**9**, and **10** (Table 1, Entries 1, 3, and 4). The product distribution for the reactions of lithium enolates (2*R*)-**8** and (2*S*)-**8** with (S_S)- and (R_S)-*N*-(*tert*-butylsulfinyl) aldimines **1**–**6** is reported in Table 1.

The (2*S*)-**8**/(S_S)-**1** pair afforded a mixture of bicyclic compound **9** and 1′-(sulfinylamino)oxazolidinone **11** (Table 1, Entry 2). Similarly, for the (2*S*)-**8**/(S_S)-**3** (Table 1,



Scheme 1.

Table 1. Product distribution for the reactions of lithium enolates (2*R*)-**8** and (2*S*)-**8** with (S_S)- and (R_S)-*N*-(*tert*-butylsulfinyl) aldimines **1**–**6**.



Entry	Imine	Enolate	R	Products	% *de*[a]	% Yield
1	(R_S)-**1**	(2*S*)-**8**	phenyl	(3*S*,7*R*,7a*R*)-**9**	>96	80
2	(S_S)-**1**	(2*S*)-**8**	phenyl	(S_S,2*S*,4*R*,1′*S*)-**11**/(3*S*,7*R*,7a*R*)-**9**	0	80
3	(S_S)-**1**	(2*R*)-**8**	phenyl	*ent*-**9**	>96	81
4	(R_S)-**2**	(2*S*)-**8**	2-thiophene	(3*S*,7*S*,7a*R*)-**10**	>96	83
5	(S_S)-**3**	(2*S*)-**8**	2-isobutyl	(S_S,2*S*,4*R*,1′*S*)-**12**/(3*S*,7*R*,7a*R*)-**13**	76	89
6	(R_S)-**3**	(2*R*)-**8**	2-isobutyl	*ent*-**12**/*ent*-**13**	76	83
7	(R_S)-**3**	(2*S*)-**8**	2-isobutyl	(3*S*,7*R*,7a*R*)-**13**	–	Trace
8	(S_S)-**4**	(2*S*)-**8**	isopropyl	(S_S,2*S*,4*R*,1′*S*)-**14**	>96	82
9	(R_S)-**4**	(2*R*)-**8**	isopropyl	*ent*-**14**	>96	83
10	(S_S)-**5**	(2*S*)-**8**	*O*-tetrabenzyl glucose	(S_S,2*S*,4*R*,1′*R*)-**15**	>96	59
11	(S_S)-**5**	(2*R*)-**8**	*O*-tetrabenzyl glucose	[b]	–	<15
12	(R_S)-**5**	(2*S*)-**8**	*O*-tetrabenzyl glucose	(R_S,2*S*,4*R*,1′*R*)-**16**	>96	63
13	(R_S)-**5**	(2*R*)-**8**	*O*-tetrabenzyl glucose	(3*R*,7*S*,7a*R*)-**17**	90	79[c]
14	(S_S)-**6**	(2*S*)-**8**	di-OTBDMS-uridine	(S_S,2*S*,4*R*,1′*R*)-**18**	>96	89

[a] Calculated on the crude reaction mixture by ^{1}H NMR spectroscopic analysis. [b] Inseparable mixture of addition products. [c] Trace amounts (5%) of the opened compound were detected (See Experimental Section).

Entry 5) and (2*R*)-**8**/(R_S)-**3** (Table 1, Entry 6) pairs involving aliphatic branched sterically demanding *N*-isopentyl aldimines, the (sulfinylamino)oxazolidinone is favored over the bicyclic adduct.

1′-(Sulfinylamino)oxazolidinones **12** and *ent*-**12** were obtained as the major products in a 88:12 ratio along with minor amounts of bicyclic adducts **13** and *ent*-**13**, respectively. Accordingly, upon treatment of aldimine (R_S)-**3** with

(2*S*)-**8**, the formation of bicyclic adduct **13** should be favored (Table 1, Entry 7). Actually, we found that the bulkiness of the imine C-substituent inhibited the formation of the bicyclic compound, which was anyway detected as the sole product but in very low yield. The greater steric bulkiness of the isopropyl group of aldimines (R_S)- and (S_S)-**4** relative to that of aldimine **3** further enhanced the *endo* selectivity in the reactions of (2*S*)-**8** with (S_S)-**4** and (2*R*)-**8** with (R_S)-**4**, which gave homochiral 1′-(sulfinylamino)oxazolidinones **14** and *ent*-**14** exclusively. These results demonstrate that the *tert*-butylsulfinyl substituent introduces an additional element of kinetic selectivity due to matching/mismatching interactions between the two chiral partners. In particular, when the (R_S)-imine *endo* approaches the (*S*)-**8** enolate, the sterically encumbered *tert*-butyl substituent points towards the enolate ring, whereas when it approaches in an *exo* manner, the *tert*-butyl group points outwards the ring (Scheme 1). Consequently, the last pathway, which leads to the formation of the bicyclic oxazole-1,5-dione, is strongly favored. Alternatively, when an (S_S)-configured imine reacts with enolate (*S*)-**8**, the *tert*-butyl substituent points outwards in the *endo* approach and inwards in the *exo* one so that the 1′-(sulfinylamino)oxazolidinone may compete for the product distribution. Besides the stereochemistry of the *tert*-butylsulfinyl group, the size of the substituent at the imine carbon atom also strongly influences the chemical yields and product distributions. For instance, the bulky sugar moiety (aldimines **5** and **6**) exerts a key role in terms of *endo* diastereoselectivity when treated with (2*S*)-**8**, leading to 1′-(sulfinylamino)oxazolidinones **15**, **16**, and **18** as sole products (Table 1, Entries 10, 12, and 14).[21] Instead, *exo* selectivity was observed in the reaction of enolate (2*R*)-**8** with (R_S)-**5**, which affords bicyclic compound **17** along with trace amounts (<5%) of the opened compound (Table 1, Entry 13). Only trace amounts of an inseparable mixture of addition products were detected in the crude mixture for the reaction involving imine (S_S)-**5** and (2*R*)-**8** (Table 1, Entry 11).

Nuclear Overhauser effect (nOe) experiments allowed the assessment of the C4 stereocenter of the 1′-(sulfinylamino)-oxazolidinones and that at the C7a center of the bicyclic oxazole-1,5-diones, by selective irradiation of the *t*Bu substituent. Moreover, by means of nOe experiments it was possible to assign the absolute configuration of bicyclic adducts **9**, **10**, **13**, **17**, and uridine derivative **18**, which adopts a restricted (4*R*,1′*R*)-conformation (Figure 2). In detail, irradiation of the *t*Bu-C2 group (δ =0.75 ppm) provided a 1.3% nOe effect on the C4 methyl group at δ = 1.69 ppm and 6.0% on the H1, which thus suggests (*R*) stereoconfiguration at the C4 carbon atom. Selective irradiation of the C4-Me group produced an 11% nOe effect on H1′, which suggests (1′*R*) conformation. Other significant nOe effects, which would further confirm the restricted conformation of **18**, were observed between the *tert*-butyl group on the sulfur atom and NH (1.0%), H7 (1.0%), and H6 (3%). Furthermore, irradiation of one the methyl protons attached to the silicon atom, centered at δ = 0.37 ppm, induced a 2.2% nOe effect on H3′ and a 4.2% effect on H1′.

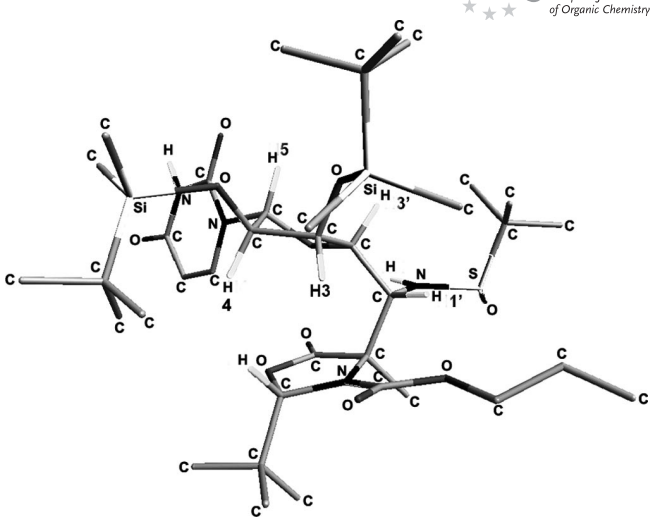


Figure 2. Spatial view of (S_S,2*S*,4*R*,1′*R*)-**18**.

The absolute stereochemistry of **15** was assigned by chemical correlation methods (see compound **24**). However, nOe analysis of **15** was performed in order to compare this result with that obtained from nOe analysis of **18** (Figure 3). In detail, irradiation of the C2-*t*Bu group (δ =1.00 ppm) produces a 7.0% nOe effect on C4-Me (δ =1.90 ppm) and a 22% effect on C2-H, which thus suggests (*R*) stereoconfiguration of the C4 carbon atom. Irradiation of the C4-Me group produces an 8.0% nOe effect on the H-C1′ position, which suggests a C1′ (*R*) configuration. Other

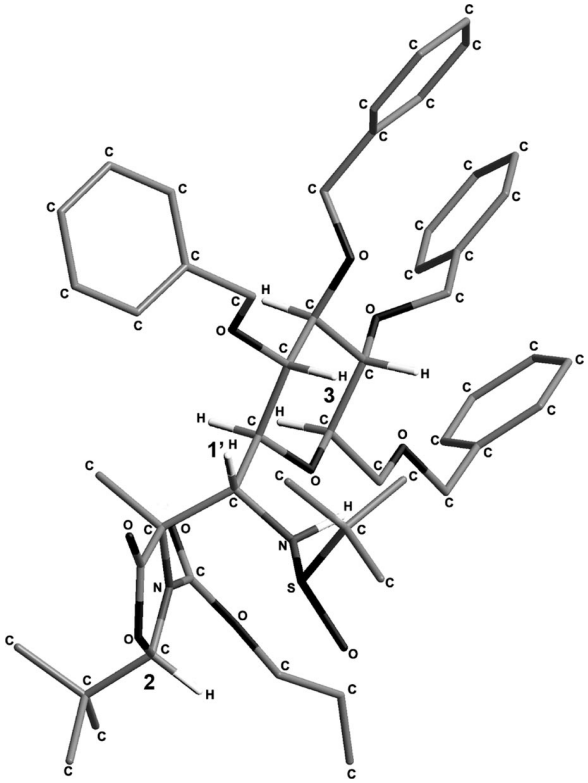
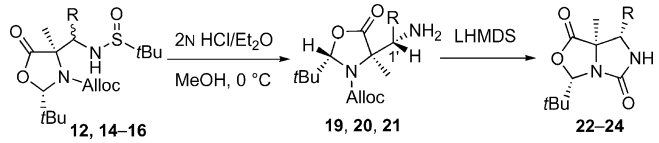


Figure 3. Spatial view of (S_S,2*S*,4*R*,1′*R*)-**15**.

Table 2. Nitrogen sulfinyl deprotection and cyclizations of free amines **19**–**21**.



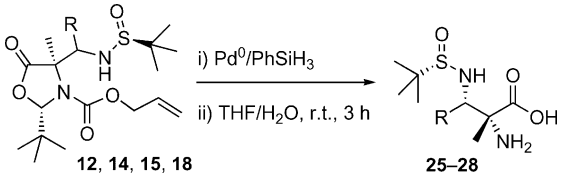
Entry	1′-(Sulfinylamino)-oxazolidinones	R	1′-Amino-oxazolidinones	% Yield	Imidazo[1,5-*c*]oxazoles	% Yield
1	(S_S,2*S*,4*R*,1′*S*)-**12**	isobutyl	(2*S*, 4*R*, 1′*S*)-**19**	90	(3*S*,7*R*,7a*S*)-**22**	80
2	(S_S,2*S*,4*R*,1′*S*)-**14**	isopropyl	(2*S*, 4*R*, 1′*S*)-**20**	85	(3*S*,7*R*,7a*S*)-**23**	40
3	(S_S,2*S*,4*R*,1′*R*)-**15**	*O*-tetrabenzyl glucose	(2*S*,4*R*,1′*R*)-**21**	90	(3*S*,7*R*,7a*R*)-**24**	40
4	(R_S,2*S*,4*R*,1′*R*)-**16**	*O*-tetrabenzyl glucose	(2*S*,4*R*,1′*R*)-**21**	90	–	–

significant nOe effects, which would further confirm this configuration, are observed between the *t*Bu group on the S(O) moiety and NH (12%) and C3-H (8%).

1′-(Sulfinylamino)oxazolidinones can be considered as orthogonally N^1,N^2-protected-α,β-diamino acids. This feature was confirmed by a number of deprotection experiments of compounds **12**, **14**, **15**, and **16**. Treatment with ethereal 2 N HCl in anhydrous MeOH afforded the corresponding *N*-unprotected 1-aminooxazolidinones **19**, **20**, and **21** in good yields. Subsequent LHMDS-induced cyclization of compounds **19**–**21** afforded bicyclic derivatives **22**–**24**, whose stereochemistry assessment (n.O.e. experiments; see Experimental Section) served also to assign the stereoconfiguration of their precursors **12**, **14**–**16** (Table 2 and Experimental Section for details).

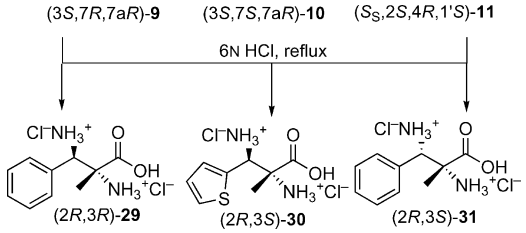
Selective Alloc-group deprotection was accomplished under neutral conditions on derivatives **12**, **14**, **15**, and **18** by catalyzed hydrogen transfer with the use of tetrakis(triphenylphosphane)palladium(0) catalyst and $PhSiH_3$. By standing at 20 °C for 3 h in THF/water, the free NH cyclic compounds smoothly afforded the corresponding NH-sulfinyl protected *syn* amino acids **25**–**28** (Table 3 and Experimental Section). This soft deprotection methodology, which can be applied to sensitive substrates such as nucleosides and sugars, proved the orthogonality between the two nitrogen protecting groups.

Table 3. Alloc Removal and amino acid formation.



Entry	Reagent	R	Product	% Yield
1	**12**	isobutyl	(S_S,2*R*,3*S*)-**25**	98
2	**14**	isopropyl	(S_S,2*R*,3*S*)-**26**	98
3	**15**	*O*-tetrabenzyl glucose	(S_S,2*R*,3R)-**27**	98
4	**18**	di-OTBDMS-uridine	(S_S,2*R*,3*R*)-**28**	98

Compounds **9**, **10**, and **11** were deprotected in refluxing 6 M HCl, which provided the corresponding *anti* amino acids **29**, **30**, and *syn*-(2*R*,3*S*)-**31**, respectively, in 98% yield (Scheme 2).



Scheme 2.

Conclusions

We developed a simple and general protocol for the synthesis of homochiral trisubstituted $\alpha^{2,2}$,β^3-diamino acids. The efficiency of this method relies on the possibility to obtain a wide pool of aromatic, heteroaromatic, aliphatic, glycosyl, and nucleoside homochiral diamino acids by using relatively inexpensive reagents, such as chiral *N*-sulfinyl aldimines and oxazolidinones. Moreover, we reported the first *C*-glycosyl-α,β-diamino acids bearing either a sugar moiety or a nucleobase, which can potentially serve as new building blocks for the synthesis of important biologically active compound analogs, such as antibiotics,[22] antifungals,[23] and peptidomimetics.[2] In particular, compound **28** can be considered as a new analog of polyoxin C; thus, it could function as an antifungal agent as is, or as a versatile building block for the preparation of a new family of polyoxin C isosters[23a] (Figure 4).

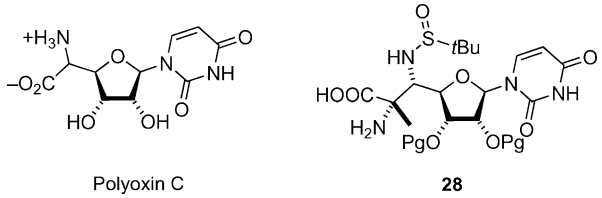


Figure 4. Polyoxin C and compound **28**.

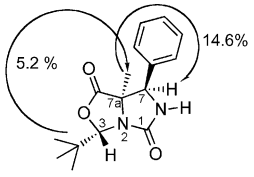
Experimental Section

General: All reactions were performed under an atmosphere of dry nitrogen by using oven-dried glassware. Tetrahydrofuran, toluene, and ethyl ether were distilled from sodium benzophenone ketal. Dichloromethane and acetonitrile were distilled from calcium hy-

dride. All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) with E. Merck silica gel 60-F254 plates. Flash column chromatography was performed with Merck silica gel (0.04–0.63 μm, 240–400 mesh) under high pressure. NMR spectra were recorded with a 400 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the $CHCl_3$ signal. All ^1H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; dd = quadruplet; dt = doublet of triplets, m = multiplet; br. = broad signal). Coupling constants *J* are given in Hz. Assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments or by correlated spectroscopy. IR spectra were recorded with an FTIR E.S.P. spectrometer as thin films on NaCl plates. Mass spectra were recorded with an ion trap spectrometer with an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000. The commercially available reagents were used as received without further purification.

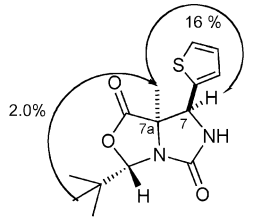
General Procedure for the Reactions of Lithium Enolates (2*R*)- and (2*S*)-8 with (S_S)- and (R_S)-*N*-(*tert*-Butylsulfinyl) Aldimines 1–6: To a solution of LHMDS (4.5 equiv. for aromatic sulfinamides and 3.5 equiv. for aliphatic ones; 1 M in THF) in THF (16 mL), cooled to –78 °C, was dropwise added a solution of oxazolidin-5-one (4.5 equiv. for aromatic aldimines and 3.5 equiv. for aliphatic ones) in THF (3.5 mL). After 20 min, the reaction mixture was further cooled to –85 to –90 °C and a solution of THF/HMPA (2 mL of THF and 3 mL of HMPA) was added dropwise. The selected sulfinamide (0.53 mmol, 1 equiv.) in THF (4.5 mL) was then added to the reaction mixture by a syringe pump (addition rate: 1.5 mL/h) keeping the temperature below –75 °C (not lower than –80 °C). Once the addition was over, the temperature was raised to –60 °C in 1 h and 0.2 M HCl was added. The solution was brought to room temperature, and the organic phase was extracted with EtOAc (2×). The organic layer was than washed with HCl (0.2 M, 2×) and saturated NH_4Cl (1×) and then dried with Na_2SO_4. Filtration of the salt and solvent removal afforded the crude material, which was purified by flash column chromatography (Table 1).

(3*S*,7*R*,7a*R*)-9 and (S_S,2*S*,4*R*,1′*S*)-11: Reaction between (2*S*)-**8** and (S_S)-**1** afforded a mixture (80%) of (S_S,2*S*,4*R*,1′*S*)-**11** and **9** in a 1:1 ratio, which was separated by flash column chromatography (hexane/$CHCl_3$/EtOAc, 10:8:2). Compound **11** was isolated as sticky oil, slightly contaminated by an inseparable byproduct. Data for **11**: ^1H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.30–7.20 (m, 3 H, arom.), 7.20–7.05 (m, 2 H, arom.), 6.20–5.80 (br. m, 1 H), 5.50–5.20 (br. m, 3 H), 5.05 (m, 1 H), 4.85–4.40 (br. m, 2 H), 4.55 (s, 1 H, C*H*-NH), 2.03 (s, 3 H, Me), 1.11 (s, 9 H, *t*BuS), 0.86 (s, 9 H, *tBu*CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C; relevant resonances): δ = 174.5, 153–150 (br.), 139–138 (br.), 131.7, 128.7, 127.5, 119.7, 95.3, 74.8, 66.7, 65.5, 56.4, 38.5, 25.6, 22.6 ppm. IR ($CDCl_3$): ṽ = 2962, 1775, 1715, 1394, 1325 cm^{-1}. HRMS: calcd. for $C_{22}H_{34}N_2O_5S$ $[M]^+$ 450.2188; found 450.2177. The (5*R*) stereoconfiguration was assessed by homonuclear nOe experiments ($CDCl_3$). A nOe effect of 2.8% was observed on the Me group at C5 position (δ =2.03 ppm) upon irradiation of the *t*Bu-C2 signal at δ = 0.86 ppm. Data for **9**: $[\alpha]_D^{20}$ = –38.3 (*c* = 0.6, $CHCl_3$). M.p. 224–226 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 3 H), 7.20–7.10 (m, 2 H), 5.65 (s, 1 H, NH), 5.21 (s, 1 H, C3-H), 4.56 (s, 1 H, C7-H), 1.79 (s, 3 H, Me), 0.98 (s, 9 H, 3 Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 165.0, 137.5, 129.5, 129.1, 126.1, 97.9, 68.1, 67.6, 36.0, 26.2, 24.5 ppm. IR ($CDCl_3$): ṽ = 2972, 1789, 1723, 1188 cm^{-1}. $C_{16}H_{20}N_2O_3$ (288.34): calcd. C 66.65, H 6.99, N 9.72; found C 66.72, H 6.91, N 9.77. The (7*R*,7a*R*) stereoconfiguration was assessed by homonuclear nOe experiments (CD_3COCD_3). Upon irradiation of the C3-*t*Bu group (δ =0.98 ppm), a 23.8% nOe effect was registered at the C3-H proton (δ =5.22 ppm) and a 5.2% effect on the Me group at the C7a position (δ =1.79 ppm), which thus confirms the (*R*) stereoconfiguration for the 7a stereocenter. In addition, irradiation of the C7a-Me protons produced a 14.6% nOe effect on the proton at the C7 position.



(3*S*,7*R*,7a*R*)-**9**

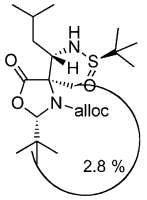
(3*S*,7*S*,7a*R*)-10: Reaction between (2*S*)-**8** and (R_S)-**2** afforded compound **10** in 83% yield as a white solid after crystallization from hexane/diethyl ether, 5:1. $[\alpha]_D^{20}$ = –10.2 (*c* = 0.6, $CHCl_3$). M.p. 158–160 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 1 H), 6.95–6.90 (m, 2 H), 5.40 (s, 1 H, NH), 5.15 (s, 1 H, C3-H), 4.73 (s, 1 H, C7-H), 1.69 (s, 3 H, Me), 0.91 (s, 9 H, 3 Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 164.4, 141.1, 128.0, 126.7, 126.1, 98.1, 68.5, 63.6, 36.3, 25.8, 24.7 ppm. IR (neat): ṽ = 2973, 1790, 1724, 1190 cm^{-1}. $C_{14}H_{18}N_2O_3S$ (294.37): calcd. C 57.12, H 6.16, N 9.52; found C 57.24, H 6.09, N 9.59. The (3*S*,7*R*,7a*S*) stereoconfiguration was assigned by homonuclear nOe experiments ($CDCl_3$). Upon irradiation of the Me group at δ = 1.69 ppm, a 16% nOe effect was observe on the proton at the C7 position (4.73 ppm). Irradiation of the Me_3C group at δ = 0.91 ppm only produced a 2.0% nOe effect on the Me group at δ = 1.69 ppm.



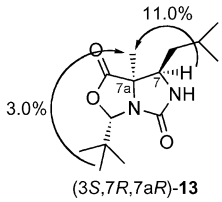
(3*S*,7*S*,7a*R*)-**10**

(S_S,2*S*,4*R*,1′*S*)-12 and (3*S*,7*R*,7a*R*)-13: Reaction between (2*S*)-**8** and (S_S)-**3** afforded a mixture of **12** and **13** (89% overall yield) in a 88:12 ratio, which was separated by flash column chromatography (cyclohexane/$CHCl_3$/Et_2O, 7:8:5) as a white solid. Data for **12**: $[\alpha]_D^{20}$ = +12.5 (*c* = 0.5, $CHCl_3$). M.p. 162 °C. ^1H NMR (400 MHz, CD_3COCD_3): δ = 6.03 (m, 1 H, C*H*=CH_2), 5.64 (s, 1 H, C2 H), 5.44 (d, *J* = 17.0 Hz, 1 H, CH=CH_2), 5.29 (dd, *J* = 1.2 Hz, *J* = 10.5 Hz, 1 H, CH=CH_2), 4.84–4.72 (br., 1 H, O-CH_2), 4.64 (d, *J* = 8.5 Hz, 1 H, NH), 4.58 (dd, *J* = 6.0 Hz, *J* = 13.2 Hz, 1 H, O-CH_2), 4.40–4.20 (br., 1 H, C1′-H), 1.87 (s, 3 H, Me), 1.90–1.80 (m, 1 H, C*H*Me_2), 1.23 (s, 9 H, *t*Bu-S), 1.20–1.15 (m, 1 H, CH-CH_2), 0.98 (s, 9 H, *t*Bu-C2), 1.00–0.90 (m, 1 H, CH-CH_2), 0.88 (d, *J* = 6.5 Hz, 3 H, Me), 0.82 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 58 °C): δ = 174.9, 156.0–154.0 (br.), 131.9, 118.5, 95.9, 66.8, 64.4, 60.0–58.0 (br.), 57.3, 41.4, 38.2, 24.7, 24.0, 23.0, 22.2, 21.5, 20.0 ppm. MS: *m*/*z* = 431 $[M]^+$, 241, 196, 156, 135. IR (neat): ṽ = 2960, 1778, 1720, 1389, 1339 cm^{-1}. $C_{21}H_{38}N_2O_5S$ (430.6): calcd. C 58.57, H 8.89, N 6.51; found C 58.70, H 8.82, N 6.45. The (4*R*) stereoconfiguration was assessed by homonuclear nOe experiments (CD_3COCD_3). A 2.8% nOe effect was observed on the C5-Me protons (1.87 ppm) upon irradiation of the *t*Bu-C2 signal at δ = 0.98 ppm. Data for **13**: $[\alpha]_D^{20}$ = +67.0 (*c* = 0.4, $CHCl_3$). M.p. 198–

200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.57–5.42 (br., 1 H, NH), 5.19 (s, 1 H, C3-H), 3.53 (dd, J = 3.0 Hz, J = 11.5 Hz, 1 H, C7-H), 1.70–1.60 (m, 1 H, C*H*Me$_2$), 1.62 (s, 3 H, Me), 1.62–1.52 (m, 1 H, CHCH_2), 1.18–1.10 (m, 1 H, CHCH_2), 0.98 (s, 9 H, 3 Me), 0.93 (d, J = 6.5 Hz, 3 H, Me), 0.89 (d, J = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 164.5, 98.6, 65.9, 61.3, 41.7, 36.1, 26.3, 24.8, 24.7, 24.0, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 1785, 1713, 1243 cm^{-1}. $C_{14}H_{24}N_2O_3$ (268.35): calcd. C 62.66, H 9.01, N 10.44; found C 62.58, H 9.03, N 10.47. The (7*R*,7a*R*) stereoconfiguration for the major product was assessed by means of homonuclear nOe experiments ($CDCl_3$). A 3.0% nOe effect was observed on the Me group at the C7a position (δ =1.62 ppm) upon irradiation of the *t*Bu group centered at δ = 0.98 ppm, and a 11.0% nOe effect was detected on the C7a-Me signal upon irradiation of the C7-H proton centered at δ = 3.53 ppm, which thus confirms the (*R*) stereoconfiguration both at the 7 and 7a stereocenters. Reaction between sulfinamide (R_S)-**3** and enolate (2*R*)-**8** afforded a mixture of *ent*-**12** and *ent*-**13** (76% *de*) in an 83% overall yield. NMR and IR spectroscopic data and mass analysis for *ent*-**12** and *ent*-**13** are identical to those of **12** and **13**, respectively. *ent*-**12**: $[\alpha]_D^{20}$ = –12.8 (c = 0.5, $CHCl_3$). *ent*-**13**: –67.2 (c 0.4, $CHCl_3$).



(S_S,2*S*,4*R*,1′*S*)-**12**

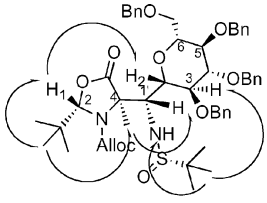


(3*S*,7*R*,7a*R*)-**13**

(S_S,2*S*,4*R*,1′*S*)-14: Reaction between (2*S*)-**8** and (S_S)-**4** afforded compound **14** as a sticky oil, which crystallized upon standing, in 82% isolated yield. $[\alpha]_D^{20}$ = +32.0 (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3COCD_3, 50 °C): δ = 6.03 (dq, J = 6.0 Hz, J = 10.5 Hz, J = 17.2 Hz, 1 H, C*H*=CH$_2$), 5.71 (s, 1 H, C2 H), 5.43 (d, J = 17.2 Hz, 1 H, CH=CH_2), 5.30 (d, J = 10.5 Hz, 1 H, CH=CH_2), 4.78 (m, 1 H, O-CH_2), 4.76 (m, 1 H, O-CH_2), 4.80–4.60 (br., 1 H, NH), 4.20–4.0 (br., 1 H, C1′-H), 1.85 (s, 3 H, Me), 1.75–1.64 (m, 1 H, CHMe$_2$), 1.27 (s, 9 H, *t*Bu-S), 1.02 (s, 9 H, *t*Bu-C2), 0.90 (d, J = 6.5 Hz, 3 H, Me), 0.77 (d, J = 6.5 Hz, 3 H, Me) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, relevant resonances): δ = 1.86 (s, 3 H, Me), 0.99 (s, 9 H, *t*Bu-C2) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3, 50 °C): δ = 175.3, 156.0–154.0 (br.), 132.5, 118.6, 95.6, 66.6, 63–62 (br.), 62.8, 56.8, 38.4, 28.5, 25.1, 22.7, 22.1, 14.5 ppm. IR (neat): $\tilde{\nu}$ = 2960, 1781, 1725, 1390, 1336 cm^{-1}. $C_{20}H_{36}N_2O_5S$ (416.57): calcd. C 57.66, H 8.71, N 6.72; found C 57.52, H 8.80, N 6.79.

General Procedure for the Addition of Sugar Aldimines to Enolates *cis*- and *trans*-8: To a solution of LHMDS (5.5 equiv.; 1 M in THF) in THF (15 mL), cooled to –78 °C, was dropwise added a solution of oxazolidin-5-one (5.5 equiv.) in THF (3.0 mL). After 20 min, the reaction mixture was further cooled to –85 to –90 °C and a solution of THF/HMPA (2 mL of THF and 3 mL of HMPA) was added dropwise. The selected sulfinamide (0.23 mmol, 1 equiv.) in THF (4.0 mL) was then added to the reaction mixture by a syringe pump (addition rate: 1.5 mL/h) keeping the temperature below –75 °C (not lower than –80 °C). Once the addition was over, the temperature was raised to –60 °C in 1 h and 0.2 M HCl was added. The solution was brought to room temperature, and the organic phase was extracted with EtOAc (2×). The organic layer was than washed with 0.2 M HCl (2×) and saturated NH_4Cl (1×) and then dried with Na_2SO_4. Filtration of the salt and solvent removal afforded the crude material, which was purified by flash column chromatography.

(S_S,2*S*,4*R*,1′*R*)-15: Reaction between (2*S*)-**8** and (S_S)-**5** afforded compound **15**, which was separated by silica-gel flash column chromatography (cyclohexane/CH_2Cl_2/Et_2O, 6:3:1), as a sticky oil. Yield: 59%, >96% *de*. $[\alpha]_D^{20}$ = +36.0 (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3COCD_3, 53 °C): δ = 7.42–7.20 (m, 20 H, arom.), 5.80–5.50 [br., 2 H, (C*H*=CH$_2$) + (*t*BuC*H*)], 5.18 (br., 1 H, NH), 5.25–4.50 [m, 12 H (C=CH_2) + 10 H (3× CH_2C$_6$H$_5$)], 4.65–4.55 [br., 1 H, (C*H*NH)], 3.90 (dd, J = 2.8 Hz, J = 11.5 Hz, 1 H, OCH_2CH=CH$_2$), 3.75 (dd, J = 1.63 Hz, J = 11.5 Hz, 1 H, OCH_2CH=CH$_2$), 3.80–3.65 (m, 1 H, H4), 3.69 (t, J = 8.8 Hz, 1 H, H5), 3.61 (t, J = 8.8 Hz, 1 H, H3), 3.52 (d, J = 9.2 Hz, 1 H, H6), 3.23 (d, J = 8.8 Hz, 1 H, H2), 1.90 (s, 3 H, Me), 1.27 (s, 9 H, *t*Bu-S), 1.00 (s, 9 H, *tBu*-CH) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3, 58 °C, relevant resonances): δ = 174.3, 153.2, 139.4, 139.1, 139.0, 138.9, 132.7, 128.4–127.3 (arom.), 117.5, 95.1, 87.6, 79.7, 78.3, 77.3, 77.2, 75.2, 74.6, 73.7, 68.5, 66.3, 59.9, 57.0, 38.5, 25.2, 22.9, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 1778, 1716, 1454, 1334 cm^{-1}. $C_{51}H_{64}N_2O_{10}S$ (897.13): calcd. C 68.28, H 7.19, N 3.12; found C 68.21, H 7.25, N 3.18. The absolute stereochemistry of **15** was assigned by chemical correlation methods (see compound **24**). However, n.O.e. analysis of **15** was performed in order to compare this result with that obtained from n.O.e. analysis of **18**. In detail, irradiation of the C2-*t*Bu group (δ =1.00 ppm) produces a 7.0% nOe effect on C4-Me (δ =1.90 ppm) and a 22% effect on C2-H, which thus suggests an (*R*) stereoconfiguration of the C4 carbon atom. Irradiation of the C4-Me group produces an 8.0% nOe effect on the H-C1′ position, which suggests a C1′ (*R*) configuration. Other significant nOe effects that further confirm this configuration are observed between the *t*Bu group of the SO moiety and the NH (12%) group and the C3-H (8%) proton; furthermore, irradiation of H1 centered at δ = 4.61 ppm produces a 3.0% nOe effect on H2 (δ =3.23 ppm).

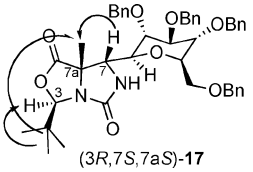


(S_S,2*S*,4*R*,1′*R*)-**15**

(R_S,2*S*,4*R*,1′*R*)-16: Reaction between (2*S*)-**8** and (R_S)-**5** afforded compound **16**, which was separated by silica-gel flash column chromatography (cyclohexane/CH_2Cl_2/Et_2O, 6:3:1). Yield: 63%, >96% *de* (still contaminated by impurities). ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.40–7.20 (m, 20 H, arom.), 5.43 (s, 1 H, *t*BuC*H*), 5.60–5.20 (br., 1 H, C*H*=CH$_2$), 5.10–4.90 (m, 5 H), 4.82–4.75 (m, 2 H), 4.66–4.58 (m, 3 H), 4.50–4.40 (m, 3 H), 4.10 (t, J = 9.2 Hz, 1 H), 3.82 (dd, J = 2.8 Hz, J = 11.2 Hz, 1 H), 3.78 (t, J = 9.6 Hz, 1 H), 3.72–3.60 (m, 3 H), 3.36 (d, J = 9.2 Hz, 1 H, H6), 3.12 (d, J = 9.6 Hz, 1 H, H2), 1.74 (s, 3 H, Me), 1.29 (s, 9 H, *t*Bu-S), 0.96 (s, 9 H, *t*Bu-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 58 °C, relevant resonances): δ = 172.6, 139.6, 138.9, 138.8, 138.70, 132.3, 128.4–127.3 (arom.), 117.5 (b), 94.9, 88.3, 79.8, 77.9, 77.4, 76.3, 76.1, 75.2, 75.1, 74.6, 74.0, 68.6, 66.6, 60.2, 57.5, 38.9, 25.6, 23.2, 22.8 ppm. IR (neat): $\tilde{\nu}$ = 1778, 1716, 1454, 1334 cm^{-1}. HRMS: calcd. for $C_{51}H_{64}N_2O_{10}S$ $[M]^+$ 896.4282; found 896.4294.

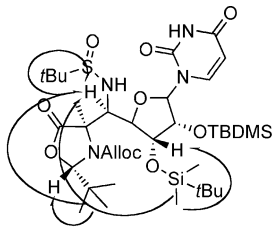
(3*R*,7*S*,7a*S*)-17: Reaction between (2*R*)-**8** and (R_S)-5 afforded compound **17** as a white solid, along with trace amounts (5%) of the opened compound. The mixture was separated by silica-gel flash column chromatography (cyclohexane/CH_2Cl_2/Et_2O, 6:3:1). Overall yield: 79%, 90% *de*. $[\alpha]_D^{20}$ = –90.0 (c = 1.0, $CHCl_3$). M.p. 83–

85 °C. ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 7.22–7.42 (m, 20 H, arom.), 6.63 (br., 1 H, NH), 5.09 (s, 1 H, C_3H), 4.96 (d, J = 11.0 Hz, 1 H, OCH_2), 4.94 (d, J = 11.0 Hz, 1 H, OCH_2), 4.89 (d, J = 11.0 Hz, 1 H, OCH_2), 4.81 (d, J = 11.0 Hz, 1 H, OCH_2), 4.78 (d, J = 11.0 Hz, 1 H, OCH_2), 4.68 (d, J = 11.0 Hz, 1 H, OCH_2), 4.63 (d, J = 12.5 Hz, 1 H, OCH_2), 4.54 (d, J = 12.5 Hz, 1 H, OCH_2), 3.85 (d, J = 1.5 Hz, 1 H, C7*H*), 3.81 (dd, J = 3.2 Hz, J = 11.6 Hz, 1 H, C3-CH_2), 3.76–3.68 (m, 3 H, C4*H* + C5*H* + C6*H*), 3.62 (dd, J = 2.0 Hz, J = 11.6 Hz, 1 H, C3-CH_2), 3.56–3.52 (m, 1 H, C2*H*), 3.29 (m, J = 3.2 Hz, J = 2.0 Hz, J = 9.5 Hz, 1 H, C3*H*), 1.58 (s, 3 H, Me), 0.93 (s, 9 H, *t*Bu-C3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 164.4, 138.7 (C arom.), 138.5 (C arom.), 138.4 (C arom.), 137.8 (C arom.), 129.1 (2 CH), 129.0 (2 CH), 128.9 (CH), 128.7 (2 CH), 128.6 (2 CH), 128.5 (2 CH), 128.0 (2 CH), 127.9 (2 CH), 127.8 (2 CH), 127.7 (CH), 127.6 (2 CH), 97.8, 87.6, 78.7, 78.1, 75.7, 75.6, 75.0, 74.8, 74.4, 73.4, 67.8, 63.8, 62.0, 35.7, 26.5, 24.7 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2871, 1784, 1719, 1249, 1096 cm^{-1}. $C_{44}H_{50}N_2O_8$ (734.88): calcd. C 71.91, H 6.86, N 3.81; found C 71.83, H 6.90, N 3.87. The stereochemistry of **17** was determined by n.O.e. experiments. In detail, irradiation of C7-H (3.85 ppm) produced a 3% n.O.e. effect on the C7a methyl group (δ =1.58 ppm). Irradiation of the *t*Bu group (δ =0.93 ppm) furnished a 2.5% n.O.e. effect on the C7a methyl group and a 25% effect on C3-H. Relevant resonances for the opened compound: ^{1}H NMR (400 MHz, CD_3Cl_3, 55 °C): δ = 0.98 (s, 9 H, *t*Bu), 1.18 (s, 9 H, *t*Bu), 1.77 (s, 3 H, Me), 3.45 (m, 1 H), 3.99 (m, 1 H), 5.45 (br. s, 1 H) ppm.



(3*R*,7*S*,7a*S*)-**17**

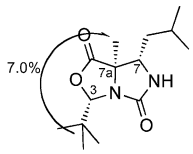
(*S*$_S$,2*S*,4*R*,1′*R*)-18: Reaction between (2*S*)-**8** and (*S*$_S$)-**6** afforded compound **18**, which was purified by silica-gel flash column chromatography (cyclohexane/ethyl acetate, 7:3) to obtain a sticky oil. Overall yield: 89%, >96% *de*. $[\alpha]_D^{20}$ = +24.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6, 75 °C): δ = 8.75 (br., 1 H, N*H*-CO, H8′), 7.68 (br., 1 H, *H*C=CH-C=O, H6′), 6.10 (br., 1 H, H5′), 5.80–5.64 (m, 1 H, C*H*=CH_2, H12′), 5.62 (m, 1 H, NH, H9′), 5.60–5.45 (m, 1 H, HC=C*H*-C=O, H7′), 5.49 (s, 1 H, C*H*t*Bu*, H10′), 5.10 (d, J = 17.2 Hz, 1 H, CH=CH_2, H13′), 5.00 (d, J = 10.4 Hz, 1 H, CH=CH_2, H13′), 4.72 (t, J = 5.6 Hz, 1 H, H3′), 4.47 (t, J = 4.8 Hz, 1 H, H4′), 4.30–4.15 (m, 3 H, 2 H, OCH_2CH=CH_2 + H2′), 4.20 (d, J = 10.0 Hz, 1 H, C*H*-NH), 1.69 (s, 3 H, Me), 1.12 (s, 9 H, *t*BuS), 1.02 (s, 9 H, *t*BuSi), 0.94 (s, 9 H, *t*BuSi), 0.75 (s, 9 H, *t*BuCH), 0.37 (s, 3 H, Me), 0.19 (s, 3 H, Me), 0.15 (s, 3 H, Me), 0.14 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, C_6D_6, 58 °C, relevant resonances): δ = 173.0, 162.1, 154.7, 150.4, 142.0, 131.8, 118.9, 102.9, 94.8, 92.0, 84.5, 74.0, 72.9, 66.8, 66.6, 65.0, 57.3, 38.4, 26.1, 26.0, 25.5, 23.1, 21.6, 18.1 ppm. IR (neat): $\tilde{\nu}$ = 1798, 1702, 1698, 1463, 1389 cm^{-1}. $C_{37}H_{66}N_4O_{10}SSi_2$ (815.17): calcd. C 54.52, H 8.16, N 6.87; found C 54.66, H 8.09, N 6.83. The stereochemistry of **18** was determined by n.O.e. experiments. In detail, irradiation of the *t*Bu-C2 group (δ =0.75 ppm) showed a 1.3% nOe effect on C4-Me at δ = 1.69 ppm and 6.0% with H1, which thus suggests the (*R*) stereoconfiguration for the C4 carbon atom. Selective irradiation of C4-Me produced an 11% nOe effect on H1′, which suggests an (1′*R*) conformation. Other significant nOe effects that further confirm the restricted conformation of **18** were observed between *t*BuS and CH-N*H* (1.0%), H7 (1.0%), and H6 (3%) and between one of the methyl protons of Me_2Si centered at δ = 0.37 ppm and H3′ (2.2%) and C*H*-NH (4.2%).



(*S*$_S$,2*S*,4*R*,1′*R*)-**18**

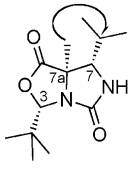
General Procedure for Nitrogen Sulfinyl Deprotection and Cyclization of the Corresponding Free Amines 19–21: Unless otherwise stated, a MeOH solution of the 1′-(sulfinylamino)oxazolidinone (2 mL per 0.03 g of dioxolanone) was added to an ethereal 2 N HCl solution (16 equiv.) under a nitrogen atmosphere at 0 °C. After 30 min, the temperature was raised to 25 °C, and the mixture was stirred for 2 h. The solvent was removed under vacuum, and the residue was treated with a 10% aqueous solution of $NaHCO_3$, diluted with H_2O, and extracted with ethyl acetate (3×). The organic phase was dried with Na_2SO_4 and concentrated under vacuum. The residue was placed in a 50-mL two-necked round-bottom flask, equipped with a nitrogen inlet, an injection septum, and a magnetic stirring bar, and diluted with freshly distilled THF (1.0 mL per 0.03 g of starting material). The reaction mixture was cooled to –30 °C, and a solution of LHMDS (4 equiv.; 1 M in THF) and HMPA (4 equiv.) was added dropwise. The reaction mixture was warmed to –5 °C over 3 h and then quenched with 1.0 N HCl. The bicyclic compounds were isolated according to the following standard procedure: the reaction mixture was extracted with ethyl acetate (3 × 20 mL), and the collected organic phase was washed with saturated NH_4Cl and then dried with Na_2SO_4. After filtration, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (Table 2).

(2*S*,4*R*,1′*S*)-19 and (3*S*,7*S*,7a*R*)-22: Reaction of **12** (0.2 g, 0.46 mmol) with 2.0 N HCl (3.7 mL) afforded **19** (0.13 g, 0.42 mmol, 90%). Treatment of **19** (crude compound) with LHMDS (1 M in THF, 1.7 mL) afforded, after silica-gel flash chromatography (cyclohexane/ethyl acetate, 5:1), **22** (0.096 g, 0.35 mmol, 80%) as a white solid. Data for **19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (dq, J = 6.2 Hz, J = 10.8 Hz, J = 17.6 Hz, 1 H, C*H*=CH_2), 5.52 (s, 1 H, C2 H), 5.34 (dd, J = 1.2 Hz, J = 17.6 Hz, 1 H, CH=CH_2), 5.27 (dd, J = 1.2 Hz, J = 10.8 Hz, 1 H, CH=CH_2), 4.78–4.64 (m, 1 H, O-CH_2), 4.80 (m, 1 H, O-CH_2), 3.80–3.40 (br., 1 H, C1′-H), 1.80–1.60 (m, 1 H, $CHMe_2$), 1.78 (s, 3 H, Me), 1.55–1.45 (br., 2 H, NH_2), 1.00–0.85 (m, 2 H, $CHCH_2$), 0.98 (s, 9 H, *t*Bu-C2), 0.91 (d, J = 6.5 Hz, 3 H, Me), 0.80 (d, J = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 154.5, 132.0, 119.1, 95.1, 66.7, 65.9, 56.0–54.0 (br.), 41.5, 38.7, 29.9, 25.5, 25.0, 24.3, 21.2 ppm. IR (neat): $\tilde{\nu}$ = 2958, 1770, 1715, 1389, 1339 cm^{-1}. Data for **22**: $[\alpha]_D^{20}$ = –32.0 (c = 0.5, $CHCl_3$). M.p. 194–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26 (s, 1 H, C3-H), 5.20–5.15 (br., 1 H, NH), 4.03 (dd, J = 4.5 Hz, J = 19.6 Hz, 1 H, C7-H), 1.68–1.60 (m, 1 H, C*H*Me_2), 1.60–1.48 (m, 2 H, $CHCH_2$), 1.51 (s, 3 H, Me), 1.01 (s, 9 H, 3 Me), 0.99 (d, J = 6.5 Hz, 3 H, Me), 0.93 (d, J = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 164.9, 99.5, 64.3, 58.7, 39.4, 36.0, 25.8, 25.0, 24.7, 21.5, 19.3 ppm. IR (neat): $\tilde{\nu}$ = 1785, 1716, 1240 cm^{-1}. $C_{14}H_{24}N_2O_3$ (268.35): calcd. C 62.66, H 9.01, N 10.44; found C 62.61, H 9.07, N 10.50. The (7*S*,7a*R*) stereoconfiguration was assessed by homonuclear nOe experiments. An nOe effect of 7.0% was observed with the C7a-Me protons at δ = 1.51 ppm upon irradiation of the C3-*t*Bu signal at δ = 1.01 ppm.



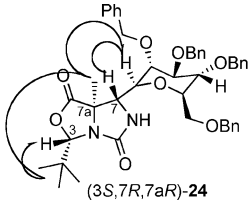
(3*S*,7*S*,7a*R*)-**22**

(2*S*,4*R*,1′*S*)-20 and (3*S*,7*S*,7a*R*)-23: Reaction of (*S*$_S$,2*S*,4*R*,1′*S*)-**14** (0.2 g, 0.48 mmol) with 2.0 N HCl (3.84 mL) afforded **20** (0.13 g, 0.40 mmol, 85%). Treatment of **20** (crude compound) with LHMDS (1 M in THF, 1.63 mL) afforded, after silica-gel flash chromatography (cyclohexane/Et_2O, 3:1), **23** (0.04 g, 0.16 mmol, 40%) as a white solid. Data for **20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (dq, *J* = 6.2 Hz, *J* = 10.8 Hz, *J* = 17.6 Hz, 1 H, C*H*=CH_2), 5.52 (br. s, 1 H, C_2H), 5.34 (dd, *J* = 1.2 Hz, *J* = 17.6 Hz, 1 H, CH=CH_2), 5.27 (dd, *J* = 1.2 Hz, *J* = 10.8 Hz, 1 H, CH=CH_2), 4.78–4.64 (m, 1 H, O-CH_2), 4.80 (m, 1 H, O-CH_2), 3.80–3.40 (br., 1 H, C1′-H), 1.78 (s, 3 H, Me), 1.55–1.45 (br., 2 H, NH_2), 1.30 (br. s, 1 H), 0.98 (s, 9 H, *t*Bu-C2), 0.91 (d, *J* = 6.5 Hz, 3 H, Me), 0.80 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 154.5, 132.0, 119.9, 119.6, 95.1, 66.7, 65.9, 56.0–54.0 (br.), 41.5, 38.7, 29.9, 25.5, 25.0, 24.3, 21.2 ppm. IR (neat): $\tilde{\nu}$ = 1790, 1715 cm^{-1}. Data for **23**: $[\alpha]_D^{20}$ = –21 (*c* = 0.3, $CHCl_3$). M.p. 191–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.27 (s, 1 H, C3-H), 4.72–4.68 (br., 1 H, NH), 3.55 (dd, *J* = 1.2 Hz, *J* = 9.5 Hz, 1 H, C7-H), 2.10–1.96 (m, 1 H, C*H*Me$_2$), 1.58 (s, 3 H, Me), 1.07 (d, *J* = 5.0 Hz, 3 H, Me), 1.01 (s, 9 H, 3 Me), 0.98 (d, *J* = 5.0 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 166.6, 99.0, 67.2, 64.7, 36.0, 28.3, 25.0, 20.4, 20.1, 19.1 ppm. IR (neat): $\tilde{\nu}$ = 1787, 1714, 1242 cm^{-1}. $C_{13}H_{22}N_2O_3$ (254.32): calcd. C 61.39, H 8.72, N 11.01; found C 61.28, H 8.78, N 11.10. The (7a*R*,7*S*) stereoconfiguration was assessed by homonuclear nOe experiments ($CDCl_3$). An nOe effect of 3.6% was observed on the C*H*Me$_2$ signal at 2.10–1.96 ppm upon irradiation of the 7a-Me signal at δ = 1.58 ppm.



(3*S*,7*S*,7a*R*)-**23**

(2*S*,4*R*,1′*R*)-21 and (3*S*,7*R*,7a*R*)-24: Reaction of (*S*$_S$,2*S*,4*R*,1′*R*)-**15** (0.2 g, 0.23 mmol) with 2.0 N HCl (1.82 mL) afforded **21** (0.16 g, 0.20 mmol, 90%). Treatment of **21** (crude compound) with LHMDS (1 M in THF, 0.8 mL) afforded, after silica-gel flash chromatography (cyclohexane/Et_2O, 1:1), **24** (0.06 g, 40%) as a sticky solid. Data for **21**: ^{1}H NMR (400 MHz, $CDCl_3$, 53 °C): δ = 7.35–7.20 (m, 20 H, arom.), 5.90–5.50 (br., 1 H), 5.41 (s, 1 H), 5.20–5.05 (m, 2 H), 4.90–4.75 (m, 5 H), 4.75–4.60 (m, 5 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.20–4.00 (br., 1 H), 3.90–3.75 (m, 3 H), 3.75–3.60 (m, 3 H), 3.35 (m, 1 H), 3.07 (d, *J* = 9.5 Hz, 1 H), 1.77 (s, 3 H, Me), 1.60–1.45 (br., 2 H, NH_2), 0.97 (s, 9 H, *tBu*-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 53 °C, relevant resonances): δ = 173.6, 139.1, 139.0, 138.9, 138.7, 132.3, 128.4–127.3 (arom.), 118.0 (br.), 94.6, 87.7, 80.3, 78.4, 77.8, 77.7, 75.5, 75.0, 74.8, 74.2, 68.8, 66.6, 63.0, 38.7, 29.8, 25.7 ppm. Data for **24**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.40 (m, 20 H, arom.), 5.20 (s, 1 H, C_3H), 4.95 (d, *J* = 11.0 Hz, 1 H, OCH_2), 4.90 (d, *J* = 11.0 Hz, 1 H,OCH_2), 4.84 (d, *J* = 11.5 Hz, 1 H, OCH_2), 4.80 (d, *J* = 11.0 Hz, 1 H, OCH_2), 4.63 (d, *J* = 11.5 Hz, 1 H, OCH_2), 4.58 (d, *J* = 11.0 Hz, 1 H, OCH_2), 4.55 (d, *J* = 12.5 Hz, 1 H, OCH_2), 4.51 (d, *J* = 12.5 Hz, 1 H, OCH_2), 4.20 (br., 1 H, NH), 3.99 (d, *J* = 1.2 Hz, 1 H, C7*H*), 3.76 (t, *J* = 8.0 Hz, 1 H, C5*H*), 3.63 (d, *J* = 10.0 Hz, 1 H, C2-*H*), 3.54–3.40 (m, 3 H, C4-*H* + C2-*H*), 3.37 (dd, *J* = 1.2 Hz, *J* = 9.0 Hz, 1 H, C2-*H*), 3.21 (dd, *J* = 8.0 Hz, *J* = 9.0 Hz, 1 H, C6-*H*), 1.59 (s, 3 H, Me), 0.97 (s, 9 H, *t*Bu-C3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, relevant resonances): δ = 176.4, 165.3, 138.5, 138.4, 138.0, 137.1, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.1, 128.0, 127.9, 127.7, 127.6, 101.9, 87.5, 79.4, 78.7, 75.9, 75.8, 75.7, 75.3, 74.5, 73.6, 69.1, 64.5, 56.4, 35.5, 26.5, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2871, 1784, 1719, 1249, 1096 cm^{-1}. $C_{44}H_{50}N_2O_8$ (734.88): calcd. C 71.91, H 6.86, N 3.81; found C 71.86, H 6.91, N 3.88. The (7a*R*,7*R*) stereoconfiguration was assessed by homonuclear nOe experiments. Selective irradiation of the C2-*t*Bu group at δ = 0.97 ppm produced a 2.1% n.O.e. effect on C7a-Me and a 25.5% effect on C3-H. Irradiation of the C7a-Me (δ =1.58 ppm) protons produced a 1.6% enhancement on the *t*Bu group (δ =0.97 ppm) and 3.5% on C2-H. Irradiation of C2-H induced a 4% n.O.e. effect on C7a-Me, a 5.5% effect on C5-H, and an 8.8% effect on C7-H. Irradiation of C7-H induced a 5.5% enhancement of the C2-H signal, and a 3.0% effect on the NH proton. No nOe effect was detected on C7a-Me.



(3*S*,7*R*,7a*R*)-**24**

General Procedure for Nitrogen Alloc-Group Deprotection and Subsequent Hydrolysis to the Corresponding Sulfinyl-Protected Amino Acids 25–28: To a solution of 1′-(sulfinylamino)oxazolidinone (1 equiv.) in CH_2Cl_2 (1.0 mL per equiv.) was added Ph_3SiH (6 equiv.) followed by $Pd(PPh_3)_4$ (10 mol-%). The reaction course was monitored by TLC analysis, and after approximately 2 h, the solvent was removed under vacuum and THF and water were added (few drops each). The solution was left to stand at room temperature for 3 h, dried, and the free amino acids were purified by crystallization or column chromatography (Table 3).

(*S*$_S$,2*S*,3*S*)-25: Reaction of (*S*$_S$,2*S*,4*R*,1′*S*)-**12** (0.08 g, 0.19 mmol) with Ph_3SiH (1.12 mmol) and $Pd(PPh_3)_4$ (0.019 mmol) in CH_2Cl_2 (0.2 mL) followed by treatment with water and THF afforded **25** (0.052 g, 98%) after crystallization (Et_2O). $[\alpha]_D^{20}$ = +17.5 (*c* = 0.3, MeOH). ^{1}H NMR (400 MHz, CD_3OD, 45 °C): δ = 3.36 (dd, *J* = 11.6 Hz, *J* = 11.6 Hz, 1 H, C1′-H), 1.85–1.76 (m, 1 H, C*H*Me$_2$), 1.52 (s, 3 H, Me), 1.49–1.40 (m, 1 H of CH_2), 1.38–1.29 (m, 1 H, of CH_2), 1.29 (s, 9 H, *t*Bu-S), 0.93 (d, *J* = 6.5 Hz, 3 H, Me), 0.91 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 54 °C): δ = 173.7, 62.7, 60.4, 57.0, 40.8, 24.1, 23.0, 22.3, 20.4, 19.8 ppm. $C_{12}H_{26}N_2O_3S$ (278.17): calcd. C 51.77, H 9.41, N 10.06; found C 51.69, H 9.46, N 10.11.

(*S*$_S$,2*R*,3*S*)-26: Reaction of (*S*$_S$,2*S*,4*R*,1′*S*)-**14** (0.08 g, 0.19 mmol) with Ph_3SiH (1.12 mmol) and $Pd(PPh_3)_4$ (0.019 mmol) in CH_2Cl_2 (0.2 mL) followed by treatment with water and THF afforded **26** (0.05 g, 98%) as a white solid after crystallization (EtOAc). $[\alpha]_D^{20}$ = +25.5 (*c* = 0.5, H_2O). M.p. 241–243 °C. ^{1}H NMR (400 MHz, CD_3OD, 62 °C): δ = 4.54 (br. s, 3 H, NH_2 + OH), 3.41 (dd, *J* = 11.6 Hz, *J* = 2.4 Hz, 1 H, C1′-H), 1.85–1.76 (m, 1 H, C*H*Me$_2$), 1.52 (s, 3 H, Me), 1.29 (s, 9 H, *t*Bu-S), 0.96 (d, *J* = 6.5 Hz, 3 H, Me), 0.87 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, D_2O, 40 °C): δ = 176.95, 66.38, 60.64, 57.90, 28.86, 23.97, 22.99,

21.58, 14.20 ppm. $C_{11}H_{24}N_2O_3S$ (264.38): calcd. C 49.97, H 9.15, N 10.60; found C 49.88, H 9.20, N 10.68.

(S_S,2*R*,3*R*)-27: Reaction of (S_S,2*S*,4*R*,1′*R*)-**15** (0.08 g, 0.091 mmol) with Ph_3SiH (0.54 mmol) and $Pd(PPh_3)_4$ (0.009 mmol) in CH_2Cl_2 (0.1 mL) followed by treatment with water and THF afforded **27** (0.07 g, 98%) as a sticky solid after purification by silica-gel flash column chromatography ($CHCl_3$/MeOH, 8.5:1.5). $[\alpha]_D^{20}$ = +17.5 (*c* = 0.5, acetone). ^{1}H NMR (400 MHz, CD_3COCD_3, 51 °C): δ = 7.36–7.27 (m, 20 H, arom.), 5.17 (d, *J* = 9.2 Hz, 1 H, NH), 4.97 (d, *J* = 11.2 Hz, 2 H), 4.89–4.84 (m, 2 H), 4.78–4.69 (m, 3 H), 4.57 (d, *J* = 12.5 Hz, 1 H), 4.12 (d, *J* = 9.0 Hz, 1 H), 3.86 (dd, *J* = 3.9 Hz, *J* = 11.2 Hz, 1 H), 3.79 (t, *J* = 8.8 Hz, 1 H), 3.74 (dd, *J* = 1.5 Hz, *J* = 11.5 Hz, 1 H), 3.72–3.60 (m, 3 H), 3.54–3.49 (m, 1 H, O-C*H*-CH_2-O), 1.60 (s, 3 H, Me), 1.31–1.23 (br., 9 H, *tBu*-CH) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3, 51 °C): δ = 176.9, 139.4, 139.3, 139.1 (2 C), 128.4–127.3 (12 CH), 87.5, 79.0, 78.7, 77.9, 76.6, 75.1, 74.6, 74.4, 73.6, 69.1, 62.0, 61.2, 56.8, 25.6, 22.9 ppm. $C_{42}H_{52}N_2O_8S$ (744.94): calcd. C 67.72, H 7.04, N 3.76; found C 67.83, H 6.99, N 3.71.

(S_S,2*R*,3*R*)-28: Reaction of (S_S,2*S*,4*R*,1′*R*)-**18** (0.08 g, 0.09 mmol) with Ph_3SiH (0.59 mmol) and $Pd(PPh_3)_4$ (0.01 mmol) in CH_2Cl_2 (0.1 mL) followed by treatment with water and THF afforded **28** (0.64 g, 98%) as a white solid after after crystallization (CH_3CN/Et_2O, 1:4). $[\alpha]_D^{20}$ = –31.0 (*c* = 0.4, THF). ^{1}H NMR (400 MHz, CD_3COCD_3, 53 °C): δ = 7.65 (d, *J* = 7.2 Hz, 1 H, *H*C=CH-C=O), 5.68 (d, *J* = 8.0 Hz, 1 H, H5′), 5.56 (m, *J* = 10.0 Hz, 1 H, N*H*SO), 5.47 (m, *J* = 7.2 Hz, 1 H, HC=C*H*-C=O), 4.88 (m, 1 H), 4.64 (m, 1 H), 4.41 (m, 1 H), 3.51 (dd, *J* = 10.0 Hz, *J* = 1.5 Hz, 1 H, C*H*-NH), 1.44 (s, 3 H, Me), 1.342 (s, 9 H, *t*BuS), 0.96 (s, 9 H, *t*BuSi), 0.90 (s, 9 H, *t*BuSi), 0.21 (s, 3 H, Me), 0.17 (s, 3 H, Me), 0.14 (s, 3 H, Me), 0.04 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, 58 °C, CD_3COCD_3): δ = 177.1, 162.2, 151.1, 145.2, 102.6, 95.9, 87.0, 74.0, 71.1, 66.6, 63.4, 57.4, 25.7, 25.6, 25.2, 23.1, 17.9, 17.7, –4.6, –4.7 (2 C), –5.6 ppm. $C_{28}H_{54}N_4O_8SSi_2$ (662.99): calcd. C 50.72, H 8.21, N 8.45; found C 50.81, H 8.17, N 8.41.

(2*R*,3*R*)-29: (3*S*,7*R*,7a*R*)-**9** (100 mg, 0.35 mmol) was heated at reflux for 2 h in 6 M HCl (2 mL). Upon crystallization (MeOH/Et_2O, 2:1), **29** was isolated from the reaction mixture in quantitative yield as a solid. Data for (2*R*,3*R*)-**29**·2HCl: $[\alpha]_D^{20}$ = +22.0 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.60–7.50 (br., 5 H, ArH), 4.98 (s, 1 H, C3-H), 1.74 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 170.4, 130.7, 130.6, 129.8, 129.5, 60.9, 57.9, 17.7 ppm. $C_{10}H_{16}Cl_2N_2O_2$ (267.15): calcd. C 44.96, H 6.04, N 10.49; found C 44.88, H 6.09, N 10.53.

(2*R*,3*S*)-30: (3*S*,7*S*,7a*R*)-**10** (100 mg, 0.34 mmol) was heated at reflux for 2 h in 6 M HCl (2 mL). Upon crystallization (MeOH/Et_2O, 2:1), **30** was isolated from the reaction mixture in quantitative yield as a solid. Data for (2*R*,3*S*)-**30**·2HCl: $[\alpha]_D^{20}$ = +29.0 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.71 (d, *J* = 7.1 Hz, 1 H, ArH), 7.57–7.59 (m, 1 H, ArH), 7.21–7.24 (m, 1 H, ArH), 5.39 (s, 1 H), 1.81 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 169.80, 130.96, 130.50, 128.98, 128.12, 61.04, 53.73, 17.82 ppm. $C_8H_{14}Cl_2N_2O_2S$ (273.18): calcd. C 35.17, H 5.17, N 10.25; found C 35.11, H 5.15, N 10.22.

(2*R*,3*S*)-31: (S_S,2*S*,4R,1′*R*)-**11** (100 mg, 0.23 mmol) was heated at reflux for 2 h in 6 M HCl (2 mL). Upon crystallization (MeOH/Et_2O, 2:1), **31** was isolated from the reaction mixture in quantitative yield as a solid, slightly contaminated by impurities. Data for (2*R*,3*S*)-**31**·2HCl: ^{1}H NMR (400 MHz, CD_3OD): δ = 7.55 (br. s, 5 H, ArH), 4.85 (s, 1 H, C3-H), 1.91 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 169.9, 130.9, 130.7, 129.9, 128.4, 60.8, 58.8, 20.8 ppm. $C_{10}H_{16}Cl_2N_2O_2$ (267.15): calcd. C 44.96, H 6.04, N 10.49; found C 44.89, H 6.10, N 10.41.

Supporting Information (see footnote on the first page of this article): Selected ^{1}H and ^{13}C NMR spectra.

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