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A Cyclic Enamine Derived from 1,2-*O*-Isopropylidene-α-D-xylofuranose As a Novel Carbohydrate Intermediate To Achieve Skeletal Diversity

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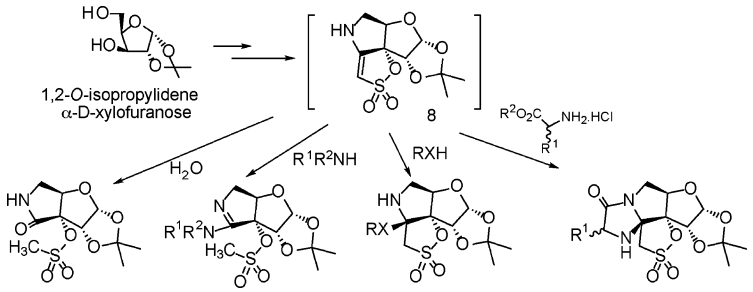

The commercially available carbohydrate 1,2-*O*-isopropylidene-α-D-xylofuranose was efficiently transformed into the high-added-value synthetic scaffold **8**. The transformation requires the synthesis of the 5-*O*-tosyl derivative **7** and its subsequent intramolecular cyclization under basic conditions to give the cyclic enamine **8**. Reaction of **8** with *O*-, *N*-, *S*-, and *C*-nucleophiles and amino acids allowed its efficient transformation (one-step, high yields, and easy purifications) into fused cyclic sugar derivatives with rather unusual molecular skeletons in a completely regio- and stereoselective manner. The characteristics of the sugar derivative **8** established here, high reactivity, synthetic accessibility, and the potential for conversion into a vast collection of products by the action of different nucleophiles, indicate that it will prove to be a useful chiral intermediate for achieving skeletal diversity. The constrained structures and dense functionalization of the polycyclic sugar derivatives generated from **8** make these compounds promising candidates for use as starting agents for the production of new analogues and as drugs.

Introduction

Carbohydrates have received much attention over the years as valuable synthetic intermediates and as a source of chirality. They can be used as scaffolds for the synthesis of naturally occurring compounds[1] as well as carbohydrate-derived bioactive compounds[2] and to mimic non-carbohydrate bioactive compounds.[3−5] In addition, a variety of C−C bond-forming reactions and ring annulations have been accomplished using carbohydrates either as chiral auxiliaries[6] or as chiral building blocks.[7] On the other hand, carbohydrates are privileged structures with a high density of functionalized and stereocontrolled centers that can be used as molecular templates to display pharmacophoric groups in well-defined spatial orientations.[8] These findings, together with the easy accessibility of simple carbohydrate derivatives, make carbohydrates attractive building blocks for organic synthesis.

In recent years carbohydrates have become established as particularly attractive scaffolds for combinatorial chemistry[9] and

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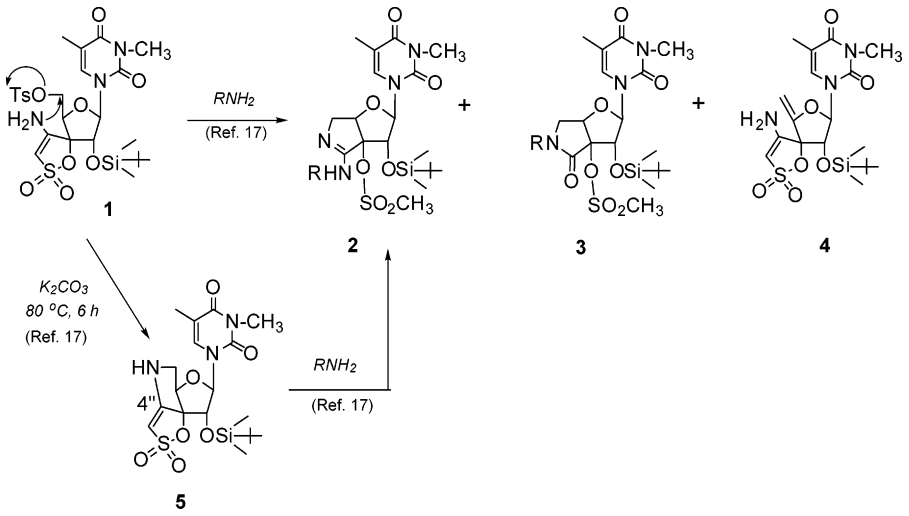
SCHEME 1. Reaction of 5′-*O*-Tosyl TSAO-m^{3}T 1 and Cyclic Enamine 5 with Alkylamines



for peptidomimetics.[10] In this context, there has been great interest in the synthesis of carbohydrate-derived scaffolds that have enhanced conformational constraints but still retain functionalities suitable for further functionalization. One possible way to constrain the molecular conformation of carbohydrates is through the synthesis of condensed cyclic compounds. The design and synthesis of this class of compounds has attracted the attention of the synthetic organic chemists in recent years.[11]

For more than a decade, our research has been directed toward synthesizing hypermodified nucleosides as potential anti-HIV agents.[12−16] In this context, we have developed a family of potent and highly specific inhibitors of HIV-1 reverse transcriptase[15,16] whose prototype is the thymine derivative [1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]thymine]-3′-spiro-5″-(4″-amino-1″,2″-oxathiole-2″,2-dioxide) named TSAO-T.

In an earlier work aimed at improving the activity/toxicity profile of TSAO derivatives, we subjected 5′-*O*-Tosyl TSAO-m^{3}T **1**,[17] derived from TSAO-T,[15] to nucleophilic attack by different alkylamines in order to obtain the corresponding 5′-alkylamino-substituted TSAO derivatives (Scheme 1). However, our attempts were unsuccessful; instead of the desired product, the bicyclic nucleosides **2** and **3** were unexpectedly obtained, albeit in moderate yield (18%), together with the unsaturated compound **4** in higher yield (25%). In our exploration of this novel reaction, a key proposed intermediate (**5**) was isolated in 70% yield under basic non-nucleophilic conditions (potassium carbonate, 80 °C and 6 h) as a result of an intramolecular attack of the amino group on the tosyl leaving group at the 5′ position of the sugar.[17] In the same study, we showed that the conjugated double bond of the α,*β*-unsaturated cyclic sulfonate ester in **5** is very reactive toward nucleophiles.[17] In fact, formation of the bicyclic nucleoside **2** could be explained by attack at the conjugated double bond of **5** by an alkylamine followed by opening of the spiroaminooxatioldioxide ring (Scheme 1).

Encouraged by this preliminary result, we investigated whether this reaction could be used as the basis for the synthesis of different classes of bi-, tri-, and tetracyclic nucleosides. In a

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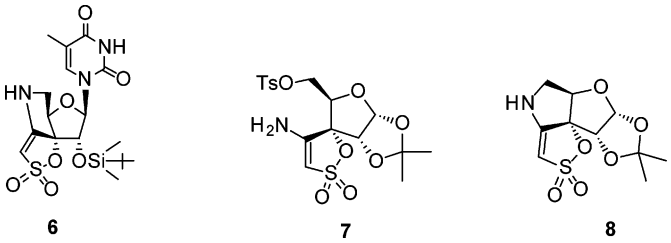

FIGURE 1. Structures of compounds **6**, **7**, and **8**.

subsequent study of the reactivity of the non-methylated thymine cyclic enamine **6** against different nucleophiles (Figure 1), we found that this enamine is in fact a very useful and versatile intermediate that can be used to prepare novel types of polycyclic nucleosides in high yields in a regio- and stereoselective manner.[18]

In the present work, we studied whether simple sugar derivatives, such as the 1,2-*O*-isopropylidene-5-*O*-tosyl α-D-ribofuranose **7**, could be converted to a cyclic enamine **8** that could then be used to achieve skeletal diversity (Figure 1). We were also interested in the possibility that the unique reactivity of the cyclic enamine in **8** would cause the compound to be transformed into unusual classes of condensed cyclic compounds. Moreover, we speculated that **8** might be used as a common sugar precursor in glycosylation reactions to give a variety of nucleosides or *O*-, *S*-, or *N*-glycosides.

Results

Chemistry. Originally, the tosylate precursor **7** of the cyclic enamine **8** was prepared following a protocol similar to that established by our group for the synthesis of 5′-*O*-tosyl TSAO-m^{3}T **1**.[17] Briefly, the 5′-TBDMS derivative **9**[19] was first synthesized via five steps starting from 1,2-*O*-isopropylidene-α-D-xylofuranose. Then, **9** was selectively deprotected with 0.1 N methanolic HCl to yield **10**,[19] which was subsequently activated with tosyl chloride to give the 5′-*O*-tosyl derivative **7** (Scheme 2).

Next we sought to establish an alternative, shorter synthetic route to 5-*O*-tosyl derivative **7**. In this second route, the tosyl moiety was introduced into the sugar during the very first stage, avoiding the two protection/deprotection steps with TBDMS used in the original scheme. Thus, this route started from commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose, which was selectively monotosylated at the primary hydroxyl group to afford **11** (95%)[20,21] (Scheme 3). Oxidation of the remaining 3-hydroxyl group with pyridinium dichromate/Ac_2O afforded the 3-ulose **12**, which was not purified. Addition of sodium cyanide to **12** followed by mesylation of the corresponding cyanohydrin **13** afforded the α-mesyloxynitrile **14** (67%). The high stereoselectivity observed in the formation of **13** could be explained by the presence of the conformationally rigid 1,2-*O*-isopropylidene functionality, which dictates the approach of the cyanide ion from the sterically less-hindered *β*-face of the ulose.[19] Subsequent treatment of **14** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at −20 °C caused **14** to undergo an aldol-type cyclocondensation to afford the *C*-branched-3-spiro derivative **7** (60%). Compared to the original synthetic route, this second route involved two less steps and gave double the yield (38% versus 19%).

Next, we attempted to obtain the cyclic enamine **8** via the intramolecular nucleophilic substitution of **7** (Scheme 4). By analogy with the conditions used for the synthesis of the cyclic enamine nucleosides **5** and **6** derived from thymine, the reaction was carried out at 80 °C for 6 h in the presence of potassium carbonate as a non-nucleophilic base. However, **8** was not formed under these conditions; instead, the unexpected crystalline compound **15** (mp 151 °C) was isolated in 80% yield.

In the ^{1}H NMR spectrum of **15**, two sets of equivalent peaks for protons H-1, H-2, H-4, and H-5 were observed, suggesting that **15** has a dimeric structure comprised of two fragments, which we denote **A** and **B**. In addition, the spectrum also contained two singlet peaks, at δ 6.43 (broad) and 6.08 (narrow) ppm, corresponding to the NH and H-3′ protons of fragments **A** and **B** (Figure 2), respectively. On the other hand, an AB system with signals at δ 4.38 and 4.47 ppm (J_{gem} = 15.5 Hz) corresponding to the H-3′ protons of fragment **B** was observed.

Unambiguous assignment of each subunit of the sugar-derivative **15** was achieved by two-dimensional NMR spectroscopy techniques, namely, the gradient heteronuclear multiple-bond correlation (gHMBC)[22] and gradient heteronuclear single quantum correlation (gHSQC)[23] techniques. The gHMBC experiment (Figure 2) was crucial for the identification of this compound. For fragment **A**, a long-range correlation between the H-5 protons (δ 3.47 and 3.65 ppm) and the C-4′ carbon (δ 155.6 ppm) was observed, whereas for fragment **B**, a long-range correlation between the H-5 protons (δ 3.40 and 3.70 ppm) and the C-4′ carbon (δ 97.6 ppm) was observed. In addition, for fragment **B** a correlation was observed between the H-3′ protons (δ 4.38 and 4.47 ppm) and the C-4′ carbon (δ 97.6 ppm).

The formation of the dimer **15** was further supported by the mass spectrum, which showed a molecular peak of 551.3 *m*/*z*.

The formation of **15** as the major product indicates that the cyclic enamine **8**, once formed, readily undergoes self-condensation via an intermolecular attack between the NH and C-4′ positions of distinct molecules, leading to the formation of a dimer. These findings stand in contrast to those for the 5′-*O*-tosyl derivative of nucleoside **1**, which under similar conditions afforded the cyclic enamine **5** in very good yield (Scheme 1). Furthermore, it became apparent that the change from the thymine in **1** to the 1,2-*O*-isopropylidene functionality in **7** greatly enhanced the reactivity of the molecule, leading to the formation of the dimer **15** as the major product of the reaction.

To further investigate the above-mentioned transformation, we performed the reaction under the conditions described above while carefully monitoring the composition of the reaction mixture using thin-layer chromatography (TLC). After 2 h, not only was the expected dimer **15** detected, but also another compound that had not been detected in the product mixture when we ran the reaction for 6 h. Next, we sought to determine the structure of the novel component, which was found to be more polar than **15** on TLC. Immediate isolation of the novel component from the reaction mixture by centrifugal circular thin-layer chromatography (CCTLC) in which nucleophilic

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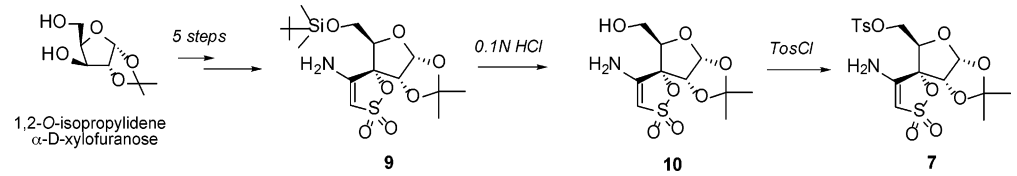
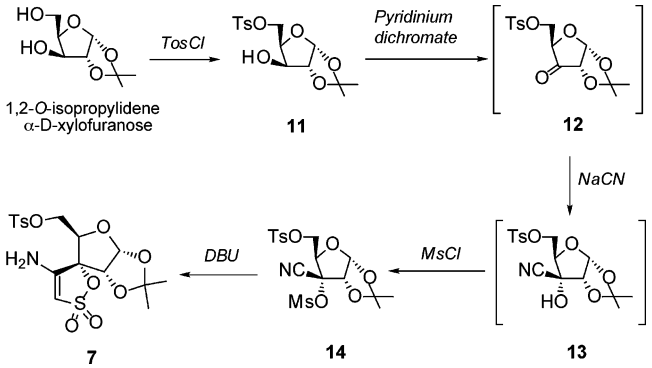
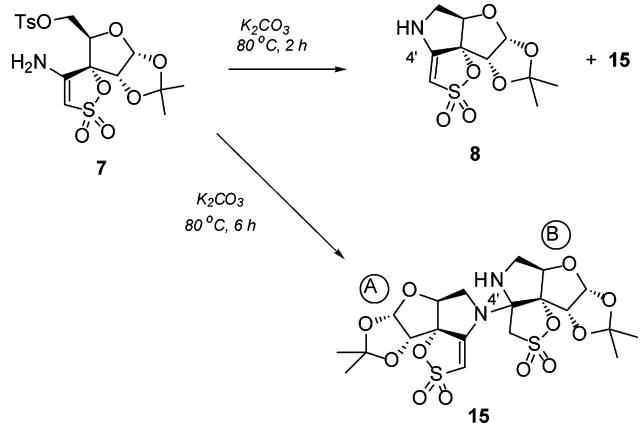
SCHEME 2. Original Method for Synthesizing 1,2-*O*-Isopropylidene-5′-*O*-tosyl Ribofuranose 7



SCHEME 3. Improved Route for Synthesizing 1,2-*O*-Isopropylidene-5′-*O*-tosyl Ribofuranose 7



SCHEME 4. Reaction of 1,2-*O*-Isopropylidene-5′-*O*-tosyl Ribofuranose 7 with Potassium Carbonate



solvents (ethanol, methanol, etc.) were avoided resulted in a reasonable amount of the component. The ^{1}H NMR spectrum of this compound was fully consistent with the structure of the desired cyclic enamine **8**.

To identify conditions that afforded **8** in higher yields, we analyzed the conversion of the tosyl derivative **7** to the desired cyclic enamine **8** as a function of reaction time, temperature, and base used. The reaction was monitored using HPLC (Table 1).

For comparison purposes, the reaction was repeated at 80 °C in the presence of potassium carbonate as a non-nucleophilic

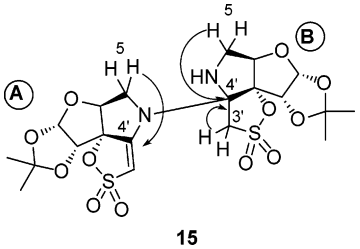
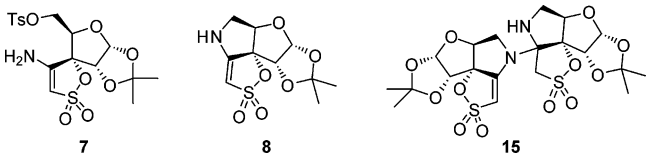


FIGURE 2. gHMBC NMR correlations, indicated by arrows.

TABLE 1. DifFerent Conditions Used for the Optimization of the Yield of Cyclic Enamine 8



entry	base	temp (°C)	time	**7** (%) $t_R = 7.53$	**8** (%) $t_R = 1.83$	**15** (%) $t_R = 5.31$
1	K_2CO_3	80	2 h	65	27	8
2			6 h	2	8	90
3	pyridine	80	24 h	100	-	-
4	Et_3N	80	24 h	100	-	-
5	DBU	40	15 min	43	52	5
6			30 min	34	59	7
7			45 min	18	69	13
8			1 h	11	69	20
9	DBU	80	15 min	5	76	19
10			30 min	3	55	42
11			45 min	8	36	56
12			1 h	2	31	67
13	DBU	80	10 min	4	90	6

base. After 2 h, starting compound **7** (retention time, $t_R = 7.53$) was detected in 65% yield. The dimer **15** (8%) ($t_R = 5.31$) and the cyclic enamine **8** (27%) ($t_R = 1.83$) were also detected (entry 1). After 6 h, the yield of **8** had decreased to 8% and the yield of **15** had increased to 90% (entry 2).

When pyridine or Et_3N were used as the base at 80 °C, only the unreacted starting 5-*O*-tosyl derivative **7** was detected in the reaction mixture, even after 24 h (entries 3 and 4).

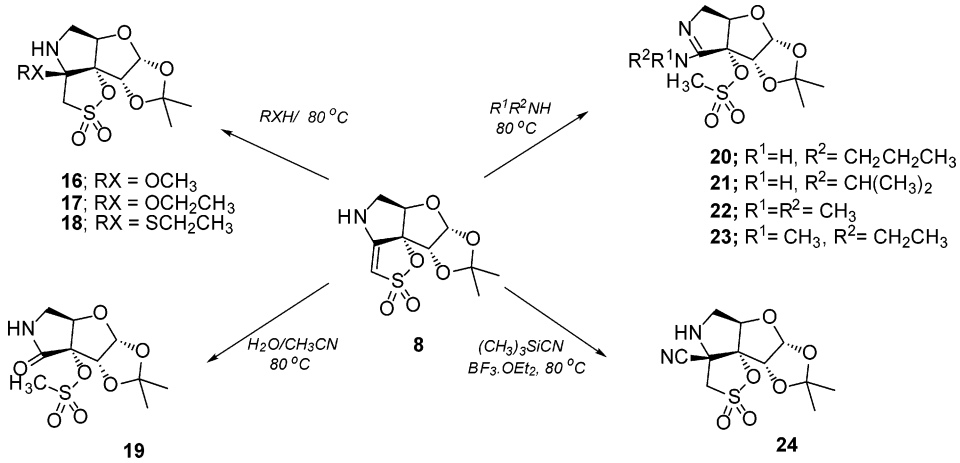
By contrast, when DBU was used as the base at 40 °C, a mixture in which compound **8** was the major component (69%) resulted after a reaction time of 1 h (entry 8). Starting compound **7** (11%) and **15** (20%) were also detected. On increasing the temperature to 80 °C, however, starting compound **7** was consumed in a shorter time (entry 9). Moreover, consistent with the behavior observed during the reaction of **7** with K_2CO_3 (entries 1 and 2), the amount of **15** increased and the amount of **8** decreased with increasing reaction time (entries 9−12).

Among the sets of reaction conditions tested, the best conditions were found to be basic media (DBU), 80 °C, and 10 min reaction time (entry 13). Under these conditions, the cyclic enamine **8** was obtained in 90% yield, with the dimer **15** as a minor derivative (6%).

It should be emphasized that **8** is not sufficiently stable to be efficiently isolated. Thus, after 10 min of reaction, the process must be quenched by addition of acetic acid (pH adjusted to 5−6), and the residue (compound **8**) left to react in situ with a nucleophile. For this reason, the reaction yields described here are the result of two consecutive steps starting from **7** (intramolecular cyclization to afford **8** and nucleophilic attack) carried out in a "one-pot" fashion.

Having established a convenient protocol for efficiently producing **8**, we next focused on exploring its reactivity toward

SCHEME 5. Reaction of 8 with (Thio)alcohols, Sodium Cyanide, Water, and Amines



oxygen-, sulfur-, carbon-, and nitrogen-based nucleophiles. In addition, we examined the reaction of **8** with amino acids.

First, the reaction of **8** with primary alcohols, specifically, methanol or ethanol (where the alcohol was used as both solvent and nucleophile), were carried out. These reactions afforded the corresponding *O*-substituted tricyclic sugars **16** (70%) and **17** (68%) in a completely regio- and stereoselective manner (Scheme 5).

When, under the same conditions, **8** was reacted with thioethanol as the nucleophile, the tricyclic sugar **18** (60%) was obtained. Thus, all three nucleophiles, methanol, ethanol, and thioethanol, behaved similarly in the reaction with **8**. By contrast, more hindered alcohols such as *i*-PrOH and *t*-ButOH reacted with **8** to exclusively afford the unexpected bicyclic sugar derivative **19**, in which a γ-lactam ring is fused to the ribose moiety. This compound was also obtained (52% yield) when **8** was reacted with a 1:1 mixture of acetonitrile and water. The facile formation of **19** again highlighted the differences in reactivity that exist between the nucleoside **6** and the sugar **8**, in that the γ-lactam ring in **6** only formed when potassium carbonate was present in the reaction medium.

Next, we focused on the reaction of the cyclic enamine **8** with primary and secondary amines (Scheme 5). When **8** was reacted with an excess of a primary amine (propyl or isopropylamine), the bicyclic sugars **20** (55% yield) and **21** (76% yield) were obtained. The fact that we obtained almost identical results for isopropylamine and propylamine indicates that, in contrast to the reactions of **8** with alcohols, branching at the C-α has little effect on the course of the reaction with primary amines. A similar treatment of **8** with secondary amines such as dimethylamine (2 M in THF) or *N*,*N*-ethylmethylamine afforded the bicyclic sugars **22** and **23** in 45% and 30% yields, respectively.

Next, we examined the reaction with a *C*-nucleophile. Sodium cyanide (NaCN) was found to be a poor source of cyanide ions because of its low solubility in the reaction solvent (acetonitrile). When, as an alternative, NaCN, sodium bicarbonate, and **8** were reacted in a 1:1 mixture of ethyl acetate/water with vigorous stirring, only the sugar derivative **19**, in which a γ-lactam ring is fused to the ribose moiety, was obtained (data not shown). However, reaction of **8** with trimethylsilylcyanide (TMSCN), a cyanide species that is soluble in acetonitrile, afforded the nitrile tricyclic sugar **24** in 60% yield (Scheme 5). It should be highlighted that all of the above-mentioned transformations were fully regio- and stereoselective.

We assigned the structures of the novel compounds **16**−**24** on the basis of their analytical and spectroscopic data. The structures of the polycyclic sugar derivatives were assigned by ^{1}H and ^{13}C NMR spectroscopic analysis using mono- and bidimensional techniques (gHMBC[22] and gHSQC[23]) and by comparison with the corresponding nucleoside derivatives.

The stereochemistry of the new stereogenic center created on C-4′ in compounds **16**−**18** was determined as *S* on the basis of NOE difference experiments carried out on **16**, which was chosen as a representative compound. Specifically, irradiation of the signal corresponding to the methyl group of the OCH_3 moiety caused the enhancement of the signals of the protons of the sugar H-2 and H-5 (Figure 3), indicating that these protons and the methanol group were on the same upper side of the furanose ring. This result confirms that the conjugate addition of the nucleophile proceeded with complete stereoselectivity on the β-face of the sugar-fused cyclic enamine.

The ^{13}C NMR spectrum for compounds **20** and **21** recorded in acetone contained broadened signals for the carbon atoms C-5, C-3, CH_2−NH, and C═N, suggesting the existence of an equilibrium between the unsaturated endo- and exocyclic amidines (**C** and **D**). This equilibrium was studied for compound **20**, which was chosen as a representative compound (Figure 4). According to literature data,[24] the methylene carbon atom appearing at δ 44.6 ppm is compatible with a CH_2NH grouping and therefore with tautomer **C**, whereas the methylene of a CH_2N═ grouping (as in tautomer **D**) should appear at lower field (around δ 56 ppm). Therefore, our observations for com-

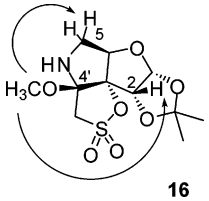


FIGURE 3. Relevant NOE, indicated by arrows.

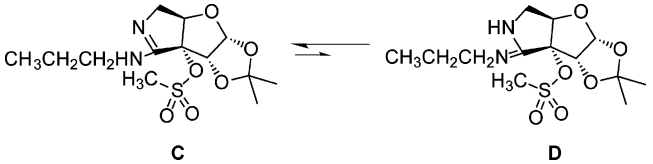
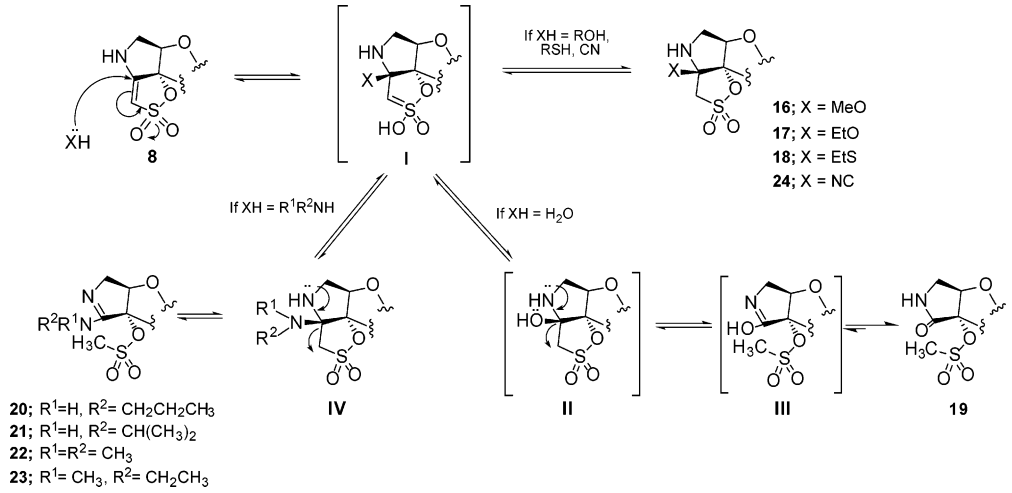
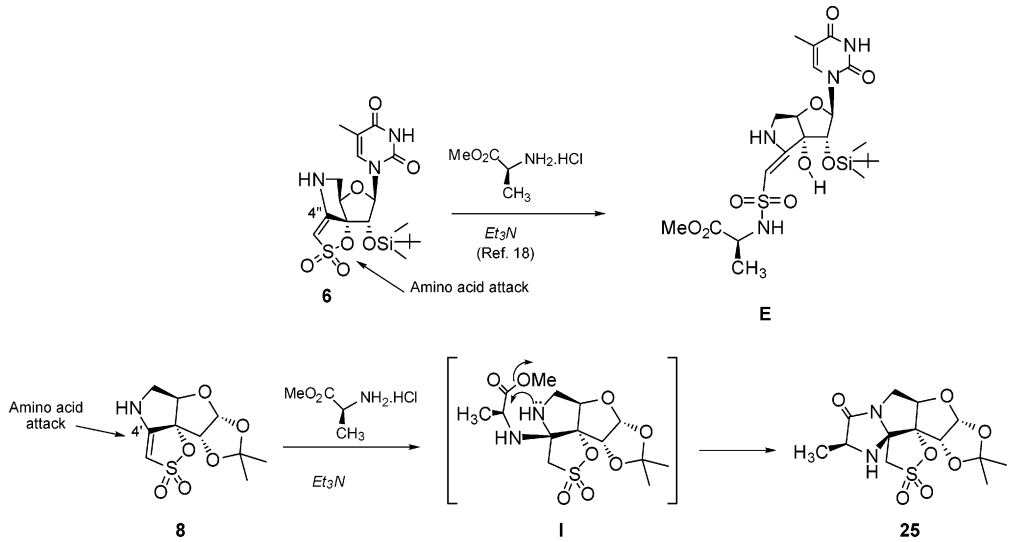


FIGURE 4. Tautomeric forms of compound **20**.

SCHEME 6. Proposed Mechanism for the Reaction of 8 with (thio)Alcohols, Water and Amines



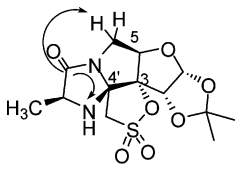
SCHEME 7. Comparison of the Reactivity of 6 and 8 against L-Alanine [*H*-L-Ala-OMe·HCl]



pound **20** in acetone solution suggests that both tautomers are present, and that the equilibrium is shifted toward tautomer **C**.

The experimental results presented above for the reactions of the sugar **8** with (thio)alcohols, water, amines, or trimethylsilylcyanide indicate that when **8** is reacted with these compounds, it behaves in a manner similar to the nucleoside **6**. These results can be explained by our previously reported mechanism (Scheme 6):[17,18] the reaction is initiated by the attack of the nucleophile on the C-4′ carbon atom of the spiroaminoxathiole ring to give intermediate **I**, and then proton transfer gives the tricyclic derivatives **16**−**18** and **24**. When the nucleophile is water, formation of intermediate **II** and subsequent ring opening of the spiroaminoxathiole moiety may occur to afford the intermediate **III**. Although this intermediate can exist in two tautomeric forms, **III** and **19**, only the bicyclic sugar **19** with a γ-lactam ring fused to the ribose moiety was observed. In the case of amines, the intermediate **IV** may undergo ring opening of the spiroaminoxathiole moiety to give the bicyclic sugar derivatives **20**−**23**, in which a pyrroline ring is fused to the ribose moiety.

Finally, we investigated the reactivity of the cyclic sugar derivative **8** with amino acids. We have previously observed that, when the nucleoside **6** reacts with the methyl ester derivative of L-alanine [*H*-L-Ala-OMe·HCl], the attack by the amino acid occurs regioselectively at the sulfur of the SO_2 group to give compound **E**. In the case of **8**, however, no reaction was observed at this position. By contrast, treatment of **8** with the same amino acid afforded the highly strained tetracyclic compound **25** in very good yield (76% overall yield, after two reaction steps) (Scheme 7). One explanation for the formation of this compound is that the amino group attacks the C-4′ position of the sugar to give the intermediate **I**, and then the NH of the pyrroline ring spontaneously displaces the ester group of the amino acid to form a new fused five-membered ring (Scheme 7). This extremely facile intramolecular attack is consistent with the previously observed high reactivity of the

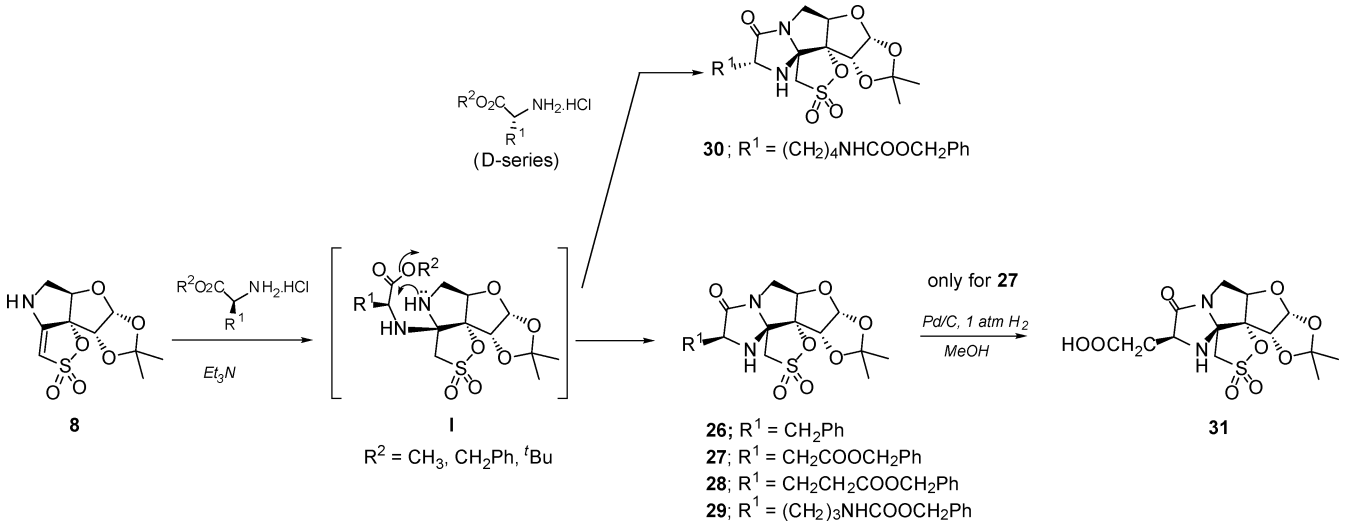


25

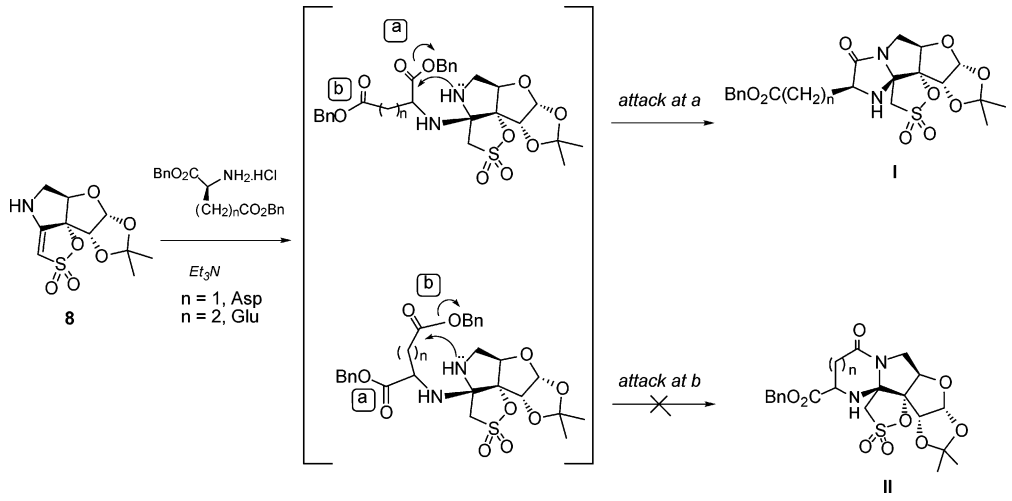
FIGURE 5. gHMBC NMR correlations, indicated by arrows.

(24) Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; John Wiley & Sons: Chichester, 1988.

SCHEME 8. Reaction of 8 with α-Amino Acids



SCHEME 9. Formation of Five- versus Six- or Seven-Membered Extra Rings with Aspartic or Glutamic Amino Acids, Respectively



NH of the pyrroline ring toward reagents that contain carbonyl groups reported by our group.[18]

The ^{1}H NMR spectrum of **25** was crucial for the identification of this compound. Specifically, the spectrum contained a singlet at δ 1.27 and a multiplet at δ 4.05 ppm, corresponding respectively to the methyl side chain of the mesylate and H-α protons of the amino acid, but did not contain signals corresponding to the ester group. In the gHMBC experiment (Figure 5), a long-range correlation between the H-5 protons (δ 3.15 and 4.13 ppm) and the CO carbon (δ 175.8 ppm) was observed, consistent with a cyclized structure.

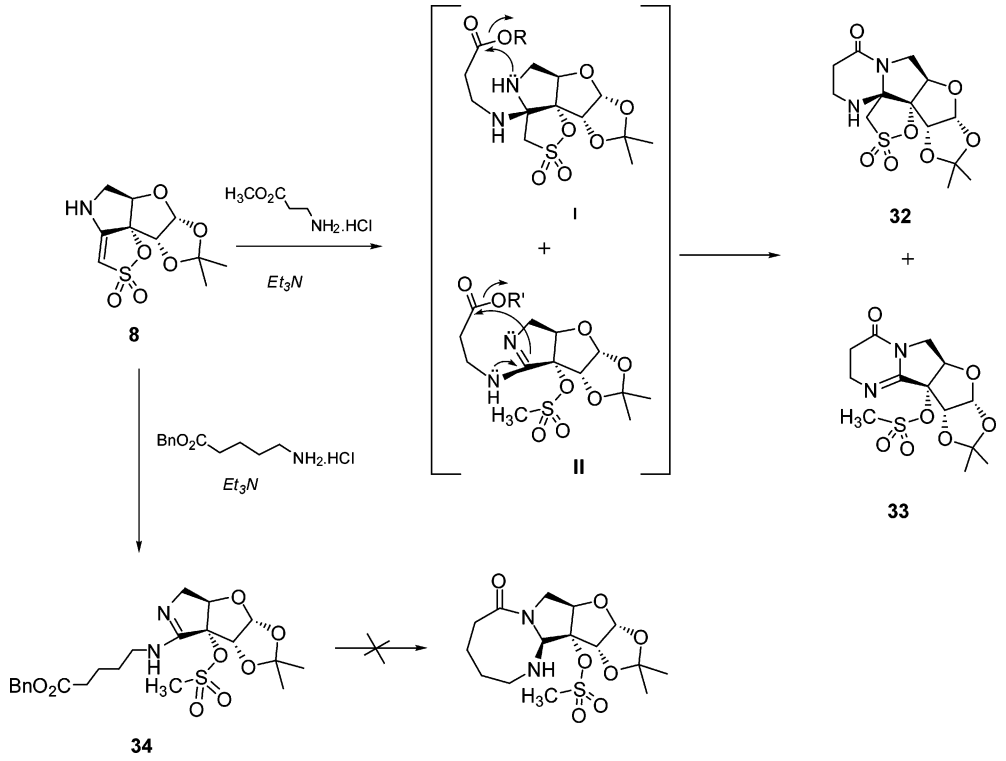
This interesting result encouraged us to investigate the reactions of **8** with various α-amino acids, to confirm whether the reaction is always regioselective and to generalize the methodology (Scheme 8). Thus, we studied the reactions of **8** with an aromatic (Phe) amino acid, and with amino acids with acidic (Asp, Glu) or basic (Orn) side-chains. The reactions with amino acids with acidic or basic side chains were examined for two reasons. First, these compounds may allow the introduction of carboxyl or amine functionalities into the five-membered ring upon deprotection of the side chain, modifications that may give rise to carbohydrates that are more suitable for use as building blocks. Second, by examining the reactions of Asp and Glu amino acids in which the side chain is protected as benzyl ester, it should be possible to determine whether there exists competition in the intramolecular cyclization between the benzyl ester groups of the side chain and the α-carboxy group. In addition, we also investigated the compatibility of the reaction with the most common protecting moieties used for the α-carboxy group of the amino acid (methyl, benzyl, *tert*-butyl).

We found that the reaction of **8** with the corresponding α-amino acid, carried out in the presence of triethylamine, afforded the tetracyclic nucleosides **26**−**29** with an extra five-membered ring in good yields (40−63%, two reaction steps), regardless of the nature of the amino acid and the protected ester form of the α-carboxy group (Scheme 8).

We additionally investigated whether the spatial disposition of the side chain of the amino acid affected the formation of the extra five-membered ring. To clarify this issue, we reacted **8** with the D-amino acid, *H*-D-Lys-(*Z*)-OMe, under the same conditions as described above (Scheme 8). This reaction afforded the corresponding tetracyclic derivative **30** in good yield (43%), indicating that the intramolecular attack is independent of the stereochemistry of the amino acid.

To generate carbohydrates that are more suitable for derivatization, we sought to incorporate at least one amine or

SCHEME 10. Reaction of 8 with β- and δ-Amino Acids



carboxylic acid functional group into the sugar ring. For this purpose, hydrogenation of **27** and **29** in the presence of Pd/C was attempted. Hydrogenation of **27** afforded the corresponding carboxy deprotected derivative **31** in 70% yield (Scheme 8); however, hydrogenation of **29** only gave a mixture of unidentified compounds.

As mentioned above, in the case of Asp and Glu amino acids in which the side chain is protected as a benzyl ester, the benzyl ester groups of the side chain (**b** in the scheme) and the α-carboxy group (**a** in the scheme) may compete in the cyclization reaction (Scheme 9). If this were to occur, Asp and Glu could lead to the formation of six- and seven-membered extra rings **II**, respectively, instead of or in addition to the five-membered extra ring **I**. However, our results indicate that the five-membered ring is preferentially formed.

To investigate whether reaction with a β-amino acid would effectively enable the formation of an extra six-membered ring, we examined the reaction of **8** with β-L-alanine (Scheme 10). In this case, the tetracyclic derivative **32** (20%) was obtained along with the tricyclic derivative **33** (25%). Formation of **33** could be explained by the attack of the amino acid and the subsequent opening of the spiro ring to give **II**. This intermediate is similar to the compounds **20** and **21** obtained from the reaction of **8** with primary and secondary amines (Scheme 6), although formation of **33** involved an extra ring-closing step in which the ester moiety was attacked by the N of the pyrroline ring.

Figure 6 shows the most important long-range correlations observed in the gHMBC experiments for compounds **32** and **33**.

Finally, we examined the reaction of **8** with a δ-amino acid, namely, *H*-δ-aminovaleric acid. In this case, the amino acid attacked the 4′ position, following by opening of the spiro ring to give **34** (35%) as the only product. The corresponding eight-membered cyclized product was not detected (Scheme 10).

These experimental results show that in the intramolecular attack of the ester moiety of the amino acid by the NH of the pyrroline or pyrrolidine ring, the formation of a five or six-membered extra ring is much more favorable than the formation of larger rings.

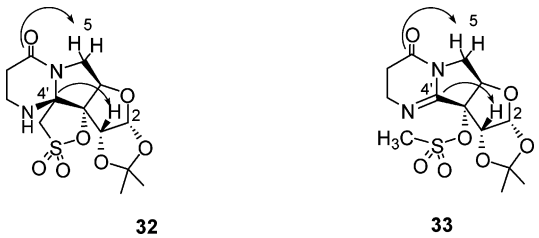


FIGURE 6. gHMBC NMR correlations, indicated by arrows.

Conclusions

We have reported a high-yielding method for synthesizing the novel sugar cyclic enamine **8** from the commercially available carbohydrate 1,2-*O*-isopropylidene-α-D-xylofuranose. Compound **8** can be prepared in situ by cyclization of the corresponding precursor, the *O*-tosyl derivative **7**, under basic conditions (DBU, 10 min, 80 °C).

The regio- and stereochemical behavior of **8** when reacted with *O*-, *N*-, and *S*-nucleophiles allowed its efficient transformation (one-step reaction, high yields, and easy purifications) into novel highly functionalized bi- and tricyclic sugar derivatives with different molecular skeletons. A notable feature of **8** is its reactivity with amino acids, which afforded a novel type of highly strained tetracylic derivative. Similar behavior was not detected when the nucleoside cyclic enamines **5** and **6** derived from thymine were reacted with amino acids.

The constrained structures and dense functionalization of the polycyclic sugar derivatives generated from **8** make these

compounds promising candidates for use as starting agents for the production of new analogues and as drugs. In addition, condensation of **8** with different nucleobases or with glycosyl acceptors could be used to access a variety of nucleosides or *O*-, *S*-, or *N*-glycosides, respectively, highlighting the potential of this cyclic enamine as a precursor.

In conclusion, the high reactivity of the sugar derivative **8**, its synthetic accessibility, and the vast collection of products into which it can be converted by the action of different nucleophiles make this compound a very useful synthetic intermediate to achieve skeletal diversity. We believe that on the basis of its unique reactivity, compound **8** could play an interesting role in the chemistry of carbohydrates.

Experimental Section

The names of polycyclic furanoses in this section are given according to the IUPAC recommendations for polycyclic compounds (extension of the Von Baeyer system).[25] However, for easy comparison, the assignments of the signals of the NMR spectra follow standard carbohydrate numbering (i.e., the furanose skeleton numbered 1−5).

1,2-*O*-Isopropylidene-3-spiro-5′-(4′-amino-1′,2′-oxathiole-2′,2′-dioxide)-5-*O*-tosyl-α-D-ribofuranose (7). Method A. To a solution of **10**[19] (2.0 g, 6.81 mmol) in dry pyridine (50 mL) was added *p*-toluensulfonyl chloride (2.86 mL, 15.0 mmol). The reaction mixture was kept at room temperature for 16 h, and then solvent was evaporated and coevaporated with ethanol and toluene. A solution of the residue in dichloromethane (30 mL) was washed with cold 1 N HCl (2 × 30 mL), saturated solution of $NaHCO_3$ (2 × 30 mL), and finally with brine (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. Flash-column chromatography (hexane/ethyl acetate, 2:1) of the residue afforded 2.65 g of **7** (87%) as a white solid: mp 87−89 °C. $[\alpha]^{20}_D$ +29.8 (*c* 0.5, $CHCl_3$). HPLC: t_R = 7.53 (40:60). ^{1}H NMR [$(CD_3)_2$CO, 300 MHz] δ: 1.33−1.48 (2s, 6H), 2.45 (s, 3H), 4.23−4.37 (m, 3H), 4.77 (d, 1H, J = 3.9 Hz), 5.67 (s, 1H), 5.97 (bs, 2H), 6.12 (d, 1H, J = 3.9 Hz), 7.46−7.83 (m, 5H). ^{13}C NMR [$(CD_3)_2$CO, 75 MHz] δ: 20.6 (CH_3), 25.8 (CH_3), 66.5 (CH_2), 75.9 (CH), 80.9 (CH), 87.6 (C), 89.2 (CH), 104.1 (CH), 113.9 (C), 127.8−148.2 (CH), 152.2 (C). MS (ES+) *m*/*z*: 448.3 $(M + H)^+$. Anal. Calcd for $C_{17}H_{21}NO_9S_2$: C, 45.63; H, 4.73; N, 3.13. Found: C, 45.48; H, 4.85; N, 3.29.

Method B. To a cooled (0 °C) solution of **14** (2.0 g, 4.46 mmol) in dry acetonitrile (50 mL) was added DBU (0.66 mL, 4.46 mmol). The reaction was stirred at 0 °C for 20 min and then quenched with acetic acid, and the solvent was evaporated under reduced pressure. Flash-column chromatography (dichloromethane/methanol, 50:1) of the residue afforded 1.2 g of **7** (60%).

5,*N*^{4} Cyclo-3-spiro-5′-(4′-amino-1′,2′-oxathiole-2′,2′-dioxide)-1,2-*O*-isopropilidene-α-D-ribofuranose (8). To a solution of the 5-*O*-tosyl derivative **7** (0.1 g, 0.22 mmol) in dry acetonitrile (2 mL) was added DBU (0.067 g, 0.44 mmol). The solution was heated in a sealed tube at 80 °C for 10 min, then acetic acid was added until pH = 5−6, and the cyclic enamine **8**, thus formed, was treated in situ with the corresponding nucleophile. HPLC: t_R = 1.83 (40:60). ^{1}H NMR [$(CD_3)_2$CO, 300 MHz] δ: 1.34−1.43 (2s, 6H), 2.52 (m, 1H), 3.23 (m, 1H), 3.98 (m, 1H), 4.95 (d, 1H, J = 3.4 Hz), 5.58 (s, 1H), 5.86 (d, 1H, J = 3.4 Hz).

1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-erythro-pentofuranose-3-ulose (12). To a suspension of pyridinium dichromate (5.89 g, 15.7 mmol) in dry dichloromethane (40 mL) was added acetic anhydride (7.26 mL, 70.6 mmol). The resulting mixture was stirred at room temperature for 1 h. Then a solution of 1,2-*O*-isopropilidene-5-*O*-tosyl-α-D-xylofuranose **11**[20,21] (5.4 g, 15.7 mmol) in dry dichloromethane (40 mL) was added. After refluxing for 3−4 h, the solvent was removed, and residues were taken up in ethyl acetate (100 mL). The mixture was filtered though a wet (ethyl acetate) short column of silica gel using ethyl acetate as the eluent. The eluent was concentrated and the residue was coevaporated with toluene (3 × 25 mL) to give **12** (crude yield 4.93 g) as a yellow syrup, which was used immediately without further purification. IR (KBr): ν 1770 cm^{-1} (CO).

3-*C*-Cyano-1,2-*O*-isopropilidene-3-*O*-mesyl-5-*O*-tosyl-α-D-ribofuranose (14). To a solution of the crude ulose **12** (4.93 g) in diethyl ether (40 mL) were added water (20 mL), sodium hydrogencarbonate (2.63 g, 31.82 mmol), and sodium cyanide (0.76 g, 15.69 mmol). The heterogeneous mixture was stirred vigorously at room temperature for 4 h. The two layers were separated, and the aqueous phase was washed with diethyl ether (2 × 30 mL). The combined ethereal phases were dried (Na_2SO_4), filtered, and evaporated to give cyanohydrin **13** as a yellow syrup that was used inmediately in the next step without purification.

To a cooled (0 °C) solution of the previously obtained cyanohydrin **13** (∼15.69 mmol) in dry pyridine (60 mL) was added dropwise methane sulfonyl chloride (1.83 mL, 23.53 mmol). The mixture was stirred at 5 °C overnight. The eluent was concentrated, and the residue was coevaporated with ethanol (3 × 25 mL) and toluene (3 × 25 mL). The residue was dissolved in dichloromethane (50 mL) and washed with cold 1 N HCl (2 × 50 mL), a saturated solution of $NaHCO_3$ (2 × 50 mL), and finally with brine (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography (hexane/ethyl acetate, 2:1) of the residue afforded 4.7 g of **14** (67%) as a yellow syrup. $[\alpha]^{20}_D$ −3.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR [$(CD_3)_2$CO, 400 MHz] δ: 1.39−1.52 (2s, 6H), 2.46 (s, 3H), 3.39 (s, 3H), 4.33−4.48 (m, 3H), 5.23 (d, 1H, J = 3.6 Hz), 6.09 (d, 1H, J = 3.6 Hz), 7.5−7.8 (m, 4H). ^{13}C NMR [$(CD_3)_2$CO, 100 MHz] δ: 21.5 (CH_3), 26.2−26.8 (CH_3), 40.8 (CH_3), 67.6 (CH_2), 77.3 (CH), 79.45 (C), 82.2 (CH), 105.3 (CH), 115.4 (CN), 128.9−146.5 (CH). MS (ES+) *m*/*z*: 448.1 $(M + H)^+$. Anal. Calcd for $C_{17}H_{21}NO_9S_2$: C, 45.63; H, 4.73; N, 3.13. Found: C, 45.54; H, 4.87; N, 3.08.

[5,*N*$^{4'}$Cyclo-3-spiro-5′-(4′-amino-1′,2′-oxathiole-2′,2′-dioxide)-1,2-*O*-isopropilidene-α-D-ribofuranosyl] (*N*$^{4'}$→ 4′) 5,*N*$^{4'}$cyclo-3-spiro-5′-(4′-amino-1′,2′-oxathiolane-2′,2′-dioxide)-1,2-*O*-isopropilidene-α-D-ribofuranose (15). To a solution of the 5-*O*-tosyl derivative **7** (0.1 g, 0.22 mmol) in dry acetonitrile (4 mL) was added dry potassium carbonate (0.034 g, 0.25 mmol). The solution was refluxed for 6 h and evaporated to dryness. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by CCTLC (hexane/ethyl acetate, 1:1) to give 0.05 g (80%) of **15** as a white solid: mp 151 °C. $[\alpha]^{20}_D$ +20.0 (*c* 0.25, $CHCl_3$). HPLC: t_R = 5.31 (40:60). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.32−1.54 (4s, 12H, $C(CH_3)_2$ **A** and **B**), 3.40 (dd, 1H, H-5a **B**, J = 2.6 Hz, J = 11.1 Hz), 3.47 (d, 1H, H-5a **A**, J = 11.0 Hz), 3.65 (dd, 1H, H-5b **A**, J = 2.9 Hz, J = 11.0 Hz), 3.70 (dd, 1H, H-5b **B**, J = 5.7 Hz, J = 11.1 Hz), 4.38 (d, 1H, H-3′a **B**, J = 15.5 Hz), 4.46 (d, 1H, H-4 **A**, J = 2.9 Hz), 4.47 (d, 1H, H-3′b **B**, J = 15.5 Hz), 4.60 (d, 1H, H-2 **A**, J = 3.5 Hz), 4.89 (m, 1H, H-4 **B**), 5.04 (d, 1H, H-2 **B**, J = 4.0 Hz), 5.83 (d, 1H, H-1 **A**, J = 3.5 Hz), 6.08 (s, 1H, H-3′ **A**), 6.09 (d, 1H, H-1 **B**, J = 4.0 Hz). 6.43 (bs, 1H, NH-4′ **B**). ^{13}C NMR [DMSO-d_6, 75 MHz] δ: 26.9−27.3 ($2CH_3$ **A** and **B**), 48.6 (CH_2 **B**), 49.4 (CH_2 **B**), 51.6 (CH_2 **A**), 78.1 (CH **B**), 80.1 (CH **A**), 80.6 (CH **B**), 82.1 (CH **A**), 86.2 (C **A**), 86.6 (C **B**), 91.8 (CH **A**), 97.6 (C **B**), 105.1 (CH **A**), 105.7 (CH **B**), 112.8 (C **A**), 113.3 (C **B**), 155.6 (C **A**). MS (ES+) *m*/*z*: 551.3 $(M + H)^+$. Anal. Calcd for $C_{20}H_{26}N_2O_{12}S_2$: C, 43.63; H, 4.76; N, 5.09. Found: C, 43.54; H, 4.58; N, 5.22.

General Procedure for the Synthesis of Sugars 16−24. The 5-*O*-tosyl derivative 7 (0.1 g, 0.22 mmol) was treated with DBU as described above to give the cyclic enamine **8** that was inmediately treated in situ with the corresponding nucleophile. The solution was heated at 80 °C for 3 h. Solvent was evaporated and the residue

(25) IUPAC nomenclaure home page. http://www.chem.qmul.ac.uk/iupac/

was purified by CCTLC. The chromatography eluent and yield of the isolated products (**16**−**24**) are indicated below for each reaction.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-4,4-dimethyl-13,13-dioxide-11-methoxy-3,5,7,14-tetraoxa-13-thio-tetracyclo[6.6.0.0$^{2-6}$.0$^{1-11}$]-tetradecane (16). Following the general procedure the cyclic enamine **8** was treated in situ with methanol (1 mL). Chromatography with hexane/ethyl acetate (1:1) gave 0.05 g of **16** (70%) as a yellow solid: mp 83−85 °C. $[\alpha]^{20}_D$ +37.4 (*c* 0.4, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.28−1.49 (2s, 6H), 3.11 (d, 1H, J = 12.8 Hz), 3.34 (s, 3H), 3.48 (m, 1H), 3.63 (bs, 1H), 3.87 (s, 2H), 4.69 (d, 1H, J = 4.0 Hz), 4.84 (d, 1H, J = 3.4 Hz), 5.73 (d, 1H, J = 3.4 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 26.7−27.5 (CH_3), 51.4 (CH_3), 51.5 (CH_2), 55.9 (CH_3), 79.6 (CH), 83.2 (CH), 97.5 (C), 106.7 (C), 108.3 (CH), 114.2 (C), MS (ES+) *m*/*z*: 308.1 (M + H)$^+$, 330.1 (M +Na)$^+$. Anal. Calcd for $C_{11}H_{17}NO_7S$: C, 42.99; H, 5.58; N, 4.56. Found: C, 42.91; H, 5.49; N, 4.62.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-4,4-dimethyl-13,13-dioxide-11-ethoxy-3,5,7,14-tetraoxa-13-thio-tetracyclo[6.6.0.0$^{2-6}$.0$^{1-11}$]-tetradecane (17). Following the general procedure the cyclic enamine **8** was treated in situ with ethanol (1 mL). Chromatography with hexane/ethyl acetate (1:1) gave 0.05 g of **17** (68%) as a yellow solid: mp 73−75 °C. $[\alpha]^{20}_D$ +25.9 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, 3H, J = 6.9 Hz), 1.43−1.62 (2s, 6H), 3.21−3.46 (m, 3H), 3.53 (d, 1H, J = 13.4 Hz), 3.64 (d, 1H, J = 13.4 Hz), 3.79 (m, 1H), 4.76 (d, 1H, J = 3.5 Hz), 4.84 (d, 1H, J = 3.4 Hz), 4.79 (d, 1H, J = 3.4 Hz).^{13}C NMR [75 MHz, ($CDCl_3$] δ: 15.2 (CH_3), 26.9−27.3 (CH_3), 50.6 (CH_2), 55.1 (CH_2), 59.8 (CH_2), 78.2 (CH), 82.2 (CH), 98.2 (C), 100.1 (C), 107.1 (C), 113.9 (C). MS (ES+) *m*/*z*: 322.1 (M + H)$^+$. Anal. Calcd for $C_{12}H_{19}NO_7S$: C, 44.85; H, 5.96; N, 4.36. Found: C, 44.65; H, 5.76; N, 4.06.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-4,4-dimethyl-13,13-dioxide-11-ethylthio-3,5,7,14-tetraoxa-13-thio-tetracyclo[6.6.0.0$^{2-6}$.0$^{1-11}$]-tetradecane (18). Following the general procedure the cyclic enamine **8** was treated in situ with ethanethiol (1 mL). Chromatography with hexane/ethyl acetate (1:1) gave 0.04 g of **18** (60%) as a yellow solid: mp 69−71 °C. $[\alpha]^{20}_D$ +33.5 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (t, 3H, J = 7.5 Hz), 1.42−1.63 (2s, 6H), 2.83 (m, 2H), 3.18 (m, 2H), 3.53 (d, 1H, J = 13.9 Hz), 3.76 (d, 1H, J = 13.9 Hz), 4.71 (d, 1H, J = 2.3 Hz), 4.94 (d, 1H, J = 3.5 Hz), 5.79 (d, 1H, J = 3.5 Hz).^{13}C NMR [75 MHz, ($CDCl_3$)] δ: 14.4 (CH_3), 24.9 (CH_2), 26.8 (CH_3), 49.5 (CH_2), 57.3 (CH_2), 66.1 (C), 79.5 (CH), 83.5 (CH), 100.2 (C), 106.4 (CH), 114.2 (C). MS (ES+) *m*/*z*: 338.1 (M + H)$^+$. Anal. Calcd for $C_{12}H_{19}NO_6S_2$: C, 42.72; H, 5.68; N, 4.15. Found: 42.79; H, 5.75; N, 4.24.

(1*R*,2*R*,6*R*,8*R*)-10-Aza-4,4-dimethyl-1-mesyloxy-11-oxo-3,5,7-trioxa-tricyclo[6.3.0.0$^{2-6}$]undecane (19). Following the general procedure the cyclic enamine **8** was treated in situ with water (2 mL). Chromatography with hexane/ethyl acetate (1:1) gave 0.03 g of **19** (52%) as a white solid: mp 154−156 °C. $[\alpha]^{20}_D$ +14.8 (*c* 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42−1.63 (2s, 6H), 3.28 (s, 3H), 3.35 (d, 1H, J = 11.2 Hz), 3.85 (dd, 1H, J = 3.6 Hz, J = 11.2 Hz), 4.89 (d, 1H, J = 3.6 Hz), 4.96 (d, 1H, J = 3.6 Hz), 5.9 (d, 1H, J = 3.6 Hz), 7.62 (bs, 1H). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 26.7−27.4 (CH_3), 40.5 (CH_3), 46.7 (CH_2), 79.8 (CH), 81.6 (CH), 88.1 (C), 105.6 (CH), 114.8 (C), 169.9 (CO). MS (ES+) *m*/*z*: 315.9 (M + Na)$^+$. Anal. Calcd for $C_{10}H_{15}NO_7S$: C, 40.95; H, 5.15; N, 4.78. Found: C, 40.84; H, 5.03; N, 4.85.

(1*R*,2*R*,6*R*,8*R*)-10-Aza-4,4-dimethyl-1-mesyloxy-11-propylamino-3,5,7-trioxa-triciclo[6.3.0.0$^{2-6}$]undec-10-ene (20). Following the general procedure the cyclic enamine **8** was treated in situ with propylamine (0.01 mL, 1.1 mmol). Chromatography with dichloromethane: methanol: ammonium hydroxide (10:1:0.01) gave 0.04 g of **20** (55%) as a yellow syrup. $[\alpha]^{20}_D$ +57.0 (*c* 2.0, $CHCl_3$). ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ: 0.91 (t, 3H, J = 7.4 Hz) 1.35−1.53 (2s, 6H), 1.59 (m, 2H), 3.13−3.26 (m, 2H), 3.21 (s, 3H), 3.49 (d, 1H, J = 14.8 Hz), 3.76 (dd, 1H, J = 3.5 Hz, J = 14.8 Hz), 4.78 (d, 1H, J = 3.5 Hz), 4.97 (d, 1H, J = 3.8 Hz), 5.84 (d, 1H, J = 3.8 Hz). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ: 10.9 (CH_3), 22.5 (CH_2), 26.6 (CH_3), 39.4 (CH_3), 44.6 (CH_2), 58.7 (CH_2), 80.1 (CH), 84.4 (CH), 96.2 (C), 106.2 (CH), 113.1 (C), 158.8 (C═N). MS (ES+) *m*/*z*: 335.0 (M + H)$^+$. Anal. Calcd for $C_{13}H_{22}N_2O_6S$: C, 46.69; H, 6.63; N, 8.38. Found: C, 46.58; H, 6.76; N, 8.44.

(1*R*,2*R*,6*R*,8*R*)-10-Aza-4,4-dimethyl-11-isopropylamino-1-mesyloxy-3,5,7-trioxa-tricyclo[6.3.0.0$^{2-6}$]undec-10-ene (21). Following the general procedure the cyclic enamine **8** was treated in situ with isopropylamine (0.01 mL, 1.1 mmol). Chromatography with dichloromethane/methanol/ammonium hydroxide (10:1:0.01) gave 0.06 g of **21** (76%) as a yellow syrup. $[\alpha]^{20}_D$ +56.1 (*c* 0.4, $CHCl_3$). ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ: 1.15 (d, 3H, J = 6.6 Hz), 1.18 (d, 3H, J = 6.6 Hz), 1.35−1.53 (2s, 6H), 3.23 (s, 3H), 3.53 (d, 1H, J = 15.0 Hz), 3.74 (dd, 1H, J = 3.5 Hz, J = 15.0 Hz), 3.85 (m, 1H), 4.78 (d, 1H, J = 3.5 Hz), 4.95 (d, H-2, J = 3.8 Hz), 5.83 (d, 1H, J = 3.8 Hz). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ: 21.4−21.8 (CH_3), 26.6 (CH_3), 39.5 (CH_3), 44.2 (CH), 59.2 (CH_2), 80.2 (CH), 84.2 (CH), 96.4 (C), 106.2 (CH), 113.1 (C), 158.8 (C═N). MS (ES+) *m*/*z*: 335.0 (M + H)$^+$. Anal. Calcd for $C_{13}H_{22}N_2O_6S$: C, 46.69; H, 6.63; N, 8.38. Found: C, 46.74; H, 6.72; N, 8.38.

(1*R*,2*R*,6*R*,8*R*)-10-Aza-4,4-dimethyl-11-*N*,*N*-(dimethylamino)-1-mesyloxy-3,5,7-trioxa-tricyclo[6.3.0.0$^{2-6}$]undec-10-ene (22). Following the general procedure the cyclic enamine **8** was treated in situ with *N*,*N*-dimethylamine (0.06 mL, 1.1 mmol). The residue was purified by CCTLC using dichloromethane/methanol/ammonium hydroxide (10:1:0.01). The fastest moving fractions gave 0.01 g (9%) of the dimer derivative **15** and 0.08 g (13%) of the bicyclic sugar derivative **19**. From the slowest moving fractions, 0.02 g (31%) of **22** was isolated as a yellow syrup. $[\alpha]^{20}_D$ +25.2 (*c* 0.4, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.41−1.61 (2s, 6H), 3.12 (1s, 6H), 3.25 (s, 3H), 3.61 (d, 1H, J = 14.6 Hz), 4.01 (dd, 1H, J = 4.6 Hz, J = 14.6 Hz), 4.92 (d, 1H, J = 3.9 Hz), 5.15 (d, 1H, J = 4.6 Hz), 6.02 (d, 1H, J = 3.9 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 27.6−28.2 (CH_3), 40.1 (CH_3), 40.3 (CH_3), 58.3 (CH_2), 82.9 (CH), 85.7 (CH), 94.4 (C), 107.2 (CH), 114.8 (C), 162.9 (C═N). MS (ES+) *m*/*z*: 321.1 (M + H)$^+$ *m*/*z*: 343.1 (M + Na)$^+$. Anal. Calcd for $C_{12}H_{20}N_2O_6S$: C, 44.99; H, 6.29; N, 8.74. Found: C, 44.84; H, 6.12; N, 8.87.

(1*R*,2*R*,6*R*,8*R*)-10-Aza-4,4-dimethyl-1-mesyloxy-11-*N*,*N*-ethylmethylamino-3,5,7-trioxa-tricyclo[6.3.0.0$^{2-6}$]undec-10-ene (23). Following the general procedure the cyclic enamine **8** was treated in situ with *N*,*N*-ethylmethylamine (0.06 mL, 1.1 mmol). The residue was purified by CCTLC using dichloromethane/methanol/ammonium hydroxide (10:1:0.01) to give 0.02 g (30%) of **23** as a yellow syrup. $[\alpha]^{20}_D$ +2.3 (*c* 3.4, $CHCl_3$). ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ: 1.13 (t, 3H, J = 7.1 Hz) 1.35−1.54 (2s, 6H), 2.98 (s, 3H), 3.21 (s, 3H), 3.25−3.45 (m, 2H), 3.52 (d, 1H, J = 14.7 Hz), 3.95 (dd, 1H, J = 4.2 Hz, J = 14.7 Hz), 4.78 (d, 1H, J = 4.3 Hz), 5.18 (d, 1H, J = 4.2 Hz), 5.93 (d, 1H, J = 4.3 Hz). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ: 10.9 (CH_3), 26.7 (CH_3), 34.6 (CH_3), 39.1 (CH_3), 44.9 (CH_2), 59.3 (CH_2), 81.4 (CH), 85.8 (CH), 94.4 (C), 105.9 (CH), 112.9 (C), 160.3 (C═N). MS (ES+) *m*/*z*: 335.0 (M + H)$^+$. Anal. Calcd for $C_{13}H_{22}N_2O_6S$: C, 46.69; H, 6.63; N, 8.38. Found: C, 46.72; H, 6.84; N, 8.53.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-11-cyano-4,4-dimethyl-13,13-dioxide-3,5,7,14-tetraoxa-13-thio-tetracyclo[6.6.0.0$^{2-6}$.0$^{1-11}$]-tetradecane (24). Following the general procedure the cyclic enamine **8** was treated in situ with trimethylsilyl cyanide (0.09 mL, 0.67 mmol) and boron trifluoride etherate (BF_3•OEt_2, 2 drops). The residue was purified by CCTLC using hexane/ethyl acetate (1:1) to give 0.04 g (60%) of **24** as a white solid: mp 82−84 °C. IR (KBr) ν 2243 cm^{-1} (CN). $[\alpha]^{20}_D$ +60.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42−1.63 (2s, 6H), 3.02−3.39 (m, 3H), 3.40 (d, 1H, J = 14.1 Hz), 4.03 (d, 1H, J = 14.1 Hz), 4.76 (m, 1H), 5.05 (d, 1H, J = 3.7 Hz), 5.98 (d, 1H, J = 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: ?26.8−27.9 (CH_3), 49.8 (CH_2), 55.1 (CH_2), 64.2 (C), 80.1 (CH), 82.1 (CH), 98.4 (C), 105.6 (CH), 115.1 (C), 115.9 (CN). MS (ES+) *m*/*z*: 303.1 (M + H)$^+$. Anal. Calcd for

$C_{11}H_{14}N_2O_6S$: C, 43.70; H, 4.67; N, 9.27. Found: C, 43.82; H, 4.73; N, 9.35.

General Procedure for the Reaction of 8 with Amino Acids (Compounds 25−29 and 31−34). To a solution of the 5-*O*-tosyl derivative **7** (0.1 g, 0.22 mmol) in dry acetonitrile (2 mL) was added DBU (0.067 g, 0.44 mmol). The solution was heated in a sealed tube at 80 °C for 10 min, then acetic acid was added until pH = 5−6, and the cyclic enamine **8**, thus formed, was treated in situ with the corresponding C-protected amino acid (0.44 mmol) and triethylamine (0.06 mL, 0.44 mmol). The reaction was refluxed for 4 h and then evaporated to dryness. The residue was dissolved in ethyl acetate (20 mL) and washed with cold 1 N HCl (2 × 30 mL), a saturated solution of $NaHCO_3$ (2 × 30 mL), and finally with brine (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by CCTLC. The yield of the isolated products together with the analytic, and spectroscopic dates are indicated below for each reaction.

(1*R*,2*R*,6*R*,8*R*,12*S*,14*S*)-10,13-Diaza-16,16-dioxide-11-oxo-3,5,7,17-tetraoxa-16-thio-4,4,12-trimethyl-pentacyclo-[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (25). Following the general procedure the cyclic enamine **8** was treated in situ with *H*-L-Ala-OMe·HCl (0.06 g, 0.44 mmol). The residue was purified by CCTLC using hexane/ethyl acetate (1:1) to give 0.06 g (76%) of **25** as a white solid: mp 128−130 °C. $[\alpha]^{20}_D$ +8.04 (*c* 4.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (d, 3H, *J* = 6.6 Hz), 1.38−1.57 (2s, 6H), 2.73 (d, 1H, *J* = 5.8 Hz), 3.15 (dd, 1H, *J* = 2.2 Hz, *J* = 13.4 Hz), 3.58 (s, 2H), 4.05 (m, 1H), 4.13 (d, 1H, *J* = 13.4 Hz), 4.71 (d, 1H, *J* = 2.2 Hz), 4.97 (d, 1H, *J* = 3.7 Hz), 5.78 (d, 1H, *J* = 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.71 (CH_3), 27.6−28.4 (CH_3), 47.3 (CH_2), 55.2 (CH), 56.2 (CH_2), 79.4 (CH), 82.8 (CH), 87.4 (C), 97.4 (C), 106.7 (CH), 114.7 (C), 175.8 (CO). MS (ES+) *m*/*z*: 347.1 (M + H)$^+$; 369.1 (M + Na)$^+$. Anal. Calcd for $C_{13}H_{18}N_2O_7S$: C, 45.08; H, 5.24; N, 8.09. Found: C, 45.17; H, 5.18; N, 8.25.

(1*R*,2*R*,6*R*,8*R*,12*S*,14*S*)-12-Benzyl-10,13-diaza-4,4-dimethyl-16,16-dioxide-11-oxo-3,5,7,17-tetraoxa-16-thio-pentacyclo-[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (26). Following the general procedure the cyclic enamine **8** was treated in situ with *H*-L-Phe-OMe·HCl (0.09 g, 0.44 mmol) or with *H*-L-Phe-O^{t}But·HCl (0.097 g, 0.44 mmol). The residue was purified by CCTLC using hexane/ethyl acetate (1:1) to give 0.05 (40%) or 0.06 g (50%) of **26** as a white solid: mp 65−68 °C. $[\alpha]^{20}_D$ +1.16 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.38−1.57 (2s, 6H), 2.51 (d, 1H, *J* = 5.6 Hz), 2.63 (m, 1H), 3.12 (m, 2H), 3.53 (d, 2H, *J* = 13.7 Hz), 4.18 (m, 2H), 4.63 (d, 1H, *J* = 2.4 Hz), 4.91 (d, 1H, *J* = 3.7 Hz), 5.23 (d, 1H, *J* = 3.7 Hz), 7.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.4 (CH_3), 38.8 (CH_2), 47.1 (CH_2), 56.1 (CH_2), 61.2 (CH), 79.1 (CH), 82.9 (CH), 87.5 (CH), 97.1 (C), 106.6 (CH), 114.6 (C), 127.5−137.5 (CH), 173.8 (CO). MS (ES+) *m*/*z*: 423.1 (M + H)$^+$, *m*/*z*: 445.1 (M + Na)$^+$. Anal. Calcd for $C_{19}H_{22}N_2O_7S$: C, 54.02; H, 5.25; N, 6.63. Found: C, 54.18; H, 5.13; N, 6.72.

(1*R*,2*R*,6*R*,8*R*,12*S*,14*S*)-12-Benzyloxycarbonylmethyl-10,13-diaza-4,4-dimethyl-16,16-dioxide-11-oxo-3,5,7,17-tetraoxa-16-thio-pentacyclo[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (27). Following the general procedure the cyclic enamine **8** was treated in situ with *H*-L-Asp-(OBn)-OBn·HCl (0.21 g, 0.44 mmol). The residue was purified by CCTLC using dichloromethane/methanol (10:1) to give 0.04 g (63%) of **27** as a white solid: mp 82−85 °C. $[\alpha]^{20}_D$ +32.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, MeOD) δ: 1.38−1.57 (2s, 6H), 2.18 (m, 1H), 2.61 (dd, 1H, *J* = 4.1 Hz, *J* = 16.6 Hz), 3.28 (dd, 1H, *J* = 2.2 Hz, *J* = 13.4 Hz), 3.68 (m, 3H), 3.95 (d, 1H, *J* = 6.1 Hz), 4.20 (m, 1H), 4.42 (d, 1H, *J* = 2.4 Hz), 4.65 (d, 1H, *J* = 3.7 Hz), 4.84 (d, 1H, *J* = 12.3 Hz), 4.93 (d, 1H, *J* = 12.3 Hz), 5.43 (d, 1H, *J* = 3.7 Hz), 7.15 (m, 5H). ^{13}C NMR (75 MHz, MeOD) δ: 27.9−28.1 (CH_3), 39.9 (CH_2), 49.7 (CH_2), 55.6 (CH_2), 58.1 (CH), 68.5 (CH_2), 80.9 (CH), 84.6 (CH), 89.9 (C), 98.7 (C), 108.4 (CH), 115.9 (C), 128.8−138.1 (CH), 173.3 (CO), 177.9 (CO). MS (ES+) *m*/*z*: 481.1 (M + H)$^+$. Anal. Calcd for $C_{21}H_{24}N_2O_9S$: C, 52.49; H, 5.03; N, 5.83. Found: C, 52.53; H, 5.16; N, 5.94.

(1*R*,2*R*,6*R*,8*R*,12*S*,14*S*)-12-Benzyloxycarbonylethyl-10,13-diaza-4,4-dimethyl-16,16-dioxide-11-oxo-3,5,7,17-tetraoxa-16-thio-pentacyclo[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (28). Following the general procedure the cyclic enamine **8** was treated in situ with *H*-L-Glu-(OBn)-OBn·HCl (0.21 g, 0.44 mmol). The residue was purified by CCTLC using dichloromethane/methanol (10:1) to give 0.06 g (43%) of **28** as a white solid: mp 80−82 °C. $[\alpha]^{20}_D$ +36.9 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40−1.60 (2s, 6H), 1.78 (m, 1H), 2.19 (m, 1H), 2.48 (m, 2H), 2.73 (d, 1H, *J* = 5.8 Hz), 3.30 (dd, 1H, *J* = 2.4 Hz, *J* = 13.5 Hz), 3.42 (d, 1H, *J* = 13.9 Hz), 3.58 (d, 1H, *J* = 13.9 Hz), 3.98 (m, 1H), 4.16 (d, 1H, *J* = 13.5 Hz), 4.68 (d, 1H, *J* = 2.4 Hz), 4.92 (d, 1H, *J* = 3.8 Hz), 5.10 (d, 1H, *J* = 12.3 Hz), 5.13 (d, 1H, *J* = 12.3 Hz), 5.7 (d, 1H, *J* = 3.8 Hz), 7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.7 (CH_3), 27.8 (CH_2), 30.3 (CH_2), 46.8 (CH_2), 55.6 (CH_2), 58.1 (CH), 66.5 (CH_2), 78.6 (CH), 82.3 (CH), 87.1 (C), 96.6 (CH), 106.2 (CH), 114.2 (C), 128.4−135.5 (CH), 172.7 (CO), 174.3 (CO). MS (ES+) *m*/*z*: 495.1 (M + H)$^+$; 517.1 (M + Na)$^+$. Anal. Calcd for $C_{22}H_{26}N_2O_9S$: C, 53.43; H, 5.30; N, 5.66. Found: C, 53.32; H, 5.42; N, 5.72.

(1*R*,2*R*,6*R*,8*R*,12*S*,14*S*)-12-Benzyloxycarbonylaminopropyl-10,13-diaza-4,4-dimethyl-16,16-dioxide-11-oxo-3,5,7,17-tetraoxa-16-thio-pentacyclo[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (29). Following the general procedure the cyclic enamine **8** was treated in situ with *H*-L-Orn-(Z)-OMe·HCl (0.14 g, 0.44 mmol). The residue was purified by CCTLC using hexane/ethyl acetate (1:1) to give 0.06 g (54%) of **29** as a white solid: mp 80−82 °C. $[\alpha]^{20}_D$ +54.2 (*c* 0.1, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.41−1.59 (2s, 6H), 1.42−1.64 (m, 4H), 2.03 (d, 1H, *J* = 5.9 Hz), 3.02 (m, 2H), 3.63 (dd, 1H, *J* = 2.3 Hz, *J* = 13.4 Hz), 3.91 (m, 4H), 4.62 (d, 1H, *J* = 2.3 Hz), 5.05 (s, 2H), 5.09 (d, 1H, *J* = 3.5 Hz), 5.62 (d, 1H, *J* = 3.5 Hz), 6.31 (bs, 1H), 7.23 (m, 5H). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 25.8 (CH_2), 26.2 (CH_3), 28.9 (CH_2), 40.1 (CH_2), 46.8 (CH_2), 54.8 (CH_2), 63.0 (CH), 65.2 (CH_2), 79.3 (CH), 82.3 (CH), 87.3 (C), 96.8 (C), 106.1 (CH), 113.2 (C), 127.2−137.7 (CH), 156.1 (CO), 175.4 (CO). MS (ES+) *m*/*z*: 546.1 (M + Na)$^+$. Anal. Calcd for $C_{23}H_{29}N_3O_9S$: C, 52.76; H, 5.58; N, 8.03. Found: C, 52.58; H, 5.49; N, 8.16.

(1*R*,2*R*,6*R*,8*R*,12*R*,14*S*)-12-Benzyloxycarbonylaminopropyl-10,13-diaza-4,4-dimethyl-16,16-dioxide-11-oxo-3,5,7,17-tetraoxa-16-thio-pentacyclo[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (30). Following the general procedure the cyclic enamine **8** was treated in situ with *H*-D-Lys-(*Z*)-OMe·HCl (0.14 g, 0.44 mmol). The residue was purified by CCTLC using hexane/ethyl acetate (1:1) to give 0.05 g (43%) of **30** as a white solid: mp 70−72 °C. $[\alpha]^{20}_D$ +43.13 (*c* 0.5, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.33−1.51 (2s, 6H), 1.42−1.64 (m, 4H), 1.82 (m, 2H), 1.95 (d, 1H, *J* = 5.5 Hz), 3.14 (m, 2H), 3.49 (m, 2H), 4.03 (dd, 1H, *J* = 2.1 Hz, *J* = 13.4 Hz), 4.13 (m, 2H), 4.65 (d, 1H, *J* = 2.1 Hz), 5.03 (m, 3H), 5.72 (d, 1H, *J* = 3.6 Hz), 5.62 (d, 1H, *J* = 3.5 Hz), 6.31 (bs, 1H), 7.35 (m, 5H). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 24.2 (CH_2), 27.5 (CH_3), 30.5 (CH_2), 34.3 (CH_2), 41.3 (CH_2), 49.2 (CH_2), 56.8 (CH_2), 62.1 (CH), 67.1 (CH_2), 80.0 (CH), 83.4 (C), 90.4 (C), 98.7 (C), 107.5 (CH), 114.9 (C), 129.2−139.1 (CH), 158.2 (CO), 179.2 (CO). MS (ES+) *m*/*z*: 560.1 (M + Na)$^+$. Anal. Calcd for $C_{24}H_{31}N_3O_9S$: C, 53.62; H, 5.81; N, 7.82. Found: C, 52.58; H, 5.49; N, 8.16.

(1*R*,2*R*,6*R*,8*R*,12*S*,14*S*)-12-Carboxyethyl-10,13-diaza-4,4-dimethyl-16,16-dioxide-11-oxo-3,5,7,17-tetraoxa-16-thio-pentacyclo[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (31). A solution of **27** (0.1 g, 0.21 mmol) in methanol (10 mL) containing Pd/C (10%) (0.010 g) was hydrogenated under atmospheric hydrogen pressure at 40 °C for 4 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by CCTLC on the chromatotron using dichloromethane/methanol (10:1) to give 0.08 g (70%) of **31** as a white solid: mp 132−135 °C. $[\alpha]^{20}_D$ +52.7 (*c* 0.5, MetOH). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.32−1.58 (2s, 6H), 2.34 (dd, 1H, *J* = 9.8 Hz, *J* =

17.1 Hz), 2.82 (dd, 1H, J = 3.4 Hz, J = 17.1 Hz), 3.55 (dd, 1H, J = 2.4 Hz, J = 13.4 Hz), 3.98 (d, 1H, J = 13.4 Hz), 4.12 (d, 1H, J = 13.9 Hz), 4.23 (d, 1H, J = 13.9 Hz), 4.46 (m, 1H), 4.72 (d, 1H, J = 2.4 Hz), 5.05 (d, 1H, J = 3.7 Hz), 5.78 (d, 1H, J = 3.7 Hz), ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 27.4 (CH_3), 39.1 (CH_2), 49.3 (CH_2), 55.4 (CH_2), 57.2 (CH), 80.6 (CH), 84.1 (CH), 89.2 (C), 98.8 (C), 107.4 (CH), 114.8 (C), 173.3 (CO), 176.4 (CO). MS (ES+) m/z: 391.1 $(M + H)^+$. Anal. Calcd for $C_{14}H_{18}N_2O_9S$: C, 43.07; H, 4.65; N, 7.18. Found: C, 43.24; H, 4.53; N, 7.36.

(1*R*,2*R*,6*R*,8*R*,15*S*)-10,14-Aza-4,4-dimethyl-17,17-dioxide-11-oxo-3,5,7,18-tetraoxa-17-thio-pentacyclo[10.6.0.0$^{2-6}$.0$^{1-15}$.0$^{10-15}$]-octadecane (32) and (1*R*,2*R*,6*R*,8*R*,15*S*)-10,14-Aza-4,4-dimethyl-11-oxo-1-mesyloxy-3,5,7-trioxa-tetracyclo[7.6.0.0$^{2-6}$.0$^{10-15}$]-pentadecane (33). Following the general procedure the cyclic enamine **8** was treated in situ with β-Ala-OMe·HCl (0.06 g, 0.44 mmol). The residue was purified by CCTLC using hexane/ethyl acetate (1:1). The fastest moving fractions gave 0.02 g (20%) of **32** as a white solid: mp 75−77 °C. $[\alpha]^{20}_D$ +84.7 (c 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42−1.63 (2s, 6H), 2.54 (m, 2H), 2.65 (bs, 1H, NH), 3.13−3.52 (m, 5H), 3.78 (d, 1H, J = 13.4 Hz), 4.63 (dd, 1H, J = 5.7 Hz, J = 8.1 Hz), 4.92 (d, 1H, J = 3.7 Hz), 5.82 (d, 1H, J = 3.7 Hz). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 27.6 (CH_3), 31.6 (CH_2), 39.9 (CH_2), 47.3 (CH_2), 52.1 (CH_2), 79.3 (CH), 80.4 (CH), 84.1 (C), 98.4 (C), 106.1 (CH), 114.4 (C), 166.7 (CO). MS (ES+) m/z: 347.1 $(M + H)^+$. Anal. Calcd for $C_{13}H_{18}N_2O_7S$: C, 45.08; H, 5.24; N, 8.09. Found: C, 45.18; H, 5.44; N, 8.29.

From the slowest moving fractions 0.02 g (25%) of **33** was isolated as a white solid: mp 78−80 °C. $[\alpha]^{20}_D$ +20.7 (c 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41−1.65 (2s, 6H), 2.53 (m, 2H), 3.22 (s, 3H), 3.83 (m, 4H), 4.82 (d, 1H, J = 3.4 Hz), 5.16 (d, 1H, J = 3.7 Hz), 5.8 (d, 1H, J = 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.3 (CH_3), 31.2 (CH_2), 40.6 (CH_3), 45.8 (CH_2), 47.4 (CH_2), 78.4 (CH), 80.9 (CH), 90.4 (C), 105.6 (CH), 114.6 (C), 154.3 (C=N), 168.5 (CO). MS (ES+) m/z: 349.1 $(M + H)^+$. Anal. Calcd for $C_{13}H_{20}N_2O_7S$: C, 44.82; H, 5.79; N, 8.04. Found: C, 44.95; H, 5.64; N, 8.14.

(1*R*,2*R*,6*R*,8*R*)-10-Aza-11-*N*,*N*-benzyloxybutylamino-4,4-dimethyl-1-mesyloxy-3,5,7-trioxa-tricyclo[6.3.0.0$^{2-6}$]-undec-10-ene (34). Following the general procedure the cyclic enamine **8** was treated in situ with *H*-δ-aminovaleric-(OBn)·pTos (0.09 g, 0.44 mmol). The residue was purified by CCTLC using hexane/ethyl acetate (1:1) to give 0.03 g (35%) of **34** as a yellow solid: mp 77−79 °C. $[\alpha]^{20}_D$ +27.0 (c 0.1, $CHCl_3$). ^{1}H NMR [300 MHz, $CDCl_3$] δ: 1.33−1.51 (2s, 6H), 1.53−1.82 (m, 4H), 2.38 (m, 2H), 3.19 (s, 3H), 3.23 (m, 2H), 3.68 (d, 1H, J = 15.4 Hz), 3.79 (dd, 1H, J = 3.3 Hz, J = 15.4 Hz), 4.65 (d, 1H, J = 3.3 Hz), 4.84 (d, 1H, J = 3.7 Hz), 5.13 (s, 2H), 5.82 (d, 1H, J = 3.7 Hz), 6.23 (bs, 1H), 7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.4 (CH_2), 27.5 (CH_3), 28.2 (CH_2), 34.1 (CH_2), 40.6 (CH_3), 43.3 (CH_2), 58.1 (CH_2), 66.6 (CH_2), 80.1 (CH), 88.7 (CH), 98.7 (C), 106.9 (CH), 114.2 (C), 129.2−139.4 (CH), 159.7 (C=N), 173.6 (CO). MS (ES+) m/z: 483.1 $(M + H)^+$. Anal. Calcd for $C_{22}H_{30}N_2O_8S$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.84; H, 6.12; N, 5.69.

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Supporting Information Available: General experimental methods and NMR procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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