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Synthesis of Highly Condensed Polycyclic Carbohydrates by Reaction of a Spirocyclic Enamino Sulfonate Derived from D-Xylofuranose with Bifunctional Reagents

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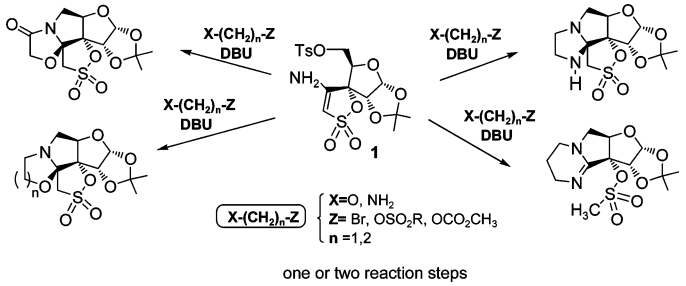

The appropriately substituted 5-*O*-tosyl derivative (**1**), easily prepared from 1,2-*O*-isopropylidene-α-D-xylofuranose, serves as a useful precursor for the preparation of highly condensed cyclic carbohydrates. The synthesis involves a first cyclization of the 5-*O*-tosyl sugar derivative **1** to a highly reactive cyclic enamine, which subsequently undergoes the nucleophilic attack of a bifunctional reagent $X(CH_2)_nZ$ in a regio- and stereospecific way. Finally, a spontaneous cyclization step allows the formation of a stereochemically defined extra ring, fused to the sugar backbone. The functionalization and size of this ring can be varied by the proper choice of the bifunctional reagent. X-ray diffraction analysis and intensive NMR studies with one of these carbohydrates were performed to highlight the strained nature of these compounds.

Introduction

Carbohydrates are natural products of great interest, due to their widespread occurrence, structural diversity, well-defined stereochemistry, and high functional (mostly hydroxyl) group density. These properties make this class of compounds particularly attractive as chiral scaffolds for the synthesis of naturally occurring[1] as well as carbohydrate[2] and non-carbohydrate bioactive compounds.[3−5] After the successful use of carbohydrates as scaffolds to mimic particular peptide folds[6] there has been a growing interest in these compounds as tools for the drug-discovery process.[7] More recently, solution-[8] and solid-phase libraries[9] have been generated by using carbohydrates and carbohydrate-derived scaffolds as molecular templates to display pharmacophoric groups in well-defined spatial orientations.

A potential disadvantage in the application of monosaccharide scaffolds may be their propensity, depending on the nature and spatial orientation of the substituents, to adopt more than one conformation. One possible method for the reduction of molecular flexibility is the introduction of a second or even further

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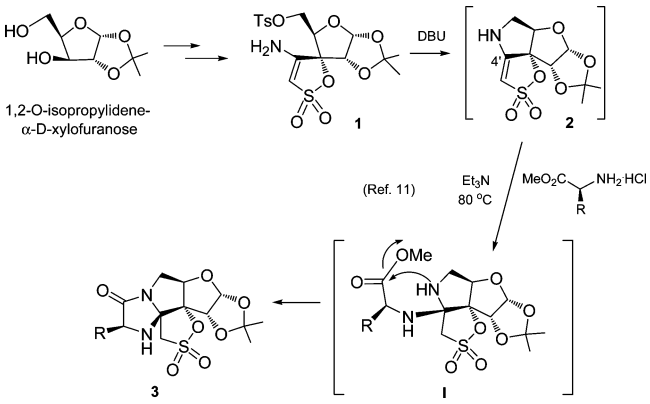
SCHEME 1. Reaction of Cyclic Enamine 2 with Amino Acids



rings fused to the sugar backbone. Toward this aim, synthesis of extra fused ring sugar derivatives from a simple synthon with a high degree of chemo-, regio-, and stereoselectivity has been a major challenge to organic chemists over the years.[10]

In an earlier work, we described the efficient transformation of a simple carbohydrate (1,2-*O*-isopropylidene-α-D-xylofuranose) into a high-added value synthetic scaffold **2** (Scheme 1).[11] The cyclic enamine **2**, obtained by cyclization of isopropylidene-5-*O*-tosyl-α-D-ribofuranose (**1**)[11] under basic non-nucleophilic (DBU) conditions (Scheme 1), is an unstable compound that has to be used immediately in the subsequent reaction without purification. Reaction of **2** with nucleophiles (i.e., water, amines, alcohols) afforded novel polycyclic sugar derivatives with rather unusual molecular skeletons and skeletal diversity.[11]

A notable feature of **2** is its reactivity with amino acids, which afforded a novel type of highly condensed tetracyclic carbohydrates of general formula **3** (Scheme 1).[11] Formation of **3** could be explained by attack of the amino group of the amino acid to the C-4′ position of the sugar **2** to give the intermediate **I**, followed by the spontaneous displacement of the ester group of the amino acid by the NH of the pyrroline ring to form a new five-membered ring fused to the sugar backbone (Scheme 1).

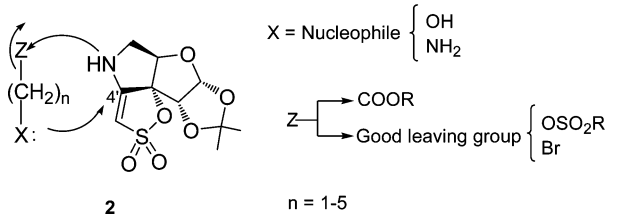


FIGURE 1. Reaction of cyclic enamine **2** with bifunctional reagents.

The present investigation aims to explore the reactivity of the cyclic enamine **2** with other classes of bifunctional reagents [$X(CH_2)_nZ$] that contain a nucleophile (X = OH, NH_2) at one end and a carboxylic ester (Z = COOR) or a good leaving group (Z = OSO_2R, halide) at the other, connected by an adequate spacer (polymethylene chain containing one, two, three, or five methylenes) (Figure 1).

Results

Chemistry. First, hydroxyalkyl esters (X = OH and Z = COOR) were studied as bifunctional reagents (Scheme 2). Thus, the reaction of **2** with the commercially available methyl 2-hydroxyacetate, at 80 °C, afforded the pentacyclic sugar derivative **4** in 40% yield, reproducing the result obtained with amino acids. In this case, compound **II** might be the intermediate of the reaction.

Next, other hydroxyalkyl esters with longer polymethylene chains were used to increase the size of the extra ring fused to the sugar backbone. In this case, the required hydroxyalkyl esters **5**−**7** were not commercially available and should be prepared as described in the literature.[12] When the reaction of **2** was carried out with the freshly prepared hydroxyalkyl esters **5**−**7**,[12] only the tricyclic derivatives **8**−**10** (40−70% yield) were observed indicating that in these cases the key intramolecular cyclization did not occur (Scheme 2). These experimental findings show that in the intramolecular attack of the ester moiety by the NH of the pyrrolidine ring, the formation of a five-membered extra ring is much more favorable than the formation of six-membered or larger rings.

We reasoned that perhaps basic reaction conditions could be employed to induce the cyclization needed to create the extra cyclic ring system. However, this was not the case, since treatment of **8** (used as model compound) under different basic conditions (K_2CO_3, Cs_2CO_3) at 80 °C only afforded, after long reaction times, compound **11** (55% yield) in which opening of the spirosultone ring was observed (Scheme 2).

Next, other reagents containing a hydroxyl group (X = OH) at one end and a good leaving group (Z = OSO_2R) at the other were studied. In this case, the required monotosyl alcohols were not commercially available and should be prepared by tosylation of the corresponding alkyl diol and separation of the mono- and ditosyl derivatives. To avoid tedious intermediate preparation and purifications we decided to postpone the tosylation

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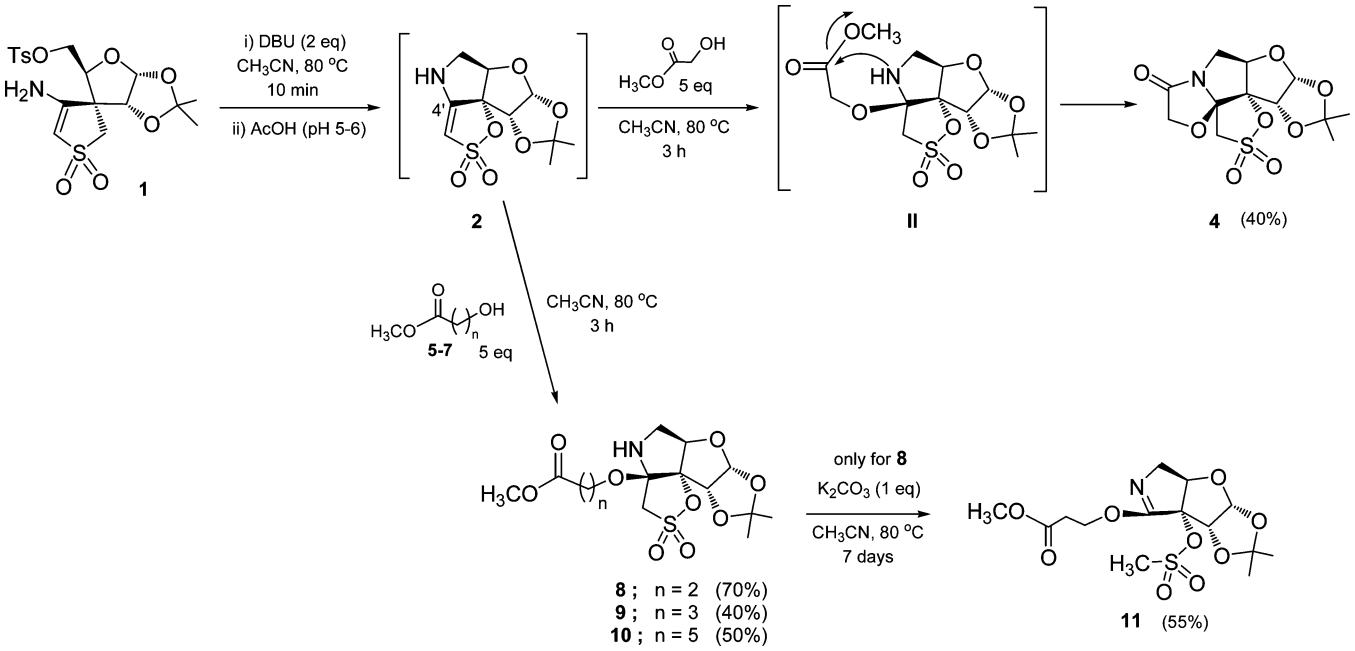
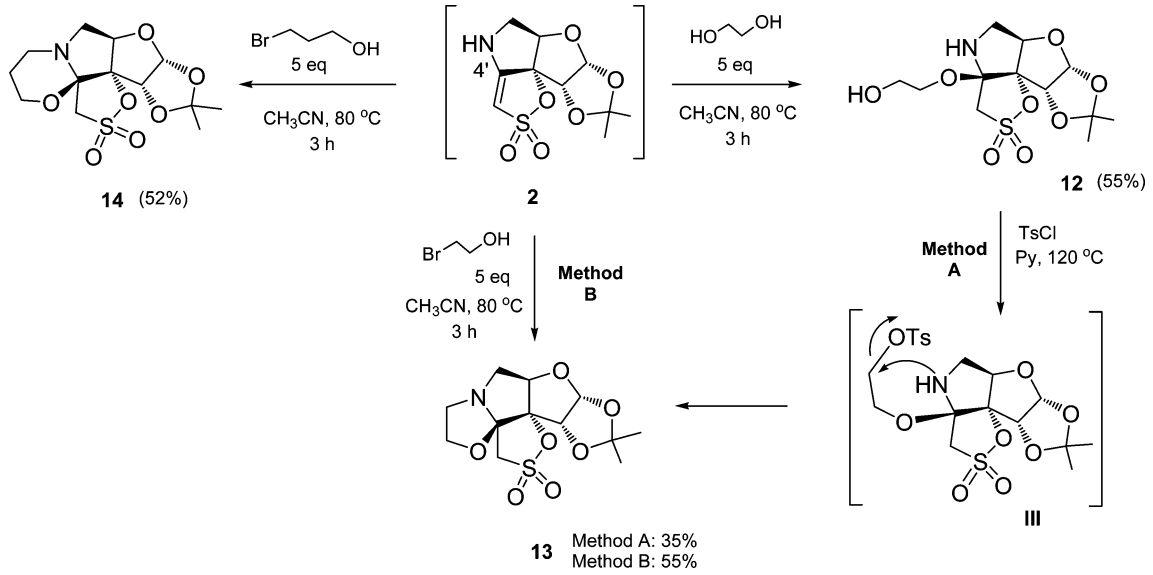
SCHEME 2. Synthesis of Carbohydrates 4 and 8−11



SCHEME 3. Synthesis of Carbohydrates 12−14



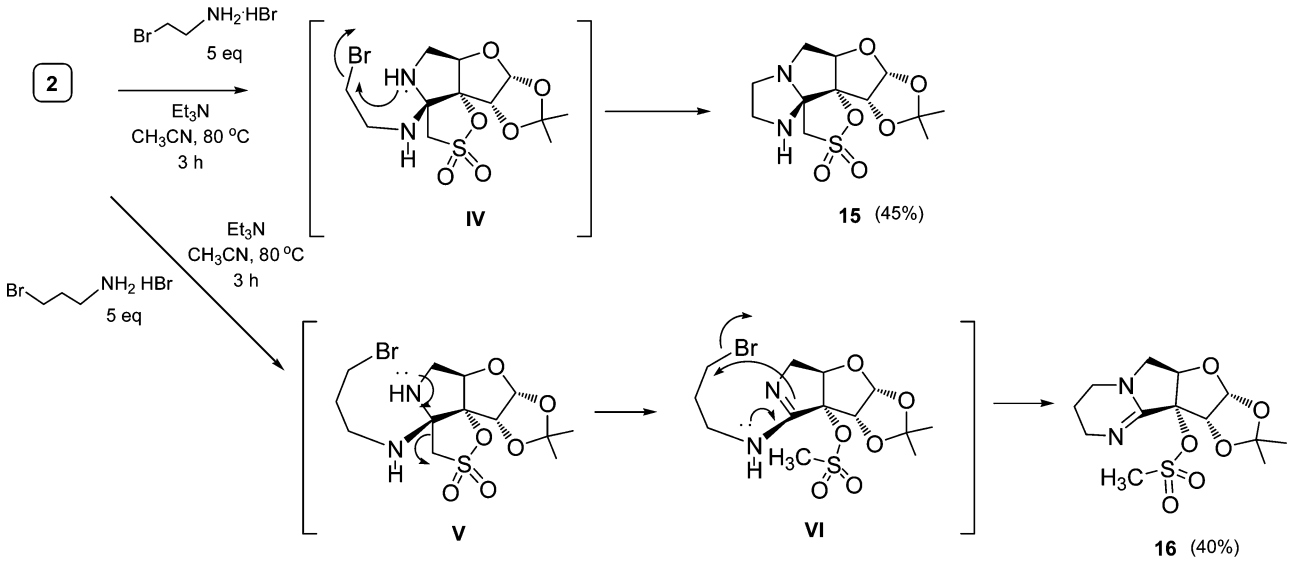
activation until the attack of one of the hydroxyl groups of the diol at the C-4′ position of **2** was completed.

To test this strategy the starting material **2** was treated with 1,2-ethanediol at 80 °C (Scheme 3). In this reaction compound **12** was isolated in 55% yield. Our aim was to convert **12** into the corresponding tosyl intermediate **III**, which subsequently should be used in the cyclization reaction. Interestingly, this approach enables the direct synthesis of **13** (35%) in which a new five-membered ring with a CH_2-N bond instead of the CO−N bond present in **4** was formed. In this case, tosylation and also the desired cyclization were carried out simultaneously in a single operation

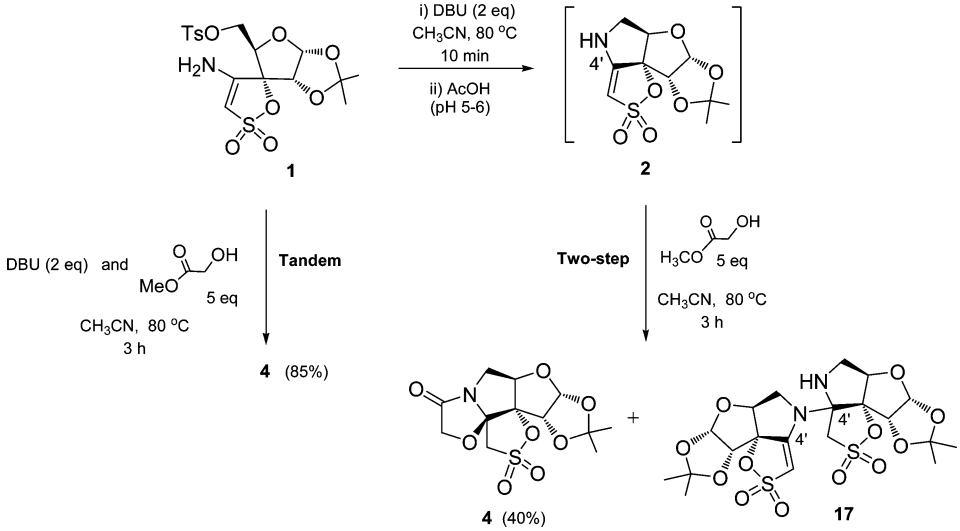
Following with our study, we decided to carry out the reaction of **2** with bromoalkyl alcohols that incorporate at one end Br as a good leaving group instead of OSO_2R. Thus, reaction of the sugar derivative **2** with commercially available bromoethanol afforded **13** (Scheme 3). In this later case, a better yield of **13** was obtained as compared to the corresponding result with the tosyl intermediate **III** (55% versus 35%). In addition, the new route obviates the need for the tosylation step, facilitating considerably the preparation of **13**. Similarly, **2** was reacted with bromopropanol leading to the cyclic sugar derivative **14** (52% yield) in which a new fused 6-membered ring was formed (Scheme 3).

Having successfully generated carbohydrates with an oxygenated fused ring, we next decided to prepare compounds wherein the oxygen was replaced by a nitrogen atom. With this aim, reaction of **2** with bromoethyl and bromopropylamine ($X = NH_2$ and $Z = Br$) hydrobromides was investigated (Scheme 4). In this case, the reaction was carried out in the presence of triethylamine to liberate the attacking amino group in the reagent. As was observed with bromoalkyl alcohols, attack of the amino group of the bromoethylamine to the C-4′ position

SCHEME 4. Synthesis of Carbohydrates 15 and 16



SCHEME 5. Synthesis of 4 by the Two-Step and Tandem Processes



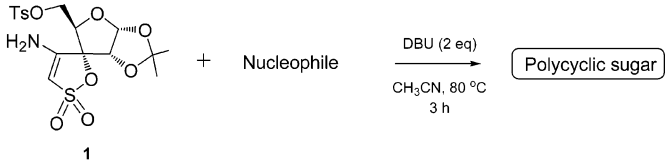
of **2** was followed by subsequent intramolecular cyclization yielding **15** (55%) with an extra five-membered ring.

On the other hand, when bromopropylamine was used as bifunctional reagent, compound **16** (40%) was isolated. In this case, opening of the spiro sultone moiety and formation of an extra six-membered ring was observed. Formation of **16** could be explained by the attack of the bromopropyl amine to the C-4′ position of **2** to afford intermediate **V**. The subsequent opening of the spirosultone ring would give intermediate **VI** that undergoes an extra ring-closing step to give **16**. A similar result was observed in the reaction of **2** with β-L-alanine.[11] Opening of the spirosultone ring was not observed in the reaction of **2** with bromoethylamine because the intramolecular cyclization that led to a five-membered ring might occur earlier and preferentially in the intermediate **IV**, which is finally locked and does not proceed further.

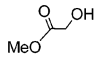
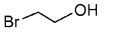
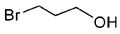
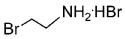
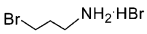
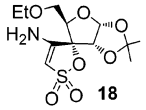
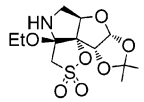
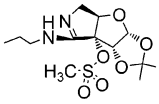
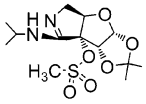
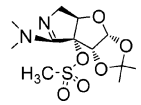
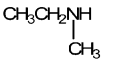
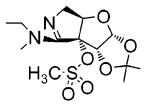
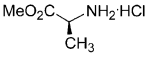
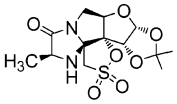
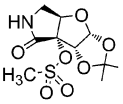
Synthesis of the Polycyclic Sugar Derivatives Based on a Tandem Process. It is worth mentioning that the synthesis of the compounds described so far were carried out in two consecutive steps, starting from the 5′-*O*-tosyl sugar derivative **1**.[11] The first step was the intramolecular cyclization of **1**[11] at 80 °C in the presence of DBU. This reaction afforded the cyclic enamine **2** that is not sufficiently stable to be efficiently isolated. Thus, after 10 min of reaction, the intramolecular cyclization of **1** must be quenched by addition of acetic acid (pH adjusted to 5−6) and the residue (compound **2**[11]) left to react "in situ", in a second step, with the corresponding nucleophile. Although these two consecutive steps were carried out under careful experimental conditions a variable amount of the dimer **17**[11] (Scheme 5) was always recovered after workup decreasing the yield of the desired polycyclic sugars. In the particular case of the polycyclic sugar derivative **4** (Scheme 5), formation of the dimer **17** makes the purification process highly difficult since the retention factor of **17** ($R_F = 0.66$) was similar to that shown by **4** ($R_F = 0.71$).

Formation of **17** indicates that the cyclic enamine **2**, once formed, readily undergoes self-condensation via an intermolecular attack between the NH and C-4′ position of distinct molecules.[11] Therefore, in order to study whether it should be possible to avoid the self-condensation of **2** and to improve the yields of the final compounds we planned to carry out the instantaneous trapping of the cyclic enamine **2** as soon as it was generated. With this aim, we decided to develop a tandem procedure in which the cyclization of the tosyl derivative **1** was

TABLE 1. Comparative Results between Sequential and Tandem Protocols



1

Entry	Nucleophile	Product[a]	Two step Yield (%)[b]	Tandem Yield. (%)[b]
1		**4**	40	85
2		**13**	55	5
3		**14**	52	15
4		**15**	45	5
5		**16**	40	5
6	EtOH (solvent and reagent)	 **18**	–	97
7	EtOH (5-20 eq)	 **19**[11]	68	85
8	$CH_3(CH_2)_2NH_2$	 **20**[11]	55	89
9	$(CH_3)_2CHNH_2$	 **21**[11]	55	76
10	$(CH_3)_2NH$	 **22**[11]	30	45
11		 **23**[11]	30	30
12		 **24**[11]	76	5
13	H_2O	 **25**[11]	52	85

[a] All reactions were conducted in a sealed tube at 80 °C for 3 h in the presence of the appropriate nucleophilic reagent (5 equiv) and DBU (2 equiv) and with acetonitrile as the solvent except for **18** (entry 6). [b] Isolated yields of chromatographically purified compounds.

carried out in the presence of the attacking nucleophile. The process is not obvious and only will be successful if the nucleophilic reagent present in the media attacks once all of the tosyl derivative **1** has been converted into the cyclic enamine **2**. Only in this case, the competitive substitution of the 5′-*O*-tosyl moiety and/or its elimination will be avoided.

The method was initially tested for **4**. Thus, reaction of 5′-*O*-tosyl derivative **1** with 5 equiv of the commercially available methyl 2-hydroxyacetate afforded the pentacyclic sugar derivative **4** with excellent yield (85%). In this case, the intramolecular cyclization of **1**, nucleophilic attack of the reagent, and subsequent ring-closure proceed in a concerted fashion. In this way, dimerization of the reactive cyclic enamine **2** was largely avoided and only traces of dimer **17** were detected. Thus, the tandem procedure allowed a significant improvement in the yield of **4** (85% versus 40%).

With this result in our hands, we next examined the scope and limitations of the tandem methodology using different types of nucleophiles. The protocol was first studied with bifunctional reagents. Next, we evaluated the tandem methodology for the synthesis of bicyclic sugars **19**−**25**, previously obtained under the two-step procedure as described in a previous paper.[11] Comparative results between sequential and tandem protocols are shown in Table 1.

Reaction of **1** with bromoethanol and bromopropanol afforded the polycyclic sugar derivatives **13** and **14** in very poor yields (entries 2 and 3). Similarly, reaction with bromoethyl and bromopropylamine hydrobromides only gave mixtures of compounds from which **15** and **16** were obtained in very low yields (entries 4 and 5). In contrast with the results observed for **4** (entry 1), in these cases the tandem protocol does not improve the results observed in the sequential protocol.

Reaction of ethanol (used as the solvent and nucleophile) with compound **1** afforded the 5′-substituted derivative **18** (97%) (entry 6) as a result of the competitive substitution of the 5′-*O*-tosyl moiety by the alcohol, instead of the expected intramolecular cyclization and nucleophilic attack. However, when only 5−20 equiv of ethanol were used, the *O*-substituted tricyclic sugar **19**[11] derivative was obtained with excellent yield (entry 7).

Next, the tandem reaction with primary amines (propyl- and isopropylamine) was investigated. In both cases the corresponding tricyclic derivatives **20**[11] and **21**[11] were obtained in good yields (89% and 76%, respectively) (entries 8 and 9).

The tandem protocol was also investigated with secondary amines (dimethylamine and ethylmethylamine). In these cases, as was observed in the two-step sequence method, a large amount of dimer **17** was detected, caused probably by the higher basicity of the secondary amines used as reagents. For this reason, the overall yields of the products **22**[11] and **23**[11] (entries 10 and 11) are similar in both methods. However, the tandem protocol is experimentally much more convenient because it simplifies the exhaustive control of the reaction conditions employed for the intramolecular cyclization of **1** in the two-step sequence method. On the other hand, when the tandem protocol was used with an amino acid such as the methyl ester derivative of L-alanine [*H*-L-Ala-OMe. HCl], a complex mixture of products was observed from which only compound **24** was isolated in very low yield (entry 12).

Finally, the tandem protocol was examined with water. In this case, lactam **25**[11] was obtained in excellent yield (entry 13).

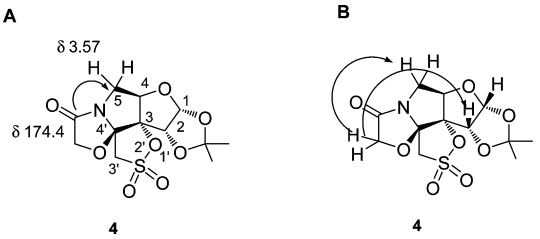


FIGURE 2. (A) gHMBC NMR correlations and (B) relevant NOE indicated by arrows.

The experimental results shown in Table 1 indicate that the yield of the tandem protocol depends on the attacking nucleophile. When alcohols, primary amines, water, and methyl glycolate were used this method gave superior yields (76−89%) than those of the sequential method (40−68%). Yields of both methods are comparable when secondary amines were used. Unfortunately, the tandem protocol with bromo alcohols. bromoalkylamines, and amino acids proved to be challenging and no bicyclic sugar derivatives were obtained in good yields. We are currently developing alternative conditions for the tandem process involving these reagents.

Structural Assignments. The structures of the novel polycyclic sugar derivatives **4**, **8**−**11**, and **13**−**16** were assigned by ^{1}H and ^{13}C NMR spectroscopic analysis, using mono- and bidimensional techniques (gHMBC[13] and gHSQC[14]) and by comparison with those of the previously reported sugar derivatives.[11] Figure 2 shows the correlations observed in the gHMBC and NOE difference experiments carried out on compound **4** as an example of a polycyclic sugar derivative.[15,16]

In the gHMBC experiment (Figure 2A) compound **4** showed a long-range correlation between the H-5 protons (δ 3.57 ppm) and the CO carbon (δ 174.4 ppm) that is consistent with a cyclized structure. Similarly, the gHMBC experiments of the derivatives **13**−**16** satisfactorily established information about the presence of a new ring fused to **2**.

NOE difference experiments carried out on compounds **4** (Figure 2B) and **13**−**16** showed that there is a correlation between the methylene protons of the new five- or six-membered ring and the sugar protons H-2 and H-5, indicating that all of these protons were on the same upper side of the furanose ring and close proximity in space. This result confirms that the conjugate addition of the nucleophilic end of the reagent proceeded with complete stereoselectivity on the β-face of the sugar-fused cyclic enamine **2** as was previously observed with other nucleophiles.[11] Semiempirical calculations (using the Hyperchem package[17]) indicated that the *S* isomer **II** (intermediate in the formation of **4**, Scheme 2) ($E = -339.67$ kcal·mol^{-1}) is more stable than its respective *R* isomer ($E = -315.05$ kcal·mol^{-1}) by 24.62 kcal·mol^{-1} in the gas phase.

Conformational Behavior of 4. With the aim to study whether the conformational freedom of the furanose ring was

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(15) Assignments of NMR spectra follow standard carbohydrate nomenclature (i.e., the furanose skeleton numbered 1−5) and the spirosultone skeleton was numbered 1′−4′ (see Figure 2A), even though the systematic compound names of the polycyclic structures are given according to the von Baeyer nomenclature.[16]
(16) IUPAC nomenclature home page: http://www.chem.qmul.ac.uk/iupac/.
(17) **HyperChem**, Release 5.1, Windows Molecular Modelling System; HyperCube: Waterloo, Ontario, Canada, 1997.

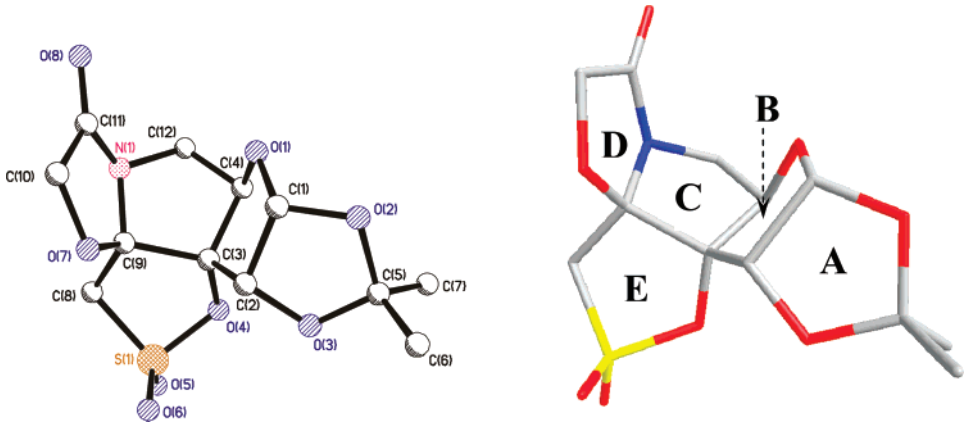

FIGURE 3. ORTEP molecular structure and ChemDraw 3D representation of **4**.

TABLE 2. Comparison of Vicinal Coupling Constants (in Hz) of 4 in Solution and Solid State

vicinal protons	$^3J_{HH}$ C_6D_6	$^3J_{HH}$ $CDCl_3$	$^3J_{HH}$ $(CD_3)_2CO$	$^3J_{HH}$ CD_3OD	$^3J_{HH}$ $(CD_3)_2SO$	HH torsion angle (ϕ, deg)	$^3J_{HH}$ calcd[a]
H-1−H-2	3.7	3.7	3.7	3.5	4.0	−2.2	6.8
H-4−H-5_a	2.5	2.5	2.0	2.0	2.0	40.9	3.6
H-4−H-5_b	0	0	0	0	0	−81.2	0.1

[a] Calculated coupling constant from the torsional angle (ϕ, deg) measured in the solid state, using the equation developed by Altona.[22]

restricted by the presence of fused rings, we decided to study the solid and solution state structures for compound **4**, which was chosen as an example of a polycyclic sugar derivative. The furanose conformation in solution was determined experimentally by NMR spectroscopic methods. In addition, an X-ray diffraction analysis was performed to establish whether in the crystalline state the furanose ring possesses the conformation that corresponds to the majority one existing in solution.

(a) Structure of 4 in the Solution State. In solution, carbohydrates are usually found in a low-energy conformation, but there may be a lower proportion of other conformers. Variable-temperature ^{1}H NMR experiments have proved useful to detect mixtures of conformers in solution.[18−20] For this reason, with the purpose of detecting a possible equilibrium between different conformational states we recorded ^{1}H NMR spectra of **4** in solvents of different polarity (C_6D_6, $CDCl_3$, $(CD_3)_2CO$, CD_3OD, and $(CD_3)_2SO$) at different temperatures. We found small changes in the chemical shifts and coupling constants between the different solvents (Table 2) and/or the high- and low-temperature spectra (data not shown). Consequently, the situation could be explained as a dynamic equilibrium between two or more conformations that is shifted toward a major conformer. As expected, the presence of one ketal moiety and three pentacyclic rings fused to the furanose decreases its conformational mobility and for this reason the sugar conformation is nonsensitive toward the solvent polarity and temperature. Similarly, small changes in the chemical shifts and coupling constants between different solvents and/or temperature spectra were observed for the novel polycyclic sugar derivatives **13**−**16** (data not shown).

(b) Structure of 4 in the Solid State. Crystals of **4**, well-suited for X-ray diffraction, could be obtained when ethyl acetate was used as solvent. Figure 3 shows an ORTEP representation of **4** in the crystalline state that reveals that the ketal moiety (**A**) and the three pentacyclic rings (**C**, **D**, **E**) were oriented toward the β- (**C**, **D**) and α-faces (**A**, **E**) of the furanose moiety (**B**).

It is worth noting that the furanose ring (**B**) adopts an envelope (*E*-type) conformation with a phase angle of pseudorotation $P = 36°$ consistent with a C4-exo ($_4E$) conformation.[21] The pyrrolidine ring (**C**) adopts an envelope form with atoms C-4, C-3, C-9, and N-1 in a plane and the C-12 atom out of this plane, oriented toward the α-face of the furanose. Sulfur (S1) is the only out-of-plane atom in the sultone ring (**E**) and it was oriented toward the β-face of the furanose. Rings **A** and **D** adopt an almost planar form.

(c) Comparison of the Conformation of 4 in Solution and Solid States. In solution, the observed coupling constants $^3J_{4,5a} = 2.5$ Hz and $^3J_{4,5b} = 0$ Hz in low and high polar solvents are in agreement with those calculated ($^3J_{4,5a} = 3.6$ Hz and $^3J_{4,5b} = 0.1$ Hz) from the X-ray analysis with the equation developed by Altona (Table 2).[22] Thus, it is apparent that the solid state (crystal structure) conformation around the C-4−C-5 bond is retained in solution. However, the $^3J_{1,2}$ value observed in solution ($^3J_{1,2} = 3.7$ Hz) does not show concordance with that calculated ($^3J_{1,2} = 6.8$ Hz) from the torsional angle measured in the solid state (Table 2). So, the $^3J_{1,2} = 3.7$ Hz value suggests that, in solution, there exists a gauche−gauche disposition of H-1 and H-2 compatible with a ^3E conformation ($P = 18°$) while in the solid state disposition of H-1 and H-2 is compatible with a $_4E$ conformation ($P = 36°$).[21]

Conclusions

We have reported a simple cyclization reaction between the cyclic enamine **2** and bifunctional reagents of the type $X(CH_2)_nZ$

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(22) Altona, C.; Ippel, J. H.; Aldert, J. A.; Hoekzema, W.; Erkelens, C.; Groesbeek, M.; Donders, L. A. *Magn. Reson. Chem.* **1989**, *27*, 564.

that allows the preparation of enantiomerically pure polycyclic sugar derivatives containing a new, stereochemically defined extra fused ring. The functionalization and size of this ring depends on the adecuate choice of the attacking nucleophile (X), leaving group (Z), and length of the chain connecting them. The constrained structures, structural diversity, well-defined stereochemistry, and dense functionalization of the condensed cyclic carbohydrates generated from **2** make these compounds attractive as chiral scaffolds. In addition, we have developed a tandem process that represents a new and efficient method for the synthesis of these and other types of polycyclic sugar derivatives previously obtained under a two-step procedure. Compared to the reported two-step method, the tandem procedure has the advantage that it does not require a careful experimental control, is simple, and in general improves the yields of the final products. The scope of the tandem methodology depends on the attacking nucleophile.

The X-ray crystal structure of **4** is also described, together with a comparison of its conformation in solution with that in the solid state. This conformational analysis revealed that **4** adopts, around the C-4 and C-5 bond, similar conformations in solid and solution states, while the conformation around the C-1 and C-2 bond shows slight differences.

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).[16] 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). The spirosultone skeleton was numbered 1′−4′ starting from the oxygen.

General Two-Step Procedure for the Synthesis of Sugars 4, 8−10, 12, and 13−16. To a solution of the 5-*O*-tosyl derivative **1**[11] (0.1 g, 0.22 mmol) in dry acetonitrile (2 mL) was added DBU (0.067 mL, 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 **2**,[11] thus formed, was treated "in situ" with the corresponding nucleophile (1.1 mmol). The solution was heated at 80 °C for 3 h. Solvent was evaporated and the residue was purified by preparative CCTLC (centrifugal circular thin layer chromatography). The chromatography eluent and yield of the isolated products are indicated below for each reaction.

(1*R*,2*R*,6*R*,8*R*,14*S*)-10-Aza-4,4-dimethyl-16,16-dioxide-11-oxo-3,5,7,13,17-pentaoxa-16-thio-4,4-dimethylpentacyclo-[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (4). Following the general procedure, the cyclic enamine **2**[11] was treated "in situ" with methyl 2-hydroxyacetate (0.09 g, 1.1 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:1) to give 0.03 g (40%) of **4** as a white solid: mp 152−154 °C. $[\alpha]^{20}_D$ +64.8 (*c* 0.12, $CHCl_3$). ^{1}H NMR [500 MHz, $(CD_3)_2CO$] δ 1.35 (s, 3H), 1.52 (s, 3H), 3.57 (dd, 1H, J = 2.0 Hz, J = 13.1 Hz), 4.05 (m, 2H), 4.18 (d, 1H, J = 14.1 Hz), 4.37 (d, 1H, J = 13.5 Hz), 4.65 (d, 1H, J = 13.5 Hz), 4.77 (d, 1H, J = 2.1 Hz), 5.02 (d, 1H, J = 3.7 Hz), 5.87 (d, 1H, H-1, J = 3.7 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 26.7 (CH_3), 26.9 (CH_3), 48.6 (CH_2), 54.5 (CH_2), 69.3 (CH_2), 78.9 (CH), 82.4 (CH), 96.5 (C), 105.8 (C), 106.4 (CH), 114.2 (C), 174.4 (CO). MS (ES+) *m*/*z* 356.1 (M + Na)$^+$. Anal. Calcd for $C_{12}H_{15}NO_8S$: C, 43.24; H, 4.54; N, 4.20. Found: C, 43.35; H, 4.43; N, 4.52.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-4,4-dimethyl-13,13-dioxide-11-methoxycarbonylethoxy-3,5,7,14-tetraoxa-13-thiotetracyclo-[6.6.0.0$^{2-6}$.0$^{1-11}$]tetradecane (8). Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with freshly prepared methyl 3-hydroxypropionate **5**[12] (0.11 g, 1.1 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:1) to give 0.06 g (70%) of **8** as a yellow syrup. $[\alpha]^{20}_D$ +51.7 (*c* 0.35, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.31 (s, 3H), 1.48 (s, 3H), 2.61 (t, 2H, J = 6.1 Hz), 3.12 (m, 1H), 3.47 (m, 1H), 3.64 (s, 3H), 3.66 (m, 1H), 3.89 (s, 2H), 4.04 (m, 1H), 4.68 (dd, 1H, J = 1.5 Hz, J = 4.9 Hz), 4.79 (d, 1H, J = 3.5 Hz), 5.71 (d, 1H, J = 3.5 Hz). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 27.8 (CH_3), 28.3 (CH_3), 35.8 (CH_2), 51.9 (CH_2), 52.5 (CH_3), 56.6 (C), 60.7 (CH_2), 79.9 (CH), 83.5 (CH), 99.7 (C), 101.1 (C), 108.6 (CH), 114.5 (C), 173.1 (CO). MS (ES+) *m*/*z* 380.1 (M + H)$^+$. Anal. Calcd for $C_{14}H_{21}NO_9S$: C, 44.32; H, 5.58; N, 3.69. Found: C, 44.24; H, 5.45; N, 3.78.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-4,4-dimethyl-13,13-dioxide-11-methoxycarbonylpropyloxy-3,5,7,14-tetraoxa-13-thiotetracyclo-[6.6.0.0$^{2-6}$.0$^{1-11}$]tetradecane (9). Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with freshly prepared methyl 4-hydroxybutanoate **6**[12] (0.13 g, 1.1 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:4) to give 0.04 g (40%) of **9** as a yellow syrup. $[\alpha]^{20}_D$ +14.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.31 (s, 3H), 1.49 (s, 3H), 1.85 (m, 2H), 2.39 (t, 2H, J = 7.3 Hz), 3.12 (m, 1H), 3.43 (m, 2H), 3.61 (s, 3H), 3.82 (m, 1H), 3.87 (s, 2H), 4.68 (dd, 1H, J = 1.3 Hz), 4.88 (d, 1H, J = 3.3 Hz), 5.76 (d, 1H, J = 3.3 Hz). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 26.3 (CH_2), 27.8 (CH_3), 28.3 (CH_3), 31.8 (CH_2), 51.8 (CH_2), 52.3 (CH_3), 56.5 (CH_2), 63.8 (CH_2), 79.9 (CH), 83.5 (CH), 99.6 (C), 101.1 (C), 108.7 (CH), 114.5 (C), 174.6 (CO). MS (ES+) *m*/*z* 394.0 (M + H)$^+$. Anal. Calcd for $C_{15}H_{23}NO_9S$: C, 45.79; H, 5.89; N, 3.56. Found: C, 45.87; H, 5.72; N, 3.71.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-4,4-dimethyl-13,13-dioxide-11-methoxycarbonylpentyloxy-3,5,7,14-tetraoxa-13-thiotetracyclo-[6.6.0.0$^{2-6}$.0$^{1-11}$]tetradecane (10). Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with freshly prepared methyl 6-hydroxyhexanoate **7**[12] (0.16 g, 1.1 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:4) to give 0.047 g (50%) of **10** as a yellow syrup. $[\alpha]^{20}_D$ +36.7 (0.24, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.35 (s, 3H), 1.43 (s, 3H), 1.38−1.63 (m, 6H), 2.29 (t, 2H, J = 7.3 Hz), 3.12 (m, 1H), 3.13−3.51 (m, 2H), 3.59 (s, 3H), 3.81 (m, 3H), 3.87 (s, 2H), 4.69 (dd, 1H, J = 5.1 Hz), 4.87 (d, 1H, J = 3.3 Hz), 5.75 (d, 1H, J = 3.3 Hz). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 24.3 (CH_2), 26.4 (CH_2), 27.5−28.1 (CH_3), 30.9 (CH_2), 34.1 (CH_2), 41.3 (CH_2), 41.8 (CH_3), 55.8 (CH_2), 63.8 (CH_2), 78.4 (CH), 82.3 (CH), 99.4 (C), 101.8 (C), 108.1 (CH), 114.1 (C), 174.3 (CO). MS (ES+) *m*/*z* 422.0 (M + H)$^+$. Anal. Calcd for $C_{17}H_{27}NO_9S$: C, 48.45; H, 6.46; N, 3.32. Found: C, 48.34; H, 6.58; N, 3.45.

(1*R*,2*R*,6*R*,8*R*)-10-Aza-4,4-dimethyl-1-mesyloxy-11-methoxycarbonylethoxy-3,5,7-trioxatricyclo[6.3.0.0$^{2-6}$]undec-10-ene (11). To a solution of **8** (0.06 g, 0.16 mmol) in dry acetonitrile (4 mL) was added dry K_2CO_3 (0.024 g, 0.17 mmol). The solution was refluxed for 7 days. The mixture was filtered and the eluent was concentrated. The residue was purified by CCTLC with hexane: ethyl acetate (1:1) to give 0.03 g (55%) of **11** as a yellow syrup. $[\alpha]^{20}_D$ +8.1 (*c* 0.25, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.36 (s, 3H), 1.52 (s, 3H), 2.62 (t, 2H, J = 6.9 Hz), 3.23 (s, 3H), 3.37 (d, 1H, J = 11.4 Hz), 3.47−3.69 (m, 5H), 3.85 (dd, 1H, J = 3.9 Hz, J = 11.4 Hz), 4.81 (d, 1H, J = 3.9 Hz), 4.83 (d, 1H, J = 3.7 Hz), 5.81 (d, 1H, J = 3.7 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 27.3 (CH_3), 27.6 (CH_3), 31.7 (CH_2), 39.8 (CH_2), 40.4 (CH_3), 51.9 (CH_3), 52.3 (CH_2), 78.4 (CH), 82.2 (CH), 89.7 (C), 106.7 (CH), 114,4 (C), 167.3 (C═N), 172.2 (CO). MS (ES+) *m*/*z* 402.0 (M + Na)$^+$. Anal. Calcd for $C_{14}H_{21}NO_9S$: C, 44.32; H, 5.58; N, 3.69. Found: C, 44.43 H, 5.68; N, 3.52.

(1*R*,2*R*,6*R*,8*R*,11*S*)-10-Aza-4,4-dimethyl-13,13-dioxide-11-(2-hydroxyethoxy)-3,5,7,14-tetraoxa-13-thiotetracyclo[6.6.0.0$^{2-6}$.0$^{1-11}$]-tetradecane (12). Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with 1,2-ethanediol (0.07 g, 1.1 mmol). The residue was purified by CCTLC with ethyl acetate: methanol (10:1) to give 0.04 g (55%) of **12** as a yellow syrup. $[\alpha]^{20}_D$ +2.62 (*c* 0.9, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.31 (s, 3H), 1.52 (s, 3H), 2.81 (br s, 1H), 3.12 (d, 1H, J = 11.5 Hz), 3.44−3.57 (m, 2H), 3.64−3.67 (m, 2H), 3.81−3.85 (m, 1H), 3.89 (s, 2H), 4.69 (d, 1H), 4.94 (d, 1H, J = 3.3 Hz), 5.81 (d, 1H,

J = 3.3 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 27.9 (CH_3), 28.3 (CH_3), 51.7 (CH_2), 57.2 (CH_2), 62.4 (CH_2), 67.1 (CH_2), 80.1 (CH), 83.5 (CH), 99.8 (C), 101.2 (C), 108.7 (CH), 114.5 (C). MS (ES+) m/z 338.1 $(M + H)^+$. Anal. Calcd for $C_{12}H_{19}NO_8S$: C, 42.72; H, 5.68; N, 4.15. Found: C, 42.65; H, 5.48; N, 4.32.

(1*R*,2*R*,6*R*,8*R*,14*S*)-10-Aza-4,4-dimethyl-16,16-dioxide-3,5,7,-13,17-pentaoxa-16-thiopentacyclo[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]-heptadecane (13). Method A: To a solution of **12** (0.032 g, 0.09 mmol) in dry pyridine (2 mL) was added *p*-toluensulfonyl chloride (0.035 g, 0.18 mmol). The reaction mixture was refluxed for 2 h, and then solvent was evaporated and coevaporated with ethanol and toluene. A solution of the residue in dichloromethane (15 mL) was washed with cold 1 N HCl (2 × 15 mL), a saturated solution of $NaHCO_3$ (2 × 15 mL), and finally brine (2 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by flash column chromatography with hexane:ethyl acetate (2:1) to give 0.01 g (35%) of **13** as a white solid: mp 131−133 °C. $[\alpha]^{20}_D$ +65.26 (*c* 1.0, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.35 (s, 3H), 1.51 (s, 3H), 3.12 (d, 1H, J = 13.6 Hz), 3.25 (m, 2H), 3.57 (dd, 1H, J = 3.4 Hz, J = 13.6 Hz), 3.7 (s, 2H), 3.91 (m, 2H), 4.62 (d, 1H, J = 3.4 Hz), 4.93 (d, 1H, J = 3.9 Hz), 5.74 (d, 1H, J = 3.9 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 27.7 (CH_3), 28.1 (CH_3), 55.1 (CH_2), 56.2 (CH_2), 58.9 (CH_2), 68.3 (CH_2), 80.2 (CH), 84.1 (CH), 99.9 (C), 107.7 (CH), 109.4 (C), 114.7 (C). MS (ES+) m/z 320.1 $(M + H)^+$. Anal. Calcd for $C_{12}H_{17}NO_7S$: C, 45.13; H, 5.37; N, 4.39. Found: C, 45.24; H, 5.28; N, 4.43.

Method B: Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with 2-bromoethanol (0.08 mL, 1.1 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:1) to give 0.04 g (55%) of **13**.

(1*R*,2*R*,6*R*,8*R*,14*S*)-10-Aza-4,4-dimethyl-17,17-dioxide-3,5,7,-14,18-pentaoxa-17-thiopentacyclo[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]-octadecane (14). Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with 3-bromopropanol (0.15 g, 1.1 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:1) to give 0.04 g (52%) of **14** as a white solid: mp 138−140 °C. $[\alpha]^{20}_D$ +28.8 (*c* 0.12, $CHCl_3$). ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 1.32 (s, 3H), 1.48 (s, 3H), 1.18 (m, 1H), 2.15 (m, 1H), 2.88 (m, 1H), 3.21 (dd, 1H, J = 3.1 Hz, J = 10.3 Hz), 3.34 (m, 1H), 3.43 (dd, 1H, J = 6.2 Hz, J = 10.3 Hz), 3.72 (d, 1H, J = 13.4 Hz), 3.85 (m, 1H), 4.04 (m, 1H), 4.17 (d, 1H, J = 13.4 Hz), 4.72 (dd, 1H, J = 3.1 Hz, J = 6.2 Hz), 4.78 (d, 1H, J = 3.5 Hz), 5.82 (d, 1H, J = 3.5 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 18.8 (CH_2), 26.7 (CH_3), 27.1 (CH_3), 40.9 (CH_2), 53.7 (CH_2), 56.2 (C-5), 65.1 (CH_2), 78.1 (CH), 81.2 (CH), 96.4 (C), 98.9 (C), 107.9 (CH), 113.5 (C). MS (ES+) m/z 334.1 $(M + H)^+$. Anal. Calcd for $C_{13}H_{19}NO_7S$: C, 46.84; H, 5.74; N, 4.20. Found: C, 46.73; H, 5.64; N, 4.32.

(1*R*,2*R*,6*R*,8*R*,14*S*)-10,13-Diaza-4,4-dimethyl-16,16-dioxide-3,5,7,17-tetraoxa-16-thio-4,4-dimethylpentacyclo-[9.6.0.0$^{2-6}$.0$^{1-14}$.0$^{10-14}$]heptadecane (15). Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with 2-bromoethylamine hydrobromide (0.24 g, 1.1 mmol) and triethylamine (0.15 mL, 1.1 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:1) to give 0.03 g (45%) of **15** as a yellow syrup. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.31 (s, 3H), 1.47 (s, 3H), 2.82 (d, 1H, J = 13.5 Hz), 2.89−3.14 (m, 4H), 3.43 (dd, 1H, J = 3.1 Hz, J = 13.5 Hz), 3.60 (d, 1H, J = 13.5 Hz), 3.64 (d, 1H, J = 13.5 Hz), 4.55 (d, 1H, J = 3.1 Hz), 4.93 (d, 1H, J = 3.6 Hz), 5.70 (d, 1H, J = 3.6 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 27.0 (CH_3), 27.5 (CH_3), 46.2 (CH_2), 55.7 (CH_2), 56.5 (CH_2), 56.9 (CH_2), 80.6 (CH), 84.5 (CH), 94.5 (C), 100.3 (C), 107.2 (CH), 113.6 (C). MS (ES+) m/z 319.1 $(M + H)^+$. Anal. Calcd for $C_{12}H_{18}N_2O_6S$: C, 45.27; H, 5.70; N, 8.80. Found: C, 45.17; H, 5.94; N, 8.50.

(1*R*,2*R*,6*R*,8*R*,15*S*)-10,14-Aza-4,4-dimethyl-1-mesyloxy-3,5,7-trioxatetracyclo[7.6.0.0$^{2-6}$.0$^{10-15}$] pentadecane (16). Following the general procedure the cyclic enamine **2**[11] was treated "in situ" with 3-bromopropylamine hydrobromide (0.24 g, 1.1 mmol) and triethylamine (0.06 mL, 0.44 mmol). The residue was purified by CCTLC with hexane:ethyl acetate (1:1) to give 0.03 g (40%) of **16** as a yellow syrup. $[\alpha]^{20}_D$ +22.6 (*c* 1.7, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.36, 1.53 (2s, 6H), 1.73 (m, 2H), 3.18−3.39 (m, 8H), 3.69 (dd, 1H, J = 3.4 Hz, J = 10.7 Hz), 4.72 (d, 1H, J = 3.4 Hz), 4.94 (d, 1H, J = 3.6 Hz), 5.81 (d, 1H, J = 3.6 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 21.3 (CH_2), 28.3 (CH_3), 41.8 (CH_3), 44.6 (CH_2), 45.2 (CH_2), 55.8 (CH_2), 81.2 (CH), 83.2 (CH), 93.1 (C), 106.9 (CH), 125.2 (C), 155.7 (C=N). MS (ES+) m/z 333.1 $(M + H)^+$. Anal. Calcd for $C_{13}H_{20}N_2O_6S$: C, 46.98; H, 6.07; N, 8.43. Found: C, 47.24; H, 5.92; N, 8.33.

General Tandem Procedure for the Synthesis of Compounds 4, 13−16, and 18−25. To a solution of the 5-*O*-tosyl derivative **1**[11] (0.1 g, 0.22 mmol) in dry acetonitrile (2 mL) was added simultaneously DBU (0.067 mL, 0.44 mmol) and the corresponding nucleophile (1.1 mmol). Triethylamine (1.1 mmol) was additionally added for the synthesis of compounds **15**, **16**, and **24**. The solution was heated at 80 °C for 3 h. Solvent was evaporated and the residue was purified by CCTLC. The chromatography eluent has been previously described in this (for compounds **4** and **13**−**16**) and in a previous paper (for compounds **19**−**25**).[11] Yields of the isolated products are indicated in Table 1 for each protocol.

5-*O*-Ethyl-1,2-*O*-isopropylidene-3-spiro-5′-(4′-amino-1′,2′-oxathiole-2′,2′-dioxide)-α-D-ribofuranose (18). To a solution of the 5-*O*-tosyl derivative **1**[11] (0.1 g, 0.22 mmol) in ethanol (2 mL) was added DBU (0.067 mL, 0.44 mmol). The solution was heated at 80 °C for 3 h. Solvent was evaporated and the residue was purified by CCTLC with dichloromethane:methanol (10:1) to give 0.07 g (97%) of **18** as a white syrup. $[\alpha]^{20}_D$ +40.7 (*c* 0.25, $CHCl_3$). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.26 (t, 3H, J = 7.1 Hz), 1.34 (s, 3H), 1.51 (s, 3H), 3.55 (dd, 1H, J = 1.5 Hz, J = 12.0 Hz,), 3.68 (dd, 1H, J = 1.5 Hz, J = 12.0 Hz), 4.01 (q, 2H, J = 7.1 Hz), 4.42 (dd, 1H, J = 3.4 Hz, J = 12.0 Hz), 4.68 (d, 1H, J = 3.9 Hz), 4.86 (s, 1H), 5.00 (br s, 1H), 5.84 (d, 1H, J = 3.9 Hz), 7.00 (br s, 1H). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 15.0 (CH_3), 27.0 (CH_3), 27.2 (CH_3), 51.5 (CH_2), 65.4 (CH_2), 80.7 (CH), 82.1 (CH), 82.3 (CH), 89.6 (C), 106.4 (CH), 113.5 (C), 161.8 (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, 45.17; H, 6.08; N, 4.18.

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Supporting Information Available: General experimental methods, NMR procedures, X-ray crystal structure of **4** (CIF and tables), and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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