A flexible route to new spirodioxanes, oxathianes and morpholines

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Abstract

This work describes a modular efficient route to 10-aza-4-thia-, 10-aza-4-oxa-, and 10-oxa-4-thia-1,7-dioxaspiro[5.5]undecanes. The synthetic pathway relies upon the iterative nucleophilic substitution of 1,3-dichloropropan-2-one *O*-benzyloxime by solketal derivatives. The oxime key-intermediates, submitted to an acidic deprotection–spiroacetalization process, afforded these original spiroketal compounds in three steps, few purifications, and very good yields.

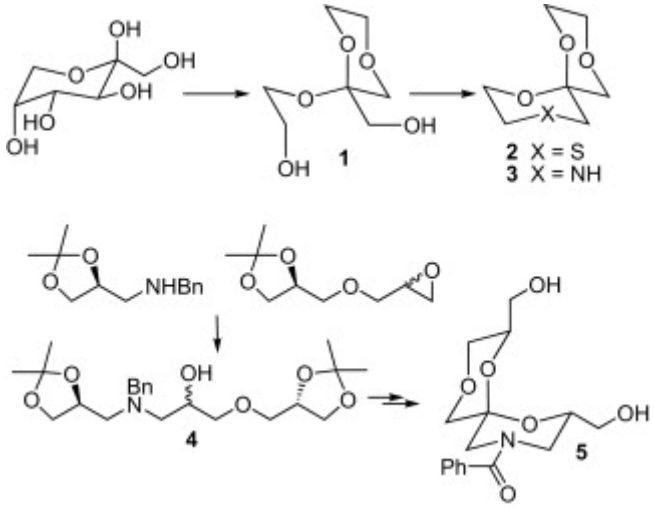
1. Introduction

Spiroketals are found as crucial substructures in a wide variety of natural compounds of diverse origins.[1], [1a], [1b], [1c] and [1d] Due to their broad spectrum of biological activities, these moieties have therefore attracted considerable synthetic interest leading to numerous strategies, which have been described and reviewed.[1], [1a], [1d], [2], [2a], [2b], [2c], [2d], [2e], [2f] and [2g]

Recently, it has been recognized that for spiroketal-containing drug compounds, the incorporation of a heteroatom at the C-4 position in one cycle of the spiranic core led to an enhancement of their activity. Thus, a series of new spiroketal derivatives possessing a nitrogen atom were evaluated as tachykinin antagonists; these spiromorpholino compounds showed a high affinity and excellent CNS penetration.[3], [3a] and [3b] By the same way, preparation of aza-[4] and [4b] or thia-[5] analogues of the GM_3 ganglioside lactone led to useful compounds that revealed hydrolytically stable immunogens. Lastly, the modification of the functionality of the tonghaosu skeleton afforded new substrates showing obvious antifeedant activity.[6], [6a] and [6b]

The main approach for the synthesis of spiroketal units involves (i) elaboration of a key acyclic keto-diol or its equivalent[7], [7a], [7b], [7c], [7d], [7e], [7f], [7g] and [7h] via intermolecular C–C bond formations followed by (ii) an intramolecular acid-catalyzed dehydrative ketalization. In this approach, the control of the stereochemistry of the anomeric center is usually based on the relative stabilities of the different isomers in the spiroketalization process: when maximum anomeric effects and minimum steric interactions are conjugated, a thermodynamically most favored isomer is formed as the almost sole product. However, although this strategy has been largely reported for the synthesis of numerous spiroketal skeletons, it has been rarely used for the elaboration of diheteroatom-containing spiroketals.

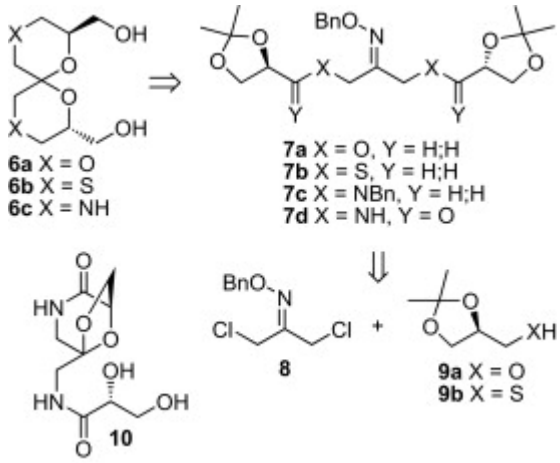
Indeed, and to our knowledge, only two syntheses of 1,7-dioxaspiro[5.5]undecanes incorporating heteroatoms at the C-4 and C-10 positions were reported (Scheme 1). The first one rested on the use of a d-fructose unit as chiral source.[8], [8a] and [8b] The authors employed a step-by-step nucleophilic substitution by chloroethanol followed by an oxidative fructose-ring opening to prepare the key intermediate **1**, from which the 10-thia- or the 10-aza-1,4,7-trioxaspiro[5.5]undecanes **2** and **3** were elaborated, once again, through nucleophilic displacements. The targeted spiroketals were thus isolated as sole isomers, in seven steps from fructose in 19% and 33% overall yields, respectively. This approach has not been extended to substituted derivatives, probably because of the choice of the starting material.



Scheme 1.

The second method[8c] consisted of the regioselective ring opening of the 2,2-dimethyl-4-[(oxiran-2-ylmethoxy)methyl]-1,3-dioxolane (obtained from solketal and epichlorohydrin) by the (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine, leading to the key alcohol **4**. Finally, oxidation and acid-catalyzed deprotection–spiroketalization conduced to the 10-aza-1,4,7-trioxaspiro[5.5]undecane **5** (seven steps, 22% overall yield) but only after modification of the nitrogen protective group. The use of an oxidation step in this synthetic scheme disfavored the direct introduction of a sulfur atom at C-4.

For our part, we have recently demonstrated[9] that the synthesis of 'symmetrical' new 1,4,7,10-tetraoxaspiro[5.5]undecane **6a** and 4,10-dithia-1,7-dioxaspiro[5.5]undecane **6b** could be efficiently achieved through a one-step acid-catalyzed deprotection–spiroketalization from the elaborated key oximes **7a**,**b**; these latter being readily synthesized by a one-step double substitution of 1,3-dichloropropan-2-one *O*-benzyloxime **8** by solketal **9a** or its thiol derivative **9b** (Scheme 2). Disappointingly, this synthetic pathway revealed ineffective to elaborate the biologically interesting 4,10-aza-1,7-dioxaspiro[5.5]undecane framework **6c** and led to the 3-aza-6,8-dioxabicyclo[3.2.1]octan-2-one **10** in place of the spiranic system (Scheme 2). With oxime **7c**, the presence of amine functions made critical the final spirocyclization and gave numerous by-products.[10]



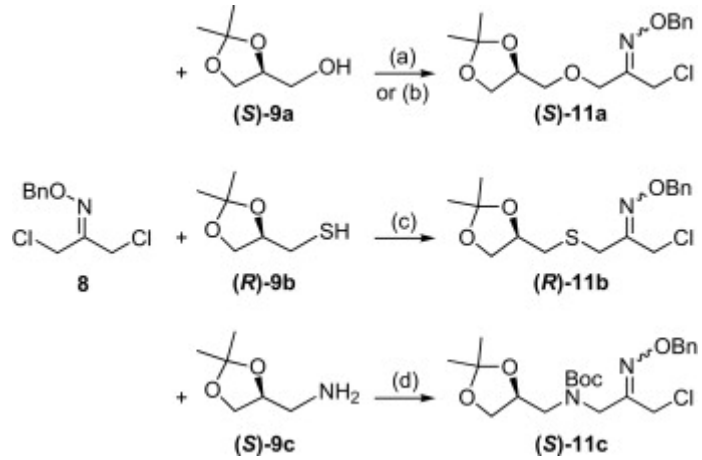
Scheme 2.

Nevertheless, and even if spirobismorpholines could not be obtained, we pursued the study of this strategy to elaborate this time 'dissymmetrical' spiroketals possessing different heteroatoms in C-4 and C-10 positions. In this paper, we would like to present our results toward the successful syntheses of three families of original compounds owning a 2,8-dihydroxymethyl-4-thia-1,7,10-trioxaspiro[5.5]undecane, a 2,8-dihydroxymethyl-10-aza-4-thia-1,7-dioxaspiro[5.5]undecane, and a 2,8-dihydroxymethyl-10-aza-1,4,7-trioxaspiro[5.5]undecane skeleton.

2. Results and discussion

The crucial point for the elaboration of these spiroketals was the efficient control of the monosubstitution of 1,3-dichloropropan-2-one *O*-benzyloxime **8** by solketal derivatives **9**.

In the conditions used for oxa- and thia-series **6a**,**b**—alkali hydrides treatment—mono-substituted oximes were detected during the TLC monitoring as the first product of the reaction but usually very fast accompanied with the disubstituted compounds.[9] We therefore undertook a study of the best operating conditions in terms of base, concentration *ratio*, solvent, and temperature to obtain oximes **11a**,**b** from **8** and **9a**,**b** and avoid the more favored double substitution. In all cases, reactions were TLC-monitored and quenched at the appearance of disubstituted oximes **7**. From alkali hydrides, best results were obtained by carrying out the reaction in tetrahydrofuran (1 mmol of **8**/3 mL of solvent) at 20 °C, with an addition of 1 equiv of alcohol **9a** or freshly prepared thiol **9b** on a mixture of oxime **8** and 2 equiv of alkali hydride. These conditions led to the expected chlorides **11a** and **11b** in 30% and 64% yields, respectively, accompanied with only 5–10% of the corresponding undesired *bi*-adduct **7a** or **7b**. Unreacted starting materials **9a** and **9b** could be recycled from flash column chromatography. In the case of **11a**, better yields— even if more wavering, from 40% to 60% yield—were obtained using a similar procedure as that previously described for the synthesis of 4-hydroxymethyl-1,3-dioxolane ethers:[11] namely, treatment of solketal by potassium hydroxide in toluene at 70 °C followed by the slow addition of an excess (1.5 equiv) of oxime **8** (Scheme 3).

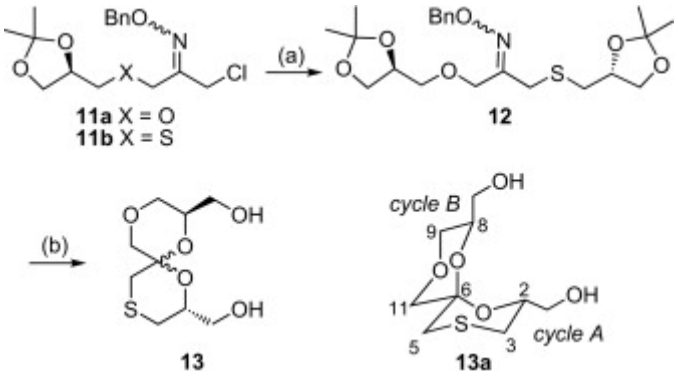


Scheme 3. Reagents and conditions: (a) KH (2 equiv), THF, 20 °C, 30%; (b) KOH (1 equiv), 18-C-6 (0.5 equiv), toluene, 70 °C, 40–60%; (c) NaH (2 equiv), THF, 20 °C, 64%; (d) two steps, 28% overall yield.[10]

Compound **11a** appeared as a mixture of *Z* and *E* isomers in a 1/1 *ratio* determined from the ^{1}H NMR spectrum, whereas compound **11b** was a mixture of the two isomers in a 3/2 *ratio* in favor of the *Z* one.[12]

Concerning the synthesis of 'aza-monooximes', our exploratory work in this area[10] has shown that nitrogen atoms implied in amine function (i.e., oxime **7c**, Scheme 2) hindered the final spiroketalization carried out under acidic conditions. Furthermore, the extensive study toward aza-substitution of oxime **8** allowed us to prepare the monochlorooxime **11c**[10] issued from **8** and the Boc-derivative of **9c** in a correct yield of 33% (Scheme 3). Consequently, this kind substrate had also been considered for the synthesis of new 'dissymmetrical' 4-aza-1,7-dioxaspiro[5.5]undecanes.

With the mono-substituted chlorooximes **11a**–**c** in hands, we engaged them in spiroketal synthesis. Considering our previous results in the symmetrical series, we first explored the access to 2,8-dihydroxymethyl-4-thia-1,7,10-trioxaspiro[5.5]undecane **13**. This was realized according to two parallel pathways using both **11a** and **11b** as key building blocks (Scheme 4). Thus, conversion of **11a**,**b** to the required oxime **12** was achieved using KH in tetrahydrofuran at 20 °C, and gave, after purification, oxime **12** in 86% yield (from **11a** and **7b**) and 54% yield (from **11b** and **7a**), respectively. Compound **12** appeared as a mixture of *Z* and *E* isomers (3/2 *ratio* determined on ^{1}H NMR spectrum) easily identified by the chemical shift of the methylene group in the α position of the benzyloxime function.[12] Lastly, oxime **12** was heated under reflux for 2 days in an acetone/water solution in the presence of Amberlyst® 15. In this case and as in 4,10-dithia-1,7-dioxaspiro[5.5]undecane series, the addition of 10 equiv of paraformaldehyde was necessary to achieve efficiently the ketone deprotection and promote the spiroketalization (Scheme 4). Spiroketal **13** was thus obtained in 79% yield as a mixture of two inseparable isomers **13a/13b** in a 19/1 *ratio* as determined on the quantitative ^{13}C NMR spectrum.



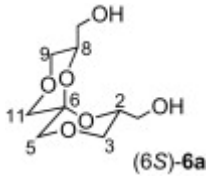
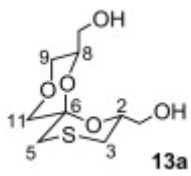
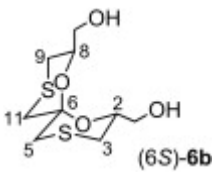
Scheme 4. Reagents and conditions: (a) KH, THF, **7b** or **7a**, 20 °C (86% from **11a**, 54% from **11b**); (b) Amberlyst® 15, $(CH_2O)_n$, acetone/H_2O (10:1), Δ, 48 h, 79%.

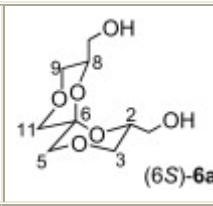
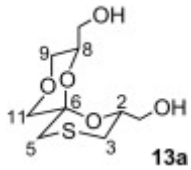
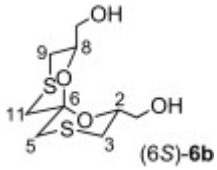
This result was in agreement with those observed in the symmetrical series.[9] Indeed, in our spirocyclisation acid-catalyzed conditions, dioxa-spiroketal **6a** (Scheme 1) was isolated as a sole isomer, possessing a *C*2 symmetry with a double anomeric effect, having two cycles in a chair conformation and the hydroxymethyl groups in an equatorial position. Conversely, we observed for dithia-spiroketal **6b** a loss of stereoselectivity due to the presence of the less electron-withdrawing sulfur atom. Thus, starting from enantiopure solketal **9a**, we isolated a mixture of two C-6 epimers.

The major isomer **13a** could be isolated and characterized after a classical TBDPS-protection/deprotection sequence. Its ^{13}C NMR spectrum comprised nine peaks with a spiranic carbon detected at 92.3 ppm (see Table 1). In the ^{1}H NMR spectrum, H-2 (δ=4.06 ppm) and H-8 (δ=4.02 ppm) exhibited vicinal coupling constants ^{3}J with H-3 and H-9 of 11.0 and 2.0 Hz, 11.0 and 2.5 Hz, respectively. Thus, **13a** adopted a chair conformation for its two cycles with H-2 and H-8 in an axial position. Moreover, structural data for **13a** fitted with those of (6*S*)-2,8-dihydroxymethyl-4,10-dithia-1,7-dioxaspiro[5.5]undecane **6b** for its A cycle and (6*S*)-2,8-dihydroxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane **6a** for its B cycle (see Table 1): for instance, C-3 was found at 27.5 ppm and C-9 at 68.7 ppm. The values of the chemical shifts of C-2 and C-8 in **13a**, are also similar to those observed in the symmetrical series. Because of the oxathiane–dioxane sequence, the chemical shifts of C-5 and C-11 were slightly modified and were observed, now, at 31.0 ppm and 72.9 ppm, respectively. Their corresponding hydrogens were shielded for H-5 and deshielded for H-11.

Table 1.

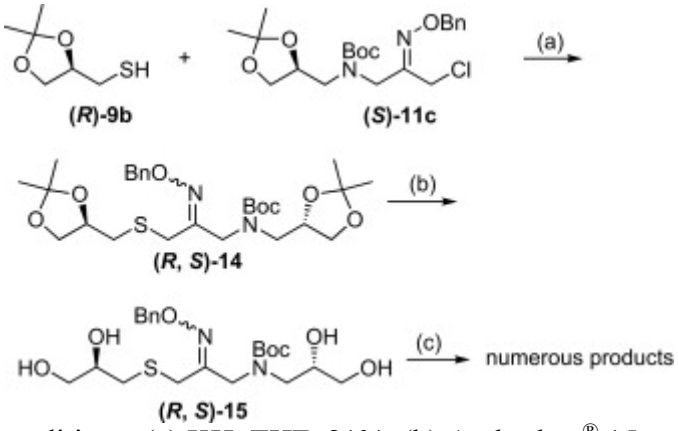
NMR data for 'symmetrical' and 'dissymmetrical' spirobisdioxanes **6a**,[9] spirobisoxathianes **6b**,[9] and spirodioxane–oxathiane **13a** (recorded at 400 MHz, measured in CD_3OD)

	 (6*S*)-**6a**		 **13a**		 (6*S*)-**6b**	
	δ_H, *J* in Hz	δ_C	δ_H, *J* in Hz	δ_C	δ_H, *J* in Hz	δ_C
2	4.03, dtd, 11.0, 5.0, 3.0	70.2	4.06, dddd, 11.0, 6.0, 5.0, 2.0	*72.0*	3.97, dt, 11.5, 5.0	*72.4*
3	3.37, t, 11.0; 3.80, dd, 11.0, 3.0	68.8	*2.37*, dt, 13.0, 2.0; *2.57*, dd, 13.0, 11.0	*27.5*	*2.37*, d, 11.5; *2.54*, t, 11.5	*27.8*
5	3.24, d, 11.5; 3.55, d, 11.5	69.6	2.31, dd, 13.5, 1.5; 2.68, d, 13.5	31.0	2.40, d, 13.5; 2.76, d, 13.5	35.2
6		93.0		92.3		91.9
8	4.03, dtd, 11.0, 5.0, 3.0	*70.2*	4.02, dtd, 11.0, 5.0, 2.5	*70.4*	3.97, dt, 11.5, 5.0	72.4

	 (6*S*)-**6a**		 **13a**		 (6*S*)-**6b**	
	δ_H, *J* in Hz	**δ_C**	**δ_H, *J* in Hz**	**δ_C**	**δ_H, *J* in Hz**	**δ_C**
9	*3.37*, t, 11.0; *3.80*, dd, 11.0, 3.0	*68.8*	*3.41*, t, 11.0; *3.84*, dd, 11.5, 2.5	*68.7*	2.37, d, 11.5; 2.54, t, 11.5	27.8
11	3.24, d, 11.5; 3.55, d, 11.5	69.6	3.34, d, 11.5; 3.62, d, 11.5	72.9	2.40, d, 13.5; 2.76, d, 13.5	35.2
CH_2OH	3.51, dd, 12.0, 5.0; 3.55, dd, 12.0, 5.0	62.9	3.49, dd, 11.5, 5.0; 3.56, dd, 11.5, 6.0	65.9	3.48, dd, 11.5, 5.0; 3.56, dd, 11.5, 5.0	65.9
CH_2OH	3.51, dd, 12.0, 5.0; 3.55, dd, 12.0, 5.0	62.9	3.57, dd, 12.0, 5.0; 3.60, dd, 12.0, 5.0	62.8	3.48, dd, 11.5, 5.0; 3.56, dd, 11.5, 5.0	65.9

From all these data, and as the configuration of C-2 and C-8 was governed by that of starting materials **9a** and **9b**, isomer **13a** adopted necessarily a structure stabilized by a double anomeric effect and equatorial positions for its substituents, with a (2*R*,6*S*,8*R*) configuration. Starting from 1,3-dichloropropan-2-one, this spiranic oxathiane–dioxane system was obtained in four steps, and 28–34% range overall yield depending of the order of introduction of oxa- and thia-synthons **9a**,**b**.

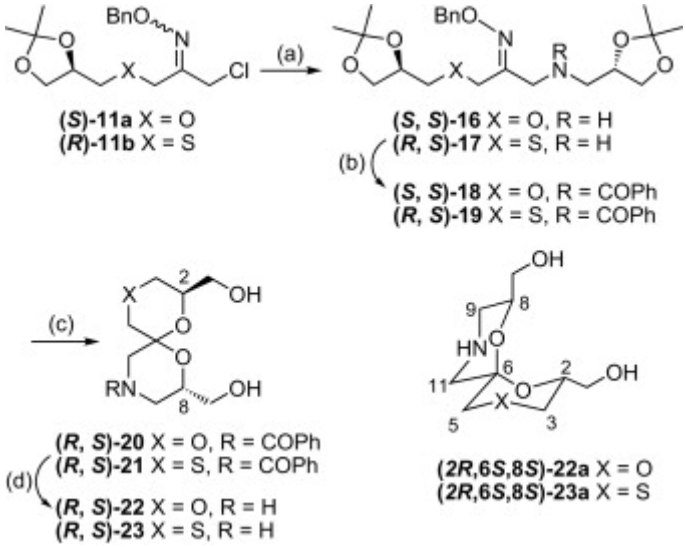
At this stage of the work, the examination of the more doubtful synthesis of aza-spiroketals remained unsolved. We began our investigation starting from the monochlorooxime **11c**, from which oxa- and thia-compounds could be envisioned. Substitution of **11c** by the thio-solketal **9b** was efficiently accomplished using KH in THF and furnished **14** in 81% yield (Scheme 5). The assignment of all signals in the ^1H and ^{13}C NMR spectra was in this case complicated by the existence of rotamers due to the carbamate group, together with the presence of the two *Z* and *E* isomers.



Scheme 5. Reagents and conditions: (a) KH, THF, 81%; (b) Amberlyst® 15, acetone/H_2O (10:1), Δ, 4 h, 33%; (c) Δ.

Treatment of **14** in our classical acidic medium afforded after 4 h at reflux the tetraol **15** as the sole product of the reaction. Pursuing the heating, we observed the disappearance of **14** (TLC monitoring) accompanied by the formation of numerous side-products lacking the Boc group in their skeleton (checked by ^1H NMR spectrum). At ambient temperature and even after 4 days, the oxime function of **15** remained unchanged.

At this stage, the reactivity of the Boc group under our acid-heating conditions, together with the trouble to obtain in good yields aza-protected chlorooximes **11**,[10] prompted us to investigate the synthesis of spiromorpholines from the monochlorooximes **11a**,**b**, testing their reactivity toward amine **9c** (Scheme 6).



Scheme 6. Reagents and conditions: (a) MeOH, Δ, **9c**, 8 h, 61% from **11a**, 67% from **11b**; (b) PhCOCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, 90% from **16**, 95% from **17**; (c) Amberlyst® 15, $(CH_2O)_n$, acetone/H_2O (10:1), Δ, 61% from **18**, 65% from **19**; (d) $LiAlH_4$, THF, nearly quantitative.

Oximes **11a**,**b** were heated in boiling methanol during 8 h in the presence of 3 equiv of amine **9c**. Under these conditions, only monosubstitution was observed, leading to oxime **16** in 61% yield as a mixture of *E*/*Z* isomers (5/3 *ratio* determined on the ^{1}H NMR spectrum) and oxime **17** in 67% yield as a 1/3 mixture of *E*/*Z* isomers. Compounds **16** and **17** were then treated by freshly distilled benzoylchloride in presence of NEt_3 and DMAP in dichloromethane to furnish the attempted amides **18** and **19** in 90% and 95% yields, respectively. The final deprotection–spiroketalization step was then carried out as usual, through the addition of paraformaldehyde to regenerate the keto-function. The targeted spiromorpholinoketals **20** and **21** were obtained in 61% and 65% yields, respectively. No other derivatives were detected in the crude reaction mixture.

Finally, compounds **20** and **21** were obtained from 1,3-dichloropropan-2-one in five steps in 17% and 26% overall yields, respectively. Full structural characterization of **20** and **21** could not be achieved at ambient temperature, as ^{1}H spectra were typical of coalescence phenomena and ^{13}C NMR spectra revealed mixtures of spiranic compounds. From ^{13}C NMR spectrum recorded at 70 °C, each compound, **20** and **21**, appeared clearly as a mixture of two inseparable isomers. The attribution of ^{13}C chemical shifts of the major and minor ones could be realized at this stage and, in the case of **20**, spectroscopic data were correlated with those already published in the literature.[8c]

To overcome the problem of coalescence and determine without ambiguity the structure of each major isomer of **20** and **21**, we reduced their amide function. The full cleavage of the amido group was efficiently accomplished using a large excess of $LiAlH_4$ in THF,[13], [13a] and [13b] furnishing the spiromorpholines **22** and **23** as, once again, a mixture of inseparable isomers in a 4/1 *ratio* for **22** and 9/1 *ratio* for **23**. Finally, major compounds could be isolated and characterized through their derivatization as silylether derivatives (TBDPS-protection/Bu_4NF deprotection).

Spiranic carbons of major isomers **22a** and **23a** were detected at 91.6 ppm (**22a**) and 90.9 ppm (**23a**). These values were once again in agreement with those observed for (6*S*)-spiro[5.5]undecane series. The C-3 and C-9 appeared at 67.2 ppm (**22a**)–66.2 ppm (**23a**) and 46.1 ppm (**22a** and **23a**), respectively. Major isomers adopted a chair conformation for the two cycles as evidenced by (i) H-9_{ax} and H-3_{ax} that were detected as triplets with ^2J=^3J=12.0 Hz, and (ii) H-9_{eq} and H-3_{eq} resonating either as broad doublets (^2J=12.0 Hz) or dedoubled doublet (^2J=12.0 Hz, ^3J=2.5 Hz). From all spectroscopic data, we assumed that majors isomers were the (2*R*,6*S*,8*S*)-**22a** and the (2*R*,6*S*,8*S*)-**23a**.

3. Conclusion

To summarize, we have developed an original and efficient pathway to new 1,7-dioxaspiro[5.5]undecanes incorporating in their skeleton two different heteroatoms in positions 4 and 10. Starting from commercially available (*S*)-solketal and 1,3-dichloropropan-2-one, we have shown that, in few steps and

with good overall yields, we were able to elaborate in a modular way, spiranic systems based on the association of dioxane–oxathiane, dioxane–morpholine, and oxathiane–morpholine cores. Finally, this work completed and generalized our previous study in the 'symmetrical' series, namely spirobisdioxane and spirobisoxathiane systems.

4. Experimental section

4.1. General experimental methods

Infrared spectra were recorded on a Perkin–Elmer 881 instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a BRUKER AC 400 spectrometer. Chemical shifts (δ values) are expressed in parts per million (ppm), coupling constants (J) are expressed in hertz, and multiplicities are mentioned as follows: s (singlet), d (doublet), t (triplet), q (quartet), Q (quintet), m (multiplet). NMR spectra were recorded in $CDCl_3$, CD_3OD or DMSO-d_6, using the solvent signals as reference. Mass spectra were recorded with a Hewlett Packard 5989B instrument and high resolution mass spectra (HRMS) were performed with a Q-TOF micromass. Chromatography was performed using silica gel 60 (230–400 mesh) and thin layer chromatography (TLC) was performed on silica gel $60PF_{254}$ plates (20×20 cm). Compounds were identified using UV fluorescence (λ=254 nm) and/or staining with a 5% phosphomolybdic acid solution in ethanol following by heating. Commercially reagents (Aldrich, Acros, Lancaster) were used as received without additional purification. Tetrahydrofuran (THF) was distilled from potassium/benzophenone while dichloromethane (CH_2Cl_2) was dried over calcium hydride prior to use.

4.2. Synthesis

4.2.1. (2*E*)- and (2*Z*)-1-Chloro-3-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}propanone *O*-benzyloxime (11a)

Method A. To a solution of oxime **8** (2.11 g, 9.1 mmol) and KH (2.44 g, 18.2 mmol) in THF (3 mL) was added (*S*)-**9a** (1.21 g, 9.1 mmol) and the resulting mixture was stirred until disubstituted compound was detected on TLC. The reaction was stopped by addition of a saturated solution of NH_4Cl. After extraction with ethyl acetate, the crude solution was concentrated in vacuo and purified by flash chromatography using (19:1→7:3) cyclohexane/ethyl acetate as eluent to give pure **11a** as a colorless liquid (0.90 g, 30%).
Method B. To a solution of (*S*)-**9a** (0.330 g, 2.5 mmol) in toluene (10 mL) were added KOH (0.165 g, 2.5 mmol) and 18-crown-6 (0.330 g, 1.25 mmol). The resulting mixture was heated at 70 °C for 1 h before addition, at 70 °C and over a period of 1 h, of a solution of oxime **8** (0.580 g, 2.5 mmol) in toluene (5 mL). At the appearance of disubstituted compound, reaction is stopped by addition of water. The resulting mixture is concentrated in vacuo and layers were separated. After extraction of the aqueous one by ethyl acetate, the combined organic layers are dried and concentrated. A final purification by flash chromatography using (4:1→1:1) cyclohexane/ethyl acetate as eluent furnished pure **11a** in a 40–60% yield.
*Compound **11a***: IR ν_{max} (neat, cm^{-1}) 1600 (C═N), 1250–1040 (C–O); ^{1}H NMR ($CDCl_3$) δ/ppm 7.40–7.30 (m, 10H, H–Ar, *E* and *Z*), 5.17 (s, 2H, CH_2Ph, *Z*), 5.11 (s, 2H, CH_2Ph, *E*), 4.48 (d, *J*=15.0 Hz, 1H, O–CH_2–C═, *E*), 4.44 (d, *J*=15.0 Hz, 1H, O–CH_2–C═, *E*), 4.27 (Q, *J*=6.0 Hz, 1H, CH–O, *E*), 4.26 (m, 1H, CH–O, *Z*), 4.23 (d, *J*=11.5 Hz, 1H, CH_2Cl, *E*), 4.21 (d, *J*=11.5 Hz, 1H, CH_2Cl, *E*), 4.21 (m, 2H, O–CH_2–C═, *Z*), 4.20 (m, 1H, CH_2Cl, *Z*), 4.19 (d, *J*=11.5 Hz, 1H, CH_2Cl, *Z*), 4.05 (t, *J*=7.0 Hz, 1H, CH_2–O, *E*), 4.03 (t, *J*=6.5 Hz, 1H, CH_2–O, *Z*), 3.77 (dd, *J*=8.0, 6.5 Hz, 1H, CH_2–O, *E*), 3.70 (dd, *J*=8.0, 6.5 Hz, 1H, CH_2–O, *Z*), 3.55 (dd, *J*=10.0, 5.5 Hz, 1H, CHO–CH_2O, *E*), 3.50 (dd, *J*=10.0, 5.0 Hz, 1H, CHO–CH_2O, *E*), 3.49 (dd, *J*=10.0, 5.5 Hz, 1H, CHO–CH_2O, *Z*), 3.44 (dd, *J*=10.0, 5.0 Hz, 1H, CHO–CH_2O, *Z*), 1.42 (s, 6H, Me, *E* and *Z*), 1.36 (s, 6H, Me, *E* and *Z*); ^{13}C NMR ($CDCl_3$) δ/ppm 154.9 (C═N, *E*), 152.4 (C═N, *Z*), 137.1 (C–Ar, *Z*), 137.0 (C–Ar, *E*), 128.4 (C–Ar, *Z* and *E*), 128.1 (C–Ar, *Z*), 128.0 (C–Ar, *E*), 127.9 (C–Ar, *Z* and *E*), 109.5 (C–$(CH_3)_2$, *E*), 109.4 (C–$(CH_3)_2$, *Z*), 76.7 (CH_2Ph, *E*), 76.5 (CH_2Ph, *Z*), 74.4 (*C*H–O, *E*), 74.3 (*C*H–O, *Z*), 72.3 (CHO–CH_2O, *E*), 71.3 (CHO–CH_2O, *Z*), 69.3 (O–CH_2–C═, *Z*), 66.5 (CH_2–O, *E* and *Z*), 63.9 (O–CH_2–C═, *E*), 41.1 (CH_2Cl, *E*), 32.7 (CH_2Cl, *Z*), 26.7 (CH_3, *E*), 26.6 (CH_3, *Z*), 25.3 (CH_3, *Z* and *E*). Anal. Calcd for $C_{16}H_{22}ClNO_4$: C, 58.62; H, 6.76; Cl, 10.82; N, 4.27. Found C, 58.57; H, 6.79; Cl, 10.72; N, 4.25.

4.2.2. (2*E*)- and (2*Z*)-1-Chloro-3-({[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}thio)propanone *O*-benzyloxime (11b)

To a solution of oxime **8** (0.254 g, 1.1 mmol) and NaH (0.090 g, 2.2 mmol) in THF (3 mL) was added (*R*)-**9b** (0.200 g, 1.1 mmol) and the resulting mixture was stirred until disubstituted compound was detected on TLC. The reaction was stopped by addition of a saturated solution of NH_4Cl (2 mL). After extraction with ethyl acetate, the crude solution was concentrated in vacuo and purified by flash chromatography using (19:1→4:1) cyclohexane/ethyl acetate as eluent to give pure **11b** as a colorless oil (0.255 g, 64%). IR ν_{max} (neat, cm^{-1}) 1618 (C═N), 1250–1040 (C–O); ^1H NMR ($CDCl_3$) δ/ppm 7.38–7.30 (m, 10H, H–Ar, *E* and *Z*), 5.14 (s, 2H, CH_2Ph, *Z*), 5.11 (s, 2H, CH_2Ph, *E*), 4.37 (s, 2H, CH_2Cl, *Z*), 4.29 (d, *J*=11.5 Hz, 1H, CH_2Cl, *E*), 4.26 (d, *J*=11.5 Hz, 1H, CH_2Cl, *E*), 4.19 (Q, *J*=6.0 Hz, 1H, CH–O, *E*), 4.17 (Q, *J*=6.0 Hz, 1H, CH–O, *Z*), 3.99 (dd, *J*=8.5, 6.0 Hz, 1H, CH_2–O, *Z*), 3.95 (dd, *J*=8.5, 6.0 Hz, 1H, CH_2–O, *E*), 3.60 (d, *J*=13.5 Hz, 1H, S–CH_2–C═, *E*), 3.55 (d, *J*=13.5 Hz, 1H, S–CH_2–C═, *E*), 3.59 (dd, *J*=8.5, *J*=6.0 Hz, 1H, CH_2–O, *E*), 3.57 (dd, *J*=8.5, 6.0 Hz, 1H, CH_2–O, *Z*), 3.40 (d, *J*=14.0 Hz, 1H, S–CH_2–C═, *Z*), 3.37 (d, *J*=14.0 Hz, 1H, S–CH_2–C═, *Z*), 2.63 (dd, *J*=13.5, 6.0 Hz, 1H, CH–CH_2S, *E*), 2.56 (dd, *J*=13.5, 6.5 Hz, 1H, CH–CH_2S, *Z*), 2.52 (dd, *J*=13.5, 6.5 Hz, 1H, CH–CH_2S, *E*), 2.45 (dd, *J*=13.5, 6.0 Hz, 1H, CH–CH_2S, *Z*), 1.41 (s, 3H, Me, *Z*), 1.40 (s, 3H, Me, *E*), 1.34 (s, 3H, Me, *Z*), 1.32 (s, 3H, Me, *E*); ^{13}C NMR ($CDCl_3$) δ/ppm 153.4 (C═N, *E*), 152.0 (C═N, *Z*), 137.3 (C–Ar, *Z*), 136.7 (C–Ar, *E*), 128.4 (C–Ar, *Z* and *E*), 128.1 (C–Ar, *E*), 128.0 (C–Ar, *Z*), 127.9 (C–Ar, *Z* and *E*), 109.5 (C–$(CH_3)_2$, *Z* and *E*), 76.6 (CH_2Ph, *E*), 76.4 (CH_2Ph, *Z*), 74.9 (CH–O, *Z*), 74.8 (CH–O, *E*), 68.6 (CH_2–O, *Z*), 68.5 (CH_2–O, *E*), 42.5 (CH_2Cl, *E*), 35.1 (CHO–*C*H_2S, *E*), 34.0 (CHO–*C*H_2S, *Z*), 33.7 (CH_2Cl, *Z*), 32.9 (S–*C*H_2–C═, *Z*), 26.9 (CH_3, *Z* and *E*), 25.5 (CH_3, *Z*), 25.4 (CH_3, *E*), 24.4 (S–*C*H_2–C═, *E*); HRMS (ESI): calculated for $C_{16}H_{22}ClNO_3Na$ $[M+Na]^+$ 366.0907, found 366.0892.

4.2.3. (2*Z*)- and (2*E*)-1-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}-3-({[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}thio)propanone *O*-benzyloxime (12)

To a pre-washed KH (1.35 g, 10.4 mmol) solution in THF (10 mL) was added, under argon, thiol (*R*)-**9b** (0.850 mg, 5.7 mmol) in THF (10 mL) followed after 15 min by a solution of **11a** (1.70 g, 5.2 mmol) in THF (20 mL). After the completion of the reaction (disappearance of **11a**), water was added and the resulting solution was extracted with dichloromethane. The organic layer was concentrated in vacuo and purified by flash chromatography using (9:1) cyclohexane/ethyl acetate to give **12** (2.0 g, 86%) as a colorless oil of a mixture of *Z* and *E* isomers.

The same protocol applied to **11b** (0.200 g, 0.58 mmol) and (*S*)-solketal **9a** (0.092 mg, 0.70 mmol) using KH (0.155 g, 1.16 mmol) gave, after purification, **12** (0.138 g, 54%).

*Compound **12***: IR ν_{max} (neat, cm^{-1}) 1600 (C═N), 1250–1050 (C–O); ^1H NMR ($CDCl_3$) δ/ppm 7.40–7.25 (m, 10H, H–Ar, *E* and *Z*), 5.09 (s, 2H, CH_2Ph, *Z*), 5.06 (s, 2H, CH_2Ph, *E*), 4.46 (d, *J*=15.0 Hz, 1H, O–CH_2–C═N, *E*), 4.43 (d, *J*=15.0 Hz, 1H, O–CH_2–C═N, *E*), 4.25 (Q, *J*=6.0 Hz, 1H, CH–O, *E*), 4.24 (Q, *J*=6.0 Hz, 1H, CH–O, *Z*), 4.20 (Q, *J*=6.5 Hz, 1H, CH–O, *Z*), 4.20 (d, *J*=12.0 Hz, 1H, O–CH_2–C═N, *Z*), 4.18 (Q, *J*=6.0 Hz, 1H, CH–O, *E*), 4.17 (d, *J*=12.0 Hz, 1H, O–CH_2–C═N, *Z*), 4.03 (dd, *J*=8.5 and 6.5 Hz, 1H, O–CH_2–CHO, *E*), 4.02 (dd, *J*=8.5 and 6.5 Hz, 1H, O–CH_2–CHO, *Z*), 4.00 (dd, *J*=8.5 and 6.0 Hz, 1H, O–CH_2–CHO, *E*), 3.95 (dd, *J*=8.5 and 6.0 Hz, 1H, O–CH_2–CHO, *Z*), 3.74 (dd, *J*=8.5 and 6.5 Hz, 1H, O–CH_2–CHO, *E*), 3.68 (dd, *J*=8.5 and 6.5 Hz, 1H, O–CH_2–CHO, *Z*), 3.59 (dd, *J*=8.5 and 6.5 Hz, 2H, O–CH_2–CHO, *E* and *Z*), 3.53 (dd, *J*=10.0 and 5.5 Hz, 1H, CHO–CH_2–O–CH_2–, *E*), 3.48 (d, *J*=13.5 Hz, 1H, S–CH_2–C═N, *Z*), 3.48 (dd, *J*=10.0 and 5.5 Hz, 1H, CH_2–OCH_2C═N, *E*), 3.47 (dd, *J*=10.0 and 6.0 Hz, 1H, CH_2–OCH_2C═N, *Z*), 3.46 (d, *J*=13.5 Hz, 1H, S–CH_2–C═N, *Z*), 3.42 (dd, *J*=10.0 and 5.0 Hz, 1H, CH_2–OCH_2C═N, *Z*), 3.34 (d, *J*=13.5 Hz, 1H, S–CH_2–C═N, *E*), 3.30 (d, *J*=13.5 Hz, 1H, S–CH_2–C═N, *E*), 2.68 (dd, *J*=13.5 and 6.0 Hz, 1H, S–CH_2–CHO, *Z*), 2.62 (dd, *J*=13.5 and 6.0 Hz, 1H, S–CH_2–CHO, *E*), 2.55 (dd, *J*=13.5 and 6.5 Hz, 1H, S–CH_2–CHO, *Z*), 2.49 (dd, *J*=13.5 and 6.5 Hz, 1H, S–CH_2–CHO, *E*), 1.41 (s, 9H, Me), 1.40 (s, 3H, Me), 1.35 (s, 6H, Me), 1.34 (s, 3H, Me), 1.32 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ/ppm 155.9 (C═N, *E*), 154.6 (C═N, *Z*), 137.6 (C–Ar, *E*), 137.1 (C–Ar, *Z*), 128.4 (C–Ar, *Z* and *E*), 128.3 (C–Ar, *Z*), 128.2 (C–Ar, *Z*), 128.0 (C–Ar, *E*), 127.9 (C–Ar, *E*), 109.5 (*C*–$(CH_3)_2$, *Z*),109.4 (*C*–$(CH_3)_2$, *E*), 76.2 (CH_2Ph *Z*), 76.1 (CH_2Ph, *E*), 74.9 (CH–O, *E*), 74.8 (CH–O, *Z*), 74.5 (CH–O, *Z*), 74.4 (CH–O, *E*), 72.2 (CHO–*C*H_2O, *E*), 71.2 (CHO–*C*H_2O, *Z*), 69.4 (O–*C*H_2–C═N, *Z*), 68.8 (O–*C*H_2–CHO, *E*), 68.6 (O–*C*H_2–CHO, *Z*), 66.5 (O–*C*H_2–CHO, *Z* and *E*), 64.5 (O–*C*H_2–C═N, *E*), 35.2 (S–*C*H_2–CHO, *Z*), 34.1 (S–*C*H_2–CHO, *E*), 31.2 (N═C–*C*H_2–S, *E*), 26.9 (CH_3, *Z* and *E*), 26.7 (CH_3, *Z* and *E*), 25.6 (CH_3, *Z* and *E*), 25.4 (CH_3, *E*), 25.3 (CH_3, *Z*), 24.5 (N═C–*C*H_2–S, *Z*). Anal. Calcd for $C_{22}H_{33}NO_6S$: C, 60.11; H, 7.57; N, 3.1. Found: C, 60.21; H, 7.51; N, 3.29.

4.2.4. 2,8-Dihydroxymethyl-4-thia-1,7,10-trioxaspiro-[5.5]undecane (13)

A solution of (*S*,*R*)-**12** (0.500 g, 1.14 mmol) in 10 mL of a mixture (10:1, v/v) of acetone/water, Amberlyst®15 (0.250 g), and paraformaldehyde (0.034 g, 1.14 mmol) was heated under reflux for 48 h. After cooling, the mixture was filtered on a Celite® pad. The residue was purified by column chromatography on silica gel using gradient (1:0→49:1) ethyl acetate/methanol as eluent, which gave a 19:1 mixture of isomers **13** (0.185 g, 79%). IR ν_{max} (neat, cm^{-1}) 3400 (O–H); ^{13}C NMR (CD_3OD) δ/ppm 107.0–92.3 (C-6), 75.6–72.9 (C-11), 75.9–72.0 (C-2), 72.1–70.4 (C-8), 74.4–68.7 (C-9), 65.9 (C-12), 64.3–62.8 (C-13), 32.2–31.0 (C-5), 29.8–27.5 (C-3).

Major compound: (2*R*,6*S*,8*R*)-**13a**: ^1H NMR ($CDCl_3$) δ/ppm 4.06 (dddd, J_{2ax3ax}=11.0 Hz, J_{2ax12a}=6.0 Hz, J_{2ax12b}=5.0 Hz, J_{2ax3eq}=2.0 Hz, 1H, H-2_{ax}), 4.02 (dtd, J_{8ax9ax}=11.0 Hz, J_{8ax13}=5.0 Hz, J_{8ax9eq}=2.5 Hz, 1H, H-8_{ax}), 3.84 (dd, J_{9eq9ax}=11.5 Hz, J_{9eq8ax}=2.5 Hz, 1H, H-9_{eq}), 3.62 (d, $J_{11eq11ax}$=11.5 Hz, 1H, H-11_{eq}), 3.60 (dd, J_{13a13b}=12.0 Hz, J_{13a8}=5.0 Hz, 1H, H-13a), 3.57 (dd, J_{13b13a}=12.0 Hz, J_{13b8}=6.0 Hz, 1H, H-13b), 3.56 (dd, J_{12a12b}=11.5 Hz, J_{12a2}=6.0 Hz, 1H, H-12a), 3.49 (dd, J_{12b12a}=11.5 Hz, J_{12b2}=5.0 Hz, 1H, H-12b), 3.41 (t, J_{9ax9eq}=J_{9ax8ax}=11.0 Hz, 1H, H-9_{ax}), 3.34 (d, $J_{11ax11eq}$=11.5 Hz, 1H, H-11_{ax}), 2.68 (d, J_{5ax5eq}=13.5 Hz, 1H, H-5_{ax}), 2.57 (dd, J_{3ax3eq}=13.0 Hz, J_{3ax2ax}=11.0 Hz, 1H, H-3_{ax}), 2.37 (dt, J_{3eq3ax}=13.0 Hz, J_{3eq2ax}=J_{3eq5eq}=2.0 Hz, 1H, H-3_{eq}), 2.31 (dd, J_{5eq5ax}=13.5 Hz, J_{5eq3eq}=1.5 Hz, 1H, H-5_{eq}); ^{13}C NMR ($CDCl_3$) δ/ppm 92.3 (C-6), 72.9 (C-11), 72.0 (C-2), 70.4 (C-8), 68.7 (C-9), 65.9 (C-12), 62.8 (C-13), 31.0 (C-5), 27.5 (C-3); HRMS (ESI): calculated for $C_9H_{16}O_5NaS$ $[M+Na]^+$ 259.0616, found 259.0620.

4.2.5. *tert*-Butyl {[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}(3-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}thio)-{2-[(benzyloxy)imino]propyl}carbamate (14)

To a suspension of KH (0.125 g, 0.92 mmol) in mineral oil, was added, under argon, a solution of (*S*)-**11c** (0.200 g, 0.46 mmol) in THF (3 mL), followed, after 30 min, by a solution of thiol (*R*)-**9b** (0.082 mg, 0.55 mmol) in THF (1 mL). The reaction was monitored by TLC. After adjunction of water, the mixture was extracted with dichloromethane (3×10 mL) and the organic extracts combined before being dried ($MgSO_4$), filtered, and then the solvent was removed using a rotary evaporator. The residue was purified by flash chromatography on silica gel using (1:0→4:1) cyclohexane/ethyl acetate as an eluent to give **14** as a mixture of two rotamers (0.200 g, 81%, colorless oil). IR ν_{max} (neat, cm^{-1}) 1697 (C═O), 1250–1060 (C–O); ^1H NMR ($CDCl_3$) δ/ppm 7.36–7.27 (m, 10H, H–Ar), 5.08 (s, 2H, CH_2Ph), 5.06 (s, 2H, CH_2Ph), 4.41–4.28 (m, 4H, CH_2S), 4.21 (m, 2H, C*H*O–CH_2N), 4.17 (Q, *J*=6.5 Hz, 2H, SCH_2–C*H*O), 3.98 (dd, ^2J=8.5 Hz, ^3J=6.0 Hz, 2H, CH_2O), 4.02–3.95 (m, 2H, CH_2O), 3.59 (dd, ^2J=8.5 Hz, ^3J=6.5 Hz, 2H, CH_2O), 3.56 (dd, ^2J=8.5 Hz, ^3J=6.5 Hz, 2H, CH_2O), 3.45–3.25 (m, 4H, O–CH–CH_2N), 3.22 (s, 2H, NCH_2), 3.18 (s, 2H, NCH_2), 2.58 (dd, ^2J=13.5 Hz, ^3J=6.0 Hz, 2H, SCH_2), 2.46 (dd, ^2J=13.5 Hz, ^3J=6.5 Hz, 2H, SCH_2), 1.44 (s, 9H, *t*-Bu), 1.42 (s, 6H, Me), 1.41 (s, 6H, Me), 1.39 (s, 9H, *t*-Bu), 1.34 (s, 6H, Me), 1.33 (s, 6H, Me); ^{13}C NMR ($CDCl_3$) δ/ppm 155.5 (CO_2*t*-Bu), 155.4 (CO_2*t*-Bu), 155.0 (C═N), 137.7 (C–Ar), 128.3 (C–Ar), 128.1 (C–Ar), 127.8 (C–Ar), 109.5 (C–$(CH_3)_2$), 109.3 (C–$(CH_3)_2$), 80.7 (C–$(CH_3)_3$), 80.5 (C–$(CH_3)_3$), 76.2 (CH_2Ph), 76.1 (CH_2Ph), 75.1 (CHO), 74.9 (CHO), 68.7 (CH_2O), 67.2 (CH_2O), 67.1 (CH_2O), 51.0 (CH_2N), 50.7 (CH_2N), 44.1 (NCH_2), 44.0 (NCH_2), 34.0 (SCH_2), 33.8 (SCH_2), 32.6 (CH_2S), 32.0 (CH_2S), 28.3 (*t*-Bu), 26.9 (CH_3), 26.8 (CH_3), 25.6 (CH_3), 25.5 (CH_3); HRMS (ESI): calculated for $C_{27}H_{42}N_2O_7NaS$ $[M+Na]^+$ 561.2610, found 561.2603.

4.2.6. *tert*-Butyl [(2*S*)-2,3-dihydroxypropyl]3-{[(2*R*)-2,3-dihydroxypropyl]thio}-{2-[(benzyloxy)imino]propyl}carbamate (15)

To a solution of (*S*,*R*)-**14** (0.050 g, 0.093 mmol) in a mixture of acetone/water (10:1 (v:v), 600 µL) was added Amberlyst® 15 (0.023 g). After stirring at reflux for 4 h, the solution was filtered on a Celite® pad and concentrated. The residue was purified by flash chromatography on silica gel using ethyl acetate as eluent to give pure (*S*, *R*)-**15** (0.014 g, 33%) as a colorless oil. ^1H NMR ($CDCl_3$) two isomers *E* (min) and *Z* (maj) δ/ppm 7.38–7.26 (m, 10H, H–Ar, *Z* and *E*), 5.08 (s, 2H, CH_2Ph, *E*), 5.07 (s, 2H, CH_2Ph, *Z*), 4.42 (d, *J*=16.0 Hz, 1H, CH_2S, *Z*), 4.30–4.15 (m, 3H, CH_2S, *Z* and *E*), 3.82 (m, 2H, CHO–CH_2N, *Z* and *E*), 3.73 (Q, *J*=6.0 Hz, 1H, C*H*O–CH_2S, *Z*), 3.68 (Q, *J*=5.5 Hz, 1H, C*H*O–CH_2S, *E*), 3.54–3.41 (m, 10H, CH_2O, *Z* and *E*, CH_2N and NCH_2), 3.37–3.30 (m, 3H, CH_2N and NCH_2), 3.28–3.10 (m, 3H, CH_2N and NCH_2), 2.67 (m, 1H, SCH_2, *E*), 2.56 (m, 1H, SCH_2, *E*), 2.56 (dd, ^2J=14.0 Hz, ^3J=7.0 Hz, 1H, SCH_2, *Z*), 2.44 (dd, ^2J=14.0 Hz, ^3J=7.0 Hz, 1H, SCH_2, *Z*); ^{13}C NMR (CD_3OD) δ/ppm 157.0 and 156.8 (CO_2*t*-Bu, *Z*), 155.6 (C═N, *Z*), 155.4 (C═N, *E*), 153.8 and 153.7 (CO_2*t*-Bu, *E*), 139.3 (C–Ar, *E*), 139.1 (C–Ar, *Z*), 129.4 (C–Ar, *Z* and *E*), 129.2 (C–Ar, *Z*), 129.1 (C–Ar, *E*), 128.9 (C–Ar, *Z* and *E*), 81.8 and 81.7 (C–$(CH_3)_3$), 77.2 (CH_2Ph, *E*), 77.1 (CH_2Ph, *Z*), 72.3 (SCH_2–*C*HO, *Z*), 72.2 (SCH_2–*C*HO, *E*), 71.8 and 71.7 (NCH_2–*C*HO), 66.1 (SCH_2CH–*C*H_2O, *E*), 66.0 (SCH_2CH–*C*H_2O, *Z*), 65.4 (NCH_2CH–*C*H_2O, *E*), 65.1 (NCH_2CH–*C*H_2O, *Z*), 53.2 (N*C*H_2CH–CH_2O, *E*), 52.4 (N*C*H_2CH–CH_2O, *Z*), 51.1 and 50.8 (N═*C*CH_2S),

46.2 and 45.8 (N=C*C*H$_2$S), 36.9 and 36.7 (S*C*H$_2$–CHO, *E*), 35.5 and 35.3 (N=C*C*H$_2$N, *Z*), 33.5 and 33.1 (N=CH$_2$, *Z*), 28.7 (CH$_3$), 26.6 and 26.2 (CH$_3$).

4.2.7. (2*E*)- and (2*Z*)-1-({[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}amino)-3-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}propanone *O*-benzyloxime (16)

To a solution of (*S*)-**11a** (0.166 g; 0.51 mmol) in anhydrous methanol (1.5 mL) was added a solution of amine (*S*)-**9c** (0.200 g; 1.53 mmol) in methanol (0.5 mL). The resulting mixture was heated at reflux for 4 h. The solvent was then concentrated and a saturated aqueous $NaHCO_3$ (10 mL) solution was added. The mixture was extracted with dichloromethane (3×10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography using (7:3) ethyl acetate/cyclohexane as eluent to give **16** as a yellow oil (0.132 g, 61%). IR ν_{max} (neat, cm^{-1}) 3345 (N–H), 1590 (C=N), 1255–1050 (C–O); ^{1}H NMR ($CDCl_3$) δ/ppm 7.35–7.26 (m, 10H, H–Ar, *E* and *Z*), 5.09 (s, 2H, CH$_2$Ph, *E*), 5.06 (s, 2H, CH$_2$Ph, *Z*), 4.43 (d, ^2J=15.5 Hz, 1H, O–C*H*$_2$–C=N, *Z*), 4.40 (d, ^2J=15.5 Hz, 1H, O–C*H*$_2$–C=N, *Z*), 4.27–4.15 (m, 4H, H–CHO, *E* and *Z*), 4.14 (d, ^2J=12.0 Hz, 1H, O–C*H*$_2$–C=N, *E*), 4.12 (d, ^2J=12.0 Hz, 1H, O–C*H*$_2$–C=N, *E*), 4.05–3.96 (m, 4H, CHO–CH$_2$O, *Z* and *E*), 3.72 (dd, $^2J'$=8.0 Hz, ^3J=6.5 Hz, 1H, O–C*H*$_2$–CHO, *Z*), 3.67 (dd, ^2J=8.5 Hz, ^3J=6.5 Hz, 1H, O–C*H*$_2$–CHO, *E*), 3.62 (dd, ^2J=8.0 Hz, ^3J=7.0 Hz, 2H, NHCH$_2$CH–C*H*$_2$O, *E* and *Z*), 3.58 (d, ^2J=15.0 Hz, 1H, CH$_2$NH, *E*), 3.57 (d, ^2J=15.0 Hz, 1H, CH$_2$NH, *E*), 3.53–3.40 (m, 6H, C*H*$_2$–O–CH$_2$C=N, *E* and *Z*, =C–C*H*$_2$NH, *Z*), 2.72–2.62 (m, 4H, NH–C*H*$_2$, *Z* and *E*), 1.91 (br s, 2H, NH, *E* and *Z*), 1.40 and1.38 (s, 12H, Me, *Z* and *E*), 1.34 and 1.33 (s, 12H, Me, *Z* and *E*); ^{13}C NMR ($CDCl_3$) δ/ppm 156.9 (C=N, *Z*), 156.6 (C=N, *E*), 137.6 (C–Ar, *Z*), 137.5 (C–Ar, *E*), 128.3 (C–Ar, *Z* and *E*), 128.0 (C–Ar, *Z* and *E*), 127.8 (C–Ar, *Z* and *E*), 109.4 (C–(CH$_3$)$_2$, *Z* and *E*), 109.0 (C–(CH$_3$)$_2$, *Z* and *E*), 76.0 (CH$_2$Ph, *Z* and *E*), 75.3 (NHCH$_2$*C*HO, *Z*), 75.1 (NHCH$_2$*C*HO, *E*), 74.4 (*C*HOCH$_2$O, *E*), 74.3 (*C*HOCH$_2$O, *Z*), 72.3 (CHO*C*H$_2$O, *Z*), 71.2 (CHO*C*H$_2$O, *E*), 70.6 (O–*C*H$_2$–C=N, *E*), 67.5 (NHCH$_2$CHO*C*H$_2$, *Z*), 67.4 (NHCH$_2$CHO*C*H$_2$, *E*), 66.6 (OHCH$_2$CHO*C*H$_2$, *E*), 66.5 (OHCH$_2$CHO*C*H$_2$, *Z*), 66.3 (OCH$_2$C=N, *Z*), 52.2 (NH–*C*H$_2$–CHO, *E*), 51.5 (NH–*C*H$_2$–CHO, *Z*), 49.1 (N=C–*C*H$_2$–NH, *Z*), 44.9 (N=C–*C*H$_2$–NH, *E*), 26.9 (CH$_3$, *Z*), 26.8 (CH$_3$, *E*), 26.8 (CH$_3$, *Z* and *E*), 25.4 (CH$_3$, *Z* and *E*), 25.3 (CH$_3$, *Z* and *E*); HRMS (ESI): calculated for $C_{22}H_{35}N_2O_6$ $[M+H]^+$ 423.2495, found 423.2497.

4.2.8. (2*E*)- and (2*Z*)-1-({[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}amino)-3-({[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}thio)propanone *O*-benzyloxime (17)

To a solution of (*R*)-**11b** (0.150 g, 0.44 mmol) in 1 mL of anhydrous methanol was added a solution of amine (*S*)-**9c** (0.172 g; 1.31 mmol) in methanol (0.5 mL). The resulting mixture was stirred under reflux for 8 h. The solution was then concentrated in vacuo and a saturated aqueous solution of $NaHCO_3$ (7 mL) followed by dichloromethane (15 mL) was introduced. After extraction, the organic layer was dried ($MgSO_4$) and concentrated. The crude product was then purified by flash chromatography using (1:1→7:3) ethyl acetate/cyclohexane as eluent to give pure **17** as a yellow oil (0.128 mg; 67%). Compound **17** appeared as a mixture of *Z* and *E* isomers. IR ν_{max} (neat, cm^{-1}) 3341 (N–H), 1624 (C=N), 1250–1050 (C–O); ^{1}H NMR ($CDCl_3$) δ/ppm 7.36–7.27 (m, 10H, H–Ar, *Z* and *E*), 5.08 (s, 4H, CH$_2$Ph, *Z* and *E*), 4.24–4.14 (m, 4H, CHO, *Z* and *E*), 4.00 (dd, ^2J=8.0 Hz, ^3J=6.5 Hz, 1H, NCH$_2$CHC*H*$_2$O, *Z*), 4.02–3.96 (m, 2H, NCH$_2$CHC*H*$_2$O, *E* and SCH$_2$CHC*H*$_2$O, *E*), 3.95 (dd, ^2J=8.5 Hz, ^3J=6.0 Hz, 1H, SCH$_2$CHC*H*$_2$O, *Z*), 3.67–3.55 (m, 6H, SCH$_2$CHC*H*$_2$O (*Z* and *E*), NCH$_2$CHC*H*$_2$O (*Z* and *E*), N=CC*H*$_2$N, *E*), 3.48 (s, 2H, N=CC*H*$_2$N, *Z*), 3.46 (s, 2H, N=CC*H*$_2$N, *Z*), 3.32 (d, ^2J=13.5 Hz, 1H, SCH$_2$C=N, *E*), 3.29 (d, ^2J=13.5 Hz, 1H, SCH$_2$C=N, *E*), 2.70 (dd, ^2J=13.5 Hz, ^3J=6.5 Hz, 1H, OCHC*H*$_2$S, *Z*), 2.67 (d, ^3J=6.0 Hz, 4H, NHC*H*$_2$CHO, *E* and *Z*), 2.59 (dd, ^2J=13.5 Hz, ^3J=6.5 Hz, 1H, OCHC*H*$_2$S, *E*), 2.56 (dd, ^2J=13.5 Hz, ^3J=6.5 Hz, 1H, OCHC*H*$_2$S, *Z*), 2.47 (dd, ^2J=13.5 Hz, ^3J=6.5 Hz, 1H, OCHC*H*$_2$S, *E*), 1.64 (br s, 2H, NH, *E* and *Z*), 1.41 (s, 6H, Me, *E* and *Z*), 1.40 (s, 6H, Me, *E* and *Z*), 1.34 (s, 6H, Me, *E* and *Z*), 1.32 (s, 6H, Me, *E* and *Z*); ^{13}C NMR ($CDCl_3$) δ/ppm 156.5 (C=N, *E*), 155.8 (C=N, *Z*), 137.7 (C–Ar, *E*), 137.4 (C–Ar, *Z*), 128.3 (C–Ar, *Z* and *E*), 128.0 (C–Ar, *Z* and *E*), 127.9 (C–Ar, *Z*), 127.8 (C–Ar, *E*), 109.4 (C–(CH$_3$)$_2$, *Z* and *E*), 109.1 (C–(CH$_3$)$_2$, *Z* and *E*), 76.0 (CH$_2$Ph, *Z* and *E*), 75.2 (NHCH$_2$–*C*HO, *Z*), 75.1 (NHCH$_2$–*C*HO, *E*), 74.8 (SCH$_2$–*C*HO, *Z* and *E*), 68.6 (SCH$_2$CH*C*H$_2$O, *Z* and *E*), 67.4 (NHCH$_2$CH*C*H$_2$O, *Z*), 67.3 (NHCH$_2$CH*C*H$_2$O, *E*), 52.1 (NH–*C*H$_2$–CHO, *E*), 51.5 (NH–*C*H$_2$–CHO, *Z*), 50.2 (N=C–*C*H$_2$, *Z*), 45.0 (N=C–*C*H$_2$, *E*), 35.2 (S–*C*H$_2$–CHO, *Z*), 33.8 (S–*C*H$_2$–CHO, *E*), 33.2 (S–*C*H$_2$–C=N, *E*), 26.9 (CH$_3$, *E*), 26.8 (CH$_3$, *Z*), 25.6 (CH$_3$, *E*), 25.4 (CH$_3$, *Z*), 25.5 (CH$_3$, *Z* and *E*), 25.3 (S–*C*H$_2$–C=N, *Z*); HRMS (ESI): calculated for $C_{22}H_{35}N_2O_5S$ $[M+H]^+$ 439.2267, found 439.2251.

4.2.9. *N*-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-*N*-3-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-2-{[(benzyloxy)imino]propyl}benzamide (18)

To (*S*,*S*)-**16** (0.317 g, 0.75 mmol) in anhydrous dichloromethane (8 mL) were added at 0 °C and under argon, triethylamine (155 µL, 1.13 mmol) and 4-dimethylaminopyridine (0.018 mg, 0.15 mmol). After 15 min, benzoylchloride (105 µL, 0.90 mmol) was added dropwise to the reaction mixture. The solution was quenched with H_2O after 2 h and the mixture was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography using (3:2) cyclohexane/ethyl acetate as eluant to give **18** as a colorless oil (0.355 g, 90%). Compound **18** is made of a mixture of the two isomers *Z* and *E*. IR ν_{max} (neat, cm^{-1}) 1635 (C═O), 1260–1000 (C–O); ^{1}H NMR ($CDCl_3$) δ/ppm 7.40–7.20 (m, 10H, H–Ar), 5.16–5.00 (m, 2H, CH_2Ph), 4.69–3.75 (m, 8H, CHO, CH_2O, O–CH_2–C═), 3.75–3.15 (m, 6H, CHO–CH_2–O, N–CH_2–CHO, ═C–CH_2–N), 1.40–1.20 (m, 12H, Me); ^{13}C NMR ($CDCl_3$) δ/ppm 172.6 (C═, *E* and *Z*), 153.8 (NCO, *E* and *Z*), 137.7 (C–Ar–Bn, *E* and *Z*), 136.2 (C–Ar, *Z*), 135.8 (C–Ar, *E*), 129.5 (C–Ar, *E*), 129.3 (C–Ar, *Z*), 128.3 (C–Ar–Bn, *E* and *Z*), 128.2 (C–Ar, *E* and *Z*), 128.0 (C–Ar–Bn, *E* and *Z*), 127.0 (C–Ar–Bn, *E* and *Z*), 126.4 (C–Ar, *E* and *Z*), 109.4 (*C*–$(CH_3)_2$, *Z*), 109.1 (*C*–$(CH_3)_2$, *E*), 76.4 (*C*H_2–Ph, *Z*), 76.2 (*C*H_2–Ph, *E*), 75.1 (NCH_2–*C*HO, *Z*), 74.4 (NCH_2–*C*HO, *E*), 74.2 (OCH_2–*C*HO, *E* and *Z*), 72.5 (CHO–*C*H_2–O, *E*), 72.0 (CHO–*C*H_2–O, *Z*), 67.4–66.9–66.6–66.3–65.8–65.5 (CH_2–O, O–*C*H_2–C═, *E* and *Z*), 51.8 (N–*C*H_2–CHO, *E*), 50.3 (N–*C*H_2–CHO, *Z*), 48.1 (═C–*C*H_2–N, *Z*), 44.6 (═C–*C*H_2–N, *E*), 26.8–26.7–26.6–25.4–25.3 (CH_3, *E* and *Z*); HRMS (ESI): calculated for $C_{29}H_{38}N_2O_7Na$ $[M+Na]^+$ 549.2577, found 549.2572.

4.2.10. *N*-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-*N*-[3-({[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-thio)-2-[(benzyloxy)imino]propyl]benzamide (19)

Compound **17** (0.350 g; 0.80 mmol) was dissolved in anhydrous dichloromethane (8 mL) at 0 °C and under argon. Triethylamine (170 µL, 1.20 mmol) and 4-dimethylaminopyridine (0.020 g, 0.16 mmol) were added followed by benzoylchloride (110 µL, 0.96 mmol). The mixture was stirred at 0 °C for 2 h whereupon the reaction was stopped by addition of water, extracted with ethyl acetate, and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by flash chromatography using (7:3) cyclohexane/ethyl acetate as eluent to give pure **19** (0.412 mg, 95%) as a colorless oil. IR ν_{max} (neat, cm^{-1}) 1638 (C═O), 1260–1060 (C–O); ^{1}H NMR ($CDCl_3$) δ/ppm 7.40–7.26 (m, 10H, H–Ar), 5.09 (s, 2H, CH_2Ph), 4.67–3.74 (m, 6H, CHO, CH_2O), 3.73–3.00 (m, 6H, N–C*H*$_2$–CHO, S–CH_2–C═N and N═C–CH_2N), 2.82–2.20 (m, 2H, CHO–C*H*$_2$–S), 1.45–1.20 (m, 12H, Me); ^{13}C NMR ($CDCl_3$) δ/ppm 172.5 (C═N, *E*), 172.4 (C═N, *Z*), 152.1 (C═O, *E* and *Z*), 137.3 (COC–Ar, *E* and *Z*), 135.9 (COC–Ar, *Z*), 135.7 (COC–Ar, *E*), 129.6 (COC–Ar, *E*), 129.4 (COC–Ar, *Z*), 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.0 and 126.5 (C–Ar, *E* and *Z*), 109.4 (C–$(CH_3)_2$, *Z*), 109.2 (C–$(CH_3)_2$, *E*), 76.4 (CH_2Ph, *E*), 76.3 (CH_2Ph, *Z*), 74.9, 74.8 and 74.6 (CHO, *E* and *Z*), 68.6 (CH_2–CHOCH_2S, *E*), 68.5 (CH_2–CHOCH_2S, *Z*), 67.2 (CH_2–CHOCH_2N, *Z*), 66.8 (CH_2–CHOCH_2N, *E*), 51.6 (N–*C*H_2–CHO, *Z*), 47.9 (N═C*C*H_2, *Z*), 46.1 (N–*C*H_2–CHO, *E*), 42.6 (N═C*C*H_2, *E*), 35.5 (CHO–*C*H_2S, *E*), 34.7 (CHO–*C*H_2S, *Z*), 34.1 and 33.4 (S–*C*H_2–C═N, *E*), 26.8 (CH_3, *E* and *Z*), 26.0 (S–*C*H_2–C═N, *Z*), 25.4 (CH_3, *E* and *Z*); HRMS (ESI): calculated for $C_{29}H_{38}N_2O_6NaS$ $[M+Na]^+$ 565.2348, found 565.2374.

4.2.11. (2*R*,8*S*)-2,8-Dihydroxymethyl-10-benzoyl-10-aza-1,4,7-trioxaspiro[5.5]undecane (20)

A solution of (*S*,*S*)-**18** (0.150 g, 0.28 mmol) in 2.8 mL of a 10:1 (v/v) mixture of acetone/water and Amberlyst® 15 (0.070 g) was heated for 2 days under reflux with 2.8 mmol of paraformaldehyde. After cooling and filtration on a Celite® pad, the solvent was evaporated in vacuo and the crude mixture was purified by flash chromatography using (49:1) ethyl acetate/MeOH as eluent to give a mixture of isomers **20** as a colorless oil (0.056 g, 61%). IR ν_{max} (neat, cm^{-1}) 3400 (O–H), 1618 (C═O), 1051 (C–O); ^{13}C NMR (DMSO-d_6, 293 K) δ/ppm 170.6–170.4–170.0–169.6 (C–Ar), 136.7–135.3 (C–Ar), 129.7–129.4 (C–Ar), 128.4–128.2 (C–Ar), 127.3–127.0–126.8 (C–Ar), 92.1–91.6 (C-6), 73.4–73.2–71.9–69.0–67.8–67.4 (C-3 and C-5), 72.8–72.4–70.5–70.3–68.6 (C-2 and C-8), 63.0–62.9–62.8–61.9–61.6–61.0 (C-12 and C-13), 52.2–50.7–50.3–48.6–46.4–45.1–44.9–43.4 (C-9 and C-11); HRMS (ESI): calculated for $C_{16}H_{21}NO_6Na$ $[M+Na]^+$ 346.1267, found 346.1261.

4.2.12. (2*R*,8*S*)-2,8-Dihydroxymethyl-10-benzoyl-10-aza-4-thia-1,7-dioxaspiro[5.5]undecane (21)

A solution of oxime (*R*,*S*)-**19** (0.112 g, 0.20 mmol) in 2 mL of a 10:1 (v/v) mixture of acetone/water with Amberlyst®15 (0.050 g) and 2 mmol of paraformaldehyde was heated under reflux for 2 days. After cooling and filtration on a Celite® pad, the solvent was evaporated in vacuo and the crude mixture purified by silica gel chromatography using (1:0→49:1) ethyl acetate/MeOH as eluent to give **21** as a white syrup (0.045 g, 65%). IR ν_{max} (neat, cm^{-1}) 3394 (O–H), 1618 (C═O), 1047 (C–O); ^{13}C NMR (DMSO-d_6, 293 K) δ/ppm 170.1–169.4 (N–CO), 135.7 (C–Ar), 129.4 (C–Ar), 128.4–128.2 (C–Ar),

127.3–126.6 (C–Ar), 91.6–91.2 (C-6), 70.3–70.2 (C-2), 68.7 (C-8), 63.9–63.8–61.9–61.5 (C-12 and C-13), 54.1–48.5–43.5 (C-9 and C-11), 30.8–30.5 (C-5), 26.6 (C-3); HRMS (ESI): calculated for $C_{16}H_{21}NO_5NaS$ $[M+Na]^+$ 362.1038, found 362.1021.

4.2.13. 2,8-Dihydroxymethyl-10-benzoyl-10-aza-1,4,7-trioxaspiro[5.5]undecane (22)

To a solution of spiroketal **20** (0.056 g, 0.17 mmol) in THF (1 mL) was added at 0 °C and under argon, a 1.0 M solution of $LiAlH_4$ in THF (693 μL, 0.68 mmol). After 3 h, the reaction is quenched by adjunction of water and the residue filtered over $MgSO_4$. The solvent was eliminated to give nearly quantitatively a crude and inseparable mixture of isomers **22**, in a 4:1 *ratio* as determined from ^{13}C NMR. ^{13}C NMR ($CDCl_3$) δ/ppm 105.9–91.6 (C-6), 75.0–70.0 (C-8), 72.6–70.0 (C-5), 70.6–69.0 (C-2), 68.4–67.2 (C-3), 63.7–63.4 (CH_2OH), 62.5–62.0 (CH_2OH), 49.9–49.1 (C-11), 47.9–46.1 (C-9).

Major isomer: (2*R*,6*S*,8*S*)-**22a**: ^1H NMR ($CDCl_3$) δ/ppm 4.06 (m, 1H, H-2), 3.90 (m, 1H, H-8), 3.60–3.48 (m, 4H, CH_2OH), 3.74 (dd, J_{3eq3ax}=11.0 Hz, J_{3eq2ax}=2.5 Hz, 1H, H-3_{eq}), 3.60 (d, ^2J=11.5 Hz, 1H, H-5), 3.33 (t, J_{3ax3eq}=J_{3ax2ax}=11.0 Hz, 1H, H-3_{ax}), 3.26 (d, ^2J=11.5 Hz, 1H, H-5), 3.13 (br d, 1H, NH), 2.83 (br d, J_{9eq9ax}=12.0 Hz, 1H, H-9_{eq}), 2.73 (d, ^2J=13.0 Hz, 1H, H-11), 2.57 (t, J_{9ax9eq}=J_{9ax8ax}=12.0 Hz, 1H, H-9_{ax}), 2.52 (d, ^2J=13.0 Hz, 1H, H-11); ^{13}C NMR ($CDCl_3$) δ/ppm 91.6 (C-6), 70.0 (C-8), 70.0 (C-5), 69.0 (C-2), 67.2 (C-3), 63.4 (CH_2OH), 62.0 (CH_2OH), 49.1 (C-11), 46.1 (C-9); HRMS (ESI): calculated for $C_9H_{18}NO_5$ $[M+H]^+$ 220.1185, found 220.1175.

4.2.14. 2,8-Dihydroxymethyl-10-benzoyl-10-aza-4-thia-1,7-dioxaspiro[5.5]undecane (23)

To a solution of spiroketal **21** (0.060 g, 0.18 mmol) in THF (1 mL) was added at 0 °C and under argon, a 1.0 M solution of $LiAlH_4$ in THF (710 μL, 0.72 mmol). After 3 h, the reaction is quenched by adjunction of water and the residue filtered over $MgSO_4$. The solvent was eliminated to give nearly quantitatively a crude and inseparable mixture of isomers **23**, in a 9:1 *ratio* (determined from ^{13}C NMR). ^{13}C NMR ($CDCl_3$) δ/ppm 99.9–90.9 (C-6), 71.4–70.8 (C-2), 70.8–70.2 (C-8), 68.8–63.3 (CH_2OH), 65.2–65.2 (CH_2OH), 53.0–51.6 (C-11), 47.7–46.1 (C-9), 37.0*–32.0 (C-5), 36.6*–26.2 (C-3).

Major isomer: (2*R*,6*S*,8*S*)-**23a**: ^1H NMR ($CDCl_3$) δ/ppm 4.04 (m, 1H, H-2), 3.89 (m, 1H, H-8), 3.58–3.45 (m, 4H, CH_2OH), 2.81 (br d, J_{9eq9ax}=12.0 Hz, 1H, H-9_{eq}), 2.79 (d, ^2J=13.0 Hz, 1H, H-11), 2.67 (d, ^2J=13.5 Hz, 1H, H-5), 2.57 (d, ^2J=13.0 Hz, 1H, H-11), 2.51 (t, J_{9ax9eq}=J_{9ax8ax}=12.0 Hz, 1H, H-9_{ax}), 2.48 (t, J_{3ax3eq}=J_{3ax2ax}=12.0 Hz, 1H, H-3_{ax}), 2.29 (d, ^2J=13.5 Hz, 1H, H-5), 2.18 (br d, J_{3eq3ax}=13.0 Hz, 1H, H-3_{eq}); ^{13}C NMR ($CDCl_3$) δ/ppm 90.9 (C-6), 70.8 (C-2), 70.2 (C-8), 65.2 (CH_2OH), 63.3 (CH_2OH), 53.0 (C-11), 46.1 (C-9), 32.0 (C-5), 26.2 (C-3); HRMS (ESI): calculated for $C_9H_{18}NO_4S$ $[M+H]^+$ 236.0957, found 236.0946.

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