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Synthesis and Ring-Chain-Ring Tautomerism of Bisoxazolidines, Thiazolidinyloxazolidines, and Spirothiazolidines

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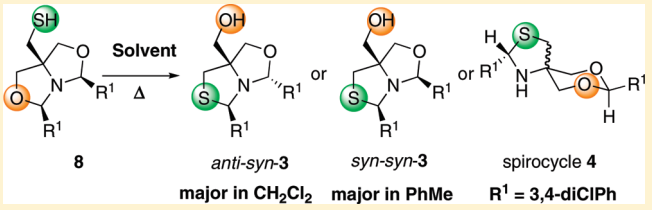
Supporting Information

ABSTRACT: The synthesis of fused heterocycles such as thiazolidinyl-oxazolidine **3** is described starting from Tris·HCl. The mercaptomethyl bisoxazolidine **8** was found to convert to the corresponding thiazolidinyloxazolidine **3** and the spiro-heterocycle **4** by a ring-chain-ring tautomerism, depending on the electronic nature of the ring substituents as well as the reaction conditions. This equilibration pathway is absent in the hydroxymethyl bisoxazolidines **2**. Computational studies confirm that both kinetic and thermodynamic control features play a role in the product distribution.



INTRODUCTION

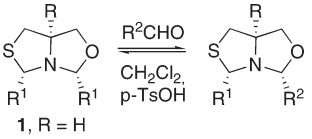
Ring-chain tautomerism is a process that involves the reversible movement of a proton accompanied by a change from an open structure to a ring, often the result of an addition of a heteroatom to a heteropolar double bond to form a heterocycle. The reaction is usually acid-catalyzed and represents a key step in the synthesis of five- and six-membered 1,3-heterocycles containing oxygen, nitrogen, or sulfur atoms.[1] This process can be exploited in the construction of dynamic combinatorial libraries[2] and has been applied to the discovery of new materials and pharmacologically active compounds.[3] The transformation has been studied thoroughly in the past decade, mainly in the context of ring-chain tautomeric equilibria involving 1,3-*X*,*N*-heterocyclic systems (X = S, O, N).[4]

As a continuation of our investigations on new reactions and scaffolds suitable to Dynamic Combinatorial Chemistry, we have explored readily available building blocks useful for the exchange of carbonyl units in a dynamic library pool. Recently, we have reported the synthesis of thiazolidinyloxazolidine **1**, which is capable of exchanging carbonyl units in the oxazolidine moiety, retaining the thiazolidine heterocycle, in the presence of *p*-TsOH in CH_2Cl_2 (Scheme 1).[5]

A logical extension of these studies was to investigate the bisoxazolidine **2**, a compound that had been reported in the literature a number of years ago.[6] We decided to prepare an analogous heterocycle, i.e., the fused thiazolidinyloxazolidine **3** (Figure 1). Bisoxazolidines **2** have been intensely studied during the past decades,[7] and some derivatives show interesting chemical and biological properties as chiral catalysts,[8] anticancer,[9] and neuroprotective agents.[10]

It is important to note that the replacement of the oxygen by a sulfur atom leads to a significant increase in the complexity of the system due to a break in the symmetry, allowing the potential formation of 2^3 fused bicycles upon variation of the substituents R and R^1.

Scheme 1. Dynamic Equilibrium and Carbonyl Group Exchange Reaction of Thiazolidinyloxazolidine 1



The present paper describes our findings in the synthesis of the thiazolidinyloxazolidine **3**, a new bicyclic fused scaffold, and its structural isomer, the spirothiazolidine **4** (see Figure 1).

RESULTS AND DISCUSSION

Our first objective was the synthesis of the fused thiazolidinyloxazolidine **3**, the sulfur analogue of bicycle **2**. Since this was a hitherto unknown building block, we had to develop a new synthetic strategy to access it. Tris·HCl reagent (**5**) was used as a starting material, and we explored two alternatives for its use in the synthesis of bicycle **3**. The key step was the replacement of a hydroxyl group with a thiol in either the Tris·HCl building block or the fused bicycle (Scheme 2).

Path a) applied an early thiolation strategy involving as the key step the synthesis of thiazolidinone-2-thione **7** starting from Tris·HCl and carbon disulfide.[11] Subsequently, a hydrolysis was followed by a cyclization to afford the target compound **3**. Path b) represents an alternative methodology that began with the protection of a diol unit in Tris·HCl, followed by the substitution of the free hydroxyl group in **2** with thioacetic acid under Mitsunobu conditions.

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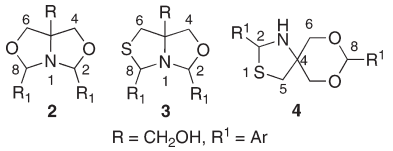
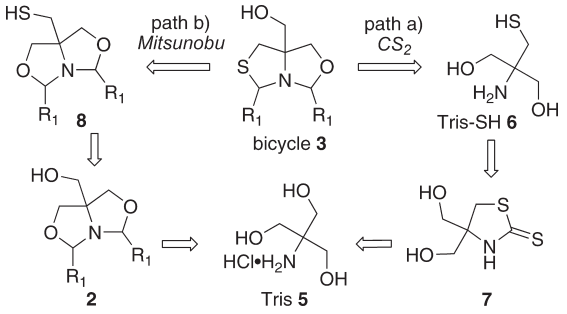
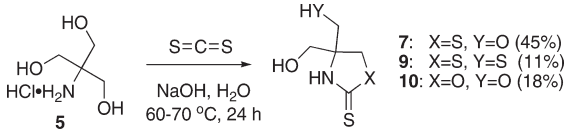


Figure 1. Structures of bisoxazolidine **2**, thiazolidinyloxazolidine **3**, and spirothiazolidine **4**.

Scheme 2. Retrosynthetic Analysis of Bicycle 3



Scheme 3. Preparation of Thiazolidin-2-thiones (7 and 9) and Oxazolidin-2-one 10



Thioester hydrolysis and an oxazolidine−thiazolidine interconversion in acidic media led to compound **3** (Scheme 2).

Recently, Darabantu et al. reported a synthesis of thiazolidinyloxazolidine **3** (R^1 = H), similarly starting from Tris **5** but otherwise using a different sequence.[12] A more detailed discussion of these routes is provided below.

Path a). The thiazolidine-2-thione **7** was prepared in moderate yields by heating a mixture of 5 M NaOH, Tris·HCl, and carbon disulfide at reflux for several hours.[13] Various conditions were attempted in order to improve the selectivity and yield, but our best result was achieved by simply heating the reaction mixture for 1 day at 60−70 °C. A mixture of two thiazolidin-2-thiones (**7** and **9**) and the oxazolidin-2-thione **10** was obtained (Scheme 3).

Thiazolidin-2-thiones **7** and **9** were subjected to a monocyclization protocol in MeCN in the presence of *p*-TsOH and R^1CHO under microwave irradiation (90 °C, 12 min). Under these conditions, these substrates yielded exclusively the corresponding spirocycles **11a** and **12a**, instead of the expected fused bicycle **13a**, in analogy to the results obtained under conventional heating (Scheme 4).

The spiro product *syn*-**12a** shows long-range couplings (^4J) due to the characteristic W-arrangement of the connecting bonds between H_a and H_b ("W-coupling"). The hydrogen atoms H_a and H_b are close to coplanar equatorial positions (Scheme 4).

The formation of the spiro products corresponding to a 6-*endo*-*trig* cyclization is a favored process according to Baldwin's rules. The corresponding 5-*endo*-*trig* process leading to bicycle **13** could not be observed; this cyclization process is disfavored by Baldwin's rules.

Scheme 4. Cyclization and Product Distribution for Thiazolidin-2-thiones 7 and 9

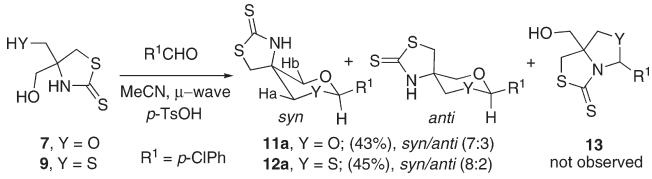
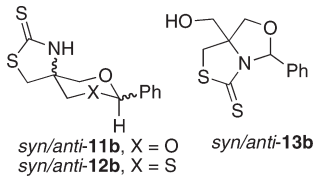


Table 1. Relative Energies for compounds *syn*/*anti*-11b, -12b, and -13b



entry	compounds	relative energies [kcal/mol]
1	*syn*-**11b** vs *anti*-**11b**	−0.6
2	*syn*-**12b** vs *anti*-**12b**	−0.7
3	*syn*-**13b** vs *anti*-**13b**	−3.0
4	*syn*-**11b** vs *syn*-**13b**	−8.9

In order to gain further insight into these results, we undertook a theoretical calculation using a geometry optimization with Spartan 10 (DFT/B3LYP/6-311G*). The relative energy (E) for selected compounds is shown in Table 1. In order to simplify the calculations, we used a simple Ph subtituent.

The spirocycles **11a** and **12a** were obtained as mixtures of *syn*- and *anti*-diastereomers. The theoretical calculations of the relative energies of the analogous products **11b** and **12b** predicted the *syn*-configurations to have a slightly lower energy in accordance with the experimental data and the configurations of the major diastereomers assigned by NOESY experiments. The differences in energy were −0.6 and −0.7 kcal/mol for spirocycles **11b** and **12b**, respectively (see Table 1, entries 1 and 2).

These calculations were also able to suggest a rationale why the fused bicycle **13a** was not observed: the difference in energy between spirocycle *syn*-**11b** and fused bicycle *syn*-**13b**, the more stable of the two stereoisomers, was about −9 kcal/mol (Table 1, entries 3 and 4), in preference for the formation of the spirocycle as the major thermodynamically favored isomer.

Hydrolysis of thiazolidin-2-thione **7** in conc HCl at reflux led to formation of Tris-SH·HCl **6** in 90% yield (Scheme 5). Cyclization in PhMe/DMF (9:1) with *p*-ClPhCHO and *p*-TsOH acid for 3 h using a Dean−Stark trap led to a mixture of the fused bicycle *syn*-**3a** (32%) and a small amount of spiro compound **4a** (3%). The presence of spirocycle **4a** was unexpected because it had not been described for the oxygen analogues **2**.

Attempts to synthesize other fused heterocycles, using aldehydes such as *p*-FPhCHO and *p*-CF_3PhCHO, led to complex reaction mixtures with low recovery of the desired products, *syn*-**3b** (R^1 = *p*-FPh, 8%), spiro-**4b** (R^1 = *p*-FPh, 3%), and *syn*-**3c** (R^1 = *p*-CF_3Ph, 2%).

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Scheme 5. Synthesis of Fused Bicycle 3a

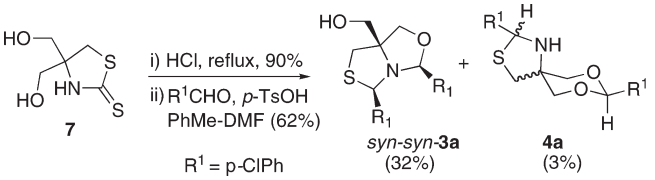
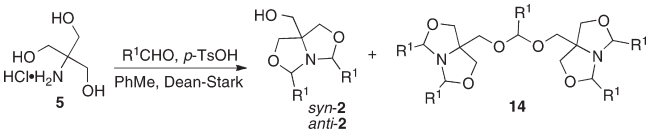


Table 2. Product Yields and Diastereomeric Ratios for Compounds 2a−e, 14a and 14c−e



entry	R^1	compd **2**, yield % (*syn*:*anti*)[b]	compd **14**, yield %
1	*p*-ClPh	**2a**, 77, (98:2)	
2	*p*-FPh	**2b**, 34, (98:2)	
3	*p*-CF_3Ph	**2c**, 32, (81:19)	**14c**, 13
4	*m*-BrPh	**2d**, 30, (80:20)	**14d**, 25
5	*p*,*m*-diClPh	**2e**, 20, (83:17)	**14e**, 35

[b] Ratio based on integration of separated ^{1}H NMR signals.

Our methodology for the synthesis of **6** provides a 40% overall yield in a two-step sequence; reported synthesis of Tris-SH was achieved in three steps with 48% overall.[12] The authors only report the synthesis of bicycle **3** derived from formaldehyde, possibly indicating the limitation of the cyclization process starting from **6**.

Due to the difficulties we encountered in path a), i.e., the low yield and limited scope for the formation of **7** and **3**, the tedious purification steps, the instability of Tris-SH **6**, and the low solubility of the intermediate **6** under several reaction conditions, we decided to explore path b) as a new alternative.

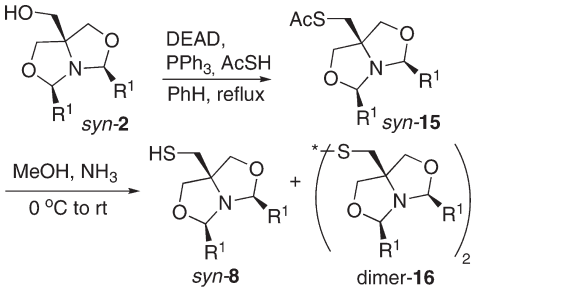
For this purpose, we studied the direct substitution of the alcohol moiety in bisoxazolidine **2**, using Mitsunobu conditions. Oxabicycles **2a**−**d** were synthesized as described previously by heating Tris·HCl, *p*-TsOH, and aldehydes in PhMe at reflux, using a Dean−Stark trap.[4]

Using these conditions, we obtained the desired product *syn*-**2a**−**e** in moderate yields, mainly due to the formation of the dimer **14** (Table 2). The proportion of the side product **14** seemed to increase with the electron-withdrawing character of the aldehyde side chain R^1.

For the continuation of the synthesis of target molecule **3**, the substitution of the hydroxyl group present in the bicycles **2a**−**d** with thioacetic acid was achieved under Mitsunobu conditions to give bicycles *syn*-**15a**−**d** in good yield, as shown in Table 3.

Smooth solvolisis of esters **15** in MeOH/NH_3 at room temperature led to the 5-thiomethyl-bisoxazolidines **8**, in good yields, except when R^1 = *m*-BrPh and 3,4-diClPh, where the dimeric compound **16** was obtained as a byproduct. This methodology allowed us to prepare the new bisoxazolidines *syn*-**8a**−**e**, substituted at C_5 with a thiomethyl group (Table 3). Disulfur dimers **16d** and **16e** could be recycled to the corresponding thiols **8d** (70%) and **8e** (60%) by treatment with $NaBH_4$ in MeOH at room temperature.

Table 3. Product Yields and Diastereomeric Ratios for Compounds 15a−e and 8a−e



entry	R^1	*syn*-**15**, yield (%)	*syn*-**8**, yield (%)
1	*p*-ClPh	**15a** (75)	**8a** (66)
2	*p*-FPh	**15b** (54)	**8b** (62)
3	*p*-CF_3Ph	**15c** (71)	**8c** (65)
4	*m*-BrPh	**15d** (84)	**8d** (44) + **16d** (43)
5	*p*,*m*-diClPh	**15e** (78)	**8e** (25) + **16e** (53)

According to our previous work, which is relevant to the ability of this class of bicycles to exchange carbonyl units at the oxazolidine site,[5] we decided to explore such an interconversion in these new heterocycles. When using CH_2Cl_2 at reflux for 6 h, in the presence of *p*-TsOH acid (cat.) and aldehyde (1 equiv) for the re-equilibration of *syn*-**8a**−**d**, we obtained thiazolidinyloxazolidines *anti*-*syn*-**3a**−**d** as main products (Table 4, entries 1, 3−5). These results were in accordance with our previous work with regard to the ability of these compounds to establish an equilibrium in favor of the most stable bicycle thiazolidinyloxazolidine **3** versus the bisoxazolidine **2**.

For the thiols **8d** and **8e**, the situation was different under the same re-equilibration conditions. Starting from **8d** (R^1 = *m*-BrPh derivative), we observed the formation of a mixture of fused **3d** and the corresponding spiro compound **4d**. Starting from **8e** (R^1 = *m*,*p*-diClPh), we observed the exclusive formation of spirocycle **4e** instead of the bicycle **3e**, (Table 4, entry 7). In contrast, when using PhMe/*p*-TsOH at reflux, we observed a different product distribution. For thiols **8a** and **8d**, we obtained a mixture of *syn*-*syn*-fused-**3** and spiro-**4** (Table 4, entries 2 and 6).

It is noteworthy that the product distribution was strongly dependent on the electronic character of the substituents R^1, the solvent, and the temperature. Bicycle **8e**, bearing the most electron-withdrawing group, only equilibrated to the spiro compound **4e.**

The new spiro-**4a,d,e** compounds were fully characterized in order to confirm their structure. Important evidence was the long-range coupling constant ^4J indicative of a typical W arrangement for H_a and H_b in the ^{1}H NMR spectra. In addition, a significant shift in some carbon signals, such as the quaternary carbon C_2, the CH_2OR C_3, and the acetal carbon of the oxazolidine or oxazine C_1, indicated the presence of compound **4** (Table 5). The absence of the hydroxyl-stretching band in the IR spectra confirmed the spiro structure **4**.

Intrigued by the formation of spirocycle **4**, we calculated the difference in energy for the fused bicycle **3f** and the spirocycle **4f** (R^1 = Ph). According to the computation the spirocycle **4f** is more stable than the thiazolidinyloxazolidine **3f** by about 5 kcal/mol (Figure 2). In agreement with the computational results for fused bicycles **3**, the diastereomer *syn*-*syn*-**3f** is 1.9 kcal more stable than the *anti*-*syn*-**3f**. This result was also experimentally confirmed since the apparent kinetic product *anti*-*syn*-**3** was obtained at a lower

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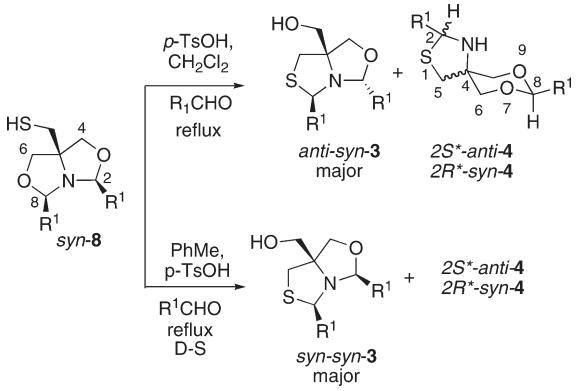
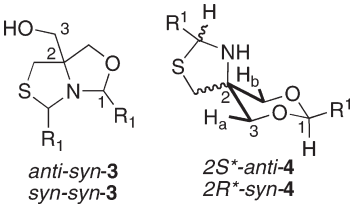
Table 4. Product Distribution for Compounds 3 and 4



				product distribution, yield	
entry	R^1	starting material	reaction conditions	**3** [%], (*anti-syn*:*syn-syn*)[c]	**4** [%]
1	*p*-ClPh	**8a**	A[a]	62, (99:1)	
2	*p*-ClPh	**8a**	B[b]	41, (10:90)	46
3	*p*-FPh	**8b**	A[a]	44, (90:10)	
4	*p*-CF_3Ph	**8c**	A[a]	64, (81:19)	
5	*m*-BrPh	**8d**	A[a]	64, (95:5)	20
6	*m*-BrPh	**8d**	B[b]	66, (7:93)	20
7	*m*,*p*-di-ClPh	**8e**	A[a]		80

[a] A: R^1CHO, *p*-TsOH, CH_2Cl_2, reflux 6 h; [b] B: R^1CHO, *p*-TsOH, PhMe, Dean−Stark, reflux 4 h; [c] ratio based on integration of distinct ^{1}H NMR signals.

Table 5. Characteristic ^{13}C NMR δ Signals for Fused-3 and Spiro-4 Heterocycles



	^{13}C NMR δ (ppm)		
compound	C_1	C_2	C_3
fused *anti-syn*-**3a**	94.6	79.8	65.8
fused *syn-syn*-**3a**	98.4	79.7	66.9
spiro *anti*-**4a**	101.1	64.1	73.4
fused *anti-syn*-**3d**	94.1	79.6	65.9
fused *syn-syn*-**3d**	98.3	79.8	66.9
spiro *anti*-**4d**	100.8	64.1	73.4

temperature in CH_2Cl_2, while higher temperatures in toluene yielded the thermodynamically preferred *syn-syn*-**3**.

However, attempts to obtain the spiro compound by further heating the fused *anti-syn*-**3a** at reflux using different solvents (MeCN, PhMe) and acidic conditions (*p*-TsOH or $HClO_4$/SiO_2[14]) led only to the isomerization of the starting material into the thermodynamic *syn-syn*-**3** bicycle, without an apparent formation of the spiro product (Scheme 6).

The proposed mechanism for bicycle and spirocycle formation is depicted in Figure 3. In acidic media, fused bicycle **3** can be

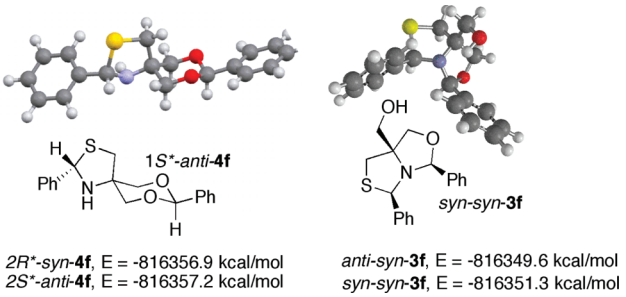
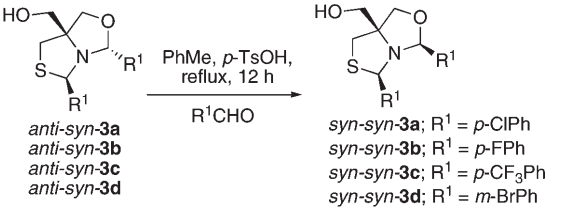


Figure 2. Calculated energies for spiro **4f** and fused **3f**.

Scheme 6. Isomerization of *anti-syn*-3 into *syn-syn*-3



opened by ring-chain tautomerism, leading to the formation of two possible intermediates: oxonium ion I_1 and the probably more stable iminium ion I_2. Under kinetic conditions, intermediate I_2 is preferentially formed and reacts faster than I_1, leading again to the 5-*endo-trig* cyclization product **3**. In contrast, under thermodynamic conditions, the more stable spiro-thiazolidine **4** is formed. The selectivity of this product distribution can be explained on the basis of the ring-chain tautomeric equilibration of the intermediates,

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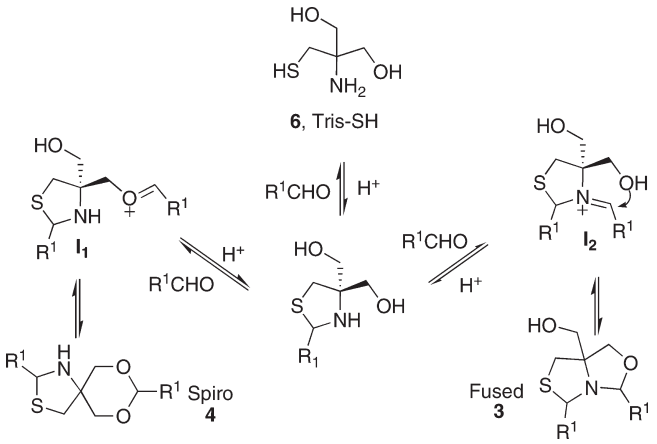

Figure 3. Mechanistic proposal for the formation of fused bicycles **3** and spirocycle **4**.

with a kinetic preference for the formation of the bicyclic product **3** under mild conditions, or a complete equilibration toward the spiro product **4** under more forcing conditions.

The reaction conditions are critical to the product distribution. There is a correlation with lower temperatures favoring the kinetic products and higher temperatures establishing a thermodynamic equilibrium.

There is no clear correlation between the electronic effect of substituents at R^1 and the product distribution bicycle versus spirocycle. The values of the Hammet coefficients are $\sigma = 0.60$ (*m*,*p*-diCl) > 0.54 (*p*-CF_3) > 0.39 (*m*-Br) > 0.23 (*p*-Cl) > 0.06 (*p*-F).[15] Electron-withdrawing groups at R^1 destabilize cationic intermediates I_1 and I_2, but probably more so in the iminium ion I_2 than the alkoxycarbenium ion I_1, thus for example favoring, in CH_2Cl_2, the formation of spirocycles **4d** (*m*,*p*-diCl) and **4e** (*m*-Br). Otherwise compound **8c** (*p*-CF_3) having also a high σ value did not evolve to the spiro and led exclusively to bicycle **3c** formation (Table 4).

CONCLUSIONS

We were able to synthesize the fused thiobicycles **3a**−**e** for the first time. As described in the literature, the oxygen-containing heterocycles **2b** and **2c** have attractive biological properties as neuroprotectives, which is likely shared or further enhanced by the sulfur analogues **3b** and **3c**. The methodology developed in path b allowed the selective preparation of both diastereomers of these heterocycles, the *syn-syn*-**3** in PhMe as well as the *anti-syn*-**3**, in CH_2Cl_2. The replacement of oxygen by a sulfur atom in the structure of Tris (**5**) to form Tris-SH (**6**) has a remarkable impact in the cyclization process in the presence of aldehydes compared to Tris.

The spirocyclic compound **4** represents a novel molecular scaffold. It was obtained in a ring-chain-ring tautomeric equilibration of mercaptomethyl bisoxazolidine **8**. These compounds can be synthesized in acidic media by tuning the reaction conditions (temperature, solvent), and their formation is strongly dependent on the electronic properties of the substituents R^1. Thiazolidines are known to be more stable than oxazolidines,[16] this property is likely the reason why thiazolidin-spirocycle **4** is formed, but the corresponding analogue oxazolidin-spirocycle remains unknown.

These findings represent a significant extension of the number of small but densely functionalized scaffolds that can be obtained from relatively simple and readily available buildings blocks. We anticipate that this information can be utilized for the construction of new dynamic combinatorial libraries.

EXPERIMENTAL SECTION

Path a

4,4-Bis(hydroxymethyl)thiazolidine-2-thione (7). To an ice-cooled solution of NaOH (5.0 g, 0.12 mol) in H_2O (9 mL) were added with stirring Tris·HCl (5.0 g, 31.8 mmol), CS_2 (4.8 mL, 79.2 mmol), and PEG 400 (2 drops). The mixture was heated at 60 °C for 24 h, then cooled down, poured into H_2O (100 mL), extracted with EtOAc (3 × 100 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure. The yellow oil crude was purified chromatography on SiO_2 (1:2, EtOAc/hexanes) to afford **7** (2.57 g, 45%), **9** (0.65 g, 11%), and **10** (0.91 g, 18%).

Thiazolidinethione **7**: white solid; mp 90−91 °C; ^{1}H NMR (CD_3OD) δ 3.45 (s, 2 H), 3.63 (d, J = 11.5 Hz, 2 H), 3.70 (d, J = 11.5 Hz, 2 H), 4.88 (bs, 2 H); ^{13}C NMR (CD_3OD) δ 36.5, 63.3, 76.4, 202.0; HRMS calcd for $C_5H_9NO_2S_2$ $[M]^+$ 179.0075, found 179.0035.

4-Hydroxymethyl-4-thiomethyl-thiazolidine-2-thione (**9**): oil; IR (NaCl) ν = 3300−3200 bs, 2926, 2513, 1732, 1458, 1007; ^{1}H NMR (CD_3CN) δ 1.78 (dd, J = 9.7, 8.4 Hz, 1 H_{SH}), 2.79 (dd, J = 14.3, 9.7 Hz, 1 H), 2.93 (dd, J = 14.3, 8.4 Hz, 1 H), 3.41 (d, J = 11.6 Hz, 1 H), 3.44 (t, J = 5.9 Hz, 1 H_{OH}), 3.53 (d, J = 11.6 Hz, 1 H), 3.62 (dd, J = 11.4, 5.9 Hz, 1 H), 3.68 (dd, J = 11.4, 5.9 Hz, 1 H) 7.96 (s, 1 H_{NH}); ^{13}C NMR (CD_3CN) δ 30.0, 38.4, 64.8, 75.5, 201.4 (C═S); HRMS calcd for $C_5H_{10}NOS_3$ $[M + H]^+$ 195.9925, found 195.9957.

4,4-Bis(hydroxymethyl)oxazolidine-2-thione (**10**): solid; mp 111−112 °C; ^{1}H NMR (DMSO-d_6) δ 3.37 (d, J = 5.6 Hz, 4 H), 4.36 (s, 2 H), 5.16 (t, J = 5.6 Hz, 1 H), 5.17 (t, J = 5.6 Hz, 1 H), 9.84 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 62.1, 67.9, 73.1, 188.0; HRMS calcd for $C_5H_{10}NO_3S$, $[M + H]^+$ 164.0381, found 164.0389.

(*syn*/*anti*)-8-(4-Chlorophenyl)-7,9-dioxa-3-thia-1-azaspiro-[4.5]decane-2-thione (11a). To a stirred solution of **7** (300 mg, 1.68 mmol) in MeCN (1 mL) were added *p*-Cl-benzaldehyde (0.47 g, 3.4 mmol) and *p*-TsOH acid (30 mg, 0.17 mmol). The reaction mixture was heated with stirring under microwave irradiation for 12 min at 90 °C. Then it was cooled, poured into H_2O, neutralized with $NaHCO_3$ (satd solution), and extracted with EtOAc (3 × 30 mL). The solvent was removed under reduced pressure, and the crude was purified by chromatography on SiO_2 (1:4, EtOAc/hexanes) to afford compound **11a** (206 mg, 43%, diasteromeric ratio = 7:3). Major diastereomer: white solid; mp 208−209 °C; IR (NaCl) ν = 3098, 2914, 1489, 1317, 1010, 829, 750; ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 2 H), 3.87 (d, J = 11.0 Hz, 2 H), 4.20 (d, J = 11.0 Hz, 2 H), 5.56 (s, 1 H), 7.46 (m, 4 H), 10.29 (bs, 1 H_{NH}); ^{13}C NMR (DMSO-d_6) δ 39.7, 64.8, 71.0, 100.3, 128.6, 128.7, 134.1, 136.9, 199.8; HRMS calcd for $C_{12}H_{11}ClNO_2S_2$ $[M - H]^-$ 299.9925, found 299.9932.

(5*RS*,*syn*/*anti*)-8-(4-Chlorophenyl)-7-oxa-3,9-dithia-1-azaspiro[4.5]decane-2-thione (12a). Prepared in an analogous route as described for **11a** to give compound **12a** (225 mg, 45%, diastereomeric ratio = 8:2). Major diastereomer: solid; mp 75−76 °C; IR (NaCl) ν = 3209, 2993, 2853, 1489, 1190, 1032, 817; ^{1}H NMR (DMSO-d_6) δ 3.11 (dd, J = 12.9, 2.5 Hz, 1 H), 3.38 (d, J = 12.9 Hz, 1 H), 3.65 (d, J = 11.5 Hz, 1 H), 3.77 (d, J = 11.6 Hz, 1 H), 3.90 (d, J = 11.6 Hz, 1 H), 4.11 (dd, J = 11.5, 2.5 Hz, 1 H), 5.99 (s, 1 H), 7.45 (m, 4 H), 10.33 (s, 1 H_{NH}); ^{13}C NMR (DMSO-d_6) δ 35.6, 39.7, 64.4, 71.7, 81.9, 128.1, 128.4, 133.2, 137.0, 198.7 (C═S); HRMS calcd for $C_{12}H_{11}ClNOS_3$ $[M - H]^-$ 315.9697, found 315.9704.

2-Amino-2-(thiomethyl)propane-1,3-diol Tris-SH·HCl (6). Diol **7** (400 mg, 2.24 mmol) was dissolved with stirring in conc HCl (3 mL) and heated at reflux for 24 h. Then, water (15 mL) was added, and the mixture was washed with EtOAc (30 mL). The aqueous layer was evaporated at reduced pressure to afford compound **6** (350 mg,

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90%). This residue was used without further purification. The ^{1}H NMR signals are in agreement with the reported spectroscopic data:[12] ^{1}H NMR (DMSO-d_6) δ 2.70 (d, J = 9.0 Hz, 2 H), 2.86 (t, J = 9.0 Hz, 1 H_{SH}), 3.48 (d, J = 11.5 Hz, 2 H) 3.54 (d, J = 11.5 Hz, 2 H), 5.44 (bs, 2 H), 7.95 (s, 2 H).

(2*S*,5*S*,8*R*)- and (2*R*,5*R*,8*S*)-2,8-Di(*p*-chlorophenyl)-5-hydroxymethyl-1-aza-3-oxa-7-thiabicyclo [3.3.0]octane (*syn-syn*-3a). To a suspension of Tris-SH (**6**) (200 mg, 1.16 mmol) in PhMe (5 mL) and DMF (0.5 mL) were added *p*-Cl-benzaldehyde (404 mg, 2.87 mmol) and catalytic *p*-TsOH (2 mg, 0.01 mmol). The mixture was heated at reflux in a Dean−Stark trap for 3 h. Then, it was cooled, poured into a saturated solution of $NaHCO_3$, extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4), and filtered. The residue was purified by chromatography on SiO_2 (1:5, EtOAc/hexanes) to give *syn-syn*-**3a** (140 mg, 32%) and spiro-*anti*-**4a** (15 mg, 3%).

syn-syn-**3a**: oil; IR (NaCl) ν = 3450−3350 bs, 2924, 1599, 1487, 1275, 1088, 1015, 825, 750; ^{1}H NMR ($CDCl_3$) δ 1.65 (t, J = 5.3 Hz, 1 H), 2.93 (d, J = 12.0 Hz, 1 H), 2.98 (d, J = 12.0 Hz, 1 H), 3.49 (dd, J = 10.5, 5.3 Hz, 1 H), 3.56 (dd, J = 10.5, 5.3 Hz, 1 H), 3.86 (d, J = 8.8 Hz, 1 H), 4.29 (d, J = 8.8 Hz, 1 H), 5.19 (s, 1 H), 5.31 (s, 1 H), 7.24 (d, J = 8.4 Hz, 2 H), 7.37 (m, 4 H), 7.46 (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 39.2, 66.9, 73.4, 74.2, 79.7, 98.4, 128.5, 128.7, 128.9, 129.0, 133.6, 135.2, 137.3, 139.2; HRMS calcd for $C_{18}H_{17}Cl_2NO_2SNa$ $[M + Na]^+$ 404.0249, found 404.0239.

(2*SR*,*anti*)-2,8-Bis(3-chlorophenyl)-7,9-dioxa-3-thia-1-azaspiro[4.5]-decane (**4a**): white solid; mp 164−165 °C; IR (NaCl) ν = 2868, 1603, 1493, 1385, 1094, 1015, 824; ^{1}H NMR ($CDCl_3$) δ 3.25 (dd, J = 11.3 Hz, ^4J = 1.1 Hz, 1 H), 3.58 (d, J = 11.3 Hz, 1 H), 3.82 (dd, J = 10.8 Hz, ^4J = 1.1 Hz, 1 H), 4.01 (m, 2 H), 4.25 (dd, J = 10.8 Hz, ^4J = 2.2 Hz, 1H), 5.46 (s, 1 H), 5.48 (s, 1 H), 7.34 (m, 4 H), 7.44 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 42.1, 64.1, 69.3, 73.4, 73.7, 101.1, 127.5, 128.5, 128.6, 128.8, 134.3, 135.0, 136.0; HRMS calcd for $C_{18}H_{18}Cl_2NO_2S$ $[M + H]^+$ 382.0430, found 382.0443.

Path b

Representative Procedure for the Synthesis of Bisoxazolidines *syn*-2a−e. (2*R*,8*S*)-2,8-Di(*p*-chlorophenyl)-5-hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-2a). To a stirred suspension of Tris·HCl (**5**) (1.0 g, 6.4 mmol) in toluene (25 mL) were added *p*-Cl-benzaldehyde (2.0 g, 14.0 mmol) and catalytic *p*-TsOH (0.1 g, 0.6 mmol). The mixture was heated at reflux in a Dean−Stark trap for 12 h. Then, it was cooled, poured into a saturated solution of $NaHCO_3$, extracted with EtOAc (3 × 100 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residue was purified by chromatography on SiO_2 (1:9, EtOAc/hexanes) to afford **2a** (1.8 g, 77%, *syn*/*anti*: 98:2): yellow oil; IR (NaCl) ν = 3500−3400 bs, 2872, 1597, 1489, 1379, 1207, 1088, 1014, 812; ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 2 H), 3.91 (d, J = 9.0 Hz, 2 H), 4.02 (d, J = 9.0 Hz, 2 H), 5.53 (s, 2 H), 7.35 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 65.5, 72.6, 74.9, 96.6, 128.1, 128.8, 134.6, 137.9; HRMS calcd for $C_{18}H_{18}Cl_2NO_3$ $[M + H]^+$ 366.0664, found 366.0632.

(2*R*,8*S*)-2,8-Di(*p*-fluorophenyl)-5-hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-2b). Prepared in an analogous route as described for *syn*-**2a** to give compound **2b** (34%, *syn*/*anti*: 98:2).

syn-**2b**: the sample had spectroscopic data in agreement with the literature data;[10] IR (NaCl) ν = 3500−3400 b, 2935, 2874, 2367, 2345, 1607, 1508, 1225, 1078, 1007, 837; ^{1}H NMR ($CDCl_3$) δ 3.47 (s, 2 H), 3.92 (d, J = 9.2 Hz, 2 H), 4.03 (d, J = 9.2 Hz, 2 H), 5.54 (s, 2 H), 7.04 (m, 4 H), 7.41 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 65.6, 72.6, 74.9, 96.6, 115.4 (d, J_{CF} = 21.4 Hz), 115.5 (d, J_{CF} = 21.2 Hz), 128.5 (d, J_{CF} = 7.7 Hz), 128.6 (d, J_{CF} = 7.5 Hz), 135.2 (d, J_{CF} = 3.0 Hz), 162.9 (d, J_{CF} = 245.8 Hz).

(2*R*,8*S*)-2,8-Di(*p*-trifluoromethylphenyl)-5-hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-2c). Prepared in an analogous route as described for *syn*-**2a** to give compounds **2c** (32%, *syn*/*anti*: 81:19) and dimer **14c** (13%).

syn-**2c**: the sample had spectroscopic data in agreement with the literature data;[10] white solid; mp 100−101 °C; IR (NaCl) ν = 2936, 2874, 1618, 1412, 1327, 1165, 1124, 1018, 827; ^{1}H NMR ($CDCl_3$) δ 1.58 (t, J = 5.6 Hz, 1 H_{OH}), 3.49 (d, J = 5.6 Hz, 2 H), 3.97 (d, J = 9.0 Hz, 2 H), 4.06 (d, J = 9.0 Hz, 2 H), 5.63 (s, 2 H), 7.56 (d, J = 8.3 Hz, 4 H), 7.64 (d, J = 8.3 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 65.6, 72.7, 75.1, 96.8, 123.9 (q, J_{CF} = 270.5 Hz), 125.6 (q, J_{CF} = 3.6 Hz), 127.12, 131.0 (q, J_{CF} = 32.5 Hz), 143.4.

(2*R*,8*S*)-{Bis(2,8-di(*p*-trifluoromethylphenyl)-1-aza-3,7-dioxabicyclo-[3.3.0]octane 5-methoxy)methyl)}-4-trifluoromethylbenzene (**14c**): pale yellow oil; IR (NaCl) ν = 3067, 2879, 1620, 1412, 1327, 1124, 1067, 827; ^{1}H NMR ($CDCl_3$) δ 3.23 (d, J = 8.9 Hz, 2 H), 3.30 (d, J = 8.9 Hz, 2 H), 3.76 (d, J = 9.0 Hz, 2 H), 3.82 (d, J = 9.0 Hz, 2 H), 3.84 (s, 4 H), 5.36 (s, 1 H), 5.55 (s, 2 H), 5.56 (s, 2 H), 7.23 (d, J = 8.1 Hz, 2 H), 7.53 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 69.4, 73.0, 73.2, 73.3, 96.4, 96.5, 96.5, 100.7, 123.9 (q, J_{CF} = 271.8 Hz), 125.3 (q, J_{CF} = 3.6 Hz), 126.4, 126.5, 126.7, 127.2, 127.3, 130.9 (q, J_{CF} = 32.0 Hz), 140.3, 143.1; HRMS calcd for $C_{48}H_{38}F_{15}N_2O_6$ $[M + H]^+$ 1023.2490, found 1023.2466.

(2*R*,8*S*)-2,8-Di(*m*-bromophenyl)-5-hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-2d). Prepared in analogous route as described for **2a** to give compounds **2d** (30% yield, *syn*/*anti*: 80:20) and dimer **14d** (25% yield).

syn-**2d**: white solid; mp 103−104 °C; IR (NaCl) ν = 3500−3400, 2934, 2874, 1570, 1202, 1082, 1007, 773; ^{1}H NMR ($CDCl_3$) δ 1.64 (bs, 1 H), 3.49 (s, 2 H), 3.93 (d, J = 9.0 Hz, 2 H), 4.04 (d, J = 9.0 Hz, 2 H), 5.52 (s, 2 H), 7.24 (t, J = 7.8 Hz, 2 H), 7.35 (d, J = 7.8 Hz, 2 H), 7.47 (m, 2 H), 7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 65.6, 72.6, 74.7, 95.9, 126.1, 128.7, 130.6, 132.7, 132.8, 139.6; HRMS calcd for $C_{18}H_{17}Br_2NO_3Na$ $[M + Na]^+$ 475.9467, found 475.9448.

anti-**2d**: pale yellow oil; IR (NaCl) ν = 3500−3400, 2870, 1572, 1475, 1433, 1377, 1207, 1070, 758; ^{1}H NMR ($CDCl_3$) δ 2.36 (bs, 1 H_{OH}), 3.70 (d, J = 11.1 Hz, 1 H), 3.75 (d, J = 11.1 Hz, 1 H), 3.82 (d, J = 8.8 Hz, 1 H), 3.86 (d, J = 8.9 Hz, 1 H), 4.08 (d, J = 8.9 Hz, 1 H), 4.19 (d, J = 8.8 Hz, 1 H), 5.08 (s, 1 H), 5.46 (s, 1 H), 6.86 (d, J = 7.6 Hz, 1 H), 7.03 (d, J = 7.6 Hz, 1 H), 7.06 (s, 1 H), 7.08 (d, J = 7.6 Hz, 1 H), 7.20 (d, J = 7.6 Hz, 1 H), 7.34 (m, 1 H), 7.40 (m, 1 H), 7.45 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 65.1, 71.7, 74.4, 74.5, 92.5, 93.1, 122.0, 122.4, 125.6, 125.7, 129.5, 129.6, 130.2, 130.3, 131.6, 131.8, 136.0, 141.7; HRMS calcd for $C_{18}H_{18}NO_3Br_2$ $[M + H]^+$ 453.9653, found 453.9665.

(2*R*,8*S*)-{Bis(2,8-di(*m*-bromophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]-octane 5-methoxy)methyl)}-3-bromobenzene (**14d**): pale yellow oil; IR (NaCl) ν = 3061, 2870, 1572, 1469, 1377, 1199, 1086, 779; ^{1}H NMR ($CDCl_3$) δ 3.25 (d, J = 9.1 Hz, 2 H), 3.28 (d, J = 9.1 Hz, 2 H), 3.77 (d, J = 9.0 Hz, 2 H), 3.81 (s, 2 H), 3.84 (s, 2H), 3.89 (d, J = 9.0 Hz, 2 H), 5.31 (s, 1 H), 5.44 (s, 2 H), 5.48 (s, 2 H), 7.18 (m, 5 H), 7.31 (m, 5 H), 7.44 (m, 5 H), 7.58 (bs, 5 H); ^{13}C NMR ($CDCl_3$) δ 69.4, 72.9, 73.2, 73.5, 96.0, 96.4, 100.7, 122.4, 122.5, 125.6, 125.7, 129.4, 129.9, 130.0, 130.1, 131.7, 131.8, 132.0, 139.1, 141.5, 141.6; HRMS calcd for $C_{43}H_{37}N_2O_6Br_5Na$ $[M + Na]^+$ 1098.8425, found 1098.8402.

(2*R*,8*S*)-2,8-Di(3,4-dichlorophenyl)-5-hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-2e). Prepared in an analogous route as described for **2a** to give **2e** (20% yield, *syn*/*anti* 83:17) and dimer **14e** (35% yield).

syn-**2e**: oil; IR (NaCl) ν = 3500 bs, 2936, 2874, 1468, 1204, 1086, 1032, 828, 756; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 2 H), 3.92 (d, J = 9.0 Hz, 2 H), 4.03 (d, J = 9.0 Hz, 2 H), 5.49 (s, 2 H), 7.23 (m, 2 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 65.7, 72.7, 74.9, 96.1, 126.1, 128.8, 130.7, 132.8, 132.9, 139.7; HRMS calcd for $C_{18}H_{15}Cl_4NO_3Na$ $[M + Na]^+$ 455.9698, found 455.9683.

anti-**2e**: white solid; mp 122−124 °C; IR (NaCl) ν = 3500−3400 bs, 2870, 1472, 1412, 1366, 1213, 1082, 1032, 827; ^{1}H NMR ($CDCl_3$) δ 3.71 (d, J = 11.1 Hz, 1 H), 3.76 (d, J = 11.1 Hz, 1 H), 3.83 (J = 8.9 Hz, 1 H), 3.88 (d, J = 9.0 Hz, 1 H), 4.09 (d, J = 9.0 Hz, 1 H), 4.19 (d, J = 8.9 Hz, 1 H), 5.04 (s, 1 H), 5.45 (s, 1 H), 6.82 (dd, J = 8.3, 2.0 Hz, 1 H), 7.03 (d, J = 2.0 Hz, 1 H), 7.12 (dd, J = 8.3, 1.7 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 1 H),

7.31 (d, J = 8.3 Hz, 1 H), 7.38 (d, J = 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 65.1, 72.0, 74.4, 74.5, 92.0, 92.6, 126.3, 126.4, 129.2, 129.3, 130.1, 130.2, 132.3, 132.6, 132.7, 133.1, 134.0, 139.7; HRMS calcd for $C_{18}H_{16}NO_3Cl_4$ $[M + H]^+$ 433.9884, found 433.9862.

(2*R*,8*S*)-{Bis(2,8-di(*m*,*p*-dichlorophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]-octane 5-methoxy)methyl)}-3,4-dichlorobenzene (**14e**): pale yellow solid; mp 79−90 °C; IR (NaCl) ν = 3065, 2872, 1566, 1469, 1367, 1204, 1032, 825, 737; ^{1}H NMR ($CDCl_3$) δ 3.22 (d, J = 9.1 Hz, 2 H), 3.26 (d, J = 9.1 Hz, 2 H), 3.75 (d, J = 9.1 Hz, 2 H), 3.82 (d, J = 9.1 Hz, 2 H), 3.83 (d, J = 9.2 Hz, 2 H), 3.86 (d, J = 9.2 Hz, 2 H), 5.30 (s, 1H), 5.41 (s, 2 H), 5.44 (s, 2 H), 6.95 (dd, J = 8.3, 2.0 Hz, 1H), 7.19 (m, 4 H), 7.25 (d, J = 2.0 Hz, 1H), 7.37 (t, J = 8.3 Hz, 5 H), 7.49 (d, J = 1.9 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 69.1, 73.0, 73.2, 95.7, 95.9, 126.2, 126.3, 128.9, 129.0, 130.5, 132.6, 132.8, 132.9, 139.4; HRMS calcd for $C_{43}H_{32}Cl_{10}N_2O_6Na$ $[M + Na]^+$ 1044.9038, found 1044.9040.

Representative Procedure for the Synthesis of 5-Acetylhythiomethyl-bisoxazolidines 14a−e. (2*R*,8*S*)-2,8-Di(4-chlorophenyl)-5-acetylthiomethyl-1-aza-3,7-dioxabicyclo [3.3.0]-octane (*syn*-15a). To an ice-cold solution of triphenylphosphine (5.7 g, 21.6 mmol) in benzene (30 mL) was added diethyl azodicarboxylate (3.4 mL, 21.6 mmol) over 5 min. After 30 min of stirring, compound *syn*-**2a** (3.0 g, 9.8 mmol) was added, and stirring was continued for 10 min. To the resulting suspension was added dropwise a solution of thioacetic acid (1.6 mL, 21.6 mmol) in benzene (5 mL), and stirring was continued for another 1 h at 0 °C. The mixture was stirred at rt overnight and heated for 5 h to reflux. The solvent was removed under reduced pressure, and the crude residue was purified by chromatography on SiO_2 (1:4, EtOAc/hexanes) to afford compound *syn*-**15a** (1.09 g, 75%) as a light yellow oil: IR (NaCl) ν = 2868, 1693, 1489, 1267, 1121, 1089, 1015, 812, 627; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.04 (s, 2 H), 3.85 (d, J = 9.0 Hz, 2 H), 3.90 (d, J = 9.0 Hz, 2 H), 5.48 (s, 2 H), 7.34 (d, J = 8.4 Hz, 4 H), 7.44 (d, J = 8.4 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 30.5, 36.2, 73.7, 74.3, 96.8, 128.5, 128.6, 132.2, 132.3, 134.6, 137.6, 194.9; HRMS calcd for $C_{20}H_{19}Cl_2NO_3SNa$ $[M + Na]^+$ 446.0355, found 446.0349.

(2*R*,8*S*)-2,8-Di(*p*-fluorophenyl)-5-acetylthiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-15b). Prepared in an analogous route as described for **15a**, in 54% yield, as a white solid; mp 78−79 °C; IR (NaCl) ν = 2932, 2868, 1701, 1605, 1508, 1225, 1078, 1015, 837; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 3.05 (s, 2 H), 3.86 (d, J = 9.0 Hz, 2 H), 3.90 (d, J = 9.0 Hz, 2 H), 5.49 (s, 2 H), 7.05 (t, J = 8.6 Hz, 4 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.50 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 30.5, 36.4, 73.6, 74.4, 96.8, 115.3 (d, J_{CF} = 21.6 Hz), 129.0 (d, J_{CF} = 8.3 Hz), 134.8 (d, J_{CF} = 2.9 Hz), 163.0 (d, J_{CF} = 245.7 Hz), 195.0; HRMS calcd for $C_{20}H_{19}F_2NO_3SNa$ $[M + Na]^+$ 414.0946, found 414.0927.

(2*R*,8*S*)-2,8-Di(*p*-trifluoromethylphenyl)-5-acetylthiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-15c). Prepared in an analogous route as described for *syn*-**15a**, in 71% yield as a white solid; mp 71−72 °C; IR (NaCl) ν = 3022, 2872, 1695, 1327, 1126, 1018, 827, 762; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3 H), 3.05 (s, 2 H), 3.87 (d, J = 9.1 Hz, 2 H), 3.94 (d, J = 9.1 Hz, 2 H), 5.58 (s, 2 H), 7.64 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 30.5, 36.0, 73.9, 74.3, 97.0, 124.0 (q, J_{CF} = 271.0 Hz), 125.5 (q, J_{CF} = 3.7 Hz), 127.5, 130.8 (q, J_{CF} = 32.3 Hz), 130.9 (q, J_{CF} = 32.3 Hz), 143.0, 194.8; HRMS calcd for $C_{22}H_{19}F_6NO_3SNa$ $[M + Na]^+$ 514.0882, found 514.0909.

(2*R*,8*S*)-2,8-Di(*m*-bromophenyl)-5-acetylthiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-15d). Prepared in an analogous route as described for **15a**, in 84% yield as white solid; mp 101 °C dec; IR (NaCl) ν = 2934, 2868, 1701, 1686, 1560, 1123, 1070, 773; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 3.06 (s, 2 H), 3.86 (d, J = 9.0 Hz, 2 H), 3.90 (d, J = 9.0 Hz, 2 H), 5.48 (s, 2 H), 7.25 (m, 2 H), 7.46 (m, 4 H), 7.67 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 30.5, 36.1, 73.8, 74.3, 96.8, 122.6, 125.8, 130.1, 130.3, 131.8, 141.4, 194.8; HRMS calcd for $C_{20}H_{19}Br_2NO_3SNa$ $[M + Na]^+$ 533.9345, found 533.9347.

(2*R*,8*S*)-2,8-Di(*m*,*p*-Dichlorophenyl)-5-acetylthiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-15e). Prepared in an analogous route as described for **15a** in 78% yield as white solid; mp 134−135 °C; IR (NaCl) ν = 2932, 2868, 1757, 1701, 1466, 1259, 1105, 1030; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 3.05 (s, 2 H), 3.85 (d, J = 9.0 Hz, 2 H), 3.90 (d, J = 9.0 Hz, 2 H), 5.45 (s, 2 H), 7.32 (dd, J = 8.2, 2.0 Hz, 2 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.59 (d, J = 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 30.5, 36.0, 73.9, 74.3, 96.3, 126.5, 129.1, 130.6, 132.2, 132.3, 132.7, 132.9, 139.3, 194.7; HRMS calcd for $C_{20}H_{17}Cl_4NO_3SNa$ $[M + Na]^+$ 513.9575, found 513.9584.

Representative Procedure for the Preparation of Thiols *syn*-8a−e. (2*R*,8*S*)- and (2*R*,8*S*)-2,8-Di(4-Chlorophenyl)-5-thiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-8a). To an ice-cooled solution of MeOH saturated with NH_3 was added compound *syn*-**15a** (100 mg, 0.27 mmol). The reaction mixture was stirred at rt overnight under N_2. The solvent was removed under reduced pressure, and the residue was purified by chromatography (1:6 EtOAc/hexanes) to afford *syn*-**8a** (55 mg, 66% yield) as an oil: IR (NaCl) ν = 2868, 2804, 1701, 1605, 1508, 1225, 1078, 837; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 8.8 Hz, 1 H_{SH}), 2.61 (d, J = 8.8 Hz, 2 H), 3.94 (d, J = 9.0 Hz, 2 H), 4.01 (d, J = 9.0 Hz, 2 H), 5.52 (s, 2 H), 7.33 (d, J = 8.2 Hz, 4 H), 7.42 (d, J = 8.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 32.0, 73.8, 75.2, 96.9, 128.4, 129.6, 134.5, 137.8; HRMS calcd for $C_{18}H_{17}Cl_2NO_2SNa$ $[M + Na]^+$ 404.0249, found, 404.0230.

(2*R*,8*S*)- and (2*R*,8*S*)-2,8-Di(4-fluorophenyl)-5-thiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-8b). Prepared in an analogous route as described for **8a**, to afford **8b** (62%) as an oil: IR (NaCl) ν = 3073, 2934, 2868, 1605, 1506, 1225, 1153, 1076, 1015, 839; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 8.6 Hz, 1 H_{SH}), 2.63 (d, J = 8.6 Hz, 2 H), 3.94 (d, J = 9.0 Hz, 2 H), 4.02 (d, J = 9.0 Hz, 2 H), 5.53 (s, 2 H), 7.04 (m, 4 H), 7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 32.1, 73.9, 75.2, 97.0, 115.3 (d, J_{CF} = 21.7 Hz), 128.8 (d, J_{CF} = 8.3 Hz), 135.0 (d, J_{CF} = 3.0 Hz), 162.9 (d, J_{CF} = 245.7 Hz); HRMS calcd for $C_{18}H_{18}F_2NO_2S$ $[M + H]^+$ 350.1021, found 350.1025.

(2*R*,8*S*)- and (2*R*,8*S*)-2,8-Di(4-trifluoromethylphenyl)-5-thiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-8c). Prepared in an analogous route as described for **8a**, to afford **8c** (65%) as a white solid; mp 63−64 °C; IR (NaCl) ν = 2938, 2870, 1412, 1327, 1124, 1067, 827; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 8.6 Hz, 1 H_{SH}), 2.63 (d, J = 8.6 Hz, 2 H), 3.99 (d, J = 9.1 Hz, 2 H), 4.03 (d, J = 9.1 Hz, 2 H), 5.62 (s, 2 H), 7.62 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 31.8, 73.9, 75.5, 97.1, 123.9 (q, J_{CF} = 270.6 Hz), 125.5 (q, J_{CF} = 3.7 Hz), 127.4, 131.0 (q, J_{CF} = 32.0 Hz), 143.2; HRMS calcd for $C_{20}H_{17}F_6NO_2SNa$ $[M + Na]^+$ 472.0776, found 472.0767.

(2*R*,8*S*)- and (2*R*,8*S*)-2,8-Di(3-bromophenyl)-5-thiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-8d). Prepared in an analogous route as described for **8a**, except that the mixture was stirred for 3 h, to give a mixture of **8d** (44%), disulfide **16d** (43%), and recovered starting material **15d** (10%).

syn-**8d**: white solid; mp 79−80 °C; IR (NaCl) ν = 3065, 2932, 2868, 1570, 1202, 1121, 997, 773; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 8.6 Hz, 1 H_{SH}), 2.64 (d, J = 8.6 Hz, 2 H), 3.95 (d, J = 9.1 Hz, 2 H), 4.02 (d, J = 9.1 Hz, 2 H), 5.52 (s, 2 H), 7.24 (t, J = 7.8 Hz, 2 H), 7.40 (d, J = 7.8 Hz, 2 H), 7.46 (m, 2 H), 7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 31.9, 73.8, 75.4, 96.9, 122.6, 125.7, 130.1, 131.8, 141.6; HRMS calcd for $C_{18}H_{16}Br_2NO_2S$ $[M - H]^-$ 467.9274, found 467.9294.

(2*R*,8*S*)- and (2*R*,8*S*)-Bis(2,8-di(3-bromophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane 5-methyldisulfide (*syn*-**16d**): oil; IR (NaCl) ν = 2868, 1572, 1469, 1435, 1199, 1119, 1069, 1009, 775; ^{1}H NMR ($CDCl_3$) δ 2.86 (s, 4 H), 3.87 (d, J = 9.1 Hz, 4 H), 4.01 (d, J = 9.1 Hz, 4 H), 5.47 (s, 4 H), 7.23 (t, J = 7.8 Hz, 4 H), 7.41 (d, J = 7.8 Hz, 4 H), 7.47 (d, J = 7.8 Hz, 4 H), 7.65 (s, 4 H); ^{13}C NMR ($CDCl_3$) 47.5, 73.9, 74.4, 96.5, 122.5, 125.7, 130.0, 130.1, 131.8, 141.3; HRMS calcd for $C_{36}H_{33}Br_4N_2O_4S_2$ $[M + H]^+$ 936.8610, found 936.8592.

(2*R*,8*S*)- and (2*R*,8*S*)-2,8-Di(3,4-dichlorophenyl)-5-thiomethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (*syn*-8e). Prepared in an analogous route as described for **8a**, except that the mixture was

stirred for 3 h, to give a mixture of *syn*-**8e** (25%), disulfide **16e** (53%), and recovered starting material **15e** (10%).

syn-**8e**: oil; IR (NaCl) ν = 2932, 2868, 1701, 1686, 1466, 1130, 1030, 827, 625; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 8.6 Hz, 1 H_{SH}), 2.62 (d, J = 8.6 Hz, 2 H), 3.95 (d, J = 9.1 Hz, 2 H), 4.01 (d, J = 9.1 Hz, 2 H), 5.49 (s, 2 H), 7.30 (dd, J = 8.2, 2.1 Hz, 2 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.57 (d, J = 2.1 Hz, 2 H) ; ^{13}C NMR ($CDCl_3$) δ 31.9, 73.8, 75.4, 96.4, 126.3, 129.0, 130.6, 132.7, 132.9, 139.5; HRMS calcd for $C_{18}H_{16}Cl_4NO_2S$ $[M + H]^+$ 449.9656, found 449.9647.

(2*R*,8*S*)- and (2*R*,8*S*)-Bis(2,8-di(3,4-dichlorophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane 5-methyldisulfide (*syn*-**16e**): white solid; mp 147−148 °C; IR (NaCl) ν = 2932, 2870, 1468, 1367, 1204, 1113, 1030, 737; ^{1}H NMR ($CDCl_3$) δ 2.84 (s, 4 H), 3.87 (d, J = 9.2 Hz, 4 H), 3.99 (d, J = 9.2 Hz, 4 H), 5.43 (s, 4 H), 7.30 (dd, J = 8.3, 2.0 Hz, 4 H), 7.43 (d, J = 8.3 Hz, 4 H), 7.57 (d, J = 2.0 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 47.6, 73.9, 74.4, 96.1, 126.4, 129.1, 130.6, 132.7, 133.0, 139.2; HRMS calcd for $C_{36}H_{29}Cl_8N_2O_4S_2$ $[M + H]^+$ 896.9072, found 896.9058.

Reduction of Disulfide 16d. To a stirred solution of dimer **16d** (90 mg, 0.10 mmol) in MeOH (3 mL) and CH_2Cl_2 (1 mL) was added portionwise $NaBH_4$ (21 mg, 0.60 mmol). The mixture was stirred at rt for 4 h. Then, the solvent was removed under reduced pressure. The crude residue was poured into H_2O (15 mL), the pH was adjusted to 6 with HCl 5%, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The solvent was removed under reduced pressure,and the residue was purified by chromatography on SiO_2 (1:4, EtOAc/hexanes) to afford *syn*-**8d** (20 mg, 25% yield, 60% yield based on recovered starting material **16d**).

Reduction of Disulfide 16e. Prepared in an analogous route as described for the reduction of disulfide **16d** to give **8e** (40%, 70% yield based on recovered starting material **16e**).

Representative Procedure for the Synthesis of *anti-syn*-Thiazolidinyl-oxazolidines 3a−d, Conditions A. (2*R*,5*S*,8*R*)- and (2*S*,5*R*,8*S*)-2,8-Di(*p*-chlorophenyl)-5-hydroxymethyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (*anti-syn*-3a). To a stirred solution of thiol *syn*-**8a** (40 mg, 0.10 mmol) in CH_2Cl_2 (8 mL) was added *p*-TsOH ac. (4 mg, 0.02 mmol). The mixture was heated to reflux for 6 h and left overnight at rt. The solvent was removed under reduced pressure, and the crude residue was poured into a saturated solution of $NaHCO_3$, extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure and the crude residue was purified by chromatography on SiO_2 (1:4 EtOAc/hexanes) to afford compound **3a** as an oil (25 mg, 62%, *anti-syn/syn-syn* 99:1).

anti-syn-**3a**: white solid; mp 106−107 °C; IR (NaCl) ν = 3500−3400 bs, 2932, 2872, 1560, 1491, 1089, 1045, 1014, 827; ^{1}H NMR ($CDCl_3$) δ 2.33 (bs, 1 H_{OH}), 3.07 (d, J = 11.8 Hz, 1 H), 3.24 (d, J = 11.8 Hz, 1 H), 3.76 (d, J = 10.8 Hz, 1 H), 3.86 (d, J = 10.8 Hz, 1 H), 3.88 (d, J = 8.7 Hz, 1 H), 4.02 (d, J = 8.7 Hz, 1 H), 5.13 (s, 1 H), 5.54 (s, 1 H), 6.96 (d, J = 8.5 Hz, 2 H), 7.10 (d, J = 8.5 Hz, 2 H), 7.19 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 39.8, 65.8, 69.4, 72.8, 79.8, 94.6, 128.1, 128.2, 128.3, 128.7, 132.6, 133.1, 134.7, 140.3; HRMS calcd for $C_{18}H_{17}Cl_2NO_2SNa$ $[M + Na]^+$ 404.0249, found 404.0235.

(2*R*,5*S*,8*R*)- and (2*S*,5*R*,8*S*)-2,8-Di(4-fluorophenyl)-5-hydroxymethyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (*anti-syn*-3b). Prepared under conditions A, in an analogous route as described for *anti-syn*-**3a**, to give **3b** (44% yield, *anti-syn/syn-syn* 90:10).

anti-syn-**3b**: white solid; mp 90−91 °C; IR (NaCl) ν = 3500−3400 bs, 2929, 2872, 1605, 1510, 1385, 1227, 1155, 1047, 839; ^{1}H NMR ($CDCl_3$) δ 2.37 (bs, 1 H_{OH}), 3.09 (d, J = 11.8 Hz, 1 H), 3.23 (d, J = 11.8 Hz, 1 H), 3.77 (d, J = 10.9 Hz, 1 H), 3.86 (d, J = 10.9 Hz, 1 H), 3.87 (d, J = 8.8 Hz, 1 H), 4.02 (d, J = 8.8 Hz, 1 H), 5.18 (s, 1 H), 5.53 (s, 1 H), 6.80 (t, J = 8.8 Hz, 2 H), 6.87 (t, J = 8.8 Hz, 2 H), 6.97 (dd, J_{HH} = 8.5 Hz, J_{HF} = 5.5 Hz, 2 H), 7.23 (dd, J_{HH} = 8.5 Hz, J_{HF} = 5.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 39.9, 65.8, 69.4, 72.7, 79.6, 94.6, 114.8 (d, J_{CF} = 21.5 Hz), 114.9 (d, J_{CF} = 21.4 Hz), 128.4 (d, J_{CF} = 8.0 Hz), 129.2 (d, J_{CF} = 8.2 Hz), 129.8 (d, J_{CF} = 3.3 Hz), 137.1 (d, J_{CF} = 2.8 Hz), 162.0 (d, J_{CF} = 244.7 Hz), 162.8 (d, J_{CF} = 246.5 Hz); HRMS calcd for $C_{18}H_{18}F_2NO_2S$ $[M + H]^+$ 350.1021, found 350.1022.

syn-syn-**3b**: pale yellow oil; IR (NaCl) ν = 3350−3450 bs, 2924, 2855, 1604, 1508, 1226, 1045, 837; ^{1}H NMR ($CDCl_3$) δ 2.93 (d, J = 12.0 Hz, 1 H), 3.00 (d, J = 12.0 Hz, 1 H), 3.50 (d, J = 10.0 Hz, 1 H), 3.55 (d, J = 10.0 Hz, 1 H), 3.86 (d, J = 8.8 Hz, 1 H), 4.28 (d, J = 8.8 Hz, 1 H), 5.21 (s, 1 H), 5.32 (s, 1 H), 6.95 (t, J = 8.6 Hz, 2 H), 7.10 (t, J = 8.6 Hz, 2 H), 7.41 (dd, J_{HH} = 8.6 Hz, J_{HF} = 5.2 Hz, 2 H), 7.51 (dd, J_{HH} = 8.6 Hz, J_{HF} = 5.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 39.3, 67.0, 73.4, 74.3, 79.7, 98.4, 115.2 (d, J_{CF} = 21.3 Hz), 115.6 (d, J_{CF} = 21.8 Hz), 129.1 (d, J_{CF} = 8.2 Hz), 129.5 (d, J_{CF} = 8.7 Hz) 134.7 (d, J_{CF} = 2.8 Hz), 136.3 (d, J_{CF} = 3.1 Hz), 162.3 (d, J_{CF} = 247.0 Hz), 163.3 (d, J_{CF} = 247.6 Hz); HRMS calcd for $C_{18}H_{17}F_2NO_2S$ $[M + H]^+$ 350.1021, found 350.1024.

(2*R*,5*S*,8*R*)- and (2*S*,5*R*,8*S*)-2,8-Di(4-trifluoromethylphenyl)-5-hydroxymethyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (*anti-syn*-3c). Prepared in an analogous route as described for *anti-syn*-**3a**, to give **3c** (64%, *anti-syn/syn-syn* 81:19).

anti-syn-**3c**: white solid; mp 106−107 °C; IR (NaCl) ν = 3309, 2932, 2870, 1738, 1697, 1327, 1163, 1126, 1069, 837; ^{1}H NMR ($CDCl_3$) δ 2.30 (t, J = 5.6 Hz, 1 H), 3.12 (d, J = 11.9 Hz, 1 H), 3.30 (d, J = 11.9 Hz, 1 H), 3.81 (dd, J = 10.9, 5.6 Hz, 1 H), 3.91 (d, J = 8.8 Hz, 1 H), 3.93 (dd, J = 10.9, 5.6 Hz, 1 H), 4.06 (d, J = 8.8 Hz, 1 H), 5.15 (s, 1 H), 5.61 (s, 1 H), 7.10 (d, J = 8.2 Hz, 2 H), 7.36 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 39.7, 66.0, 69.5, 73.0, 79.7, 94.2, 124.9 (q, J_{CF} = 3.5 Hz), 126.4 (q, J_{CF} = 276.0 Hz), 127.14, 127.72, 129.7 (q, J_{CF} = 32.0 Hz), 130.9 (q, J_{CF} = 32.1 Hz), 137.78, 145.2; HRMS calcd for $C_{20}H_{17}F_6NO_2SNa$ $[M + Na]^+$ = 472.0776 found: 472.0773.

syn-syn-**3c**: oil; IR (NaCl) ν = 3500−3400 b, 2934, 2876, 1419, 1327, 1124, 1069, 839; ^{1}H NMR ($CDCl_3$) δ 1.64 (t, J = 5.0 Hz, 1 H), 2.98 (s, 2 H), 3.52 (dd, J = 10.6, 5.0 Hz, 1 H), 3.63 (dd, J = 10.6, 5.0 Hz, 1 H), 3.90 (d, J = 8.8 Hz, 1 H), 4.34 (d, J = 8.8 Hz, 1 H), 5.28 (s, 1 H), 5.41 (s, 1 H), 7.53 (d, J = 8.7 Hz, 2 H), 7.57 (d, J = 8.7 Hz, 2 H), 7.64 (d, J = 8.6 Hz, 2 H), 7.68 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 39.2, 67.0, 73.7, 74.3, 80.0, 98.4, 123.9 (q, J_{CF} = 270.8 Hz), 125.3 (q, J_{CF} = 3.4 Hz), 125.7 (q, J_{CF} = 3.7 Hz), 127.7, 127.9, 130.1 (q, J_{CF} = 32.4 Hz), 131.5 (q, J_{CF} = 32.1 Hz) 142.8, 144.7 (q, J_{CF} = 1.0 Hz); HRMS calcd for $C_{20}H_{17}F_6NO_2S$ $[M + H]^+$ 450.0957, found 450.0953.

(2*R*,5*S*,8*R*)- and (2*S*,5*R*,8*S*)-2,8-Di(3-bromophenyl)-5-hydroxymethyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (*anti-syn*-3d). Prepared in an analogous route as described for *anti-syn*-**3a**, to give a mixture of **3d** (64%, *anti-syn/syn-syn* (95:5) and spiro-**4d** (20%, diastereomeric ratio = 7:3).

anti-syn-**3d**: oil; IR (NaCl) ν = 3500−3400 b, 3067, 2928, 2872, 1570, 1213, 1045, 997, 787, 727; ^{1}H NMR ($CDCl_3$) δ 2.46 (bs, 1 H_{OH}), 3.08 (d, J = 11.9 Hz, 1 H), 3.26 (d, J = 11.9 Hz, 1 H), 3.77 (d, J = 10.9 Hz, 1 H), 3.86 (d, J = 8.7 Hz, 1 H), 3.87 (d, J = 10.9 Hz, 1 H), 4.01 (d, J = 8.7 Hz, 1 H), 5.11 (s, 1 H), 5.49 (s, 1 H), 6.99 (m, 3 H), 7.10 (t, J = 1.8 Hz, 1 H), 7.15 (d, J = 7.8 Hz, 1H), 7.25 (m, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 7.42 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 39.7, 65.9, 69.5, 72.7, 79.6, 94.1, 121.9, 122.3, 125.5, 125.9, 129.4, 129.5, 130.0, 130.6, 130.7, 131.9, 136.0, 143.5; HRMS calcd for $C_{18}H_{18}Br_2NO_2S$ $[M + H]^+$ 469.9420, found 469.9432.

syn-syn-**3d**: oil; IR (NaCl) ν = 3500−3400 bs, 2928, 2870, 1574, 1469, 1433, 1367, 1209, 1068, 997, 785; ^{1}H NMR ($CDCl_3$) δ 1.65 (bs, 1 H), 2.94 (d, J = 12.1 Hz, 1 H), 3.00 (d, J = 12.1 Hz, 1 H), 3.51 (d, J = 10.6 Hz, 1 H), 3.60 (d, J = 10.6 Hz, 1 H), 3.86 (d, J = 8.8 Hz, 1 H), 4.30 (d, J = 8.8 Hz, 1 H), 5.20 (s, 1 H), 5.29 (s, 1 H), 7.15 (t, J = 7.9 Hz, 1 H), 7.29 (t, J = 7.9 Hz, 1 H), 7.35 (m, 2 H), 7.44 (d, J = 7.9 Hz, 1 H), 7.52 (d, J = 7.9 Hz, 1 H), 7.66 (d, J = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 39.2, 66.9, 73.4, 74.3, 79.8, 98.3, 122.6, 122.7, 126.0, 126.3, 129.9, 130.3, 130.5, 130.8, 130.9, 132.5, 141.1, 143.1; HRMS calcd for $C_{18}H_{17}Br_2NO_2SNa$ $[M + Na]^+$ 491.9239, found 491.9215.

(2*SR*,*syn*/*anti*)-2,8-Bis(3-bromophenyl)-7,9-dioxa-3-thia-1-azaspiro-[4.5]decane (spiro-**4d**), major product: pale yellow oil; IR (NaCl) ν = 3065, 2857, 1570, 1474, 1425, 1379, 1207, 1107, 783; ^{1}H NMR ($CDCl_3$) δ

2.71 (d, J = 10.9 Hz, 1 H), 2.85 (d, J = 10.9 Hz, 1 H), 3.83 (d, J = 11.7 Hz, 1 H), 4.07 (d, J = 11.4 Hz, 1 H), 4.15 (dd, J = 11.4 Hz, ^4J = 2.9 Hz, 1 H), 4.35 (dd, J = 11.7, ^4J = 2.9 Hz, 1 H), 5.53 (s, 1 H), 5.58 (s, 1 H), 7.22 (m, 2 H), 7.42 (m, 4 H), 7.67 (m, 1 H), 7.74 (m, 1 H); HRMS calcd for $C_{18}H_{18}Br_2NO_2S$ $[M + H]^+$ 469.9420, found 469.9432.

(2*SR*,*syn*/*anti*)-2,8-Bis(3,4-dichlorophenyl)-7,9-dioxa-3-thia-1-azaspiro[4.5]decane (spiro-4e). Prepared in an analogous route as described for *anti-syn*-**3a**, to give spiro-**4e** (80%, *syn*/*anti* 8:2).

syn-**4e**: solid; mp 108−109 °C; IR (NaCl) ν = 3323.35, 2926, 2855, 1472, 1375, 1101, 1031, 822; ^{1}H NMR ($CDCl_3$) δ 2.70 (d, J = 10.9 Hz, 1 H), 2.84 (d, J = 10.9 Hz, 1 H), 2.93 (bs, 1H), 3.83 (d, J = 11.5 Hz, 1 H), 4.05 (d, J = 11.5 Hz, 1 H), 4.13 (dd, J = 11.5, 2.9 Hz, 1 H), 4.33 (dd, J = 11.5, 2.9 Hz, 1 H), 5.51 (s, 1 H), 5.55 (s, 1 H), 7.33 (td, J = 8.4, 2.0 Hz, 2 H), 7.40 (d, J = 8.3 Hz, 1 H), 7.44 (d, J = 8.3 Hz, 1 H), 7.61 (d, J = 2.0 Hz, 1 H), 7.68 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 36.4, 63.6, 66.4, 71.3, 74.8, 100.1, 125.4, 126.8, 128.2, 129.4, 130.2, 130.3, 132.2, 132.5, 132.6, 133.1, 137.4, 140.8; HRMS calcd for $C_{18}H_{16}Cl_4NO_2S$ $[M + H]^+$ 449.9650, found 449.9634.

Representative Procedure for the Synthesis of *syn-syn*-3a and -3d, Conditions B. (2*S*,5*S*,8*R*)- and (2*R*,5*R*,8*S*)-2,8-Di(*p*-chlorophenyl)-5-hydroxymethyl-1-aza-3-oxa-7-thiabicyclo-[3.3.0]octane (*syn-syn*-3a). To a stirred solution of thiol *syn*-**8a** (100 mg, 0.28 mmol) in PhMe (10 mL) were added *p*-TsOH acid (10 mg, 0.058 mmol) and *p*-Cl benzaldehyde (40 mg, 0.28 mmol). The mixture was heated at reflux in a Dean−Stark trap for 5 h. The solvent was removed under reduced pressure and the crude residue was poured into a saturated solution of $NaHCO_3$, extracted with EtOAc (3 × 50 mL), dried, and filtered. The solvent was removed under reduced pressure, and the crude residue was purified by chromatography on SiO_2 (1:5, EtOAc/hexanes) to afford a mixture of **3a** (41 mg, 41%, *anti-syn*/*syn-syn* 10:90) and spiro-*anti*-**4a** (46 mg, 46% yield).

Synthesis of *syn-syn*-3d, Conditions B. Prepared in analogous route as described for *syn-syn*-**3a** (method B), except the reaction mixture was heated for 2 h, to give a mixture of *syn-syn*-**3d** (66% yield, *anti-syn*/*syn-syn* 7:93) and spiro-**4d** (20% yield, *anti*/*syn* 8:2).

(2*RS*,*anti*)-**4d**: oil, ^{1}H NMR ($CDCl_3$) δ 3.25 (dd, J = 11.2 Hz, ^4J = 1.4 Hz, 1 H), 3.58 (d, J = 11.2 Hz, 1 H), 3.82 (dd, J = 10.8 Hz, ^4J = 1.4 Hz, 1 H), 4.01 (s, 1 H), 4.02 (d, ^4J = 2.4 Hz, 1 H), 4.25 (d, J = 10.8 Hz, ^4J = 2.4 Hz, 1 H), 5.46 (s, 1 H), 5.47 (s, 1 H), 7.24 (m, 2 H), 7.45 (m, 4 H), 7.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) 42.1, 64.1, 69.2, 73.4, 73.8, 100.8, 122.4, 122.7, 124.8, 126.0, 129.3, 129.9, 130.2, 130.3, 131.6, 132.2, 139.5, 142.1; HRMS calcd for $C_{18}H_{17}Br_2NO_2SNa$ $[M + Na]^+$ 491.9239, found 491.9215.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C spectra for **2c**−**e**, **3a**−**d**, **4a**, **4d**, **4e**, **9**, **11a**, **12a**, **8a**−**e**, **15a**−**e**, and **16e**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Lambert, J. B.; Wang, G. T.; Huseland, D. E.; Takiff, L. C. *J. Org. Chem.* **1987**, *52*, 68–71.
(2) Selected reviews: (a) Ladame, S. *Org. Biomol. Chem.* **2008**, *6*, 219–226. (b) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711.
(3) (a) Lazar, L.; Fulöp, F. *Act. Pharm. Hung.* **1999**, *69*, 202–207. (b) Botti, P.; Pallin, T. D.; Tam, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10018–10024.
(4) (a) Talancón, D.; Bosque, R.; López, C. *J. Org. Chem.* **2010**, *75*, 3294–3300. (b) Keiko, N. A.; Vchislo, N. V.; Stepanova, L. G.; Larina, L. I.; Chuvashev, Y. A.; Funtikova, E. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 1466–1471. (c) Lazar, L.; Fulöp, F. *Eur. J. Org. Chem.* **2003**, 3025–3042.
(5) Saiz, C.; Wipf, P.; Manta, E.; Mahler, S. G. *Org. Lett.* **2009**, *11*, 3170–3173.
(6) Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515–1519.
(7) Darabantu, M.; Maiereanu, C.; Silaghi-Dumitrescu, I.; Toupet, L.; Condamine, E.; Ramondenc, Y.; Berghian, C.; Plé, G.; Plé, N. *Eur. J. Org. Chem.* **2004**, *12*, 2644–2661.
(8) Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638–6639.
(9) Shintani, Y.; Tanaka, T.; Nozaki, Y. *Cancer Chemother. Pharmacol.* **1997**, *40*, 513–520.
(10) Desino, K. E.; Ansar, S.; Georg, G. I.; Himes, R. H.; Michaelis, M. L.; Powell, D.; Reiff, E. A.; Telikepalli, H.; Audus, K. L. *J. Med. Chem.* **2009**, *52*, 7537–7543.
(11) Handrick, G. R.; Atkinson, E. R. *J. Med. Chem.* **1966**, *9*, 558–562.
(12) But, A.; Lameiras, P.; Silaghi-Dumitrescu, I.; Batiu, C.; Guillard, S.; Ramondenc, Y.; Darabantu, M. *Lett. Org. Chem.* **2010**, *7*, 283–290.
(13) For a discussion of S vs O nucleophilic attack, see:Baiget, J.; Cosp, A.; Gálvez, E.; Gómez-Pinal, L.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 5637–5644.
(14) Kumar, R.; Kumar, D.; Chakraborti, A. K. *Synthesis* **2007**, *2*, 299–303.
(15) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
(16) Fulop, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron* **1990**, *46*, 6545–6552.