



HAL
open science

An expedient route to new spiroheterocycles: synthesis and structural studies.

Marlène Goubert, Isabelle Canet, Marie-Eve Sinibaldi

► **To cite this version:**

Marlène Goubert, Isabelle Canet, Marie-Eve Sinibaldi. An expedient route to new spiroheterocycles: synthesis and structural studies.. *European Journal of Organic Chemistry*, 2006, pp.4805-4812. 10.1002/ejoc.200600448 . hal-00119575

HAL Id: hal-00119575

<https://hal.science/hal-00119575>

Submitted on 27 Feb 2007

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

An Expedient Route to New Spiroheterocycles: Synthesis and Structural Studies

Marlène Goubert,^[a] Isabelle Canet,^{*[a]} and Marie-Eve Sinibaldi^{*[a]}

Keywords: Spiro compounds / Heterocycles / Nucleophilic substitution / Cyclization

We have developed a short, efficient and enantioselective synthesis of 1,4,7,10-tetraoxa- and 1,7-dioxa-4,10-dithia-spiro[5.5]undecanes. The method involved the reaction of solketal **5** or thiol derivative **6** with 1,3-dichloropropanone *O*-benzyloxime (**4**) which affords the conveniently protected symmetrical ketones **7** and **8**. Elaboration of the required 4,10-disubstituted-1,7-dioxaspiro[5.5]undecane systems **1**

and **2** entailed a final "one-pot" deprotection–spirocyclization process in an acidic medium. The structures and configurations of the spiroketals were established unambiguously by NMR spectroscopy.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

Introduction

Significant attention has been focused on the synthesis of the 1,7-dioxaspiro[5.5]undecane moiety which is the prevalent underlying motif in several groups of bioactive natural products, from the simple spiroketals used as pheromones^[1] by a large number of insect species, to more complex molecules such as polyether antibiotics^[2] and antitumour compounds.^[3] This diversity has led to interest in the development of original methods for the preparation of this framework and a number of strategies have been investigated.^[4] Moreover, new spiroketal compounds with a supplementary heteroatom at the position β to the spiranic carbon atom have been reported that possess interesting biological activities, such as the NK1 antagonists^[5] or anthelmintic agents^[6] (Figure 1).

We recently described an efficient diastereoselective approach to spiroketals^[7] and spiroaminoketals^[8] based upon an acidic deprotection–cyclization key step of a linear α,ω -dihydroxy- or an α -amino- ω -hydroxy ketone, protected as its dimethylhydrazone, respectively.

As a continuation of our research program devoted to the synthesis and biological evaluation of various spiroketal analogues, we have explored the viability of incorporating heteroatoms into the skeleton of spiroketals. We describe here a new and expedient route towards 4,10-disubstituted-1,7-dioxaspiro[5.5]undecanes **1** and **2** as well as full conformational and structural studies on these spiroketals based on various NMR experiments.

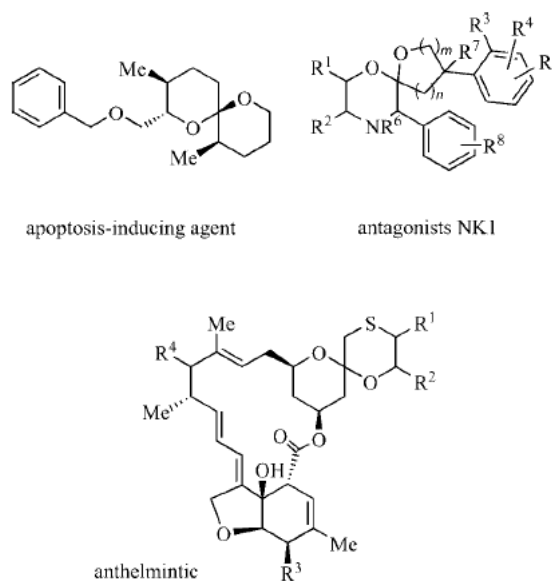


Figure 1. New spiroketal compounds with interesting biological properties.

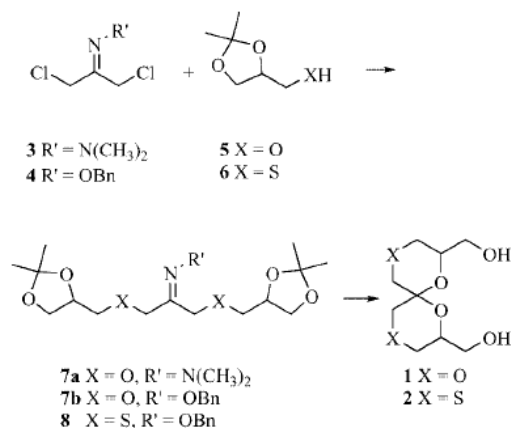
Results and Discussion

Chemistry

We first tried to introduce heteroatoms into the 4- and 10-positions of the spiroketal framework using a strategy similar to the one we reported for simple spiroketals.^[7] In this way, we envisioned constructing the target skeleton by substitution of the hydrazone **3** with commercially available solketal **5** or its thiol derivative **6**. In situ acidic deprotection of the bis-alkylated intermediates **7** or **8** would lead to a nonisolated symmetrical keto-tetraol, which should spontaneously undergo spirocyclization into the required spirohet-

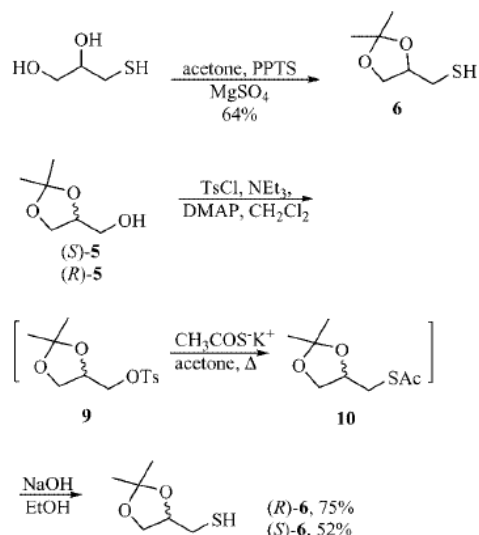
[a] Laboratoire de Synthèse et d'Etude de Systèmes à Intérêt Biologique, UMR CNRS 6504, Université Blaise Pascal, 63177 Aubière Cedex, France
E-mail: isabelle.canet@univ-bpclermont.fr
m-eve.sinibaldi-troin@univ-bpclermont.fr

erocyclic compounds **1** or **2** (Scheme 1). However, in spite of numerous attempts, we unfortunately never obtained hydrazone **7a**. Therefore, we focused on a new approach to scaffold **1** and **2**, modifying the nature of the protective group on **3**, namely by using the benzyloxime **4** (Scheme 1).



Scheme 1. Preparative routes to 4,10-disubstituted-1,7-dioxaspiro[5.5]undecanes.

The starting point was the synthesis of precursors **4** and **6**. Condensation of 1,3-dichloropropanone in EtOH with benzylhydroxylamine hydrochloride^[9] led quantitatively to oxime **4**. Racemic thiol **6** (Scheme 2) was obtained from commercially available 3-mercapto-1,2-propanediol by simple treatment with acetone using a catalytic amount of PPTS in the presence of MgSO₄^[10] and was isolated in 64% yield. Enantiopure (*R*)- and (*S*)-**6** were obtained from (*S*)- and (*R*)-solketal **5** in 75 and 52% overall yields, respectively, in three steps. Compounds (*S*)- or (*R*)-**5** were first converted to tosylate **9** using *p*-toluenesulfonyl chloride and a mixture of NEt₃/DMAP in dry CH₂Cl₂. The tosyl ether was then displaced with potassium thioacetate in boiling acetone.^[11a] Cleavage of the crude thioacetate **10** with a 5 M aqueous solution of NaOH in EtOH furnished the expected thiols.^[11b]



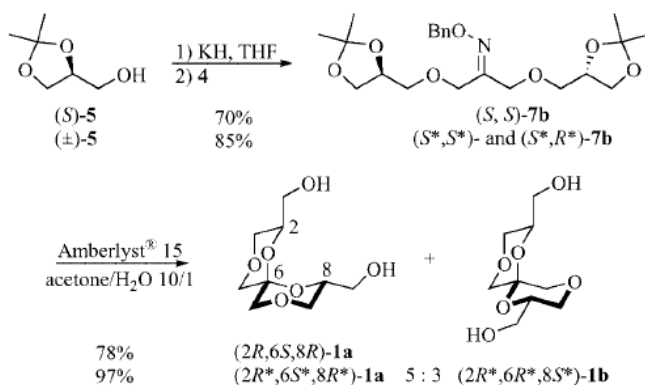
Scheme 2. Preparation of thiols **6**.

Having the precursors in hand, we then studied their condensation reactions with oxime **4** under basic conditions. The double substitution^[9] of **4** (Scheme 3) by the sodium or the potassium salt of **5** in DMF or THF afforded the expected oxime **7b** in good yields (see Table 1). The best results were obtained with KH in THF. Consequently, these reaction conditions were applied to the condensation of **4** with **6** and led as expected to **8** in 80–90% yields (Scheme 4).

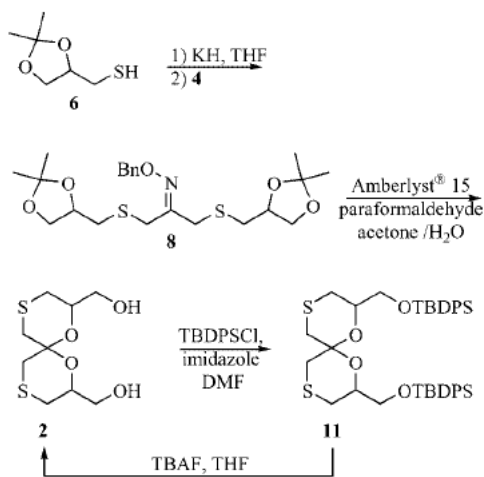
Table 1. Substitution of oxime **4** with solketal **5**.

| Entry | Compound 7b | Solvent | Base | Isolated yield [%] |
|-------|---|---------|------|--------------------|
| 1 | <i>(R*,S*)</i> - and <i>(S*,S*)</i> - 7b | DMF | NaH | 79 |
| | | THF | KH | 85 |
| 2 | <i>(S,S)</i> - 7b | DMF | NaH | 28 ^[a] |
| | | THF | KH | 70 |
| 3 | <i>(R,R)</i> - 7b | DMF | NaH | 61 |
| | | THF | KH | 87 |

[a] Sodium alcoholate of (*S*)-solketal led surprisingly to a gelled solution, which showed poor reactivity.



Scheme 3. Synthesis of 1,4,7,10-tetraoxaspiro[5.5]undecane **1**.



Scheme 4. Synthesis of 1,7-dioxo-4,10-dithiaspiro[5.5]undecanes **2** and **11**.

The second step involved concomitant deprotection of the diol and the keto functions of **7b** and **8** and spirocyclization into **1** and **2**. For this purpose, we first treated **7b** with Amberlyst® 15 in a 10:1 mixture of acetone/water. In this way, spiroketals (2*R*,6*S*,8*R*)- and (2*S*,6*R*,8*S*)-**1a** were cleanly obtained from (*S*)- and (*R*)-**5** in 55 and 52% overall yields, respectively (Scheme 3). Spiroketal **1a** presents, as expected, a double anomeric effect and has *C*₂ symmetry with both cycles adopting a chair conformation.^[12] Compound (±)-**5** led, in an 82% overall yield, to a mixture of (2*R*^{*},6*S*^{*},8*R*^{*})-**1a** and (2*R*^{*},6*R*^{*},8*S*^{*})-**1b** (5:3 ratio determined by quantitative ¹³C NMR spectroscopy), which were easily separated by purification on silica gel and fully characterized.^[12]

Applying the same conditions to oxime **8** led unfortunately to the sole deprotection of the diol function. The deprotection–spirocyclization sequence was finally achieved by adding paraformaldehyde to the acidic medium (Scheme 4).^[13] Enantiopure (*R,R*)-**8** furnished, in a 75% yield, an inseparable mixture of *C*-6 epimers (2*R*,6*S*,8*R*)-**2a** and (2*R*,6*R*,8*R*)-**2b** in a 10:7 ratio (Figure 2). Their enantiomers were obtained efficiently starting from enantiopure (*S,S*)-**8** (71% yield). The cyclization step proceeded with a lower stereoselectivity than was the case for the tetraoxa series; the importance of the anomeric effect in the cyclization process was reduced by the presence of the less electron-withdrawing atoms in the molecule.

In order to isolate **2a** and **2b**, we prepared their TBDPS derivatives **11a,b** (Scheme 4) using TBDPSCl/imidazole in DMF. Flash column chromatography on SiO₂ allowed the clean separation of **11a** of **11b**. Alcohols **2a** and **2b** were then recovered by classical treatment with TBAF in THF.

Starting from (±)-**6**, oximes (*R*^{*},*R*^{*})- and (*R*^{*},*S*^{*})-**8** furnished four diastereomers, (2*R*^{*},6*S*^{*},8*R*^{*})-**2a**, [(2*R*^{*},6*R*^{*},8*R*^{*})-**2b** + (2*R*^{*},6*S*^{*},8*S*^{*})-**2c**] and (2*R*^{*},6*R*^{*},8*S*^{*})-**2d**, in a 78% yield and a 5:7:1 ratio, as determined by quantitative ¹³C NMR spectroscopy. Isomer **2d** could be separated at this stage from the three others. A TBDPS protection–chromatography–deprotection sequence allowed us to obtain **2a** cleanly, but **2b** and **2c** remained

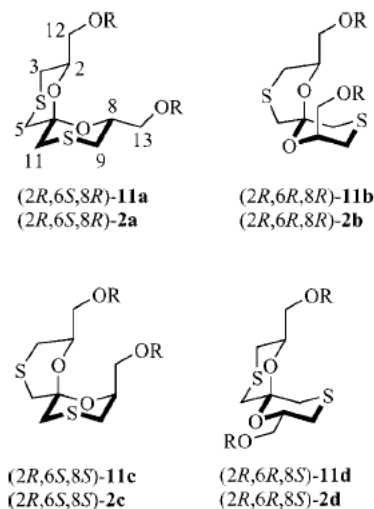


Figure 2. Structures of the isomers of the spiroketals **11** (R = TBDPS) and **2** (R = H).

inseparable. In order to characterize (2*R*^{*},6*S*^{*},8*S*^{*})-**2c**, we therefore conducted the reaction on (*R,S*)-**8**. We isolated the two *C*-6 epimers (2*R*,6*S*,8*S*)-**2c** and (2*R*,6*R*,8*S*)-**2d** in 44% yield, with **2d**, as before, the minor compound (Figure 2).

Structural and Conformational Studies of Spiroketal **2**

Analysis of the ¹H and ¹³C NMR spectra of isomers (2*R*,6*S*,8*R*)-**2a**, (2*R*,6*R*,8*R*)-**2b**, (2*R*,6*S*,8*S*)-**2c** and (2*R*,6*R*,8*S*)-**2d** with the help of COSY, HETCOR and in particular NOESY experiments permitted us to assign all the ¹H and ¹³C resonances (Figure 2, Table 2).

Compound **2a** presented a simplified ¹H NMR spectrum and only five peaks were detected in its ¹³C NMR spectrum, which is in good agreement with a *C*₂ symmetrical structure. As the deprotection–spirocyclization sequence was conducted under thermodynamic control, we concluded that the configuration was unambiguously (2*R*,6*S*,8*R*). As for **1a**, 2-H and 8-H are in an axial position on the cycles adopting a chair conformation, as illustrated by the large coupling constants (11.5 Hz) measured between 2-H and 3-H^{ax}, 8-H and 9-H^{ax}, and the small ones (not measurable in the ¹H NMR spectrum, crosspeak on COSY) between 2-H/3-H^{eq} and 8-H/9-H^{eq}, respectively.

As compound **2b** is the *C*-6 epimer of **2a**, we assumed its configuration was (2*R*,6*R*,8*R*). The small coupling constants (less than 2.0 Hz, not measurable in the ¹H NMR spectrum) for 8-H (br. d, δ = 4.77 ppm) with both 9-H atoms (d, δ = 2.19 ppm and δ = 3.11 ppm) and the distances between 8-H and 9-H (obtained from NOESY of **11b**, see Figure 3) indicated an equatorial position of 8-H on the cycle that adopted a chair conformation. The coupling constants of 7.0 and 5.0 Hz observed between 2-H (dq, δ = 3.71 ppm) and 3-H^a (δ = 2.77 ppm) and 3-H^b (δ = 2.64 ppm) led to the assignment of a “boat” deformation for the upper cycle, and thus a pseudoaxial position for 2-

Table 2. ¹H and ¹³C NMR spectroscopic data of isomers of **2**.

| | <i>(2R,6S,8R)</i> - 2a | | <i>(2R,6R,8R)</i> - 2b | | <i>(2R,6S,8S)</i> - 2c | | <i>(2R,6R,8S)</i> - 2d | |
|-----------|-------------------------------|--|-------------------------------|--|-------------------------------|--|-------------------------------|---|
| | δ_c | δ_H | δ_c | δ_H | δ_c | δ_H | δ_c | δ_H |
| 2 | 72.4 | 3.97 (dt) (<i>J</i> 11.5; 5.0) | 72.9 | 3.71 (dq) (<i>J</i> 7.0; 5.0) | 72.9 | 3.69 (dq) (<i>J</i> 7.0; 5.0) | 72.1 | 3.81 (dddd) (<i>J</i> 10.5; 6.0; 5.0; 2.0) |
| 3 | 27.8 | 2.37 (d) (<i>J</i> 11.5) 2.54 (t) (<i>J</i> 11.5) | 37.8 | 2.64 (ddd) (<i>J</i> 13.5; 7.0; 2.0) 2.77 (dd) (<i>J</i> 13.5; 5.5) | 37.8 | 2.63 (dd) (<i>J</i> 13.5; 7.0) 2.75 (dd) (<i>J</i> 13.5; 5.0) | 29.7 | 2.42 (br. d) (<i>J</i> 13.5) 2.54 (dd) (<i>J</i> 13.5; 10.5) |
| 5 | 35.2 | 2.40 (d) (<i>J</i> 13.5) 2.76 (d) (<i>J</i> 13.5) | 40.6 | 2.83 (d) (<i>J</i> 14.0) 2.84 (d) (<i>J</i> 14.0) | 40.6 | 2.80 (d) (<i>J</i> 15.0) 2.83 (d) (<i>J</i> 15.0) | 28.7 | 2.42 (d) (<i>J</i> 13.5) 2.69 (d) (<i>J</i> 13.5) |
| 6 | 91.9 | | 108.3 | | 108.3 | | 94.7 | |
| 8 | 72.4 | 3.97 (dt) (<i>J</i> 11.5; 5.0) | 76.3 | 4.77 (br. d) (<i>J</i> 6.0) | 76.3 | 4.75 (br. d) (<i>J</i> 6.0) | 76.3 | 4.36 (dtd) (<i>J</i> 11.0; 5.0; 2.0) |
| 9 | 27.8 | 2.37 (d) (<i>J</i> 11.5) 2.54 (t) (<i>J</i> 11.5) | 29.7 | 2.19 (d) (<i>J</i> 13.0) 3.11 (d) (<i>J</i> 13.0) | 29.7 | 2.18 (br. d) (<i>J</i> 13.0) 3.09 (br. d) (<i>J</i> 13.0) | 28.3 | 2.37 (dt) (<i>J</i> 13.0; 2.0) 2.55 (dd) (<i>J</i> 13.0; 11.0) |
| 11 | 35.2 | 2.40 (d) (<i>J</i> 13.5) 2.76 (d) (<i>J</i> 13.5) | 33.9 | 2.44 (d) (<i>J</i> 13.0) 3.01 (d) (<i>J</i> 13.0) | 33.9 | 2.42 (d) (<i>J</i> 13.0) 2.99 (d) (<i>J</i> 13.0) | 35.9 | 2.64 (d) (<i>J</i> 14.5) 3.58 (dd) (<i>J</i> 14.5; 2.0) |
| 12 | 65.9 | 3.48 (dd) (<i>J</i> 11.5; 5.0) 3.56 (dd) (<i>J</i> 11.5; 5.0) | 66.0 | 3.49 (dd) (<i>J</i> 11.0; 5.5) 3.54 (dd) (<i>J</i> 11.0; 5.0) | 66.0 | 3.47 (dd) (<i>J</i> 11.0; 5.0) 3.52 (dd) (<i>J</i> 11.0; 5.5) | 65.9 | 3.53 (dd) (<i>J</i> 11.0; 6.0) 3.61 (dd) (<i>J</i> 11.0; 5.0) |
| 13 | 65.9 | 3.48 (dd) (<i>J</i> 11.5; 5.0) 3.56 (dd) (<i>J</i> 11.5; 5.0) | 70.8 | 3.94 (t) (<i>J</i> 6.0) 4.33 (d) (<i>J</i> 6.5) | 70.8 | 3.93 (t) (<i>J</i> 6.0) 4.31 (d) (<i>J</i> 6.0) | 66.0 | 3.41 (dd) (<i>J</i> 11.0; 5.0) 3.47 (dd) (<i>J</i> 11.0; 5.0) |

H. This conformation was also confirmed by the NOE contacts determined for **11b** between 2-H ($\delta = 3.71$ ppm) and 3-H^b ($\delta = 2.64$ ppm), 2-H and 5-H^a ($\delta = 2.83$ ppm), and 5-H^a ($\delta = 2.83$ ppm) and 3-H^b ($\delta = 2.64$ ppm) (Figure 3). The deshielding of 5-H ($\delta = 2.83$ and 2.84 ppm in **2b** and $\delta = 2.40$ and 2.76 ppm in **2a**) and of C-5 ($\delta = 40.6$ ppm in **2b** and $\delta = 35.2$ ppm in **2a**) favour an (*R*) configuration for C-6. Moreover, the deshielding of C-13 ($\delta = 70.8$ ppm in **2b** and $\delta = 65.9$ ppm in **2a**) and 13-H ($\delta = 4.33$ and 3.94 ppm in **2b** vs. $\delta = 3.56$ and 3.48 ppm in **2a**) implied a 1,3-diaxial position for C-13 and O-1, which is in agreement with the conformation depicted in Figure 2 for **2b**.

The determination of the C-6 configuration for the other isomers **2c** and **2d** did not appear so trivial. In the minor isomer **2d**, 2-H and 8-H appeared in an axial position: indeed, we observed for 2-H ($\delta = 3.81$ ppm) a coupling constant of 10.5 Hz with 3-H^{ax} and of 2.0 Hz with 3-H^{eq}. In the same manner, 8-H presented coupling constants of 11.0 and 2.0 Hz with 9-H^{ax} and 9-H^{eq}, respectively. Moreover, we detected in this isomer a deshielding of 11-H^{eq} ($\delta = 3.58$ ppm) and a shielding of C-5 which is in complete agreement with an equatorial position of the C-6–O-7 bond. These results were corroborated by the NOE contacts determined for **11d** between 11-H^{ax} and 5-H^{ax} and between

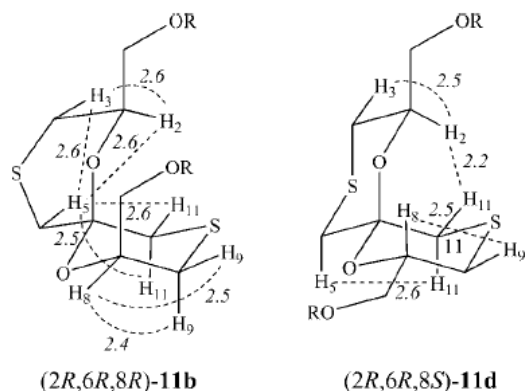


Figure 3. Selected NOE interactions in **11b** and **11d**. The relative distances (in Å) calculated from the NOEs are indicated.

2-H and 11-H^{eq} (Figure 3). All these data are in good agreement with a (2*R*,6*R*,8*S*) configuration for **2d**.

Isomer **2c**, whose *R_f* is identical to that of isomer **2b**, presented a ¹³C NMR spectrum identical to that of isomer **2b**. In the ¹H NMR spectrum only slight differences could be detected: indeed, only three protons exhibited “de-doubled” signals. These spectroscopic data indicate a structure for **2c** similar to that of **2b**. As compound **2c** is the C-6 epimer of **2d**, all these observations are in agreement with a “boat” conformation for the O-1 cycle and an (*S*) configuration for C-6. Therefore we concluded that the configuration of **2c** should be (2*R*,6*S*,8*S*).

Conclusions

In summary, we have developed a concise and original method for the synthesis of new spiroketals with supplementary heteroatoms in the 4- and 10-positions of the cycles. The key step involved the condensation of 1,3-disubstituted-propanone *O*-benzyloxime **4** with alcohol **5** or thiol **6**. The versatility and the efficiency of our approach have been demonstrated by the synthesis, in a few steps with good yields, of symmetrical elaborated molecules of the 1,4,7,10-tetraoxa- and 1,7-dioxa-4,10-dithiaspiro[5.5]undecane series from commercially available solketal and 1,3-dichloropropanone.

Experimental Section

General Remarks: NMR spectra were recorded with a Bruker AC 400 spectrometer operating at 400 MHz. ¹H and ¹³C NMR were recorded in CDCl₃ or CD₃OD; chemical shifts are calibrated to the residual proton and carbon resonances of the solvent (CDCl₃: δ_H = 7.26, δ_C = 77.0 ppm; CD₃OD: δ_H = 3.34, δ_C = 49.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br. d = broad doublet; when coupling constants ²*J* and ³*J* are identical, the multiplicity “t” is attributed, a doublet when ²*J* is different of ³*J*), coupling constants (Hz), integration and assignment. Mass spectra were recorded with a Hewlett–Packard 5989B instrument. High-resolution mass spectra were performed with a Q-TOF micromass spectrometer. Optical rotations were measured

at the sodium D line (589 nm) using a 1-dm quartz cell with a JASCO DIP-370 apparatus. Infrared spectra were recorded with a Perkin–Elmer spectrometer. Melting points were determined with a hot-stage Reichert apparatus and are uncorrected. Flash column chromatography was performed using silica gel 60 (Macherey–Nagel, 0.04–0.063 mm). Dry tetrahydrofuran was distilled from potassium and benzophenone, whereas dry dichloromethane was distilled from CaH₂. Reactions were generally run under argon. All commercially available compounds (Acros, Aldrich) were used as received. TLC analysis was conducted using the spray reagent molybdic acid and by further heating until development of colour. Compound **4** was synthesized according to ref.^[9].

1,3-Bis[(4*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]propanone *O*-Benzyloxime (7b**):** Solketal (*S*)-**5** (630 mg, 4.76 mmol) in THF (4 mL) was slowly added to a stirred suspension of potassium hydride (25–35% in mineral oil, 870 mg, 6.50 mmol) in anhydrous THF (9 mL) under argon at 20 °C. When bubbling had ceased (ca. 30 min), 1,3-dichloropropanone *O*-benzyloxime **4** (500 mg, 2.16 mmol) in THF (3 mL) was added in one portion. The reaction mixture was stirred at room temperature for 2 h. Additional KH could be added if starting material was left. The reaction was quenched by the addition of H₂O (7 mL) followed by CH₂Cl₂ (30 mL). The aqueous phase was extracted with CH₂Cl₂ (2 × 15 mL) and the combined organic layers were washed with brine (15 mL) and dried with MgSO₄. After filtration, the solvent was removed. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate, 4:1) to afford **7b** as a colourless oil.

(*S,S*)-**7b**: Yield 70% (640 mg). *R_f* = 0.51 (cyclohexane/EtOAc, 7:3). [α]_D²⁵ = +13.9 (*c* = 1.2, CHCl₃). IR (neat): ν̄ = 1680 (C=N) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.37–7.28 (m, 5 H, Ar-H), 5.10 (s, 2 H, CH₂-Ar), 4.40 (d, ²*J* = 14.5 Hz, 1 H, N=C-CH₂-O), 4.38 (d, ²*J* = 14.5 Hz, 1 H, N=C-CH₂-O), 4.24 (quint, ³*J* = 6.0 Hz, 2 H, CH-O), 4.17 (s, 2 H, N=C-CH₂-O), 4.02 (t, ²*J* = ³*J* = 6.5 Hz, 2 H, CH₂-O), 3.71 (t, ²*J* = ³*J* = 6.5 Hz, 1 H, CH₂-O), 3.69 (t, ²*J* = ³*J* = 6.5 Hz, 1 H, CH₂-O), 3.51 (dd, ²*J* = 10.0, ³*J* = 5.5 Hz, 1 H, OCH-CH₂-O), 3.48 (m, 2 H, OCH-CH₂-O), 3.44 (dd, ²*J* = 10.0, ³*J* = 6.0 Hz, 1 H, OCH-CH₂-O), 1.40 (s, 6 H, CH₃), 1.35 (s, 6 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 155.4 (C=N), 137.4 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 109.4 (O-C-O), 76.3 (CH₂-Ar), 74.5 (CH-O), 72.3 (CH₂-O), 71.4 (CH₂-O), 68.7 (CH₂-O), 66.7 (CH₂-O), 66.6 (CH₂-O), 64.4 (CH₂-O), 26.7 (CH₃), 25.4 (CH₃) ppm. C₂₂H₃₄N₂O₇ (423.50): calcd. C 62.39, H 7.85, N 3.31; found C 62.58, H 8.03, N 3.24.

(*R,R*)-**7b**: Yield 87% (795 mg). [α]_D²⁵ = -11.6 (*c* = 1.5, CHCl₃).

(*S*^{*},*S*^{*})- and (*S*^{*},*R*^{*})-**7b**: Yield 85% (780 mg).

2,8-Dihydroxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane (1**):** Amberlyst[®] 15 (1.15 g, 250 mg/mmol) was added to a solution of oxime **7b** (1.94 g, 4.59 mmol) in a mixture of acetone and water (10:1 v/v, 33 mL). The resulting solution was refluxed for 2 d. After filtration of the insoluble material through a Celite[®] pad, the solvent was eliminated and the residue purified by SiO₂ column chromatography (EtOAc/MeOH, 49:1) to give **1a** as a white powder. The racemic product was obtained in 97% yield (1.08 g) as a 5:3 mixture of two isomers, (±)-(2*R*^{*},6*S*^{*},8*R*^{*})-**1a** and (±)-(2*R*^{*},6*R*^{*},8*S*^{*})-**1b**, which could be separated by flash column chromatography (EtOAc/MeOH, 1:0 → 49:1).

(2*R*,6*S*,8*R*)-**1a**: Yield 78% (791 mg). *R_f* = 0.35 (EtOAc/MeOH, 9:1). M.p. 146 °C (EtOAc). [α]_D²⁵ = +3.1 (*c* = 1.6, MeOH). IR (KBr): ν̄ = 3430 (OH) cm⁻¹. ¹H NMR (400 MHz, CD₃OD): δ = 4.03 (dtd, ³*J* = 11.0, ²*J* = 5.0, ³*J* = 3.0 Hz, 2 H, 2-H^{ax} and 8-H^{ax}), 3.80 (dd,

$^2J = 11.0$, $^3J = 3.0$ Hz, 2 H, 3-H^{eq} and 9-H^{eq}), 3.55 (d, $^2J = 11.5$ Hz, 2 H, 5-H^{eq} and 11-H^{eq}), 3.55 (dd, $^2J = 12.0$, $^3J = 5.0$ Hz, 2 H, CH₂OH), 3.51 (dd, $^2J = 12.0$, $^3J = 5.0$ Hz, 2 H, CH₂OH), 3.37 (t, $^2J = ^3J = 11.0$ Hz, 2 H, 3-H^{ax} and 9-H^{ax}), 3.24 (d, $^2J = 11.5$ Hz, 2 H, 5-H^{ax} and 11-H^{ax}) ppm. ¹³C NMR (100 MHz, CD₃OD): $\delta = 93.0$ (C-6), 70.2 (C-2 and C-8), 69.6 (C-5 and C-11), 68.8 (C-3 and C-9), 62.9 (C-12 and C-13) ppm. HRMS (ESI): calcd. for C₉H₁₆O₆Na: 243.0845; found 243.0855 [M + Na]⁺.

(2*S*,6*R*,8*S*)-1a: Yield 60% (600 mg). $[\alpha]_D^{25} = -5.8$ ($c = 1.5$, MeOH).

(2*R,6*R**,8*S**)-1b**: Yield 36% (401 mg). $R_f = 0.45$ (EtOAc/MeOH, 9:1). M.p. 118 °C (EtOAc). ¹H NMR (400 MHz, CD₃OD): $\delta = 4.22$ (dtd, $^3J = 11.5$, $^2J = 5.0$, $^3J = 3.0$ Hz, 1 H, 8-H^{ax}), 3.99 (d, $^2J = 12.0$ Hz, 1 H, 11-H^{eq}), 3.80 (dd, $^2J = 11.5$, $^3J = 3.0$ Hz, 1 H, 9-H^{eq}), 3.78 (m, 1 H, 2-H), 3.77 (m, 1 H, CH₂OH), 3.74 (dd, $^2J = 11.5$, $^3J = 3.0$ Hz, 1 H, 3-H^{eq}), 3.69 (m, 1 H, CH₂OH), 3.57 (dd, $^2J = 11.5$, $^3J = 6.0$ Hz, 1 H, 3-H^{ax}), 3.50 (dd, $^2J = 11.5$, $^3J = 5.0$ Hz, 1 H, CH₂OH), 3.48 (d, $^2J = 11.5$ Hz, 1 H, 5-H^{eq}), 3.47 (dd, $^2J = 11.5$, $^3J = 5.0$ Hz, 1 H, CH₂OH), 3.37 (t, $^2J = ^3J = 11.5$ Hz, 1 H, 9-H^{ax}), 3.35 (d, $^2J = 11.5$ Hz, 1 H, 5-H^{ax}), 3.23 (d, $^2J = 12.0$ Hz, 1 H, 11-H^{ax}) ppm. ¹³C NMR (100 MHz, CD₃OD): $\delta = 92.7$ (C-6), 73.5 (C-2), 71.3 (C-5), 70.4 (C-8), 69.0 (C-9), 68.5 (C-11), 68.2 (C-3), 62.9 (C-12), 62.8 (C-13) ppm.

(±)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methanethiol (6): 3-Mercapto-1,2-propanediol (3 g, 27.7 mmol) was dissolved in acetone (40 mL). Pyridinium *p*-toluenesulfonate (700 mg, 2.77 mmol) and MgSO₄ (5 g) were added. The mixture was stirred for 3 d at 20 °C before being filtered through a Celite[®] pad. After elimination of the solvent, the residue was purified by flash column chromatography (pentane/Et₂O, 24:1) to afford the thiol **6** (2.6 g, 17.7 mmol, 64%) as a colourless liquid.

[(4*R*)- or (4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methanethiol (6): A solution of toluene-*p*-sulfonyl chloride (5.2 g, 27.2 mmol) in dry CH₂Cl₂ (30 mL) was added to a solution of (*S*)- or (*R*)-solketal **5** (3 g, 22.7 mmol), DMAP (0.01 equiv., 28 mg, 0.23 mmol) and triethylamine (7.3 mL, 52.2 mmol) in dry CH₂Cl₂ (50 mL) at 0 °C. The flask was kept in a fridge for 2 d. After dilution with CH₂Cl₂ (225 mL), the solution was washed twice with water (45 mL). After evaporation of the solvent, the residue was dissolved in diethyl ether (75 mL) and the organic layer was dried with MgSO₄, filtered and concentrated under reduced pressure. The crude tosylate **9** was dissolved in acetone (120 mL) and potassium thioacetate (2.95 g, 25.8 mmol) was added. The resulting solution was refluxed for 24 h. After filtration and concentration, the residue was treated with water (20 mL) and extracted with diethyl ether (2 × 100 mL). The organic layer was dried with MgSO₄, filtered and concentrated to give the thioacetate **10**. This was dissolved in EtOH (3 mL) and 5 N NaOH (5.5 mL, 27.7 mmol) was added. The resulting solution was stirred for 9 h at 20 °C. The reaction was carefully neutralized with acetic acid and the EtOH was evaporated. After extraction with ether (3 × 10 mL), the combined organic layers were washed with a saturated solution of NaHCO₃, dried with MgSO₄ and concentrated. The residue was finally purified by flash column chromatography (C₅H₁₂/Et₂O, 24:1) to afford (*R*)- or (*S*)-**6** as a colourless liquid:

(*R*)-6: Yield 75% (2.52 g). $[\alpha]_D^{25} = +35.6$ ($c = 1.4$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): $\delta = 4.18$ (q, $^3J = 6.0$ Hz, 1 H, CH-O), 4.08 (dd, $^2J = 8.0$, $^3J = 6.0$ Hz, 1 H, CH₂-O), 3.74 (dd, $^2J = 8.0$, $^3J = 6.0$ Hz, 1 H, CH₂-O), 2.72 (ddd, $^2J = 13.5$, $^3J = 8.0$, $^3J = 6.0$ Hz, 1 H, CH₂-S), 2.58 (ddd, $^2J = 13.5$, $^3J = 9.0$, $^3J = 6.0$ Hz, 1 H, CH₂-S), 1.45 (t, $^3J = 8.5$ Hz, 1 H, SH), 1.41 (s, 3 H, CH₃), 1.34 (s, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 109.6$ (O-C-O), 76.9 (CH-O), 68.2 (CH₂O), 27.6 (CH₂S), 26.8 (CH₃), 25.4 (CH₃) ppm.

(*S*)-6: Yield 52% (1.78 g). $[\alpha]_D^{25} = -31.1$ ($c = 1.4$, CHCl₃).

1,3-Bis[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylthio]propanone *O*-Benzyloxime (8): According to the procedure described for the preparation of **7b**, starting from thiol **6** (1.21 g, 8.17 mmol) and oxime **4** (860 mg, 3.72 mmol), oxime **8** was obtained after purification by SiO₂ column chromatography (cyclohexane/EtOAc, 9:1) as a colourless oil.

(*R*,*R*)-8: Yield 91% (1.55 g). $[\alpha]_D^{25} = +22.6$ ($c = 1.4$, CHCl₃). IR (NaCl): $\tilde{\nu} = 2985$, 2933, 2876, 1373, 1253, 1216, 1153, 1059, 858, 753, 700 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.37$ –7.28 (m, 5 H, Ar-H), 5.08 (s, 2 H, Ar-H), 4.22 (quint, $^3J = 6.0$ Hz, 1 H, CH-O), 4.18 (quint, $^3J = 6.0$ Hz, 1 H, CH-O), 4.00 (dd, $^2J = 6.0$, $^3J = 2.0$ Hz, 1 H, CH₂-O), 3.97 (dd, $^2J = 6.0$, $^3J = 2.0$ Hz, 1 H, CH₂-O), 3.63–3.52 (m, 4 H, N=C-CH₂-S, CH₂-O), 3.37 (s, 2 H, N=C-CH₂-S), 2.69 (dd, $^2J = 13.5$, $^3J = 6.0$ Hz, 1 H, S-CH₂), 2.58 (dd, $^2J = 13.5$, $^3J = 6.5$ Hz, 1 H, S-CH₂), 2.57 (dd, $^2J = 13.5$, $^3J = 6.5$ Hz, 1 H, S-CH₂), 2.46 (dd, $^2J = 13.5$, $^3J = 6.5$ Hz, 1 H, S-CH₂), 1.42 (s, 3 H, CH₃), 1.41 (s, 3 H, CH₃), 1.35 (s, 3 H, CH₃), 1.33 (s, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 154.1$ (CN), 137.4 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar), 109.6 (O-C-O), 76.2 (CH₂-Ar), 74.9 (CH-O), 68.7 (CH₂-O), 35.2 (CH₂-S), 34.1 (CH₂-S), 33.1 (S-CH₂), 26.9 (CH₃), 25.5 (CH₃), 25.1 (S-CH₂) ppm. C₂₂H₃₃NO₅S₂ (455.63): calcd. C 57.99, H 7.30, N 3.07, S 14.08; found C 58.30, H 7.47, N 3.11, S 13.93.

(*S*,*S*)-8: Yield 90% (1.52 g). $[\alpha]_D^{25} = -25.8$ ($c = 1.5$, CHCl₃).

(*R,*R**)- and (*R**,*S**)-8**: Yield 83% (1.41 g).

General Procedure for the Cyclization of 8: Amberlyst[®] 15 (250 mg) and paraformaldehyde (10 mmol) were added to a solution of oxime **8** (1 mmol) in acetone (10 mL) and water (1 mL). The resulting mixture was refluxed for 2 d. After removing insoluble material by filtration through a Celite[®] pad, the solvent was evaporated. The residue was purified by SiO₂ column chromatography (EtOAc/cyclohexane, 9:1).

General Procedure for TBDPS Protection of 2: Imidazole (4.4 mmol) followed by *tert*-butylchlorodiphenylsilane (2.2 mmol) were added at 0 °C to a mixture of **2** (1 mmol) in DMF (5 mL). The resulting solution was stirred overnight and then taken up in diethyl ether (100 mL) and the organic layer was washed with water (15 mL) followed by a saturated aqueous NH₄Cl solution (15 mL). Filtration and evaporation of the dried (MgSO₄) organic layer afforded derivatives **11** which could be separated by two consecutive flash column chromatography (cyclohexane/EtOAc, 49:1 then cyclohexane/Et₂O, 100:1 → 50:1).

General Procedure for TPDPS Cleavage of 11: Tetrabutylammonium fluoride (1.0 M in THF, 2.4 mmol) was added to a solution of TBDPS-protected spirocompound **11** (1 mmol) in anhydrous THF (5 mL). After stirring at 20 °C overnight, the reaction mixture was diluted with ethyl acetate (100 mL) and then washed with water (10 mL) followed by brine (10 mL). The organic layer was dried with MgSO₄. The solvent was evaporated and the residue was purified by SiO₂ column chromatography (EtOAc/cyclohexane, 4:1).

(2*R*,6*S*,8*R*)- and (2*R*,6*R*,8*R*)-2,8-Dihydroxymethyl-1,7-dioxo-4,10-dithiaspiro[5.5]undecane (2a) and (2b): According to the general procedure of cyclization, starting from (*R*,*R*)-oxime **8**, an inseparable mixture of (2*R*,6*S*,8*R*)-**2a** and (2*R*,6*R*,8*R*)-**2b** was obtained in a 10:7 ratio and 75% yield. The isomers were separated by preparing their TBDPS derivatives **11a** and **11b** using the general procedure of protection followed by deprotection under the conditions described in the general procedure.

(2*R*,6*S*,8*R*)-11a: Viscous oil. $R_f = 0.74$ (cyclohexane/EtOAc, 9:1). $[\alpha]_D^{25} = -76.0$ ($c = 1.2$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): $\delta =$

7.73 (m, 8 H, Ar-H), 7.39 (m, 12 H, Ar-H), 4.16 (dtd, $^3J = 11.0$, $^3J = 5.5$, $^3J = 2.0$ Hz, 2 H, 2-H^{ax} and 8-H^{ax}), 3.76 (dd, $^2J = 10.5$, $^3J = 5.5$ Hz, 2 H, CH₂OSi), 3.60 (dd, $^2J = 10.5$, $^3J = 5.5$ Hz, 2 H, CH₂OSi), 2.76 (d, $^2J = 13.5$ Hz, 2 H, 5-H and 11-H), 2.58 (dd, $^2J = 13.0$, $^3J = 11.0$ Hz, 2 H, 3-H^{ax} and 9-H^{ax}), 2.44 (d, $^2J = 13.0$ Hz, 2 H, 3-H^{eq} and 9-H^{eq}), 2.40 (d, $^2J = 13.5$ Hz, 2 H, 5-H and 11-H), 1.07 (s, 18 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 135.7$ (C-Ar), 133.2 (C-Ar), 129.7 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 90.4 (C-6), 70.6 (C-2 and C-8), 66.5 (CH₂OSi), 34.6 (C-5 and C-11), 27.3 (C-3 and C-9), 26.8 (CH₃), 19.2 [C(CH₃)₃] ppm. MS (ESI): *m/z* (%) = 767 (53) [M + K]⁺, 751 (100) [M + Na]⁺, 288 (22).

(2R,6R,8R)-11b: Viscous oil. *R_f* = 0.48 (cyclohexane/EtOAc, 9:1). [α]_D²⁵ = -2.2 (*c* = 3.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.26$ – 7.68 (m, 20 H, Ar), 4.65 (br. d, $^3J = 5.0$ Hz, 1 H, 8-H), 4.30 (d, $^2J = 6.0$ Hz, 1 H, CH₂OSi), 3.93 (qd, $^3J = 5.0$, $^3J = 7.0$ Hz, 2 H, 2-H), 3.87 (dd, $^2J = 6.0$ Hz, $^3J = 7.0$ Hz, 1 H, CH₂OSi), 3.74 (dd, $^2J = 10.5$, $^3J = 5.0$ Hz, 1 H, CH₂OSi), 3.71 (dd, $^2J = 10.5$, $^3J = 5.0$ Hz, 1 H, CH₂OSi), 3.14 (br. d, $^2J = 13.0$ Hz, 1 H, 9-H^{ax}), 2.98 (dd, $^2J = 13.5$, $^3J = 7.0$ Hz, 1 H, 3-H^{ax}), 2.91 (d, $^2J = 13.0$ Hz, 1 H, 11-H), 2.66 (dd, $^2J = 13.5$, $^3J = 5.0$ Hz, 1 H, 3-H^{eq}), 2.55 (d, $^2J = 14.0$ Hz, 1 H, 5-H), 2.50 (d, $^2J = 14.0$ Hz, 1 H, 5-H), 2.33 (d, $^2J = 13.0$ Hz, 1 H, 11-H), 2.11 (dd, $^2J = 13.0$, $^3J = 2.0$ Hz, 1 H, 9-H^{eq}), 1.04 (s, 9 H, CH₃), 1.01 (s, 9 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 136.0$ (C-Ar), 135.8 (C-Ar), 135.6 (C-Ar), 135.5 (C-Ar), 133.9 (C-Ar), 133.8 (C-Ar), 133.5 (C-Ar), 133.4 (C-Ar), 129.6 (C-Ar), 129.5 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 106.8 (C-6), 74.6 (C-8), 73.1 (C-2), 69.5 (CH₂OSi), 65.4 (CH₂OSi), 39.7 (C-5), 36.5 (C-3), 33.1 (C-11), 28.9 (C-9), 26.9 (CH₃), 26.8 (CH₃), 19.2

[C(CH₃)₃] ppm. MS (ESI): *m/z* (%) = 767 (13) [M + K]⁺, 751 (18) [M + Na]⁺, 288 (100).

(2R,6S,8R)-2a: White solid. *R_f* = 0.37 (EtOAc). [α]_D²⁵ = -137.5 (*c* = 0.6, CH₃OH). M.p. 98 °C (EtOAc). ¹H NMR (400 MHz, CD₃OD): $\delta = 3.97$ (dt, $^3J = 11.5$, $^3J = 5.0$ Hz, 2 H, 2-H^{ax} and 8-H^{ax}), 3.56 (dd, $^2J = 11.5$, $^3J = 5.0$ Hz, 2 H, CH₂OH), 3.48 (dd, $^2J = 11.5$, $^3J = 5.0$ Hz, 2 H, CH₂OH), 2.76 (d, $^2J = 13.5$ Hz, 2 H, 5-H and 11-H), 2.54 (t, $^2J = ^3J = 11.5$ Hz, 2 H, 3-H^{ax} and 9-H^{ax}), 2.40 (d, $^2J = 13.5$ Hz, 2 H, 5-H and 11-H), 2.37 (d, $^2J = 11.5$ Hz, 2 H, 3-H^{eq} and 9-H^{eq}) ppm. ¹³C NMR (100 MHz, CD₃OD): $\delta = 91.9$ (C-6), 72.4 (C-2 and C-8), 65.9 (CH₂OH), 35.2 (C-5 and C-11), 27.8 (C-3 and C-9) ppm. C₉H₁₆O₄S₂ (252.35): calcd. C 42.84, H 6.39, S 25.41; found C 42.67, H 6.36, S 25.54.

(2R,6R,8R)-2b: Colourless oil. *R_f* = 0.37 (EtOAc). ¹H NMR (400 MHz, CD₃OD): $\delta = 4.77$ (br. d, $^3J = 6.0$ Hz, 1 H, 8-H^{eq}), 4.33 (d, $^2J = 6.5$ Hz, 1 H, CH₂OH), 3.94 (t, $^2J = ^3J = 6.0$ Hz, 1 H, CH₂OH), 3.71 (dq, $^3J = 7.0$, $^3J = ^3J_{2,3b} = 5.0$ Hz, 1 H, 2-H), 3.54 (dd, $^2J = 11.0$, $^3J = 5.0$ Hz, 1 H, CH₂OH), 3.49 (dd, $^2J = 11.0$, $^3J = 5.5$ Hz, 1 H, CH₂OH), 3.11 (d, $^2J = 13.0$ Hz, 1 H, 9-H^{ax}), 3.01 (d, $^2J = 13.0$ Hz, 1 H, 11-H^{ax}), 2.84 (d, $^2J = 14.0$ Hz, 1 H, 5-H^a), 2.83 (d, $^2J = 14.0$ Hz, 1 H, 5-H^b), 2.77 (dd, $^2J = 13.5$, $^3J = 5.5$ Hz, 1 H, 3-H^a), 2.64 (ddd, $^2J = 13.5$, $^3J_{3,2} = 7.0$, $^4J = 2.0$ Hz, 1 H, 3-H^b), 2.44 (d, $^2J = 13.0$ Hz, 1 H, 11-H^{eq}), 2.19 (d, $^2J = 13.0$ Hz, 1 H, 9-H^{eq}) ppm. ¹³C NMR (100 MHz, CD₃OD): $\delta = 108.3$ (C-6), 76.3 (C-8), 72.9 (C-2), 70.8 (CH₂OH), 66.0 (CH₂OH), 40.6 (C-5), 37.8 (C-3), 33.9 (C-11), 29.7 (C-9) ppm.

(2S,6R,8S)- and (2S,6S,8S)-2,8-Dihydroxymethyl-1,7-dioxo-4,10-dithia-spiro[5.5]undecane (2a) and (2b): The general procedure applied to (S,S)-oxime **8** led to the isomers (2S,6R,8S)-**2a** and (2S,6S,8S)-**2b** in a 10:7 ratio.

(2S,6R,8S)-11a: [α]_D²⁵ = +62.8 (*c* = 1.1, CHCl₃).

(2S,6S,8S)-11b: [α]_D²⁵ = +2.7 (*c* = 0.3, CHCl₃).

(2S,6R,8S)-2a: [α]_D²⁵ = +137.2 (*c* = 0.8, CH₃OH), m.p. 95 °C (EtOAc).

(2S,6S,8S)-2b: [α]_D²⁵ = +33.3 (*c* = 1.0, CH₃OH).

(2R*,6S*,8R*)-, (2R*,6R*,8R*)-, (2R*,6S*,8S*)- and (2R*,6R*,8S*)-2,8-Dihydroxymethyl-1,7-dioxo-4,10-dithiaspiro[5.5]undecane (2): The general cyclization conditions applied to (R*,R*)- and (R*,S*)-**8** gave a mixture of four diastereoisomers: (2R*,6S*,8R*)-**2a**, [(2R*,6R*,8R*)-**2b** + (2R*,6S*,8S*)-**2c**] and (2R*,6R*,8S*)-**2d** in a 5:7:1 ratio. Isomer (2R*,6R*,8S*)-**2d** was directly isolated from the others by SiO₂ column chromatography (EtOAc/cyclohexane, 9:1). Isomer **2a** was obtained after TBDPS protection followed by cleavage. (2R*,6R*,8R*)-**2b** and (2R*,6S*,8S*)-**2c** could not be separated even with TBDPS protection.

(2R*,6R*,8S*)-2d: Colourless oil. *R_f* = 0.46 (EtOAc). ¹H NMR (400 MHz, CD₃OD): $\delta = 4.36$ (dtd, $^3J = 5.0$, $^3J = 11.0$, $^3J = 2.0$ Hz, 1 H, 8-H), 3.81 (dddd, $^3J = 5.0$, $^3J = 6.0$, $^3J = 10.5$, $^3J = 2.0$ Hz, 1 H, 2-H), 3.61 (dd, $^2J = 11.0$, $^3J = 5.0$ Hz, 1 H, CH₂OH), 3.58 (dd, $^2J = 14.5$, $^4J = 2.0$ Hz, 1 H, 11-H^{eq}), 3.53 (dd, $^2J = 11.0$, $^3J = 6.0$ Hz, 1 H, CH₂OH), 3.47 (dd, $^2J = 11.0$, $^3J = 5.0$ Hz, 1 H, CH₂OH), 3.41 (dd, $^2J = 11.0$, $^3J = 5.0$ Hz, 1 H, CH₂OH), 2.69 (d, $^2J = 13.5$ Hz, 1 H, 5-H^{eq}), 2.64 (d, $^2J = 14.5$ Hz, 1 H, 11-H^{ax}), 2.55 (dd, $^2J = 13.0$, $^3J = 11.0$ Hz, 1 H, 9-H^{ax}), 2.54 (dd, $^2J = 13.5$, $^3J = 10.5$ Hz, 1 H, 3-H^{ax}), 2.42 (br. d, $^2J = 13.5$ Hz, 2 H, 3-H^{eq}), 2.42 (d, $^2J = 13.5$ Hz, 1 H, 5-H^{ax}), 2.37 (dt, $^2J = 13.0$, $^3J = 2.0$, $^4J = 2.0$ Hz, 1 H, 9-H^{eq}) ppm. ¹³C NMR (100 MHz, CD₃OD): $\delta = 94.7$ (C-6), 76.3 (C-8), 72.1 (C-2), 66.0 (CH₂OH), 65.9 (CH₂OH), 35.9 (C-11), 29.7 (C-3), 28.7 (C-5), 28.3 (C-9) ppm.

(2R,6S,8S)- and (2R,6R,8S)-2,8-Dihydroxymethyl-1,7-dioxo-4,10-dithiaspiro[5.5]undecane (2c and 2d): The general procedure of cyclization applied to (R,S)-**8** led to isomers (2R,6S,8S)-**2c** and (2R,6R,8S)-**2d** with isomer **2c** as the major compound.

(2R,6S,8S)-2c: Colourless oil. *R_f* = 0.37 (EtOAc). [α]_D²⁵ = +10.0 (*c* = 0.1, CH₃OH). ¹H NMR (400 MHz, CD₃OD): $\delta = 4.75$ (br. d, $^3J = 6.0$ Hz, 1 H, 8-H^{eq}), 4.31 (d, $^2J = 6.5$ Hz, 1 H, CH₂OH), 3.93 (t, $^2J = ^3J = 6.0$ Hz, 1 H, CH₂OH), 3.69 (dq, $^3J = 7.0$, $^3J = 5.0$ Hz, 1 H, 2-H), 3.52 (dd, $^2J = 11.0$, $^3J = 5.5$ Hz, 1 H, CH₂OH), 3.47 (dd, $^2J = 11.0$, $^3J = 5.0$ Hz, 1 H, CH₂OH), 3.09 (br. d, $^2J = 13.0$ Hz, 1 H, 9-H^{ax}), 2.99 (d, $^2J = 13.0$ Hz, 1 H, 11-H^{ax}), 2.83 (d, $^2J = 15.0$ Hz, 1 H, 5-H^a), 2.80 (d, $^2J = 15.0$ Hz, 1 H, 5-H^b), 2.75 (dd, $^2J = 13.5$, $^3J = 5.0$ Hz, 1 H, 3-H^a), 2.63 (dd, $^2J = 13.5$, $^3J = 7.0$ Hz, 1 H, 3-H^b), 2.42 (d, $^2J = 13.0$ Hz, 1 H, 11-H^{eq}), 2.18 (br. d, $^2J = 13.0$ Hz, 1 H, 9-H^{eq}) ppm. ¹³C NMR (100 MHz, CD₃OD): $\delta = 108.3$ (C-6), 76.3 (C-8), 72.9 (C-2), 70.8 (CH₂OH), 66.0 (CH₂OH), 40.6 (C-5), 37.8 (C-3), 33.9 (C-11), 29.7 (C-9) ppm.

Acknowledgments

The authors thank Anne-Sophie Martin for performing the NOESY experiments. This research was supported by a grant from the Ministère de l'Enseignement Supérieur et de la Recherche (M.G.).

- [1] For example, see: a) Y. Qiu, A. Hübener, H. Zhang, C. J. Moore, M. T. Fletcher, P. Hayes, K. Dettner, W. Francke, C. S. P. McErlean, W. Kitching, *Synthesis* **2000**, 13, 1956–1978; b) W. Francke, W. Kitching, *Curr. Org. Chem.* **2001**, 5, 233–251.
- [2] For example, see: a) M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, 100, 2407–2473; b) J. A. Marshall, M. M. Yanik, *J. Org. Chem.* **2001**, 66, 1373–1379.

- [3] For example, see: a) E. Hamel, *Med. Res. Rev.* **1996**, *16*, 207–231; b) F. M. Uckun, C. Mao, A. O. Vassilev, H. Huang, S. T. Jan, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541–545; c) O. Barun, K. Kumar, S. Sommer, A. Lgerak, T. U. Mayer, O. Müller, H. Waldmann, *Eur. J. Org. Chem.* **2005**, *22*, 4773–4788; for inhibitors of the mitogenic activity of epidermal growth factors (EGF), see: d) T. Takahashi, H. Osada, H. Koshino, M. Sasaki, R. Onose, M. Nakakoshi, M. Yoshihama, K. Isono, *J. Antibiot.* **1992**, *45*, 1414–1419; e) H. Takahashi, Y. Yamashita, H. Takaoka, J. Nakamura, M. Yoshihama, H. Osada, *Oncol. Res.* **1997**, *9*, 7–11; for new apoptosis-inducing agents, see: f) S. Mitsuhashi, H. Shima, T. Kawamura, K. Kikuchi, M. Oikawa, A. Ichihara, H. Oikawa, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2007–2012; g) K. Kikuchi, H. Shima, S. Mitsuhashi, M. Suzuki, H. Oikawa, *Drugs Future* **2000**, *25*, 501–507.
- [4] K. T. Mead, B. N. Brewer, *Curr. Org. Chem.* **2003**, *7*, 227–256.
- [5] a) E. M. Seward, E. Carlson, T. Harrison, K. R. Haworth, R. Herbert, F. J. Kelleher, M. M. Kurtz, J. Moselev, S. N. Owen, A. P. Owens, S. J. Sadowski, C. J. Swain, B. J. Williams, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2515–2518; b) J. D. Moseley, C. J. Swain, WO 97/30056, **1997**.
- [6] P. T. Meinke, H. Mrozik, US 5162363, **1992**.
- [7] A. Tursun, B. Aboab, I. Canet, M.-E. Sinibaldi, *Tetrahedron Lett.* **2005**, *46*, 2291–2294.
- [8] A. Tursun, B. Aboab, A.-S. Martin, M.-E. Sinibaldi, I. Canet, *Synlett* **2005**, *15*, 2397–2399.
- [9] a) P. M. Sher, R. D. Kronenthal, *J. Labelled Compd. Radiopharm.* **1997**, *39*, 21–28; b) M. Hashimoto, Y. Hatanaka, J. Yang, J. Dhesi, G. D. Holman, *Carbohydr. Res.* **2001**, *331*, 119–127.
- [10] A.-H. Li, S. Moro, N. Forsyth, N. Melman, X.-D. Ji, K.-A. Jacobson, *J. Med. Chem.* **1999**, *42*, 706–721.
- [11] a) A. K. M. Anisuzzaman, L. N. Owen, *J. Chem. Soc., C* **1967**, *11*, 1021–1026; b) P. C. Braga, US 4910220, **1988**.
- [12] The physical data for (2*R*,6*S*,8*R*)-1a and (2*R*,6*R*,8*S*)-1b were in good agreement with those previously reported by M. Lemaire, G. Jeminet, J.-G. Gourcy, G. Dauphin, *Tetrahedron: Asymmetry* **1993**, *4*, 2101–2108.
- [13] R. J. Mears, H. E. Sailes, J. P. Watts, A. Whiting, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3250–3263.

Received: May 23, 2006

Published Online: September 8, 2006