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A short and versatile route to chiral spiroketal skeletons

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Abstract—Different chiral spiroketal skeletons are obtained, in a versatile manner, by iterative alkylations of acetone *N*,*N*-dimethylhydrazone with iodides **2** followed by a one-pot deprotection/spirocyclization sequence. This methodology has been applied successfully to the synthesis of 1,7-dioxaspiro[5.5]undecane and 1,6-dioxaspiro[4.5]decane systems.

The 1,7-dioxaspiro[5.5]undecane and the 1,6-dioxaspiro[4.5]decane systems are important subunits of natural products from various sources, including insects, microbes, plants, fungi and marine organisms.[1] In particular, these moieties occur in a large number of biologically active compounds such as polyether ionophores, insect pheromones and antibiotic macrolides. They have also been employed as scaffold in the synthesis of conformationally restrained glycomimetics.[2]

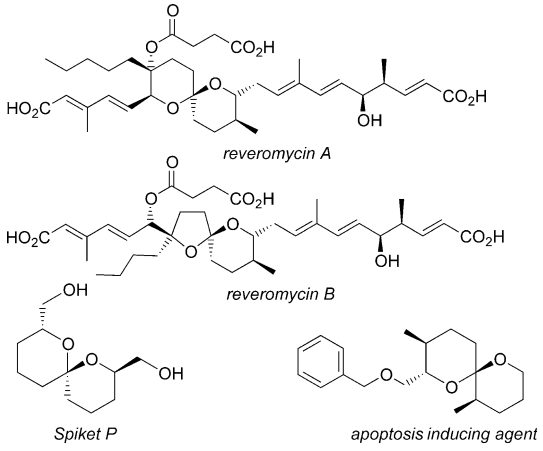

Figure 1.

As a part of our research programme is devoted to the synthesis of novel antimitotic spiroketal derivatives, we focused our attention on the epidermal growth factor inhibitors reveromycins A and B.[3] In contrast with other natural antitumour compounds bearing a spiroketal framework in their skeleton (i.e., spongistatin) these products show a more simplified structure while maintaining interesting activity. Additionally, it was recently reported that poorly substituted spiroketals exhibit biological effects such as tubulin modulation[4] (Spiket P) and cytotoxicity against tumour cell lines[5] (Fig. 1).

Therefore, in order to prepare analogues (modulations of sizes and substituents) of spiroketal units, we developed a short and versatile synthesis of frameworks **1**. The key step of our approach is based upon an acidic spirocyclization of a chiral diketalketone **4** obtained in three steps from *N*,*N*-dimethylhydrazones and isopropylidene iodides **2** (Scheme 1).

To check the validity of our approach, we first addressed the synthesis of unsubstituted spiroketals **1** (Scheme 1, R = H).

First part of our work was devoted to the preparation of synthons **2a** and **2b**. Iodide **2a** was synthesized from L-malic acid using an improved sequence (Scheme 2), inspired from the procedure previously described by Mori and Watanabe.[6] Thus, **2a** was obtained in six steps in 47% overall yield. Compound **2b** was prepared in two steps from commercially available (*S*)-solketal.[7]

Alkylation of the lithiated acetone *N*,*N*-dimethylhydrazone[8] with (*S*)-iodide **2a** provided, nearly quantitatively,

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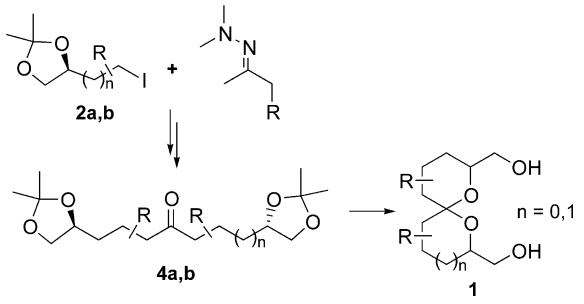


Scheme 1.

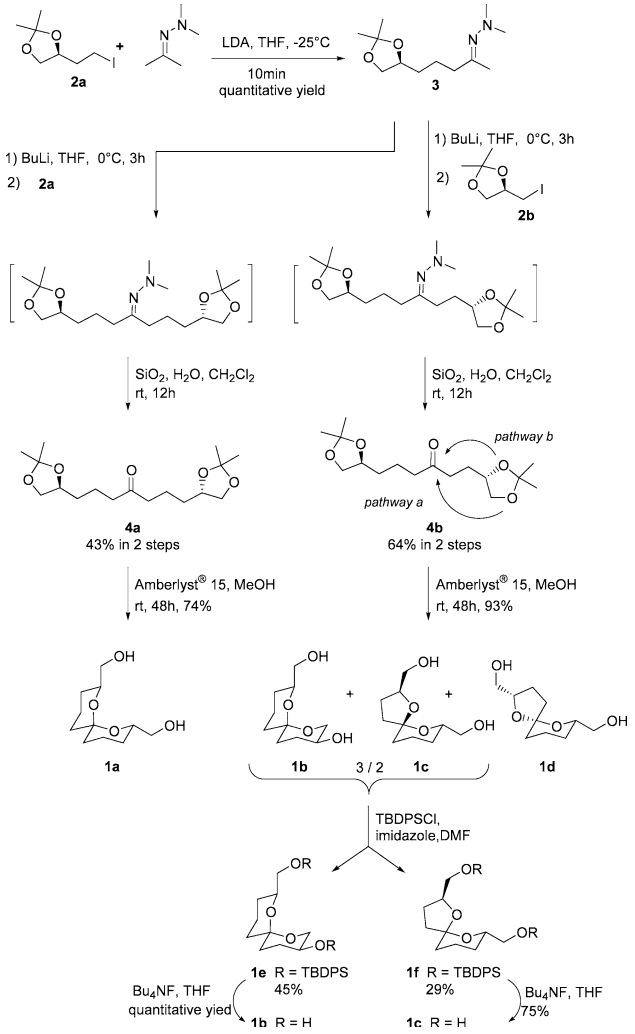
the monoalkylated hydrazone **3**, which was immediately used in the next step without further purification. A second alkylation using either iodide (*S*)-**2a**, or (*R*)-**2b** led, after SiO_2-induced cleavage[9] of the hydrazone function, to the appropriate ketones **4a**,**b**[10] in 43% and 64% overall yield, respectively (Scheme 3).

Deprotection of the two acetal groups concomitant with spirocyclization was achieved by simple treatment of **4a**,**b** with Amberlyst® 15 in MeOH at room temperature during 48 h (Scheme 3).

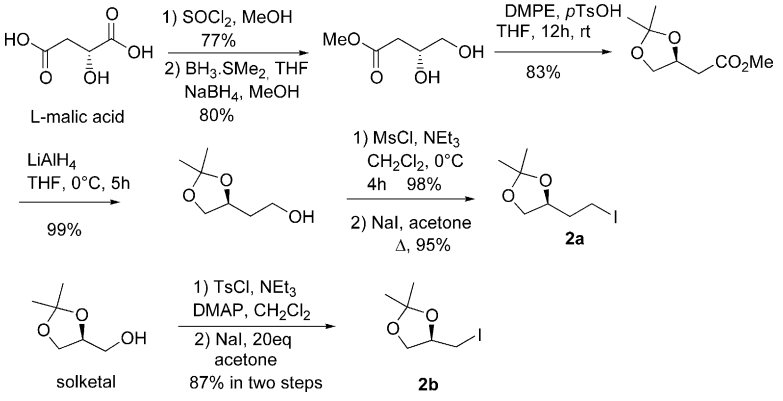
In this way, the (2*S*,6*S*,8*S*)-**1a** isomer[10] was efficiently obtained from **4a** as the sole product. The absolute configuration at the central spirocarbon of **1a** is controlled by steric and anomeric effects[11] whereas the configurations of the carbons bearing the side chains resulted from the configuration of the iodide precursor **2a**.

Finally, compound **1a** is obtained, without racemization, from L-malic acid in 10 steps and 15% overall yield. Our methodology is therefore competitive with that reported by Uckun et al.[4a] (10 steps, 8.6% yield) or Chattopadhyay and co-workers[4d] (eight steps, 15.5% yield).

In the case of compound **4b** the acidic tandem deprotection/cyclization reaction provided, as expected,[12] a mixture of 1,7-dioxaspiro[5.5]undecane **1b** (Scheme 3, pathway a) and 1,6-dioxaspiro[4.5]decanes **1c** and **1d** (Scheme 3, pathway b), in 93% yield. Although compound **1d**[13] could be isolated in 9% yield, compounds **1b** and **1c** were obtained, in 84% yield, as an inseparable mixture of isomers (3/2 ratio determined from quantitative ^{13}C NMR spectrum). This mixture was then treated with TBDPSCl in DMF in the presence of imidazole, furnishing silylated derivatives **1e** and **1f**, which could be separated by flash chromatography. Transformation



Scheme 3.



Scheme 2.

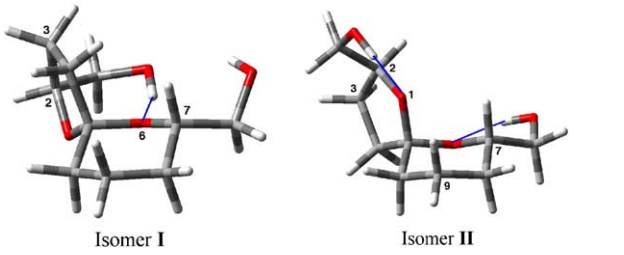


Figure 2. Calculated structures for (2*S*,5*R*,7*S*)- and (2*S*,5*S*,7*S*)-1,6-dioxaspiro[4.5]decanes. Hydrogen bonds are represented by a line.

of compounds **1e** and **1f** to the corresponding alcohols **1b**[13] and **1c**[13] was achieved by a classical method using Bu_4NF in THF (Scheme 3).

For the same reasons as **1a**, the configuration of compound **1b** is (3*S*,6*S*,8*S*) as confirmed by the equatorial position of the hydroxyl group at C_3 (H_3 gave a triplet of triplet, $J = 10.0$ and 4.5 Hz).[14] We assumed that by taking into account the factors that determine the stereochemistry of **1a** the major isomer **1c** has configuration (2*S*,5*S*,7*S*). In order to confirm this hypothesis, we compared the experimental data to those obtained by molecular modeling (Fig. 2).[15]

The isomer **I** of (2*S*,5*R*,7*S*) configuration (highest energy, $\Delta H_f^0 = -189.57$ kcal mol^{-1}) presented a structure in which the lost of one anomeric effect is counterbalanced by an intercyclic hydrogen bond (calculated distance between O*H* and O_6: 1.82 Å). The isomer **II** of (2*S*,5*S*,7*S*) configuration, is the more stable isomer ($\Delta H_f^0 = -193.42$ kcal mol^{-1}) exhibiting the attempted double anomeric structure (Fig. 2). In this isomer, the existence of an 1,3-diaxial relationship between H_7, H_{9ax} and O_1 should lead to a deshielded position of the resonances for these two hydrogens. Both calculated structures were in close agreement with the experimental NMR data[13] as illustrated by (i) the chemical shifts observed for H_7 and H_9 (**1c**: $\delta_{H7} = 3.91$ ppm, $\delta_{H9ax} = 1.82$ ppm, $\delta_{H9eq} = 1.70$ ppm; **1d**: $\delta_{H7} = 3.70$ ppm, $\delta_{H9} = 1.52$ and 1.31 ppm) supporting a *trans*-configured tetrahydropyran ring for **1c**, (ii) the calculated and measured scalar coupling constants (Table 1).

In summary, we have developed an efficient and stereoselective approach to 1,7-dioxaspiro[5.5]undecane and to 1,6-dioxaspiro[4.5]decane ligands **1a**,**b**,**c**,**d** from readily available starting materials. By this route, **1a**, **1b**, **1c** and **1d** were obtained, from iodides **2a** and **2b**, in 32% (four steps), 29% (six steps), 14% (six steps) and 6% (six steps) overall yield, respectively. Furthermore, as the enantiomers of the starting materials are readily available, this approach is also applicable to the synthesis of the antipode spiroketals.

Application of this methodology to the synthesis of substituted spiroketals from modified iodide derivatives **2** is actually in progress in our laboratory. In addition, the antitumoural activity of all synthesized spiroketals will be evaluated in due course.

Table 1. Selected calculated and observed scalar coupling constants for **1c** and **1d**

		Calculated dihedral angle (deg)	Calculated *J* (Hz)	Observed *J* (Hz)
Isomer **I** (**1d**)	H_2–H_{3a}	1.7	9.6	8.0
	H_2–H_{3b}	120.4	4.7	2.5
Isomer **II** (**1c**)	H_2–H_{3a}	6.7	9.5	8.0
	H_2–H_{3b}	125.2	5.5	5.0
	H_7–H_{8a}	172.3	12.2	12.0
	H_7–H_{8b}	55.1	3.9	3.0

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6. Selected data for compound **2a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (tdd, 1H, $J = 6.0$, 7.5, 4.5 Hz), 4.08 (dd, 1H, $J = 8.0$, 6.0 Hz), 3.57 (dd, 1H, $J = 8.0$, 6.0 Hz), 3.27 (ddd, 1H, $J = 10.0$, 5.5, 8.0 Hz), 3.22 (dt, 1H, $J = 10.0$, 7.5 Hz), 2.10 (tdd, 1H, $J = 7.5$, 14.0, 5.5 Hz), 2.03 (tdd, 1H, $J = 8.0$, 14.0, 4.5 Hz), 1.41 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.1, 75.6, 68.6, 37.8, 26.9, 25.5, 1.2; $[\alpha]_D^{25}$ −23.8 (*c* 2.1, $CHCl_3$) lit. $[\alpha]_D^{25}$ −22.3 (*c* 2.12, $CHCl_3$) Mori, K.; Watanabe, H. *Tetrahedron Lett.* **1986**, *42*, 295–304.
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10. Compounds **4a**, **4b** and **1** were characterized by ^{1}H and ^{13}C NMR measurements and mass spectra. In the case of **1a** comparison with an authentical sample of our laboratory was also realized. All the data of **1a** were in good agreement with the proposed structure **1a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (dddd, 2H, J = 11.5, 7.0, 3.0, 2.5 Hz), 3.60 (dd, 2H, J = 11.0, 3.0 Hz), 3.50 (dd, 2H, J = 11.0, 7.0 Hz), 2.20 (2H, OH), 1.89 (qt, 2H, J = 13.0, 4.5 Hz), 1.62 (m, 4H), 1.50 (md, 2H, J = 13.0 Hz), 1.41 (td, 2H, J = 13.0, 4.5 Hz), 1.30 (tdd, 2H, J = 13.0, 11.5, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.3 (C6), 70.0 (C2 and C8), 66.5 (CH_2OH), 35.5 (C5 and C11), 26.6 (C3 and C9), 18.5 (C4 and C10); $[\alpha]_D^{25}$ +70.0 (c 0.46, $CHCl_3$). For (2*R*,6*R*,8*R*)-Spiket P[4a] $[\alpha]_D^{22}$ −59.4 (c 0.7, $CHCl_3$).
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13. Compound **1b**: ^{1}H NMR (400 MHz, C_6D_6): δ 4.1 (br s, 2H, OH), 3.76 (ddd, 1H, J = 10.0, 4.5, 2.0 Hz), 3.71 (m, 1H), 3.66 (tt, 1H, J = 10.0, 4.5 Hz), 3.57 (t, 1H, J = 10.0 Hz), 3.51 (dd, 1H, J = 11.5, 6.5 Hz), 3.48 (dd, 1H, J = 11.5, 4.0 Hz), 2.0 (m, 1H), 1.88 (qt, 1H, J = 13.0, 4.0 Hz), 1.77 (m, 1H), 1.65 (dt, 1H, J = 13.0, 3.5 Hz), 1.46 (d, 1H, J = 13 Hz), 1.37 (m, 1H), 1.37 (td, 1H, J = 13.0, 4.0 Hz), 1.22 (m, 2H), 1.05 (qd, 1H, J = 12.5, 4.0 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 95.0 (C6), 71.0 (C2), 66.4 (CH_2OH), 66.3 (C9), 64.8 (C8), 35.2 (C11), 34.6 (C5), 28.3 (C10), 26.8 (C3), 19.0 (C4); IR (film) 3401, 2944, 1660, 1446, 1377, 1227, 1177, 1054, 1018; $[\alpha]_D^{25}$ +76.43 (c 1.26, $CHCl_3$). Compound **1c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (dtd, 1H, J = 8.0, 5.5, 3.0 Hz), 3.91 (ddt, 1H, J = 11.5, 6.5, 3.0 Hz), 3.73 (dd, 1H, J = 11.5, 3.0 Hz), 3.58 (dd, 1H, J = 11.5, 3.0 Hz), 3.52 (dd, 1H, J = 11.5, 6.0 Hz), 3.48 (dd, 1H, J = 11.5, 6.5 Hz), 2.3 (br s, 2H, OH), 2.1 (m, 1H), 1.96 (m, 1H), 1.82 (qt, 1H, J = 13.0, 4.0 Hz), 1.70 (m, 5H), 1.50 (dq, 1H, J = 13.0, 3.0 Hz), 1.32 (qd, 1H, J = 13.0, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 106.6 (C5), 78.2 (C2), 71.0 (C7), 66.0 (CH_2OH), 64.7 (CH_2OH), 37.7 (C10), 32.9 (C4), 26.2 (C8), 25.3 (C3), 19.6 (C9); IR (film) 3335, 2941, 1150, 1380, 1222, 1042; $[\alpha]_D^{25}$ +70.87 (c 1.38, $CHCl_3$). Compound **1d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (tt, 1H, J = 8.0, 2.5 Hz), 3.84 (dd, 1H, J = 12.0, 2.5 Hz), 3.70 (m, 1H), 3.65 (br s, 2H, OH), 3.62 (m, 2H), 3.48 (dd, 1H, J = 12.0, 8.0 Hz), 2.4 (m, 1H), 2.1 (m, 1H), 1.90 (m, 2H), 1.74 (m, 1H), 1.62 (m, 2H), 1.52 (m, 2H), 1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 107.6 (C5), 81.2 (C7), 75.6 (C2), 66.3 (CH_2OH), 64.0 (CH_2OH), 34.0 (C4), 33.3 (C6), 26.2 (C3), 24.2 (C8), 21.1 (C9); $[\alpha]_D^{25}$ +18.84 (c 0.34, $CHCl_3$).
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