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An entry to 1,6-dioxaspiro[4.6]undecanes and 1,7-dioxaspiro[5.6]dodecanes

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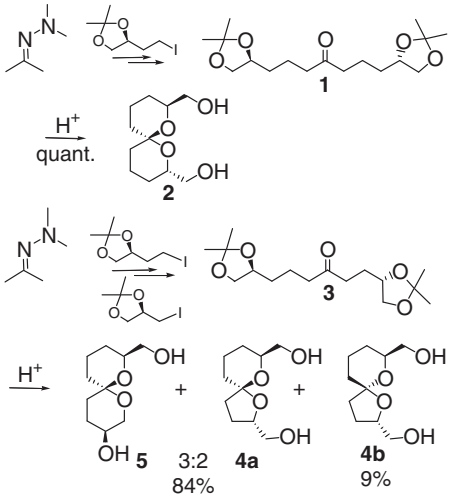
ABSTRACT

Ketones **11a–c** obtained by iterative alkylation of acetone *N,N*-dimethylhydrazone with iodides **6** and **8a,b** or epoxide **9** followed by SiO_2/H_2O-induced cleavage of the hydrazone were quantitatively transformed into 1,6-dioxaspiro[4.6]undecanes **12a,c** and 1,7-dioxaspiro[5.6]dodecanes **12b** using $Yb(OTf)_3$ in CH_3CN.

Spiroketals form the common structural part of many biologically active, naturally occurring products issued from various sources including insects, plants, fungi, and marine organisms.[1] The mainly encountered structural variations relate to the size of the two spiranic cycles (spiro[4.4], spiro[4.5], and spiro[5.5] systems) and the presence or not of alkyl or alkoxy substituents on the spirocyclic skeleton. Because of their wide range of biological activities, spiroketals have seen a sustained interest in the development of methods for their preparation—mainly for 1,7-spiro[5.5]undecane and 1,6-spiro[4.5]decane systems—and numerous strategies have been reported and reviewed.[2] An interesting but rarer structural variation is exhibited by seven-membered ring spiroketals which could be formed stereoselectively but often in moderate yields.[3]

We investigated these last years' short routes to spiroketals and analogues. Our general strategy led to the elaboration of linear key-ketones of type **1–3**, obtained by iterative substitution of conveniently protected acetone,[4] followed by a one-step deprotection—spiroketalization cascade. Thus, in spiro[5.5] series, we described the efficient synthesis of dihydroxymethyl-substituted 1,7-dioxaspiro[5.5]undecane **2**[5] and demonstrated the facility in incorporating supplementary heteroatoms in the two cycles, starting from acetone *O*-benzyloxime.[6] In spiro[4.5] series, we evaluated our strategy through the elaboration of 1,6-dioxaspiro[4.5]decane.[5] Exposure of ketone intermediate **3** to acidic conditions led to a mixture of the targeted [4.5]-spiroketal, as the anomeric **4a** and non-anomeric **4b** forms, but and contrarily to spiro[5.5] series, accompanied with the 1,7-dioxaspiro[5.5]undecane **5**—resulting from a double attack of primary alcohol functions on the keto group (Scheme 1).

To further evaluate the scope of this sequence, we decided to extend it to the preparation of 1,6-dioxaspiro[4.6]undecane and 1,7-dioxaspiro[5.6]dodecane systems. Herein are disclosed details of our investigations in this area. In this course, we chose to prepare the spiro precursors **11** (Scheme 2).



Scheme 1. Synthesis of 1,7-dioxaspiro[5.5]undecanes and 1,6-dioxaspiro[4.5]-decanes.

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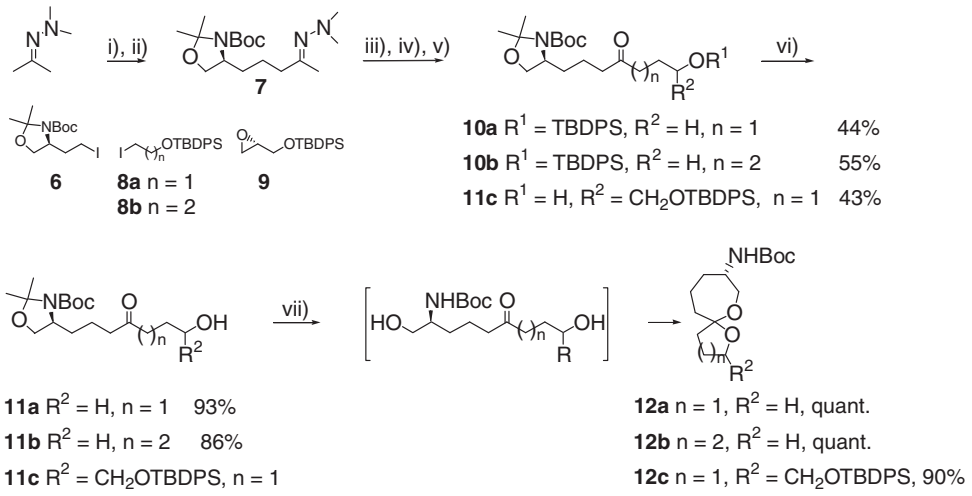
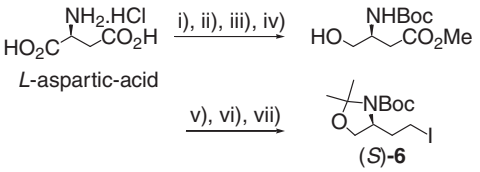


Scheme 2. (i) *n*-BuLi, THF, −10 °C; (ii) **6**, THF, quant.; (iii) LDA, −78 °C, THF; (iv) **8a**, **8b** or **9**, −20 °C, 12 h; (v) SiO_2/H_2O, CH_2Cl_2, 20 °C, 48 h, (vi) for **10a**,**b**, TBAF, THF, 20 °C, quant.; (vii) $Yb(OTf)_3$, CH_3CN, 20 °C, 24 h.



Scheme 3. Synthesis of iodide (*S*)-**6**. (i) $SOCl_2$, −10 °C, MeOH, 91%; (ii) Boc_2O, Na_2CO_3, dioxane/H_2O, 20 °C, 12 h, 89%; (iii) *N*-hydroxysuccinimide, DCC, CH_2Cl_2, 20 °C, 12 h; (iv) $NaBH_4$, THF/EtOH (3/1), 0 °C, 15 min, 89% in two steps; (v) DMPE, *p*-TsOH, CH_2Cl_2, 20 °C, 87%; (vi) $LiAlH_4$, THF, 0 °C then 20 °C, 12 h, quant.; (vii) I_2, imidazole, PPh_3, Et_2O/CH_3CN (3/2), 20 °C, 48 h, 95%.

Thus, treatment of the lithiated acetone *N*,*N*-dimethylhydrazone by iodide **6** (see Scheme 3 for an access to **6** by an adaptation of the reported synthesis[7] of this substrate) led quantitatively (^{1}H NMR of the crude) to hydrazone intermediate **7**. Compound **7** submitted to basic treatment (LDA) underwent a second alkylation step with the known iodides **8a,b**[8] furnishing the disubstituted hydrazones that delivered after their selective SiO_2/H_2O induced cleavage, ketones **10a** and **10b** in 44% and 55% yields, respectively (three steps, one final purification). Subsequent removal of the silyl ether protecting group of **10a,b** was then classically accomplished using TBAF in THF and afforded the key hydroxy-ketones **11a** and

Table 1
^{13}C and ^{1}H NMR data for **12a** and **12b** isomers ($CDCl_3$)

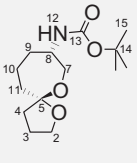
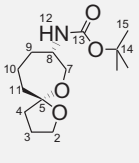
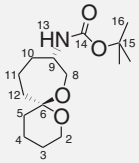
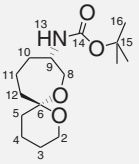
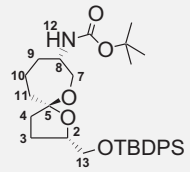
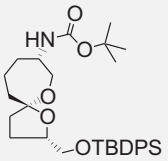
		(5*R*,8*S*)-**12a**		(5*S*,8*S*)-**12a**		(6*R*,9*S*)-**12b**		(6*S*,9*S*)-**12b**
	δ_H, *J* in Hz	δ_C	δ_H, *J* in Hz	δ_C	δ_H, *J* in Hz	δ_C	δ_H, *J* in Hz	δ_C
2	3.63, td (8.0, 5.0) 3.66, br t (7.5)	66.8	3.67, td (8.0, 6.0) 3.77, td (8.0, 6.5)	66.9	3.42, dd (11.0, 5.0) 3.53, td (12.0, 2.5)	61.0	3.49, dd (10.0, 4.0) 3.66, m	61.1
3	1.41, m 1.71, m	24.9	1.46, m 1.80, m	24.7	1.14, m 1.33, qt (13.0, 4.0)	25.7	1.20, m 1.39, m	25.8
4	1.22, m 1.66, m	38.1	1.29, m 1.89, m	38.2	1.21, m 1.64, qt (13.5, 3.5)	19.2	1.33, m 1.85, m	19.2
5		110.5		110.1	1.02, td (13.0, 4.0) 1.44, m	35.2	1.12, m 1.71, m	35.4
6						100.0		99.6
7	3.37, dt (12.5, 2.5) 3.68, dd (13.0, 1.0)	64.0	3.45, dd (12.0, 10.0) 3.60, br d (12.0)	65.4				
8	3.85, dq (8.0, 2.0)	49.7	3.91, m	51.1	3.32, dt (12.5, 2.5) 3.60, d (12.5)	62.9	3.37, td (11.0, 5.0) 3.62, m	64.2
9	1.11, m 1.93, br d (13.5)	35.7	0.90, dt (11.0, 10.5) 1.65, m	36.1	3.88, m	49.7	3.87, m	51.0
10	1.14, m 1.23, m	19.2	1.21, m 1.37, m	20.5	1.10, m 1.92, br d (13.0)	35.9	0.74, m 1.68, m	36.5
11	1.63, dt (14.5, 7.5) 1.77, dd (14.5, 11.0)	38.6	1.65, m 1.85, m	38.1	1.10, m 1.21, m	18.1	1.22, m	19.6
12	5.38, d (8.0)		4.20, br s		1.53, d (11.0) 1.59, m	41.7	1.68, m	41.2
13		155.1		155.0	5.41, d (8.5)		4.07, br s	
14		78.6		78.5		155.1		155.0
15	1.47, s	28.6	1.43, s	28.5		78.6		78.6
16					1.47, s	28.6	1.45, s	28.5

Table 2
^{13}C and ^{1}H NMR data for **12c** isomers

	 (2*S*,5*S*,8*S*)-**12c**		 (2*S*,5*R*,8*S*)-**12c**	
	δ_H, *J* in Hz	δ_C	δ_H, *J* in Hz	δ_C
2	4.18, dq (8.0, 4.5)	78.9	4.21, q (6.5)	80.5
3	1.68, m 2.01, ddt (14.5, 11.5, 8.5)	26.9	1.67, m	27.8
4	1.51, dt (11.0, 8.0) 1.91, m	38.0	1.16, m 1.69, m	38.2
5		110.8		110.5
7	3.60, m 3.47, dd (11.5, 10.0)	65.5	3.11, br d (12.5) 3.53, d (13.0)	63.7
8	3.91, m	51.31	3.81, m	49.6
9	1.66, m 0.95, m	36.2	1.08, m 1.91, br d (13.5)	35.6
10	1.23, m 1.40, m	20.4	1.19, m	19.2
11	1.70, m 1.91, m	38.3	1.60, dd (15.0, 7.5) 1.76, dd (15.0, 11.5)	38.5
12	4.26, br d (8.0)		5.29, d (8.5)	
13	3.68, dd (10.5, 4.0) 3.58, dd (10.5, 4.5)	66.7	3.53, dd (10.0, 5.5) 3.78, dd (10.0, 6.5)	68.7
N-Boc	1.43, s	155.0, 78.6, 28.5	1.46, s	155.0, 78.5, 28.6
Si-*t*Bu	1.15, s	19.6, 27.1	1.17, s	

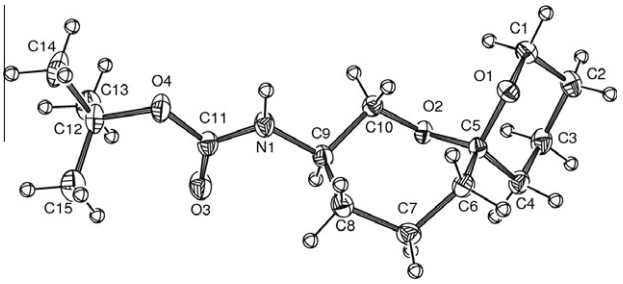


Figure 1. ORTEP of **12b**.

11b in good yields. In a same manner, the attack of the anion of hydrazone **7** on epoxide **9**[9] permitted its ring opening, leading directly to the keto-diol **11c** in 43% yield.

Finally, *p*-TsOH/MeOH mediated deprotection-spirocyclization of **11a,b,c** afforded, as the sole cleanly isolated derivatives, 1,6-dioxaspiro[4.6]undecanes **12a,c** and 1,7-dioxaspiro[5.6]dodecane **12b** (Scheme 2). In an attempt to increase the formation of these spirocyclic compounds, we modified the nature of the acid. Treatment of **11** by HCl/methanol or Amberlyst® 15 led unfortunately to degradation of the reaction mixture. Conversely, the use of $Yb(OTf)_3$ in CH_3CN revealed efficient[3d] and gave nearly quantitatively and exclusively the spirocyclic epimers **12** in a 1/1 ratio.

These diastereomers could be cleanly separated on neutral alumina and fully characterized (Tables 1 and 2). Furthermore, in the spiro[5.6] series, if the (6*R*,9*S*)-isomer of **12b** occurred as an oil, its (6*S*,9*S*) epimer could be obtained as a fine white powder easily recrystallized from ethanol. Its structure and the relative stereochemistry of the spiranic center were then confirmed by an X-ray crystallographic analysis as shown as ORTEP plot in Figure 1.[10]

In summary, we demonstrated here the efficiency of our strategy to prepare in a few steps and good yields the 1,6-dioxaspiro[4.6]undecanes **12a,c** (five steps, 41% yield for **12a**; four steps, 39% yield for **12c**) and 1,7-dioxaspiro[5.6]dodecane **12c** (five steps, 47% yield) as a 1/1 separable mixture of the two spiranic epimers. Our approach allowed the introduction of substitutions on the β and γ positions relative to the spiranic center, using simple iodides or epoxide precursors. Extension to the synthesis of others spiroketals will be reported in due course.

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