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Spiranes synthesis based on samarium diiodide-mediated reductive cyclization

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ABSTRACT

A general and efficient method for the preparation of spiro compounds is described. Enone–aldehydes were exposed to samarium diiodide under mild conditions and various spirocyclic γ-hydroxyketones were obtained in good yields.

Many natural products having the spiro core and exhibiting significant biological activities are known to exist (Fig. 1). Further, owing to the biological importance of the spiro core in nature, the development of new and efficient strategies for constructing it has become a major focal point of synthetic chemistry.[1] Therefore, our aim was to develop a general and efficient method for preparing spiro compounds.

Samarium (II) diiodide (SmI_2) is a powerful one-electron reducing agent that has found widespread use in organic synthesis.[2] One of the widely applied processes involving the use of SmI_2 includes the intramolecular ketyl olefin radical coupling reaction to achieve carbon–carbon bond formation between aldehydes or ketones and olefins.[3] Recently, cyclization reactions involving the use of SmI_2 have been proved to be valuable tools for the synthesis of natural products.[4] Therefore, our developed method for preparing spiranes focuses on the intramolecular cyclization reactions of aldehydes onto cyclic α,β-unsaturated ketones.

Spirane precursors, enone–aldehydes **6**–**9**, were prepared from 3-alkoxyenones **1**–**4**, which were either purchased from commercial suppliers or obtained from corresponding cyclic 1,3-diones using a method reported in the literature.[5] The 1,2-addition of Grignard reagents **5a**–**c**[6] to **1**–**4** and subsequent treatment of the resulting addition products with an acidic aqueous solution gave enone–aldehydes **6**–**8** in good yields, with an exception of **9a** (Table 1). Thus, enone–aldehydes **9** were prepared from another substrate, 2-cyclohepten-1-one (**10**), as shown in Scheme 1. Similarly, the 1,2-addition of **5a**–**b** generated the tertiary allylic alcohols **11**. This addition was followed by the oxidation of pyridinium chlorochromate (PCC) to give enones **12**. Hydrolysis of the acetal moiety under acidic conditions gave the desired enone–aldehydes **9** in good overall yields.

Having obtained the enone–aldehydes, we first used **6a** to examine the reaction conditions. SmI_2 (0.1 M in THF, 4 equiv) was added to a solution of **6a** in THF in the presence of MeOH at room temperature. We found that **6a** was completely consumed within 1 min and gave cyclized product **13** in 72% yield (Table 2, entry 1). However, under these conditions, the ketone was also reduced to alcohol owing to an excess of the reducing agent.

Then, we reduced the 4 equiv of SmI_2 to 2 equiv. In this case, the desired spirocyclic γ-hydroxyketones **14a** and **14a′** were obtained in 60% yield as a 1:1 mixture of inseparable diastereoisomers (entry 2). When an attempt was made to improve the diastereoselectivity by decreasing the reaction temperature to 0 °C, **14a** and **14a′** were obtained in 75% yield in a ratio of 3:2 (entry 3). A similar diastereoselectivity was observed when the reaction was carried out at −20 °C or at lower temperatures; however, at these temperatures, the yield decreased and the required reaction time increased

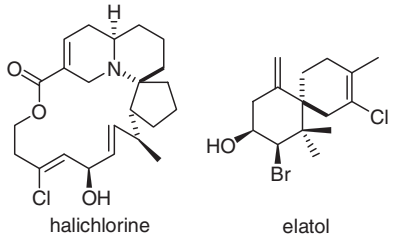

Figure 1. Natural products containing the spiro core structures.

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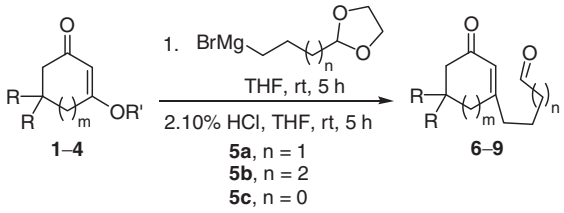
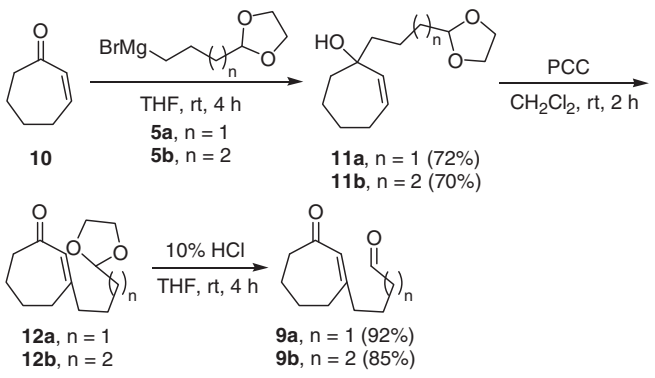
Table 1
Preparation of enone–aldehydes **6**–**9** from 3-alkoxyenones **1**–**4**

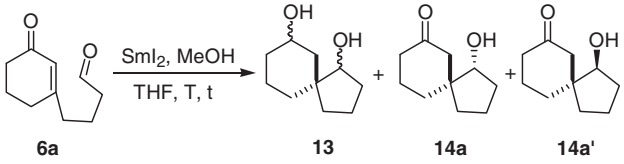


Entry	3-Alkoxyenone	Grignard	Product		Yield (%)
1		**5a**		**6a**, $n = 1$	75
2		**5b**		**6b**, $n = 2$	80
3	OEt **1**	**5c**		**6c**, $n = 0$	47
4		**5a**		**7a**, $n = 1$	63
5	OMe **2**	**5b**		**7b**, $n = 2$	57
6		**5a**		**8a**, $n = 1$	65
7	OMe **3**	**5b**		**8b**, $n = 2$	68
8	OEt **4**	**5a**		**9a**, $n = 1$	20



Scheme 1. Preparation of enone–aldehydes **9** from 2-cyclohepten-1-one (**10**).

Table 2
Intramolecular reductive cyclization of **6a** with SmI_2



Entry	SmI_2 (equiv)	T (°C)	t (min)	Product/yield (%)	**14a**:**14a′**[a]
1	4	rt	1	**13**/72	–
2	2	rt	5	**14a** + **14a′**/60	1:1
3	2	0	10	**14a** + **14a′**/75	1.5:1
4	2	−20	20	**14a** + **14a′**/65	1.5:1
5	2	−30	40	**14a** + **14a′**/60	1.7:1
6	2	−40	100	**14a** + **14a′**/50	1.5:1
7	2	−50	200	**14a** + **14a′**/56	1.5:1

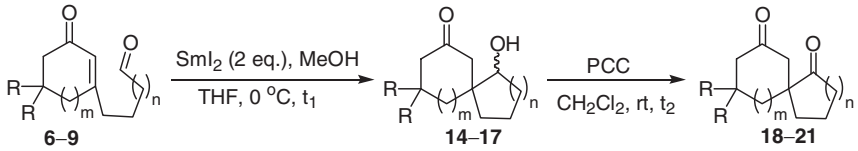
[a] The ratios were determined by ^1H NMR.

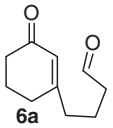
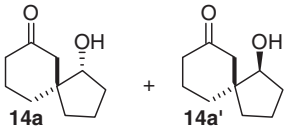
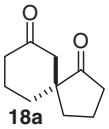
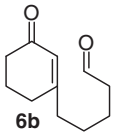
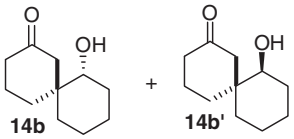
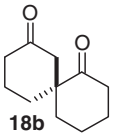
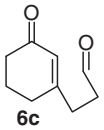
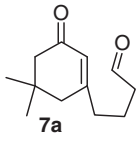
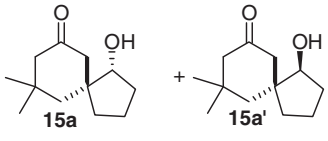
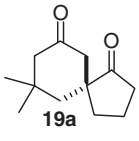
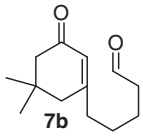
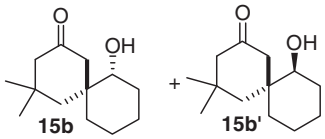
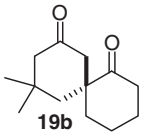
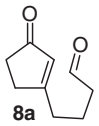
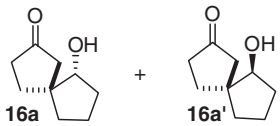
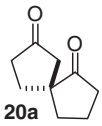
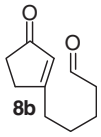
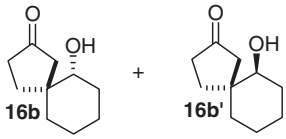
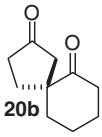
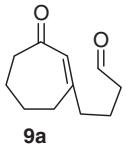
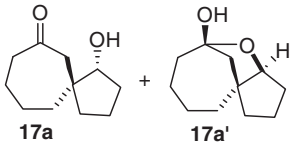
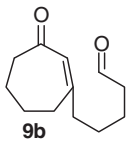
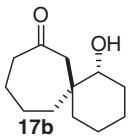
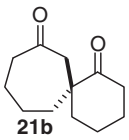
(entries 4–7). Thus, in the reductive cyclization of **6a**, the best yield and the optimum diastereoselectivity were observed when the reaction was carried out at 0 °C with 2 equiv of SmI_2.

Other enone–aldehydes **6**–**9** were examined to the optimized conditions, and the desired spirocyclic γ-hydroxyketones **14**–**17** were obtained as inseparable diastereoisomers in moderate to good yields in various diastereomeric ratios (Table 3). With a three-carbon side chain in the substrate, the desired spiro[3.5]nonane skeleton could not be observed, and this resulted in a complex mixture (entry 3). The spiro[3.5]nonane skeleton could not be observed probably because of the ring strain. Formation of a cyclobutane ring under these conditions was difficult. Surprisingly, cycloheptenone substrates **9** showed different results (entries 8 and 9). One of the spirocyclic diastereomers spontaneously cyclized and formed a tricyclic hemiketal **17a′** (entry 8). Further, a single diastereomer **17b** was obtained (entry 9) but its yield was considerably low (25%). Fortunately, its yield increased to 58% when the reaction was carried out at −20 °C. In order to confirm that the obtained inseparable spirocyclic γ-hydroxyketones are diastereomers, the mixture of diastereomers **14**–**16** was oxidized by PCC to give a single 1,4-dione in each case (Table 3).

The structures of **14**–**17** were satisfactorily characterized by IR, ^1H, ^{13}C NMR, and low- and high-resolution MS analyses. The stereostructures of **14**–**17** were determined by NOESY experiments (Fig. 2). The NOESY spectra of **14a**–**17b** showed a cross-peak between C_1H and the α-hydrogen of the ketone, whereas those of **14a′**–**16b′** did not show a cross-peak.

Table 3
Intramolecular reductive cyclization and oxidation



Entry	Enone–aldehyde	t_1 (min)	Products	d.r.[a]	Yield[b] (%)	t_2 (h)	Product	Yield[b] (%)
1	 6a	10	 14a + 14a'	1:5:1	75	1	 18a	90
2	 6b	25	 14b + 14b'	5:1	70	2	 18b	93
3	 6c	30	–	–	–[c]	–	–	–
4	 7a	25	 15a + 15a'	16:1	57	2	 19a	96
5	 7b	30	 15b + 15b'	5:1	53	2	 19b	98
6	 8a	30	 16a + 16a'	3:1	62	4	 20a	90
7	 8b	30	 16b + 16b'	1:5:1	70	4	 20b	90
8	 9a	10	 17a + 17a'	–	33 + 52	–	–	–
9	 9b	10	 17b	–	25(58)[d]	5	 21b	94

[a] The ratios were determined by ^{1}H NMR.
[b] Isolated yield.
[c] Complex mixture.
[d] The reaction was carried out at −20 °C.

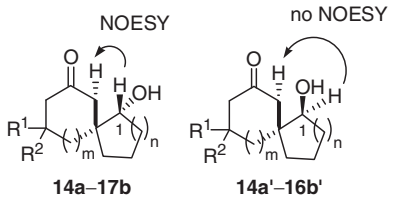


Figure 2. NOESY investigations of **14**–**17**.

In conclusion, we have developed a general method for preparing various spirocyclic γ-hydroxyketones under mild conditions. The ring size of the spiro compounds can be controlled easily either by using different cyclic enones or by altering the length of the side chain. The application of this efficient method to natural product synthesis is currently under investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.068.

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