COMMUNICATION

Facile construction of spirobicyclic skeletons by intramolecular aldol reaction: simple formal syntheses of (±)-spirojatamol and (±)-erythrodiene

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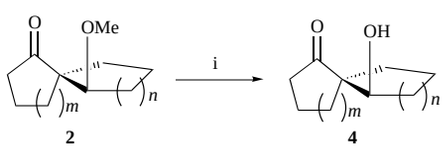
An intramolecular aldol reaction of keto acetals 1, regioselectively performed with Me_3SiI–$(Me_3Si)_2NH$ leading to spirobicyclic compounds 2 and 3, has been applied to the syntheses of (±)-spirojatamol and (±)-erythrodiene.

The aldol reaction is one of the most versatile methods for carbon–carbon bond formation in organic synthesis.[1] In particular, the intramolecular version is a useful method for the synthesis of a variety of ring structures. A new methodology for the construction of polycyclic ring systems fused to cyclobutane has recently been developed using a tandem intramolecular Michael–aldol reaction, carried out with Me_3SiI in the presence of $(Me_3Si)_2NH$.[2] Here we report a regioselective intramolecular aldol reaction of keto acetals **1** using Me_3SiI–$(Me_3Si)_2NH$ and the successful use of this methodology for syntheses of (±)-spirojatamol and (±)-erythrodiene.

The results of the intramolecular aldol reaction of keto acetals **1**† are summarized in Table 1. Reaction of **1a** with Me_3SiI–$(Me_3Si)_2NH$ in CH_2Cl_2 at 0 °C gave a mixture of spiro compounds **2a** and **3a** in 78% yield. Thus, the aldol reaction regioselectively takes place at the more substituted α-carbon atom. Using the same procedure, **1b–f** were converted into the corresponding spiro compounds **2b–f** and **3b–f** in good yields.

The stereostructures of **2c**, **d** and **f** were determined by their transformation into the known alcohols **4c**, **d** and **f**[3] by treatment with BBr_3 (Scheme 1)‡ while the structures of the other products were assigned by spectral analysis.



c $m = 2, n = 1$
d $m = 2, n = 2$
f $m = 3, n = 2$

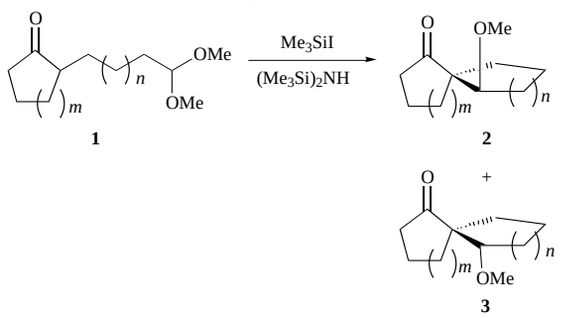
Scheme 1 *Reagents and conditions:* i, BBr_3, CH_2Cl_2, −78 to −40 °C

Spirojatamol **5**, isolated from the roots of *Naldostuchys jatamansi*,[4] and erythrodiene **6**, found in the encrusting Caribbean gorgonian coral *Erythropodium caribaeorum*,[5] have a spiro[4.5]decane framework. Recently, Forsyth[6a] and we[6b] independently accomplished total syntheses of these natural products. The present approach for the preparation of these natural products has been designed by way of the above intramolecular aldol reaction.

N-Cyclohexyl-4-isopropylcyclohexanimine **7**[6b] was treated with lithium diisopropylamide (LDA) in the presence of hexamethylphosphoric triamide (HMPA) and then with 4-bromobutanal dimethyl acetal to give ketone **8** as a mixture of two diastereoisomers (Scheme 2). The aldol reaction of **8** with Me_3SiI–$(Me_3Si)_2NH$ furnished, in excellent yield, a mixture of **9a–d** in the ratio of 2.4:1.3:1.0:1.2. After separation of the four diastereoisomers, **9a–d** were demethylated with BBr_3. Though isomerization at the C-1 and C-5 positions of the products occurred to some extent during the transformation, alcohols **10a–d**§ were obtained as the major products from the corresponding stereoisomers, respectively. Treatment of **10a** and **b** with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[7] provided **11** which has been correlated with (±)-spirojatamol **5** and (±)-erythrodiene **6**.[6b] On the other hand, oxidation of **10c** and **d** gave diketone **12**.

The above method conducted under mild reaction conditions should be useful for the assembly of spiro skeletons and for syntheses of various natural products.

Table 1 Synthesis of spiro compounds **2** and **3** from keto acetals **1**



Substrate	Yield (%)	Ratio **2**:**3**
1a ($m = 1, n = 1$)	78	1.1[a]
1b ($m = 1, n = 2$)	70	1.2[b]
1c ($m = 2, n = 1$)	83	1.6[a]
1d ($m = 2, n = 2$)	92	2.4[a]
1e ($m = 3, n = 1$)	87	1.5[a]
1f ($m = 3, n = 2$)	89	1.5[a]

[a] Isolated ratio. [b] Determined by integration of peaks in the ^1H NMR spectrum.

Experimental

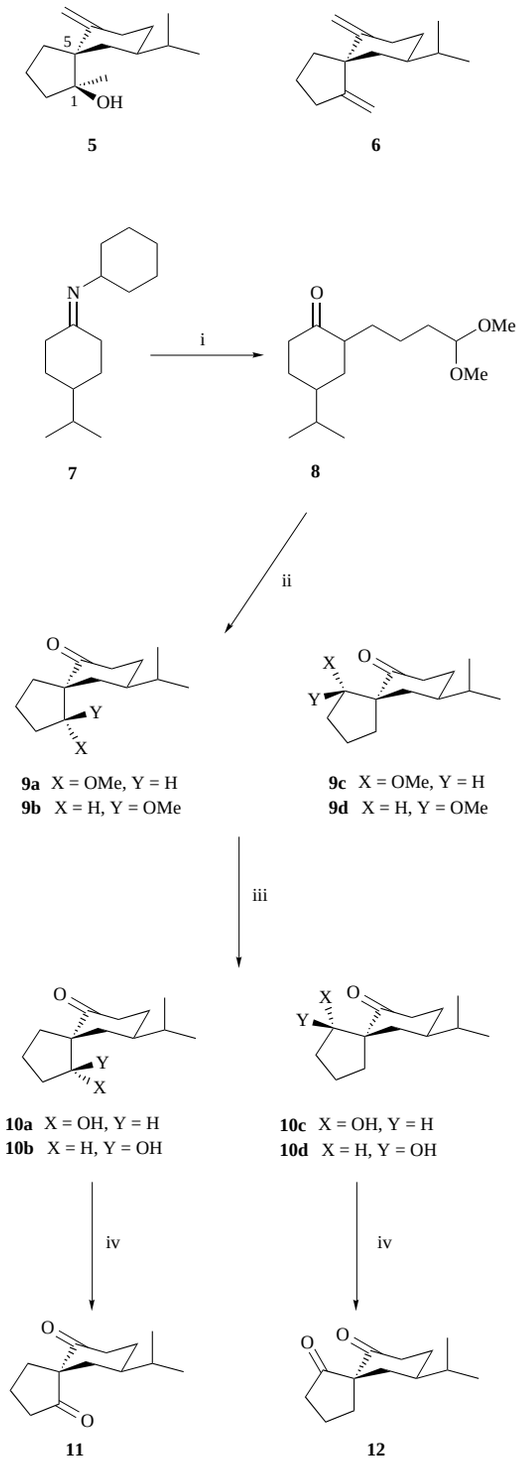
Typical reaction procedure for 1-methoxyspiro[4.5]decan-6-ones 2c and 3c

To a stirred solution of the keto acetal **1c** (0.837 g, 3.91 mmol) and $(Me_3Si)_2NH$ (1.24 cm^3, 5.87 mmol) in dry CH_2Cl_2 (25 cm^3) at 0 °C was added Me_3SiI (0.67 cm^3, 4.70 mmol) and the mixture was stirred for 30 min at the same temperature. After addition of 10% hydrochloric acid followed by stirring of the mix-

† Keto acetals **1a–f** were prepared from the corresponding cyclic ketones in two steps; formation of the cyclohexyl imines, followed by alkylation.

‡ The isomerization at the C-1 and C-5 positions of **4c** occurred during the conversion.

§ The stereostructures of **9a** and **9b** were assigned by comparison with spectral data for **2c** and **3c**. On the other hand, that of **10d** was established on the basis of the intramolecular hydrogen bond between the hydroxy group and the carbonyl group.



Scheme 2 *Reagents and conditions:* i, LDA, HMPA, 4-bromobutanal dimethyl acetal, THF, 0 °C, 88%; ii, Me_3SiI, $(Me_3Si)_2NH$, CH_2Cl_2, 0 °C, 94%; iii, BBr_3, CH_2Cl_2, −78 to −40 °C, 50–61%; iv, TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, room temp., 85–96%

ture for 30 min, the resulting mixture was extracted with diethyl ether. The extract was washed with 10% aqueous sodium thiosulfate and brine, dried over potassium carbonate and the solvent evaporated. The residue was subjected to chromatography on silica gel with ethyl acetate–hexane (1 : 6 v/v) to give **3c** (0.228 g, 32%) as an oil and **2c** (0.366 g, 51%) as an oil.

3c: ν_{max}(neat)/cm^{-1} 1720; δ_H(300 MHz; $CDCl_3$) 1.42–1.95 (12 H, m), 2.35–2.42 (2 H, m, 7-H_2), 3.30 (3 H, s, OMe), 4.07 (1 H, br t, *J* 7,¶ 1-H); δ_C(75 MHz; $CDCl_3$) 20.6, 22.0, 27.0, 29.4, 32.0, 34.1, 39.8, 57.5, 59.7, 83.5, 214.0; *m/z* 182 (M^+) (HRMS: found M^+, 182.1299. $C_{11}H_{18}O_2$ requires *M*, 182.1307).

2c: ν_{max}(neat)/cm^{-1} 1706; δ_H(300 MHz; $CDCl_3$) 1.04–1.14 (1 H, m), 1.38–1.90 (10 H, m), 2.01–2.10 (1 H, m), 2.35–2.61 (2 H, m, 7-H_2), 3.87 (3 H, s, OMe), 3.84–3.89 (1 H, m, 1-H); δ_C(75 MHz; $CDCl_3$) 21.2, 22.6, 27.7, 29.1, 32.0, 38.4, 41.6, 56.6, 61.3, 87.1, 211.5; *m/z* 182 (M^+) (HRMS: found M^+, 182.1308).

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¶ *J* Values given in Hz.

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