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Internal chirality transfer in the reaction of substituted cyclic (*S,O*)-ketene ortho esters with aldehydes catalysed by Lewis acid†

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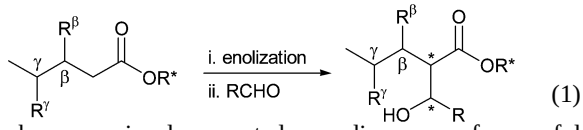
Internal chirality transfer of 1a and 1b with aldehydes in the presence of Lewis acid catalyst resulted in high diastereoselectivities in the construction of a highly functionalised acyclic system.

The development of efficient synthetic methods for achieving absolute and relative stereocontrol *via* catalytic processes in the construction of acyclic systems is of considerable current interest in synthetic chemistry.[1] During the past decades, substantial progress has been made, and as a result, many stereoselective synthetic routes are extensively explored.[2] For example, significant advances in diastereocontrol have been made in the formation of β-hydroxy esters through the aldol reaction.[3] Even though there have been elegant reports regarding stereoselectivity of the aldol processes in the literature,[4] the limited data concerning the internal chiralty trasfer of β- or γ-substituents presumably due to a lack of stereoselectivity surprised us, in view of their synthetic potential (eqn 1). We became quite interested in a systematic study on the substituent effect of **1** in influencing chirality transfer during the catalytic process. This research led to the discovery of the remarkable chirality transfer providing high levels of diastereoselectivity.

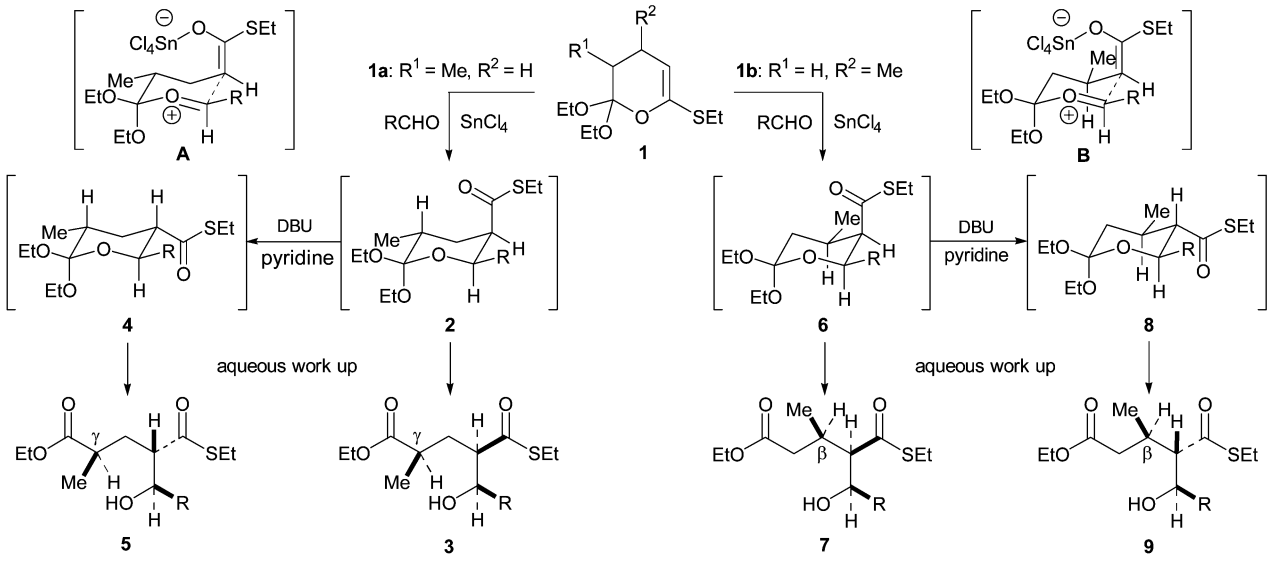


(1)

We have previously reported our discovery of a useful method for the assembly of aldol products of a glutarate derivative containing a *threo* stereochemical relationship, from reaction of dihydro-2*H*-pyran derivatives **1** (R^1 = R^2 = H) with aldehydes in the presence of a Lewis acid catalyst.[5] Recently this approach provided a diastereoselective protocol for achieving *erythro* diastereoselectivities[6] and enantioselective versions by utilisation of a chiral Lewis acid.[7] It was envisaged that the internal chirality transfer of **1** for the diastereoselective synthesis of **3** and **7** through cyclic ortho ester intermediates **2** and **6** could be realized in a predictable fashion if **A** and **B** are stereochemical models. The key to this prediction is the geometrical preference of the substituents (R^1 and R^2) at **A** and **B** to be located in equatorial positions as depicted in Scheme 1. This highly stereocontrolled transformation for the synthesis of **3** and **7** involves the diastereoselective generation of a C–C bond and the introduction of an ester functionality from hydrolysis of the ortho ester intermediate. Furthermore, we anticipated that this investigation could provide a better understanding of the mechanistic insight for this chemical phenomenon.

To investigate the sequence outlined in Scheme 1, the starting point was the availability of starting materials **1**. These were prepared in quantity by a two step sequence, purified by distillation, and were stable to storage.‡ Treatment of **1a** (R^1 = Me, R^2 = H) with benzaldehyde in the presence of $SnCl_4$ (20 mol%) at −78 °C in CH_2Cl_2 for 1 h afforded only two adducts **3a** and **5a** in 87% yield in a ratio of 96 : 4 as judged by 500 MHz ^{1}H NMR of crude products. This result clearly indicated that the chirality transfer of **1** turned out to be very efficient, nearly perfect. With the notion that this approach might lead to a general and efficient method for diastereoselective chirality transfer, we set out to determine the scope of reaction with various aldehydes. Indeed, the method is successful with a variety of aldehydes and affords products of high diaster-

† Electronic supplementary information (ESI) available: Experimental details. See http://www.rsc.org/suppdata/cc/b3/b305003c/



Scheme 1 Internal chirality transfer of **1** with aldehydes.

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eomeric purity as can be seen in Table 1. It is worthy of note that reactions at −78 °C for 1 h in CH_2Cl_2 were the optimal conditions in terms of diastereoselectivities and chemical yields, while with longer reaction times, especially more than 2 h, diminished diastereoselectivity was observed mainly due to the partial epimerisation of **2** to **4**.

Table 1 Synthesis of **3** from reaction of **1a** with aldehydes[a]

Entry	RCHO	**3**	Dr (**3** : **5**)[c]	Yield (%)[d]
1	Ph	a	96 : 4	87
2	$PhCH_2CH_2$	b	97 : 3	81
3	$PhCH_2$	c	95 : 5	83
4	C_6H_{13}	d	91 : 9	90
5	c-C_6H_{11}	e	98 : 2	67
6[b]	PhCH=CH	f	91 : 9	59

[a] Reactions were carried out with $SnCl_4$ (20 mol%) in CH_2Cl_2 at −78 °C for 1 h. [b] 30 mol% of $SnCl_4$ for 30 min. [c] Diastereomeric ratio was determined by the analysis of 500 MHz ^{1}H NMR spectra of crude products (all entries) and by GC analysis using HP-1 (Hewlett-Packard, cross linked methyl siloxane, 25m × 0.32 mm × 0.52 μm, entries 2, 4, 5). [d] Yields refer to isolated and purified products.

In order to obtain **5** from **1a**, epimerisation of **2** to **4** under basic conditions was carried out.[6] Indeed, the reaction produced the same products **3** and **5** but in different ratios. The reaction was performed by addition of $SnCl_4$ (20 mol%) to a solution of **1a** and benzaldehyde in toluene at −78 °C. After 3 h at −78 °C, freshly distilled pyridine (15 equiv.) and DBU (7 equiv.) was added during which time white precipitate was formed. After stirring for 30 min at −78 °C, the temperature was allowed to rise to 50 °C and stirring was continued for 7 h. After cooling to 0 °C, the reaction mixture was quenched with 2 M aqueous HCl in EtOH followed by work up and silica gel chromatography to afford **5a** with **3a** in a ratio of > 98 : 2 as judged by the 500 MHz ^{1}H NMR of crude products. The reliability of the reaction was further examined with various aldehydes as listed in Table 2. It is worthy of note that the reaction produced only a trace or less than 2% of minor product **3**.

Table 2 Synthesis of **5** from reaction of **1a** with aldehydes[a]

Entry	RCHO	**5**	D r (**5** : **3**)	Yield (%)
1	Ph	a	> 98 : 2	84
2	$PhCH_2CH_2$	b	> 98 : 2	74
3	$PhCH_2$	c	> 98 : 2	80
4	C_6H_{13}	d	> 98 : 2	81
5	c-C_6H_{11}	e	> 98 : 2	67
6	PhCH=CH	f	> 98 : 2	55

[a] Reactions were carried out in toluene at −78 °C to 50 °C for 7 h and other conditions were identical with those of Table 1.

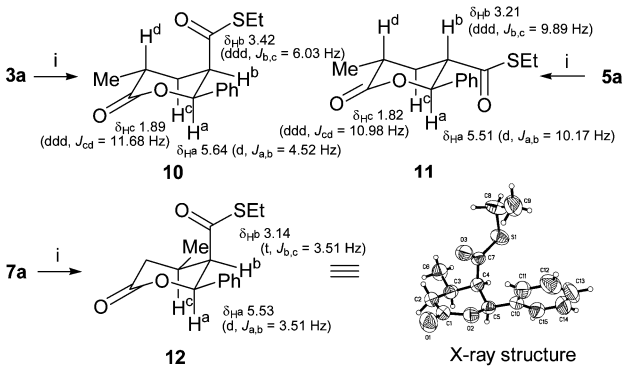
With our research scope of the internal chirality transfer of **1a**, we turned our attention next to examining the possibility of this approach for **1b**. Under optimal conditions, the reaction was performed by addition of $SnCl_4$ (20 mol%) in CH_2Cl_2 to a solution of **1b** (R^1 = H, R^2 = Me) and benzaldehyde in CH_2Cl_2 at −78 °C. After stirring for 1 h, the reaction mixture was quenched with 2 M aqueous HCl followed by work up and silica gel chromatography to afford **7a** with **9a** in a ratio of 95 : 5 as judged by the 500 MHz ^{1}H NMR of crude products. From Table 3 it can be seen that the reactions of **1b** were conducted on a variety of aldehydes under identical conditions to furnish **7** with high levels of diastereoselectivity.

Surprisingly, we encountered unexpected difficulties in the conversion of **1b** to **9** using the conditions for the synthesis of **5** from **1a**. Reaction of **1b** with benzaldehyde under the same conditions {i. 20 mol% of $SnCl_4$, −78 °C, 3 h, toluene, ii pyridine (15 equiv), DBU (7 equiv), −78 °C to 50 °C, 7 h} afforded **9a** and **7a** in 77% yield, but diastereoselectivity turned out to be only 71 : 29. Also, increasing the temperature to 80 °C resulted in diminished chemical yield (dr 81 : 19, 41% yield). This result could be explained by difficulties in the enolization of **6** and also strong *gauche* interactions in **8**.

Table 3 Synthesis of **7** from reaction of **1b** with aldehydes[a]

Entry	RCHO	**7**	Dr (**7** : **9**)	Yield (%)
1	Ph	a	95 : 5	77
2	$PhCH_2CH_2$	b	97 : 3	78
3	$PhCH_2$	c	93 : 7	75
4	C_6H_{13}	d	92 : 8	81
5	c-C_6H_{11}	e	98 : 2	54
6	PhCH=CH	f	89 : 11	51

[a] Reactions were carried out in CH_2Cl_2 at −78 °C for 1 h and other conditions were identical with those of Table 1.



Scheme 2 *Reagents and conditions*: i. Et_2AlCl, Pr^i_2NEt, −20–20 °C, 4 h, CH_2Cl_2, 77–83% yield.

The relative stereochemical relations of all products were unambiguously established after conversion to structurally rigid lactones by ^{1}H NMR analysis. The stereochemical assignments were based on the magnitudes of the vicinal coupling constants of the major component for each case. As illustrated in Scheme 2 the NMR data for each component is comparable to the stereochemical structures. The stereochemical relationship of compound **12** was also confirmed by X-ray crystallography.§

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Notes and references

‡ Compounds **1a** and **1b** were prepared under previous reaction conditions,[5] see ESI.

§ Chemical formula $C_{15}H_{18}O_3S$, formula weight 278.35, crystal system monoclinic, space group $P2_1/c$, a = 10.2348(18) Å, b = 23.217(3) Å, c = 20.626(5) Å, β = 99.96(2)°, V = 1466.9(7) Å^3, Z = 4, D_{calcd} = 1.260 g·cm^{-3}, μ(MoKα) = 0.222 mm^{-1}, T = 297(2) K. Total of 2806 reflections were collected, among which 2558 reflections were independent [R(int) = 0.0441]. $wR2/R1$ = 0.1233/0.0695 ($I > 2\sigma$) and 0.1694/0.1851 (all data). CCDC 210261. See http://www.rsc.org/suppdata/cc/b3/b305003c/ for crystallographic data in .cif or other electronic format.

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