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Highly Stereocontrolled Synthesis of Substituted Propiolactones and Butyrolactones from Achiral Lithium Enolates and Homochiral Aldehydes

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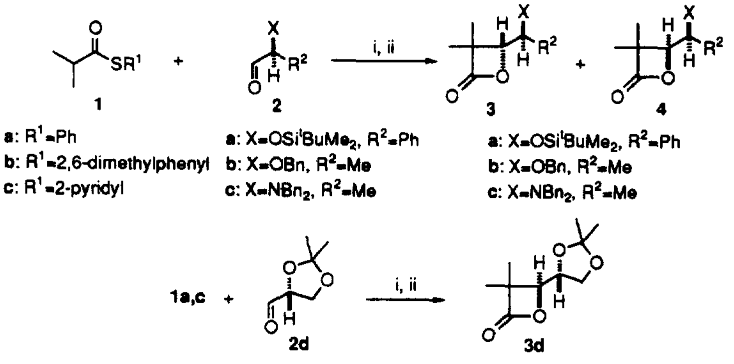
Abstract. Lithium enolates derived from achiral thiol esters react in a highly stereoselective fashion with homochiral aldehydes to yield the corresponding 2-oxetanones. The stereochemical outcome of the reaction corresponds to a non-chelation control, except when O-silylated mandelaldehyde is used. The propiolactones thus formed are efficiently transformed into δ-lactones *via* Lewis acid promoted dyotropic rearrangements.

In the course of the last decade, 2-oxetanones have received increasing attention, since these compounds exhibit interesting biological properties and are useful and versatile synthetic intermediates[1]. Quite recently, Danheiser *et al.*[2] have reported a general reaction between aldehydes or ketones and thiol ester enolates. These authors have applied this procedure to the synthesis of alkenes[2a] and allenes[2b]. However, the potential usefulness of the Danheiser method in asymmetric synthesis of propiolactones remains unexplored. We report herein our preliminary results on the aldol reaction between thiol esters derived from isobutyric acid (**1a-c**) and homochiral aldehydes (**2a-d**) (Scheme 1).



Scheme 1. Reagents and conditions: (i) LDA(1.1eq.), THF, -78°C→r.t., very slow addition of **2** *via* precooled (-78°C) cannula. (ii) NH_4Cl-H_2O (sat.sol.) or 10% citric acid in water in the case of aldehyde **2c**.

The reaction between **1a** and the tert-butyldimethylsilyloxy protected aldehyde **2a** was tested first, under the reaction conditions reported by Danheiser. The diastereomeric 2-oxetanones **3a** and **4a** were obtained in a ratio of 12:88 respectively (see Table 1). When the bulkier thiol ester **2b** (R^1=2,6-dimethylphenyl) was used instead of **1a**, the diastereomeric ratio was 23:77, the chelation control diastereomer **4a** was the major product.

Furthermore, thiol ester **1c** (R^1=2-pyridyl) with an additional nitrogen atom amenable to coordination, increased the chemical yield as well as the proportion of the non-chelation control diastereomer **3a** (see Table 1). On the

Table 1[a,b].

Reaction	Yield, %	3:4	Reaction	Yield, %	3:4
1a+2a→3a+4a	41	12:88	**1c+2b→3b**	61	>98:2
1b+2a→3a+4a	57	23:77	**1a+2c→3c**	61[c]	>98:2
1c+2a→3a+4a	70	31:69	**1a+2d→3d**	38	>98:2
1a+2b→3b	39	>98:2	**1c+2d→3d**	55	>98:2

[a] Yields of isolated pure products after column chromatography. [b] Diastereomeric ratios determined by 300 MHz ^{1}H-NMR on crude reaction mixtures. [c] Yield of crude product determined by ^{1}H-NMR (see text and Scheme 4).

other hand, we have found that aldehydes **2b-d** react with virtually complete stereocontrol with **1a** to yield exclusively the non-chelation control diastereomers **3b-d**[3]. It is interesting to note that thiol ester **1c** was again more effective than **1a**, the yields of the corresponding 2-oxetanones being significantly higher without loss of stereocontrol (see Table). The configuration of the new chiral centers in 2-oxetanones **3** and **4** was established on the basis of dyotropic rearrangements promoted by Lewis acids[4] (*vide infra*). This methodology could not be applied to compound **3d**, and its configuration at the new chiral center was assigned by analogy with compounds **3a-c**. We have examined the origins of the non-chelation stereocontrol observed in this reaction

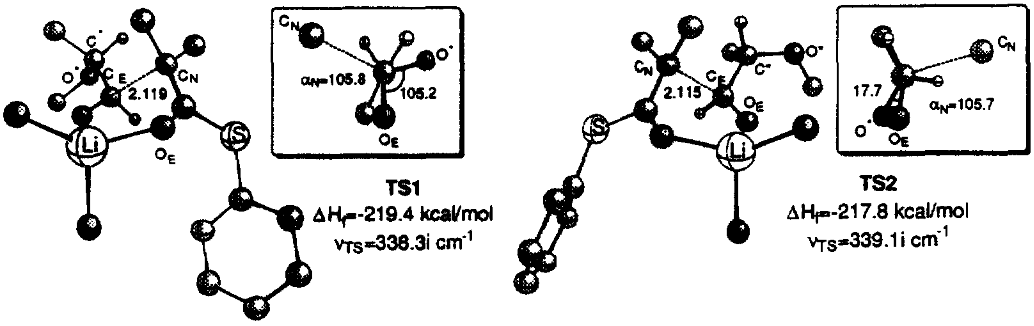
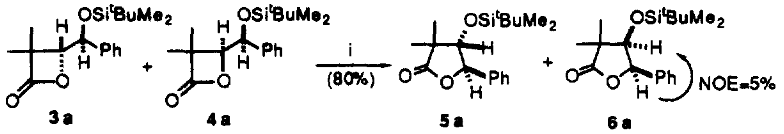


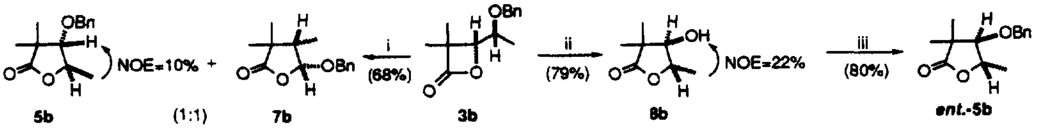
Figure 2. RHF/PM3 fully optimized structures of TS1 and TS2, corresponding to the reaction between (*S*)-2-methoxypropionaldehyde and lithium enolate of **1a** (see text). Distances and angles are given in Å and deg., respectively. The insets include Newman projections of the corresponding transition structures above the C_E-C^* bond. Most of the hydrogen atoms have been omitted for clarity.

when non-silylated protecting groups are present in the starting aldehydes. As model reaction we chose the coupling between the lithium enolate of **1a** and (*S*)-2-methoxypropionaldehyde, a 2-methoxy analogue of lactaldehyde **2b**. We have performed semi-empirical calculations by means of the PM3[5] hamiltonian at the Restricted Hartree Fock (RHF) level and using the parameters for lithium recently developed by Anders *et al.*[6]. We have also included two molecules of water to model the ethereal solvent and to provide a tetrahedral environment for lithium. The fully optimized transition structures (TS's) corresponding to the two possible interaction modes, denoted as **TS1** and **TS2**, are depicted in Figure 2. Inspection of such a Figure reveals that in both TS's the critical bond distances $C_N \cdots C_E$ are very similar. The α_N=$C_N \cdots C_E$-O_E bond angles are also similar, with a value of *c.a.* 106°, consistent with the Bürgi-Dunitz trajectories[7]. The main difference between **TS1** and **TS2** is that in the former the value of the dihedral angle τ=O^*-C^*-C_E-O_E is of 105.2°, whereas in the latter TS the calculated value of τ is of only 17.7° (see Figure 2). Therefore, in **TS1** the values of τ is closer to that expected from the Felkin-Ahn model[8] (τ=90°), although slightly higher in order to minimize the Coulombic repulsion between the O* and O_E atoms. In contrast, the smaller value of τ in **TS2** generates a major repulsion between these atoms and a lower efficiency of the $\sigma^* \rightarrow \sigma^*_{CX}$ two-electron interaction. Consequently, the heat of formation of this latter TS is calculated to be 1.6 kcal/mol higher than that of **TS2**, in qualitative agreement with the exclusive formation of **3d** observed experimentally.

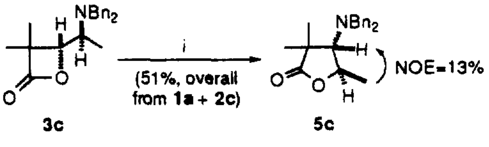
We have also explored the transformation of the 2-oxetanones previously obtained into the corresponding δ-lactones, in order to verify the geometry of compounds **3** and **4**, as well as to study the possibility of using 2-oxetanones as synthetic precursors of enantiopure butyrolactones. The reaction used has been the Lewis acid promoted dyotropic rearrangement[4]. Following the experimental procedure reported by Black[9], we treated a mixture of 2-oxetanones **3a** and **4a** with magnesium bromide in diethyl ether at room temperature for 12 h. Under these conditions, a mixture of butyrolactones **5a** and **6a** was obtained in good yield, and their structures were confirmed by the IR and ^{1}H-NMR spectra (Scheme 2) and by nuclear Overhauser effect (NOE) experiments. However, when compound **3b** was subjected to the same reaction conditions, a *ca.* 1:1 mixture of butyrolactones **5b** and **7b** was observed in the crude reaction mixture, thus indicating that magnesium dibromide promotes migration of both the benzyloxy and the methyl groups[10] (Scheme 3). By contrast, when titanium tetrachloride was used as Lewis acid, only butyrolactone **8b** was obtained[11]. Benzylation of **8b** gave the enantiomer of **5b**, thus proving that $TiCl_4$ promotes deprotection of the benzyloxy group and concomitant transesterification (Scheme 3). This result is especially interesting given the importance of chiral 3-hydroxybutirolactones in natural product chemistry[12]. Finally, we have found that conversion of **3c** into **5c**[13] is specially facile, since this rearrangement takes place during purification of **3c** by flash chromatography[14] (Scheme 4).



Scheme 2. Reagents and conditions: (i) $MgBr_2$ (2.0 eq.), Et_2O, r.t., 12 h.



Scheme 3. Reagents and conditions: (i) $MgBr_2$ (2.0 eq.), Et_2O, r.t., 12 h. (ii) $TiCl_4$ (1.0 eq.), CH_2Cl_2, r.t., 12 h. (iii) BnBr (1.2 eq), NaH(1.0 eq.), DMF, THF, r.t., 24 h.



Scheme 4. Reagents and conditions: (i) Flash chromatography on Silicagel 60-230 mesh, ethyl acetate/hexanes 1:20 as eluent.

In summary, we have found that the Danheiser method for the preparation of 2-oxetanones is useful in the stereoselective synthesis of these compounds. In addition, the propiolactones thus formed can be stereospecifically transformed into γ-lactones, the behavior of the starting 2-oxetanones being sensitive to the nature of the Lewis acid used to promote the dyotropic rearrangement.

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3. Selected data: **3b**: Colorless oil; $[\alpha]_{D/25}$=+26.5° (c=1.3, CH_2Cl_2); IR(film) 1825 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.36-7.26(m, 5H), 4.66(d, 1H, J=-11.2Hz), 4.43(d, 1H, J=-11.2Hz), 4.02(d, 1H, J=8.7Hz), 3.78(dq, 1H, J=8.7Hz, J'=6.0Hz), 1.44(s, 3H), 1.35(d, 3H, J=6.0Hz), 1.32(s, 3H); ^{13}C-NMR($CDCl_3$) δ 175.2, 137.6, 128.5, 127.9, 104.4, 83.3, 73.2, 70.6, 23.1, 16.7, 16.1. **3c**: Colorless oil; IR(film) 1821 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.52-7.14(m, 10H), 4.10(d, 1H, J=9.7Hz), 3.73(d, 2H, J=-13.4Hz), 3.47(d, 2H, J=-13.4Hz), 3.14(dq, 1H, J=6.6Hz, J'=9.7Hz), 1.28(s, 3H). **3d**: White crystals; mp 55-56°C (from ethyl acetate in hexanes); $[\alpha]_{D/25}$=+19° (c=0.1, CH_2Cl_2); IR(KBr) 1830 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.24(ddd, 1H, J=9.3Hz, J'=5.9Hz, J"=3.9Hz), 4.16(dd, 1H, J=5.9Hz, J'=-8.9Hz), 4.05(d, 1H, J=9.3Hz), 3.97(dd, 1H, J=3.9Hz, J'=-8.9Hz), 1.46(s, 3H), 1.43 (s, 3H), 1.39(s, 3H), 1.36(s, 3H); ^{13}C-NMR($CDCl_3$) δ 174.4, 110.2, 80.7, 73.8, 67.1, 54.2, 27.0, 25.1, 22.6, 16.4.
4. It is well known that this reaction takes place with double inversion of configuration for the two stationary carbon atoms. See for example: (a) Reetz, M.T.; Schmitz, A.; Holdgrün, X. *Tetrahedron Lett.* **1989**, *30*, 5421. (b) Mulzer, J.; Brüntrup, G. *Angew.Chem. Int. Ed. Engl.* **1979**, *18*, 793. (c) Black, T.H.; Hall, J.A.; Sheu, R.G. *J.Org.Chem.* **1988**, *53*, 2371.
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9. Black, T.H.; DuBay III, W.J.; Tully, P.S. *J.Org.Chem.* **1988**, *53*, 5922.
10. A related observation on the dependence of the migrating group with the Lewis acid has recently been reported by Mulzer. See Mulzer, J.; Pointner, A.; Straßer, R.; Hoyer, K.; Nagel, V. *Tetrahedron Lett.* **1995**, *36*, 3679.
11. Selected data of **8b**: White crystals; mp 70-71°C (from ethyl acetate in hexanes); $[\alpha]_{D/25}$=-46.0° (c=0.1 CH_2Cl_2); IR(KBr) 3415, 1736 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 4.24(dq, 1H, J=6.2Hz, J'=7.9Hz), 3.75(dd, 1H, J=5.9Hz, J'=7.9Hz), 2.58(d, 1H, J=6.2Hz), 1.47(d, 3H, J=6.2Hz), 1.26(s, 3H), 1.18(s, 3H). ^{13}C-NMR($CDCl_3$) δ 180.2, 81.5, 78.0, 43.8, 22.7, 18.2, 17.6. **5b**: Colorless oil; $[\alpha]_{D/25}$=+40.0° (c=0.3 CH_2Cl_2); IR(film) 1776 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.39-7.26(m, 5H), 4.68(d, 1H, J=-11.5Hz), 4.58(d, 1H, J=-11.5Hz), 4.28(dq, 1H, J=6.3Hz, J'=7.7Hz), 3.56(d, 1H, J=7.7Hz), 1.42(d, 3H, J=6.3Hz), 1.31((s, 3H), 1.24(s, 3H); ^{13}C-NMR($CDCl_3$) δ 179.7, 137.3, 128.6, 128.2, 127.7, 88.4, 76.6, 73.2, 43.8, 24.3, 18.9, 18.5.
12. See for example: (a) Toshima, H.; Goto, T.; Ichihara, A. *Tetrahedron Lett.* **1995**, *36*, 3373. (b) Takahata, H.; Uchida, Y.; Momose, T. *J.Org.Chem.* **1994**, *59*, 7201.
13. Reetz has observed *in situ* dyotropic rearrangement in aldol reactions using N,N-dibenzyl-α-aminoaldehydes. see ref. 4a
14. Selected data of **5c**: Colorless oil; $[\alpha]_{D/25}$=+18.3° (c=0.3, CH_2Cl_2); IR(film) 1768 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.50-7.19(m, 10H), 4.73(dq, 1H, J=6.3Hz, J'=7.0Hz), 3.92(d, 2H, J=-13.8Hz), 3.62(d, 2H, J=-13.8Hz), 3.01(d, 1H, J=7.0Hz), 1.50(d, 3H, J=6.3Hz), 1.33(s, 3H, CH_3)1.04(s, 3H). ^{13}C:NMR($CDCl_3$) δ 180.8, 138.7, 128.5, 128.4, 127.3, 73.7, 73.5, 69.2, 43.8, 25.6, 21.1, 19.9.

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