## Highly Diastereoselective Aldol Reactions of 4-Thianone: A New Strategy for Synthesis of Polypropionate Frames<sup>1</sup>

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Abstract The aldol reactions of the lithium enolate of 4-thianone with aldehydes yield the threo-isomers of aldols in a highly stereoselective manner and also showed high diastereoface selectivity. Other metal enolates of this reagent exhibited different behabiors from those of the corresponding cyclohexane enolates.

The last two decades have witnessed a drastic growth in the development and the use of the aldol strategy in the context of acyclic stereoselective synthesis <sup>2</sup> Recently, attention is increasingly directed toward the aldol reactions in the cyclic system, such as cyclic ketones, <sup>3-9</sup> heterocyclic ketones, <sup>10-12</sup> lactones, <sup>13</sup> or lactames, <sup>14</sup> whose seochemical attributes are found to be somewhat different from those in the acyclic analogs. It is established in the acyclic system that when the counter cation of an enolate belongs to group I, II, or III, [Z]-enolates lead to the *erythro* aldols, whereas [E]-enolates yield the *threo* aldols <sup>2c</sup>. In the cyclic systems there is no ambiguity about the geometry of the enolates, which by necessity have [E]-configuration. Current reports<sup>3</sup> on the aldol reactions of lithium enolate of cyclohexanone have raised a question to the data commonly accepted (*anti syn* = 52 48) <sup>15,16</sup>. The present paper deals with the stereochemistry of the aldol reactions of thianone 1, which can be regarded as a synthetic equivalent of 3-pentanone 2, because 1 can be formally shaped by connecting the two terminal carbons of 2 with a sulfur atom and reproduced by simple reductive desulfurization of 1.<sup>17,18</sup>. The C <sub>2</sub> symmetry of this reagent suggests the possibility that 1 might be employed for simplificition of the macrolide synthesis by using the sequential aldol condensation of 1 with suitable simple aldehydes, followed by reductive steps (Scheme 1) <sup>19</sup>.



All the reactions of the lithium enolate of 1 with aldehydes showed substantial *anti* -selectivity 20-22 The results was summarized in Table 1. The observed ratios are close to the real kinetic ratios, because the 3-*anti* isomer (R = isopropyl) in a CDC13 solution, when allowed to stand at rom temperature for a month, reached to the eqlibrium (*anti syn* =36 64). The reaction of 1 with pivalaldehyde (entry 1) yielded a *anti-syn* ratio of 95 5, which exhibits a striking contrast to the result obtained in the reaction of [E]-enolate of 2 with the aldehyde by

Dubois and his coworker (anti.syn = 54.46) <sup>23</sup> This drastic increment in the stereoselectivity level suggests the presence of the additional effect attributed to *ring formatiom*, which is still not elucidated. The selectivity of the reaction with benzaldehyde (entry 5) is comparable to that of the reaction of cyclohehanone with the aldehyde <sup>3</sup> The reactions of 1 with the aldehydes having a branch at the  $\alpha$ -position afforded high *anti*-selectivity. The re-



Table 1 Reactions of 4-thianone with aldehydes

action with two aldehydes 4 and 5 having a chiral carbon at the  $\alpha$ -position were undertaken, in order to gain information about the level of diastereoface selectivity of the reagent 1. The ratio of 6:7:8:9 = 90:6:2:2 was obtained for aldehyde 4, and almost only one isomer 10 was produced for the reaction with aldehyde 5<sup>24</sup>. These results can be explained by Felkin-Anh model. The high Cram-selectivity of aldehyde 5 may be attributed to the bulkiness of the ketal ring and the favorable orbital interaction between the p-orbital of the aldehyde and the two lone pairs of the ketal oxygens <sup>25</sup>. Thus, this reaction generates three consecutive stereogenic centers in one step.

The strategy can be utilized for the synthesis of the right-half of denticulatins <sup>26</sup>

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Attempts were made to reverse the stereoserectivity of reagent 1 by changing the counter cation of its enoate The results were listed in Table 2. It is suprising that borane, stannane, and titanium enolates, except for zirconium one, all showed *anti* selectivity, which makes a striking contrast to the facts that the corresponding cyclohexanone enolates exhibit *syn* selectivity 6-9

Table 2 Reactions of metal enolates of 4-thianone with 2-methylpropanal



 $^{a}$  The reactions were performed on the same conditions as those of the corresponding cyclohexanone enolates  $^{66.76.8.9}$ 

A preliminary experiment for desulfurization was performed using Raney Nickel W-2, according to the method described in the literature 17 The desulfurization of diol 12, which was obtained from the stereoselective reduction of aldol 11 by sodium borohydride, produced diol 13 in 75% yield 27



The chiral version of this methodology will be reported in due course.

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- 20 A typical procedure for the aldol reaction of 1 is as follows A solution of disopropylamine (0.4 ml, 2.2 mmol) in dry THF (3.0 ml) was cooled to -30°C and 1.60 M butyllithium in hexane (1 4 ml, 2.0 mmol) was added under nitrogen. After stirring for 10 min, 4-thianone 1 (0.232 g, 2.0 mmol) in THF (3.0 ml) was added dropwise to the solution and the mixture was stirred for 30 min at -78°C. Isobutylaldehyde (2 5 mmol) in THF (3 0 ml) was added and the solution was quenched with saturated NH4Cl solution within 30 sec The solution was extracted with ether repeatedly and the extracts were submitted to HPLC
- 21. In all cases, the aldols show a profound tendency toward retroaldolization , and some retroaldolization always occurs upon silica gel and alumina chromatography Neverthless, for cases in which the aldol is not crystalline, purification is conveniently accomplished by this technique if the contact time of the aldol with the silica gel is minimized (HPLC). All new compounds were fully characterized by elementary analysis (C, H, S), IR, HPLC, and <sup>1</sup>H NMR Ratios were determined on the crude reaction mixtures by HPLC and NMR, integrating the typical HA and Me signals
- 22. In intramolecularly hydrogen-bonded aldols, the vicinal coupling constant JAB is larger for the anti isomer (7-10 Hz) than for the syn isomer (2-6 Hz).<sup>2c,3</sup> In addition, HA always resonates at higher field for the anti isomer than for the syn isomer.
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- 27 H<sup>1</sup> NMR of 13 (CDCl<sub>3</sub>, 500MHz),  $\delta$  0.98 (t, 3H, J =7 5 Hz), 1 15 (d, 3H, J =7 2Hz), 1.4-1 5 (m, 2H) 3 63 (dt, 1H, J = 4 0, 7 2Hz), 4 63 (d, 1H, J = 9 5Hz), 7 40 (m, 5H).

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