

Expeditious Asymmetric Synthesis of Optically Pure δ -Lactones
Bearing Consecutive Three Asymmetric Centers

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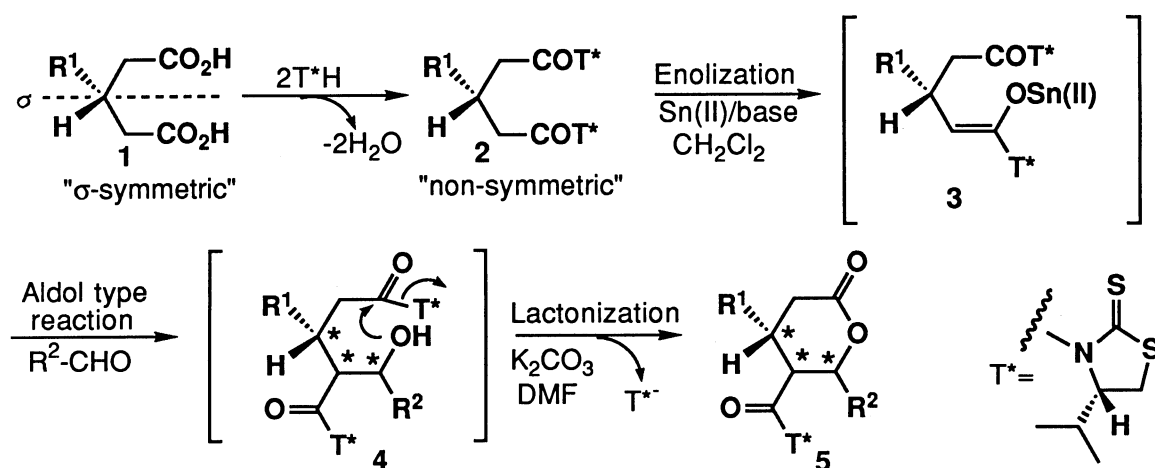
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The (4*S*)-isopropyl-1,3-thiazolidine-2-thione diamides of 3-substituted glutaric acids were submitted to enolization with $\text{Sn}(\text{CF}_3\text{SO}_3)_2$ and *N*-ethylpiperidine. The resultant tin(II) enolate was treated with several aldehydes to give the aldols, which readily undergo basic lactonization affording the corresponding chiral δ -lactones bearing consecutive three asymmetric centers.

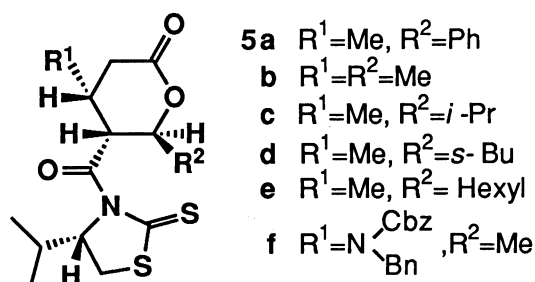
Since development of highly selective differentiation method between two identical carboxyl groups in a prochiral σ -symmetric dicarboxylic acid based on the new concept,¹⁾ we have expanded the application of this methodology employing C4-chiral thiazolidines in order to establish the generality and the availability.²⁾ Previously, we reported a highly enantioselective Dieckmann reaction of (4*S*)-isopropyl-1,3-thiazolidine-2-thione [(4*S*)-IPTT]³⁾ amide of *meso-cis*-cyclohex-4-ene-1,2-bis(acetic acid),⁴⁾ in which we realized that diastereoselective enolization of two sets of the active methylene groups might be possible. We now designed an expeditious asymmetric synthesis of the δ -lactones bearing consecutive three asymmetric centers by utilizing stereoselective enolization of "non-symmetric" diamide **2** obtained from " σ -symmetric" dicarboxylic acid **1** and then aldol type reaction³⁾ of the resultant enolate **3** with suitable aldehydes ($\text{R}^2\text{-CHO}$). The process including lactonization of aldol **4** is outlined in Scheme 1.

After several attempts, all reactions were carried out as follows. Diamide **2** ($\text{R}^1=\text{Me}$, 0.3 mmol), obtained by dehydrative condensation (66% yield) of 3-methylglutaric acid (**2**: $\text{R}^1=\text{Me}$) with (4*S*)-IPTT, was treated with a suspension of tin(II) trifluoromethanesulfonate (1.0 mmol)⁵⁾ and *N*-ethylpiperidine (1.1 mmol)⁵⁾ in CH_2Cl_2 (7.5 ml) at -40°C for 2 h. After addition of benzaldehyde (1.1 mmol), the mixture was stirred at -40°C for 1 h and then submitted to the usual work-up³⁾ to give an oily residue. A solution of the residue in DMF (1 ml) was treated with

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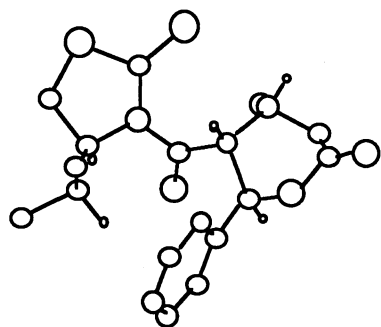
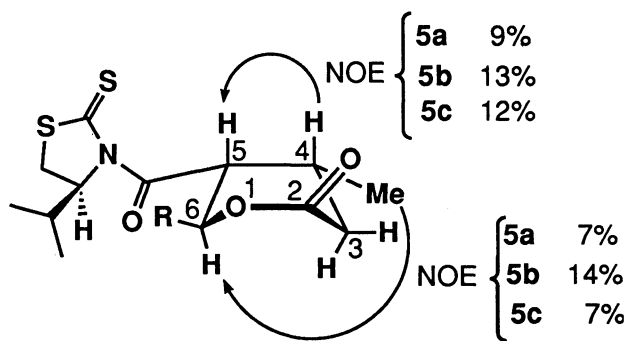


Scheme 1.

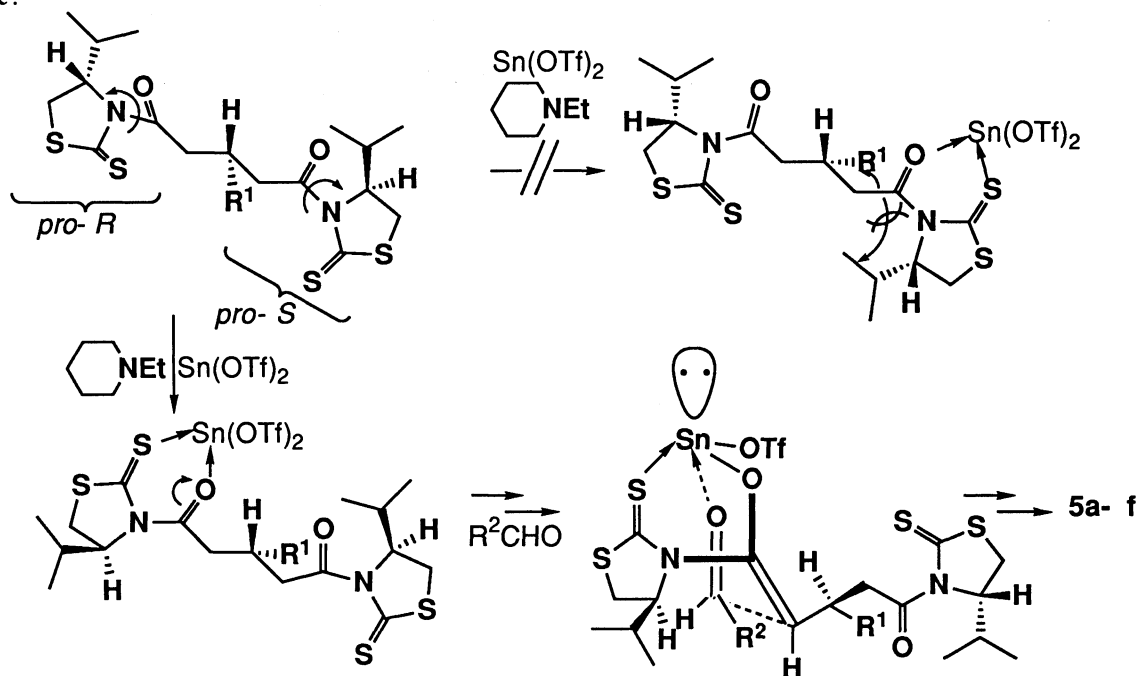


potassium carbonate (0.3 mmol) at room temperature for 1 h. The reaction mixture was poured into excess aqueous NH_4Cl and then treated as usual. The residue was purified on the preparative TLC (silica gel) plate with AcOEt -hexane (1:1) to give δ -lactone **5a** [yellow needles (*i*-PrOH), mp 152-154 °C, $[\alpha]_{\text{D}}^{23} +75.4^\circ$ (*c*0.7, CHCl_3)] as the sole product⁶⁾ in 52% yield from **2** ($R^1 = \text{Me}$). Similar reactions of **2** ($R^1 = \text{Me}$) with acet-, isopropyl, *s*-butyl, and hexyl aldehydes furnished the corresponding chiral δ -lactones **5b** [23% yield,⁶⁾ yellow needles (*i*-PrOH), mp 68-72 °C, $[\alpha]_{\text{D}}^{23} +128.3^\circ$ (*c*0.42, CHCl_3)], **5c** [30% yield,⁶⁾ yellow needles (*i*-PrOH), mp 82-83 °C, $[\alpha]_{\text{D}}^{23} +110.5^\circ$ (*c*0.97, CHCl_3)], **5d** [22% yield,⁶⁾ yellow oil, $[\alpha]_{\text{D}}^{23} +128.8^\circ$ (*c*1.4, CHCl_3)], **5e** [30% yield,⁶⁾ yellow oil, $[\alpha]_{\text{D}}^{23} +99.8^\circ$ (*c*1.4, CHCl_3)], respectively. Similar treatment of **2** ($R^1 = \text{N} \begin{smallmatrix} \text{Cbz} \\ \text{Bn} \end{smallmatrix}$) with acetaldehyde afforded the desired chiral δ -lactone **5f** [25% yield,⁶⁾ yellow oil, $[\alpha]_{\text{D}}^{23} +216.8^\circ$ (*c*1.33, CHCl_3)] and an unidentified compound⁷⁾ [yellow oil, $[\alpha]_{\text{D}}^{23} -307.7^\circ$ (*c*0.8, CHCl_3)]. All chiral δ -lactones **5a-f** were confirmed to be optically pure by their HPLC and $^1\text{H-NMR}$ ⁸⁾ analyses. Although chemical yield of the desired lactones is low, this particular synthetic method must be fairly considerable from the viewpoints of simultaneous diastereoselective construction of the consecutive three asymmetric centers and of their convenient procedure.

The absolute configuration of three asymmetric centers in the molecule **5a** was determined by the X-ray crystallographic analysis as shown in Fig. 1.

Fig. 1. Perspective view of the crystallographic structure of **5a**.Fig. 2. NOE experiment for compounds **5a-c**.

On the basis of Allinger's report⁹⁾ and the crystallographic structure of **5a**, the δ -lactone ring of compounds **5a-f** bearing three substituents should predominantly adopt a boat conformation (See Fig. 2) in the CDCl_3 solution. Thus, we confirmed the stereochemistry of **5b** and **5c** by utilizing NOE experiments in their 500 MHz ^1H -NMR analyses. The NOE aspects ($\text{C4-H} \rightarrow \text{C5-H}$ and $\text{C4-Me} \rightarrow \text{C6-H}$) of **5b, c** are consistent with those of **5a** as shown in Fig. 2. The stereochemistry of chiral δ -lactones **5d-f** was tentatively assigned on the basis of their similar ^1H -NMR data (**5d, e**)⁸⁾ in CDCl_3 and/or the similar mechanistic consideration (**5f**) to the case of **5a-c**.

Fig. 3. Plausible reaction pathway to give **5a-f**.

Formation of the consecutive three asymmetric centers toward the chiral δ -lactones may be rationalized in terms of diastereoselective enolization of the *pro-R* site active methylene followed by diastereoselective aldol type reaction *via* a six-membered transition state³⁾ illustrated in Fig. 3. Namely, similar diastereoselective enolization at the *pro-S* site maintaining

predominant conformation¹⁾ of the glutaloyl moiety should be difficult because of steric hindrance between R¹ group and isopropyl group of the *pro-S* site thiazolidine.

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- 6) In the production of δ -lactones **5a-f**, the corresponding diamides **2** were recovered in a range of 5-32% yields. However, under other reaction conditions using large excess reagents, each desired δ -lactone could not be obtained at all.
- 7) Its structure determination is now in progress.
- 8) **5a**: δ 0.63 (3H, d, J=7.1 Hz), 0.74 (3H, d, J=7.1 Hz), 1.11 (3H, d, J=6.4 Hz), 1.81 (1H, m), 2.58 (1H, dd, J=6.4, 16.7 Hz), 2.65 (1H, m), 2.75 (1H, dd, J=6.4, 16.7 Hz), 2.91 (1H, d, J=11.9 Hz), 3.41 (1H, dd, J=7.9, 11.9 Hz), 5.15 (1H, dd, J=6.4, 7.9 Hz), 5.71 (1H, dd, J=5.6, 8.7 Hz), 5.77 (1H, d, J=8.7 Hz), 7.28-7.42 (5H, m); **5b**: δ 0.99 (3H, d, J=6.4 Hz), 1.01 (3H, d, J=6.4 Hz), 1.08 (3H, d, J=6.4 Hz), 1.43 (3H, d, J=6.4 Hz), 2.33-2.37 (1H, m), 2.50 (1H, dd, J=5.6, 15.9 Hz), 2.56 (1H, m), 2.61 (1H, dd, J=4.8, 15.9 Hz), 3.04 (1H, d, J=11.9 Hz), 3.78 (1H, dd, J=7.9, 11.9 Hz), 4.92 (1H, m), 5.09 (1H, dd, J=4.8, 8.7 Hz), 5.20 (1H, t, J=7.9 Hz); **5c**: δ 0.97 (3H, d, J=7.1 Hz), 0.99 (3H, d, J=7.1 Hz), 1.02 (3H, d, J=7.1 Hz), 1.07 (3H, d, J=7.1 Hz), 1.08 (3H, d, J=7.1 Hz), 1.87-1.91 (1H, m), 2.31-2.35 (1H, m), 2.45-2.54 (3H, m), 3.02 (1H, d, J=11.1 Hz), 3.44 (1H, dd, J=7.1, 11.1 Hz), 4.74 (1H, dd, J=3.6, 9.9 Hz), 5.21 (1H, t, J=7.1 Hz), 5.46 (1H, dd, J=5.2, 9.9 Hz); **5d**: δ 0.93 (3H, d, J=6.4 Hz), 0.95 (3H, d, J=6.4 Hz), 0.99 (3H, d, J=7.2 Hz), 1.05 (3H, d, J=7.2 Hz), 1.08 (3H, d, J=6.4 Hz), 1.31-1.39 (1H, m), 1.65-1.70 (1H, m), 1.94-2.00 (1H, m), 2.32-2.38 (1H, m), 2.49-2.61 (3H, m), 3.03 (1H, d, J=11.1 Hz), 3.47 (1H, dd, J=7.9, 11.1 Hz), 4.85 (1H, dt, J=7.9, 2.4 Hz), 5.14 (1H, dd, J=4.8, 7.9 Hz), 5.17 (1H, t, J=7.9 Hz); **5e**: δ 0.87 (3H, t, J=6.8 Hz), 0.99 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 1.27 (6H, br s), 1.43 (1H, m), 1.54 (1H, m), 1.62-1.70 (2H, m), 2.40 (1H, m), 2.45-2.63 (3H, m), 3.03 (1H, d, J=11.7 Hz), 3.47 (1H, dd, J=7.8, 11.7 Hz), 4.80 (1H, m), 5.20 (2H, m); **5f**: δ 0.96 (6H, d, J=6.4 Hz), 1.04 (3H, d, J=6.4 Hz), 1.46 (3H, s), 2.20-2.35 (1H, m), 2.60-2.80 (1H, m), 2.95 (1H, br s), 3.40 (2H, m), 4.30 (1H, br s), 4.50 (2H, br s), 4.70 (1H, br s), 4.90 (1H, br s), 5.15 (2H, br s), 5.70 (1H, br s), 7.20-7.50 (10H, m).
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