

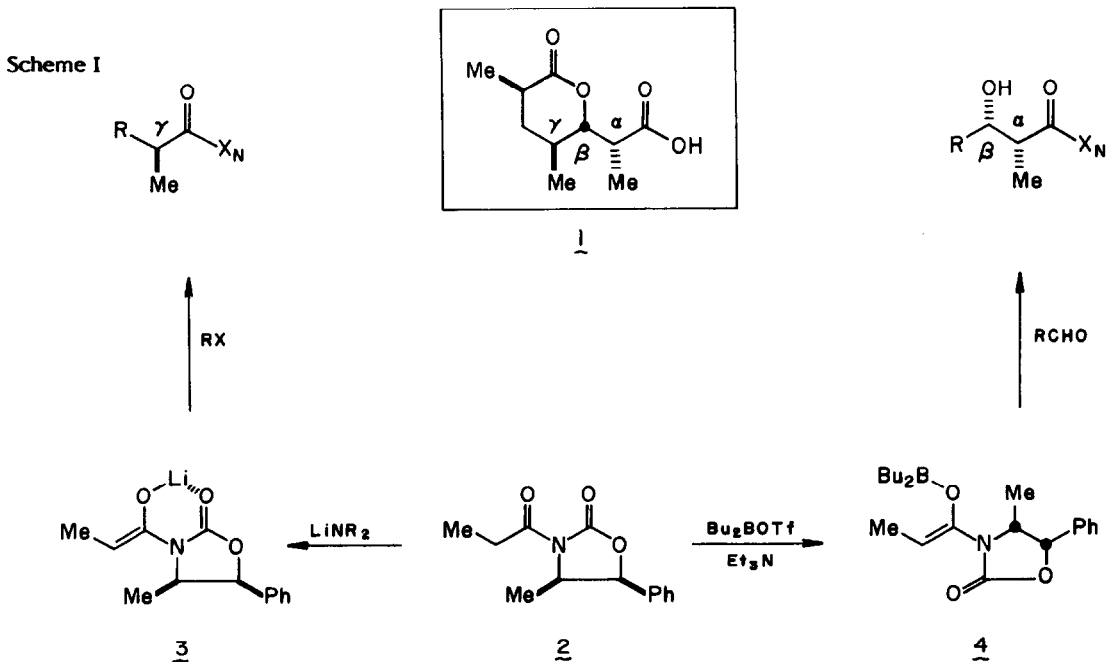
**Stereoselective Reactions of Chiral Enolates.**  
**Application to the Synthesis of (+)-Prelog-Djerassi Lactonic Acid.**

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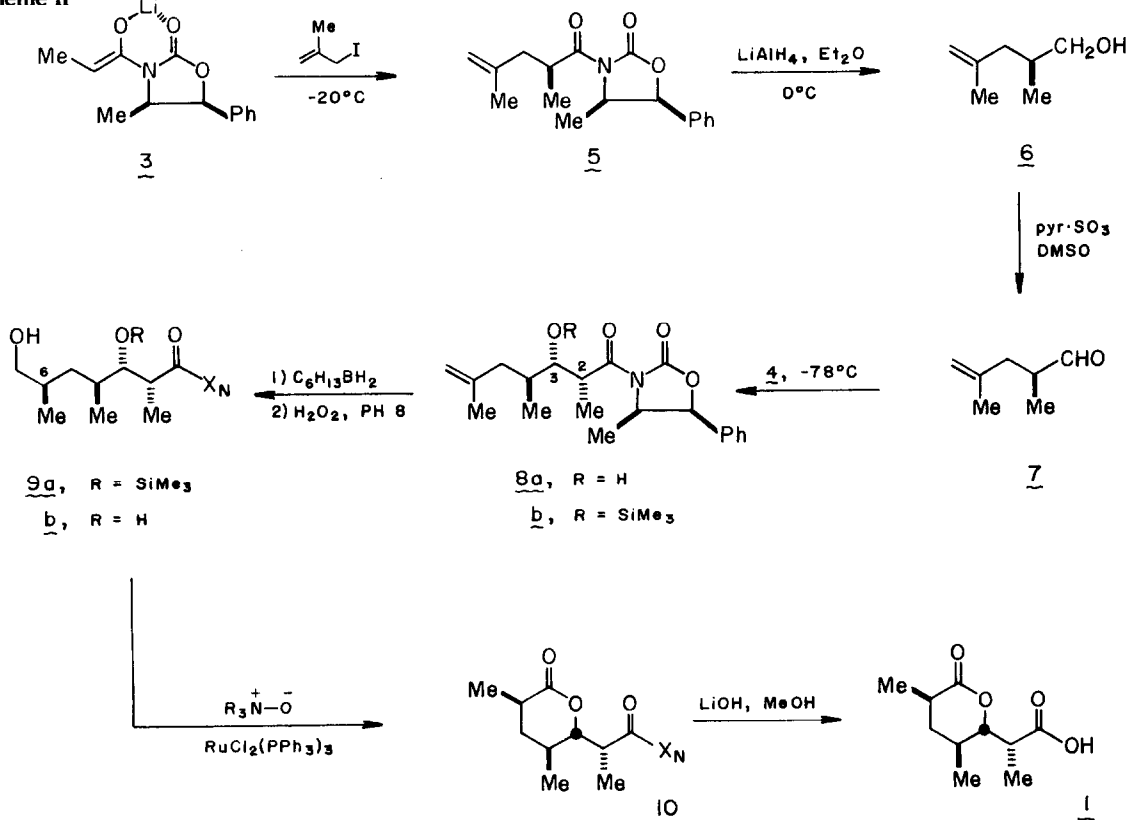
**Summary:** The application of chiral metal enolates **3** and **4** have been employed in an efficient synthesis of (+)-Prelog-Djerassi lactone (**1**).

The Prelog-Djerassi lactonic acid (**1**), derived via the degradation of either methymycin or narbomycin,<sup>1</sup> embodies important architectural features common to a range of macrolide antibiotics. Consequently, this structure has served as a focal point for the development of a diversity of new stereoselective chemical operations.<sup>2</sup> In this communication we wish to describe the utility of chiral propionimide **2**, via the derived enolates **3** and **4**, in highly diastereoselective alkylation<sup>3</sup> and aldol<sup>4</sup> processes as applied to the construction of this target structure (Scheme I).



As illustrated in Scheme II, the chiral propionimide **2**, derived from (1*S*,2*R*)-norephedrine, was transformed into the lithium enolate **3** (LDA, THF,  $-78^{\circ}\text{C}$ , 0.5 h) and treated with methallyl iodide (2.0 equiv,  $-50^{\circ}\text{C} \rightarrow -20^{\circ}\text{C}$ , 3 h) to give a 97:3 ratio of diastereomeric alkylation products. The major (2*S*)-diastereomer **5**, readily purified by medium pressure chromatography<sup>6</sup> (2*S*:2*R* > 500:1),<sup>5</sup> was obtained in 73% yield [mp  $42\text{--}44^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}} = +33.7^{\circ}$  ( $c$  6,  $\text{CH}_2\text{Cl}_2$ )]. The staging of the aldol bond construction in the synthesis (c.f. **7**  $\rightarrow$  **8**) required the transformation of imide **5** to the (*S*)-aldehyde **7**. Through our own experience associated with the selective reductions of oxazolidone imides, we have found that the above transformation is most efficiently carried out in two steps. Reduction of **5** with lithium aluminum hydride (1.0 molar equiv,  $\text{Et}_2\text{O}$ ,  $0^{\circ}\text{C}$ , 5 min)<sup>3</sup> afforded, after bulb-to-bulb distillation, an 85% yield of the (*S*)-alcohol **6** [bp  $73^{\circ}\text{C}/15$  mm,  $[\alpha]_{\text{D}} = -3.9^{\circ}$  ( $c$  4,  $\text{CH}_2\text{Cl}_2$ )] and the recovered oxazolidone chiral auxiliary. The oxidation of **6** to the (*S*)-aldehyde **7** was effected by the Parikh modification<sup>7</sup> of the Moffatt oxidation [ $\text{C}_5\text{H}_5\text{N}\cdot\text{SO}_3$  (3.0 equiv),  $\text{Et}_3\text{N}$  (7.0 equiv), DMSO,  $25^{\circ}\text{C}$ , 1.0 h)] in 85–91% yields. This method has been found by us to be exceptional in that no more than 0.1% racemization accompanies this oxidation process; in contrast, the analogous Collins and silica gel-supported chromate oxidations afford 5% and 22% racemization respectively.<sup>8,9</sup> The aldol condensation of the propionimide-derived boron enolate **3** with (*S*)-**7** according to the previously described conditions<sup>4</sup> afforded, after recrystallization, the diastereomerically homogeneous erythro anti-Cram aldol adduct

Scheme II

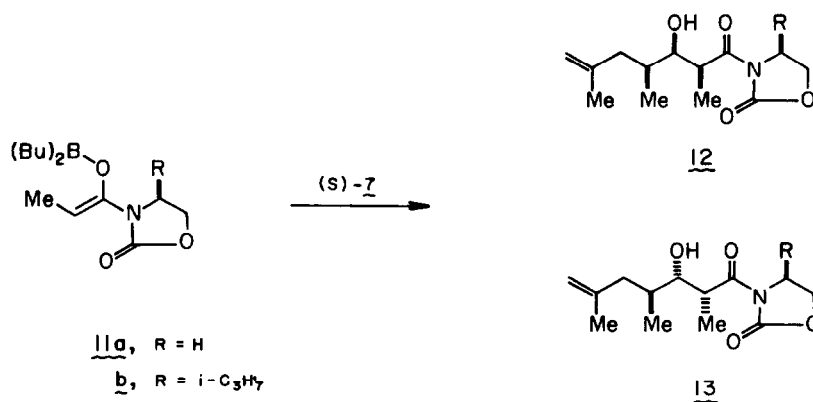


**8a** [mp 110-111°C,  $[\alpha]_D = +17^\circ$  ( $c$  3, CH<sub>2</sub>Cl<sub>2</sub>)] in 86% yield. The stereochemical control in this process was truly remarkable. Diastereomer analysis on the unpurified aldol adduct **8b** revealed that total erythro:threo diastereoselection was 400:1 while asymmetric induction within the erythro product manifold was 660:1.<sup>5</sup> In subsequent passes through the synthesis it was found to be unnecessary to chromatographically separate the minor C<sub>2</sub>-epimer of **5** accompanying the initial alkylation (**3** → **5**). This diastereomeric impurity was conveniently removed in the recrystallization of the aldol adduct **8a**.

The final methyl-bearing asymmetric center was introduced by the hydroboration process. Conversion of **8a** to the silyl ether **8b** [Me<sub>3</sub>SiNEt<sub>2</sub> (1.5 equiv), DMAP (0.2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25°C, 2 h] followed by hydroboration with thexylborane [C<sub>6</sub>H<sub>13</sub>BH<sub>2</sub> (2 molar equiv), THF, 0°C, 5 h] with a subsequent bicarbonate peroxide oxidation afforded an 85:15 mixture of the 6(R)-alcohol **9a** (X<sub>N</sub> = norephedrine auxiliary) and its C<sub>6</sub>-epimer. Flash chromatographic resolution conveniently afforded **9a** [ $[\alpha]_D = -20.6^\circ$  ( $c$  5, CH<sub>2</sub>Cl<sub>2</sub>)] in 79% yield uncontaminated by its C<sub>6</sub>-diastereomer.<sup>5</sup> The 1,3-asymmetric induction observed in this hydroboration is noteworthy, and more detailed studies on the generality of this process will appear shortly.<sup>10</sup>

The synthesis was completed by acid hydrolysis of **9a** to **9b** (oxalic acid, MeOH, 25°C, 5 min) and subsequent ruthenium-catalyzed oxidation<sup>11</sup> [N-methylmorpholine-N-oxide, 1% (PPh<sub>3</sub>)<sub>3</sub>RuCl<sub>2</sub>, acetone, 25°C, 3 h] to the crystalline lactone **10** [mp 123.5-124.5°C,  $[\alpha]_D = +51.5^\circ$  ( $c$  6.2, CH<sub>2</sub>Cl<sub>2</sub>)] in 73% yield after chromatography. Gas chromatographic analysis of lactone **10** (X<sub>N</sub> = norephedrine auxiliary) confirmed that it was >99% diastereomerically pure. The (+)-Prelog-Djerassi lactonic acid (**1**) was obtained by hydrolysis of **10** [1.0  $\underline{N}$  LiOH, MeOH, 0°C, 5 min]. Recrystallization from hot n-pentane-ether afforded (+)-**1** [mp 122.5-123.5°C,  $[\alpha]_D = +41.3^\circ$  ( $c$  2.1, CHCl<sub>3</sub>)].<sup>12</sup> Transformation of (+)-**1** to its corresponding methyl ester and subsequent gas chromatographic analysis established its chemical and diastereomeric purity at >99.9%. A spectral comparison of (+)-**1** constructed via the present route and that derived from the Ireland carbohydrate-based total synthesis<sup>2a</sup> established the identity of the two samples.

In complementary studies designed to more fully define the stereoregulation observed in the previously described aldol condensation (c.f. **4** + (**S**)-**7** → **8a**), we have also examined the condensation of boron enolates **11a** and **11b** with aldehyde (**S**)-**7**. For the achiral enolate **11a**, a slight preference was noted for the anti-Cram aldol diastereomer **13a** (**13a**:**12a** = 64:36). In the analogous condensation of the chiral enolate **11b**, the erythro



diastereoselection was approximately the same (**12b:13b**  $\geq$  400:1) as that noted for enolate **4** but with the opposite sense of asymmetric induction. It may thus be concluded from this and related studies in this laboratory that enolate chirality transfer in these systems strongly dominates the condensation process with chiral aldehydes.<sup>13</sup>

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### References and Notes

- (1) (a) Anliker, R.; Dvornik, D.; Gubler, K.; Heusser, H.; Prelog, V. *Helv. Chim. Acta* **1956**, *39*, 1785-1790. (b) Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 6390-6395.
- (2) For recent enantioselective syntheses of (+)-**1** see: (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479-485. (b) Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.* **1981**, *22*, 4287-4290. (c) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568-1571. (d) Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 2533-2534. (e) Grieco, P. A.; Ohfuné, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749-4752. (f) Nakano, A.; Takimoto, S.; Inanaga, J.; Katsuki, T.; Ouchida, S.; Inoue, K.; Aiga, M.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1019-1020.
- (3) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* in press.
- (4) Evans, D. A.; Bartroli, J.; Shih, T. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.
- (5) Diastereomer analysis was carried out on a 5880A Hewlett-Packard gas chromatograph employing 30 x 0.32 M WCOT columns (Carbowax 20 M, Methyl Silicone SE-54).
- (6) Chromatographic resolutions were carried out with Merck LoBar Silica Gel columns.
- (7) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.
- (8) (a) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-4002. (b) Santaniello, E.; Ponti, F.; Manzocchi, A. *Synthesis* **1978**, 534-535.
- (9) A gas chromatographic<sup>5</sup> racemization assay for **7** was developed by a total diastereomer analysis of the subsequent aldol step (**7**  $\rightarrow$  **8**). All possible diastereomers at C<sub>2</sub>-C<sub>4</sub> in **8b** may be resolved.
- (10) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* in press.
- (11) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, 2503-2506.
- (12) Other physical data reported for (+)-**1**: mp 124-125°C,  $[\alpha]_D = +33^\circ$  (c 0.797, CHCl<sub>3</sub>);<sup>1a</sup> mp 126-128°C,  $[\alpha]_D = +38^\circ$ ; <sup>1b</sup> mp 123.5-125°C,  $[\alpha]_D = +47.7^\circ$  (c 1.93, CHCl<sub>3</sub>);<sup>2a</sup>  $[\alpha]_D = +47.5^\circ$  (c 1.1, CHCl<sub>3</sub>);<sup>2c</sup> mp 123.5°C,  $[\alpha]_D = +38.6^\circ$  (c = 1.92);<sup>2b</sup> mp 123.5-125.0°C,  $[\alpha]_D = +38.7^\circ$  (c 1.90, CHCl<sub>3</sub>).<sup>2e</sup>
- (13) All compounds prepared during the course of this study afforded consistent elemental analyses and spectral data.