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Enantioselective synthesis of prelactone B using a proline-catalyzed crossed-aldol reaction

Petri M. Pihko* and Anniina Erkkilä

Helsinki University of Technology, Laboratory of Organic Chemistry, POB 6100, FIN-02015 HUT, Finland

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Abstract—Catalytic enantioselective synthesis of prelactone B has been achieved in only four steps. A direct proline-catalyzed aldehyde–aldehyde aldol reaction is employed as the sole source of chirality.
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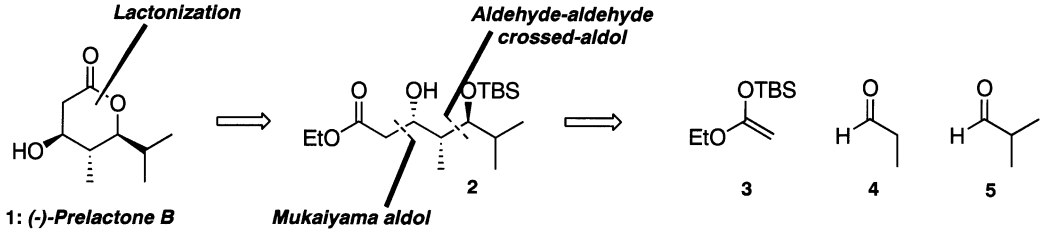
Recent discoveries from the laboratories of List,[1] Barbas,[2] MacMillan[3] and Jørgensen[4] in proline-catalyzed direct aldol reactions[5] have established that highly enantioselective couplings both between aldehydes and ketones as well as between two aldehydes can be achieved with inexpensive proline. In spite of its importance, the latter variant, the highly enantioselective aldehyde-aldehyde cross-coupling reaction,[3] has not yet been employed in the context of total synthesis. Herein, we report a very short, highly enantioselective synthesis of prelactone B where all chirality derives from a catalytic quantity of proline.[6]

Prelactone B is a natural product isolated from bafilomycin-producing *Streptomyces griseus* (strain Tü 2599 ana 18), representing an early metabolite in the biosynthesis of polyketide antibiotics.[7] Inspired by its biogenesis, we envisioned that prelactone B could be readily accessed by two consecutive aldol reactions, the first one of these being an organocatalytic crossed-aldol (Scheme 1).

Our synthesis (Scheme 2)[8] began with the MacMillan variant of the proline-catalyzed crossed-aldol reaction[3] between isobutyraldehyde and propionaldehyde, affording the aldol product **6** in >99% ee and 40:1 *anti*:*syn* selectivity.[9] In comparison with the MacMillan procedure,[3] we found it advantageous to employ a substantial excess (4 equiv.) of isobutyraldehyde in this reaction to suppress the formation of the propionaldehyde dimerization side product. The capricious nature of the β-hydroxyaldehyde product **6**[10] necessitated that the precious aldol product be immediately processed further before decomposition could set in. After some experimentation, we found that the crude aldol product **6** could be cleanly protected as a TBS ether **7** in a mixture of Et_2O and CH_2Cl_2 (61% overall from propionaldehyde).[11]

Setting up the remaining stereocenter required a Felkin-selective aldol reaction between an ester enolate equivalent and **7**. Similar highly diastereoselective Mukaiyama-type aldol reactions between α,β-chiral aldehydes and silyl enol ethers derived from ketones



Scheme 1. Retrosynthetic analysis of prelactone B and the building blocks.

Keywords: prelactone B; proline-catalyzed aldol; Mukaiyama aldol; diastereoselection.
* Corresponding author. Tel.: +358 9 451 2536; fax: +358 9 451 2538; e-mail: petri.pihko@hut.fi

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have been extensively studied by Evans[12] and others.[13] However, to the best of our knowledge, diastereoselective aldol reactions between chiral α,β-disubstituted aldehydes and ketene silyl acetals derived from *esters* have not been previously documented. To our delight, exposure of aldehyde **7** to ketene silyl acetal **3** in the presence of $BF_3{\cdot}Et_2O$ afforded the desired Felkin product **2** in 65% yield as the only observed diastereomer.[14] This result thus supports the Evans model.[12]

With the carbon skeleton of prelactone B in place, final global deprotection and lactonization with HF in $MeCN/H_2O$[15] gave (−)-prelactone B **1** as a highly crystalline solid (mp 98–99°C). Synthetic **1** proved to be identical to the natural product in all respects (mp, IR, NMR, HRMS)[16] with the exception of its optical rotation, which was similar in magnitude but opposite in sign ($[\alpha]_D = -46$ (*c* 0.42, MeOH); lit.[7] $[\alpha]_D = +38.3$ (*c* 0.6, MeOH). Thus, the unnatural enantiomer of **1** was produced; the natural (+)-**1** enantiomer could similarly be accessed starting with D-proline as the catalyst.

In summary, we have achieved a short, catalytic, enantioselective and nearly completely diastereoselective synthesis of (−)-prelactone B in only four steps and 22% overall yield. Our synthesis is the shortest reported so far and requires only inexpensive reagents.[17] Studies to combine the proline-catalyzed aldol reactions with the realm of aqueous Mukaiyama aldol chemistry are in progress.

Acknowledgements

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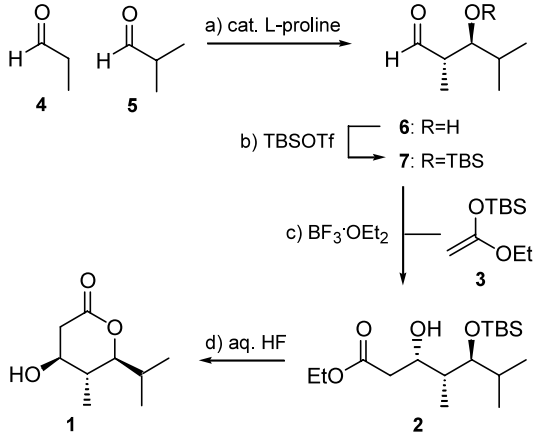

Scheme 2. *Reagents and conditions*: (a) **5** (400 mol%), L-proline (10 mol%), DMF, addition of **4** by syringe pump over 30 h; then 10 h, 5°C; (b) crude **6** (dried over 4 Å MS), TBSOTf (170 mol%), 2,6-lutidine (330 mol%), 1:1 Et_2O/CH_2Cl_2, −20 to 10°C, 2.5 h, 61% (two steps); (c) $BF_3{\cdot}Et_2O$ (100 mol%), **3** (300 mol%), CH_2Cl_2, −78°C, 65%; (d) 48% HF, H_2O, MeCN (1:2:17), 4.5 h, rt, 55%.

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9. The enantioselectivity was determined by GC analysis of the 5,5-dimethyl-1,3-dioxane derivative of **6** as described in Ref. 3. Conditions: Supelco γ-DEX 120 column, 30 m×0.25 mm (110°C isotherm 45 min, then raised to 180°C at a rate of 2°C/min, He carrier gas, velocity 28 cm/s); (2*S*,3*S*) *anti* isomer $t_r = 55.1$ min, (2*R*,3*R*) *anti* isomer $t_r = 56.0$ min, (2*R*,3*S*) and (2*S*,3*R*) *syn* isomers $t_r = 54.2$ min.
10. β-Hydroxyaldehydes such as **6** are notorious for the facility by which they undergo oligomerization, elimination and other decomposition reactions. For recent documented examples, see: (a) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319–1333; (b) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993–2012.
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14. We also observed the formation of a TBS-protected (−)-prelactone B in this reaction (ca. 10% yield), presumably via silyl migration and subsequent lactonization.
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16. Selected physical data of **1**. $R_f = 0.12$ (50% EtOAc in hexanes); mp 98–99°C; $[\alpha]_D = -46$ (*c* 0.42, MeOH); IR (thin film, cm^{-1}) 3270, 3055, 2971, 1732, 1265, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (m, 2H), 2.91 (dd, 1H, $J = 17.2$, 5.9 Hz), 2.46 (dd, 1H, $J = 17.2$, 8.0 Hz), 1.97 (dsept., 1H, $J = 2.1$, 6.9 Hz), 1.73 (ddq, 1H, $J = 6.6$, 8.1 Hz, 10.2 Hz), 1.09 (d, 3H, $J = 6.9$ Hz), 1.07 (d, 3H, $J = 6.6$ Hz), 0.91 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 86.2, 69.9, 39.1, 39.0, 28.9, 20.0, 14.0, 13.6; high resolution mass spectrum (ESI+) m/z 195.0988 [$(M+Na)^+$; calcd for $C_9H_{16}O_3Na$: 195.0997].
17. In fact, the most expensive reagent in our synthesis is *t*-butyldimethylsilyl triflate (TBSOTf)! This remains true even if D-proline were to be employed as the catalyst to produce (+)-prelactone B.