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# Stereoselective synthesis of polyketide fragments using a novel intramolecular Claisen-like condensation/reduction sequence

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**Abstract**—Intramolecular Claisen-type cleavage of the Evans-oxazolidinone with an acetate enolate followed by reduction of the resulting ketone using a borane–amine complex yielded β-hydroxy-δ-lactones as fully functionalized polyketide precursors stereoselectively. Consequently, this reaction sequence constitutes a highly practical alternative to an acetate–aldol reaction.


Chiral polyketide units are important fragments of many natural products, especially macrolide antibiotics,[1] ionophores[2] and the immunosuppressive natural products FK506,[3] Rapamycin[4] and Sanglifehrin A.[5] In order to investigate derivatives of immunosuppressants with novel modes of action, we needed an efficient synthesis of unknown polyketide fragments **1** and **2** (Fig. 1).

Using the Evans-oxazolidinone, the stereocenters at C4 and C5 can be established efficiently in *syn*-[6] and *anti*-selective[7] propionate aldol reactions. However, setting the stereochemistry at C3 requires a non-trivial selective acetate–aldol reaction (or equivalent thereof), for which novel synthetic methodologies are still urgently needed.[8] Indeed, initial studies with nucleophilic additions of acetate enolates and allyl-Ti reagents to aldehydes **3** and **4** were met by limited success. Therefore, we reasoned that an *intramolecular* cleavage of the Evans-auxiliary by an acetate enolate to form the δ-lactones **5** and **6**,[9] followed by a stereoselective reduction of the ketone would constitute an attractive alternative to the acetate aldol reaction. This synthetic sequence obviates the need to liberate **3** and **4** from the initial aldol adducts and to perform protecting group manipulations. Herein we report the successful implementation of this strategy.

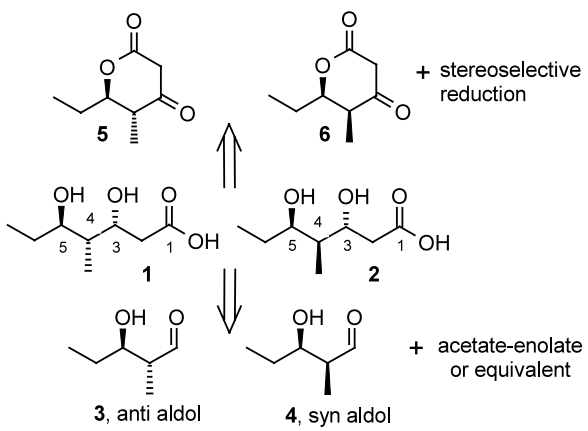


**Figure 1.**

As shown in Scheme 1, anti aldol **7**[10] was transformed into the corresponding acetate **8** by treatment with acetic anhydride in the presence of DMAP and $NEt_3$. No epimerization occurred during this step, as detected by NMR. Exposure of compound **8** to a solution of LiHMDS (Li-bistrimethylsilylamide) in THF at −78°C for 3 h led to the clean formation of β-keto-δ-lactone **5**,[11] with the free oxazolidinone as the only detectable by-product.[12] Acidic lactone **5** was isolated conveniently by a simple extraction procedure, which also allowed for efficient recovery of the chiral auxiliary. Chemoselective reduction of the keto-function in **5** turned out to be troublesome, since conventional reducing agents either afforded enolization only or complex reaction mixtures.[13] Clean conversion of ketone **5** into secondary alcohol **9**,[14] however, was achieved using *t*-$BuNH_2$-$BH_3$ in combination with citric acid.[15] The ratio of C3 epimers was determined by NMR to be equal to 13/1. NOE experiments revealed that relative

*Keywords*: acetate–aldol reaction; polyketides; Evans-auxiliary; β-keto-δ-lactones.

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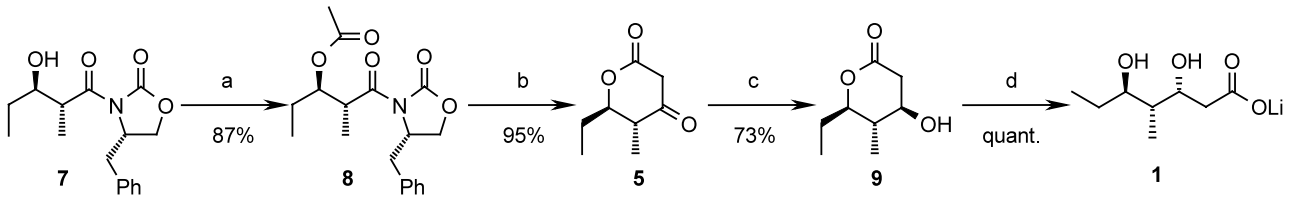


**Scheme 1.** *Reagents and conditions*: (a) $Ac_2O$, $NEt_3$, DMAP, $CH_2Cl_2$, rt; (b) LiHMDS, THF, −78°C; (c) *t*-$BuNH_2{\cdot}BH_3$, citric acid, MeOH, $H_2O$, −5 to 0°C; (d) LiOH, $H_2O$, THF.

stereochemistry and conformation of the major stereoisomer are as shown in Fig. 2: lactone **9** adopts a boat-conformation with all substituents in equatorial positions.

Although the exact conformation of ketone **5** is unknown,[16] the relatively high facial selectivity is presumably the consequence of steric hindrance of two axial protons next to the reacting carbonyl center

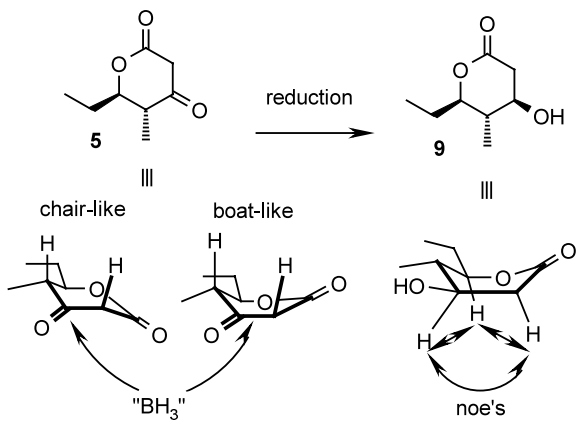


**Figure 2.** Rationalization of stereoselective reduction and observed NOEs in boat conformation of **9**.

present in chair- and boat-like conformations of keto-lactone **5**. Treatment of lactone **9** with one equivalent of LiOH in $THF/H_2O$ completed the synthesis of stereotriad **1** as its Li-salt. The same reaction sequence proved effective to transform *syn*-aldol **10**[17] into β-hydroxy-δ-lactone **12** and subsequently into carboxylate **2** (Scheme 2). Again the reduction of keto-lactone **6** yielded one major isomer of **12**.[18] Its relative stereochemistry was determined by NOE experiments to be as shown in Scheme 2. The face selectivity can be rationalized by the fact that either the ethyl- or methyl-substituent in lactone **6** is forced into an axial position and prevents attack of the reducing agent.

In summary, we described a novel and highly practical alternative to a selective acetate–aldol reaction for the synthesis of polyketide fragments. The conversion of *syn*- and *anti*-aldols **7** and **10** into stereotriads **1** and **2** can be achieved in only four steps and proceeds in good overall yield (44–60%).

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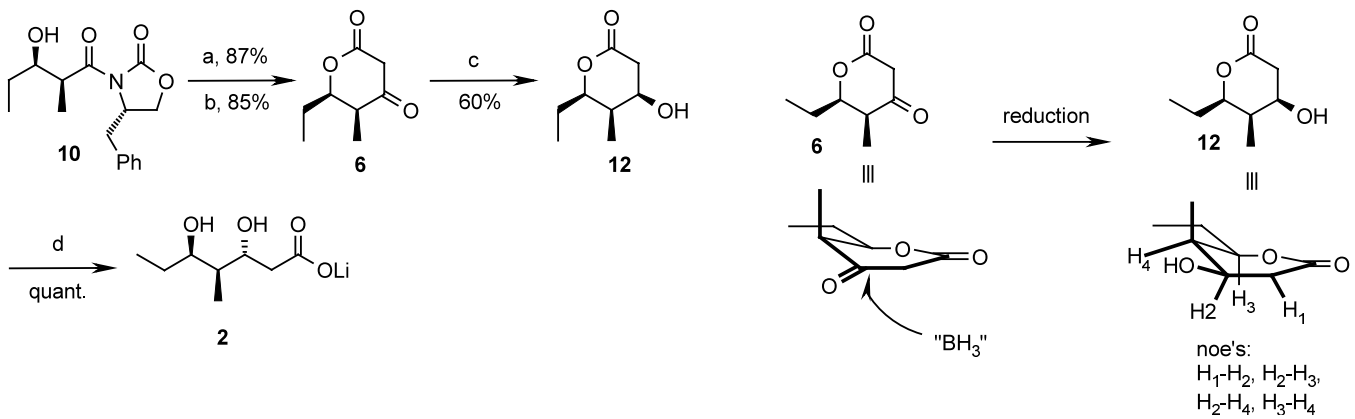


**Scheme 2.** *Reagents and conditions*: (a) $Ac_2O$, $NEt_3$, DMAP, $CH_2Cl_2$, rt; (b) LiHMDS, THF, −78°C; (c) *t*-$BuNH_2{\cdot}BH_3$, citric acid, MeOH, $H_2O$, −5 to 0°C; (d) LiOH, $H_2O$, THF.

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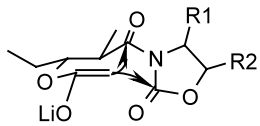
11. Experimental procedure: A solution of acetate **4** (1.2 g, 3.2 mmol) in THF (25 ml) was added at −78°C to a stirred solution of LiHMDS (1 M in THF, 9.6 ml, 9.6 mmol) in THF (20 ml). After stirring for 3 h, the reaction mixture was quenched at −78°C by the addition of satd $NH_4Cl/MeOH/H_2O$ (100 ml, 1/1/1, v/v/v). Ethylacetate (100 ml) and water (30 ml) were added and the layers separated. The organic phase contained the chiral auxiliary in quantitative yield and 90% purity. The aqueous, basic layer (pH 9–10) was titrated with 0.3N HCl to pH 2–3 and then extracted with $CH_2Cl_2$ (3×100 ml). Drying with $MgSO_4$ and concentration of the organic layer yielded the product as an off-white solid in quantitative yield and 90% purity. Chromatography (ethylacetate/hexane = 1/2) gave pure **5** as a white solid (485 mg, 3.1 mmol, 95%): $R_f = 0.35$ in ethylacetate/hexane = 1/2 mp: 78–79°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ ppm (t, $J = 7$ Hz, 3H, $CH_2C\underline{H}_3$), 1.19 (d, $J = 7$ Hz, 3H, $CHC\underline{H}_3$), 1.68–1.77 (ddq, $J = 8$ Hz, 1H, $C\underline{H}_2CH_3$), 1.92–2.00 (ddq, $J = 3$ Hz, $J = 8$ Hz, 1H, $C\underline{H}_2CH_3$), 2.43 (dq, $J = 10$ Hz, $J = 7$ Hz, 1H, $C\underline{H}CH_3$), 3.45 (d, $J = 19$ Hz, 1H, $C\underline{H}_2CO$), 3.56 (d, $J = 19$ Hz, 1H, $C\underline{H}_2CO$), 4. 28 (ddd, $J = 10$ Hz, $J = 7$ Hz, $J = 3$ Hz, 1H, CHO); MS (EI): 156 ($M^+$), 127 ($M-C_2H_5^+$), 98, 85, 56, 42; HRMS calcd for $C_8H_{12}O_3$ 155.0708, found 155.0710; $[\alpha]_D^{25} = +144$, $c = 5.5$ mg/ml in $Et_2O$. NMR data are in accordance with that of racemic **5**: Brandänge, S.; Leijonmarck, H. *J. Chem. Soc., Chem. Commun.* **1983**, 1097–1098.
12. This result is remarkable in the light of Brandänges findings (see Ref. 9). In a related experiment using a Norephedrin-derived oxazolidinone he observed predominant attack at the *endo*-carbonyl function, yielding the 11-membered ring structure. Subtle effects of substituents on the oxazolidinone therefore seem to govern the course of the reaction.




13. K-Selectride and DIBAH led to enolization, $LiBH_4$ and $NaBH_4$ in solvents such as MeOH, THF to complex reaction mixtures detected by TLC, while the use of $Me_3N$-$BH_3$ gave no conversion.
14. Experimental procedure: To a stirred solution of ketone **5** (35 mg, 0.22 mmol) in MeOH (2 ml) was added at −5°C a solution of *t*-$BuNH_2$-$BH_3$ (62 mg, 0.67 mmol) in MeOH (2 ml), immediately followed by a 1 M solution of citric acid in water (1.6 ml). After 2.5 h at −5°C, $CH_2Cl_2$ (15 ml) and water (5 ml) were added. Layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3×10 ml). After drying with $MgSO_4$ and concentration of the organic layer, chromatography (ethylacetate/hexane = 2/1) yielded 26 mg (0.16 mmol, 73%) of a colorless oil. $R_f = 0.21$ in ethylacetate/hexane = 1/1; $^1$H NMR (500 MHz, DMSO): $\delta = 0.90$ ppm (d, $J = 7.4$ Hz, 3H, $CHC\underline{H}_3$), 0.94 (t, $J = 6.8$ Hz, 3H, $CH_2C\underline{H}_3$), 1.47 (m, 2H, $C\underline{H}_2CH_3$), 1.70 (m, 1H, $C\underline{H}CH_3$), 2.25 (dd, $J = 6.4$ Hz, $J = 16.5$ Hz, 1H, $CH_2CO$), 2.78 (dd, $J = 5.6$ Hz, $J = 16.5$ Hz, 1H, $CH_2CO$), 3.60 (m, 1H, CHOCO), 3.85 (ddd, $J = 2.9$ Hz, $J = 7.6$ Hz, $J = 10.4$ Hz, 1H, $C\underline{H}OH$), 5.12 (d, $J = 4.7$ Hz, 1H, OH); MS (ES+): 159 ($MH^+$), 141 ($M^+-H_2O$), 129 ($M^+-C_2H_5$), 116, 87, 58; HRMS calcd for $C_8H_{14}O_3$+OH 175.0970, found 175.0971; IR: 3430 (m, OH), 2971, 2937, 2883 (m, CH), 1729 (s, lacton CO), 1462 (m), 1379, 1360 (m), 1250 (s, lacton CO), 1190, 1098, 1042, 999 (m); $[\alpha]_D^{25} = +41.9$, $c = 8$ mg/ml in $Et_2O$.
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18. The ratio of C3 epimers was detected by NMR to be equal to 4/1. Chromatographic separation of epimers gave pure **10** in 60% yield.