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Intramolecular Claisen-type Condensations of β-Acetoxy Amides or Imides

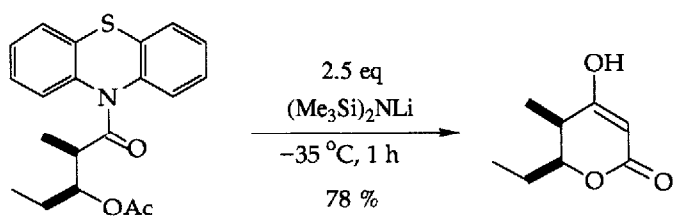
Svante Brandänge* and Hans Leijonmarck

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

Abstract: Intramolecular Claisen-type condensation of amide **1** or imide **7** leads to the same δ-lactone in racemic (**2**) or enantiomerically pure form (**4**) respectively. A side-reaction producing the 11-membered ring compound **6** makes imide **3** unsuitable as a starting material for the synthesis of **4**. A clean two-step reduction of **4** to **9** is also described.

β-Acetoxy esters having one or two α–alkyl substituents undergo intramolecular Claisen condensation when treated with lithium hexamethyldisilazide at low temperature.[1,2] The products are formed stereospecifically[2] and are tautomeric mixtures of β-keto-δ-lactones and the corresponding enols (*e.g.* **2**) in which the latters sometimes predominate. We here report an extension of the previous work which involves unprecedented Claisen-type cyclizations of some β-acetoxy amides or imides. The new reactions represent two-carbon chain elongations and lead, as before, to β-keto-δ-lactones. These products are versatile synthetic intermediates[3,4] which now have been synthesized in either diastereomerically or enantiomerically pure form.

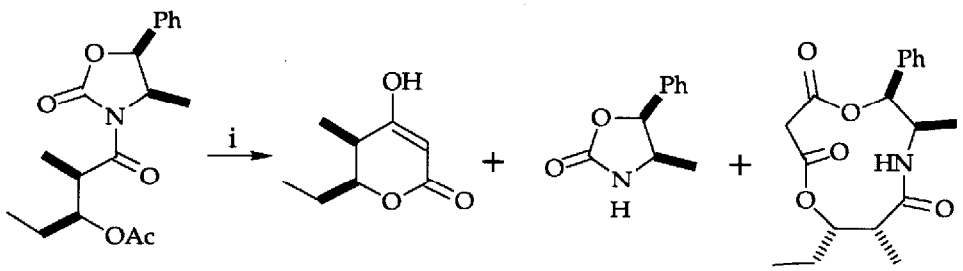
Racemic, diastereomerically pure **2** was prepared in three steps from *N*-propionylphenothiazine. Thus, a highly diastereoselective aldol-type condensation[5] with propionaldehyde followed by acetylation (Ac_2O, pyridine) afforded **1**, m.p. 126-9 °C. A solution of **1** in tetrahydrofuran (THF) was added to lithium hexamethyldisilazide[6] in THF (2.5 eq, N_2, –78 °C). Reaction at –78 °C→–35 °C, then 1 h at –35 °C and work-up involving separation of acidic **2** from the neutral compounds by partition between Et_2O and aqueous $NaHCO_3$ gave racemic **2** in a 78 % yield; m.p. 95-103 °C; solutions in $CDCl_3$ showed (NMR) both **2** and its



1 (racemic) **2** (racemic)

keto tautomer. No or little α,β-elimination of acetic acid from **1** had occurred. Compared to the previous synthesis of **2** from β-acetoxy ester[2], this new route to **2** is two steps shorter, gives a higher yield in the cyclization step and less elimination.

In order to prepare **2** in enantiomerically pure form, we first investigated a route based on Evans' asymmetric aldol condensation.[7] The condensation product was acetylated and a THF solution of the acetate (**3**) was added dropwise to a solution of lithium hexamethyldisilazide[6] (2.5 eq, THF, –78 °C). Workup after 2 h and analysis by ^{1}H NMR spectroscopy showed an 88 % conversion of **3**. Beside the δ-lactone **4** (37 %) and the chiral auxiliary **5** (45 %), there was also formed a byproduct (43 %), m.p. 73-5 °C. Its EI-MS showed, supported by FAB-MS, that it was a structural isomer of the starting material: M^+ = 333.1574 ± 0.0010 (base peak), calc. for $C_{18}H_{23}NO_5$; M^+ = 333.1577. We assigned the 11-membered ring structure **6** to the byproduct. The malonate unit was seen in the ^{1}H NMR spectrum as an AB-spectrum (2 H) centered at δ

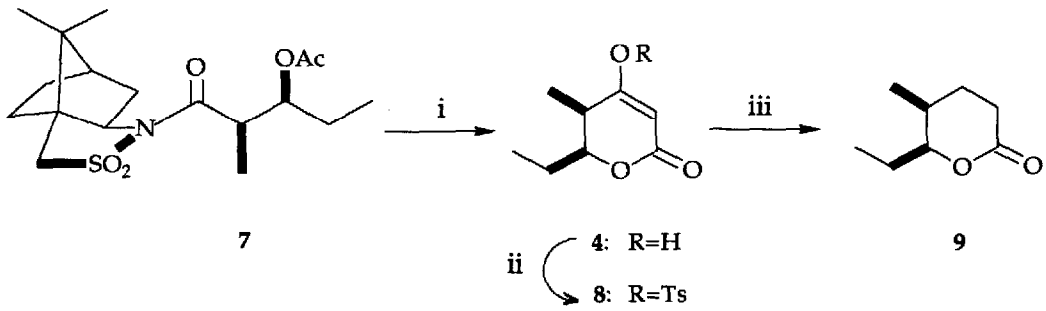


3 **4** **5** **6**

Reagent: i) $(Me_3Si)_2NLi$ (2.5 eq), –78 °C, 2 h

3.50 (*J* 15.2 Hz) and the amide NH as a doublet (*J* 7.8 Hz) at δ 5.40.[8] On exchange with CD_3OD (22 °C) the NH signal disappeared and the ddq multiplet (1 H) at δ 4.26, ascribed to the N-methine group, turned into a dq signal (loss of a 7.8 Hz coupling). The formation of the byproduct most likely involves deprotonation of the acetoxy group, attack of the resulting enolate on the remote carbonyl of the *N*-acyl carbamate group, and subsequent opening of the five-membered ring. The C-C bond-forming steps of the reactions leading to **4** and **6** are probably practically irreversible. This means that the six-membered ring transition state which eventually leads to **4** and the eight-membered ring transition state which eventually leads to **6** are comparable in energy. A similar product mixture was obtained from the *sodium* enolate of **3**.

To avoid the side-reaction which lowered the yield of **4**, we changed chiral auxiliary and carried out an asymmetric aldol condensation according to Oppolzer.[9] Subsequent acetylation gave the crystalline acetate **7**,[10] m.p. 97-9 °C, which was subjected to intramolecular Claisen-type condensation. Lithium hexamethyldisilazide (3.0 eq) in THF (initially –78 °C but probably somewhat warmed during the transfer) was added during 25 min to a solution of **7** (2.50 g) in THF (–78 °C) and the mixture then allowed to react for 1 h (–78 °C) before workup. Crystalline **4** was obtained in 77 % yield; m.p. 94-9 °C; $[\alpha]_D^{21}$ +8.3° (*c* 1.0,



Reagents: i) $(Me_3Si)_2NLi$ (3.0 eq), −78 °C, 1 h, 77 %; ii) TsCl, $NEtPr_2^i$, $CHCl_3$, reflux, 0.5 h, 91 %; iii) H_2 (1 atm), Pd, 73 %

$CHCl_3$); the chiral sultam auxiliary was recovered in 95 % yield. The base-induced elimination of HOAc from **7** was negligible (<1 %).

Exhaustive reduction in the β position of β-keto-δ-lactones has previously been carried out by preparation of the corresponding enol acetate and subsequent reduction with H_2 and PtO_2.[3] However, the conversion of **4** into **9** by this technique suffered from an incomplete hydrogenolysis in the second step (Et_2O as solvent); 5-7 % of the saturated β-acetoxy lactone was formed along with **9** (setting all GLC response factors equal). It was thus evident that a more efficient leaving group was to be preferred. The enol tosylate **8**[11] (91 %), and also an enol phosphate, were reduced to **9** with increased efficiency using H_2 and PtO_2, but the purest product was obtained when **8** (2.90 g) was reduced with H_2 (1 atm, EtOAc) and Pd/C, using $MgHPO_4 \cdot 7H_2O$ (5 eq) as acid scavenger. Crude **9** (GLC purity: 94.9 %; 0.6 % trans isomer + 4.5 % others) was purified by silica gel chromatography (Et_2O-hexane) and subsequent distillation (50-54 °C, 0.3 mbar); 73 % (GLC purity: 98.8 %; 0.6 % trans isomer + 0.6 % others); $[\alpha]_D^{21}$ −92° (*c* 1.1, alcohol-free $CHCl_3$); lit.[12] value: $[\alpha]_D^{24}$ −65.82° (*c* 1.0, $CHCl_3$).[13] When methanol-containing chloroform (ca. 1 %, v/v) was used as solvent for **9**, the specific rotation decreased during the measurement until $[\alpha]_D^{21}$ −78° was reached (0.5 -1 h). This was due to a methanolysis of **9** forming a methyl ester (^1H NMR, GLC); the equilibrium content of the latter under the actual conditions was 20 %. An inversion of configuration at *both* asymmetric carbons in the side chain of **7** during the conversion of **7** into **9** seems almost impossible. Therefore, the enantiomeric purity of **9** should not be lower than the diastereomeric purity[10] of **7** (>98 %).

Compound **9** has been converted by two steps into the pheromone serricornin.[14] Previous routes to **9** involve several steps[12,14] but shorter routes have been used for some similar lactones.[15-17]

It is thus clear that the β-acetoxy amide **1** and the β-acetoxy imide **7** are better suited starting materials for intramolecular Claisen-type condensations than the previously studied β-acetoxy esters. This means that improved routes to the synthetically versatile β-keto-δ-lactones have been found.

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8. Compound **6**: IR ($CHCl_3$): 3445, 1765, 1735, 1680 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, Me_4Si): δ 7.39-7.22 (m, 5 H), 5.97 (d, 1 H, *J* 4.3 Hz), 5.40 (d, 1 H, *J* 7.8 Hz), 4.94 (ddd, 1 H, *J* 10.3, 5.9, 4.0 Hz), 4.26 (ddq, 1 H, *J* 7.8, 7.1 (q), 4.3 Hz), 3.57 and 3.43 (AB-spectrum, 2 H, *J* 15.2 Hz), 2.82 (pentet, 1 H, *J* 6.6 Hz), 1.71 (ddq, 1 H, *J* 14.5, 10.3, 7.3 (q)), 1.65 (ddq, 1 H, *J* 14.5, 7.3 (q), 4.0 Hz), 1.18 (d, 3 H, *J* 6.9 Hz), 0.90 (d, 3 H, *J* 7.3 Hz), 0.90 (t, 3 H, *J* 7.3 Hz). ^{13}C NMR (67 MHz, $CDCl_3$, Me_4Si): δ 171.9 (s), 166.4 (s), 165.9 (s), 137.1 (s), 128.5 (d), 127.8 (d), 125.1 (d), 78.7 (d), 77.2 (d), 49.3 (d), 43.1 (t), 42.8 (d), 21.5 (t), 13.8 (q), 11.8 (q), 10.3 (q). EI–MS (70 eV): *m/z* (% rel. abundance) = 334 (20), 333 (100), 227 (4), 200 (9), 199 (9); remaining peaks were weak (<4 %).
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10. The alcoholic precursor of **7** showed m.p. 119-120 °C; $[\alpha]_D^{21}$ –100° (*c* 1.1, $CHCl_3$). Lit.[9] values: m.p. 120-121 °C; $[\alpha]_D^{20}$ –99.3° (*c* 1.06, $CHCl_3$). Compound **7** showed $[\alpha]_D^{21}$ –99° (*c* 1.0, $CHCl_3$). No signals from any diastereomer (<2 %) was seen in the ^1H NMR spectrum of **7**.
11. Enol tosylate **8**: ^1H NMR (270 MHz, $CDCl_3$, Me_4Si): δ 7.85 (d, 2 H, *J* 8.4 Hz), 7.40 (d, 2 H, *J* 7.9 Hz), 5.81 (s, 1 H), 4.26 (ddd, 1 H, *J* 8.3, 6.1, 3.2 Hz), 2.48 (s, 3 H), 2.40 (dq, 1 H, *J* 7.1 (q), 3.2 Hz), 1.9-1.7 (m, 1 H), 1.65-1.45 (m, 1 H), 0.99 (d, 3 H, *J* 7.1 Hz), 0.99 (t, 3 H, *J* 7.4 Hz). ^{13}C NMR (67 MHz, $CDCl_3$, Me_4Si): δ 168.3, 164.8, 146.7, 131.8, 130.3, 128.4, 104.3, 80.3, 35.6, 24.0, 21.8, 9.7, 9.5.
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13. Compound **9**: ^1H NMR (270 MHz, $CDCl_3$, Me_4Si): δ 4.21 (ddd, 1 H, *J*≈8.6, 5.3, 2.8 Hz), 2.54 (t, 2 H, *J* 7.1 Hz), 2.1-1.9 (m, 2 H), 1.8-1.4 (m, 3 H), 1.01 (t, 3 H, *J* 7.5 Hz), 0.96 (d, 3 H, *J* 7.0 Hz). Somewhat different values were obtained for **9** in CCl_4.[14] Our ^{13}C NMR shifts (67 MHz, $CDCl_3$, internal Me_4Si) were consistently 0.6 ppm higher than those published[14] ($CDCl_3$).
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