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Aldol-type transformations of levoglucosenone-derived medium-sized keto lactones

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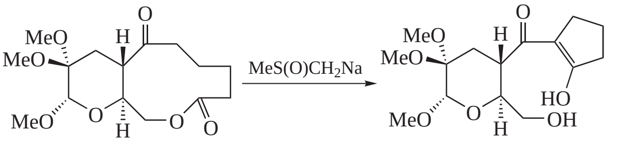
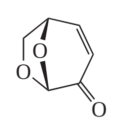
Action of bases on levoglucosenone-derived 6-oxononan-9-olide and 7-oxodecan-10-olide causes the transannular reaction of the aldol type affording stable 2-acylcyclopent-1-en-1-ol and 2-acylcyclohex-1-en-1-ol, respectively. The lower homologue, 5-oxooctan-8-olide derivative, under the similar conditions gives a complex mixture of products, which may be explained by the poor stability of the intermediate 2-acyl-cyclobut-1-en-1-ol.

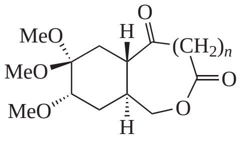


Levoglucosenone, enone of carbohydrate nature,[1] is attractive for the preparation of natural-like compounds due to reliable stereo control at the synthetic stages.[1,2] For instance, chloriolide, a twelve-membered macrocyclic lactone, was obtained based on levoglucosenone.[3] We also used this enone in the three-step synthesis of medium and large size lactones **1**–**3**.[4] These lactones seem interesting for studying their intramolecular, in particular transannular, reactions (see, for example, the properties of decarestrictins[5]). The lactone cycle of compounds **1**–**3** is annulated at the β,γ-position in respect of the oxy group with the pyran ring, while their ester and keto groups are separated from one to another by 3, 4 and 5 carbon units, respectively. The most feasible transformation of this series is an aldol-type reaction stimulated by the cleavage of medium-sized cycles and formation of ordinary ones. The possibility of acyloin-like transformations is not ruled out either. Unlike linear dicarboxylic acid esters, in medium-sized lactones there is a ‘proximity effect’,[6] or ‘transannular promotion’. In this communication, we report on the behaviour of lactones **1**–**3** under the Dieckmann reaction conditions with varying the nature of base applied.

Boiling of octanolide **1** in THF in the presence of NaH[7] led to a complex mixture of products which were difficult to identify. The result can be explained by the decomposition of the labile intermediate cyclobutenol **4** (Scheme 1). The products of possible competing condensation involving pyran atom α to the keto group to form a spiro derivative were not detected, which was probably due to steric reasons. Decanolide **3** under similar conditions is converted into acylcyclohexenol **5**[†] in 69% yield (see Scheme 1).



levoglucosenone

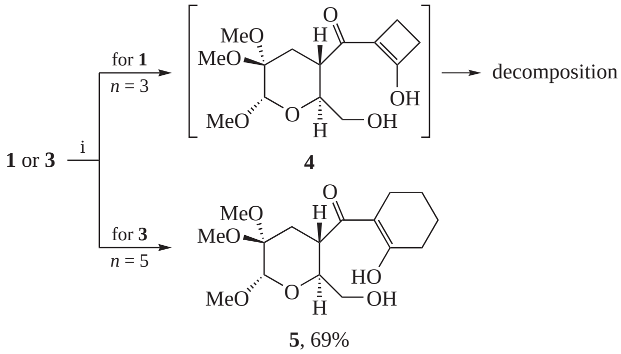


1–**3**

1 $n = 3$
2 $n = 4$
3 $n = 5$

The similar ring opening in nonanolide **2** resulted in acylcyclopentenol **6**[‡] derivative in a yield of 71% (Scheme 2). This substrate was chosen for the optimization of the conditions and base nature.

Optimal results were achieved using dimsyl sodium in DMSO[8] or colloidal potassium (generated by ultrasonic action) followed by EtOH treatment.[9] Less effective were the applications of KOEt in ethanol and toluene or Bu^{t}OK in THF.[10]

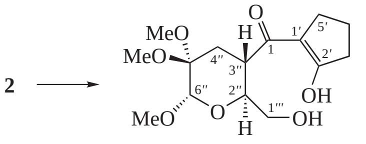


Scheme 1 *Reagents and conditions:* i, NaH, THF, boiling.

[†] *(2-Hydroxycyclohex-1-en-1-yl)[(2*S*,3*S*,6*S*)-2-hydroxymethyl-5,5,6-trimethoxytetrahydro-2*H*-pyran-3-yl]methanone* **5**. Lactone **3** (0.16 g, 0.47 mmol) in THF (1.0 ml) was added to a suspension of NaH (0.02 g, 0.94 mmol, obtained by washing a 60% dispersion of NaH in mineral oil with hexane and removing the residual hexane) in THF (2.0 ml), and this was boiled under inert atmosphere until the starting material disappeared (TLC monitoring). The mixture was then treated with HCl (1% aq., 2.0 ml), and the product was extracted EtOAc (3×5 ml). The combined organic layers were dried over MgSO$_4$, the solvent was distilled off, and the residue was chromatographed on a column of silica gel. Yield 0.10 g (60%).

[‡] *(2-Hydroxycyclopent-1-en-1-yl)[(2*S*,3*S*,6*S*)-2-hydroxymethyl-5,5,6-trimethoxytetrahydro-2*H*-pyran-3-yl]methanone* **6**.

Method A. A solution of nonanolide **2** (0.10 g, 0.30 mmol) in DMSO (0.5 ml) was added to the solution of NaH (0.03 g, 1.2 mmol, obtained by washing a 60% dispersion of NaH in mineral oil with hexane and removing the residual hexane) in DMSO (0.5 ml) in the argon atmosphere for 30 min at room temperature. The stirring was stopped after the disappearance of the starting material (TLC monitoring). The mixture was then treated with H$_2$O (1.0 ml). The products were extracted EtOAc (3×5.0 ml), dried with MgSO$_4$, the solvent was distilled off, the residue was chromatographed on a column of silica gel. Yield 0.085 g (89%).



6

Conditions	Yield of **6** (%)
K (colloidal) in toluene, then EtOH	93
MeS(O)CH$_2$Na	89
NaH, THF, boiling	71
KOEt, EtOH	63
KOEt, toluene	60
Bu^{t}OK, THF	33

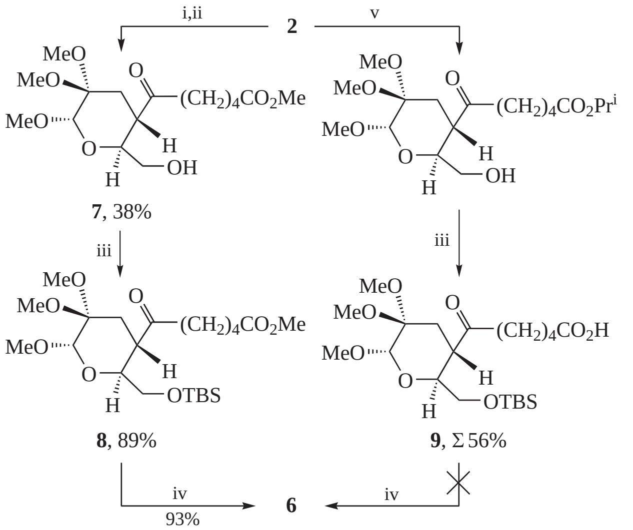
Scheme 2

The effect of the preparation way of KOEt on the efficiency of the transformation of nonanolide **2** is of note. The use of KOEt in EtOH without replacement of the solvent[11] provided 63% yield of product **6** over 12 h. When KOEt is generated directly in the reaction mixture by the addition of EtOH to potassium metal as pieces in a toluene solution of nonanolide **2**, cyclopentenol **6** is formed in 30 min in 28% yield. The ultrasonic treatment of a toluene solution of nonanolide **2** in the presence of colloidal potassium in an effort to trigger acyloin-type condensation[12] was unsuccessful. However, addition of ethanol to this mixture results in the instantaneous formation of cyclopentenol **6** in a yield of 93%. The reason for the inertness of nonanolide **2** under the conditions of acyloin condensation,[12] in all probability, is the steric hindrance created by the pyran ring at the α-position to the keto group. When EtOH is added to the finely dispersed potassium, an instant condensation of the aldol type at the α′-position of the keto group free from the steric influence of the pyran ring can start.

The formation of keto enol **6** is indicated by signals of the carbonyl group at 207.68 ppm, carbon atoms C$^{1'}$ and C$^{2'}$ at 174.61 and 110.21 ppm. respectively. Signals C$^{2''}$ and C$^{6''}$ are manifested at 69.63 ppm (δ_H 4.08) and 97.82 ppm (δ_H 4.61). In the H–H COSY spectra, the correlation peaks H$^{2''}$/H$^{3''}$, H$^{3''}$/H$^{4''}$ and H$^{2''}$/H$^{1''}$ are observed. The correlation peak of H$^{3''}$/C=O and H$^{5'}$/C=O in the HMBC spectrum indicates that the carbonyl carbon atom is in the C^1 position rather than in C$^{2'}$ one. Since the configuration of the C$^{2''}$ center during the reaction is not affected, the value of the CCRB $^3J_{2'',3''}$ 10.6 Hz indicates an anti-location of the protons H$^{2''}$ and H$^{3''}$.

An attempt to carry out intramolecular carbocyclization of lactone **2** under conditions of effective acyloin condensation[13] by sonication of its solution in a mixture of Na and TMSCl in THF[12] was unsuccessful. Probably, there is a strong steric counteraction as in the case of condensation involving the α-carbon atom of the keto group.

To detect a possible transannular effect on the Dieckmann reaction, we synthesized a linear analogue of nonanolide **2**. For this purpose, methanolysis of nonanolide **2** in the presence of MeONa was performed to produce keto ester **7** whose hydroxyl group was protected as a TBS-ester to afford substrate **8**. The latter was treated with dimsyl sodium under the same conditions for nonanolide **2**, and cyclopentenol derivative **6** was obtained in 93% yield (Scheme 3). Thus, such differences in the structures of the substrates do not significantly affect the yield of the Dieckmann product.



Scheme 3 *Reagents and conditions:* i, MeONa–MeOH; ii, CH$_2$N$_2$, Et$_2$O; iii, TBSCl, imidazole, CH$_2$Cl$_2$; iv, MeS(O)CH$_2$Na, then H$^+$; v, Pr^{i}ONa– Pr^{i}OH; vi, NH$_4$OH, Δ.

The herein synthesized keto acid **9** (see Scheme 3) turned to be resistant to dimsyl sodium in DMSO. This experiment allows us to exlude participation of compound **9** in the process in question.

In conclusion, in the formation of 5- or 6-membered cycles by the Dieckmann reaction, the transannular effect of medium-sized lactones is leveled by the high reactivity of the substrate. The decrease in product yields depending on the reaction conditions is most likely caused by the lactone opening with the formation of non-reactive carboxylic acids or their salts. The compounds obtained seem promising for studying the structure–activity relationship in the lactone-carbocyclic derivative series.

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Analyses were carried out using the equipment of the Center for Collective Usage ‘Chemistry’, Ufa Institute of Chemistry, Russian Academy of Sciences.

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Method B. Potassium metal (0.012 g, 0.30 mmol) was added to dry toluene (2.0 ml), and this was subjected to sonication for 15 min at 0 °C. Then nonanolide **2** (0.10 g, 0.30 mmol) in toluene (0.5 ml) was added. After 5 min, the mixture was treated with ethanol (2.0 ml), neutralized with 3% HCl (aq.), and the products were extracted with EtOAc (3 × 3 ml). The extract was dried with MgSO$_4$, the solvent was distilled off, the residue was chromatographed on a column of silica gel. Yield 0.89 g (93%).

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