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Reversible intramolecular Dieckmann-type condensation of 2-(2-hydroxymethyl-5,5,6-trimethoxytetrahydropyran-3-ylcarbonyl)-cyclopentanone: an alternative access to medium-sized lactones

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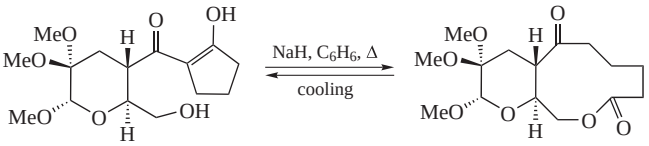
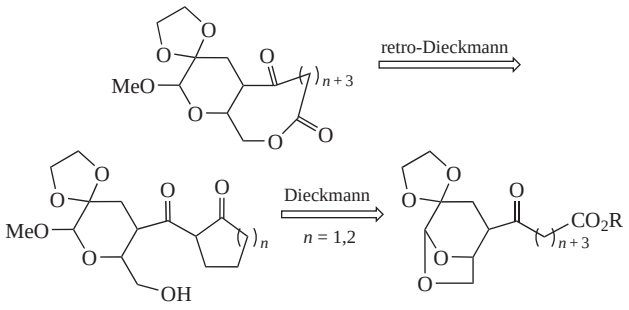
Levoglucosenone-derived 2-[(2*S*,3*S*,6*S*)-2-hydroxymethyl-5,5,6-trimethoxytetrahydro-2*H*-pyran-3-ylcarbonyl]cyclopentanone upon boiling in benzene in the presence of NaH undergoes the retro-Dieckmann-type reaction to afford 10-membered lactone, while storing this reaction mixture at room temperature brings about the starting cyclopentanone derivative. Several structurally analogous compounds were examined in respect of similar transformations.



In our ongoing investigations, we used levoglucosenone, an available enantiopure natural compound, as a starting material for the preparation of new polyfunctional chiral compounds of potent biological utility.[1] For instance,[1(c)] we reported on the Dieckmann-type transformations of lactones prepared by the Michael addition of cycloalkanones at levoglucosenone. The thus obtained compounds contain 1,3-dicarbonyl system and remote hydroxyl group. Relative 2-alkyl-2-(ω-hydroxyalkyl)cyclohexa-1,3-diones are known to undergo the retro-Dieckmann reaction with the formation of medium or large cycle lactones.[2] Such transformations are classified by Ho[3] as *a1a* fragmentations. Since enolizable 1,3-diketones tend to be stabilized under the action of bases,[3] one may reason on reverse conversion of cycloalkenones derived from medium-sized cyclic keto lactones. In this case, to accomplish the retro-Dieckmann reaction seems to be attractive in terms of preparation of new chiral medium-sized lactones from levoglucosenone-derived 1,3-dicarbonyl compounds (Scheme 1).

In fact, boiling cyclopentenol **la**[1] in benzene in the presence of NaH for 7 h leads to its complete conversion into lactone **2**[†]

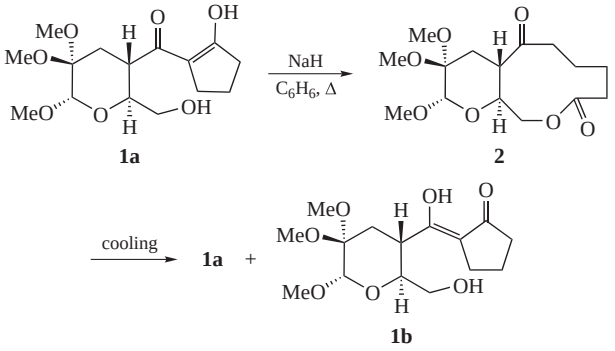


Scheme 1

[†] *(2S,4aS,12aS)-2,3,3-Trimethoxydecahydropyrano[2,3-c]oxecine-5,10-dione* **2** and *2-{1-hydroxy-1-[(2S,3S,6S)-2-hydroxymethyl-5,5,6-trimethoxytetrahydro-2H-pyranyl]methylidene}cyclopentanone* **1b**.

Method A. To a benzene (1.0 ml) solution of cyclopentenol **1a** (40 mg, 0.13 mmol), suspension of NaH (9 mg, 0.39 mmol) in benzene (2.0 ml) was added, and this was boiled under inert atmosphere until the starting **1a** was consumed (TLC). The mixture was treated with aq. HCl (1%) and extracted with EtOAc (3 × 5.0 ml). After drying ($MgSO_4$), concentrating and column chromatography, a 2 : 1 mixture of **1a**,**b** (17 mg, 40%) and lactone **2** (17 mg, 41%) were obtained.

(Scheme 2). However, after cooling the reaction mixture to room temperature and usual work up, in addition to the product **2** (yield 41%), the starting cyclopentenol **1a** was recovered along with formation of its tautomer **1b** (2 : 1 ratio, inseparable mixture). Moreover, after cooling the reaction mixture and keeping it for 12 h, a complete reverse conversion of lactone **2** into cyclopentanes **1a**,**b** occurred. To obtain only lactone **2**, it was necessary to immediately work up the reaction mixture after the complete conversion of the starting compound **1a**. When a benzene solution of lactone **2** was kept in contact with NaH at room temperature for 24 h, it was completely transformed into cyclopentanone **1b**. On the other hand, boiling the solution of cyclopentenol **la** in benzene in the presence of a catalytic amount of DBU irreversibly



Scheme 2

Method B. To a benzene (3.0 ml) solution of compound **1a** (50 mg, 0.16 mmol), DBU (~5 μl) was added, and this was boiled under inert atmosphere until the starting **1a** was consumed (TLC). The solvent was distilled off, the residue was chromatographed on SiO_2 to afford lactone **2** (38 mg, 75%) and compound **1b** (9 mg, 18%).

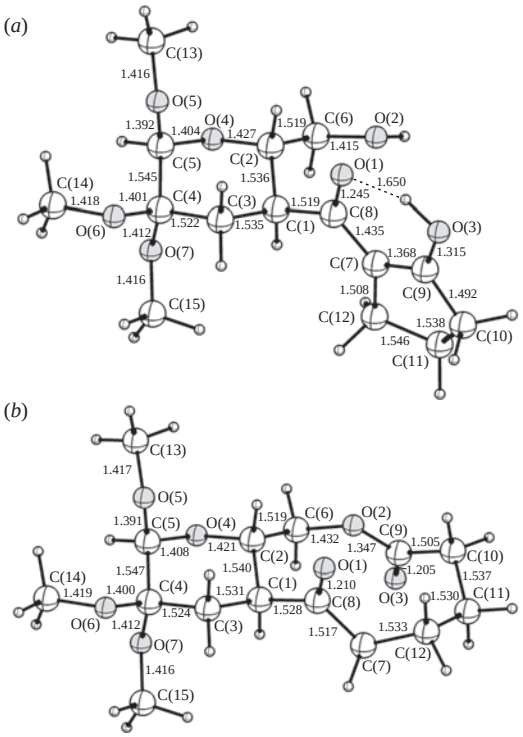
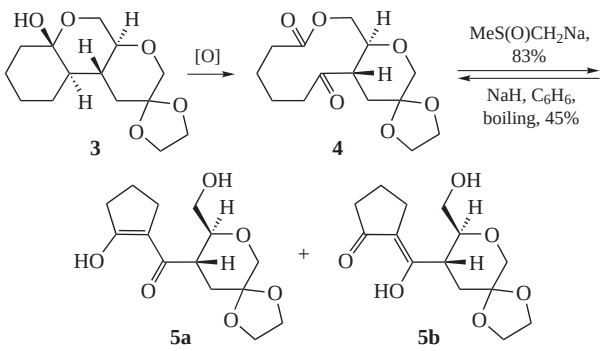


Figure 1 B97-2/6-311+G(d,p)-optimized geometry of molecular structures of compounds (*a*) **1a** and (*b*) **2**. Bond distances are given in Å.

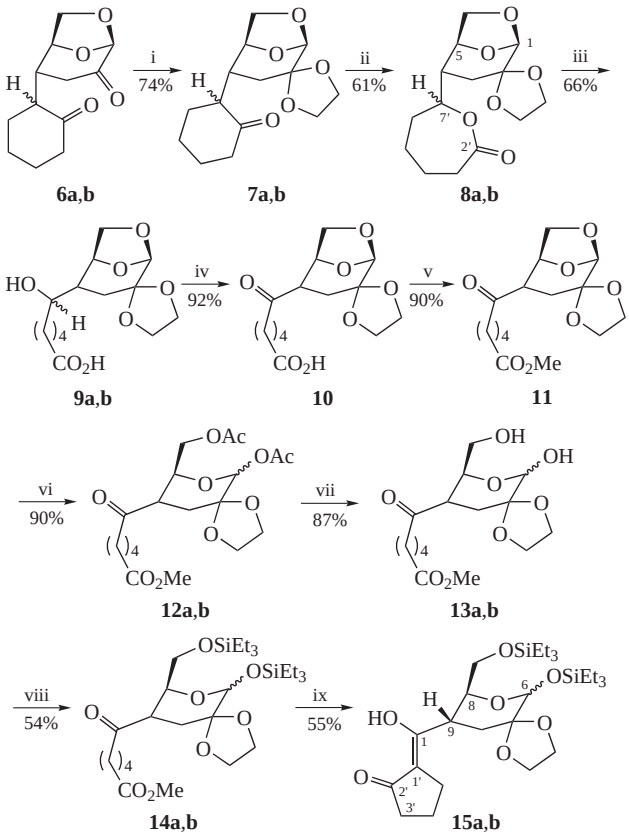
led to lactone **2** (yield 75%) and tautomer **1b** (yield 18%). The tautomer **1b** is less active since it is prone to stabilization as a conjugated base.

DFT quantum chemical calculations [B97-2/6-311+G(d,p)] were carried out to evaluate relative thermodynamic stability of compounds **1a** and **2**. In accordance with chosen theoretical approximation, enthalpy (ΔH_{298}) and Gibbs free energy (ΔG_{298}) of **1a**→**2** transformation (see Scheme 2) were found to be 39.2 and 29.0 kJ mol^{-1}, respectively. Consequently, the reverse reaction is more preferable under standard conditions. According to Figure 1, the high stability of **1a** may be caused by two factors: compound **1a** has hydrogen bond O(1)···HO(3) as well as O(3)=C(9)–C(7)=C(12) conjugation. Note that along with the thermodynamic stability of the structures relating to valleys of reactant **1a** and product **2** on the reaction potential energy surface, the influence of the intermediates forming the chemical trajectory of the reaction should be a topic of a separate study.

Protective groups slightly affect the condensation results. Under similar conditions, lactone **4** (obtained from compound **3**[4]) is converted into keto enols **5a**,**b** in a yield of 83% (Scheme 3). Retro-reaction of cyclopentenol **5a** under the action of NaH in C_6H_6 led to lactone **4** (45% yield) and 2 : 1 tautomeric mixture of **5a** and **5b** (20% total yield).



Scheme 3

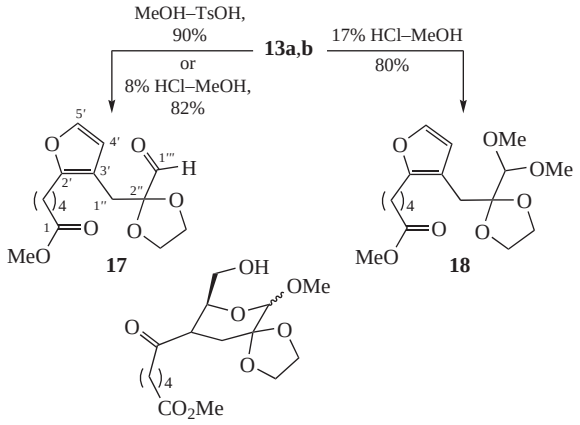


Scheme 4 *Reagents and conditions:* i, $HO(CH_2)_2OH$, $BF_3{\cdot}Et_2O$; ii, *m*-CPBA; iii, 10-camphorsulfonic acid, acetone, Δ; iv, H_2CrO_4, acetone; v, MeOH, TsOH; vi, Ac_2O, $ZnCl_2$; vii, MeOH, MeONa; viii, Et_3SiOTf, Et_3N, CH_2Cl_2; ix, NaH, C_6H_6, Δ.

Based on these results, we anticipated of finding shorter ways towards such 1,3-diketones by intramolecular transformations of the corresponding keto ester moieties at the carbohydrate residue. The good models for our purpose were obtained from available[5] diastereomeric mixture **6a**,**b** (Scheme 4). One keto group in diketones **6a**,**b** was selectively protected to give dioxolanes **7a**,**b**. Further Bayer–Villiger oxidation of the latter, opening of the lactone cycles in compounds **8a**,**b**, oxidation of the hydroxyl group to furnish keto acid **10**, and its esterification brought about keto ester **11**. The opening of the 1,6-anhydro bridge in keto ester **11** was carried out with Ac_2O in the presence of $ZnCl_2$ to afford anomers **12a**,**b**. After deacetylation and TES-protection of the hydroxyl groups, keto esters **14a**,**b** were obtained. Their boiling in benzene in the presence of NaH led to cyclopentenols **15a**,**b** in 55% yield.

Using the selective TOCSY method, all signals for protons of isomers **8a** and **8b** were assigned. The proton $H^{7'}$ resonates as a doublet-doublet at 4.76 and 4.77 ppm for isomers **8a** and **8b**, respectively. In the ^{13}C NMR spectrum, the $C^{7'}$ signals are observed at 78.27 and 78.35 ppm, while the carbonyl atoms $C^{2'}$ are manifested at 175.38 and 175.67 ppm for isomers **8a** and **8b**, respectively. The presence of the correlation peak $H^{7'}$/C=O in the HMBC spectra indicates the ester nature of lactones **8a**,**b**. The structure of enols **15a**,**b** was confirmed based on the signals for the quaternary carbons $C^{1'}$ at 110.06/109.42 ppm and C^1 at 176.17/176.74 ppm, as well as the correlations $H^{3'}/C^{1'}$, H^9/C^1 and $H^{3'}/C^{2'}$ in the HMBC spectrum. Since during the reaction the configuration of the centre C^9 would retain, the value $^3J_{9–8}$ 10.1 Hz allows us to refer the center of C^9 to the *R*-configuration.

Treatment of keto ester **11** with dimsyl sodium in DMSO[6] did not afford the Dieckmann products but caused its destruction. Other attempts comprising colloidal potassium in toluene or NaH



Scheme 5

in THF[7] proved to be equally unsuccessful. The blocking of the hydroxyl group after opening the 1,6-anhydro bridge with bulky protective groups also did not improve the efficiency of the desired transformation (*cf*. ref. 1). Most probably, the 1,6-anhydro bridge in keto ester **11** serves as a site controlling this transformation and preventing the introduction of the bulky substituent at the axial position of the preferred pyran conformation. Attempted simultaneous trans-acetalization–deacetylation of compounds **12a**,**b** with MeOH in the presence of TsOH or montmorillonite clay was unsuccessful, and the starting acetates remained unchanged.

The methoxylation of lactols **13a**,**b** with MeOH catalyzed by TsOH or HCl (8 or 17% in MeOH) gave, instead of the expected methyl acetals **16a**,**b**, furan derivatives **17** or **18** with loss of all asymmetric centers (Scheme 5). The formation of furan **18** is indicated by the characteristic signals of quaternary carbon $C^{2'}$ at 153.03 ppm and $C^{3'}$ at 112.73 ppm, as well as $C^{4'}$ at 113.36 ppm. (δ_H 6.29) and $C^{5'}$ at 139.62 ppm (δ_H 7.19). In the HMBC spectrum, the correlation peaks $H^5/C^{2'}$, $H^{1''}/C^{3'}$ are observed.

In conclusion, we revealed some factors responsible for the direct and reverse Dieckmann-type reactions in lactone **2** with the final formation of thermodynamically more stable cyclopentanes **1a**,**b**. The reverse reaction seems promising alternative access to medium-sized levoglucosenone-derived lactones. The polyfunctional chiral compounds obtained in this work may be of interest for medicinal chemistry.

Analyses were carried out on the equipment of the Center of Collective Usage ‘Chemistry’, Ufa Institute of Chemistry, Russian Academy of Sciences. The study was performed within the framework of topics AAAA-A17-117011910022-5 and AAAA-A17-117011910027-0 of the state assignment and supported by the Russian Foundation for Basic Research (grant no. 17-43-020166-p_ povolzh’e_a).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.021.

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