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Intramolecular aldol condensation of Michael adducts of levoglucosenone and cyclododecanone

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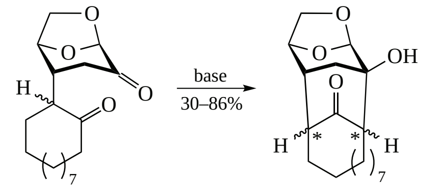
Base-promoted intramolecular aldol condensation of diastereomeric Michael adducts of levoglucosenone and cyclododecanone affords 12-hydroxy-14,20-dioxatetracyclo[9.6.1.1^{12,17}.1^{13,16}]icosan-18-one as a mixture of three diastereomers. The products thus obtained are promising for synthesizing 14-membered macrocyclic compounds, including cembranoids and their analogues.



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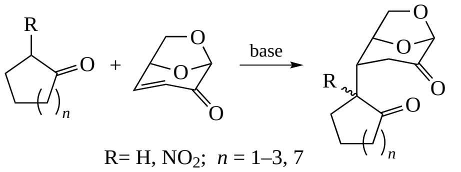
1,5-Dicarbonyl compounds of cycloalkanone series containing second carbonyl group in the side chain are capable of intramolecular aldol condensation to give bicyclic products with a ketone bridge.[1] Cleavage of the latter results in ring expansion by three carbon atoms. Building such bicyclic systems with a ketone bridge seems promising in the development of new construction of the core of natural biologically active cyclic compounds. Such systems are not always accessible by cyclization of two cycloalkanone moieties of suitable adducts because of steric restrictions. Nevertheless, these transformations are implemented in other ways, for example, by additional incorporation of some other electrophilic center.[2] The use of chiral 1,5-diketones as starting materials is important for synthesizing cyclic natural compounds. The suitable substrates for this purpose are exemplified, for instance, by the Michael adducts of levoglucosenone with cycloalkanones (Scheme 1) previously used to prepare chiral lactones with medium and large ring sizes.[3] The capabilities of intramolecular aldol cyclization of Michael adducts of levoglucosenone with a number of CH-acids having a linear structure of a 1,5-keto moiety were demonstrated for the adducts with acetyl- and pivaloylacetones, ethyl acetoacetate and 2-acetylcyclododecanone.[3,4]

In this study, we first tried to perform the intramolecular aldol condensation of the adduct of levoglucosenone with cyclohexanone **1** (Scheme 2). Unfortunately, multiple attempts to implement this reaction under various conditions failed. Interestingly, under high static pressure the intermolecular aldol condensation between two molecules of compound **1** occurred through the addition of the α-carbon atom of the cyclohexanone fragment to the keto group of the levoglucosenone moiety with the final trapping of water molecule, which afforded product **2**, a bis-semi-ketal of tetrahydropyran-2,6-diol series.

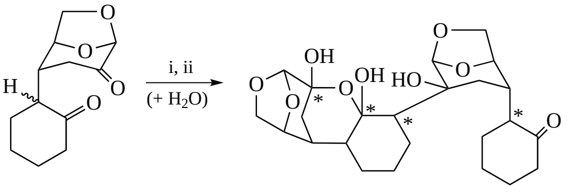


R= H, NO_2; *n* = 1–3, 7

Scheme 1 (*cf.* ref. 3).

Apparently, the realization of intramolecular aldol condensation in cyclohexanone derivative **1** is hindered by significant steric factors, the most essential ones being α,α′-diaxial addition of bulky substituent, as well as the mutual repulsion of oxygen atoms of the keto group and the pyran ring in the conformation fixed by the 1,6-anhydro bridge. These obstacles should play smaller role in cases of homologues with larger cycle size possessing higher conformational flexibility.

The intramolecular aldol condensation was then performed using diastereomeric Michael adducts of levoglucosenone with cyclododecanone **3**.[3] In fact, treatment of this substance with KOH in EtOH–H_2O for 2 h gave the target condensation product **4** in 30% yield, the reaction having been accompanied by significant resinification (Scheme 3). Crystalline compound **4** was obtained in 48% yield (59% conversion) on stirring a solution of reactant **3** in CH_2Cl_2 in the presence of tetramethylguanidine (TMG) for 2 days. Brief heating (15 min, 150–160 °C) of the diastereomers **3** in DMSO in the presence of an equimolar amount of $NaHCO_3$ afforded product **4** in 86% yield.[†]



1 **2** (single diastereomer, 17%)

Scheme 2 *Reagents and conditions*: i, DBU, PhMe, 6000 atm, 100 °C, 3 h; ii, H_2O, HCl.

[†] *12-Hydroxy-14,20-dioxatetracyclo[9.6.1.1^{12,17}.1^{13,16}]icosan-18-one* **4**. Sodium bicarbonate (0.027 g, 0.32 mmol) was added to adduct **3** (diastereomeric mixture, 0.100 g, 0.32 mmol) in DMSO (5.0 ml), and the resulting suspension was heated at 150–160 °C for 15 min until the

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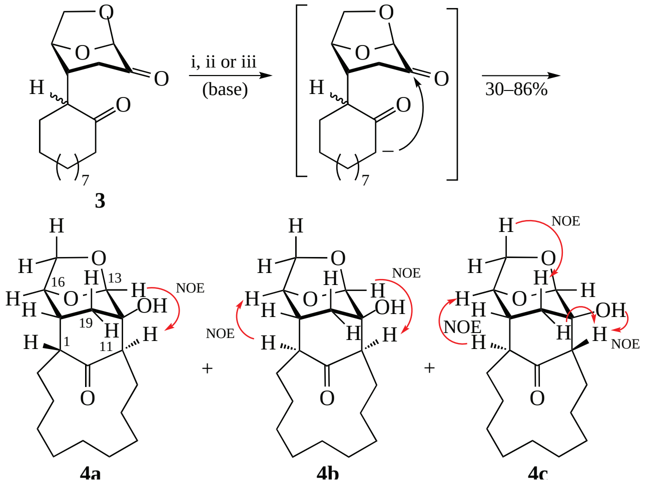

Scheme 3 *Reagents and conditions*: i, KOH, EtOH, H_2O, room temperature, 2 h (30%, **4a**/**4b**/**4c** = 3 : 2 : 1); ii, TMG (cat.), CH_2Cl_2, room temperature, 48 h (48%, **4a**/**4b**/**4c** = 2 : 1 : 1); iii, $NaHCO_3$ (1 equiv.), DMSO, 150–160 °C, 15 min (86%, **4a**/**4b**/**4c** = 2 : 1 : 1).

As a result of the reaction, three diastereomers **4a–c** were obtained of four possible ones (see Scheme 3), column chromatography having afforded **4a**,**b** mixture and individual compound **4c**. These compounds had the same mass numbers. Their structure was determined by ^{1}H and ^{13}C NMR spectroscopy using standard HHCosy, HSQC, HMBC, and NOESY two-dimensional correlation techniques (for details, see Online Supplementary Materials, Tables S2 and S3). The configuration of each diastereomer was derived from the NOESY experiment in which the diagnostic correlations were observed (see Scheme 3). The NOESY spectrum of diastereomer **4c** shows correlation peaks between the C^{1}H protons and C^{16}H, C^{11}H and C^{19}H$^{\beta}$, which supports the *S*-configuration of the C^1 and C^{11} centers and the *R*-configuration of the C^{12} atom. The existence of the Overhauser effect between C^{11}H and C^{13}H in both diastereomers **4a**,**b** allows one to assign the C^{11} center to the *R*-configuration whereas this effect is not observed in diastereomer **4c**. Since the configuration of the C^{16} center does not change in the reaction, the NOE coupling between C^{1}H and C^{16}H makes it possible to assign the C^1 center to the *S*-configuration in diastereomer **4b** (Scheme 3). Since the firmly bound atoms C^{13}, C^{17} and C^{16} of the bicyclic system of diastereomeric Michael adducts **3** are not involved in the reaction, they retain their absolute configuration in products **4a**,**b**,**c**.

Most probably, like in the majority of levoglucosenone reactions, the ring closure is controlled by the 1,6-anhydro bridge and occurs on the α-side of the keto group of levoglucosenone, as it is confirmed by the stereochemistry of the C^{12} center in all the three diastereomers **4a–c**. It should be noted that, unlike Michael adducts of levoglucosenone with cyclohexanone **1**, the homologous adducts with cyclopentanone or cycloheptanone did not give carbocyclization products under these conditions. Attempts to perform a similar reaction with adducts containing a nitro or ethoxycarbonyl groups at the α-position with respect to the keto group of the cycloalkanone moiety were accompanied by a retro Michael decay.

In conclusion, the intramolecular aldol condensation of diastereomeric Michael adducts of levoglucosenone with cyclododecanone by treatment with various bases has been developed. The diastereomers **4a–c** thus obtained seem promising materials for synthesizing cembranoids and their analogues[5] for the studies on the structure–activity relationship.

The authors are grateful to the Circa Group for providing industrial grade levoglucosenone. The study was performed within the subject no. AAAA-A20-120012090028-3 of the state assignment. NMR spectra were recorded using the equipment of the Center for Collaborative Use of Scientific Equipment ‘Chemistry’ and the Regional Center for Collaborative Use of Unique Equipment ‘Agidel’ of the Ufa Institute of Chemistry, Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.07.018.

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starting compound disappeared (TLC monitoring). The mixture was then treated with brine, and the products were extracted with Et_2O (3 × 7.0 ml). The extract was dried with $MgSO_4$ and concentrated on a rotary evaporator, the **4a**/**4b**/**4c** ratio in a crude material was 2 : 1 : 1. The residue was subjected to column chromatography (SiO_2) to afford individual diastereomer **4c** and **4a**,**b** mixture, white crystals; total yield, 0.086 g (86%).

(1*S*,11*S*,12*R*,13*R*,16*S*,17*S*)-**4C**, mp 101 °C, $[\alpha]_D^{20}$ –48.1° (*c* 1, $CHCl_3$), R_f 0.18 (EtOAc–light petroleum, 1 : 1). (1*RS*,11*R*,12*R*,13*R*,16*S*,17*S*)-**4a**,**b**, mp 151 °C, $[\alpha]_D^{20}$ –52.8° (*c* 1, $CHCl_3$), R_f 0.17 (EtOAc–light petroleum, 1 : 1).