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A convenient synthesis of enantiopure (4a*S*,7a*R*)-1,4,4a,7a-tetrahydrocyclopenta[*c*]pyran-3,7-dione

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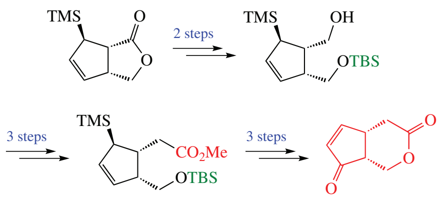
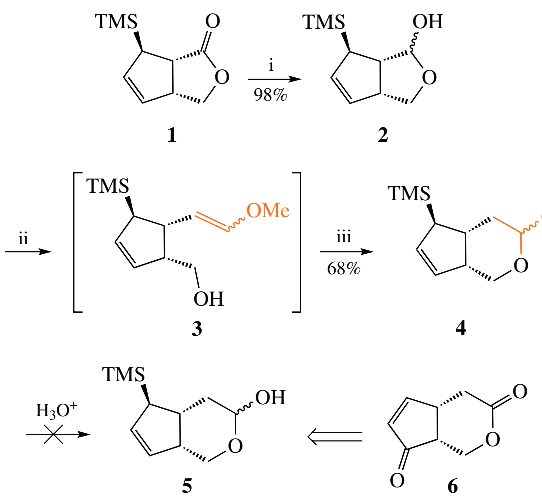
The title compound, as the new chiral building block for bioactive cyclopentenones, was prepared in 8 steps with 15% overall yield. The key steps involve selective homologation in intermediate [(1*S*,2*R*,5*R*)-5-trimethysilylcyclopent-3-ene-1,2-diyl]dimethanol by regioselective silylation followed by oxidation and the Wittig reaction.



Keywords: bicyclic δ-lactones, cyclopentenones, bioactive compounds, cyclopentanoids, asymmetric synthesis, lactonization, epoxidation, allylsilanes, silylation, ion-exchange resins.

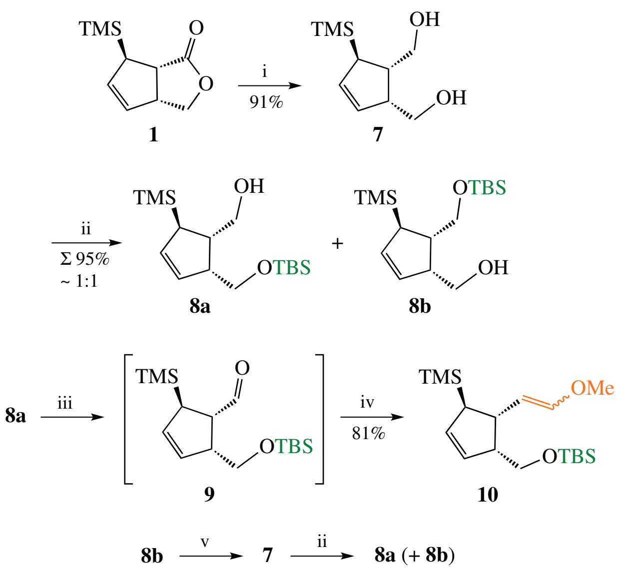
Bicyclic δ-lactones are the fragmentary parts of a number of biologically active compounds, such as jasmonic acid,[1] (+)-coronatine,[2] harringtonolide.[3,4] Some of their derivatives and monocyclic synthetic equivalents are used for the preparation of anticancer cross-conjugated cyclopentenone prostaglandins,[5–7] as a bioisosteric analogues of cytotoxic exomethylidene-cyclopentenone[8] and cyclic precursor of homosarcomycin.[9] Surprisingly, syntheses on racemic or scalemic (4a*S*,7a*R*)-1,4,4a,7a-tetrahydrocyclopenta[*c*]pyran-3,7-dione **6** (Scheme 1), a promising multifunctional bicyclic keto lactone, are lacking in the literature.

In attempted access to enone lactone **6**, we started with previously described compound **1**[10] (see Scheme 1). Herein, the formal task was the regioselective introduction of methylene unit into the lactone part of compound **1**. The first option for homologation was the Wittig olefination of lactol **2**[11] with ylide $Ph_3P{=}CHOMe$. However, the primary olefination product **3** underwent intramolecular cyclization into stable methyl acetal **4** in the course of work up and chromatography purification on SiO_2. The attempted acid hydrolysis of acetal function in compound **4** caused simultaneous protodesilylation of the TMS-group.

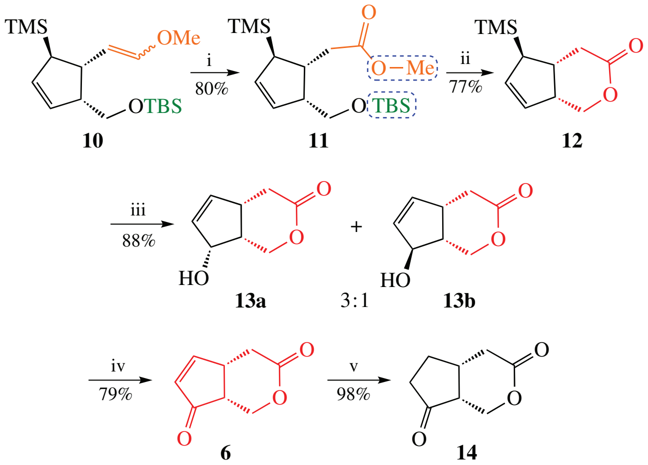


Scheme 1 *Reagents and conditions*: i, DIBAL–H, CH_2Cl_2, –78 °C; ii, $[Ph_3PCH_2OMe]^+Cl^-$, NaHMDS, PhMe, –78 °C; iii, SiO_2.

As an alternative pathway, conversion of compound **1** into enol ether **10** (Scheme 2) through the step of monosilyl ether **8a** was chosen. Lactone **1** was reduced into diol **7** and silylated with 1.0 equiv. of TBSCl to give a 1 : 1 mixture of silyl ethers **8a**,**b** which were easily separated on SiO_2. Regioisomer **8b** can be transformed into **8a** *via* repeating the cycle through diol **7**.[11] Homologation in hydroxymethyl moiety of compound **8a** was carried out through aldehyde **9** that was subjected to olefination with ylide $Ph_3P{=}CHOMe$ to produce enol ether **10** (*E*/*Z* = 5 : 1) (see Scheme 2).



Scheme 2 *Reagents and conditions*: i, $LiAlH_4$, THF, 0 °C; ii, TBSCl (1.0 equiv.), imidazole (0.9 equiv.), CH_2Cl_2, room temperature, then column chromatography; iii, DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N; iv, $[Ph_3PCH_2OMe]^+Cl^-$, NaHMDS, PhMe, –78 °C; v, Dowex/Amberlyst, MeOH.



Scheme 3 *Reagents and conditions*: i, PCC, SiO_2, $NaHCO_3$, CH_2Cl_2, 0 → 20 °C; ii, Dowex/Amberlyst, MeOH, room temperature; iii, Oxone, $NaHCO_3$, acetone, then column chromatography; iv, Jones reagent, 0 °C; v, H_2, Pd/C, MeOH.

In the next step, enol ether **10** was oxidized to ether **11** with pyridinium chlorochromate (PCC) in the presence of SiO_2 (100% weight of enol ether) and $NaHCO_3$ (Scheme 3). The addition of silica gel allows one to absorb the reduction products of the oxidant, which greatly facilitates the work up of the reaction mixture. The use of PDC or the Jones reagent at this step was unsuccessful. Subsequent removal of the TBS-protecting group in ether **11** was carried out using combination of an ion exchange resins Dowex and Amberlyst (1 : 1) in methanol. Under these conditions, lactone **12** was obtained a good yield. The next transformation **12** → **13** can be regarded as an example of employing the chemistry of allylsilanes for creating a fragment of allylic alcohol along with a transfer on the allylic part. This reaction has been performed through epoxidation of olefinic lactone **12**, which caused the *in situ* Peterson-type fragmentation affording epimeric allylic alcohols **13a**,**b**.[12]

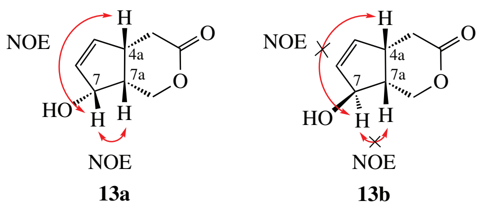


Figure 1 NOE-interactions in alcohols **13a** and **13b**.

The ascription of the spatial arrangement of the C^7 protons in compounds **13a** and **13b** was based on the NOE-interaction between C^7H with C^{7a}H and C^7H with C^{4a}H in the allylic alcohol **13a** and the absence of such phenomenon in alcohol **13b** (Figure 1).

At the final stage, oxidation of allylic alcohols **13a**,**b** into enone **6**, individually or in mixture, was performed, the highest yields having been achieved using Jones reagent (see Scheme 3). Subsequent hydrogenation of the double bond in compound **6** yielded cyclic derivative of homosarcomycin **14**.

In conclusion, we have accomplished the synthesis of the new bicyclic δ-lactone **6** as a useful platform for obtaining various bioactive compounds, such as cyclic derivative of homosarcomycin **14**. The key stage of this approach is the selective homologation of the lactone part in cyclopentabutanolide **1**.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.01.003.

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