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Synthetically attractive chiral cyclopentenone building blocks conjugated with tetrahydro- and 2-oxotetrahydrofurans

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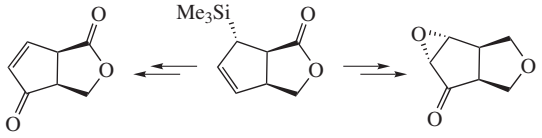
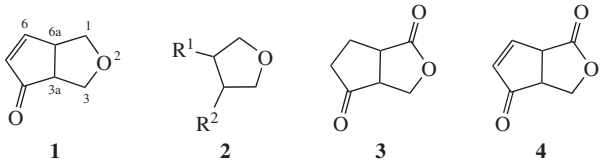
Synthetically useful chiral building blocks (3a*S*,6a*R*)-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one and (3a*S*,6a*R*)-3a,6a-dihydro-1*H*-cyclopenta[*c*]furan-1,4(3*H*)-dione have been synthesized *via* a key allylsilane–allyl alcohol fragmentation pathway using (3a*S*,6*S*,6a*R*)-6-(trimethylsilyl)-3,3a,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-1-one as an illustrative example.



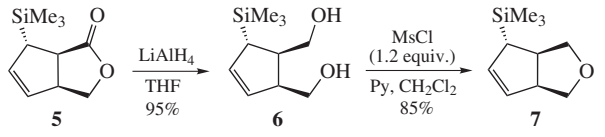
The cyclopentenone block **1** in 3a,6a-coupling with the THF ring is a poorly studied substructure in the series of tetrahydrofuryl-containing bi- and polycycles.[1–3] The synthesis of racemic compound **1** from 2,5-dihydrofuran and an acetylenic complex of cobalt hexacarbonyl *via* the Pauson–Khand reaction was reported by Billington.[2]

Regarding to the prospective synthetic applications of compound **1**, oxidative cleavage of its double bond to give 3,4-disubstituted tetrahydrofurans **2** or oxidation of lactone **3**, a saturated analogue of **1**, look promising. It should also be noted that cyclopentenone **1** and corresponding building blocks **2** and **3** are of interest as synthons only in the chiral version. The 3,4-disubstituted THF moiety is a part of the structures in a broad range of natural compounds: polyether antibiotic Ionomycin,[4,5] Lasalocid[6] and Nonactin[7] ionophores, polyketides of acetogenin series,[8] *etc*.[9] Chiral lactone **3** was used in a synthesis of cyclosarcomicin.[10] The synthetic potential of the cyclopentene block in compound **4** is even more obvious and significant. It is a chemorational key precursor in approaches to cyclopentanone antibiotics and prostaglandins,[11] carbanucleosides,[12] *etc*.[13]



1 **2** **3** **4**

In this work, we accomplished the syntheses of chiral compounds (–)-(3a*S*,6a*R*)-**1** and (–)-(3a*S*,6a*R*)-**4** from (+)-lactone **5**.[14] Initially, (+)-(3a*S*,6*R*,6a*R*)-**5** was reduced with LAH in THF to give compound **6**.[15] Numerous attempts to perform intramolecular cyclization of diol **6** under acid catalysis conditions using concentrated H_2SO_4, $Ce(NH_4)_2(NO_3)_6$ in MeCN, Dowex® and Amberlyst® ion exchange resins did not provide acceptable results. At the same time, THF derivative (3a*R*,4*S*,6a*S*)-**7** was obtained† under standard conditions of alcohol mesylation at 0 °C (Scheme 1).

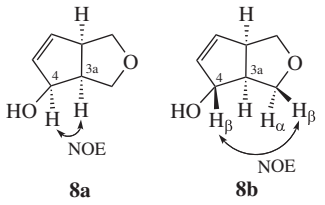


5 **6** **7**

Scheme 1

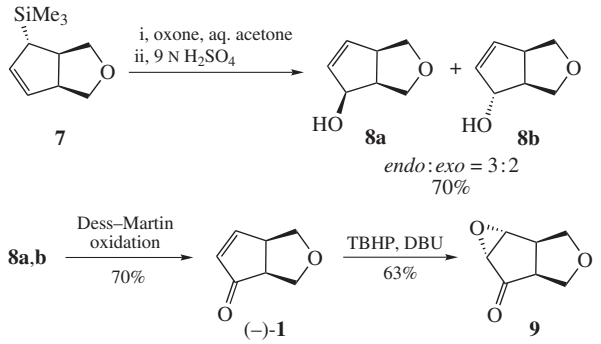
We intended to perform the subsequent transformations of compound **7** towards target product (–)-**1** using the potential of its allylsilane moiety, by converting **7** to TMS-epoxides and engaging them in Peterson-type fragmentation reactions to obtain the corresponding allyl alcohols. The epoxidation of **7** with mCPBA failed to provide the epoxide for subsequent conversion. However, the use of dimethyldioxirane for epoxidation of **7** allowed us to obtain in one step a mixture of allyl alcohols **8a**,**b** at a ratio of *endo*- and *exo*-isomers of 3 : 2 (Scheme 2).

The stereochemical assignments of diastereomeric alcohols **8a** and **8b** were based on NOE data, where strong C^4–H and



8a **8b**

† *Trimethyl[(3a*R*,4*S*,6a*S*)-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-1-yl]silane* **7**. Pyridine (0.12 ml, 1.53 mmol) and mesyl chloride (0.05 ml, 0.61 mmol) were added to a solution of diol **6** (0.1 g, 0.51 mmol) in anhydrous CH_2Cl_2 (10 ml) at 0 °C. The mixture was stirred at this temperature for 8 h, and then refluxed for 1 h (TLC monitoring). The mixture was cooled to room temperature, water was added, and the product was extracted with EtOAc (3×10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on SiO_2 (light petroleum–ethyl acetate, 5 : 1). The product **7** was isolated as transparent viscous oil in 85% yield. R_f 0.5; $[\alpha]_D^{20}$ +120.2 (*c* 0.80, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.66 (dt, 1H, CH=C*H*CHSiMe_3, *J* 2.13, 5.5 Hz), 5.43 (dt, 1H, C*H*=CHCHSiMe_3, *J* 2.14, 5.5 Hz), 3.93 (t, 1H, C^1H_2O, *J* 8.24 Hz), 3.85 (t, 1H, C^1H_2O, *J* 8.24 Hz), 3.60 (dd, 1H, C^3H_2O, *J* 3.36, 8.54 Hz), 3.38 (dd, 1H, C^3H_2O, *J* 5.80, 8.54 Hz), 3.35–3.29 (m, 1H, C^{6a}H), 2.70 (qd, 1H, C^{3a}H, *J* 2.14, 6.10 Hz), 1.74 (quintet, 1H, C^4HO, *J* 2.14 Hz), –0.01 (s, 9H, Me_3Si). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 132.43, 128.56, 76.91, 73.18, 51.99, 43.69, 41.01, –3.32. IR (ν/cm^{-1}): 2954, 2927, 2848, 1248, 1085, 1063, 1046, 973, 957, 921, 839, 746, 698. Found (%): C, 65.70; H, 9.78. Calc. for $C_{10}H_{18}OSi$ (%): C, 65.93; H, 9.89.

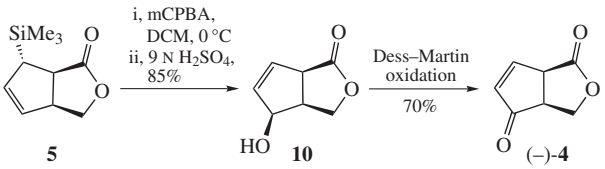


Scheme 2

C^{3a}–H couplings were observed in the case of *endo*-isomer **8a**, and between $C^{4\beta}$–H and $C^{3\beta}$–H for *exo*-**8b**, respectively. The vicinal coupling constants of the protons at C^4 and C^{3a} were also characteristic: $^3J_{4,3a}$ 7.8 Hz for **8a** and $^3J_{4,3a}$ 2.0 Hz for **8b**.

At the final step, the oxidation of individual allyl alcohols **8a** and **8b** or their mixture with the Dess–Martin reagent provided the target enone (–)-**1** in a good yield (see Scheme 2).‡ Epoxidation of this enone with *tert*-butyl hydroperoxide catalyzed by DBU gave epoxy derivative **9**, a precursor for periodate cleavage on the synthetic route to compound **2**.

The approaches to chiral cyclopentanone lactone **4** were also based on allylsilane **5**. Epoxidation of substrate **5** in the presence of mCPBA followed by treatment with 9 N H_2SO_4 in THF resulted in allyl alcohol **10**, whose oxidation with Dess–Martin reagent under mild conditions provided (–)-lactone **4** (Scheme 3).‡



Scheme 3

Therefore, we have reported the syntheses of the two novel chiral cyclopentenones, (–)-(3a*S*,6a*R*)-**1** and (–)-(3a*S*,6a*R*)-**4**, from the previously suggested bicyclic allylsilane **5**. The obtained compounds contain the coupled tetrahydro- and 2-oxotetrahydrofuran rings, respectively. Taking the availability of starting reactant **5** in both enantiomeric forms into account, one can state that the proposed synthetic pathways are practically applicable to the preparation of enantiomers of the above target structures.

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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.2018.07.006.

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‡ For syntheses and characteristics of compounds **1**, **4**, **8a**, **8b**, **9** and **10**, see Online Supplementary Materials.

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