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Synthesis of (4*S*,5*S*)-4,5-*O*-isopropylidene-cyclopent-2-ene-1-one via the intramolecular Reformatsky reaction

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ABSTRACT

Isomeric mixtures of bromo- and iodohydrins produced via bromohydroxylation and iodohydroxylation of *exo*-methylene derivative **2** undergo an intramolecular aldol cyclization–dehydration sequence under Reformatsky reaction conditions to give cyclopentenone **1**.

Chiral cyclopentenone **1**, its enantiomer, and related structures are used widely in the synthesis of cyclopentenone antibiotics,[1] prostaglandins,[2] carbanucleosides,[3] etc.[4] A number of methods have been reported for the synthesis of compound **1**, for example, early approaches using cyclopentadiene[5] via (±)-**1** with further optical resolution using Johnson's sulfoximine method,[6] Hudlicky's microbiological approach[7] involving toluene oxidation to afford the chiral *cis*-toluenediol. The most effective approaches to **1**, employing natural chiral pool compounds, were based on the reaction of ribonolactone and its derivatives with dimethylmethylphosphonate anions,[8,9] $LiAlH(OBu)_3$,[10] etc.[11] An extremely convenient and practical approach to **1** and related structures is based on intramolecular cyclization of the corresponding α,ω-diolefins derived from sugars. The cyclization was promoted with Grubbs'[12–16] and Schrock[17] catalysts (RCM).

Herewith we report a new and practical method for the synthesis of cyclopentenone **1**. The approach is based on the use of an intramolecular Reformatsky aldol cyclization–dehydration procedure of 1,4-dioxo compounds derived from D-ribose. The initial *exo*-methylene derivative **2**, easily prepared from D-ribose, was transformed via bromohydroxylation (NBS–H_2O) to a mixture of isomeric bromohydrins **3** and **4**.[18] Treatment of this mixture with NaI and Zn powder led to a mixture of cyclopentenone **1**[19] and methoxypyranoside **5** in the ratio 3.2:1 (HPLC) (Scheme 1).[20] The yield of the target product **1**[21] was 40% (calculated based on **2**).

The formation of minor bicyclic compound **5**[22] in this reaction is probably the result of a Williamson type of intramolecular ether-formation of an acyclic form of hemiacetal **3** followed by HBr elimination. The same carbacyclization of separated **3** also led to a mixture of **1** and **5** in the ratio 1.4:1 (HPLC). Under the same conditions **4** gave cyclopentenone **1** only, in a yield of 43%. Attempts to use $CrCl_2$ and SmI_2 instead of Zn in this reaction were unsuccessful.

The preparation of iodo derivatives **6** and **7** considerably improved the transformation of **2**→**1**. Iodohydrins **6** and **7** (Scheme 2) were generated from **2** using 1.5 equiv of I_2 in THF–H_2O (3:1). The reaction proceeded rapidly and in quantitative yield. The mixture of **6** and **7** was subjected to the Reformatsky reaction with Zn in refluxing benzene.[23] When all of the iodohydrins **6** and **7** had reacted (TLC) the reaction was worked up and the residue was purified by column chromatography on SiO_2. Compounds **1** and **8** were obtained in yields of 50% and 8%, respectively.

A possible mechanism for the formation of **8** involves cross-aldol condensation between ketol **10**, a precursor of enone **1**, and lactol **7** followed by elimination of H_2O. The structure of **8** was identified from NOE and COSY studies of acetate **9**,[24] obtained by acylation of **8** (Ac_2O, Py). The location of the cyclic furanyl fragment at C-2 of the enone unit in **8** and **9** was confirmed by the coupling constant $^4J_{3,1'} = 1.9$ Hz between olefin protons H-3 and H-1′. The vicinal constant $^3J_{1'2'} = 4.0$ Hz indicates on the cis-orientation of protons H-1′ and H-2′ and consequently on the cis-orientation of cyclic fragments. The observed NOE between protons H-1′ and H-2′ ($\eta = 4.3\%$) also confirms their cis-orientation. The arrangement of the CH_2I- and AcO-groups was proposed in accordance with the NOE ($\eta = 1.9\%$) observed between the methylene protons of the

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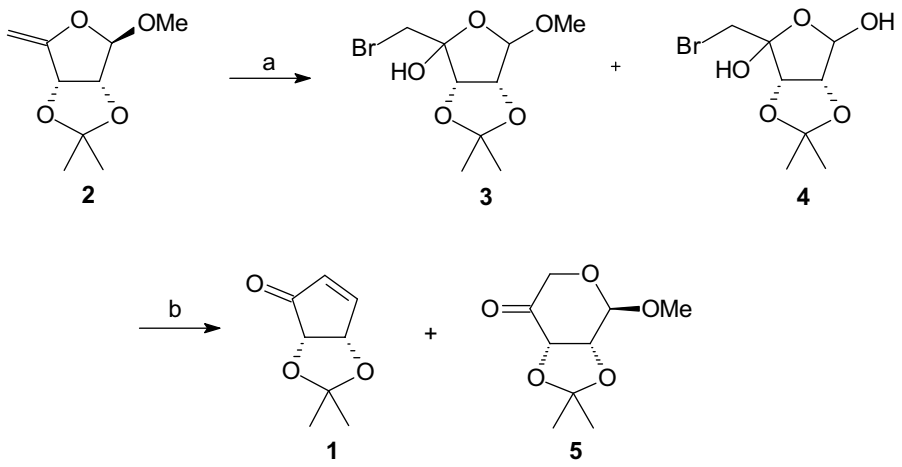
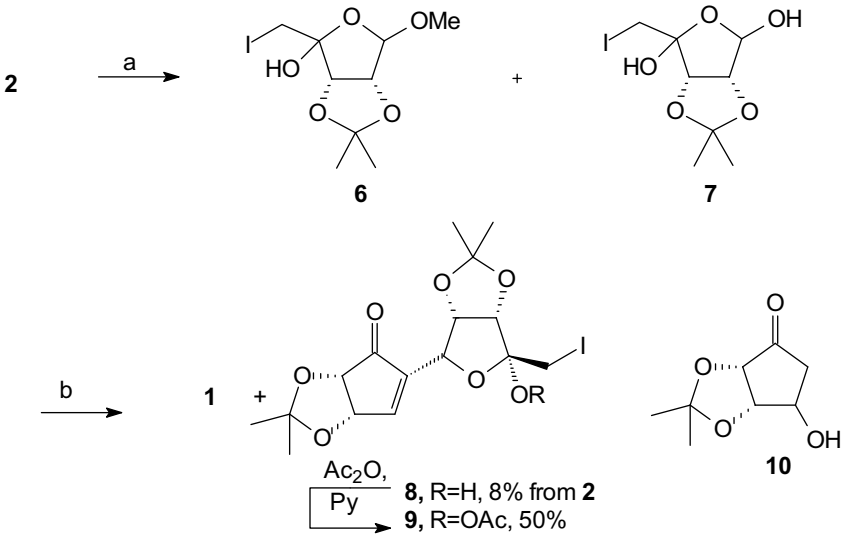


Scheme 1. Synthesis of cyclopentenone **1** via bromohydrins **3** and **4**. Reagents and conditions: (a) 1.2 equiv NBS, THF–H_2O (3:1), 20 °C, 5 min (98%); (b) 1.3 equiv NaI, 2.3 equiv Zn, THF, Δ, 2 h (40% from **2**).



Scheme 2. Synthesis of cyclopentenone **1** via iodohydrins **6** and **7**. Reagents and conditions: (a) 1.5 equiv I_2, THF–H_2O (3:1), 20 °C, 5 min (quant.); (b) 2.3 equiv Zn, C_6H_6, Δ, 3 h (50% from **2**).

CH_2I- group and proton H-3′. The NOE of **9** revealed the interactions as shown in Figure 1, which clearly confirmed the assigned structure.

The principal advantages of using **2** as starting material (easily prepared in three steps from D-ribose[18]) were the use of inexpensive and available reagents, and mild and simple reaction conditions for the transformation to **1**. The synthetic protocol avoids the use of any explosive and inflammable materials (such as *n*-BuLi and O_3), as well as expensive organometallics (Ru-catalysts) or toxic organo-phosphorous compounds. In addition, the by-products **5** and **8** are of interest as novel chiral synthetic blocks.

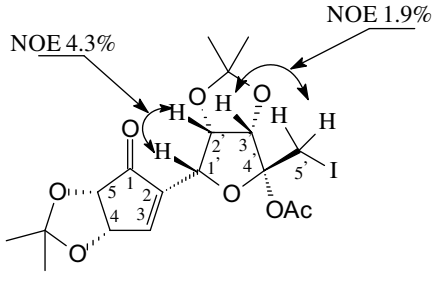


Figure 1. NOE correlations in **9**.

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20. *Preparation of compound* **1** *by intramolecular cyclization of bromohydrins* **3** *and* **4**: To a stirred solution of bromohydrins **3** and **4** (0.085 g) in dry THF (8 mL) was added NaI (0.057 g, 0.39 mmol) under an argon atmosphere. The mixture was stirred for 10 min, and then Zn powder (0.046 g, 0.69 mmol) was added. The mixture was stirred under reflux for 2 h, then filtered and concentrated. The residue was separated by column chromatography on silica gel using petroleum ether–ethyl acetate (95:5) as the eluent to give cyclopentenone **1** (0.019 g, 40% from **2**) and methoxypyranoside **5** (0.011 g, 13% from **2**).
21. *Compound* **1**: White crystal; mp 66–67 °C (lit.[19] 68.5–69.5 °C); $[\alpha]_D^{20}$ +66.3 (*c* 1.0, $CHCl_3$) [lit.[19] +69.1 (*c* 1.98, $CHCl_3$)]; IR (Nujol) ν 1720, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.42 (s, 6H, CH_3), 4.48 (d, $^3J_{5,4}$ = 5.5 Hz, 1H, H^5), 5.27 (dd, $^3J_{4,3}$ = 2.2, $^3J_{4,5}$ = 5.5 Hz, 1H, H^4), 6.22 (d, $^3J_{2,3}$ = 5.9 Hz, 1H, H^2), 7.10 (dd, $^3J_{3,4}$ = 2.2, $^3J_{3,2}$ = 5.9 Hz, 1H, H^3); ^{13}C (75 MHz, $CDCl_3$), δ 26.33 (Me), 27.59 (Me), 76.69 (C^2), 78.78 (C^3), 115.69 (C), 134.49 (C^5), 159.83 (C^4), 203.17 (C^1). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54%. Found: C, 62.28; H, 6.59%.
22. *Compound* **5**: Colorless oil; $[\alpha]_D^{20}$ −3.94 (0.9, $CHCl_3$); IR (Nujol) ν 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.38 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 4.11 (d, ^2J = 16.8 Hz, 1H, CH_2O), 4.20 (d, ^2J = 16.8 Hz, 1H, CH_2O), 4.41 (m 2H), 4.78 (br s, 1H); ^{13}C (75 MHz, $CDCl_3$), δ 25.3 (CH_3), 26.6 (CH_3), 56.1 (OCH_3), 65.7 (C^6), 75.27 (C^2), 77.57 (C^3), 99.93 (C^4), 111.9 (C), 203.2 (C^1); MS *m/z:* M^+ (not observed), 187 (21%, $M-CH_3)^+$, 171 (3%, $M-OCH_2I)^+$, 144 (32%, $M-CH_3-COCH_3)^+$, 113 [100%, $M-OC(CH_3)_2-CH_3$], 85 [72%, $M-OC(CH_3)_2-OCOCH_3$], 59 (21%, CH_3OCO), 43 (91%, CH_3CO). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98%. Found: C, 53.38; H, 7.09%.
23. *Preparation of compound* **1** *by intramolecular cyclization of iodohydrins* **6** *and* **7**: (a) To a stirred solution of enol-ether **2** (0.20 g, 1.07 mmol) in a mixture of THF–H_2O (3:1, 8 mL) was added iodine (0.35 g, 1.40 mmol). The mixture was stirred for 5 min (TLC), then the solvent was removed under vacuum and the product was extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated solution of $Na_2S_2O_3$, brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel column using petroleum ether–ethyl acetate (95:5→7:3) as a eluent gave a mixture of methoxy- and oxy-iodohydrins **6** and **7** (0.29 g). (b) To a stirred solution of a mixture of iodohydrins **6** and **7** (0.29 g) in dry benzene (8 mL) was added Zn powder (0.17 g, 2.61 mmol) under an argon atmosphere. The reaction mixture was stirred for 2.5 h under reflux, then filtered and the filtrate was concentrated under vacuum. The product was purified by column chromatography on silica gel (CH_2Cl_2) to give cyclopentenone **1** (0.083 g, 50% from **2**) and dimeric compound **8** (0.038 g, 8% from **2**).
24. *Compound* **9**: $[\alpha]_D^{20}$ −59.9 (1.0, $CHCl_3$); IR (Nujol) ν 1730, 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.25 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.90 (d, ^2J = 11.1 Hz, 1H, CH_2I), 3.97 (d, ^2J = 11.1 Hz, 1H, CH_2I), 4.54 (d, $^3J_{5,4}$ = 5.4 Hz, 1H, H^5), 4.90 (m, 1H, H^4), 4.93 (d, $^3J_{3',2'}$ = 5.8 Hz, 1H, $H^{3'}$), 5.11 (dd, $^3J_{2',3'}$ = 5.8, $^3J_{2',1'}$ = 4.1 Hz, 1H, $H^{2'}$), 5.25 (m, 1H, $H^{1'}$), 7.53 (br s, 1H^3); ^{13}C (75 MHz, $CDCl_3$), δ 14.17 (CH_2I), 21.69 (CH_3), 24.61 (CH_3), 25.04 (CH_3), 27.11 (CH_3), 27.66 (CH_3), 76.95 (C^4), 77.35 ($C^{3'}$), 80.17 ($C^{2'}$), 83.75 (C^5), 109.14 ($C^{1'}$), 113.62 (C), 115.55 (C), 141.78 (C^2), 155.44 (C^3), 169.26 (C=O), 200.96 (C^1); MS *m/z:* M^+ (not observed), 479 (68.5%, $M-CH_3)^+$, 434 (100%, $M-AcOH)^+$, 367 (72%, $M-I)^+$. Anal. Calcd for $C_{18}H_{23}IO_8$: C, 43.74; H, 4.69; I, 25.67%. Found: C, 43.59; H, 4.80; I, 25.81%.