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Synthesis of chiral hydroxylated cyclopentanones and cyclopentanes

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Abstract—A method for the synthesis of enantiomeric 1,3-dihydroxy and 2,3-dihydroxy cyclopentanones, starting from a commercially available 3-methyl-cyclopentane-1,2-dione **1**, is described. Dione **1** was subjected to asymmetric 3-hydroxylation to afford 3-methyl-3-hydroxy-1,2-dione **2**. The carbonyl groups in **2** were selectively differentiated by converting them either in dimethylacetal **5** or acetonide **6**. Stereoselective reduction of those acetals by using $NaBH_4$ afforded chiral methyl 1,2-dihydroxy cyclopentanone **9** and 1,3-dihydroxy cyclopentanone **10**, respectively. The diols obtained were further converted to the corresponding diastereomeric triols **11**–**13** by hydride reduction.

1. Introduction

The chiral multihydroxylated cyclopentane structure unit is present in various bioactive compounds, such as prostaglandins,[1,2] neurokinin-1,[3] glycosidase inhibitors[4] and natural lipid analogues.[5] These compounds are most widely used as building blocks in the synthesis of carbocyclic nucleoside analogues, which exhibit activity against a variety of diseases, for example, HIV, HSV, cancer and hepatitis.[6–9]

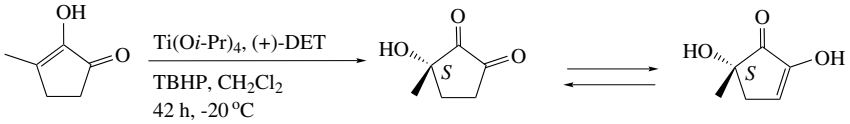
Many synthetic methods for the synthesis of polyhydroxy cyclopentanes and cyclopentanones rely on natural chiral compounds[7,10,11] or enzymatic processes.[12,13] Only a few examples of asymmetric synthesis of these compounds are described in the literature (e.g., Refs. 14 and 15).

In our laboratory, a method for the asymmetric oxidation of 3-alkyl-1,2-diketones **1** with Ti(O*i*Pr)$_4$-tartaric ester complex affording 3-hydroxylated 3-alkyl diketones **2** in high enantiomeric purity and with defined absolute configuration has recently been developed (Scheme 1).[16] Herein, we report our results of synthesizing different chiral dihydroxy cyclopentanones **9** and **10**, and cyclopentanetriols **11**–**13** starting from diketone **2**. The approach is based on differentiating the 1- and 2-oxo groups in hydroxylated diketone **2** via the formation of different types of acetals.

2. Results and discussion

2.1. Differentiation of C-1 and C-2 carbonyl groups

The starting diketone **2** is isolated from the reaction mixture of the asymmetric oxidation of 3-methyl-1,2-cyclopentanedione with a Ti(O*i*Pr)$_4$-tartaric ester complex



1 **2** **2a**

Scheme 1. Asymmetric oxidation with Ti(O*i*Pr)$_4$-tartaric ester complex.

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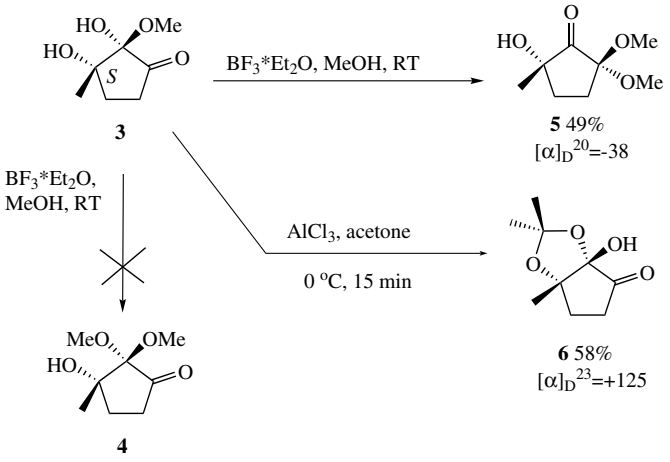
usually in a stable hemiacetal form **3**. In order to obtain a 1,3-dihydroxy compound we first made an attempt to reduce **3** directly with $NaBH_4$. However, from these experiments, a complex mixture of diols and triols in low total yield together with some amount of unreacted starting material was obtained. This prompted us to look for a more stable carbonyl protecting group. Also, we expected that using distinct protecting groups it would be possible to differentiate the carbonyl functions at C-1 and C-2 in diketone **2**.

To convert hemiacetal **3** to acetal **4**, first we used ordinary reaction conditions for acetalization (catalytic amount of *p*-TsOH and MeOH). However, our attempts failed even when up to 2 equiv of the catalyst were used. Surprisingly enough, when 0.5 equiv of boron trifluoride etherate with MeOH were used, hemiacetal **3** converted to the methyl acetal **5** in a 49% yield (the carbonyl group at C-1 was protected and the group at C-2 free for further transformations). Increasing the amount of Lewis acid to 1 equiv did not improve the yield, instead, the yield decreased considerably (17%) (Scheme 2).



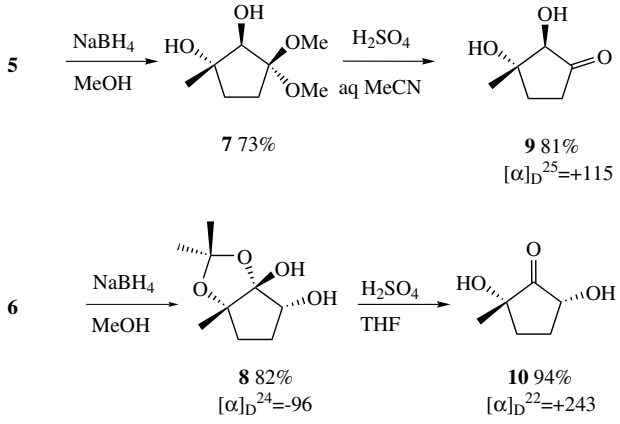
Scheme 2. Differentiation of C-1 and C-2-carbonyl groups.

In order to protect the C-2 carbonyl group, we selected the transformation of hemiacetal **3** to acetonide **6**. Under typical conditions,[17] when the substrate was refluxed in a solvent (usually toluene or benzene) in the presence of acid catalyst (*p*-TsOH, H_2SO_4) and 2,2-dimethoxypropane, the yield of **6** was low and acetalization was accompanied by side reactions (the elimination of tertiary hydroxyl group, deacetalization of hemiacetal **3** and formation of ketoenol **2a**). Also, using acetone or 2-methoxypropene as a reagent and/or applying lower reaction temperature (from rt to 60 °C) and long reaction times, resulted in acetonide **6** only but in low yield (13–32%). Neither was the change of a Brønsted acid to a Lewis acid ($BF_3{\cdot}Et_2O$) successful. Finally, using the procedure proposed by Lal et al.[18] (3 equiv of $AlCl_3$ in a dry 1:1 mixture of acetone and ether), we obtained acetonide **6** in an acceptable yield (58%). According to that procedure we obtained the intermediate **6** with C-2 carbonyl group protected and C-1 carbonyl free (Scheme 2).

2.2. Stereoselective reduction of C-1 and C-2 carbonyl groups

The reduction of acetal **5** with 1.2 equiv of $NaBH_4$ in MeOH led stereoselectively with good yield (73%) to diol **7**. The same exclusive stereoselectivity and excellent yield was observed in the case of reduction of acetal **6**. Thus, compound **8** was obtained as a single isomer in a 82% yield.

The deprotection of hydroxy acetals **7** and **8** with sulfuric acid in MeCN or THF furnished dihydroxyketones **9** and **10**, respectively, in a good yield (81% and 94%, Scheme 3). It should be noted that using HCl as an acid catalyst in deprotection resulted in the elimination of tertiary hydroxyl groups in **9** and **10**. Also, during the purification of the crude reaction mixture on silica gel, a tendency towards elimination of the OH-group was observed. Therefore, the crude product was only filtered through a Celite pad after water–ethyl acetate extraction. The obtained products **9** and **10** were identified and characterized by the NMR analysis and found to be stereochemically homogeneous.



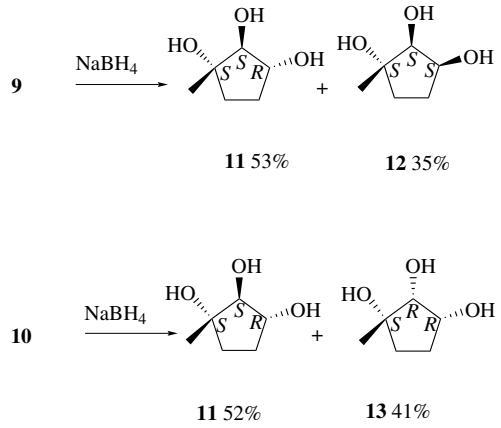
Scheme 3. Synthesis of ketodiols **9** and **10**.

However, NMR spectroscopic data was insufficient to determine the relative stereochemistry of acetonide **8** and dihydroxyketone **10**. Therefore, the diols were converted to triols and their NMR spectra together with the spectra of the model compounds **15** and **16** were additionally investigated.

2.3. The relative and the absolute configuration of hydroxylated cyclopentanones and cyclopentanes

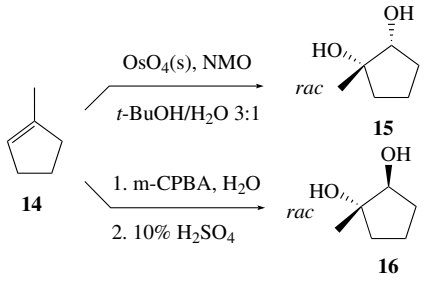
Dihydroxyketones **9** and **10** were further reduced with $NaBH_4$ affording, in both cases, a mixture of triols **11**–**13** (in a 88% yield as a sum of isomers for **9** and in a 93% for **10**; Scheme 4). The NMR spectra of the triols **11**–**13** were thoroughly investigated. Also, the information obtained enabled us to verify the established relative stereochemistry of acetonide **8** and dihydroxyketone **10** that was presented above.

It is known that the ^{13}C chemical shift of the methyl group vicinal to a hydroxyl group in cyclic alkanols is dependent



Scheme 4. Reduction of 3-methyl-2,3-dihydroxy-cyclopentanone and 2-methyl-2,5-dihydroxy-cyclopentanone to 1-methyl-1,2,3-cyclopentanetriols.

on the relative configuration of the substituents.[19–21] That phenomenon was also observed in the case of compounds **9**, **11**–**13**. To confirm the proposed stereochemistry for these compounds, model 1-methyl-1,2-cyclopentanols **15** and **16** were separately synthesized from cyclopentene **14**, using two different pathways: the dihydroxylation of **14** with an OsO_4/NMO system which should afford a *cis*-diol **15** and the epoxidation of **14** with MCPBA in water, followed by the treatment with H_2SO_4 which should afford a *trans*-diol **16** (Scheme 5).



Scheme 5. Synthesis of 1-methyl-1,2-cyclopentanediols **15** and **16**.

Although the difference in chemical shifts was larger (3.78 ppm) in the case of diols than that for triols, the general trend is clearly expressed: when the methyl group is located *cis* to the neighbouring hydroxyl group, the shift is 2.02–2.65 ppm upfield relative to that for the compounds with *trans* configuration of those groups. This regularity enabled us to determine the configuration of the substituents around carbons C1 and C2 as follows: *cis* for compounds **9**, **11** and **12** and *trans* for compound **13**.

The chemical shifts of three adjacent carbon atoms attached to hydroxyl groups are also determined by the relative configuration of the corresponding substituents (see Table 1). The ^{13}C chemical shifts of the compounds where OH-groups at carbons C2 and C3 are *cis* to each other were approximately 4 ppm upfield compared to the corresponding *trans*-compounds.[20] In the case of compounds **11**–**13** a difference of 5 ppm was observed, which allows us to make suggestions about the relative configurations of groups around atoms C2 and C3 as follows: in compound **11** the C2 and C3 hydroxyls are in *trans*- and in compounds **12** and **13** in *cis*-configuration.

Thus, the results obtained from NMR spectra enable us to assign correct stereochemical structures to all diol and triol compounds synthesized. Furthermore, the absolute configuration of the carbon C1 in triols is determined by the oxidation step and it is already well established. This way, the relative and absolute stereochemistry of the triols was unambiguously determined as depicted in Scheme 4.

3. Conclusions

A useful regioselective method for the differentiation of the carbonyl groups in 3-alkyl-3-hydroxy cyclopentane-1,2-dione was developed. The synthesized acetals **5** and **6** were converted in a stereoselective manner to dihydroxy ketones **9** and **10**, respectively. The NMR investigation of diastereomeric triols **11**–**13** and diols **15** and **16** enables us to draw regularities in the chemical shifts from relative configuration of hydroxyl groups in the compounds. The data obtained help to establish the stereochemical structure of similar cyclopentanols.

4. Experimental

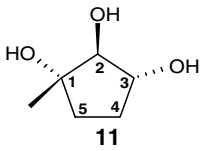
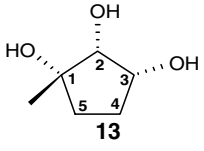
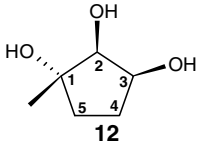
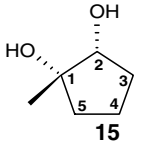
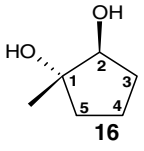
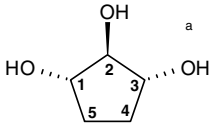
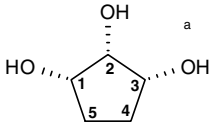
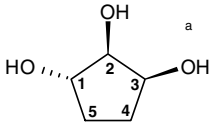
4.1. Materials and methods

Chemicals were purchased from Aldrich Chemical Co. or Lancaster and were used as received. DCM was distilled over CaH_2 and stored on the 3 Å molecular sieve pellets. THF and ether were distilled over $LiAlH_4$. Acetone was refluxed on $KMnO_4$ after persisting colour distilled, dried over K_2CO_3 2d, then distilled and stored over 4 Å molecular sieve pellets. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40–100 μm was used. NMR spectra were determined in $CDCl_3$, CD_3OD or DMSO-d_6 on Bruker AMX-500 spectrometer. 2D FT methods were used for the analysis of synthesized compounds. IR spectra were measured on a Perkin–Elmer Spectrum BX FTIR spectrometer. Mass spectra were recorded on a Hitachi M80B spectrometer using EI (70 eV) or CI (isobutane) mode. Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. All reactions sensitive to the moisture or oxygen were carried out under Ar atmosphere in an oven-dried glassware. Chiral starting material **3** was synthesized according to the conditions described in the literature from commercially available 2-methyl-1,2-cyclopentanedione. The reference compounds **15** and **16** were obtained from 1-methyl-cyclopent-1-ene purchased from Lancaster, following the recommendations of FiberCat™ catalyst manufacturer (Johnson Matthey) and an example of Fringuelli et al.,[22] respectively.

4.2. (2*S*)-2-Hydroxy-5,5-dimethoxy-2-methyl-cyclopentanone 5

To hemiacetal **3** (72 mg, 0.45 mmol) in dry MeOH (5 mL) under Ar atmosphere at 0 °C $BF_3{\cdot}Et_2O$ (29 μL, 0.23 mmol)

Table 1. ^{13}C Chemical shifts of cyclopentanols

Compound	C-1	C-2	C-3	C-4	C-5	CH_3
 **11**	*77.63*	*85.08*	*76.87*	29.25	36.27	**23.27**
 **13**	*76.51*	*77.46*	*71.61*	29.61	35.70	25.92
 **12**	*78.71*	*79.23*	*71.96*	29.91	35.88	**23.90**
 **15**	*78.32*	*78.40*	*31.57*	19.14	37.10	25.28
 **16**	*80.80*	*79.96*	*30.94*	18.76	36.95	**21.50**
 [a]	*76.60*	*85.10*	*76.60*	29.10	29.10	—
 [a]	*72.8*	*74.8*	*72.8*	29.90	29.90	—
 [a]	*76.80*	*79.90*	*72.50*	29.00	29.00	—

[a] Chemical shifts were abstracted directly from Ref. 21.

was added. The reaction mixture was allowed to reach ambient temperature and stirred for 26 h. To neutralize the solution, 5% $NaHCO_3$ (8 mL) was added at 0 °C. MeOH was removed from the mixture by evaporation and the water phase was extracted with dry AcOEt (6×25 mL). The organics were dried over Na_2SO_4, filtered, concentrated and purified over silica gel column (hexanes/acetone 20:1–10:1) to yield dimethylacetal (38 mg,

0.22 mmol, 49%) as a light yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 3H, 2-CH_3), 1.96 and 2.15 (m, 2H, H-4), 1.98 (m, 2H, H-3), 2.45 (br s, 1H, 2-OH), 3.28 (s, 3H, 5-OCH_3), 3.34 (s, 3H, 5-OCH_3); ^{13}C (125 MHz, $CDCl_3$): δ 24.44 (2-CH_3), 29.83 (C-4), 32.38 (C-3), 50.23 (OCH_3), 50.32 (OCH_3), 74.77 (C-2), 100.64 (C-5), 210.18 (C-1); IR (neat): 3417, 2983 2949, 2839, 1760, 1455, 1391, 1373, 1220, 1208, 1145, 1094, 1048, 1024; $[\alpha]_D^{20} = -38$ (*c* 2.47, $CHCl_3$); MS: *m*/*z*: 174, 156, 141, 126 (base), 113, 94, 81, 69, 55, 41, 27, 15.

4.3. (3a*S*,6a*S*)-3a-Hydroxy-2,2,6a-trimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-one 6

To ketone **3** (91 mg, 0.364 mmol) dissolved in dry acetone (1.5 mL) was added $AlCl_3$ (207 mg, 1.091 mmol) in dry Et_2O (1.5 mL) dropwise at 0 °C. After stirring for 15 min, the reaction mixture was quenched with cold $NaHCO_3$ (2.0 mL). Et_2O (10 mL) was added and the layers were separated. Water phase was extracted with Et_2O (4 × 10 mL). Combined organics were dried over $MgSO_4$, filtered and purified by column chromatography (silica gel, petroleum ether/acetone 20:1). Product **6** was obtained as a white solid (39 mg, 0.209 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 3H, 2-CH_3), 1.46 (s, 3H, 6a-CH_3), 1.55 (s, 3H, 2-CH_3), 1.71 (ddd, $J = 8.2$, 11.9 and 13.7 Hz, 1H, H-6), 2.22 (ddd, $J = 2.9$, 10.2 and 13.7 Hz, 1H, H-6), 2.27 (ddd, $J = 2.9$, 8.2 and 17.4 Hz, 1H, H-5), 2.86 (ddd, $J = 10.2$, 11.9 and 17.4 Hz, 1H, H-5), 3.92 (br s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.73 (6a-CH_3), 28.06 (2-CH_3), 28.47 (2-CH_3), 32.35 (C-5), 32.49 (C-6), 86.60 (C-6a), 101.52 (C-3a), 112.02 (C-2), 208.79 (C-4); IR (CCl_4): 3341, 2996, 2946, 1764, 1452, 1412, 1380, 1264, 1215, 1153, 1098, 1029; $[\alpha]_D^{23.5} = +125$ (*c* 1.75, $CHCl_3$); MS 10 eV *m*/*z*: 186, 171, 141, 128, 113, 100 (base), 82, 69, 59; HRMS calcd for $(M-CH_3)^+$ $C_8H_{11}O_4$: 171.0656; found: 171.0655.

4.4. (1*S*,2*R*)-3,3-Dimethoxy-1-methyl-cyclopentane-1,2-diol 7

To the starting ketone **5** (141 mg, 0.81 mmol) in 1 mL dry MeOH on the ice bath $NaBH_4$ (40 mg, 0.97 mmol) in three portions was added. After 15 min of stirring, the reaction mixture was quenched by adding acetone (200 μL) and subsequent filtering through Celite path. Concentrated mixture was purified by flash chromatography (silica gel, petroleum ether/acetone 5:1) to furnish alcohol **7** (105 mg, 0.60 mmol, 73.5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, 3H, 1-CH_3), 1.74 and 1.84 (m, 2H, H-5), 1.87 and 1.93 (m, 2H, H4), 3.26 and 3.29 (2s, 6H, OCH_3), 3.69 (br s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.52 (1-CH_3), 30.55 (C-4), 34.97 (C-5), 49.40 (OCH_3), 49.57 (OCH_3), 79.31 (C-1), 80.55 (C-2), 108.32 (C-3).

4.5. (3a*R*,4*R*,6a*S*)-2,2,6a-Trimethyl-tetrahydro-cyclopenta[1,3]dioxole-3a,4-diol 8

Compound **6** (38 mg, 0.204 mmol) was dissolved in MeOH (1.5 mL) and treated with $NaBH_4$ (9 mg, 0.238 mmol) at −5 °C. After stirring for 0.5 h, the excess of hydride was destroyed by adding acetone (0.5 mL) to the solution. The mixture was quenched with brine (10 mL) and extracted with AcOEt (1 × 20 mL and 3 × 10 mL). The resulting organic solution was dried over Na_2SO_4. The concentrated filtrate was purified by flash chromatography (silica gel, hexanes/acetone 5:1) to afford product **8** (28 mg, 0.149 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H, 6a-CH_3), 1.43 and 1.53 (2s, 2 × 3H, 2-CH_3), 1.35 and 1.82 (m, 2H, H-6), 1.53 and 1.83 (m, 2H, H-5), 3.02 (d, $J = 10.9$ Hz, 1H, 4-OH), 3.73 (m, 1H, H-4), 4.93 (s, 1H, 3a-OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.59 (6a-CH_3), 27.78 (2-CH_3), 28.27 (2-CH_3), 29.01 (C-5), 34.14 (C-6), 78.74 (C-4), 88.09 (C-6a), 108.49 (C-3a), 109.93 (C-2); $[\alpha]_D^{24} = -96$ (*c* 3.55, $CHCl_3$).

4.6. (2*R*,3*S*)-2,3-Dihydroxy-3-methyl-cyclopentanone 9

Acetal **7** (70 mg, 0.40 mmol) was dissolved in MeCN (3.0 mL). To the obtained solution was added aq 0.2 M H_2SO_4 (1.5 mL) dropwise. After stirring for 1.5 h at ambient temperature, the reaction was quenched with 2 M $NaHCO_3$ (0.4 mL). MeCN was removed under reduced pressure and the remaining water phase was extracted with AcOEt (8 × 10 mL). The solution was dried over $MgSO_4$, filtered through Celite path and the solvents evaporated to give ketodiol **9** (47 mg, 0.36 mmol, 80.5%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 3H, CH_3), 2.09 and 2.11 (m, 2H, H-4), 2.24 and 2.56 (m, 2H, H-5), 4.22 (d, $J = 1.5$ Hz, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.33 (CH_3), 31.40 (C-4), 32.97 (C-5), 76.88 (C-3), 83.82 (C-2), 214.25 (C-1); $[\alpha]_D^{25} = +115$ (*c* 0.34, acetone); MS *m*/*z*: 130, 112, 97, 84, 71, 58 (base), 43, 27, 15; HRMS calcd for M^+ $C_6H_{10}O_3$: 130.0629; found: 130.0626.

4.7. (2*S*,5*R*)-2,5-Dihydroxy-2-methyl-cyclopentanone 10

To the solution of **8** (55.2 mg, 0.277 mmol) in THF (1.5 mL) aq 2 N H_2SO_4 (0.5 mL) was added. The mixture obtained was stirred at room temperature for 3 h, after which the reaction mixture was treated with 5% $NaHCO_3$ (1 mL). AcOEt (20 mL) was added and the layers separated. Water phase was extracted with AcOEt (10 × 10 mL), dried over Na_2SO_4 and filtered through Celite plug to yield ketodiol **10** (34 mg, 0.261 mmol, 94%) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD): δ 1.22 (s, 3H, 2-CH_3), 1.70 (ddd, $J = 6.8$, 11.0 and 13.7 Hz, 1H, H-3), 1.82 (dddd, $J = 7.3$, 10.1, 11.0 and 12.2 Hz, 1H, H-4), 2.00 (ddd, $J = 3.0$, 7.3 and 13.7 Hz, 1H, H-3), 2.19 (dddd, 1H, $J = 3.0$, 6.8, 8.5 and 12.2 Hz, H-4), 4.14 (dd, $J = 8.5$ and 10.1 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD): δ 23.59 (2-CH_3), 27.27 (C-4), 32.90 (C-3), 73.27 (C-2), 73.59 (C-5), 218.28 (C-1). $[\alpha]_D^{22} = +243$ (*c* 0.80, MeOH); MS *m*/*z*: 130, 112, 84, 69, 58 (base), 43, 27, 15; HRMS calcd for $(M)^+$ $C_6H_{10}O_3$: 130.0629; found: 130.0630.

4.8. (1*S*,2*S*,3*R*)-1-Methyl-cyclopentane-1,2,3-triol 11 and (1*S*,2*S*,3*S*)-1-methyl-cyclopentane-1,2,3-triol 12

(2*R*,3*S*)-2,3-Dihydroxy-3-methyl-cyclopentanone **9** (10.8 mg, 0.083 mmol) was dissolved in MeOH (1 mL). The obtained solution was treated with $NaBH_4$ (3.8 mg, 0.100 mmol) at −5 °C for 1 h, after which acetone (0.2 mL) was added. The reaction mixture was filtered through Celite and concentrated. The product was purified

by flash chromatography (silica gel, DCM/MeOH, 15:1–10:1) to yield a mixture of two isomers as oil (9.7 mg, 0.073 mmol, 88%): (1*S*,2*S*,3*R*)-1-methyl-cyclopentane-1,2,3-triol **11** and (1*S*,2*S*,3*S*)-1-methyl-cyclopentane-1,2,3-triol **12** in 3:2 ratio by proton NMR. Compound **11**: (500 MHz, DMSO-d_6): δ 1.02 (s, 3H, 1-CH_3), 1.44 (m, 1H, H-4), 1.48 (m, 1H, H-5), 1.63 (m, 1H, H-5), 1.77 (m, 1H, H-4), 3.42 (t, 1H, H-2), 3.63 (m, 1H, H-3), 4.32 (s, 1H, 1-OH), 4.62 (d, 1H, 3-OH), 4.67 (d, 1H, 2-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.27 (1-CH_3), 29.25 (C-4), 36.27 (C-5), 76.87 (C-3), 77.63 (C-1), 85.08 (C-2). Compound **12**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14 (s, 3H, 1-CH_3), 1.39 and 1.64 (m, 2H, H-5), 1.39 and 1.87 (m, 2H, H-4), 3.31 (m, 1H, H-2), 4.17 (m, 1H, H-3), 4.22 (d, $J = 4.1$ Hz, 1H, 2-OH), 4.24 (s, 1H, 1-OH), 4.32 (d, $J = 7.0$ Hz, 1H, 3-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.90 (1-CH_3), 29.91 (C-4), 35.88 (C-5), 71.96 (C-3), 78.71 (C-1), 79.23 (C-2).

4.9. (1*S*,2*S*,3*R*)-1-methyl-cyclopentane-1,2,3-triol (11) and (1*S*,2*R*,3*R*)-1-methyl-cyclopentane-1,2,3-triol (13)

(2*S*,5*R*)-2,5-dihydroxy-2-methyl-cyclopentanone **10** (9.3 mg, 0.071 mmol) was dissolved in MeOH (1 mL). The obtained solution was treated with $NaBH_4$ (3.2 mg, 0.086 mmol) at -5 °C for 1 h, after which acetone (0.1 mL) was added. The reaction mixture was filtered through Celite and concentrated. Diastereomers were separated by flash chromatography (silica gel, DCM/MeOH, 15:1–10:1) to yield (1*S*,2*S*,3*R*)-1-methyl-cyclopentane-1,2,3-triol **11** (4.9 mg, 0.037 mmol, 52%) and (1*S*,2*R*,3*R*)-1-methyl-cyclopentane-1,2,3-triol **13** (3.9 mg, 0.030 mmol, 41%). Compound **11**: NMR spectra identical to the data given in Section 4.8. Compound **13**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (s, 3H, 1-CH_3), 1.42 and 1.72 (m, 2H, H-5), 1.57 and 1.76 (m, 2H, H-4), 3.25 (m, 1H, H-3), 3.88 (bs, 1H, H-2), 4.15 (bs, 1H, 1-OH), 4.50 (bs, 2H, 2-OH, 3-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.92 (1-CH_3), 29.61 (C-4), 35.70 (C-5), 71.61 (C-3), 76.51 (C-1), 77.46 (C-2).

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