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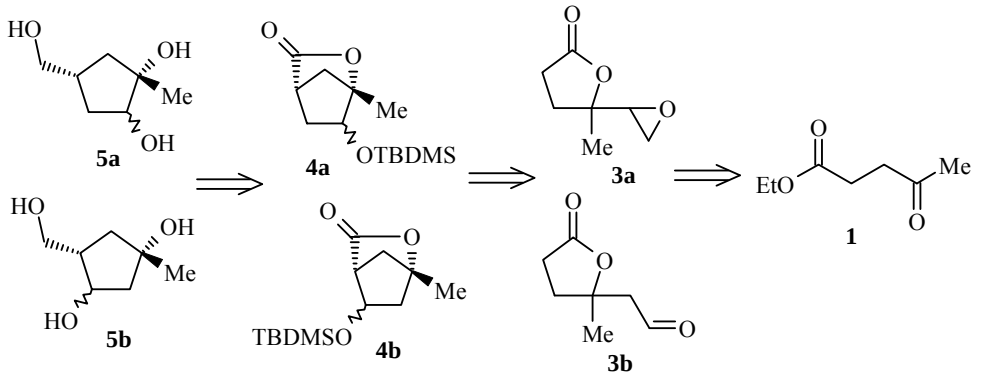
STEREOSELECTIVE SYNTHESIS OF 1-METHYL-1,2- AND 1,3-CYCLOPENTANEDIOLS *via* γ-LACTONES

A method for the synthesis of derivatives of 1-methylcarbapentofuranoses was developed. 1,2-*cis*- and 1,2-*trans*-4-hydroxymethyl-1-methylcyclopentanediols were obtained from intramolecular opening of 4-epoxy-4-methyl-γ-lactone. 1,3-*cis*- and 1,3-*trans*-4-hydroxymethyl-1-methylcyclopentanediols were obtained from intramolecular aldol reaction of 4-methyl-4-(2-oxoethyl)-γ-lactone derivatives.

Keywords: carbaribose, cyclopentane-1,2-diols, cyclopentane-1,3-diols, γ-lactone derivatives, oxabicyclo[2.2.1]heptanone, cyclization, epoxide opening.

Substituted cyclopentanediol structural subunits are essential parts of many important natural compounds and their analogues. Prostaglandins F [1, 2] and phytoprostanes, [3] antiviral [4–6] and anticancer [7–9] carbacyclic nucleoside analogues present only a few examples of those compounds. It is obvious that the synthesis of differently substituted cyclopentane structures and pentofuranose carba-analogues has attained considerable interest in the last few decades [10–12]. Also, several methods for stereoselective synthesis of compounds with the structures of this type have been published [13–15].

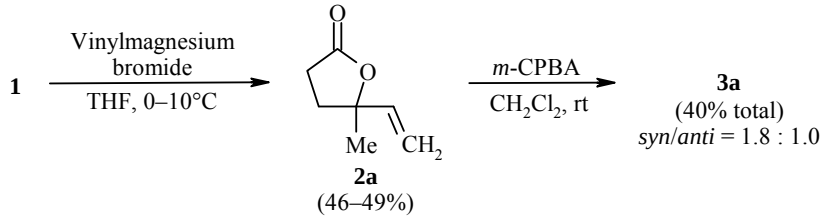
We have been engaged in the synthesis of different 4'-substituted nucleoside analogues [16–18]. Now we have developed synthetic routes to obtain 1'-methyl-substituted carbocyclic ribose analogues **5a**,**b** with controlled regio- and stereo-selective chemistry, from the key intermediates **3a**,**b** *via* bicyclic lactones **4a**,**b**.



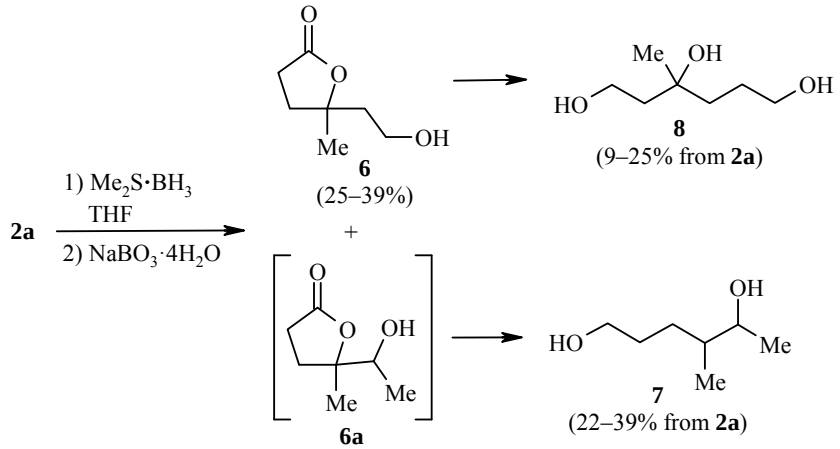
The location of the secondary OH group in the cyclopentane ring is determined by selection of the key intermediate **3**: compounds with 2-OH group are obtained from epoxide **3a** and compounds with 3-OH group – from aldehyde **3b**.

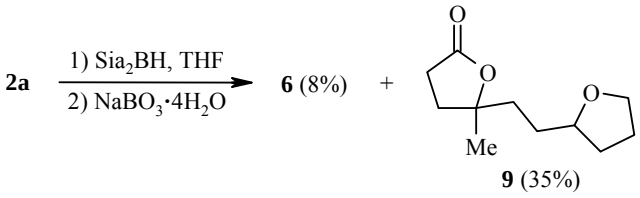
Lactone intermediates **2a**,**b** were prepared starting from ethyl levulinate **1**. Thus, an addition of vinylic Grignard reagent to compound **1** [19], followed by intramolecular cyclization afforded lactone **2a** (49% after distillation). The double

bond of lactone **2a** was epoxidized with *m*-chloroperbenzoic acid (*m*-CPBA), resulting in a diastereomeric mixture of epoxy lactones **3a** in the ratio of *syn*/*anti*-isomers 1.8 : 1.0, in 40% overall separated yield.



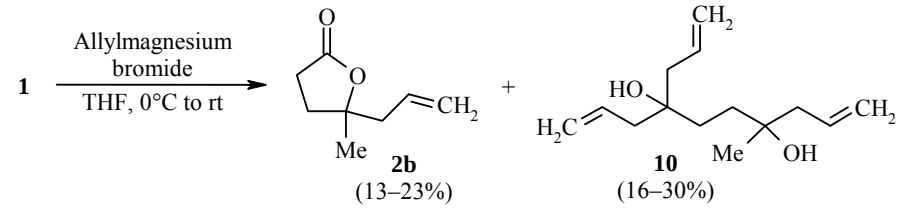
We also intended to obtain lactone aldehyde **3b** directly from vinyl lactone **2a** (*via* lactone alcohol **6**) using hydroboration–oxidation sequence. Despite of many attempts using $Me_2S{\cdot}BH_3$ in THF at different substrate/reactant ratios and reaction conditions, we always obtained a mixture of different products with the yield of the target lactone alcohol **6** after oxidation of borane with $NaBO_3{\cdot}4H_2O$ in the range of 25–39%, together with compound **7**, which very likely forms from regioisomer **6a**, after hydroboration–elimination–rehydroboration sequence [20] in the range of 22–39%. Also, we have isolated the reduction product **8** (9–25%). Even use of a sterically bulky boron reagent disiamylborane (Sia_2BH) (110 mol %, from 0°C to rt, 44 h) did not improve the results – after 44 h at rt compound **6** was formed in only 8% yield; instead, a radical coupling reaction of alkene **2a** with THF occurred, yielding compound **9** in 35% yield.



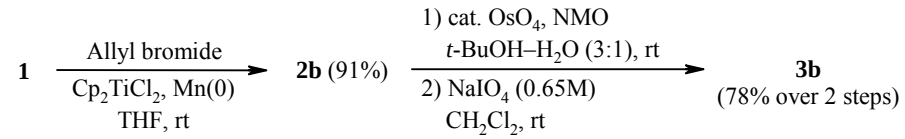


Poor chemo- and regioselectivity (only 2:1 in favor of primary alcohol **6**, calculated from **6**/**7** ratio) prompted us to pursue other synthetic path towards the key intermediate **3b**. Thus, a synthesis *via* allylic γ-lactone **2b** was performed. Direct Grignard reaction of ethyl levulinate **1** with allylmagnesium bromide gave unsatisfactory results, leading to the mixtures of monoaddition adduct **2b** (after

lactonization) and triaddition adduct **10** in various ratios. The yield of mono-addition adduct **2b** did not exceed 23% in the best case.

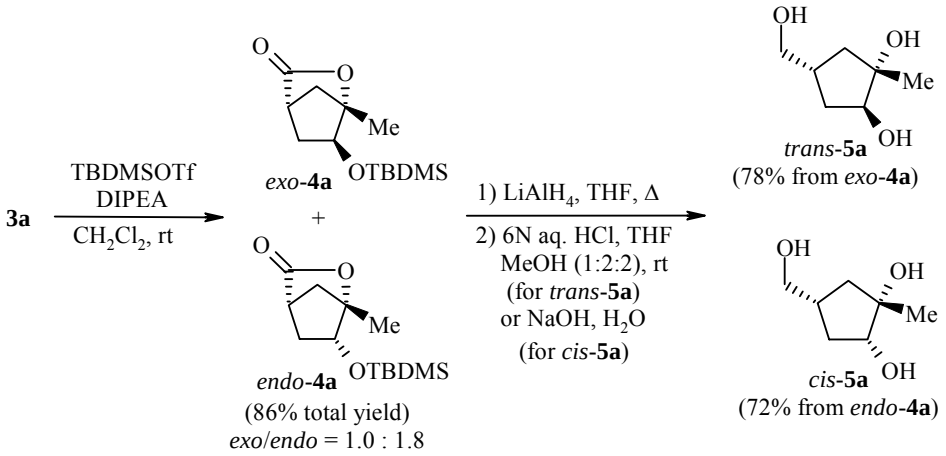


Fortunately, Ti(III)-mediated Barbier type allylation of ethyl levulinate **1** according to Estevez [21] with 1.5 excess of allyl bromide afforded allylic lactone **2b** in 91% yield. Two-step oxidation of γ-lactone **2b**, osmium-catalyzed dihydroxylation followed by $NaIO_4$-induced oxidative cleavage [22–24], afforded the key intermediate **3b** in 78% overall yield.



There are several reports in the literature where the intramolecular epoxide opening has been used to construct functionalized cyclopentane structural units. Some of the examples include NaH-assisted synthesis of bicyclic skeleton of 9-Deoxyenglerin A, [25] Lewis acid (BF_3)-catalyzed intramolecular epoxide opening to synthesize Brefeldin A, [26] and a radical Ti-catalyzed stereoselective epoxide opening to construct functionalized cyclopentane structural units of terpenic compounds. [27]

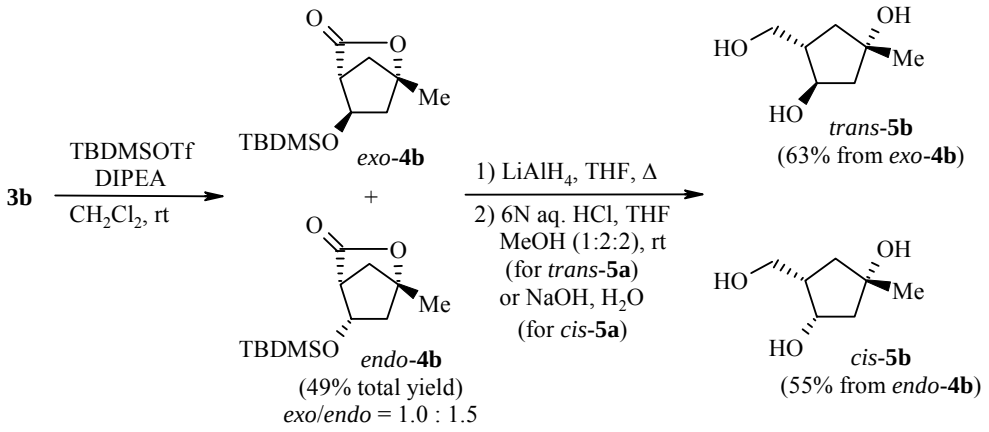
We found that lactone epoxide **3a** cyclizes smoothly in regioselective manner by the use of TBDMSOTf–DIPEA reagent system [28].



The cyclization affords stable diastereomeric silyl-protected alcohols **4a** in good yield (86%) as the primary reaction product, in the similar *exo*/*endo* diastereomer ratio as of the initial epoxide (1.8 : 1.0). This result indicates that the reaction is fully regio- and stereoselective. The diastereomers were easily separated on silica gel and subjected separately to reduction. Diastereomer *exo*-**4a** was treated with $LiAlH_4$ in refluxing THF, quenched with aqueous NaOH, and deprotected with 6N

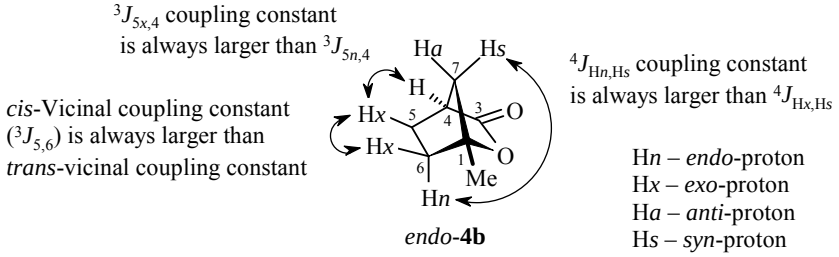
HCl in a mixture of MeOH and THF to afford diol *trans*-**5a** in 78% yield over two steps. The compound *cis*-**5a** was obtained similarly from *endo*-**4a** in 72% after treatment of the reaction mixture with NaOH solution in water without deprotection step.

Cyclization of the second key intermediate **3b** was performed under the same conditions used for compound **3a**. After separation on silica gel, isomers *exo*-**4b** and *endo*-**4b** were obtained in 49% total isolated yield, with the *exo*/*endo* ratio of isomers ~1.0 : 1.5.



The subsequent transformations were carried out with the *exo*- and *endo*-isomers separately. Thus, compound *exo*-**4b** was treated with $LiAlH_4$ in THF, quenched with aqueous NaOH followed by deprotection with 1:2:2 mixture of aqueous 6N HCl, MeOH and THF to afford isomer *trans*-**5b** in 63% yield over two steps. The similar transformation of compound *endo*-**4b** resulted directly after quenching the mixture with aq. NaOH in isomer *cis*-**5b** in one step with 55% yield.

To assign the configurations of bicyclic intermediates **4a**,**b** well known regularities in NMR spectra of related bicyclo[2.2.1]heptane derivatives were used [29–31]. It is known that when C-5 or C-6 atoms have *exo*-OX substituent, the signal of C-7 carbon in ^{13}C NMR spectrum is shifted upfield [32, 33]. In the case of compound **4a** the signal of C-7 atom has chemical shift 40.7 ppm for *exo*-isomer and 42.7 ppm for *endo*-isomer, in the case of compound **4b** the corresponding values are 41.9 and 43.4 ppm. In ^1H NMR spectra, $^3J_{H\text{-}5x,H\text{-}4}$ is always larger than $^3J_{H\text{-}5n,H\text{-}4}$. In the case of compound **4b**, the corresponding values are 4.3 and 1.3 Hz, thus revealing the configuration of H-5 proton. In the case of compound **4a**, both H-5 protons are present with $^3J_{H\text{-}5x,H\text{-}4}$ values of 4.6 Hz (for *endo*-isomer) and 4.3 Hz (for *exo*-isomer) and $^3J_{H\text{-}5n,H\text{-}4}$ values of 0.6 and 0.7 Hz, respectively (Figure).



Relevant interactions for the structure determination.
(TBDMSO group at position 5*n* is not shown)

As a rule, vicinal proton-proton coupling constants ^3J have higher values when protons are *cis*-oriented. In the case of compounds **4a**, H-5*x* and H-5*n* protons being assigned, the relative configuration of H-6 is revealed by inspecting relevant ^3J coupling values H-5*x*,H-6 and H-5*n*,H-6, which for isomer *exo*-**4a** are 2.7 and 6.6 Hz and for isomer *endo*-**4a** 9.0 and 3.3 Hz, respectively. Equally informative in ^{1}H NMR spectra of compounds **4a** and **4b** for the determination of configuration are ^4J between H-7*s* and H-6 (and H-5) *endo*-protons which are always larger in the case of *endo*-protons than in the case of *exo*-protons [29]. The proton H-6*n* of compound **4a** is coupled to H-7*s* with value of 1.6 Hz, whereas proton H-5*n* of compound **4b** is coupled to H-7*s* with value of 1.3 Hz.

Taking into account all the relevant information given above, the relative configuration of bicyclic compounds **4a**,**b** was unambiguously determined, thus letting us to establish also the relative configurations of diols **5a**,**b**. On the other hand, the relative configuration of compounds **5a** could have been determined based on our previous observation [34], that ^{13}C chemical shifts of 1-methyl-substituted vicinal diols are dependent on *cis*-*trans* substitution pattern. The methyl group should have ^{13}C chemical shift upfield in *trans*-diol relative to *cis*-diol; in the case of isomer *trans*-**5a** the methyl group has chemical shift 22.1 ppm and in case of isomer *cis*-**5a** – 25.2 ppm. Furthermore, the C-1 and C-2 carbons in compound **5a** should have chemical shifts upfield, when *cis*-substitution is observed relative to the *trans*-substituted diol. Indeed, chemical shifts for C-1 and C-2 carbons in isomer *cis*-**5a** are 79.1 and 78.6 ppm, whereas in isomer *trans*-**5a** the corresponding shifts are 81.8 and 81.1 ppm. These results correlate with the observation, that reduction of compounds *exo*-**4a** and *endo*-**4a** should give triols *trans*-**5a** and *cis*-**5a**, respectively, and thus confirms the assignment of relative configuration of bicyclic intermediates **4a**.

Thus, through unprecedented use of a reagent system TBDMSOTf–DIPEA a regio- and stereospecific epoxide opening reaction is described and efficiently applied to the synthesis of novel methyl branched cyclopentane derivatives *via* heterocyclic bicyclo[2.2.1]heptanes. Appropriate substrate selection allowed to achieve the synthesis of regioisomeric 5- and 6-silyloxy-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one derivatives, starting from (2-methyl-5-oxotetrahydrofuran-2-yl)acetaldehyde and 5-methyl-5-oxiranyldihydrofuran-2-one, respectively.

EXPERIMENTAL

IR spectra were measured on a Perkin Elmer Spectrum BX FTIR spectrometer. NMR spectra were determined in $CDCl_3$ or CD_3OD on Bruker Avance USLA 400 or Bruker Avance 800 spectrometer. Residual solvent signals were used as references. Mass spectra were recorded on a Hitachi M80B or Shimadzu GCMSQP2010 spectrometer using EI as ionization method (70 eV). High resolution mass spectra were recorded on Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer and utilizing AJ-ESI or APCI ion sources. Elemental analyses were performed on a Perkin Elmer C,H,N,S-Analyzer 2400. Precoated silica gel 60 F254 plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40-100 μm was used. All reactions sensitive to the moisture or oxygen were carried out under Ar atmosphere in oven-dried glassware. Vinyl lactone **2a** and allyl lactone **2b** were synthesized according to previously published methods (except for allylation reaction allyl bromide instead of allyl chloride was used as alkylating reagent) and their physical and spectroscopic properties were in accordance with data given in literature [19, 21]. Epoxides **3a** synthesized by literature method [35]. Chemicals were purchased from Aldrich Chemical Co or Alfa Aesar and were used as received. MeOH was distilled from sodium. DCM was distilled over CaH_2 and

stored on the 4Å molecular sieves pellets. THF was distilled from sodium benzophenone complex.

5-Methyl-5-oxiranyldihydrofuran-2-one (3a) (mixture of diastereomers). To the solution of γ-vinyl lactone **2a** (253.6 mg, 2.01 mmol) in CH_2Cl_2 (5 ml) *m*-CPBA (551.3 mg, 2.46 mmol, 1.22 equiv) was added portionwise at 22°C. The resulting solution was stirred at 22°C for 25 h during which precipitation occurred. Second portion of *m*-CPBA (764.4 mg, 3.10 mmol) was added and stirring was continued for another 19 h (44 h total). The reaction was quenched with successive addition of 10% aq. solution of $Na_2S_2O_3$ (5 ml) and 5% aq. solution of $NaHCO_3$ (5 ml) with vigorous stirring. The layers were separated and water phase extracted with CH_2Cl_2 (4 × 10 ml). Combined organic phase were washed sequencially with $NaHCO_3$ (10 ml) and saturated NaCl (10 ml), then dried over Na_2SO_4. Filtration and evaporation of volatiles afforded crude product from which, after purification by flash chromatography (SiO_2, CH_2Cl_2–MeOH, 200:1) diastereomeric epoxides **3a** were obtained as light yellow oil (112 mg, 40%, *syn/anti* = 1.8 : 1.0). IR spectrum (thin layer), ν, cm^{-1}: 2984 (CH), 1778 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.20 (0.36H, *J* = 4.2, *J* = 2.7, 2'-CH *anti*); 3.03 (0.64H, dd, *J* = 4.0, *J* = 2.8, 2'-CH *syn*); 2.84 (0.36H, t, *J* = 4.3, 3'-CH_A *anti*); 2.80 (0.64H, dd, *J* = 5.0, *J* = 2.6, 3'-CH_A *syn*); 2.78–2.69 (1.28H, m, 3-CH_A *syn*, 3'-CH_B *syn*); 2.66–2.57 (1.08H, m, 3-CH_2 *anti*, 3'-CH_B *anti*); 2.55–2.39 (1.28H, m, 3-CH_B *syn*, 4-CH_A *syn*); 2.13–2.01 (1H, m, 4-CH_B *syn*, 4-CH_A *anti*); 1.90–1.78 (0.36H, m, 4-CH_B *anti*); 1.50 (1.92H, s, CH_3 *syn*); 1.48 (1.08H, s, CH_3 *anti*). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 176.5 (C-2 *syn*); 176.2 (C-2 *anti*); 84.7 (C-5 *anti*); 81.6 (C-5 *syn*); 56.7 (C-2' *syn*); 55.3 (C-2' *anti*); 43.6 (C-3' *anti*); 43.5 (C-3' *syn*); 32.5 (C-4 *syn*); 29.0 (C-3 *syn*); 29.0 (C-3 *anti*); 27.7 (C-4 *anti*); 23.5 (CH_3 *anti*); 23.3 (CH_3 *syn*). Mass spectrum, *m/z* (I_{rel}, %): 142 $[M]^+$ (1), 127 $[M–CH_3]^+$ (2), 112 $[M–CH_2O]^+$ (1), 99 $[M–C_2H_3O]^+$ (100). Found, %: C 58.90; H 7.09. $C_7H_{10}O_3$. Calculated, %: C 59.14; H 7.09.

(2-Methyl-5-oxotetrahydrofuran-2-yl)acetaldehyde (3b). To the solution of γ-allyl lactone **2b** (93%, 536.3 mg, 3.55 mmol) in *t*-BuOH (8.9 ml) and H_2O (3.0 ml) were consecutively added OsO_4 in *t*-BuOH (2.5%, 2.2 ml, 0.175 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (50% in water, 1.1 ml, 5.32 mmol). After stirring at 22°C for 23 h the reaction mixture was treated with Na_2SO_3 (20%, 10 ml) and Florisil (1 g) at the same temperature for 45 min. The resulting slurry was filtered through a pad of Celite and the latter washed with acetone (3 × 15 ml). The organic volatiles were evaporated, and to the residue 1M $NaHSO_4$ (2 ml) was added to adjust pH 2. Water phase was extracted with EtOAc (15 × 15 ml, 2 g of NaCl was added to the water phase after 10th extract), dried over $MgSO_4$, and filtered through short pad of silica to yield crude 5-(2,3-dihydroxypropyl)-5-methyldihydrofuran-2-one (562.5 mg) as 1:1 mixture of diastereomers, which was used in the next synthetic step without further purification. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.98–3.89 (1H, m, 2'-CH); 3.62–3.52 (1H, m) and 3.49–3.40 (1H, m, 3'-CH_2); 2.72–2.55 (2H, m, 3-CH_2); 2.49–2.21 (1H, m) and 2.12–1.99 (1H, m, 4-CH_2); 1.92–1.71 (2H, m, 1'-CH_2); 1.49 (1.5H, s) and 1.47 (1.5H, s, CH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 177.0 (C-2); 86.1 and 85.9 (C-5); 68.4 and 67.9 (C-2'); 66.6 and 66.6 (C-3'); 42.7 and 42.6 (C-1'); 33.4 and 32.7 (C-4); 28.7 and 28.5 (C-3); 26.4 and 25.6 (CH_3).

To the obtained intermediate diol (479 mg, 2.75 mmol) dissolved in CH_2Cl_2 (55.0 ml), $NaIO_4$ (0.65M, 5.3 ml) and SiO_2 (5.22 g) were added at 22°C. The resulting slurry was stirred for 40 min and then filtered through the pad of SiO_2. The solids on the filter were washed with CH_2Cl_2 (3 × 25 ml) and EtOAc (2 × 25 ml) and the solvents evaporated to yield a crude aldehyde **3b** as light brown liquid. Yield 392.4 mg (78%). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1766 (CO), 1723 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.79 (1H, t, *J* = 1.9, CHO); 2.85 (2H, qd, *J* = 16.7, *J* = 1.8, C$\underline{H}_2$CHO); 2.71–2.62 (2H, m, 4-CH_2); 2.30–2.16 (2H, m, 3-CH_2); 1.52 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 198.6 (CHO); 175.7 (C-5); 83.2 (C-2); 53.3 (C$\underline{H}_2$CHO); 33.0 (C-4); 28.3 (C-3); 26.3 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 143 $[M+H]^+$ (1), 127 $[M–CH_3]^+$ (8), 114 $[M+H–CH_2O]^+$ (27), 99 $[M–C_2H_3O]^+$ (92). Found, *m/z*: 165.0521 $[M+Na]^+$. $C_7H_{10}O_3Na$. Calculated, *m/z*: 165.0522.

Synthesis of cyclization products *exo*-4a, *endo*-4a, *exo*-4b and *endo*-4b (General Method).

6-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (4a). To the mixture of DIPEA (255 μl, 1.45 mmol) and TBDMSOTf (340 μl, 1.45 mmol) in CH_2Cl_2 (6 ml) a solution of diastereomeric mixture of epoxides **3a** (69 mg, 0.49 mmol) in CH_2Cl_2 (3 ml) was added at 25°C dropwise over period of 10–15 min. Resulting solution (0.06M in substrate) was stirred for 0.5 h at 25°C, after which the reaction mixture was added to saturated aq. solution of NH_4Cl solution and the layers separated. Organic phase was extracted with CH_2Cl_2 (4×10 ml), dried over $MgSO_4$, filtered, and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, heptane–acetone, 40:1 to 10:1) to yield the compound *exo*-**4a** (66.6 mg, 54%) and *endo*-**4a** (39.0 mg, 32%) in a form of light yellow oils.

6-*exo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*exo*-4a). IR spectrum (thin layer), ν, cm^{-1}: 1776 (CO). ^{1}H NMR spectrum (800 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.82 (1H, ddd, *J* = 6.6, *J* = 2.7, *J* = 1.6, 6-CH*n*); 2.72 (1H, dddd, *J* = 4.3, *J* = 1.6, *J* = 1.2, *J* = 0.7, 4-CH); 2.17 (1H, dddd, *J* = 13.2, *J* = 6.6, *J* = 2.3, *J* = 0.7, 5-CH*n*); 1.98 (1H, dd, *J* = 10.6, *J* = 1.2, 7-CH*a*); 1.88 (1H, ddt, *J* = 10.6, *J* = 2.3, *J* = 1.6, 7-CH*s*); 1.59 (1H, ddd, *J* = 13.2, *J* = 4.3, *J* = 2.7, 5-CH*x*); 1.47 (3H, s, 1-CH_3); 0.87 (9H, s, $C(CH_3)_3$); 0.06 (3H, s) and 0.05 (3H, s, $Si(CH_3)_2$). ^{13}C NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 178.1 (C-3); 90.8 (C-1); 73.3 (C-6); 41.1 (C-4); 40.7 (C-7); 36.2 (C-5); 25.6 ($SiC(\underline{C}H_3)_3$); 17.8 ($Si\underline{C}(CH_3)_3$); 15.6 (1-CH_3); –4.8 ($SiCH_3$); –5.1 ($SiCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 257 $[M+H]^+$ (1), 241 $[M–CH_3]^+$ (2), 211 $[M–COOH]^+$ (1), 199 $[M–t\text{-Bu}]^+$ (31), 171 $[M–t\text{-Bu}–CO]^+$, (41), 155 $[M–t\text{-Bu}–COOH]^+$ (26), 141 $[M–TBDMS]^+$ (1), 127 $[M+1–TBDMS–CH_3]^+$ (9), 115 $[TBDMS]^+$ (28), 75 $[C_2H_7SiO]^+$ (100). Found, %: C 60.81; H 9.48. $C_{13}H_{24}O_3Si$. Calculated, %: C 60.89; H 9.43.

6-*endo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*endo*-4a). IR spectrum (thin layer), ν, cm^{-1}: 1779 (CO). ^{1}H NMR spectrum (800 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.14 (1H, dd, *J* = 9.0, *J* = 3.3, 6-CH*x*); 2.79 (1H, dddd, *J* = 4.6, *J* = 1.9, *J* = 1.0, *J* = 0.6, 4-CH); 2.31 (1H, ddd, *J* = 13.3, *J* = 9.0, *J* = 4.6, 5-CH*x*); 1.95 (1H, ddd, *J* = 10.8, *J* = 3.4, *J* = 1.9, 7-CH*s*); 1.72 (1H, dd, *J* = 10.8, *J* = 1.0, 7-CH*a*); 1.50 (1H, dtd, *J* = 13.3, *J* = 3.3, *J* = 0.6, 5-CH*n*), 1.48 (3H, s, 1-CH_3); 0.88 (9H, s, $C(CH_3)_3$); 0.06 (s, 3H) and 0.04 (s, 3H, $Si(CH_3)_2$). ^{13}C NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 178.2 (C-3); 90.1 (C-1); 74.6 (C-6); 43.6 (C-4); 42.7 (C-7); 35.6 (C-5); 25.6 ($SiC(\underline{C}H_3)_3$); 18.0 ($Si\underline{C}(CH_3)_3$); 16.1 (1-CH_3), –4.7 ($SiCH_3$); –5.0 ($SiCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 241 $[M–CH_3]^+$ (1), 211 $[M–COOH]^+$ (1), 199 $[M–t\text{-Bu}]^+$ (12), 171 $[M–t\text{-Bu}–CO]^+$ (23), 155 $[M–t\text{-Bu}–COOH]^+$ (46), 141 $[M–TBDMS]^+$ (1), 127 $[M+1–TBDMS–CH_3]^+$ (13), 115 $[TBDMS]^+$ (22), 75 $[C_2H_7SiO]^+$ (100). Found, %: C 60.89; H 9.48. $C_{13}H_{24}O_3Si$. Calculated, %: C 60.89, H 9.43.

5-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (4b) was obtained using aldehyde **3b** as starting material in 2.75 mmol scale. Yield of isomer *exo*-**4b** 143 mg (20%), light yellow liquid. Yield of isomer *endo*-**4b** 204 mg (29%), light yellow amorphous solid.

5-*exo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*exo*-4b). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1783 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.33 (1H, ddt, *J* = 6.6, *J* = 2.0, *J* = 1.3, 5-CH*n*); 2.79 (1H, quint, *J* = 1.3, 4-CH); 2.25 (1H, dd, *J* = 10.4, *J* = 1.4, 7-CH*a*); 2.25 (1H, ddd, *J* = 13.8, *J* = 6.6, *J* = 2.8, 6-CH*n*); 1.98 (1H, ddt, *J* = 10.4, *J* = 2.8, *J* = 1.3, 7-CH*s*); 1.59 (3H, s, 1-CH_3); 1.59 (1H, ddd, *J* = 13.8, *J* = 2.0, *J* = 1.3, 6-CH*x*); 0.88 (9H, s, $C(CH_3)_3$); 0.08 (3H, s) and 0.07 (3H, s, $Si(CH_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 176.5 (C-3); 90.2 (C-1); 70.2 (C-5); 53.3 (C-4); 47.0 (C-6); 41.9 (C-7); 25.7 ($C(\underline{C}H_3)_3$); 18.7 (1-CH_3); 17.9 ($\underline{C}(CH_3)_3$); –4.8 ($SiCH_3$); –5.0 ($SiCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 256 $[M]^+$ (1), 241 $[M–CH_3]^+$ (1), 199 $[M–t\text{-Bu}]^+$ (33), 171 $[M–t\text{-Bu}–CO]^+$ (4), 155 $[M–t\text{-Bu}–COOH]^+$ (7), 115 $[TBDMS]^+$ (2), 75 $[C_2H_7SiO]^+$ (100). Found, *m/z*: 279.1391 $[M+Na]^+$. $C_{13}H_{24}NaO_3Si$. Calculated, *m/z*: 279.1387.

5-*endo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*endo*-4b). IR spectrum (KBr), ν, cm^{-1}: 1776 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz):

4.54 (1H, ddd, *J* = 8.7, *J* = 4.3, *J* = 3.1, 5-CH*x*); 2.92 (1H, dt, *J* = 4.3, *J* = 1.4, 4-CH); 2.10 (1H, dd, *J* = 13.7, *J* = 8.7, 6-CH*x*); 1.96 (1H, ddd, *J* = 10.7, *J* = 3.9, *J* = 1.6, 7-CH*s*); 1.65 (1H, dd, *J* = 10.7, *J* = 1.2, 7-CH*a*); 1.64 (1H, ddd, *J* = 13.7, *J* = 3.9, *J* = 3.1, 6-CH*n*); 1.51 (3H, s, 1-CH_3); 0.87 (9H, s, $C(CH_3)_3$); 0.09 (s, 3H) and 0.06 (s, 3H, $Si(CH_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 174.8 (C-3); 88.6 (C-1); 70.6 (C-5); 51.7 (C-4); 43.7 (C-6); 43.4 (C-7); 25.7 ($C(\underline{C}H_3)_3$); 19.3 (CH_3); 18.0 ($\underline{C}(CH_3)_3$); –4.8 ($SiCH_3$); –5.0 ($SiCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 241 $[M–CH_3]^+$ (1), 199 $[M–t\text{-Bu}]^+$ (30); 171 $[M–t\text{-Bu–CO}]^+$ (8); 155 $[M–t\text{-Bu–COOH}]^+$ (6); 75 $[C_2H_7SiO]^+$ (100). Found (ESI), *m/z*: 279.1392 $[M+Na]^+$. $C_{13}H_{24}NaO_3Si$. Calculated, *m/z*: 279.1387.

1,2-*trans*-4-Hydroxymethyl-1-methylcyclopentane-1,2-diol (*trans*-5a). $LiAlH_4$ (91 mg, 2.28 mmol) was suspended in THF, and solution of compound *exo*-**4a** (167 mg, 0.65 mmol) in THF (10 ml) was added at 0°C. The resulting suspension was heated to reflux for 1 h, then the reaction mixture was cooled to 0°C and water added (100 μl). Stirring was continued for 0.5 h with gradual rise of temperature to 23°C. Then aqueous 10% NaOH (100 μl) at 23°C was added and the stirring continued for additional 0.5 h to complete the precipitation. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield crude protected diol. Mass spectrum, *m/z* (I_{rel}, %): 243 $[M+H–H_2O]^+$ (1), 227 $[M–H_2O–CH_3]^+$ (1), 203 $[M–t\text{-Bu}]^+$ (12), 185 $[M–H_2O\text{-}t\text{-Bu}]^+$ (42), 129 $[M+H–H_2O–TBDMS]^+$ (2), 75 $[C_2H_7SiO]^+$ (100).

To the solution of the protected diol (130.3 mg, 0.50 mmol) in mixture of THF (2 ml) and MeOH (2 ml) 6N HCl (1 ml) was added dropwise at 25°C. The resulting solution was stirred for 1 h at 25°C, then the volatiles were evaporated to yield the crude product as light yellow oil. Further purification was achieved by flash chromatography on SiO_2 eluting with CH_2Cl_2–MeOH, 10:1. Yield 57 mg (78%). Colorless oil. IR spectrum (thin layer), ν, cm^{-1}: 3341 (OH), 1118 (C–O), 1038 (C–O). ^{1}H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 3.75 (1H, dd, *J* = 5.6, *J* = 3.3, 2-CH); 3.47 (2H, d, *J* = 6.0, $C\underline{H}_2OH$); 2.44–2.27 (1H, m, 4-CH); 1.98–1.80 (2H, m, 3-CH_A, 5-CH_A); 1.77–1.65 (1H, m, 3-CH_B); 1.43 (1H, dd, *J* = 13.7, *J* = 5.3, 5-CH_B); 1.25 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 81.8 (C-1); 81.1 (C-2); 67.6 (CH_2OH); 41.5 (C-5); 38.4 (C-4); 36.2 (C-3); 22.1 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 146 $[M]^+$ (1), 128 $[M–H_2O]^+$ (3), 115 $[M–CH_2OH]^+$ (28), 98 $[M+H–H_2O–CH_2OH]^+$ (17), 97 $[M–H_2O–CH_2OH]^+$ (37). Found, *m/z*: 169.0829 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

1,2-*cis*-4-Hydroxymethyl-1-methylcyclopentane-1,2-diol (*cis*-5a). $LiAlH_4$ (50 mg, 1.29 mmol) was suspended in THF (7 ml), and solution of compound *endo*-**4a** (88 mg, 0.34 mmol) in THF (7 ml) was added at 0°C. The resulting suspension was heated to reflux for 1 h, then the reaction mixture was cooled to 0°C and water added (100 μl). Stirring was continued for 0.5 h with gradual rise of temperature to 23°C. Then aqueous 10% NaOH (100 μl) at 23°C was added and the stirring continued for additional 0.5 h to complete the precipitation. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield crude diol *cis*-**5a** which was purified by flash chromatography on SiO_2, eluent CH_2Cl_2–MeOH, 10:1. Yield 36.4 mg (72%). Light colorless oil. IR spectrum (thin layer), ν, cm^{-1}: 3381 (OH), 1086 (C–O), 1043 (C–O). ^{1}H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 3.63 (1H, dd, *J* = 7.9, *J* = 6.4, 2-CH); 3.48 (2H, d, *J* = 6.0, $C\underline{H}_2OH$); 2.17–2.01 (2H, m, 4-CH, 3-CH_A); 1.79 (1H, dd, *J* = 13.8, *J* = 9.3) and 1.56 (1H, dd, *J* = 13.8, *J* = 5.7, 5-CH_2); 1.48 (1H, dt, *J* = 12.7, *J* = 7.5, 3-CH_B); 1.22 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 79.1 (C-1); 78.6 (C-2); 67.7 ($\underline{C}H_2OH$); 41.2 (C-5); 36.4 (C-4); 35.6 (C-3); 25.2 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 146 $[M]^+$ (1), 128 $[M–H_2O]^+$ (5), 115 $[M–CH_2OH]^+$ (32), 98 $[M+H–H_2O–CH_2OH]^+$ (14), 97 $[M–H_2O–CH_2OH]^+$ (36). Found, *m/z*: 169.0828 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

1,3-*trans*-4-Hydroxymethyl-1-methylcyclopentane-1,3-diol (*trans*-5b). $LiAlH_4$ (41 mg, 1.06 mmol) was suspended in THF (2.5 ml), and solution of compound *exo*-**4b** (130.3 mg, 0.51 mmol) in THF (2.5 ml) was added at 0°C. The resulting suspension was heated to reflux for 1 h, then the reaction mixture was cooled to 0°C and water added (41 μl). Stirring was continued for 0.5 h with gradual rise of temperature to 23°C. Then aqueous 10% NaOH (41 μl) at 23°C was added and the stirring continued for additional 0.5 h, upon which water (123 μl) was added. The

reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield crude protected diol, which was dissolved in CH_2Cl_2 (5 ml), and 6N HCl (200 μl) was added. Resulting two phase system was stirred vigorously for 5 min and then the volatiles were removed *in vacuo* to yield crude diol *trans*-**5b** which was purified by flash chromatography on SiO_2, eluent with CH_2Cl_2–MeOH, 20:1 to 10:1. Yield 46.7 mg (63%). Light yellow oil. IR spectrum (thin layer), ν, cm^{-1}: 3331 (OH), 1057 (C–O), 1031 (C–O). ^{1}H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 4.10 (1H, dd, *J* = 13.6, *J* = 7.6, 3-CH); 3.68 (1H, dt, *J* = 9.5, *J* = 5.9) and 3.58–3.55 (1H, m, C<u>H</u>$_2$OH); 2.07 (1H, ddd, *J* = 13.2, *J* = 7.1, *J* = 1.4, 4-CH); 2.01–1.94 (2H, m) and 1.67–1.52 (2H, m, 2,5-CH_2); 1.33 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 77.8 (C-1); 75.2 (C-3); 65.4 (<u>C</u>H_2OH); 50.8 (C-4); 50.7 (C-2); 43.8 (C-5); 29.5 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 128 $[M–H_2O]^+$ (1), 113 $[M–H_2O–CH_3]^+$ (15), 98 $[M+H–H_2O–CH_2OH]^+$ (11), 97 $[M–H_2O–CH_2OH]^+$ (4). Found, *m/z*: 169.0824 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

1,3-*cis*-4-hydroxymethyl-1-methylcyclopentane-1,3-diol (*cis*-5b). $LiAlH_4$ (43.5 mg, 1.12 mmol) was suspended in THF (2.5 ml), and solution of compound *endo*-**4b** (135.2 mg, 0.53 mmol) in THF (2.5 ml) was added at 0°C. The resulting suspension was heated to reflux for 1h, then the reaction mixture was cooled to 0°C and water added (44 μl). Stirring was continued for 0.5 h with gradual rise of temperature to 19°C. Then aqueous 10% NaOH (100 μl) at 19°C was added and the stirring continued for additional 0.5 h, upon which water (132 μl) was added. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield crude diol *cis*-**5b** which was purified by flash chromatography on SiO_2, eluent with CH_2Cl_2–MeOH 40:1 to 20:1 mixture. Yield 44.3 mg (55%). Light yellow oil. IR spectrum (thin layer), ν, cm^{-1}: 3383 (OH), 1033 (C–O). ^{1}H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 4.26 (1H, td, *J* = 4.9, *J* = 2.8, 3-CH); 3.79 (1H, dd, *J* = 10.7, *J* = 7.5) and 3.66–3.58 (1H, m, C<u>H</u>$_2$OH); 2.20–2.10 (1H, m, 4-CH); 1.90–1.81 (3H, m, 2-CH_2, 5-CH_A); 1.77–1.68 (1H, m, 5-CH_B); 1.30 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 79.4 (C-1); 74.8 (C-3); 63.2 (<u>C</u>H_2OH); 50.8 (C-2); 47.7 (C-4); 43.8 (C-5); 29.8 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 147 $[M+H]^+$ (1), 128 $[M–H_2O]^+$ (2), 113 $[M–H_2O–CH_3]^+$ (2), 98 $[M+H–H_2O–CH_2OH]^+$ (10), 97 $[M–H_2O–CH_2OH]^+$ (5). Found, *m/z*: 169.0825 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

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