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

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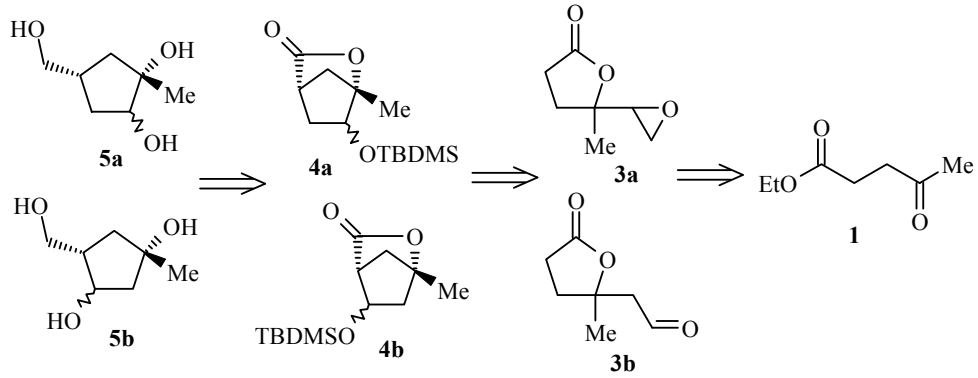
A method for the synthesis of 1-methylcarbapentofuranose derivatives was developed, where 1,2-cis- and 1,2-trans-4-hydroxymethyl-1-methylcyclopentanediols were obtained from intramolecular opening of a 4-epoxy-4-methyl-γ-lactone. An intramolecular aldol reaction of 4-methyl-4-(2-oxoethyl)-γ-lactone derivatives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

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 analogs. Prostaglandins F [1, 2] and phytoprostanes [3], antiviral [4-6] and anticancer [7-9] carbacyclic nucleoside analogs present only a few examples of such compounds. It is obvious that the synthesis of differently substituted cyclopentane structures and pentofuranose carba analogs has attained considerable interest in the last few decades [10-12]. Also, several methods for stereoselective synthesis of compounds with structures of this type have been published [13-15].

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



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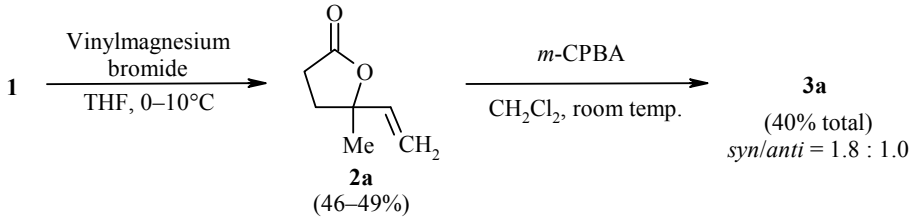
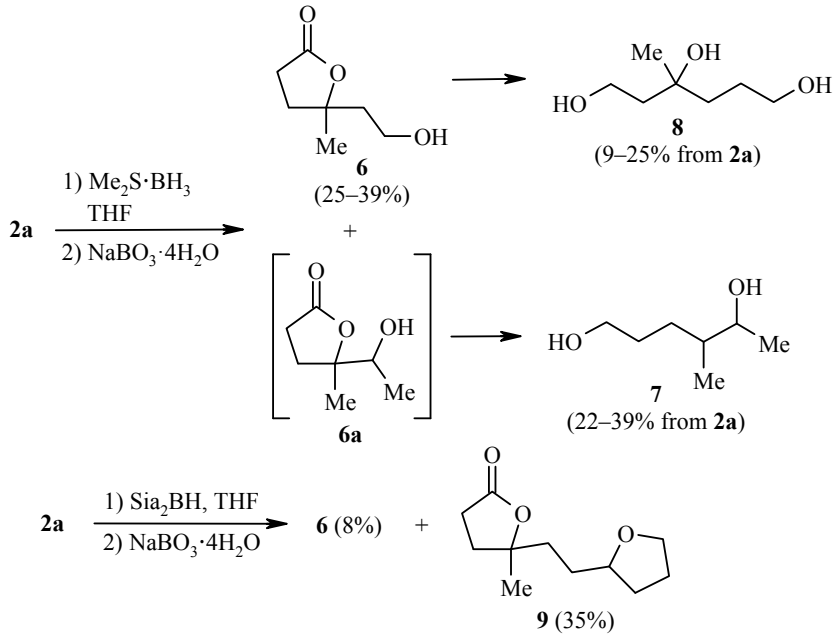
The location of the secondary OH group in the cyclopentane ring was determined by the key intermediate 3: compounds with 2-OH group are obtained from epoxide 3a, and compounds with 3-OH group, from the aldehyde 3b.

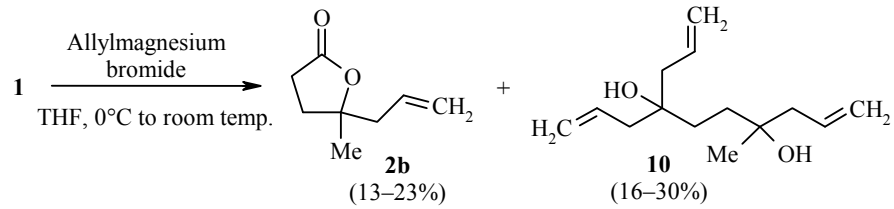
Lactone intermediates **2a**,**b** were prepared starting from ethyl levulinate **1**. Thus, addition of vinylic Grignard reagent to compound **1** [19], followed by intramolecular cyclization, afforded lactone **2a** (49% yield after distillation). The double bond of lactone **2a** was epoxidized with *m*-chloroperbenzoic acid (*m*-CPBA), resulting in a diastereomeric mixture of epoxy lactones **3a** in the *syn*/*anti* isomers ratio of 1.8:1.0, in 40% overall isolated yield.



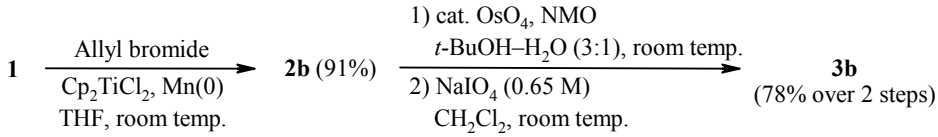
We also intended to obtain lactone aldehyde **3b** directly from vinyl lactone **2a** (*via* lactone alcohol **6**), by using a hydroboration–oxidation sequence. Despite our many attempts using $Me_2S{\cdot}BH_3$ in THF at different substrate/reactant ratios and reaction conditions, we always obtained 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%, along with compound **7**, which very likely formed in 22-39% yield from regioisomer **6a**, after a hydroboration–elimination–rehydroboration sequence [20]. Also, we isolated 9-25% of the reduction product **8**. Even using a sterically bulky boron reagent disiamylborane (Sia_2BH) (110 mol%, from 0°C to room temperature, 44 h) did not improve the results – compound **6** was formed in only 8% yield after 44 h at room temperature; 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 the **6**/**7** ratio) prompted us to pursue another 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 mixtures of monoaddition adduct **2b** (after lactonization) and triple addition adduct **10** in variable ratios. The yield of monoaddition adduct **2b** did not exceed 23% in the best case.

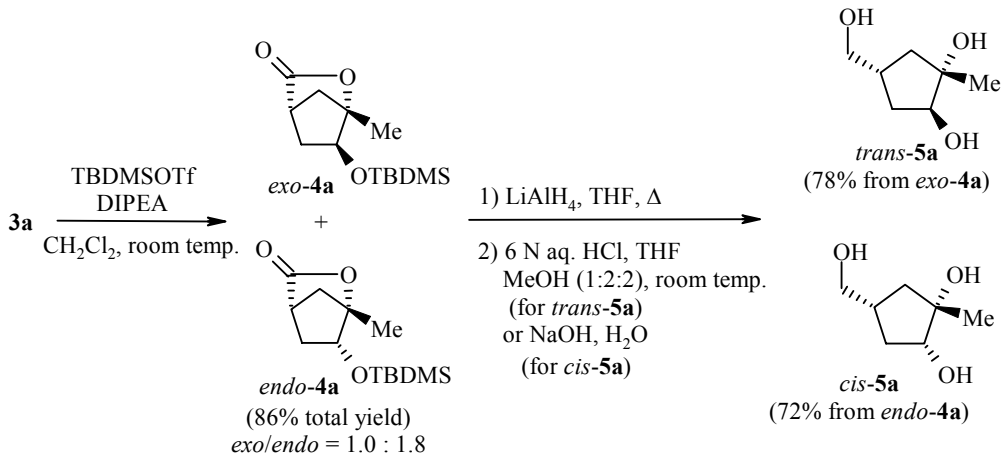


Fortunately, Ti(III)-mediated Barbier type allylation of ethyl levulinate **1** according to Estevez [21] with 1.5-fold excess of allyl bromide afforded allylic lactone **2b** in 91% yield. Two-step oxidation of γ-lactone **2b** and osmium-catalyzed dihydroxylation followed by $NaIO_4$-induced oxidative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



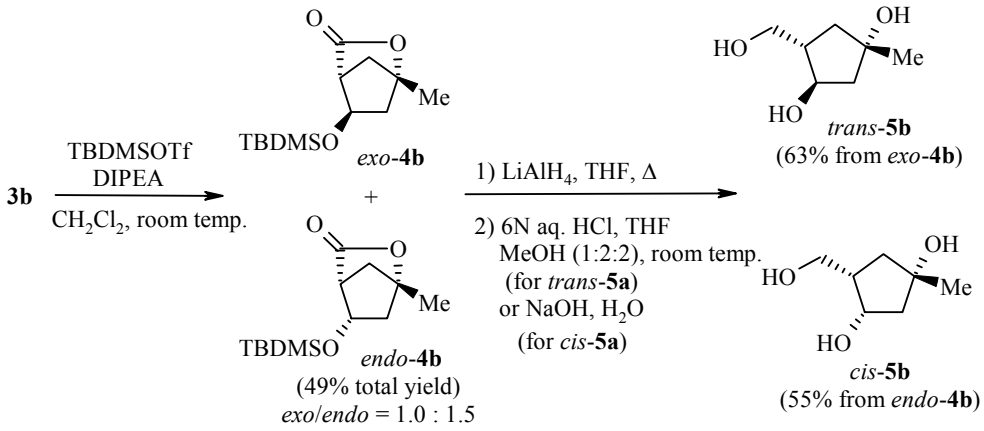
There are several reports in the literature where the intramolecular epoxide opening has been used to construct functionalized cyclopentane structural units. Some of the examples include NaH-assisted synthesis of the bicyclic skeleton of 9-deoxyenglerin A [25], Lewis acid (BF_3)-catalyzed intramolecular 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 a regioselective manner by the use of TBDMSOTf–DIPEA reagent system [28].



The cyclization afforded stable diastereomeric silyl-protected alcohols **4a** in a good yield (86%) as the primary reaction products, in a similar *exo*/*endo* diastereomer ratio as 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 6 N 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 compound *endo*-**4a** in 72% yield after treatment of the reaction mixture with aqueos NaOH solution without the 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 ~1.0:1.5.



The subsequent transformations were carried out separately 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 a 1:2:2 mixture of aqueous 6 N HCl, MeOH, and THF to afford isomer *trans*-**5b** in 63% yield over two steps. A similar transformation of compound *endo*-**4b** to isomer *cis*-**5b** was achieved in 55% yield by a direct one-step quenching the mixture with aqueous NaOH.

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

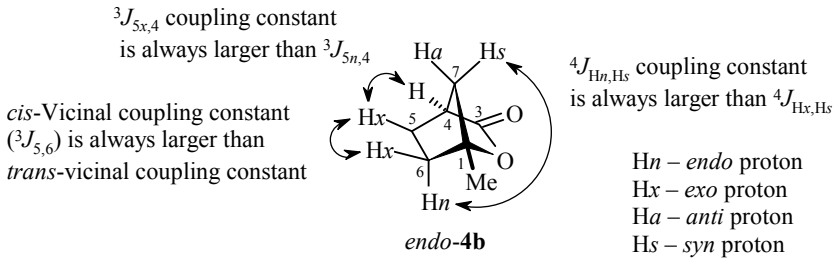


Fig. 1. Relevant interactions for the structure determination.
(TBDMSO group at position 5*n* is not shown)

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

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

Thus, through unprecedented use of the TBDMSOTf–DIPEA reagent system, a regio- and stereospecific epoxide opening reaction was investigated and efficiently applied to the synthesis of novel methyl branched cyclopentane derivatives *via* heterocyclic bicyclo[2.2.1]heptanes. Appropriate substrate selection allowed us to achieve the synthesis of regioisomeric 5- and 1-methyl-6-silyloxy-2-oxa-bicyclo[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

The IR spectra were measured on a Perkin-Elmer Spectrum BX FTIR spectrometer. The NMR spectra were determined in $CDCl_3$ or CD_3OD on Bruker Avance USLA 400 or Bruker Avance 800 spectrometers. Residual solvent signals were used for reference. Mass spectra were recorded on Hitachi M80B or Shimadzu GCMSQP2010 spectrometers using EI ionization (70 eV). High-resolution mass spectra were recorded on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer 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 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 that, 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 the literature [19, 21]. Epoxides **3a** were synthesized by the 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). *m*-CPBA (551.3 mg, 2.46 mmol, 1.22 equiv) was added portionwise at 22°C to a solution of γ-vinyl lactone **2a** (253.6 mg, 2.01 mmol) in CH_2Cl_2 (5 ml). The resulting solution was stirred at 22°C for 25 h, during which precipitation occurred. A 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% aqueous solution of $Na_2S_2O_3$ (5 ml) and 5% aqueous solution of $NaHCO_3$ (5 ml) with vigorous stirring. The layers were separated and the water phase extracted with CH_2Cl_2 (4×10 ml). The combined organic phases were washed sequentially with $NaHCO_3$ (10 ml) and saturated NaCl (10 ml), then dried over Na_2SO_4. Filtration and evaporation of volatiles afforded the crude product, from which, after purification by flash chromatography (silica gel, CH_2Cl_2–MeOH, 200:1), diastereomeric epoxides **3a** were obtained as a light-yellow oil (112 mg, 40%, *syn/anti* = 1.8:1.0). IR spectrum (thin layer), ν, cm^{-1}: 2984 (CH), 1778 (CO). ^1H 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). 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) were consecutively added to a 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). After stirring at 22°C for 23 h, the reaction mixture was treated with 20% aqueous Na_2SO_3 (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 1 M $NaHSO_4$ (2 ml) was added to the residue to adjust the pH to 2. The water phase was extracted with EtOAc (15×15 ml, NaCl (2 g) was added to the water phase after the 10th extract), dried over $MgSO_4$, and filtered through a short pad of silica to yield crude 5-(2,3-dihydroxypropyl)-5-methyldihydrofuran-2-one (562.5 mg) as a 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), $NaIO_4$ (0.65 M, 5.3 ml) and silica (5.22 g) were added at 22°C. The resulting slurry was stirred for 40 min and then filtered through a pad of silica. The solids on the filter were washed with CH_2Cl_2 (3×25 ml) and EtOAc (2×25 ml), and the solvents were evaporated to yield the crude aldehyde **3b** as a 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 ($\underline{C}H_2$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 a diastereomeric mixture of epoxides **3a** (69 mg, 0.49 mmol) in CH_2Cl_2 (3 ml) was added dropwise at 25°C over a period of 10-15 min. The resulting solution (0.06 M of substrate) was stirred for 0.5 h at 25°C, after which the reaction mixture was added to a saturated aqueous NH_4Cl solution, and the layers were separated. The 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 (silica gel, heptane–acetone, 40:1 to 10:1) to yield compounds *exo*-**4a** (66.6 mg, 54%) and *endo*-**4a** (39.0 mg, 32%) in the 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*-Bu]$^+$ (31), 171 [M-*t*-Bu-CO]$^+$, (41), 155 [M-*t*-Bu-COOH]$^+$ (26), 141 [M-TBDMS]$^+$ (1), 127 [M+1-TBDMS-CH$_3$]$^+$ (9), 115 [TBDMS]$^+$ (28), 75 [C$_2$H$_7$SiO]$^+$ (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*-Bu]$^+$ (12), 171 [M-*t*-Bu-CO]$^+$ (23), 155 [M-*t*-Bu-COOH]$^+$ (46), 141 [M-TBDMS]$^+$ (1), 127 [M+1-TBDMS-CH$_3$]$^+$ (13), 115 [TBDMS]$^+$ (22), 75 [C$_2$H$_7$SiO]$^+$ (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 on a 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*-Bu]$^+$ (33), 171 [M-*t*-Bu-CO]$^+$ (4), 155 [M-*t*-Bu-COOH]$^+$ (7), 115 [TBDMS]$^+$ (2), 75 [C$_2$H$_7$SiO]$^+$ (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*-Bu]$^+$ (30); 171 [M–*t*-Bu–CO]$^+$ (8); 155 [M–*t*-Bu–COOH]$^+$ (6); 75 [C$_2$H$_7$SiO]$^+$ (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 a 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 was 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 an additional 0.5 h to complete the precipitation. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield the crude protected diol. Mass spectrum, *m/z* (I_{rel}, %): 243 [M+H-H$_2$O]$^+$ (1), 227 [M-H$_2$O-CH$_3$]$^+$ (1), 203 [M-*t*-Bu]$^+$ (12), 185 [M-H$_2$O-*t*-Bu]$^+$ (42), 129 [M+H-H$_2$O-TBDMS]$^+$ (2), 75 [C$_2$H$_7$SiO]$^+$ (100).

To a solution of the protected diol (130.3 mg, 0.50 mmol) in a mixture of THF (2 ml) and MeOH (2 ml), 6 N 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 a light-yellow oil. Further purification was achieved by

flash chromatography on silica gel 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). ^1H 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<u>H</u>$_2$OH); 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 a solution of the 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 (100 μl) was added. 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 an additional 0.5 h to complete the precipitation. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield the crude diol *cis*-**5a**, which was purified by flash chromatography on silica gel, eluent CH_2Cl_2–MeOH, 10:1. Yield 36.4 mg (72%). Light to colorless oil. IR spectrum (thin layer), ν, cm^{-1}: 3381 (OH), 1086 (C–O), 1043 (C–O). ^1H 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<u>H</u>$_2$OH); 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 (<u>C</u>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 a solution of the 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 (41 μl) was added. 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 was continued for an 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 the crude protected diol, which was dissolved in CH_2Cl_2 (5 ml), and 6 N HCl (200 μl) was added. The resulting two-phase system was stirred vigorously for 5 min and then the volatiles were removed *in vacuo* to yield the crude diol *trans*-**5b**, which was purified by flash chromatography on silica gel, eluent 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). ^1H 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 a solution of the 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 (44 μl) was added. Stirring was continued for 0.5 h with gradual rise of temperature to 19°C. Then aqueous 10% NaOH (100 μl) was added at 19°C, and the stirring continued for an 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 the crude diol *cis*-**5b** which was purified by flash chromatography on silica gel, eluent 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). ^1H 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 ($\underline{C}H_2OH$); 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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