# Enzyme-Catalyzed Stereoselective Synthesis of Two Novel Carbasugar Derivatives

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Enzymatic resolution of racemic 1,4,5,6-tetrachloro-2-(hydroxymethyl)-7,7-dimethoxybicyclo[2.2.1]-hept-5-ene (*rac*-**1**) using various lipases in vinyl acetate as acetyl source was studied. The obtained enantiomerically enriched (+)-(1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)methyl acetate ((+)-**2**; 94% ee), upon treatment with Na in liquid $NH_3$, followed by *Amberlyst-15* resin in acetone, provided (−)-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-one ((−)-**7**), which is a valuable precursor for the synthesis of carbasugar derivatives. Subsequent *Baeyer–Villiger* oxidation afforded a nonseparable mixture of bicyclic lactones, which was subjected to $LiAlH_4$ reduction and then acetylation. The resultant compounds (−)-**11** and (+)-**12** were submitted to a *cis*-hydroxylation reaction, followed by acetylation, to afford the novel carbasugar derivatives (1*S*,2*R*,3*S*,4*S*,5*S*)-4,5-bis(acetoxymethyl)cyclohexane-1,2,3-triyl triacetate ((−)-(**13**)) and (1*R*,3*R*,4*R*,6*R*)-4,6-bis(acetoxymethyl)cyclohexane-1,2,3-triyl triacetate ((−)-(**14**)), respectively, with *pseudo*-$C_2$-symmetric configuration. The absolute configuration of enantiomerically enriched unreacted alcohol (−)-**1** (68% ee) was determined by X-ray single-crystal analysis by anchoring optically pure (*R*)-1-phenylethanamine. Based on the configurational correlation between (−)-**1** and (+)-**2**, the absolute configuration of (+)-**2** was determined as (1*R*,2*R*,4*S*).

**1. Introduction.** – Polyhydroxylated cyclohexanoids are widespread in the nature, and they usually possess a wide range of important biological activities [1]. In view of their potential as therapeutic agents for the treatment of a variety of carbohydrate-mediated diseases like diabetes, AIDS, viral infections, and cancers, many structural variants of conduritol and carbasugar have been synthesized [2]. A novel approach for the synthesis of several carbasugars emanating from norbornyl systems has been developed by *Mehta et al.* [3].

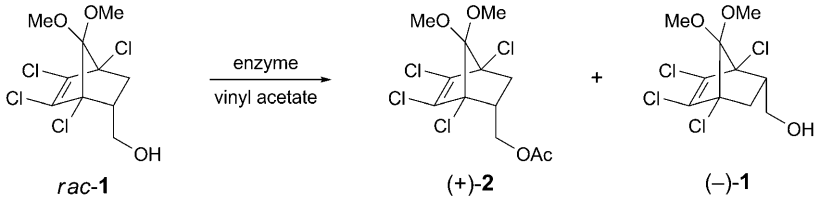
The increasing demand for the synthesis of enantiomerically pure compounds has led to the investigation of different approaches for obtaining chiral cyclitol derivatives. One of the most promising methods is the use of a microbial enzyme, *Pseudomonas putida* [4], to convert achiral aromatic compounds to the optically active key compounds of cyclitol derivatives [5].

The pursuit for novel approaches in enantiomerically pure compound (EPC) syntheses is a major topic in modern organic synthesis [6]. The chemo-enzymatic approach for asymmetric synthesis has been increasingly included in synthetic strategies, while the use of biocatalysts as routine chiral catalysts has already found widespread application in preparative organic chemistry over the last decade [7]. Lipases can catalyze asymmetric hydrolysis [8] as well as esterification [9]. This property has attracted a great deal of attention from synthetic chemists, since lipases do

not require cofactors, and are readily available and easily handled. Polychlorinated norbornene adducts can be given as an interesting example of the extensive application area of lipases. In the literature, there are only a few examples of enzymatic resolution of hexa- and tetrachlorinated norbornene and norbornadiene derivatives [10]. Recently, we reported the enzymatic resolution of various hydroxymethyl-substituted hexachlorinated norbornene and norbornadiene derivatives [11]. In connection with these biotransformations, we turned our attention to the enzymatic resolution of *rac*-1,4,5,6-tetrachloro-2-*endo*-(hydroxymethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-ene, which involves versatile structural benefits. High *endo* selectivity can be obtained during the *Diels–Alder* reactions of 1,2,3,4-tetrachloro-5,5-dimetoxycyclopentadiene because of the steric repulsion of its MeO groups at C(5). Moreover, it is well documented by *Mehta et al.* [3] that the dimethoxy-substituted bridge C-atom of similar cycloadducts may serve as a precursor of OH and $HOCH_2$ groups in the synthesis of carbasugar derivatives. On the basis of the versatility of 2-*endo*-(acetoxymethyl)-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene (**2**), here, we report the resolution of *rac*-**1** and the highly efficient enantioselective conversion of the resulting enantiomerically enriched acetate (+)-**2** to carbasugar derivatives (1*S*,2*R*,3*S*,4*S*,5*S*)-4,5-bis(acetoxymethyl)cyclohexane-1,2,3-triyl triacetate ((−)-**13**) and *pseudo*-$C_2$-symmetric (1*R*,3*R*,4*R*,6*R*)-4,6-bis(acetoxymethyl)cyclohexane-1,2,3-triyl triacetate ((−)-**14**). To the best of our knowledge, this is the first stereoselective synthesis of novel carbasugar derivatives.

**2. Results and Discussion.** – 2.1. *Synthesis and Enzymatic Resolution of* rac-**1**. The key substrate *rac*-**1** was synthesized, in its pure *endo*-form, through a *Diels–Alder* reaction by heating a mixture of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and allyl alcohol (1:1.2 molar ratio) to 150° for 50 h in a sealed tube [12]. Then, various lipases were tested with *rac*-**1** in the presence of vinyl acetate as acetyl source (*Scheme 1*).

*Scheme 1*




*rac*-**1** (+)-**2** (−)-**1**

The first bioconversion was performed using porcine pancrease lipase (PPL) according to the following procedure (*Table 1*). To a stirred solution of *rac*-**1** (500 mg) in vinyl acetate (5 ml) was added PPL (50 mg) in one portion, and the mixture was shaken at 25°. The conversion was monitored by TLC, and 38% conversion was achieved after 45 h. The products were separated by flash column chromatography, and (+)-**2** was isolated in 45% yield with 64% ee (*Entry 1*). The next attempts involved the resolutions achieved by *Candida rugosa* lipase (CRL; 50 mg) and *Novazyme 435*

(100 mg) under the same conditions as described above (*Entries 2* and *3*, resp.). CRL appeared to be the best enzyme tested, since (+)-(1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)methyl acetate ((+)-**2**) was isolated in 44% yield with 94% ee, whereas *Novazyme 435* (*Entry 3*) showed an acceptable level of enantioselectivity (86% ee) and appeared to be the most efficient in terms of reaction duration (20 h). All of the enzymes afforded the acetylated derivative **2** with the same configuration. To improve the ee value, experimental conditions were tested in detail using various co-solvents such as $(i\text{-}Pr)_2O$, i-PrOH, *t*-BuOMe, and BuOH, and changing the amount of CRL used. No increase in the enantioselectivity was observed. In all cases, the acetylation was interrupted after 40% conversion, since a longer reaction time and conversion near 50% gave (+)-**2** with a lower ee value. On the other hand, this approach caused a decrease in the ee value of the unreacted alcohol (−)-**1**. All ee determinations were performed with the acetylated derivative **2**, since it was effectively resolved by HPLC. Hence, the unreacted alcohol (−)-**1** was acetylated by $Ac_2O$ in pyridine, and, then, the ee value was determined by HPLC.

Table 1. *Results of the Enzyme-Catalyzed Acetylation of* rac-**1**

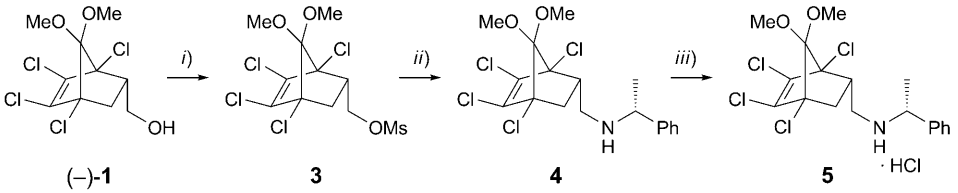
| *Entry* | Lipase | Time [h] | Esters $ee_p$ [%][a]) | Alcohols $ee_s$ [%][b]) | *c* [%][c]) | *E*[d]) |
|---|---|---|---|---|---|---|
| *1* | PPL | 45 | 64 | 39 | 38 | 7 |
| *2* | CRL | 68 | 94 | 68 | 42 | 65 |
| *3* | *Novazyme 435* | 20 | 86 | 54 | 39 | 21 |

[a]) Enantiomeric excess (ee) values were determined by HPLC using *Chiralcel OD-H* chiral column. [b]) ee was calculated after transforming to corresponding acetate. [c]) $c = ee_s/(ee_s + ee_p)$. [d]) Calculated by the method of *Sih* and co-workers: $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$ [13].

2.2. *Determination of Absolute Configuration of (−)-***1** *and (+)-***2**. The absolute configuration of (+)-**2** was not known, and its assignment was crucial since we used it as a reference for the determination of the absolute configuration of newly generated stereogenic centers in the target carbasugar derivatives. We decided to utilize recovered unreacted alcohol (−)-**1** with low ee (68%), which was found to be useful and economical, since we were able to determine accurately the ee value of (−)-**1**. The absolute configuration of (−)-**1** was determined by X-ray single-crystal analysis. We planned to anchor an optically pure chiral unit with a known configuration as a reference. For this purpose, enantiomerically enriched unreacted alcohol (−)-**1** was transformed into the 1-phenylethanamine derivative **4** *via* first mesylation of **3** and subsequent substitution with optically pure (*R*)-1-phenylethanamine (*Scheme 2*). We were unable to grow single crystals of **4**, but then, it was converted to its HCl salt by passing HCl gas through the solution to afford suitable crystals of **5**.

The crystal-structure analysis of **5** confirmed the compound as 1-phenyl-*N*-[(1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)methyl]ethanammonium chloride (*Fig. 1*). There are four ion pairs (I to IV) in the asymmetric unit (triclinic non-centrosymmetric space group *P*1). In the crystal, 84.1% of the cations (namely, the cations I to III, and 36.4(3)% of the cations IV) show the (*R*,*S*,*S*,*R*)-configuration (related to the asymmetric C-atoms at C(1), C(4), C(5), and C(17) in molecule **5**), and 15.9% (namely, 63.6(3)% of the cations IV) show the (*S*,*R*,*R*,*R*)-configuration (*Fig. 2*).

*Scheme 2*




*i*) MsCl, $Et_3N$, $CH_2Cl_2$. *ii*) (+)-(*R*)-1-Phenylethanamine. *iii*) HCl (gas) in $Et_2O$.

Due to this disorder, two of the four $Cl^-$ ions are disordered as well. Nevertheless, each N-atom has exactly two H-bonds by each of its bonded H-atoms to a $Cl^-$ ion (*Table 2*). By these H-bonds, an isolated tetrameric aggregate consisting of four $Cl^-$ ions and four almost coplanar $NH_2^+$ groups is formed (*Fig. 3*). Due to the configurational correlation between (–)-**1** and (+)-**2**, the absolute configuration of (+)-**2** was determined as (1*R*,2*R*,4*S*).

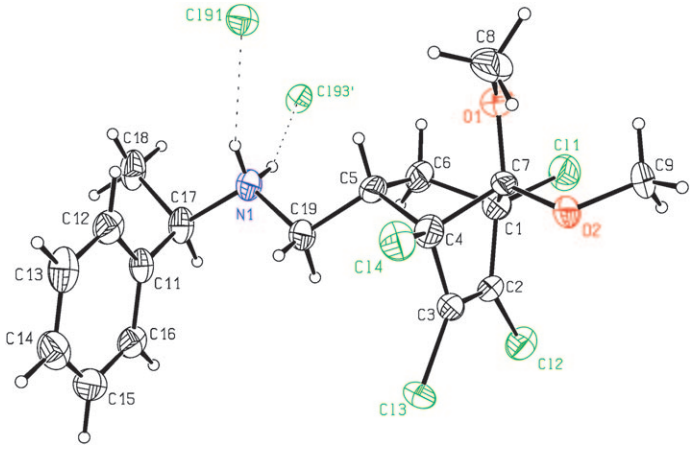



Fig. 1. *ORTEP* [14] *Plot of one cation of* **5** (together with its coordinating anions showing the atomic numbering scheme). The presumed H-bonds are indicated with dotted lines.

2.3. *Stereoselective Syntheses.* After successful enzymatic resolution and absolute-configuration determination of the key compound (+)-(1*R*,2*R*,4*S*)-**2**, we turned our attention to the reductive dechlorination. Tetrachloro derivative (+)-(1*R*,2*R*,4*S*)-**2** was successfully converted to the desired dechlorinated derivative (–)-(1*S*,2*S*,4*S*)-**6** by treatment of (+)-**2** with Na in liquid $NH_3$ [15]. During the course of this reaction, deacetylation occurred, as expected. The structure of (–)-(1*S*,2*S*,4*S*)-**6** was assigned on the basis of the $^1$H-NMR spectrum. The most distinctive features were the olefinic H-atom resonances. The olefinic H-atoms of (–)-**6** resonating at $\delta$(H) 6.18 (*dd*, $J = 3.2$, 6.0 Hz) and 6.04 (*dd*, $J = 3.2$, 6.0 Hz) show further splitting with adjacent bridgehead H-atoms. Compound (–)-**6** was readily and almost quantitatively deprotected by

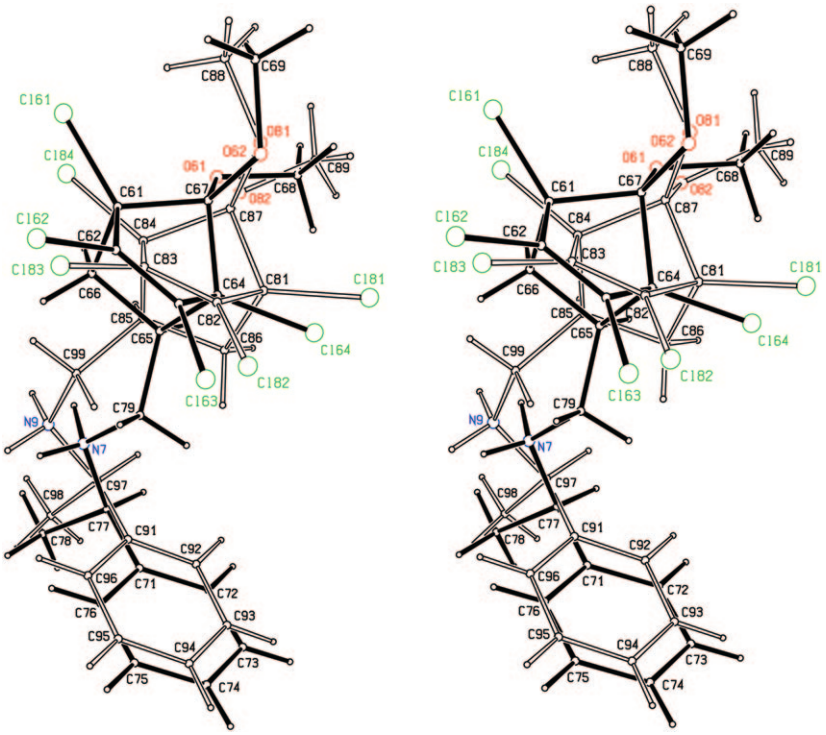



Fig. 2. *ORTEP* [14] *plot of the disordered cation IV of* **5**. The atoms are drawn with arbitrary radii. The cation with the (*S*,*R*,*R*,*R*)-configuration (site occupation factors of 0.636(3)) is drawn with full bonds, the cation with the (*R*,*S*,*S*,*R*)-configuration (site occupation factors of 0.364(3)) is drawn with open bonds.

*Amberlyst-15* resin in acetone to afford the ketone (−)-(1*S*,2*S*,4*S*)-**7** in 99% yield [16]. In particular, the $^{13}$C-NMR spectrum consisting of a characteristic ketone resonance signal at $\delta$(C) 204.6 was a good evidence for the structure of (−)-(1*S*,2*S*,4*S*)-**7**. So far, since only the C−Cl bonds were cleaved, and subsequently the ketal group was transferred to the corresponding oxo group in these reactions, the configuration at all C-atoms were preserved (*Scheme 3*).

In our synthetic design, the norbornen-7-one ((−)-**7**) is an ideal substrate for the synthesis of carbasugar derivatives. We planned to use the oxo group as the source of $HOCH_2$ and OH groups. The OH group of compound (−)-**7** was protected by the Ac group prior to the *Baeyer–Villiger* oxidation to avoid possible side-reactions. The reaction of acetyl derivative (−)-**8** with *m*-CPBA resulted in the formation of a mixture of two lactone isomers, **9** and **10**, in 75% total yield. Although many attempts were made to separate the mixture **9**/**10**, we did not obtain satisfactory results and decided to proceed to the next step, in which the mixture **9**/**10** was subjected to $LiAlH_4$ reduction in dry THF. After acetylation of the mixture with $Ac_2O$ in pyridine, the products (−)-**11** and (+)-**12** were isolated in 36 and 45% yields, respectively. The structures of (−)-**11** and (+)-**12** were assigned on the basis of the $^1$H-NMR spectra. The most characteristic features of (−)-**11** and (+)-**12** are the resonances of the AcO-bearing CH groups. The

Table 2. *H-Bonds of* **5**. The N–H distances were restrained to 0.92 Å. The atoms Cl(93), Cl(94), N(7), H(701), and H(702) have site occupation factors of 0.636(3), the corresponding atoms Cl(95), Cl(96), N(9), H(901), and H(902) have site occupation factors of 0.364(3).

| D–H···A | $d$(H···A) [Å] | $d$(D···A) [Å] | <(DHA) [°] |
|---|---|---|---|
| N(1)–H(102)···Cl(91) | 2.36 | 3.232(4) | 158.0 |
| N(1)–H(101)···Cl(93)[a]) | 2.40 | 3.291(6) | 162.5 |
| N(1)–H(101)···Cl(95)[a]) | 2.25 | 3.117(9) | 156.1 |
| N(3)–H(301)···Cl(91)[b]) | 2.39 | 3.271(4) | 160.6 |
| N(3)–H(302)···Cl(93) | 2.39 | 3.274(6) | 161.6 |
| N(3)–H(302)···Cl(95) | 2.07 | 2.919(8) | 152.2 |
| N(5)–H(501)···Cl(92) | 2.19 | 3.082(3) | 163.8 |
| N(5)–H(502)···Cl(91)[c]) | 2.32 | 3.221(3) | 167.0 |
| N(7)–H(702)···Cl(93) | 2.29 | 3.179(7) | 161.3 |
| N(7)–H(701)···Cl(94) | 2.24 | 3.072(6) | 150.2 |
| N(9)–H(902)···Cl(95) | 2.32 | 3.126(13) | 146.5 |
| N(9)–H(901)···Cl(96) | 2.08 | 2.997(14) | 171.1 |

Symmetry transformations used to generate equivalent atoms: [a]) $x, y, z-1$. [b]) $x, y, z+1$. [c]) $x, y+1, z$.

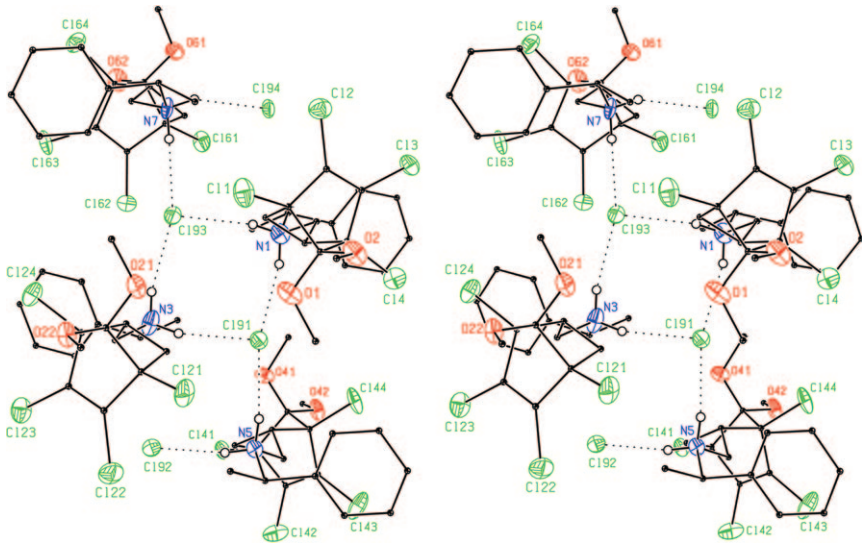
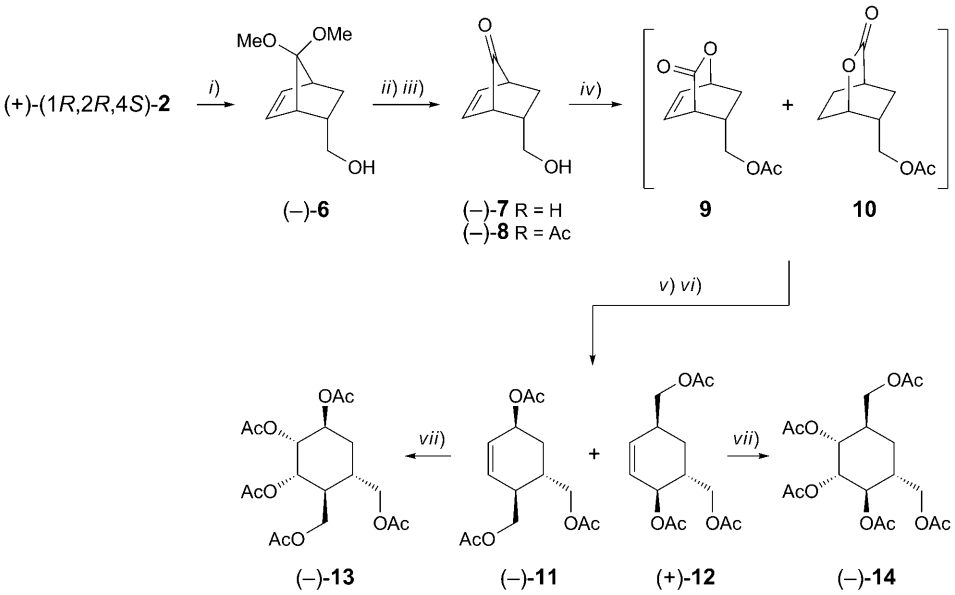



Fig. 3. *Stereoscopic ORTEP* [14] *plot of the H-bonded aggregate of* **5**. The probability ellipsoids are drawn at the 50% probability level, the C- and H-atoms bonded to N-atoms are drawn with arbitrary radii, the other H-atoms as well as the atoms with site occupation factors less than 0.5 are omitted for clarity. The presumed H-bonds are drawn with dotted lines.

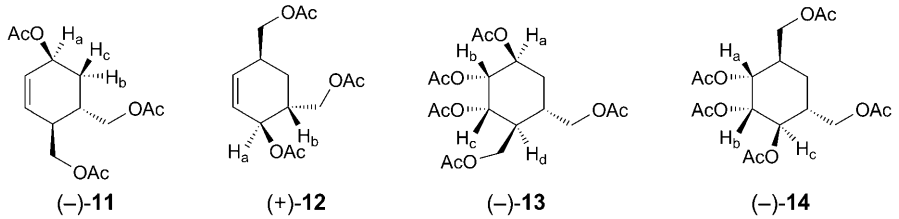
CH H-atom, $H_a$, of (–)-**11** resonates at $\delta$(H) 5.17 ($J = 3.6$ Hz) as a *quartet*, whereas $H_a$ of (+)-**12** gives rise to a signal at $\delta$(H) 5.09 ($J = 5.0, 1.6$ Hz) as a *dd*. The positions of the AcO groups in (–)-**11** and (+)-**12** were determined with the help of the COSY spectra: $H_a$ of (–)-**11** shows cross-peaks with the neighboring diastereotopic $CH_2$ H-atoms, $H_b$

*Scheme 3*




*i*) Na, $NH_3$ (liq.). *ii*) *Amberlyst-15* resin. *iii*) AcCl, pyridine, $CH_2Cl_2$. *iv*) *m*-CPBA, $CH_2Cl_2$. *v*) $LiAlH_4$, THF. *vi*) AcCl, pyridine, $CH_2Cl_2$. *vii*) $OsO_4$-NMO (*N*-methylmorpholine *N*-oxide) and then $Ac_2O$, pyridine.

and $H_c$, resonating at $\delta$(H) 1.82 ($J = 14.1$ and 3.5 Hz) as a *dt* and 1.67 ($J = 14.1$, 11.1, 4.5 Hz) as a *ddd*, respectively. In the COSY spectrum of (+)-**12**, $H_a$ exhibits a cross-peak with the neighboring $H_b$ resonating at $\delta$(H) 2.12–2.04 as a *multiplet*.




Finally, for further functionalization of the C=C bond, we studied the *cis*-hydroxylation of compounds (–)-**11** and (+)-**12**. Triacetate (–)-**11** was reacted with $OsO_4$-NMO (*N*-methylmorpholine *N*-oxide) followed by acetylation to afford pentaacetate (–)-**13**. The NMR data confirmed the formation of a single isomer. The stereochemical course of the *cis*-hydroxylation may be *syn* or *anti* with respect to 1,4-substituted AcO and $AcOCH_2$ groups. To determine the exact configuration of pentaacetate (–)-**13**, first we made complete assignments for the CH H-atoms $H_a$, $H_b$, and $H_c$ with the help of the COSY spectrum. The H-atoms $H_a$, $H_b$, and $H_c$ resonate at $\delta$(H) 4.97 ($J = 3.2$ Hz) as a *quartet*, 5.19 ($J = 3.4$ Hz) as a *triplet*, and 5.04 ($J = 10.9$,

3.1 Hz) as a *dd*, respectively. The $H_a$-atom shows a cross-peak with neighboring $CH_2$ H-atoms ($\delta$(H) 1.84–1.67 as a *multiplet*), whereas $H_c$ exhibits a cross-peak with the neighboring $H_d$-atom. In particular, $H_c$ resonating as a *dd* with coupling constants of $J = 10.9$ and 3.1 Hz strongly supports the *trans*-relation of $H_c$ and $H_d$, and the *cis*-relation of $H_c$ and $H_b$, respectively.

Triacetate (+)-**12** was submitted to a *cis*-hydroxylation reaction as described above, followed by acetylation to afford pentaacetate (−)-**14** with *pseudo*-$C_2$-symmetry. The spectroscopic data confirmed the formation of a single isomer. We determined the positions of the CH H-atoms $H_a$, $H_b$, and $H_c$ by the COSY spectrum: $H_b$ reveals cross-peaks with both neighboring $H_a$ and $H_c$. The signal of $H_a$ appears at $\delta$(H) 5.01 as a *dd* with coupling constants of $J = 8.2$ and 3.1 Hz, which obviously supports the *trans*-relation between $H_a$ and the neighboring CH H-atom attached to the $AcOCH_2$ group and the *cis*-relation between $H_a$ and $H_b$, respectively. The $H_c$-atom resonates at $\delta$(H) 5.10 as a *triplet* with a coupling constant of $J = 8.2$ Hz, clearly indicating that $H_c$ is in *trans*-relations with both $H_b$ and the neighboring $AcOCH_2$-attached CH H-atom.

**3. Conclusions.** – In summary, we achieved the stereoselective synthesis of the two novel carbasugar derivatives (−)-**13** and (−)-**14** *via* a chemo-enzymatic approach. Enzymatic resolution of *rac*-1,4,5,6-tetrachloro-2-*endo*-(hydroxymethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-ene (*rac*-**1**) employing CRL-catalyzed esterification afforded enantiomerically enriched unreacted alcohol (−)-**1** and (+)-**2** with 68 and 94% ee, respectively. The absolute configuration was determined by X-ray single-crystal analysis of unreacted alcohol (−)-**1** anchored by optically pure (*R*)-1-phenylethanamine. Due to the configurational correlation between (−)-**1** and (+)-**2**, the absolute configuration of (+)-**2** was determined as (1*R*,2*R*,4*S*). This is crucial since we used it as a reference for the absolute-configuration determination of newly generated stereogenic centers in the target carbasugar derivatives. The key compound (+)-**2** was successfully converted to nonchlorinated derivative (−)-**6** and subsequently transformed into oxo-bridged derivative (−)-**7**, which preserves the configuration at all C-atoms. The OH group of (−)-**7** was protected with the Ac group prior to *Baeyer–Villiger* oxidation, followed by $LiAlH_4$ reduction and acetylation. For further functionalization of the C=C bond, (−)-**11** and (+)-**12** were submitted to a *cis*-hydroxylation with $OsO_4$-NMO, followed by acetylation to give the novel carbasugar derivatives (−)-**13** and (−)-**14**. The spectral data confirmed the formation of a single isomer for each case. The stereochemical course of the hydroxylation may be *syn* or *anti* with respect to the AcO and $AcOCH_2$ groups. The exact configuration of these carbasugars, (−)-**13** and (−)-**14**, was established by NMR spectroscopy. In particular, (−)-**14** possesses a very interesting stereochemical property, namely a *pseudo*-$C_2$-symmetry. This chemo-enzymatic approach may be extended to the stereoselective synthesis of further targets.

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## Experimental Part

1. *General*. Flash column chromatography (FC): silica gel ($SiO_2$; 60 mesh, *Merck*). The relative proportion of solvents in chromatography solvent mixtures refers to the *v*/*v* ratio. The reactions were monitored by TLC using $SiO_2$ *60* $F_{254}$ anal. aluminium plates (0.2 mm, *Merck*). HPLC: *Thermo Separation Products, Inc.*, *P1500-SN-4000-UV2000* instrument using a *Chiralcel OD-H* anal. column (250 × 4.60 mm). Optical rotations: *Rudolph* research analytical, *Autopol III* automatic polarimeter in a 1-dm cell. IR Spectra: *Varian 1000* FT-IR spectrophotometer; KBr pellets; $\tilde{\nu}$ in $cm^{-1}$. $^1$H- and $^{13}$C-NMR spectra: *Bruker Spectrospin Avance DPX 400* spectrometer in $CDCl_3$ at 400 ($^1$H) and 100 ($^{13}$C) MHz, resp.; $\delta$ in ppm rel. to $Me_4Si$ or the residual solvent peak as internal standard, *J* in Hz. HR-MS: *Waters SYNAPT*; in *m*/*z*.

2. *Starting Materials.* CRL (*Candida rugosa* lipase) was purchased from *Aldrich*. *Novazyme 435* was donated by *Novo Nordisk AS*, Bagsverd, Denmark. $CH_2Cl_2$ was distilled over $P_2O_5$, and THF was dried over Na under Ar.

3. *Enzymatic Resolution of* rac-**1**. To a stirred soln. of *rac*-**1** (500 mg) in vinyl acetate (5 ml) was added CRL (50 mg) in one portion, and the mixture was stirred at 25° (TLC monitoring). Then, the mixture was filtered, and vinyl acetate was evaporated under reduced pressure. The products (−)-**1** and (+)-**2** were purified by FC (AcOEt/hexane 1:4).

*(1S,2S,4S)-(1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)methanol* ((−)-**1**). Yield 54% (0.27 g). $[\alpha]_D^{20} = -15.1$ ($c = 1.8$, MeOH) for 68% ee.

*(1S,2R,4S)-(1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)methyl Acetate* ((+)-**2**). Yield 44% (0.25 g). HPLC-Analysis of (+)-**2**: *Chiralcel OD-H* at r.t., hexane/i-PrOH 99:1, flow rate 0.3 ml/min; $\lambda$, 230 nm; $t_1$, 19.8 min (minor); $t_2$, 21.3 min (major). $[\alpha]_D^{20} = +11.4$ ($c = 1.8$, MeOH) for 94% ee.

4. *Anchoring of (*R*)-1-Phenylethanamine to* (−)-**1**. 4.1. *[(1S,2R,4S)-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]methyl Methanesulfonate* (**3**). To a soln. of (−)-**1** (1 g, 3.1 mmol) and $Et_3N$ (0.87 ml, 6.2 mmol) in $CH_2Cl_2$ at 0° was slowly added MsCl (0.36 ml, 4.6 mmol). After stirring for 10 min, the mixture was diluted with $H_2O$, and the layers were separated. The org. layer was washed with $H_2O$ and brine, dried ($MgSO_4$), filtered, and concentrated at r.t. under reduced pressure to afford the crude methanesulfonate. Product **3** was purified by FC (AcOEt/hexane 1:3): 1.22 g (98%). $^1$H-NMR: 4.29 (*dd*, *J* = 10.3, 5.2, 1 H); 3.91 (*dd*, *J* = 10.2, 8.0, 1 H); 3.61 (*s*, 3 H); 3.55 (*s*, 3 H); 3.09–3.05 (*m*, 1 H); 3.03 (*s*, 3 H); 2.56 (*dd*, *J* = 11.9, 9.2, 1 H); 1.73 (*dd*, *J* = 12.1, 4.1, 1 H). $^{13}$C-NMR: 131.0; 127.7; 111.9; 77.4; 74.1; 67.4; 52.7; 51.7; 46.3; 39.3; 37.6.

4.2. *(*R*)-1-Phenyl-*N*-{[(1S,2R,4S)-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]methyl}ethanamine* (**4**). Compound **3** (0.5 g, 1.25 mmol) and (+)-(*R*)-1-phenylethanamine (1.5 ml) were stirred at 90° under Ar overnight. After disappearance of **3** (TLC), the mixture was dissolved in $CH_2Cl_2$ and washed with aq. $Na_2CO_3$ soln. The org. layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by FC (AcOEt/hexane 1:10 + 1% $Et_3N$) to afford **4** (0.32 g, 60%). $^1$H-NMR: 7.26–7.15 (*m*, 5 H); 3.65–3.60 (*m*, 1 H); 3.51 (*s*, 3 H); 3.48 (*s*, 3 H); 2.63–2.54 (*m*, 2 H); 2.43–2.37 (*m*, 1 H); 2.10 (*dd*, *J* = 11.9, 8.4, 1 H); 1.42 (*dd*, *J* = 11.5, 9.0, 1 H); 1.24 (*d*, *J* = 5.7, 3 H). $^{13}$C-NMR: 144.9; 129.4; 127.9; 127.7; 126.5; 126.0; 111.3; 77.5; 74.1; 57.9; 52.3; 51.0; 47.7; 46.6; 40.6; 23.8.

4.3. *(*R*)-1-Phenyl-*N*-{[(1S,2R,4S)-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]methyl}ethanammonium Chloride* (**5**). Compound **4** (0.32 g, 0.75 mmol) was dissolved in $Et_2O$ (15 ml). HCl Gas produced from the reaction of NaCl with $H_2SO_4$ was passed through the amine soln. Ammonium salt **5** precipitated as white crystals.

5. *X-Ray Crystal-Structure Determination of* **5**. All measurements were performed using graphite-monochromatized Mo$K_\alpha$ radiation at 100 K. $C_{18}H_{22}Cl_5NO_2$; $M_r$ 461.64; triclinic; space group *P*1; *a* = 12.6456(6) Å, *b* = 13.7775(6) Å, *c* = 14.1907(7) Å, $\alpha = 62.2039(15)°$, $\beta = 74.7209(17)°$, $\gamma = 88.2506(16)°$, *V* = 2097.39(17) Å$^3$, *Z* = 4, $D_{calc} = 1.462$ g cm$^{-3}$, $\mu = 0.705$ mm$^{-1}$. A total of 31320 reflections were collected ($\Theta_{max} = 26.0°$), of which 14943 were unique ($R_{int} = 0.0239$), with 14465 having $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares techniques against $F^2$ (SHELXL-97) [14][17]. The absolute configuration was established by anomalous dispersion effects in the diffraction measurements on the crystal. Due to the enantiomeric impurity of the compound

containing 15.9% of the (*S*,*R*,*R*)-enantiomer besides 84.1% of the (*R*,*S*,*S*)-enantiomer (related to the asymmetric C-atoms at C(1), C(4), and C(5) in molecule I), the molecule IV is disordered over two orientations and was refined with site-occupation factors of 0.636(3) for the (*S*,*R*,*R*)-enantiomer and of 0.364(3) for the (*R*,*S*,*S*)-enantiomer. This disorder of the molecule IV has influences on the neighboring molecules, mainly on the Ph ring of molecule II, and on two $Cl^-$ ions (Cl(93)/Cl(95) and Cl(94)/Cl(96)). A rigid bond restraint was applied to this disordered Ph ring and to the molecules IVa/IVb, and the equivalent bonds in the bicycle of the molecules IVa/IVb were restrained to have the same lengths. The C-atoms of the disordered Ph rings were fitted to a regular hexagon with C–C distances of 1.39 Å. There was also a slight disorder observable in molecule I (the two largest peaks in the difference *Fourier* map are near this molecule), which could not be resolved. The entire molecules show (*R*)-configuration at the stereogenic C-atom bonded to the N-atom (C(17) in molecule I).

The other non-H-atoms were refined with anisotropic displacement parameters without any constraints. The H-atoms were refined with appropriate positional constraints and with common isotropic displacement parameters $U_{iso}$ for equivalent H-atoms. The H-atoms of the Me groups were refined with an idealized geometry with tetrahedral angles, enabling rotation around the X–C bond, and C–H distances of 0.98 Å. Some H-atoms showing $U_{iso}$ smaller than the equivalent isotropic displacement parameters $U_{eq}$ of the C-atoms they are bonded to be included at calculated positions with their $U_{iso}$ are fixed to 1.2 times $U_{eq}$ of the C-atom they are bonded to. The C–H distances were fixed to 0.99, 1.00, and 0.95 Å for the secondary, tertiary, and Ph H-atoms, resp. The H-atoms of the $NH_2^+$ groups were refined with common isotropic displacement parameters for the H-atoms of the same group and idealized geometry with approximately tetrahedral angles and C–H distances of 0.92 Å. For 1222 parameters, final *R* indices of $R^1 = 0.0436$ and $wR^2 = 0.1165$ (GOF = 1.049) were obtained. The largest peak in the difference *Fourier* map was 1.270 e $Å^{-3}$. The structural data for **5** have been deposited with the *Cambridge Crystallographic Data Centre* (CCDC-739825).

6. *Synthesis of Carbasugar Derivatives (–)-***13** *and (–)-***14**. 6.1. *Synthesis of [(1*S*,2*S*,4*S*)-7,7-Dimethoxybicyclo[2.2.1]hept-5-en-2-yl]methanol* ((–)-**6**). Liq. $NH_3$ (150 ml) was distilled into a 250-ml three-necked round-bottomed flask equipped with a condenser. Small pieces of freshly cut Na were added to the flask with stirring at $-33°$, and a dark blue color appeared. Compound (+)-**2** (6 g, 16.5 mmol) was dissolved in a dry $Et_2O$/EtOH 1:1 (40 ml) and introduced into the mixture. The mixture was stirred at $-33°$ for 30 min. During the reaction, the blue color should persist. If necessary, more Na pieces can be added. Then, solid $NH_4Cl$ was added until the soln. became colorless. The excess $NH_3$ was allowed to evaporate, and a cold aq. sat. $NH_4Cl$ soln. and $H_2O$ were added to the resulting residue, which was subsequently extracted with AcOEt (3 × 100 ml). Removal of the solvent, followed by purification of the crude product by FC (AcOEt/hexane 1:3), afforded (–)-**6**. (2.4 g, 79%). Colorless oil. $[\alpha]_D^{20} = -18.7$ ($c = 1$, MeOH). IR (neat): 3403, 2935, 1290, 1114, 1077, 1050, 720. $^1$H-NMR: 6.04 (*dd*, $J = 6.0$, 3.2, 1 H); 6.18 (*dd*, $J = 6.0$, 3.5, 1 H); 3.38–3.28 (*m*, 2 H); 3.22 (*s*, 3 H); 3.15 (*s*, 3 H); 2.96 (*m*, 1 H); 2.79 (*m*, 1 H); 2.54–2.46 (*m*, 1 H); 2.05–1.99 (*m*, 1 H); 1.44 (br. *s*, 1 H); 0.55 (*dd*, $J = 11.6$, 4.2, 1 H). $^{13}$C-NMR: 134.2; 130.6; 119.3; 64.7; 51.8; 49.5; 46.3; 44.6; 38.8; 27.0. HR-MS: 184.1100 ($M^+$, $C_{10}H_{16}O_3^+$; calc. 184.1099).

6.2. *Synthesis of (1*S*,2*S*,4*S*)-5-(Hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-one* ((–)-**7**). To a stirred soln. of (–)-**6** (2.4 g, 13 mmol) in acetone (50 ml) containing $H_2O$ (0.75 ml) was added *Amberlyst-15* (0.52 g). The mixture was stirred overnight. The resin was filtered, and the filtrate was evaporated to afford (–)-**7** (1.78 g, 99%). Colorless oil. $[\alpha]_D^{20} = -40.0$ ($c = 1$, MeOH). IR (neat): 3396, 2937, 1770, 1030, 732, 706. $^1$H-NMR: 6.59 (*dd*, $J = 6.6$, 3.7, 1 H); 6.44 (*dd*, $J = 6.6$, 3.4, 1 H); 3.43 (*ddd*, $J = 14.5$, 9.7, 4.6, 1 H); 3.35 (*ddd*, $J = 14.6$, 9.6, 4.6, 1 H); 3.08–3.06 (*m*, 1 H); 2.87 (*t*, $J = 3.4$, 1 H); 2.56–2.48 (*m*, 1 H); 2.13 (*ddd*, $J = 12.1$, 9.7, 4.1, 1 H); 1.43 (br. *s*, 1 H); 0.75 (*dd*, $J = 12.1$, 5.4, 1 H). $^{13}$C-NMR: 204.6; 133.6; 130.0; 64.2; 48.5; 46.3; 36.1; 25.3. HR-MS: 138.0679 ($M^+$, $C_8H_{10}O_2^+$; calc. 138.0681).

6.3. *Synthesis of [(1*S*,2*S*,4*S*)-7-Oxobicyclo[2.2.1]hept-5-en-2-yl]methyl Acetate* ((–)-**8**). To a stirred soln. of (–)-**7** (2.4 g, 13.0 mmol) in $CH_2Cl_2$ (50 ml) was added dry pyridine (1.47 g, 18.6 mmol) at 0°, and the mixture was stirred for 30 min under Ar. AcCl (1.12 g, 14.1 mmol) was added dropwise. The resultant mixture was stirred for 3 h at r.t. The mixture was extracted with 0.1M HCl (3 × 50 ml), sat. $NaHCO_3$ (3 × 50 ml), and brine (2 × 50 ml). The collected org. phase was dried ($MgSO_4$), and the solvent was concentrated *in vacuo*. The crude product was purified by FC (AcOEt/hexane 1:3) to afford (–)-**8**

(3.07 g, 98%). Colorless liquid. $[\alpha]_D^{20} = -53.2$ ($c = 1$, MeOH). $^1$H-NMR: 6.60 (*dd*, $J = 6.6, 3.4$, 1 H); 6.42 (*dd*, $J = 6.6, 3.5$, 1 H); 3.87 (*dd*, $J = 10.9, 5.9$, 1 H); 3.74 (*dd*, $J = 10.9, 5.9$, 1 H); 2.99–2.98 (*m*, 1 H); 2.88–2.87 (*m*, 1 H); 2.63–2.59 (*m*, 1 H); 2.17–2.11 (*m*, 1 H); 2.04 (*s*, 3 H); 0.78 (*dd*, $J = 12.0, 5.3$, 1 H). $^{13}$C-NMR: 203.3; 170.7; 134.0; 130.0; 65.3; 48.6; 46.2; 32.7; 25.6; 20.8.

6.4. Baeyer–Villiger *Oxidation of [(1*S*,2*S*,4*S*)-7-Oxobicyclo[2.2.1]hept-5-en-2-yl]methyl Acetate* (**8**). *m*-CPBA (70%, 3.20 g, 13.0 mmol) was added to a stirred suspension of (−)-**8** (2.34 g, 13 mmol) and $Na_2CO_3$ (1.38 g, 13.0 mmol) in $CH_2Cl_2$ (50 ml) at 0°. The mixture was stirred for 6 h at r.t., before the reaction was quenched with 10% aq. soln. of $Na_2S_2O_5$ (25 ml). The org. layer was separated, and the aq. phase was extracted with $CH_2Cl_2$ (2 × 50 ml). The combined org. phase was washed with sat. aq. $NaHCO_3$ soln. (50 ml), followed by brine (50 ml), prior to drying (anh. $Na_2SO_4$). After filtration, the soln. was concentrated *in vacuo* followed by FC (AcOEt/hexane 1:3) to afford the regioisomeric mixture of lactones **9** and **10** (1.91 g, 75% total yield).

*$LiAlH_4$ Reduction of the Mixture* **9**/**10**. To a soln. of **9**/**10** (1.91 g, 9.7 mmol) in dry THF (45 ml), cooled at −15°, was added $LiAlH_4$ (114 mg, 29 mmol), and the mixture was stirred for 2 h at the same temp. The reaction was cautiously quenched with AcOEt (50 ml), followed by sat. $Na_2SO_4$ soln. (25 ml), to precipitate out Al salts. The filtrate was concentrated *in vacuo* to afford a mixture of trihydroxylated cyclohexene derivatives, which was directly subjected to an acetylation reaction prior to separation according to the procedure described for the synthesis of compound (−)-**8**. The isomers were separated by FC (AcOEt/hexane 1:5) to afford (−)-**11** (0.99 g, 36%) and (+)-**12** (1.25 g, 45%).

6.4.1. *[(1*S*,2*S*,5*S*)-5-(Acetyloxy)cyclohex-3-ene-1,2-diyl]dimethanediyl Diacetate* (−)-(**11**). Colorless oil. $[\alpha]_D^{20} = -22.0$ ($c = 1$, MeOH). IR (neat): 2952, 1732, 1368, 1229, 1032. $^1$H-NMR: 5.83 (*ddd*, $J = 10.1, 4.1, 2.1$, 1 H); 5.78 (*dd*, $J = 10.1, 2.3$, 1 H); 5.17 (*q*, $J = 3.6$, 1 H); 4.14 (*dd*, $J = 11.1, 5.5$, 1 H); 4.08 (*dd*, $J = 11.3, 5.8$, 1 H); 4.04 (*dd*, $J = 11.3, 5.8$, 1 H); 3.99 (*dd*, $J = 11.1, 6.2$, 1 H); 2.29–2.23 (*m*, 1 H); 2.00 (*s*, 7 H); 1.98 (*s*, 3 H); 1.82 (*dt*, $J = 14.1, 3.5$, 1 H); 1.67 (*ddd*, $J = 14.1, 11.1, 4.5$, 1 H). $^{13}$C-NMR: 170.5; 170.4; 170.1; 132.5; 126.5; 66.0; 65.8; 65.5; 37.2; 31.5; 30.2; 21.2; 20.7. HR-MS: 307.1150 ($[M + Na]^+$, $C_{14}H_{20}NaO_6^+$; calc. 307.1158).

6.4.2. *[(1*R*,3*S*,6*S*)-6-(Acetyloxy)cyclohex-4-ene-1,3-diyl]dimethanediyl Diacetate* (+)-(**12**). Colorless oil. $[\alpha]_D^{20} = +11.6$ ($c = 1$, MeOH). IR (neat): 2952, 1731, 1367, 1223, 1018. $^1$H-NMR: 5.74 (*dd*, $J = 10.2, 1.6$, 1 H); 5.69 (*dd*, $J = 10.2, 2.6$, 1 H); 5.09 (*dd*, $J = 5.0, 1.6$, 1 H); 4.01–3.91 (*m*, 4 H); 2.44–2.43 (*m*, 1 H), 2.12–2.04 (*m*, 1 H); 2.02 (*s*, 9 H), 1.66 (*t*, $J = 6.3$, 2 H). $^{13}$C-NMR: 169.5; 169.4; 169.1; 129.7; 126.6; 67.6; 65.2; 63.3; 33.9; 31.7; 23.8; 20.0; 19.8; 19.7. HR-MS: 307.1150 ($[M + Na]^+$, $C_{14}H_{20}NaO_6^+$; calc. 307.1158).

6.5. *Dihydroxylation of (−)-*(**11**) *and (+)-*(**12**). To the soln. of (−)-(**11**) or (+)-(**12**) (142 mg, 0.5 mmol) in acetone/$H_2O$ 4:1 (5 ml) was added $OsO_4$ (12 mg, 0.05 mol) and 50% NMO soln. (0.3 ml). The resulting soln. was stirred overnight until the complete consumption of the starting material. The reaction was quenched with $Na_2S_2O_5$ (100 mg, 0.526 mmol), and the mixture was filtered. The filtrate was concentrated *in vacuo* and dried ($Na_2SO_4$). The crude product was dissolved in pyridine (2 ml). To the mixture was added $Ac_2O$ (0.25 ml, 2.6 mmol), followed by stirring for 30 h at r.t., until the starting material was consumed. The mixture was concentrated *in vacuo* and then dissolved in $H_2O$ (2 ml). It was extracted with AcOEt (3 × 15 ml). The combined org. layer was washed with 5% HCl (3 ml), $H_2O$ (3 ml), and brine (10 ml), and dried ($Na_2SO_4$). The filtrate was concentrated *in vacuo*, and the crude product was purified by FC (AcOEt/hexane 2:5).

6.5.1. *(1*S*,2*R*,3*S*,4*S*,5*S*)-4,5-Bis(acetoxymethyl)cyclohexane-1,2,3-triyl Triacetate* (−)-(**13**). Yield 70% (0.14 g). Colorless oil. $[\alpha]_D^{20} = -2.3$ ($c = 1$, MeOH). IR (neat): 2963, 1734, 1367, 1213, 1021. $^1$H-NMR: 5.19 (*t*, $J = 3.4$, 1 H); 5.04 (*dd*, $J = 10.9, 3.1$, 1 H); 4.97 (*q*, $J = 3.2$, 1 H); 4.16–4.01 (*m*, 4 H); 2.07 (*s*, 3 H); 2.05 (*s*, 3 H); 2.03–2.01 (*m*, 2 H); 2.00 (*s*, 3 H); 1.99 (*s*, 3 H); 1.94 (*s*, 3 H), 1.84–1.67 (*m*, 2 H). $^{13}$C-NMR: 171.5; 170.9; 170.7; 170.2; 170.0; 69.8; 69.3; 68.9; 66.3; 60.8; 38.3; 32.4; 29.5; 22.0; 21.8; 21.7. HR-MS: 425.1418 ($[M + Na]^+$, $C_{18}H_{26}NaO_{10}^+$; calc. 425.1424).

6.5.2. *(1*R*,3*R*,4*R*,6*R*)-4,6-Bis(acetoxymethyl)cyclohexane-1,2,3-triyl Triacetate* (−)-(**14**). Yield 65% (0.13 g). Colorless oil. $[\alpha]_D^{20} = -2.2$ ($c = 1$, MeOH). IR (neat): 2959, 1738, 1367, 1223, 1038. $^1$H-NMR: 5.21 (*dd*, $J = 5.2, 3.1$, 1 H); 5.10 (*t*, $J = 8.2$, 1 H); 5.01 (*dd*, $J = 8.2, 3.1$, 1 H); 4.11 (*dd*, $J = 11.2, 6.8$, 1 H); 4.04 (*dd*, $J = 10.0, 6.6$, 2 H); 3.97 (*dd*, $J = 11.2, 5.1$, 1 H); 2.04 (*s*, 3 H); 2.03 (*s*, 3 H); 2.00 (*s*, 3 H); 1.99 (*s*, 3 H); 1.97–2.04 (*m*, overlapping with H-atoms of the Ac group, 2 H); 1.95 (*s*, 3 H); 1.79–1.72 (*m*, 1 H);

1.69 – 1.63 (*m*, 1 H). $^{13}$C-NMR: 171.9; 171.1; 171.0; 71.8; 71.3; 71.2; 65.4; 64.9; 38.0; 36.9; 26.4; 22.4; 22.2; 22.1. HR-MS: 425.1418 ($[M+Na]^+$, $C_{18}H_{26}NaO_{10}^+$; calc. 425.1424).

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