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A Graphical Abstract

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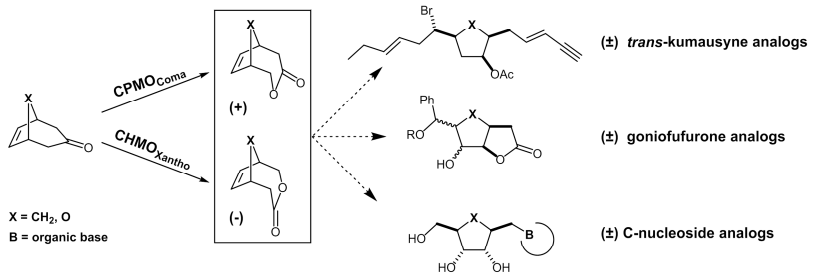

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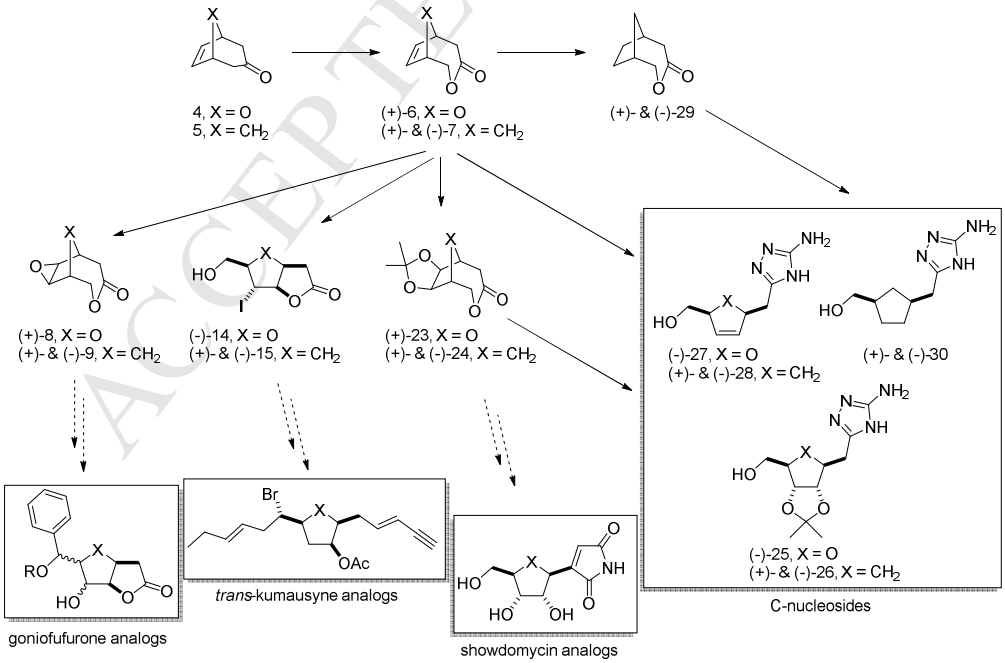
ABSTRACT

In this work we present efficient formal syntheses of several biologically interesting natural products (showdomycin, goniofufurone, *trans*-kumausyne) and their novel carba analogues by applying different Baeyer-Villiger monooxygenases. This strategy provides access to tetrahydrofuran-based natural products, C-nucleosides and both antipodes of the corresponding carba analogues in high optical purities (up to >95% ee) starting from simple achiral and commercially available building blocks (tetrabromoacetone, furan and cyclopentadiene). The striking key features of this chemo-enzymatic approach are the introduction of four stereogenic centers in as few as three reaction steps within a desymmetrization approach and the short-cut of several reaction sequences by the implementation of a biocatalytic step.



Scheme 1. Schematic overview of the syntethic strategy towards natural products containing a tetrahydrofuran motif employed within this work.

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1. Introduction

Tetrahydrofuran is a common motif in several important classes of biologically active compounds such as showdomycin, goniofufurone and *trans*-kumausyne (Scheme 1). Showdomycin displayed antitumor[1] and antibiotic[2] activity, whereas goniofufurone has been described as cytotoxic to human tumor cells.[3] The structural characteristics of *trans*-kumausyne have attracted remarkable interest by synthetic chemists and a number of total syntheses have recently been published.[4-8]

C-nucleosides represent another structural class, which attracts notable attention in the scientific community, with the above mentioned showdomycin being one example. C-nucleosides are compounds containing a C-C bond between the carbohydrate and the base rather than a C-N bond (N-nucleosides). This structural feature provides increased stability as the glycosidic C-C bond cannot be cleaved hydrolytically (increased *in vivo* stability). An additional characteristic is the increased enzymatic stability. Therefore, C-nucleosides exhibit several special biological features such as antibiotic, anticancer and/or antiviral activity in combination with an interesting pharmacological behavior.[9-13]

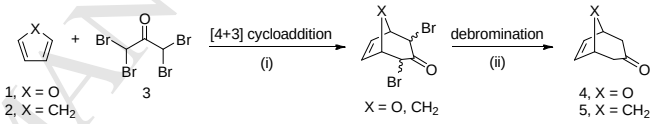
While common nucleosides are usually derived from pentoses, their carba analogs (the tetrahydrofuran ring is substituted by a cyclopentane ring) may not be accessed in this way and often require a more complex synthetic strategy. Hence, carba-C-nucleosides are a class of potential bio-active compounds combining common features of classical C-nucleosides and a non-carbohydrate core structure that are underrepresented in the literature so far. In the same way carba analogs of tetrahydrofuran containing natural products may offer interesting biological behavior.

Since the first publication by Adolf Baeyer and Victor Villiger in 1899[14], the Baeyer-Villiger oxidation has become an important method in synthesis of esters and lactones from acyclic and cyclic ketones, respectively.[15-18] In recent years several methods for the stereoselective Baeyer-Villiger oxidation became available.[19-21] Due to the fact that the chemical Baeyer-Villiger oxidation requires a peracid as an oxidant in combination with often harsh reaction conditions, several problems arise, in particular safety issues imposed by the explosive character of reactants and low functional group tolerance. The development of a biocatalytic variant of this transformation by applying Baeyer-Villiger monooxygenases (BVMOs) enabled synthetic chemists to circumvent some of these disadvantages and, moreover, achieve significantly higher regio-, chemo- and stereoselectivity for the oxygen insertion products. Therefore, BVMO mediated reactions evolved as an attractive alternative and an important tool for the preparation of chiral esters and lactones in synthetic chemistry.[22-27]

A large number of BVMOs are known by now and were successfully applied for the synthesis of chiral building blocks aiming at the preparation of bioactive compounds. In order to assist the selection process to identify the most suitable enzyme for a given substrate, we recently published some decision guidance for quantitative and comparative evaluation of chiral catalysts[28]. Consequently, enzymes of choice for this preparative work turned out to be cyclopentanone monooxygenase (CPMO; CE 1.14.13.16)[29,30]_ from *Comamonas* sp. NCIMB 9872 (EC; $CPMO_{Coma}$) and cyclohexanone monooxygenase (CHMO) from *Xanthobacter* sp. ZL5 ($CHMO_{Xantho}$).[31] Both enzymes were overexpressed in *Escherichia coli* in order to circumvent elaborate cofactor recycling strategies and troublesome isolation of NADPH-dependent instable BVMOs, and successful recombinant whole-cell biotransformations were applied.[32,33]

Within this contribution we present a conclusive methodology for the (formal) synthesis of above mentioned bio-active substances and present additional examples to previously reported preliminary results of our research effort in this area.[34,35] Tetrahydrofuran- and cyclopentane-based compounds were successfully accessed starting from the very simple achiral starting materials furan and cyclopentadiene, respectively. Subsequent enzyme-mediated Baeyer-Villiger oxidation is used to successfully introduce chirality by exploiting the above mentioned enzymes. Furthermore, the Baeyer-Villiger biooxidation of the cyclopentane based starting material afforded both antipodes selectively when using enzymes $CPMO_{Coma}$ and $CHMO_{Xantho}$, respectively. This behavior is in line with our recently identified correlation of sequence clustering and stereopreference of BVMOs.[36] Consequently, all compounds emerging from these Baeyer-Villiger products were accessed in an enantiocomplementary form. Up to four stereogenic centers were established in only three chemo-enzymatic steps with high optical purity. The precursors presented in this work may serve as efficient shortcuts for the synthesis of the mentioned tetrahydrofuran-based natural products as well as their carba analogs in comparison to current total syntheses. To our knowledge, carba analogs of these compounds have not been described in the literature, so far, and are therefore potentially interesting in means of studying their biological behavior.

2. Results and Discussion



Scheme 2. Preparation of bicyclic ketones **4** and **5** via Cu/Zn-couple mediated [3+4] cycloaddition (i) followed by reductive debromination (ii)..

We envisioned the [4+3] cycloaddition as a powerful tool for the construction of the desired seven-membered bicyclic ketones **4**[37] and **5**, which act as precursors for a subsequent Baeyer-Villiger oxidation. This cyclization involves a perbromo ketone (1,1,3,3-tetrabromoacetone **3** was synthesized according to the literature[38]) as dienophile, which generates the reactive oxyallyl species in the course of the reaction. The cyclization reaction was conducted with freshly prepared Cu/Zn-couple[39] and an excess of the reagent was used for the subsequent debromination. In line with previous reports on facilitating such heterogeneous cycloaddition reactions by ultrasound irradiation [40,41], the synthesis of bicyclic ketones **4** and **5** was carried out according to a sonochemical protocol developed in our group.[42]

Furan **1**, tetrabromoacetone **3**, Cu/Zn-couple and catalytic amount of dibromoethane were reacted under sonication and at 30°C. After filtration the crude solution of 2,4-dibromo-8-oxabicyclo[3.2.1]oct-6-en-3-one was used without further purification for the debromination step. After reduction with Cu/Zn-couple in the presence of NH_4Cl at -78°C and subsequent extractive work-up oxo-ketone **4** was obtained as beige crystals in good yield and purity (72%; m.p. 36-38 °C). Reaction of cyclopentadiene **2** with tetrabromoacetone **3**, activated Zn and catalytic amount of I_2 gave crude 2,4-dibromobicyclo[3.2.1]oct-6-en-3-one via an analogous protocol. Debromination with activated Zn and work-up provided carba-ketone **5** in adequate yield and purity (58%).

2.1. Microbial Baeyer-Villiger oxidation of bicyclic ketones

Having the symmetric ketones **4** and **5** in hands several different BVMOs from our enzyme collection were tested for their ability to convert the bicyclic ketones **4** and **5** into the desired lactones **(+)-6**

and **(+)-** and **(-)-7**. All tested BVMOs were overexpressed in *Escherichia coli* and conversion was monitored by GC. Screening results are shown in **Table 1**.

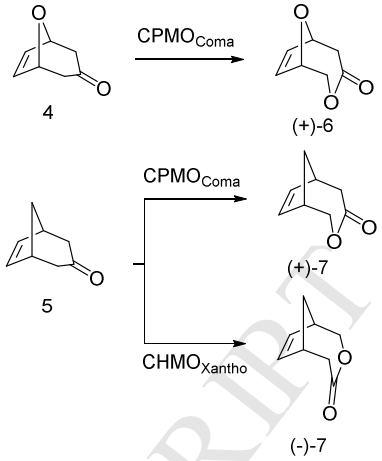
Table 1. Results of screening different BVMOs on their ability to convert the ketones of interest.

	Bicyclic oxo ketone **4**		Bicyclic carba ketone **5**	
Strain	conversion[a]	ee[b]	conversion[a]	ee[b]
CDMO	-	-	-	-
$CHMO_{Acineto}$	-	-	+	91 (-)
$CHMO_{Arthro1}$	-	-	+	96 (-)
$CHMO_{Brachy}$	-	-	+	98 (-)
$CHMO_{Brevi1}$	-	-	-	-
$CHMO_{Brevi2}$	+++	93 (+)	++	59 (+)
$CPMO_{Coma}$	+++	95 (+)	++	89 (+)
$CHMO_{Rhodo1}$	-	-	+	97 (-)
$CHMO_{Rhodo2}$	-	-	+	98 (-)
$CHMO_{Xantho}$	-	-	++	99 (-)
CPDMO	-	-	-	-
$BVMO_{Paer}$	-	-		
$BVMO_{Mtub5}$	-	-		
$HAPMO_{Pfl}$	-	-		

[a]Conversion: -: no conversion, +: <50% conversion, ++: 50% - 90% conversion, +++:.>90% conversion.
[b] sign of optical rotation in parentheses

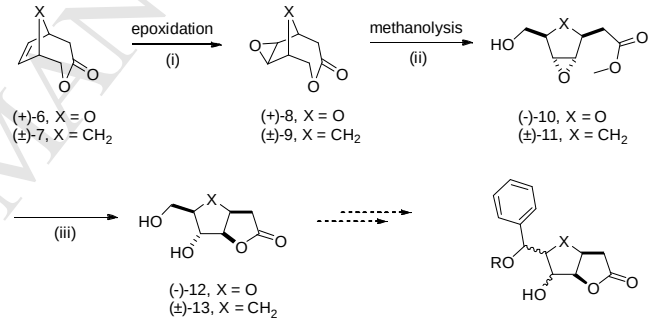
$CPMO_{Coma}$ and $CHMO_{Brevi2}$ transformed ketones **4** and **5** to the corresponding lactones **(+)-6** and **(+)-7**. $CPMO_{Coma}$ was preferred over $CHMO_{Brevi2}$ based on higher stereoselectivity. $CHMO_{Xantho}$ was also identified to convert both bicyclic ketones **4** and **5**. In the case of substrate **5** the corresponding lactone **(-)-7** was formed but when substrate **4** was supplied, the corresponding epoxide was formed exclusively while the ketone did not react at all.[43] By using these two different BVMOs we achieved facile access to the antipodal carba-lactones **(+)-7** and **(-)-7**. Hence, we were able to prepare all subsequent carba-products in an enantiocomplementary manner. Biotransformations proceeded with perfect chemoselectivity, very good enantioselectivity in the case of **(+)-6** and **(-)-7** and reasonable optical purity for **(+)-7**. According to screening results, the biotransformation in large scale was carried out with *Escherichia coli* DH5α expressing $CPMO_{Coma}$ and BL21 (DE3) cells expressing $CHMO_{Xantho}$ either under controlled conditions in a bioreactor or in shake flask experiments.

The fermentation of oxo-ketone **4** to the corresponding lactone **(+)-6** was optimized by exploiting the *in situ* substrate feeding / product removal concept (SFPR).[44] This approach enables higher compound concentrations which otherwise would be toxic for cells.[44-46] After sequential extraction of the resin and the fermentation broth and subsequent purification by column chromatography the desired lactone **(+)-6** was isolated in good yield (70%) and very good optical purity (95% ee; $[\alpha]_D^{20}$: +85.2 (c = 0.2, $CHCl_3$)). In contrast carba-ketone **5** was transformed into the corresponding lactone **(+)-7** catalyzed by $CPMO_{Coma}$ applying shake flask experiments. The desired product was obtained in reasonable yield (63%) and good optical purity (89% ee; $[\alpha]_D^{21}$ = +80.2 (c = 0.52, $CHCl_3$)). Transforming the same ketone **5** using $CHMO_{Xantho}$ as the catalyst, the enantiocomplementary lactone **(-)-7** was obtained in again good yield (71%) and excellent optical purity (>99% ee; $[\alpha]_D^{21}$ = −83.3 (c = 0.51, $CHCl_3$)). Compounds **(+)-6** and **(+)-** and **(-)-7** were then used as a platform for comprehensive chemical transformations.



Scheme 3. Enzyme-mediated Baeyer-Villiger oxidations: 95% ee and 70% yield for **(+)-6**, 89% ee and 63% yield for **(+)-7** and >99% ee and 61% yield for **(-)-7**.

2.2. Synthesis of goniofufurone analogs

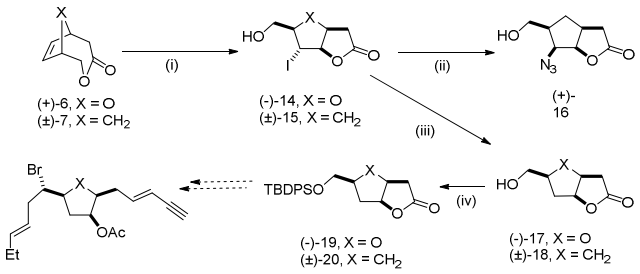


Scheme 4. Preparation of goniofufurone analogs: (i) *m*-CPBA, CH_2Cl_2, reflux for synthesis of **(+)-8**, rt for synthesis of **(±)-9**, **8**: yield: 98%, **(+)-9**: yield: 69%, **(-)-9**: yield: 75%; (ii) $MeOH/H_2O$, K_2CO_3, rt, **(-)-10**: yield: 98%, **(+)-11**: yield: 67%, **(-)-11**: yield: 74%; (iii) $SnCl_4$, CH_2Cl_2, -78 °C for synthesis of **(-)-12**, rt for synthesis of **(±)-13**, **(-)-12**: yield: 98%, **(+)-13**: yield: 85%, **(-)-13**: yield: 79%.

After one chemoenzymatic step we were able to synthesize the key building blocks **(+)-6** and **(+)-** and **(-)-7** to get access to goniofufurone and their carba analogs. In **Scheme 4** all synthetic steps including reaction conditions for formal syntheses of goniofufurone analogs starting from lactones **(+)-6** and **(+/-)-7** are displayed. In the first step, a diastereoselective epoxidation was carried out using *m*-chloroperbenzoic acid (*m*-CPBA) as oxidant reagent. This procedure[47,48] afforded selectively *exo*-epoxide **(+)-8** in excellent yield (98%) as well as the carba-epoxides **(+)-9** (69% yield) and **(-)-9** (75% yield). Interestingly the shielding effect from the bridging CH_2 group or the oxygen atom in addition to the geometry of the bicyclic ring characteristics resulted in a perfectly stereochemically controlled epoxidation. Subsequent methanolysis was succcessfully applied to obtain compound **(-)-10** in 98% yield, compound **(+)-11** was isolated in 67% yield and compound **(-)-11** in 74% yield. Intramolecular ring opening of the epoxide via Lewis acid activation resulted in formation of bicyclic lactone **(-)-12** again in excellent yield (98%). Transformation of **(+)-11** gave access to both antipodes **(+)-13** (85% yield) and **(-)-13** (79% yield). Preparation of these key intermediates enables access to various goniofufurone analogs as interesting natural products

containing a fused tetrahydrofuran or cyclopentane ring respectively according to previous references.[49,50]

2.3. Synthesis of trans-kumausyne analogs

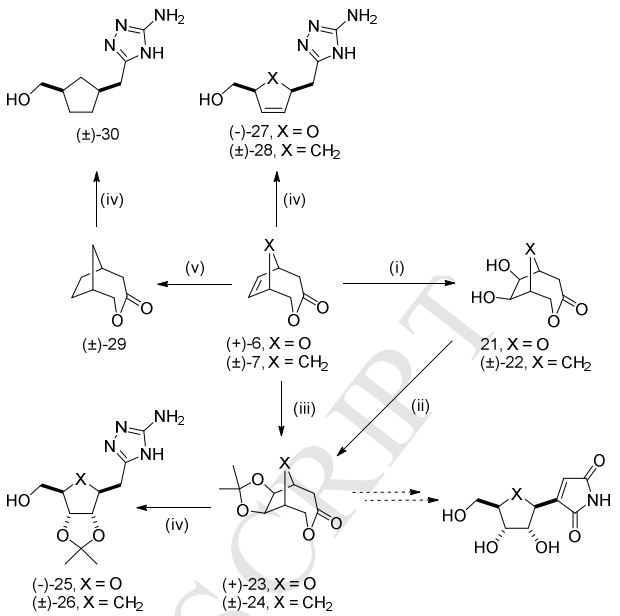


Scheme 5. Preparation of *trans*-kumausyne analogs: (i) 1) KOH, MeCN/H_2O 2) I_2/KI, 40°C for synthesis of **(-)-14**, rt for synthesis of **(±)-15**, **(-)-14**: yield: 75%, **(+)-15**: yield: 92%, **(-)-15**: yield: 100%; (ii) NaN_3, DMSO, 75°C, yield: 100%; (iii) $HSn(Bu)_3$, toluene, 60°C, **(-)-17**: yield: 99%, **(+)-18**: yield: 85%, **(-)-18**: yield: 81%; (iv) *tert*-butylchlorodiphenylsilane, imidazole, DMF, rt, **(-)-19**: yield: 92%, **(+)-20**: yield: 95%, **(-)-20**: yield: 89%.

Furthermore we exploited the geometry of the biotransformation products (+)-**6** as well as **(+)-** and **(-)-7** and introduced two new stereogenic centers by applying an iodolactonization reaction. This approach provides goniofufurone analog precursors from the previous section additionally bearing an iodine atom in position of the previous hydroxyl as a good leaving group. Following this route we aimed for the accessibility of another interesting natural compound, namely *trans*-kumausyne. **Scheme 5** shows the synthetic strategy carried out for the formal preparation of *trans*-kumausyne analogs starting from chiral bicyclic lactones (+)-**6** and **(+)-** and **(-)-7**. Lactones were hydrolyzed in situ using KOH in MeCN/H_2O. Subsequent iodolactonization adding I_2/KI enabled a one pot reaction to give iodolactone (-)-**14** in good yield (75%). Applying the same protocol carba analogs **(+)-** and **(-)-15** were obtained in excellent yields (**(+)-15** 92% yield; **(-)-15** 100% yield). Again, two new stereogenic centers were incorporated with perfect selectivity. Additionally, these iodide intermediates enable further chemical transformations. As an example we synthesized the corresponding azide **(+)-16** starting from **(+)-15** in the presence of sodium azide. Azidolactone **(+)-16** was obtained quantitatively with complete inversion of the stereogenic center in position 6. Next, the iodolactones were dehalogenated using tributyltin hydride as the reducing agent and gave lactone (-)-**17** after purification as colorless oil with identical spectral properties as described in the literature[51] in perfect yield (99%). Transformation of the carba analogs gave antipodal products **18** in very good yields (**(+)-18** 85%; **(-)-18** 81%). Discrepancies in published data about the absolute configuration based on the specific optical rotation of alcohol (-)-**17** prompted us to extend our synthetic investigations towards the protected alcohol compounds (-)-**19/(+)-** and **(-)-20**. Finally the alcohol functionality was masked by using *tert*-butylchlorodiphenylsilane and all three compounds were obtained in very good yields ((-)-**19**: 92%; **(+)-20**: 95%, **(-)-20**: 89%).

By comparing the specific rotation of **(-)-19** with published data[51] we were able to conclude that chiral information was conserved completely. This is probably true for the carba analogs but to our knowledge no reference data is available yet. With the synthesis of these key intermediates, the formal synthesis of *trans*-kumausyne and its carba analogs were formally completed.

2.4. Synthesis of C-nucleosides



Scheme 6. Preparation of C-nucleosides: (i) NMO/OsO_4, DCM/*t*-BuOH, rt, **21**: yield: 55%, **(+)-22**: yield: 56%, **(-)-22**: yield: 50%; (ii) 2-methoxypropene or 2,2-dimethoxypropane, *p*-toluenesulfonic acid, acetone, rt, **(+)-23**: yield: 76%, **(+)-24**: yield: 60%, **(-)-24**: yield: 80%; (iii) NMO/OsO_4, DCM/*t*-BuOH, rt, then $AlCl_3$, acetone, rt, **(+)-23**: yield: 47%; (iv) aminoguanidine bicarbonate, pyridine, reflux, **(-)-25**: yield: 78%, **(+)-26**: yield: 43%, **(-)-26**: yield: 50%, **(-)-27**: yield: 67%, **(+)-26**: yield: 71%, **(-)-26**: yield: 71%, **(+)-30**: yield: 69%, **(-)-30**: yield: 67%; (v) H_2, Pd/C, EtOAc, rt, **(+)-29**: yield: 83%, **(-)-29**: yield: 79%.

Special interest was given to the very broad field of C-nucleosides with showdomycin being one prominent example. Synthesis of compounds **(+)-23** and **(+)-** and **(-)-24** provide suitable precursors for the formal total synthesis of showdomycin and its carba analogs They may also act as precursors for the synthesis of other C-nucleosides like pseudouridines. In **Scheme 6** all transformations including the preparation of other C-nucleosides are summarized. Conversion of the bio-oxidation products **(+)-6** and **(+)-** and **(-)-7** to the key intermediates **(+)-23** and **(+)-** and **(-)-24** for modified nucleosides turned out to be challenging due to the high water solubility of the intermediate diols **21** and **(+)-** and **(-)-22**. Among several protecting groups for the diol structural motif, the acetonide turned out to be most suitable for subsequent transformations. Several methods were investigated in order to obtain an acceptable yield for the target compounds. First a stepwise synthesis was applied. Olefin **6** was dihydroxylated using catalytic amount of OsO_4 and N-methylmorpholine oxide (NMO) as the re-oxidant achieving two new stereogenic centers selectively. Using only little amounts of an aqueous solution of Na_2SO_3 for quenching and intensive re-extraction, diol **21** was obtained with a reasonable yield of 55% after purification. The diol **21** was then reacted further with 2,2-dimethoxypropane and *para*-toluenesulfonic acid (*p*-TsOH) as a catalyst to yield acetonide **(+)-23** as colorless crystals in good yield (76%). The most suitable strategy turned out to avoid work-up of the reaction after the dihydroxylation but rather use the crude product directly for the protection step. Crude diol **21** was dissolved in dry acetone and freshly sublimed $AlCl_3$ was added. After full conversion and purification the acetonide **(+)-23** was obtained in 47% yield over two steps, which was only a slight improvement. Upon comparison of physical data[52] for **(+)-23** the absolute configuration of bio-oxidation product **(+)-6** could be confirmed to be (1*S*,6*S*). Similar conditions were applied to

convert the carba analogs **(+)-** and **(-)-7**. When synthesizing the diols **(+)-** and **(-)-22**, aqueous conditions were avoided during work-up by adsorbing the reaction solution directly on silica gel. After purification by column chromatography comparable yields of 56% for **(+)-22** and 50% for **(-)-22** were achieved. Protection of the diol moiety was performed as described before and acetonide**(+)-24** was obtained in 60% and **(-)-24** in 80% yield respectively. These compounds have been established as key intermediates for analogs of the natural *C*-nucleoside showdomycin. Finally the lactone moiety was addressed to synthesize other *C*-nucleosides. As an example 5-amino-4*H*-1,2,4-triazol was installed as a base using available oxo- and carba lactones (**Scheme 6**). This represents a formal access to novel non-natural C-nucleosides *via* the bio-oxidative approach in this work. Within the general procedure for the preparation of C-nucleosides the corresponding lactone was refluxed with aminoguanidine bicarbonate in pyridine under argon atmosphere till conversion was proved to be complete by TLC analysis. Purification by column chromatography provided products **(-)-25, (+)-** and **(-)-26, (-)-27, (+)-** and **(-)-28** and **(+)-** and **(-)-30**. For the elaboration of saturated lactones **(+)-** and **(-)-29**, olefins **(+)-** and **(-)-7** were hydrogenated using a balloon filled with hydrogen and Pd/C (10% w/w) as catalyst to provide 83% of **(+)-29** and 79% of **(-)-29**.

3. Conclusions

In summary, we were able to provide facile access to several biological interesting natural products (showdomycin, goniofufurone, *trans*-kumausyne) as well as C-nucleosides. Furthermore, enantiocomplementary carba analogs of all presented compounds were successfully synthesized. An enzyme-mediated Baeyer-Villiger oxidation was applied to introduce chirality efficiently. The obtained optically active lactones were used as a convenient platform for several stereoselective transformations. Not only can the presented compounds serve as versatile precursors for the synthesis of above mentioned natural products (formal synthesis) but the corresponding enantiocomplementary carba precursors may also be transformed further to carba analogs of the described compounds which have not been described in the literature yet. It would be interesting to study their biological behavior in contrast to the original tetrahydrofuran based compounds.

4. Experimental Section

Unless otherwise noted, chemicals and microbial growth media were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Flash column chromatography was performed on silica gel 60 from Merck (40-63µm). Abbreviations are used as the following: LP = light petroleum, o/n = over night, rt = room temperature. Basic silica gel was obtained by mixing NEt_3 (5%), the desired solvent mixture and silica gel. This suspension was stirred for 5 minutes and was used for column chromatography. Medium pressure column chromatography was performed on a regular silica gel column with a Büchi 681 Chromatography Pump with Automatic Fraction Collector. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. Biotransformations were carried out in a New Brunswick Bioflow 110 fermenter equipped with pH probe, oxygen probe, flow controller and temperature control. Monitoring of all fermentation parameters was performed using the BiocommandPlus 3.30 software by New Brunswick. Glucose concentrations were determined with Roche AccuChek-go. NMR-spectra were recorded from $CDCl_3$, CD_3OD or DMSO-d6 solutions on a Bruker AC 200 (200 MHz) spectrometer and chemical shifts are reported in ppm using TMS as internal standard. Combustion analysis was carried out in the Microanalytic Laboratory, University of Vienna. General conversion control and examination of purified products were performed with GC Top 8000 / MS Voyager (quadropol, EI+) using a standard capillary column BGB5 (30mx0.32mm ID). Enantiomeric excess was determined via GC using a BGB 175 column (30mx0.25mm ID, 0.25µm film) and a BGB 173 column (30mx0.25mm ID, 0.25µm film) on a ThermoQuest Trace GC 2000 and a Thermo Focus GC. Specific rotation $[\alpha]^D_{20}$ was determined using a Perkin Elmer Polarimeter 241 by the following equation: $[\alpha]^D_{20} = 100*\alpha / [c]*l$; c[g/100mL], l[dm]

4.1. Biocatalyst performance screening on analytical scale

A baffled Erlenmeyer flask was charged with LB medium with appropriate antibiotics supplement (10 mL), inoculated with a bacterial single colony from an Agar plate and incubated at 37 °C in an orbital shaker o/n. The biotransformation medium, supplemented with ampicillin (200 mg/L), was then inoculated with 2% v/v of the preculture and incubated for approx. 1–2 h under the same conditions until an optical density of 0.2–0.6 was reached. Inducing agent and β-cyclodextrin (1 equiv.) were added, the mixture was thouroughly mixed and split in 1.0 mL aliquots into 24-well plates. Substrates were added as 0.8 M solutions in 1,4-dioxane to a final concentration of 4 mM. The plates were sealed with adhesive film and incubated at the appropriate temperature in an orbital shaker for up to 24 h. Analytical samples were prepared by extraction of 0.5 mL of biotransformation culture with 1.0 mL dichloromethane (supplemented with 1 mM methyl benzoate as internal standard) after centrifugal separation of the cell mass (approx. 15 kRCF, 1 min, rt) and measured by chiral GC..

*4.2. 8-Oxabicyclo-[3.2.1]oct-6-en-3-one (**4**)*

Cu/Zn couple (20.6 g, 0.31 mol), furan **1** (100 mL, 1.39 mol) and catalytic amount of dibromoethane were suspended in dry MeCN (80 mL). The reaction mixture was cooled to 10 °C under nitrogen atmosphere and was sonicated for 30 min under subsequent addition of tetrabromoacetone **3** (38.2 g, 1.02 mol) dissolved in dry MeCN. The temperature was maintained below 25 °C. The conversion of the reaction was monitored by GC-MS. After complete conversion the reaction mixture was filtered through a pad of Celite®. The crude solution of 1,5-dibromo-8-oxabicyclo-[3.2.1]oct-6-en-3-one was used without further purification for the next reaction step. Cu/Zn couple (47.3 g, 0.72 mol) and NH_4Cl (26.0 g, 0.49 mol) were suspended in dry EtOH and cooled to -78 °C. Maintaining a reaction temperature below -50 °C, 80% of crude 1,5-dibromo-8-oxabicyclo-[3.2.1]oct-6-en-3-one in MeCN was added slowly. After 15 min the remaining 20% of the solution were added and the reaction mixture was warmed to room temperature. Reaction monitoring was performed by GC-MS. After conversion had reached completion, Cu/Zn couple was removed by filtration and the solid residue was washed with dichloromethane. The combined organic phases were vacuum evaporated. The crude product was cooled with an ice bath upon neutralization with saturated bicarbonate. The obtained suspension was filtered again and solids were washed intensively with dichloromethane. Layers were separated and the organic phase was dried over Na_2SO_4 and concentrated (bath temperature below 30 °C!). The purity of the crude product was checked by NMR and GC/MS. After evaporation of all volatiles and drying in vacuo compound **4** was obtained as beige crystals; yield 72%; m.p. 36-38 °C (lit.[53] 37 – 39 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.30 (d, J = 16 Hz, 2 H), 2.80 (dd, J = 16 Hz & 5 Hz, 2 H), 5.05 (d, J = 5 Hz, 2 H), 6.20 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 46.6, 77.1, 133.3, 205.2 ppm.

*4.3. Bicyclo-[3.2.1]oct-6-en-3-one (**5**)*

Cyclopentadiene **2** was obtained by distillation of dicyclopentadiene (T_{dist} = 38-40 ºC). Tetrabromoacetone **3** was prepared by reaction of acetone and bromine under acidic conditions. Cu/Zn couple (20.2 g, 0.309 mol) and catalytic amount of I_2 were suspended in dry MeCN (100 mL) under nitrogen atmosphere and with sonication (approx. 10 min). The reaction mixture was cooled to 0 ºC with subsequent dropwise addition of cyclopentadiene (9.17 g, 0.139 mol) and tetrabromoacetone (37.1 g, 0.099 mol) while sonicated and the temperature was maintained below room temperature throughout the experiment. The reaction was monitored by TLC until complete conversion was observed (approx. 3-7 h). Activated Zn (20.0 g, 0.306 mol), NH_4Cl (20.0 g, 0.374 mol) and dry MeOH (100 mL) were added under nitrogen atmosphere at 0 ºC and with sonication. The reaction was followed by TLC until complete conversion. Remaining Zn was removed by filtration through a pad of Celite® and the solid residue was washed with diethylether. The suspension was cooled with an ice bath and neutralized with sodium bicarbonate. The obtained suspension was filtered again, washed with diethylether and concentrated in vacuo. The crude was extracted with pentane (3 times), trying to achieve a selective extraction of the desired product taking advantage of its high carbon nature. The combined organic layers were dried over Na_2SO_4 and concentrated (bath temperature below 30 °C!) in vacuo. The purity of the crude product was checked by NMR, where we can see small amounts of impurities but the purity of the crude is sufficient for its use in the next step. After evaporation of all volatiles and drying *in vacuo* compound **5** was obtained; yield 58%; To increase the purity of the product sublimation can be applied to obtain beige crystals; m.p. 98-100 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.75 (d, *J* = 10.9 Hz, 1 H), 2.03-2.16 (m, 1 H), 2.31 (dd, J = 17.2 Hz & 2.4 Hz, 2 H), 2.44 (dd, *J* = 17.2 Hz & 3.3 Hz, 2 H), 2.90 (br. s, 2 H), 6.00 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.2, 41.7, 46.3, 135.4, 210.4 ppm.

*4.4. (1S,6S)-3,9-Dioxabicyclo[4.2.1]non-7-en-4-one ((**+**)-**6**)*

A New Brunswick Bioflow 110 fermenter containing 1 L of sterile TB medium supplemented with 200 mg/L ampicillin was inoculated with 20 mL (2 vol%) overnight culture of DH5α/CPMO grown on LB medium (50 mg/L ampicillin). The temperature was maintained at 37 °C and the pH was kept constant at 7.00 ± 0.05 by adding 3N NaOH or 3N H_3PO_4 automatically. The 1 L culture was grown with an air flow of 5 L/min and stirring rates at 500 rpm. The growth was continued until the culture density reached 3.01 - 3.44 g/L dcw and the temperature was decreased to 25 °C. IPTG was added to a final concentration of 0.25mM and after an additional hour the fermentation culture was supplemented with 4 g/L glucose (20% sterile solution). Two hours after induction 20 mL of cell culture were taken and activity tests were performed. After passing the activity tests the pre-loaded resin and any additives were added. The glucose level was measured periodically as the bioconversion progressed. Compound **4** (5 g, 40 mmol) was dissolved in ethanol (10 mL) and was subsequently added to the resin (50 g wet resin, load X^{eq} = 0.2) and 100 mL of LBAmp. β-cyclodextrin (10 mol%) and the substrate-resin mixture were added to the fermentation broth. After 36 h and purification via column chromatography (LP/EtOAc = 2/1; 200 g SiO_2) the desired lactone **(+)-6** was isolated; yield 70% (95% ee); m.p.: 98-100°C; $[\alpha]_D^{20}$: +85.2 (c = 0.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.90 (dd, *J* = 16 Hz & 5 Hz, 1 H), 3.20 (dd, *J* = 16 Hz & 3 Hz, 1 H), 4.05 (dd, *J* =12 Hz & 3 Hz, 1 H), 4.40 (d, *J* = 12 Hz, 1 H), 4.70 (d, *J* = 3 Hz, 1 H), 4.85 (d, *J* = 3 Hz, 1 H), 6.10 (d, *J* = 6 Hz, 1 H), 6.35 (d, *J* =6 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 46.7, 71.0, 76.3, 81.6, 129.0, 133.4, 172.0 ppm.

*4.5. 3-Oxabicyclo[4.2.1]non-7-en-4-one ((**+**)- and (**-**)-**7**)*

A 1 L Erlenmeyer flask containing 200 mL of sterile TB medium supplemented with 0.2 mg/mL of ampicillin and a drop of antifoam was inoculated with 2 mL (1% vol) overnight culture BL21(DE3)/p11X5.1 grown on LB medium (0.2 mg/mL ampicillin). The culture was growing at 30 ºC and 120 rpm until the optical density at 590 nm reached a value between 10-18 (approx. 8-11 h). Then the temperature was decreased to 24 ºC and IPTG was added to a final concentration of 0.1 mM. After one hour, β-cyclodextrin (930 mg; 0.820 mmol), compound **5** (100 mg, 0.82 mmol) and 1,4-dioxan (1 mL) were added. The reaction was followed using GC-MS until 80-90% of conversion (approx. 14-20 h). The cells were separated from the broth by centrifugation (9600 rpm, 15 min), and the broth was continuously extracted using dichloromethane (8-10 h). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (LP/EtOAc = 3/1) gave the desired compounds **(+)-** and **(-)-7** as a colorless solid; yield 71% (ee > 99%) ($CHMO_{Xantho}$); yield 63% (ee = 89%) ($CPMO_{Coma}$); m.p. 50-52 °C; $[\alpha]_D^{21}$ = −83.3 (c = 0.51, $CHCl_3$) ($CHMO_{Xantho}$); $[\alpha]_D^{21}$ = +80.2 (c = 0.52, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.64 (d, *J* = 11.5 Hz, 1 H), 2.20 - 2.45 (m, 1 H), 2.65 - 2.87 (m, 2 H), 2.89 - 3.07 (m, 1 H), 4.00 - 4.24 (m, 2 H), 5.83 (dd, *J* = 5.7 Hz & 2.9 Hz, 1 H), 6.10 (dd, *J* = 5.7 Hz & 2.9 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.7, 42.6, 44.4, 44.7, 70.7, 131.1, 137.0, 174.1 ppm. $C_8H_{10}O_2$ (138.16): calcd. C 69.55, H 7.30; found C 69.29, H 7.25.

*4.6. (1R,6S,7S,9R)-3,8,10-Trioxatricyclo[4.3.1.0^{7,9}]decan-4-one ((**+**)-**8**)*

m-CPBA (3891 mg, 22.7 mmol) was added to a solution of compound **(+)-6** (390 mg, 2.27 mmol) in dichloromethane (100 mL) at room temperature. The reaction mixture was refluxed for 2 days until no starting material could be detected by TLC. After that, the residue was purified by column chromatography on silica gel (Hexane/EtOAc) gave compound **(+)-8** as colorless crystals; yield 98%; m.p. 78-80 °C; $[\alpha]_D^{22}$ = +94.9 (c = 0.79, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.92 (dd, *J* = 16.5 Hz & 3.8, 2 H), 3.05 (dd, *J* = 16.5 Hz & 2.5 Hz, 1 H), 3.76 (s, 2H), 4.19 (dd, *J* = 3.6 Hz & 2.7 Hz, 1 H), 4.20 - 4.50 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.9, 52.6, 54.2, 69.3, 71.3, 74.2, 171.5 ppm. $C_7H_8O_4$ (156.14): calcd. C 53.35, H 5.16; found C 53.55, H 5.12.

*4.7. 3,8-Dioxatricyclo[4.3.1.0^{7,9}]decan-4-one ((**+**)- and (**-**)-**9**)*

m-CPBA (190 mg (purity 70%), 0.77 mmol) was added to a solution of compound **(+)-** or **(-)-7** (71 mg, 0.51 mmol) in dry dichloromethane (5 mL) under nitrogen atmosphere. The reaction was carried out at room temperature and after 17 h no starting material could be detected by TLC. The reaction mixture was cooled to -20 ºC, filtered and washed with cold dichloromethane. The filtrate was neutralized with saturated sodium bicarbonate and extracted with dichloromethane (x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography (LP/EtOAc = 1/1) gave compounds **(+)-** and **(-)-9**; yield 75% ($CHMO_{Xantho}$); yield 69% ($CPMO_{Coma}$); $[\alpha]_D^{24}$ = −95.5 (c = 1.0, $CHCl_3$) ($CHMO_{Xantho}$); $[\alpha]_D^{24}$ = +82.8 (c = 1.2, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 12.5 Hz, 1 H), 1.88 (dt, *J* = 12.5 Hz & = 6.4 Hz, 1 H), 2.45 (t, *J* = 6.4 Hz, 1 H), 2.60 (m, 2 H), 2.93 (ddd, *J* = 16.0 Hz & = 6.5 Hz & = 2.0 Hz, 1 H), 3.48 (s, 2 H), 4.18 (d, *J* = 12.8 Hz, 1 H), 4.41 (ddd, *J* = 12.8 Hz & = 5.5 Hz & = 1.7 Hz, 1 H) ppm. ^{13}C NMR (50

MHz, $CDCl_3$): δ = 31.2, 33.9, 36.8, 39.5, 54.1, 55.7, 71.6, 173.5 ppm.

4.8. (1S,2S,4R,5R)-Methyl-2(-4-(hydroxymethyl)-3,6-dioxabicyclo[3.1.0]hexan-2-yl)-acetate ((-)-10)

K_2CO_3 (20 mg, 0.14 mmol) was added to the stirred solution of compound **(+)-8** (47 mg, 0.25 mmol) in MeOH/H_2O (1 mL, 8:2) at room temperature. The reaction mixture was stirred until the starting material had reacted completely (checked by TLC, reaction time < 10 seconds). The mixture was quenched with saturated aqueous solution of ammonium chloride and extracted with EtOAc (5 x 15). The organic layer was dried over Na_2SO_4 and evaporated. Purification by column chromatography on silica gel (Hexane/EtOAc) gave compound **(-)-10** as a colorless oil; yield 98%; $[\alpha]_D^{22}$ = -32.09 (c = 6.19, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.43 (br s, 1 H), 2.57 (d, *J* = 7.5 Hz, 2 H), 3.67 (s, 3 H), 3.50 - 3.75 (m, 4 H), 4.11 (t, *J* = 4.3 Hz, 1 H), 4.43 (t, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.2, 51.9, 57.9, 62.6, 73.7, 78.9, 171.5 ppm.

4.9. Methyl 2(-4-(hydroxymethyl)-6-oxabicyclo[3.1.0]hexan-2-yl)-acetate ((+)- and (-)-11)

K_2CO_3 (20 mg, 0.14 mmol) was added to the stirred solution of compound **(+)-** or **(-)-9** (40 mg, 0.29 mmol) in MeOH/H_2O (2.6 mL, 8:2) at room temperature. The reaction mixture was stirred until the starting material had reacted completely. The reaction mixture was directly adsorbed on silica gel and after purification by column chromatography compounds **(+)-** or **(-)-11**, respectively, were obtained as a colorless oil; yield 67% ($CHMO_{Xantho}$); yield 74% ($CPMO_{Coma}$); $[\alpha]_D^{30}$ = +13.5 (c = 1.0, $CHCl_3$) ($CHMO_{Xantho}$); $[\alpha]_D^{30}$ = -11.3 (c = 0.4, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 14.3 Hz, 1 H), 1.92 (dt, *J* = 14.3 Hz & 8.9 Hz, 1 H), 2.26 - 2.51 (m, 3 H), 2.55 – 2.70 (m, 1 H), 3.13 (bs, 1 H), 3.39 (d, *J* = 2.3 Hz, 1 H), 3.52 (d, *J* = 2.3 Hz, 1 H), 3.55 – 3.61 (m, 2 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.7, 35.2, 36.9, 42.0, 51.7, 60.0, 61.0, 63.9, 172.7 ppm.

4.10. (3aS,5R,6R,6aR)-6-Hydroxy-5-(hydroxymethyl)tetrahydrofuro[3,2-b]furan-2(5H)-one ((-)-12)

A $SnCl_4$ solution in dichloromethane (1 mL, 100 µL/mL) was added at -78°C to a solution of compound **(-)-10** (0.081 g, 0.430 mmol) in dry dichloromethane (3.0 mL). The reaction mixture was stirred for 1 h until the starting material had reacted completely (checked by TLC). Then the residue was purified by column chromatography (Hexane/EtOAc) to yield compound **(-)-12** as an amorphic, semi-crystalline form;[54] yield 98%; $[\alpha]_D^{25}$ = -30.1 (c = 0.86, MeOH). ^{1}H NMR (200 MHz, CD_3OD): δ = 2.50 (d, *J* = 18.4 Hz, 1 H), 2.72 (dd, *J* = 18.8 Hz & 4.9 Hz, 1 H), 3.21 (br s, 2 H), 3.48 (dd, *J* = 11.9 Hz & 5.9 Hz, 1 H), 3.68 (dd, *J* = 11.9 Hz & 3.7 Hz, 1 H), 3.74 (dt, *J* = 5.9 Hz & 3.7 Hz, 1 H), 4.06 (d, *J* = 5.5 Hz, 1 H), 4.76 - 4.80 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.1, 62.8, 77.2, 79.0, 88.3, 92.2, 177.8 ppm.

4.11. 6-Hydroxy-5-(hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one ((+)- and (-)-13)

To a solution of compound **(+)-** or **(-)-11** (30 mg, 0.16 mmol) in dry dichloromethane (2 mL), was added $SnCl_4$ (38 µL, 0.32 mmol) dropwise under nitrogen atmosphere at −78 ºC. After 2 h all the starting material was consumed (checked by TLC). The reaction mixture was directly adsorbed on silica gel and after purification by column chromatography (EtOAc) compounds **(+)-** and **(-)-13** were obtained as a colorless oil; yield 85% ($CHMO_{Xantho}$); yield 79% ($CPMO_{Coma}$); $[\alpha]_D^{21}$ = +35.1 (c = 0.87, MeOH) ($CHMO_{Xantho}$); $[\alpha]_D^{21}$ = -32.2 (c = 0.12, MeOH) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz, CD_3OD): δ = 1.30 (d, *J* = 11.1 Hz, 1 H), 1.89 - 2.32 (m, 3 H), 2.77 (dd, *J* = 17.9 Hz & 9.7 Hz, 1 H), 2.93 (qd, *J* = 8.0 Hz & 2.6 Hz, 1 H), 3.54 (dd, *J* = 11.0 Hz & 6.2 Hz, 1 H), 3.70 (dd, *J* = 11.0 Hz & 4.4 Hz, 1 H), 3.87 (dd, *J* = 8.8 Hz & 3.6 Hz, 1 H), 4.68 (dd, *J* = 8.0 Hz & 3.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 32.8, 34.7, 35.3, 49.4, 63.7, 78.4, 92.0, 178.4 ppm.

4.12. (3aS,5R,6R,6aR)-5-(Hydroxymethyl)-6-iodotetrahydrofuro[3,2-b]furan-2(3H)-one ((-)-14)

To a stirred solution of compound **(+)-6** (0.55 g, 3.92 mmol) in MeCN/H_2O (8.6 mL, 2.3:1) was added KOH (230 mg, 4.11 mmol). The reaction mixture was stirred at room temperature for 4 h until TLC showed full consumption of the starting material. Afterwards, a mixture of I_2 (1.09 g, 4.30 mmol) and KI (2.15 g, 12.93 mmol) was added. The resulting mixture was stirred in the dark for 5 days at 40°C. The reaction was quenched with a 10% solution of $Na_2S_2O_3$ until decoloration of the mixture was observed and then extracted with EtOAc (5 x 15). The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. Purification by column chromatography on silica gel (Hexane/EtOAc) gave compound **(-)-14** as a beige oil which solidified upon standing in the refrigerator; yield 75%; m.p. 84-86 °C; $[\alpha]_D^{22}$ = -70.2 (c = 1.28, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.90 (br s, 1 H), 2.80 (d, *J* = 3.3 Hz, 2 H), 3.70 (dd, *J* = 12.4 Hz & 4.6 Hz, 1 H), 3.86 (dd, *J* = 12.4 Hz & 3.0, 1 H), 4.22 (dd, *J* = 7.5 Hz & 2.1 Hz, 1 H), 4.33 (ddd, *J* = 7.5 Hz & 4.6 Hz & = 3.0 Hz, 1 H), 4.85 – 4.90 (m, 1 H), 5.22 (dd, *J* = 4.5 Hz & 2.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.0, 36.2, 61.2, 78.2, 90.7, 92.8, 173.8 ppm. $C_7H_9IO_4$ (284.05): calcd. C 29.60, H 3.19; found C 30.00, H 3.18.

4.13. 5-(Hydroxymethyl)-6-iodohexyhydro-2H-cyclopenta[b]furan-2-one ((+)- and (-)-15)

To a stirred solution of compound **(+)-** or **(-)-7** (100 mg, 0.73 mmol) in MeCN/H_2O (2 mL, 2.3:1) was added KOH (43 mg, 0.76 mmol). The reaction mixture was stirred at room temperature for 5 h until TLC showed full consumption of the starting material. Afterwards, a mixture of I_2 (202 mg, 0.80 mmol) and KI (397 mg, 2.39 mmol) was added. The resulting mixture was stirred in the dark for 39 h at room temperature. The reaction was quenched with a 10% solution of $Na_2S_2O_3$ until decoloration of the mixture was observed and the reaction was neutralized with saturated NH_4Cl. Then the reaction was extracted with EtOAc (3x). The organic layer was dried over Na_2SO_4 and evaporated. Purification by column chromatography (LP/EtOAc = 1/2) gave compounds **(+)-** and **(-)-15** as a colorless oil; yield 92% ($CHMO_{Xantho}$); yield 100% (CPMO); $[\alpha]_D^{24}$ = +62.5 (c = 1.2, $CHCl_3$) ($CHMO_{Xantho}$); $[\alpha]_D^{24}$ = -59.4 (c = 0.3, $CHCl_3$) (CPMO). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50 (dt, *J* = 13.2 Hz & 9.0 Hz, 1 H), 2.10 – 2.25 (m, 2 H), 2.40 – 2.48 (m, 2 H), 2.81 (dd, *J* = 18.0 Hz & 9.5 Hz, 1 H), 3.02 (qd, *J* = 9.5 Hz & 3.1 Hz, 1 H), 3.68 (dd, *J* = 10.8 Hz & 4.9 Hz, 1 H), 3.77 (dd, *J* = 10.8 Hz & 4.5 Hz, 1 H), 4.09 (dd, *J* = 9.4 Hz & 4.4 Hz, 1 H), 5.17 (dd, *J* = 7.8 Hz & 4.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.8, 33.5, 35.3, 37.1, 52.4, 61.5, 93.9, 176.2 ppm. $C_8H_{11}IO_3$ (282.08): calcd. C 34.06, H 3.93; found C 35.37, H 3.70.

4.14. 6-Azido-5-(hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one ((+)-16)

Compound **(+)-15** (27 mg, 0.10 mmol), DMSO (1 mL) and 4Å molecular sieve were warmed to 75°C. Sodium azide (62 mg, 010 mmol) was added and the solution was stirred at 75°C for 40h. The reaction was quenched with H_2O and extracted with dichloromethane (3x). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Crude mass was purified by column chromatography (LP/EtOAc = 1/2 to 1/4) to yield compound **(+)-**

16 as a colorless oil; yield 100%; $[\alpha]_D^{30}$ = +198.0 (c = 1.0, $CHCl_3$) ($CHMO_{Xantho}$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (dd, *J* = 10.7 Hz & 6.4 Hz, 1H), 1.35 (m, 1H), 2.02- 2.24 (m, 2H), 2.34 (dd, *J* = 17.9 Hz & 6.7 Hz, 1H), 2.68 - 3.03 (m, 2H), 3.67 - 3.83 (m, 2H), 4.26 (t, *J* = 4.2 Hz, 1H), 4.97 (dd, *J* = 9.2 Hz & 4.7 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.7, 34.8, 36.1, 44.3, 61.5, 64.9, 84.3 ppm.

*4.15. (3aS,5S,6aS)-5-(Hydroxymethyl)tetrahydrofuro[3,2-b]furan-2(3H)-one (**(-)-17**)*

Tributyltin hydride (0.500 mL, 1.85 mmol) was added dropwise to a solution of compound **(-)-14** (0.190 g, 0.71 mmol) in dry toluene (15 mL). The mixture was stirred for 48 h at 60 °C until the starting material had reacted completely (checked by TLC). Then, the solvent was concentrated in vacuo and the crude mass was purified by column chromatography (Hexane/EtOAc) to yield compound **(-)-17** as a colorless oil; yield 99%, $[\alpha]_D^{25}$ = -53.3 (c = 0.42, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.89 (bs, 1 H), 2.12 (ddd, *J* = 14.6 Hz & 7.1 Hz & 3.2 Hz, 1 H), 2.39 (ddd, *J* = 14.6 Hz & 7.8 Hz & 6.9 Hz, 1 H), 2.75 (d, *J* = 3.2 Hz, 2 H), 3.60 (dd, *J* = 11.8 Hz & 6.3 Hz, 1 H), 3.74 (dd, *J* = 11.9 Hz & 3.2 Hz, 1 H), 4.18 (ddd, *J* = 10.4 Hz & 7.2 Hz & 3.2 Hz, 1 H), 4.63 (dd, *J* = 7.3 Hz & 3.2 Hz, 1 H), 5.05 (ddd, *J* = 6.3 Hz & 4.2 Hz & 1.7 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.0, 36.4, 64.6, 79.0, 80.7, 84.4, 175.2 ppm.

*4.16. 5-(Hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one (**(+)-** and **(-)-18**)*

Tributyltin hydride (208 µL, 0.78 mmol) was added dropwise to a solution of compound **(+)-** or **(-)-15** (85 mg, 0.30 mmol) in dry toluene (1.5 mL). The mixture was stirred for 43 h at 60 °C under nitrogen atmosphere until the starting material had reacted completely (checked by TLC). The reaction mixture was directly adsorbed on silica gel and after purification by column chromatography (LP/EtOAc = 1/3 – 1/5) compounds **(+)-** and **(-)-18** were obtained as a colorless oil; yield 85% ($CHMO_{Xantho}$); yield 81% (CPMO); $[\alpha]_D^{21}$ = +57.5 (c = 1.0, $CHCl_3$) ($CHMO_{Xantho}$); $[\alpha]_D^{21}$ = -61.5 (c = 0.4, $CHCl_3$) (CPMO). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 – 1.45 (m, 2 H), 1.55 – 1.80 (m, 1 H), 2.00 - 2.42 (m, 4 H), 2.67 - 2.84 (m, 2 H), 3.50 – 3.65 (m, 2 H), 4.92 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.5, 35.6, 39.1, 42.1, 65.6, 86.0, 177.3 ppm. $C_8H_{12}O_3$ (156.18): calcd. C 61.52, H 7.74; found C 57.63, H 6.30.

*4.17. (3aS,5S,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3H)-one (**(-)-19**)*

Imidazole (20.0 mg, 0.29 mmol) was added to a solution of compound **(-)-17** (8.5 mg, 0.05 mmol) in dry DMF (0.5 mL) followed by *tert*-butylchlorodiphenylsilane (30 mg, 0.11 mmol). The mixture was stirred for 24 h at room temperature until the starting material had reacted completely (checked by TLC). Crude mass was purified by column chromatography (Hexane/EtOAc) to yield compound **(-)-19** as a colorless oil; yield 92%; $[\alpha]_D^{26}$ = -23.8 (c = 0.75, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (s, 9 H), 2.10 – 2.26 (m, 1 H), 2.26 – 2.45 (m, 1 H), 2.68 – 2.72 (m, 2 H), 3.63 – 3.79 (m, 2 H), 4.05 – 4.20 (m, 1 H), 4.54 – 4.61 (m, 1 H), 4.97 – 5.05 (m, 1 H), 7.30 – 7.45 (m, 6 H), 7.61 – 7.72 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.2, 26.8, 34.6, 36.4, 65.6, 78.9, 80.7, 84.3, 127.7, 129.7, 133.3, 133.4, 135.5, 135.6, 175.2 ppm.

*4.18. 5-(((tert-Butyldiphenylsilyl)oxy)methyl)hexahydro-2H-cyclopenta[b]furan-2-one (**(+)-** and **(-)-20**)*

Imidazole (53 mg, 0.78 mmol) was added to a solution of compound **(+)-** or **(-)-18** (22 mg, 0.14 mmol) in dry DMF (1.3 mL) followed by *tert*-butylchlorodiphenylsilane (75 µL, 0.29 mmol) under nitrogen atmosphere. The mixture was stirred for 1 h at room temperature until the starting material had reacted completely (checked by TLC). The reaction mixture was extracted with dichloromethane (3x), the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Crude mass was purified by column chromatography (LP – LP/EtOAc = 20/1) to yield compounds **(+)-** and **(-)-20** as a white solid; yield 95% ($CHMO_{Xantho}$); yield 89% (CPMO); m.p. 78-81 °C, $[\alpha]_D^{30}$ = +45.0 (c = 1.0, $CHCl_3$) ($CHMO_{Xantho}$); $[\alpha]_D^{30}$ = -32.4 (c = 0.3, $CHCl_3$) (CPMO). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 1.12 – 1.26 (m, 1 H), 1.65 – 1.75 (m, 1 H), 2.05 – 2.41 (m, 2 H), 2.66 – 2.81 (m, 2 H), 3.60 (dd, *J* = 10.0 Hz & 3.3 Hz, 1 H), 3.66 (dd, *J* = 10.0 Hz & 3.1 Hz, 1 H), 4.88 – 4.98 (m, 1 H), 7.36 – 7.44 (m, 6 H), 7.62 – 7.67 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.2, 26.7, 35.3, 35.5, 35.6, 39.1, 42.4, 66.3, 85.8, 127.6, 129.6, 133.5, 135.4, 177.0 ppm. $C_{24}H_{30}O_2Si$ (378.58): calcd. C 73.05, H 7.66; found C 73.04, H 7.59.

*4.19. (1R,6S,7R,8S)—7,8-Dihydroxy-3,9-dioxabicyclo[4.2.1]nonan-4-one (**21**)*

To a solution of compound **(+)-6** (109 mg, 0.78 mmol) in dichloromethane (11 mL) and *tert*-Butanol (2 mL) was added NMO (163 mg, 1.39 mmol) followed by a crystal of OsO_4. The reaction was stirred at room temperature until TLC analysis showed complete consumption of starting material (3-6 h). The reaction was quenched with 2 mL of a 10% solution of Na_2SO_3 and the mixture was stirred for an additional 45 min. Then it was filtered through a pad of Celite® which was washed with dichloromethane. The aqueous phase was extracted 5 times with dichloromethane. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Purification of the crude mass by column chromatography (stepwise gradient LP/EtOAc = 100% LP to 100% EtOAc, followed by a stepwise gradient EtOAc/EtOH = 100% EtOAc to 10% EtOH) gave compound **21**; yield 55%; ^{1}H NMR (200 MHz, CD_3OD): δ = 2.81 (dd, *J*= 16.3 Hz & 5.0 Hz, 1 H), 2.95 (dd, *J* = 16.3 Hz & 2.4 Hz, 1 H), 3.90 – 4.40 (m, 6 H), 4.8 (s, 2 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 43.8, 73.1 (2C), 76.0, 82.1, 86.6, 175.7 ppm.

*4.20. 7,8-Dihydroxy-3-oxabicyclo[4.2.1]nonan-4-one (**(+)-** and **(-)-22**)*

To a solution of compound **(+)-** or **(-)-7** (140 mg, 1.01 mmol) in dichloromethane/*tert*-Butanol (6 mL, 2/1) was added NMO•H_2O (172 mg, 1.27 mmol) under nitrogen atmosphere followed by a crystal of OsO_4. The reaction was stirred at room temperature until TLC analysis showed complete consumption of starting material (24 h). The reaction was quenched with 2 mL of a 10% solution of Na_2SO_3 and the mixture was stirred for an additional 1 h. The reaction mixture was directly adsorbed on silica gel and after purification by column chromatography (EtOAc) compounds **(+)-** and **(-)-22**, respectively, were obtained as a colorless oil; yield 50% ($CHMO_{Xantho}$); yield 56% (CPMO); $[\alpha]_D^{21}$ = -71.5 (c = 0.06, EtOH) ($CHMO_{Xantho}$); $[\alpha]_D^{21}$ = +73.1 (c = 1.27, EtOH) (CPMO). ^{1}H NMR (200 MHz, CD_3OD): δ = 1.48 (d, *J* = 11.1 Hz, 1 H), 2.21 – 2.37 (m, 3 H), 2.63 (dd, *J* = 15.8 & 1.8 Hz, 1 H), 2.84 (ddd, *J* = 15.8 Hz & 7.7 Hz & 1.3 Hz, 1 H), 3.87 (d, *J* = 6.0 Hz, 1 H), 4.12 – 4.38 (m, 3 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 37.2, 41.1, 42.8, 47.9, 72.7, 73.9, 76.7, 177.7 ppm.

*4.21. (1S,2S,6R,7R)-4,4-Dimethyl-3,5,9,12-tetraoxatricyclo[5.4.1.$0^{2,6}$]dodecan-10-one (**(+)-23**)*

To a solution of compound **21** (50 mg, 0.29 mmol) in acetone (3 mL) under nitrogen atmosphere, 2-methoxypropene (1.50 mL, 15.7 mmol) and a catalytic amount of *p*-Toluenesulfonic acid were added. When TLC proved all starting material to be gone, the reaction was hydrolyzed with saturated bicarbonate solution. The aqueous phase was extracted 5 times with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude material was purified by column chromatography (basic SiO_2, stepwise gradient LP/EtOAc = 100% LP to 100% EtOAc) yielding compound **(+)-23** as colorless crystals; yield 76%, m.p. 163 – 167 °C, $[\alpha]_D^{20}$: +73.0 (c = 0.66, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.96 (d, J = 4 Hz, 2H, H-2), 4.23-4.30 (m, 3H), 4.31-4.39 (m, 1H), 4.65 (d, J=5.0 Hz, 2H), 4.95 (d, J = 5.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$): δ 24.3, 25.9, 42.5, 71.5, 78.3, 81.5, 82.4, 83.5, 112.4, 172.2;

*4.22. 4,4-Dimethyl-3,5,9-triaoxatricyclo[5.4.1.0^{2,6}]dodecan-10-one (**(+)- and (-)-24**)*

To a solution of compound **(+)-** or **(-)-22** (43 mg, 0.25 mmol) in acetone (3 mL) under nitrogen atmosphere, 2,2-dimethoxypropane (1.50 mL, 12.2 mmol) and a catalytic amount of *p*-Toluenesulfonic acid were added. When TLC proved all starting material to be gone (after 26 h), the reaction was hydrolyzed with saturated bicarbonate solution. The aqueous phase was extracted 5 times with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude material was purified by column chromatography (LP/EtOAc = 6/1) yielding compounds **(+)-** and **(-)-(+)-** and **(-)-24** as a white solids, each; yield 80% ($CHMO_{Xantho}$); yield 60% (CPMO); m.p. 115 - 119 °C, $[\alpha]_D^{22}$ = -74.2 (c = 1.0, $CHCl_3$) ($CHMO_{Xantho}$); $[\alpha]_D^{22}$ = +69.2 (c = 1.0, $CHCl_3$) (CPMO). ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ = 1.26 (d, *J* = 0.5 Hz, 3 H), 1.36 (d, *J* = 0.5 Hz, 3 H), 1.59 (d, *J* = 11.3 Hz, 1 H), 2.22 – 2.30 (m, 2 H), 2.42 – 2.52 (m, 1 H), 2.70 – 2.83 (m, 2 H), 4.17 – 4.36 (m, 3 H), 4.69 (dd, *J* = 5.3 Hz & 1.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $(CD_3)_2CO$): δ = 23.6, 26.2, 36.8, 39.4, 39.9, 44.2, 71.0, 82.4, 84.5, 109.8, 174.1 ppm.

*4.23. ((3aR,4R,6S,6aS)-6-((3-Amino-1H-1,2,4-triazol-5-yl)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (**(-)-25**)*

Aminoguanidine bicarbonate (58 mg, 0.43 mmol) was added to a mixture of compound **(+)-23** (90 mg, 0.41 mmol) in pyridine (5 mL) at room temperature. The reaction mixture was refluxed for 1.5 h under argon atmosphere until no starting material could be detected by TLC. After that, the pyridine was removed and purification of the liquid residue by column chromatography on silica gel ($CHCl_3$/MeOH) gave compound **(-)-25** as colorless crystals; yield 78%; m.p. 65 – 67°C; $[\alpha]_D^{21}$ = -11.8 (c = 0.22, MeOH). ^{1}H NMR (200 MHz, CD_3OD): δ = 1.12 – 1.20 (m, 2 H), 1.31 (s, 3 H), 1.51 (s, 3 H), 2.66 (s, 1 H) 2.78 – 2.84 (m, 2 H), 3.50 – 3.70 (m, 3 H), 3.91 – 3.99 (m, 1 H), 4.18 – 4.25 (m, 1 H), 4.46 – 4.52 (m, 1 H), 4.59 – 4.67 (m, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 16.1, 23.4, 25.4, 61.1, 80.8, 81.8, 83.4, 84.2, 113.0 ppm.

*4.24. (6-((3-Amino-1H-1,2,4-triazol-5-yl)methyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (**(+)- and (-)-26**)*

Aminoguanidine bicarbonate (33 mg, 0.25 mmol) was added to a mixture of compound **(+)-** or **(-)-24** (30 mg, 0.15 mmol) in pyridine (3 mL) at room temperature. The reaction mixture was refluxed for 1 h under argon atmosphere until no starting material could be detected by TLC. After that, the pyridine was removed and purification of the liquid residue by column chromatography on silica gel ($CHCl_3$/MeOH) gave compounds **(+)-** and **(-)-26** as oils, each; yield 50% ($CHMO_{Xantho}$); yield 43% (CPMO); $[\alpha]_D^{24}$ = -104.1 (c = 1.0, MeOH) ($CHMO_{Xantho}$); $[\alpha]_D^{24}$ = +97.1 (c = 1.0, MeOH) (CPMO). ^{1}H NMR (200 MHz, CD_3OD): δ = 1.28 (s, 3 H), 1.50 (s, 3 H), 2.05 – 2.17 (m, 3 H), 2.31 – 2.57 (m, 2 H), 3.55 – 3.70 (m, 4 H), 4.19 – 4.41 (m, 2 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 25.4, 27.9, 34.9, 38.4, 43.4, 52.0, 64.5, 84.2, 86.7, 113.7, 174.6 ppm.

*4.25. ((2R,5R)-5-((3-Amino-1H-1,2,4-triazol-5-yl)methyl)-2,5-dihydrofuran-2-yl)methanol (**(-)-27**)*

Aminoguanidine bicarbonate (90 mg, 0.67 mmol) was added to a mixture of compound **(+)-6** (90 mg, 0.64 mmol) in pyridine (5 mL) at room temperature. The reaction mixture was refluxed for 2 h under argon atmosphere until no starting material could be detected by TLC. After that, the pyridine was removed and purification of the liquid residue by column chromatography on silica gel ($CHCl_3$/MeOH) gave compound **(-)-27** as colorless crystals; yield 67%; m.p. 87 - 89°C; $[\alpha]_D^{21}$ = -45.5 (c = 0.22, MeOH). ^{1}H NMR (200 MHz, CD_3OD): δ = 2.59 – 2.85 (m, 2 H), 3.10 – 3.27 (m, 2 H), 3.30 – 3.55 (m, 2 H), 4.60 – 4.85 (m, 3 H), 4.85 – 5.05 (m, 1 H), 5.70 – 5.77 (m, 1 H), 5.80 – 5.95 (m, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD + $CDCl_3$): δ = 34.4, 64.5, 84.4, 87.8, 128.4, 131.0, 156.5, 158.8 ppm.

*4.26. (4-((3-Amino-1H-1,2,4-triazol-5-yl)methyl)cyclopent-2-en-1-yl)methanol (**(+)- and (-)-28**)*

Aminoguanidine bicarbonate (62 mg, 0.46 mmol) was added to a mixture of compound **(+)-** or **(-)-7** (50 mg, 0.36 mmol) in pyridine (3 mL) at room temperature. The reaction mixture was refluxed for 1 h under argon atmosphere until no starting material could be detected by TLC. After that, the pyridine was removed and purification of the liquid residue by column chromatography on silica gel ($CHCl_3$/MeOH) gave compounds **(+)-** and **(-)-28**, respectively; yield 71% ($CHMO_{Xantho}$); yield 71% (CPMO); $[\alpha]_D^{21}$ = 6.63 (c = 1.0, MeOH) ($CHMO_{Xantho}$); $[\alpha]_D^{22}$ = -10.1 (c = 0.8, MeOH) (CPMO). ^{1}H NMR (200 MHz, CD_3OD): δ = 1.04 – 1.18 (m, 1 H), 2.03 – 2.15 (m, 1 H), 2.35 – 2.56 (m, 1 H), 2.59 – 3.06 (m, 1 H), 3.19 – 3.22 (m, 2H), 3.25(bs, 2 H), 5.58 (dd, *J* = 7.8 Hz & 1.4 Hz, 1 H), 5.65 (dd, *J* = 7.8 Hz & 1.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 34.0, 35.3, 45.8, 49.1, 67.5, 133.6, 136.2 ppm.

*4.27. 3-Oxabicyclo[4.2.1]nonan-4-one (**(+)- and (-)-29**)*

Compound **(+)-** or **(-)-7** (100 mg, 0.72 mmol) and Pd/C (10% w/w) were suspended in dry EtOAc (10 mL) and hydrogenated at rt overnight using a balloon filled with hydrogen. The conversion was determined by TLC analysis and after completion, the reaction mixture was filtered through a pad of Celite®. The residue was washed thoroughly with EtOAc and the filtrate was concentrated in vacuo. The purity of the product was determined to be >95% by NMR so no further purification was necessary. Compounds **(+)-** and **(-)-29** were obtained as a pale yellow oil, each; yield 79% ($CHMO_{Xantho}$); yield 83% (CPMO); $[\alpha]_D^{22}$ = -12.4 (c = 1.0, EtOAc) ($CHMO_{Xantho}$); $[\alpha]_D^{22}$ = +105.1 (c = 1.67, $CHCl_3$) (CPMO). 1H-NMR and 13C-NMR data are according to the previous results in our group (Kandioller Wolfgang Diploma Thesis)

*4.28. (3-((5-Amino-4H-1,2,4-triazol-3-yl)methyl)cyclopentyl)methanol (**(+)- and (-)-30**)*

Aminoguanidine bicarbonate (100 mg, 0.74 mmol) was added to a mixture of compound **(+)-** or **(-)-29** (90 mg, 0.64 mmol) in pyridine (5 mL) at room temperature. The reaction mixture was refluxed for 1 h under argon atmosphere until no starting material

could be detected by TLC. After that, the pyridine was removed and purification of the liquid residue by column chromatography on silica gel ($CHCl_3$/MeOH) gave compounds **(+)-** and **(-)-30** as oils, each; yield 69% ($CHMO_{Xantho}$); yield 67% (CPMO); $[\alpha]_D^{22}$ = +3.4 (c = 1.0, EtOAc) ($CHMO_{Xantho}$); $[\alpha]_D^{21}$ = -1.9 (c = 1.67, MeOH) (CPMO). ^{1}H NMR (200 MHz, CD_3OD): δ = 0.80 – 1.00 (m, 1 H), 1.20 – 1.50 (m, 2 H), 1.60 – 1.83 (m, 2 H), 1.85 – 2.40 (m, 3 H), 2.54 (d, *J* = 7.5 Hz, 2 H), 3.15 – 3.25 (m, 1 H), 3.35 (d, *J* = 6.7 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 29.1, 32.5, 34.3, 37.4, 40.4, 43.2, 67.6, 160.0 ppm.

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Supplementary Material

Supplementary data related to this article can be found at …

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