Synthesis of tetrahydrofuran-based natural products and their carba analogs via stereoselective enzyme mediated BaeyereVilliger oxidation

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a r t i c l e i n f o

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In this work we present efficient formal syntheses of several biologically interesting natural products (showdomycin, goniofufurone, trans-kumausyne) and their novel carba analogs by applying different BaeyereVilliger monooxygenases. This strategy provides access to tetrahydrofuran-based natural products, C-nucleosides and both antipodes of the corresponding carba analogs 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.

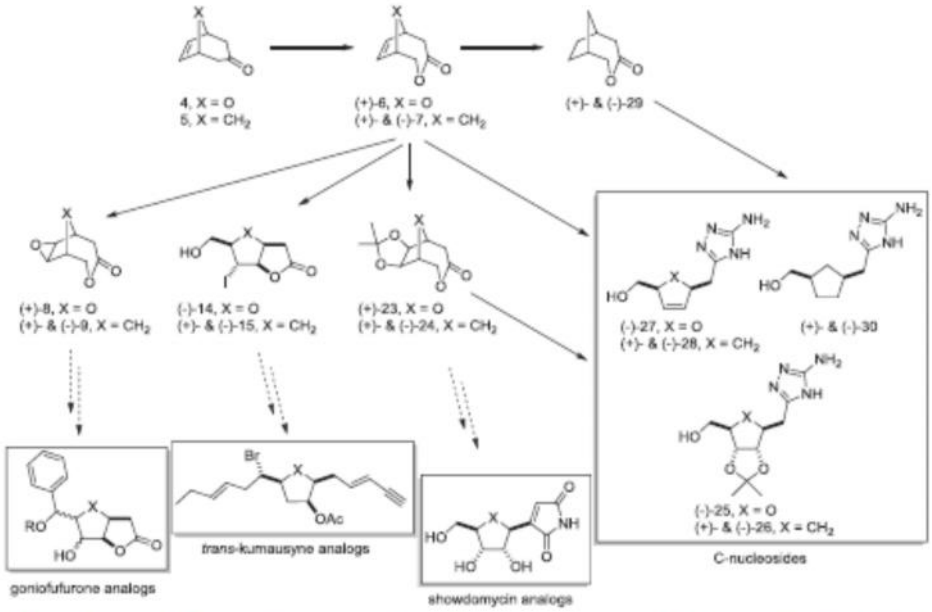
1. Introduction

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.[4e8]

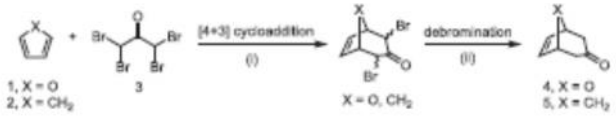
C-nucleosides represent another structural class, which attracts notable attention in the scientific community, with the above mentioned showdomycin being one example. C-nucleosides are compounds containing a CeC bond between the carbohydrate and the base rather than a CeN bond (N-nucleosides). This structural feature provides increased stability as the glycosidic CeC 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.[9e13] 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-Cnucleosides are a class of potential bio-active compounds combining common features of classical C-nucleosides and a noncarbohydrate 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 BaeyereVilliger oxidation has become an important method in synthesis of esters and lactones from acyclic and cyclic ketones, respectively.[15e18] In recent years several methods for the stereoselective BaeyereVilliger oxidation became available.[19e21] Due to the fact that the chemical BaeyereVilliger 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



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



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

functional group tolerance. The development of a biocatalytic variant of this transformation by applying BaeyereVilliger 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.[22e27] 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 (E. 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 enzymemediated BaeyereVilliger oxidation is used to successfully introduce chirality by exploiting the above mentioned enzymes.

Furthermore, the BaeyereVilliger 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 BaeyereVilliger 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

We envisioned the [4þ3] cycloaddition as a powerful tool for theconstruction of the desired seven-membered bicyclic ketones **4**[37] and **5**, which act as precursors for a subsequent BaeyereVilliger oxidation (Scheme 2). 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 oxyallylspecies 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 linewith previous reports on facilitating such heterogeneous cycloadditionreactions by ultrasound irradiation,[40,41] the synthesis of bicyclicketones 4 and 5 was carried out according to a sonochemicalprotocol developed in our group.[42]
Furan 1, tetrabromoacetone 3, Cu/Zn-couple and catalyticamount of dibromoethane were reacted under sonication and at30 _C. After filtration the crude solution of 2,4-dibromo-8-oxabicyclo[3.2.1]oct-6-en-3-one was used without further purificationfor the debromination step. After reduction with Cu/Zn couplein the presence of NH_4Cl at _78 _C and subsequent extractivework-up oxo-ketone 4 was obtained as beige crystals in good yield and purity (72%; mp 36e38 _C). Reaction of cyclopentadiene 2 with tetrabromoacetone 3, activated Zn and catalyticamount of I_2 gave crude 2,4-dibromobicyclo[3.2.1]oct-6-en-3-onevia an analogous protocol. Debromination with activated Zn andwork-up provided carba-ketone 5 in adequate yield and purity(58%).

2.1. Microbial BaeyereVilliger oxidation of bicyclic ketones

Having the symmetric ketones 4 and 5 in hands several differentBVMOs from our enzyme collection were tested for their ability toconvert the bicyclic ketones 4 and 5 into the desired lactones (þ)-6and (þ)- and (_)-7. All tested BVMOs were overexpressed in E. coliand conversion was monitored by GC. Screening results are shownin Table 1.

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

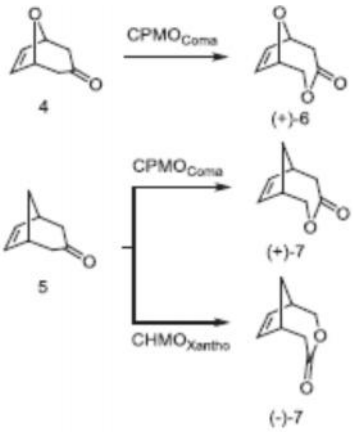
	Bicyclic oxo ketone **4**		Bicyclic carba ketone **5**	
Strain	Conversion[a]	ee[b]	Conversion[a]	ee[b]
CDMO	–	–	–	–
$CHMO_{Acineto}$	–	–	+	91 (–)
$CHMO_{Arthro1}$	–	–	+	96 (–)
$CHMO_{Brachy}$	–	–	+	98 (–)
$CHMO_{Brevi1}$	–	–	–	–
$CHMO_{Brevi2}$	+++	93 (+)	++	59 (+)
$CPMO_{Coma}$	+++	95 (+)	++	89 (+)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

[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 thecorresponding lactones (þ)-6 and (þ)-7 (Scheme 3). $CPMO_{Coma}$ was preferred over $CHMO_{Brevi2}$ based on higher stereoselectivity.$CHMO_{Xantho}$ was also identified to convert both bicyclic ketones 4and 5. In the case of substrate 5 the corresponding lactone (_)-7was formed but when substrate 4 was supplied, the correspondingepoxide was formed exclusively while the ketone did not react atall.[43] By using these two different BVMOs we achieved facile accessto the antipodal carba-lactones (þ)-7 and (_)-7. Hence, we wereable to prepare all subsequent carba-products in an enantiocomplementary manner. Biotransformations proceeded with perfectchemoselectivity, very good enantioselectivity in the case of (þ)-6and (_)-7 and reasonable optical purity for (þ)-7. According toscreening results, the biotransformation in large scale was carriedout with E. coli DH5a expressing $CPMO_{Coma}$ and BL21 (DE3) cellsexpressing $CHMO_{Xantho}$ either under controlled conditions ina bioreactor or in shake flask experiments. The fermentation of oxo-ketone 4 to the corresponding lactone(þ)-6 was optimized by exploiting the in situ substrate feeding/product removal concept (SFPR).[44] This approach enables highercompound concentrations, which otherwise would be toxic forcells.[44e46] After sequential extraction of the resin and the fermentationbroth and subsequent purification by column chromatographythe desired lactone (þ)-6 was isolated in good yield (70%) andvery good optical purity (95% ee; $[a]_{D20}$: þ85.2 (c¼0.2, $CHCl_3$)). Incontrast carba-ketone 5 was transformed into the correspondinglactone (þ)-7 catalyzed by $CPMO_{Coma}$ applying shake flask experiments.The desired product was obtained in reasonable yield (63%)and good optical purity (89% ee; $[a]_{D21}$ ¼þ80.2 (c¼0.52, $CHCl_3$)).Transforming the same ketone 5 using $CHMO_{Xantho}$ as the catalyst,the enantiocomplementary lactone (_)-7 was obtained in againgood yield (71%) and excellent optical purity (>99% ee; $[a]_{D21}$ ¼_83.3(c¼0.51, $CHCl_3$)). Compounds (þ)-6 and (þ)- and (_)-7 were thenused as a platform for comprehensive chemical transformations.

2.2. Synthesis of goniofufurone analogs

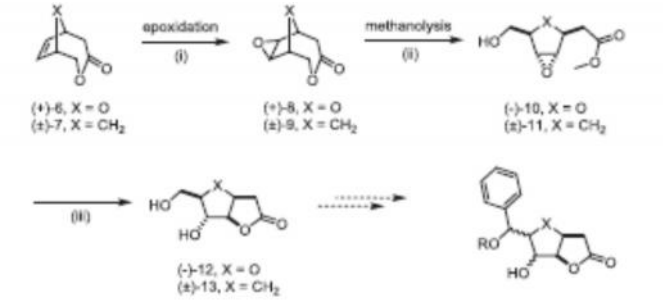
After one chemoenzymatic step we were able to synthesize thekey building blocks (þ)-6 and (þ)- and (_)-7 to get access togoniofufurone and their carba analogs. In Scheme 4 all syntheticsteps including reaction conditions for formal syntheses of goniofufuroneanalogs starting from lactones (þ)-6 and (þ)- and (_)-7are displayed. In the first step, a diastereoselective epoxidationwascarried out using m-chloroperbenzoic acid (m-CPBA) as oxidantreagent. This procedure[47,48] afforded selectively exo-epoxide (þ)-8in excellent yield (98%) as well as the carba-epoxides (þ)-9 (69%yield) and (_)-9 (75% yield). Interestingly the shielding effect fromthe bridging CH_2 group or the oxygen atom in addition to the geometryof the bicyclic ring characteristics resulted in a perfectlystereochemically controlled epoxidation. Subsequent methanolysiswas successfully applied to obtain compound (_)-10 in 98% yield,compound (þ)-11 was isolated in 67% yield and compound (_)-11in 74% yield. Intramolecular ring opening of the epoxide via Lewisacid activation resulted in formation of bicyclic lactone (_)-12again in excellent yield (98%). Transformation of (þ)-11 gave accessto both antipodes (þ)-13 (85% yield) and (_)-13 (79% yield).Preparation of these key intermediates enables access to variousgoniofufurone analogs as interesting natural products containinga fused tetrahydrofuran or cyclopentane ring, respectively accordingto previous Refs. 49,50.



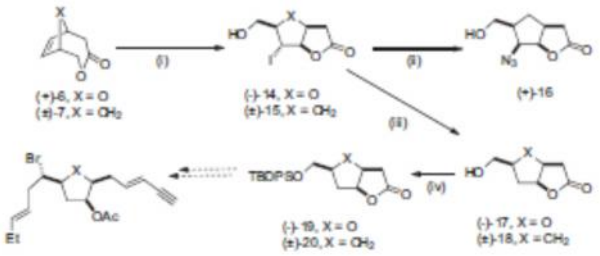
Scheme 3. Enzyme-mediated Baeyer–Villiger oxidations: 95% ee and 70% yield for (+)-**6**, 89% ee and 63% yield for (+)-**7** and >99% ee and 61% yield for (−)-**7**.

2.3. Synthesis of trans-kumausyne analogs

Furthermore we exploited the geometry of the biotransformationproducts (þ)-6 as well as (þ)- and (_)-7 and introducedtwo new stereogenic centers by applying aniodolactonization reaction. This approach provides goniofufuroneanalog precursors from the previous section additionally bearing aniodine atom in position of the previous hydroxyl as a good leavinggroup. Following this route we aimed for the accessibility of anotherinteresting natural compound, namely trans-kumausyne.Scheme 5 shows the synthetic strategy carried out for the formalpreparation of trans-kumausyne analogs starting from chiral bicycliclactones (þ)-6 and (þ)- and (_)-7. Lactones were hydrolyzedin situ using KOH in MeCN/H_2O. Subsequent iodolactonization



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%.



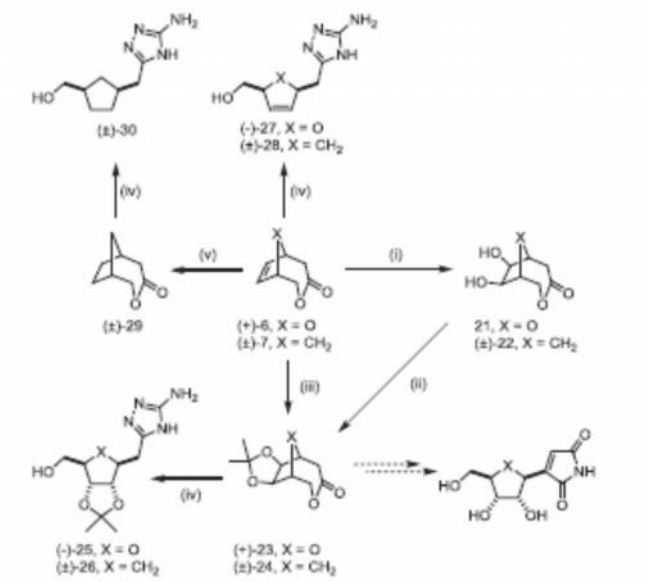
Scheme 5. Preparation of *trans*-kumausyne analogs: (i) 1) KOH, MeCN/H_2O 2) I_2/KI, 40 °C for synthesis of (−)-**14**, rt for synthesis of (±)-**15**, (−)-**14**: yield: 75%, (+)-**15**: yield: 92%, (−)-**15**: yield: quant.; (ii) NaN_3, DMSO, 75 °C, yield: quant.; (iii) $HSn(Bu)_3$, toluene, 60 °C,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

adding I_2/KI enabled a one pot reaction to give iodolactone (_)-14in good yield (75%). Applying the same protocol carba analogs (þ)-and (_)-15 were obtained in excellent yields ((þ)-15 92% yield;(_)-15 quant. yield). Again, two new stereogenic centers were incorporatedwith perfect selectivity. Additionally, these iodide intermediatesenable further chemical transformations. As an

example we synthesized the corresponding azide (þ)-16 startingfrom (þ)-15 in the presence of sodium azide. Azidolactone (þ)-16was obtained quantitatively with complete inversion of the stereogenic center in position 6. Next, the iodolactones were dehalogenatedusing tributyltin hydride as the reducing agent and gavelactone (_)-17 after purification as colorless oil with identicalspectral properties as described in the literature[51] in perfect yield(99%). Transformation of the carba analogs gave antipodal products18 in very good yields ((þ)-18 85%; (_)-18 81%). Discrepancies inpublished data about the absolute configuration based on thespecific optical rotation of alcohol (_)-17 prompted us to extendour synthetic investigations towards the protected alcohol compounds(_)-19/(þ)- and (_)-20. Finally the alcohol functionalitywas masked by using tert-butylchlorodiphenylsilane and all threecompounds were obtained in very good yields ((_)-19: 92%;(þ)-20: 95%, (_)-20: 89%).By comparing the specific rotation of (_)-19 with publisheddata[51] we were able to conclude that chiral information was conservedcompletely. This is probably true for the carba analogs but toour knowledge no reference data is available yet. With the synthesisof these key intermediates, the formal synthesis of transkumausyneand its carba analogs were formally completed.

2.4. Synthesis of C-nucleosides

Special interest was given to the very broad field of C-nucleosideswith showdomycin being one prominent example. Synthesis of compounds (þ)-23 and (þ)- and (_)-24 provide suitable precursorsfor the formal total synthesis of showdomycin and its carba analogs. They may also act as precursors for the synthesis of otherC-nucleosides like pseudouridines. In Scheme 6 all transformations including the preparation of other C-nucleosides are summarized.Conversion of the bio-oxidation products (þ)-6 and (þ)- and (_)-7 to the key intermediates (þ)-23 and (þ)- and (_)-24 for modifiednucleosides turned out to be challenging due to the high water solubility of the intermediate diols 21 and (þ)- and (_)-22. Amongseveral 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 wasapplied. Olefin 6 was dihydroxylated using catalytic amount of OsO_4 and N-methylmorpholine oxide (NMO) as the re-oxidantachieving two new stereogenic centers selectively. Using only little amounts of an aqueous solution of Na_2SO_3 for quenching andintensive re-extraction, diol 21 was obtained with a reasonable yield of 55% after purification. The diol 21 was then reacted furtherwith 2,2-dimethoxypropane and para-toluenesulfonic acid (p-TsOH) as a catalyst to yield acetonide (þ)-23 as colorless crystals ingood yield (76%). The most suitable strategy turned out to avoid work-up of the reaction after the dihydroxylation but rather use thecrude 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 (þ)-23 was obtained in 47% yield over two steps, which was only a slight improvement.Upon comparison of physical data[52] for (þ)-23 the absolute configuration of bio-oxidation product (þ)-6 could beconfirmed to be (1S,6S). Similar conditions were applied to convert the carba analogs (þ)- and (_)-7. When synthesizing the diols (þ)-and (_)-22, aqueous conditions were avoided during work-up by adsorbing the reaction solution directly on silica gel. After purificationby column chromatography comparable yields of 56% for (þ)-22 and 50% for (_)-22 were achieved. Protection of the diolmoiety was performed as described before and acetonide (þ)-24



Scheme 6. Preparation of C-nucleosides: (i) NMO/OsO_4, CH_2Cl_2/*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, CH_2Cl_2/*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%.

was obtained in 60% and (_)-24 in 80% yield, respectively. Thesecompounds have been established as key intermediates for analogs

of the natural C-nucleoside showdomycin. Finally the lactonemoiety was addressed to synthesize other C-nucleosides. As an example 5-amino-4H-1,2,4-triazol was installed as a base usingavailable oxo- and carba lactones (Scheme 6). This represents a formal access to novel non-natural C-nucleosides via the biooxidativeapproach in this work. Within the general procedure for the preparation of C-nucleosides the corresponding lactone wasrefluxed with aminoguanidine bicarbonate in pyridine under argon atmosphere till conversion was proved to be complete by TLCanalysis. Purification by column chromatography provided products (_)-25, (þ)- and (_)-26, (_)-27, (þ)- and (_)-28 and (þ)- and(_)-30. For the elaboration of saturated lactones (þ)- and (_)-29, olefins (þ)- and (_)-7 were hydrogenated using a balloon filledwith hydrogen and Pd/C (10% w/w) as catalyst to provide 83% of (þ)-29 and 79% of (_)-29.

3. Conclusions

In summary, we were able to provide facile access to severalbiological 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-mediatedBaeyereVilliger oxidation was applied to introduce chirality efficiently. The obtained optically active lactones were used as a convenientplatform for several stereoselective transformations. Not only can the presented compounds serve as versatile precursors forthe synthesis of above mentioned natural products (formal synthesis) but the corresponding enantiocomplementary carba precursorsmay also be transformed further to carba analogs of the described compounds, which have not been described in the literatureyet. It would be interesting to study their biological behavior in contrast to the original tetrahydrofuran basedcompounds.

4. Experimental section

4.1. General

Unless otherwise noted, chemicals and microbial growth mediawere purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Flashcolumn chromatography was performed on silica gel 60 from Merck (40e63 mm). Abbreviations are used as the following:LP¼light petroleum, o/n¼over night, rt¼room temperature. Basic silica gel was obtained by mixing NEt_3 (5%), the desired solventmixture and silica gel. This suspension was stirred for 5 min and was used for column chromatography. Medium pressure columnchromatography was performed on a regular silica gel column with a B€uchi 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. Biotransformationswere carried out in a New Brunswick Bioflow 110 fermenter equipped with pH probe, oxygen probe, flow controllerand temperature control. Monitoring of all fermentation parameters was performed using the BiocommandPlus 3.30 software byNew Brunswick. Glucose concentrations were determined with Roche AccuChek-go. NMR-spectra were recorded from $CDCl_3$,CD_3OD or DMSO-d_6 solutions on a Bruker AC 200 (200 MHz) spectrometer and chemical shifts are reported in ppm using TMS asinternal standard. Combustion analysis was carried out in the MicroanalyticLaboratory, University of Vienna. General conversioncontrol and examination of purified products were performed withGC Top 8000/MS Voyager (quadropol, EIþ) using a standard capillary column BGB5 (30 m_0.32 mm ID). Enantiomeric excesswas determined via GC using a BGB 175 column (30m_0.25mmID,0.25 mm film) and a BGB 173 column (30 m_0.25 mm ID, 0.25 mm film) on a ThermoQuest Trace GC 2000 and a Thermo Focus GC.Specific rotation $[a]_{D20}$ was determined using a Perkin Elmer Polarimeter241 by the following equation: $[a]_{D20}$¼100*a/[c]*l; c[g/100 mL], l[dm].

4.2. Biocatalyst performance screening on analytical scale

A baffled Erlenmeyer flask was charged with LB medium withappropriate antibiotics supplement (10 mL), inoculated witha bacterial single colony from an Agar plate and incubated at 37 _Cin an orbital shaker o/n. The biotransformation medium, supplementedwith ampicillin (200 mg/L), was then inoculated with 2% v/v of the preculture and incubated for approx. 1e2 h under the same conditions until an optical density of 0.2e0.6was reached. Inducingagent and b-cyclodextrin (1 equiv) were added, the mixture was thoroughly 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 filmand incubated at the appropriate temperature in an orbital shaker for up to 24 h. Analytical samples were prepared by extraction of0.5 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.

4.3. 8-Oxabicyclo-[3.2.1]oct-6-en-3-one (4)

Cu/Zn couple (20.6 g, 0.31 mol), furan 1 (10 mL, 0.139 mol) andcatalytic amount of dibromoethane were suspended in dry MeCN (80 mL). The reaction mixture was cooled to 10 _C under nitrogenatmosphere and was sonicated for 30 min under subsequent addition of tetrabromoacetone 3 (38.2 g, 0.102 mol) dissolved in dryMeCN. The temperature was maintained below 25 _C. The conversion of the reaction was monitored by GCeMS. After completeconversion 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 crude1,5-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 wereadded and the reaction mixture was warmed to room temperature. Reaction monitoring was performed by GCeMS. After conversionhad reached completion, Cu/Zn couple was removed by filtration and the solid residue was washed with dichloromethane. Thecombined organic phases were vacuum evaporated. The crude product was cooled with an ice bath upon neutralization withsaturated bicarbonate. The obtained suspension was filtered again and solids were washed intensively with dichloromethane. Layerswere separated and the organic phase was dried over Na_2SO_4 and concentrated (bath temperature below 30 _C!). The purity of thecrude product was checked by NMR and GC/MS. After evaporation of all volatiles and drying in vacuo compound 4 was obtained asbeige crystals; yield 72%; mp 36e38 _C (lit.[53] 37e39 _C). ^1H NMR (200 MHz, $CDCl_3$): d¼2.30 (d, J¼16 Hz, 2H), 2.80 (dd, J¼16 Hz &5 Hz, 2H), 5.05 (d, J¼5 Hz, 2H), 6.20 (s, 2H) ppm ^{13}C NMR (50 MHz,$CDCl_3$): d¼46.6, 77.1, 133.3, 205.2 ppm.

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

Cyclopentadiene 2 was obtained by distillation of dicyclopentadiene(T_{dist}¼38e40 _C). Tetrabromoacetone 3 was prepared by reaction of acetone and bromine under acidic conditions. Cu/Zncouple (20.2 g, 0.309 mol) and catalytic amount of I_2 were suspended in dry MeCN (100 mL) under nitrogen atmosphere and withsonication (approx. 10 min). The reaction mixture was cooled to0 _C with subsequent dropwise addition of cyclopentadiene (9.17 g,0.139 mol) and tetrabromoacetone (37.1 g, 0.099 mol) while sonicatedand the temperature was maintained below room temperaturethroughout the experiment. The reaction was monitored byTLC until complete conversion was observed (approx. 3e7 h). ActivatedZn (20.0 g, 0.306 mol), NH_4Cl (20.0 g, 0.374 mol) and dryMeOH (100 mL) were added under nitrogen atmosphere at 0 _C andwith sonication. The reaction was followed by TLC until completeconversion. Remaining Zn was removed by filtration through a padof Celite_ and the solid residue was washed with diethylether. Thesuspension was cooled with an ice bath and neutralized with sodiumbicarbonate. The obtained suspension was filtered again,washed with diethylether and concentrated in vacuo. The crudewas extracted with pentane (three times), trying to achieve a selectiveextraction of the desired product taking advantage of itshigh carbon nature. The combined organic layers were dried overNa_2SO_4 and concentrated (bath temperature below 30 _C!) invacuo. The purity of the crude product was checked by NMR, wherewe can see small amounts of impurities but the purity of the crudeis sufficient for its use in the next step. After evaporation of allvolatiles and drying in vacuo compound 5 was obtained; yield 58%;to increase the purity of the product sublimation can be applied toobtain beige crystals; mp 98e100 _C. ^{1}H NMR (200 MHz, $CDCl_3$):d¼1.75 (d, J¼10.9 Hz, 1H), 2.03e2.16 (m, 1H), 2.31 (dd, J¼17.2 Hz &2.4 Hz, 2H), 2.44 (dd, J¼17.2 Hz & 3.3 Hz, 2H), 2.90 (br s, 2H), 6.00 (s,2H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼38.2, 41.7, 46.3, 135.4,210.4 ppm.

4.5. (1S,6S)-3,9-Dioxabicyclo[4.2.1]non-7-en-4-one ((D)-6)A NewBrunswick Bioflow 110 fermenter containing 1 L of sterile TB medium supplemented with 200 mg/L ampicillin was inoculatedwith 20 mL (2 vol %) overnight culture of DH5a/CPMOgrown on LB medium (50 mg/L ampicillin). The temperature wasmaintained at 37 _C and the pH was kept constant at 7.00_0.05 byadding 3N NaOH or 3N H_3PO_4 automatically. The 1 L culture wasgrown with an air flowof 5 L/min and stirring rates at 500 rpm. Thegrowth was continued until the culture density reached3.01e3.44 g/L dcw and the temperature was decreased to 25 _C.IPTG was added to a final concentration of 0.25 mM and after anadditional hour the fermentation culture was supplemented with4 g/L glucose (20% sterile solution). Two hours after induction20 mL of cell culture were taken and activity tests were performed.After passing the activity tests the pre-loaded resin and any additiveswere added. The glucose level was measured periodically asthe bioconversion progressed. Compound 4 (5 g, 40 mmol) wasdissolved in ethanol (10 mL) and was subsequently added to theresin (50 g wet resin, load X_{eq}¼0.2) and 100 mL of LB_{Amp}. b-cyclodextrin(10 mol %) and the substrate-resin mixture were addedto the fermentation broth. After 36 h and purification via columnchromatography (LP/EtOAc¼2/1; 200 g SiO_2) the desired lactone(þ)-6was isolated; yield 70% (95% ee); mp: 98e100 _C; $[a]_D^{20}$: þ85.2(c¼0.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼2.90 (dd, J¼16 Hz &5 Hz, 1H), 3.20 (dd, J¼16 Hz & 3 Hz, 1H), 4.05 (dd, J¼12 Hz & 3 Hz,1H), 4.40 (d, J¼12 Hz, 1H), 4.70 (d, J¼3 Hz, 1H), 4.85 (d, J¼3 Hz, 1H),6.10 (d, J¼6 Hz, 1H), 6.35 (d, J¼6 Hz, 1H) ppm ^{13}C NMR (50 MHz,$CDCl_3$): d¼46.7, 71.0, 76.3, 81.6, 129.0, 133.4, 172.0 ppm.

4.6. 3-Oxabicyclo[4.2.1]non-7-en-4-one ((D)- and (L)-7)
A 1 L Erlenmeyer flask containing 200 mL of sterile TB mediumsupplemented with 0.2 mg/mL of ampicillin and a drop of antifoam was inoculated with 2 mL (1% vol) overnight culture BL21(DE3)/p11_5.1 grown on LB medium (0.2 mg/mL ampicillin). The culture was growing at 30 _C and 120 rpm until the optical density at590 nm reached a value between 10 and 18 (approx. 8e11 h). Then the temperature was decreased to 24 _C and IPTG was added toa final concentration of 0.1 mM. After 1 h, b-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 GCeMS until 80e90% of conversion (approx. 14e20 h). The cells were separatedfrom the broth by centrifugation (9600 rpm, 15 min), and the broth was continuously extracted using dichloromethane (8e10 h). Theorganic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (LP/EtOAc¼3/1) gave thedesired compounds (þ)- and (_)-7 as a colorless solid; yield 71% (ee>99%) ($CHMO_{xantho}$); yield 63% (ee¼89%) ($CPMO_{Coma}$); mp50e52 _C; $[a]_{D21}$ ¼_83.3 (c¼0.51, $CHCl_3$) ($CHMO_{xantho}$); $[a]_{D21}$ ¼þ80.2(c¼0.52, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.64 (d,J¼11.5 Hz, 1H), 2.20e2.45 (m,1H), 2.65e2.87 (m, 2H), 2.89e3.07 (m,1H), 4.00e4.24 (m, 2H), 5.83 (dd, J¼5.7 Hz & 2.9 Hz, 1H), 6.10 (dd,J¼5.7 Hz & 2.9 Hz, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼36.7, 42.6,4.4, 44.7, 70.7, 131.1, 137.0, 174.1 ppm. $C_8H_{10}O_2$ (138.16): calcd. C69.55, H 7.30; found C 69.29, H 7.25.

4.7. (1R,6S,7S,9R)-3,8,10-Trioxatricyclo[4.3.1.0^{7,9}]decan-4-one((D)-8)
m-CPBA (3891 mg, 22.7 mmol) was added to a solution ofcompound (þ)-6 (390 mg, 2.27 mmol) in dichloromethane (100 mL) at room temperature. The reaction mixture was refluxedfor 2 days until no starting material could be detected by TLC. After that, the residue was purified by column chromatography on silicagel (Hexane/EtOAc) gave compound (þ)-8 as colorless crystals; yield 98%; mp 78e80 _C; $[a]_{D22}$ ¼þ94.9 (c¼0.79, $CHCl_3$). ^{1}H NMR(200 MHz, $CDCl_3$): d¼2.92 (dd, J¼16.5 Hz & 3.8, 2H), 3.05 (dd, J¼16.5 Hz & 2.5 Hz, 1H), 3.76 (s, 2H), 4.19 (dd, J¼3.6 Hz & 2.7 Hz, 1H),4.20e4.50 (m, 2H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼41.9, 52.6,54.2, 69.3, 71.3, 74.2, 171.5 ppm. $C_7H_8O_4$ (156.14): calcd. C 53.35, H5.16; found C 53.55, H 5.12.4.8. 3,8-

Dioxatricyclo[4.3.1.0^{7,9}]decan-4-one ((D)- and (L)-9)
m-CPBA (190 mg (purity 70%), 0.77 mmol) was added to a solutionof compound (þ)- or (_)-7 (71 mg, 0.51 mmol) in dry dichloromethane (5 mL) under nitrogen atmosphere. The reactionwas carried out at room temperature and after 17 h no starting material could be detected by TLC. The reaction mixture was cooledto _20 _C, filtered and washed with cold dichloromethane. The filtratewas neutralized with saturated sodium bicarbonate andextracted with dichloromethane (x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by columnchromatography (LP/EtOAc¼1/1) gave compounds (þ)- and (_)-9; yield 75%($CHMO_{xantho}$); yield 69%($CPMO_{Coma}$); $[a]_{D24}$¼_95.5 (c¼1.0,$CHCl_3$) ($CHMO_{xantho}$); $[a]_{D24}$ ¼þ82.8 (c¼1.2, $CHCl_3$) ($CPMO_{Coma}$). ^{1}HNMR(200 MHz, $CDCl_3$): d¼1.29 (d, J¼12.5 Hz,1H),1.88 (dt, J¼12.5 Hz& ¼6.4 Hz, 1H), 2.45 (t, J¼6.4 Hz, 1H), 2.60 (m, 2H), 2.93 (ddd,J¼16.0 Hz & ¼6.5 Hz & ½2.0 Hz, 1H), 3.48 (s, 2H), 4.18 (d, J¼12.8 Hz,1H), 4.41 (ddd, J¼12.8 Hz & ¼5.5 Hz & ¼1.7 Hz, 1H) ppm ^{13}C NMR(50 MHz, $CDCl_3$): d¼31.2, 33.9, 36.8, 39.5, 54.1, 55.7, 71.6, 173.5 ppm.

4.9. (1S,2S,4R,5R)-Methyl-2(-4-(hydroxymethyl)-3,6-dioxabicyclo[3.1.0]hexan-2-yl)-acetate ((L)-10)
K_2CO_3 (20 mg, 0.14 mmol) was added to the stirred solution ofcompound (þ)-8 (47 mg, 0.25 mmol) in MeOH/H_2O (1 mL, 8:2) at

room temperature. The reaction mixture was stirred until thestarting material had reacted completely (checked by TLC, reaction time <10 s). The mixture was quenched with saturated aqueoussolution of ammonium chloride and extracted with EtOAc(5_15 mL). 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%;[a]$_{D22}$ ¼_32.09 (c¼6.19, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼2.43(br s, 1H), 2.57 (d, J¼7.5 Hz, 2H), 3.67 (s, 3H), 3.50e3.75 (m, 4H), 4.11(t, J¼4.3 Hz, 1H), 4.43 (t, J¼7.5 Hz, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼35.2, 51.9, 57.9, 62.6, 73.7, 78.9, 171.5 ppm.

4.10. Methyl 2(-4-(hydroxymethyl)-6-oxabicyclo[3.1.0]hexan-2-yl)-acetate ((D)- and (L)-11)

K_2CO_3 (20 mg, 0.14 mmol) was added to the stirred solution ofcompound (þ)- or (_)-9 (40 mg, 0.29 mmol) in MeOH/H_2O (2.6 mL, 8:2) at roomtemperature. The reactionmixturewas stirred until thestarting material had reacted completely. The reaction mixture was directly adsorbed on silica gel and after purification by columnchromatography compounds (þ)- or (_)-11, respectively, were obtained as a colorless oil; yield 67% ($CHMO_{xantho}$); yield 74% ($CPMO_{Coma}$);[a]$_{D30}$ ¼þ13.5 (c¼1.0, $CHCl_3$) ($CHMO_{xantho}$); [a]$_{D30}$ ¼_11.3(c¼0.4, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.22 (d, J¼14.3 Hz, 1H), 1.92 (dt, J¼14.3 Hz & 8.9 Hz, 1H), 2.26e2.51 (m, 3H),2.55e2.70 (m, 1H), 3.13 (br s, 1H), 3.39 (d, J¼2.3 Hz, 1H), 3.52 (d,J¼2.3 Hz,1H), 3.55e3.61 (m, 2H), 3.67 (s, 3H) ppm^{13}CNMR(50MHz,$CDCl_3$): d¼29.7, 35.2, 36.9, 42.0, 51.7, 60.0, 61.0, 63.9, 172.7 ppm.

4.11. (3aS,5R,6R,6aR)-6-Hydroxy-5-(hydroxymethyl)tetrahydrofuro[3,2-b]furan-2(5H)-one ((L)-12)

A $SnCl_4$ solution in dichloromethane (1 mL, 100 mL/mL) wasadded at _78 _C to a solution of compound (_)-10 (81 mg, 0.430 mmol) in dry dichloromethane (3.0 mL). The reaction mixturewas 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%; [a]$_{D25}$ ¼_30.1 (c¼0.86,MeOH). ^{1}H NMR (200 MHz, CD_3OD): d¼2.50 (d, J¼18.4 Hz, 1H), 2.72(dd, J¼18.8 Hz & 4.9 Hz, 1H), 3.21 (br s, 2H), 3.48 (dd, J¼11.9 Hz &5.9 Hz, 1H), 3.68 (dd, J¼11.9 Hz & 3.7 Hz, 1H), 3.74 (dt, J¼5.9 Hz &3.7 Hz, 1H), 4.06 (d, J¼5.5 Hz, 1H), 4.76e4.80 (m, 2H) ppm ^{13}C NMR(50 MHz, $CDCl_3$): d¼37.1, 62.8, 77.2, 79.0, 88.3, 92.2, 177.8 ppm.

4.12. 6-Hydroxy-5-(hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one ((D)- and (L)-13)

To a solution of compound (þ)- or (_)-11 (30 mg, 0.16 mmol) indry dichloromethane (2 mL), was added $SnCl_4$ (38 mL, 0.32 mmol)dropwise under nitrogen atmosphere at _78 _C. After 2 h all thestarting material was consumed (checked by TLC). The reaction mixturewas directly adsorbed on silica gel and after purification bycolumn chromatography (EtOAc) compounds (þ)- and (_)-13 wereobtained as a colorless oil; yield 85% ($CHMO_{xantho}$); yield 79%($CPMO_{Coma}$); [a]$_{D21}$ ¼þ35.1 (c¼0.87, MeOH) ($CHMO_{xantho}$); [a]$_{D21}$¼_32.2 (c¼0.12, MeOH) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz, CD_3OD):d¼1.30 (d, J¼11.1 Hz, 1H), 1.89e2.32 (m, 3H), 2.77 (dd, J¼17.9 Hz &9.7 Hz, 1H), 2.93 (qd, J¼8.0 Hz & 2.6 Hz, 1H), 3.54 (dd, J¼11.0 Hz &6.2 Hz, 1H), 3.70 (dd, J¼11.0 Hz & 4.4 Hz, 1H), 3.87 (dd, J¼8.8 Hz &3.6 Hz, 1H), 4.68 (dd, J¼8.0 Hz & 3.5 Hz, 1H) ppm ^{13}C NMR (50 MHz,CD_3OD): d¼32.8, 34.7, 35.3, 49.4, 63.7, 8.4, 92.0, 178.4 ppm.

4.13. (3aS,5R,6R,6aR)-5-(Hydroxymethyl)-6-iodotetrahydrofuro[3,2-b]furan-2(3H)-one ((L)-14)

To a stirred solution of compound (þ)-6 (0.55 g, 3.92 mmol) inMeCN/H_2O (8.6 mL, 2.3:1) was added KOH (230 mg, 4.11 mmol). The eaction mixture was stirred at room temperature for 4 h untilTLC showed full consumption of the starting material. Afterwards,a mixture f I_2 (1.09 g, 4.30 mmol) and KI (2.15 g, 12.93 mmol) wasadded. The resulting mixture was stirred in the dark for 5 days at40 _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_15 mL). The organic layer was washed with brine,dried over Na_2SO_4 and evaporated. Purification by column chromatographyon silica gel (Hexane/EtOAc) gave compound (_)-14 asa beige oil, which solidified upon standing in the refrigerator; yield75%; mp 84e86 _C; [a]$_{D22}$ ¼_70.2 (c¼1.28, $CHCl_3$). ^{1}H NMR(200 MHz, $CDCl_3$): d¼1.90 (br s, 1H), 2.80 (d, J¼3.3 Hz, 2H), 3.70 (dd,J¼12.4 Hz & 4.6 Hz, 1H), 3.86 (dd, J¼12.4 Hz & 3.0, 1H), 4.22 (dd,J¼7.5 Hz & 2.1 Hz, 1H), 4.33 (ddd, J¼7.5 Hz & 4.6 Hz &¼3.0 Hz, 1H),4.85e4.90 (m, 1H), 5.22 (dd, J¼4.5 Hz & 2.1 Hz, 1H) ppm ^{13}C NMR($CDCl_3$): d¼20.0, 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.

4.14. 5-(Hydroxymethyl)-6-iodohexyhydro-2H-cyclopenta[b]furan-2-one ((D)- and (L)-15)

To a stirred solution of compound (þ)- 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 temperaturefor 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 mixturewas stirred in the darkfor 39 h at room temperature. The reactionwas quenched with a 10%olution of $Na_2S_2O_3$ until decoloration of the mixture was observedand the reaction was neutralized with saturated NH_4Cl. Then thereactionwas extracted with EtOAc (3_). The organic layerwas dried over Na_2SO_4 and evaporated. Purification by column chromatography(LP/EtOAc¼1/2) gave compounds (þ)- and (_)-15 as a colorless oil; yield 92% ($CHMO_{xantho}$); yield quant. ($CPMO_{Coma}$); [a]$_{D24}$ ¼þ62.5(c¼1.2, $CHCl_3$) ($CHMO_{xantho}$); [a]$_{D24}$ ¼_59.4 (c¼0.3, $CHCl_3$) ($CPMO_{Coma}$).^{1}HNMR(200 MHz, $CDCl_3$): d¼1.50 (dt, J¼13.2 Hz & 9.0 Hz,1H),2.10e2.25 (m, 2H), 2.40e2.48 (m, 2H), 2.81 (dd, J¼18.0 Hz & 9.5 Hz,1H), 3.02 (qd, J¼9.5 Hz & 3.1 Hz, 1H), 3.68 (dd, J¼10.8 Hz & 4.9 Hz,1H), 3.77 (dd, J¼10.8 Hz & 4.5 Hz, 1H), 4.09 (dd, J¼9.4 Hz & 4.4 Hz,1H), 5.17 (dd, J¼7.8 Hz & 4.4 Hz, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$):d¼26.8, 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.

4.15. 6-Azido-5-(hydroxymethyl)hexahydro-2H-cyclopenta[b] furan-2-one ((D)-16)

Compound (þ)-15 (27 mg, 0.10 mmol), DMSO (1 mL) and 4 _Amolecular sieve were warmed to 75 _C. Sodium azide (62 mg,0.10 mmol)was added and the solutionwas stirred at 75 _C for 40 h.The reaction was quenched with H_2O and extracted withdichloromethane (3_). The organic layer was dried over $Na_2SO_4$and concentrated in vacuo. Crude mass was purified by columnchromatography (LP/EtOAc¼1/2 to 1/4) to yield compound (þ)-16as a colorless oil; yield quant.; [a]$_{D30}$ ¼þ198.0 (c¼1.0, $CHCl_3$)($CHMO_{Xantho}$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼0.83 (dd, J¼10.7 Hz &6.4 Hz, 1H), 1.35 (m, 1H), 2.02e2.24 (m, 2H), 2.34 (dd, J¼17.9 Hz &6.7 Hz, 1H), 2.68e3.03 (m, 2H), 3.67e3.83 (m, 2H), 4.26 (t, J¼4.2 Hz,1H), 4.97 (dd, J¼9.2 Hz & 4.7 Hz,1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$):d¼32.7, 34.8, 36.1, 44.3, 61.5, 64.9, 84.3 ppm.

4.16. (3aS,5S,6aS)-5-(Hydroxymethyl)tetrahydrofuro[3,2-b]furan-2(3H)-one ((L)-17)

Tributyltin hydride (0.500 mL, 1.85 mmol) was added dropwiseto 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 waspurified by column chromatography (Hexane/EtOAc) to yieldcompound (_)-17 as a colorless oil; yield 99%, [a]$_{D25}$ ¼_53.3(c¼0.42, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.89 (br s, 1H), 2.12(ddd, J¼14.6 Hz & 7.1 Hz & 3.2 Hz, 1H), 2.39 (ddd, J¼14.6 Hz & 7.8 Hz& 6.9 Hz, 1H), 2.75 (d, J¼3.2 Hz, 2H), 3.60 (dd, J¼11.8 Hz & 6.3 Hz,1H), 3.74 (dd, J¼11.9 Hz & 3.2 Hz, 1H), 4.18 (ddd, J¼10.4 Hz & 7.2 Hz& 3.2 Hz, 1H), 4.63 (dd, J¼7.3 Hz & 3.2 Hz, 1H), 5.05 (ddd, J¼6.3 Hz &4.2 Hz & 1.7 Hz, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼34.0, 36.4,64.6, 79.0, 80.7, 84.4, 175.2 ppm.

4.17. 5-(Hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one ((D)- and (L)-18)

Tributyltin hydride (208 mL, 0.78 mmol) was added dropwise toa solution of compound (þ)- or (_)-15 (85 mg, 0.30 mmol) in dry toluene (1.5 mL). The mixture was stirred for 43 h at 60 _C undernitrogen atmosphere until the starting material had reacted completely(checked by TLC). The reaction mixture was directly adsorbedon silica gel and after purification by column chromatography (LP/EtOAc¼1/3e1/5) compounds (þ)- and (_)-18 were obtained asa colorless oil; yield 85% ($CHMO_{Xantho}$); yield 81% ($CPMO_{Coma}$); [a]$_{D21}$¼þ57.5 (c¼1.0, $CHCl_3$) ($CHMO_{Xantho}$); [a]$_{D21}$ ¼_61.5 (c¼0.4, $CHCl_3$)($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.15e1.45 (m, 2H),1.55e1.80 (m, 1H), 2.00e2.42 (m, 4H), 2.67e2.84 (m, 2H),3.50e3.65 (m, 2H), 4.92 (m, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼35.5, 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.

4.18. (3aS,5S,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3H)-one ((L)-19)

Imidazole (20.0 mg, 0.29 mmol) was added to a solutionof 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 thestarting material had reacted completely (checked by TLC).Crude mass was purified by column chromatography (Hexane/EtOAc) to yield compound (_)-19 as a colorless oil; yield92%; [a]$_{D26}$ ¼_23.8 (c¼0.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$):d¼1.05 (s, 9H), 2.10e2.26 (m, 1H), 2.26e2.45 (m, 1H), 2.68e2.72(m, 2H), 3.63e3.79 (m, 2H), 4.05e4.20 (m, 1H), 4.54e4.61 (m,1H), 4.97e5.05 (m, 1H), 7.30e7.45 (m, 6H), 7.61e7.72 (m,4H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼19.2, 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.

4.19. 5-(((tert-Butyldiphenylsilyl)oxy)methyl)hexahydro-2Hcyclopenta[b]furan-2-one ((D)- and (L)-20)

Imidazole (53 mg, 0.78 mmol) was added to a solution ofcompound (þ)- or (_)-18 (22 mg, 0.14 mmol) in dry DMF (1.3 mL)followed by tert-butylchlorodiphenylsilane (75 mL, 0.29 mmol)under nitrogen atmosphere. The mixturewas stirred for 1 h at roomtemperature until the starting material had reacted completely(checked by TLC). The reaction mixture was extracted withdichloromethane (3_), the organic layerwas dried over Na_2SO_4 andconcentrated in vacuo. Crude mass was purified by column chromatography(LPeLP/EtOAc¼20/1) to yield compounds (þ)- and(_)-20 as a white solid; yield 95% ($CHMO_{Xantho}$); yield 89%($CPMO_{Coma}$); mp 78e81 _C, [a]$_{D30}$ ¼þ45.0 (c¼1.0, $CHCl_3$) ($CHMO_{Xantho}$);[a]$_{D30}$ ¼_32.4 (c¼0.3, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz,$CDCl_3$): d¼1.06 (s, 9H), 1.12e1.26 (m, 1H), 1.65e1.75 (m, 1H),2.05e2.41 (m, 2H), 2.66e2.81 (m, 2H), 3.60 (dd, J¼10.0 Hz & 3.3 Hz,1H), 3.66 (dd, J¼10.0 Hz & 3.1 Hz, 1H), 4.88e4.98 (m, 1H), 7.36e7.44 starting material had reacted completely (checked by TLC). Then,the solvent was concentrated in vacuo and the crude mass waspurified by column chromatography (Hexane/EtOAc) to yieldcompound (_)-17 as a colorless oil; yield 99%, [a]$_{D25}$ ¼_53.3(c¼0.42, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.89 (br s, 1H), 2.12(ddd, J¼14.6 Hz & 7.1 Hz & 3.2 Hz, 1H), 2.39 (ddd, J¼14.6 Hz & 7.8 Hz& 6.9 Hz, 1H), 2.75 (d, J¼3.2 Hz, 2H), 3.60 (dd, J¼11.8 Hz & 6.3 Hz,1H), 3.74 (dd, J¼11.9 Hz & 3.2 Hz, 1H), 4.18 (ddd, J¼10.4 Hz & 7.2 Hz& 3.2 Hz, 1H), 4.63 (dd, J¼7.3 Hz & 3.2 Hz, 1H), 5.05 (ddd, J¼6.3 Hz &4.2 Hz & 1.7 Hz, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼34.0, 36.4,64.6, 79.0, 80.7, 84.4, 175.2 ppm.

4.17. 5-(Hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one ((D)- and (L)-18)

Tributyltin hydride (208 mL, 0.78 mmol) was added dropwise toa solution of compound (þ)- or (_)-15 (85 mg, 0.30 mmol) in drytoluene (1.5 mL). The mixture was stirred for 43 h at 60 _C undernitrogen atmosphere until the starting material had reacted completely(checked by TLC). The reaction mixture was directly adsorbedon silica gel and after purification by column chromatography(LP/EtOAc¼1/3e1/5) compounds (þ)- and (_)-18 were obtained asa colorless oil; yield 85% ($CHMO_{Xantho}$); yield 81% ($CPMO_{Coma}$); [a]$_{D21}$¼þ57.5 (c¼1.0, $CHCl_3$) ($CHMO_{Xantho}$); [a]$_{D21}$ ¼_61.5 (c¼0.4, $CHCl_3$)($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.15e1.45 (m, 2H),1.55e1.80 (m, 1H), 2.00e2.42 (m, 4H), 2.67e2.84 (m, 2H),3.50e3.65 (m, 2H), 4.92 (m, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$):d¼35.5, 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.

4.18. (3aS,5S,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3H)-one ((L)-19)

Imidazole (20.0 mg, 0.29 mmol) was added to a solutionof 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 thestarting material had reacted completely (checked by TLC).Crude mass was purified by column chromatography (Hexane/EtOAc) to yield compound (_)-19 as a colorless oil; yield92%; [a]$_{D26}$ ¼_23.8 (c¼0.75, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$):d¼1.05 (s, 9H), 2.10e2.26 (m, 1H), 2.26e2.45 (m, 1H), 2.68e2.72(m, 2H), 3.63e3.79 (m, 2H), 4.05e4.20 (m, 1H), 4.54e4.61 (m,1H), 4.97e5.05 (m, 1H), 7.30e7.45 (m, 6H), 7.61e7.72 m,4H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼19.2, 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.

4.19. 5-(((tert-Butyldiphenylsilyl)oxy)methyl)hexahydro-2Hcyclopenta[b]furan-2-one ((D)- and (L)-20)

Imidazole (53 mg, 0.78 mmol) was added to a solution ofcompound (þ)- or (_)-18 (22 mg, 0.14 mmol) in dry DMF (1.3 mL)followed by tert-butylchlorodiphenylsilane (75 mL, 0.29 mmol)under nitrogen atmosphere. The mixturewas stirred for 1 h at roomtemperature until the starting material had reacted completely(checked by TLC). The reaction mixture was extracted withdichloromethane (3_), the organic layerwas dried over Na_2SO_4 andconcentrated in vacuo. Crude mass was purified by column chromatography(LPeLP/EtOAc¼20/1) to yield compounds (þ)- and(_)-20 as a white solid; yield 95% ($CHMO_{antho}$); yield 89%($CPMO_{Coma}$); mp 78e81 _C, [a]$_{D30}$ ¼þ45.0 (c¼1.0, $CHCl_3$) ($CHMO_{antho}$);[a]$_{D30}$ ¼_32.4 (c¼0.3, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz,$CDCl_3$): d¼1.06 (s, 9H), 1.12e1.26 (m, 1H), 1.65e1.75 (m, 1H),2.05e2.41 (m, 2H), 2.66e2.81 (m, 2H), 3.60 (dd, J¼10.0 Hz & 3.3 Hz,1H), 3.66 (dd, J¼10.0 Hz & 3.1 Hz, 1H), 4.88e4.98 (m, 1H), 7.36e7.44 starting material had reacted completely (checked by TLC). Then,the solvent was concentrated in vacuo and the crude mass waspurified by column chromatography (Hexane/EtOAc) to yieldcompound (_)-17 as a colorless oil; yield 99%, [a]$_{D25}$ ¼_53.3(c¼0.42, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.89 (br s, 1H), 2.12(ddd, J¼14.6 Hz & 7.1 Hz & 3.2 Hz, 1H), 2.39 (ddd, J¼14.6 Hz & 7.8 Hz& 6.9 Hz, 1H), 2.75 (d, J¼3.2 Hz, 2H), 3.60 (dd, J¼11.8 Hz & 6.3 Hz,1H), 3.74 (dd, J¼11.9 Hz & 3.2 Hz, 1H), 4.18 (ddd, J¼10.4 Hz & 7.2 Hz& 3.2 Hz, 1H), 4.63 (dd, J¼7.3 Hz & 3.2 Hz, 1H), 5.05 (ddd, J¼6.3 Hz &4.2 Hz & 1.7 Hz, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼34.0, 36.4,64.6, 79.0, 80.7, 84.4, 175.2 ppm.

4.17. 5-(Hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one ((D)- and (L)-18)

Tributyltin hydride (208 mL, 0.78 mmol) was added dropwise toa solution of compound (þ)- or (_)-15 (85 mg, 0.30 mmol) in dry toluene (1.5 mL). The mixture was stirred for 43 h at 60 _C undernitrogen atmosphere until the starting material had reacted completely (checked by TLC). The reaction mixture was directly adsorbedon silica gel and after purification by column chromatography (LP/EtOAc¼1/3e1/5) compounds (þ)- and (_)-18 were obtained asa colorless oil; yield 85% ($CHMO_{antho}$); yield 81% ($CPMO_{Coma}$); [a]$_{D21}$¼þ57.5 (c¼1.0, $CHCl_3$) ($CHMO_{antho}$); [a]$_{D21}$ ¼_61.5 (c¼0.4, $CHCl_3$)($CPMO_{Coma}$). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.15e1.45 (m, 2H),1.55e1.80 (m, 1H), 2.00e2.42 (m, 4H), 2.67e2.84 (m, 2H),3.50e3.65 (m, 2H), 4.92 (m, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼35.5, 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.

4.18. (3aS,5S,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3H)-one ((L)-19)

Imidazole (20.0 mg, 0.29 mmol) was added to a solutionof 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; yield92%; [a]$_{D26}$ ¼_23.8 (c¼0.75, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$):d¼1.05 (s, 9H), 2.10e2.26 (m, 1H), 2.26e2.45 (m, 1H), 2.68e2.72(m, 2H), 3.63e3.79 (m, 2H), 4.05e4.20 (m, 1H), 4.54e4.61 (m,1H), 4.97e5.05 (m, 1H), 7.30e7.45 (m, 6H), 7.61e7.72 (m,4H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼19.2, 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.

4.19. 5-(((tert-Butyldiphenylsilyl)oxy)methyl)hexahydro-2Hcyclopenta[b]furan-2-one ((D)- and (L)-20)

Imidazole (53 mg, 0.78 mmol) was added to a solution ofcompound (þ)- or (_)-18 (22 mg, 0.14 mmol) in dry DMF (1.3 mL)followed by tert-butylchlorodiphenylsilane (75 mL, 0.29 mmol)under nitrogen atmosphere. The mixturewas stirred for 1 h at roomtemperature until the starting material had reacted completely(checked by TLC). The reaction mixture was extracted withdichloromethane (3_), the organic layerwas dried over Na_2SO_4 andconcentrated in vacuo. Crude mass was purified by column chromatography(LPeLP/EtOAc¼20/1) to yield compounds (þ)- and(_)-20 as a white solid; yield 95% ($CHMO_{antho}$); yield 89%($CPMO_{Coma}$); mp 78e81 _C, [a]$_{D30}$ ¼þ45.0 (c¼1.0, $CHCl_3$) ($CHMO_{antho}$);[a]$_{D30}$ ¼_32.4 (c¼0.3, $CHCl_3$) ($CPMO_{Coma}$). ^{1}H NMR (200 MHz,$CDCl_3$): d¼1.06 (s, 9H), 1.12e1.26 (m, 1H), 1.65e1.75 (m, 1H),2.05e2.41 (m, 2H), 2.66e2.81 (m, 2H), 3.60 (dd, J¼10.0 Hz & 3.3 Hz,1H), 3.66 (dd, J¼10.0 Hz & 3.1 Hz, 1H), 4.88e4.98 (m, 1H), 7.36e7.44 starting material had reacted completely (checked by TLC). Then,the solvent was concentrated in vacuo and the crude mass waspurified by column chromatography (Hexane/EtOAc) to yieldcompound (_)-17 as a colorless oil; yield 99%, [a]$_{D25}$ ¼_53.3(c¼0.42, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): d¼1.89 (br s, 1H), 2.12(ddd, J¼14.6 Hz & 7.1 Hz & 3.2 Hz, 1H), 2.39 (ddd, J¼14.6 Hz & 7.8 Hz& 6.9 Hz, 1H), 2.75 (d, J¼3.2 Hz, 2H), 3.60 (dd, J¼11.8 Hz & 6.3 Hz,1H), 3.74 (dd, J¼11.9 Hz & 3.2 Hz, 1H), 4.18 (ddd, J¼10.4 Hz & 7.2 Hz& 3.2 Hz, 1H), 4.63 (dd, J¼7.3 Hz & 3.2 Hz, 1H), 5.05 (ddd, J¼6.3 Hz &4.2 Hz & 1.7 Hz, 1H) ppm ^{13}C NMR (50 MHz, $CDCl_3$): d¼34.0, 36.4,64.6, 79.0, 80.7, 84.4, 175.2 ppm.

4.17. 5-(Hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one ((D)- and (L)-18)

Tributyltin hydride (208 mL, 0.78 mmol) was added dropwise toa solution of compound (þ)- or (_)-15 (85 mg, 0.30 mmol) in drytoluene (1.5 mL). The mixture was stirred for 43 h at 60 _C undernitrogen atmosphere until the starting material had reacted completely(checked by TLC). The reaction mixture was directly adsorbedon silica gel and after purification by column chromatography(LP/EtOAc¼1/3e1/5)

compounds (þ)- and (_)-18 were obtained asa colorless oil; yield 85% (CHMOXantho); yield 81% (CPMOComa); [a]D21¼þ57.5 (c¼1.0, CHCl3) (CHMOXantho); [a]D21 ¼_61.5 (c¼0.4, CHCl3)(CPMOComa). 1H NMR (200 MHz, CDCl3): d¼1.15e1.45 (m, 2H),1.55e1.80 (m, 1H), 2.00e2.42 (m, 4H), 2.67e2.84 (m, 2H),3.50e3.65 (m, 2H), 4.92 (m, 1H) ppm 13C NMR (50 MHz, CDCl3):d¼35.5, 35.6, 39.1, 42.1, 65.6, 86.0, 177.3 ppm. C8H12O3 (156.18):calcd. C 61.52, H 7.74; found C 57.63, H 6.30.

4.18. (3aS,5S,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3H)-one ((L)-19)

Imidazole (20.0 mg, 0.29 mmol) was added to a solutionof 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 thestarting material had reacted completely (checked by TLC).Crude mass was purified by column chromatography (Hexane/EtOAc) to yield compound (_)-19 as a colorless oil; yield92%; [a]D26 ¼_23.8 (c¼0.75, CHCl3). 1H NMR (200 MHz, CDCl3):d¼1.05 (s, 9H), 2.10e2.26 (m 1H), 2.26e2.45 (m, 1H), 2.68e2.72(m, 2H), 3.63e3.79 (m, 2H), 4.05e4.20 (m, 1H), 4.54e4.61 (m,1H), 4.97e5.05 (m, 1H), 7.30e7.45 (m, 6H), 7.61e7.72 (m,4H) ppm 13C NMR (50 MHz, CDCl3: d¼19.2, 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.

4.19. 5-(((tert-Butyldiphenylsilyl)oxy)methyl)hexahydro-2Hcyclopenta[b]furan-2-one ((D)- and (L)-20)

Imidazole (53 mg, 0.78 mmol) was added to a solution ofcompound (þ)- or (_)-18 (22 mg, 0.14 mmol) in dry DMF (1.3 mL)followed by tert-butylchlorodiphenylsilane (75 mL, 0.29 mmol)under nitrogen atmosphere. The mixturewas stirred for 1 h at roomtemperature until the starting material had reacted completely(checked by TLC). The reaction mixture was extracted withdichloromethane (3_), the organic layerwas dried over Na2SO4 andconcentrated in vacuo. Crude mass was purified by column chromatography(LPeLP/EtOAc¼20/1) to yield compounds (þ)- and(_)-20 as a white solid; yield 95% (CHMOXantho); yield 89%(CPMOComa); mp 78e81 _C, [a]D30 ¼þ45.0 (c¼1.0, CHCl3) (CHMOXantho);[a]D30 ¼_32.4 (c¼0.3, CHCl3) (CPMOComa). 1H NMR (200 MHz,CDCl3): d¼4.06 (s, 9H), 1.12e1.26 (m, 1H), 1.65e1.75 (m, 1H),2.05e2.41 (m, 2H), 2.66e2.81 (m, 2H), 3.60 (dd, J¼10.0 Hz & 3.3 Hz,1H), 3.66 (dd, J¼10.0 Hz & 3.1 Hz, 1H), 4.88e4.98 (m, 1H), 7.36-7.44 (m, 6H), 7.62e7.67 (m, 4H) ppm 13C NMR (50 MHz, CDCl3): d¼19.2,26.7, 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. C24H30O2Si (378.58): calcd. C 73.05, H 7.66; found C73.04, H 7.59.

4.20. (1R,6S,7R,8S)d7,8-Dihydroxy-3,9-dioxabicyclo[4.2.1]nonan-4-one (21)

To a solution of compound (þ)-6 (109 mg, 0.78 mmol) indichloromethane (11 mL) and tert-butanol (2 mL) was added NMO (163 mg, 1.39 mmol) followed by a crystal of OsO4. The reactionwasstirred at room temperature until TLC analysis showed completeconsumption of starting material (3e6 h). The reaction wasquenched with 2 mL of a 10% solution of Na2SO3 and the mixturewas stirred for an additional 45 min. Then it was filtered througha pad of Celite_, which was washed with dichloromethane. The aqueous phase was extracted five times with dichloromethane. Thecombined organic layers were dried over Na2SO4 and the solvent was removed in vacuo. Purification of the crude mass by columnchromatography (stepwise gradient LP/EtOAc¼100% LP to 100% EtOAc, followed by a stepwise gradient EtOAc/EtOH¼100% EtOAc to0% EtOH) gave compound 21; yield 55%; 1H NMR (200 MHz, CD3OD): d¼2.81 (dd, J¼16.3 Hz & 5.0 Hz, 1H), 2.95 (dd, J¼16.3 Hz &2.4 Hz, 1H), 3.90e4.40 (m, 6H), 4.8 (s, 2H) ppm 13C NMR (50 MHz,CD3OD): d¼43.8, 73.1 (2C), 76.0, 82.1, 86.6, 175.7 ppm.

4.21. 7,8-Dihydroxy-3-oxabicyclo[4.2.1]nonan-4-one ((D)- and (L)-22)

To a solution of compound (þ)- or (_)-7 (140 mg, 1.01 mmol) indichloromethane/tert-butanol (6 mL, 2/1) was added NMO$H2O(172 mg, 1.27 mmol) under nitrogen atmosphere followed bya crystal of OsO4. The reaction was stirred at room temperatureuntil TLC analysis showed complete consumption of starting material(24 h). The reactionwas quenched with 2mL of a 10% solutionof Na2SO3 and the mixture was stirred for an additional 1 h. Thereaction mixture was directly adsorbed on silica gel and after purificationby column chromatography (EtOAc) compounds (þ)- and(_)-22, respectively, were obtained as a colorless oil; yield 50%(CHMOXantho); yield 56% (CPMOComa); [a]D21 ¼_71.5 (c¼0.06, EtOH)(CHMOXantho); [a]D21 ¼þ73.1 (c¼1.27, EtOH) (CPMOComa). 1H NMR(200 MHz, CD3OD): d¼1.48 (d, J¼11.1 Hz, 1H), 2.21e2.37 (m, 3H),2.63 (dd, J¼15.8 & 1.8 Hz, 1H), 2.84 (ddd, J¼15.8 Hz & 7.7 Hz & 1.3 Hz, 1H), 3.87 (d, J¼6.0 Hz, 1H), 4.12e4.38 (m, 3H) ppm 13C NMR(50 MHz, CD3OD): d¼37.2, 41.1, 42.8, 47.9, 72.7, 73.9, 76.7,177.7 ppm.

4.22. (1S,2S,6R,7R)-4,4-Dimethyl-3,5,9,12-tetraoxatricyclo[5.4.1.02,6]dodecan-10-one ((D)-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 wereadded. When TLC proved all starting material to be gone, the reactionwas hydrolyzed with saturated bicarbonate solution. Theaqueous phase was extracted five times with EtOAc. The combinedorganic layers were dried over Na2SO4 and the solvent was removedin vacuo. The crude material was purified by column chromatography(basic SiO2, stepwise gradient LP/EtOAc¼100% LP to100% EtOAc) yielding compound (þ)-23 as colorless crystals; yield76%, mp 163e167 _C, [a]D20: þ73.0 (c¼0.66, CHCl3). 1H NMR (200MHz, CDCl3): d 1.32 (s, 3H, CH3), 1.49 (s, 3H, CH3), 2.96 (d, J¼4 Hz,2H, H-2), 4.23e4.30 (m, 3H), 4.31e4.39 (m, 1H), 4.65 (d, J¼5.0 Hz,2H), 4.95 (d, J¼5.0 Hz, 2H) ppm. 13C NMR (50 MHz, CDCl3): d 24.3, 25.9, 42.5, 71.5, 78.3, 81.5, 82.4, 83.5, 112.4, 172.2 ppm.

4.23. 4,4-Dimethyl-3,5,9-trioxatricyclo[5.4.1.02,6]dodecan-10-one ((D)- and (L)-24)

To a solution of compound (þ)- or (_)-22 (43 mg, 0.25 mmol) inacetone (3 mL) under nitrogen atmosphere, 2,2-dimethoxypropane(1.50 mL, 12.2 mmol) and a catalytic amount of p-toluenesulfonicacid were added. When TLC proved all starting material to be gone(after 26 h), the reaction was hydrolyzed with saturated bicarbonatesolution. The aqueous phase was extracted five timeswith EtOAc. The combined organic layers were dried over Na2SO4and the solvent was removed in vacuo. The crude material waspurified by column

chromatography (LP/EtOAc¼6/1) yieldingcompounds (þ)- and (_)-24 as a white solids, each; yield80% (CHMOXantho); yield 60% (CPMOComa); mp 115e119 _C, [a]D22 ¼_74.2 (c¼1.0, CHCl3) (CHMOXantho); [a]D22 ¼þ69.2 (c¼1.0, CHCl3)(CPMOComa). 1H NMR (200 MHz, (CD3)2CO): d¼1.26 (d, J¼0.5 Hz,3H), 1.36 (d, J¼0.5 Hz, 3H), 1.59 (d, J¼11.3 Hz, 1H), 2.22e2.30 (m,2H), 2.42e2.52 (m, 1H), 2.70e2.83 (m, 2H), 4.17e4.36 (m, 3H), 4.69(dd, J¼5.3 Hz & 1.4 Hz, 1H) ppm. 13C NMR (50 MHz, (CD3)2CO):d¼23.6, 26.2, 36.8, 39.4, 39.9, 44.2, 71.0, 82.4, 84.5, 109.8, 174.1 ppm.

4.24. ((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 ((L)-25)

Aminoguanidine bicarbonate (58 mg, 0.43 mmol) was added toa mixture of compound (þ)-23 (90 mg, 0.41 mmol) in pyridine (5 mL) at room temperature. The reaction mixture was refluxed for1.5 h under argon atmosphere until no starting material could be detected by TLC. After that, the pyridine was removed and purificationof the liquid residue by column chromatography on silica gel (CHCl3/MeOH) gave compound (_)-25 as colorless crystals; yield78%; mp 65e67 _C; [a]D21 ¼_11.8 (c¼0.22, MeOH). 1H NMR(200 MHz, CD3OD): d¼1.12e1.20 (m, 2H), 1.31 (s, 3H), 1.51 (s, 3H),2.66 (s, 1H) 2.78e2.84 (m, 2H), 3.50e3.70 (m, 3H), 3.91e3.99 (m, 1H), 4.18e4.25 (m, 1H), 4.46e4.52 (m, 1H), 4.59e4.67 (m, 1H) ppm13C NMR (50 MHz, CD3OD): d¼16.1, 23.4, 25.4, 61.1, 80.8, 81.8, 83.4,84.2, 113.0 ppm.

4.25. (6-((3-Amino-1H-1,2,4-triazol-5-yl)methyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol ((D)- and (L)-26)

Aminoguanidine bicarbonate (33 mg, 0.25 mmol) was added toa mixture of compound (þ)- or (_)-24 (30 mg, 0.15 mmol) in pyridine3 mL) at room temperature. The reaction mixture wasrefluxed for 1 h under argon atmosphere until no starting materialcould be detected by TLC. After that, the pyridine was removed andpurification of the liquid residue by column chromatography onsilica gel (CHCl3/MeOH) gave compounds (þ)- and (_)-26 as oils,each; yield 50% (CHMOXantho); yield 43% (CPMOComa); [a]D24¼_104.1 (c¼1.0, MeOH) (CHMOXantho); [a]D24 ¼þ97.1 (c¼1.0, MeOH)(CPMOComa). 1H NMR (200 MHz, CD3OD): d¼1.28 (s, 3H), 1.50 (s, 3H), 2.05e2.17 (m, 3H), 2.31e2.57 (m, 2H), 3.55e3.70 (m, 4H),4.19e4.41 (m, 2H) ppm. 13C NMR (50 MHz, CD3OD): d¼25.4, 27.9, 34.9, 38.4, 43.4, 52.0, 64.5, 84.2, 86.7, 113.7, 174.6 ppm.

4.26. ((2R,5R)-5-((3-Amino-1H-1,2,4-triazol-5-yl)methyl)-2,5-dihydrofuran-2-yl)methanol ((L)-27)

Aminoguanidine bicarbonate (90 mg, 0.67 mmol) was added toa mixture of compound (þ)-6 (90 mg, 0.64 mmol) in pyridine (5 mL) at room temperature. The reaction mixture was refluxed for2 h under argon tmosphere until no starting material could be detected by TLC. After that, the pyridine was removed and purificationof the liquid residue by column chromatography on silica gel (CHCl3/MeOH) gave compound (_)-27 as colorless crystals; yield67%; mp 87e89 _C; [a]D21 ¼_45.5 (c¼0.22, MeOH). 1H NMR (200 MHz, CD3OD): d¼2.59e2.85 (m, 2H), 3.10e3.27 (m, 2H),3.30e3.55 (m, 2H), 4.60e4.85 (m, 3H), 4.85e5.05 (m, 1H),5.70e5.77 (m, 1H), 5.80e5.95 (m, 1H) ppm 13C NMR (50 MHz,CD3ODþCDCl3): d¼34.4, 64.5, 84.4, 87.8, 128.4, 131.0, 156.5,158.8 ppm.

4.27. (4-((3-Amino-1H-1,2,4-triazol-5-yl)methyl)cyclopent-2-en-1-yl)methanol ((D)- and (L)-28)

Aminoguanidine bicarbonate (62 mg, 0.46 mmol) was added toa mixture of compound (þ)- or (_)-7 (50 mg, 0.36 mmol) in pyridine (3 mL) at room temperature. The reaction mixture wasrefluxed for 1 h under argon atmosphere until no starting material could be detected by TLC. After that, the pyridine was removed andpurification of the liquid residue by column chromatography on silica gel (CHCl3/MeOH) gave compounds (þ)- and (_)-28, respectively;yield 71% (CHMOXantho); yield 71% (CPMOComa); [a]D 21¼6.63 (c¼1.0, MeOH) (CHMOXantho); [a]D22 ¼_10.1 (c¼0.8, MeOH)(CPMOComa). 1H NMR (200 MHz, CD3OD): d¼1.04e1.18 (m, 1H),2.03e2.15 (m, 1H), 2.35e2.56 (m, 1H), 2.59e3.06 (m, 1H), 3.19e3.22(m, 2H), 3.25(br s, 2H), 5.58 (dd, J¼7.8 Hz & 1.4 Hz, 1H), 5.65 (dd,.8 Hz & 1.4 Hz, 1H) ppm 13C NMR (50 MHz, CD3OD): d¼34.0,35.3, 45.8, 49.1, 67.5, 133.6, 136.2 ppm.

4.28. 3-Oxabicyclo[4.2.1]nonan-4-one ((D)- and (L)-29)

Compound (þ)- 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 conversionwasdetermined by TLC analysis and after completion, the reaction mixture was filtered through a pad of Celite_. The residue waswashed thoroughly with EtOAc and the filtrate was concentrated in vacuo. The purity of the product was determined to be >95% byNMR so no further purificationwas necessary. Compounds (þ)- and (_)-29 were obtained as a pale yellow oil, each; yield 79%(CHMOXantho); yield 83% (CPMOComa); [a]D ¼_12.4 (c¼1.0, EtOAc) (CHMOXantho); [a]D22 ¼þ105.1 (c¼1.67, CHCl3) (CPMOComa). 1H NMRand 13C NMR data are according to the previous results in ourgroup (Kandioller Wolfgang Diploma Thesis).

4.29. (3-((5-Amino-4H-1,2,4-triazol-3-yl)methyl)cyclopentyl) methanol ((D)- and (L)-30)

Aminoguanidine bicarbonate (100 mg, 0.74 mmol) was added toa mixture of compound (þ)- or (_)-29 (90 mg, 0.64 mmol) inpyridine (5 mL) at room temperature. The reaction mixture wasrefluxed for1 h under argon atmosphere until no starting materialcould be detected by TLC. After that, the pyridine was removed anduri fication of the liquid residue by column chromatography onsilica gel (CHCl3/MeOH) gave compounds (þ)- and (_)-30 as oils,each; yield 69% (CHMOXantho); yield 67% (CPMO); [a]D22 ¼þ3.4(c¼1.0, EtOAc) (CHMOXantho); [a]D21 ¼_1.9 (c¼1.67, MeOH) (CPMO).1H NMR (200 MHz, CD3OD): d¼0.80e1.00 (m, 1H), 1.20e1.50 (m, 2H), 1.60e1.83 (m, 2H), 1.85e2.40 (m, 3H), 2.54 (d, J¼7.5 Hz, 2H),3.15e3.25 (m, 1H), 3.35 (d, J¼6.7 Hz, 2H) ppm 13C NMR (50 MHz, CD3OD): d¼29.1, 32.5, 34.3, 37.4, 40.4, 43.2, 67.6, 160.0 ppm.

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