Synthesis of γ-Lactones from Cycloocta-1,5-diene − Starting Materials for Natural-Product Synthesis

Sandra Behr,[a] Klaus Hegemann,[a] Holger Schimanski,[a] Roland Fröhlich,[a] and Günter Haufe*[a]

Keywords: Alkenes / Cyclization / Lactones / Natural products / Oxygen heterocycles

The bislactones *rac*-tetrahydro-2,2′-bifuranyl-5,5′-dione (*rac*-**12**) and its diastereomer *meso*-**25** were prepared from *endo*-5-hydroxy-9-oxabicyclo[4.2.1]nonan-2-one (*endo*-**10**) and *endo*-6-hydroxy-9-oxabicyclo[3.3.1]nonan-2-one (*endo*-**11**) or *exo*-5-hydroxy-9-oxabicyclo[4.2.1]nonan-2-one (*exo*-**23**), respectively, under the conditions of a Baeyer–Villiger oxidation with trifluoroperacetic acid. The latter compounds were obtained by *O*-heterocylization of *cis*,*cis*-cycloocta-1,5-diene (**1**) by either reaction with peracids followed by hydrolysis and Jones oxidation or ruthenium tetraoxide oxidation, respectively. The optically active bislactone (*R*,*R*)-(−)-**12** was prepared in a similar manner from (1*S*,5*R*,6*R*)-(+)-**10** and (1*R*,5*R*,6*R*)-(+)-**11**, which, in turn, were obtained by lipase-catalyzed asymmetric acetylation of the corresponding diols *meso*-**2** and *rac*-**3** and subsequent Jones oxidation of the formed hydroxy esters (1*S*,2*S*,5*R*,6*R*)-(+)-**4** and (1*R*,2*R*,5*R*,6*R*)-(+)-**5**. Since the regioisomeric hydroxy-9-oxabicyclo[4.2.1]- and -[3.3.1]nonan-2-ones (1*S*,5*R*,6*R*)-(+)-**10** and (1*R*,5*R*,6*R*)-(+)-**11** yielded the same bislactone [(*R*,*R*)-(−)-**12**] it is presumed that the sequence proceeds via open-chain intermediates. Applying this strategy to the enantiopure acetoxy ketones (1*S*,5*R*,6*R*)-(+)-**8** and (1*R*,5*R*,6*R*)-(+)-**9**, followed by Kolbe electrolysis of the formed (*R*,*R*)-5-acetoxy-7-carboxyheptan-4-olide [(*R*,*R*)-**27**], (*R*,*R*)-5-acetoxydecan-4-olide [(*R*,*R*)-**29**] was accessible in a five-step synthesis. The absolute configuration of (+)-**8** was determined by X-ray analysis of the dithiepane derivative **14**.

Introduction

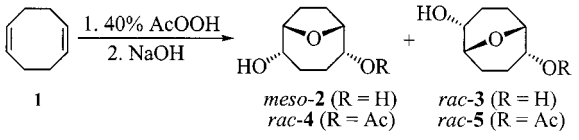
In general, γ-butyrolactones are versatile starting materials in synthetic organic chemistry since countless compounds containing this function show interesting biological activities. Many publications deal with the synthesis of 5-hydroxy-γ-heptadecalactone (muricatacin, obtained from the seeds of *Annona muricata*),[1−3] which is a potent cytotoxic agent on different tumor cell lines.[4] 5-Hydroxy-γ-decalactone, a lower homologue of muricatacin, was assumed to be the autoregulatory factor (L-factor) of the antibiotic-producing Gram-positive actinomycete *Streptomyces griseus*.[5] Although this effect was subsequently contradicted,[6] great efforts were made to synthesize this enantiopure target molecule.[7−10]

In this paper we describe a new approach to the bislactones **12** and *meso*-**25** and compounds **27**, **28** and **29** containing a single γ-butyrolactone ring. These compounds can serve as starting materials for the above-mentioned type of natural products and other biologically active compounds. The sequence starts with an *O*-heterocylization reaction of *cis*,*cis*-cycloocta-1,5-diene (**1**) using peracids, a reaction which has been known for several years.[11−14] According to these procedures the diene **1** was transformed into a mixture of skeletal isomers of 9-oxabicyclononanediols **2** and **3**, which were then separated by simultaneous desymmetrization of *meso*-**2** and kinetic resolution of *rac*-**3** using *Candida rugosa* lipase generating enantiopure monoacetates **4** and **5**.[15,16]

[a] Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster
Corrensstr. 40, 48149 Münster, Germany
Fax: + 49-251-83-39772
E-mail: haufe@uni-muenster.de

Results and Discussion

At the beginning of our investigation the known procedures[13,14,16] for the *O*-heterocylization of cycloocta-1,5-diene (**1**) were improved. Using commercially available 40% peracetic acid (Wofasteril®), followed by neutral workup, 30% of a 41:59 mixture of two racemic bicyclic skeletal isomeric monoacetates **4** and **5** as well as 63% of a 63:37 mixture containing the diols **2** and **3** was isolated (Scheme 1).

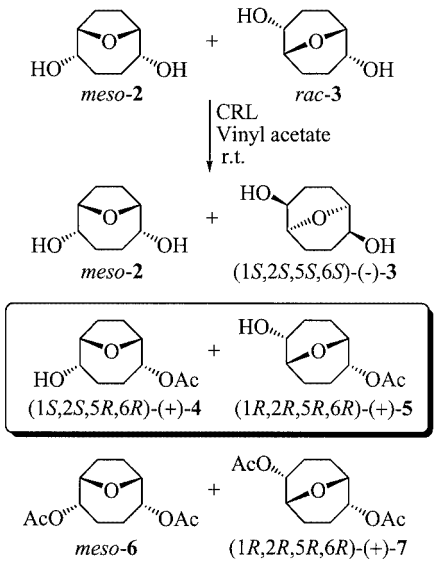


Scheme 1. Synthesis of racemic monoacetates **4** and **5** as well as diols **2** and **3** by transannular *O*-heterocyclization

  DOI: 10.1002/ejoc.200400219

In contrast, workup at pH 10 gave a 45:55 mixture of *meso*-**2** and *rac*-**3** in 92% yield. In the past these diols were known to be produced in 65−70% yield using performic acid, generated in situ from formic acid and 30% hydrogen peroxide.[14,16]

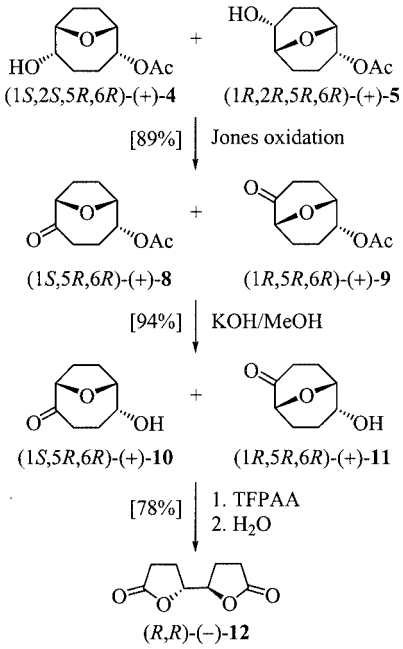
Since these mixtures are difficult to separate, compounds **2** and **3** were used together for the next step. The lipase-catalyzed kinetic resolution of *rac*-**3** and the desymmetrization of *meso*-**2** by acetylation with vinyl acetate gave different ratios of (1*S*,2*S*,5*R*,6*R*)-(+)-5-acetoxy-9-oxabicyclo[4.2.1]nonan-2-ol [(1*S*,2*S*,5*R*,6*R*)-(+)-**4**] and (1*R*,2*R*,5*R*,6*R*)-(+)-6-acetoxy-9-oxabicyclo-[3.3.1]nonan-2-ol [(1*R*,2*R*,5*R*,6*R*)-(+)-**5**] with different enantiomeric purity depending on the applied lipase and rate of conversion (Scheme 2).[15,16]



Scheme 2. Synthesis of a mixture of enantiopure monoacetates **4** and **5** by lipase-catalyzed esterification

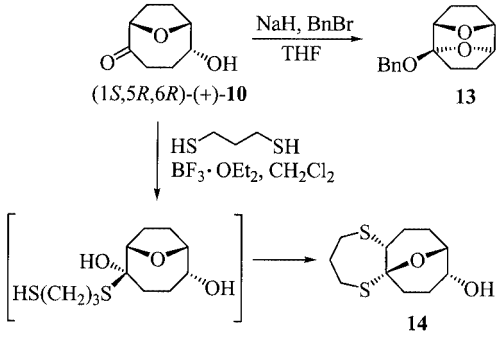
Additionally, the diacetates *meso*-**6** and (1*R*,2*R*,5*R*,6*R*)-(+)-**7** were produced, which were easily separated from the monoacetates by column chromatography. The remaining diols *meso*-**2** (traces) and the enantiopure (1*S*,2*S*,5*S*,6*S*)-(−)-**3** were separated from the product mixture by crystallization. Using the most selective enzyme (*Candida rugosa* lipase) compounds (−)-**3** (14% yield) and (+)-**7** (10% yield) were isolated as pure isomers with >98% *ee* each. Additionally, an 80:20 mixture of the monoesters (+)-**4** (>98% *ee*) and (+)-**5** (80% *ee*) was isolated with 40% yield.[15] The absolute configuration of the products of lipase-catalyzed acetylation of *meso*-**2** and *rac*-**3**, except for compound (+)-**4**, has already been described.[16] The absolute configuration of (+)-**4** was determined indirectly (vide infra).

In the next step Jones' reagent was used to oxidize the free hydroxyl function of the enantiopure monoacetates (1*S*,2*S*,5*R*,6*R*)-(+)-**4** and (1*R*,2*R*,5*R*,6*R*)-(+)-**5** to form the acetoxy ketones (1*S*,5*R*,6*R*)-(+)-**8** and (1*R*,5*R*,6*R*)-(+)-**9**. Hydrolysis with methanolic potassium hydroxide gave the hydroxy ketones (1*S*,5*R*,6*R*)-(+)-**10** and (1*R*,5*R*,6*R*)-(+)-**11** in high yield and without affecting the enantiopurity (Scheme 3).



Scheme 3. Reaction sequence leading to bislactone **12**

The absolute configuration of compound (+)-**4** could not be determined directly or from simple derivatives formed at the hydroxyl function.[16] Thus, we first tried benzylation of compound (+)-**10** with sodium hydride as the base, but this reaction led to the tricyclic acetal **13** by transannular nucleophilic attack of the intermediary alkoxide at the carbonyl group. The pure product **13** was isolated chromatographically as an oily compound (Scheme 4).



Scheme 4. Derivatizations of hydroxy ketone **10**

Consequently, we tried to protect the carbonyl group and to determine the absolute configuration after eventual derivatization of the remaining OH function. Therefore, similar to a known protocol,[17] we treated the ketone (+)-**10** [contaminated with 30% of (+)-**11**] with propane-1,3-thiol in the presence of BF_3·diethyl ether, but we did not get the expected 1,3-dithiolane. Instead, the solid dithiepane **14** and its skeletal isomer were formed as a 72:28 mixture by inter-

mediary skeletal rearrangement (Scheme 4). A similar rearrangement was observed earlier by Mann et al.[18] By careful crystallization single crystals of the major product 11-hydroxy-14-oxa-2,6-dithiatricyclo[8.3.1.0^{1,7}]tetradecane (**14**) were grown. These crystals were suitable to determine the absolute configuration to be (1*S*,7*R*,10*R*,11*R*) by X-ray structural analysis (Figure 1).

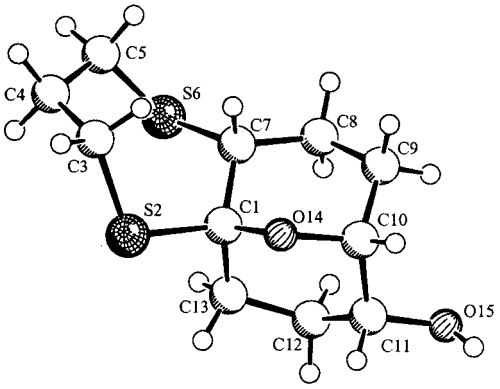


Figure 1. X-ray structure of (1*S*,7*R*,10*R*,11*R*)-11-hydroxy-14-oxa-2,6-dithiatricyclo[8.3.1.0^{1,7}]tetradecane (1*S*,7*R*,10*R*,11*R*)-(**14**)

Since no reaction occurred at carbons number 10 and 11 during the S_N2-type skeletal rearrangement, the configuration of the original acetoxy alcohol is (1*S*,2*S*,5*R*,6*R*)-**4** (Scheme 3).

Continuing the synthetic sequence, Baeyer−Villiger oxidation[19] of the acetoxy ketones (1*S*,5*R*,6*R*)-(+)-**8** and (1*R*,5*R*,6*R*)-(+)-**9** and of the hydroxy ketones (1*S*,5*R*,6*R*)-(+)-**10** and (1*R*,5*R*,6*R*)-(+)-**11** was planned. Normally peracids or hydrogen peroxide are used for such oxidations. However, all attempts to react the acetoxy ketones **8** and **9** by "classical" reagents such as 32% peracetic acid or *m*-chloroperbenzoic acid failed. These reagents seem to be too weak for Baeyer−Villiger oxidation of the mentioned ketones, which are deactivated due to the adjacent ether functionality. Trifluoroperacetic acid (TFPAA) has been described as a strong oxidizing agent in Baeyer−Villiger oxidation. However, starting with trifluoroacetic acid and 90% hydrogen peroxide[20] would provide an extensive safety risk, which can be easily avoided by preparing trifluoroperacetic acid in situ from trifluoroacetic acid and sodium percarbonate ($Na_2CO_3 \cdot 1.5H_2O_2$).[21] According to this protocol an 81:19 mixture of the hydroxy ketones (1*S*,5*R*,6*R*)-(+)-**10** and (1*R*,5*R*,6*R*)-(+)-**11** was transformed into bislactone (*R*,*R*)-(−)-**12** in 78% yield in the presence of six equivalents of trifluoroperacetic acid generated in situ (Table 1, entry 1). From the isolated yield it remained unclear whether (*R*,*R*)-(−)-**12** is formed exclusively from (1*S*,5*R*,6*R*)-(+)-**10** or also from (1*R*,5*R*,6*R*)-(+)-**11**, although the slightly decreased enantiomeric excess of (*R*,*R*)-(−)-**12** (95% *ee*) might indicate that both (1*S*,5*R*,6*R*)-(+)-**10** (>98% *ee*) and (1*R*,5*R*,6*R*)-(+)-**11** (60% *ee*) might have been oxidized to **12**. Unfortunately, we were not able to isolate optically active (1*R*,5*R*,6*R*)-(+)-**11** as a pure skeletal isomer.

Table 1. Baeyer−Villiger oxidation of different mixtures of **10** and **11**; comparison of yield and enantiomeric excess of product **12**

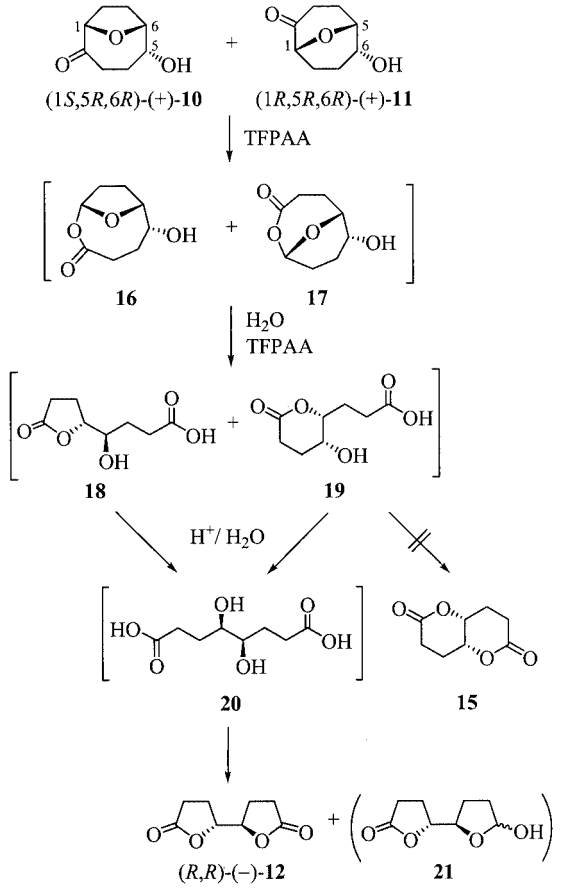
	Reactant ratio (*ee*)[a] (1*S*,5*R*,6*R*)-(+)-**10**	(1*R*,5*R*,6*R*)-(+)-**11**	Yield (*R*,*R*)-(−)-**12** [*ee* found][b] (*ee* calcd.)[c]
1	81 (>98%)	19 (60%)	78 [95%] (92%)
2	81 (>98%)	19 (30%)[d]	78 [80%] (75%)
3	56 (>98%)	44 (83%)	74 [93%] (93%)
4	37 (>98%)	63 (>98%)	72 [>98%] (>98%)
5	59 (*rac*)	41 (*rac*)	75 [*rac*]

[a] According to enantiopurity of acetates **4** and **5**, measured by chiral GC (Betadex™ 120, 165 °C, isothermic). [b] Measured by chiral GC (Betadex™ 120, 165 °C, isothermic). [c] Expected *ee* with complete conversion of both **10** and **11** presumed. [d] (1*S*,5*S*,6*S*)-(−)-**11**, prepared by lipase-catalyzed hydrolysis of *rac*-**7**.[16]

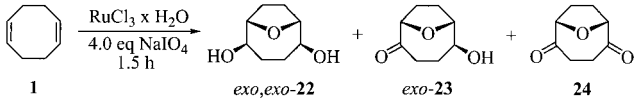
However, according to the different ratio and enantiomeric purity of the skeletal isomers **10** and **11** (Table 1, entries 1−4) used in the Baeyer−Villiger oxidation it is presumed that the 9-oxabicyclo[3.3.1]nonan-2-one system **11** also generates the bislactone **12**. Isomerization of the hydroxy ketones can be excluded under these conditions. Entries 3−5 in Table 1 show that the yield of **12** exceeds the portion of [4.2.1]bicyclic hydroxy ketone **10** in the mixture of starting materials. In addition, the enantiomeric excess of **12** becomes lower with decreasing *ee* of ketone **11** (Entries 1−3, Table 1). Furthermore no comparative δ-bislactone **15** (Scheme 5) was observed.

Thus, the following mechanism is proposed. First the bicyclic lactones **16** and **17** are formed, which are not stable in the acidic medium and undergo ring opening and subsequent oxidation of the intermediate lactols under the oxidative conditions to give γ- and δ-lactono hydroxy acids **18** and **19**. Since no δ-lactone was found as a product a translactonization might occur via an open-chain intermediate **20**, which, under the reaction conditions, forms the stable bislactone **12** exclusively. In some reactions with a smaller excess of the peracid, the lactololactol **21** was formed in 14−16% yield. This observation supports the presumed mechanism. Thus, this five-step procedure provides enantiopure (*R*,*R*)-(−)-**12** from bulk *cis*,*cis*-cycloocta-1,5-diene (**1**) in 26% overall yield.

In order to amplify the variety of stereochemical information in intermediates of natural-product syntheses we did not confine ourselves to application of peracids in *O*-heterocyclization reactions. In due course we also used transition-metal-catalyzed oxidative cyclizations. For oxidation of open-chain 1,5-dienes to form *cis*-2,5-disubstituted tetrahydrofurans potassium permanganate,[22] ruthenium tetraoxide,[23,24] perruthenate[25] or osmium tetraoxide[26] have been applied in the literature. Using catalytic amounts of $RuCl_3$ hydrate and excess sodium periodate as oxidant *cis*,*cis*-cycloocta-1,5-diene (**1**) was converted into a 6:85:9 mixture of *exo*,*exo*-9-oxabicyclo[4.2.1]nonane-2,5-diol (*exo*,*exo*-**22**), *exo*-5-hydroxy-9-oxabicyclo[4.2.1]nonan-5-one (*exo*-**23**) and 9-oxabicyclo[4.2.1]nonane-2,5-dione (**24**; Scheme 6). The major product was isolated in 53% yield after complete conversion of **1** in the presence of four equiv-



Scheme 5. Presumed mechanism of Baeyer−Villiger oxidation of hydroxy ketones *endo*-**10** and *endo*-**11** leading to **12** as the major product



Scheme 6. RuO_4 oxidation of diene **1**

alents of sodium periodate in a mixture of water, acetonitrile and acetone (v/v/v = 1:1:1, Table 2, entry 3). No 9-oxabicyclo[3.3.1]nonane derivative was observed under these conditions. The relative stereochemistry of the products was assigned by spectroscopic data and a mechanism proposed.[23]

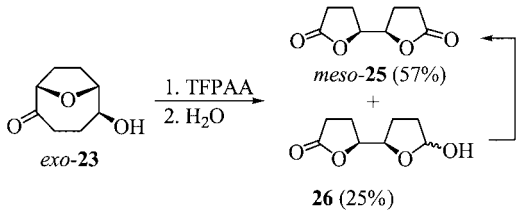
Table 2. Oxidative cyclization of **1** using catalytic amounts of $RuCl_3$ hydrate and four equivalents of $NaIO_4$

	Solvent mixture (total volume in mL)[b]	Product ratio[a] *exo,exo*-**22**	*exo*-**23**	24	Yield *exo*-**23**
1	**A** 1:2:1 (25)	6	85	9	44[c]
2	**A** 1:1:1.5 (35)	10	68	22	50[d]
3	**B** 1:1:1 (30)	2	72	26	53[d]
4	**C** 1:1 (20)	7	68	25	47[d]

[a] Determined by GC. [b] **A**: water/ethyl acetate/acetone; **B**: water/acetonitrile/acetone; **C**: water/acetonitrile; per 1 mmol of **1**. [c] Aqueous workup with sat. sodium thiosulfate solution, then continuous extraction with ethyl acetate for three days. [d] Filtration of precipitate, then continuous extraction with ethyl acetate for three days.

For comparison, permanganate was applied to oxidize *cis,cis*-cycloocta-1,5-diene (**1**) under the conditions mentioned in the literature, except that a lower temperature (0 °C) was used.[22] After 1.5 hours conversion reached just 52% (GC) and diketone **24** was identified as the main product (75%) by GC. Desired compounds *exo,exo*-**22** and *exo*-**23** were detected as side products in only 14% and 11% yields, respectively. Due to the fact that the conversion was not complete at this point, the mixture was just analyzed by GC and no further attempts at optimization were made.

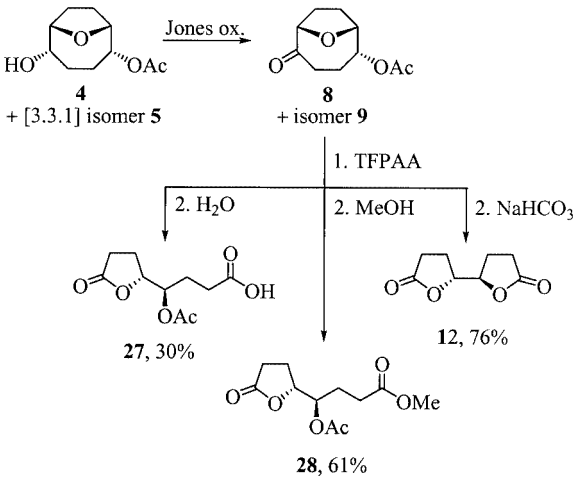
Under the conditions described above, the hydroxy ketone *exo*-**23** underwent Baeyer−Villiger oxidation giving the bislactone *meso*-**25** in 57% yield. The lactololactol **26** was identified as a minor product in ratios of 2−25% (Scheme 7). Jones oxidation of the crude product mixture of another run of Baeyer−Villiger oxidation (*meso*-**25**:**26** = 75:25, GC) gave the pure bislactone *meso*-**25** in 68% yield. Thus, this three-step procedure provided *meso*-**25** from bulk *cis,cis*-cycloocta-1,5-diene (**1**) in 36% overall yield.



Scheme 7. Baeyer−Villiger oxidation of *exo*-**23** and subsequent Jones oxidation

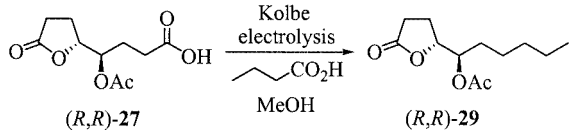
In principle there are other syntheses known in which either the stereochemistry of the bislactones **12** and **25** and corresponding monolactones is provided already in the starting material, for example D- and L-gulono-1,4-lactone, D-mannono-1,4-lactone[27−29] or D-tartric acid and D-mannitol,[30] or in which conventional asymmetric steps are used, for example the Sharpless bishydroxylation of γ-unsaturated mono-esters[31] and diesters.[32,33] Our approach, however, also gives the possibility of preparing enantiopure or racemic **12** and *meso*-bislactone **25** as well as enantiopure monolactones by minimal modifications of the workup conditions. Therefore, we applied Jones oxidation directly to a 74:26 mixture of monoacetates (1*S*,2*S*,5*R*,6*R*)-(+)-**4** (>98% *ee*) and (1*R*,2*R*,5*R*,6*R*)-(+)-**5** (80% *ee*) which gave acetoxy ketones (1*S*,5*R*,6*R*)-(+)-**8** and (1*R*,5*R*,6*R*)-(+)-**9** in good yield. These were treated with a threefold excess of trifluoroperacetic acid, leading to almost enantiopure (*R*,*R*)-5-acetoxy-7-carboxyheptane-4-olide [(*R*,*R*)-**27**] in 35% yield after aqueous workup of the acidic reaction mixture and continuous extraction with dichloromethane (Scheme 8). When the reaction mixture was quenched with methanol, continuous extraction gave the methyl ester [(*R*,*R*)-(−)-**28**] in 61% yield[34,35] When using saturated sodium hydrogencarbonate solution for workup the bislac-

tone [(*R*,*R*)-(−)-**12** was again isolated in 76% yield after column chromatography. No other product was isolated. The mechanism presumed to operate for hydroxy ketones *endo*-**10** and *endo*-**11** (Scheme 6) should also be valid for the acetoxy ketones **8** and **9** and will also be useful for the synthesis of other derivatives of **10** and **11** containing a protected OH group.



Scheme 8. Baeyer−Villiger oxidation of acetoxy ketones **8** and **9** leading either to bislactone **12**, lactono acid **27** or methyl ester **28**

In an additional step (*R*,*R*)-**27** was transformed into (*R*,*R*)-5-acetoxydecan-4-olide (*R*,*R*)-**29** (Scheme 9), the *O*-acetyl derivative of the already mentioned 5-hydroxy-γ-decalactone. Kolbe electrolysis of (*R*,*R*)-5-acetoxy-7-carboxyheptane-4-olide (*R*,*R*)-**27** and butanoic acid gave (*R*,*R*)-**29** in 10% yield after purification by column chromatography. The application of other co-acids might give access to other biologically active lactones.



Scheme 9. Kolbe electrolysis of lactono acid (*R*,*R*)-**27** and butanoic acid

Conclusion

Herein we have reported Baeyer−Villiger oxidations of 9-oxabicyclononan-2-ones, which were readily accessible by transannular *O*-heterocyclizations of cycloocta-1,5-diene (**1**) with in-situ-generated trifluoroperacetic acid as the key step. Depending on the workup conditions either the corresponding bislactones or functionalized γ-butyrolactones were synthesized in moderate to good yields. Both series of compounds are useful intermediates in synthesis since the stereochemistry is easily controllable. Dependent upon the reagent used for the oxidation of **1** — either peracetic acid or transition metal oxidants like RuO_4 — the relative stereochemistry of the 9-oxabicyclononanone, the starting material for Baeyer−Villiger oxidation, can be chosen. Enantiopure compounds were achieved by lipase-catalysed simultaneous desymmetrization and kinetic resolution, as reported recently.[15]

Experimental Section

General Remarks: All reagents and solvents were obtained from commercial sources and used as received, unless otherwise specified. Tetrahydrofuran was dried by distillation over sodium benzophenone. Products were separated by column chromatography (silica gel 60, Merck 0.063−0.200 mm, 70−230 mesh). The composition of the crude reaction products and the conversions of substrates were monitored by GC using quartz capillary columns: 25 m × 0.33 mm × 0.52 μm HP-1 (Hewlett−Packard) and 30 m × 0.32 mm × 0.25 μm SPB-1™ (Supelco). Enantiomeric excesses (*ee*) were determined by GC: 30 m × 0.25 mm × 0.25 μm chiral Beta-Dex™ 120 (Supelco), isothermic (165 °C). Optical rotations were determined at λ = 589 nm (sodium D-line). ^{1}H NMR (400.1 MHz or 300.1 MHz) and ^{13}C NMR (100.6 MHz or 75.5 MHz) were recorded in $CDCl_3$. Chemical shifts are reported as δ values (ppm) relative to TMS as internal standard. The multiplicities of ^{13}C signals were determined by the DEPT pulse sequence. The assignment of the ^{1}H and ^{13}C signals is based on 2D NMR spectra (^{1}H,^{1}H-COSY or ^{1}H,^{13}C-HECTOR). Signals of inseparable mixtures were assigned to the respective compounds using 1D-TOCSY difference spectra. Mass spectra (electron impact ionisation, 70 eV) were recorded by GC/MS coupling. Elementary analyses were carried out by the "Mikroanalytisches Laboratorium, Organische Chemie", University of Münster. The X-ray data set was collected with a four-circle diffractometer. Programs used: data collection EXPRESS (Nonius B.V., 1994), data reduction MolEN (K. Fair, Enraf−Nonius B.V., 1990), structure solution SHELXS-97,[36] structure refinement SHELXL-97,[37] graphics SCHAKAL.[38]

(1*S*,5*R*,6*R*)-(+)-5-Hydroxy-9-oxabicyclo[4.2.1]nonane-2-one (*endo*-10) and (1*R*,5*R*,6*R*)-(+)-6-Hydroxy-9-oxabicyclo[3.3.1]nonane-2-one (*endo*-11): According to known procedures for corresponding racemic compounds[13] an 81:19 mixture of acetates (1*S*,2*S*,5*R*,6*R*)-(+)-**4** (>98% *ee*) and (1*R*,2*R*,5*R*,6*R*)-(+)-**5** (60% *ee*) (1.19 g, 5.94 mmol)[15] was dissolved in acetone (50 mL). At 0 °C Jones' reagent (2.5 mL portion, made from 26.0 g of CrO_3, 23 mL of concd. H_2SO_4 and 77 mL of H_2O) was added slowly. The mixture was warmed up to room temperature and stirred for 1 h. Excess oxidant was destroyed with 2-propanol (13 mL) at 0 °C, and then the mixture was treated with water (30 mL) to dissolve the precipitate and extracted with dichloromethane (5 × 25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was then dissolved in methanol (30 mL) and treated slowly with 2 N methanolic KOH (25 mL) at room temperature. After stirring for three more hours, water (20 mL) was added and the mixture was neutralized with 4 N HCl. After evaporation of methanol to the greatest possible extent, the aqueous residue was extracted continuously with ethyl acetate for three days. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 1:1) to give (1*S*,5*R*,6*R*)-(+)-**10** (>98% *ee*) and (1*R*,5*R*,6*R*)-(+)-**11** (60% *ee*) as a colorless oil with an unchanged ratio of the skeletal isomers (81:19, GC). Yield: 0.78 g (84% over two steps). Previously spectroscopic data

were just partially described.[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.55−4.62 (m, 1 H [**10**], 6-CH), 4.38 (dd, J = 10.1, 2.0 Hz, 1 H, [**10**], 1-CH), 4.22−4.30 (m, 1 H [**11**], 5-CH), 4.05 (dt, J = 11.1, 4.7 Hz, 1 H [**10**], 5-CH), 4.00−4.07 (m, 1 H [**11**], 1-CH), 3.92 (dt, J = 12.3, 4.9 Hz, 1 H [**11**], 6-CH), 2.88 (dt, J = 14.0, 2.4 Hz, 1 H [**10**], *exo*-3-CH), 2.73−2.86 (m, 1 H [**11**], *exo*-3-CH), 1.35−2.42 (m, 7 H [**10**], *endo*-3-CH, 4-CH_2, 7-CH_2, 8-CH_2; 7 H [**11**], *endo*-3-CH, 4-CH_2, 7-CH_2, 8-CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 219.4 (s, [**10**], 2-C=O), 218.2 (s, [**11**], 2-C=O), 85.5 (d, [**10**], 6-CH), 84.2 (d, [**10**], 1-CH), 78.4 (d, [**11**], 5-CH), 73.3 (d, [**10**], 5-CH), 71.4 (d, [**11**], 1-CH), 69.1 (d, [**11**], 6-CH), 38.3 (t, [**10**], 3-CH_2), 35.8 (t, [**11**], 3-CH_2), 32.4 (t, [**10**], 8-CH_2), 28.5 (t, [**11**], 7-CH_2), 28.1 (t, [**10**], 7-CH_2), 26.1 (t, [**11**], 8-CH_2), 23.8 (t, [**10**], 4-CH_2), 20.1 (t, [**11**], 4-CH_2) ppm.

1-Benzyloxy-9,10-dioxatricyclo[4.2.1.1^{2,5}]decane (13): A suspension of a 60% sodium hydride (0.11 g, 2.8 mmol) in mineral oil was added under argon to a 70:30 mixture of (1*S*,5*R*,6*R*)-5-hydroxy-9-oxabicyclo[4.2.1]nonan-2-one (**10**) and (1*R*,5*R*,6*R*)-6-hydroxy-9-oxabicyclo[3.3.1]-nonan-2-on (**11**) (0.40 g, 2 mmol) in 40 mL of abs. THF. The reaction mixture was refluxed for 30 min and then benzyl bromide (0.34 g, 2 mmol) in 2 mL of abs. THF was added over a period of 20 min and refluxed for 18 hours. The reaction mixture was then poured into 50 mL of water and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried over magnesium sulfate and the solvent was removed in vacuo. The remaining residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give **13** as an oil. Yield: 0.24 g (49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21−7.38 (m, 5 H, 14-CH, 14′-CH, 15-CH, 15′-CH, 16-CH), 4.55−4.80 (m, 2 H, 12-CH_2), 3.91−4.06 (m, 3 H, 2-CH, 5-CH, 6-CH), 1.72−2.38 (m, 8 H, 3-CH_2, 4-CH_2, 7-CH_2, 8-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (s, 13-C), 128.3 (2d, 15-CH, 15′-CH), 127.4 (d, 16-CH), 127.3 (2d, 14-CH, 14′-CH), 108.0 (s, 1-C), 81.8 (d, 2-CH), 79.4 (d, 6-CH), 79.1 (d, 5-CH), 63.7 (t, 12-CH_2), 27.6 (2t, 4-CH_2, 7-CH_2), 27.3 (t, 8-CH_2), 26.1 (t, 3-CH_2) ppm. GC-MS (70 eV): *m*/*z* (%) = 246 (0.4) [M^+], 200 (0.6), 156 (12) [$M^+ - C_7H_6$], 155 (96) [$M^+ - C_7H_7$], 138 (4), 137 (2) [155 − H_2O], 111 (78) [137 − C_2H_2], 99 (6), 92 (11), 91 (100) [$M^+ - C_8H_{11}O_3$], 85 (12) [111 − C_2H_2], 81 (16), 67 (4), 65 (11), 57 (4), 55 (14), 41 (6). $C_{15}H_{18}O_3$ (246.3): calcd. C 73.15, H 7.37; found C 73.22, H 7.55.

Synthesis of (1*S*,7*R*,10*R*,11*R*)-11-Hydroxy-14-oxa-2,6-dithiatricyclo[8.3.1.0^{1,7}]tetradecane (14): Propane-1,3-dithiol (0.32 g, 3.0 mmol) was added dropwise at room temperature to a 70:30 mixture of (1*S*,5*R*,6*R*)-5-hydroxy-9-oxabicyclo[4.2.1]nonan-2-one (**10**) and (1*R*,5*R*,6*R*)-6-hydroxy-9-oxabicyclo[3.3.1]nonan-2-one (**11**) (0.45 g, 2.9 mmol) in 30 mL of dry dichloromethane. Then, five drops of BF_3·Et_2O were added and the mixture was stirred for 4 h. Subsequently the solvent was removed in vacuo and the crude product was purified by column chromatography (cyclohexane/ethyl acetate, 1:1). A 72:28 mixture of **14** and **15** remained as a solid. Yield: 0.52 g (72%). $[\alpha]_D^{20}$ = −10.1 (*c* = 1.03, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.70−4.73 (m, 1 H [**15**], 10-CH), 4.41−4.45 (m, 1 H [**15**], 11-CH), 4.04−4.12 (m, 1 H [**14**], 11-CH), 3.95−4.00 (m, 1 H [**14**], 10-CH), 3.10−3.16 (m, 1 H [**14**], 7-CH; 1 H [**15**], 7-CH), 2.65−3.01 (m, 5 H [**14**], 3-CH_2, 8-CH_2, *endo*- or *exo*-13-CH_2; 4 H [**15**], 9-CH_2, 12-CH_2), 1.71−2.47 (m, 9 H [**14**], 4-CH_2, 5-CH_2, 9-CH_2, 12-CH_2, *endo*- or *exo*-13-CH_2; 10 H [**15**], 3-CH_2, 4-CH_2, 5-CH_2, 8-CH_2, 13-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 87.9 (s, 1-C [**14**], 1-C [**15**]), 84.4 (d, 10-CH [**15**]), 81.2 (d, 11-CH [**15**]), 73.2 (d, 10-CH [**14**]), 67.6 (d, 11-CH [**14**]), 54.2 (d, 7-CH_2 [**14**], 7-CH_2 [**15**]), 33.9 (t, 3-CH_2 [**14**]), 33.7 (t, 3-CH_2 [**15**]), 32.7 (t, 5-CH_2 [**14**]), 31.4 (t, 13-CH_2 [**14**]), 29.7 (t, 9-CH_2 [**14**]), 29.6 (t, 12-CH_2 [**14**]), 28.8 (t, 5-CH_2 [**15**]), 28.0 (t, 8-CH_2 [**14**]), 27.8 (t, 13-CH_2 [**15**]), 26.5 (t, 12-CH_2 [**15**]), 26.3 (t, 9-CH_2 [**15**]), 24.7 (t, 8-CH_2 [**15**]), 22.6 (2 t, 4-CH_2 [**14**], 4-CH_2 [**15**]) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 248 (9) [M^+ + 2], 247 (15) [M^+ + 1], 246 (100) [M^+], 244 (4), 171 (6), 153 (9), 134 (31) [247 − $C_6H_9O_2$], 133 (6) [$M^+ - C_6H_9O_2$], 119 (36) [$M^+ - C_7H_{11}O_2$], 106 (65) [$C_3H_6S_2^+$], 97 (10), 85 (18) [$C_5H_9O^+$], 71 (33) [$C_4H_7O^+$], 81 (17), 72 (22) [$C_4H_8O^+$], 71 (100) [$C_4H_7O^+$], 67 (34) [95 − C_2H_4], 66 (7), 58 (10), 55 (20), [$C_4H_7^+$], 45 (18), 41 (32) [$C_3H_5^+$].

X-ray Crystallographic Study: Careful recrystallization from acetone gave single crystals of **14** suitable for X-ray structural analysis: formula $C_{11}H_{18}O_2S_2$, M = 246.37, colorless crystal 0.30 × 0.25 × 0.10 mm, a = 15.420(2), c = 9.686(1) Å, V = 1994.5(4) Å^3, $\rho_{calcd.}$ = 1.231 g cm^{-3}, μ = 34.74 cm^{-1}, empirical absorption correction by ψ-scan data (0.422 ≤ T ≤ 0.723), Z = 6, hexagonal, space group $P6_1$ (no. 169), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 1600 reflections collected ($-h$, $-k$, $-l$), [(sinθ)/λ] = 0.62 Å^{-1}, 1439 independent (R_{int} = 0.048) and 1366 observed reflections [$I \geq 2\ \sigma(I)$], 137 refined parameters, R = 0.061, wR^2 = 0.183, max. residual electron density 1.20 (−0.31) e·Å^{-3}, remaining electron density is located around 0,0,*z* and cannot be assigned in a chemically meaningful way, Flack parameter 0.08(4), hydrogens calculated and refined as riding atoms.

CCDC-233051 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

***exo*-5-Hydroxy-9-oxabicyclo[4.2.1]nonane-2-one (*exo*-23). a) Oxidation by RuO_4:** $NaIO_4$ (21.4 g, 0.1 mol) was dissolved in water (250 mL) in a 1-L flask and a catalytic amount of $RuCl_3$·xH_2O dissolved in acetone (250 mL) was added. Diene **1** (2.71 g, 3.07 mL, 25 mmol) was dissolved in acetonitrile (250 mL) and added to the ruthenium tetraoxide solution within 45 min. After stirring for an additional 40 min the slurry was filtered and the remaining solution was extracted continuously with ethyl acetate. The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of cyclohexane/ethyl acetate (2:1) to give *exo*-**23** as a colorless oil. Yield: 2.06 g (53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61 (m, 1 H, 6-CH), 4.40 (dd, J = 9.4, 2.6 Hz, 1 H, 1-CH), 3.80 (m, 1 H, 5-CH), 3.23 (dt, J = 13.9, 2.9 Hz, 1 H, 3-CH or 3′-CH), 2.85 (br. s, 1 H, -OH), 2.22−2.32 (m, 1 H, 8-CH or 8′-CH), 2.11−2.18 (m, 2 H, 3-CH or 3′-CH, 7-CH or 7′-CH), 2.02−2.09 (m, 1 H, 8-CH or 8′-CH), 1.88−1.96 (m, 1 H, 4-CH or 4′-CH), 1.73-1.82 (m, 1 H, 4-CH or 4′-CH), 1.54−1.63 (m, 1 H, 7-CH or 7′-CH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 217.4 (s, 2-C=O) 83.9 (d, 6-CH), 83.6 (d, 1-CH), 71.4 (d, 5-CH), 35.2 (t, 3-CH_2), 29.8 (t, 8-CH_2), 25.9 (t, 4-CH_2), 25.5 (t, 7-CH_2) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 156 (5) [M^+], 138 (5) [$M^+ - H_2O$], 128 (6) [M^+ − CO], 113 (5) [M^+ − 43], 110 (8) [138 − CO or 128 − H_2O], 100 (16) [128 − CO or C_2H_4], 95 (6), 85 (33) [113 − CO or C_2H_4], 84 (21), 83 (18), 82 (21) [110 − CO or C_2H_4], 81 (22), 72 (30) [100 − CO or C_2H_4], 71 (100), 67 (36), 57 (47) [85 − CO or C_2H_4], 55 (28) [85 − CH_2O], 44 (60) [72 − CO or C_2H_4], 43 (46), 41 (46), 39 (18). $C_8H_{12}O_3$ (156.2): calcd. C 61.52, H 7.74; found C 61.05, H 7.49.

***exo*,*exo*-2,5-Dihydroxy-9-oxabicyclo[4.2.1]nonane (22):** ^{1}H NMR (400 MHz, [D_4]methanol): δ = 4.29 (m, 2 H, 1-CH, 6-CH), 3.60 (m, 2 H, 2-CH, 5-CH), 2.03−2.11 (m, 2 H, 7-CH or 7′-CH, 8-CH or 8′-CH), 1.83−1.92 (m, 2 H, 3-CH or 3′-CH, 4-CH or 4′-CH),

1.58−1.71 (m, 4 H, 3-CH or 3′-CH, 4-CH or 4′-CH, 7-CH or 7′-CH, 8-CH or 8′-CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 85.9 (d, 1-CH, 6-CH), 76.8 (d, 2-CH, 5-CH), 29.2 (t, 7-CH_2, 8-CH_2), 27.8 (t, 3-CH_2, 4-CH_2) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 158 (0) [M^+], 140 (5) [$M^+ - H_2O$], 124 (6), 122 (5) [140 − H_2O], 115 (3), 112 (28) [140 − CO or C_2H_4], 97 (23), 96 (32), 84 (84) [112 − CO or C_2H_4], 79 (91), 71 (63), 68 (93), 67 (82), 57 (98) [$C_4H_9^+$], 55 (69), 44 (37), 43 (57), 42 (23), 41 (100), 39 (30).

9-Oxabicyclo[4.2.1]nonane-2,5-dione (24): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59 (m, 2 H, 1-CH, 6-CH), 2.95 (m, 2 H, 3-CH or 3′-CH, 4-CH or 4′-CH), 2.38 (m, 2 H, 3-CH or 3′-CH, 4-CH or 4′-CH), 2.21−2.29 (m, 2 H, 7-CH or 7′-CH, 8-CH or 8′-CH), 1.94−1.99 (m, 2 H, 7-CH or 7′-CH, 8-CH or 8′-CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 212.0 (s, 2-C=O, 5-C=O) 85.2 (d, 1-CH, 6-CH), 35.3 (t, 3-CH_2, 4-CH_2), 28.6 (t, 7-CH_2, 8-CH_2) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 154 (13) [M^+], 126 (56) [M^+ − CO], 111 (14) [M^+ − 43], 98 (85) [126 − CO or C_2H_4], 83 (42) [111 − CO or C_2H_4], 70 (100) [98 − CO or C_2H_4], 69 (66), 56 (34), 55 (100) [83 − CO or C_2H_4], 54 (58), 42 (85) [70 − CO or C_2H_4], 41 (56), 39 (43). $C_8H_{10}O_3$ (158.2): calcd. C 62.33, H 6.54; found C 61.97, H 6.58.

b) Oxidation by $KMnO_4$: $KMnO_4$ (1.58 g, 10 mmol, 2.5 equiv.) was dissolved in acetone (72 mL) and water (6 mL) and was then slowly added to a solution of diene **1** (0.5 mL, 4 mmol) in acetone (2 mL) at 0 °C. After stirring for 30 min the precipitate was filtered off and acetone was removed almost completely in vacuo. The aqueous layer was extracted with dichloromethane (3 × 100 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was analysed by GC showing 48% of remaining diene **1**. The reaction products were identified as the diketone **24** (75%), the hydroxy ketone *exo*-**23** and diol **22** (14% and 11%, respectively).

General Procedure for the Baeyer−Villiger Oxidation: The bicyclic ketone (2.0 mmol) and trifluoroacetic acid (4 mL) were dissolved in abs. dichloromethane (10 mL). Sodium percarbonate (1.32 g, 8.4 mmol) was then added in portions within one hour at 0 °C. The heterogeneous mixture was warmed up to room temperature and stirred vigorously for four hours. After addition of water (15 mL) the two-phase mixture was stirred for an additional 18 h. The mixture was then cautiously neutralized by addition of solid and a saturated solution of sodium hydrogencarbonate. The aqueous phase was extracted continuously with dichloromethane for 3 d. The organic phase was then stirred over $FeSO_4$ to destroy the remaining peroxides, and then dried over $MgSO_4$ and concentrated in vacuo.

(2*R*,2′*R*)-(−)-Tetrahydro-2,2′-bifuranyl-5,5′-dione (12): A 37:63 mixture of the hydroxy ketones (1*S*,5*R*,6*R*)-(+)-**10** (>98% *ee*) and (1*R*,5*R*,6*R*)-(+)**11** (>98% *ee*) (312 mg, 2.0 mmol) was transformed as described above. The residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 1:2) as eluent to give (2*R*,2′*R*)-(−)-**12**. Yield: 245 mg (72%). Spectroscopic data have been reported previously.[27] $[\alpha]_D^{20}$ = −78.5 (*c* = 1.0, chloroform, ref.[27] $[\alpha]_D^{20}$ = −81, *c* = 0.99, chloroform), >98% *ee* (chiral GC, Beta-Dex™ 120). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57−4.63 (m, 2 H, 2-CH, 2′-CH), 2.69 (ddd, *J* = 17.8, 10.1, 6.1 Hz, 2 H, *endo*-4-CH, *endo*-4′-CH or *exo*-4-CH, *exo*-4′-CH), 2.54 (ddd, *J* = 17.8, 9.9, 7.7 Hz, 2 H, *endo*-4-CH, *endo*-4′-CH or *exo*-4-CH, *exo*-4′-CH), 2.24−2.44 (m, 4 H, 3-CH_2, 3′-CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.6 (s, 5-C=O, 5′-C=O), 80.1 (d, 2-CH, 2′-CH), 27.9 (t, 4-CH_2, 4′-CH_2), 23.9 (t, 3-CH_2, 3′-CH_2) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 170 (2) [M^+], 142 (2) [M^+ − CO], 115 (2) [$C_5H_7O_3^+$], 87 (2), 86 (28), 85 (100) [$C_4H_5O_2^+$], 57 (27) [85 − CO], 56 (7), 55 (5) [85 − CH_2O], 42 (4), 41 (3), 39 (5).

In some cases 5′-hydroxytetrahydro-2,2′-bifuranyl-5-one (**21**) was identified as a side-product of this reaction in 14−16% yield (GC). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.57−5.58 (br. d, 1 H, *cis*- and *trans*-5′-CH), 4.50 (m, 1 H, 2-CH), 4.31 (m, 1 H, 2′-CH), 2.61−2.72 (m, 2 H, 4-CH_2), 2.20−2.33 (m, 2 H, 3-CH_2), 2.08 (m, 2 H, 4′-CH_2), 1.86 (m, 2 H, 3′-CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.9 (s, 5-C=O), 99.4 (d, 5′-C-OH), 81.8 (d, 2′-CH), 81.2 (d, 2-CH), 32.9 (t, 4′-CH_2), 28.0 (t, 4-CH_2), 25.6 (t, 3-CH_2), 24.9 (t, 3′-CH_2) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 172 (1) [M^+], 154 (2) [$M^+ - H_2O$], 129 (2), 115 (9), 98 (11), 87 (100) [$C_4H_7O_2^+$], 86 (44), 85 (49) [$C_4H_5O_2^+$], 69 (28) [87 − H_2O], 57 (18) [85 − CO], 43 (25), 41 (21).

(2*R*,2′*S*)-Tetrahydro-2,2′-bifuranyl-5,5′-dione (*meso*-25): Hydroxy ketone *exo*-**23** (493 mg, 3.16 mmol) was transformed as described above. The crude residue containing a mixture of *meso*-**25** and **26** (75:25, GC) was dissolved in acetone (20 mL). At 0 °C Jones' reagent (1 mL portion, made of 26.0 g of CrO_3, 23 mL of concd. H_2SO_4 and 77 mL of H_2O) was added slowly. The mixture was warmed up to room temperature and stirred for 1 h. Excess oxidant was destroyed with 2-propanol (5 mL) at 0 °C. After dissolving the precipitate in water (15 mL), the mixture was extracted with dichloromethane (5 × 25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give *meso*-**25** (365 mg, 2.15 mmol, 68%). Spectroscopic data agree with previously published ones.[27]

A mixture of the *cis*- and *trans*-isomers of 5′-hydroxytetrahydro-2,2′-bifuranyl-5-one (**26**) was identified as a side product of this reaction in 2−25% yield (GC). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.62−5.76 (br. d, 2 H, *cis*- and *trans*-5′-CH), 4.49−4.57 (m, 2 H, 2-CH), 4.22−4.34 (m, 2 H, 2′-CH), 2.46−2.67 (m, 2 H, 4-CH_2), 1.62−2.46 (m, 12 H, 3-CH_2, 3′-CH_2, 4′-CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.9, 176.7 (s, 5-C=O), 106.2, 107.6 (d, 5′-C-OH), 80.4 (2d, 2-CH), 79.1, 78.9 (d, 2′-CH), 28.7, 28.6 (t, 4′-CH_2), 27.9, 27.8 (t, 4-CH_2), 24.9 (2t, 3′-CH_2), 23.0, 22.8 (t, 3-CH_2) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 172 (0) [M^+], 154 (4) [$M^+ - H_2O$], 129 (3), 115 (7), 98 (8), 87 (100) [$C_4H_7O_2^+$], 86 (43), 85 (58) [$C_4H_5O_2^+$], 69 (35) [87 − H_2O], 57 (16) [85 − CO], 43 (23), 41 (17).

(1*S*,5*R*,6*R*)-(+)-5-Acetoxy-9-oxabicyclo[4.2.1]nonane-2-one (8) and (1*R*,5*R*,6*R*)-6-(+)-Acetoxy-9-oxabicyclo[3.3.1]nonane-2-one (9): According to known procedures for the corresponding racemic compounds[13] a 74:26 mixture of acetates (1*S*,2*S*,5*R*,6*R*)-(+)-**4** (>98% *ee*) and (1*R*,2*R*,5*R*,6*R*)-(+)-**5** (80% *ee*) (1.50 g, 7.5 mmol)[15] was dissolved in acetone (150 mL). At 0 °C Jones' reagent (5 mL portion, made of 26.0 g of CrO_3, 23 mL of concd. H_2SO_4 and 77 mL of H_2O) was added slowly within one hour. After stirring for an additional hour the mixture was warmed up to room temperature and stirred for 18 h. 2-Propanol (50 mL) was then added to destroy excess oxidant. The precipitate was then dissolved in water (50 mL), and the mixture was extracted with chloroform (4 × 75 mL). The combined organic phases were washed with water (2 × 50 mL), dried over $MgSO_4$ and concentrated in vacuo to give a 74:26 mixture of **8** and **9** as a yellowish oil. Yield: 1.20 g (81%). Spectroscopic data of the racemates have been partially reported.[13] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.15 (dt, *J* = 11.4, 4.8 Hz, 1 H [**8**], 5-CH), 5.01 (dt, *J* = 11.4, 4.8 Hz, 1 H [**9**], 6-CH), 4.57−4.71 (m, 1 H [**8**], 6-CH), 4.34−4.48 (m, 1 H [**8**], 1-CH, 1 H [**9**], 5-CH), 4.01−4.18 (m, 1 H [**9**], 1-CH), 2.71−2.96 (m, 1 H [**8**], *exo*-3-CH, 1 H [**9**], *exo*-3-CH), 2.06 (s, 3 H [**9**], 12-CH_3), 2.09 (s, 3 H [**8**], 12-CH_3), 1.50−2.48 (m, 7 H [**8**], *endo*-3-CH, 4-CH_2, 7-CH_2, 8-CH_2, 7

H [**9**], *endo*-3-CH, 4-CH_2, 7-CH_2, 8-CH_2) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 216.5 (s, 2-C=O [**8**]), 215.3 (s, 2-C=O [**9**]), 169.9 (s, 11-C=O [**9**], 11-C=O [**8**]), 83.7 (d, 1-CH [**8**]), 82.1 (d, 1-CH [**9**]), 79.6 (d, 6-CH [**8**]), 71.7 (d, 5-CH [**8**]), 69.8 (d, 5-CH [**9**]), 66.3 (d, 6-CH [**9**]), 36.5 (t, 3-CH_2 [**8**]), 30.7 (t, 4-CH_2 [**8**]), 28.5 (t, 3-CH_2 [**9**]), 26.4 (t, 7-CH_2 [**9**]), 23.4 (t, 7-CH_2 [**8**]), 23.2 (t, 8-CH_2 [**8**]), 22.2 (t, 4-CH_2 [**9**]), 21.7 (t, 8-CH_2 [**9**]), 20.9 (2q, 12-CH_3 [**8**], 12-CH_3 [**9**]) ppm.

(*R*,*R*)-5-Acetoxy-7-carboxyheptane-4-olide (27): A 74:26 mixture of bicyclic acetoxy ketones (1*S*,5*R*,6*R*)-(+)-**8** and (1*R*,5*R*,6*R*)-(+)-**9** (0.40 g, 2.00 mmol) was transformed as described above with trifluoroacetic acid (7 mL) and sodium percarbonate (0.66 g, 4.2 mmol). Water (20 mL) was added after the reaction mixture had been stirring for 18 h. After continuous extraction with dichloromethane (50 mL) the organic layer was extracted five times with 0.1 N $NaHCO_3$ (each 30 mL). Then the aqueous layer was acidified to pH 2 with 2 N HCl and was extracted continuously with dichloromethane (100 mL). The mixture was treated with $MgSO_4$ and concentrated in vacuo to give **25** as colorless oil. Yield: 0.16 g (35%). No other products were detected by GC. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.01−5.10 (m, 1 H, 5-CH), 4.51−4.60 (m, 1 H, 4-CH), 2.09 (s, 3 H, 10-CH_3), 1.68−2.72 (m, 8 H, 2-CH_2, 3-CH_2, 6-CH_2, 7-CH_2) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 192.0 (s, 8-C=O), 177.4 (s, 1-C=O), 170.9 (s, 9-C=O), 80.3 (d, 5-CH), 73.1 (d, 4-CH), 28.0 (t, 7-CH_2), 27.8 (t, 2-CH_2), 25.4 (t, 6-CH_2), 23.7 (q, 10-CH_3), 20.6 (t, 3-CH_2) ppm. GC-MS (70 eV, Ion Trap, as trimethylsilyl ester): *m*/*z* (%) = 302 (0) [M^+], 287 (7) [$M^+ - CH_3$], 246/245 (5/35) [$287 - C_2H_2O$], 227 (38) [$287 - C_2H_4O_2$], 217 (28) [245 − CO], 199 (15), 185 (13), 175 (63), 153 (10), 129 (8), 125(16), 117 (36), 111 (24), 98 (8), 86/85 (5/100) [$C_4H_5O_2^+$], 75 (75), 73 (42) [$Si(CH_3)_3^+$], 72 (4), 55 (20) [$C_4H_7^+$], 45 (8), 43 (48) [$C_2H_3O^+$].

(*R*,*R*)-(−)-5-Acetoxy-7-(methoxycarbonyl)heptane-4-olide (28): A 69:31 mixture of bicyclic acetoxy ketones (1*S*,5*R*,6*R*)-(+)-**8** and (1*R*,5*R*,6*R*)-(+)-**9** (0.40 g, 2.00 mmol) was transformed as described above with trifluoroacetic acid (4 mL) and sodium percarbonate (0.66 g, 4.2 mmol). Abs. methanol (8 mL) was added cautiously instead of water and the mixture stirred for 30 min. After adding dichloromethane (20 mL) the organic layer was extracted twice with 1% $NaHCO_3$ solution (each 50 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of cyclohexane/ethyl acetate (1:2) to yield (*R*,*R*)-(−)-**28** as colorless oil. Yield: 0.30 g (61%)[34]. $[\alpha]_D^{20}$ = −37.9 (*c* = 1.0, chloroform), >98% *ee* [chiral GC, Beta-Dex™ 120, after hydrolysis to (−)-**12**]. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.07 (ddd, *J* = 8.7, *J* = 4.3, *J* = 4.3 Hz, 1 H, 5-CH), 4.58 (ddd, *J* = 7.7, *J* = 6.5, *J* = 4.3 Hz, 1 H, 4-CH), 3.64 (s, 3 H, 9-CH_3), 2.51−2.55 (m, 2 H, 2-CH, 2-CH′), 2.39 (dd, *J* = 7.7, *J* = 3.4 Hz, 1 H, 7-CH′ or 7-CH), 2.10 (s, 3 H, 11-CH_3), 2.37 (dd, *J* = 7.7, *J* = 4.3 Hz, 1 H, 7-CH or 7-CH′), 2.28−2.35 (m, 1 H, 3-CH′ or 3-CH),1.90−2.13 (m, 3 H, 6-CH_2, 3-CH or 3-CH′) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 176.4 (s, 1-C=O), 172.9 (s, 8-C=O), 170.4 (s, 10-C=O), 80.0 (d, 4-CH), 73.1 (d, 5-CH), 51.8 (q, 9-CH_3), 29.6 (t, 7-CH_2), 28.1 (t, 2-CH_2), 25.8 (t, 6-CH_2), 23.9 (t, 3-CH_2), 20.8 (q, 11-CH_3) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 244 (22) [M^+], 185 (16) [$M^+ - C_2H_3O_2$], 171 (5) [$M^+ - C_3H_5O_2$], 159 (23) [$M^+ - C_4H_5O_2$], 152 (14), 124 (17) [152 − CO], 97 (11), 85 (39) [$C_3H_5O_2^+$], 43 (100) [$C_2H_3O^+$]. $C_{11}H_{16}O_6$ (244.2): calcd. C 54.09, H 6.60; found C 53.88, H 6.87.

(*R*,*R*)-5-Acetoxydecane-4-olide (29): Absolute methanol (30 mL) was added to a mixture of **27** (0.23 g, 2.00 mmol) and butanoic acid (1.9 mL, 20.0 mmol) in an undivided beaker-type cell equipped with a stirrer and a platinum anode and cathode. In order to adjust 5% neutralization, 1 N methanolic KOH (1.05 mL) was added. The electrolysis was carried out at 25 °C with a current density of 0.1 A/cm^2 for 23 min at a potential of 50 V. The reaction mixture was added to water (50 mL) and the whole solution was extracted four times with diethyl ether (each 50 mL). NaCl was then added to separate the layers. The combined organic layers were dried over $MgSO_4$, the solvent was evaporated in vacuo and the residue was purified by column chromatography (diethyl ether/pentane, 5:1). Compound **29** was obtained as a yellow oil. Yield: 22 mg (10%). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.99 (ddd, *J* = 10.3, 7.4, 4.1 Hz, 1 H, 5-CH), 4.58 (ddd, *J* = 10.3, 6.4, 4.1 Hz, 1 H, 4-CH), 2.07 (s, 3 H, 12-CH_3), 1.23-2.60 (m, 12 H, 2-CH_2, 3-CH_2, 6-CH_2, 7-CH_2, 8-CH_2, 9-CH_2), 0.85−0.96 (t, 3 H, 10-CH_3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 176.5 (s, 1-C=O), 170.4 (s, 11-C=O), 79.8 (d, 4-CH), 74.3 (d, 5-CH), 31.4 (t, 8-CH_2), 30.4 (t, 6-CH_2), 28.1 (t, 2-CH_2), 24.8 (t, 7-CH_2), 23.9 (t, 9-CH_2), 22.4 (t, 3-CH_2), 20.9 (q, 12-CH_3), 13.8 (q, 10-CH_2) ppm. GC-MS (70 eV, Ion Trap): *m*/*z* (%) = 229/228 (3/39) [M^+], 227 (3) [$M^+ - 1$], 168 (3) [$M^+ - CH_3CO_2H$], 150 (3) [$168 - H_2O$], 125 (3), 111 (3), 95 (2), 85 (40) [$C_4H_5O_2^+$], 67 (2), 55 (6) [$C_4H_7^+$], 43 (100) [$C_2H_3O^+$].

Acknowledgments

Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. We wish to thank Prof. Dr. H.-J. Schäfer and Dr. S. Kratschmer for their assistance with the Kolbe electrolyses.

[1] V. Popsavin, I. Krstic, M. Popsavin, *Tetrahedron Lett.* **2003**, *44*, 8897−8900 and references cited therein.
[2] T. Yoshimitsu, T. Makino, H. Nagaoka, *J. Org. Chem.* **2003**, *68*, 7548−7550 and references cited therein.
[3] M. Carda, S. Rodríguez, F. González, E. Castillo, A. Villanueva, J. A. Marco, *Eur. J. Org. Chem.* **2002**, 2649−2655 and references cited therein.
[4] M. J. Rieser, J. F. Kozlowski, K. V. Wood, J. L. McLaughlin, *Tetrahedron Lett.* **1991**, *32*, 1137−1140.
[5] U. Gräfe, G. Reinhardt, W. Schade, D. Krebs, I. Eritt, W. F. Fleck, E. Heinrich, L. Radics, *J. Antibiot.* **1982**, *35*, 609−614.
[6] U. Gräfe, I. Eritt, *J. Antibiot.* **1983**, *36*, 1592−1593.
[7] L. A. Garbe, R. Tressl, *Helv. Chim. Acta* **2003**, *86*, 2349−2363 references cited therein.
[8] R. W. Friesen, A. Giroux, *Can. J. Chem.* **1994**, *72*, 1857−1865.
[9] S. K. Kang, H. S. Cho, H. S. Sim, B. K. Kim, *J. Carbohydr. Chem.* **1992**, *11*, 807−812.
[10] M. Plewe, R. R. Schmidt, *Synthesis* **1989**, 534−536.
[11] P. Lafont, G. Vivant, Fr. Pat. 1,336,187, **1963**; *Chem. Abstr.* **1964**, *60*, 2803.
[12] A. H. Frazer, US Pat. 3,347,826, **1967**; *Chem. Abstr.* **1968**, *68*, 2819b.
[13] R. O. Duthaler, K. Wicker, P. Ackermann, C. Ganter, *Helv. Chim. Acta* **1972**, *55*, 1809−1829.
[14] P. E. Eaton, R. Millikan, *Synthesis* **1990**, 483−484.
[15] K. Hegemann, H. Schimanski, U. Höweler, G. Haufe, *Tetrahedron Lett.* **2003**, *44*, 2225−2229.
[16] K. Hegemann, R. Fröhlich, G. Haufe, *Eur. J. Org. Chem.* **2004**, 2181−2192.
[17] J. A. Marshall, J. L. Belletire, *Tetrahedron Lett.* **1991**, 871−874.
[18] M. M. M. Rubinger, J. Mann, M. G. B. Drew, *Tetrahedron* **1995**, *51*, 11295−11304.
[19] G. R. Krow, *Org. React.* **1993**, *43*, 251−798.
[20] M. Hudlický, *Oxidations in Organic Chemistry*, ACS Monograph 186, American Chemical Society, Washington, **1990**, p. 189.
[21] G. A. Olah, Q. Wang, N. J. Trivedi, G. K. S. Prakash, *Synthesis* **1991**, 739−740.

[22] E. Klein, W. Rojahn, *Tetrahedron* **1965**, *21*, 2353−2358.
[23] L. Albarella, D. Musumeci, D. Sica, *Eur. J. Org. Chem.* **2001**, 997−1003.
[24] N. Cavallo, V. Piccialli, *Tetrahedron Lett.* **2001**, *42*, 4695−4699.
[25] V. Piccialli, T. Caserta, *Tetrahedron Lett.* **2004**, *45*, 303−308.
[26] T. J. Donohoe, S. Butterworth, *Angew. Chem.* **2003**, *115*, 978−981; *Angew. Chem. Int. Ed.* **2003**, *42*, 948−951.
[27] J. A. J. M. Vekemans, C. W. M. Dapperens, R. Claessen, A. M. J. Koten, E. F. Godefroi, G. J. F. Chittenden, *J. Org. Chem.* **1990**, *55*, 5336−5344.
[28] J. A. J. M. Vekemans, G. A. M. Franken, C. W. M. Dapperens, E. F. Godefroi, G. J. F. Chittenden, *J. Org. Chem.* **1988**, *53*, 627−633.
[29] J. A. J. M. Vekemans, G. A. M. Franken, E. F. Godefroi, G. J. F. Chittenden, *Tetrahedron Lett.* **1987**, *28*, 2299−2230.
[30] H. Kotsuki, H. Nishikawa, Y. Mori, M. Ochi, *J. Org. Chem.* **1992**, *57*, 5036−5040.
[31] P. A Evans, J. D. Roseman, *Tetrahedron Lett.* **1997**, *38*, 5249−5252.
[32] J. M. Holland, M. Lewis, A. Nelson, *J. Org. Chem.* **2003**, *68*, 747−753.
[33] M. E. Maier, S. Reuter, *Synlett* **1995**, 1029−1030.
[34] The yield was increased to 76% in another experiment by using an 80:20 mixture of the enantiomers (1*R*,5*S*,6*S*)-(−)-(**8**) (94% *ee*) and (1*R*,5*R*,6*R*)-(+)-(**9**) (>98% *ee*), which lead to enantiomerically enriched (*S*,*S*)-methyl ester (+)-**26**. The enantiomers were obtained by enzyme-catalyzed hydrolysis[16] of fully acetylated *rac*-diols **2** and **3** (52%) followed by Jones oxidation of the free hydroxyl group.
[35] Several years ago, the diastereomeric (*R*,*S*)-methyl ester was synthesized: V. N. Odinokov, L. P. Zhemaiduk, G. Yu. Ishmuratov, G. A. Tolstikov, *Zh. Org. Khim.* **1978**, *14*, 1617−1627; *J. Org. Chem. Russ. Ed.* **1978**, *14*, 1511−1518.
[36] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467−473.
[37] G. M. Sheldrick, University of Göttingen, **1997**.
[38] E. Keller, University of Freiburg, **1997**.

Received April 1, 2004

