Stereoselective Synthesis of 1,6,9-Trioxaspiro[4.5]decanes From d-Glucose: Novel Structural Motifs of Spiroacetal Natural Products

Eckehard Cuny1

Abstract
Spiroacetals are the central structural core element of numerous natural products and are essential for their biological activity. A typical structural representative of a spiroacetal is the bicyclic 1,6-dioxaspiro[4.5]decane ring system. It represents the complete or partial structure of many biologically potent natural products such as the Pararepsila pheromone 1, the antibiotic (+)-monensin A 2, the anticancer agent (−)-berkelic acid 3, the antimitotic ingredient spirastrellolide F, characterized after methylation as (+)-methyl ester 4, and the marine toxin (−)-calycin A 5. In these compounds, the 1,6-dioxaspiro[4.5]decane ring system is found in either spiro (R)-6 or (S)-6 configuration. The corresponding 1,6,9-trioxaspiro[4.5]decane framework (S)-7 and (R)-7 with opposite chirality at the spiro center due to an additional oxygen atom at position 9 in the pyran portion has so far not been found in living organisms or been synthesized. To close this gap and enable structure–activity relationship studies, potentially leading to novel antibiotics and selective anticancer agents, we have developed an efficient and stereocontrolled route to the (R)- and (S)-configured 1,6,9-trioxaspiro[4.5]decane ring system leading to oxa analog motifs of the above natural products.

Keywords
spiroacetal, bioactivity, pheromone, antibiotic, marine toxin

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Spiroacetals are the central structural core element in a multitude of natural products of insect, marine, bacterial, or plant origin.1-6 A typical example of an organism producing a spiroacetal compound is the wasp Paravespula vulgaris, a social insect constructing and living in communal nests. The wasps emit an aggregation pheromone with spiroacetal molecular structure (Figure 1) for the purpose of mating and overwhelming predators. This aggregation pheromone is the minor bouquet component and a mixture of 2 diastereomers of 2-methyl-1,6-dioxaspiro[4.5]decane with either cis or trans geometry in the furan ring of the methyl group and the pyran oxygen atom 7 (I in Figure 2). The absolute stereochemistry with regard to the biological activity is still unknown, although all 4 possible stereoisomers have been synthesized.8-14 More complex structures with bicyclic 1,6-dioxaspiro[4.5]decane ring system and spiro (R)- as well as spiro (S)-configuration are found in the following natural products: (1) (+)-monensin A 2, a polyether ionophorous antibiotic and formed as a metabolite in a biosynthesis of Streptomyces cinnamonensis bacteria;15-18 (2) (−)-berkelic acid 3, a novel spiroketal and unique secondary metabolite with selective anticancer activity isolated from an extremophilic Penicillium species;19,25 (3) spirastrellolide F, a potent antimitotic agent of the marine sponge Spirastrella coccinea, whose structure has been characterized after methylation as (−)-methyl ester 426-30, and (4) (−)-calycin A 5, a toxin blocking calcium influx and inhibiting protein Ser/Thr phosphatase isolated from the marine sponge Disodermia calyx.31-34

Biological studies disclosed that the spiroacetal framework is essential for biological activity in these types of natural compounds.35-40 Given their diverse biological activity, Zinzalla et al41 designed and synthesized spiroketal derivatives, leading to a collection of new small molecules for biological evaluation as orally bioavailable lead compounds. The use of spirocyclic scaffolds in drug discovery has been reviewed.42 With regard to

1Department of Chemistry, Clemens-Schöpf-Institute of Organic Chemistry and Biochemistry, Darmstadt Technical University, Darmstadt, Germany

Corresponding Author: Eckehard Cuny, Department of Chemistry, Clemens-Schöpf-Institute of Organic Chemistry and Biochemistry, Darmstadt Technical University, Alarich-Weiss-Straße 4, 64287, Darmstadt, Germany. Email: cuny@cuny.de

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drug design, in 2017, Scheepstra et al. published a paper entitled “Designed Spiroketal Protein Modulation”, describing that spiroketals are arguably well-suited for 2 approaches: (1) diversity-oriented synthesis and (2) biology-oriented synthesis.

The 1,6-dioxaspiro[4.5]decane ring system is found in nature with either spiro (R)- or spiro (S)-configuration (structures (R)-6 and (S)-6 marked in red in Figure 2). The corresponding 1,6,9-trioxaspiro[4.5]decane framework (S)-7 and (R)-7 with opposite chirality at the spiro center, due to the additional oxygen atom in the dioxane portion (oxygen marked in blue), has not yet been found in nature. To close this gap and enable the characterization of these compounds in view of structure–activity relationship studies, we here describe an efficient and stereocontrolled route to derivatives with (R)- as well as (S)-configured 1,6,9-trioxaspiro[4.5]decane ring system. These novel compounds contain the oxa analog motifs of the aforementioned natural products depicted in Figure 2.

**Syntheses**

The chemical elaboration of the 1,6,9-trioxaspiro[4.5]decane ring system is difficult and only a few racemic approaches are known. These include the electrolysis of mono furfuryl ethers, a carbon–carbon bond formation reaction of a diazoketone and the selective reduction of analogs of the secondary metabolite and antifeedant tonghaosu. A newer US patent describes the cyclization of keto diols with 1 stereogenic center, which yields derivatives of 1, but with unspecified stereochemistry at the spiro center and in the dioxane portion. The 1,6,9-trioxaspiro[4.5]decanes described are potentially useful for the diagnosis and treatment of diseases of cell membrane lipid asymmetry. Interestingly, the reaction of anhydrous hydrogen fluoride with d-fructose, sucrose, or inulin leads among others to d-fructose anhydride I, a tricyclic molecule with 2 1,6,9-trioxaspiro[4.5]decanes 1,8, a tricyclic molecule with 2 1,6,9-trioxaspiro[4.5]decanes 1,8.

In the early 1980s, we developed a practical method for the conversion of the 2 literature-known d-glucose-derived 2-hydroxyglycal esters 9a and 9b into the corresponding ulosyl bromides 10a and 10b. We subsequently published the glycosylation of 10a with the diol ethylene glycol to the bicyclic pyranodioxane (1,4,5-trioxa-cis-decaline) 11a. In the same paper, we also reported the ring contraction of 11a to the 2 1,6,9-tri-oxaspiro[4.5]decanes 14a and 15a together with consecutive bromide 16a and its dehalogenated derivative 17a.

Here we describe for the first time the glycosylation of the 6-deoxyulosyl bromide 10b with ethylene glycol to the β-cis-annulated bicyclic pyranodioxane 11b. Its further spiroacetalization by adopting our synthetic strategy leads to novel 1,6,9-tri-oxaspiro[4.5]decane derivatives possessing a methyl instead of a benzoyloxymethyl group in the 5-membered furan moiety. Consequently, their structure is more closely related to the naturally occurring spiroacetal motifs. Furthermore, the structural elucidation of all new...
shown by the arrows. The hydroxyl group of (10R)-cussed and presented.

Scheme 1. Conversion of the d-glucose-derived ulosyl bromides 10 into the bicyclic pyranodioxanes 11 furnished by acid-catalyzed ring contraction and acylation (via protonated 11, oxonium cation 12 and (10R)-13 the 1,6,9-tri-oxaspiro[4.5]decane derivatives 14a, and 15a as well as 14b and 15b. Their bromination (through intermediates 16a, 16b) and successive dehalogenation gave the 2 Paravespula pheromone derivatives 17a and 17b. Further reaction of 16a with different alcohols afforded the spiroketal glycosides 18, 19, 20, and 21, which are lead structures for drug design.

and known 1,6,9-tri-oxaspiro[4.5]decane derivatives is discussed and presented.

Derivatives with Spiroacetal Motif (R)-7

The stereoselective synthesis of compounds with the spiroacet- tal motif (R)-7 (1,6,9-tri-oxaspiro[4.5]decane-structure) from d-glucose is shown in Scheme 1.

The reaction of the 6-deoxy-ulosyl bromide 10b with ethylene glycol in dichloromethane in the presence of silver carbonate (Koenigs–Knorr conditions) gave the 6-deoxy-pyranodioxane 11b as colorless crystals in 95% yield. Under these reaction conditions, only β-glycosylation took place (C-1 attack), which is immediately followed by ketalization through β-attack at C-2. Further reaction of 11b with acetic acid anhydride or benzoic acid anhydride in the presence of perchloric acid (70%) gave, after protonation in an equilibrium reaction, 12, which undergoes ring contraction to (10R)-13, as shown by the arrows. The hydroxyl group of (10R)-13 was immediately trapped by acylation to afford the spiro[4.5]ketalts 14b and 15b in 94% and 77% yield, respectively (see Scheme 1).

As shown by a comparison experiment, no appreciable conversion occurred by the reaction of 11a with perchloric acid (70%) in dichloromethane and the absence of an acylating agent at room temperature. At reflux temperature (40°C), a continuous conversion arose and after 2 hours, a 1:3 equilibrium mixture of 11a and (10R,S)-13a has been achieved. The mixture of (10R,S)-13 was also obtained by hydrolysis of 16a (see the section Experimental).

Subsequent bromination of 15b gave 16b, which could be radically dehalogenated to 17b. Reaction of 16a with methanol, isopropanol, cyclohexanol and cholesterol afforded under Koenigs–Knorr conditions the corresponding glycosides 18, 19, 20, and 21, all in over 86% yield. No side products were formed because a stereospecific Sn2-attack is guaranteed under these reaction conditions with silver carbonate as acid scaven- ger (see Scheme 1).

The synthesized compounds possess the (5R)-1,6,9-tri-oxaspiro[4.5]decane framework (R)-7, which corresponds to structure (S)-6, the spiroacetal motif found in (−)-berkelic acid 3, (−)-spirastrellolide F methyl ester 4, and (−)-calyculin A 5. They resemble those motifs even more, because of the newly implemented methyl group. In particular, the spiroacetal 17b represents an oxo derivative of the Paravespula pheromone 1.

Derivative with Spiroacetal Motif (S)-7

The stereospecific conversion of the pyranodioxane 22 to a derivative with framework (S)-7 could also be achieved. But in contrast to its (R)-configured counterpart, the yield was lower and the reaction process less homogenous. For that reason, we also studied this stereoselective ring contraction of 22.

The pyranodioxane 22 is obtainable from ulosyl bromide 10a and ethylene glycol in dimethylformamide. Further reaction with benzoic acid anhydride and perchloric acid (70%) gave via protonation (through intermediate 23) and rearrangement (through intermediate 24) spiro compound 25 in 61% yield. A more detailed examination of the reaction revealed that the open-chain side product 26 was formed as well (30%). The reason for its formation is the reduced stability of the pyranodioxane 22, compared with its isomer 11a under these acidic reaction conditions. Thus, the ketal function of 22 at C-2 is split off and the resulting open-chain form was immediately benzoylated to the glycoside 26 (Scheme 2).
The synthesized 1,6,9-tri-oxaspiro[4.5]decane derivative 25 contains the framework (S)-7, which corresponds to the structure (R)-6, the spiroacetal motif of (+)-monensin A 2.

**Structural Elucidation**

The configuration and conformation of the aforementioned 1,6,9-tri-oxaspiro[4.5]decanes with either (R)- or (S)-spiro framework could be resolved on the basis of 1H and 13C NMR data.

**Furan Portion**

The relevant proton chemical shifts and coupling constants of the ring protons in the tetrahydrofuran portion are listed in Table 1.

The chemical shifts for 2H, 3H, and 4H of compounds with the spiroacetal motif (R)-7 are as expected of the same order of magnitude in each case of (A) and (B) in Table 1. In contrast to this, the ring proton 3H of 25 with framework (S)-7 (C in Table 1) has a pronounced high field shift of 0.43 ppm, as compared to its corresponding (R)-7 counterpart, the compound 15a. This distinctive difference is caused by the lack of 1,3-diaxial interaction of the furan 3H with the dioxane oxygen O-6 in 25, a finding, that could be used to determine the configuration of the spiro center in these kinds of spiroacetals with 1,6,9-tri-oxaspiro[4.5]decane ring system.

The same result was also found by Lemieux and Nagarajan in the hexaacetate of di-α-fructofuranosyl-β-d-fructofuranose 27, a finding, that could be used to determine the configuration of the spiro center in these kinds of spiroacetals with 1,6,9-tri-oxaspiro[4.5]decane ring system.

Table 1. Selected Proton Chemical Shifts and 1H-1H Coupling Constants of 1,6,9-Triaspiro[4.5]decanes in the Tetrahydrofuran Portion (300 MHz in CDCl3, δ in ppm, J in Hz).

| Comp. | X | 2H | 3H | 4H | J2,3 | J3,4 |
|-------|---|----|----|----|------|------|
| (A) Spiroacetal motif (R)-7 and X axial | | | | | | |
| 14a | OAc | 4.59 | 5.91 | 5.91 | n.d. | n.d. |
| 15a | OBz | 4.63 | 5.94 | 6.02 | 5.5 | 7.1 |
| 16a | Br | 4.59 | 5.79 | 5.89 | 5.4 | 6.5 |
| 14b | OAc | 4.34 | 5.56 | 5.83 | 5.2 | 6.8 |
| 15b | OBz | 4.37 | 5.58 | 5.89 | 5.2 | 6.8 |
| 16b | Br | 4.33 | 5.42 | 5.81 | 5.0 | 5.9 |
| (B) Spiroacetal motif (R)-7 and X equatorial | | | | | | |
| 18 | OMe | 4.64 | 6.02 | 5.91 | 5.2 | 6.8 |
| 19 | OiPr | 4.66 | 5.97 | 5.84 | 5.1 | 6.0 |
| 20 | OC6H11 | 4.69 | 5.97 | 5.85 | 5.1 | 5.6 |
| 21 | OChol | 4.70 | 5.93 | 5.82 | 4.3 | 5.4 |
| (C) Spiroacetal motif (S)-7 and X axial | | | | | | |
| 25 | OBz | 4.62 | 5.51 | 5.76 | 4.4 | 0.4 |

The complete data are listed in the Experimental Part and in Cuny et al. The n. d. indicates not determined, due to the overlap of the shifts of 3H and 4H. Overlap with the shift of 7Ha.

The examination of the acid catalyzed ring contraction of the pyranodioxane 22 revealed that in the presence of benzoic acid anhydride, not only the required 25 was formed but also the undesired open-chain side product 26. Protonated starting material 22 and structures 23 and 24 are intermediates on the reaction path to 25. The starting material 22 is readily obtainable from β-glucose-derived ulosyl bromide 10a.

![Scheme 2](image)

**Figure 3.** Molecular geometry and 1H-1H coupling constants of the hexaacetate of di-α-fructofuranosyl-β-d-fructofuranose 27 with carbohydrate numbering as published by Lemieux and Nagarajan. For a better understanding, the underlying 1,6,9-triaspiro[4.5]decane motifs (R)-7 and (S)-7, with chair conformation and IUPAC numbering, are also given.
derivatives in Table 1 correspond to $J_{4,5}, J_{6,7}$ and $J_{3,9}, J_{5,6}$ of 27. The values of the coupling constants demonstrate also that the compounds 14–21 with framework (R)-7 possess a (E)-envelope conformation in solution, whilst this is (E'-E)-configuration 27.

Due to the large geminal and axial coupling constants, 7Hₐ and 8Hₐ possess broad ddd-shifts whereas 7Hₑ and 8Hₑ are characterized by narrow pdd-shifts, because only one large geminal coupling constant is found.

7Hₑ and 8Hₑ could be further differentiated on the basis of the strong downfield shift for 8Hₑ (4.45–4.54 ppm vs 4.12–4.33 for 7Hₑ) in compounds with an axial substituent at C-10 (A and C in Table 2). Responsible for this extensive effect is the 1,3-diaxial interaction of the electronegative substituent X at C-10 with 8Hₑ.

The determination of 8Hₑ in compounds possessing an equatorial substituent X at C-10 was substantiated by the observed NOE interactions of 10 H → 8 Hₑ (B in Table 2).

### 1,4-Dioxane Portion

The chemical shifts of the ring protons in the dioxane portion are listed in Table 2. Their axial/equatorial orientation could be easily distinguished by the width of their chemical shifts.

Due to the large geminal and axial coupling constants, 7Hₐ and 8Hₐ possess broad ddd-shifts whereas 7Hₑ and 8Hₑ are characterized by narrow pdd-shifts, because only one large geminal coupling constant is found.

7Hₑ and 8Hₑ could be further differentiated on the basis of the strong downfield shift for 8Hₑ (4.45–4.54 ppm vs 4.12–4.33 for 7Hₑ) in compounds with an axial substituent at C-10 (A and C in Table 2). Responsible for this extensive effect is the 1,3-diaxial interaction of the electronegative substituent X at C-10 with 8Hₑ.

The determination of 8Hₑ in compounds possessing an equatorial substituent X at C-10 was substantiated by the observed NOE interactions of 10 H → 8 Hₑ (B in Table 2).

### Table 2. Selected Proton Chemical Shifts of 1,6,9-Trioxaspiro[4.5]decanes in the 1,4-Dioxane Portion with Either (R)- or (S)-Configuration (300 MHz in CDCl₃, δ in ppm)

| Comp. | X | 7Hₐ | 7Hₑ | 8Hₐ | 8Hₑ | 10H |
|-------|---|-----|-----|-----|-----|-----|
| (A) Spiroacetal motif (R)-7 and X axial | | | | | | |
| 14a⁵⁸ | OAc | 4.12 | 3.55 | 4.46 | 3.67 | 5.99 |
| 15a⁵⁸ | OBz | 4.23 | 3.61 | 4.49 | 3.75 | 6.23 |
| 16a⁵⁸ | Br | 4.30 | 3.67 | 4.45 | 3.76 | 6.28 |
| 14b | OAc | 4.14 | 3.59 | 4.46 | 3.74 | 5.93 |
| 15b | OBz | 4.24 | 3.64 | 4.54 | 3.81 | 6.20 |
| 16b | Br | 4.33⁵ | 3.70 | 4.50 | 3.83 | 6.23 |
| (B) Spiroacetal motif (R)-7 and X equatorial | | | | | | |
| 18 | OMe | 4.19 | 3.46 | 3.82 | 3.88 | 6.44 |
| 19 | OPr | 4.18 | 3.46 | 3.83 | 3.83 | 4.81 |
| 20 | OCH₂H₁₁ | 4.19 | 3.46 | 3.83 | 3.83 | 4.89 |
| 21 | OChol | 4.17 | 3.45 | 3.83 | 3.83 | 4.86 |
| (C) Spiroacetal motif (S)-7 and X axial | | | | | | |
| 25⁵⁸ | OBz | 4.27 | 3.69 | 4.45 | 3.78 | 6.38 |

⁵The multiplicity of the shifts and the coupling constants are listed in the section Experimental and in Cuny et al.⁵⁸
⁶Overlap with the shifts of 2H₁.

### 13C NMR Spectral Data

The ¹³C NMR spectral data of the synthesized 1,6,9-trioxaspiro[4.5]decanes are listed in Table 3. For each of these compounds, the values of the chemical shifts correlate well. As expected, notable differences are found for the carbon atom C-10, because it possesses different substituents. Thus, the values for the chemical shifts for 14a, 14b, 15a, 15b, 25 (R = OAcyl) are around δ = 89 ppm, for 16a, 16b (R = Br) around δ = 87 ppm and for 18, 19, 20, 21 (R = Oalkyl) around δ = 98 ppm. The axial or equatorial orientation of the substituent at C-10 could also be determined from the chemical shift of the dioxane carbon C-8. Compounds with an axial orientation (A and C) possess values around 60 ppm, whereas their equatorial counterparts (C) have all the same values of 65.2 ppm.

### Concluding Remarks

The 1,6-dioxaspiro[4.5]decanes 1,2- and 3,4- are essential for biological activity and found in nature in the aggregation pheromone 1, the antibiotic (+)-monensin A 2, the antitumoriferous agent (−)-berkelic acid 3, the antimitotic agent spirastrellolide.

### Table 3. Selected ¹³C Nuclear Magnetic Resonance Data of 1,6,9-Trioxaspiro[4.5]decanes (75.5 MHz in CDCl₃, δ in ppm)

| Comp. | C-2 | C-3 | C-4 | C-5 | C-7 | C-8 | C-10 | C-2' |
|-------|-----|-----|-----|-----|-----|-----|------|------|
| (A) Spiroacetal motif (R)-7 and X axial | | | | | | | | |
| 14a⁵⁸ | 79.0 | 77.1 | 75.5 | 98.6 | 59.1 | 60.0 | 89.5 | 65.1 |
| 15a⁵⁸ | 79.1 | 77.1 | 75.5 | 99.1 | 59.4 | 60.1 | 89.9 | 65.2 |
| 16a | 78.7 | 77.1 | 76.6 | 99.3 | 60.2 | 60.4 | 86.3 | 64.8 |
| 14b | 78.2 | 81.7 | 76.0 | 98.7 | 59.8 | 59.3 | 89.6 | 21.3 |
| 15b | 78.3 | 81.9 | 76.0 | 99.0 | 59.5 | 60.0 | 90.1 | 21.3 |
| 16b | 78.6 | 82.2 | 77.5 | 100.2 | 60.7 | 60.0 | 87.1 | 21.1 |
| (B) Spiroacetal motif (R)-7 and X equatorial | | | | | | | | |
| 18 | 79.3 | 76.7 | 76.2 | 100.9 | 60.2 | 65.2 | 99.4 | 64.9 |
| 19 | 79.4 | 77.4 | 76.6 | 101.3 | 60.3 | 65.2 | 97.6 | 64.7 |
| 20 | 81.1 | 76.7 | 77.5 | 101.3 | 60.3 | 65.2 | 97.2 | 64.6 |
| 21 | 79.6 | 77.6 | 76.6 | 101.4 | 60.3 | 65.2 | 97.4 | 64.6 |
| (C) Spiroacetal motif (S)-7 and X axial | | | | | | | | |
| 25⁵⁸ | 82.1 | 78.6 | 81.1 | 102.8 | 59.6 | 59.5 | 88.2 | 63.5 |

⁵The complete data are listed in the section Experimental and in Cuny et al.⁵⁸
F (characterized after methylation as (+)-methyl ester 4), and the toxin (−)-calyculin A 5. We developed an efficient and stereocontrolled preparation of oxo analogs of these motifs with either (R)- or (S)-configuration and 1,6,9-tri-oxaspiro[4.5]decane framework.\(^5\) In view of structure–activity relationship studies, here we describe additional spiroacetals that resemble the natural products even more than previously published spiroacetal structures. These novel compounds possess a methyl instead of a benzoyloxymethyl group in the 5-membered furan moiety.

The 6-deoxy-pyranodioxane 11b was obtained in 95% yield by starting from the β-glucose derived 6-deoxy-ulosyl bromide 10b and ethylene glycol. Further reaction with acetic acid anhydride or benzoic acid anhydride in the presence of perchloric acid (70%) gave the spiro[4.5]ketal 14b and 15b in 94% and 77% yield, respectively. Diastereomers were not detectable, showing that the ring contraction takes place in a stereospecific manner. Subsequent bromination of 15b yielded the halide 16b, which could be radically dehalogenated to 17b. Glycosylation of 16a with methanol, isopropanol, cyclohexanol, and cholesterol afforded the corresponding derivatives 18, 19, 20, and 21, each in over 80% yield.

The synthesized compounds possess the (5R)-1,6,9-tri-oxaspiro[4.5]decane framework (R)-7, which corresponds to structure (S)-6, the spiroacetal motif of (−)-berkelic acid 3, (+)-spirastrellolide F methyl ester 4, (−)-calyculin A 5, and in particular, the Paravespula pheromone 1.

The synthesis of the (5S)-1,6,9-trioxaspiro[4.5]decanes with opposite chirality is also possible.\(^1\) To further clarify the reaction process, we studied the formation of the (5S)-1,6,9-trioxaspiro[4.5]decane 25, too. The reaction of the pyranodioxane 22 with benzoic acid anhydride in the presence of perchloric acid revealed that apart from 25 (in 61% yield) the open-chain side product 26 was also formed (30%). Respectable for the generation of 26 is the low stability of the starting acetal 22 in the acidic reaction media. Both compounds, 25 and 26, could be characterized after separation. The key product, the (5S)-1,6,9-trioxaspiro[4.5]decane 25, possesses the spiroacetal motif of the oxo analogs of the antibiotic (+)-monensin A 2.

The \(^1\)H and \(^13\)C NMR data of 1,6,9-trioxaspiro[4.5]decanes that are published and described herein are summarized in Tables 1–3. On the basis of these data, together with a X-ray analysis of compound 15a,\(^8\) their configuration and conformation could be resolved. The chemical shifts of the above spiroacetals are of the same order of magnitude for the appropriate ring protons in the tetrahydrofuran portion. Only 3H of the (5S)-diastereomer 25 has a pronounced high-field shift of 0.43 ppm (see Table 1). This effect is caused by the loss of the 1,3-diaxial interaction of 3H with the dioxane oxygen O-6. The observed coupling constants of all 1,6,9-trioxaspiro[4.5]decane derivatives (see Table 1) correlate well with those of the hexaacetate of di-D-fructose anhydride 27. In this molecule, both the (SR)- and the (5R)-1,6,9-trioxaspiro[4.5]decane entity are realized. In 27 and the other structures described here the configurations of the furan portion are identical. These are a (E)-envelope conformation for all (5R)-configured compounds 15-21 and a (Z)-envelope conformation for the (5S) representative 25.

The axial or equatorial arrangement of the substituent at C-10 could be established from the chemical shift value of the 8H\(_a\) dioxane proton, which is 4.45-4.50 ppm for an axial arrangement and 3.82-3.84 ppm for an equatorial configuration (see Table 2). The influence of the C-10 substituent on the values of the chemical shifts of the tetrahydrofuran ring protons is not significant because it is relatively far away.

The synthesized 1,6,9-trioxaspiro[4.5]decane motifs 14b, 15b, 16b, 17b, 18, 19, 20, and 21 are new and unique, and their altered chemical properties make them promising lead structures for pharmacological evaluation. Bioactivity and cytotoxicity tests would be logical first steps toward uncovering the pharmacological and medical potential of these compounds, in particular, with respect to cancer treatment.

**Experimental**

TLC was performed on POLYGRAM SILG/UV\(_{254}\) (Macherey Nagel & Co.). Preparative chromatographic separations were carried out on columns with Merck silica gel 60 (15–40 µm) and Merck precoated silicagel plates 60 F\(_{254}\), 20 × 20 cm, 0.25 mm. Melting points (m.p.) were determined on a Bock-Monoskop VS or a Büchi SMP-20 and are uncorrected. Specific optical rotations were determined on a Perkin-Elmer Polarimeter 241 in 1 dm cuvettes at a wavelength of 589 nm. NMR spectra were measured on a Bruker WM 300 spectrometer at 303 K using TMS as an internal reference. The abbreviation of the multiplicities of the shifts is indicated as s for singlet, d for doublet, t for triplet, q for quartet, sext for sextet, oct for octet, m for multiplet, br for broad, and p for pseudo. Mass spectra were run on a MAT 311 mass spectrometer (Varian). Elemental analyses were performed on a Perkin Elmer 240 Elementar Analyser.

\((−)-(4R,6R,7R,8S,8aS)-7,8-Bis-Benzoyloxy-6-Methyl-8a-Hydroxy-1,4,5-Trioxa-Cis-Decaline (11b)\)

A mixture of silver carbonate (662 mg, 2.40 mmol), ethylene glycol (134 µL, 149 mg, 2.40 mmol) in water-free dichloromethane (25 mL) was stirred in the presence of a freshly annealed molecular sieve 4 Å (2 g) at room temperature for 15 minutes. 6-Deoxy-ulosyl bromide 10b (867 mg, 2.00 mmol) was then added and stirring continued for 1 hour at room temperature in the dark. Filtration through a pad of kieselguhr and evaporation of the filtrate in vacuo gave a crystalline residue of 787 mg (95 %) of 11b with R\(_o\) 0.23 (n-hexane/diethyl ether 1:1). An analytical sample was obtained by flash chromatography on a silica gel column (12 × 2 cm, n-hexane/diethyl ether 10:1 → 1:1) as colorless crystals with m.p. 139°C to 142°C and [α\(_D\)\(_{20}\)] = −80.1 (c = 0.9, CHCl\(_3\)).

C\(_{22}\)H\(_{22}\)O\(_8\) (414.4): calcld. C 63.76, H 5.35; found C 63.85, H 5.25.

MS (FD, 20 mA): m/z = 415 (100%, M + 1).

\(^1\)H NMR (300 MHz, CDCl\(_3\) δ 1.38 (d, 3H, 6-C\(_H\)), 3.57, 4.33 (each 2 H-m, 2H\(_a\), 3H\(_a\)), 3.82 (dq, 1 H, 6 H), 4.71 (s, 1 H, 4a H), 5.12 (d, 1 H, 8 H), 5.29 (s, 1 H, OCH\(_3\)), 5.51 (dd, 1 H, 7 H),
7.2-8.2 (m, 10 H, 2C₆H₅CO). J₆,CH₃ = 6.1, J₆,7 = 9.8, J₇,8 = 9.7 Hz.

1³C NMR (75.5 MHz, CDCl₃) δ 17.5 (CH₃), 59.1, 59.3 (C-2, C-3), 70.0 (C-6), 72.2 (C-7), 72.5 (C-8), 81.1 (C-8a), 95.2 (C-4b), 128.3-134.8 (2 C₆H₅), 165.5, 168.6 (2 C₂H₅CO).

**Diastereomeric mixture of (−)-(2R, 3R, 4S, 5S, 10R, S)-3,4-Bis-Benzoyloxy-2-Benzoyloxymethyl-10-Hydroxy-1,6,9-Trioxaspiro[4.5]decane (10R, S) (13a)**

Aqueous perchloric acid (70 %, 0.8 mL, 9.3 mmol) was added to a stirred solution of the 1,4,5-trioxaspiro-5-decaline 11a (1.07 g, 20 mmol) in dichloromethane (20 mL) with a syringe at 0°C. The mixture was removed from the ice bath and stirred at room temperature.

Monitoring of the reaction (TLC) revealed that no appreciable conversion occurred. By refluxing the mixture (40°C), a continuous conversion of 11a into 13a took place. After a reaction time of 2 H a 3:1 equilibrium of products was established. By refluxing the mixture (40°C), 11a with dichloromethane (100 mL) and washed consecutively with water (2 × 50 mL), saturated NaHCO₃ solution (2 × 50 mL), and water (2 × 50 mL). Drying (Na₂SO₄) and evaporation to dryness in vacuo left a syrup which was purified by flash chromatography on a silica gel column (5 × 5 cm, n-hexane/diethyl ether 1:1). This procedure yielded 6.2 g (94%) of chromatographic uniform 14b (Rf 0.75, tolune/ethanol acetate 4:1) as a colorless syrup which spontaneous crystallized and could be used without additional purification for subsequent reactions.

Analytical pure material was obtained by treating with diethyl ether and had m.p. 162°C to 164°C. For all other shifts see Table 3.

**C₂₉H₂₆O₉ (518.5): calcd. C 67.17, H 5.05; found C 67.25, H 5.29.**

MS (FD, 20 mA): m/ξ = 456 (100%, M⁺).

1⁵H NMR (300 MHz, CDCl₃) δ 1.65 (d, 3 H, 2-CH₃), 1.86 (s, 3 H, CH₃CO), 3.59 (dd, 1 H, 7 H, 8 H), 3.74 (dd, 1 H, 8 H, 9 H), 4.14 (dd, 1 H, 7 H), 4.34 (psx, 1 H, 2 H), 4.46 (dd, 1 H, 8 H), 4.73 (dd, 1 H, 8 H, 9 H), 5.56 (dd, 1 H, 3 H), 5.83 (d, 1 H, 4 H), 5.93 (s, 1 H, 10 H), 7.15-7.3 (m, 2 H, CH₃CO); J₃,4 = 3.5, J₄,5 = 4.4, J₅,6 = 1.1, CHCl₃).

C₂₉H₂₆O₉ (456.0): calcd. C 63.15, H 4.90; found C 63.20, H 5.02.

MS (FD, 20 mA): m/ξ = 533 (25 %, M⁺ - 1), 412 (100%, M⁺ - C₂H₅COOH).

Main (10S)-13a determined from the mixture:

1⁵H NMR (300 MHz, CDCl₃) δ 3.47 (dd, 1 H, 7 H, 8 H), 3.84 (m, 2 H, 7 H, 8 H), 4.10 (m, 1 H, 8 H), 4.66 (m, 2 H, 2 H, 2' H), 7.47 (m, 1 H, 2' H), 5.50 (s, 1 H, 10 H, after treatment with D₂O), 5.01 (br s, 1 H, O), 5.91 (d, 1 H, 4 H), 5.97 (dd, 1 H, 3 H); J₂,3 = 4.6, J₃,₄ = 5.9, J₆,₂₈ = 11.8, J₇,₈,₉ = 2.1 Hz, all other shifts are overlapped.

1³C NMR (75.5 MHz, CDCl₃) δ 60.1 (C-2, CH₃O), 64.7 (CH₂OBe), 65.3 (C-8), 76.3 (C-4), 77.5 (C-3), 80.1 (C-2), 91.8 (C-10), 102.0 (C-5), 128.0-134.0 (3 C₆H₅CO), 165.6, 165.8, 166.2 (3 C₂H₅CO).

Minor (10R)-13a determined from the mixture:

1⁵H NMR (300 MHz, CDCl₃) δ 3.47 (dd, 1 H, 7 H, 8 H), 3.77 (m, 2 H, 7 H, 8 H), 4.01 (m, 1 H, 8 H), 4.70 (m, 2 H, 2 H, 2' H), 7.29 (m, 1 H, 2' H), 4.99 (s, 1 H, 10 H, after treatment with D₂O), 5.04 (br s, 1 H, O), 5.83 (d, 1 H, 4 H), 5.89 (dd, 1 H, 3 H); J₂,₃ = 3.9, J₃,₄ = 5.1 Hz, all other shifts are overlapped.

1³C NMR (75.5 MHz, CDCl₃) δ 57.2 (C-8), 61.0 (C-7), 64.7 (CH₂OBe), 77.5 (C-4), 77.8 (C-3), 79.7 (C-2), 91.5 (C-10), 100.8 (C-5), 128.0-134.0 (3 C₆H₅CO), 165.6, 165.8, 166.2 (3 C₂H₅CO).

**C₂₉H₂₆O₉ (518.5): calcd. C 67.17, H 4.90; found C 67.25, H 5.12.**

MS (FD, 20 mA): m/ξ = 518 (100%, M⁺).
1H NMR (300 MHz, CDCl3) δ: 1.68 (d, 3 H, 2-CH3), 3.64 (pdd, 1 H, 7 H), 3.81 (pdd, 1 H, 8 H), 4.24 (dd, 1 H, 7 H), 4.37 (pdx, 1 H, 2 H), 4.54 (dd, 1 H, 8 H), 5.58 (dd, 1 H, 3 H), 5.89 (d, 1 H, 4 H), 6.20 (s, 1 H, 10 H), 6.9-8.2 (m, 15 H, 3 C6H5CO); J1,2Me = 6.5, J7a,8 = 5.2, J9,10 = 6.8, Jgem = 11.7, J7a,8 = 12.2, J7a,8 = 2.8, Jgem = 2.7, J7,8 = 0, J8gem = 11.6 Hz.

13C NMR (75.5 MHz, CDCl3) δ: 164.5, 164.8, 166.1 (3 C6H5CO). For all other shifts see Table 3.

(−)-(2R,3R,4S,5S,10S)-3,4-Bis-Benzoyl oxy-2-Benzoyloxymethyl-10-Bromo-1,6,9-Trioxaspiro[4.5]decane (16a)

Preparation, physical and spectral data see Cuny et al.58

13C NMR (75.5 MHz, CDCl3) δ: 124.2-144.2 (3 C6H5CO); 1H NMR (300 MHz, CDCl3) δ: 1.68 (d, 3 H, 2-CH3), 3.46 (pdd, 1 H, 7 H), 3.68 (pdd, 1 H, 8 H), 4.33 (m, 2 H, 2 H and 7 H), 4.50 (dd, 1 H, 8 H), 5.42 (dd, 1 H, 3 H), 5.81 (d, 1 H, 4 H), 6.23 (s, 1 H, 10 H), 7.3-8.2 (m, 10 H, 2 C6H5CO); J1,2Me = 6.5, J7a,8 = 5.0, J7,8 = 5.9, Jgem = 11.7, J7a,8 = 12.2, J7a,8 = 3.1, Jgem = 2.9, Jgem = 0, Jgem = 11.5 Hz.

C32H24O10 (548.5): calcd. C 65.69, H 5.15; found C 65.48, H 5.06.

MS (FD, 20 mA): m/z = 548 (100 %, M+).

1H NMR (300 MHz, CDCl3) δ: 3.46 (pdd, 1 H, 7 H), 3.68 (s, 3 H, OCH3), 3.82 (dd, 1 H, 8 H), 3.88 (pdd, 1 H, 8 H), 4.19 (dd, 1 H, 7 H), 4.68 (s, 1 H, 10 H and m, 1 H, 2 H), 4.65 (dd, 1 H, Hα of CH2OBz), 4.77 (dd, 1 H, Hα of CH2OBz), 5.91 (d, 1 H, 4 H), 6.02 (dd, 1 H, 3 H), 7.3-8.2 (m, 15 H, 3 C6H5CO); J1,2Ha = 5.4, J2,3HB = 6.3, J11a,11b = 13.6, J2,3J5,6 = 5.2, J5,6 = 4.8, J5,6 = 11.6, J7a,8 = 11.4, J7a,8 = 3.5, J7,8J8,9 = 2.3, J7,8J8,9 = 0, J8gem = 11.8 Hz.

NOE interactions 10 H (4.64) → OCH3 (3.68), 8 Hα (3.82) and 4 H (5.91 ppm).

C39H38B6O14 (757.5): calcd. C 67.82, H 5.05; found C 67.95, H 4.85.

Bromide 16a (120 mg, 0.20 mmol) was dissolved in anhydrous methanol (10 mL) followed by the addition of silver carbonate (55 mg, 0.23 mmol) and freshly dried molecular sieve 4 Å (1 g).

After the mixture was stirred for 20 minutes at room temperature and under the absence of light, the silver salts were removed by filtration through a pad of kieselguhr and the filtrate evaporated with dichloromethane. The eluate was evaporated under vacuum to yield 101 mg (92%) of 18 as a syrup with Rf 0.49 (n-hexane/diethyl ether 1:1). An analytical sample was obtained by chromatography on a silica gel column (15 × 2 cm, diethyl ether/n-hexane 2:1) and had [α]D20 = −50.3 (c = 0.9, CHCl3).

C30H28O10 (548.5): calcd. C 65.69, H 5.15; found C 65.48, H 5.06.

Bromide 16a (140 mg, 0.23 mmol) was dissolved in anhydrous isopropanol (10 mL) followed by the addition of silver carbonate (63 mg, 0.23 mmol) and freshly dried molecular sieve 4 Å (1 g) and gave 244 mg (75%) of 16b, the identical product as described above in (A).

(−)-(2R,3R,4S,5R)-3,4-Bis-Benzoyloxy-2-Methyl-1,6,9-Trioxaspiro[4.5]decane (17b)

Azobisobutyronitrile (AIBN) (25 mg, 0.15 mmol) and tributyltin hydride (350 µL, 1.33 mmol) were successively added to a solution of bromide 16b (195 mg, 0.41 mmol) in toluene (25 mL). The mixture was stirred and refluxed in a nitrogen atmosphere for 0.5 hours. The reaction solution was diluted with acetonitrile (200 mL), washed with n-hexane (3 × 50 mL) and concentrated in vacuo. The remaining syrup of 125 mg (77%) of 17b had Rf 0.34 (n-hexane/diethyl ether 1:1) and after flash column chromatography on silica gel (n-hexane/diethyl ether 1:1) [α]D20 = −108.7 (c = 1.3, CHCl3).

MS (FD, 20 mA): m/z = 398 (80 %, M+), 397 (100 %, M+ - 1).

1H NMR (300 MHz, CDCl3) δ: 1.64 (d, 3 H, 2-CH3), 3.60-3.80 (m, 3 H, 7 Hα 8 Hα and 8 Hβ), 3.79 (d, 1 H, 10 H), 3.85 (d, 1 H, 10-H), 4.20-4.40 (m, 2 H, 2 H and 7 H), 5.50 (d, 1 H, 4 H), 5.65 (dd, 1 H, 3 H), 7.3-8.2 (m, 10 H, 2 C6H5CO); J1,2Me = 6.5, J2,3 = 4.8, Jgem = 6.3, Jgem = 11.8 Hz.

Spectroscopic data see Table 3.
After the mixture was stirred for 3 hours at room temperature under the absence of light, the silver salts were removed by filtration through a pad of kieselguhr and the filter rewashed with dichloromethane. The filtrate was evaporated under vacuum to yield 118 mg (89%) of \(\text{C}_{35}\text{H}_{36}\text{O}_{10}\) as a syrup with \(m/z = 576\) (100% \(M^+\)).

\[\begin{align*}
\text{MS (FD, 20 mA; m/z = 576 (100 \%), M^+).}
\end{align*}\]

\[\begin{align*}
\text{Cyclohexanol (170 mg, 1.67 mmol) was dissolved in anhydrous dichloromethane (50 mL) followed by the addition of silver carbonate (138 mg, 0.50 mmol) and freshly dried molecular sieve 4 Å (2 g). After the mixture was stirred for 15 minutes at room temperature under the absence of light, bromide 16a (299 mg, 0.50 mmol) was added in 1 portion and the mixture heated at reflux for 45 minutes under the exclusion of moisture. The silver salts were removed by filtration through a pad of kieselguhr and the filter rewashed with dichloromethane. The filtrate was evaporated under vacuum to yield 387 mg (86%) of 21 as colorless crystals with \(R_f = 0.79\) (toluene/ethyl acetate 8:1), melting point 135°C to 136°C and \([\alpha]_{D}^{20} = +20.2 (c = 0.9, \text{CHCl}_3)\).
\end{align*}\]

\[\begin{align*}
\text{C}_{35}\text{H}_{36}\text{O}_{10} \text{ (905.2): calcd. C 74.31, H 8.02; found C 73.84, H 7.96.}
\end{align*}\]

\[\begin{align*}
\text{MS (FD, 20 mA; m/z = 904 (100 \%), M^+ - 1).}
\end{align*}\]

\[\begin{align*}
\text{1H NMR (300 MHz, CDCl}_3\text{): 1,6,9-trioxaspiro[4.5]decane \text{ portion: } \delta = 3.45 (\text{pdd, 1 H, H}_3, 3.83 (\text{m, 2 H, H}_8, \text{and H}_{14}), 4.17 (\text{m, 1 H, H}_7), 4.70 (\text{m, 3 H, H}_1, \text{H}_4, \text{and H}_5, \text{of CH}_3\text{OBz}), 4.86 (\text{s, 1 H, H}_1, 10\text{ H}), 5.82 (\text{d, 1 H, H}_4), 5.93 (\text{dd, 1 H, H}_3, 7.2–8.2 (\text{m, 15 H, 3 C}_6\text{H}_5\text{CO}), J_{2,3} = 4.3, J_{3,4} = 5.4 \text{ Hz, all other shifts are overlapped.}}
\end{align*}\]

Main shifts of cholestane portion: \(\delta = 0.65 (\text{s, 3 H, H}_3), 0.76 (\text{s, 3 H, H}_3), 0.86 (2\text{H-d, 26 H}_3 \text{ and 27 H}_3), 0.90 (\text{d, 3 H, 21 H}_3), 3.73 (\text{m, 1 H, 3 H}), J_{20,21} = 6.5, J_{25,26} = 6.6, J_{25,27} = 6.6 \text{ Hz.}
\]

\[\begin{align*}
\text{13C NMR (75.5 MHz, CDCl}_3\text{): cyclohexyl CH}_2: \delta = 21.2 (C-18), 26.0, 23.8, 25.5, 24.1, 25.5, 23.8, 26.0, 25.5, 24.1, 21.2 (C-18), 22.6 (C-21), 22.8 (C-22), 28.0, 28.3, 29.7, 31.2, 36.2, 36.9, 39.5, 40.0; steroid CH: 28.0, 35.5, 35.8, 44.9, 54.3, 56.3, 56.5, 79.4; steroid C: 35.5, 42.6, 128.0–134.0 (3 C}_6\text{H}_5\text{CO), 2 × 165.8, 166.2 (3 C}_6\text{H}_5\text{CO). For all other shifts see Table 3.}
\end{align*}\]

\[\begin{align*}
\text{C}_{35}\text{H}_{36}\text{O}_{10} \text{ (905.2): calcd. C 74.31, H 8.02; found C 73.84, H 7.96.}
\end{align*}\]
The remaining residue was filtered through a silica gel column (15 x 2 cm, n-hexane/diethyl ether 3:1) to remove excessive benzoic acid anhydride and polar impurities. The eluate was concentrated in vacuo and the remaining colorless syrup, containing \textit{25} and \textit{26}, was chromatographically separated on a silica gel column (15 x 2 cm, \textit{25} and \textit{26}). The eluate with [\(\alpha\)]\textsubscript{D}\textadd{20} = +43.2 (\(c = 0.8\), CHCl\textsubscript{3}) and with identical physical data as published in Cuny et al. \textit{38}

The fraction with [\(\alpha\)]\textsubscript{D}\textadd{20} = 0.9, CHCl\textsubscript{3}. afforded 107 mg (30%) of colorless amorphous solid with identical physical data as published in Cuny et al. \textit{58}

\begin{align*}
\text{[\(\alpha\)]\textsubscript{D}\textadd{20}} & = +43.2 \quad (c = 0.8, \text{CHCl}_3) \quad \text{and with identical physical data as published in Cuny et al.} \textit{38}.
\end{align*}

The fraction with [\(\alpha\)]\textsubscript{D}\textadd{20} = 0.9, CHCl\textsubscript{3}. afforded 107 mg (30%) of colorless amorphous solid with identical physical data as published in Cuny et al. \textit{58}

\begin{align*}
\text{[\(\alpha\)]\textsubscript{D}\textadd{20}} & = +43.2 \quad (c = 0.8, \text{CHCl}_3) \quad \text{and with identical physical data as published in Cuny et al.} \textit{38}.
\end{align*}

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\textbf{ORCID ID}

Eckehard Cuny \(\text{https://orcid.org/0000-0003-2077-9536}\)

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