

Article

Double Intramolecular Transacetalization of Polyhydroxy Acetals: Synthesis of Conformationally-Restricted 1,3-Dioxanes with Axially-Oriented Phenyl Moiety

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Abstract: The synthesis of conformationally-restricted 1,3-dioxanes with a phenyl moiety fixed in an axial orientation at the acetalic center is described. Starting with diethyl 3-hydroxyglutarate (**15**), benzaldehyde acetal **12a** and acetophenone ketal **12b** bearing a protected 1,3,5-trihydroxypentyl side chain in the *o*-position were prepared. The first acid-catalyzed intramolecular transacetalization gave a mixture of diastereomeric 2-benzofurans **18** (ratio of diastereomers 2:2:1:1). After OH group deprotection, the second intramolecular transacetalization afforded tricyclic alcohol **14a** (2-(1,5-epoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl)ethan-1-ol). Analogous cyclizations led to the corresponding silyl ether **22a** (19%) and azide **23a** (13%). Whereas tricyclic alcohol **14a** was obtained as a 1:1 mixture of diastereomers, the silyl ether **22a** and the azide **23a** afforded only one diastereomer. This observation indicates a faster cyclization of the minor diastereomers providing the thermodynamically-favored compounds with equatorially-oriented substituents in the 3-position of the tricyclic 1,5-epoxy-2-benzoxepine system. In general, acetophenone-derived ketalic compounds (**b**-series) required very mild reaction conditions and gave lower yields than the corresponding acetalic compounds (**a**-series).

Keywords: double intramolecular transacetalization; polyhydroxy acetals; conformationally-restricted 1,3-dioxanes; axially-oriented phenyl moiety; tricyclic alcohols; 1,5-epoxy-2-benzoxepines

1. Introduction

Heterocycles with two *O*-atoms in the acetalic position, such as 1,3-dioxoles, 1,3-dioxolanes, and homologous 1,3-dioxanes, are found in several important biologically-active compounds. The 1,3-dioxole ring is present in the natural product galipinine (**1**), found in the roots of *Galipea officinalis*, which is active against some chloroquine-resistant *Plasmodium falciparum* strains [1]. The broad-spectrum antifungal agents ketoconazole (**2**), terconazole (**3**), and itraconazole (**4**) [2–4], contain the 1,3-dioxolane ring. This five-membered heterocycle is also found in dexoadrol (**5**) and etoadrol (**6**), showing analgesic and anesthetic activity due to uncompetitive antagonism at the *N*-methyl-D-aspartate (NMDA) receptor [5–7] (Figure 1).

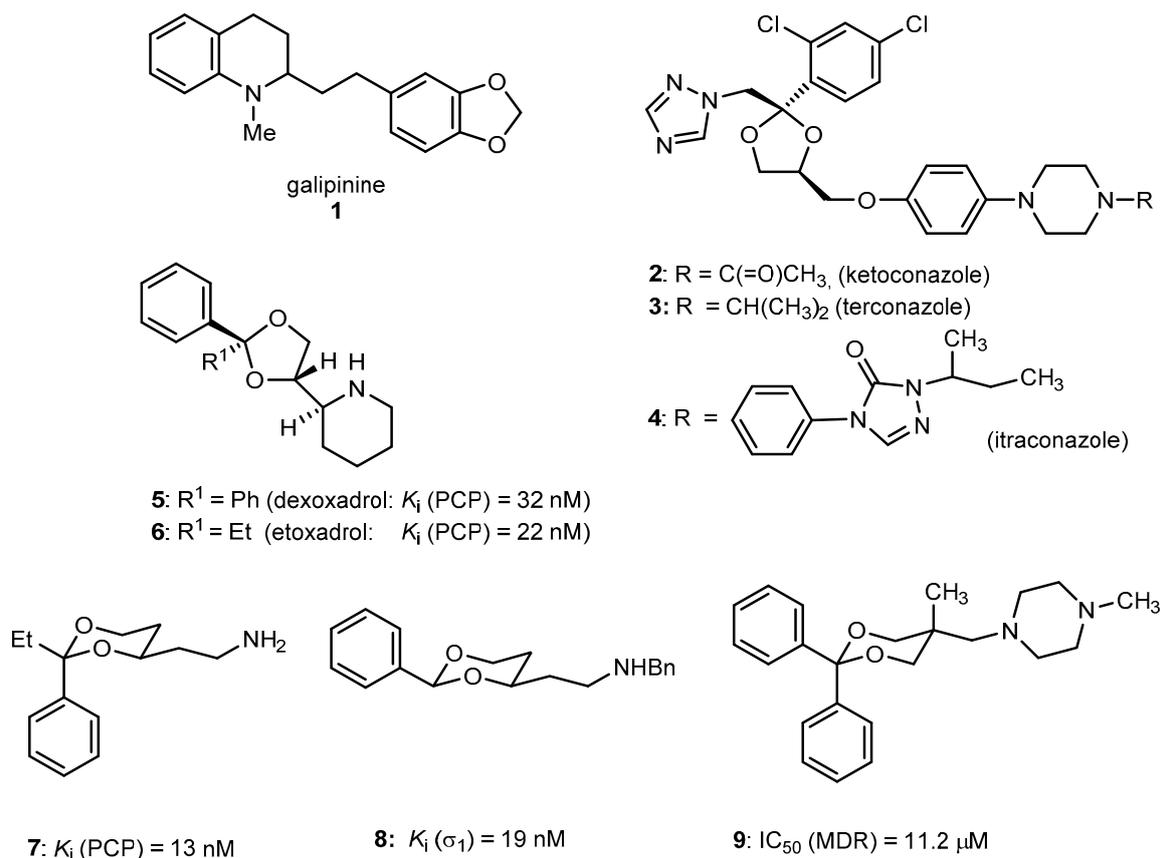


Figure 1. Some biologically-important compounds containing the 1,3-dioxole, 1,3-dioxolane, and 1,3-dioxane scaffold.

Enlargement of the 1,3-dioxolane ring of dexoadrol (5) and etoadrol (6) led to 1,3-dioxanes with high NMDA and σ_1 receptor antagonistic activity. The 1,3-dioxane 7 with an aminoethyl substituent at the 4-position is a potent uncompetitive antagonist at the phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) binding site of the NMDA receptor ($K_i = 13$ nM [6], Figure 1). The PCP affinity of the 1,3-dioxane 7 is even higher than the PCP affinity of the corresponding 1,3-dioxolane derivative [6]. Removal of the ethyl moiety at the acetalic position and the introduction of a benzyl moiety at the N-atom led to 1,3-dioxane 8 with very high σ_1 receptor affinity ($K_i = 19$ nM). Moreover, 1,3-dioxane 8 shows very high analgesic activity in the capsaicin assay [5]. 1,3-Dioxane 9 with substituents at the 5-position in addition to two phenyl moieties at the 2-position, reveals multi-drug resistance (MDR) modulatory properties ($IC_{50} = 11.2$ μM [8]), which are even higher than the MDR modulatory activities of the analogous 1,3-dioxolane with a similar substitution pattern [6,8,9].

A common structural feature of the pharmacologically-active compounds 2–9 shown in Figure 1 is the phenyl moiety at the acetalic position. Structure-activity-relationship (SAR) studies with flexible 1,3-dioxolane- and 1,3-dioxane-based NMDA receptor antagonists led to the hypothesis that one phenyl moiety in an axially perpendicular orientation at the acetalic 2-position of the oxygen heterocycle is required for high NMDA receptor affinity [5,10,11]. 1,3-Dioxane 8 with an equatorially oriented phenyl moiety at the 2-position shows rather low PCP affinity, but rather high σ_1 receptor affinity [5].

In order to obtain insight into the preferred orientation of the phenyl moiety at the 1,3-dioxane ring, conformationally-restricted 1,3-dioxanes of type 14 (Figure 2) were envisaged bearing a phenyl moiety, which is forced to adopt an axial orientation. Herein we report on the synthesis of the tricyclic compounds 14 resulting from the 1,3-dioxanes 7–9 by connecting a phenyl moiety with the carbon atom at the 6-position of the 1,3-dioxane ring. In the tricyclic compounds 14 the phenyl ring is fixed in the axial orientation and, moreover, its rotation along the phenyl-C(acetal) bond is blocked.

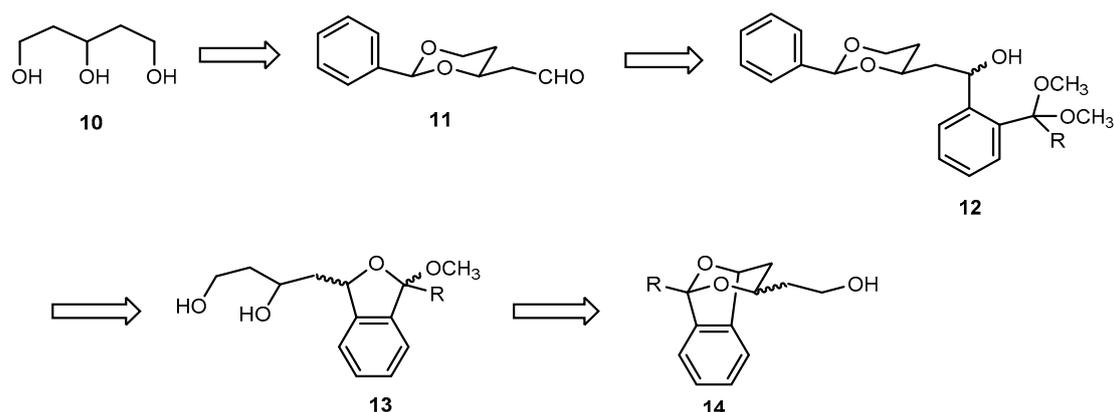
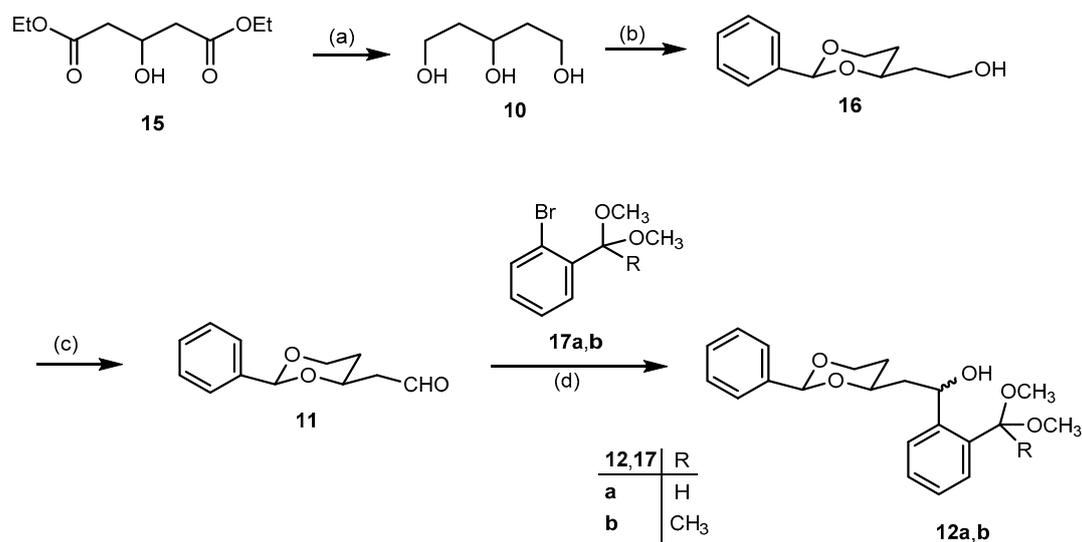


Figure 2. Plan for the synthesis of tricyclic compounds **14**. The phenyl ring of **14** is fixed in the axial position of the 1,3-dioxane ring without any rotational freedom.

2. Synthesis

The plan for the synthesis of tricyclic compounds **14** is based on two subsequent intramolecular transacetalization reactions. At first, aldehyde **11** will be prepared by acetalization of pentane-1,3,5-triol (**10**) with benzaldehyde and subsequent oxidation of the primary alcohol. Reaction of **11** with an arylmetal derivative bearing an acetalic substituent in the *o*-position will provide the secondary alcohols **12** (Scheme 1). Starting from **12**, the first intramolecular transacetalization will establish the benzofuran ring, and the second intramolecular transacetalization after cleavage of the 1,3-dioxane ring (**13**) will afford the tricyclic system **14**.

For the synthesis of pentane-1,3,5-triol (**10**) the diester **15** was reduced with LiAlH_4 . Careful workup resulted in 97% yield of triol **10** [12]. (Scheme 1) Acetalization of benzaldehyde with triol **10** afforded stereoselectively the *cis*-configured 1,3-dioxane **16** in 85% yield [13–15]. Swern oxidation [16] of the primary alcohol **16** with DMSO and oxalyl chloride provided aldehyde **11** in 92% yield [13].

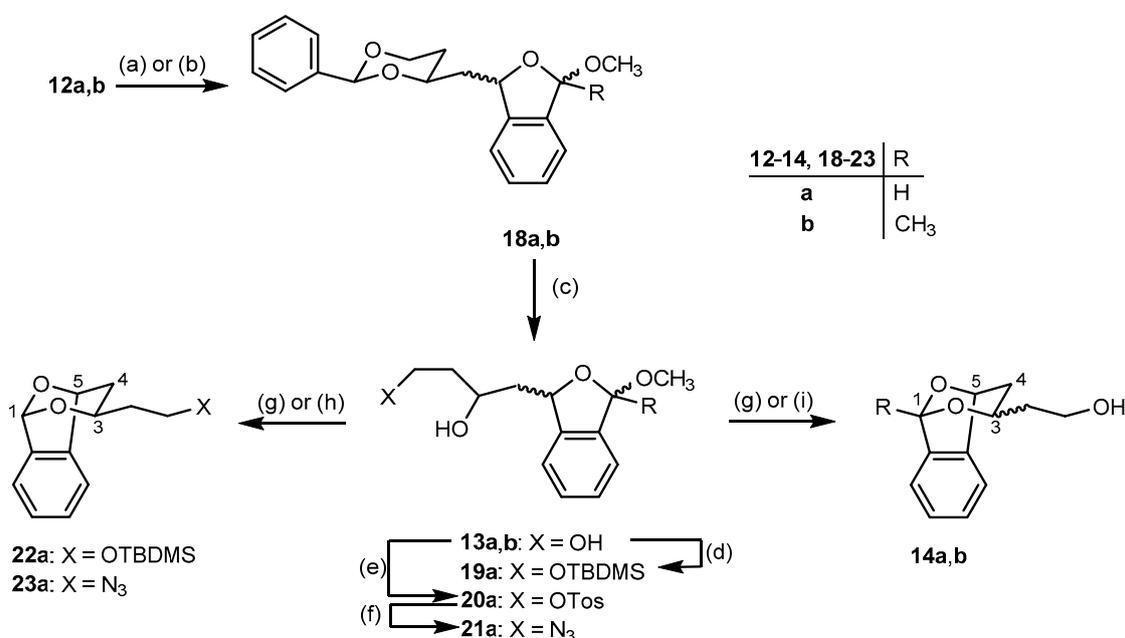


Scheme 1. Synthesis of alcohols **12a,b** as key intermediates for the preparation of conformationally-restricted 1,3-dioxanes. Reagents and reaction conditions: (a) LiAlH_4 , THF, 66 °C, 72 h, 97%; (b) PhCH=O , TosOH, Na_2SO_4 , CH_2Cl_2 , r.t., 24 h, 85%; (c) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78 °C, 92%; (d) *n*-BuLi, THF, -78 °C to r.t., 16 h, 93% (**12a**), 97% (**12b**).

Treatment of aryl bromides **17a,b** [17,18] with *n*-butyllithium at $-78\text{ }^{\circ}\text{C}$ led to the corresponding aryllithium intermediates, which reacted with the aldehyde **11** to give the secondary alcohols **12a,b**. Both alcohols **12a** and **12b** were isolated as a mixture of two diastereomers in the ratio 2:1. The ratio of diastereomeric alcohols **12a** and **12b** was determined by integration of characteristic methyne signals ($\text{PhCH}(\text{dioxane})$, R_2CHOH , $\text{PhCH}(\text{OCH}_3)_2$) in the $^1\text{H-NMR}$ spectra.

The intramolecular transacetalization of **12a** required careful optimization of the reaction conditions in order to avoid the cleavage of the 1,3-dioxane moiety. Various acid catalysts in different solvents (e.g., *p*TosOH in CH_2Cl_2 , AcOH in CH_2Cl_2 , and AcOH in CHCl_3) were investigated. The highest yield of the 2-benzofuran **18a** (89%) was obtained using *p*TosOH in toluene within 2 h at room temperature. However, the concentration of *p*TosOH has to be carefully controlled in order to avoid complete decomposition of the compounds (Scheme 2).

Unexpectedly, treatment of the alcohol **12b** with the optimized reaction conditions for the cyclization of **12a** to **18a** led to decomposition within 45 min. It is assumed that the higher reactivity of the ketal of **12b** (forming a more stable carbenium ion) compared to the acetal **12a** is responsible for this decomposition reaction. Therefore, milder reaction conditions were investigated. Low amounts of *p*TosOH in a 1:1-mixture of cyclohexane and toluene afforded the desired benzofuran **18b** in 71% yield.



Scheme 2. Synthesis of conformationally restricted 1,3 dioxanes **14**, **22** and **23**. Reagents and reaction conditions: (a) *p*TosOH, toluene, r.t., 2 h, 89% (**18a**); (b) *p*TosOH (0.5 mg/mL), toluene/cyclohexane (1:1), r.t., 2 h, 71% (**18b**); (c) *p*TosOH, MeOH/H₂O (4:1), r.t., 36–72 h, 87% (**13a**), 55% (**13b**); (d) ^tBuMe₂SiCl, imidazole, DMF, r.t., 24 h, 58%; (e) *p*TosCl, Bu₂SnO, Et₃N, CH₂Cl₂, 40 °C, 48 h, 51%; (f) NaN₃, DMF, 90 °C, 3 h, 92%; (g) *p*TosOH (0.5 mg/mL), toluene, 85 °C, 72 h, 17% (**14a**), 13% (**23a**); (h) 0.1 M HCl in AcOH (15 μL), toluene (5 mL), 65 °C, 60 h, 19% (**22a**); and (i) toluene/AcOH (4:1), r.t., 72 h, 6% (**14b**). *p*TosOH = *p*-toluenesulfonic acid.

For the second intramolecular transacetalization the benzaldehyde acetal of **18** protecting the hydroxy moieties of the side chain had to be cleaved. Catalytic amounts of *p*-toluenesulfonic acid (*p*TosOH) in a mixture of methanol and water (4:1) led to cleavage of the 1,3-dioxane ring, providing the diols **13a** and **13b** in 87% and 55% yields, respectively. The conversion of benzofuran **18b** with ketalic substructure into diol **13b** was slower and gave lower yields (55%) than the preparation of diol **13a** (87%) from the acetalic benzofuran **18a** (Scheme 2). In general, it was observed that substrates with

a ketalic substructure (**12b**, **18b**) require milder reaction conditions than the corresponding analogues **12a** and **18a** with an acetalic system.

The benzofurans **18a,b**, as well as the diols **13a,b**, were obtained as mixtures of four diastereomers in the ratio 2:2:1:1. The ratio of diastereomers was derived from the relative intensities of the four signals for 1-H of the 2-benzofuran ring.

Although it was expected that the intramolecular transacetalization of diols **13** should easily provide six-membered acetals **14** (1,3-dioxane in the tricyclic scaffold), the synthesis of **14** was rather challenging. Several variations were investigated in order to detect the best reaction conditions. The transformation of **13a** into **14a** was performed in polar and nonpolar solvents (DMF, AcOH, CHCl₃, toluene), with different acids (*p*TosOH, AcOH and HCl in AcOH), at r.t. up to 90 °C for periods between 3 h and 7 d producing **14a** in yields between 10%–46%. However, due to purification problems the yield of pure tricyclic alcohol **14a** (1:1 mixture of diastereomers) did not exceed 17% (*p*TosOH, toluene, 85 °C, 72 h).

As shown for the reactions of ketals **12b** and **18b**, the final cyclization starting with the ketal **13b** required very mild reaction conditions in order to avoid decomposition. Finally, the tricyclic alcohol **14b** was obtained as a 1:1 mixture of diastereomers in 6% yield after stirring the diol **13b** in a toluene/AcOH mixture at r.t. for 72 h.

It was hypothesized that the low yields of the tricyclic alcohols **14a** and **14b** could be due to competition between the secondary and primary alcohol of **13** leading to the desired compounds **14** or compounds with an eight-membered acetalic ring. Therefore, the primary alcohol of **13a** was protected regioselectively with TBDMS-Cl to provide the silyl ether **19a** in 58% yield. Treatment of the silyl ether **19a** with HCl in AcOH led to the tricyclic silyl ether **22a** in 19% yield. Although a mixture of four diastereomers (ratio 2:2:1:1) was employed in this reaction, only one diastereomer of the tricyclic silyl ether was isolated (see discussion of the stereochemistry below). The ¹H-NMR spectrum of the recovered starting material **19a** indicated that the minor diastereomers of the silyl ether **19a** had reacted faster than the major diastereomers.

Next, the primary alcohol of **13a** should be converted into an azide. For this purpose, the diol **13a** was reacted with *p*TosCl in the presence of catalytic amounts of Bu₂SnO [19] in refluxing CH₂Cl₂ to afford, regioselectively, the tosylate **20a** as a mixture of four diastereomers (ratio 2:2:1:1) in 51% yield. Substitution of the tosylate **20a** with NaN₃ led to the azide **21a** in 92% yield (Scheme 2). It was assumed that the intramolecular transacetalization of azide **21a** should result in higher yields than the reaction of diol **13a**, since the competing primary alcohol was no longer present. The conversion of azidoalcohol **21a** into tricyclic azide **23a** was achieved with *p*TosOH in toluene (85 °C). Unexpectedly, only one isomer of **23a** was isolated in 13% yield (see discussion of the stereochemistry below). The ¹H-NMR spectrum of the recovered starting material **21a** showed only signals for the two major diastereomers of **21a**. It was concluded that the minor diastereomers of **21a** reacted faster to form the tricyclic azide **23a** than the major diastereomers. The lower reactivity of the major diastereomers may explain the low yields of the tricyclic azide **23a**.

In order to determine the relative configuration of the diastereomerically-pure silyl ether **22a** and the azide **23a**, the ¹H-NMR signals produced by the protons in the 3-, 4-, and 5-positions were analyzed. In both compounds the axially-oriented proton in the 4-position causes a ddd signal with two large coupling constants of 13 Hz and 11 Hz, and one small coupling constant of 3.7 Hz. The largest coupling constant (13 Hz) belongs to the geminal coupling of 4-H_{ax} with 4-H_{eq}. The small coupling constant reflects the interaction between 4-H_{ax} and the equatorially-oriented 5-H. The remaining coupling constant of 11 Hz can only be explained by an 1,2-diaxial position of adjacent protons. Therefore, the proton in the 3-position has to adopt an axial orientation resulting in equatorial position of the substituted ethyl moiety in the 3-position.

3. Experimental Section

3.1. General

Unless otherwise stated, moisture-sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Similarly, dichloromethane and methanol were distilled from calcium hydride and magnesium methanolate, respectively. For the regulation of temperature below 0 °C a cryostat (EK 90, Thermo Haake, Karlsruhe, Germany) or acetone/dry ice bath (−78 °C) was used. Solvents and liquid reagents were added to the reaction mixture with disposable syringes. Thin layer chromatography (TLC): silica gel 60 F₂₅₄ plates (Merck, Darmstadt, Germany). Flash chromatography (fc): silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, length of column, fraction size, eluent, *R_f* value. IR: IR spectrophotometer IRAffinity with MIRacle 10 accessory FT-ATR-IR (Shimadzu, Duisburg, Germany). ¹H-NMR (400 MHz), ¹³C-NMR (100 MHz): Mercury plus 400 spectrometer (Varian, Willich, Germany); ¹H-NMR (600 MHz), ¹³C-NMR (151 MHz): Agilent Technologies (Waldbronn, Germany) 600/54 premium spectrometer: δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution; ¹H- and ¹³C-NMR spectra are shown in the Supplementary Materials. MS: EI = electron impact, ESI = electro spray ionization: MicroTof (Bruker Daltronics, Bremen, Germany), calibration with sodium formate clusters (ESI) and fatty acid esters (atmospheric pressure chemical ionization (APCI)) before measurement.

3.2. HPLC Method to Determine the Purity of the Compounds

Merck Hitachi equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method A: column: LiChrospher[®] 60 RP-select B (5 μm), 250–4 mm cartridge; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection λ = 210 nm; solvents: A: water with 0.05% (*v/v*) trifluoroacetic acid; B: acetonitrile with 0.05% (*v/v*) trifluoroacetic acid: gradient elution: (A%): 0–4 min: 90%, 4–29 min: gradient from 90% to 0%, 29–31 min: 0%, 31–31.5 min: gradient from 0% to 90%, 31.5–40 min: 90%.

3.3. Synthetic Procedures

Pentane-1,3,5-triol (**10**) [12]. Under N₂ atmosphere and ice cooling (0 °C), diethyl 3-hydroxyglutarate (**15**, 5.31 g, 26 mmol) in dry THF (10 mL) was added dropwise to a suspension of LiAlH₄ (2.43 g, 64 mmol) in dry THF (60 mL). The reaction mixture was heated at 66 °C for 72 h. The excess of LiAlH₄ was quenched with cold water (50 mL) under ice cooling until a completely white precipitate was observed. A solution of H₂SO₄ (1/4 conc.) was added dropwise to the mixture under ice cooling until the precipitate dissolved completely (pH 1). The reaction mixture was then heated to reflux for 12 h and the THF was removed under reduced pressure. The resulting aqueous mixture was alkalinized with NH₃ solution (25%) until a gelatinous precipitate of Al(OH)₃ was observed (pH 10). The precipitate was removed by suction filtration, and the residue was washed with water (3 × 50 mL). The filtrate was concentrated in vacuo, and the residue was heated to reflux in CH₃OH (150 mL) for 4 h. The mixture was then filtered to remove the insoluble Li₂SO₄. The residue was washed with CH₃OH (3 × 50 mL). The combined filtrate was concentrated in vacuo, and the crude product was purified by fc (Ø = 6 cm, h = 15 cm, ethyl acetate:methanol = 9:1, V = 20 mL, *R_f* = 0.21). Colorless oil, yield 2.9 g (97%). C₅H₁₂O₃ (120.1). Exact mass (APCI): *m/z* = 121.0871, calcd. 121.0859 for C₅H₁₂O₃ [MH]⁺. ¹H-NMR (400 MHz, CD₃OD): δ [ppm] = 1.58–1.75 (m, 4H, CH₂CHOHCH₂), 3.69 (t, *J* = 6.5 Hz, 4H, CH₂OH), 3.87 (tt, *J* = 8.4/4.5 Hz, 1H, CHOH). Signals for the OH protons are not observed in the spectrum. ¹³C-NMR (100 MHz (CD₃)₂SO): δ [ppm] = 40.6 (2C, CH₂CHOH), 58.3 (2C, CH₂OH), 65.2 (1C, CHOH). FTIR (neat): ν (cm^{−1}) = 3298 (O-H), 2940, 2886 (C-H), 1042 (C-O).

2-[(2*RS*,4*SR*)-2-Phenyl-1,3-dioxan-4-yl]ethanol (**16**). *p*-Toluenesulfonic acid (50 mg, 0.3 mmol) was added to a solution of pentane-1,3,5-triol (**10**, 0.64 g, 5.3 mmol) and benzaldehyde (1.1 mL, 1.1 g, 11 mmol) in

dry CH_2Cl_2 (25 mL). Then anhydrous Na_2SO_4 (3.80 g, 27 mmol) was added and the reaction mixture was stirred at r.t. for 24 h. The reaction mixture was filtered to remove Na_2SO_4 , and the residue was washed with CH_2Cl_2 (3×10 mL). The combined filtrate was washed with saturated aqueous solution of NaHCO_3 (3×10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the crude product was purified by fc ($\varnothing = 3$ cm, $h = 18$ cm, cyclohexane:ethyl acetate = 1:1, $V = 20$ mL, $R_f = 0.25$). Colorless oil, yield 0.90 g (85%). $\text{C}_{12}\text{H}_{16}\text{O}_3$ (208.3). Exact mass (APCI): $m/z = 209.1155$, calcd. 209.1172 for $\text{C}_{12}\text{H}_{16}\text{O}_3$ $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CD_2Cl_2): δ [ppm] = 1.52 (dtd, $J = 13.3/2.5/1.4$ Hz, 1H, 5- H_{eq}), 1.79 (dddd, $J = 14.5/6.6/5.2/4.0$ Hz, 1H, $\text{CH}_2\text{CH}_2\text{OH}$), 1.83–1.90 (m, 2H, $\text{CH}_2\text{CH}_2\text{OH}$ (1H), 5- H_{ax} (1H)), 2.07 (t, $J = 4.6$ Hz, 1H, CH_2OH), 3.73–3.84 (m, 2H, CH_2OH), 3.98 (ddd, $J = 12.4/11.4/2.6$ Hz, 1H, 6- H_{ax}), 4.10 (tdd, $J = 11.1/4.0/2.4$ Hz, 1H, 4- H_{ax}), 4.25 (ddd, $J = 11.4/5.1/1.4$ Hz, 1H, 6- H_{eq}), 5.53 (s, 1H, 2- H_{ax}), 7.32–7.40 (m, 3H, H_{arom}), 7.43–7.50 (m, 2H, H_{arom}). $^{13}\text{C-NMR}$ (100 MHz, CD_2Cl_2): δ [ppm] = 31.8 (1C, C-5 $_{dioxane}$), 38.9 (1C, $\text{CH}_2\text{CH}_2\text{OH}$), 60.4 (1C, CH_2OH), 67.5 (1C, C-6 $_{dioxane}$), 76.7 (1C, C-4 $_{dioxane}$), 101.7 (1C, C-2 $_{dioxane}$), 126.6 (2C, C_{arom}), 128.7 (2C, C_{arom}), 129.2 (1C, C_{arom}), 139.5 (1C, C_{qarom}). FTIR (neat): ν (cm^{-1}) = 3410, 3383 (O-H), 2947, 2859 (C-H), 1454, 1400, 1366 (C= C_{arom}), 1215, 1138, 1099 (C-O), 748, 698 (C- H_{arom} monosubst).

2-[(2*RS*,4*RS*)-2-Phenyl-1,3-dioxan-4-yl]acetaldehyde (**11**). Under N_2 atmosphere, a solution of oxalyl chloride in CH_2Cl_2 (3.0 mL, 6.0 mmol) was added in one portion to dry CH_2Cl_2 (10 mL) and the resulting solution was cooled down to -78 °C. Then a solution of dry $(\text{CH}_3)_2\text{SO}$ (0.6 mL, 8.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise (10 mL/h via a syringe pump). The reaction mixture was stirred at -78 °C for 15 min. Then a solution of alcohol **16** (0.84 g, 4.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise (10 mL/h via a syringe pump), and the mixture was stirred at -78 °C for another 20 min. Finally, Et_3N (2.9 mL, 20 mmol) was added in one portion, and the mixture was stirred at -78 °C for additional 10 min. The mixture was allowed to warm to r.t. The reaction mixture was diluted with Et_2O (20 mL) and the precipitate was filtered off. The residue was washed with Et_2O (2×20 mL) and the combined filtrate was concentrated in vacuo. The crude product was purified by fc ($\varnothing = 3$ cm, $h = 17$ cm, cyclohexane:ethyl acetate = 8:2, $V = 20$ mL, $R_f = 0.30$). Colorless oil, yield 0.70 g (92%). $\text{C}_{12}\text{H}_{14}\text{O}_3$ (206.2). Exact mass (APCI): $m/z = 207.1008$, calcd. 207.1016 for $\text{C}_{12}\text{H}_{15}\text{O}_3$ $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CD_2Cl_2): δ [ppm] = 1.61 (dtd, $J = 13.3/2.5/1.4$ Hz, 1H, 5- H_{eq}), 1.86 (dddd, $J = 13.2/12.2/11.3/5.0$ Hz, 1H, 5- H_{ax}), 2.60 (ddd, $J = 16.8/4.8/1.6$ Hz, 1H, CH_2CHO), 2.74 (ddd, $J = 16.8/7.6/2.4$ Hz, 1H, CH_2CHO), 3.95–4.04 (m, 1H, 6- H_{ax}), 4.25 (ddd, $J = 11.5/5.0/1.4$ Hz, 1H, 6- H_{eq}), 4.42 (dddd, $J = 11.2/7.5/4.8/2.5$ Hz, 1H, 4- H_{ax}), 5.55 (s, 1H, 2- H_{ax}), 7.30–7.41 (m, 3H, H_{arom}), 7.41–7.50 (m, 2H, H_{arom}), 9.81 (dd, $J = 2.4/1.6$ Hz, 1H, CH_2CHO). $^{13}\text{C-NMR}$ (100 MHz, CD_2Cl_2): δ [ppm] = 31.6 (1C, C-5 $_{dioxane}$), 50.0 (1C, CH_2CHO), 67.3 (1C, C-6 $_{dioxane}$), 72.8 (1C, C-4 $_{dioxane}$), 101.7 (1C, C-2 $_{dioxane}$), 126.6 (2C, C_{arom}), 128.6 (2C, C_{arom}), 129.3 (1C, C_{arom}), 139.2 (1C, C_{qarom}), 200.8 (1C, CH_2CHO). FTIR (neat): ν (cm^{-1}) = 2855 (C-H), 1721 (C=O), 1238, 1142, 1099 (C-O), 752, 698 (C- H_{arom} monosubst).

2-[(1*RS*)-2-[(2*RS*,4*RS*)- and (2*SR*,4*SR*)-4-Phenyl-1,3-dioxan-2-yl]-1-hydroxyethyl]benzaldehyde dimethyl acetal (**12a**). Under N_2 atmosphere, a solution of bromoacetal **17a** (0.72 g, 3.1 mmol) in dry THF (10 mL) was cooled down to -78 °C. Then 1.6 M *n*-butyllithium in *n*-hexanes (2.0 mL, 3.1 mmol) was added dropwise over 15 min, and the reaction mixture was stirred at -78 °C for 10 min. Then a solution of aldehyde **11** (0.43 g, 2.1 mmol) in dry THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred at -78 °C for 2 h, and was then allowed to warm to r.t. overnight. Under ice cooling, water (15 mL) was added dropwise to the reaction mixture. THF was removed in vacuo from the mixture and the resulting aqueous layer was extracted with CHCl_3 (3×20 mL). The combined organic layer was washed with brine (15 mL), dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The crude product was purified by fc ($\varnothing = 3$ cm, $h = 18$ cm, cyclohexane:ethyl acetate = 8:2, $V = 20$ mL, $R_f = 0.26$). Pale yellow oil, yield 0.70 g (93%), mixture of two diastereomers (2:1). $\text{C}_{21}\text{H}_{26}\text{O}_5$ (358.4). Exact Mass (APCI): $m/z = 325.1437$, calcd. 325.1434 for $\text{C}_{20}\text{H}_{21}\text{O}_4$ $[\text{M} - \text{HOCH}_3 - \text{H}]^+$; $m/z = 295.1325$, calcd. 295.1329 for $\text{C}_{19}\text{H}_{19}\text{O}_3$ $[\text{M} - \text{HOCH}_3 - \text{OCH}_3]^+$. MS (ESI): $m/z = 381$

[M + Na]⁺, 295 [M – HOCH₃ – OCH₃]⁺. ¹H-NMR (400 MHz, CD₃OD-*d*₄): δ [ppm] = 1.54 (dtd, *J* = 13.3/2.6/1.4 Hz, 0.33H, 5-*H*_{eq}^o), 1.59 (dtd, *J* = 13.3/2.5/1.4 Hz, 0.67H, 5-*H*_{eq}^m), 1.68–1.97 (m, 2.34H, CH₂CHOH^m (2 × 0.67H), 5-*H*_{ax}^{o+m} (1H)), 2.14 (dt, *J* = 13.9/7.5 Hz, 2 × 0.33H, CH₂CHOH^o), 3.18 (s, 3 × 0.67H, OCH₃^m), 3.22 (s, 3 × 0.33H, OCH₃^o), 3.27 (s, 3 × 0.67H, OCH₃^m), 3.27 (s, 3 × 0.33H, OCH₃^o), 3.84–4.04 (m, 2H, 6-*H*_{eq}^o (0.33H), 4-*H*_{ax}^m (0.67H), 6-*H*_{ax}^{o+m} (1H)), 4.12–4.28 (m, 1H, 4-*H*_{ax}^o (0.33H), 6-*H*_{eq}^m (0.67H)), 5.36 (dd, *J* = 7.9/5.8 Hz, 0.67H, CHO^m), 5.42–5.47 (m, 1H, CHO^o (0.33H), (CH(OCH₃)₂)^m (0.67H)), 5.51 (s, 0.33H, 2-*H*_{ax}^o), 5.57 (s, 0.67H, 2-*H*_{ax}^m), 5.59 (s, 0.33H, CH(OCH₃)₂^o), 7.20–7.29 (m, 2 × 0.67H, H_{arom}), 7.30–7.40 (m, 4H, H_{arom}), 7.44–7.48 (m, 2H, H_{arom}), 7.49–7.55 (m, 0.67H, H_{arom}), 7.59 (ddd, *J* = 7.8/4.1/1.3 Hz, 1H, H_{arom}). Ratio of diastereomers 67:33. ^o = minor isomer; ^m = major isomer. ¹³C-NMR (151 MHz, DMSO-*d*₆): δ [ppm] = 30.6^m (0.67C, C-5_{dioxane}), 31.4^o (0.33C, C-5_{dioxane}), 45.3^m (0.67C, CH₂CHOH), 46.2^o (0.33C, CH₂CHOH), 53.3^m (2 × 0.67C, OCH₃), 53.5^o (2 × 0.33C, OCH₃), 63.5^o (0.33C, CHO), 64.1^m (0.67C, CHO), 66.3^{o+m} (1C, C-6_{dioxane}), 73.4^o (0.33C, C-4_{dioxane}), 74.4^m (0.67C, C-4_{dioxane}), 100.2^o (0.33C, CH(OCH₃)₂), 100.3^m (0.67C, CH(OCH₃)₂), 100.97^m (0.67C, C-2_{dioxane}), 101.0^o (0.33C, C-2_{dioxane}), 125.6^m (0.67C, C_{arom}), 125.7^o (0.33C, C_{arom}), 126.06^m (0.67C, C_{arom}), 126.08^m (2 × 0.67C, C_{arom}), 126.10^o (2 × 0.33C, C_{arom}), 126.13^o (0.33C, C_{arom}), 126.3^o (0.33C, C_{arom}), 126.5^m (0.67C, C_{arom}), 127.9^m (0.67C, C_{arom}), 128.0^m (2 × 0.67C, C_{arom}), 128.4^o (0.33C, C_{arom}), 128.5^{o+m} (1C, C_{arom}), 128.53^m (0.67C, C_{arom}), 133.9^o (0.33C, C_{qarom}), 134.1^m (0.67C, C_{qarom}), 139.0^m (0.67C, C_{qarom}), 139.2^o (0.33C, C_{qarom}), 144.2^m (0.67C, C_{qarom}), 144.8^o (0.33C, C_{qarom}). Ratio of diastereomers 67:33. ^o = minor isomer; ^m = major isomer. FTIR (neat): ν (cm⁻¹) = 3460 (O-H), 2947 (C-H), 1454 (C=C_{aromatic}), 1099 (C-O), 752, 698 (C-H_{arom} mono- and 1,2-disubst).

1-{2-[(1RS)-2-[(2RS,4RS)- and (2SR,4SR)-2-Phenyl-1,3-dioxan-4-yl]-1-hydroxyethyl]phenyl}ethanone dimethyl ketal (**12b**). Under N₂ atmosphere, a solution of 2'-bromoacetophenone dimethyl ketal (**17b**, 0.95 g, 3.7 mmol) in dry THF (12 mL) was cooled down to –78 °C. Then 2.5 M *n*-butyllithium in *n*-hexanes (1.5 mL, 3.7 mmol) was added dropwise over 15 min. The reaction mixture was stirred at –78 °C for 10 min. A solution of aldehyde **11** (0.51 g, 2.5 mmol) in dry THF (6 mL) was added dropwise over 18 min. The reaction mixture was stirred at –78 °C for 2 h, then it was allowed to warm to r.t. overnight. Under ice cooling, water (15 mL) was added dropwise to the reaction mixture. THF was removed in vacuo from the mixture and the resulting aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layer was washed with brine (15 mL), dried (Na₂SO₄), filtered, and the solvent removed in vacuo. The crude product was purified by fc (Ø = 2 cm, h = 15 cm, cyclohexane:ethyl acetate = 8:2, V = 20 mL, R_f = 0.40). Pale yellow oil, yield 0.89 g (97%), mixture of two diastereomers (2:1). C₂₂H₂₈O₅ (372.5). Exact Mass (APCI): *m/z* = 310.1536, calcd. 310.1569 for C₂₀H₂₂O₃ [M – HOCH₃ – OCH₃ + H]⁺. MS (ESI): *m/z* = 395 [M + Na]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 1.46 (s, 3 × 0.33H, CH₃C(OCH₃)₂^o), 1.50 (s, 3 × 0.67H, CH₃C(OCH₃)₂^m), 1.53–1.79 (m, 3.34H, 5-*H*_{eq}^{o+m} (1H), 5-*H*_{ax}^{o+m} (1H), CH₂CHOH^m (2 × 0.67H)), 1.91–2.02 (m, 2 × 0.33H, CH₂CHOH^o), 3.01 (s, 3 × 0.67H, OCH₃^m), 3.07 (2s, 6 × 0.33H, OCH₃^o), 3.10 (s, 3 × 0.67H, OCH₃^m), 3.93 (qd, *J* = 11.4/2.7 Hz, 1H, 6-*H*_{ax}^{o+m}), 4.05–4.25 (m, 2H, 4-*H*_{ax}^{o+m} (1H), 6-*H*_{eq}^{o+m} (1H)), 4.97 (2d, *J* = 4.8 Hz, 1H, CHO^{o+m}), 5.34 (ddd, *J* = 10.0/5.0/3.0 Hz, 0.67H, CHO^m), 5.51 (s, 1H, 2-*H*_{ax}^m (0.67H), CHO^o (0.33H)), 5.55 (s, 0.33H, 2-*H*_{ax}^o), 7.18 (dtd, *J* = 8.3/7.1/1.5 Hz, 2 × 0.67H, H_{arom}^m), 7.25–7.36 (m, 4H, H_{arom}^{o+m}), 7.36–7.41 (m, 2 × 0.67H, H_{arom}^m), 7.44 (ddd, *J* = 8.0/6.5/1.8 Hz, 2 × 0.67H, H_{arom}^m), 7.60 (td, *J* = 8.0/1.4 Hz, 1H, H_{arom}^{o+m}). Ratio of diastereomers 67:33. ^o = minor isomer; ^m = major isomer. ¹³C-NMR (101 MHz, DMSO-*d*₆): δ [ppm] = 25.7^o (0.33C, CH₃), 25.9^m (0.67C, CH₃), 30.9^m (0.67C, C-5_{dioxane}), 32.0^o (0.33C, C-5_{dioxane}), 45.9^m (0.67C, CH₂CHOH), 46.8^o (0.33C, CH₂CHOH), 48.85^m (2 × 0.67C, OCH₃), 48.88^o (2 × 0.33C, OCH₃), 63.8^o (0.33C, CHO), 64.4^m (0.67C, CHO), 66.77^m (0.67C, C-6_{dioxane}), 66.80^o (0.33C, C-6_{dioxane}), 74.1^o (0.33C, C-4_{dioxane}), 75.2^m (0.67C, C-4_{dioxane}), 100.6^o (0.33C, C-2_{dioxane}), 100.9^m (0.67C, C-2_{dioxane}), 102.1^o (0.33C, C(OCH₃)₂), 102.3^m (0.67C, C(OCH₃)₂), 126.5^o (2 × 0.33C, C_{arom}), 126.54^m (2 × 0.67C, C_{arom}), 126.6^o (0.33C, C_{arom}), 126.61^o (0.33C, C_{arom}), 126.7^m (0.67C, C_{arom}), 126.8^m (0.67C, C_{arom}), 128.15^o (0.33C, C_{arom}), 128.16^m (0.67C, C_{arom}), 128.2^m (0.67C, C_{arom}), 128.24^o (0.33C, C_{arom}), 128.3^o (2 × 0.33C, C_{arom}), 128.34^m (2 × 0.67C, C_{arom}), 128.8^o (0.33C, C_{arom}), 128.9^m (0.67C, C_{arom}), 138.5^o (0.33C, C_{qarom}), 138.7^m (0.67C, C_{qarom}), 139.5^m (0.67C, C_{qarom}), 139.7^o (0.33C, C_{qarom}), 144.9^m

(0.67C, C_qarom), 145.6° (0.33C, C_qarom). Ratio of diastereomers 67:33. ° = minor isomer; ^m = major isomer. FTIR (neat): ν (cm⁻¹) = 3487 (OH), 2924, 2851 (C-H), 1450 (C=C_{aromatic}), 1099 (C-O), 760, 698 (C-H_{arom} mono- and 1,2-disubst).

1-Methoxy-3-[(2-phenyl-1,3-dioxan-4-yl)methyl]-1,3-dihydro-2-benzofuran (18a) (four diastereomers). A solution of *p*-toluenesulfonic acid in toluene (0.5 mg/mL, 18 mL) was added to alcohols **12a** (0.33 g, 0.9 mmol). The reaction mixture was stirred vigorously at r.t. for 2 h. Saturated aqueous solution of NaHCO₃ (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layer was washed with brine (20 mL), dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was purified by fc (Ø = 2 cm, h = 15 cm, cyclohexane: ethyl acetate = 9:1, V = 10 mL, R_f = 0.39). Colorless oil, yield 0.27 g (89%), mixture of four diastereomers (2:2:1:1). C₂₀H₂₂O₄ (326.4). Exact Mass (APCI): m/z = 295.1330, calcd. 295.1329 for C₁₉H₁₉O₃ [M – OCH₃]⁺; m/z = 221.0973, calcd. 221.1172 for C₁₃H₁₇O₃ [M – PhCO]⁺. MS (ESI): m/z = 349 [M + Na]⁺, 295 [M – OCH₃]⁺, 277 [M – OCH₃ – H₂O]⁺, 221 [M – PhCO]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 1.59–2.02 (m, 3.34H, 5-*H*_{eq}^{o+m} (1H), 5-*H*_{ax}^{o+m} (1H), CHCH₂CH^{o+m+o} (2 × 0.67H)), 2.04–2.27 (m, 2 × 0.33H, CHCH₂CH^m), 3.33 (s, 3 × 0.17H, OCH₃^o), 3.34 (s, 3 × 0.33H, OCH₃^m), 3.40 (s, 3 × 0.17H, OCH₃^o), 3.41 (s, 3 × 0.33H, OCH₃^m), 3.95–4.08 (m, 1.34H, 6-*H*_{ax}^{o+m} (1H), 4-*H*_{ax}^o (2 × 0.17H)), 4.16–4.34 (m, 1.66H, 4-*H*_{ax}^m (2 × 0.33H), 6-*H*_{eq}^{o+m} (1H)), 5.34 (dt, *J* = 10.4/4.6 Hz, 0.50H, 3-*H*_{bf}^{o+m}), 5.43–5.50 (m, 0.50H, 3-*H*_{bf}^{o+m}), 5.58 (s, 0.33H, 2-*H*_{ax}^m), 5.61 (s, 0.33H, 2-*H*_{ax}^m), 5.66 (2s, 2 × 0.17H, 2-*H*_{ax}^o), 6.12 (s, 0.33H, 1-*H*_{bf}^m), 6.14 (s, 0.17H, 1-*H*_{bf}^o), 6.20 (d, *J* = 2.1 Hz, 0.17H, 1-*H*_{bf}^o), 6.22 (d, *J* = 2.1 Hz, 0.33H, 1-*H*_{bf}^m), 7.34–7.45 (m, 16 × 0.33H + 18 × 0.17H, H_{arom}), 7.48–7.54 (m, 2 × 0.33H, H_{arom}). Ratio of diastereomers 33:33:17:17. ° = minor isomer; ^m = major isomer; _{bf} = benzofuran. ¹³C-NMR (101 MHz, DMSO-*d*₆): δ [ppm] = 31.0^m (0.33C, C-5_{dioxane}), 31.2^m (0.33C, C-5_{dioxane}), 32.1^o (2 × 0.17C, C-5_{dioxane}), 41.9^m (0.33C, CHCH₂CH), 43.0^o (0.17C, CHCH₂CH), 43.5^m (0.33C, CHCH₂CH), 44.7^o (0.17C, CHCH₂CH), 54.0^o (0.17C, OCH₃), 54.1^m (0.33C, OCH₃), 54.3^o (0.17C, OCH₃), 54.5^m (0.33C, OCH₃), 66.6^{o+m} (0.50C, C-6_{dioxane}), 66.7^m (0.33C, C-6_{dioxane}), 67.4^o (0.17C, C-6_{dioxane}), 73.8^m (0.33C, C-4_{dioxane}), 74.0^o (0.17C, C-4_{dioxane}), 74.1^m (0.33C, C-4_{dioxane}), 74.2^o (0.17C, C-4_{dioxane}), 78.8^o (0.17C, C-3), 79.0^o (0.17C, C-3), 79.03^m (0.33C, C-3), 79.3^m (0.33C, C-3), 100.5^m (0.33C, C-2_{dioxane}), 100.6^m (0.33C, C-2_{dioxane}), 100.7^o (0.17C, C-2_{dioxane}), 100.74^o (0.17C, C-2_{dioxane}), 106.2^o (0.17C, C-1), 106.3^m (0.33C, C-1), 106.6^o (0.17C, C-1), 106.7^m (0.33C, C-1), 121.6^o (0.17C, C_{arom}), 121.8^o (0.17C, C_{arom}), 121.84^m (0.33C, C_{arom}), 122.0^m (0.33C, C_{arom}), 123.4^m (2 × 0.33C, C_{arom}), 123.42^o (2 × 0.17C, C_{arom}), 126.4^m (2 × 0.33C, C_{arom}), 126.42^m (2 × 0.33C, C_{arom}), 126.5^o (2 × 0.17C, C_{arom}), 126.53^o (2 × 0.17C, C_{arom}), 128.06^m (0.33C, C_{arom}), 128.10^{o+m} (0.50C, C_{arom}), 128.2^o (0.17C, C_{arom}), 128.26^m (2 × 0.33C, C_{arom}), 128.3^m (2 × 0.33C, C_{arom}), 128.38^o (2 × 0.17C, C_{arom}), 128.39^o (2 × 0.17C, C_{arom}), 128.8^m (0.33C, C_{arom}), 128.81^o (2 × 0.17C, C_{arom}), 128.9^m (0.33C, C_{arom}), 129.6^{o+m} (0.50C, C_{arom}), 129.61^{o+m} (0.50C, C_{arom}), 137.7^o (0.17C, C_qarom), 137.74^o (0.17C, C_qarom), 137.8^m (2 × 0.33C, C_qarom), 139.3^o (2 × 0.17C, C_qarom), 139.34^m (0.33C, C_qarom), 139.4^m (0.33C, C_qarom), 143.3^m (0.33C, C_qarom), 143.4^m (0.33C, C_qarom), 143.5^o (0.17C, C_qarom), 143.51^o (0.17C, C_qarom). Ratio of diastereomers 33:33:17:17. ° = minor isomer; ^m = major isomer. FTIR (neat): ν (cm⁻¹) = 2947, 2858 (C-H), 1458 (C=C_{aromatic}), 1096 (C-O), 752, 698 (C-H_{arom} mono- and 1,2-disubst).

1-Methoxy-1-methyl-3-[(2-phenyl-1,3-dioxan-4-yl)methyl]-1,3-dihydro-2-benzofuran (18b) (four diastereomers). A solution of *p*-toluenesulfonic acid in toluene (25 mL, 1 mg/mL) was added to a solution of alcohols **12b** (0.89 g, 2.4 mmol) in cyclohexane (25 mL). The reaction mixture was stirred vigorously at r.t. for 2 h. Saturated aqueous solution of NaHCO₃ (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layer was washed with brine (20 mL), dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was purified by fc (Ø = 2 cm, h = 15 cm, cyclohexane:ethyl acetate = 9:1, V = 10 mL, R_f = 0.40). Pale yellow oil, yield 0.58 g (71%), mixture of four diastereomers (2:2:1:1). C₂₁H₂₄O₄ (340.4). MS (ESI): m/z = 657 [2(M – OCH₃) + K]⁺, 363 [M + Na]⁺, 309 [M – OCH₃]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 1.55–1.65 (m, 3.66H, CH₃C(OCH₃)^{o+m} (3H), 5-*H*_{eq}^m (2 × 0.33H)), 1.70–1.83 (m, 1.34H,

5- H_{eq}° ($2 \times 0.17H$), 5- H_{ax}^{o+m} (1H)), 1.91–2.19 (m, 2H, $CHCH_2CH^{o+m}$), 2.82 (s, $3 \times 0.17H$, OCH_3°), 2.84 (s, 1.5H, OCH_3^{o+m}), 2.94 (s, $3 \times 0.33H$, OCH_3^m), 3.94 (dd, $J = 11.7/2.9$ Hz, $2 \times 0.33H$, 6- H_{ax}^m), 3.97–4.04 (m, 0.67H, 6- H_{ax}° ($2 \times 0.17H$), 6- H_{eq}^m (0.33H)), 4.12–4.16 (m, $2 \times 0.33H$, 4- H_{ax}^m), 4.19 (ddd, $J = 8.9/5.6/3.2$ Hz, 0.33H + $2 \times 0.17H$, 6- H_{eq}^{o+m+o}), 4.23 (dt, $J = 7.1$, 2.1 Hz, $2 \times 0.17H$, 4- H_{ax}°), 5.24 (ddd, $J = 16.6/9.6/3.5$ Hz, $2 \times 0.17H$, 3- H_{bf}°), 5.39–5.47 (m, $2 \times 0.33H$, 3- H_{bf}^m), 5.52 (s, 0.33H, 2- H_{ax}^m), 5.60 (s, 0.33H, 2- H_{ax}^m), 5.63 (2s, $2 \times 0.17H$, 2- H_{ax}°), 7.23 (qd, $J = 3.8/1.6$ Hz, 1H, H_{arom}^{o+m}), 7.26–7.43 (m, 7H, H_{arom}^{o+m}), 7.46 (ddd, $J = 7.4/3.8/1.9$ Hz, 1H, H_{arom}^{o+m}). Ratio of diastereomers 33:33:17:17. $^{\circ}$ = minor isomer; m = major isomer; $_{bf}$ = benzofuran. ^{13}C -NMR (101 MHz, DMSO- d_6): δ [ppm] = 26.1 m (0.33C, $CH_3C(OCH_3)$), 26.2 $^{\circ}$ (0.17C, $CH_3C(OCH_3)$), 26.8 m (0.33C, $CH_3C(OCH_3)$), 27.1 $^{\circ}$ (0.17C, $CH_3C(OCH_3)$), 30.3 m (0.33C, C-5 $_{dioxane}$), 30.5 $^{\circ}$ ($2 \times 0.17C$, C-5 $_{dioxane}$), 31.5 m (0.33C, C-5 $_{dioxane}$), 41.6 m (0.33C, $CHCH_2CH$), 41.8 m (0.33C, $CHCH_2CH$), 42.4 $^{\circ}$ (0.17C, $CHCH_2CH$), 43.2 $^{\circ}$ (0.17C, $CHCH_2CH$), 48.9 m (0.33C, OCH_3), 48.99 $^{\circ}$ (0.17C, OCH_3), 49.2 m (0.33C, OCH_3), 49.26 $^{\circ}$ (0.17C, OCH_3), 66.0 $^{o+m}$ (1C, C-6 $_{dioxane}$), 73.1 m (0.33C, C-4 $_{dioxane}$), 73.37 $^{\circ}$ (0.17C, C-4 $_{dioxane}$), 73.4 $^{\circ}$ (0.17C, C-4 $_{dioxane}$), 73.44 m (0.33C, C-4 $_{dioxane}$), 76.6 m (0.33C, C-3), 76.66 $^{\circ}$ (0.17C, C-3), 78.4 $^{\circ}$ (0.17C, C-3), 78.7 m (0.33C, C-3), 99.8 m (0.33C, C-2 $_{dioxane}$), 100.0 $^{o+m}$ (0.50C, C-2 $_{dioxane}$), 100.1 $^{\circ}$ (0.17C, C-2 $_{dioxane}$), 109.8 $^{o+m}$ (0.50C, C-1), 110.1 m (0.33C, C-1), 110.2 $^{\circ}$ (0.17C, C-1), 121.0 $^{\circ}$ (0.17C, C_{arom}), 121.2 $^{o+m}$ (0.50C, C_{arom}), 121.4 m (0.33C, C_{arom}), 121.8 $^{\circ}$ (0.17C, C_{arom}), 121.83 $^{\circ}$ (0.17C, C_{arom}), 121.9 m ($2 \times 0.33C$, C_{arom}), 125.7 m ($2 \times 0.33C$, C_{arom}), 125.8 m ($2 \times 0.33C$, C_{arom}), 125.9 $^{\circ}$ ($2 \times 0.17C$, C_{arom}), 126.0 $^{\circ}$ ($2 \times 0.17C$, C_{arom}), 127.6 m ($2 \times 0.33C$, C_{arom}), 127.7 m ($2 \times 0.33C$, C_{arom}), 127.77 m ($4 \times 0.33C$, C_{arom}), 127.8 $^{\circ}$ (0.17C, C_{arom}), 127.9 $^{\circ}$ (0.17C, C_{arom}), 128.1 m (0.33C, C_{arom}), 128.2 m (0.33C, C_{arom}), 128.3 $^{\circ}$ (0.17C, C_{arom}), 128.31 $^{\circ}$ (0.17C, C_{arom}), 128.8 $^{o+m+m}$ ($2 \times 0.33C + 0.17C$, C_{arom}), 128.9 $^{\circ}$ (0.17C, C_{arom}), 138.6 m ($2 \times 0.33C$, C_{qarom}), 138.7 $^{\circ}$ ($2 \times 0.17C$, C_{qarom}), 138.72 $^{\circ}$ (0.17C, C_{qarom}), 138.8 m (0.33C, C_{qarom}), 139.0 $^{\circ}$ (0.17C, C_{qarom}), 139.08 m (0.33C, C_{qarom}), 142.3 m (0.33C, C_{qarom}), 142.4 $^{\circ}$ (0.17C, C_{qarom}), 142.7 m (0.33C, C_{qarom}), 142.8 $^{\circ}$ (0.17C, C_{qarom}). Ratio of diastereomers 33:33:17:17. $^{\circ}$ = minor isomer; m = major isomer. FTIR (neat): ν (cm^{-1}) = 2932, 2855 (C-H), 1454 (C= C_{arom}), 1099 (C-O), 748, 698 (C- H_{arom} mono- and 1,2-disubst).

4-(3-Methoxy-1,3-dihydro-2-benzofuran-1-yl)butane-1,3-diol (**13a**) (four diastereomers). A solution of 2-benzofuran **18a** (0.32 g, 1.3 mmol) in a mixture of methanol and water (20 mL, 4:1) was treated with *p*-toluenesulfonic acid (0.17 g, 1.0 mmol). The reaction mixture was stirred at r.t. for 48 h. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added. Methanol was evaporated in vacuo and the resulting aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The crude product was purified by fc ($\emptyset = 2$ cm, $h = 13$ cm, ethyl acetate (100%), $V = 10$ mL, $R_f = 0.44$). Pale yellow oil, yield 0.27 g (87%), mixture of four diastereomers (2:2:1:1). $C_{13}H_{18}O_4$ (238.3). Exact Mass (APCI): $m/z = 413.2047$, calcd. 413.1959 for $C_{24}H_{30}O_6$ [$2(M - HOCH_3) + H$] $^+$; $m/z = 207.1090$, calcd. 207.1016 for $C_{12}H_{15}O_3$ [$M - OCH_3$] $^+$. MS (ESI): $m/z = 467$ [$M + C_{12}H_{14}O_3 + Na$] $^+$, 261 [$M + Na$] $^+$, 207 [$M - OCH_3$] $^+$, 189 [$M - H_2O - OCH_3$] $^+$. 1H -NMR (400 MHz, DMSO- d_6): δ [ppm] = 1.33–1.98 (m, 4H, $CH_2CH_2OH^{o+m}$ (2H), CH_2CHOH^{o+m} (2H)), 3.24 (s, $3 \times 0.33H$, OCH_3^m), 3.28 (s, $3 \times 0.17H$, OCH_3°), 3.27 (s, $3 \times 0.17H$, OCH_3°), 3.31 (s, $3 \times 0.33H$, OCH_3^m), 3.46–3.57 (m, 2H, CH_2OH^{o+m}), 3.84–3.97 (m, 1H, $CHOH^{o+m}$), 4.29–4.38 (m, 1H, CH_2OH^{o+m}), 4.48 (d, $J = 5.1$ Hz, 0.33H, $CHOH^m$), 4.52 (d, $J = 5.1$ Hz, 0.33H, $CHOH^m$), 4.60 (d, $J = 2.5$ Hz, 0.17H, $CHOH^{\circ}$), 4.62 (d, $J = 2.6$ Hz, 0.17H, $CHOH^{\circ}$), 5.22 (dd, $J = 7.4/6.2$ Hz, 0.33H, 1- H_{bf}^m), 5.27 (dd, $J = 10.4/2.5$ Hz, 0.17H, 1- H_{bf}°), 5.34 (ddd, $J = 7.4/5.1/2.0$ Hz, 0.33H, 1- H_{bf}^m), 5.40 (dt, $J = 10.2/2.3$ Hz, 0.17H, 1- H_{bf}°), 6.01 (s, 0.33H, 3- H_{bf}^m), 6.03 (s, 0.17H, 3- H_{bf}°), 6.09 (2s, Hz, 0.50H, 3- H_{bf}^{o+m}), 7.24–7.41 (m, 4H, H_{arom}). Ratio of diastereomers 33:33:17:17. $^{\circ}$ = minor isomer; m = major isomer; $_{bf}$ = benzofuran. ^{13}C -NMR (101 MHz, DMSO- d_6): δ [ppm] = 39.8 m ($2 \times 0.33C$, CH_2CH_2OH), 41.1 $^{\circ}$ (0.17C, CH_2CH_2OH), 41.14 $^{\circ}$ (0.17C, CH_2CH_2OH), 44.0 m (0.33C, CH_2CHOH), 44.7 $^{\circ}$ (0.17C, CH_2CHOH), 45.5 m (0.33C, CH_2CHOH), 46.3 $^{\circ}$ (0.17C, CH_2CHOH), 53.5 m (0.33C, OCH_3), 53.7 $^{\circ}$ ($2 \times 0.17C$, OCH_3), 53.9 m (0.33C, OCH_3), 58.0 $^{\circ}$ (0.17C, CH_2OH), 58.05 $^{o+m}$ (0.50C, CH_2OH), 58.06 m (0.33C, CH_2OH), 64.3 $^{\circ}$ (0.17C, $CHOH$), 64.7 $^{\circ}$ (0.17C, $CHOH$), 64.72 m (0.33C, $CHOH$), 64.8 m (0.33C, $CHOH$), 79.2 $^{\circ}$ (0.17C, C-1), 79.6 $^{\circ}$ (0.17C, C-1), 79.7 m (0.33C, C-1), 80.0 m (0.33C, C-1), 105.6 m (0.33C, C-3), 105.7 $^{\circ}$ (0.17C, C-3), 106.0 $^{\circ}$ (0.17C, C-3), 106.1 m (0.33C, C-3), 121.0 $^{\circ}$ (0.17C,

C_{arom}), 121.2^o (0.17C, C_{arom}), 121.3^m (0.33C, C_{arom}), 121.6^m (0.33C, C_{arom}), 122.9^m (2 × 0.33C, C_{arom}), 123.0^o (2 × 0.17C, C_{arom}), 127.5^o (0.17C, C_{arom}), 127.55^m (0.33C, C_{arom}), 127.59^o (0.17C, C_{arom}), 127.6^m (0.33C, C_{arom}), 129.1^m (0.33C, C_{arom}), 129.13^o (0.17C, C_{arom}), 129.14^m (0.33C, C_{arom}), 129.2^o (0.17C, C_{arom}), 137.3^o (0.17C, C_{qarom}), 137.4^m (0.33C, C_{qarom}), 137.42^m (0.33C, C_{qarom}), 137.5^o (0.17C, C_{qarom}), 143.46^m (0.33C, C_{qarom}), 143.50^m (0.33C, C_{qarom}), 143.7^o (0.17C, C_{qarom}), 143.8^o (0.17C, C_{qarom}). Ratio of diastereomers 33:33:17:17. ^o = minor isomer; ^m = major isomer. FTIR (neat): ν (cm⁻¹) = 3375 (O-H), 2936, 2889 (C-H), 1431 (C=C_{aromatic}), 1080 (C-O), 752 (C-H_{arom 1,2-disubst}).

4-(3-Methoxy-3-methyl-1,3-dihydro-2-benzofuran-1-yl)butane-1,3-diol (**13b**) (four diastereomers). A solution of 2-benzofuran **18b** (0.22 g, 0.6 mmol) in a mixture of methanol and water (12 mL, 4:1) was treated with *p*-toluenesulfonic acid (40.0 mg, 0.2 mmol). The reaction mixture was stirred at r.t. for 72 h. Saturated aqueous solution of NaHCO₃ (10 mL) was added. Methanol was removed in vacuo and the resulting aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was purified by fc (Ø = 2 cm, h = 10 cm, ethyl acetate (100%), V = 10 mL, R_f = 0.40). Yellow oil, yield 88.4 mg (55%), mixture of four diastereomers (2:2:1:1). C₁₄H₂₀O₄ (252.31). MS (ESI): m/z = 463 [2(M - HOCH₃) + Na]⁺, 275 [M + Na]⁺, 203 [M - OCH₃ - H₂O]⁺, 221 [M - OCH₃]⁺, ¹H-NMR (400 MHz, CD₃OD): δ [ppm] = 1.55–2.07 (m, 7H, CH₃^{o+m} (3H), CH₂CHOHCH₂^{o+m} (4H)), 2.94 (s, 3 × 0.33H*, OCH₃^m), 2.95 (s, 3 × 0.17H*, OCH₃^o), 3.01 (s, 3 × 0.17H*, OCH₃^o), 3.04 (s, 3 × 0.33H*, OCH₃^m), 3.41–3.62 (m, 0.33H, CH₂CH₂OH^m), 3.65–3.87 (m, 3 × 0.33H + 4 × 0.17H, CH₂CH₂OH^{o+m}), 3.95–4.25 (m, 1H*, CH₂CHOH^{o+m}), 5.17–5.36 (m, 0.50H, 1-H_{bf}^{o+m}), 5.38–5.48 (m, 0.33H, 1-H_{bf}^m), 5.53 (dd, J = 10.2/2.3 Hz, 0.17H, 1-H_{bf}^o), 7.20–7.49 (m, 4H, H_{arom}^{o+m}). Ratio of diastereomers 33:33:17:17. Signals of the OH protons are not observed in the spectrum. * The integrals of these signals are slightly lower than expected. ^o = minor isomer; ^m = major isomer; _{bf} = benzofuran. ¹³C-NMR (101 MHz, CD₃OD): δ [ppm] = 26.7^o (0.17C, CCH₃(OCH₃)), 26.73^m (0.33C, CCH₃(OCH₃)), 27.7^m (0.33C, CCH₃(OCH₃)), 27.8^o (0.17C, CCH₃(OCH₃)), 40.2^m (0.33C, CH₂CH₂OH), 40.4^m (0.33C, CH₂CH₂OH), 41.6^o (0.17C, CH₂CH₂OH), 41.63^o (0.17C, CH₂CH₂OH), 45.0^m (0.33C, CH₂CHOH), 45.6^o (0.17C, CH₂CHOH), 45.8^m (0.33C, CH₂CHOH), 46.6^o (0.17C, CH₂CHOH), 50.1^m (2 × 0.33C, OCH₃), 50.5^o (0.17C, OCH₃), 50.6^o (0.17C, OCH₃), 60.2^{o+m} (1C, CH₂CH₂OH), 67.0^o (2 × 0.17C, CH₂CHOH), 68.0^m (0.33C, CH₂CHOH), 68.1^m (0.33C, CH₂CHOH), 80.6^m (0.33C, C-1), 81.4^o (2 × 0.17C, C-1), 82.4^m (0.33C, C-1), 111.9^m (0.33C, C-3), 112.1^m (0.33C, C-3), 112.5^o (2 × 0.17C, C-3), 122.0^m (0.33C, C_{arom}), 122.3^o (0.17C, C_{arom}), 122.34^m (0.33C, C_{arom}), 122.5^o (0.17C, C_{arom}), 123.26^o (0.17C, C_{arom}), 123.3^m (0.33C, C_{arom}), 123.4^o (0.17C, C_{arom}), 123.42^m (0.33C, C_{arom}), 129.1^o (0.17C, C_{arom}), 129.2^m (0.33C, C_{arom}), 129.3^o (0.17C, C_{arom}), 129.33^m (0.33C, C_{arom}), 130.3^o (0.17C, C_{arom}), 130.36^o (0.17C, C_{arom}), 130.4^m (2 × 0.33C, C_{arom}), 140.1^o (0.17C, C_{qarom}), 140.2^o (0.17C, C_{qarom}), 140.4^m (0.33C, C_{qarom}), 140.6^m (0.33C, C_{qarom}), 144.2^o (0.17C, C_{qarom}), 144.6^m (2 × 0.33C, C_{qarom}), 144.9^o (0.17C, C_{qarom}). Ratio of diastereomers 33:33:17:17. ^o = minor isomer; ^m = major isomer. FTIR (neat): ν (cm⁻¹) = 3395 (O-H), 2935, 2881 (C-H), 1431, (C=C_{aromatic}), 1041 (C-O), 764 (C-H_{arom 1,2-disubst}).

[(*tert*-Butyldimethylsilyl)oxy]-1-(3-methoxy-1,3-dihydro-2-benzofuran-1-yl)butan-2-ol (**19a**) (four diastereomers). In DMF (0.50 mL), diols **13a** (34.1 mg, 0.14 mmol) were treated with imidazole (29.2 mg, 0.43 mmol) and *tert*-butyldimethylsilyl chloride (22.2 mg, 0.14 mmol). The reaction mixture was stirred at r.t. for 24 h, diluted with EtOAc (10 mL) and washed with water (4 × 5 mL). The organic phase was separated, dried (Na₂SO₄), filtered and was concentrated under reduced pressure. The crude product was purified by fc (Ø = 2 cm, h = 10 cm, cyclohexane: ethyl acetate (8:2), V = 10 mL, R_f = 0.44). Colorless oil, yield 26.6 mg (58%). C₁₉H₃₂O₄Si (352.5). Ratio of diastereomers 33:33:17:17. ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 0.02–0.04 (m, 6H, (CH₃)₂^tBuSi^{o+m}), 0.86–0.87 (m, 9H, Me₂ (C(CH₃)₃Si^{o+m}), 1.43–1.95 (m, 4H, CH₂CHOHCH₂^{o+m}), 3.28 (s, 3 × 0.33H, OCH₃^m), 3.29 (s, 3 × 0.17H*, OCH₃^o), 3.32 (s, 3 × 0.17H *, OCH₃^o), 3.34 (s, 3 × 0.33H, OCH₃^m), 3.68–3.78 (m, 2H, CH₂OH^{o+m}), 3.90–3.96 (m, 1H, CHOH^{o+m}), 4.51 (d, J = 5.3 Hz, 0.33H, CHOH^m), 4.53 (d, J = 5.3 Hz, 0.33H, CHOH^m), 4.63 (d, J = 3.3 Hz, 0.17H*, CHOH^o), 4.64 (d, J = 3.2 Hz, 0.17H *, CHOH^o), 5.26 (dd, J = 7.4/6.4 Hz, 0.33H, 1-H_{bf}^m), 5.31 (dd,

$J = 10.4/2.4$ Hz, 0.17H, 1- H_{bf}°), 5.34–5.39 (dd, $J = 10.4/3.7$ Hz, 0.33H, 1- H_{bf}^{m}), 5.43 (dd, $J = 11.4/1.4$ Hz, 0.17H, 1- H_{bf}°), 6.04 (s, 0.33H, 3- H_{bf}^{m}), 6.06 (s, 0.17H, 3- H_{bf}°), 6.12 (2s, 0.5H, 3- $H_{\text{bf}}^{\circ+\text{m}}$), 7.28–7.44 (m, 4H, H_{arom}). Ratio of diastereomers 33:33:17:17. * Signals were slightly lower than expected. $^{\circ}$ = minor isomer, $^{\text{m}}$ = major isomer, bf = benzofuran.

[3-Hydroxy-4-(3-methoxy-1,3-dihydro-2-benzofuran-1-yl)butyl]-4-methylbenzenesulfonate (**20a**) (four diastereomers). A solution of diols **13a** (0.20 g, 0.84 mmol) in dry CH_2Cl_2 (4 mL) was treated with Bu_2SnO (10.7 mg, 0.04 mmol), Et_3N (176 μL , 1.3 mmol) and *p*-toluenesulfonyl chloride (0.18 g, 0.9 mmol). The reaction mixture was heated to reflux for 16 h. The solvent was removed under reduced pressure at 30 °C. The crude product was purified by fc ($\varnothing = 2$ cm, $h = 12$ cm, cyclohexane: ethyl acetate (7:3), $V = 10$ mL, $R_f = 0.36$ (1st spot); 0.19 (2nd spot)). Colorless oil, yield 0.16 g (51%), mixture of four diastereomers (2:2:1:1). $\text{C}_{20}\text{H}_{24}\text{O}_6\text{S}$ (392.5). MS (ESI): $m/z = 361$ [$\text{M} - \text{OCH}_3$] $^+$, 343 [$\text{M} - \text{H}_2\text{O} - \text{OCH}_3$] $^+$, 171 [$\text{M} - \text{C}_{13}\text{H}_{17}\text{O}_3$] $^+$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 1.41–2.21 (m, 4H, $\text{CH}_2\text{CH}_2\text{OSO}_2\text{PhCH}_3^{\circ+\text{m}}$ (2H), $\text{CH}_2\text{CHOH}^{\circ+\text{m}}$ (2H)), 2.41 (2s, 3 $\text{H}^{\circ+\text{m}}$, CH_3Ph), 3.26 (s, 3 \times 0.33H, OCH_3^{m}), 3.28 (s, 3 \times 0.17H * , OCH_3°), 3.30 (s, 3 \times 0.33H, OCH_3°), 3.68–3.77 (m, 2 \times 0.17H, $\text{CH}_2\text{CHOH}^{\circ}$), 3.81 (dt, $J = 10.2/5.5$ Hz, 2 \times 0.33H, $\text{CH}_2\text{CHOH}^{\text{m}}$), 3.88–4.19 (m, 2H $\text{CH}_2\text{CH}_2\text{OSO}_2\text{PhCH}_3^{\circ+\text{m}}$), 4.70–4.82 (m, 2 \times 0.33H, $\text{CH}_2\text{CHOH}^{\text{m}}$), 4.87–5.01 (m, 2 \times 0.17H, $\text{CH}_2\text{CHOH}^{\circ}$), 5.18 (dd, $J = 8.1/5.3$ Hz, 0.33H, 1- H_{bf}^{m}), 5.22–5.27 (m, 0.17H, 1- H_{bf}°), 5.29 (ddd, $J = 7.3/4.6/1.9$ Hz, 0.33H, 1- H_{bf}^{m}), 5.33–5.40 (m, 0.17H, 1- H_{bf}°), 6.03 (s, 0.33H, 3- H_{bf}^{m}), 6.05 (s, 0.17H, 3- H_{bf}°), 6.08 (d, $J = 2.0$ Hz, 0.33H, 3- H_{bf}^{m}), 6.10 (d, $J = 2.0$ Hz, 0.17H, 3- H_{bf}°), 7.24–7.31 (m, 1H, $H_{\text{arom}}^{\circ+\text{m}}$), 7.31–7.42 (m, 10 \times 0.33H, $H_{\text{arom}}^{\circ+\text{m}}$), 7.47 (dd, $J = 8.3/3.1$ Hz, 2H, $H_{\text{arom}}^{\circ+\text{m}}$), 7.78 (dt, $J = 8.3/2.1$ Hz, 5 \times 0.33H, $H_{\text{arom}}^{\circ+\text{m}}$). Ratio of diastereomers 33:33:17:17. * A signal (3 \times 0.17H) for the OCH_3 moiety of the fourth isomer cannot be observed in the spectrum, because the water peak of $\text{DMSO-}d_6$ is overlapping with this signal. $^{\circ}$ = minor isomer; $^{\text{m}}$ = major isomer; bf = benzofuran. $^{13}\text{C-NMR}$ (151 MHz, $\text{DMSO-}d_6$): δ [ppm] = 28.7 $^{\circ}$ (2 \times 0.17C, CH_3Ph), 29.6 $^{\text{m}}$ (0.33C, CH_3Ph), 30.9 $^{\text{m}}$ (0.33C, CH_3Ph), 35.2 $^{\text{m}}$ (2 \times 0.33C, $\text{CH}_2\text{CH}_2\text{OSO}_2\text{PhCH}_3$), 35.3 $^{\circ}$ (2 \times 0.17C, $\text{CH}_2\text{CH}_2\text{OSO}_2\text{PhCH}_3$), 43.1 $^{\text{m}}$ (0.33C, CH_2CHOH), 43.9 $^{\circ}$ (0.17C, CH_2CHOH), 44.7 $^{\text{m}}$ (0.33C, CH_2CHOH), 45.6 $^{\circ}$ (0.17C, CH_2CHOH), 53.2 $^{\text{m}}$ (0.33C, OCH_3), 53.7 $^{\text{m}}$ (0.33C, OCH_3), 54.6 $^{\circ}$ (2 \times 0.17C, OCH_3), 63.2 $^{\circ}$ (2 \times 0.17C, CH_2CHOH), 63.3 $^{\text{m}}$ (2 \times 0.33C, CH_2CHOH), 68.1 $^{\circ}$ (2 \times 0.17C, $\text{CH}_2\text{CH}_2\text{OSO}_2\text{PhCH}_3$), 68.2 $^{\text{m}}$ (2 \times 0.33C, $\text{CH}_2\text{CH}_2\text{OSO}_2\text{PhCH}_3$), 79.0 $^{\circ}$ (2 \times 0.17C, C-1), 79.2 $^{\text{m}}$ (2 \times 0.33C, C-1), 105.4 $^{\text{m}}$ (0.33C, C-3), 105.5 $^{\circ}$ (0.17C, C-3), 105.8 $^{\circ}$ (0.17C, C-3), 105.9 $^{\text{m}}$ (0.33C, C-3), 120.9 $^{\circ+\text{m}}$ (0.50C, C_{arom}), 121.2 $^{\circ+\text{m}}$ (0.50C, C_{arom}), 122.7 $^{\circ+\text{m}+\circ}$ (0.33C + 2 \times 0.17C, C_{arom}), 122.71 $^{\text{m}}$ (2 \times 0.33C, C_{arom}), 127.3 $^{\circ+\text{m}}$ (2C, C_{arom}), 127.33 $^{\circ+\text{m}}$ (0.50C, C_{arom}), 127.4 $^{\circ+\text{m}}$ (0.50C, C_{arom}), 128.8 $^{\circ+\text{m}}$ (0.50C, C_{arom}), 128.9 $^{\circ+\text{m}}$ (0.50C, C_{arom}), 129.9 $^{\circ+\text{m}}$ (2C, C_{arom}), 132.2 $^{\text{m}}$ (0.33C, C_{qarom}), 137.0 $^{\circ+\text{m}}$ (0.50C, C_{qarom}), 137.06 $^{\circ}$ (0.17C, C_{qarom}), 142.9 $^{\text{m}}$ (0.33C, C_{qarom}), 142.92 $^{\text{m}}$ (0.33C, C_{qarom}), 143.0 $^{\circ}$ (0.17C, C_{qarom}), 143.2 $^{\circ}$ (0.17C, C_{qarom}), 144.5 $^{\circ+\text{m}}$ (1C, C_{qarom}). Ratio of diastereomers 33:33:17:17. $^{\circ}$ = minor isomer; $^{\text{m}}$ = major isomer. FTIR (neat): ν (cm^{-1}) = 3506 (O-H), 2920 (C-H), 1173 (RO-SO $_2$ R 1), 1096(C-O), 752, 737, 664 (C-H $_{\text{arom}1,2}$ - and 1,4-disubst).

4-Azido-1-(3-methoxy-1,3-dihydro-2-benzofuran-1-yl)butan-2-ol (**21a**) (four diastereomers). A solution of tosylates **20a** (46.6 mg, 0.12 mmol) in dry DMF (1 mL) was treated with NaN_3 (23.2 mg, 0.36 mmol). The reaction mixture was heated to 90 °C for 3 h. The solvent was removed in vacuo. The crude product was purified by fc ($\varnothing = 2$ cm, $h = 12$ cm, cyclohexane: ethyl acetate (7:3), $V = 10$ mL, $R_f = 0.48$). Pale yellow oil, yield 28.7 mg (92%), mixture of four diastereomers (2:2:1:1). $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3$ (263.3). Exact Mass (APCI): $m/z = 234.1121$, calcd. 234.1125 for $\text{C}_{13}\text{H}_{16}\text{NO}_3$ [$\text{M} - \text{N}_2 - \text{H}$] $^+$; $m/z = 204.1027$, calcd. 204.1019 for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ [$\text{M} - \text{N}_2 - \text{OCH}_3$] $^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 1.64–2.16 (m, 4H, $\text{CH}_2\text{CHOHCH}_2^{\circ+\text{m}}$), 3.26–3.74 (m, 5H, $\text{OCH}_3^{\circ+\text{m}}$ (3H), $\text{CH}_2\text{CH}_2\text{N}_3^{\circ+\text{m}}$ (2H)), 3.87–4.06 (m, 2 \times 0.17H, $\text{CH}_2\text{CHOH}^{\circ}$), 4.20 (dddd, $J = 9.5/6.9/5.1/2.2$ Hz, 2 \times 0.33H, $\text{CH}_2\text{CHOH}^{\text{m}}$), 5.35–5.42 (m, 0.33H, 1- H_{bf}^{m}), 5.46 (dd, $J = 7.8/3.3$ Hz, 0.17H, 1- H_{bf}°), 5.54 (dt, $J = 10.4/2.5$ Hz, 0.33H, 1- H_{bf}^{m}), 5.63 (d, $J = 7.6$ Hz, 0.17H, 1- H_{bf}°), 6.11 (s, 0.17H, 3- H_{bf}°), 6.16 (s, 0.33H, 3- H_{bf}^{m}), 6.18 (d, $J = 2.0$ Hz, 0.17H, 3- H_{bf}°), 6.20 (d, $J = 2.1$ Hz, 0.33H, 3- H_{bf}^{m}), 7.17–7.22 (m, 1H, H_{arom}), 7.35–7.42 (m, 3H, H_{arom}). Ratio of diastereomers 33:33:17:17. Signals due to the OH protons are not observed in the spectrum. $^{\circ}$ = minor isomer; $^{\text{m}}$ = major isomer; bf = benzofuran. $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ [ppm] = 36.7 $^{\circ}$ (0.17C,

CH₂CH₂N₃), 36.8° (0.17C, CH₂CH₂N₃), 36.84^m (0.33C, CH₂CH₂N₃), 36.9^m (0.33C, CH₂CH₂N₃), 42.4° (0.17C, CH₂CHOH), 43.4^m (0.33C, CH₂CHOH), 44.1° (0.17C, CH₂CHOH), 44.6^m (0.33C, CH₂CHOH), 48.5^m (0.33C, CH₂CH₂N₃), 48.6^m (0.33C, CH₂CH₂N₃), 48.8° (2 × 0.17C, CH₂CH₂N₃), 55.1^{o+m} (0.50C, OCH₃), 55.7^m (0.33C, OCH₃), 56.1° (0.17C, OCH₃), 66.5° (0.17C, CH₂CHOH), 66.7° (0.17C, CH₂CHOH), 68.8^m (0.33C, CH₂CHOH), 69.0^m (0.33C, CH₂CHOH), 81.1° (0.17C, C-1), 81.6° (0.17C, C-1), 83.8^m (0.33C, C-1), 84.0^m (0.33C, C-1), 107.1° (0.17C, C-3), 107.3^m (0.33C, C-3), 108.2^{o+m} (0.50C, C-3), 121.27^m (0.33C, C_{arom}), 121.30° (0.17C, C_{arom}), 121.5^m (0.33C, C_{arom}), 121.53° (0.17C, C_{arom}), 123.6° (0.17C, C_{arom}), 123.62^m (0.33C, C_{arom}), 123.64^m (0.33C, C_{arom}), 123.7° (0.17C, C_{arom}), 128.6° (0.17C, C_{arom}), 128.7^{o+m} (0.50C, C_{arom}), 128.8^m (0.33C, C_{arom}), 130.0^{o+m} (0.50C, C_{arom}), 130.04^{o+m} (0.50C, C_{arom}), 137.2^m (0.33C, C_{qarom}), 137.3^m (0.33C, C_{qarom}), 137.9° (0.17C, C_{qarom}), 138.0° (0.17C, C_{qarom}), 142.5° (0.17C, C_{qarom}), 142.7° (0.17C, C_{qarom}), 142.8^m (0.33C, C_{qarom}), 142.9^m (0.33C, C_{qarom}). Ratio of diastereomers 33:33:17:17. ° = minor isomer; ^m = major isomer. FTIR (neat): ν (cm⁻¹) = 3464 (O-H), 2932 (C-H), 2091 (N=N=N), 1084 (C-O), 752 (C-H_{arom 1,2-disubst}).

2-[(1RS,3RS,5RS)- and (1RS,3SR, 5RS)-1,5-Epoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (**14a**). A solution of *p*-toluenesulfonic acid in toluene (4 mL, 0.5 mg/mL) was added to diols **13a** (49.2 mg, 0.21 mmol). The reaction mixture was heated to 85 °C for 72 h. Saturated aqueous solution of NaHCO₃ (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layer was dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was purified by fc (Ø = 2 cm, h = 12 cm, CH₂Cl₂:ethyl acetate (6:4), V = 10 mL, R_f = 0.46 (1st isomer), 0.35 (2nd isomer)). Colorless solid, yield 7.23 mg (17%), mixture of two diastereomers (1:1). C₁₂H₁₄O₃ (206.2). Exact mass (APCI): *m/z* = 207.1014, calcd. 207.1016 for C₁₂H₁₅O₃ [MH]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 1.52–1.93 (m, 2.5H, 4-*H*_{eq} (1H), CH₂CH₂OH (1.5H)), 2.00 (m, 1.5H, CH₂CH₂OH (0.5H), 4-*H*_{ax} (1H)), 3.66–3.81 (m, 2H, CH₂CH₂OH), 3.82–3.93 (m, 1H, 3-*H*_{ax} (0.5H), 3-*H*_{eq} (0.5H)), 4.61 (d, *J* = 4.4 Hz, 0.5H, CH₂CH₂OH), 4.73 (d, *J* = 5.7 Hz, 0.5H, CH₂CH₂OH), 5.33 (d, *J* = 10.8 Hz, 0.5H, 5-*H*_{eq}), 5.41 (dd, *J* = 7.9/3.6 Hz, 0.5H, 5-*H*_{eq}), 6.05 (s, 0.5H, 1-*H*_{eq}), 6.09 (s, 0.5H, 1-*H*_{eq}), 7.26–7.44 (m, 4H, H_{arom}). Ratio of diastereomers 50:50. FTIR (neat): ν (cm⁻¹) = 3372 (O-H), 2874 (C-H), 1462 (C=C_{arom}), 1080 (C-O), 748 (C-H_{arom 1,2-disubst}).

2-[(1RS,3RS,5RS)- and (1RS,3SR,5RS)-1-Methyl]-1,5-epoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (**14b**). A solution of diols **13b** (50.0 mg, 0.2 mmol) in a mixture of toluene/AcOH (4:1, 5 mL) was stirred at r.t. for 72 h. Saturated aqueous Solution of NaHCO₃ (5 mL) was added. The mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was purified by fc (Ø = 2 cm, h = 10 cm, ethyl acetate/cyclohexane (1:1)), V = 10 mL, R_f = 0.45 (1st spot) and 0.25 (2nd spot). Yellow oil, yield 2.6 mg (6%) mixture of two diastereomers (1:1). C₁₄H₂₀O₄ (220.27). ¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 1.26 (2s, 3H, 6 × 0.5H, CH₃), 1.62–1.89 (m, 1H, 4-*H*_{eq} (0.5H) *, CH₂CH₂OH (0.5H)), 1.89–2.15 (m, 1.5H, CH₂CH₂OH), 2.17–2.33 (m, 1H, 2 × 0.5H, 4-*H*_{ax}), 3.88 (dd, *J* = 12.0/4.7 Hz, 1H**, 2 × 0.5H, CH₂CH₂OH), 3.94–3.98 (m, 1H **, 2 × 0.5H, CH₂CH₂OH), 4.01–4.09 (m, 0.5H, 3-*H*_{ax}), 4.08–4.14 (m, 0.5H, 3-*H*_{ax}), 5.31–5.36 (m, 0.5H, 5-*H*_{eq}), 5.67 (dd, *J* = 6.1/2.7 Hz, 0.5H, 5-*H*_{eq}), 7.19 (m, 1H, 2 × 0.5H, H_{arom}), 7.29–7.47 (m, 3H, 6 × 0.5H, H_{arom}). Ratio of diastereoisomers 50:50. * Signals for one isomer is overlapping with other signals including the signal for the residual water in CDCl₃. ** Signals are slightly higher than expected due to impurities. Due to the low amount of **18b** the ¹³C-NMR, IR and MS spectra could not be recorded.

(1RS,3SR,5RS)-3-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-1,5-epoxy-1,3,4,5-tetrahydro-2-benzoxepine (**22a**). In toluene (5 mL), silyl ethers **19a** (26.6 mg, 0.08 mmol) were treated with 0.1 M HCl in AcOH (15 µL) and was heated to 65 °C for 60 h. The reaction mixture was diluted with EtOAc (10 mL) and was washed with saturated aqueous solution of NaHCO₃ (3 × 5 mL). The pooled organic phase was dried (Na₂SO₄), filtered, and the solvent was removed in vacuo. The crude product was purified by fc (Ø = 2 cm, h = 10 cm, cyclohexane: ethyl acetate (9:1), V = 10 mL, R_f = 0.48). Colorless oil, yield 4.5 mg (19%). C₁₈H₂₈O₃Si (320.5). ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = -0.12 (s, 3H, (CH₃)₂^tBuSi),

−0.14 (s, 3H, $(\text{CH}_3)_2^t\text{BuSi}$), 0.68 (s, 9H, $\text{Me}_2(\text{C}(\text{CH}_3)_3\text{Si})$), 1.44 (ddd, $J = 13.8/7.7/1.9$ Hz, 1H, 4- H_{eq}), 1.50–1.62 (m, 2H, $\text{CH}_2\text{CH}_2\text{OTBDMS}$), 2.01 (ddd, $J = 13.2/11.2/3.7$ Hz, 1H, 4- H_{ax}), 3.20–3.28 (m, 1H, 3- H_{ax}), 3.44–3.53 (m, 2H, CH_2OTBDMS), 5.23 (dd, $J = 3.7/1.8$ Hz, 1H, 5- H_{eq}), 6.12 (s, 1H, 1- H_{eq}), 7.25–7.37 (m, 4H, H_{arom}).

(1*RS*,3*SR*,5*RS*)-3-(2-Azidoethyl)-1,5-epoxy-1,3,4,5-tetrahydro-2-benzoxepine (**23a**). A solution of *p*-toluenesulfonic acid in toluene (5 mL, 0.5 mg/mL) was added to azide **21a** (69.8 mg, 0.27 mmol). The reaction mixture was heated to 85 °C for 72 h. Saturated aqueous solution of NaHCO_3 (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The crude product was purified by fc ($\varnothing = 2$ cm, $h = 12$ cm, cyclohexane: ethyl acetate (8:2), $V = 10$ mL, $R_f = 0.45$). Yellow oil, yield 7.7 mg (13%). $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$ (231.3). After fc purification, only one diastereomer was isolated. MS (ESI): $m/z = 424$ [$2(\text{M} - \text{OCH}_3) + \text{Na} + \text{H}$] $^+$, 232 [MH] $^+$, 204 [$\text{M} - \text{N}_2 + \text{H}$] $^+$. $^1\text{H-NMR}$ (400 MHz, CD_2Cl_2): δ [ppm] = 1.54–1.66 (m, 2H, 4- H_{eq} (1H), $\text{CH}_2\text{CH}_2\text{N}_3$ (1H)), 1.76 (ddt, $J = 14.5/8.7/5.8$ Hz, 1H, $\text{CH}_2\text{CH}_2\text{N}_3$), 2.17 (ddd, $J = 13.0/11.1/3.7$ Hz, 1H, 4- H_{ax}), 3.22–3.35 (m, 3H, $\text{CH}_2\text{CH}_2\text{N}_3$ (2H), 3- H_{ax} (1H)), 5.22 (dd, $J = 3.8/1.8$ Hz, 1H, 5- H_{eq}), 6.11 (s, 1H, 1- H_{eq}), 7.28–7.40 (m, 4H, H_{arom}). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ [ppm] = 35.1 (1C, $\text{CH}_2\text{CH}_2\text{N}_3$), 37.6 (1C, C-4), 47.2 (1C, $\text{CH}_2\text{CH}_2\text{N}_3$), 65.3 (1C, C-3), 77.9 (1C, C-5), 100.8 (1C, C-1), 119.6 (1C, C_{arom}), 121.3 (1C, C_{arom}), 128.0 (1C, C_{arom}), 128.6 (1C, C_{arom}), 138.7 (1C, C_{qarom}), 143.0 (1C, C_{qarom}). FTIR (neat): ν (cm^{-1}) = 2874 (C-H), 2095 (N=N=N), 1015 (C-O), 756 (C- H_{arom} 1,2-disubst).

4. Conclusions

Herein the synthesis of 1,3-dioxanes is reported, which are bearing a phenyl moiety in the axial orientation at the acetalic center without any freedom to rotate around the phenyl-C-bond. Two subsequent intramolecular transacetalization reactions represent the key steps in the synthesis of the tricyclic compounds **14**, **22**, and **23**. The central hydroxyacetals **12** were prepared in a three-step sequence starting from pentane-1,3,5-triol (**10**). Whereas the first intramolecular transacetalization of **12** under mild reaction conditions resulted in high yields of 2-benzofurans **18**, the second intramolecular transacetalization of **13** gave only low yields of tricyclic alcohols **14** even after several optimization experiments. Protection or substitution of the competing primary alcohol of **13a** did not result in higher yields of tricyclic silyl ether **22a** or azide **23a**. Since only one isomer of **22a** and **23a** was isolated and the major isomer remained partly unchanged after cyclization of **19a** and **21a**, it was postulated that the minor isomers of **19a** and **21a** reacted faster than the major isomers. Due to fast decomposition, the transformations of ketalic compounds (**b**-series) required milder reaction conditions than the acetalic compounds (**a**-series).

Supplementary Materials: Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/21/11/1503/s1>.

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