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Substituent effects on the reaction mode between 2-hydroxybenzyl alcohol derivatives and MEM chloride: synthesis and mechanistic aspects of seven- and ten-membered benzo-fused *O*,*O*-acetals

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Abstract—The synthesis of (*RS*)-2- or (*RS*)-3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins and (*RS*)-5- or (*RS*)-3-methoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecins has been developed. The mechanism of such a reaction via the boron trifluoride etherate-promoted transformation of 2-(methoxyethoxymethoxy)benzyloxyacetaldehyde dimethyl acetals or 2-(methoxyethoxymethoxymethyl)phenyloxy-acetaldehyde dimethyl acetals has been proposed. Transannular versions of the reaction results in the facile ring contraction of 12-membered intermediates to the 10- and to 7-membered benzene-fused *O*,*O*-acetals. The characterization of the by-products strongly supports the mechanisms proposed.

1. Introduction

Selective protection and deprotection of functional groups is one of the major issues in multistep synthetic strategies of organic compounds. In particular, hydroxyl groups are targets for selective protection, because selectively accessible OH-groups are often required for the following reaction. Many OH-protecting groups are known and the ability to protect a primary hydroxyl group in the presence of a secondary one was found with a variety of protecting reagents.[1,2] It has lately been shown that hydroxyalkyl phenols undergo selective protection either at the hydroxyl or at the phenol group by simply choosing the protecting reagent under essentially the same reaction conditions.[3] A literature survey revealed no reports on the regioselective protection of 2-hydroxybenzyl alcohol derivatives as a function of the electronic nature of the substituents at positions 3 or 5 of the aromatic ring. Accordingly, we decided to fill this gap in scientific literature and, at the same time, to use this synthetic tool for the preparation of isomeric seven-membered benzo-fused *O*,*O*-acetals, and isomeric ten-membered benzo-fused analogues.

We have recently reported the synthesis and biological activities of 2,3-dihydro-5*H*-1,4-benzodioxepin derivatives condensed with the 5-fluorouracil (5-FU) moiety on position 3 (**1**).[4] For these compounds the starting materials were the 2,3-dihydro-5*H*-1,4-benzodioxepin synthons **2a**–**c**. We embarked on a programme of synthesis and study of the biological properties of 2,3-dihydro-5*H*-1,4-benzodioxepin fragments that have the pyrimidine base linked in all the possible sites of the seven-membered ring, and directed our efforts in a second phase to the preparation of the cyclic *O*,*O*-acetal **3a**,**d**,**e**, with the acetalic methoxy group on position 2. The mechanistic aspects of the reaction between the acyclic *O*,*O*-acetals **4a**–**g** or the cyclic ones **2a**–**c** and 5-fluorouracil (5-FU) have been reported.[5] In the course of our present studies, the benzo-fused ten-membered *O*,*O*-acetals **5a**,**d**,**e** were also obtained. Here we report the three-step synthesis of **3a**,**d**,**e** and **5a**,**d**,**e**, together with their mechanisms. When the 2-hydroxybenzyl alcohol has a 5-OMe group or a 3-OMe substituent, the final compounds are the seven-membered *O*,*O*-acetals **2b**,**c**, together with **6c**. The importance of the ten-membered *O*,*O*-acetals **5a**,**d**,**e** and **6c** lies in the following: (a) These unreported structures could be the starting synthons for the preparation of the

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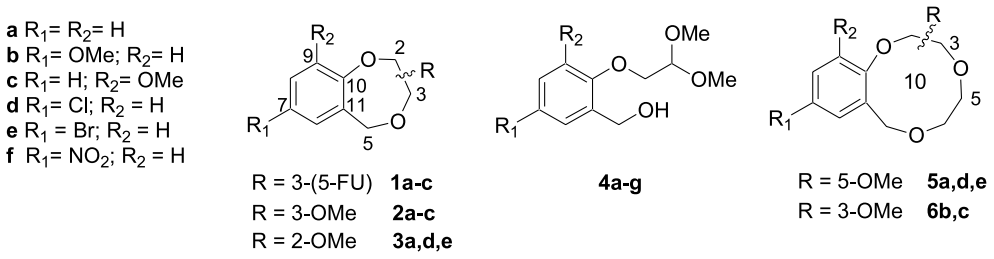


Chart 1.

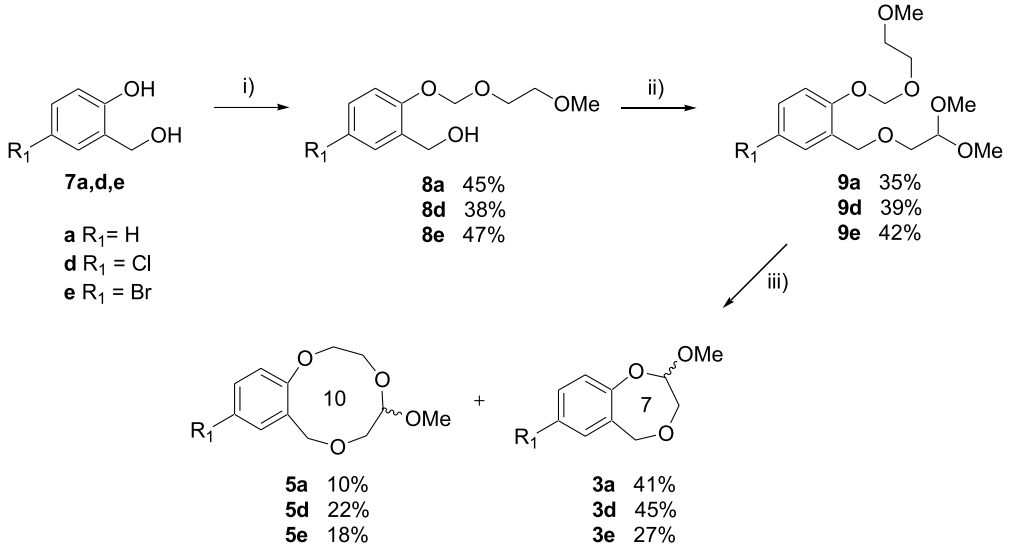
corresponding ten-membered *O*,*N*-acetals that, in a similar way to what was reported for the fourteen-membered bis(5-FU *O*,*N*-acetals), could exhibit notable biological activities against breast cancer cells; and (b) their formation sheds light on the mechanism of reaction in which the neighbouring-group participation plays a pivotal role (Chart 1).

2. Results and discussion

2.1. Reaction between 2-hydroxybenzyl alcohols 7a,d,e and 2-methoxyethoxymethyl chloride

Before carrying out the synthesis of **3a**,**d**,**e** it is necessary to protect the phenolic hydroxy group of the 2-hydroxybenzyl alcohol **7a**. Among other functionalities, the 2-methoxyethoxylmethyl (MEM) group was developed as a protective group of alcohols[6] and phenols.[7] Nevertheless, this protective group does not present enough selectivity and also leads to the blocking of the benzylic alcohol. Accordingly, the protection reaction with MEMCl has been carried out under several conditions, with the object of improving its modest selectivity in favour of **8a** and to the detriment of 2-(methoxyethoxymethoxymethyl)phenol, by using several bases and solvents. Such a study was performed on 2-hydroxybenzyl alcohol (salicyl alcohol) **7a**. We have studied three experimental conditions: (a) acetone and potassium carbonate; (b) sodium hydride and tetrahydrofuran (THF); and (c) diisopropylethylamine (DIPEA) and methylene chloride. The better yield in compound **6a** was obtained using conditions (a) (See Section 4).

Both MEM ethers [2-(methoxy-2-ethoxymethoxymethyl) phenol and **8a**] possess similar polarities (very close R_f, 0.3 and 0.2, respectively, using diethyl ether/hexane: 3/1 as eluant) and spectroscopic properties. Both compounds show the same molecular-ion peak of M^+ (calculated for $C_{11}H_{16}O_4Na$ $(M+Na)^+$ 235.0946, found 235.0946) in their high resolution liquid secondary ion mass spectrum (HR LSIMS) spectra, confirming that both have incorporated the MEM moiety into their structures. We thought that in the corresponding ^1H NMR spectra the chemical shift of the –O–CH_2–O– group could serve as a probe to decide the identity of both isomers: in compound **8a** such a group should appear at a lower field (δ 5.34 ppm) than in compound 2-(methoxy-2-ethoxymethoxymethyl)phenol (δ 4.85 ppm), due to the electron-withdrawing effect originated by the phenoxy moiety. Once the structure of **8a** had been demonstrated we decided to extend the reaction starting with 2-hydroxybenzyl alcohols with different substituents on the aromatic ring (**8d**,**e**). The synthesis of the cyclic *O*,*O*-acetals was carried out in a three-step process: (a) the formation of MEM ethers **8a**,**d**,**e** using MEMCl (1.5 equiv), K_2CO_3 (1.1 equiv), the salicyl alcohols (1 equiv) in acetone as solvent at 0 °C, under an inert atmosphere; (b) preparation of the intermediate acyclic *O*,*O*-acetals **9a**,**d**,**e** by alkylation of the benzylic hydroxy group with bromoacetaldehyde dimethyl acetal, using sodium hydride as a base and anhydrous



Scheme 1. Reagents: (i) K_2CO_3, anhydrous acetone, MEMCl; (ii) $BrCH_2CH(OMe)_2$, NaH, anhydrous DMF; (iii) $BF_3 \cdot OEt_2$ in anhydrous Et_2O.

dimethylformamide (DMF) as solvent; and (c) the cleavage of the MEM moiety and subsequent cyclization to yield the target molecules **3a**,**d**,**e**. In the original paper, which introduced the MEM group as a protective group for the hydroxyl function,[6] the advantages of using anhydrous $ZnBr_2$ or $TiCl_4$ over other Lewis acids were highlighted. We have reported the $BF_3 \cdot OEt_2$-mediated seven-membered cyclization of acyclic *O*,*O*-acetals[4,8,9] and accordingly, we supposed that the use of such a catalyst could lead to the target molecules **3a**,**d**,**e** in a one-step/pot reaction, as a consequence of the simultaneous deblocking/cyclization process. The experimental results confirmed our hypothesis but, in addition to the expected benzofused seven-membered *O*,*O*-acetals **3a**,**d**,**e**, the ten-membered *O*,*O*-acetals **5a**,**d**,**e** were also produced (Scheme 1).

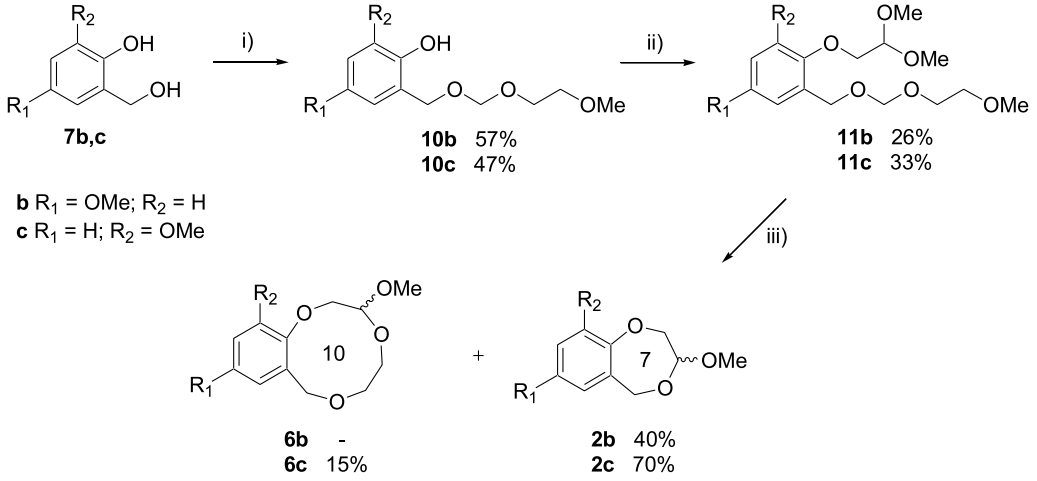
In order to confirm the structures of the compounds, we focused our attention on the NMR chemical shift of the benzylic carbon atoms and found that in the case of **8a**,**d**,**e**, the range covers a narrow interval of ≈ 1 ppm (in $CDCl_3$): δ 61.58 ppm (**9a**), δ 60.62 ppm (**9d**), and δ 60.41 ppm (**9e**).

2.2. Reaction between 2-hydroxybenzyl alcohols 7b,c and 2-methoxyethoxymethyl chloride

Nevertheless, when we tried to extend this series of reactions with the aim of obtaining **8b**,**c**, starting from the salicyl alcohols **7b**,**c**, their ^{13}C NMR chemical behaviour was not compatible with such structures on the basis of the chemical shifts of the benzylic carbon atoms, that is, δ 66.80 ppm when the benzene ring had a 5-OMe group or δ 64.55 ppm when the aromatic substituent was the 3-OMe moiety. These two low field chemical shifts, in relation to the corresponding values of **9a**,**d**,**e** cannot be explained by the field/inductive effects of the aromatic methoxy fragments because the distance between the two centres involved is very high in both cases. However, such a chemical shift difference could be justified should the oxygen atom of the benzylic alcohol be alkylated by the MEM moiety, instead of the oxygen atom of the phenol group. Should this be the case, the sequence of reactions (Scheme 2) would lead to the previously reported seven-membered *O*,*O*-acetals **2b**,**c** (with the acetalic –OMe fragment in position 3), together with **6c** in the case of starting from **7c**. Scheme 2 depicts the synthetic route followed whose difference with respect to Scheme 1 is based on the different alkylation site by MEMCl.

Another key point is the chemical shift of the benzylic carbon atoms of both target molecules **3a**,**d**,**e** and **2b**,**c**. For compounds **2b**,**c**, such carbons are located γ (an 1,3-relationship) in relation to the acetalic methoxy groups, their ^{13}C chemical shifts being very sensitive to the steric compression. As a rule, it is found that the ^{13}C NMR chemical shifts of carbon atoms in spatially crowded alkyl groups are more upfield than similar carbon atoms in unperturbed systems. Therefore, such an effect is negligible for compounds **3a**,**d**,**e** because the proximity relationship between both groups is even higher (delta or an 1,4-relationship). Table 1 shows the ^{13}C chemical shifts of the corresponding seven-membered moieties of the cyclic *O*,*O*-acetals.

In spite of the accurate ^{13}C NMR reasoning carried out to prove the structures of **2b**,**c**, the confirmation of such compounds needed to be corroborated because this point is



Scheme 2. Reagents: (i) K_2CO_3, anhydrous acetone, MEMCl; (ii) $BrCH_2CH(OMe)_2$, NaH, anhydrous DMF; (iii) $BF_3 \cdot OEt_2$ in anhydrous Et_2O.

Table 1. ^{13}C NMR chemical shifts[a] (ppm) for the 2,3-dihydro-5*H*-1,4-dioxepin moiety in **3a**,**d**,**e** and **2b**,**c** for $CDCl_3$ solutions

	3a	3d	3e	2b[b]	2c[b]
C-2	103.99	103.99	104.04	73.00	72.37
C-3	74.86	74.85	74.85	101.54	101.25
C-5	72.87	72.37	72.32	63.23	62.85
C-10	154.30	152.85	153.45	152.91	147.90
C-11	133.26	134.80	135.27	131.15	130.49

[a] Each reading was quoted to the nearest 0.05 ppm.
[b] See Ref. 4.

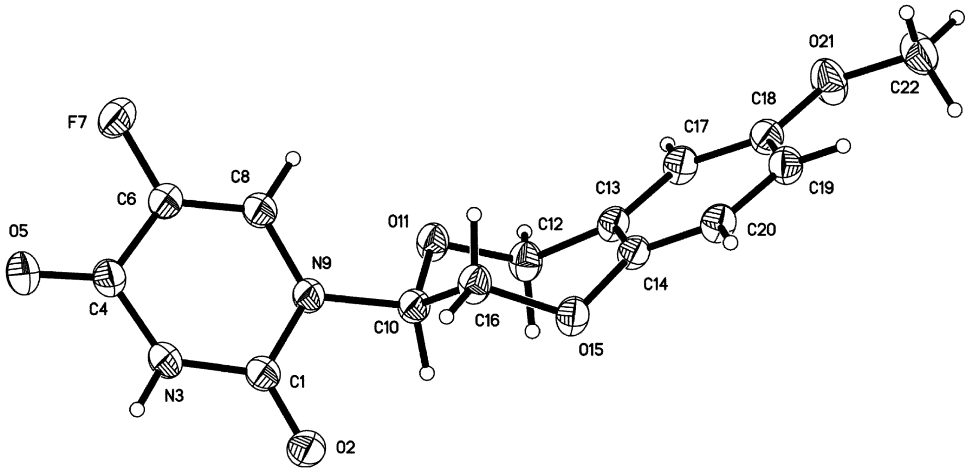


Figure 1. Molecular structure of (*RS*)-1-(7-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil (ORTEP drawing at 50% probability).

critical for the confirmation of the alkylation site of **7b** by MEMCl. There is always the chance that the structure of **2b** with the acetalic –OMe group at position 3 could have been mistaken for the corresponding analogue having the acetalic –OMe group at position 2 (the hypothetical molecule **3b**) because their ^{1}H and ^{13}C NMR data are very close. Accordingly, we decided to unequivocally elucidate the structure of the acetal (**2b** or **3b**) by its reaction with 5-fluorouracil, 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and trimethylchlorosilane (TCS), under acid catalysis ($SnCl_4$) in acetonitrile during 144 h. Such a process led to (*RS*)-1-(7-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil,[4] whose structure was unambiguously determined by X-ray crystallography (Fig. 1). Therefore, the regioselective protection of the primary hydroxy group of the corresponding salicyl alcohol was finally proved by a synthetic method, which made secure our previous structural assignments.

The explanation of the different chemical behaviour (see Schemes 1 and 2) is very simple: the acidity of phenolic compounds is modulated by electronic effects. *ortho* and *para* electron-donating groups in relation to the phenol group decrease acidity, whilst electron-withdrawing groups at the same position act in the opposite manner. As a result of both resonance and field/inductive effects, charge concentration leads to lesser stability of phenoxy anions and to a decrease in acidity.[10] Accordingly, the electronic properties of the *ortho* and *para* substituents to the hydroxy phenoxy group modifies the selectivity of the alkylation site by MEMCl.

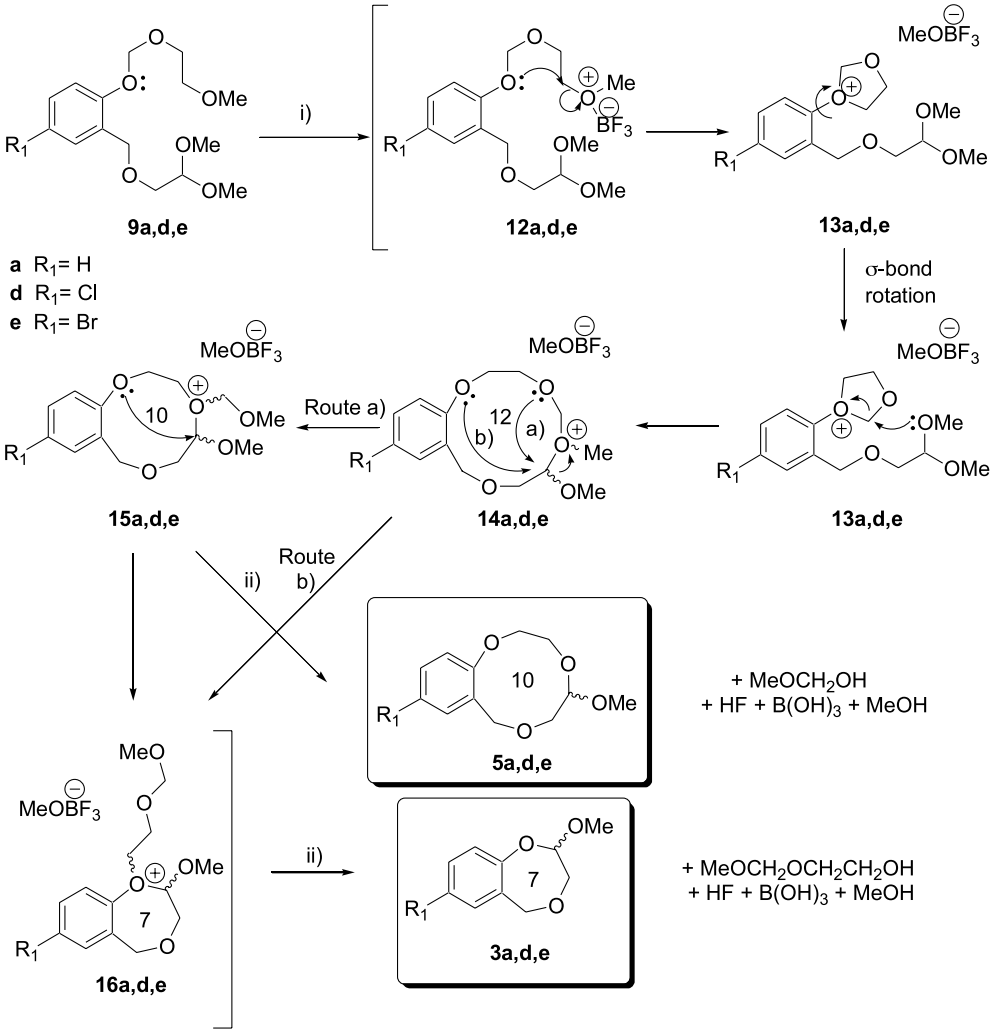
2.3. Mechanistic aspects of the synthesis of (*RS*)-2-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins 3a,d,e and (*RS*)-5-methoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecins 5a,d,e

This process is effected by the reaction of **9a**,**d**,**e** (1 equiv) in tetrahydrofuran (THF) at 0 °C under an inert atmosphere with 0.5 equiv of $BF_3 \cdot OEt_2$. If the structures of the starting material **9a**,**d**,**e** and of the final compounds **3a**,**d**,**e** and **5a**,**d**,**e** are compared, one comes to the conclusion that the MEM moiety of **9a**,**d**,**e** should suffer two different cleavage processes from a formal point of view: (a) on one hand, the breaking of the methoxyethoxymethyl moiety, then the nucleophilic attack of the phenoxy group to the acetalic functionality with the concomitant cyclization process should give rise to the seven-membered acetal **3a**,**d**,**e**; and (b) formation of the ten-membered acetal **5a**,**d**,**e** is not so obvious: the terminal methyl ether and the internal methylene-oxy group of the MEM fragment should be eliminated before or after the corresponding cyclization step takes place. Such processes are likely to occur through concerted processes and rearrangements on common intermediates. It must be emphasized that outside the protective group arena, MEMCl has been used to alkylate enolates[11] and aryllithium reagents in the presence of Ph_2TlBr.[12] MEM ethers have also proved to be a good one-carbon source for the preparation of isochromans[13] and seven- and eight-membered oxacyclic rings.[14]

Scheme 3 shows a possible mechanism for the formation of both cyclic *O*,*O*-acetals. First of all, the complexation of the ethereal oxygen atom of the methoxy group of the MEM moiety takes place with the concomitant O-*5*[†] participation of the ethereal phenoxy atom and formation of a 1,3-dioxolane-1-ylium cation. The intermediate **13a**,**d**,**e** might undergo σ-bond rotation about the C_{Ph}–O bond, and then its highly electrophilic carbon atom of the methylenedioxy fragment could be attacked by one of the acetalic –OMe groups. This would give rise to the 12-membered transition state **14a**,**d**,**e**, which could suffer a reduction of the ring size to the 10-membered intermediate **15a**,**d**,**e** by means of an intramolecular reaction and the later leaving of the methoxymethanol fragment. An O-*5* participation of the oxygen atom at position 1 and the acetalic carbon of **15a**,**d**,**e** gives rise to a ring contraction leading to **3a**,**d**,**e** through the intermediacy of the seven-membered oxonium ion **16a**,**d**,**e**.

On one hand, it could have been supposed that, rather than the formation of **16a**,**d**,**e** through the intermediates **12a**,**d**,**e**–**15a**,**d**,**e**, the synthesis of **3a**,**d**,**e** could be considered more directly and simply from the open acetals **9a**,**d**,**e** by nucleophilic attack of the phenoxy oxygen to the acetalic

[†] When describing nucleophilic participation it is frequently convenient to use the symbol G-*n*, where G is the participating group and *n* the size of the ring that is formed in the transition state.



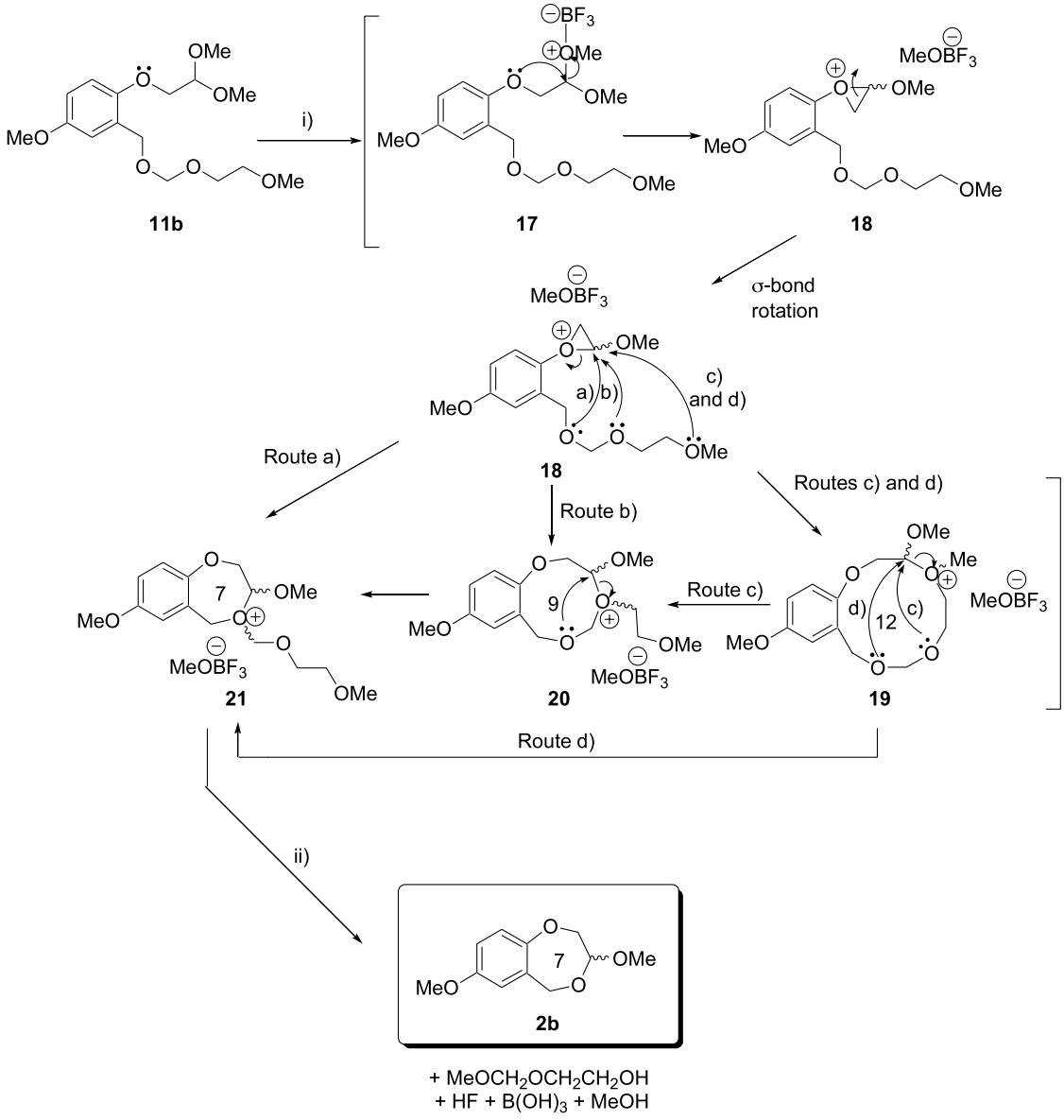
Scheme 3. Reagents: (i) $BF_3 \cdot OEt_2$, THF; (ii) H_2O.

functionality, after complexation by BF_3 of one of the acetalic oxygens. Then the intermediate analogous to **16a**,**d**,**e** should arise, but in this case substituted on the oxonium oxygen by a 2-methoxyethoxymethyl group. Cleavage of this group should also deliver **3a**,**d**,**e**. Nevertheless, the proof of the presence of the by-product 2-(methoxymethoxy)ethanol[15] (See Section 4), formed through **12a**,**d**,**e**–**15a**,**d**,**e**, and the absence of methoxyethoxymethanol, arising directly from **9a**,**d**,**e**, allow us to settle the proposed mechanism. On the other hand, it has been checked that the seven-membered rings **3a**,**d**,**e** (major products of the rearrangements) do not arise from the ten-membered rings **5a**,**d**,**e**, upon treatment of the latter with boron trifluoride diethyl etherate under the conditions of the rearrangement.

2.4. Mechanistic aspects on the synthesis of (*RS*)-3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins 2b,c and (*RS*)-3-methoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecins 6c

When the starting materials are **11b** and **11c**, both the nature and the yields of the final compounds, are determining factors to shed light on the two different mechanisms that could explain the course of the cyclization/contraction reaction. We believe that the mechanism of the transformation **11b**→**2b** is best represented as in Scheme 4. The aromatic –OMe substituent has an influence on the course of the reaction: the phenolic oxygen atom (O-1), whose nucleophilicity may be strongly influenced by the electronic character of the 4-OMe moiety, should intervene as a neighbouring group. We have previously reported a similar feature.[4] According to this hypothesis, the intermediate **17** suffers the neighbouring group attack to give the oxyranium ion **18**, much more reactive than its predecessor. After a σ-bond rotation through the $C–O^+$ bond of this highly reactive species, the acetalic-like carbon atom could be attacked by either of the three oxygen atoms of the adjacent lateral chain [routes (a), (b), or (c) and (d)]. Through any of the twelve- or nine-membered intermediates (**19** and **20**, respectively), the final destiny is the seven-membered intermediate **21**, which after work up leads to **2b**. The characterization of the by-product 2-(methoxymethoxy)-ethanol justifies the proposed mechanism (See Section 4).

The most important feature of this mechanism is the electrophilic character of the acetalic carbon atom. Nevertheless, the course of the reaction that leads to **2c** and **6c** is

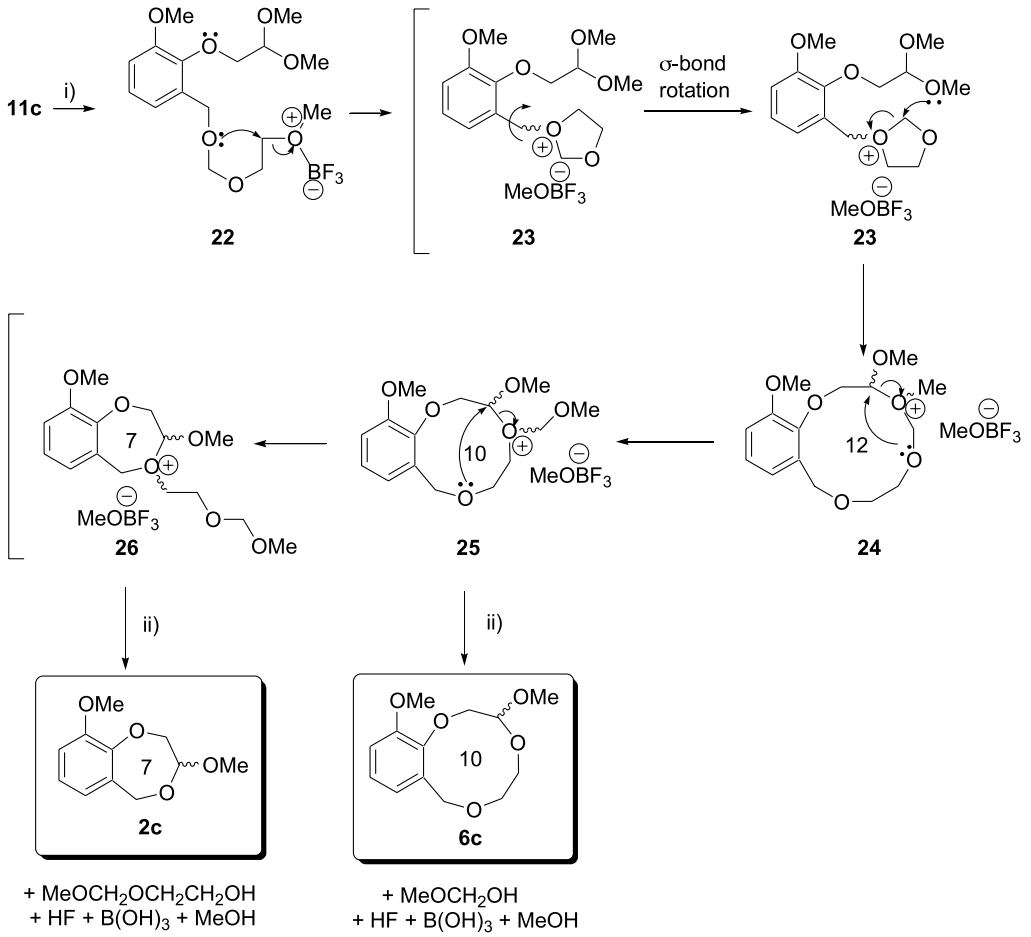


Scheme 4. Reagents: (i) $BF_3 \cdot OEt_2$, THF; (ii) H_2O.

different (Scheme 5). In this case and via a different mechanism, closely related to the one shown in Scheme 3, the acetalic –OMe group acts as a nucleophile and the MEM-derived chain as a good electrophile through the 1,3-dioxolane-1-ylium cation **23**. Again, the proof of the presence of 2-(methoxymethoxy)ethanol[15] and methoxymethanol[16] strongly supports the mechanism.

An important question that needs to be answered is the following: Why this different behaviour if in **11b** and in **11c** the aromatic –OMe groups are *para* and *ortho*, respectively, in relation to the phenolic oxygen atom that carries the acetaldehyde dimethyl acetal moiety? Although the electronic effects of the –OMe group in both positions are composed of field/inductive and resonance effects, the latter is far more important and, in principle, the mechanisms of the transformations **11b**→**2b** (Scheme 4) and **11c**→**2c**+**6c** (Scheme 5) should have been the same. Should this be the case, Chart 2 shows the two key intermediates, one of them (**27**) is highly unstable due to the closeness of both positive charges and accordingly very unlikely.

In short, when in the doubly protected salicyl alcohol the substituent R_1, *para* in relation to the phenolic oxygen atom, is electronical neutral (H), electron-withdrawing (Cl, Br) or electron-releasing groups the phenolic *O*-linked moiety acts as an electrophile and the alcoholic *O*-linked fragment acts as a nucleophile (Schemes 3 and 4). Nevertheless, the differences in nucleophilicity and electrophilicity of such groups are so subtle that the presence of an electron-releasing group *ortho* in relation to the phenolic *O*-linked fragment can invert the reactivity of both lateral chains: that is to say, the unstability of the intermediate **27** makes the upper *O*-phenolic fragment to act as electrophile and, accordingly the lower alcoholic *O*-linked moiety to work as nucleophile (Scheme 5). Such behaviour can be confirmed after the structural proofs of the by-products methoxymethanol and methoxymethoxyethanol.



Scheme 5. Reagents: (i) $BF_3 \cdot OEt_2$, THF; (ii) H_2O.

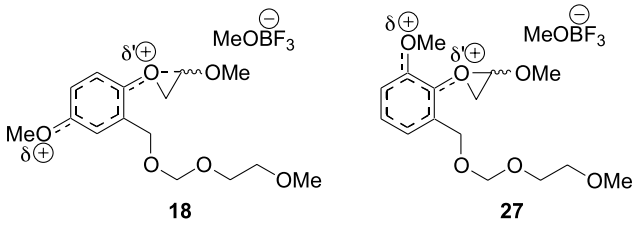


Chart 2.

2.5. Structural characteristics of the seven-membered *O*,*O*-acetals (3a,d,e and 2b,c), and the ten-membered ones (5a,d,e and 6c)

The structures of all derivatives were ascertained by their spectroscopic data (^{1}H, ^{13}C NMR, MS) and elemental analyses. In compounds **3a**,**d**,**e** the acetalic hydrogen atom (H-2) appears between δ 4.65–4.89 ppm as double of doublets (dd), whilst the H-3 atoms resonate between δ 4.00–4.22 ppm as dd with a J_{gem} in the range of 12.5–13.00 Hz. The H-5 atoms are in all cases diastereotopic and compounds **3d**,**e** show a $J_{gem} \approx 14$ Hz. Nevertheless, in the case of **2a**–**c** their chemical shifts are nearly equivalent giving an aspect of a doublet (d) with a small coupling constant ($J = 1.50$–2.10 Hz). It is noteworthy that the chemical shifts of the acetalic –OMe group of compounds **3d**,**e** are located upfield (δ 3.46–3.47 ppm) in relation to the same signals of **2a**–**c** (δ 3.56–3.62 ppm). Regarding the ^{13}C NMR spectra, the acetalic C-2 atoms of **3d**,**e** (δ 101.32–101.40 ppm) are upfield in relation to the same signals of **2a**–**c** (δ 103.99–104.04 ppm). This tendency is also observed with C-3 [**3d**,**e** (δ 72.43–72.80 ppm) and **2a**–**c** ($\delta \approx 74.8$ ppm)] and C-5 [**3d**,**e** (δ 62.93–63.05 ppm) and **2a**–**c** (δ 72.87–72.32 ppm)].

The 10-membered cycloacetals **5a**,**d**,**e** show the following characteristics: (a) The resonance of the acetalic proton H-5 appears between δ 4.77–4.81 ppm as dd with coupling constants of 1.7 and 6.6 Hz; (b) the signals of H-8 resonate as dd at a δ value between 4.56–4.65 ppm with $J = 1.2$–2.6 Hz and $J_{gem} \approx 13.3$–14.1 Hz; (c) the protons of the methylene groups H-2, H-3 and H-6 appear as multiplets; and (c) the singlet of the acetalic –OMe group presents a chemical shift close in all cases to δ 3.4 ppm. The most interesting aspects of the ^{13}C NMR spectra of the 10-membered moiety of **5a**,**d**,**e** are the following: (a) The acetalic C-5 atom is the most deshielded one and appears at δ 100.47–103.22 ppm, followed by C-6 at δ 72.19–74.92 ppm, C-2 (δ 71.85–72.72 ppm), C-8 (δ 67.20–71.58 ppm) and C-3 (δ 63.05–68.25 ppm); (b) the acetalic –OMe moiety appears close to δ 59.10 ppm, except in the case of **6c** that resonates at δ 56.14 ppm; (c) the chemical shift values of **6c** appear generally slightly upfield with regard to the rest of the compounds **5a**,**d**,**e**.

3. Conclusion

Three main conclusions can be drawn from our results: (1) It has been found that the substituents on 2-hydroxybenzylic alcohols affect the protection mode with MEMCl of the two different hydroxyl groups. The 5-methoxy *O*-alcoholic-MEM-protected phenol structure was demonstrated on the following basis: (a) by ^{1}H and ^{13}C NMR assignments, and (b) by an X-ray crystallographic determination of (*RS*)-1-(7-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil, which unambiguously proved the nature of the starting material. (2) The mild reaction conditions can be of particular interest for the preparation of seven- and ten-membered benzo-fused acetals, which are otherwise difficult to prepare, although the latter ones are obtained with low yields. (3) The formation of the ten-membered *O*,*O*-acetals **5a**,**d**,**e** and **6b**,**c** and characterization of the by-products throw light on the course of the $BF_3 \cdot OEt_2$-promoted reaction on **9a**,**d**,**e** and **11b**,**c**, respectively.

4. Experimental

All moisture-sensitive reactions were performed in flame-dried glassware equipped with rubber septa under a positive pressure of dry argon. Organic extracts were dried over $MgSO_4$. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254}, the spots being developed at the UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker at 300.13 and 400.1 MHz, and at 75.78 and 100.03 MHz, respectively in $CDCl_3$ solutions. Chemical shifts were measured in δ and referenced to $CDCl_3$ (7.25 ppm for ^{1}H NMR and 77.20 ppm for ^{13}C NMR). The accurate mass determination was carried out in an AutoSpec-Q mass spectrometer arranged in an EBE geometry (Micromass Instruments, Manchester, UK) and equipped with a FAB (LSIMS) source. The instrument was operated at 8 kV of accelerating voltage and Cs^+ cations were used as primary ions. The GC/MS was carried out on a Platfom II mass spectrometer (Micromass Instruments, Manchester, UK) coupled with a Carlo Erba gas chromatograph (ThermoInstruments, CA, USA) and equipped with an EI source at 70 eV. The analysis was performed on a HP-5MS capillary column (30 m×0.25 mm×0.25 μm) in a splitless mode, inserted directly into the ion source. The temperature programme was the following: 60 °C, 10 °C/min to 300 °C, then isothermal for 10 min. The carrier gas was helium with a flow rate of 1 mL/min. Solvents were obtained dry as follows: tetrahydrofuran (THF) was distilled from benzophenone ketyl, CH_2Cl_2 was refluxed over, and distilled from CaH_2 and then stored over molecular sieves (3 Å), CH_3OH from Mg. 2-Hydroxybenzyl alcohols were kept at 40 °C and 0.1 mm Hg for 48 h. $BF_3 \cdot OEt_2$ was distilled prior to use, in an all-glass apparatus with calcium hydroxide to remove volatile acids and to reduce bumping.

4.1. Reaction between 3- or 5-substituted-2-hydroxybenzyl alcohols and 2-methoxyethoxymethyl chloride (MEMCl)

The general procedure is exemplified with the case of 2-hydroxybenzyl alcohol. Synthesis of 2-(methoxyethoxymethoxymethyl)phenol and 2-(methoxyethoxymethoxy)benzyl alcohol **8a**. K_2CO_3 (5.6 g, 40.8 mmol) were added to a solution of 2-hydroxybenzyl alcohol **7a** (5.6 g, 45.2 mmol) in anhydrous acetone (65 mL), and the suspension was left at room temperature under stirring for 30 min. After this time, the temperature of the suspension had to fall to 0 °C before the addition of MEMCl (6.85 mL, 60 mmol) and the suspension was left under stirring at 0 °C for 6 h. K_2CO_3 was filtrated and the resulting solution was concentrated in vacuo. The resulting residue was purified by flash chromatography (diethyl ether/hexane: 1/2) and the following two fractions were obtained: the first one was identified as 2-(methoxyethoxymethoxymethyl)phenol (2.58 g, 27% yield) and the second one identified as **8a** (4.31 g, 45% yield). When other conditions were used, the corresponding yields were the following: NaH and THF [2-(methoxyethoxymethoxymethyl)phenol 17%, and **8a** 17%], and DIPEA and CH_2Cl_2 [2-(methoxyethoxymethoxymethyl)phenol 50%, and **8a** 29%]. When 5-chloro-2-hydroxybenzyl alcohol **7d**, and 5-bromo-2-hydroxybenzyl alcohol **7e** were used, the 2-[(2-methoxyethoxymethoxy)]benzyl alcohols **8d**,**e** were the only compounds obtained, the corresponding 2-(methoxyethoxymethoxymethyl)phenols were not detected. When 5-methoxy-2-hydroxybenzyl alcohol **7b**, and 3-methoxy-2-hydroxybenzyl alcohol **7c** were used, the 2-(methoxy-2-ethoxymethoxymethyl)phenols **10b**,**c** were the only compounds obtained.

4.1.1. 2-(Methoxyethoxymethoxymethyl)phenol. Compond **7a** was used as starting material. Yield: 27%. R_f (diethyl ether/hexane: 3/1): 0.3. ^{1}H NMR (300 MHz) δ 7.22 (dt, 1H, H-5; $J=1.7$, 7.7 Hz); 7.06 (dd, 1H, H-6; $J=1.5$, 7.4 Hz); 6.87 (m, 2H, H-3 and H-4); 4.85 (s, 2H, OCH_2O); 4.76 (s, 2H, PhCH_2O); 3.65 (m, 4H, OCH_2CH_2O); 3.41 (s, 3H, O*Me*). HR LSIMS calcd for $C_{11}H_{16}O_4Na$ $(M+Na)^+$ 235.0946, found 235.0946. Anal. for $C_{11}H_{16}O_4$: Calcd: C 62.25; H 7.60. Found: C 62.48; H 8.00.

4.1.2. 2-(Methoxyethoxymethoxy)benzyl alcohol 8a. Yield: 45%. R_f (diethyl ether/hexane: 3/1): 0.2. ^{1}H NMR (300 MHz,) δ 7.33 (dd, 1H, H-3 or H-6, $J=1.8$, 7.4 Hz); 7.26 (dt, 1H, H-5 or H-4, $J=1.8$, 7.9 Hz); 7.14 (dd, 1H, H-6 or H-3, $J=1.0$, 7.9 Hz); 7.02 (dt, 1H, H-4 or H-5, $J=1.0$, 7.4 Hz); 5.34 (s, 2H, OCH_2O); 4.72 (s, 2H, CH_2OH); 3.87 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.56 (m, 2H, BB′ part of the ethylenedioxy fragment); 3.37 (s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 155.07 (C-2); 130.00 (C-1); 128.98, 128.93 (C-6 and C-4); 121.96 (C-5); 114.12 (C-3); 93.57 (O*C*H$_2$O); 71.62 (*C*H$_2$OMe); 68.04 (*C*H$_2$CH$_2$OMe); 61.58 (*C*H$_2$OH); 59.04 (O*Me*). HR LSIMS calcd for $C_{11}H_{16}O_4Na$ $(M+Na)^+$ 235.0946, found 235.0946. Anal. for $C_{11}H_{16}O_4$: Calcd: C 62.25; H 7.60. Found: C 62.48; H 8.00.

4.1.3. [5-Chloro-2-(methoxyethoxymethoxy)]benzyl alcohol 8d. Compond **7d** was used as starting material. Yield: 38%. R_f (diethyl ether/hexane: 4/1): 0.3. ^{1}H NMR (300 MHz) δ 7.28 (d, 1H, H-6, $J=2.6$ Hz); 7.15 (dd, 1H, H-4, $J=2.6$, 8.7 Hz); 7.01 (d, 1H, H-3, $J=8.7$ Hz); 5.24 (s, 2H, OCH_2O); 4.60 (d, 2H, CH_2OH, $J=6.1$ Hz); 3.77 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.50 (m, 2H,

BB′ part of the ethylenedioxy fragment); 3.31 (s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 153.29 (C-2); 131.85 (C-5); 128.36 (C-4); 128.32 (C-6); 126.86 (C-1); 115.33 (C-3); 93.66 (O*C*H$_2$O); 71.56 (*C*H$_2$OMe); 68.06 (*C*H$_2$CH$_2$OMe); 60.62 (*C*H$_2$OH); 59.02 (O*Me*). HR LSIMS calcd for $C_{11}H_{15}O_4$NaCl $(M+Na)^+$ 269.0556, found 269.0553. Anal. for $C_{11}H_{15}O_4Cl$: Calcd: C 53.56; H 6.13. Found: C 53.85; H 5.83.

4.1.4. [5-Bromo-2-(methoxyethoxymethoxy)]benzyl alcohol 8e. Compound **7e** was used as starting material. Yield: 47%. R_f (diethyl ether/hexane: 2/1): 0.26. ^{1}H NMR (400 MHz) δ 7.42 (d, 1H, H-6, $J=2.5$ Hz); 7.28 (dd, 1H, H-4, $J=2.5$, 8.7 Hz); 6.95 (d, 1H, H-3, $J=8.7$ Hz); 5.23 (s, 2H, OC*H*$_2$O); 4.59 (d, 1H, 2H, C*H*$_2$OH, $J=3.5$ Hz); 3.76 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.49 (m, 2H, BB′ part of the ethylenedioxy fragment); 3.30 (s, 3H, O*Me*). ^{13}C NMR (100 MHz) δ 153.76 (C-2); 132.36 (C-1); 131.23, 131.16 (C-4, C-6); 115.77 (C-3); 114.30 (C-5); 93.61 (O*C*H$_2$O); 71.55 (*C*H$_2$OMe); 68.05 (*C*H$_2$CH$_2$OMe); 60.41 (*C*H$_2$OH); 58.95 (O*Me*). HR LSIMS calcd for $C_{11}H_{15}O_4$NaBr $(M+Na)^+$ 313.0051, found 313.0049. Anal. for $C_{11}H_{15}O_4Br$: Calcd: C 45.38; H 5.19. Found: C 44.99; H 4.84.

4.1.5. [2-(Methoxyethoxymethoxymethyl)]-4-methoxyphenol 10b. Compound **7b**[17] was used as starting material. Yield: 57%. R_f (diethyl ether/hexane: 2/1): 0.4. ^{1}H NMR (300 MHz) δ 6.75 (d, 1H, H-3, $J=7.5$ Hz); 6.70 (d, 1H, H-6, $J=3.0$ Hz); 6.68 (dd, 1H, H-4, $J=3.0$, 7.5 Hz); 4.75 (s, 2H, OC*H*$_2$O); 4.65 (s, 2H, C*H*$_2$OH); 3.69 (s, 3H, C-5-O*Me*); 3.69 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.52 (m, 2H, BB′ part of the ethylenedioxy fragment); 3.35 (s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 153.02 (C-5); 149.28 (C-2); 123.32 (C-1); 117.01 (C-3); 114.70, 114.51 (C-4, C-6); 94.44 (O*C*H$_2$O); 71.60 (*C*H$_2$OCH$_3$); 67.13 (*C*H$_2$CH$_2$-OMe); 66.80 (*C*H$_2$OH); 58.85 (O*Me*); 55.61 (C-5-O*Me*). HR LSIMS calcd for $C_{12}H_{18}O_5$ $(M+Na)^+$ 265.1051, found 265.1050. Anal. for $C_{12}H_{18}O_5$: Calcd: C 59.49; H 7.49. Found: C 59.76; H 7.22.

4.1.6. [2-(Methoxyethoxymethoxymethyl)]-6-methoxyphenol 10c. Compound **7c** was used as starting material. Yield: 47%. R_f (diethyl ether/hexane: 4/1): 0.42. ^{1}H NMR (400 MHz) δ 6.9 (dd, 1H, H-5, $J=4.3$, 5.2 Hz); 6.25 (d, 2H, H-4, H-6, $J=5.2$ Hz); 6.17 (s, 1H, OH); 4.81 (s, 2H, OC*H*$_2$O); 4.70 (s, 2H, C*H*$_2$OH); 3.85 (s, 3H, C-3-O*Me*); 3.75 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.56 (m, 2H, BB′ part of the ethylenedioxy fragment); 3.39 (s, 3H, O*Me*). ^{13}C NMR (100 MHz) δ 146.66 (C-3); 144.02 (C-2); 123.48 (C-1); 121.73 (C-5); 119.36 (C-6); 110.47 (C-4); 94.76 (O*C*H$_2$O); 71.70 (*C*H$_2$OMe); 66.78 (*C*H$_2$-CH$_2$OMe); 64.55 (*C*H$_2$OH); 58.85 (CH$_2$O*Me*); 55.94 (C-3-O*Me*). HR LSIMS calcd for $C_{12}H_{18}O_5$Na $(M+Na)^+$ 265.1051, found 265.1050. Anal. for $C_{12}H_{18}O_5$: Calcd: C 59.49; H 7.49. Found: C 59.22; H 7.76.

4.2. Synthesis of 2-(methoxyethoxymethoxy)benzyloxyacetaldehyde dimethyl acetals 9a,d,e

The general procedure is exemplified with the case of **9a**: **8a** (1 g, 4.7 mmol) was added to a suspension of NaH (0.42 g of a 80% dispersion in mineral oil) in anhydrous DMF (12.5 mL) while cooling in an ice bath and the resulting mixture was left under stirring at room temperature for 2 h. After this time, bromoacetaldehyde dimenthyl acetal (1.1 mL, 9.4 mmol) was added while cooling with ice, and the resulting mixture was left under stirring at room temperature at 50 °C for 5 h. The reaction mixture was distilled under diminished pressure and the resulting residue was diluted with water, the pH was adjusted to 2–3 by adding an aqueous solution of HCl 2N and was then extracted (EtOAc). The extract was washed with brine and dried with Na_2SO_4, filtrated, and concentrated in vacuo. The resulting residue was purified by flash chromatography (diethyl ether/hexane: 1/1.5) and **9a** was obtained (0.5 g, 35%). R_f (diethyl ether/hexane: 3/1): 0.38. ^{1}H NMR (300 MHz) δ 7.41 (dd, 1H, H$_{Ar}$; $J=1.6$, 7.4 Hz); 7.25 (dt, 1H, H$_{Ar}$; $J=1.6$, 7.4 Hz); 7.15 (d, 1H, H$_{Ar}$; $J=1.0$, 7.4 Hz); 7.02 (dt, 1H, H$_{Ar}$; $J=1.0$, 7.4 Hz); 5.41 (s, 2H, OC*H*$_2$O); 4.65 (s, 2H, C-1-C*H*$_2$O); 4.57 (t, C*H*(OMe)$_2$); $J=5.2$ Hz); 3.86 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.56 (m, 4H, BB′ part of the ethylenedioxy fragment and O–C*H*$_2$–CH); 3.41 (s, 6H, (O*Me*)$_2$); 3.39 (s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 154.88 (C-2); 129.18, 128.84 (C-6 and C-4); 127.00 (C-1); 121.73 (C-5); 114.04 (C-3); 102.74 (*C*H(OMe)$_2$); 95.46 (O*C*H$_2$O); 71.61, 69.93, 68.28, 67.71 (*C*H$_2$OMe), (*C*H$_2$CH$_2$OMe), (C-1-*C*H$_2$O), (O–*C*H$_2$–CH); 59.05 (O*Me*); 53.85 (O*Me*)$_2$. HR LSIMS calcd for $C_{15}H_{23}O_6$Na $(M+Na-1)^+$ 299.1494, found 299.1494. Anal. for $C_{15}H_{24}O_6$: Calcd: C 59.98; H 8.05. Found: C 59.95; H 8.23.

4.2.1. [5-Chloro-2-(methoxyethoxymethoxy)benzyloxyacetaldehyde dimethyl acetal 9d. Compound **8d** was used as starting material. Yield: 39%. R_f (ethyl acetate/hexane: 4/1): 0.54. ^{1}H NMR (400 MHz) δ 7.37 (d, 1H, H-6, $J=2.6$ Hz); 7.16 (dd, 1H, H-4, $J=2.6$, 8.7 Hz); 7.06 (d, 1H, H-3, $J=8.76$ Hz); 5.25 (s, 2H, OC*H*$_2$O); 4.57 (s, 2H, C-1-C*H*$_2$O); 4.55 (t, 1H, H-1′, $J=5.2$ Hz); 3.79 (m, 2H, H-2′); 3.54 (m, 4H, AA′BB′ system); 3.40 (s, 3H, O*Me*); 3.36 (s, 6H, (O*Me*)$_2$). ^{13}C NMR (100 MHz) δ 153.11 (C-2); 129.08 (C-5); 128.47 (C-4); 128.22 (C-6); 126.82 (C-1); 115.25 (C-3); 102.74 (*C*H(OMe)$_2$); 93.60 (O*C*H$_2$O); 71.53, 70.30, 67.79, 67.71 (O–*C*H$_2$–CH) (*C*H$_2$OMe), (C-1-*C*H$_2$O), (*C*H$_2$CH$_2$OMe); 58.99 (O*Me*); 53.92 (O*Me*)$_2$. HR LSIMS calcd for $C_{15}H_{23}O_6$NaCl $(M+Na)^+$ 357.1080, found 357.1078. Anal. for $C_{15}H_{23}O_6Cl$: Calcd: C 53.81; H 6.92. Found: C 53.48; H 7.23.

4.2.2. [5-Bromo-2-(methoxyethoxymethoxy)benzyloxyacetaldehyde dimethyl acetal 9e. Compound **8e** was used as starting material. Yield: 42%. R_f (ethyl acetate/hexane: 4/1): 0.38. ^{1}H NMR (400 MHz) δ 7.47 (d, 1H, H-6, $J=2.5$ Hz); 7.27 (dd, 1H, H-4, $J=2.5$, 8.7 Hz); 6.97 (d, 1H, H-3, $J=8.7$ Hz); 5.21 (s, 2H, OC*H*$_2$O); 4.53 (s, 2H, C-1-C*H*$_2$O); 4.51 (t, 1H, H-1′, $J=5.2$ Hz); 3.75 (m, 2H, H-2′); 3.50 (m, 4H, AA′BB′ system); 3.35 (s, 3H, O*Me*); 3.31 (s, 6H, (O*Me*)$_2$). ^{13}C NMR (100 MHz) δ 153.61 (C-2); 131.34 (C-4); 131.17 (C-6); 129.51 (C-1); 115.67 (C-3); 114.22 (C-5); 102.73 (*C*H(OMe)$_2$); 93.51 (O*C*H$_2$O); 71.50, 70.31, 67.78, 67.67 (O–*C*H$_2$–CH), (*C*H$_2$OMe), (C-1-*C*H$_2$O), (*C*H$_2$CH$_2$-OMe); 58.94 (O*Me*); 53.88 (O*Me*)$_2$. HR LSIMS calcd for $C_{15}H_{23}O_6$NaBr $(M+Na)^+$ 401.0575 $C_{15}H_{23}O_6$NaBr $(M+Na)^+$ 401.0575, found 401.0583. Anal. for $C_{15}H_{23}O_6Br$: Calcd: C 47.51; H 6.11. Found: C 47.9; H 5.76.

4.3. Synthesis of (*RS*)-2-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins 2a,d,e and (*RS*)-5-methoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecin 5a,d,e

The general procedure is exemplified with the case of **2a** and **5a**: **9a** (1.5 g, 4.9 mmol) was dissolved in anhydrous THF (15 mL), and $BF_3 \cdot OEt_2$ (0.3 mL) was added at 0 °C and the mixture was kept at this temperature under stirring for 24 h. After this time the solution was washed with an aqueous solution of K_2CO_3 (10%) and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography with diethyl ether/hexane (1/3) yielding 0.36 g of **3a** (41%), and 0.12 g of **5a** (6%). After concentrating the organic layer, the residue was subjected to a simple combination of directly-coupled gas chromatography-mass spectrometry (GC-MS): t_R of methoxymethanol: 4.14 min; t_R of methoxymethoxyethanol: 6.76 min. The identity of methoxymethanol[14] and methoxymethoxyethanol[15] were confirmed by comparison of their retention times with pure authentic samples.

Compound **3a**. R_f (diethyl ether/hexane: 2/1): 0.61. ^{1}H NMR (300 MHz) δ 7.31 (dt, 1H, H_{Ar}, J=1.7, 7.7 Hz); 7.20 (dd, 1H, H_{Ar}, J=1.7, 7.7 Hz); 7.17 (dd, 1H, H_{Ar}, J=1.3, 7.7 Hz); 7.09 (dt, 1H, H_{Ar}, J=1.3, 7.7 Hz); 4.70 (dd, 1H, H-2, J=1.6, 6.3 Hz); 4.68 (d, 2H, H-5, 1.6); 4.07 (dd, 1H, H-3, J=1.6, 12.5 Hz); 3.81 (dd, 1H, H-3, J=6.3, 12.5 Hz); 3.62 (s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 154.30 (C-10); 133.26 (C-11); 129.49, 129.04 (C-6 and C-8); 124.00 (C-9); 121.48 (C-7); 103.99 (C-2); 74.86 (C-3); 72.87 (C-5); 56.50 (O*Me*). HR LSIMS calcd for $C_{10}H_{12}O_3Na$ $(M+Na)^+$ 203.0694, found 203.0683. Anal. for $C_{10}H_{12}O_3$: Calcd: C 66.65; H 6.71. Found: C 66.19; H 6.85.

Compound **5a**. R_f (diethyl ether/hexane: 4/1): 0.39. ^{1}H NMR (400 MHz) δ 7.29 (dt, 1H, H-11 or H-10, J=1.7, 7.8 Hz); 7.17 (dd, 1H, H-9 or H-12, J=1.7, 7.4 Hz); 7.13 (dd, 1H, H-12 or H-9, J=1.1, 7.8 Hz); 7.07 (dt, 1H, H-10 or H-11, J=1.1, 7.4 Hz); 4.81 (dd, 1H, H-5, J=1.7, 6.8 Hz); 4.65 (dd, 2H, H-8, J=2.6, 13.3 Hz); 4.14 (m, 2H, H-6, H-2); 3.81 (m, 2H, H-6, H-2); 3.61 (m, 2H, H-3, H-3); 3.39 (s, 3H, O*Me*). ^{13}C NMR (100 MHz) δ 154.44 (C-13); 133.43 (C-14); 129.52 (C-11); 129.05 (C-9); 124.05 (C-10); 121.40 (C-12); 103.16 (C-5); 74.91 (C-6); 72.72 (C-2); 71.58 (C-8); 68.08 (C-3); 59.12 (O*Me*). HR LSIMS calcd for $C_{12}H_{16}O_4Na$ $(M+Na)^+$ 247.0946, found 247.0945. Anal. for $C_{12}H_{16}O_4 \cdot 0.1H_2O$: Calcd: C 64.27; H 7.19. Found: C 64.00; H 7.20.

4.3.1. (*RS*)-7-Chloro-2-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin 3d and (*RS*)-10-chloro-5-methoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecin 5d.

Compound **9d** was used as a starting material. **3d**: Yield: 45%. R_f (ethyl acetate/hexane: 4/1): 0.7. ^{1}H NMR (400 MHz) δ 7.23 (dd, 1H, H-8, J=2.5, 8.4 Hz); 7.15 (d, 1H, H-6, J=2.5 Hz); 7.07 (d, 1H, H-9, J=8.4 Hz); 4.68 (dd, 1H, H-2, J=1.5, 6.0 Hz); 4.60 (d, 2H, H-5, J=1.7 Hz); 4.03 (dd, 1H, H-3, J=1.5, 12.6 Hz); 3.80 (dd, 1H, H-3, J=6.0, 12.6 Hz); 3.59 (s, 3H, O*Me*). ^{13}C NMR (100 MHz) δ 152.85 (C-10); 134.80 (C-11); 134.79 (C-7); 129.20 (C-8); 128.83 (C-6); 122.94 (C-9); 103.99 (C-2); 74.85 (C-3); 72.37 (C-5); 56.61 (O*Me*). HR LSIMS calcd for $C_{10}H_{11}O_3NaCl$ $(M+Na)^+$ 237.0294, found 237.0299. Anal. for $C_{10}H_{11}O_3Cl$: Calcd: C 55.96; H 5.17. Found: C 56.22; H 4.87.

Compound **5d**. Yield: 22%. R_f (ethyl acetate/hexane: 4/1): 0.6. ^{1}H NMR (400 MHz) δ 7.23 (dd, 1H, H-11, J=2.5, 8.4 Hz); 7.15 (d, 1H, H-9, J=2.5 Hz); 7.05 (d, 1H, H-12, J=8.4 Hz); 4.8 (dd, 1H, H-5, J=1.6, 6.6 Hz); 4.59 (dd, 2H, H-8, J=1.2, 13.6 Hz); 4.11 (m, 2H, H-6, H-2); 3.8 (m, 2H, H-6, H-2); 3.6 (m, 2H, H-3, H-3); 3.39 (s, 3H, O*Me*). ^{13}C NMR (100 MHz) δ 153.00 (C-13); 134.97 (C-10); 129.22 (C-11); 128.92 (C-9); 128.85 (C-14); 122.87 (C-12); 103.18 (C-5); 74.91 (C-6); 72.22 (C-2); 71.54 (C-8); 68.20 (C-3); 59.15 (O*Me*). HR LSIMS calcd for $C_{12}H_{15}O_4NaCl$ $(M+Na)^+$ 281.0556, found 281.0563. Anal. for $C_{12}H_{15}O_4Cl$: Calcd: C 55.71; H 5.84. Found: C 55.83; H 6.03.

4.3.2. (*RS*)-7-Bromo-2-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin 3e and (*RS*)-10-bromo-5-methoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecin 5e.

Compound **9e** was used as a starting material. **3e**: Yield: 27%. R_f (diethyl ether/hexane: 2/1): 0.6. ^{1}H NMR (400 MHz) δ 7.35 (dd, 1H, H-8, J=2.4, 8.4 Hz); 7.27 (d, 1H, H-6, J=2.4 Hz); 6.99 (d, 1H, H-9, J=8.4 Hz); 4.65 (dd, 1H, H-2, J=1.6, 6.1 Hz); 4.57 (d, 2H, H-5, J=2.1 Hz); 4.00 (dd, 1H, H-3, J=1.6, 12.6 Hz); 3.76 (dd, 1H, H-3, J=6.1, 12.6 Hz); 3.56 (s, 3H, O*Me*). ^{13}C NMR (100 MHz) δ 153.45 (C-10); 135.27 (C-11); 132.25 (C-8); 131.76 (C-6); 123.32 (C-9); 116.46 (C-7); 104.04 (C-2); 74.85 (C-3); 72.32 (C-5); 56.63 (O*Me*). HR LSIMS calcd for $C_{10}H_{12}O_3Br$ $(M^+ + 1)$ 258.9969, found 258.9976. Anal. for $C_{10}H_{11}O_3Br$: Calcd: C 46.36; H 4.28. Found: C 45.97; H 4.11.

Compound **5e**. Yield: 18%. R_f (diethyl ether/hexane: 2/1): 0.46. ^{1}H NMR (400 MHz) δ 7.34 (dd, 1H, H-11, J=2.4, 8.4 Hz); 7.26 (d, 1H, H-9, J=2.4 Hz); 6.97 (d, 1H, H-12, J=8.4 Hz); 4.77 (dd, 1H, H-5, J=1.7, 6.6 Hz); 4.56 (dd, 2H, H-8, J=1.5, 14.1 Hz); 4.07 (m, 2H, H-6, H-2); 3.76 (m, 2H, H-6, H-2); 3.56 (m, 2H, H-3, H-3); 3.35 (s, 3H, O*Me*). ^{13}C NMR (100 MHz) δ 153.60 (C-13); 135.45 (C-10); 132.28 (C-11); 131.82 (C-9); 123.35 (C-12); 116.53 (C-14); 103.22 (C-5); 74.92 (C-6); 72.19 (C-2); 71.61 (C-8); 68.25 (C-3); 59.17 (O*Me*). HR LSIMS calcd for $C_{12}H_{15}O_4NaBr$ $(M+Na)^+$ 325.0051, found 325.0053. Anal. for $C_{12}H_{15}O_4Br$: Calcd: C 47.54; H 4.99. Found: C 47.81; H 5.13.

4.4. Synthesis of 2-(methoxyethoxymethoxymethyl)-phenyloxyacetaldehyde dimethyl acetals 11b and 11c

The procedure was similar to the one used in 4.3, but changing **9a** by **10b**, and **9a** by **10c**.

4.4.1. [4-Methoxy-2-(methoxyethoxymethoxymethyl)]-phenyloxyacetaldehyde dimethyl acetal 11b.

Compound **10b** was used as starting material. Yield: 26%. R_f (ethyl acetate/hexane: 2/1): 0.4. ^{1}H NMR (300 MHz) δ 6.95 (d, 1H, H-3, J=2.8 Hz); 6.76 (t, 1H, H-6, J=8.8 Hz); 6.73 (dd, 1H, H-5, J=2.8, 8.8 Hz); 4.82 (s, 2H, OCH_2O); 4.66 (t, 1H, H-1′, J=5.2 Hz); 4.63 (s, 2H, C-2-CH_2O); 3.94 (d, 2H, H-2′, J=5.2 Hz); 3.73 (s, 1H, C-4-OMe); 3.73 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.54 (m, 2H, BB′ part of the ethylenedioxy fragment); 3.41 (s, 6H, $(OMe)_2$); 3.37

(s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 154.05 (C-4); 150.20 (C-1); 128.22 (C-2); 114.75 (C-6); 113.16 (C-5); 113.12 (C-3); 102.37 (*C*H(OMe)$_2$); 95.29 (O*C*H$_2$O); 71.82, 68.97, 66.86, 64.55 (O-*C*H$_2$–CH), (*C*H$_2$OMe), (C-2-*C*H$_2$O), (*C*H$_2$-CH$_2$OMe); 59.03 (O*Me*); 55.72 (C-4-O*Me*); 54.17 (O*Me*)$_2$. HR LSIMS calcd for $C_{16}H_{26}O_7$ $(M+Na)^+$ 353.1576, found 353.1577. Anal. for $C_{16}H_{26}O_7$: Calcd: C 58.17; H 7.93. Found: C 57.82; H 8.27.

4.4.2. [6-Methoxy-2-(methoxyethoxymethoxymethyl)-phenyloxyacetaldehyde dimethyl acetal 11c. Compond **10c** was used as starting material. Yield: 33%. R_f (diethyl ether/hexane: 2/1): 0.35. ^{1}H NMR (300 MHz) δ 7.00 (d, 1H, H-4, $J=7.7$ Hz); 6.96 (dd, 1H, H-3 or H-5, $J=1.9$, 7.7 Hz); 6.82 (dd, 1H, H-5 or H-3, $J=1.9$, 7.7 Hz); 4.80 (s, 2H, OC*H*$_2$O); 4.70 (t, 1H, H-1′, $J=5.4$ Hz); 4.67 (s, 2H, C-2-C*H*$_2$O); 4.01 (d, 2H, H-2′, $J=5.4$ Hz); 3.81 (s, 3H, C-6-O*Me*); 3.72 (m, 2H, AA′ part of the ethylenedioxy fragment); 3.55 (m, 2H, BB′ part of the ethylenedioxy fragment); 3.40 (s, 6H, (O*Me*)$_2$); 3.37 (s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 152.31 (C-6); 145.84 (C-1); 131.84 (C-2); 124.06 (C-4); 121.24 (C-3); 111.95 (C-5); 102.47 (*C*H(OMe)$_2$); 95.15 (O*C*H$_2$O); 71.87, 71.82, 66.87, 64.50 (O-*C*H$_2$–CH), (*C*H$_2$OMe), (C-1-*C*H$_2$O), (*C*H$_2$CH$_2$OMe); 59.05 (O*Me*); 55.77 (C-6-O*Me*); 53.85 (O*Me*)$_2$. HR LSIMS calcd for $C_{16}H_{26}O_7Na$ $(M+Na)^+$ 353.1576, found 353.1573. Anal. for $C_{16}H_{26}O_7$: Calcd: C 58.17; H 7.93. Found: C 57.85; H 8.02.

4.5. Synthesis of (*RS*)-3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins 2b,c and (*RS*)-3,12-dimethoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecin 6c

The procedure is similar to the one used in 4.3, but changing **9a** by **11b**, and **9a** by **11c**.

4.5.1. (*RS*)-2,7-Dimethoxy-2,3-dihydro-5*H*-1,4-benzodioxepin 2b. Compond **11b** was used as a starting material, yielding 40% of **2b**, whose spectroscopical characteristics were identical to the ones previously described.[4] The organic residue was subjected to a simple combination of directly-coupled gas chromatography-mass spectrometry (GC-MS): t_R of methoxymethoxyethanol: 6.76 min.

4.5.2. (*RS*)-3,9-Dimethoxy-2,3-dihydro-5*H*-1,4-benzodioxepin 2c and (*RS*)-3,12-dimethoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecin 6c. Compond **11c** was used as a starting material, yielding 70% of **2c** and 15% of **6c**. The spectroscopic characteristics of **2c** were identical to the ones previously described.[5] The aqueous layer was freeze-dried and the residue was subjected to a simple combination of directly-coupled gas chromatography-mass spectrometry (GC-MS): t_R of methoxymethanol: 4.14 min; t_R of methoxymethoxyethanol: 6.76 min.

Compound **6c**. Yield: 15%. R_f (2/1, diethyl ether/hexane): 0.27. ^{1}H NMR (300 MHz) δ 6.88 (d, 1H, H-10, $J=7.6$ Hz); 6.80 (d, 1H, H-9, $J=1.5$ Hz); 6.64 (dd, 1H, H-11, $J=1.5$, 7.6 Hz); 5.24 (d, 1H, H-8, $J=14.5$ Hz); 5.05 (dd, 1H, H-5, $J=3.4$, 7.6 Hz); 4.38 (dd, 1H, H-8, $J=14.5$ Hz); 4.29 (dd, 1H, H-6, $J=3.4$, 13.1 Hz); 4.13 (dd, 1H, H-6, $J=7.6$, 13.1 Hz); 3.95 (m, 1H, H-2); 3.83 (s, 3H, C-12-O*Me*); 3.69 (m, 1H, H-2); 3.56 (m, 2H, H-3, H-3); 3.38 (s, 3H, O*Me*). ^{13}C NMR (75 MHz) δ 150.47 (C-12); 147.87 (C-13); 130.12 (C-14); 122.48 (C-10); 120.18 (C-9); 111.38 (C-11); 100.47 (C-5); 72.19 (C-6); 71.85 (C-2); 67.20 (C-8); 63.05 (C-3); 59.16 (C-12-O*Me*); 56.14 (C-5-O*Me*). HR LSIMS calcd for $C_{13}H_{18}O_5Na$ $(M+Na)^+$ 277.1052, found 277.1055. Anal. for $C_{13}H_{18}O_5$: Calcd: C 61.4; H 7.13. Found: C 61.02; H 6.88.

4.6. X-ray crystallographic study of (*RS*)-1-(7-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil

A colourless crystal was mounted on a glass fibre and used for data collection. Crystal data were collected at 298(2) K, using a Bruker SMART CCD 1000 diffractometer. Graphite monochromated Mo Kα radiation ($\lambda=0.71073$ Å) was used throughout. The data were processed with SAINT[18] and corrected for absorption using SADABS (transmissions factors: 0.976–0.971).[19] The structure was solved by direct methods using the programme SHELXS-97[20] and refined by full-matrix least-squares techniques against F^2 using SHELXL-97.[21] Positional and anisotropic atomic displacement parameters were refined for all nonhydrogen atoms. Hydrogen atoms were located in difference maps and included as fixed contributions riding on attached atoms with isotropic thermal parameters 1.2 times those of their carrier atoms. Criteria of a satisfactory complete analysis were the ratios of rms shift to standard deviation less than 0.001 and no significant features in final difference maps. Atomic scattering factors from 'International Tables for Crystallography'.[22] Molecular graphics and geometrical calculatioons from PLATON[23] and SHELTXL.[24] Relevant crystal data: formula $C_{14}H_{13}FN_2O_5$, formula weight 308.26, $T=298(2)$ K, crystal system triclinic, space group *P*-1, unit cell dimensions $a=6.491(2)$, $b=7.588(3)$ and $c=14.037(2)$ Å, and $\alpha=89.41(2)°$, $\beta=87.70(2)$ and $\gamma=73.72(2)$, $Z=2$, $D=1.544$ Mg m^{-3}, μ(Mo Kα)$=0.127$ mm^{-1}, measured/unique reflections 7805/3007 [R(int) 0.0191], refined parameters 200, final R_1 ($I>2\sigma(I)$)$=0.0408$ and w$R_2=0.1119$, and GOF$=1.053$. CCDC reference number 236010. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccd.cam.ac.uk].

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