Neighboring-Group Participation Involving the Oxygen Atom of the *O,O*- or *O,N*-Acetal Functional Groups

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Abstract: The application of the neighboring-group participation involving the oxygen atom of *O,O*- or *O,N*-acetals can be very fruitful. For instance, the naphthoate ester derivatives of (*Z*)-hex-3-ene-1,5-diyne were used to generate biradicals *via* γ-oxo ketene acetal intermediates, and a synthesis of tricyclic 9-crown-3 ethers bearing a chiral oxathiane ring was achieved by utilizing nucleophilic displacement of a triflic ester leaving-group assisted by neighbouring-group participation of a 1,3-dioxolane function. In a different field, the reaction between *o*-(hydroxymethyl)phenoxyacetaldehyde dimethyl acetals, or (+/-)-3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins with 5-fluorouracil was studied. The intramolecular cyclization may be explained through a neighbouring-group attack to give a 2-(5- fluorouracil-1-yl)oxyranium ion that can be attacked by the silylated benzylic hydroxyl group to yield the benzannelated seven- membered *O,N*-acetals. Before carrying out the synthesis of 7- or 9-substituted (+/-)-2-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins it is necessary to protect the phenolic hydroxy group of the 2-hydroxybenzyl alcohol. Among other functionalities, the 2- methoxyethoxylmethyl (MEM) group was developed as a protective group of alcohols and phenols. Accordingly, it was decided to use the MEM group for the preparation of 7- or 9-substituted (+/-)-2-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins and their ten-membered benzo-fused analogs. The importance of the ten-membered *O,O*-acetals sheds light on the mechanism of reaction in which the neighbour- ing-group participation plays a pivotal role. Transannular versions of the reaction result in the facile ring contraction of 12-membered in- termediates to the 10- and to 7-membered benzene-fused *O,O*-acetals. Acetals with several oxygen atoms in their side-chains have been used in the preparation of highly oxygenated cyclic ether compounds.

Keywords: Acetals, Bisfuran, Medium-ring heterocycles, Methoxyethoxymethyl group, Neighbouring group participation, γ-Oxo ketene acetal, Steroidal sapogenins, Triciclycic 9-crown-3 ether derivatives.

INTRODUCTION

Neighboring-group participation is a term which encompasses all intramolecular reactions and all reactions which involve non-electrostatic through-space interactions between groups within the same molecule. The term was invented in 1942 by Saul Winstein. Neighboring-group participation is well documented as far as the mechanism and scope of the reaction are concerned [1]. We will concentrate on neighboring-group participation on *O,O*- and/or *O,N*-acetals with one or more oxygen atoms in their side-chains. As far as we know, this subject has not been reviewed yet. We have made an attempt to take into account the largest possible number of original papers (SciFinder and PubMed), including our research and others. It is difficult to write a comprehensive review on a subject as broad as this, since too many examples are hidden away in pa- pers whose titles and, in many cases, abstracts, give no mention of a relationship to neighbouring- group participation. Publications that appeared after 1998 are included. This review is organized accord- ing to the publication date of the manuscripts, starting from the earliest ones (1998) and finishing with the most recent ones.

Several investigators have been attracted to studies of neighbor- ing-group effects in order to improve our understanding of basic chemical reactivity as well as to unravel some anomalous results. The most widely studied type of neighboring-group participation is where the neighboring group acts as a nucleophile. When describ- ing 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. Acetals or ketals partici- pate in far less displacement reactions than simple ethers.

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1. CYCLOAROMATIZATION OF ENEDIYNE COMPOUNDS *VIA* γ-OXO KETENE ACETAL INTERMEDIATES

Various acyclic (*Z*)-1,2,4-heptatrien-6-ynes, which undergo cycloaromatization to produce reactive dehydrotoluene biradicals (Myers-Saito-type cyclization) [2], have been investigated as chemical models for a class of potent antitumor antibiotics, neocarzinostatin (NCS) [3]. The preparation of enyne-allene models possessing characteristic triggering devices which initiate the generation of dehydrotoluene biradicals is a challenging problem [4]. Naoe *et al*. reported that the cis-enediyne derivative **1** generates the toluene biradical **3** *via* the fixed s-*cis*-enyne-allene intermediate **2** by means of intramolecular triggering action of the hydroxy group under acidic conditions (Fig. (**1**)) [5]. For further development of this class of cascade reaction, Suzuki *et al*. described the Myers- Saito-type cyclization *via* γ-oxo ketene acetal intermediates **4** gen- erated by the neighboring group participation of the naphthoate ester moieties of enediyne derivatives in acidic media.

In typical examples, the naphthoate esters **8a** and **8b** were synthesized having the α-hydroxy naphthoate moiety. The synthesis of naphthoate esters **8a,b** (Fig. (**2**)) started with the known (*Z*)-bromoenyne **5** [6] which was condensed with 1-methoxy-1,l-diphenyl-2-propyne to give the enediyne **6**. The alcohol **7** was obtained by reduction of the ester **6** with excess of DIBAL-H (diisobutylaluminum hydride). A naphthoate group was introduced by the reaction of **7** with 2-hydroxy-1-naphthalenecarboxylic acid or 2-hydroxy-7-methoxy-5-methyl-1-naphthalenecarboxylic acid [7] in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and subsequent desilylation with tetra-*n*-butylammonium fluoride to afford the desired naphthoate esters **8a** and **8b,** respectively.

The reaction of naphthoate **8a** with trifluoroacetic acid (0.6 v/v%) in the presence of 1,4-cyclohexadiene (50 equiv) in benzene at room temperature afforded a mixture of several products from which diphenyl acetal **9a** (10% yield), the diol **10a** (5% yield) and

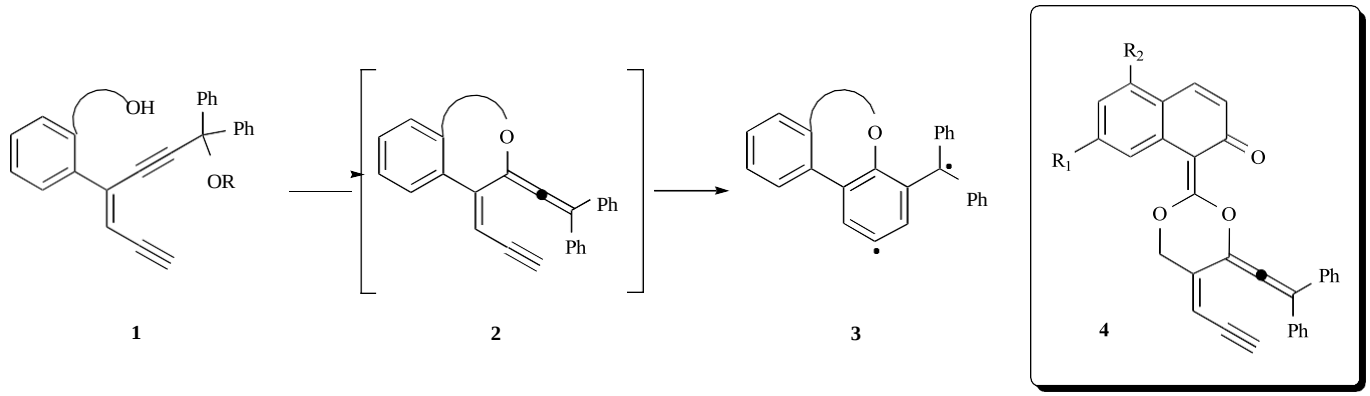


Fig. (1).

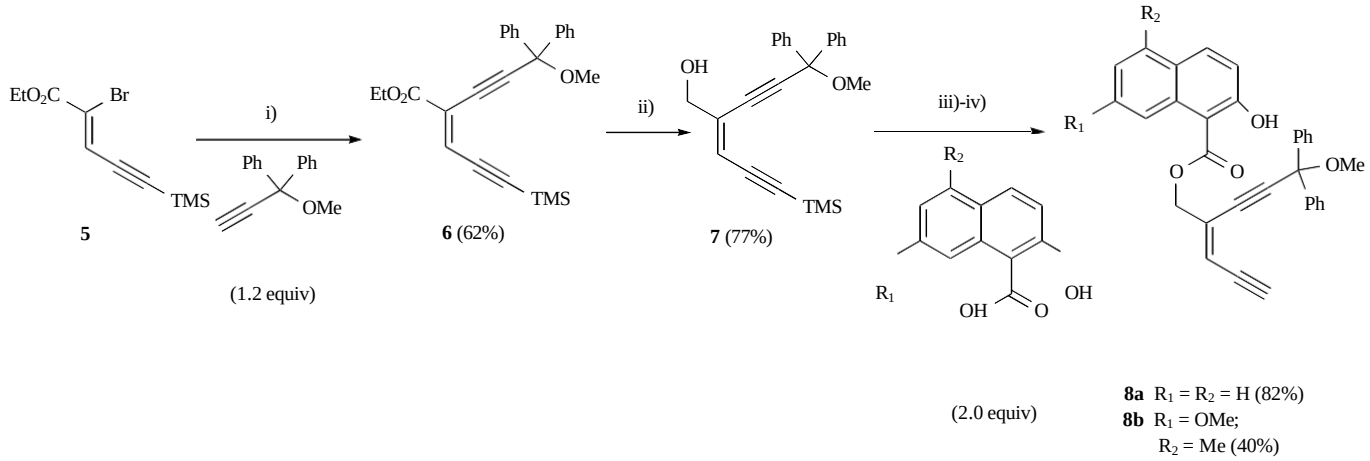


Fig. (2). *Reagents*: i) $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.2 equiv), *n*-$PrNH_2$ (1.8 equiv), toluene, 60 ºC; ii) DIBAL-H (2.1 equiv), THF, -78 ºC; iii) EDC (40 equiv), CH_2Cl_2, rt; iv) $(n\text{-}C_4H_9)_4NF$ (1.0 equiv), THF, 0 ºC.

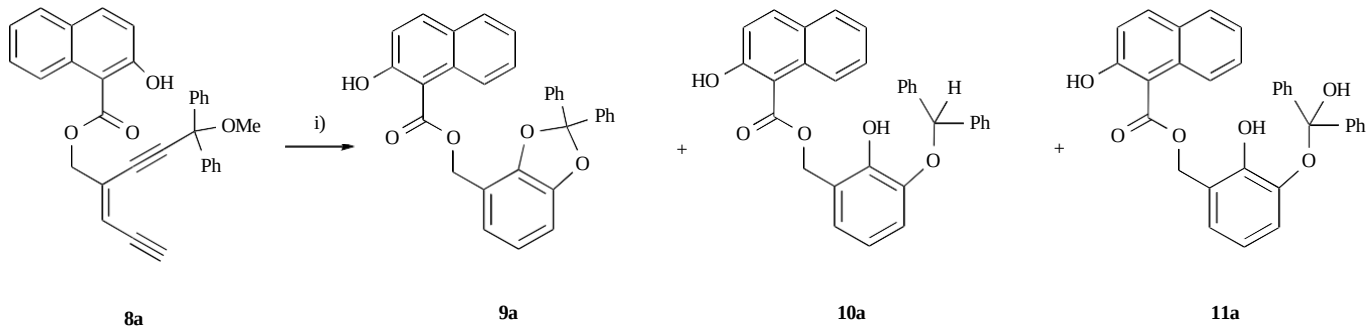


Fig. (3).

Table 1. Acid-Catalyzed Cyclization of Naphthoates 8a and 8b [CF_3CO_2H (0.3 v/v%), Cyclohexadiene (50 equiv), Benzene, 25 ºC]

Compound	Conditions	Reaction time	Products (yield)
8a	under Ar	14 h	**10a** (7%), **11a** (24%)
8a	under O_2	24 h	**9a** (65%)
8b	under Ar	15 min	**11b** (14%)
8b	under O_2	30 min	**9b** (55%)

the triol **11a** (28% yield) were isolated (Fig. (**3**)). These results suggest that the enediyne **8a** proceeded *via* an acid-catalyzed reaction to the enyne-allene intermediate followed by subsequent Myers-Saito-type reaction to form cyclized products. In order to examine the formation pathways of these products, the reaction was conducted in a degassed solvent as well as in oxygen atmosphere (Table **1**) [6]. When the reaction of **8a** was carried out in a degassed solvent, the acetal **9a** was not detected in the mixture of reaction.

On the other hand, the reaction under oxygen atmosphere afforded **9a,** but not **10a** nor **11a**. While the reactions of **8a** required more than 14 h at 25 ºC, **8b** reacted within 0.5 h under similar conditions. The latter reaction gave a more intricate mixture, from which **11b** (under Ar) and **9b** (under O_2) could be isolated.

These results strongly suggest the naphthoate participation and incorporation of molecular oxygen into the acetals **9a,b**. Thus, the

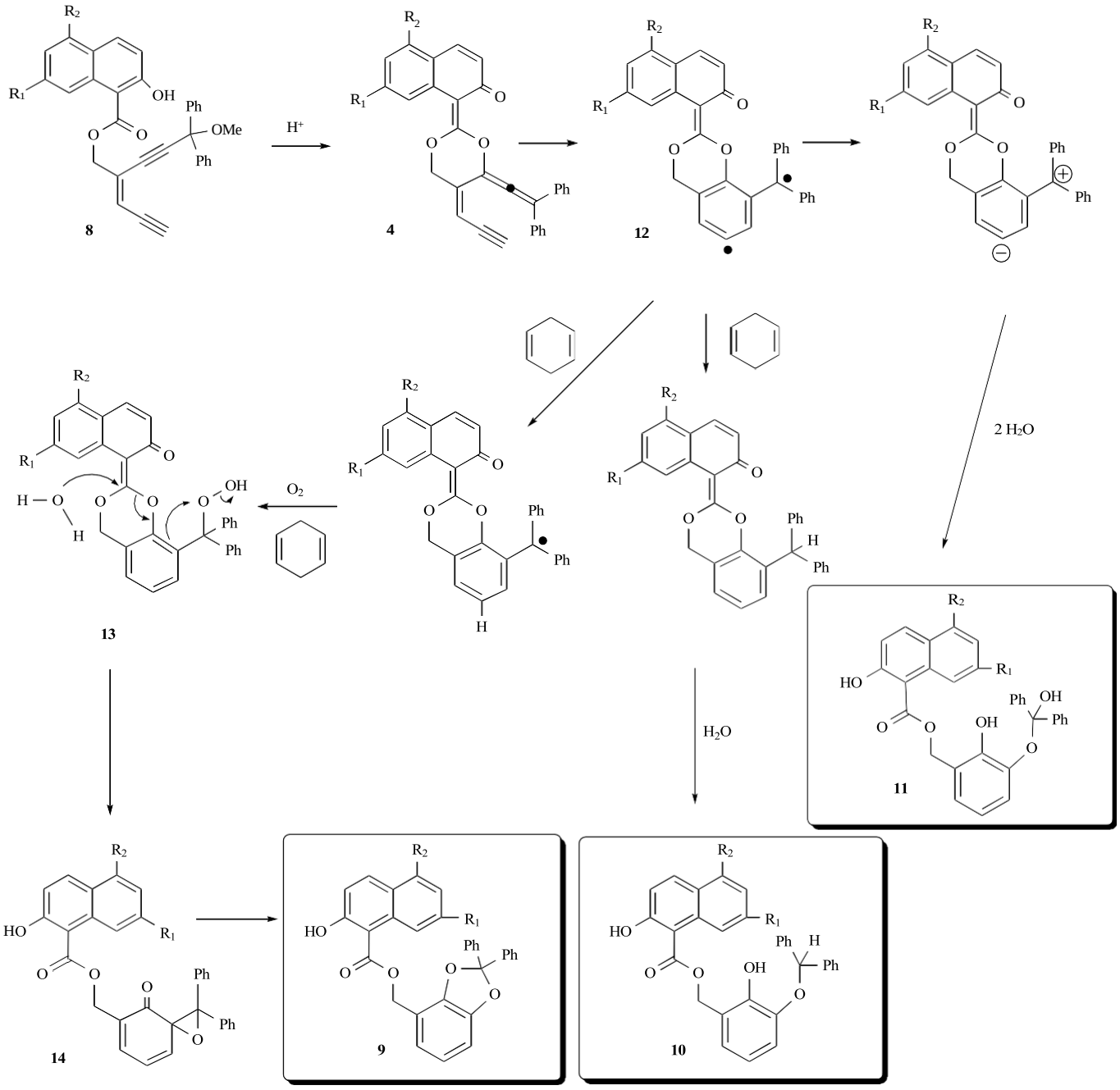


Fig. (4).

following mechanism was proposed for these cycloaromatization reactions as represented in Fig. (**4**).

In the first step, the naphthoate migration to acetylenic carbon with the concomitant elimination of the methoxy group is likely to occur in acidic media. The γ-oxo ketene acetal intermediates **4** thus formed should undergo the cycloaromatization to give the biradical intermediates **12**. Under anaerobic conditions, **12** would be converted into diol **10** by hydrogen abstraction from cyclohexadiene, followed by the addition of adventitious water or by hydrolysis under work-up conditions. Alternatively, biradicals **12** would be transformed into triol **11** *via* the ionization process [9]. When the reactions were carried out under oxygen atmosphere, hydrogenperoxy intermediates **13** would be formed by hydrogen abstraction, followed by molecular oxygen incorporation. The addition of water or trifluoroacetic acid to the ketene acetal **13** should provide **9** *via* the epoxy intermediates **14**. The final rearrangement pathway is similar to that of the well-known phenol synthesis from cumene hydroperoxide under acidic conditions [10]. The relatively fast reaction of **8b** compared with **8a** is presumably due to the presence of electron-releasing substituents on its naphthalene ring.

2. PREPARATION OF 9-CROWN-3 ETHER DERIVATIVES THROUGH THE DIOXOLANE ACETAL RING EXPANSION ON A SUGAR TRIFLATE

The nucleophilic displacement of sugar triflates by oxygen nucleophiles represents an efficient route towards substituted products with inverted configuration at the electrophilic centres [11]. Accordingly, it was assumed that solvolysis of the L-*talo*-derivative **19**, in the presence of benzoate anion as the nucleophile, might be used for the preparation of the L-*manno*-isomer **20** (Fig. (**5**)), a

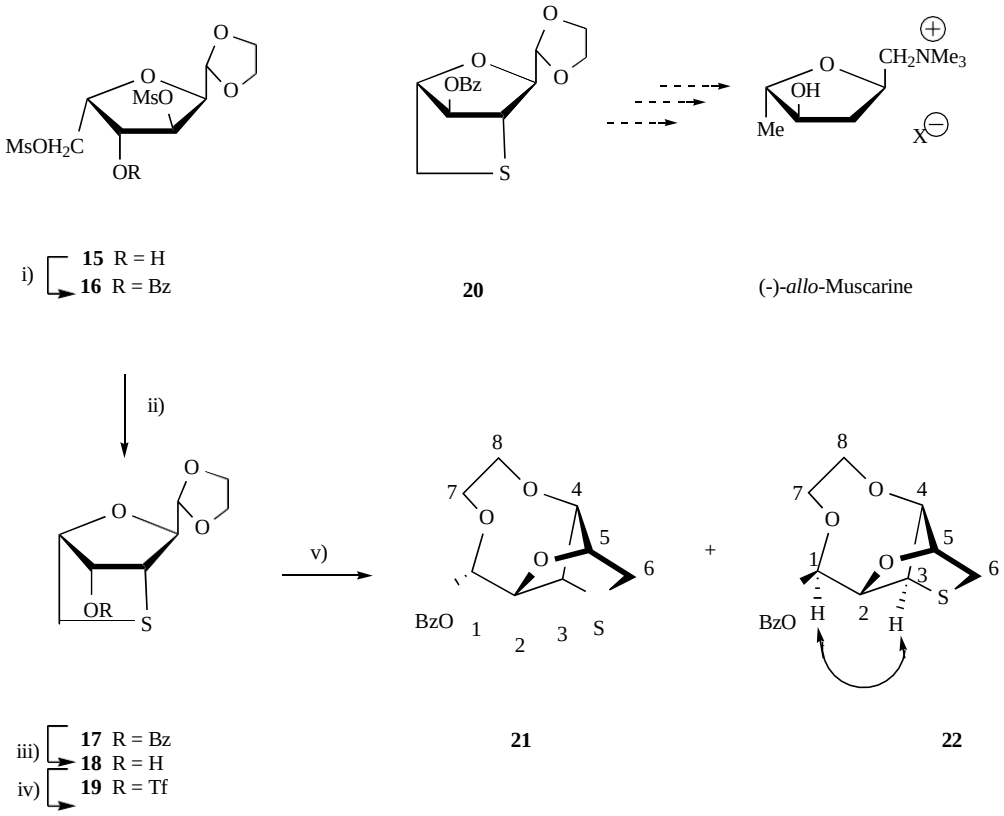


Fig. (5). *Reagents*: i) BzCl, py, rt, 24 h; ii) NaSH, DMF, N_2, 80 ºC, 40 min; iii) NaOH, MeOH, 80 ºC, 40 min; iv) Tf_2O, py, CH_2Cl_2, O ºC → rt, 30 min; v) LiOBz, DMF, 24 h.

possible intermediate in the synthesis of (-)-*allo*-muscarine from D-glucose [12]. The triflic ester **19** was thus prepared starting from the known 2,5-anhydro-L-idose derivative **15** [13].

Reaction of **15** with benzoyl chloride in dry pyridine gave the expected 4-*O*-benzoyl derivative **16** which was further treated with sodium hydrogen sulfide in DMF (*N*,*N*-dimethylformamide) to give the oxathiane derivative **17**. *O*-Debenzoylation of **17** with sodium hydroxide in dry methanol afforded the unstable alcohol **18** which was subsequently treated with triflic anhydride in a mixture of dichloromethane and pyridine to afford the triflate ester **19**. The four-step sequence **15** → **19** was carried out without purification of intermediates **16-18**, whereby the desired product **19** was isolated by flash column chromatography in an overall yield of 53% with respect to the starting compound **15** [14].

Although most sugar triflates have been shown to be rather reactive towards a variety of nucleophiles [11,15], the triflic ester **19** remained unchanged even after prolonged treatment with an excess of potassium benzoate in DMF at 140 °C. This implied that the approach of an external nucleophile to the electrophilic centre was sterically hindered by the β-orientated dioxolane acetal ring. Therefore, the reaction was carried out in boiling DMF, whereupon the conversion of the starting compound was completed after 48 h. However, this reaction did not afford the substitution product **20**, but resulted in the formation of the 9-crown-3 ether derivative **21**, isolated by flash column chromatography in 26% yield. A some- what different result was obtained by using lithium benzoate as the nucleophilic agent. Treatment of compound **19** with an excess of lithium benzoate in boiling DMF for 24 h gave an approximately 12:1 mixture of the stereoisomers **21** and **22** in a 42% combined yield.

The assignment of diastereomer configuration of **21** and **22** was discussed by Popsavin *et al.* [14].

A possible mechanism of the solvolytic reaction may involve dioxolane neighboring-group participation in the first step. As outlined in Fig. (**6**), both stereochemically distinct intermediates **19a** and **19b** might be formed from **19**. Further reaction of the *exo- oxonium* ion **19a** with benzoate anion would give the major product **21** having the *S*-configuration at C-1. Similar reaction of the *endo- oxonium* ion **19b** would lead to the 1*R*-stereoisomer **22** isolated as a minor product from the reaction mixture. Presumably this is be- cause the *endo*-oxonium ion **19b** is too strained to form readily [14]. In fact, semiempirical PM3 calculations [16] performed on both **19a** and **19b** confirmed a lower stability of **19b** (AE = 10.16 kJ/mol in favor of **19a**). This is mainly due to the repulsive van der Waals interactions between the *syn*-orientated *O*-1 and *O*-2(5) at- oms. The calculated distance between these atoms in an optimized structure **19b** is 2.68 Å, that is less than the sum of the correspond- ing van der Waals radii (2.80 Å) [17]. On the other hand, the inter- mediate **19a** is less strained since the distance between H-1 and *O*- 2(5) atom (2.59 Å) is similar to the sum of their van der Waals radii (2.60 Å), as calculated from the optimized structure **19a**. Conse- quently, the *exo*-ion is preferentially formed, leading to the stereoi- somer **21** as the major reaction product. Alternatively, the second step of the rearrangement (**19a** → **21**), may well be an S_N1 type of process the attack of the nucleophile being carried out preferentially from the less hindered face.

3. REARRANGEMENT OF SPIROSTANES TO BISFURAN SYSTEMS

The sapogenins are aglycones of saponins, a group of gly- cosides widely distributed in plants. The most common sapogenins are spirostanols with the normal-type spiroacetal form (22*R*). With regard to the configuration at C-25, there are two types: an α- oriented methyl group (25*R* as in hecogenin acetate **23**) and a β- oriented methyl group (25*S* as in sarsasapogenin acetate **27**).

It is well known that sapogenins can be selectively brominated at C-23. The observations of Morzycki and Jastrzębska [18] con- firm

the reports that 25*R*-sapogenins form two isomeric 23-bromo

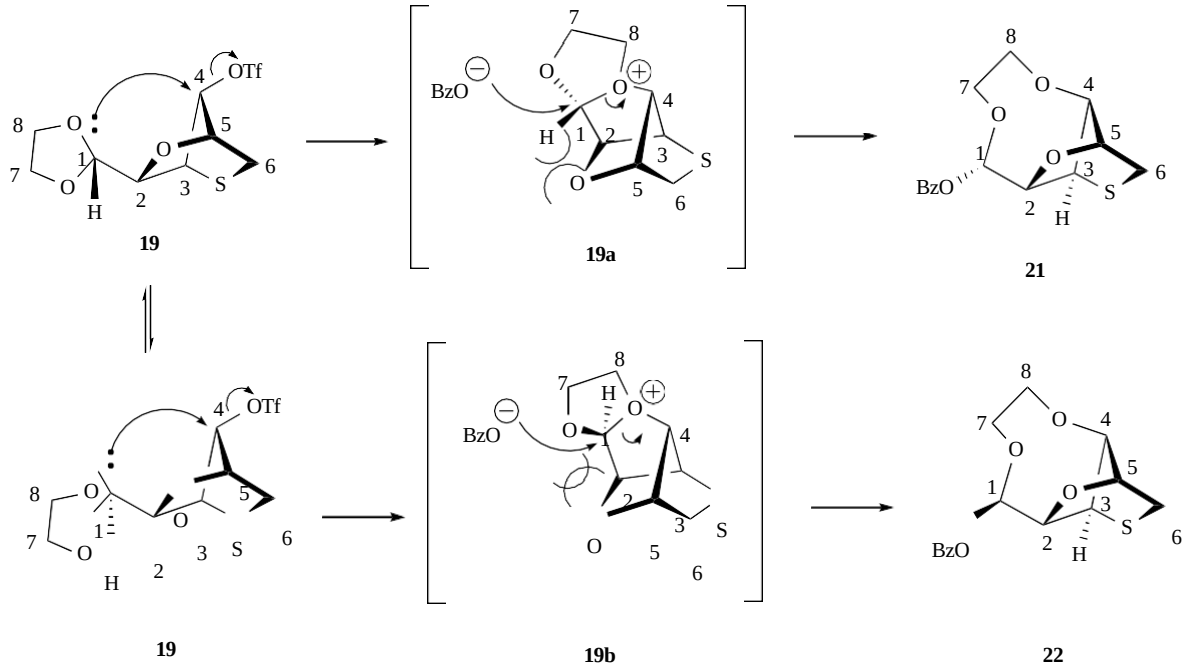


Fig. (6).

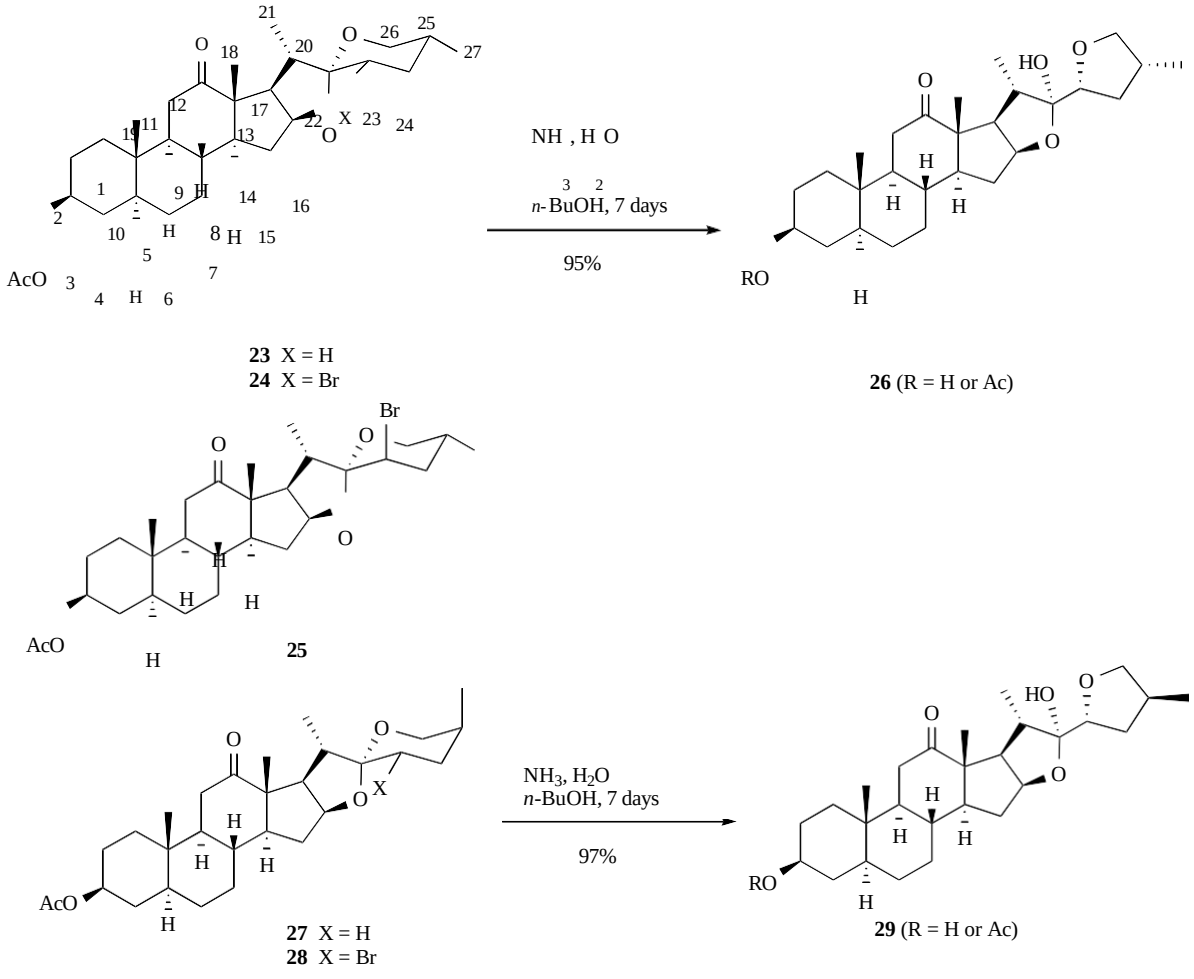


Fig. (7).

derivatives **24** and **25** (no bromination product at C-11 was detected). Bromination of the 25*S*-sapogenins yields only a single 23-bromo product **28** due to steric hindrance from the axial methyl group at C-25. All three bromo derivatives (23*S*,25*R*; 23*R*,25*R* and 23*S*,25*S*) were subjected to weak alkaline hydrolysis (NH_3 or K_2CO_3, H_2O, *n*-BuOH, under reflux several days). Compound **25** with an axial bromine atom did not react under these conditions (Fig. (**7**)). The other compounds (**24** and **28**) yielded bisfuran prod-

ucts with a tertiary hydroxy group (as proved by failure of acetylation attempts). Mass spectra showed a very characteristic pattern of molecular ion fragmentation involving loss of water or methyltetrahydrofuran ($M-C_5H_{10}O)^+$ [19]. ^1H and ^{13}C NMR spectra confirmed the hemiacetal structure of the products (**26** and **29**, respectively). The analysis of NOE effects in their ^1H NMR spectra suggests the 23*R* configuration in these compounds [18].

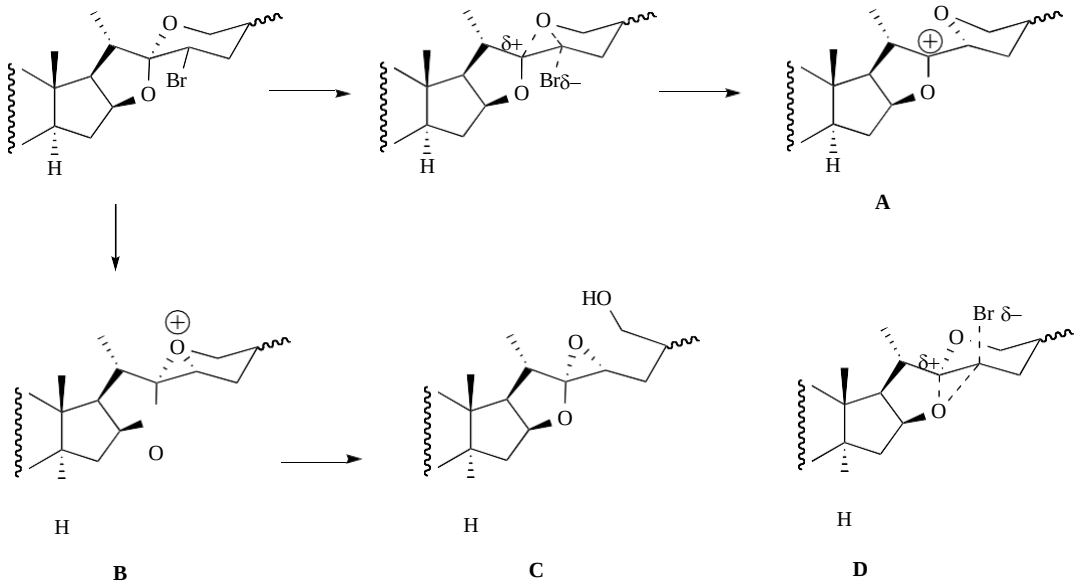
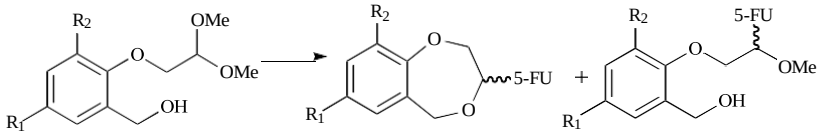


Fig. (8).

Table 2. Formation of Cyclic and Acyclic 5-FU *O,N*-acetals Starting from Acyclic *O,O*-acetals and 5-FU, HMDS, TMSCl, $SnCl_4/CH_2Cl_2$, MeCN, the Reaction Time Being 24 h



30 R_1 = OMe; R_2 = H
31 R_1 = H; R_2 = OMe
32 R_1 = Cl; R_2 = H
33 R_1 = Br; R_2 = H
34 R_1 = NO_2; R_2 = H

35 R_1 = OMe; R_2 = H

36 R_1 = OMe; R_2 = H
37 R_1 = H; R_2 = OMe
38 R_1 = Cl; R_2 = H
39 R_1 = Br; R_2 = H
40 R_1 = NO_2; R_2 = H

Entry	Starting *O,O*-acetals	Cyclic *O,N*-acetals (yield, %)	Acyclic *O,N*-acetals (yield, %)
1	**30**	**35** (26)	**36** (27)
2	**31**	-	**37** (37)
3	**32**	-	**38** (17)
4	**33**	-	**39** (4)
5	**34**	-	**40** (35)

A concerted mechanism is suggested for bisfuran formation (Fig. (**8**)) consisting of the simultaneous departure of bromide and shift of an oxygen atom from C-20 to C-22, followed by the addi- tion of water to the stabilized carbocation **A**. Non-bonded electrons of the 'pyranose' oxygen atom may, however, assist the departure of the bromine atom of compounds **24** and **28**. The oxonium ion thus formed (**B**) could be preferentially attacked by hydroxide anion at the spiro carbon atom (C-22) bearing some positive charge. The oxonium ion **B** may also be attacked at the secondary position (C- 26) to afford epoxy alcohol **C** that could be further transformed to the final product. There are different stereochemical consequences of these mechanisms. The two former mechanisms (*via* **A** or **B**) imply the inversion of configuration at C-23, whereas the latter (via **C**) proceeds through a retention of configuration as a result of a double inversion. The rearrangement described above is novel in the chemistry of spirostanes.

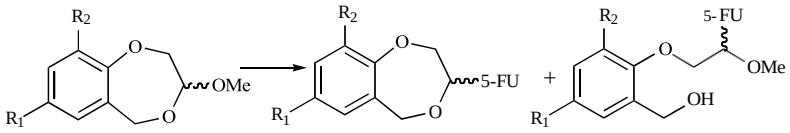
4. NEIGHBORING-GROUP PARTICIPATION AS THE KEY STEP IN THE REACTIVITY OF ACYCLIC AND CYCLIC SALICYL-DERIVED *O,O*-ACETALS WITH 5-FLUOROURACIL

4.1. Condensation Between *o*-(Hydroxymethyl)phenoxy-acetaldehyde Dimethyl Acetals and 5-Fluorouracil

The non-naturally occurring base with known antitumor activ- ity, 5-fluorouracil (5-FU) is highly toxic and accordingly novel derivatives of 5-FU possessing a broader spectrum of antitumor activity and fewer side effects than 5-FU have been sought in a number of laboratories.

Under the previously described conditions [20] the condensa- tion between the acyclic *O,O*-acetals **30-34** and 5-FU gave rise to the cyclic **35** and/or the acyclic *O,N*-acetals **36-40**, respectively through a process whose regioselectivity depended on the presence

Table 3. Formation of Cyclic and Acyclic 5-FU *O,N*-acetals[a] Starting from Cyclic *O,O*-acetals and 5-FU, HMDS, TMSCl, $SnCl_4/CH_2Cl_2$, MeCN, the Reaction Time Being 24 h



41 $R_1 = R_2 = H$
42 $R_1 = OMe$; $R_2 = H$
43 $R_1 = H$; $R_2 = OMe$
44 $R_1 = Cl$; $R_2 = H$
45 $R_1 = Br$; $R_2 = H$
46 $R_1 = NO_2$; $R_2 = H$

47 $R_1 = R_2 = H$
35 $R_1 = OMe$; $R_2 = H$
48 $R_1 = H$; $R_2 = OMe$

36 $R_1 = OMe$; $R_2 = H$
37 $R_1 = H$; $R_2 = OMe$
38 $R_1 = Cl$; $R_2 = H$
39 $R_1 = Br$; $R_2 = H$
40 $R_1 = NO_2$; $R_2 = H$

Entry	Starting acetals	Cyclic *O,N*-acetals (yield, %)	Acyclic *O,N*-acetals (yield, %)
1	**41**	**47** (43)	-
2	**42**	**35** (27)	**36** (21)
3	**42**	**35** (40)[b]	-
4	**43**	**48** (15.5)	**37** (5)
5	**44**	-	**38** (77)
6	**45**	-	**39** (33)
7	**46**	-	**40** (5)

[a]All the yields refer to compounds in which the 5-FU moiety is linked through N_1. [b]Reaction time: 144 h [20].

and nature of the substituents on the benzene ring (Table **2**), named R_1 and R_2.

In relation with the condensation reaction between the acyclic *O,O*-acetals **30-34** and 5-FU, the following can be stated [21]:

1) The nature and position of substituents R_1 and R_2 showed clear influence on both the yields and regioselectivity of the process. Thus, the effect of the substitution in position 5 of **30-34** (equivalent to 7 of **35**) was as follows (only $R_2 = H$ is considered):
   1.1 The electron-withdrawing substituents (Cl, Br and NO_2) induced the preferred formation of acyclic *O,N*-acetals **38-40** (entries 3-5).
   1.2 The only electron-donating substituent used, the OMe group, halted the regioselectivity of the reaction forming both the cyclic **35** and acyclic **36** *O,N*-acetals and, moreover, in an approximately 1/1 ratio (entry 1).
2) Finally, the substitution in C-3 of **31** by the only group studied (OMe) clearly favored the formation of the acyclic *O,N*-acetal **37** (entry 2).

4.2. Condensation Between (+/-)-3-Methoxy-7-substituted-2,3-dihydro-5*H*-1,4-benzodioxepins and 5-FU

The results obtained when the cyclic *O,O*-acetals were used as starting materials in the reaction with 5-FU are shown in Table **3**, which reproduces the reaction time and the yields obtained. In this study, the following may be generalized [21]:

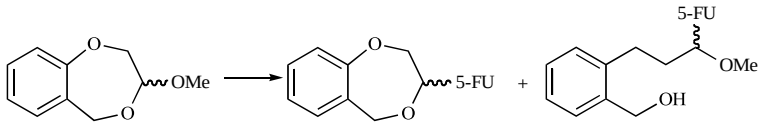
1) The better yield was obtained when R_1 and R_2 were hydrogen atoms (entry 1). The process is regioselective in the cyclic *O,N*-acetal **47**.
2) The presence of the methoxy group at positions 7 (compound **42**) or 9 (compound **43**) leads to the formation of both cyclic (compounds **35** and **36**, entry 2) and acyclic *O,N*-acetals (compounds **48** and **37**, entry 4). Nevertheless, when the reaction time was increased up to 144 h (6 days), starting from **42**, the regioselectivity formation of **35** was observed (entry 3).
3) The substituents R_1 and R_2 similarly influenced the regioselectivity of the previously described reaction; thus, the R_1 electron-withdrawing substituents (Cl, Br and NO_2, compounds **44-46**, respectively) in- duced the regioselective formation of the acyclic *O,N*-acetals **38-40** (entries 5-7).

4.3. Experimental Study of the Condensation Reaction between the Cyclic *O,O*-Acetal 41, and the Acyclic *O,O*-Acetal 50 with 5-FU: Influence of Other Factors on the Progress of the Reaction

As explained previously, the nature of the substituent on the aromatic ring is determinant for obtaining cyclic or acyclic *O,N*-acetals. Now the influence of the reaction time and the type of the Lewis acid will be described. For this study the simplest acetals have been selected. The reaction between the cyclic *O,O*-acetal **41** and 5-FU is strongly affected by the reaction time (Table **4**). Thus, a short reaction time (4 h) favors the formation of the acyclic *O,N*- acetal **49** (entry 1), whereas its increase (24 h) provokes the re- gioselective synthesis of the cyclic *O,N*-acetal **47** (entries 2 and 3), as was described previously [20]. From these experimental data it can be deduced that compound **47** is formed from the structure **49**, as will be depicted in Fig. (**10**).

Nevertheless, in the reaction between the acyclic *O,O*-acetal **50** and 5-FU with a reaction time of 24 h and using $SnCl_4/CH_2Cl_2$ as the Lewis acid, the two following reaction products have been iden- tified (Fig. (**9**)): Compound **47** and its corresponding dimer *trans*- **51** [21] that shows a 14-crown-4 ether structure with two pendant 5- FU fragments. Although the yield for obtaining *trans*-**51** was very low (7%), the structure is very attractive and will have a long pedi- gree as a result of its notable biological properties [21].

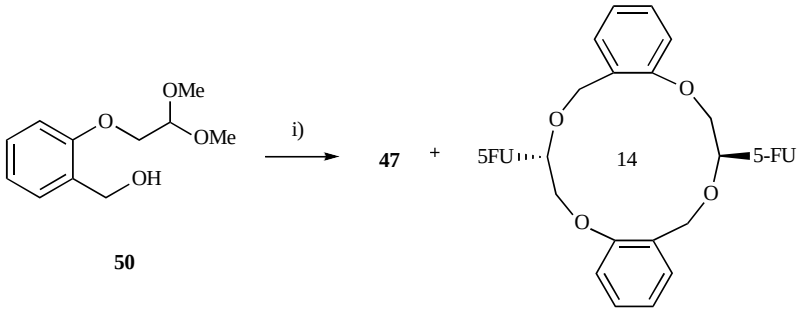
Table 4. Several Conditions in the Condensation Reaction Between the Cyclic *O,O*-acetal 41 and 5-FU, HMDS, TMSCl, $SnCl_4/CH_2Cl_2$, MeCN.[a]



41 **47** **49**

Entry	Lewis Acid	Reaction Time (h)	yield (%) of 47	yield (%) of 49
1	$SnCl_4/CH_2Cl_2$	4	4	15
2	$SnCl_4/CH_2Cl_2$	24	43	-
3	$BF_3{\cdot}Et_2O$	24	36	-

[a]All the yields refer to compounds in which the 5-FU moiety is linked through N_1.



50 *trans*-**51**

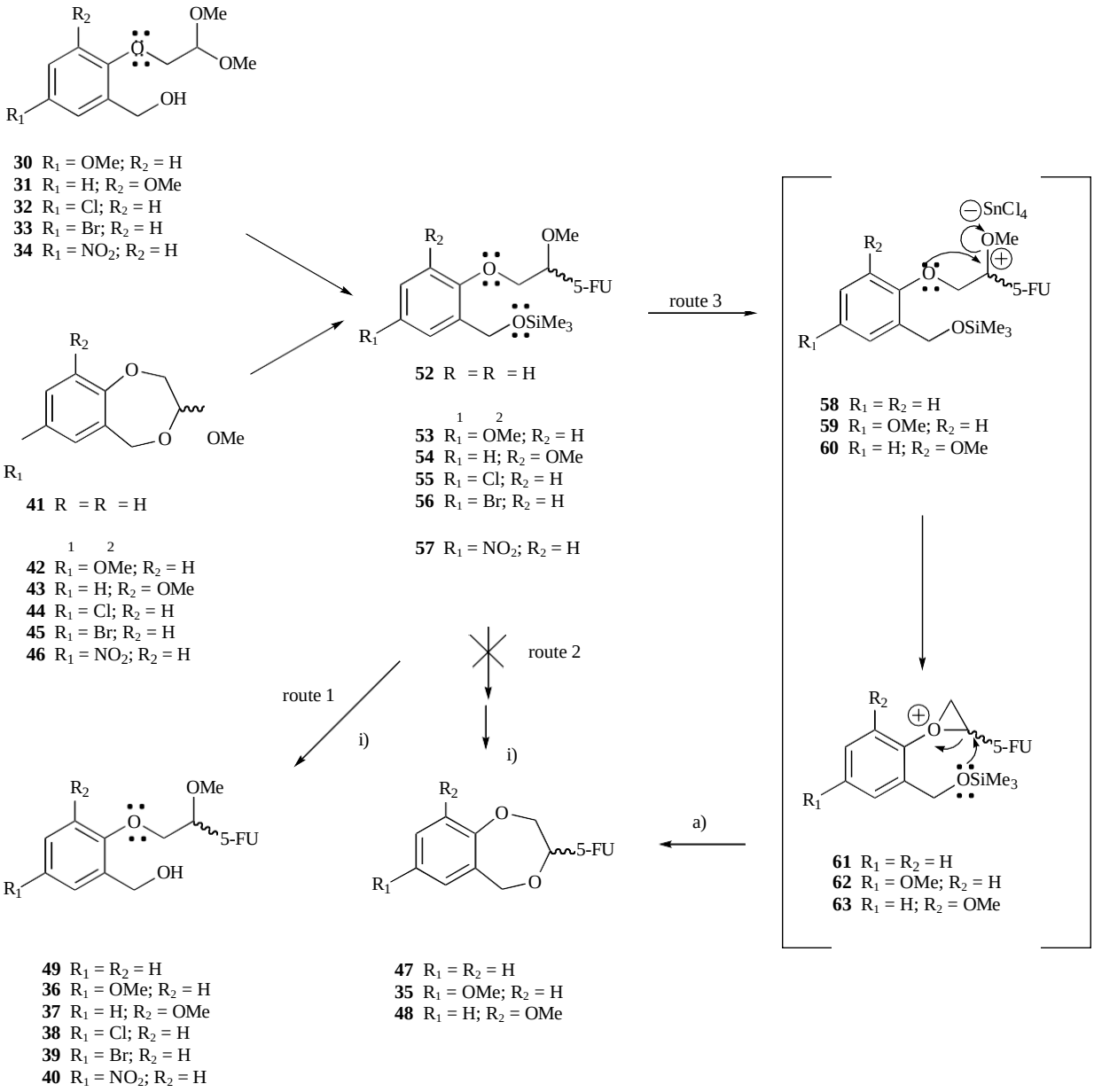
Fig. (9). *Reagents and conditions:* i) 5-FU, HMDS, TMSCl, $SnCl_4/CH_2Cl_2$, MeCN, Reaction Time 24 h.

4.4. Mechanism of the Condensation Reaction from *O,O*-Acetals and 5-FU: Neighboring-Group Participation

The mechanism represented in Fig. (**10**) (routes 1 and 3) may explain the nature of the reaction products. *O,O*-Acetals are functional groups consisting of an sp^3-carbon atom attached to two alkoxy groups. Under acidic conditions (with a Brønsted acid or a Lewis acid), an *O,O*-acetal can be activated to generate an α- heteroatom substituted carbenium ion as a reactive intermediate, which reacts with a nucleophile to form a substitution product. In this process, the acid coordinates to a lone pair of one of the oxygen atoms to cleave the O-carbon bond with the assistance of electron donation from a lone pair of the other oxygen atom. The substitution of the acetalic OMe group of **30**-**34** by the 5-FU takes place as has been reported for bis-acetals [22], leading to the intermediates **57**-**62**. The intramolecular attack of the silylated benzylic hydroxy group may explain the formation of **47**,**35**,**48** (route 2). Nevertheless, although the mechanism is simple and logical, it does not justify the influence of the R_1 substituent over the course of the reaction. A possible solution may involve a different pathway for the intramolecular cyclization in which the phenolic oxygen atom should intervene as a neighboring group, whose nucleophilicity may be strongly influenced by the electronic character of the substituent R_1. In fact, route 3 shows a possible mechanism for the intramolecular cyclization. According to this route, the intermediate **58**-**60** suffers the neighboring group attack to give the oxyranium ion **61**-**63**, much more reactive than its predecessor and that can be attacked by the silylated benzylic hydroxy group. Finally, the aqueous work-up renders **47**, **35**, **48**. Accordingly, the intramolecular cyclization product will depend on the stability of the intermediates **58**-**60**, which will in turn be influenced by the electronic character of the substituent R_1 (and R_2); in fact, electron-withdrawing groups destabilize the positive charge of the phenolic oxygen atom on generating an electronic deficiency in the carbon atom that carries the oxygen atom, making the intramolecular closing impossible. The contrary holds true for the electron-donating groups such as the methoxy moiety.

The results of the condensation reaction between the cyclic *O,O*-acetals **41**-**46** and 5-FU seem to suggest that, in the presence of $SnCl_4$, the remaining conditions and in accordance with our previous results [23], compounds **52**-**57** were formed. These intermediates are the precursors of the two types of target compounds according to Fig. (**10**) [21]. Consequently, the formation of the seven-membered ring reveals that the attack of the benzylic trimethylsilyloxy group leads to a favored 7-*Exo*-*Tet* process in accordance with Baldwin's rules [24]. It does not follow that because a process is "favored" it will necessarily occur readily in every case. The other factor such as the presence of an electron-withdrawing group at position *para* in relation to the phenolic ethereal atom exerts a negative influence and the formation of the seven-membered ring does not take place. This mechanism is supported by the fact that when the reaction was carried out in a short time (4 hours, Table **4**, entry 1) the preferential formation of the acyclic *O,N*-acetal **49** over the cyclic one **47** was observed.

According to the general mechanism of reaction explained in Fig. (**11**), the reaction of two molecules of **61** would give rise to *trans*-**51**, after work-up. Presumably, the non-formation of *cis*-**51** could be accounted for by the clashing of both 5-FU during its possible synthesis. Nevertheless, the intermolecular nucleophilic attack of the hydroxy benzylic group of **50** to the *O,O*-acetalic carbon of another molecule of **50**, and subsequent substitution of the two acetalic methoxy groups by two molecules of 5-FU cannot be ruled out.



30 R_1 = OMe; R_2 = H
31 R_1 = H; R_2 = OMe
32 R_1 = Cl; R_2 = H
33 R_1 = Br; R_2 = H
34 R_1 = NO_2; R_2 = H

41 R = R = H

42 R_1 = OMe; R_2 = H
43 R_1 = H; R_2 = OMe
44 R_1 = Cl; R_2 = H
45 R_1 = Br; R_2 = H
46 R_1 = NO_2; R_2 = H

52 R = R = H

53 R_1 = OMe; R_2 = H
54 R_1 = H; R_2 = OMe
55 R_1 = Cl; R_2 = H
56 R_1 = Br; R_2 = H

57 R_1 = NO_2; R_2 = H

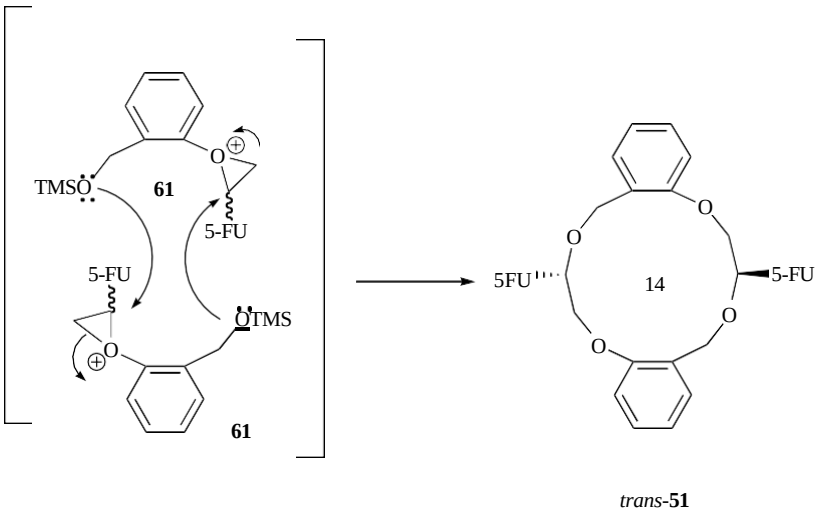
58 R_1 = R_2 = H
59 R_1 = OMe; R_2 = H
60 R_1 = H; R_2 = OMe

61 R_1 = R_2 = H
62 R_1 = OMe; R_2 = H
63 R_1 = H; R_2 = OMe

49 R_1 = R_2 = H
36 R_1 = OMe; R_2 = H
37 R_1 = H; R_2 = OMe
38 R_1 = Cl; R_2 = H
39 R_1 = Br; R_2 = H
40 R_1 = NO_2; R_2 = H

47 R_1 = R_2 = H
35 R_1 = OMe; R_2 = H
48 R_1 = H; R_2 = OMe

Fig. (10). *Reagent:* i) H_2O.



trans-**51**

Fig. (11).

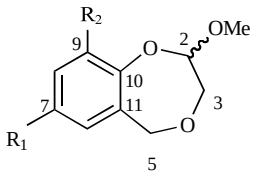
5. NEIGHBORING-GROUP PARTICIPATION BY AN OXYGEN ATOM OF AN ACETAL FUNCTIONAL GROUP

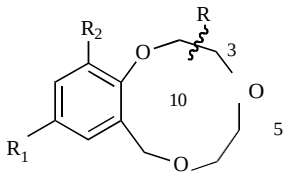
The selective protection and deprotection of functional groups is one of the major issues in multistep synthetic strategies of or- ganic

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 [25,26]. It has lately been shown that hy-

droxyalkyl 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 [27]. A literature survey revealed no reports on the regioselective protection of 2-hydroxybenzyl alcohol derivatives as a function of the elec- tronic nature of the substituents at positions 3 or 5 of the aromatic ring. Accordingly, it was decided to fill in 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 [21].

After the research explained previously, it was decided to embark on a programme of synthesis and study of the biological properties of 2,3-dihydro-5*H*-1,4-benzodioxepin fragments carrying the pyrimidine moiety in all the possible positions of the seven-membered ring, and directed our efforts in a second phase to the preparation of the cyclic *O,O*-acetals **64-66** (Fig. (**12**)), with the acetalic methoxy group on position 2. In the course of the present studies, the benzo-fused ten-membered *O,O*-acetals **67-71** (Fig. (**12**)) were also obtained. It is reported here the three-step synthesis of **64-66** and **67-71** (Fig. (**12**)), together with their mechanisms. The importance of the ten-membered *O,O*-acetals **67-69** and **71** (Fig. (**12**)) lies in the following: a) These unreported structures could be the starting synthons for the preparation of the corresponding ten-membered *O,N*-acetals that, in a similar way to that reported for the fourteen-membered bis(5-FU *O,N*-acetal) **51** [21], could exhibit notable biological activities against breast cancer cells; and b) their formation sheds light on the mechanism of reaction in which the neighboring-group participation plays a pivotal role.





64 $R_1 = R_2 = H$
65 $R_1 = Cl$; $R_2 = H$
66 $R_1 = Br$; $R_2 = H$

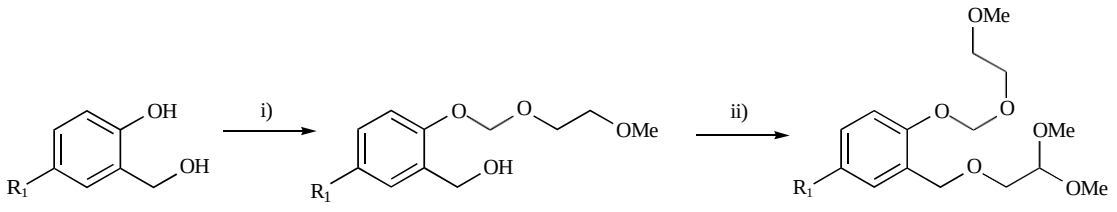
67 $R_1 = R_2 = H$; R = 5-OMe
68 $R_1 = Cl$; $R_2 = H$; R = 5-OMe
69 $R_1 = Br$; $R_2 = H$; R = 5-OMe
70 $R_1 = OMe$; $R_2 = H$; R = 3-OMe
71 $R_1 = H$; $R_2 = OMe$; R = 3-OMe

Fig. (12).

5.1. Reaction Between 2-Hydroxybenzyl Alcohols 72-74 and 2-Methoxyethoxymethyl Chloride

Before carrying out the synthesis of **64-66** it is necessary to protect the phenolic hydroxy group of the 2-hydroxybenzyl alcohol **72**. Among other functionalities, the 2-methoxyethoxymethyl (MEM) group was developed as a protective group of alcohols [28] and phenols [29]. 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 **75** 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) **72**. We have studied three experimental conditions: a) acetone and potassium carbonate; b) sodium hydride and THF (tetrahydrofuran); and c) DIPEA (diisopropylethylamine) and methylene chloride. The better yield in compound **75** was obtained using conditions a).

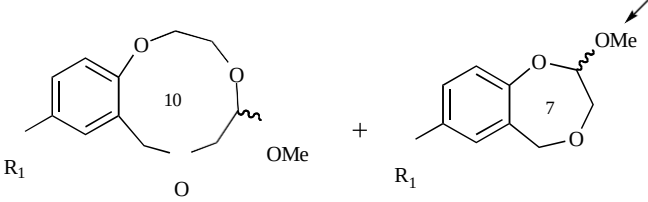
Both MEM ethers [2-(methoxy-2-ethoxymethoxymethoxymethyl)phenol and **75**] possess similar polarities (very close R_f, 0.3 and 0.2, respectively, using diethyl ether/hexane: 3/1 as eluant) and spectroscopic properties. Both compounds show the same molecular-ion peak of M^+ (calculated for $C_{11}H_{16}O_4Na$ $(M + Na)^+$ 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 **75** 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 **75** had been demonstrated we decided to extend the reaction starting with 2-hydroxybenzyl alcohols with different substituents on the aromatic ring (**82,83**). The synthesis of the cyclic *O,O*-acetals was carried out in a three-step process: a) the formation of MEM ethers **75-77** using MEMCl (1.5 equiv), K_2CO_3 (1.1 equiv), the salicyl alcohols (1 equiv) in acetone as solvent at 0 ºC, under an inert atmosphere; b) preparation of the intermediate acyclic *O,O*-acetals **78-80** by alkyla- tion of the benzylic hydroxy group with bromoacetaldehyde di-



72 R_1= H
73 R_1 = Cl
74 R_1 = Br

75 R_1 = H (45%)
76 R_1 = Cl (38%)
77 R_1 = Br (47%)

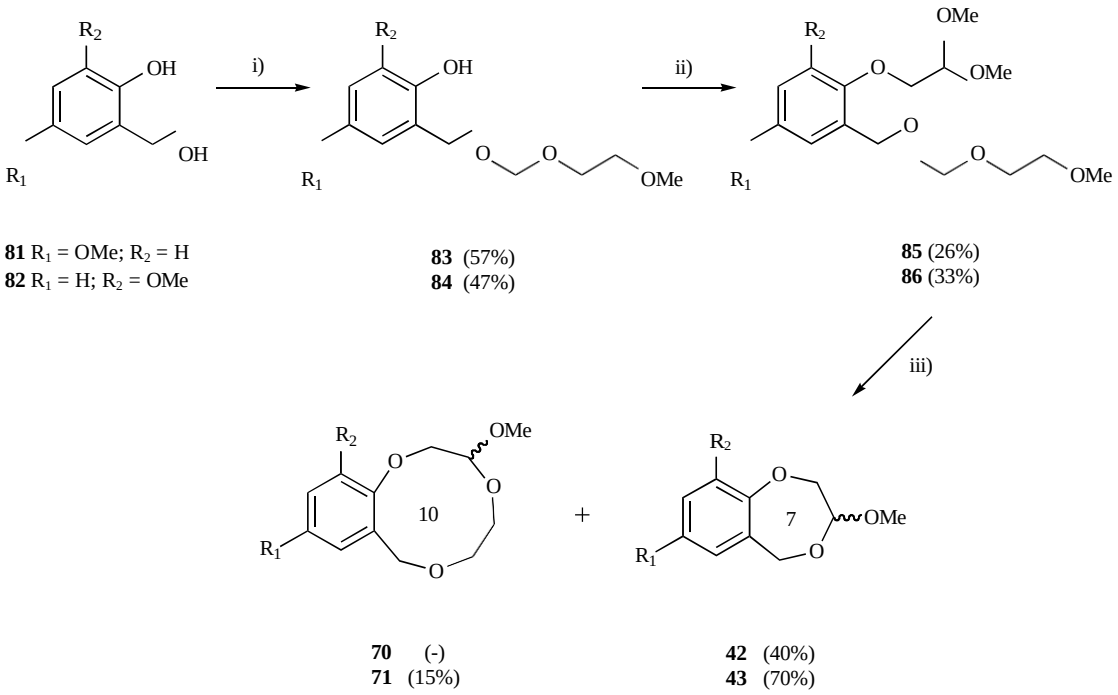
78 R_1 = H (35%)
79 R_1 = Cl (39%)
80 R_1 = Br (42%)



67 (10%)
68 (22%)
69 (18%)

64 (41%)
65 (45%)
66 (27%)

Fig. (13). *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.



81 R_1 = OMe; R_2 = H
82 R_1 = H; R_2 = OMe

83 (57%)
84 (47%)

85 (26%)
86 (33%)

70 (-)
71 (15%)

42 (40%)
43 (70%)

Fig. (14). *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 5. ^{13}C NMR Chemical Shifts (ppm) for the 2,3-dihydro-5*H*-1,4-dioxepin Moiety in 64-66 and 42,43 for $CDCl_3$ Solutions

	64	65	66	42[a]	43[a]
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]See [20]

methyl acetal, using sodium hydride as a base and anhydrous DMF as solvent; and c) the cleavage of the MEM moiety and subsequent cyclization to yield the target molecules **64-66**. In the original pa- per, which introduced the MEM group as a protective group for the hydroxyl function [28], the advantages of using anhydrous $ZnBr_2$ or $TiCl_4$ over other Lewis acids were highlighted.

It has been reported the $BF_3{\cdot}OEt_2$-mediated seven-membered cyclization of acyclic *O,O*-acetals [20,23,30] and accordingly, we supposed that the use of such a catalyst could lead to the target molecules **64-66** in a one-step/pot reaction, as a consequence of the simultaneous deblocking/cyclization process. The experimental results confirmed the hypothesis but, in addition to the expected benzofused seven-membered *O,O*-acetals **64-66**, the ten-membered *O,O*-acetals **67-69** were also produced (Fig. (**13**)).

In order to confirm the structures of the compounds, the atten- tion was focused on the NMR chemical shift of the benzylic carbon atoms and found that in the case of **75-77**, the range covers a nar- row interval of ≈ δ 1 ppm (in $CDCl_3$): δ 61.58 ppm (**75**), δ 60.62 ppm (**76**), and δ 60.41 ppm (**77**).

5.2. Reaction Between 2-Hydroxybenzyl Alcohols 81,82 and MEMCl

Nevertheless, when we tried to extend this series of reactions with the aim of obtaining the 5-methoxy-2-(2-methoxyethoxy- methoxy)benzylic and the 3-methoxy-2-(2-methoxyethoxy-

methoxy)benzylic alcohols, starting from the salicyl alcohols **81,82**, their ^{13}C NMR chemical behavior was not compatible with such structures on the basis of the chemical shifts of the benzylic carbon atoms, *i.e.* 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 **75-77** cannot be explained by the field/inductive effects of the aromatic methoxy fragments because there is a great distance between the two atoms involved 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 (Fig. (**14**)) would lead to the previously reported seven-membered *O,O*-acetals **42,43** (with the acetalic -OMe fragment in position 3), together with **71** in the case of starting from **82**. Fig. (**14**) shows the synthetic route followed, whose difference with respect to Fig. (**13**), is the different alkylation site achieved by the reactant MEMCl.

Another key point is the chemical shift of the benzylic carbon atoms of both target molecules **64-66** and **42,43**. For compounds **42,43**, such carbons are in γ position (an 1,3-relationship) in relation to the acetalic methoxy groups, their ^{13}C chemical shifts being very sensitive to 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 com-

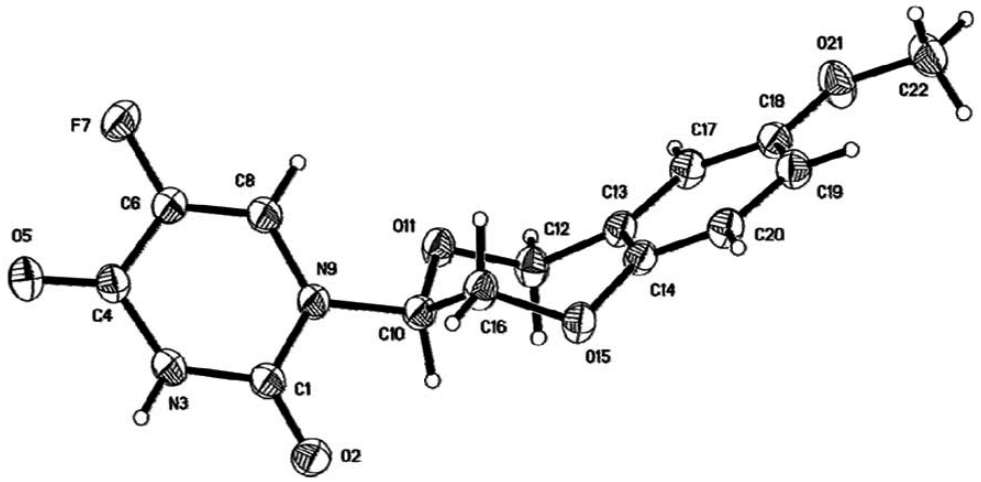


Fig. (15). Molecular structure of (+/-)-1-(7-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil **35** (ORTEP drawing at 50% probability) [31].

pounds **64-66** because the proximity relationship between both groups is even higher (delta or an 1,4-relationship). Table **5** shows the ^{13}C chemical shifts of the corresponding seven-membered moie- ties of the cyclic *O,O*-acetals.

In spite of the accurate ^{13}C NMR reasoning carried out to prove the structures of **42,43**, the confirmation of such compounds needed to be corroborated because this point is critical for the confirmation of the alkylation site of **81** by MEMCl. There is always the chance that the structure of **42** with the acetalic –OMe group at position 3 could have been mistaken for the corresponding analog having the acetalic –OMe group at position 2 (the hypothetical molecule **65**) because their ^{1}H and ^{13}C NMR data are very close. Accordingly, we decided to unequivocally elucidate the structure of the acetal (**65** or **42**) by its reaction with 5-FU, HMDS and TMSCl, under acid catalysis ($SnCl_4$) in acetonitrile during 144 h. Such a process led to 1-(7-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil **35** [20], whose structure was unambiguously determined by X-ray crystallography (Fig. (**15**)). Therefore, the regioselective protection of the primary hydroxy group of the corresponding salicyl alcohol was finally proved by a synthetic method, which ensured the previ- ous structural assignments.

The explanation of the different chemical behavior (see Figs. (**13**) and (**14**)) 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 [32]. Accordingly, the electronic properties of the *ortho* and *para* substituents to the hydroxy phenoxy group modify the selectivity of the alkylation site by MEMCl.

5.3. Mechanistic Aspects of the Synthesis of (+/-)-2-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins 64-66 and (+/-)-5-methoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecins 67-69

This process is effected by the reaction of **78-80** (1 equiv) in 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 **78-80** and of the final com- pounds **64-66** and **67-69** are compared, one comes to the conclusion that the MEM moiety of **78-80** should suffer two different cleavage processes from a formal point of view: a) on one hand, with the breaking of the methoxyethoxymethyl moiety, then the nucleophilic attack of the phenoxy group to the acetalic function with the concomitant cyclization process should give rise to the seven- membered acetal **64-66**; and b) the formation of the ten-membered acetal **67-69** 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 proc- esses and rearrangements on common intermediates. It must be emphasized that outside the protective group arena, MEMCl has been used to alkylate enolates [33] and aryllithium reagents in the presence of Ph_2TlBr [34]. MEM ethers have also proved to be a good one-carbon source for the preparation of isochromans [35].

Fig. (**16**) 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 σ_p^+ values for H, Cl and Br are the following: 0.00, 0.11 and 0.15, which means that Cl and Br are weak electron-withdrawing groups [36]). The intermediates **90-92** may 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 **93-95**, which could suffer a reduction of the ring size to the 10-membered intermediate **96-98** 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 **96-98** gives rise to a ring contraction leading to **64-66** through the intermediacy of the seven-membered oxonium ion **99- 101**.

It could be thought that, rather than the formation of **99-101** through the intermediates **87-98**, the synthesis of **64-66** could be considered more directly and simply from the open acetals **78-80** by nucleophilic attack of the phenoxy oxygen to the acetalic functionality, after complexation by BF_3 of one of the acetalic oxygens. Then the intermediate analogous to **99-101** should arise, but in this case substituted on the oxonium oxygen by a 2-methoxyethoxy- methyl group. Cleavage of this group should also deliver **64-66**. Nevertheless, the proof of the presence of the by-product 2-(methoxymethoxy)ethanol, formed through **87-98**, and the absence of methoxyethoxymethanol, arising directly from **78-80**, allow us to settle the proposed mechanism. On the other hand, it has been checked that the seven-membered rings **64-66** (major products of

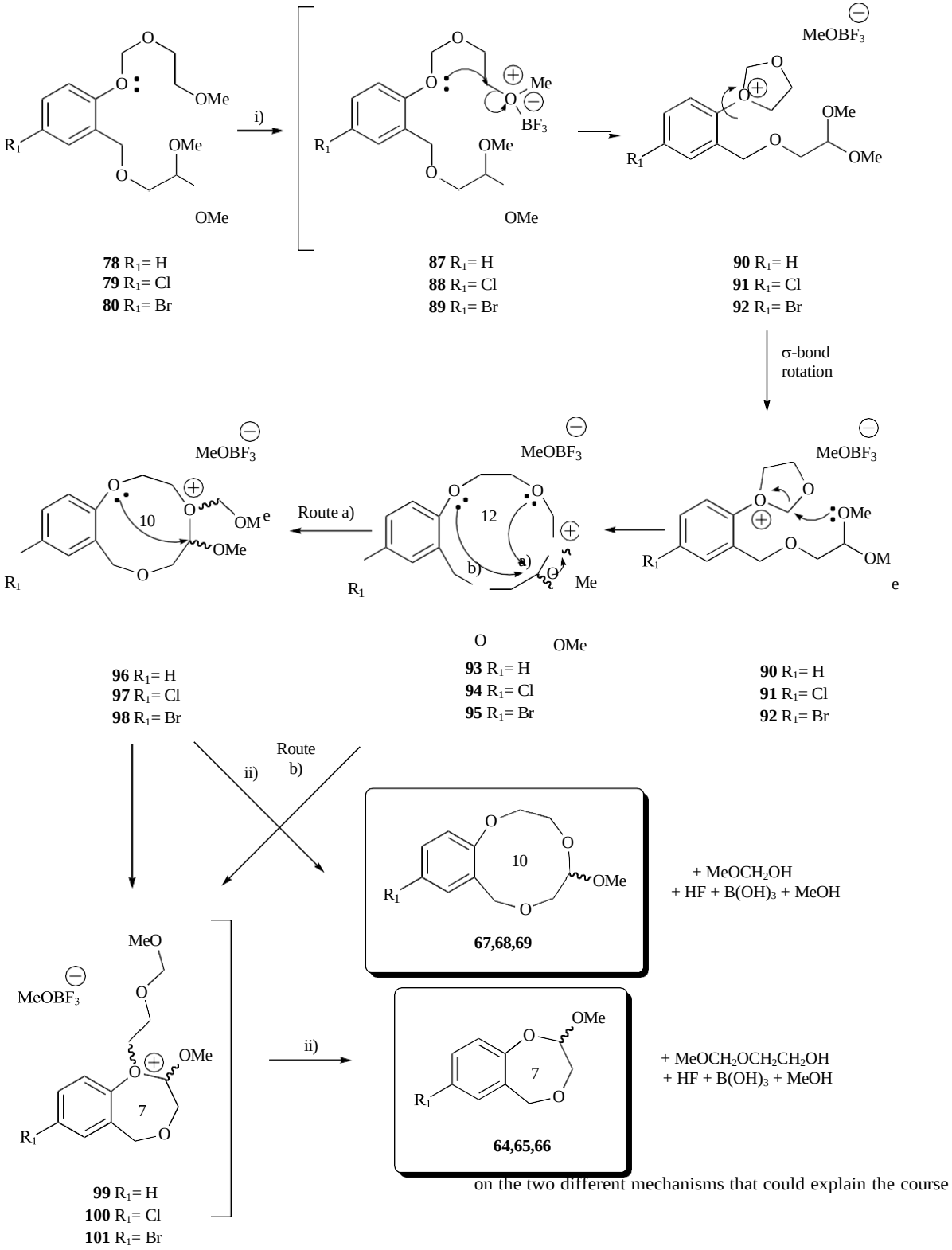


Fig. (16). *Reagents*: i) $BF_3 \cdot OEt_2$, THF; ii) H_2O.

the rearrangements) do not arise from the ten-membered rings **67- 69**, upon treatment of the latter with boron trifluoride diethyl ether- ate under the conditions of the rearrangement.

5.4. Mechanistic Aspects of the Synthesis of (+/-)-3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins 42,43 and (+/-)-3,12-dimethoxy-2,3,5,6-tetrahydro-8*H*-benzo-[1,4,7]-trioxecin 71

When the starting materials are **85** and **86**, 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. The mechanism of the transformation **85** → **42** is best represented as in Fig. (**17**). 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 neighboring group. It has been previously reported a similar feature [20]. According to this hypothesis, the intermediate **102** suffers the neighboring group attack to give the oxyranium ion **103**, which is much more reactive than its predecessor. After a σ-bond rotation through the C-O^+ bond of this highly

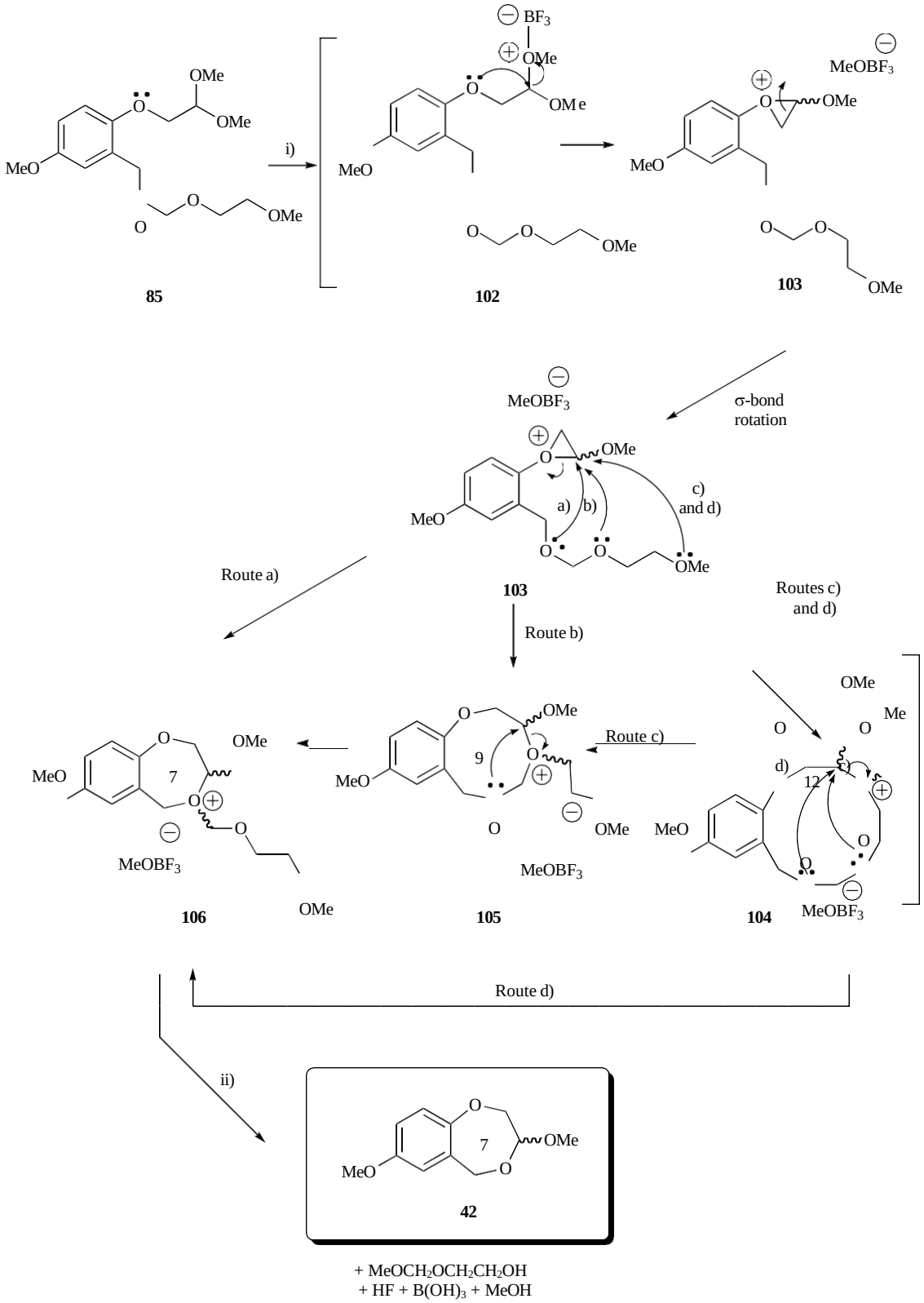


Fig. (17). *Reagents*: i) $BF_3 \cdot OEt_2$, THF; ii) H_2O.

reactive species, the acetalic-like carbon atom could be attacked by any 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 (**104** and **105**, respectively), the final destiny is the seven-membered intermediate **106**, which after work-up leads to **42**. The characterization of the by-product methoxymethoxyethanol justifies the proposed mechanism.

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 **43** and **71** is different (Fig. (**18**)). In this case, *via* a different mechanism, closely related to the one shown in Fig. (**16**), 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 **108**. Again, the proof of the presence of methoxymethoxyethanol and methoxymethanol strongly supports the mechanism.

An important question that needs to be answered is the following: Why this different behavior is observed when the aromatic –OMe groups in **85** and in **86** 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 **85** → **42** (Fig. (**17**)) and **86** → **43** + **71** (Fig. (**18**)) should have been the same. Should this be the case, the two key intermediates are shown in Fig. (**19**), one of

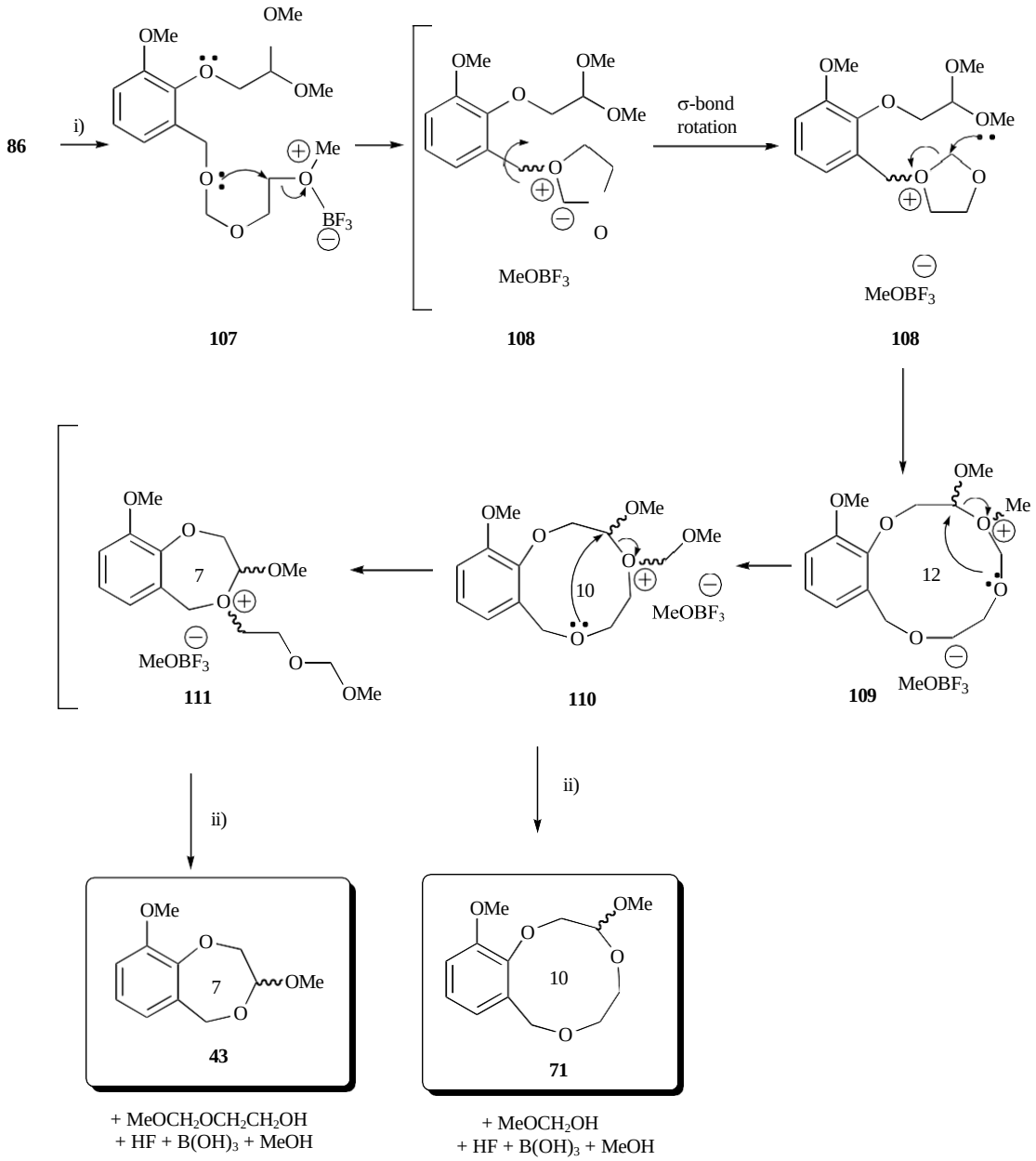


Fig. (18). *Reagents*: i) $BF_3 \cdot OEt_2$, THF; ii) H_2O.

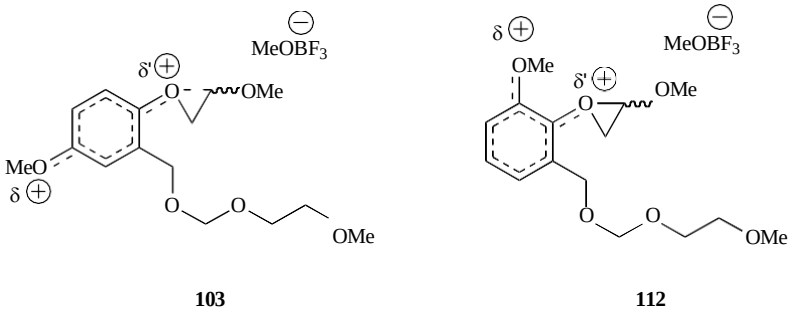


Fig. (19). Two key intermediates: **112** is highly unstable due to the closeness of both positive charges.

them (**112**) 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 electronically 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

(Figs. (**16**) and (**17**)). 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 **112** makes the upper *O*-phenolic fragment to act as electrophile and, accordingly the lower alcoholic *O*-linked moiety to work as nucleophile (Fig. (**18**)).

This behavior can be confirmed after the structural proofs of the by-products methoxymethanol and methoxymethoxyethanol.

CONCLUSIONS

It is impossible to establish a common final structure as a consequence of the neighboring-group participation involving the oxygen atom of the *O,O*- or *O,N*-acetal functions, since it depends on the starting material. The naphthoate ester derivatives of (*Z*)-hex-3- ene-1,5-diyne were used to generate biradicals *via* γ-oxo ketene acetal intermediates, and a synthesis of tricyclic 9-crown-3 ethers bearing a chiral oxathiane ring was achieved by utilizing nucleo- philic displacement of a triflic ester leaving group assisted by neighboring-group participation of a 1,3-dioxolane function. The reaction between *o*-(hydroxymethyl)phenoxyacetaldehyde dimethyl acetals, or 3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins with 5- fluorouracil was also studied. The intramolecular cyclization may be explained through a neighboring-group attack to give a 2-(5- fluorouracil-1-yl)oxyranium ion that can be attacked by the sily- lated benzylic hydroxyl group to yield the benzannelated seven- membered *O,N*-acetals. On the other hand, the substituents of 2- hydroxybenzylic alcohols affect the protection mode with MEMCl of the two different hydroxyl groups. 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. The formation of the ten-membered *O,O*-acetals **67-69** and **70-71** and characterization of the by-products throw light on the course of the $BF_3{\cdot}OEt_2$-promoted reaction on **78-80** and **85,86**, respectively. Al- though a smaller amount of data is available upon which to draw conclusions about the facility of the acetal participation, the results seem comparable to those of simple ethers. The rational design of *O,O*-acetals containing several heteroatoms located in critical posi- tions in their side-chains could be interesting chemotypes for the preparation of esoteric rings endowed with potentially remarkable biological activities. Moreover, the analysis of the course of such reactions could throw some light on the mechanistic aspects of the subject, facilitating accordingly both the fine tuning of the target molecules and the comprehension of this stereoelectronic effect. In consequence, this review endeavours to awaken the interest of re- searchers in the preparation and mechanistic features of unusual polyheteroatomic rings.

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ABBREVIATIONS

Ac	=	acetyl
Bz	=	benzoyl
DIBAL-H	=	diisobutylaluminium hydride
DIPEA	=	diisopropylethylamine
DMF	=	*N,N*-dimethylformamide
EDC	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
5-FU	=	5-fluorouracil
HMDS	=	1,1,1,3,3,3-hexamethyldisilazane
HR LSIMS	=	high resolution liquid secondary ion mass spectrum
MEM	=	2-methoxyethoxymethyl
Ms	=	methanesulfonyl
NCS	=	neocarzinostatin
NOE	=	nuclear Overhausser effect
ORTEP	=	Oak Ridge Thermal Ellipsoid Plot
Py	=	pyridine
rt	=	room temperature
THF	=	tetrahydrofuran
Tf	=	triflate
TMS	=	trimethylsilyl

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