Dilithiated synthons: synthesis of cyclic ethers*

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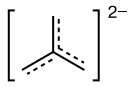
Recent advances in the generation of dilithiated synthons by arene-catalyzed lithiation of the corresponding dichloro compounds in the presence of carbonyl compounds (Barbier-type reaction conditions) as the key step are described. Further cyclization of the generated diols under different reaction conditions affords a variety of mono-, bi-, and spirocyclic ethers.

Key words: dilithiated synthons, lithiation, cyclic ethers, spirocyclic ethers.

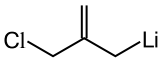
Apart from other considerations, such as biological screening, organic synthesis is based mainly on two important pillars: (a) synthetic strategy, also called retrosynthetic analysis, is the way that an organic chemist imagine on paper how to go from the starting material to the target molecule[1] and (b) synthetic methodology, which is the way to realize practically in the laboratory what in principle the synthetic strategy designed.[2] Concerning the development of new methodologies, in the last few years we have been interested in the study of functionalized organometallic compounds,[3] mainly organolithium derivatives,[4,5] which are interesting intermediates in synthetic organic chemistry because their reactions with electrophiles afford directly polyfunctionalized molecules, widely occurring in nature. One intrinsic practical problem associated with the preparation of very unstable functionalized organolithium compounds has to do with the lithiation reaction, which in many cases must be performed at low temperatures. For this purpose, about ten years ago we found out that the use of an excess of lithium and a catalytic amount of an arene as the electron carrier is a versatile and potent methodology to perform the lithiation of several substrates under very mild reaction conditions.[6—9] Thus, using the mentioned methodology (arene-catalyzed lithiation) it is possible to carry out new lithiation processes, such as the preparation of organolithium compounds starting from non-halogenated materials,[10] the generation of functionalized organolithium compounds[5] and polylithiated synthons.[11] It was necessary in many cases to work under Barbier-type reaction conditions (BTRC) (performing the lithiation in the presence of an electrophile)[12] in order to avoid decomposition of the corresponding very unstable intermediates. In this paper, we present our last results in the field of the generation of polylithiated synthons and their application to the synthesis of cyclic and spirocyclic ethers.[13]

3-Lithio-2-(lithiomethyl)propene synthon

The trimethylenemethane dianion (**I**) presents a theoretical interest in relation to the so-called "Y-aromaticity" but also a practical one, because it is possible to transfer an unsaturated four-carbon fragment to two molecules of an electrophile. However, its generation by halogen-lithium exchange fails due to the decomposition of the monolithiated intermediate (**II**) initially formed.[14a]



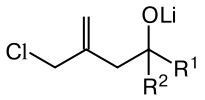
I



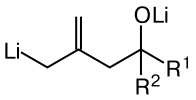
II

However, the naphthalene-catalyzed lithiation of 3-chloro-2-(chloromethyl)propene (**1**) in the presence of different carbonyl compounds (BTRC) in THF at temperatures ranging between −78 °C and room temperature yielded, after hydrolysis, the corresponding unsaturated diols **2** (Scheme 1). The step-wise process (tandem lithiation-S_E reaction) afforded dimer **3** as the only reaction product resulting from the dimerization of the initially formed intermediate (**II**).[14b]

Concerning the possible reaction pathway, intermediate **II** is probably formed after the first lithiation. This reacts with the electrophile present in the reaction medium to give the alkoxide **III**, which undergoes second lithi-



III



IV

* Materials were presented at the Mark Vol´pin Memorial International Symposium "Modern Trends in Organometallic and Catalytic Chemistry" dedicated to his 80th anniversary.

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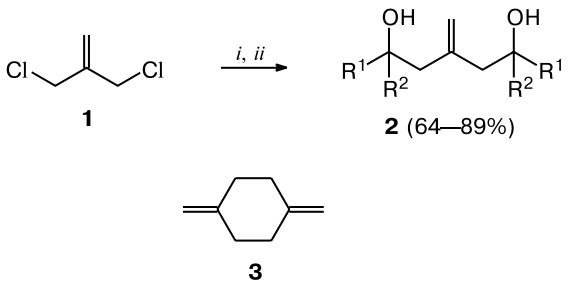
Scheme 1

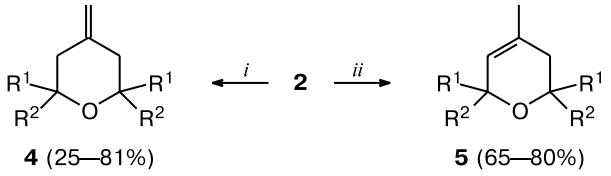


Reagents and conditions: *i*. Li, $C_{10}H_8$ (6%), R^1R^2CO = Pr^iCHO, PhCHO, Me_2CO, Et_2CO, *cyclo*-$(C_3H_5)_2CO$, Pr^i_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, THF, −78 °C → 20 °C; *ii*. H_2O.

ation affording the new intermediate **IV**. The final reaction of compound **IV** with the electrophile produces the corresponding dialkoxide precursor of the diols **2**.

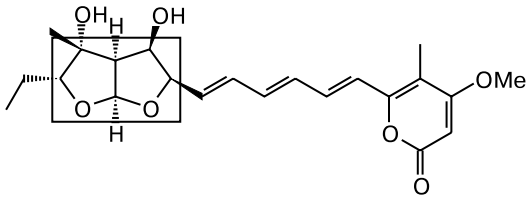
Treatment of diols **2** with hydrochloric acid gave different products depending on the concentration of the acid. Using a 6 *M* solution in ether, methylenetetrahydropyrans **4** are obtained as the main products; with 12 *M* hydrochloric acid in the same solvent and for a longer reaction time, the corresponding dihydropyrans **5** are obtained (Scheme 2). The corresponding carbenium-ion intermediates are probably involved in the cyclization and isomerization processes.[15] Tetra- and dihydropyrans are common structural elements in many biologically active natural products.[16]

Scheme 2

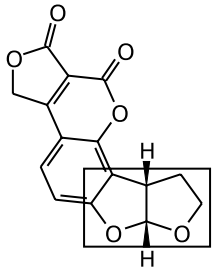


Reagents and conditions: *i*. 6 *M* HCl, Et_2O, 1—5 h; *ii*. 12 *M* HCl, Et_2O, 24 h.

In addition to cyclization producing compounds **4** or **5**, unsaturated diols **2** can be used as starting materials to prepare perhydrofurofurans, which are structural units present in many natural products. Thus this fragment is found in many clerodan-type diterpenes (*i.e.*, lupulin A, scuterepepin A_1 or scupolin B),[17] which show insect antifeedant activity as well as antibacterial properties. Asteltoxin[18] and aflatoxin B_2[19] are probably the most famous members of a family of molecules containing the perhydrofurofuran core because these mycotoxins possess very potent toxicity and carcinogenicity.



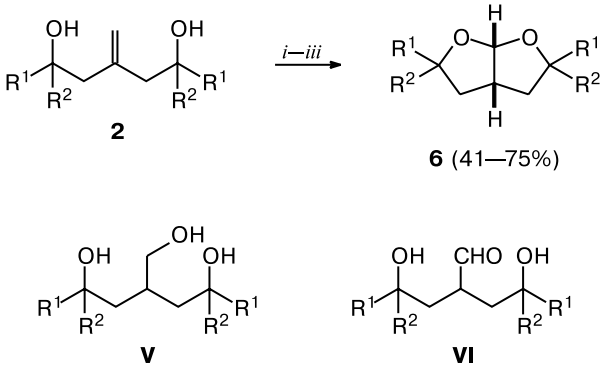
Asteltoxin



Aflatoxin B_2

In our approach to the perhydrofurofuran unit, we used diols **2** as the starting materials, using a tandem hydroboration—oxidation followed by oxidation of the primary alcohol formed to the corresponding aldehyde. Thus treatment of compounds **2** with borane in THF at 0 °C followed by oxidation with hydrogen peroxide gave crude triol (**V**), whose primary OH group was then oxidized to the corresponding aldehyde group (compound **VI**) with the $(Ph_3P)_3RuCl_2$ complex in benzene (for R^2 = H) or with PCC in dichloromethane (for $R^2 \neq$ H). After spontaneous acetalization of dihydroxyaldehyde formed, the expected perhydrofurofurans **6** were isolated (Scheme 3).[20,21]

Scheme 3

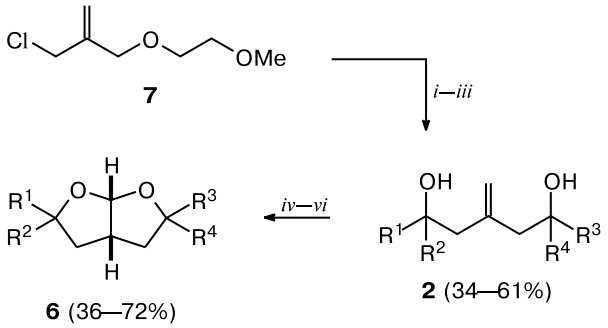


R^1, R^2 = H, Me, Et, Pr^i, Bu^t, *cyclo*-C_6H_{11}, Ph;
R^1—R^2 = $(CH_2)_5$, $O(CH_2CH_2)_2$

Reagents and conditions: *i*. $BH_3 \cdot THF$, 0 °C; *ii*. 33% H_2O_2, 3 *M* NaOH; *iii*. $(Ph_3P)_3RuCl_2$, PhH, 0 °C (R^2 = H) or PCC, CH_2Cl_2, 0 °C ($R^2 \neq$ H).

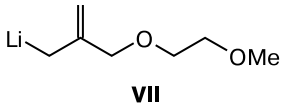
Following the strategy shown in Scheme 3, it is possible to prepare only perhydrofurofurans **6** having identical substitution at both sides of the molecule. In order to make possible the preparation of these molecules with different groups on both parts of the structure, compound **7** was used as the starting material, in which two different carbon-heteroatom bonds are ready to be lithiated. Thus the reaction of chloro ether **7** with lithium and a catalytic amount of naphthalene in the presence of different carbonyl compounds in THF at temperatures ranging between −78 and −30 °C allowed the introduction of the corresponding electrophilic fragment through the exclusive lithiation of the carbon-chlorine bond. Then a second carbonyl compound was added to the reaction mixture allowing warming up to room temperature, so the second lithiation of the allylic carbon-oxygen bond took place with an excess of lithium present in the reaction medium. After the reaction with the second electrophile and final hydrolysis, the unsymmetrically substituted unsaturated alcohols **2** were obtained. The application of the same methodology for the cyclization mentioned above allowed the preparation of perhydrofurofurans **6**, bearing different substituents at both parts of the molecule (Scheme 4).[21,22]

Scheme 4

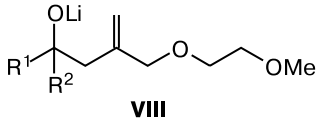


Reagents and conditions: *i*. Li, $C_{10}H_8$ (2.5%), R^1R^2CO = Bu^tCHO, Et_2CO, $(CH_2)_5CO$, $O(CH_2CH_2)_2CO$, PhCOMe, THF, −78°C → −30 °C; *ii*. R^3R^4CO = Me_2CO, Et_2CO, Bu^tCOMe, $Bu^t{}_2CO$, $(CH_2)_4CO$, $(CH_2)_5CO$, −30 °C → 20 °C; *iii*. H_2O; *iv*. $BH_3 \cdot THF$, 0 °C; *v*. 33% H_2O_2, 3 *M* NaOH; *vi*. $(Ph_3P)_3RuCl_2$, PhH, 0 °C (R^2 = H) or PCC, CH_2Cl_2, 0 °C ($R^2 \neq$ H).

From a mechanistic point of view, after lithiation of the most reactive carbon-chlorine bond, the functionalized organolithium compound **VII** is generated, which before any decomposition reacts with the first electrophile (R^1R^2CO) to give the alkoxide **VIII**. After the second lithiation involving the allylic carbon-oxygen bond at higher temperature, the new organolithium intermediate **IV** (see above) is formed, which reacts with the second electrophile (R^3R^4CO), also added to the reaction medium, to give the corresponding dialkoxide precursor of the final diols **2**.

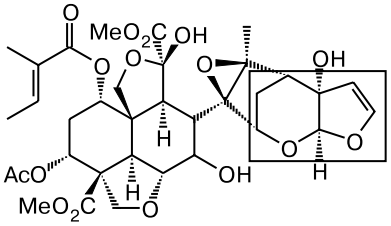


VII

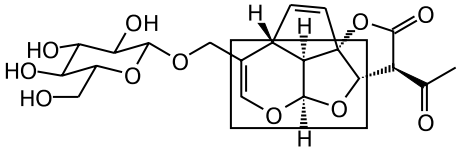


VIII

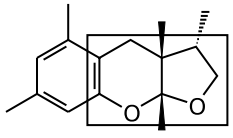
Another application of the homologous unsaturated diols of type **2** is the preparation of perhydrofuropyrans, which are also present as structural units in many natural products. Examples of such naturally occurring compounds are among others, azadirachtin[23] and duroin,[24] both showing potent growth-inhibitory activity in plants, or alboatrin, a phytotoxic metabolite that causes vascular-wilt disease on alfalfa.[25]



Azadirachtin



Duroin

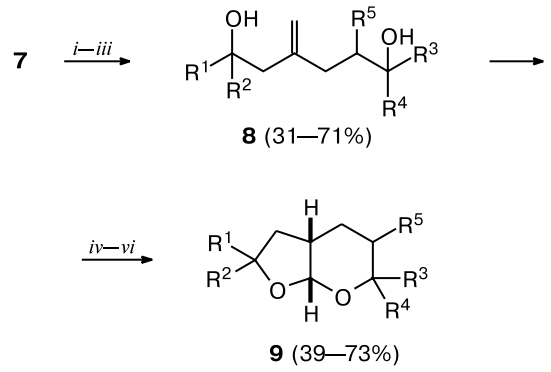


Alboatrin

In the case of the synthesis of the perhydrofuropyran core, one more carbon atom is needed in one of the two sides of diols **2**. This synthesis can be achieved starting from chloro ether **7** and using an epoxide as the second electrophile. Thus, after the first lithiation and reaction with a carbonyl compound (R^1R^2CO), as it was described in Scheme 4, second lithiation occurred in the presence of different epoxides giving, after final hydrolysis, the corresponding diols **8**. These isolated compounds were

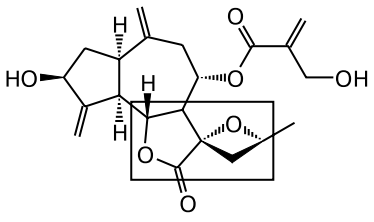
then subjected to cyclization under the same reaction conditions as shown in Schemes 3 and 4, so the expected perhydrofuropyrans **9** were directly isolated (Scheme 5).[26]

Scheme 5

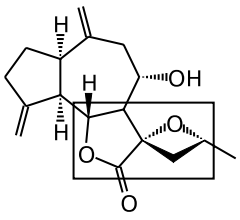


Reagents and conditions: *i*. Li, $C_{10}H_8$ (2.5%), R^1R^2CO = Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $O(CH_2CH_2)_2CO$, 2-adamantanone, THF, −78 °C → 0 °C; *ii*. $R^3R^4C(O)CHR^5$ = $MeCH(O)CH_2$, $EtCH(O)CH_2$, *n*-$C_6H_{13}CH(O)CH_2$, $(CH_2)_4CH(O)CH$, $PhCH(O)CH_2$, $PhCMe(O)CH_2$, $Et_2C(O)CH_2$, 2-methyleneadamantane oxide, $(n\text{-}C_5H_{11})_2C(O)CH_2$, $(CH_2)_5C(O)CH_2$, $O(CH_2CH_2)_2C(O)CH_2$, 0°C → 20 °C; *iii*. H_2O; *iv*. BH_3·THF, 0 °C; *v*. 33% H_2O_2, 3 *M* NaOH, 0 °C; *vi*. PCC or $(Ph_3P)_3RuCl_2$, CH_2Cl_2.

The last application of the 2-lithio-3-lithiomethyl synthon was the preparation of 1,6-dioxaspiro[3.4]octanes. This structural unit appears in a series of naturally occurring sesquiterpene lactones such as clementein[27] or subexpinnatin C,[28] which show biological activity.



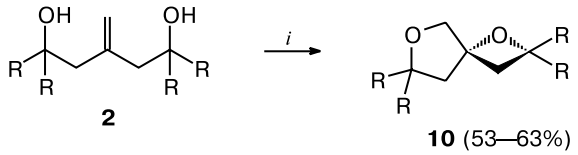
Clementein



Subexpinnatin C

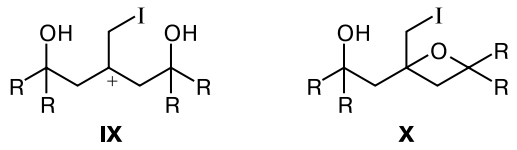
Once diols **2** ($R^1 = R^2$) were isolated, they were treated with iodine and silver(I) oxide in a mixture of water and dioxane at room temperature, so the expected 1,6-dioxaspiro[3.4]octanes **10** were isolated (Scheme 6).[29]

Scheme 6



Reagents and conditions: *i*. I_2, Ag_2O, dioxane—H_2O, 20 °C.

The spirocyclization shown in Scheme 6 can be rationalized considering that the initially formed iodonium ion suffers first attack of one of the oxygen atoms, through the most stable tertiary carbenium ion **IX**, to give the iodohydrin **X**, which finally undergoes an intramolecular nucleophilic substitution (with displacement of iodide) to yield the final spirocyclic product **10**.

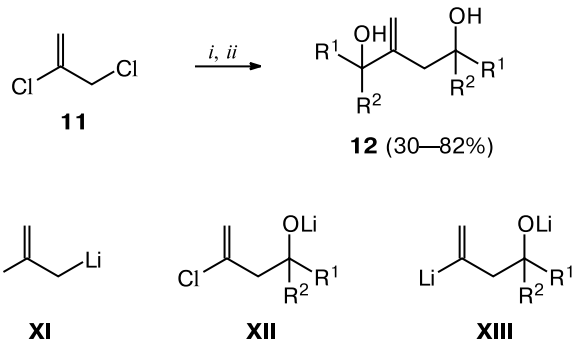


2,3-Dilithiopropene synthon

An important problem in the generation of 2,3-dilithiopropene is that the corresponding primary intermediate **XI** is a β-functionalized organolithium compound (also considered a d^2-reagent following Seebach´s nomenclature[30]), which has a great tendency to suffer β-elimination[31] giving, in this case, allene.[32] One way to overcome this problem is to work under BTRC, expecting that the reaction of intermediate **XI** with the electrophile present in the reaction medium would be faster than the corresponding β-elimination. That was the case, so the reaction of 2,3-dichloropropene (**11**) with lithium and a catalytic amount of 4,4´-di-*tert*-butylbiphenyl (DTBB) in the presence of different carbonyl compounds in THF at temperatures ranging between −78 °C and room temperature gave, after hydrolysis, the expected unsaturated diols **12** (Scheme 7).[33]

The mechanism of the reaction shown in Scheme 7 probably involves first a chlorine-lithium exchange at the most reactive allylic bond to give intermediate **XI**, which reacts with the electrophile present in the reaction medium (instead of β-elimination) giving the alkoxide **XII**. Second lithiation of this chloro alkoxide generates the second functionalized organolithium compound **XIII**, which finally reacts with a second molecule of the electrophile giving the corresponding dialkoxide precursor of diols **12**.

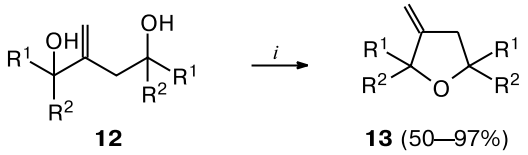
Scheme 7



Reagents and conditions: *i*. Li, DTBB (5%), R^1R^2CO = Pr^iCHO, Bu^tCHO, PhCHO, Pr^nCOMe, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOEt, THF, 0 °C; *ii*. H_2O.

Direct cyclization of diols **12** under acidic conditions (3 *M* hydrochloric acid in ether at room temperature) afforded the corresponding methylenic tetrahydrofurans **13** (Scheme 8), which are important structural units in many biologically active natural products.[34] Concerning the mechanism of the cyclization, the most stable allylic carbenium ion is probably involved in the process. It is worth noting that in this case no isomerization of the double bond (to give the endocyclic olefin) was observed.

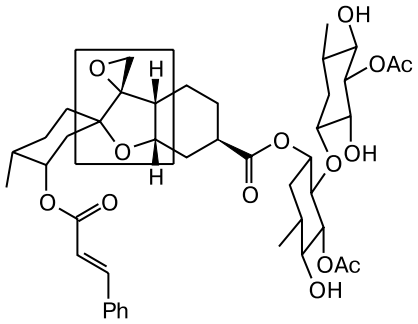
Scheme 8

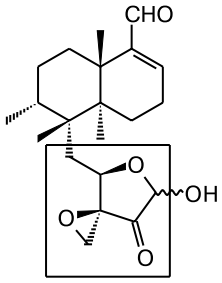


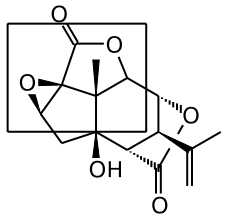
Reagents and conditions: *i*. 3 *M* HCl, Et_2O.

Finally, diols **12** were also transformed into the corresponding 1,5-dioxaspiro[2.4]heptanes using a modification of the methodology mentioned above for the preparation of spiro compounds **10** (see Scheme 6). This 1,5-dioxaspiro[2.4]heptane unit is the fragment of many natural products such as the antineoplastic glycoside phyllanthostatin 1,[34] the microbial diterpenoid clerocidin[35] and picrotoxinin,[36] one of the most toxic substances of plant origin known.

Once diols **12** were obtained, they were treated with sodium hydride and iodine in THF at temperatures ranging from 0 °C to room temperature, so the corresponding spiro compounds **14** were isolated. In addition, since in nature many compounds have the lactone functionality associated to the spiro core, we transformed compounds **14** into the related lactones **15** by oxidation with sodium periodate and a catalytic amount of ruthenium dioxide in

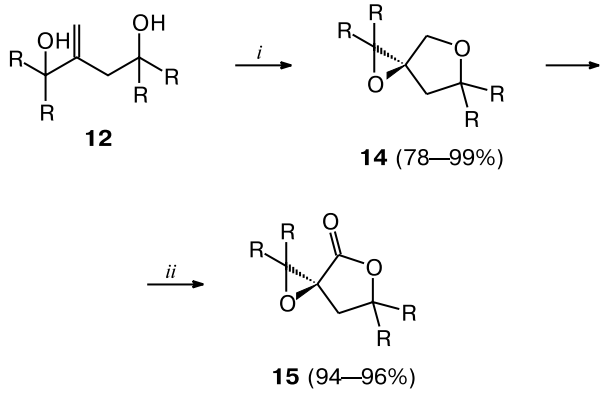






a mixture of carbon tetrachloride and water at room temperature (Scheme 9).[37]

Scheme 9



Reagents and conditions: *i*. NaH, I_2, THF, 0 °C → 20 °C; *ii*. $NaIO_4$, RuO_2 (15%), CCl_4—H_2O.

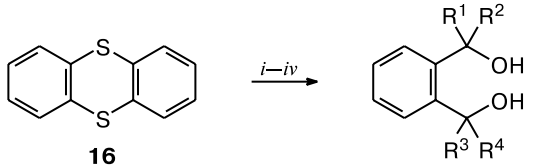
The spirocyclization shown in the first step of Scheme 9 probably involves intermediates of the same type like those (**IX** and **X**) postulated for the preparation of compounds **10**.

1,2-Dilithiobenzene synthon

The direct generation of the 1,2-dilithiobenzene dianion from the corresponding 1,2-dichlorobenzene using

an arene-catalyzed lithiation (even under BTRC) fails, only one electrophilic fragment being possible to be introduced in the molecule, giving monosubstituted benzenes, since the second chlorine atom is always substituted by hydrogen.[38] For this reason, any alternative to overcome this problem would be welcome. Recently, we found that thianthrene (**16**) can be successively lithiated allowing the introduction of two different electrophiles. Thus when this starting material **16** was lithiated with lithium and a catalytic amount of DTBB in THF at −90 °C and then reacted with a carbonyl compound (R^1R^2CO) at the same temperature, the corresponding intermediate is formed which could suffer a second lithiation. It is then possible to add a second carbonyl compound (R^3R^4CO) at temperatures ranging between −90 and −78 °C, so after final hydrolysis at low temperature the corresponding diols **17** were isolated (Scheme 10).[39]

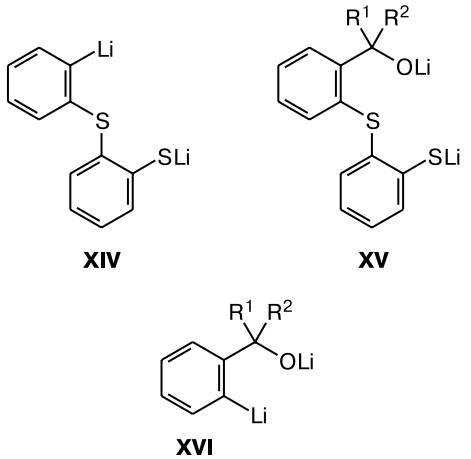
Scheme 10



16 **17** (47—81%)

Reagents and conditions: *i*. Li, DTBB (7%), THF, −90 °C; *ii*. R^1R^2CO = Bu^tCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, −90 °C; *iii*. R^3R^4CO = Bu^tCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, Et_2CO, $(CH_2)_5CO$, −90 °C → −78 °C; *iv*. H_2O, −78 °C → 20 °C.

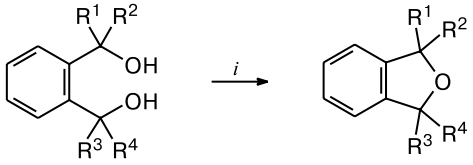
To rationalize the whole transformation shown in Scheme 10, we think that after the first lithiation a ring opening takes place yielding a functionalized organolithium intermediate **XIV**, which reacts in a second step with the first carbonyl compound to give the alkoxide **XV**. Then, the second lithiation takes place generating the organolithium intermediate **XVI**, which finally is trapped by the second electrophile affording the corresponding dialkoxide precursor of the diol **17**.



XIV **XV** **XVI**

Diols **17** were easily cyclized with 85% phosphoric acid upon reflux in toluene to yield substituted phthalans **18** (Scheme 11), which are interesting molecules related to the corresponding phthalides of biological significance.[40] A benzylic carbenium ion is probably involved in the cyclization to give compounds **18**.

Scheme 11



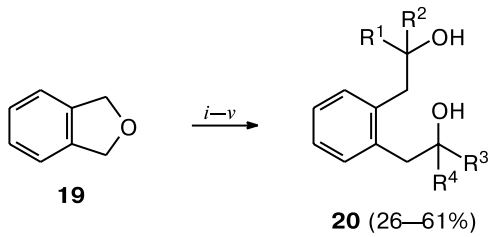
17 **18** (>95%)

Reagents and conditions: *i*. 85% H_3PO_4, refluxing toluene.

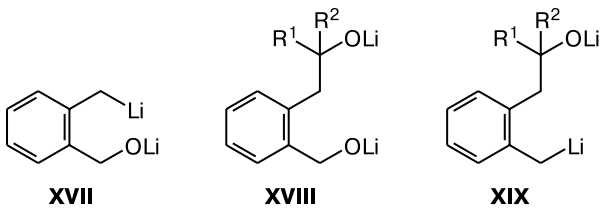
1,2-Bis(lithiomethyl)benzene synthon

The ring opening of phthalan **19** can be used to generate a 1,2-bis(lithiomethyl)benzene synthon using an approach similar to that shown in Scheme 11. The reaction of phthalan **19** with lithium and a catalytic amount of DTBB in THF at room temperature followed by addition of a first carbonyl compound in THF at −78 °C to room temperature allowed the introduction of the first electrophilic fragment, the second lithiation takes place, so a

Scheme 12



19 **20** (26—61%)



XVII **XVIII** **XIX**

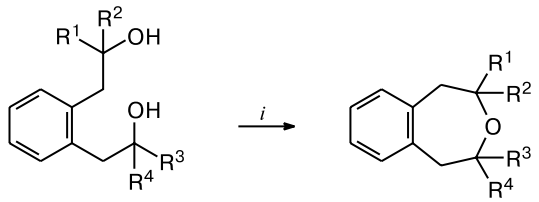
Reagents and conditions: *i*. Li, DTBB (2.5%), THF, 20 °C; *ii*. R^1R^2CO = Bu^tCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, −78 °C; *iii*. −78 °C → 20 °C; *iv*. R^3R^4CO = EtCHO, Bu^tCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, −78 °C; *v*. H_2O, −78 °C → 20 °C.

second carbonyl compound can be added to give, after hydrolysis, the corresponding diols **20** (Scheme 12).[41]

The species **XVII—XIX** have been postulated as intermediates in the process depicted in Scheme 12. Thus, after the first lithiation, the benzylic organolithium compound **XVII** is formed, which reacts with the first carbonyl compound to give the dialkoxide **XVIII**. After allowing the temperature to rise to room temperature, the second lithiation takes place cleaving the second carbon—oxygen bond, so intermediate **XIX** was obtained, which reacts finally with the second electrophile yielding the corresponding dialkoxide precursor of products **20**.

Finally, diols **20** were cyclized under acidic conditions (85% phosphoric acid, refluxing toluene) to yield benzoxepines **21** (Scheme 13). The overall process (**19** → **21**) is the double homologation of the starting material. For the cyclization shown in Scheme 13, the corresponding homobenzylic carbenium ion could be a possible intermediate.

Scheme 13



20 **21** (52—71%)

Reagents and conditions: *i*. 85% H_3PO_4, refluxing toluene.

Conclusion

From the results presented herein, we can conclude that the arene-catalyzed lithiation of dichlorinated materials, such as compounds **1** and **11**, in the presence of different carbonyl compounds (Barbier-type reaction conditions) allows the preparation of unsaturated 1,5- and 1,4-diols (**2** and **12**), respectively, which are versatile starting materials for different type of mono- (**4**, **13**) and bicyclic (**6**) ethers, as well as spiro compounds (**10**, **14**), these heterocyclic units being widely present in naturally occurring biologically active products. Using 1,2-disubstituted aromatic precursors **16** and **19** and applying a similar strategy, it is possible to introduce two equal or different electrophilic fragments at the 1,2-positions, so the corresponding diols prepared (**17** and **20**) are easily cyclized to the corresponding benzofused cyclic ethers (**18** and **21**). Note, concerning the use of naphthalene or DTBB as catalysts and the corresponding amount used (<10% in any case) were found empirically.

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