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Straightforward synthesis of 1,7-dioxaspiro[4.4]nonanes

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Abstract—The reaction of 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene with an excess of lithium powder and a catalytic amount of naphthalene (2.5%) in the presence of a carbonyl compound ($E^1 = R^1R^2CO$) in THF at −78 to 0 °C, followed by the addition of an epoxide [$E^2 = R^3R^4C(O)CHR^5$] at 0 to 20 °C leads, after hydrolysis, to the expected methylidenic diols. These diols, in the presence of iodine and silver(I) oxide in dioxane–water, undergo double intramolecular iodoetherification to give the corresponding 1,7-dioxaspiro[4.4]nonanes, which in addition can be easily oxidised to a variety of 1,7-dioxaspiro[4.4]nonan-6-ones.

The 1,7-dioxaspiro[4.4]nonane skeleton and its derived lactones are present in a wide and diverse series of natural products, some of them with important biological activities. This type of compounds are especially abundant within the family of the labdane diterpenoids, two representatives of which are prehispanolone (**I**) (a specific platelet activating factor receptor antagonist, isolated from the Chinese herbal medicine *Leonurus heterophyllus*)[1,2] and leopersin J (**II**) (from *Leonurus persicus*).[3] Some other naturally occurring compounds containing the mentioned substructure are sphydrofuran (**III**) (a secondary metabolite produced by Actinomycetes),[4] cinatrin A (**IV**) (a potent inhibitor of rat platelet phospholipase A_2, from the fermentation broth of the microorganism *Circinotrichum falcatisporum*),[5] longianone (**V**) (from *Xylaria longiana*),[6] or hyperolactone A (**VI**) (from *Hypericum chinense* L.).[7] 1,7-Dioxaspiro[4.4]nonanes have also been used as valuable polycyclic scaffolds in the synthesis of natural products (e.g., **VII**, in zaragozic acid synthesis)[8] or have been obtained as a result of carbohydrate modification (**VIII**)[9] (Chart 1).

Due to the unique structural nature of these spirocyclic compounds, their syntheses represent a major challenge for the organic chemist.[10] However, most of the available methodologies have focussed on the synthesis of spirocyclic γ-mono- and bislactones, less attention being dedicated to the 1,7-dioxaspiro[4.4]nonane itself as a polycyclic ether. These methodologies normally involve the intramolecular cyclisation of a moiety attached to a preformed γ-lactone or tetrahydrofuran ring. As representative examples we can mention: (a) the intramolecular Michael addition of a 3-hydroxyalkyl group to a 2-butenolide ring;[10] (b) Reformatsky-type reaction on a tetrahydrofuran-3-one, followed by lactonisation;[11] (c) lactonisation of 2-hydroxyalkyl-γ-lactone acids;[12] (d) radical cyclisation of a 4-(3-butynyloxy)-2,5-dihydro-2-furanone;[13] or (e) intramolecular ketalisation from a 2,2-disubstituted tetrahydrofuran.[14]

On the other hand, in the recent years we have shown an increasing interest in the synthesis of bicyclic[15–19] and spirocyclic[20,21] polyether skeletons as constituents of important biologically active compounds. In particular, and in connection with the title topic, we reported the two-step synthesis of 1,6-dioxaspiro[3.4]octanes from 3-chloro-2-(chloromethyl)prop-1-ene[20] and 1,5-dioxaspiro[2.4]heptanes from 2,3-dichloroprop-1-ene.[21] In both cases an arene-catalysed lithiation[22–24] under Barbier conditions[25,26] and an iodine-mediated double intramolecular cyclisation were utilised as the key reaction steps.

We want to describe herein a methodology that allows a straight and ready access to the title compounds, using 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**1**) as starting material. This compound underwent a selective naphthalene-catalysed lithiation with concomitant one-pot incorporation of two different electrophilic fragments,

Keywords: 1,7-Dioxaspiro[4.4]nonanes; Arene-catalysed lithiation; Spirolactones; Spirocyclisation.

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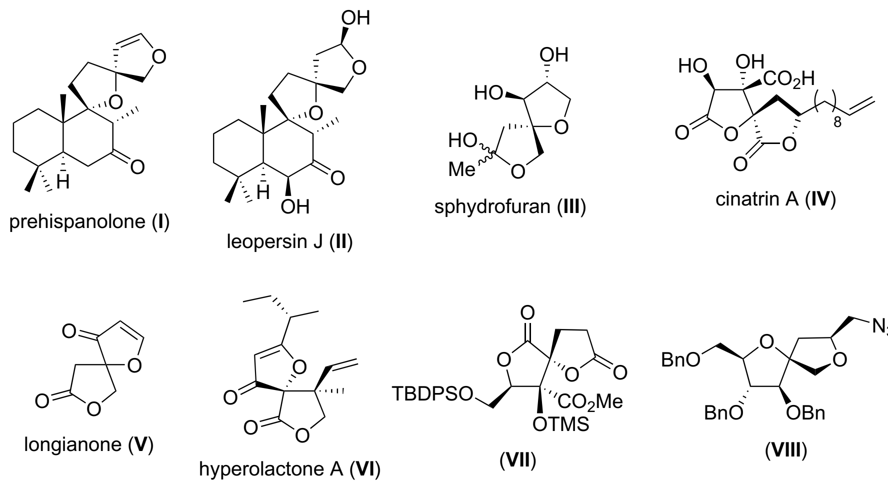


Chart 1.

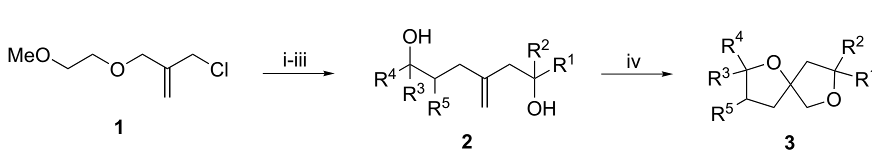
derived from a carbonyl compound and an epoxide, respectively.[19] The resulting methylidenic diols (**2**) were regioselectively cyclised in the presence of iodine and silver(I) oxide, affording the expected 1,7-dioxaspiro[4.4]nonanes (**3**) in high yields. In addition, these compounds could be easily oxidised to the corresponding 1,7-dioxaspiro[4.4]nonan-6-ones (**5**).

The reaction of 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**1**) with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of naphthalene (1:0.1 molar ratio, 2.5 mol %), in the presence of different carbonyl compounds ($E^1 = R^1R^2CO$; 1:0.95 molar ratio) in THF, at temperatures ranging from −78 to 0 °C for ca. 3.5 h, led to a reaction mixture, which was treated with an excess of an epoxide as a second electrophile [$E^2 = R^3R^4C(O)CHR^5$; 1:3 molar ratio] at 0 to 20 °C overnight giving, after hydrolysis with water, the corresponding methylidenic diols **2a–h** (Scheme 1 and Table 1). Among them, those symmetrically substituted were readily obtained using a ketone as the first electrophile and the epoxide derived from that ketone as the second electrophile (Table 1, compounds **2f**,**g**). In the case of using cyclohexene oxide as the second electrophile, only the corresponding *trans*-diastereomer was obtained (Table 1, compound **2h**).

This sequential incorporation of two electrophilic fragments arises from the different reactivity of the carbon–chlorine and carbon–oxygen bonds in arene-catalysed lithiations. Thus, the whole process is suggested to take place through an initial chlorine–lithium exchange with concomitant addition to the carbonyl compound, followed by an allylic carbon–oxygen bond cleavage (at higher temperature) and subsequent reaction with the epoxide.[19]

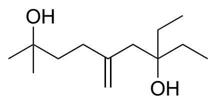
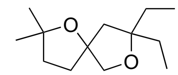
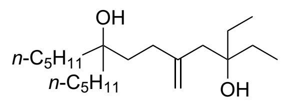
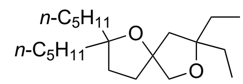
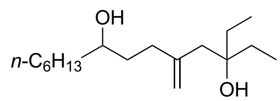
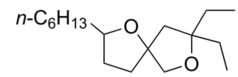
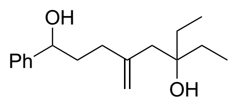
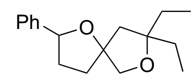
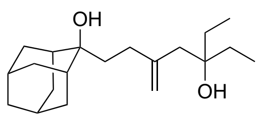
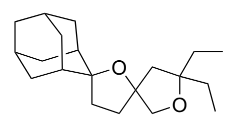
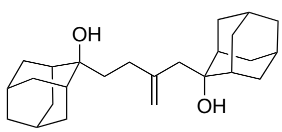
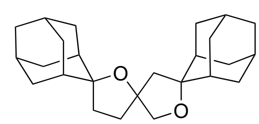
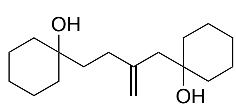
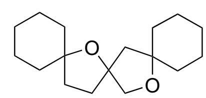
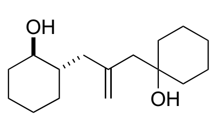
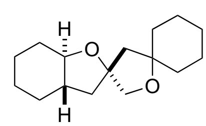
The isolated diols (**2**) were treated with iodine (1.5 equiv) and silver(I) oxide (1.5 equiv) in a 7:1 mixture of dioxane–water at room temperature overnight, to give the corresponding 1,7-dioxaspiro[4.4]nonanes **3** in excellent yields and with high purity (Scheme 1 and Table 1). In particular, compounds **3e–h** are polyspirocyclic molecules especially interesting from the structural point of view. It is worth of note that chiral racemic diols were obtained when 1-octene, styrene and cyclohexene oxides were used as second electrophiles (Table 1, compounds **2c**,**d**,**h**), and consequently some asymmetric induction could be expected in the formation of the new spirocyclic stereocentre. Spirocyclisation of diol **2d** gave a disappointing 1:1 diastereomeric ratio, whereas a 3.5:1 ratio was observed for diol **2c**. However, the cyclisation of diol **2h** led to an interesting 12:1 mixture of diastereoisomers (85% de) in favour of **3h**, the structure of which was confirmed by a NOESY experiment. This result can be promising in the synthesis of chiral nonracemic 1,7-dioxaspiro[4.4]nonanes by utilising enantiomerically pure epoxides as second electrophiles.

It must be mentioned that spirocyclisation of the diol **2f** could not be driven to completion, what explained the lower yield observed in the formation of **3f** (70%) compared to the rest of compounds **3**. However, this reaction allowed the isolation of the corresponding iodohydrin intermediate **4f** (15%). From this compound it can be inferred that the first cyclisation involves the epoxide derived moiety, followed by final intramolecular iodoetherification. Therefore, this mode of cyclisation



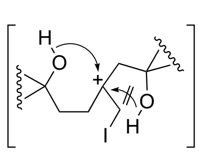
Scheme 1. Reagents and conditions: i, Li, $C_{10}H_8$ (2.5 mol %), R^1R^2CO, THF, −78 to 0 °C, 3.5 h; ii, $R^3R^4C(O)CHR^5$, 0 to 20 °C, overnight; iii, H_2O; iv, I_2, Ag_2O, dioxane–H_2O (7:1), 20 °C, overnight.

Table 1. Obtention of 1,7-dioxaspiro[4,4]nonanes **3** from diols **2**

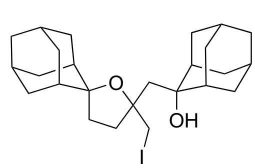
Product **2**[a]			Product **3**[a]		
No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
2a		70	**3a**		98
2b		43	**3b**		96
2c		55	**3c**		97[d]
2d		68	**3d**		88[e]
2e		41	**3e**		96
2f		33	**3f**		70[f]
2g		54	**3g**		92
2h		43	**3h**		93[g]

[a] All products were ⩾ 95% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).
[b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting chloroether **1**.
[c] Yield of pure **3** from the reaction crude (unless otherwise is stated) based on the starting diol **2**.
[d] Obtained as a 3.5:1 mixture of diastereoisomers.
[e] Obtained as a 1:1 mixture of diastereoisomers.
[f] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the corresponding diol **2f**.
[g] Obtained as a 12:1 mixture of diastereoisomers (85% de), the major diastereoisomer is shown.

leading regioselectively to the 1,7-dioxaspiro[4.4]nonanes is more favoured than the alternative one leading to the 1,6-dioxaspiro[3.5]nonanes (see **IX**).

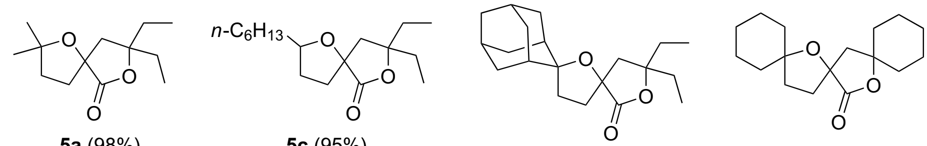


IX



4f

As shown Chart 1, not only 1,7-dioxaspiro[4.4]nonanes themselves are interesting compounds but also the derived lactones. We believed that the spirocyclic compounds synthesised **3** could be used as adequate precursors of 1,7-dioxaspiro[4.4]nonan-6-ones by oxidation adjacent to the tetrahydrofuran oxygen atom. Among the different methods available to carry out this transformation, the system composed of catalytic ruthenium(IV) oxide and sodium periodate gave excellent results (for some applications of this oxidation system, see for instance Ref. 27). Thus, by treating the 1,7-dioxaspiro[4.4]nonanes **3a**,**c**,**e**,**g** with a catalytic amount (0.15 equiv) of RuO_2 and an excess of $NaIO_4$ (4.88 equiv), in CCl_4–H_2O (1:1) at room temperature, the corresponding lactones **5a**,**c**,**e**,**g** were obtained, respectively, in remarkable yields and without any further purification (Chart 2).



5a (98%) **5c** (95%) **5e** (97%) **5g** (91%)

Chart 2.

Acknowledgements

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