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Substituted 1,7-Dioxabicyclo[3.3.0]octanes: New Easy Access to the Perhydrofurofuran Core of Aflatoxins and Analogues

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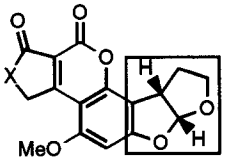
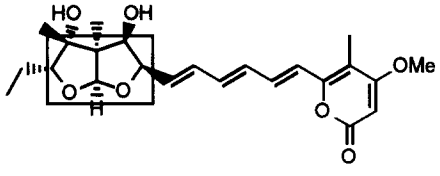
Abstract: The reaction of 3-chloro-2-(chloromethyl)-1-propene (**1**) with lithium and a catalytic amount of naphthalene in the presence of different carbonyl compounds in THF a -78°C affords, after hydrolysis, the corresponding methylenic diols **2**, which by a tandem hydroboration-oxidation with hydrogen peroxide followed by treatment with PCC (for ketone derivatives) or $RuCl_2(PPh_3)_3$ (for aldehyde derivatives) yields the expected perhydrofurofurans **3**. © 1997 Elsevier Science Ltd.

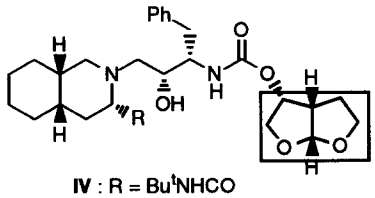
The bis-tetrahydrofuran fragment is present in many biologically active natural compounds. Among them, aflatoxins[1,2] B_2 and G_2 (**I** and **II**, respectively; metabolites of the mold *Aspergillus flavus*) are important mycotoxins due to their potent toxicity and carcinogenicity[3] and the fact that they have been detected in several foods, so intense interest from toxicologists and government regulators has been shown.[4] Other examples of interesting molecules containing the above mentioned fragment are asteltoxin[5] (**III**; isolated from *Aspergillus stellatus*, is a ATPase inhibitor with a toxicity comparable to that of aflatoxins) and compounds **IV**[6] (a non-peptidal ligand for HIV-1 protease-inhibitor complex) or **V**[7] (with strong antibacterial activity against *Pseudomonas aeruginosa*).



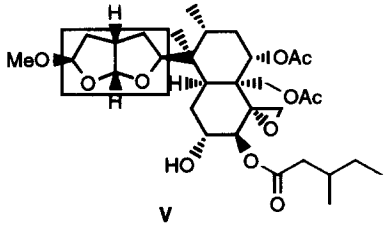
I : X = CH_2
II : X = CH_2O



III



IV : R = Bu^tNHCO

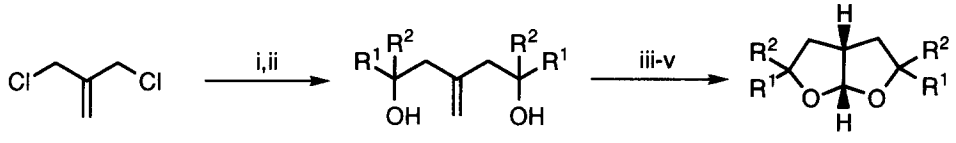


V

Chart 1.

On the other hand, in the last few years we have developed an efficient methodology consisting in carrying out lithiation processes in the presence of a catalytic amount of an arene as electron carrier under very mild reaction conditions.[8] Using this procedure we were able to develop new methods to prepare organolithium compounds starting from non-halogenated materials[9] as well as to prepare very reactive functionalised organolithium compounds[10] or polylithiated synthons.[11] In this paper we describe the application of one of the last type of polyanionic intermediates in the key step for the synthesis of the perhydrofurofuran core of compounds of type **I-V** (Chart 1).

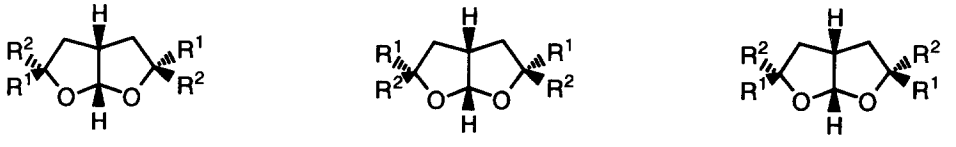
The reaction of 3-chloro-2-(chloromethyl)-1-propene (**1**)[12] with lithium and a catalytic amount of naphthalene (5 mol %) in the presence of different carbonyl compounds as electrophilic components (Barbier-type reaction conditions)[13] in THF at -78°C, yielded, after hydrolysis with water, the corresponding methylenic diols **2**.[14] Tandem hydroboration (with the complex BH_3·THF at 0°C)-oxidation[15] with hydrogen peroxide under basic conditions (3 M NaOH at 0°C) followed by treatment with PCC[16] (CH_2Cl_2, 0°C) for ketone derivatives (R^1, $R^2 \neq H$) or $RuCl_2(PPh_3)_3$ (PhH, 0°C) for aldehyde derivatives ($R^2 = H$) led to the direct formation of the corresponding perhydrofurofurans **3** (Scheme 1 and Table 1).



1 **2** **3**

Scheme 1. *Reagents and conditions*: i, Li, $C_{10}H_8$ cat. (5 %), R^1R^2CO, THF, -78°C; ii, H_2O; iii, BH_3·THF, 0°C; iv, 33% H_2O_2, 3 M NaOH, 0°C; iv, PCC, CH_2Cl_2, 0°C or $RuCl_2(PPh_3)_3$, PhH, 0°C (for $R^2 = H$).

In the case of aldehyde (**3a,b**) or unsymmetrically substituted ketones (**3f,g**) derivatives, the expected diastereoisomers mixture (*trans* + *cisI* + *cisII*) was obtained (Chart 2). However, the mentioned diastereoisomeric compounds could be separated by column chromatography (silica gel, hexane/diethyl ether) and their structures unequivocally assigned by 300 MHz ^1H NMR experiments (mainly nOe studies), considering their symmetry properties. For instance, for compound **3b**, the *trans*-isomer (t_r = 11.75 min[18]) is the only one which shows two signals for the *tert*-butyl groups (δ_H 0.89, 0.92 and δ_C 25.6, 25.95). For the other two *cis*-isomers (*cisI*: t_r = 11.99 min,[18] δ_H 0.92, δ_C 25.55; *cisII*: t_r = 11.84 min,[18] δ_H 0.87, δ_C 25.7) the structure was easily assigned by nOe experiments.[19]



trans *cisI* *cisII*

Chart 2.

Table 1. Preparation of Compounds **3**

Entry	Carbonyl compound	Diol **2** [yield (%)][b]	Oxidation method[c]	Product[a] No.	R^1	R^2	Yield (%)[d]	*trans/cisI/cisII* [e]
1	Pr^iCHO	**2a** [64][f]	A	**3a**	Pr^i	H	41	71/ - /29
2	Bu^tCHO	**2b** [61]	A	**3b**	Bu^t	H	57	53/21/26
3	Me_2CO	**2c** [74][f]	B	**3c**	Me	Me	51	-
4	Et_2CO	**2d** [72][f]	B	**3d**	Et	Et	75	-
5	$(CH_2)_5CO$	**3e** [67][f]	B	**3e**	$(CH_2)_5$		58	-
6	Bu^tCOMe	**3f** [66]	B	**3f**	Bu^t	Me	68	47/47/6
7	PhCOMe	**3g** [41]	B	**3g**	Ph	Me	53	36[g]/47/17[g]
8	$CyCOCy^h$	**2h** [50]	B	**3h**	Cy^h	Cy^h	60	-

[a] All products **3** were >95% pure (GLC and 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and mass spectrometry). [b] Isolated yield after column chromatography (silica gel, hexane/diethyl ether) based on the starting carbonyl compound. [c] Corresponding to the last step (reaction v in Scheme 1); Method A: $RuCl_2(PPh_3)_3$; Method B: PCC. [d] Isolated yield after column chromatography (silica gel, hexane/diethyl ether) based on the corresponding unsaturated diol **2**. [e] Diastereoisomers ratio determined by GLC; the corresponding assignments were made on the basis of NMR experiments on the isolated diastereoisomers (see text). [f] See reference 14. [g] These diastereoisomers could not be separated by column chromatography; assignments were carried out on the corresponding mixture. [h] Cy = cyclohexyl.

As a conclusion, we have described here the application of our previously described methodology [14] to the two-step preparation of substituted perhydrofurofurans, which constitute the heterocyclic core of important biologically active natural products.

ACKNOWLEDGEMENTS

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11. For the last paper on this topic from our laboratory, see: Guijarro, A.; Yus, M. *Tetrahedron* **1996**, *52*, 1797-1810.
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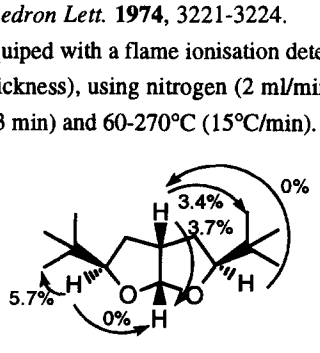
18. Measured with a HP-5890 Series Gas Chromatograph equiped with a flame ionisation detector and a 12 m HP-1 capillary column (0.2 mm diam, 0.33 μm film thickness), using nitrogen (2 ml/min) as the carrier gas, $T_{detector}$ = 300°C, $T_{injector}$ = 275°C, T_{column} = 60°C (3 min) and 60-270°C (15°C/min).
19. The obtained nOe values for *cisII*-**3b** are as follows:



cisII-**3b**

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