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## Nucleophilic opening of bis-epoxides: a new access to symmetrically functionalised macrocycles

Mohamed Faouzi Sebban,<sup>c,d</sup> Philippe Vottero,<sup>b</sup> Abdelhakim Alagui<sup>c</sup> and Claude Dupuy<sup>a,\*</sup>

<sup>a</sup>Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité, associé CNRS, Université Joseph Fourier, BP 53, F-38041 Grenoble Cedex 9, France

<sup>b</sup>Département de Recherche Fondamentale sur la Matière Condensée, Service de Chimie Inorganique et Biologique, 17, rue des Martyrs, F-38054 Grenoble Cedex 9, France

<sup>c</sup>Laboratoire de Chimie Organique Appliquée, Unité de Synthèse Organique et Structurale, Université Cadi Ayyad, BP 2390, 40000 Marrakech, Morocco

<sup>d</sup>L.M.N. Ecole Normale Supérieure, BP S41, 40000 Marrakech, Morocco

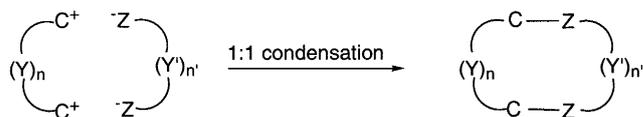
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### Abstract

A series of polyhydroxylated symmetrical macrocycles has been prepared in satisfactory yield by 1:1 condensation of several bis-epoxides with various bis-nucleophiles. Preliminary results are reported, which illustrate the synthesis of crown ethers and oxa-azacrown and oxa-thiacrown compounds. © 2000 Elsevier Science Ltd. All rights reserved.

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Syntheses of macrocyclic compounds that contain nine or more atoms in the ring, including at least three heteroatoms, have been known for a long time.<sup>1–4</sup> The condensation of two bifunctional fragments (1+1 procedure) is the most usual approach for the construction of the macrocyclic system. Nearly all of the syntheses that use this strategy link nucleophilic heteroatoms (Z=N,O,S) with electrophilic carbon atoms (Scheme 1).



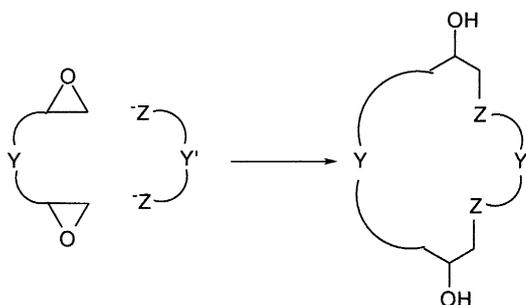
Scheme 1.

The electrophilic centre is a primary carbon bearing a good leaving group such as iodides, sulfonates, or carboxylic functions. To our knowledge, there are very few examples of macrocyclisation involving the opening of bis-epoxides by nucleophilic attack on the terminal carbon atoms affording symmetrical

\* Corresponding author. Tel: 04.76.51.45.97; fax: 04.76.51.43.82; e-mail: claude.dupuy@ujf-grenoble.fr (C. Dupuy)

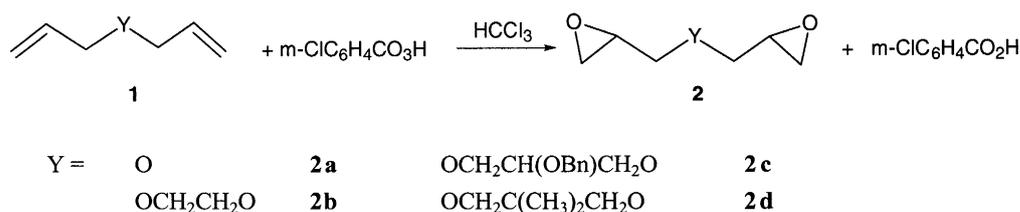
functionalised macrocycles. The only one found in the literature is the reaction of ethylene glycol with diethylene glycol diglycidyl ether, which gave a mixture of two isomeric crown derivatives in 24% yield.<sup>5</sup> Le Merrer and co-workers have also prepared, in a two steps procedure, various mono and diaza cyclic compounds by opening homochiral  $C_2$ -symmetric bis-epoxides with amines.<sup>6</sup> The acid-catalysed oligomerisation of ethylene oxide in the presence of alkali metal cations<sup>7</sup> is another approach to macrocycles but it is not under the scope of the present work.

In this preliminary communication it is shown that polyheteroatomic, symmetrical and functionalised macrocycles are easily obtained from bis-epoxides and a variety of bis-heteronucleophiles (Scheme 2).



Scheme 2.

The following bis-epoxide substrates (**2a,c,d**) were prepared by epoxidation of the corresponding bis-allyl compounds (**1**) with *m*-chloroperbenzoic acid.<sup>8</sup> Compound **2b** is commercially available (Scheme 3).



Scheme 3.

The macrocyclisation with each bis-nucleophiles was achieved without high dilution as in a simple intermolecular nucleophilic attack on an epoxide. NaH in dry THF first converted the diols and dithiols to their anions.<sup>9</sup> The diamines were added in refluxing acetonitrile or in water.<sup>10</sup>

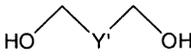
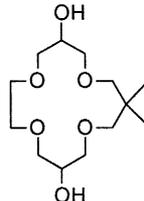
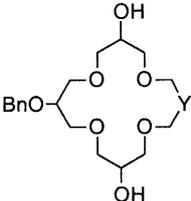
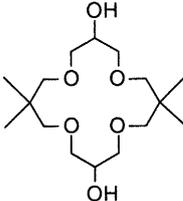
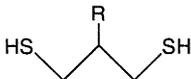
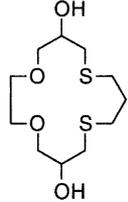
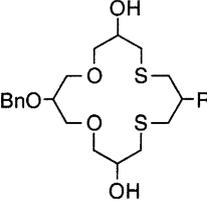
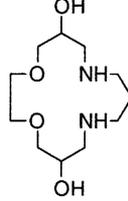
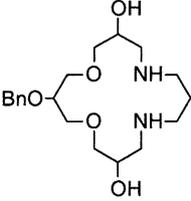
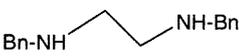
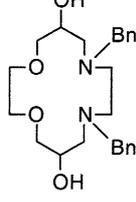
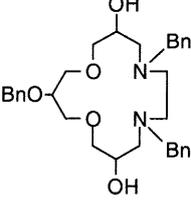
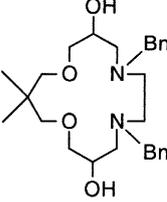
Table 1 summarises the most significant results; the yields are given for the chromatographically isolated macrocycles.<sup>11</sup>

The 15- and 16-membered rings could be prepared in satisfactory yields. Surprisingly, we observed that the reaction of the bis-epoxide **2d** with 2-benzyloxy-1,3-propanediol ( $Y'_2$ ) gave only traces of the expected macrocycles, while they are formed in excellent yield from the bis-epoxide **2c** and 2,2-dimethyl-1,3-propanediol ( $Y'_1$ ) (92%). Similarly, very poor yields have been obtained with the bis-epoxide **2a**. No convincing explanation for this result may be proposed at that time except a possible template effect of the sodium ion for **2c** which might be disfavoured by the smaller size of **2a**.

On the other hand, as mentioned by Le Merrer and co-workers,<sup>6</sup> we found that reactions of bis-epoxides with diamines afford better yields in water than in acetonitrile, due probably to a better stabilisation of the transition state during the nucleophilic attack.

Each isolated macrocycle showed only one molecular peak in their ESMS mass spectra. They gave satisfactory microanalyses for molecular formula. As proton NMR spectra exhibited good integrals but

Table 1

bis-nucleophiles	bis-epoxides		
	<b>2b</b>	<b>2c</b>	<b>2d</b>
 $Y'_1 = C(CH_3)_2$ $Y'_2 = CH(OBn)$	 <b>36%</b>	 $Y'_1 = 92\%$ $Y'_2 = 97\%$	 <b>75%</b>
 $R = H, OBn$	 <b>16%</b>	 $R = H$ <b>52%</b> $R = OBn$ <b>82%</b>	
	 <b>82<sup>a</sup>%</b>	 <b>90<sup>a</sup>%, 75<sup>b</sup>%</b>	
	 <b>80<sup>a</sup>%</b>	 <b>77<sup>b</sup>%</b>	 <b>84<sup>a</sup>%, 76<sup>b</sup>%</b>

a- in hot water b- in acetonitrile

very complex multiplets for each kind of proton found in the molecules we concluded that the observed samples were mixtures of diastereoisomers (2, 3 or 5 depending on the different substituents). Finally, carbon NMR spectra also accounted for this conclusion according to the number of carbon atoms for each type of carbon atoms.

Efforts are being made to separate these mixtures and to isolate at least the more abundant stereoisomers of these new polyhydroxylated macrocycles. The reactions of other bis-epoxides with bis-nucleophiles and the possible role of a sodium template effect<sup>5</sup> during the cyclisation are also under investigation.

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9. To a stirred suspension of NaH (2.5 equiv.) in dry THF (10 mL) cooled to 0°C was added the diol or the dithiol (3 to 5 mmol, 1.1 equiv.) under an Ar atmosphere. At the end of the hydrogen evolution, the reaction mixture was heated to reflux and the bis-epoxide (1 equiv.) in dry THF (5 mL) was added. The consumption of the bis-epoxide was monitored by TLC.
10. To a solution of the diamine in water ( $10^{-3}$  M) was added at reflux a water:acetonitrile solution (9:1) of the bis-epoxide (1 equiv.). Generally the bis-epoxide was totally consumed after 12 h.
11. The mixtures of isomeric products were isolated by column chromatography (silica gel, cyclohexane–ethylacetate or chloroform–methanol–NH<sub>4</sub>OH gradient). These homogeneous fractions were characterised by IR, <sup>1</sup>H and <sup>13</sup>C NMR, MS, and elemental analysis.