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Unusual Totally Selective Cyclodimerization of Epoxides: Synthesis of a Pair of Diastereoisomers of Enantiopure 2,5-Disubstituted-1,4-Dioxanes with C_2 Symmetry

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Abstract: The synthesis of the C_2-symmetrical (2*R*,5*R*)- and (2*S*,5*S*)-2,5-bis-[(*S*)-1-(dibenzylaminoalkyl)]-1,4-dioxanes **1** or **2** in enantiopure form is reported. Compounds **1** and **2** were obtained by a completely selective and unusual cyclodimerization of chiral (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **3** or **4** promoted by a mixture of diisopropylamine and boron trifluoride·diethyl etherate complex. The structure of the obtained dioxane was established by single-crystal X-ray diffraction analysis. A mechanism has been proposed to explain this transformation.

Keywords: amino epoxides; diastereoselectivity; dimerization; dioxanes; enantiopurity

Introduction

Epoxides are very important building blocks in organic synthesis and consequently an important number of reviews have been published on this topic.[1] The synthetic applications of epoxides are based on their versatility. Thus, oxiranes can be opened by an important number of nucleophiles, can be transformed into aldehydes, or alkenes, as well as other important functional groups. However, to the best of our knowledge, no cyclodimerization of epoxides to produce 1,4-dioxanes has been reported to date. This unusual cyclodimerization is very interesting, not only due to its novelty, but also because of the important practical applications of the 1,4-dioxanes generated. Hence, they are used in the manufacture of polycarbonates with photoreceptor properties,[2] cosmetic products,[3] flame retardant additives for flammable plastics,[4] insecticides, acaricides and ectoparasiticides,[5] or germicides and fungicides.[6] In addition, some of these also offer biomedical applications[7] such as, for example, inhibitors of epidermal growth factor receptor tyrosine kinase,[8] or as antiobesity agents.[9]

In spite of the significant applications of 1,4-dioxanes, it is surprising that very few methods for the synthesis of racemic 1,4-dioxanes have been reported in the literature.[10] Consequently, the methods to obtain 1,4-dioxanes in enantiomerically enriched form are even more scarce,[11] and no general preparation exists, apart from isolated reports based on: a) oxyselenylation of dienes with enantiopure diols;[11,12] b) Mitsunobu cyclization of diols;[13] c) photoinduction electron transfer (PET) cyclization of an appropriate diene;[14] d) condensation of glyoxalic acid with chiral hydrobenzoin,[15] or e) intramolecular ring opening of oxirane by an alcohol moiety.[16] Therefore, a general method to obtain enantiopure 1,4-dioxanes with C_2 symmetry would be desirable, due to their synthetic utility,[17] especially when the two diastereoisomers could be accessed with complete selectivity.

Previously, we reported the efficient synthesis of both enantiopure (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides, by total stereoselective reduction of enantiopure α-amino-α′-chloro ketones with $LiAlH_4$ or by a highly stereoselective addition reaction of iodomethyllithium to chiral 2-amino aldehydes, respectively.[18] More recently, we described various transformations of these amino epoxides into a variety of enantiopure compounds, based on the highly regioselective nucleophilic opening of the oxirane ring. Thus, we reported the transformation of the oxirane ring into 1,3-dioxolanes,[19] 1,3-diaminoalkan-2-ols,[20] O^1-

acyl-3-aminoalkane-1,2-diols,[21] β-amino alcohols,[22] and 1-alkylthio-3-aminoalkan-2-ols[23] by reaction with ketones, nitriles, carboxylic acids, organolithium compounds or thiols, respectively.

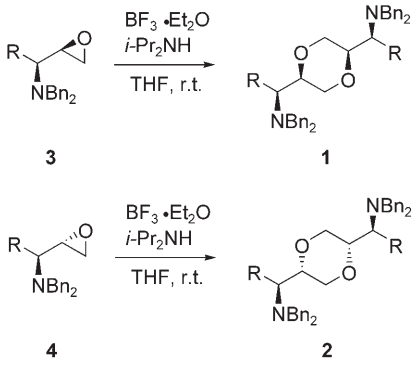
We now report the novel cyclodimerization reaction of the oxirane ring of the chiral (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **3** or **4**, promoted by a mixture of diisopropylamine and $BF_3{\cdot}OEt_2$ in THF, to afford 2,5-bis-[(*S*)-1-(dibenzylamino)alkyl)]-(2*R*,5*R*)-1,4-dioxane **1** or its 2*S*,5*S*-diastereoisomer **2** in enantiomerically pure form and with total selectivity. Interestingly, from the synthetic applications viewpoint, the 1,4-dioxanes obtained present a C_2-axis of symmetry. The proposed structures of the reported compounds were established based on single-crystal X-ray diffraction analysis of **1b**. A mechanism has been proposed to explain this unusual transformation.

Results and Discussion

The first experiments were performed using the *syn*-aminoepoxide **3b** as model substrate. Thus, a solution of **3b** in toluene was treated with *i*-Pr_2NEt and $BF_3{\cdot}OEt$ at room temperature for 12 h. The structure of the obtained major product **1b** (53% yield) could not be established from the ^{13}C and ^1H NMR spectroscopic data. As it was expected, the spectra of **1b** were different to those of the starting amino epoxide **3b**, but the number of signals of the starting and final compound was the same. The NMR spectra of **1b** showed the presence of one dibenzylamino group and two signals of a CH and CH_2 groups (DEPT experiment) at $\delta = 75.7$ and 65.8 ppm, which could be assigned to CHO and CH_2O. In addition the analysis of **1b** by mass spectrometry showed a peak for M^+ near to twice that of the starting amino epoxide **3b**. These data could suggest that the NMR spectra of **1b** showed only half of their signals, which in turn, could indicate that **1b** was a *meso* or a C_2-symmetrical diastereoisomer.

To improve the synthesis of **1b**, various different reaction conditions were tested. The best result was obtained by treatment of a solution of **3b** in THF (instead of toluene) with diisopropylamine (instead diisopropylethylamine) and $BF_3{\cdot}OEt$ at room temperature for 5 h. Hence, compound **1b** was obtained in 80% yield as single isomer, after column chromatographic purification (Scheme 1 and Table 1).

Product **1b** could be crystallized and its corresponding X-ray analysis (Figure 1) allowed the unambiguous assignment of the structure of **1b**, as depicted in Scheme 1.[24] This structure comprises a C_2 axis of symmetry, explaining that only half of their carbons and protons were seen in its ^1H and ^{13}C NMR spectra. In addition the structure of **1b** demonstrated that the absolute configurations of the stereogenic centers were the same as those in its precursor **3b**.



Scheme 1. Synthesis of enantiopure 1,4-dioxanes **1** and **2**.

Table 1. Synthesis of enantiopure 1,4-dioxanes **1** and **2**.

Entry	**1** or **2**	R	*t* [h][a]	*dr*[b]	Yield [%][c]
1	**1a**	Me	5	> 99/1	73
2	**1b**	*i*-Bu	5	> 99/1	80
3	**1c**	Bn	1	> 99/1	81
4	**1d**	$BnOCH_2$	5	> 99/1	72
5	**2a**	Me	5	> 99/1 (99/1)	70
6	**2b**	*i*-Bu	5	95/5 (95.5/4.5)	73
7	**2c**	Bn	2	96.5/3.5 (96/4)	75

[a] Reaction time.
[b] Diastereoisomeric ratios determined by ^1H NMR analysis of the crude products **1** or **2**. The *dr* values of the starting amino epoxides **4** are given in brackets.
[c] Isolated yields after column chromatography based on the starting amino epoxide **3** or **4**.

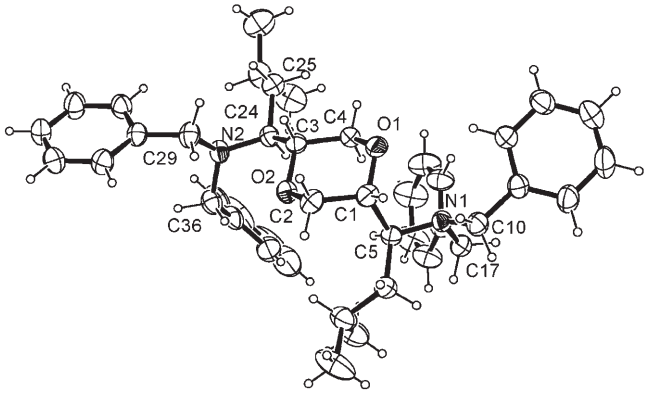


Figure 1. ORTEP drawing of structure **1b**.[25]

To test the generality of this unusual cyclodimerization reaction, *syn* amino epoxides **3a**, **3c**–**d** and *anti*-amino epoxides **4** were allowed to react under the same reaction conditions, obtaining the corresponding dimers **1** and **2** in high yield (Scheme 1 and Table 1).

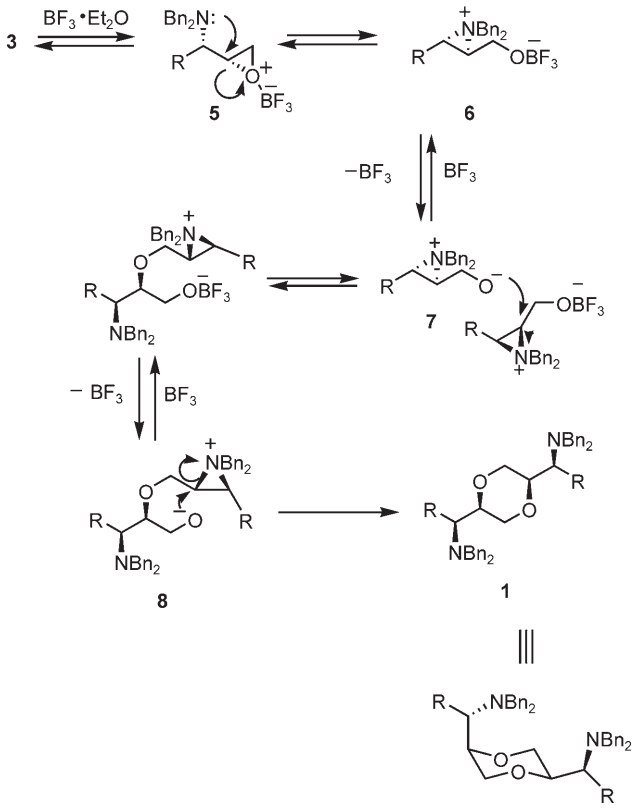
The spectroscopic data (NMR and IR) of compounds **1a**, **1c–d** and **2** were closely related to those of **1b** and the analyses of compounds **1a**, **c**, **d** and **2a–c** by high- and low-resolution mass spectrometry were also in accord with the corresponding dioxanes **1** and **2**. Therefore, the structures of **1** and **2** (Scheme 1) were assigned by anology to **1b**. An analysis of Table 1 reveals that no important differences in this cyclodimerization reaction of epoxides were observed as a consequence of structural differences on the starting amino epoxides **3** or to the change of the stereochemistry in the starting amino epoxides when amino epoxides **4** were used as starting materials instead of **3**, under the same reaction conditions.

It was noteworthy that no dry solvents were used and no inert atmosphere was necessary to perform the reaction.

Determinations of the diastereoisomeric purity of products **1** and **2** were performed by GC/MS and ^{1}H and ^{13}C NMR analysis on the crude reaction products. Hence, it could be established that, from diastereopure amino epoxides **3**,[18] all dioxanes **1** were obtained as single diastereoisomers, whereas compounds **2** were obtained as a mixture of diastereoisomers in the same relationship to that of the starting amino epoxides **4**.[18] This fact could be an indirect support of the total selectivity of the reaction. The major diastereoisomer **2** was isolated as a single diastereoisomer, after easy purification of the crude reaction products by column chromatography.

To explain the transformations of amino epoxides **3** and **4** into products **1** and **2**, respectively, we tentatively propose a mechanism based on the following experimental results: a) when 2-cyclohexyloxirane was treated under the same reaction conditions, the corresponding amino alcohol, derived from the opening of the oxirane ring by the amine at the C-3 position, instead of the dimer, was obtained. This result could suggest that the dibenzylamino group of the starting epoxides **3** or **4** could have an essential role in the transformation. b) The presence of both reagents, diisopropylamine and $BF_3{\cdot}Et_2O$, was essential to perform the transformations of **3** into **1** or **4** into **2**. In the absence of amine or $BF_3{\cdot}Et_2O$, unchanged amino epoxides **3** or **4** were fully recovered.

So, initially the oxygen of the amino epoxide **3** could selectively react with the Lewis acid, BF_3,[26] to give the activated oxirane **5** (Scheme 2). Then, the dibenzylamino group could open the activated epoxide at C-2 with inversion of its configuration, generating an aziridinium salt **6**. The intermediate **6**, in which the oxygen is coordinated to the Lewis acid, and the base could be in equilibrium with an aziridinium intermediate **7** (without the Lewis acid) and the $BF_3{\cdot}$amine salt.[27] Then, the alcoholate group of **7** could open the aziridinium ring of a second equivalent of the intermediate **6** at C-2,[28] with a second inversion of the carbon configuration, affording (after BF_3 dissociation) the intermediate **8**. The final 1,4-dioxane **1** could be obtained by a cyclization of **8**. A similar mechanism could explain the transformation of **4** into **2**.



Scheme 2. Proposed mechanism.

Taking into account that no dimerization took place from the oxide of cyclohexene, alternative mechanisms without involvement of the dibenzylamino group should be rejected. Thus, the reaction of the epoxide oxygen as a nucleophile with the terminal carbon of a second equivalent of an epoxide activated by BF_3 and followed by cyclization of the obtained alkoxide from epoxide opening onto the terminal carbon of the *O*-alkylated epoxonium ion is not supported by our experimental results.

Conclusions

We have reported the unusual cyclodimerization of chiral (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **3** or **4** to afford 2,5-bis-[(*S*)-1-(dibenzylaminoalkyl)]-(2*R*,5*R*)-1,4-dioxanes **1** or the 2*S*,5*S*-diastereoisomers **2**, both in enantiopure form and with C_2 symmetry. The transformation took place with complete selectivity, by treatment of **3** or **4** with *i*-Pr_2NH and $BF_3{\cdot}Et_2O$ in THF at room temperature. The structure of compound **1b** was established by single-crystal X-ray diffraction analysis and the corresponding mechanism

has been proposed to explain this transformation. Further studies directed toward the development of the synthetic applications of the enantiopure substituted 1,4-dioxanes prepared are currently under investigation within in our laboratory.

Experimental Section

General Procedure for the Synthesis of 1 or 2

To a stirred solution of the corresponding amino epoxide **3** or **4** (0.3 mmol), in THF (2 mL), $BF_3{\cdot}OEt_2$ (1.1 equiv, 0.33 mmol, 0.041 mL) and diisopropylamine (2 equiv. 0.6 mmol, 0.085 mL) were successively added at room temperature. After stirring at this temperature for the time indicated in Table 1, the mixture was neutralized with an aqueous saturated solution of $NaHCO_3$ (5 mL). The aqueous phase was extracted with diethyl ether (3×5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc 10:1) provided pure compounds **1** or **2.**

Analytical and spectroscopic data for products **1** and **2** and the general remarks about the equipment used made are available in the Supporting Information.

Acknowledgements

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[24] CCDC 654081 (**1b**) contains the supplementary crystallographic data for this paper. They can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif (or the Cambridge Data Centre, 12, Union Road. Cambridge CB21EZ, UK: fax: (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk.
[25] For clarity, only some relevant atoms are labelled.
[26] The coordination of the Lewis acid with the oxygen of the epoxide is favoured in comparison with the nitrogen of the dibenzylamino group due to steric hindrance of the dibenzylamino group, and it has previously been observed in other ring openings of amino epoxides **3** or **4**: see ref.[18].
[27] The synthesis of a mixture of products when the reaction was performed under the same reaction conditions, but using a tertiary amine (*i*-Pr_2NEt) instead of *i*-Pr_2NH, could support the existence of this equilibrium, due to the coordination of a tertiary amine with a Lewis acid is most difficult than a secondary amine.
[28] A ring-opening of aziridinium **6** at C-3·could be also possible. However the obtained intermediate would allow access to a 7-membered cycle, which it is disfavoured with respect to the formation of the 6-membered cycle such as dioxane. So, the hypothetical formation of this intermediate would be reversible and it would be newly transformed into intermediates **6** and **7**.

