Studies on the reactivity of *cis*-4-benzyloxy-1,2-epoxycyclohexane

Mar Sabaté,[a] Amadeu Llebaria,[b] and Antonio Delgado [a,b,] *

[a]*Research Unit on Bioactive Molecules (RUBAM); Departament de Química Orgànica Biològica, Institut d'Investigacions Químiques i Ambientals de Barcelona (IIQAB-C.S.I.C); Jordi Girona 18-26, 08034 Barcelona, Spain*

[b]*Universitat de Barcelona, Facultat de Farmàcia, Unitat de Química Farmacèutica (Unitat Associada al CSIC), Avda. Joan XXIII, s/n, 08028 Barcelona, Spain*

Email: adelgado@cid.csic.es

Dedicated to Professor Joan Bosch on the occasion of his 60th birthday

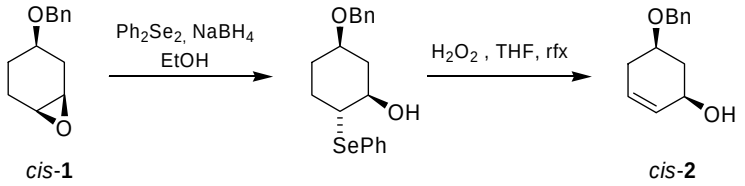
Abstract

The reaction course of the selenation-oxidation-elimination sequence carried out from *cis*-4-benzyloxy-1,2-epoxycyclohexane (*cis*-**1**) is studied. Contrary to literature precedents, this transformation leads to an unexpected diastereomeric cyclohexenol, whose formation can be interpreted by stereoelectronic grounds. In addition, the base induced rearrangement of *cis*-**1** with lithium amide bases is also discussed. In the absence of external additives, a mixture of cyclohexenols arising from the competition of *syn* and *anti* elimination processes is observed. However, in the presence of Li salts, the corresponding cyclohexenol arising from an apparent *anti* elimination pathway predominates. A mechanistic rationale is proposed to account for these observations.

Keywords: Epoxide, nucleophilic attack, elimination, selenoxide, base induced rearrangement

Introduction

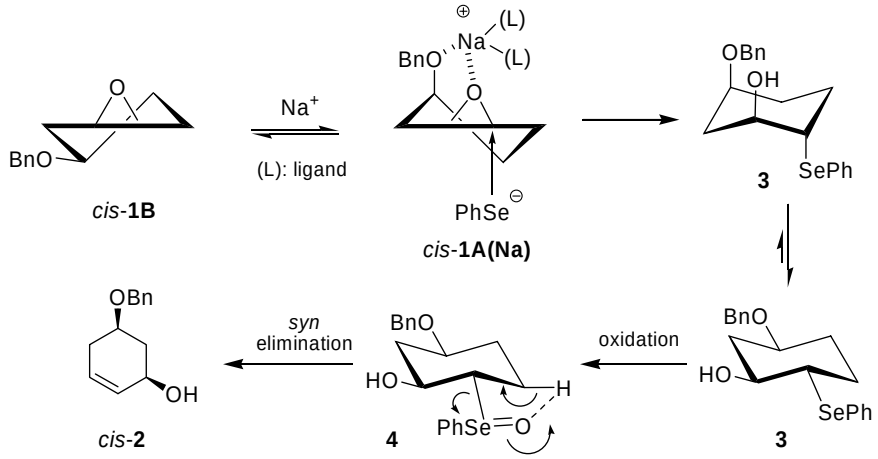
In the course of our recent research, the use of *cis*-4-benzyloxy-1,2-epoxycyclohexane (*cis*-**1**) has disclosed interesting reactivity features that deserve some attention. Thus, a literature report[1,2] describes the use of *cis*-**1** as starting material for the synthesis of *cis*-5-benzyloxy-2-cyclohexenol (*cis*-**2**) by phenyl selenation followed by oxidation to the corresponding selenoxide and *in situ* elimination (Scheme 1).



Scheme 1. Proposed synthetic pathway for alcohol *cis*-**2** from epoxide *cis*-**1**, according to reference 1.

Results and Discussion

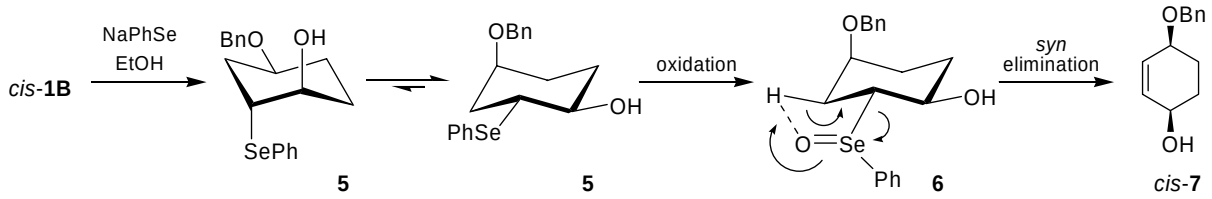
Attempts to reproduce the above sequence required the preparation of epoxide *cis*-**1**, which was obtained uneventfully from 4-benzyloxycyclohexene following literature protocols.[3] Reaction of *cis*-**1** with sodium phenylselenide (obtained *in situ* by reaction of diphenyldiselenide with $NaBH_4$ in EtOH) was carried out as described in the literature.[1,2] Mechanistic considerations concerning the putative reaction pathway involved in the transformation of *cis*-**1** into the expected allylic alcohol *cis*-**2**, would require phenylselenide attack to afford phenylselenyl derivative **3** through a chelated reactive conformation *cis*-**1A(Na)**, in agreement with the *trans*-diaxial attack imposed by the Fürst-Platner rule.[4] The above reaction course would be imperative for the subsequent *syn* elimination of selenoxide **4**[5] required to give alcohol *cis*-**2** (see Scheme 2).



Scheme 2. Proposed mechanism to account for the formation of *cis*-**2** by *syn* elimination of phenyl selenoxide intermediate **4**.

However, taking into account the relatively low chelating ability of the Na ion to force the above reactive conformation *cis*-**1A(Na)**,[6] a thorough examination of the reaction outcome was undertaken. Thus, operation of a non-chelating reactive conformation *cis*-**1B** on reaction of *cis*-**1**

with phenylselenide would afford phenylselenide **5** (Scheme 3), whose oxidation to selenoxide **6**, followed by *syn*-elimination,[5] would lead to the isomeric allylic alcohol *cis*-**7**, as depicted in Scheme 3.

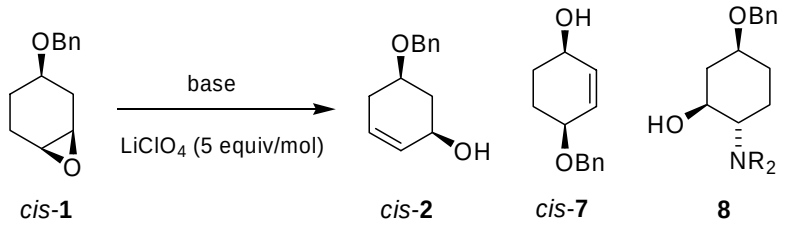


Scheme 3. Proposed mechanism to account for the formation of *cis*-**7** by *syn* elimination of phenyl selenoxide intermediate **6**.

As expected from the above hypothesis, and contrary to literature precedents,[1,2] *alcohol cis*-**7** *was formed in this process instead of cis*-**2**. Formation of *cis*-**7** was confirmed by comparison of its spectroscopical data with those described in the literature for this alcohol[7] and isomeric *cis*-**2**.[8]

In light of these results, we explored the potential of epoxide *cis*-**1** as starting material for the synthesis of isomeric alcohols *cis*-**2** and *cis*-**7**. In this context, synthesis of *cis*-**7** is described in the literature from base-induced rearrangement of epoxide *cis*-**1**.[7] However, despite the well recognised synthetic usefulness of this transformation,[9,10] the reaction outcome can be dramatically affected by the nature of the base, the solvent, and the reaction temperature, among others.[11,12] Thus, computational and experimental studies carried out on cyclohexane oxides have shown a switch from *syn*-β elimination in non polar solvents to a more energetically favourable *anti*-β elimination in polar solvents, such as HMPA.[13] Our experiments carried out from epoxide *cis*-**1** under different reaction conditions (base, solvent, temperature, and $LiClO_4$ as chelating agent) are shown in Table 1. An initial experiment in LDA/Et_2O at rt (entry 1) showed the formation of a roughly 1:1 mixture of allylic alcohols *cis*-**2** and *cis*-**7**, which can be interpreted as a result of the operation of competing *anti* and *syn* elimination processes, respectively, from the most stable conformation *cis*-**1B**, (Scheme 4).[14] Based on our previous results,[15] addition of $LiClO_4$ (5 equiv/mol) is known to drive the reaction mixture towards a chelated reactive conformation *cis*-**1A(Li)** (Scheme 5). This conformation was expected to favour the operation of a *syn* elimination leading ultimately to *cis*-**2.** However, contrary to our assumption, alcohol *cis*-**7** was the major one under the above conditions (entry 2). Similar results were obtained in the presence of THF as a solvent (entry 3), although unreacted starting epoxide *cis*-**1** was the major or exclusive one at lower temperatures (entries 5, 6).

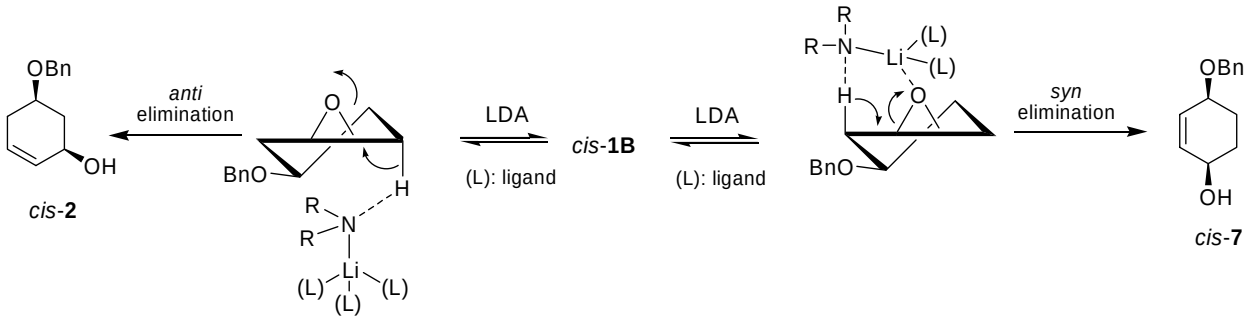
Table 1. Reactivity of epoxide *cis*-**1** under basic conditions in the presence of $LiClO_4$



Entry	Solvent	Base (equiv/mol)	temp (ºC)	t (h)	*cis*-7	*cis*-2	8	*cis*-1
1 (a)	Et_2O	LDA (1.5)	25	16	25%	25%	----	----
2	Et_2O	LDA (1.5)	25	22	52%	<5%	----	----
3	THF	LDA (1.5)	25	24	35%	<5%	----	----
4	Et_2O	LDA (3.0)	25	4	58%	<5%	19% (b)	
5	THF	LDA (1.5)	-78	7	----	----	----	100%
6	THF	LDA (1.5)	-20	22	30%	<5%	----	46%
7	THF	LDA (3.0)	reflux	5	33%	----	49% (b)	----
8	THF	$LiNEt_2$ (1.5)	25	10	23%	----	50% (c)	20%
9	THF	$LiNEt_2$ (1.5)	reflux	5	30%	----	32% (c)	----
10	Et_2O	$LiN(C_6H_{11})_2$ (1.5)	25	3.5	46%	----	----	<5%

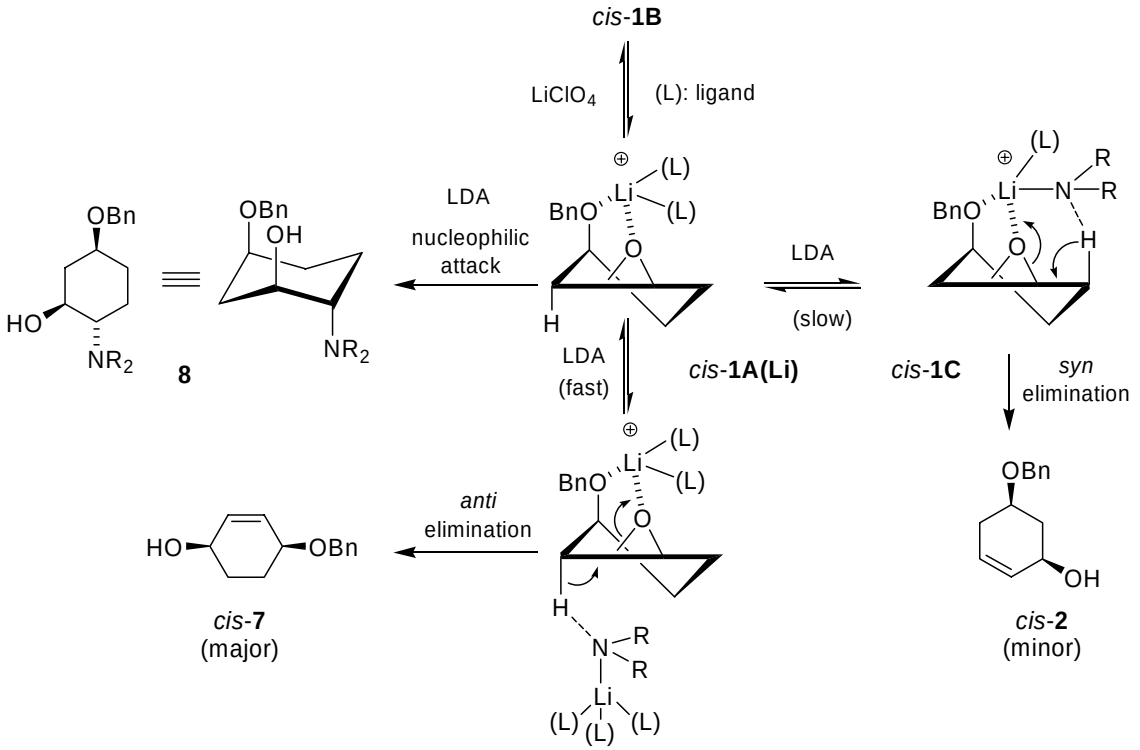
(a): No $LiClO_4$ was used in this experiment. (b): R=iPr. (c): R=Et.

The use of a larger excess LDA (3 equiv/mol, entry 4) was unsuccessful, since noticeable amounts of alcohol **8** (R=iPr) was also observed (see Scheme 5). This side reaction was even more important under reflux conditions, since **8** (R=iPr) was the major compound (entry 7). Moving from LDA to other lithium amide bases led to similar results, irrespective of their steric demand or reaction conditions (entries 8-10). In all cases, only alcohol *cis*-**7** was formed as a result of a base-induced rearrangement process. Finally, contrary to literature precedents,[7] the use of HMPA did not improve the reactivity of the lithium amides, since poor conversions were observed in all cases.



Scheme 4. Proposed reaction mechanisms to account for the formation of alcohols *cis*-**2** and *cis*-**7** from a common non-chelated reactive conformation *cis*-**1B.**

The above results, in the presence of $LiClO_4$ as chelating agent, can be interpreted by considering Scheme 5. Thus, due to the well recognized ability of Li ions to promote a reactive chelating conformation in epoxy cyclohexanes,[6,15] conformation *cis*-**1A(Li)** can account for the reactivity of epoxide *cis*-**1** in the presence of $LiClO_4$ (5 equiv/mol). The commonly accepted *syn* elimination pathway for this kind of LDA promoted rearrangements would require a previous Li-ligand exchange to accommodate the amide base in a proper orientation for a subsequent abstraction of the vicinal pseudoaxial proton[10] (conformation *cis*-**1C**, Scheme 5). This exchange process might be slower than an alternative *anti* elimination pathway leading ultimately to major alcohol *cis*-**7**. This reactive conformation would also explain formation of amino alcohols **8** as a result of nucleophilic attack of the amide base following a *trans*-diaxial pathway.



Scheme 5. Mechanistic interpretation to account for product distribution on reaction of epoxide *cis*-**1** with LDA in the presence of $LiClO_4$.

In summary, the above results represent an additional proof of the generality of the Fürst-Platner rule on the reactivity of epoxy cyclohexane derivatives, as evidenced by the results obtained from epoxide *cis*-**1** on reaction with phenyl selenide anion. On the other hand, studies on the base-induced rearrangement of epoxide *cis*-**1** in the presence of $LiClO_4$ show the ability of this additive to facilitate an *anti* elimination process leading ultimately to allylic alcohol *cis*-**7** as the major reaction product.

Experimental Section

General Procedures. Solvents were distilled prior to use and dried by standard methods. [16] Melting points are uncorrected. FT-IR spectra are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions at 300 MHz (for ^1H) and 75 MHz (for ^{13}C), respectively, unless otherwise indicated. Chemical shifts are reported in delta (δ units, parts per million (ppm) relative to the singlet at 7.24 ppm of $CDCl_3$ for ^1H and in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$ for ^{13}C.

***cis*-4-Benzyloxy-2-cyclohexenol (*cis*-7)**[7]

Sodium borohydride (950 mg, 25 mmol) is added portionwise to a solution of diphenyldiselenide (3.7 g, 12 mmol) in EtOH (10 mL) under nitrogen. The reaction mixture is stirred at rt for 10 min. The mixture is then treated with a solution of epoxide *cis*-**1** (1g, 4.89 mol) in EtOH (5 mL). After stirring for 45 min at rt, the reaction mixture is diluted with THF (7 mL), treated with 30% H_2O_2 (5.2 mL added dropwise), and heated to reflux temperature with vigorous stirring. After 8h, the mixture is concentrated *in vacuo*, treated with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts are dried over $MgSO_4$, filtered and evaporated to afford a crude residue which was flash chromatographed on hexanes/EtOAc (2/1) to afford alcohol *cis*-**7** (350 mg, 35 % yield).

^1H NMR (200 MHz, $CDCl_3$): δ 1.77-1.83 (4H, m, 2xH_5, 2xH_6), 3.89 (2H, m, H_4 and H_1), 4.12 (1H, d, *J*=12.2, C*H*$_2$-Ph), 4.60 (1H, d, *J*=12.2, C*H*$_2$-Ph), 5.91 (2H, broad, H_2, H_3), 7.34 (5H, m, Ar); ^{13}C NMR (50 MHz; $CDCl_3$): δ 24.4 (C_5), 28.1 (C_6), 65.2 (C_1), 70.3 (C*H*$_2$-Ph), 71.5 (C_4), 127.4, 128.2, 128.9, 129.9, 133.0 (Ar), 138.4 (Cq); IR (cm^{-1}): 734, 1060, 1072, 2866, 2945, 3384; HRMS, Calculated for $C_{13}H_{16}O_2$: 204.1150; Found: 204.1158.

General procedure for the reactions of epoxide *cis*-1 with lithium amide bases

Lithium amide bases were typically prepared by treatment at -78ºC of a solution of the corresponding amine (4.5 mmol) in the required solvent (4 mL) with BuLi (2.5 mL of a 1.6 *N* solution in hexanes). This affords a solution containing 4 mmol LDA, approximately. The above mixture is allowed to warm to the required temperature and next treated with a solution of epoxide *cis*-**1** (500 mg, 2.45 mmol for a base/substrate ratio of 1.5) containing $LiClO_4$ (1.3 g, 12.25 mmol) in the required solvent (6 mL). The reaction mixture was quenched by careful addition of H_2O (1 mL). The organic phase was extracted, dried, and evaporated *in vacuo* to afford a residue which was purified by flash chromatography to afford the reaction products (see Table 1).

***cis*-5-Benzyloxy-2-cyclohexenol (*cis*-2)**[8]

^1H NMR (200 MHz, $CDCl_3$): δ 1.99 (2H, t, 2xH_6), 2.21 (2H, m, 2xH_4), 3.80 (1H, q, H_5), 4.18 (1H, m, H_1), 4.99 (2H, s, C*H*$_2$-Ph), 5.65 (1H, m, H_3), 5.84 (1H, m, H_2), 7.26 (5H, complex, Ar). ^{13}C NMR (50.4 MHz; $CDCl_3$): δ 30.1 (C1), 30.1 (C6), 35.7 (C4), 64.7 (C1), 70.4 (CH_2-Ph), 72.4

(C5), 127.3, 127.5, 128.3 (CH Ar), 125.1, 130.1 (C3, C2), 138.2 (Cq); HRMS, Calculated for $C_{13}H_{16}O_2$: 204.1150; Found: 204.1142.

***c*-5-benzyloxy-*t*-2-diethylamino-*r*-cyclohexanol (8, R=Et)**[6]

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (6H, t, CH_3), 1.35 (2H, m, 2xH_4), 1.70 (1H, complex, H_6), 2.10 (1H, m, H_6), 2.36-2.45 (5H, m, 2xN-CH_2 and H_2), 2.62 (2H, m, H_3), 3.30 (2H, complex, H_1 and H_5), 4.50-4.52 (2H, broad, CH_2-Ph), 7.27 (5H, complex, Ar); ^{13}C NMR (50.4, $CDCl_3$): δ 14.5 (CH_3), 19.2 (C_4), 31.4 (C_3), 38.6 (C_6), 43.2 (N-CH_2), 65.5 (C_2), 66.5 (C_1), 70.0 (CH_2-Ph), 74.8 (C_5), 127.4 and 128.2 (CH Ar), 138.6 (Cq); HRMS, Calculated for $C_{17}H_{28}NO_2$: 278.2042 $(M+1)^+$; Found: 278.2033.

c-5-benzyloxy-t-2-diisopropylamino-r-cyclohexanol (8, R=iPr)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (12H, d, CH_3), 1.55 (2H, m, 2xH_4), 1.90-2.30 (2H, m, 2xH_6), 2.67-3.02 (5H, m, 2xN-CH, H_2 and 2xH_3), 3.35 (m, 2H, H_1 and H_5), 4.40-4.65 (2H, broad, CH_2-Ph), 7.35 (5H, complex, Ar); ^{13}C NMR (50.4, $CDCl_3$): δ 20.4 C_3), 22.1 (CH_3), 30.7 (C_4), 37.5 (C_6), 47.7 (N-CH), 60.3 (C_1), 62.2 (C_2), 72.5 (CH_2-Ph), 75.8 (C_5), 127.0 and 129.5 (CH Ar), 137.5 (Cq); HRMS, Calculated for $C_{19}H_{32}NO_2$ $(M+1)^+$: 306.2355; Found: 306.2366.

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14. Despite formation of *cis*-**2** can also be interpreted as a result of a *syn* elimination from a putative chelated conformation *cis*-**1A** (Li) (Scheme 5), operation of this reactive conformation usually requires a higher concentration of Li ions (see text).
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