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An Unexpected Chelation-Controlled $Yb(OTf)_3$-Catalyzed Aminolysis and Azidolysis of Cyclitol Epoxides

Pedro Serrano,[†,‡] Amadeu Llebaria,[‡] and Antonio Delgado*[,†,‡]

Universitat de Barcelona, Facultat de Farmàcia, Unitat de Química Farmacèutica (Unitat Associada al CSIC), Avgda. Joan XXIII, s/n, 08028 Barcelona, Spain, and RUBAM, Departament de Química Orgànica Biològica, Institut d'Investigacions Químiques i Ambientals de Barcelona (IIQAB-CSIC), Jordi Girona 18-26, 08034 Barcelona, Spain

adelgado@far.ub.es

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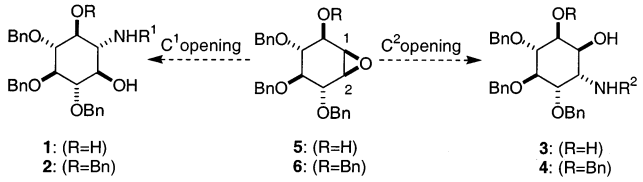
Abstract: A chelation-controlled aminolysis and azidolysis of cyclitol epoxides with $Yb(OTf)_3$ has been disclosed. The presence of a free OH group able to direct the coordination with the lanthanide seems essential for an efficient regiocontrol of the process.

Over the last few years, aminocyclitols have gained importance as pharmacological tools for the study of cellular processes linked to the inositol cycle,[1] as well as potential glycosidase inhibitors.[2] As part of our ongoing research directed toward the design and synthesis of new amino and diaminocyclitols as modulators of sphingolipid metabolism,[3] we became interested in the synthesis of libraries of aminocyclitols **3** arising from regio- and stereoselective C2 opening of epoxide **5**[4] (Scheme 1).

Toward this end, we considered the combination of a nucleophilic amine and a metal triflate Lewis acid catalyst[5] as the most suitable system for our purposes. Following the seminal papers of Crotti et al.[6] and Yamamoto et al.,[7] lanthanide triflates seem the catalysts of choice for the efficient aminolysis of epoxides in nonprotic solvents. On the basis of these precedents, we reasoned that aminolysis of epoxide **5** in the presence of $Yb(OTf)_3$ would be mainly dictated by stereoelectronic

SCHEME 1



bias to give the corresponding C2 adducts **3** arising from trans-diaxial opening[8] of an "all equatorial" conformation such as **5B** (Scheme 2).

This assumption was reinforced by the work of Crotti et al. on *cis*-4-benzyloxy-1,2-epoxycyclohexane,[6] which emphasizes the nonchelating properties of $Yb(OTf)_3$ to account for the observed regioselective aminolysis to give the corresponding C2 adducts.

Initial aminolysis experiments from epoxide **5** and Et_2-NH in toluene at room temperature in the presence of 50mol % $Yb(OTf)_3$[6] were unsuccessful, since only starting material was recovered.[9] Harsher conditions were required for the complete aminolysis of the starting epoxide **5**.[10] However, contrary to our expectations, amino alcohol **1h** (Table 1, entry 9), arising from C1 opening of epoxide **5**, was obtained instead as a single regioisomer.[11,12] The products arising from a C1 opening could be easily distinguished from its C2 opening regioisomers, since both ^{1}H and ^{13}C-RMN were in the former case simplified due to the symmetry of the molecule. Spectral data obtained for the compounds obtained are consistent with a trans-diaxial epoxide opening following the Fürst–Plattner rule. The same regio- and stereochemistry was found on aminolysis of **5** with a variety of primary and secondary amines (Table 1, entries 3–12) with the exception of the bulky amines **i** and **k**, which failed to react under these conditions. This unexpected outcome can be interpreted as a result of a stereocontrolled trans-diaxial opening of **5** through an "all-axial" conformation **5A** stabilized by lanthanide chelation (Scheme 2).[13] This

* Address correspondence to this author at IIQAB-CSIC. Fax: int + 34-932045904.

† Unitat de Química Farmacéutica.

‡ Institut d'Investigacions Químiques i Ambientals de Barcelona.

(1) (a) Brunn, G.; Fauq, A. H.; Chow, S.; Kozikowski, A. P.; Gallegos, A.; Powis, G. *Cancer Chemother. Pharmacol.* **1994**, *35*, 71–79. (b) Powis, G.; Aksoy, I. A.; Melder, D. C.; Aksoy, S.; Eichinger, H.; Fauq, A. H.; Kozikowski, A. P. *Cancer Chemother. Pharmacol.* **1991**, *29*, 95–104.

(2) (a) Lillelund, V. H.; Jensen, H. H.; Liang, X. F.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553; (b) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779–844. (c) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933–1972.

(3) For a preliminary communication, see: Delgado, A.; Serrano, P. In *XII Congreso Nacional de la Sociedad Española de Química Terapéutica*; Book of Abstracts: Sevilla, Spain, 2001; p 61.

(4) Jaramillo, C.; Chiara, J.; Martín-Lomas, M. *J. Org. Chem.* **1994**, *59*, 3135–3141.

(5) For an overview of metal triflates as catalysts for aminolysis of epoxides, see: Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287–289 and references therein.

(6) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433–436.

(7) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597–2601.

(8) For stereoelectronic effects in epoxide opening with nucleophiles, see: Rickborn, B.; Murphy, D. K. *J. Org. Chem.* **1969**, *34*, 3209. For related fully benzylated conduritol epoxide opening through a conformation similar to **5A** with all substituents in the axial position see: Montchamp, J. L.; Migaud, M. E.; Frost, J. W. *J. Org. Chem.* **1993**, *58*, 7679–7684. Takahshi, H.; Iimori, T.; Ikegami, S. *Tetrahedron Lett.* **1998**, *39*, 6939–6942.

(9) A control aminolysis with *cis*-4-benzyloxy-1,2-epoxycyclohexane and Et_2NH, as described in ref 6, afforded the expected C2 aminolysis product. The observed lack of reactivity from **5** can be thus attributed to the nature of the substrate.

(10) In general, aminolysis of cyclitol epoxides requires harsher reaction conditions than that of simpler epoxycycloalkanes. See, for example: (a) Nakata, M.; Tatsuta, K. *J. Antibiotics* **1993**, *46*, 1919–1922. (b) Letellier, P.; Ralainirina, R.; Beaupère, D.; Uzan, R. *Tetrahedron Lett.* **1994**, *35*, 4555–4558. (c) Paulsen, H.; Burkhard, M. *Liebigs Ann. Chem.* **1990**, 169–180.

(11) The regio- and the stereochemistry of all compounds was carefully checked by mono- and bidimensional NMR methods. After peak assignment and assuming a chair conformation for the final products, the coupling constants of cyclohexane hydrogen atoms were of diagnostic value (see Supporting Information).

(12) Additional evidence of the structure of this amino alcohol has also been obtained by comparison with the product of the chelation-controlled $LiClO_4$ promoted C1 aminolysis of epoxycyclitol **5**. This stereochemically well-defined process (see ref 13) gives a single amino alcohol identical in all respects to the major product obtained with $Yb(OTf)_3$.

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SCHEME 2

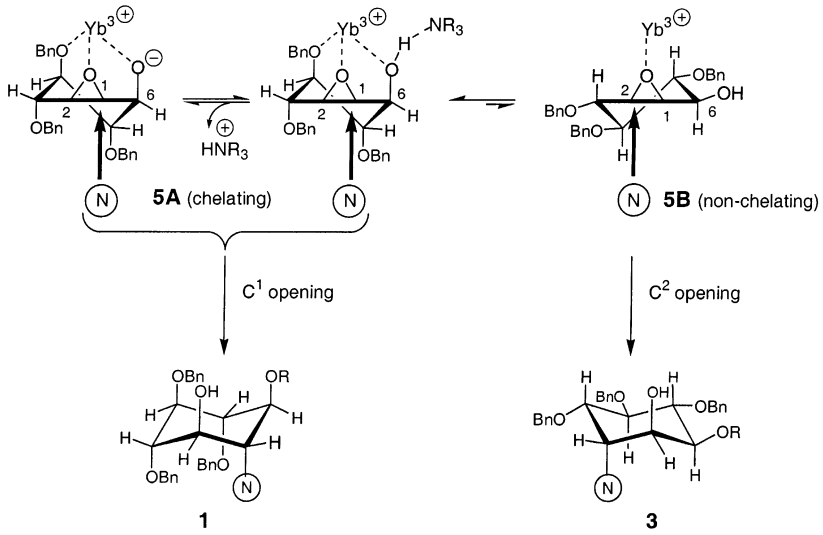
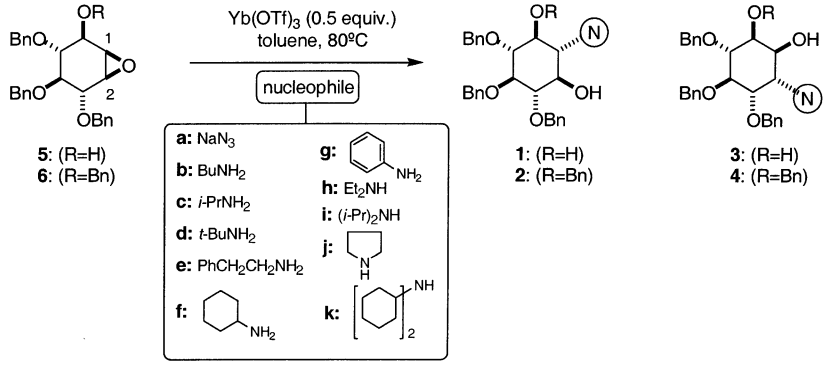


TABLE 1



entry	substrate	nucleophile	major isomer	RR[a]	yield[b] (%)	entry	substrate	nucleophile	major isomer	RR[a]	yield[b] (%)
1	**5**	**a**	–	–	–	9	**5**	**h**	**1h**	>95:5	79
2	**5**	**a**[c]	**1a**	>95:5	89	10	**5**	**i**	–	–	–
3	**5**	**b**	**1b**	>95:5	87	11	**5**	**j**	**1j**	90:10	80
4	**5**	**c**	**1c**	80:20	85	12	**5**	**k**	–	–	–
5	**5**	**d**	**1d**	90:10	88	13	**6**	**a**[c]	–	–	–
6	**5**	**e**	**1e**	90:10	80	14	**6**	**b**	**2b/4b**	55:45[d]	*e*
7	**5**	**f**	**1f**	>95:5	81	15	**6**	**h**	–	–	–
8	**5**	**g**	**1g**	80:20	85						

[a] RR: regioisomeric ratio determined by ^{1}HNMR or HPLC. [b] Isolated (major isomer). [c] Et_3N (15 mol·equiv) was added. [d] Together with variable amounts of starting material. [e] Not determined

chelation depends largely on the presence of the free C6−OH group and its activation by an external amine,[14] as evidenced by comparing the azidolysis of **5** in the presence or in the absence of Et_3N, a nonnucleophilic base (see Table 1, entries 1 and 2).[15] In addition, the enhanced acidity of the free OH group on coordination with the lanthanide[16] does not rule out an ionic stabilizing interaction.[17] Additional evidence in favor of the dramatic effect of the free OH group on Yb chelation and epoxide activation toward nucleophilic attack is found on comparison with the reactivity of perbenzylated epoxide **6**. In this case, scarce (entry 14) or no reactivity (entries 13 and 15) was observed under our conditions.[18] Moreover, the lower diastereoselectivity observed with $BuNH_2$ (compare entries 3 and 14) indicates a competition

(13) For the use of chelation-controlled aminolysis and azidolysis of 1,2-epoxycyclohexanes bearing remote polar groups, see: Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999−13022 and references therein.

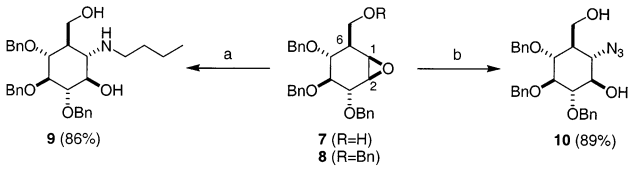
(14) (a) For a related amine-promoted coordination of a free OH with Yb, see: Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083−4084. (b) For the use of lanthanides in organic synthesis, see: (i) *Lanthanides: Chemistry and use in organic synthesis*; Kobayashi, S., Ed.; Springer-Verlag: Berlin, Heidelberg, New York, 1999; (ii) *Lanthanides in Organic Synthesis*; Imamoto, T., Ed.; Academic Press Limited: London, UK, 1994.

(15) The nucleophilic amines (10 equiv) used in the aminolysis of **5** (Table 1) can also play the role of the external base required to promote OH−Yb coordination.

(16) (a) Neverov, A. A.; Montoya-Pelaez, P. J.; Brown, R. S. *J. Am. Chem. Soc.* **2001**, *123*, 201−217. (b) Geyer, C. R.; Sen, D. *J. Mol. Biol.* **1998**, *275*, 483−489. (c) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1994**, *116*, 7893−7894.

(17) For a related example, see: Morrow, J. R.; Aures, K.; Epstein, D. *J. Chem. Soc., Chem. Commun.* **1995**, 2431−2432.

SCHEME 3[a]



[a] Conditions: (a) $BuNH_2$ (10 mol•equiv), $Yb(OTf)_3$ (0.5 mol•equiv), toluene, 80 °C, 18 h; (b) NaN_3 (10 mol•equiv), Et_3N (15 mol•equiv), $Yb(OTf)_3$ (0.5 mol•equiv), toluene, 80 °C 18 h.

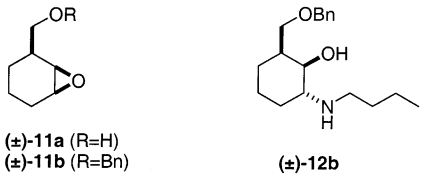


FIGURE 1.

between the chelating and the nonchelating postulated conformations.

The ability of Yb to effectively assist the opening of a cyclitol epoxide through a chelating-controlled process was also investigated on the homologue **7** bearing a hydroxymethyl group at C6 (Scheme 3). Aminolysis of **7** with $BuNH_2$ afforded a single amino alcohol **9** arising from C1 opening of the starting epoxide.[11,12] As expected, azidolysis of **7** to give azido alcohol **10** took place only in the presence of Et_3N as an external base. As above, the presence of a free OH group to promote coordination with Yb was also crucial, since the perbenzylated analogue **8** failed to react under our standard conditions.[10,18] In addition, reaction of the simplified model (±)-**11b** with $BuNH_2$ cleanly afforded the expected "C2-like" opening adduct (±)-**12b** (Figure 1). The enhanced reactivity of $Yb(OTf)_3$ to promote epoxide opening in (±)-**11b** in comparison to **8** can be explained by the establishment of fewer "unproductive" coordination complexes in this less densely functionalized substrate, in agreement with our above hypothesis.[18] Hydroxymethyl analogue (±)-**11a** led to a mixture of "C1-like" and "C2-like" regioisomers. Direct NMR analysis of this mixture was hampered presumably by traces of Yb which could not be removed even after exhaustive washings. Formation of the above mixture can be tentatively interpreted as an indirect proof of the need of at least three coordination sites for an effective chelation-controlled Yb catalysis. All these results are in full agreement with our postulated chelating model shown in Scheme 2.

In summary, a chelation-controlled aminolysis and azidolysis of cyclitol epoxides with $Yb(OTf)_3$ has been disclosed. The presence of a free OH group able to direct the coordination with the lanthanide seems essential for an efficient regiocontrol of the process. This chelation ability of a lanthanide triflate was hitherto unprecedented and should be added to the repertoire of other well-established procedures for the chelation-controlled aminolysis of epoxides.[13]

Experimental Section[19]

Starting Materials. Cyclitol epoxides **6** and **8** were obtained from benzylation of **5**[4] and **7**[20] with NaH/BnBr in DMF. Epoxide (±)-**11b** was obtained as described in the literature.[21] Epoxide (±)-**11a** was obtained from debenzylation of (±)-**11b** with $Pd(OH)_2$ in MeOH or, alternatively, by deprotection (DDQ in CH_2Cl_2/H_2O 18:1) of *c*-3-[(*p*-methoxybenzyloxy)methyl]-r-1,2-epoxycyclohexane, obtained by a modification of the method described for (±)-**11b**.

Typical Experimental Procedure for Epoxide Opening. A solution of the starting epoxide **5** or **6** (0.5 mmol) in toluene (10 mL) is added dropwise under argon over $Yb(OTf)_3$ (0.25 mmol, 155 mg) at room temperature. A solution of 5 mmol of NaN_3 and 7.5 mmol (1.0 mL) of Et_3N or the corresponding amine in toluene (1 mL) is next added and the reaction mixture is stirred at 80 °C under argon. After 18 h, the reaction mixture is cooled to room temperature, quenched with H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts are exhaustively washed with water and the residue is filtrated through a pad of silica gel (hexane/EtOAc/Et_3N 48/48/4) to remove traces of metal. The crude thus obtained is used to calculate the diastereomeric ratio (see Table 1). Flash chromatography on hexane/EtOAc/Et_3N (78/19/3) affords pure alcohols in the yield given in Table 1.

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Supporting Information Available: General experimental methods, spectral data, and ^{13}C NMR spectra for compounds **1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1j**, **2b, 6, 8, 10, 11a and 12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) A plausible explanation to account for the observed lack of reactivity should lie on the inability of the lanthanide salt to coordinate with the epoxide in these densely oxygenated substrates. The lack of a close free OH group as "coordinator assistant" and the well-known oxophilicity of Yb (ref 14b) may result in alternative, "unproductive" coordination complexes with any of the remaining benzyloxy groups. The same results were obtained with predried $Yb(OTf)_3$ (160 °C, 0.05 mmHg, 48 h).

(19) For general experimental data see the Supporting Information..

(20) Letellier, P.; Ralainairina, R.; Beaupère, D.; Uzan, R. *Synthesis* **1994**, 925−930. See also ref 10b.

(21) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1992**, *57*, 1713−18.