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Ring Opening of the Epoxide Moiety of (2*S*, 3*S*, 4*S*)-4-Amino-2,3-epoxy-1-alkanol and Its Derivatives: A Key Role of Ti(O-*i*-Pr)4 as a Mild Catalyst

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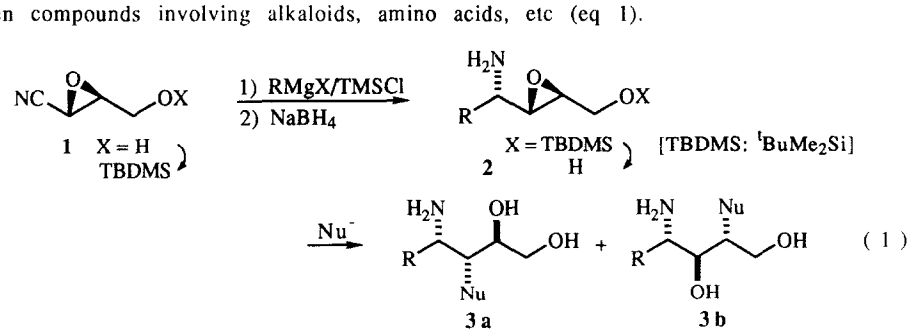
Abstract: (2*S*, 3*S*, 4*S*)-4-Amino-2,3-epoxy-1-alkanol gave 4-amino-1,3-alkanediol or 3,4-imino-1,2-alkanediol with Dibal or Ti(O-*i*-Pr)4 respectively and, after introduction of Boc group to its amino group, afforded a 4-amino-1,2,3-alkanetriol derivative under the influence of Ti(O-*i*-Pr)4.

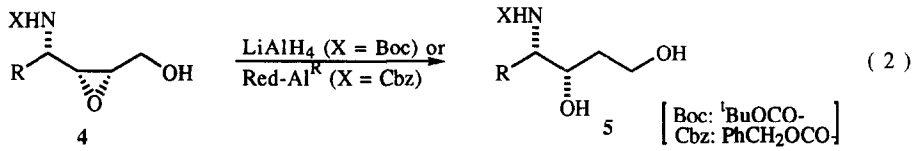
Recently we reported a concise preparation of (2*S*, 3*S*, 4*S*)-4-amino-2,3-epoxy-1-alkanols (**2**), in which the amino and epoxy groups are *anti* and the epoxide has *trans* substituents, from readily available (2*S*, 3*S*)-3-cyano-2,3-epoxy-1-propanol (**1**) via addition of Grignard reagents followed by *in situ* reduction of the resulting N-metallo-imines with $NaBH_4$.[1] The regioselective opening of their epoxide moieties with an appropriate nucleophile should provide versatile intermediates **3** for stereocontrolled construction of nitrogen compounds involving alkaloids, amino acids, etc (eq 1).



(1)

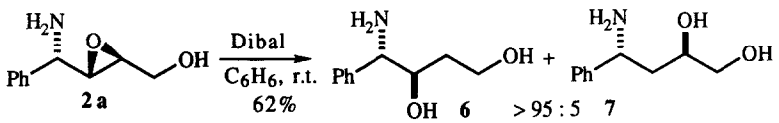
In fact, Ohfune *et al.*[2a] and Kogen *et al.*[2b] demonstrated a regioselective epoxide opening of the suitably protected **4**, a diastereoisomer of **2**, with hydride species to give selectively 1,3-diols **5** which were successfully converted to galantinamic acid and statine (eq 2). Since the reactivity and regioselectivity of such reactions depend on the structure of

substrates, and basically little is known about the regioselectivity of the ring opening of epoxides having both hydroxy[3] and amino[4] groups at their neighboring positions, we would like to disclose here our findings on the reactivity of **2** with a few nucleophiles. We initiated our study of **2** with hydride reduction.



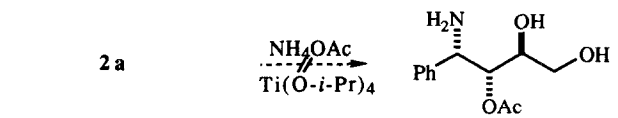
(2)

The reduction of **2a** with Dibal (diisobutylaluminum hydride) in benzene at room temperature proceeded smoothly to give the corresponding 1,3-diol **6** in a >95 : 5 selectivity (**6**/**7**) (eq 3). This is in sharp contrast to the case of analogous 2,3-epoxy-1-alkanols having no amino group where the same hydride selectively affords the corresponding *1,2-diol* under similar reaction conditions.[5] Thus the amino group of **2a** plays a very important role in determining the reaction course. However, the protection of the hydroxy group of **2a** with TBDMS group completely inhibits the reaction itself, resulting in the recovery of the starting material. Other hydrides such as $LiAlH_4$ and Red-Al^R (sodium bis(methoxyethoxy)aluminum hydride) also afforded **6** in high regioselectivities, albeit with a considerable amount of a by-product[6] and a decrease in the product yield. Thus Dibal is the hydride reagent of choice for our substrate, requiring no protection of the amino group.[7]

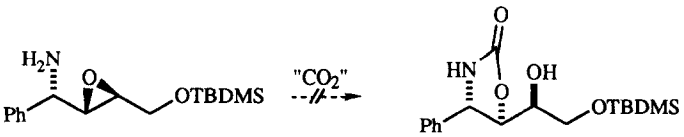


(3)

The epoxide opening of **2** with oxygen nucleophile is an attractive reaction which takes advantage of three consecutive stereogenic carbons in **2**, but was found to be much more problematic than the hydride addition. Neither treatment of **2a** with NH_4OAc-Ti(O-*i*-Pr)$_4$ under standard conditions reported by Sharpless[8] (eq 4) nor that of the TBDMS ether of **2a** with Amberlyst^R A-26 (carbonate form)[9] under forcing conditions (eq 5) afforded the desired 4-amino-1,2,3-alkanetriol derivative, at all. In the former case the product isolated was an aziridine **12** (36% yield, *vide infra*) and in the latter the starting material was recovered unchanged.

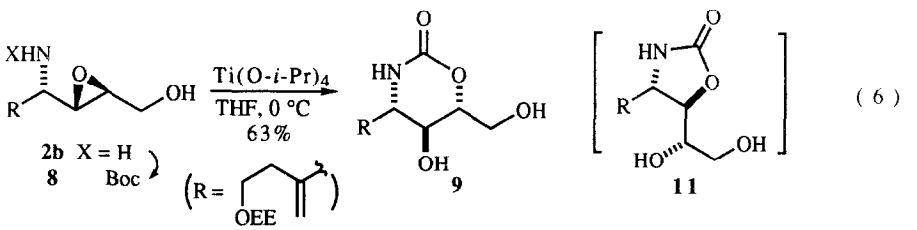


(4)



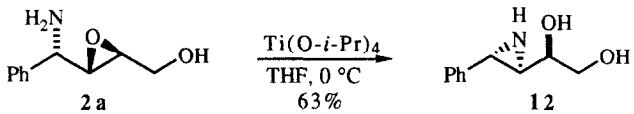
(5)

However, fortunately we eventually found that an intramolecular delivery of oxygen-functionality in the N-Boc substrate **8**, a derivative of **2b**, nicely proceeded under Ti(O-*i*-Pr)4 catalysis, affording the 4-amino-1,2,3-triol derivative **9**[10] which was isolated as a single isomer (eq 6). The structure of **9** stems from i) spectroscopic data and ii) reluctance to undergo $NaIO_4$ oxidation (which shows that it is not the regioisomer **11**). TLC analysis of a crude reaction mixture did not show the presence of another isomer **11**. As far as the catalyst is concerned, Ti(O-*i*-Pr)4 is the best one which showed high chemoselectivity, so that the acid-sensitive EE (ethoxyethyl) group survived the reaction conditions. Other catalysts involving $BF_3{\cdot}OEt_2$ and TMSOTf either in an equimolar or a catalytic amount only led to destruction of the starting material **8**.



(6)

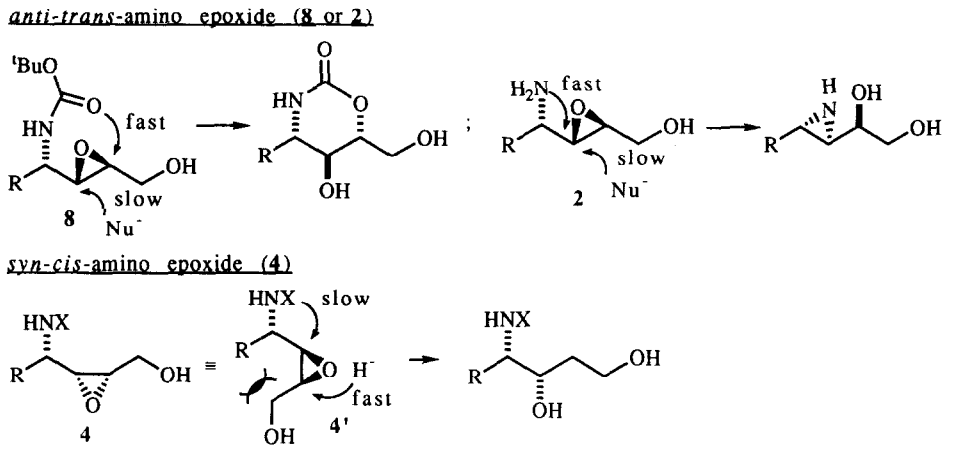
The opening of the epoxide ring of **2a** with a nitrogen nucleophile was readily achieved again in an intramolecular fashion with Ti(O-*i*-Pr)4 in THF at 0°C to give the aziridine **12** as a single product which in turn is a versatile intermediate for further transformations, for example, substitution reactions with nucleophiles such as organocopper reagents.[11] This reaction demonstrates that Ti(O-*i*-Pr)4 is an effective catalyst for promoting an aza-version of the Payne rearrangement.[12] Since the TBDMS ether of **2a** was inert under the same reaction conditions, the interaction of the hydroxy group of **2a** with Ti(O-*i*-Pr)4 seems to be critical as was illustrated in many other cases.[3]



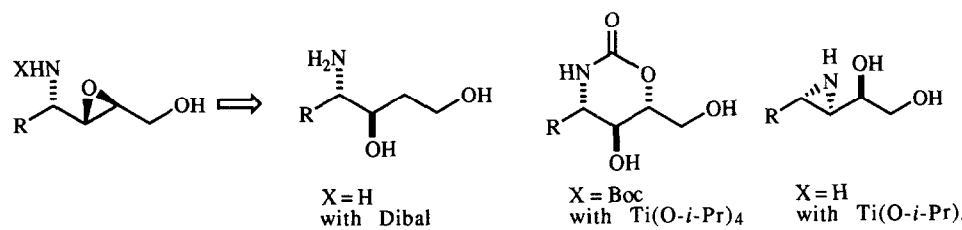
(7)

Generally, as shown above, the epoxide moiety of *anti-trans* amino epoxide (**8** or **2**) was found to be very susceptible to an intramolecular delivery of nucleophile which can sometimes block the desired intermolecular reaction,[13] while the previously reported *syn-cis*-isomer **4** underwent smooth intermolecular reaction with a nucleophile (Scheme 1). The more preferred conformation leading to an intramolecular reaction of **8** or **2** as compared to that of **4'** which suffers steric hindrance between *cis* substituents of the epoxide would account for these observations.

In summary, some useful reactions of **2** which are summarized in Scheme 2 have been developed. Application of this methodology to the synthesis of biologically active compounds is our current interest.



Scheme 1



Scheme 2

EXPERIMENTAL SECTION

General. IR spectra were recorded on a JASCO A-100 spectrometer or a JASCO FT-IR 5000 and are reported in wave numbers (cm^{-1}). ^1H nmr sprectra were taken on a Varian Gemini-300 spectrometer at 300 MHz with $CDCl_3$ as solvent and with TMS (δ = 0 ppm) as internal standard, and ^{13}C nmr spectra at 75 MHz with the middle peak of $CDCl_3$ (δ = 77.00 ppm) as internal standard. $[\alpha]_D$ values were measured on a YANAKO OR-50 polarimeter in a 20-mL cell with a 5-cm path length. All solvents used were purified and dried in a standard manner.

Starting materials: The TBDMS ethers of (2*S*, 3*S*, 4*S*)-4-amino-2,3-epoxy-4-phenyl-1-butanol (2a) and **(2*S*, 3*S*, 4*S*)-4-amino-2,3-epoxy-7-(1-ethoxyethyl)oxy-5-methylene-1-heptanol (2b)** were prepared as described elsewhere.[1]

(2*S*, 3*S*, 4*S*)-4-Amino-2,3-epoxy-4-phenyl-1-butanol (2a): To a solution of the TBDMS ether of **2a** (0.25 g, 0.85 mmol) in THF (10 mL) was added 1.0 M-TBAF (Bu_4NF) in THF (0.93 mL, 0.93 mmol) at room temperature. After stirring for 30 min at the same temperature, the solution was diluted with CH_2Cl_2 (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers

were dried with Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (eluent: MeOH-CH_2Cl_2) to afford the title compound (0.138 g, 92%).

^1H nmr 1.67 (br s, 3 H), 3.20 (m like br s, 1 H), 3.34 (m like br s, 1 H), 3.64 (d/d, J = 4.1, 12.5 Hz, 1 H), 3.91 (d/d, J = 2.4, 12.5 Hz, 1 H), 4.18 (d, J = 4.2 Hz, 1 H), 7.28--7.38 (m, 5 H).

^{13}C nmr 54.95, 56.22, 59.03, 61.21, 126.76, 127.62, 128.43, 140.97.

IR(neat) 3350, 3000, 2920, 2850, 1740, 1660, 1600, 1490, 1450, 1220, 1080, 1030, 900, 750, 695.

$[\alpha]_D^{25}$ +14.0° (c 2.74, $CHCl_3$).

(3*R*, 4*S*)-4-Amino-4-phenyl-1,3-butanediol (6): To a solution of **2a** (47.5 mg, 0.264 mmol) in benzene (2.5 mL) was added 1.0 M Dibal in hexane (0.79 mL, 0.79 mmol) at room temperature. After stirring for 30 min at the same temperature, the solution was diluted with ether (2.5 mL) and 1N-NaOH (2.5 mL). After the mixture had been stirred for 30 min, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a crude oil, ^1H nmr analysis of which showed the ratio of **6**/**7** to be > 95:5 (for the preparation of authentic **7**: see below). The crude oil was chromatographed on silica gel (eluent: MeOH-CH_2Cl_2) to afford the title compound (29.9 mg, 63%, **6**/**7** > 95:5) as an oil.

^1H nmr 1.61 (m like br s, 2 H), 2.26 (br s, 4 H), 3.79 (m, 3 H), 4.00 (br s, 1 H), 7.22--7.35 (m, 5 H).

^{13}C nmr 34.46, 60.04, 60.31, 74.38, 127.28, 127.49, 128.46, 141.58.

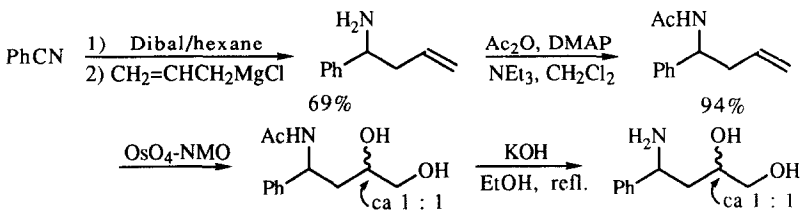
IR (neat) 3350, 2910, 1740, 1660, 1600, 1490, 1450, 1210, 1060, 970, 750, 690.

$[\alpha]_D^{25}$ +22.5° (c 0.53, $CHCl_3$) for a sample of a 95:5 mixture of **6** and **7**.

(3*R*, 4*S*)-1-Acetylamino-2,4-diacetoxy-1-phenylbutane (tri-Ac-6) (for structural confirmation): To a solution of **6** (5 mg, 0.0274 mmol) in CH_2Cl_2 (0.5 mL) were added Et_3N (0.114 mL, 0.82 mmol), Ac_2O (0.052 mL, 0.55 mmol), and DMAP (dimethylaminopyridine, 2.2 mg, 0.018 mmol) at room temperature. After stirring for 2 hr at that temperature, the solution was diluted with ether and 1N-HCl. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with satd. $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo to afford the essentially pure title compound (4.9 mg) whose ^1H nmr spectrum was consistent with the assigned structure.

^1H nmr 1.98--2.06 (m including singlet peaks at 2.00, 2.02, and 2.04 ppm for Ac's, 11 H), 4.05 (t, J = 6.2 Hz, 2 H), 5.18 (d/d, J = 4.4, 8.0 Hz, 1 H), 5.25--5.31 (m, 1 H), 6.30 (br d, J = 8.0 Hz, 1 H), 7.26--7.37 (m, 5H).

Authentic mixture of 4-amino-4-phenyl-1,2-butanediols (7 and its diastereoisomer) (for structural determination of 6) was prepared from known 4-amino-4-phenyl-1-butene[14] according to the following scheme.



^{1}H nmr 1.79 (m, 2 H), 2.1--2.8 (br s, 4 H), 3.50 (d/d, J = 4.8, 11.2 Hz, 1 H), 3.65 (d/d, J = 3.2, 11.2 Hz, 1 H), 4.03--4.09 (m, 2 H), 7.24--7.35 (m, 5 H).

(2*S*, 3*S*, 4*S*)-4-(*tert*-Butyloxycarbonyl)amino-1-(*tert*-butyl)dimethylsilyloxy-2,3-epoxy-7-(1-ethoxyethyl)oxy-5-methyleneheptane (Introduction of Boc group to the TBDMS ether of 2b): To a solution of the TBDMS ether of **2b** (0.36 g, 1 mmol) in $CHCl_3$ (4 mL) were added $NaHCO_3$ (0.126 g, 1.5 mmol) in water (2.5 mL), NaCl (0.28 g, 4.8 mmol), and $(Boc)_2O$ (0.33 g, 1.5 mmol) in $CHCl_3$ (0.7 mL) at room temperature. The mixture was heated at reflux for 2 hr and cooled to room temperature. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (eluent: AcOEt-hexane) to afford the title compound (0.39 g, 85%).

^{1}H nmr 0.06 (s, 3 H), 0.07 (s, 3 H), 0.90 (s, 9 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.33 (d, J = 5.4 Hz, 3 H), 1.44 (s, 9 H), 2.37 (t, J = 6.3 Hz, 2 H), 2.99 (d/d, J = 1.5, 6.0 Hz, 1 H), 3.12 (m like br s, 1 H), 3.45--3.88 (m, 4 H), 3.69 (d/d, J = 4.7, 12.2 Hz, 1 H), 3.85 (d/d, J = 2.7, 12.2 Hz, 1 H), 4.01 (br s, 1 H), 4.70 (q, J = 5.4 Hz, 1 H), 5.06 (s, 1 H), 5.17 (s, 1 H), 5.36 (br s, 1 H).

^{13}C nmr -5.54, -5.41, 15.24, 18.27, 19.64, 25.80, 28.30, 33.38, 55.84, 57.79, 60.45, 60.72, 62.59, 64.65, 79.40, 99.50, 114.66, 143.85, 155.25.

IR (neat) 3325, 2930, 2850, 1700, 1500, 1360, 1250, 1170, 1100, 1050, 940, 900, 830, 770, 650.

$[\alpha]_D^{25}$ -2.1° (c 6.41, $CHCl_3$).

(2*S*, 3*S*, 4*S*)-4-(*tert*-Butyloxycarbonyl)amino-2,3-epoxy-7-(1-ethoxyethyl)-oxy-5-methylene-1-heptanol (8): To a solution of the Boc derivative prepared above (0.37 g, 0.802 mmol) in THF (50 mL) was added 1.0 M-TBAF in THF (1.01 mL, 1.01 mmol) at room temperature. After stirring for 30 min at room temperature, the solution was diluted with 1:1 ether-hexane and washed with satd. $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (eluent: MeOH-CH_2Cl_2) to afford the title compound (0.25 g, 90%) as an oil.

^{1}H nmr 1.20 (t, J = 7.1 Hz, 3 H), 1.33 (d, J = 5.1 Hz, 3 H), 1.44 (s, 9 H), 1.81 (br s, 1 H), 2.38 (t, J = 6.2 Hz, 2 H,), 3.09 (d/d, J = 2.1, 6.3 Hz, 1 H), 3.23 (m like br s, 1 H), 3.42--3.99 (m, 7 H), 4.72 (q, J = 5.1 Hz, 1 H), 5.09 (s, 1 H), 5.18 (s, 1 H), 5.53 (br s, 1 H),

^{13}C nmr 15.22, 19.62, 28.28, 33.23, 55.91, 57.77, 60.48, 60.77, 61.09, 64.83, 79.53, 99.52, 115.00, 143.72, 155.42.

IR (neat) 3325, 2980, 2930, 1690, 1510, 1370, 1240, 1170, 1130, 1090, 1050, 940, 900, 865, 750.

$[\alpha]_D^{25}$ +1.4° (c 2.05, $CHCl_3$).

The 6-membered cyclic carbamate of (2*R*, 3*S*, 4*S*)-4-amino-7-(1-ethoxyethyl)oxy-5-methylene-1,2,3-heptanetriol (9): To a solution of **8** (0.1 g, 0.288 mmol) in THF (5 mL) was added dropwise Ti(O-*i*-Pr)$_4$ (0.17 mL, 0.576 mmol) at 0°C. After stirring for 3 hr at that temperature, water (0.34 mL), NaF (0.174 g, 4.15 mmol), ether (5 mL), and Celite were added at room temperature. The resulting heterogeneous mixture was stirred for 2 hr at room temperature, filtered through a pad of Celite with ether, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was chromatographed on silica gel (eluent: MeOH-CH_2Cl_2) to afford the title compound (52.5 mg, 63%).

^{1}H nmr 1.21 (t, J = 6.9 Hz, 3 H), 1.32 (d, J = 5.4 Hz, 3 H), 2.16 (br s, 1 H), 2.38 (t, J = 6.0 Hz, 2 H), 3.07 (br s, 1 H), 3.42--3.84 (m, 7 H), 4.35 (d/t, J = 4.8, 6.5 Hz, 1 H), 4.43 (d, J = 4.5 Hz, 1 H), 4.69 (q, J = 5.4 Hz, 1 H), 5.10 (s, 1 H), 5.23 (s, 1 H), 5.37 (br s, 1 H)

^{13}C nmr 15.23, 19.77, 31.04, 58.08, 61.18, 62.36, 63.87, 72.08, 80.93, 99.76, 113.29, 144.70, 159.55.

IR (neat) 3350, 2980, 2940, 1730, 1380, 1220, 1120, 1090, 1040, 940, 750.

$[\alpha]_D^{25}$ -23° (c 0.92, $CHCl_3$).

(2*R*, 3*R*, 4*S*)-3,4-Imino-4-phenyl-1,2-butanediol (12): To a solution of **2a** (48 mg, 0.277 mmol) in THF (1 mL) was added Ti(O-*i*-Pr)4 (0.12 mL, 0.416 mmol) at room temperature. After stirring for 1 hr at room temperature, water (0.24 mL), NaF (0.125 g, 3 mmol), ether (1 mL), and Celite were added. The resulting mixture was stirred for 3.5 hr at that temperature, filtered through Celite with ether, dried over Na_2SO_4, and concentrated in vacuo to give the essentially pure title compound (30 mg, 63%), which can be purified on silica gel, if necessary.

^{1}H nmr 2.02 (br s, 3 H), 2.39 (br s like t, 1 H), 3.02 (d, J = 2.7 Hz, 1 H), 3.69 (d/d, J = 5.6, 11.6 Hz, 1 H), 3.81 (d/d, J = 3.2, 11.6 Hz, 1 H), 3.88 (m, 1 H), 7.18--7.42 (m, 5 H).

The ^{1}H nmr coupling constant between the protons of aziridine (J = 2.7 Hz) established their *trans* relationship.

^{13}C nmr 35.68, 41.65, 64.90, 70.12, 125.65, 127.41, 128.64, 138.94.

IR (neat) 3350, 3025, 2940, 1660, 1450, 1220, 1080, 1040, 890, 750, 690.

$[\alpha]_D^{25}$ -62° (c 0.16, $CHCl_3$)

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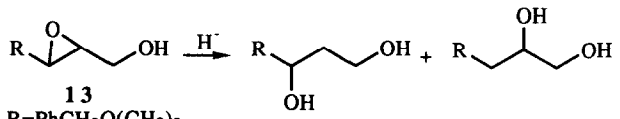
1989, *30*, 5425-5428.

5. The reduction of **13** with a few hydride reagents was reported. Dibal is exceptional to give the corresponding 1,2-diol (eq 8).



13
R=$PhCH_2O(CH_2)_2$

Red-Al^R/THF/-20°C	150	: 1
Dibal/C_6H_6/r.t.	1	: 13
LAH/THF/r.t.	1	: 1
LAH/THF/-20°C	9	: 1

(8)

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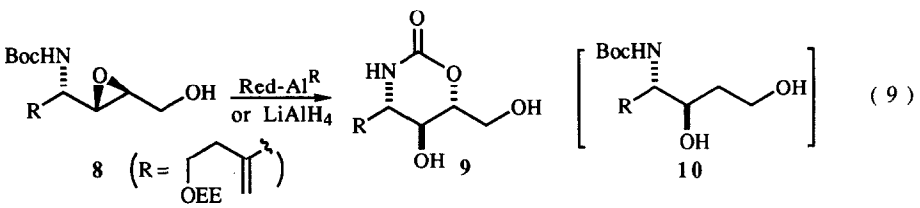
6. The by-product was aziridine **12** which was not detected when Dibal was used as the hydride (eq 3).
7. Remarkably, although the formation of **10** had been initially expected based on the previous results shown in eq 2, the reaction of the N-Boc derivative **8** with Red-Al^R afforded the cyclic carbamate **9** resulting from the intramolecular epoxide opening as a major product. The same trend was seen when the Red-Al^R was replaced with $LiAlH_4$.



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