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Regioselective Nucleophilic Ring Opening of Epoxides and Aziridines derived from Homoallylic Alcohols

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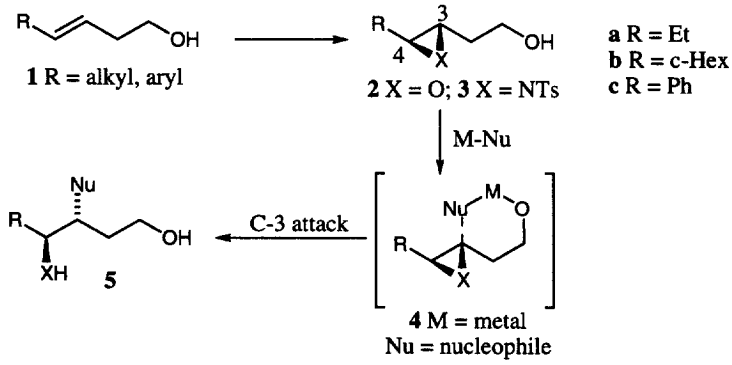
Abstract: The regioselectivity of nucleophilic ring opening of some 3,4-epoxy and 3,4-aziridino alcohols has been studied. The nucleophiles chosen were complex hydrides ($LiAlH_4$, Red-Al and DIBAL) and Lipshutz- or Gilman-type organocuprate reagents. The C-4 substituent in the substrates was varied in order to study steric and electronic effects on the ring opening reactions. For alkyl substituents at C-4, most of the results can be explained on the basis of intramolecular delivery of the nucleophile to C-3 via a six-membered transition state, leading to 1,4-diols or 1,4-amino alcohol derivatives. In general, the epoxy alcohols gave poorer regioselectivity than the *N*-tosyl aziridino alcohols, for which selectivities of >95:5 were routinely obtained. The activating effect of a phenyl group at C-4 led to a switch in regiochemistry, with the 1,3-diol or 1,3-amino alcohol derivative as the major product. © 1997 Elsevier Science Ltd.

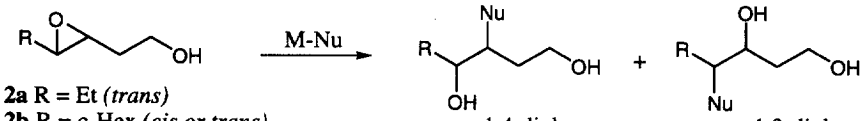
In connection with a project aimed at the stereoselective total synthesis of some natural products and analogs, we required building blocks of type **5** shown below, particularly those with X = NHTs. We reasoned that these might be easily available via regioselective ring opening reactions of 3,4-epoxy alcohols and aziridines (**2** and **3**) in analogy with chemistry developed for the 2,3-isomers.[1, 2] For the latter,[1, 2] many of the ring opening reactions using organometallic reagents are presumed to involve cyclic transition states (five- or six-membered, leading to nucleophilic attack at C-2 or C-3, respectively). In the present case, we hoped to obtain as good, or even better, selectivity (for attack at the proximal carbon of the three-membered ring) since the competing transition states would be six- and seven-membered, respectively (see structure **4**). This should lead to preferential attack at C-3, providing the desired regiochemistry in the products (Scheme 1).



Scheme 1. Proposed route to 1,4-diols or amino alcohol derivatives.

The substrates shown above were chosen to investigate both steric and electronic effects of the C-4 substituent, and for the substrates with the bulkiest C-4 substituent (**2b**, **3b**) both *cis* and *trans* isomers were

examined. All these materials were racemic, but methods[3] are available for their preparation in optically active form. In line with earlier work,[2a-c] we chose complex hydrides and organocuprates as nucleophiles, and the results are shown in Tables 1 and 2. The structure of each product (1,4- *vs.* 1,3-derivative) was assigned on the basis of extensive ^1H (200 or 500 MHz) and ^{13}C NMR spectroscopic analysis (50 or 125 MHz) including homonuclear decoupling, COSY, DEPT and HETCOR. In each case, this was done on the crude product prior to chromatographic purification. In some cases, the spectroscopic analysis was performed on acetylated derivatives (see Experimental). The epoxides were studied first (see Table 1).



2a R = Et *(trans)*
2b R = c-Hex *(cis or trans)*
2c R = Ph *(trans)*

1,4-diol 1,3-diol

Nu = H, Me

Table 1. Nucleophilic ring opening of epoxides **2a-c**.

Entry	Substrate	Reagent/Solvent	Conditions	Yield, %	1,4- : 1,3-diol[a]
1	**2a**	$LiAlH_4$/THF	2 eq., -78 to -23°C, 24 h	70	90 : 10
2	*trans*-**2b**		2 eq., -23°C, 66 h	>95	90 : 10
3	*cis*-**2b**		2 eq., -23°C, 66 h	>95	>95 : 5
4	**2c**		2.5 eq., -78 to -23°C, 115 h	66	30 : 70
5	**2a**	Red-Al/THF	3 eq., -78°C to RT, 95 h	>95	92 : 8
6	*trans*-**2b**		3 eq., RT, 100 h	>95	92 : 8
7	*cis*-**2b**		3 eq., RT, 140 h	72	>95 : 5
8	**2c**		3 eq., -78°C to RT, 112 h	>95	70 : 30
9	**2a**	DIBAL/Benzene	3 eq., 0°C to RT, 77 h	53	20 : 80
10	*trans*-**2b**		3 eq., RT, 88 h	82[b]	45 : 55
11	*cis*-**2b**		3 eq., RT, 140 h	>95	75 : 25
12	**2c**		3 eq., RT, 72 h	61	20 : 80
13	**2a**	Li_2Me_2CuCN/Et_2O	3 eq., -78 to -23°C, 34 h	47	55 : 45
14	*trans*-**2b**		3 eq., -78 to -23°C, 40 h	91	85 : 15
15	*cis*-**2b**		3 eq., -23°C to RT, 95 h	>95	93 : 7
16	**2c**		3 eq., -78 to -55°C, 34 h	45	see text
17	**2a**	$LiMe_2Cu/Et_2O$	3 eq., -78 to 0°C, 50 h	46	55 : 45
18	*trans*-**2b**		3 eq., -78 to 0°C, 55 h	93	85 : 15
19	*cis*-**2b**		3 eq., -23 to 0°C, 110 h	94	90 : 10
20	**2c**		3 eq., -78 to 0°C, 55 h	72	see text

(a) Determined by ^1H NMR spectroscopy on crude product. (b) Reaction incomplete.

Earlier experience[1a-c] with ring opening of *2,3*-epoxy alcohols by $LiAlH_4$ and Red-Al suggested that in the present case the cyclic transition state shown above should be operative, and that from **2a** and **2b** the 1,4-diol should be the major product. This was indeed the case, and the *trans* isomers of **2a** and **2b** gave synthetically useful levels of regioselectivity and acceptable chemical yields (Table 1, entries 1 and 2, 5 and 6). Interestingly, the *cis* isomer of **2b** gave better selectivity for the desired 1,4-diol, particularly with $LiAlH_4$ (Table 1, entries 3 and 7). Inspection of molecular models suggests that for both *trans* and *cis* isomers, the six-membered, chair-like transition state for attack at C-3 is relatively unhindered (Fig. 1, **A**

and **B**). The corresponding seven-membered array for attack at C-4 in the *cis* isomer (Fig. 1, **C**) suffers from steric interactions between the C-2 methylene and the 2- or 6-positions of the cyclohexyl ring; such interactions are absent during C-4 attack on the *trans* isomer (structure not shown).

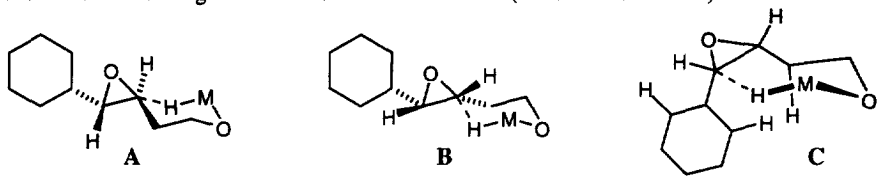


Fig. 1. Proposed chair-like transition states for C-3 attack in the *trans* and *cis* isomers of **2b** (**A** and **B**) and seven-membered transition state for C-4 attack in the *cis* isomer (**C**).

The third hydride reagent, DIBAL, is not expected[1b] to participate in the type of transition state depicted above, and regioselectivities with **2a,b** were indeed lower (Table 1, entries 9 - 11). For the *trans* isomers, the 1,3-diol is actually the major product, and this parallells results from ring opening of 2,3-epoxy alcohols.[1b] Surprisingly, however, the 1,4-diol was the major product from *cis*-**2b** (Table 1, entry 11). The regiochemistry of the ring opening by DIBAL is presumably dictated by various steric interactions during *inter*molecular reactions.

The phenyl substituent in substrate **2c** was expected to electronically favour attack at C-4, and this was found to be the case for $LiAlH_4$ and DIBAL (Table 1, entries 4 and 12). However, Red-Al, which in such reactions normally mimics[1a-c] the regioselectivity of $LiAlH_4$, provided an unexpected exception in this case (Table 1, entry 8).

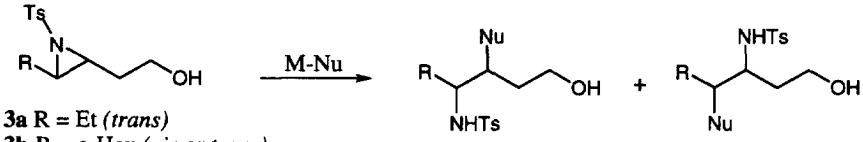
Reaction of Lipshutz- or Gilman-type cuprates with 2,3-epoxy alcohols is usually an excellent method[1d, e] for nucleophilic attack at C-2 (perhaps via an intramolecular reaction) and we were therefore disappointed to find poor regioselectivity for the corresponding attack at C-3 in *trans*-**2a,b** (Table 1, entries 13 and 14, 17 and 18). The only really satisfactory result was that from *cis*-**2b** and the Lipshutz methylcuprate (Table 1, entry 15). On the other hand, epoxide **2c** gave complete regioselectivity for attack at C-4, but this was compromised by the fact that substantial amounts of the original homoallylic alcohol were also formed. (For entries 16 and 20 in Table 1, the ratios between 1,3-diol and olefin were 66:33 and 90:10, respectively.)

The present results thus show that while there are indeed similarities in the reactivity patterns of 2,3- and 3,4-epoxy alcohols, there are also distinct differences, and our original hope for enhanced regioselectivity for the 3,4-isomers was not fulfilled. The reactions with the 3,4-isomers were also much slower than those of the 2,3-epoxy alcohols.[1]

The results from the corresponding ring opening reactions of the aziridines **3a-c** are collected in Table 2. For aziridines **3a** and **3b**, both $LiAlH_4$ and Red-Al gave gratifyingly high levels of regioselectivity, in line with the chair-like transition state model proposed above for the epoxides (Fig. 1 and Table 2, entries 1 - 3, 5 and 6). A surprising exception, however, was the reaction between Red-Al and *cis*-**3b** (Table 2, entry 7). Reactions with DIBAL are not included in Table 2, since these were extremely sluggish and not synthetically useful (e.g. < 10% isolated yield from **3a** after 96 h).

The phenyl-substituted substrate **3c** parallelled its epoxide counterpart, and once again the originally unexpected switch of regioselectivity upon going from $LiAlH_4$ to Red-Al was noted (Table 2, entries 4 and 8). At present we have no convincing explanation for this difference.

In contrast to the epoxides, the 3,4-aziridino alcohols **3a,b** gave excellent C-3 regioselectivity in ring opening by both types of cuprate, the Lipshutz reagents being the more reactive. (Table 2, entries 9 - 11, 13 - 15). Combined with generally high chemical yields, this makes the procedure a synthetically useful one, and in general the *N*-tosyl aziridines proved to be more reactive than the epoxides. For **3c**, the electronic effect of the C-4 phenyl group obviously competes well with the favourable steric effects invoked for attack at C-3 (Table 2, entries 12 and 16). Apart from longer reaction times, the results with the present 3,4-aziridino alcohols are very similar to those obtained earlier[2a - c] with the 2,3-isomers, and synthetic applications of the present methodology will be reported in due course.



3a R = Et *(trans)*
3b R = c-Hex *(cis or trans)*
3c R = Ph *(trans)*

1,4-isomer 1,3-isomer

Nu = H, Me

Table 2. Nucleophilic ring opening of aziridines **3a-c**.

Entry	Substrate	Reagent/Solvent	Conditions	Yield, %	1,4- : 1,3-isomer[a]
1	**3a**	$LiAlH_4$/THF	2 eq., -78 to -23°C, 20 h	62	>95 : 5
2	*trans*-**3b**		3 eq., -78 to -23°C, 40 h	55	>95 : 5
3	*cis*-**3b**		3 eq., -23°C, 90 h	76	>95 : 5
4	**3c**		3 eq., -23°C, 115 h	60	15 : 85
5	**3a**	Red-Al/THF	2 eq., -78 to -23°C, 20 h	>95	>95 : 5
6	*trans*-**3b**		2 eq., -78 to -23°C, 20 h	90	>95 : 5
7	*cis*-**3b**		2 eq., -23°C, 90 h	>95	80 : 20
8	**3c**		3 eq., -23°C, 120 h	70	85 : 15
9	**3a**	Li_2Me_2CuCN/Et_2O	3 eq., -78 to -23°C, 20 h	>95	>95 : 5
10	*trans*-**3b**		3 eq., -78 to -23°C, 20 h	90	>95 : 5
11	*cis*-**3b**		3 eq., -23°C, 70 h	90	>95 : 5
12	**3c**		3 eq., -78 to -23°C, 20 h	50	30 : 70
13	**3a**	$LiMe_2Cu/Et_2O$	3 eq., -23°C, 20 h	82	>95 : 5
14	*trans*-**3b**		3 eq., -23°C, 93 h	94	>95 : 5
15	*cis*-**3b**		3 eq., -23°C, 69 h	>95	>95 : 5
16	**3c**		3 eq., -23°C, 140 h	65	20 : 80

(a) Determined by ^1H NMR spectroscopy on crude product.

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EXPERIMENTAL

General remarks. ^1H (200 or 500 MHz) and ^{13}C (50 or 125 MHz) NMR spectra were recorded on a Bruker AC 200 or AM-500 spectrometer ($CDCl_3$/TMS). IR spectra were obtained on a Perkin-Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks are listed. Elemental analyses were performed at the Analytical Department of the Research Institute for Pharmacy and Biochemistry,

Prague, Czech Republic. $LiAlH_4$ (1M in THF), Red-Al (3.5M in toluene) and DIBAL (1M in hexanes) were purchased from Aldrich. MeLi (1.6M in diethyl ether) was purchased from Merck and titrated immediately before use. Ether and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone. Benzene was dried over calcium hydride and distilled under nitrogen. Silica gel for flash chromatography was purchased from Grace-Amicon, and ether-hexane mixtures were used for elution. The epoxy alcohols were prepared by standard mCPBA epoxidation of the corresponding homoallylic alcohols, which were commercially available (*trans*-3-hexen-1-ol), known in the literature[4] (*trans*-4-phenyl-3-buten-1-ol) or easily prepared[5] (*trans*- and *cis*- 4-cyclohexyl-3-buten-1-ol). The *N*-tosyl aziridines were prepared from the epoxides by previously described methods.[2a-c]

Selected physical data for the epoxy alcohols: **2a**. ^1H NMR: δ 1.00 (3H, t, J = 7.5 Hz); 1.58 (2H, m); 1.70 (1H, ddt, J = 6.5, 14.5, 6); 1.95 (1H, ddt, J = 6.5, 14.5, 6.5); 2.65 (1H, bs, OH); 2.78 (1H, dt, J = 2.5, 5.5); 2.88 (1H, ddd, J = 2.5, 4.3, 6.5); 3.77 (2H, dd, J = 6.0, 6.5). ^{13}C NMR: 9.6, 24.8, 34.2, 56.4, 59.4, 59.6. IR: 3420 (b), 1459, 1240, 1059, 884 cm^{-1}.

trans-**2b**. ^1H NMR: 1.00 - 1.40 (6H, m); 1.61 - 1.20 (7H, m); 2.22 (1H, bs, OH); 2.59 (1H, dd, J = 2.2, 6); 2.92 (1H, ddd, J = 2.2, 4.5, 7); 3.77 (2H, t, J = 6). ^{13}C NMR: 25.4, 25.6, 26.2, 28.8, 29.5, 34.3, 39.8, 55.5, 60.0, 62.5. IR: 3415 (b), 1450, 1055, 875.

cis-**2b**. ^1H NMR: 1.00 - 1.41 (6H, m); 1.50 - 1.80 (5H, m); 1.85 - 2.00 (3H, m); 2.67 (1H, dd, J = 4.5, 8); 3.10 (1H, dt, J = 4.5, 8); 3.87 (2H, m). 25.3, 25.4, 26.1, 28.6, 30.6, 36.6, 55.0, 60.8, 61.0. IR: 3420 (b), 1450, 1054.

2c. ^1H NMR: 1.86 (1H, ddt, J = 6.5,14.5, 6.0); 2.00 (1H, bs, OH); 2.11 (1H, ddt, J = 4.5, 14.5, 6.5); 3.14 (1H, ddd, J = 2.2, 4.5, 6.5), 3.72 (1H, d, J = 2.2); 3.86 (2H, m); 7.31 (5H, m). ^{13}C NMR: 34.5, 58.0, 59.7, 60.9, 125.5, 128.1, 128.4, 137.2. IR: 3416 (b), 1604, 1497, 1462, 1240, 1051, 882.

Selected physical data for the aziridino alcohols: **3a**. ^1H NMR: 0.93 (3H, t, J = 7.5); 1.76 (3H, m); 1.91 - 2.20 (2H, m); 2.42 (3H, s); 2.67 (1H, dt, J = 4.5, 6.7); 2.85 (1H, ddd, J = 4.5, 5, 7); 3.70 (2H, t, J = 6); 7.32 and 7.85 (2H + 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR (11.7, 21.5, 22.8, 32.6, 46.5, 50.9, 60.6, 127.4, 129.4, 138.0, 144.0. IR: 3461 (b), 1598, 1320, 1154. Anal. Calc. for $C_{13}H_{19}NO_3S$: C, 57.96%; H, 7.11; N, 5.20. Found: C, 57.91; H, 7.14; N, 5.18.

trans-**3b**. ^1H NMR: 0.80 - 1.40 (6H, m); 1.40 - 1.75 (5H, m); 2.14 (2H, m); 2.39 (1H, bs, OH); 2.43 (3H, s); 2.57 (1H, dd, J = 4.5, 8.5); 2.80 (1H, dt, J = 4.5, 6.5); 3.75 (2H, t, J = 6); 7.31 and 7.83 (2H + 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 21.4, 25.1, 25.3, 25.8, 29.9, 30.6, 31.8, 38.8, 46.8, 53.7, 60.7, 127.4, 129.3, 137.3, 143.8. IR: 3456 (b), 1598, 1314, 1154. Anal. Calc. for $C_{17}H_{25}NO_3S$: C, 63.12%; H, 7.79; N, 4.33. Found: C, 63.09; H, 7.81; N, 4.21.

cis-**3b**. ^1H NMR: 0.79 - 1.30 (6H, m); 1.30 - 1.80 (6H, m); 1.86 - 2.02 (1H, m); 2.39 (1H, bs, OH); 2.45 (3H, s); 2.51 (1H, dd, J = 6.5, 8); 2.97 (1H, ddd, J = 4, 6.5, 7); 3.71 (2H,m); 7.34 and 7.83 (2H + 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 21.6, 25.3, 25.8, 29.1, 29.5, 31.1, 35.6, 41.6, 50.2, 60.8, 128.1, 129.5, 134.5, 144.5. IR: 3534 (b), 1598, 1322, 1160. Anal. Calc. for $C_{17}H_{25}NO_3S$: C, 63.12%; H, 7.79; N, 4.33. Found: C, 63.10; H, 7.80; N, 4.24.

3c. ^1H NMR: 2.25 - 2.55 (2H, m); 2.39 (3H, s); 3.04 (1H, m); 3.80 - 4.00 (3H, m). 7.11 - 7.30 (7H, m); 7.80 (2H, part of *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 21.4, 31.5, 48.6, 50.4, 60.6, 126.4, 127.1, 127.9, 128.3, 129.4, 134.8, 137.2, 143.9. IR: 3500 - 3200 (b), 1599, 1326, 1160. Anal. Calc. for $C_{17}H_{19}NO_3S$: C, 64.33%; H, 6.03; N, 4.41. Found: C, 64.08; H, 6.14; N, 4.36.

Ring opening reactions. The reactions with the hydride and cuprate reagents and subsequent work-up were carried out as previously described.[2a - c] All reactions were carried out under nitrogen and were monitored by TLC. Details of reaction time, temperature etc. are given in Tables 1 and 2. The pure products were obtained as viscous oils or low-melting solids.

*Ring opening of **2a** with hydride reagents.* Data for 1,4-diol. ^{1}H NMR: 0.94 (3H, t, J = 7.5); 1.40 - 1.60 (2H, m); 1.60 - 1.71 (4H, m); 3.17 (2H, bs, 2xOH); 3.55 (1H, m); 3.65 (2H, m). ^{13}C NMR: 9.9, 29.0, 30.1, 33.8, 62.7, 73.1. Data for 1,3-diol. ^{1}H NMR: 0.94 (3H, t, J = 7.5); 1.39 - 1.60 (4H, m); 1.60 - 1.70 (2H, m); 3.17 (2H, bs, 2xOH); 3.65 (2H, m); 3.85 (1H, m). ^{13}C NMR: 13.9, 18.6, 38.1, 39.8, 61.4, 71.6.

*Ring opening of **2a** with cuprate reagents.* Data for 1,4-diol. ^{1}H NMR: 0.80 - 1.00 (6H, m, 2xMe); 1.30 -1.70 (5H, m); 3.25 (1H, ddd, J = 4, 5.5, 8); 3.30 - 3.80 (4H, m). ^{13}C NMR: 9.9, 16.5, 27.0, 35.2, 35.9, 60.1, 77.0. Data for 1,3-diol: ^{1}H NMR: 0.90 (6H, m, 2xMe); 1.30 - 1.70 (5H, m); 3.3 - 3.8 (5H, m). ^{13}C NMR: 11.4, 14.3, 24.8, 34.1, 40.6, 61.7, 75.6.

*Ring opening of trans- or cis-**2b** with hydride reagents.* The crude product was peracetylated (Ac_2O, pyridine) prior to spectroscopic analysis. Data for 1,4-diacetate. ^{1}H NMR: 0.80 - 1.41 (6H, m); 1.4 1 - 1.80 (9H, m); 2.05 (6H, s); 4.05 (2H, t, J = 6.4); 4.75 (1H, m). ^{13}C NMR: 20.8, 21.0, 24.6, 25.88, 25.90, 26.2, 27.5, 28.0, 28.8, 41.1, 64.1, 77.2, 170.8. Data for 1,3-diacetate. ^{1}H NMR: 0.80 - 1.40 (6H, m); 1.40 - 1.80 (9H, m); 2.05 (6H, s); 4.08 (2H, t, J = 6.4); 5.09 (1H, m).

*Ring opening of trans-**2b** with methylcuprates.* The spectroscopic analysis was carried out on both the diol mixture and the peracetylated crude product. Neither the diols nor the diacetates could be separated chromatographically, and the spectra of the 1,3-isomer (minor product) could not be fully assigned. Data for the 1,4-diol (major product). ^{1}H NMR: 0.95 (3H, d, J = 7); 1.00 - 1.40 (6H, m); 1.40 -1.90 (8H, m); 2.81 (2H, bs, 2xOH); 3.62 (1H, m); 3.75 (2H, m). ^{13}C NMR: 17.0, 26.0, 26.2, 26.4, 27.1, 29.9, 32.7, 34.7, 40.3, 60.1, 80.2. Data for 1,4-diacetate. ^{1}H NMR: 0.90 (3H, d, J = 7); 1.00 - 1.40 (6H, m); 1.40 - 1.90 (8H, m); 2.06 (6H, s); 4.00 - 4.20 (2H, m); 4.68 (1H, dd, J = 5, 6.5). ^{13}C NMR: 16.3, 20.7, 25.5, 25.7, 25.9, 26.1, 27.8, 29.4, 30.4, 38.7, 62.6, 81.1, 170.9.

*Ring opening of cis-**2b** with methylcuprates.* As for the *trans* isomer above, the products were not chromatographically separable. The spectroscopic analysis was best carried out on the diacetate. Data for 1,4-diacetate (major product). ^{1}H NMR: 0.90 (3H, d, J = 7); 1.00 - 1.40 (6H, m); 1.40 - 1.80 (7H, m); 1.90 (1H, m); 2.05 (6H, s); 4.10 (2H, m); 4.69 (1H, dd, J = 3.8, 8). ^{13}C NMR: 13.1, 20.7, 25.7, 25.8, 26.1, 28.6, 29.2, 30.3, 32.5, 38.7, 62.4, 79.8, 170.9.

*Ring opening of **2c** with hydride reagents.* Data for the 1,4-diol. ^{1}H NMR: 1.50 - 1.75 (2H, m); 1.80 - 1.90 (2H, m); 3.20 (2H, bs, 2xOH); 3.60 (2H, m); 4.65 (1H, t, J = 6.2); 7.20 - 7.40 (5H, m). ^{13}C NMR: 29.0, 36.2, 62.5, 74.1, 125.7, 127.2, 128.2, 144.6. Data for 1,3-diol. ^{1}H NMR: 1.80 (2H, m); 2.74 (2H, d, J = 6.5); 3.20 (2H, bs, 2xOH); 3.60 (2H, m); 3.65 - 3.80 (1H, m); 7.20 - 7.40 (5H, m). ^{13}C NMR: 37.5, 44.1, 61.2, 72.6, 126.3, 128.4, 129.3, 138.1.

*Ring opening of **2c** with methylcuprates.* The 1,4-product was not detected (see text). Data for the 1,3-diol. ^{1}H NMR: 1.26 (3H, d, J = 7); 1.80 (2H, m); 2.76 (1H, qn, J = 7); 3.70 (2H, t, J = 6.3); 3.88 (1H, ddd, J = 2.5, 8, 10); 7.30 (5H, m). ^{13}C NMR: 17.3, 35.4, 46.3, 61.4, 76.2, 125.6, 128.4, 129.3, 143.1.

*Ring opening of **3a** with hydride reagents.* The crude product consisted of essentially a single regioisomer (1,4-amino alcohol derivative, see Table 2). Data for 1,4-isomer. ^{1}H NMR: 0.74 (3H, t, J = 7.5); 1.20 - 1.60 (6H, m); 2.30 (1H, bs, OH); 2.43 (3H, s); 3.18 (1H, m); 3.55 (2H, m); 4.80 (1H, bs, NH); 7.28 and 7.77 (2H

+ 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 9.5, 21.3, 27.6, 28.0, 30.6, 55.0, 62.3, 126.8, 129.4, 138.4, 142.9. Anal. Calc. for $C_{13}H_{21}NO_3S$: C, 57.53%; H, 7.80; N, 5.17. Found: C, 57.49; H, 7.85; N, 4.99.

*Ring opening of **3a** with methylcuprates.* The crude product consisted of essentially a single regioisomer (1,4-amino alcohol derivative, see Table 2). Data for 1,4-isomer. ^{1}H NMR: 0.68 (3H, t, J = 7.5); 0.83 (3H, d, J = 7.0); 1.25 - 1.90 (5H, m); 2.42 (3H, s); 3.07 (1H, dt, J = 8, 5); 3.63 (2H, m); 5.20 (1H, bs, NH); 7.28 and 7.76 (2H + 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 9.9, 15.4, 21.4, 23.8, 33.0, 34.8, 59.7, 60.4, 126.9, 129.4, 138.4, 142.9. Anal. Calc. for $C_{14}H_{23}NO_3S$: C, 58.97%; H, 8.12; N, 4.91. Found: C, 58.51; H, 8.22; N, 4.86.

*Ring opening of trans-**3b** with hydride reagents.* The crude product consisted of essentially a single regioisomer (1,4-amino alcohol derivative, see Table 2). Data for 1,4-isomer. ^{1}H NMR: 0.70 - 1.20 (6H, m); 1.20 - 1.80 (9H, m); 2.45 (3H, s); 3.05 (1H, m); 3.50 (2H, m); 5.35 (1H, bs, NH); 7.27 and 7.76 (2H + 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 21.3, 26.0, 26.05, 26.1, 27.7, 28.3, 28.5, 41.3, 58.5, 62.2, 126.8, 129.3, 138.4, 142.3. Anal. Calc. for $C_{17}H_{27}NO_3S$: C, 62.74%; H, 8.36; N, 4.30. Found: C, 62.59; H, 8.39; N, 4.19.

*Ring opening of cis-**3b** with Red-Al.* This experiment gave a chromatographically unseparable 80:20 mixture of the 1,4- and 1,3-amino diol derivatives. The ratio was determined by integration of the tosyl-Me signals, but a full assignment of the spectrum of the minor isomer was impossible due to peak overlap.

*Ring opening of trans-**3b** with methylcuprates.* The crude product consisted of essentially a single regioisomer (1,4-amino alcohol derivative, see Table 2). Data for 1,4-isomer. ^{1}H NMR: 0.78 (3H, d, J = 7); 0.80 - 2.00 (14H, m); 2.43 (3H, s); 3.03 (1H, m); 3.60 (2H, m); 5.05 (1H, bs, NH); 7.26 and 7.74 (2H + 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 17.3, 21.4, 26.1, 26.2, 28.6, 30.9, 31.7, 34.1, 40.0, 60.3, 63.9, 126.8, 129.2, 139.3, 142.6. Anal. Calc. for $C_{18}H_{29}NO_3S$: C, 63.68%; H, 8.61; N, 4.13. Found: C, 63.47; H, 8.70; N, 4.08.

*Ring opening of cis-**3b** with methylcuprates.* The crude product consisted of essentially a single regioisomer (1,4-amino alcohol derivative, see Table 2). Data for 1,4-isomer. ^{1}H NMR: 0.78 (3H, d, J = 7); 0.80 - 2.00 (14H, m); 2.42 (3H, s); 3.13 (1H, ddd, J = 3.5, 7.5, 10); 3.58 (2H, m); 4.53 (1H, d, J = 10, NH); 7.28 and 7.74 (2H + 2H, *AA'BB'*, J_{AB} = 8.5). ^{13}C NMR: 14.3, 21.4, 26.0, 26.1, 29.6, 30.6, 30.8, 37.1, 40.6, 60.8, 62.5, 126.8, 129.3, 139.1, 142.8. Anal. Calc. for $C_{18}H_{29}NO_3S$: C, 63.68%; H, 8.61; N, 4.13. Found: C, 63.51; H, 8.71; N, 4.10.

*Ring opening of **3c** with hydride reagents.* Reactions with $LiAlH_4$ and Red-Al gave inseparable mixtures of 1,4- and 1,3-amino alcohol derivatives. The ratios were determined by integration of the TsN*H* signals, but full assignment of the ^{1}H NMR spectrum of the crude product was not possible. The regiochemistry was assigned on the basis of the ^{13}C NMR shifts. Data for 1,4-isomer: 21.3, 28.6, 34.1, 58.0, 62.0, 126.4, 126.9, 128.2, 129.1, 129.3, 129.6, 137.6, 140.9, 142.7. Data for 1,3-isomer: 21.4, 36.1, 41.6, 52.9, 58.9, 126.3, 126.9, 128.3, 129.1, 129.3, 129.5, 137.2, 137.6, 143.0. Elemental analysis was run on the inseparable mixture after flash chromatography. Anal. Calc. for $C_{17}H_{21}NO_3S$: C, 63.92%; H, 6.63; N, 4.39. Found: C, 63.72; H, 6.73; N, 4.24.

*Ring opening of **3c** with methylcuprates.* Reactions with the cuprate reagents gave inseparable mixtures of 1,4- and 1,3-amino alcohol derivatives. The ratios were determined by integration of the TsN*H* signals, but full assignment of the ^{1}H NMR spectrum of the crude product was not possible. Data for 1,4-isomer. ^{13}C NMR: 14.6, 21.4, 32.5, 42.1, 57.6, 60.3. Data for 1,3-isomer. ^{13}C NMR: 15.5, 21.4, 34.2, 43.1, 56.3, 58.8. The aromatic carbons gave a complex series of peaks between 125 and 143 ppm. Elemental analysis was

run on the inseparable mixture after flash chromatography. Anal. Calc. for $C_{18}H_{23}NO_3S$: C, 64.84%; H, 6.95; N, 4.20. Found: C, 64.79; H, 7.00; N, 4.18.

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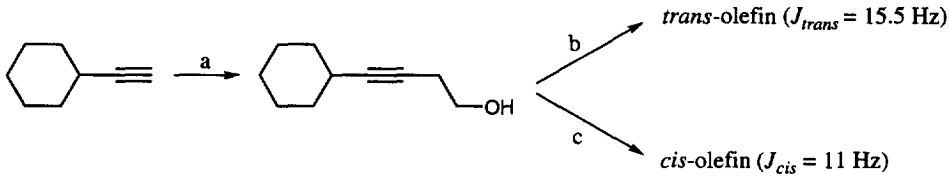
5. The precursors to the *trans* and *cis* isomers of **2b** were prepared in *ca.* 50% overall yields from commercially available cyclohexylacetylene, as shown:



(a) i) BuLi, THF; ii) Ethylene oxide, $BF_3.OEt_2$. (b) $LiAlH_4$, THF, reflux. (c) H_2, Lindlar cat., hexane

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