



## Total Synthesis of Balanol, Part 2. Completion of the Synthesis and Investigation of the Structure and Reactivity of Two Key Heterocyclic Intermediates.

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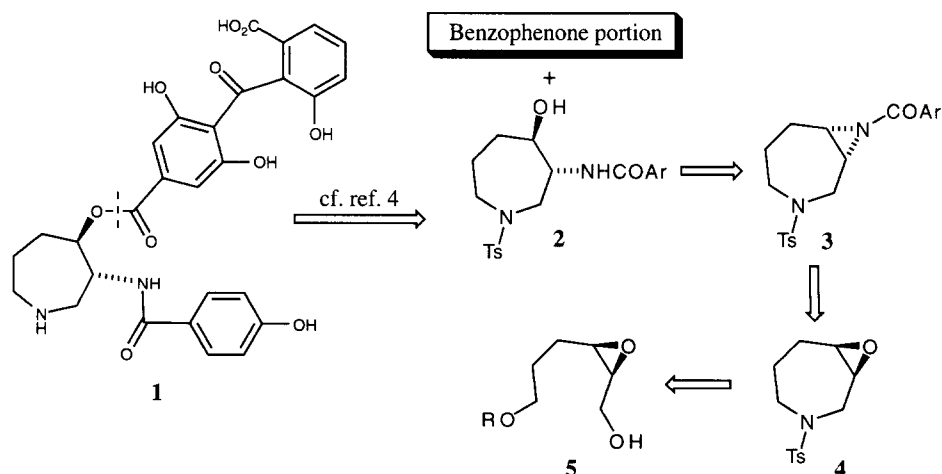
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**Abstract:** A convergent enantioselective total synthesis of the natural product (-)-balanol (**1**) is described. In addition to benzophenone fragment **8**, key intermediates are chiral bicyclic aziridine **3** and the corresponding epoxide **4**, both of which undergo highly regio- and stereoselective nucleophilic ring-opening reactions, allowing control of the two stereogenic centres of the target molecule. The structure and reactivity of **3** and **4** have been investigated in some detail.

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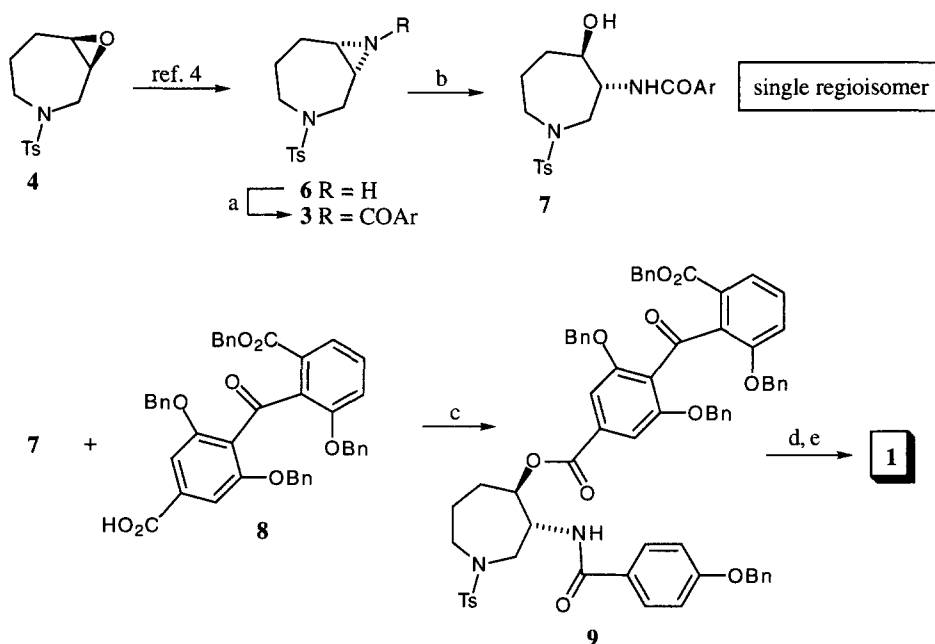
In 1993, the isolation, structure, and absolute stereochemistry of the novel natural product balanol (**1**) were reported.<sup>1</sup> The new structure and the impressive potency<sup>1</sup> of balanol in inhibition of protein kinase C soon attracted the attention of organic chemists interested in total synthesis and/or the design of analogous structures of potential therapeutic value. To date, four groups have reported the total synthesis of balanol,<sup>2</sup> and several approaches to the chiral hexahydroazepine unit<sup>3</sup> of the natural product have also been published. The latter category includes our own enantioselective route<sup>4</sup> to this key heterocyclic intermediate, which is based on the chemistry of chiral epoxides and aziridines<sup>5</sup> (Scheme 1).



Scheme 1. Retrosynthetic analysis of balanol, **1**. (Ar = *p*-BnOC<sub>6</sub>H<sub>4</sub>)

In this paper, we describe completion of the total synthesis of balanol and an investigation of the factors responsible for the remarkable regioselectivity observed in the ring-opening reactions of two key intermediates, *viz.* aziridine **3** and epoxide **4**.

*Completion of the total synthesis of balanol.* The known chiral aziridine **6**, available in excellent enantiomeric purity (>96% *e.e.*) via our published route,<sup>4</sup> was transformed into the target molecule by the short sequence shown in Scheme 2. Acylation of **6** under standard conditions gave **3** which, in line with our earlier observations,<sup>4</sup> underwent a highly stereo- and regioselective acid-catalysed ring opening reaction with water as the nucleophile. Compound **7** was obtained as a single regioisomer (selectivity >98:2 according to high-field <sup>1</sup>H NMR spectroscopy).



*Scheme 2.* Ar = *p*-BnOC<sub>6</sub>H<sub>4</sub>. (a) 4-benzyloxybenzoyl chloride, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 89%. (b) *p*-TsOH, H<sub>2</sub>O, THF, 82%. (c) 2-chloro-1-methylpyridinium iodide, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 90%. (d) Na(Hg), Na<sub>2</sub>HPO<sub>4</sub>, MeOH. (e) Pd black, HCO<sub>2</sub>H, 30% based on **9**.

The chiral hexahydroazepine was then coupled with the known<sup>6</sup> benzophenone derivative **8** by Mukaiyama esterification,<sup>7</sup> as used in the Nicolaou total synthesis of balanol.<sup>2b</sup> Fully protected balanol **9** was then taken on to the target by sequential removal of the tosyl group<sup>4</sup> and debenzoylation.<sup>2b</sup> Synthetic balanol was thus obtained in 20% overall yield, based on the readily available **6**. Aziridine **6** was itself obtained in 44% overall yield<sup>4</sup> from the simple Sharpless 2,3-epoxy alcohol **5** (Scheme 1, R = Si<sup>t</sup>BuPh<sub>2</sub>).

*Structure and reactivity of key intermediates 3 and 4.* In the course of this project we were both surprised and delighted by the remarkable regioselectivity obtained in the ring-opening reactions<sup>4</sup> of aziridine **3** and epoxide **4**, and we thus deemed it worthwhile to try to understand the factors responsible for the regiochemistry, and also to explore the scope and limitations of the ring-opening process.

Mechanistically,<sup>5</sup> there is usually little difference between nucleophilic ring-opening of epoxides and that of aziridines activated by electron-withdrawing groups on nitrogen: both processes are expected to occur with inversion of stereochemistry, and the examples presented here are no exception. Our initial studies were performed on the epoxide **4**, and a selection of results is shown in Table 1.

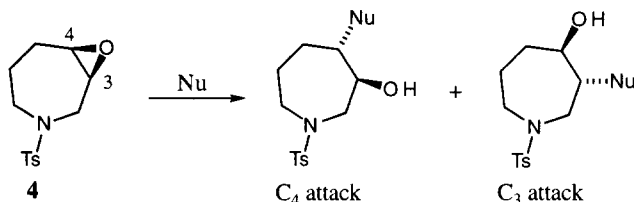


Table 1. Nucleophilic ring-opening of epoxide **4**

Entry	Nucleophile	Conditions	Time, h	Isolated yield, %	C <sub>4</sub> vs. C <sub>3</sub> attack <sup>a</sup>
1	NaN <sub>3</sub>	DMF, 90°C	48	50 <sup>b,c</sup>	97 : 3
2	LiN <sub>3</sub>	DMF, 90°C	48	89 <sup>c</sup>	97 : 3
3	Me <sub>3</sub> SiN <sub>3</sub>	DMF, 60°C	16	N.R.	
4	Me <sub>3</sub> SiN <sub>3</sub> , ZnI <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub> , reflux	16	67 <sup>b,c</sup>	97 : 3
5	KCN	DMF, 90°C	16	N.R.	
6	NaCN	DMF, 90°C	48	55 <sup>d</sup>	58 : 42
7	LiCN	DMF, 90°C	72	10 <sup>b</sup>	75 : 25
8	Me <sub>3</sub> SiCN, ZnI <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub> , reflux	0.25	92 <sup>c,e</sup>	97 : 3
9	LiMe <sub>2</sub> Cu	Et <sub>2</sub> O, -78°C to RT	3	66 <sup>c</sup>	97 : 3
10	Li <sub>2</sub> Me <sub>2</sub> CuCN	Et <sub>2</sub> O, -78°C to RT	3	76 <sup>c</sup>	97 : 3
11	AlMe <sub>3</sub>	Toluene, reflux	12	N.R.	
12	DIBAL	Toluene, reflux	12	63 <sup>c</sup>	28 : 72
13	Red-Al	THF, reflux	12	N.R.	
14	LiAlH <sub>4</sub>	Et <sub>2</sub> O, 0°C	5	88 <sup>c</sup>	94 : 6
15	Bu <sub>4</sub> NF	THF, reflux	48	35 <sup>c,d</sup>	97 : 3
16	NaSEt	THF, 60°C	24	40 <sup>c,d</sup>	97 : 3

(a) Determined by <sup>1</sup>H NMR spectroscopy on crude product. (b) Reaction incomplete. (c) Pure regioisomers obtained by flash chromatography. (d) Decomposition of starting material. (e) Product is nitrile, not isonitrile.

In all cases, the ratio of regioisomers could be measured by integration of the <sup>1</sup>H NMR spectra of the crude products before separation (flash chromatography and/or recrystallization). Assignments were made by NMR spectroscopic techniques (homonuclear decoupling, two-dimensional methods, NOE studies), a convenient starting point for each analysis being the diastereotopic protons of the C<sub>2</sub>-methylene group which gave rise to well-separated signals with characteristic coupling patterns.

The presence of the lithium cation (presumably acting as a Lewis acid) has an obvious effect on both the regioselectivity and the chemical yield (compare entries 1 and 2; entries 9, 10 and 11; entries 12, 13 and 14). Much more surprising was the difference between azide and cyanide, particularly in terms of regioselectivity (compare entries 1 and 2 with entries 6 and 7) and we have as yet no convincing explanation for this observation. The poor conversion shown in entry 7 is also unexpected (it may be noted that the same batch of LiCN in DMF (Aldrich) was later used to ring-open cyclohexene oxide in high yield under the same reaction conditions). Yet another intriguing feature is provided by entry 8: the expected

product<sup>8</sup> is the *isonitrile* but in this case the *nitrile* is formed exclusively in high yield. (These isomers can be distinguished<sup>8</sup> on the basis of their <sup>13</sup>C NMR spectra; when we used the same batches of Me<sub>3</sub>SiCN and ZnI<sub>2</sub> to ring-open cyclohexene oxide, the isonitrile was the sole product, as reported by Gassman.<sup>8</sup>) Again, it is difficult to provide a rationale for our result. Finally, as best illustrated by comparison of entries 15 and 16, we note that both hard and soft nucleophiles tend to give attack at C<sub>4</sub>, and we shall return to this point later (*vide infra*).

Bicyclic epoxide **4** is a crystalline solid, and we have determined its structure by means of X-ray crystallography. The structure in solution has been investigated by NMR spectroscopy, and the experimental results have been compared to those from theoretical studies<sup>9</sup> (molecular mechanics<sup>9a</sup> and quantum mechanics<sup>9b</sup>); theory and experiment are actually in good agreement, as discussed below. Figure 1 (left) shows the crystal structure which reveals the seven-membered ring to be in a chair conformation with a pseudoaxial tosyl group. This structure is in accord with that of one of the major conformers in solution, as determined by <sup>1</sup>H NMR spectroscopy (including COSY and NOE): the solution structure is dominated by the equilibrium shown in Fig. 1, and a long range "W" coupling is observed between H<sub>a</sub> and H<sub>b</sub>.

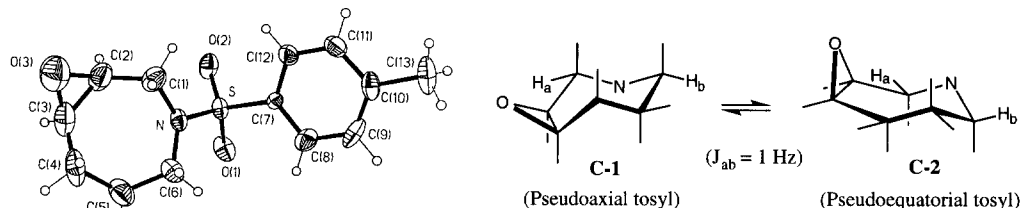


Fig. 1. Crystal structure of epoxide **4** (left) and major conformers in solution (right).

Molecular mechanics calculations also indicate that the lowest-energy conformer is a chair, with a pseudoaxial tosyl substituent (corresponding to C-1 in Fig. 1; however, C-2 is < 2 kJmol<sup>-1</sup> higher in energy.) This structure is in excellent agreement with that found in the crystal, and two representations are shown in Fig. 2.

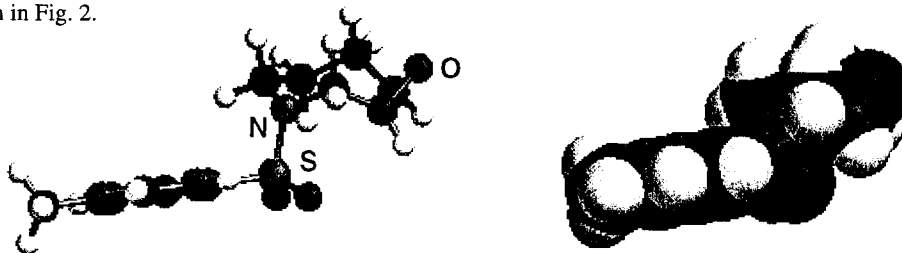


Fig. 2. Lowest-energy conformer of **4** according to molecular mechanics calculations.

In principle, the dynamic structure of **4** is characterised by two processes, *viz.* ring inversion and pyramidal inversion at nitrogen. The latter is expected to have a very low barrier (the nitrogen atom is essentially planar<sup>10</sup>) while the former was determined to be 48 kJmol<sup>-1</sup> by means of variable temperature <sup>13</sup>C NMR spectroscopy in CD<sub>2</sub>Cl<sub>2</sub> solution. A number of conformations are thus available to the molecule under the reaction conditions used for the ring-opening reactions. What, then, are the reasons for the excellent regioselectivity observed in the majority of cases listed in Table 1? MO calculations indicate that

in the LUMO of **4** the orbital coefficients<sup>9c</sup> at C<sub>3</sub> and C<sub>4</sub> are very small (the former being the larger) and that there is lower electron density at C<sub>4</sub> as compared to C<sub>3</sub>. (Fig. 3).

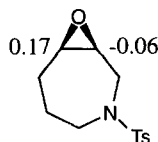
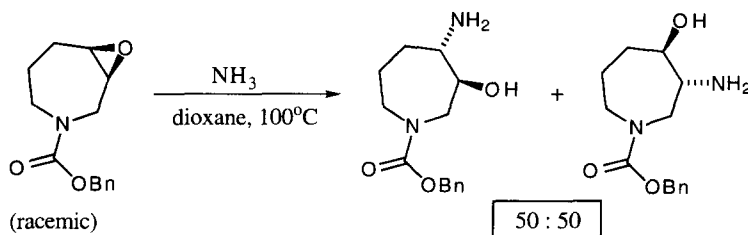


Fig. 3. Calculated charge distributions at C<sub>3</sub> and C<sub>4</sub> of epoxide **4**.

Thus, both calculation and experiment indicate that the ring-opening reactions are under charge control rather than orbital control, since both the hardest (fluoride) and the softest (thiolate) nucleophiles attack preferentially at C<sub>4</sub>. However, steric effects and the nature of the *N*-protective group are also important: in some conformers, particularly **C-1** (Fig. 1), the tosyl group efficiently blocks approach of the nucleophile to C<sub>3</sub> (see Fig. 2, right) and in this respect our results can be compared to those of König<sup>3a</sup> (Scheme 3). Inspection of models indicates that the tosyl group is effectively larger than the benzyloxycarbonyl. In addition, our calculations on König's epoxide indicate that the LUMO orbital coefficient at C<sub>3</sub> is much larger than that in **4**, implying that ring-opening (Scheme 3) may be more subject to orbital control, but as far as we are aware this has not been tested by use of soft nucleophiles.



Scheme 3. (See ref. 3a).

Conformer **C-2** (Fig. 1) is not subject to the same type of steric effects exerted by the protective group, and any ring-opening is presumably dominated by the electronic factors discussed above.

As shown in Table 2, the ring-opening reactions of aziridines of type **3** are also characterised by a preference for attack at C<sub>4</sub>. (Most of our studies have been carried out on the *p*-methoxy derivative **3'** which we had prepared earlier,<sup>4</sup> and these results will be presented here since we have observed<sup>11</sup> that the regioselectivity is not significantly dependent on the nature of the acyl group on the aziridine nitrogen.) An added complication in the aziridine case is occasional formation of the oxazoline<sup>12</sup> **10**, the stereochemistry of which was assigned by NOE studies, as indicated below.

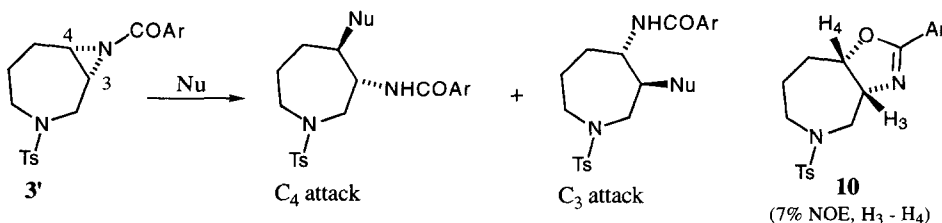


Table 2. Nucleophilic ring-opening of aziridine **3'** (Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>)

Entry	Nucleophile	Conditions	Time, h	Isolated yield, %	C <sub>4</sub> vs. C <sub>3</sub> attack <sup>a</sup>
1	NaN <sub>3</sub>	DMF, 60°C	12	48 <sup>b</sup>	98 : 2
2	LiN <sub>3</sub>	DMF, 60°C	6	82 <sup>c</sup>	98 : 2
3	NaCN	DMF, 90°C	48	d, e, f	98 : 2
4	LiCN	DMF, 90°C	48	(80% of <b>10</b> ) <sup>d</sup>	
5	NaI	DMF, 100°C	60	(80% of <b>10</b> ) <sup>g</sup>	
6	H <sub>2</sub> O	<i>p</i> -TsOH, THF, RT	12	71 <sup>f</sup>	98 : 2
7	HCO <sub>2</sub> H	neat, 0°C	0.08	76 <sup>f</sup>	98 : 2
8	CH <sub>3</sub> CO <sub>2</sub> H	neat, RT	5	84 <sup>f</sup>	98 : 2

(a) Determined by <sup>1</sup>H NMR spectroscopy on crude product. (b) Plus **10** (40%). (c) Pure major regioisomer obtained by recrystallization. (d) Reaction incomplete. (e) Ca. 30% conversion, major product is **10**. (f) Pure regioisomers obtained by flash chromatography. (g) Decomposition of starting material.

Measurement of regioisomeric ratios and the assignment of regiochemistry were performed in the same manner as for the products shown in Table 1. In line with previous experience,<sup>5</sup> the ring-opening reactions of the activated aziridine tended to be faster than those of the epoxide (compare, *e.g.*, entry 2 of Table 2 with that of Table 1). With azide as nucleophile, the regioselectivities are very similar for both types of heterocycle (compare entries 1 and 2 in Table 2 with entries 1 and 2 of Table 1). Once again, however, cyanide is an exception (compare entries 3 and 4 of Table 2 with entries 6 and 7 of Table 1) and a reasonable explanation for this is still lacking. The reactions of carboxylic acids (Table 2, entries 7 and 8) were of particular interest, since it was initially planned to maximise convergence in the balanol total synthesis by the use of carboxylic acid **8** to ring-open aziridine **3**; however, this was unsuccessful.

There are thus obvious similarities between the reactivity of the aziridine and that of the epoxide. However, according to our molecular mechanics calculations, the structure of aziridines such as **3'** differs from that of **4** in that the lowest-energy conformer is the twist-boat shown in Fig. 4. This is borne out by <sup>1</sup>H NMR experiments: the long-range W-coupling between pseudoequatorial protons on C<sub>2</sub> and C<sub>7</sub> observed for epoxide **4** is absent from the spectra of **3**, **3'**, and other related aziridines.<sup>11</sup> It may also be noted that the substituent on the aziridine nitrogen adopts the expected *exo* position with respect to the seven-membered ring.

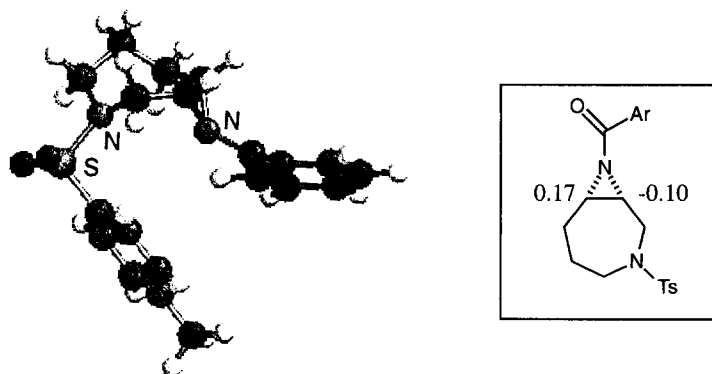


Fig. 4. Lowest-energy conformer of aziridines such as **3** and **3'** (according to molecular mechanics) and calculated charge distributions at C<sub>3</sub> and C<sub>4</sub> (right).

We have not yet obtained crystal structures for any of our fused bicyclic aziridines, nor have we performed DNMR studies, but we presume that the various dynamic processes involving the seven-membered ring are rapid on the NMR time-scale. Therefore, as for the epoxide, a number of conformations can be involved in the ring-opening process. It is nevertheless interesting to note that in the major conformers of the aziridines the C<sub>3</sub>-position will not enjoy the type of steric shielding provided by the *N*-tosyl group in the case of epoxide **4**; for the aziridines, electronic effects (charge control)<sup>13</sup> may well be the dominant factor in determining regioselectivity, as indicated by the charge distributions shown above (Fig. 4, right).

In conclusion, we have developed a convergent, enantioselective and reasonably concise total synthesis of the interesting natural product balanol, key intermediates being the chiral epoxide **4** and the aziridine **3**. Furthermore, the results collected in Tables 1 and 2 (including the oxazoline formation shown in the latter) should provide convenient entry to a number of regio- and stereoisomeric balanol analogues suitable for biological testing. This will be the subject of a separate report.

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## EXPERIMENTAL

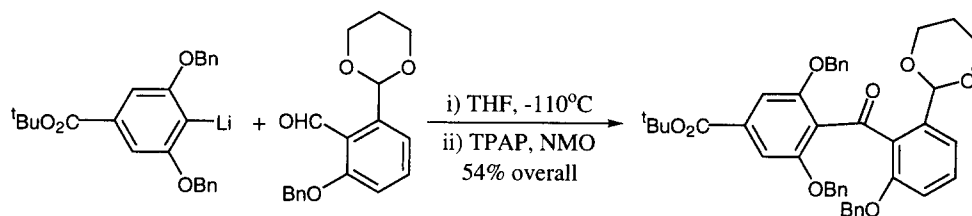
*General remarks.* <sup>1</sup>H (300 or 400 MHz) and <sup>13</sup>C (75 or 100 MHz) NMR spectra were recorded on a Varian XL 300 or a Varian Unity 400 spectrometer (CDCl<sub>3</sub>/TMS). IR spectra were obtained on a Perkin-Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks are listed. Specific rotation values were measured at 25°C on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed at the Analytical Department of the Research Institute for Pharmacy and Biochemistry, Prague, Czech Republic. Ether and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone. Dichloromethane, toluene and triethylamine were dried over calcium hydride and distilled under nitrogen. Dimethylformamide (DMF) was distilled at reduced pressure from calcium hydride. Methanol was distilled under nitrogen from magnesium turnings. Silica gel for flash chromatography was purchased from Grace-Amicon.

**Aziridine 3.** Triethylamine (0.68 mL, 5.2 mmol) and 4-benzyloxybenzoyl chloride (0.90 g, 3.9 mmol) were dissolved with stirring under nitrogen in dry dichloromethane (40 mL) and cooled to 0°C before addition of a solution of **6**<sup>4</sup> (0.70 g, 2.61 mmol) in dry dichloromethane (5 mL). The resultant solution was stirred overnight, water (20 mL) was added and the separated aqueous phase was extracted twice with dichloromethane. The combined organics were washed with brine (5 mL) and dried over MgSO<sub>4</sub> before removal of the solvent to give a residue which was flash chromatographed (gradient: ether to ethyl acetate). There was obtained 1.1 g (89%) of the product as a colorless solid, m.p. 149–151°C. [ $\alpha$ ]<sub>D</sub> +157.8 (c 1.1, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR:  $\delta$  7.92–7.88 (m, 2H), 7.71–7.67 (m, 2H), 7.45–7.32 (m, 3H), 7.28–7.24 (m, 4H),

7.02-6.98 (m, 2H), 5.13 (s, 2H), 3.91 (dd,  $J=11$ , 4 Hz, 1H), 3.47 (ddd,  $J=15$ , 7, 5, 1H), 3.38-3.30 (m, 1H), 3.22-3.14 (m, 1H), 2.90-2.84 (m, 1H), 2.72-2.67 (m, 1H), 2.35 (s, 3H), 2.32-2.14 (m, 1H), 2.00-1.90 (m, 1H), 1.82-1.72 (m, 2H).  $^{13}\text{C}$  NMR:  $\delta$  178.4, 162.5, 143.3, 135.8, 136.3, 131.2, 129.7, 128.7, 128.1, 127.4, 127.1, 125.7, 114.6, 70.1, 51.6, 48.8, 40.5, 40.1, 28.2, 25.7, 21.4. IR (CDCl<sub>3</sub>): 1671, 1604 cm<sup>-1</sup>. Anal. Calc. for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S: C, 68.04%; H, 5.92; N, 5.88. Found: C, 68.00; H, 5.89; N, 5.78.

**Amido alcohol 7.** Aziridine **3** (0.020 g, 42.0  $\mu\text{mol}$ ) was dissolved with stirring in a mixture of THF (1 mL) and water (0.8 mL). *p*-Toluenesulfonic acid (0.010 g) was added and the resultant mixture stirred for 6 h at ambient temperature. The THF was removed on the rotary evaporator and to the residue was added saturated aqueous NaHCO<sub>3</sub> solution (2 mL). Extraction with dichloromethane (3 x 5 mL), drying the combined organics over MgSO<sub>4</sub>, and solvent removal left a residue which was purified by flash chromatography (hexane/EtOAc). There was obtained 0.017 g (82%) of the desired product.  $[\alpha]_{\text{D}}^{+11.76}$  (*c* 0.19, CH<sub>2</sub>Cl<sub>2</sub>).  $^1\text{H}$  NMR: 8.00 (d,  $J=5$ , -NH), 7.93-7.89 (m, 2H), 7.70-7.67 (m, 9H), 7.05-7.01 (m, 2H), 5.13 (s, 2H), 4.74 (s, -OH), 4.04-3.98 (m, 2H), 3.94 (bd,  $J=12$ , 1H), 3.71 (d,  $J=15$ , 1H), 3.16 (dd,  $J=15$ , 3, 1H), 2.66-2.57 (m, 1H), 2.44 (s, 3H), 2.02-1.77 (m, 4H).  $^{13}\text{C}$  NMR: 168.2, 161.7, 144.0, 136.4, 135.0, 130.0, 129.2, 128.6, 128.1, 127.4, 127.0, 125.8, 114.8, 78.0, 70.1, 58.3, 51.6, 50.4, 31.6, 26.4, 21.5. IR (CDCl<sub>3</sub>): 3400-3200 (b), 1612, 1511. Anal. Calc. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>S: C, 65.56%; H, 6.11; N, 5.66. Found: C, 65.27; H, 6.08; N, 5.57.

**Benzophenone 8.** This was prepared according to the literature,<sup>6</sup> with the modifications shown below (coupling performed at -110°C instead of -78°C, and TPAP oxidation<sup>14</sup> instead of MnO<sub>2</sub>).



**Fully protected balanol 9.** The amido alcohol from above (0.012 g, 24.3  $\mu\text{mol}$ ) was dissolved in dry dichloromethane (2 mL) and added under nitrogen to a stirred solution of carboxylic acid **8** (0.013 g, 24.3  $\mu\text{mol}$ ) and 2-chloro-1-methylpyridinium iodide (0.007 g, 27  $\mu\text{mol}$ ) in dry dichloromethane (5 mL). triethylamine (4  $\mu\text{L}$ , 30  $\mu\text{mol}$ ) was added and the mixture was stirred for 0.5 h before addition of DMAP (0.0009 g). Stirring was continued for 3 h then the solvent was removed and the residue subjected to flash chromatography (gradient hexane/EtOAc, 75/25 to 50/50) to yield the desired product (0.0243 g, 90%) as a colorless oil.  $[\alpha]_{\text{D}}^{+8.23}$  (*c* 0.51, CH<sub>2</sub>Cl<sub>2</sub>).  $^1\text{H}$  NMR (mixture of amide rotamers): 7.89-7.84 (m, 2H), 7.75-7.69 (m, 2H), 7.43-6.96 (m, 30H), 6.92-6.89 (m, 2H), 6.85-6.80 (m, 2H), 5.38-5.31 (m, 1H), 5.13 (s, 2H), 5.07 (s, 2H), 4.79 (s, 4H), 4.72 (s, 2H), 4.58-4.50 (m, 1H), 3.96-3.51 (m, 1H), 3.77-3.71 (m, 1H), 3.70 (d,  $J=15$ , 1H), 3.15 (dd,  $J=15$ , 3, 1H), 2.79-2.69 (m, 1H), 2.42 (s, 3H), 2.19-1.95 (m, 4H). (The  $^{13}\text{C}$  NMR spectrum was complex due to the presence of rotamers; at least 52 signals could be observed). IR (CH<sub>2</sub>Cl<sub>2</sub>): 3685, 1732, 1660, 1605.



(-)-**Balanol 1**. (i) *Detosylation*. The fully protected balanol derivative from above (0.015 g, 12.9  $\mu$ mol) was dissolved with stirring in methanol (2.5 mL),  $\text{Na}_2\text{HPO}_4$  (0.015 g) was added followed by freshly prepared 6% sodium amalgam (0.040 g) and the mixture heated at reflux for 6 h. The reaction mixture was cooled, the supernatant transferred to a fresh flask *via* pipette, and the solvent removed to yield a residue which was used directly in the next step. (ii) *Debenzylation* and final purification were carried out according to Nicolaou.<sup>2b</sup> There was obtained 0.0021 g (30% based on **9**) of synthetic balanol as a yellow solid. This material was spectroscopically, chiroptically and chromatographically identical to authentic samples kindly provided by Prof. Nicolaou and Dr. Lampe.

*Ring-opening reactions of 4 and 3'*. The reaction of **4** with  $\text{LiN}_3$  and the reaction of **3'** with  $p\text{-TsOH}/\text{H}_2\text{O}$  have been described earlier and the products fully characterised.<sup>4</sup> However, not all of the ring-opened products listed in Tables 1 and 2 have been fully characterised; selected procedures and data for some of the more significant products are collected below.

*Product from reaction of 4 with  $\text{Me}_3\text{SiCN}$  and  $\text{ZnI}_2$* .  $\text{ZnI}_2$  (0.0036 g, 1.12  $\mu$ mol) was dissolved with stirring under nitrogen in dry dichloromethane (1 mL),  $\text{Me}_3\text{SiCN}$  (0.41 mL, 0.03 mmol) was added and the resultant solution stirred for 5 min before addition of a solution of the epoxide (0.020 g, 76  $\mu$ mol) in dry dichloromethane (1 mL). The reaction mixture was heated under reflux for 15 min, cooled, and poured into ice-water. The separated aqueous phase was extracted with dichloromethane (3 x 2 mL) and the combined organics were dried over  $\text{MgSO}_4$ . Removal of the solvent gave a residue which was purified by flash chromatography (pentane/ether, 40/60) to yield the pure major regioisomer (0.025 g, 92%) as an oil.  $[\alpha]_D^{25} +0.69$  (*c* 1.13,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR: 7.65 and 7.31 (AA'BB',  $J_{AB}=8$ , 4H), 4.06 (ddd,  $J=11$ , 9, 3, 1H), 3.90 (ddd,  $J=11$ , 9, 4, 1H), 3.59-3.50 (m, 2H), 2.96-2.89 (m, 1H), 2.78 (dd,  $J=15$ , 9, 1H), 2.46-2.38 (m, 1H), 2.42 (s, 3H), 2.23-2.13 (m, 1H), 1.93-1.85 (m, 1H), 1.59-1.50 (m, 1H).  $^{13}\text{C}$  NMR: 143.3, 135.8, 129.7, 126.9, 122.6, 78.6, 49.7, 46.4, 39.7, 33.5, 27.5, 21.5. (The absence of  $^{13}\text{C}$ - $^{14}\text{N}$  coupling<sup>8</sup> confirms the structure as the nitrile, rather than the isonitrile). IR: 3155, 3032, 2253.

*Product from reaction of 4 with tetrabutylammonium fluoride*. (Experiment carried out on racemic material.) Major regioisomer:  $^1\text{H}$  NMR: 7.68 and 7.33 (AA'BB',  $J_{AB}=8$ , 4H), 4.65-4.50 (m,  $J_{\text{HF}}=46$ , 1H), 3.93-3.86 (m, 1H), 3.54-3.46 (m, 1H), 3.42-3.35 (dd,  $J=15$ , 5, 1H), 3.29-3.23 (dt,  $J=15$ , 2, 1H), 3.08-3.02 (m, 1H), 2.96 (d,  $J=5$ , -OH), 2.44 (s, 3H), 2.11-1.87 (m, 3H), 1.79-1.64 (m, 1H).

*Product from reaction of 4 with the sodium salt of ethanethiol*. (Experiment carried out on racemic material.) Major regioisomer:  $^1\text{H}$  NMR: 7.68 and 7.31 (AA'BB',  $J_{AB}=8$ , 4H), 3.71-3.65 (m, 1H), 3.51-3.46 (dd,  $J=15$ , 3, 1H), 3.41-3.34 (m, 1H), 3.26-3.10 (m, 2H), 2.71-2.66 (m, 1H), 2.62-2.53 (m, -SCH<sub>2</sub>-), 2.43 (s, 3H), 2.20-2.12 (m, 1H), 1.97-1.88 (m, 1H), 1.84-1.66 (m, 2H), 1.26 (t,  $J=7.5$ , 3H).  $^{13}\text{C}$  NMR: 143.5, 135.6, 129.8, 127.1, 72.3, 52.3, 49.6, 47.8, 27.9, 25.2, 24.4, 21.5, 15.0.

*X-ray crystallographic analysis of 4*. Single crystals of **4** ( $\text{C}_{13}\text{H}_{17}\text{NO}_3\text{S}$ ,  $M_w=267.34$ ) were grown from toluene/pentane in the refrigerator. Crystal data: orthorhombic (*Pbca*, No. 61),  $a=11.132(2)$ ,  $b=18.348(3)$ ,  $c=12.591(2)$  Å,  $V_c=2571.7(7)$  Å<sup>3</sup>,  $Z=8$ ,  $D_c=1.381$  Mg m<sup>-3</sup>,  $\mu=0.252$  mm<sup>-1</sup>,  $F(000)=1136$ . Crystal dimensions: 0.41x0.36x0.42 mm.

Intensity data were collected at 153(2) K using a STOE/AED2 diffractometer, MoK $\alpha$  radiation ( $\lambda=0.71073$  Å,  $\theta_{\max}=25^\circ$ ) and  $\omega$ -2 $\theta$  scan technique. The intensities of 2253 unique reflections ( $0\leq h\leq 13$ ,  $0\leq k\leq 21$ ,  $0\leq l\leq 14$ ) were measured and corrected for background, Lorentz and polarization effects. The five standard reflections, measured repeatedly at 90-minute intervals, indicated that the crystal was stable during the data collection (intensity instability <2%). In the refinement of the unit cell dimensions the  $\theta$  values of 38 well centred reflections with  $17.5<2\theta<36.5^\circ$  were used.

The structure was solved by direct methods (SHELXS)<sup>15</sup> and refined by full matrix least-squares treatment based upon  $F^2$  (SHELXL-93).<sup>16</sup> The hydrogens were assumed to be in idealized positions, calculated using geometric evidence, taking into account the effects of both the chemical environment and the temperature.<sup>16</sup> The C, N, O and S atoms were treated anisotropically, whereas isotropic displacement parameters were refined for the H atoms. The flexible bicyclic system is disordered in the crystal, as indicated by the atomic displacement parameters of the ring atoms as well as by spurious electron density peaks detected in the vicinity of the epoxide ring (final  $\Delta\rho_{\max}=1.12$  and  $\Delta\rho_{\min}=-0.489$  eÅ<sup>-3</sup>). The disorder, however, could not be modelled in a chemically reasonable way. Thus, refinement of 184 variables converged to  $R=0.0834$  [for 1530  $F$  with  $F_o>4\sigma(F_o)$ ], and  $wR=0.2518$  (for 2540  $F^2$  with goodness-of-fit [ $S$ ]=1.088). The weights of the structure factors were assumed to be  $w=1/[\sigma^2(F_o^2)+(0.11P^2)+12.6P]$  where  $P=(F_o^2+2F_c^2)/3$ .<sup>15</sup> The geometric features were calculated using the PARST program.<sup>17</sup>

*Product from reaction of 3' with lithium azide.* The aziridine (0.190 g, 0.48 mmol) was dissolved with stirring under nitrogen in dry DMF (12 mL) and lithium azide (0.116 g, 2.38 mmol) was added. The mixture was stirred at 60°C for 6 h and the solvent was evaporated at reduced pressure. The residue was partitioned between dichloromethane (20 mL) and water (10 mL) by stirring for 10 min, then the separated aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organics were washed with brine, dried over MgSO<sub>4</sub> and the solvent was removed to give a residue which was purified by flash chromatography (pentane/EtOAc, 60/40). The major regioisomer (0.172 g, 82%) was further purified by recrystallization from benzene/pentane, to give 0.160 g of product, m.p. 177–179°C.  $[\alpha]_D^{+102.5}$  ( $c$  0.6, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR: 7.92 and 6.95 (AA'BB',  $J_{AB}=8.5$ , 4H), 7.68 and 7.33 (AA'BB',  $J_{AB}=8$ , 4H), 7.48 (d,  $J=7$ , N-H), 4.19 (m, 2H), 3.84 (s, 3H), 3.79 (m, 1H), 3.62 (dd,  $J=15$ , 3.5, 1H), 3.07 (dd,  $J=15$ , 2, 1H), 2.87 (m, 1H), 2.43 (s, 3H), 2.00–1.82 (m, 4H). <sup>13</sup>C NMR: 166.5, 162.3, 144.1, 134.4, 130.0, 129.0, 127.1, 126.0, 113.8, 61.8, 55.3, 52.0, 48.6, 47.0, 25.1, 21.5, 21.2. IR: 3290, 2090, 1630, 1607, 1530, 1505. Anal. Calc. for C<sub>21</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub>S: C, 56.87%; H, 5.68; N, 15.79. Found: C, 56.72; H, 5.61; N, 15.58.

*Oxazoline 10.* Aziridine 3' (0.020 g, 0.050 mmol) was dissolved with stirring under nitrogen in dry DMF (5 mL) and NaI (0.037 g, 0.25 mmol) was added. The reaction mixture was stirred at 100°C for 60 h, cooled, and poured into a mixture of ice-water and pentane/ether. The separated aqueous phase was extracted with pentane/ether (3 x 4 mL) and the combined organics were dried over MgSO<sub>4</sub>. The solvents were removed and the crude product was purified by recrystallization (ethyl acetate/hexane) to yield the oxazoline (0.016 g, 80%).  $[\alpha]_D^{-36.7}$  ( $c$  0.98, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR: 7.84 and 7.27 (AA'BB',  $J_{AB}=9$ , 4H), 7.69 and 6.89 (AA'BB',  $J_{AB}=8$ , 4H), 4.86 (ddd,  $J=9$ , 8, 4, 1H; H-3), 4.67 (ddd,  $J=9$ , 8, 4, 1H; H-2), 4.03 (bdd,  $J=14$ , 4, 1H), 3.88–3.82 (m, 1H), 3.84 (s, 3H), 2.74 (m, 1H), 2.63 (m, 1H), 2.41 (s, 3H), 2.19–2.11 (m, 1H), 1.98–1.57 (m, 3H). <sup>13</sup>C NMR: 156.9, 144.9, 144.0, 139.7, 136.8, 129.9, 128.7, 128.6, 127.1, 108.1, 96.2,

54.8, 51.7, 48.3, 25.6, 23.0, 21.5. IR (CCl<sub>4</sub>): 1731. Anal. Calc. for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S: C, 62.98%; H, 6.04; N, 6.99. Found: C, 62.76; H, 5.89; N, 6.83.

*Products from reaction of 3' with carboxylic acids. (a) Reaction with HCO<sub>2</sub>H.* Aziridine **3'** (0.251 g, 0.627 mmol) was dissolved with stirring in cold (0°C) formic acid (3 mL) and the reaction was monitored by TLC (ether). After 5 min, no starting material could be detected, and the formic acid was evaporated at reduced pressure. The residue was purified by flash chromatography (ether) to yield the pure major regioisomer as a colorless solid, m.p. 173-175°C. [ $\alpha$ ]<sub>D</sub> +119 (c 0.9, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR: 8.08 (s, 1H), 7.90 and 6.95 (AA'BB', J<sub>AB</sub>=8.5, 4H), 7.68 and 7.33 (AA'BB', J<sub>AB</sub>=8.3, 4H), 7.34 (d, J=8, -NH), 5.34 (bs, 1H), 4.30 (bs, 1H), 3.87 (m, 1H), 3.85 (s, 3H), 3.68 (dd, J=15, 2, 1H), 3.15 (dd, J=15, 2.5, 1H), 2.83 (td, J=12, 6, 1H), 2.43 (s, 3H), 2.14-1.80 (m, 4H). <sup>13</sup>C NMR: 166.4, 162.3, 160.0, 144.0, 134.6, 129.9, 129.1, 127.1, 126.1, 113.8, 73.9, 55.4, 52.1, 49.4, 48.3, 26.4, 22.1, 21.5. IR: 3310, 2934, 1720, 1637, 1607, 1534, 1506. Anal. Calc. for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>S: C, 59.17%; H, 5.87; N, 6.27. Found: C, 59.02; H, 5.69; N, 6.14.

*(b) Reaction with CH<sub>3</sub>CO<sub>2</sub>H.* The aziridine (0.225 g, 0.56 mmol) was dissolved with stirring in acetic acid (5 mL) and stirring was continued at ambient temperature for 5 h, at which point TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated at reduced pressure and the residue was purified by flash chromatography (ether) to give the pure major regioisomer as a colorless solid, m.p. 216-217°C. [ $\alpha$ ]<sub>D</sub> +109.4 (c 0.64, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR: 7.88 and 6.95 (AA'BB', J<sub>AB</sub>=8, 4H), 7.67 and 7.31 (AA'BB', J<sub>AB</sub>=8, 4H), 7.22 (d, J=7.5, -NH), 5.19 (ddd, J=6, 4, 2, 1H), 4.30 (b"s", 1H), 3.89 (m, 1H), 3.85 (s, 3H), 3.66 (dd, J=15, 3, 1H), 3.15 (dd, J=15, 3, 1H), 2.82 (td, J=12, 6, 1H), 2.43 (s, 3H), 2.02 (s, 3H), 2.08-1.78 (m, 4H). <sup>13</sup>C NMR: 169.8, 166.4, 162.2, 143.9, 129.9, 129.0, 127.0, 126.3, 113.7, 74.0, 55.3, 52.2, 49.5, 48.6, 26.6, 22.5, 21.5, 21.1. IR: 3321, 2934, 1734, 1637, 1607, 1534, 1506. Anal. Calc. for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub>S: C, 59.98%; H, 6.13; N, 6.08. Found: C, 59.85; H, 5.98; N, 6.01.

## REFERENCES AND NOTES

1. Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452.
2. (a) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147; Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572. (b) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402; Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem. Eur. J.* **1995**, *1*, 454. (c) Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2355. (d) Barbier, P.; Stadlwieser, J. *Chimia* **1996**, *50*, 530.
3. (a) Müller, A.; Takyar, D. K.; Witt, S.; König, W. A. *Liebigs Ann. Chem.* **1993**, 651. (b) Hughes, P. F.; Smith, S. H.; Olson, J. T. *J. Org. Chem.* **1994**, *59*, 5802. (c) Hu, H.; Jagdmann Jr., G. E.; Hughes, P. F.; Nichols, J. B. *Tetrahedron Lett.* **1995**, *36*, 3659. (d) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Synlett* **1996**, 29. (e) Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624. (f) Tuch, A.; Sanière, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron: Asymmetry* **1996**, *7*, 2901.

4. Tanner, D.; Almario, A.; Högberg, T. *Tetrahedron* **1995**, *51*, 6061.
5. Reviews: (a) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; *Angew. Chem.* **1994**, *106*, 625. (b) Tanner, D. *Pure Appl. Chem.* **1993**, *65*, 1319. (c) For some very recent interesting examples, see: Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M. *Tetrahedron* **1997**, *53*, 1417.
6. Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994**, *59*, 6703.
7. Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707; *Angew. Chem.* **1979**, *91*, 798.
8. Gassman, P. G.; Guggenheim, T. L. *J. Am. Chem. Soc.* **1982**, *104*, 5849; Gassman, P. G.; Gremban, R. S. *Tetrahedron Lett.* **1984**, *25*, 3259.
9. (a) Molecular mechanics calculations: Amber\* (Macromodel version 4.5: Mohamadi, F.; Rickards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Change, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 44. (b) MO calculations: PM3 (Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209; Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 221; Spartan version 4.0: Wavefunction, Inc., 18401 Von Karman Avenue, Suite 370, Irvine, California 92715, USA). (c) In the LUMO of **4**, the largest orbital coefficients are located on the *N*-tosyl moiety, the next largest at C<sub>2</sub> and C<sub>6</sub>.
10. See, however: Hoppe, I.; Hoppe, D.; Wolff, C.; Egert, E.; Herbst, R. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 67; *Angew. Chem.* **1989**, *101*, 65, for an example of pyramidal nitrogen in a tosyl amide.
11. Tanner, D.; Tedenborg, L. *Unpublished results*.
12. Related examples: (a) Heine, H. W.; Fetter, M. E.; Nicholson, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 2202. (b) McManus, S. P.; Hearn, R. A.; Pittman, C. U. *J. Org. Chem.* **1976**, *41*, 1895. (c) Bates, G. S.; Varelas, M. A. *Can. J. Chem.* **1980**, *58*, 2562. (d) Dumić, M.; Filic, D.; Vinković, M.; Jamnický, B.; Kamenar, B. *Tetrahedron Lett.* **1993**, *34*, 3639. (e) Umezawa, J.; Takahashi, O.; Furuhashi, K.; Nohira, H. *Tetrahedron: Asymmetry* **1994**, *5*, 491. (f) Sepúlveda-Arques, J.; Armero-Alarte, T.; Acero-Alarcon, A.; Zaballo-Garcia, E.; Solesio, B. Y.; Carrera, J. E. *Tetrahedron* **1996**, *52*, 2097.
13. For a recent theoretical and experimental study of charge vs. orbital control in the nucleophilic ring-opening of *N*-acyl and *N*-Cbz aziridines, see: Dauban, P.; Dubois, L.; Tran Huu Dau, M. E.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035.
14. Review: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
15. Sheldrick, G. M.; *Acta Crystallogr.* **1990**, *A46*, 467.
16. Sheldrick, G. M. *SHELXL-93*: Program for the Refinement of Crystal Structures. Univ. of Göttingen, Germany (1993).
17. Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.

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