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On the Use of C_2-Symmetric Aziridines as Chiral Auxiliaries

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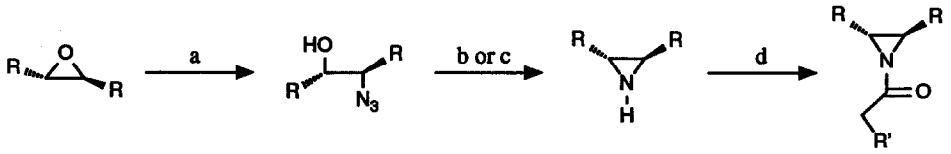
Abstract: A systematic study has been made of the utility of readily available C_2-symmetric aziridines as auxiliaries for asymmetric alkylation and aldol reactions of amide enolates. Aziridines with suitably placed oxygen atoms in the side chains proved to be useful for alkylation reactions (d.e. values up to >98%) and the results are explained in terms of an intramolecularly chelated Z-enolate species, which could be observed directly by means of NMR spectroscopy. In contrast, aziridine auxiliaries lacking side-chain oxygens performed better in aldol reactions (syn selectivity up to 98% d.e.) for which a Zimmerman-Traxler transition state is proposed. After reaction, the auxiliaries can be cleaved off non-destructively under mild conditions to afford either optically pure aldehydes or carboxylic acids.

Introduction

In an earlier communication[1] we presented some promising preliminary results regarding the use of C_2-symmetric aziridines as chiral auxiliaries for asymmetric alkylations and aldol reactions. In this paper we describe in detail the synthesis of enantiomerically pure C_2-symmetric aziridines and report the results of a systematic study of the factors responsible for the asymmetric induction observed in the reactions of the corresponding amide enolates.

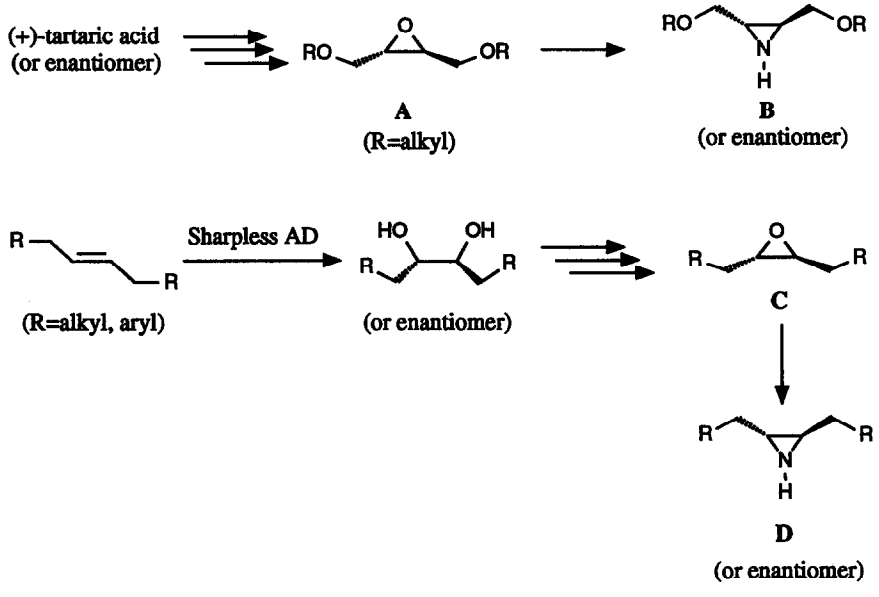
Aziridine synthesis

Our chosen route (Scheme 1) relies on the availability, in enantiomerically pure form, of the relevant epoxides and the stereospecific conversion[2] of these to aziridines. The epoxides were first ring-opened by the azide anion and the resultant azido alcohols were ring-closed either directly (PPh_3) or via the corresponding mesylates ($LiAlH_4$). Overall, the epoxide-to-aziridine transformation occurs with clean inversion at both carbons of the original epoxide and with no loss of enantiomeric purity. Standard acylation then provides the desired amides in good to excellent overall yields.



Scheme 1. (a) NaN_3; (b) PPh_3; (c) (i) MsCl (ii) $LiAlH_4$; (d) $R'CH_2COCl$ or $(R'CH_2CO)_2O$

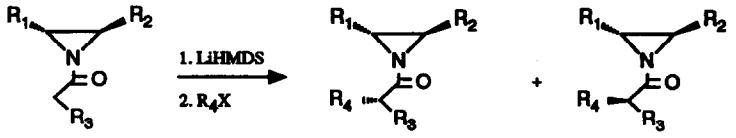
As shown schematically below, the requisite epoxides are easily available in both enantiomeric forms (Scheme 2). The enantiomers of tartaric acid can be converted to epoxides of type **A** by the method of Nicolaou[3], thus providing aziridines **B** with ethereal side-chains. Alternatively, the products of Sharpless asymmetric dihydroxylation[4] (AD) of symmetrical *trans* olefins were used[5] to prepare epoxides **C** which were transformed to aziridines **D** lacking oxygens in the side-chains.



Scheme 2. *Routes to enantiomerically pure epoxides and aziridines.*

Diastereoselective alkylation

The alkylation reactions (Eq. 1 and Table 1) were carried out by formation of the enolate at -78°C in THF solution, using lithium hexamethyldisilazide (LiHMDS) as base, followed by addition of the electrophile. Use of lithium diisopropylamide (LDA) as base gave poorer and less reproducible results: both chemical yields and diastereoselectivities were lower.



(1)

Aziridine substrate

1. R_1=R_2=CH_2OBn, R_3=CH_3
2. R_1=R_2=CH_2OCH_3, R_3=CH_3
3. R_1=R_2=^nBu, R_3=CH_3
4. R_1=R_2=Ph, R_3=CH_3
5. R_1=R_2=CH_2Ph, R_3=CH_3
6. R_1=R_2=Ph, R_3=CH_2OBn
7. R_1=R_2= R_3=CH_2OBn

Table 1. Electrophilic alkylation of aziridine amides.

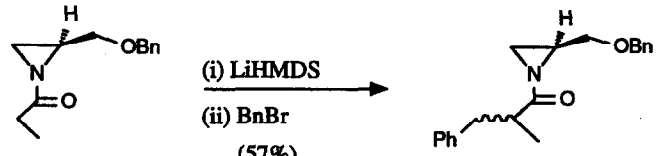
Entry	Aziridine	R_4X	Ratio	Abs. config.	Isolated yield[a]
1	**1**	BnBr	>99:1	(*R*)	88%
2	**2**	BnBr	>99:1	(*R*)	63%
3	**3**	BnBr	80:20		74%
4	**4**	BnBr	55:45		59%
5	**5**	BnBr	80:20		70%
6	**6**	MeI	91:9		65%
7	**7**	MeI	60:40		65%

a. After flash chromatography. No attempts to optimize the yields have been made. Unreacted starting material gives mass balance.

For entries 1,2, and 7 in Table 1, enantiomerically pure aziridines prepared from (+)-tartaric acid were used, while racemic materials were used for entries 3-6. This was done because the aziridines **3-6** with non-oxygenated side-chains were *not* expected to give as good diastereoselectivity (*vide infra*) - an expectation which was borne out in practice; preparation of the racemic aziridines **3-6** (via the products of mCPBA epoxidation) was a rapid and very simple matter, and the diastereoselectivity of the amide alkylation reaction could easily be screened by means of NMR spectroscopy. Had any of compounds **3-6** given good levels of diastereoselectivity, the appropriate enantiomerically pure auxiliaries could have been produced according to Scheme 2 (*cf.* the discussion of the aldol reactions below).

In contrast to substrates **3-6**, the aziridines **1** and **2** gave excellent results in alkylation with benzyl bromide (Table 1, entries 1 and 2) with a single diastereoisomer being detected in the crude product mixture by means of high-field ^1H NMR spectroscopy. For determination of the absolute stereochemistry at the new stereogenic centre, the possible diastereomeric products were prepared independently from the amines and the appropriate enantiomerically pure acid chlorides[6]; these amides were readily distinguished by NMR spectroscopy, and allowed assignment of the *(R)* stereochemistry for both alkylations.

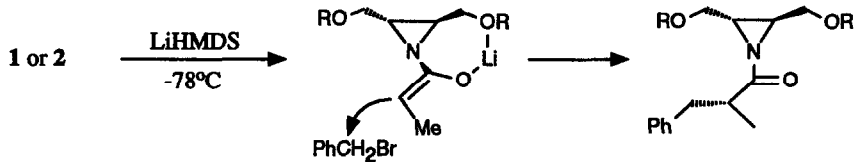
That the C_2-symmetry of the oxygenated auxiliaries is indeed important was shown by the result shown in Eq. 2., optically pure **8** being prepared from commercially available *(S)*-glycidol.



8

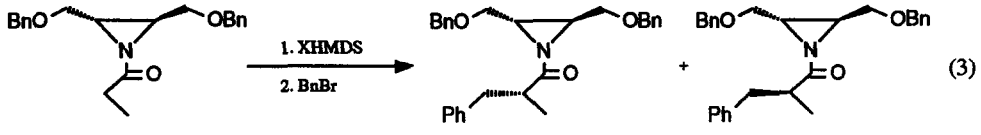
Diastereomeric ratio: 75:25 (2)

The alkylation of the C_2-symmetric aziridine amides shown above is thus highly dependent on the presence of side-chain oxygens (Table 1: compare entries 1 and 2 with 3-6) but seems to be independent of the size of the ethereal group (benzyl *vs.* methyl, entries 1 and 2). These results can be explained (Scheme 3) on the basis of an internally chelated lithium enolate[7], the possibility of which had guided the design of these auxiliaries.



Scheme 3. *A chelated Z-enolate is alkylated on the less hindered α-face.*

The reaction conditions used were expected[8] to lead to formation of the Z-enolate, the nitrogen of which is presumably pyramidalized[9]. Due to the C_2-symmetry of the substrate it is immaterial on which face of the aziridine ring the chelate is formed, and alkylation on the less-hindered enolate diastereoface would produce the absolute configuration actually observed. The chelate hypothesis is further supported by the results shown in Eq. 3 and Table 2 since, of the three metal ions, lithium would be expected to most easily form a chelate of the type proposed above.



1 (3)

Table 2. *Variation of the counter-ion in electrophilic alkylation of aziridine* **1**.

Entry	Counterion (X)	Product Ratio
1	Li	>99:1
2	Na	75:25
3	K	67:33

Molecular mechanics calculations on aziridine 1 (see Experimental) revealed, not unexpectedly, a large number of possible conformers but with most of the lower-energy ones resembling that shown in

Fig. 1, with the side- chain oxygens nicely poised to engage in a chelate. Figure 1 also shows a Chem 3 D representation of the chelated Li-enolate, under the simplifying assumption of a monomeric structure.

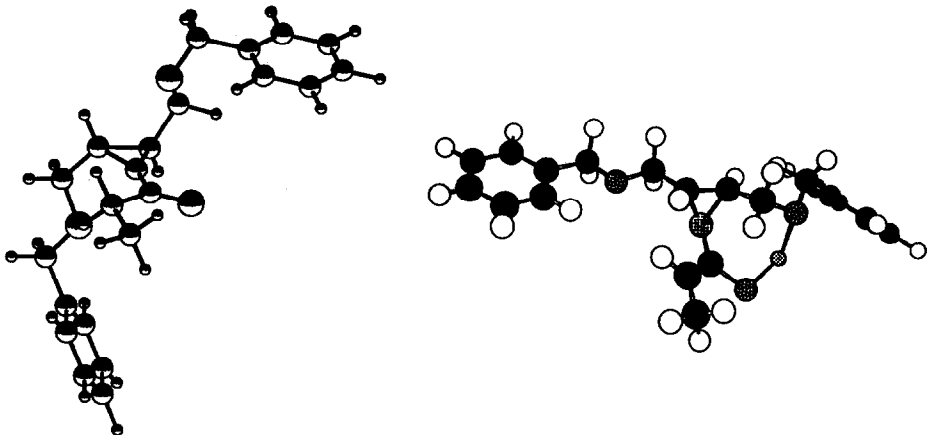


Figure 1. *Calculated low-energy conformation of 1, and a simplified representation of the corresponding Lithium enolate (see also Figs. 3 and 4).*

Structure and dynamics of the enolate of 1. NMR spectroscopic studies.

Having accumulated evidence for internal chelation in the enolates of **1** and **2**, we undertook an NMR spectroscopic study of the former species. The study included a comparison of the Li and K enolates, and typical ^{1}H NMR spectra are shown in Fig. 2.

In our interpretation of the results we have concentrated on the lithium species, in which we presume[7] that the metal is tetracoordinated in solution. Four possible structures are considered: (i) a monomer, with lithium coordinated to the enolate oxygen, a side-chain oxygen, and two THF molecules (cf. Fig. 1); (ii) a C_2-symmetric dimer with a Li-O-Li-O core, the two aziridine moieties being positioned on the same face of the quadrangle; each lithium is coordinated to one side-chain oxygen, the enolate oxygens are shared, and THF molecules occupy the fourth coordination site on each metal (see Fig. 4); (iii) a C_1-symmetric dimer, i.e. with the aziridine moieties on opposite faces of the Li-O-Li-O core (structure not shown); (iv) a D_2-symmetric tetramer built from two C_2-symmetric dimers, with the four enolate oxygens and four lithiums defining a cube and each lithium coordinated to one side-chain oxygen (structure not shown).

For the possible candidates, literature precedents[7] suggest that a monomeric structure in solution is unlikely and that dimers and/or tetramers are the most probable. As discussed below for the Li-enolate, our results are in accordance with the existence of the C_2-symmetric dimer (Fig. 4) and the D_2-symmetric tetramer.

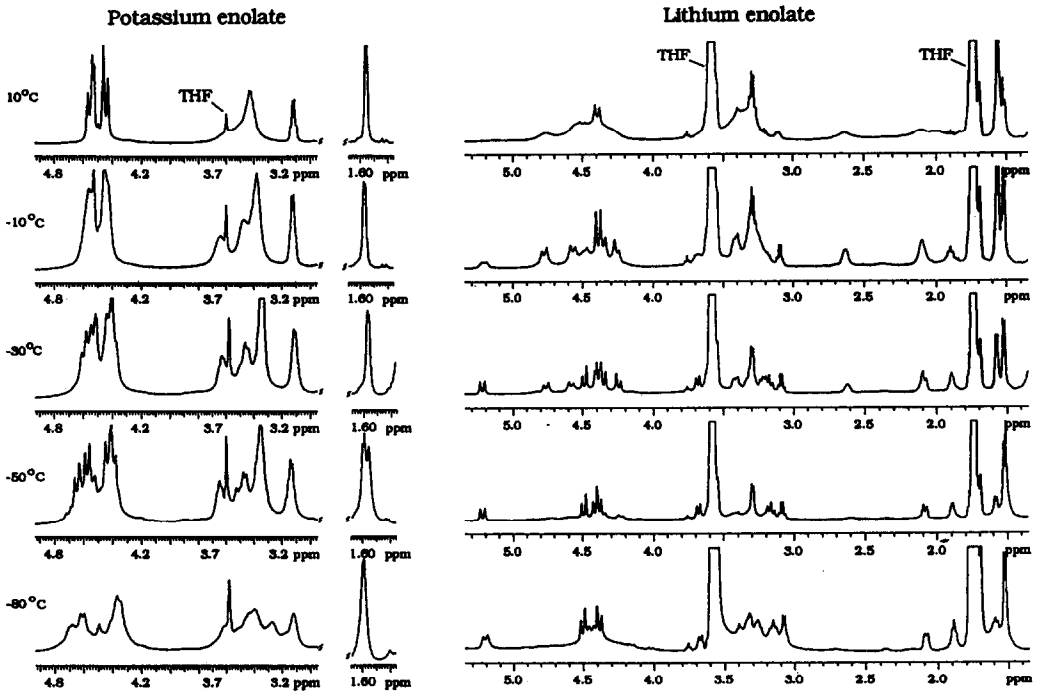


Figure 2. *Portions of the 400 MHz ^1H NMR spectra of the enolates of 1 at various temperatures*

The enolate was generated at -80°C, and spectra were then recorded at a variety of temperatures (Fig. 2). Two species were observed, one of which gave rise to very broad signals at -80°C, and a complete assignment (Fig. 3 and Table 3) of the sharper set of signals observed at this temperature was made by means of a TOCSY experiment[10]. A particularly well-resolved spectrum was obtained at -30°C and this clearly showed that in both species the aziridine moieties were no longer C_2-symmetric, i.e. the faces of each aziridine ring are no longer equivalent[11]. Simple inspection of the number of AB-type subspectra observed for the benzylic protons then rules out the C_1-symmetric dimer, leaving some combination of the monomer, the C_2-symmetric dimer, and the tetramer as possible structures. A portion of the ^1H-^1H NOESY spectrum[12] obtained at -80°C is shown in Fig. 3, and these data combined with information from the one-dimensional spectrum can be interpreted in terms of the enolate substructure shown in Figs. 1 and 3, with a pyramidalized nitrogen and a seven-membered ring reminiscent of the boat conformer of cycloheptane. There is no observable spin-spin coupling between H_A and H_B which implies an angle of ca. 90° between them. The *Z* geometry of the enolate follows from the observation of a strong NOE between $H_{A'}$ and H_F and the absence of an NOE between $H_{A'}$ and the methyl group. There are also significant NOEs between $H_{A'}$ and the trio ($H_CH_{B'}H_{C'}$) while H_A has NOEs to ($H_BH_{B'}H_{C'}$). Thus far, the data do not allow a definite structural assignment to the species which gives rise to the sharper set of signals at -80°C, but the important observation of NOEs between the enolate methyl and both H_D and H_E (Fig. 3) is consistent only with the C_2-symmetric dimer or the tetramer: these NOEs must arise from interactions between two discrete but spectroscopically equivalent aziridine moieties, since inspection of models suggests that in the monomer (and in the C_1-symmetric dimer) the distance between the methyl

group and (H_DH_E) would be too great for any NOE to be observed. If the "well-resolved" species observed at -80°C is assigned the C_2-symmetric dimer structure shown in Fig. 4, it is reasonable to assume that the component which gives rise to very broad signals at -80°C is the tetramer, the line-broadening being due to decreased mobility and/or solubility of the cluster at low temperature. The nature of the dynamic processes which are obviously occurring at higher temperatures (Fig. 2) has not been investigated in detail but it appears that the two species are interconverting.

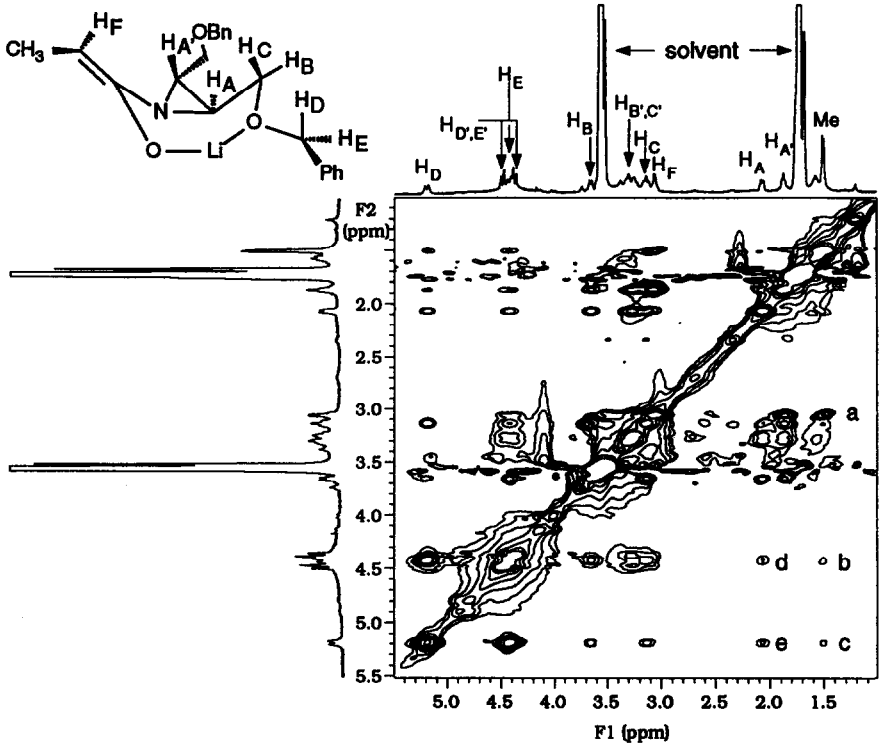


Figure 3. *Part of the NOESY spectrum of the lithium enolate (THF-d_8, -80°C). Structurally significant cross-peaks are marked: a, Me-H_F, b, Me-H_E, c, Me-H_D, d, H_A-H_E, e, H_A-H_D. Cross peaks b and c indicate the arrangement of the two enolate molecules in the proposed dimeric complex (see also Fig. 4).*

While NMR spectroscopy investigations of the type discussed here can reveal many details of enolate structure in solution, they may be uninformative as to the nature of the actual reactive species[7]. The aggregates described above may thus react as such, or may simply be pre-equilibrium precursors of more reactive monomeric species. However, inspection of molecular models of the proposed species indicates that internal chelation effects should force the incoming electrophile to react with the same diastereoface of the enolate, regardless of the aggregation state of the lithium species.

Table 3.
Comparison between some chemical shifts of the aziridine 1 and an enolate species observed at -80°C

Starting Material (1)			Enolate		
Benzylic H	-O-CH_2-	Aziridine ring H	Benzylic H	-O-CH_2-	Aziridine ring H
4.5 (s)	3.7 (m)	2.8 (m)	5.2 and	3.6 (d)[a]	2.1 (d)
	3.6 (m)		4.4 (AX)	3.3 (m)	1.9 (m)
			4.5 and	3.2 (m)	
			4.3 (AB)	3.1 (m)	

a. see text for discussion

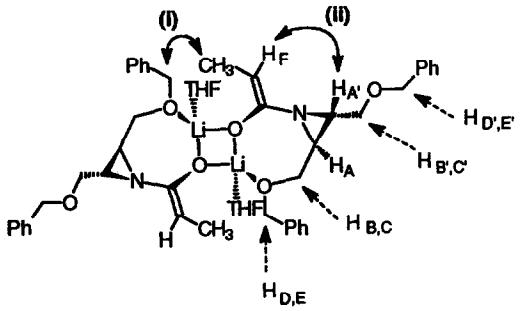


Figure 4. *Structure of the proposed dimeric lithium enolate. Structurally significant NOEs: (i) Me-$H_{D,E}$ (ii) H_F-H_A'.*

The ^{1}H NMR spectrum of the potassium enolate (Fig. 2) is also temperature dependent. In contrast to the lithium enolate, one apparently symmetrical species dominates at 10°C with chemical shifts for the benzylic and other methylene protons very similar to those observed for **1** itself. The spectral changes which occur as the temperature is lowered are consistent with slow pyramidal inversion at nitrogen. This process is rapid in aziridine **1** over the same temperature range, but would be expected to have a higher barrier in the enolate due to electrostatic repulsion between the anion and the nitrogen lone-pair in the planar transition state for inversion. We have not attempted to deduce the aggregation state of this enolate, but we conclude that internal chelation of the type proposed for the lithium species is of lesser importance in the potassium case.

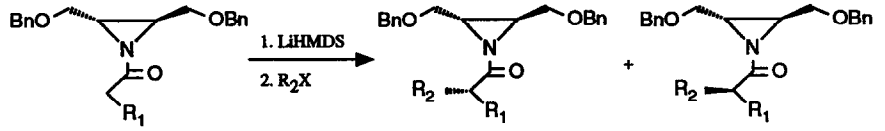
The lithium enolate of aziridine **3** was also studied at various temperatures but no detailed conclusions could be drawn, since the spectra consisted of a series of broad, featureless peaks; several enolate species seemed to be present.

At this point it is also instructive to compare the results of the alkylation of **1** and **2** with those from the alkylation of the corresponding C_2-symmetric 2,6-disubstituted piperidine[13] and 2,5-disubstituted pyrrolidine[14] auxiliaries which, with benzyl bromide, both give the *opposite* sense of chirality to that obtained with our aziridines. For the pyrrolidine case, chelation within the enolate has been discounted on the basis that *trans* 2,5-dimethyl pyrrolidine was almost as good an auxiliary as the species carrying two ethereal side-chains (-CH_2OMEM) and that the alkylation of the latter enolate

showed no dependence on the nature of the metal counter-ion[14].

Returning to Table 1, entry 7, the very poor diastereoselectivity observed in this case may thus be the result of alkylation of two competing chelates (seven- *vs.* five-membered ring) one of which would lack the diastereofacial bias present in the other.

The dependence of the steric course of the alkylation of **1** on the nature of the electrophile was also studied (Eq. 4) and some results are gathered in Table 4.



(4)

1. R_1=CH_3

9. R_1=$(CH_2)_7CH_3$

Table 4. *Variation of the electrophile in alkylation of aziridines* ***1*** a *nd* ***9.***

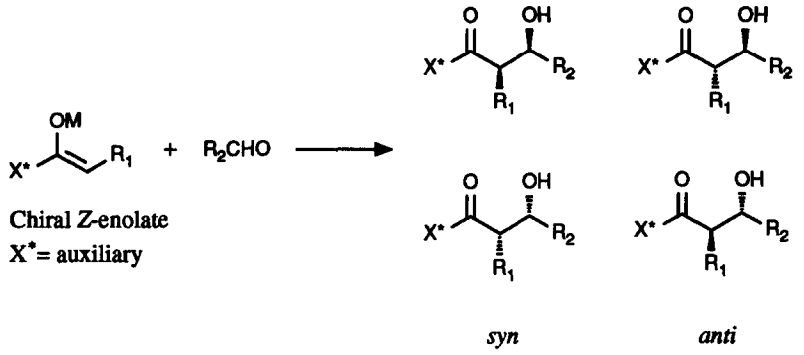
Entry	Aziridine	R_2X	Ratio	Isolated yield[a]
1	**1**	BnBr	>99:1	88%
2	**1**	AllylBr	91:9	67%
3	**1**	OctylI	75:25	40%
4	**9**	MeI	85:15	74%

a. After flash chromatography. No attempts to optimize the yields have been made. Unreacted starting material gives mass balance.

The results imply that for reactive and relatively bulky electrophiles (Table 4, entries 1 and 2) good to excellent diastereoselectivity can be obtained in reactions run at -78°C. The much less reactive electrophile shown in entry 3 required higher temperature in order to react at all, with obviously deleterious effects on selectivity. Switching the order of introduction of the alkyl groups (entry 4) led to the opposite diastereoisomer of the product, with better chemical yield and stereoselectivity. However, the reactivity of MeI (reacts at -78°C) is offset by its lack of steric bulk, and the only really encouraging aspect of entry 4 was that the diastereoisomeric products could be separated easily by flash chromatography; the corresponding chiral carboxylic acids are useful intermediates in the asymmetric synthesis of insect pheromones[15].

Diastereoselective aldol reaction

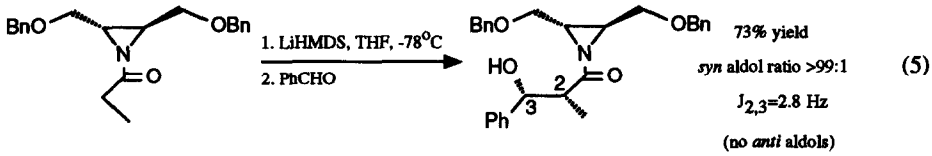
In recent years, few reactions have attracted so much interest as the stereoselective aldol process[8]. The challenge is of course the control of both relative and absolute stereochemistry in a reaction which entails carbon-carbon bond formation with the generation of two stereogenic centres. Since one way of achieving this is the use of stereochemically well-defined enolates attached to chiral auxiliaries, a variety of which is now available[16], it was of interest to test our aziridines in the aldol reaction (Scheme 4).



Scheme 4. *The four possible diastereoisomeric aldols from reaction of a chiral enolate.*

Of the various factors which can affect the relative stereochemical outcome (i.e. *syn* vs. *anti*) of a crossed aldol reaction, an important one[8] is enolate geometry (*Z* vs. *E*). Thus, for reactions run under kinetic control, *Z* amide enolates such as that shown in Scheme 4 tend to produce *syn* aldols predominantly or even exclusively, a correlation which can be rationalized on the basis of a Zimmerman-Traxler transition state model[8,17] (six-membered chair-like TS).

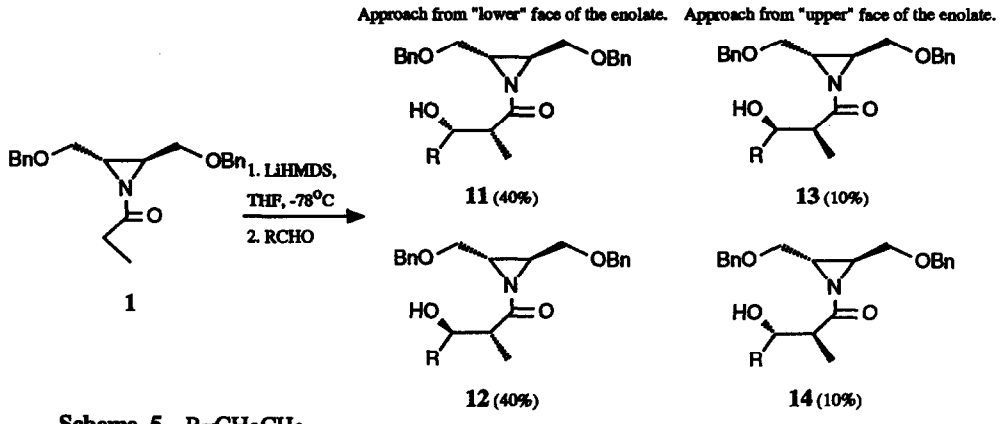
In the present study, the *Z* enolate of aziridine **1** was the first to be tested in the aldol reaction with benzaldehyde (Eq. 5).



1 **10**

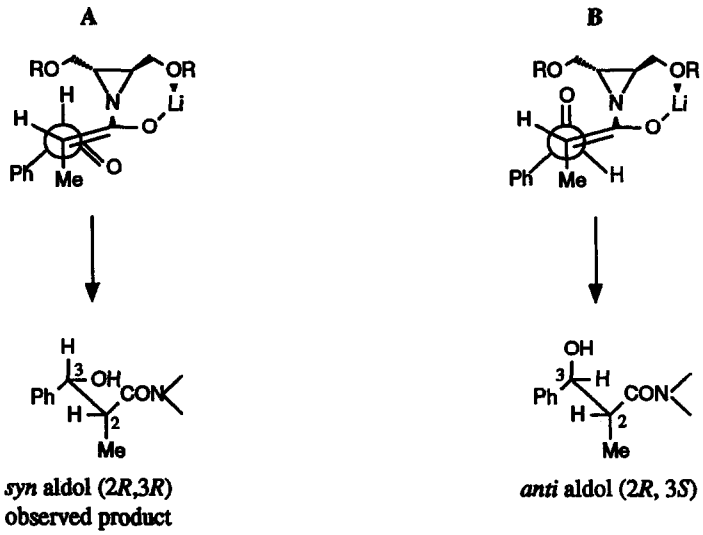
The results were very encouraging in that a single diastereoisomer was produced in good yield. (In our earlier communication[1] we inadvertently reported a 98:2 ratio). That the relative stereochemistry was *syn* was suggested by an analysis of the appropriate coupling constants[8] in the ^{1}H NMR spectrum of the aldol product, and that the absolute stereochemistry was (2*R*,3*R*) was deduced from the chiroptical data of the carboxylic acid obtained upon removal of the auxiliary (see discussion below and Experimental). However, when other aldehydes were tested, it soon became apparent that benzaldehyde was atypical, as illustrated by the results shown in Scheme 5.

The results with propionaldehyde and other short-chain aliphatic aldehydes were initially very discouraging but, as discussed below, they led us to the design of the alternative set of aziridine auxiliaries in which internal chelation of the metal ion is of no importance.



Scheme 5. R=CH_2CH_3

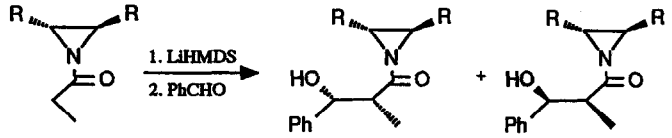
As described earlier, there is good reason to assume a chelated structure for the enolate and, while this is advantageous for alkylations, it is not difficult to rationalize why this could have a deleterious effect on the stereoselectivity of aldol reactions. For the Zimmerman-Traxler transition state to be operative, the metal ion of the enolate must be able to coordinate to both the enolate oxygen and to that of the incoming aldehyde. This can become impossible if the metal is already engaged in a chelate involving a side-chain of the auxiliary, and the approach of a "small" aldehyde can then become stereorandom (**11** *vs.* **12**). However, the chelate can still be instrumental in directing the electrophile mainly to the less hindered face of the enolate (**11** + **12** *vs.* **13** + **14**). The anomalous results obtained with benzaldehyde could be explained on the basis of "open" transition states, two of which are drawn as Newman projections in Scheme 6.



Scheme 6. ***Possible "open" transition states for the reaction of 1 and benzaldehyde.***

In both cases the aldehyde approaches the less hindered face of the nucleophile, with the phenyl group as far as possible from the bulkiest part of the enolate. Studies of molecular models indicate that the major difference between **A** and **B** is that the former has the smallest portion of the aldehyde directed toward the "lower" side-chain of the auxiliary.

The results shown in Scheme 7 lend further support to the contention that, for aldol reactions, the steric bulk of the aziridine side-chains is more important than the ability to coordinate to metals.

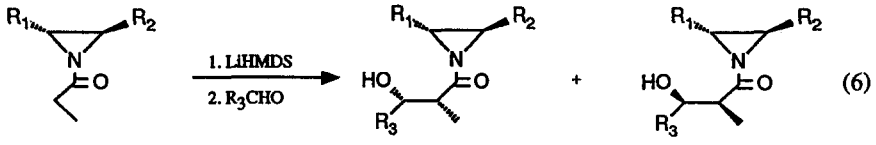


1, 2, 4 **A** **B**

R	Ratio A:B
CH_2OBn (1)	>99:1
CH_2OMe (2)	87:13
Ph (4)	80:20

Scheme 7.

These results can be compared and contrasted with those shown for the alkylation reactions in Table 1. For alkylation, there was no apparent difference between **1** and **2** (Table 1, entries 1 and 2) but **1** is clearly superior in the aldol reaction shown above. Aziridine **4**, which performed very poorly in the alkylation process (Table 1, entry 4) now actually begins to rival **2** in the aldol reaction. These observations prompted us to screen the aziridines shown in Eq. 6, and the results are collected in Table 5. (Diastereomeric ratios were measured on the crude product mixtures).



(6)

3. $R_1=R_2={}^nBu$ **4.** $R_1=R_2=Ph$

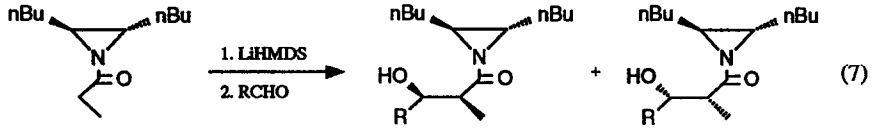
5. $R_1=R_2=CH_2Ph$ **15.** $R_1=R_2=CH(CH_3)_2$

Table 5. *Aziridines 3, 4, 5 and 15 in aldol reactions.*

Entry	Aziridine	Aldehyde (R_3CHO)	Ratio [a]	Isolated yield[b]
1	3	PhCHO	>99:1	69%
2	3	CH_3CH_2CHO	87:13	84%
3	4	PhCHO	80:20	45%
4	4	CH_3CH_2CHO	55:45	52%
5	5	PhCHO	91:9	53%
6	5	CH_3CH_2CHO	85:15	76%
7	15	CH_3CH_2CHO	80:20	c

a. No anti products could be detected by ^1H or ^{13}C NMR spectroscopy. b. After flash chromatography. No attempts to optimize the yields have been made. Unreacted starting material gives mass balance. c. Not determined.

For the initial studies, racemic materials were used. On the basis of Table 5, aziridine **3** was selected for preparation in optically active form according to Scheme 2. The enantioselectivity[4] of the Sharpless AD process (employing *trans*-5-decene and the AD-mix β) was at least 95% and delivered correspondingly pure aziridine **16**. The results of aldol reactions with representative aldehydes (Eq. 7) are shown in Table 6.



(7)

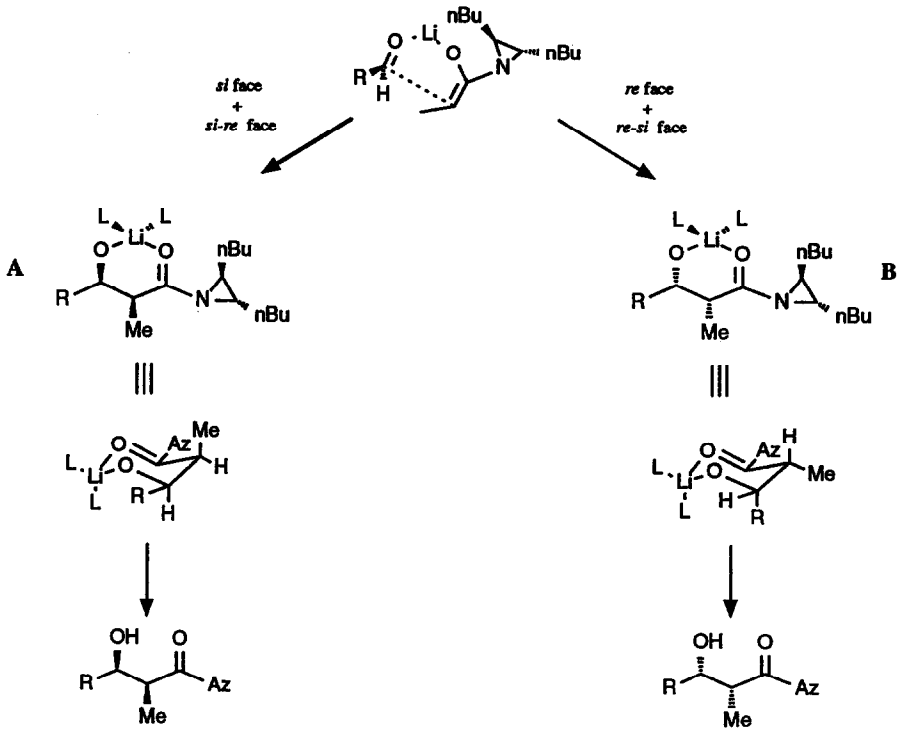
16

Table 6. *Aziridine 16 in aldol reactions with different aldehydes.*

Entry	Aldehyde (RCHO)	Ratio [a]	Isolated yield[b]
1	PhCHO	>99:1	66%
2	CH_3CH_2CHO	87:13	88%
3	CH_3CH:CHCHO	88:12	59%
4	$CH_3(CH_2)_4CHO$	80:20	87%
5	$(CH_3)_2CHCHO$	>99:1	87%
6	$(CH_3)_3CCHO$	>99:1	91%
7	PhCH:CHCHO	81:19	75%
8	1-naphthaldehyde	85:15 [c]	88%
9	2-naphthaldehyde	75:25 [c]	66%
10	(*R*)-CH_3CH(OTBDMS)CHO	>99:1	56%
11	(*S*)-CH_3CH(OTBDMS)CHO	60:40[d]	37%
12	2,5-dimethoxy-3-nitrobenzald.	>99:1	63%

a. No anti products could be detected by ^1H and ^{13}C NMR spectroscopy unless otherwise stated. Absolute configuration assigned after cleavage of the auxiliary. b. After flash chromatography. No attempts to optimise the yields have been made. Unreacted starting material gives mass balance. c. The minor diastereomer is an anti aldol product. d. Both products are anti aldols.

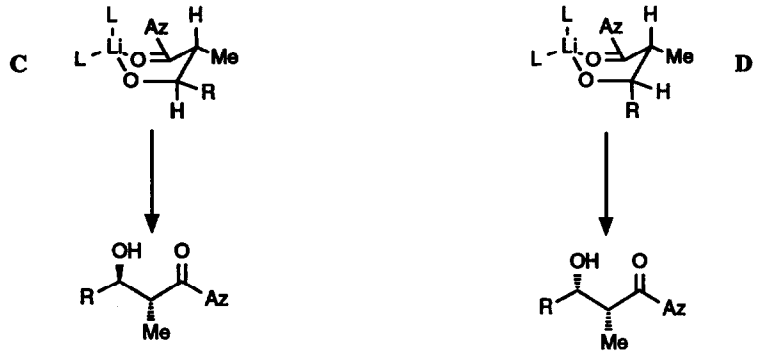
Certain "large" aldehydes (Table 6, entries 1, 5, 6, 10 and 12) gave excellent results, with exclusive formation of a single *syn* aldol, as expected[8] from reaction of the *Z* enolate via the sterically more favourable Zimmerman-Traxler chair-like transition state. Sterically less demanding aldehydes (entries 2, 3, 4 and 7) gave poorer diastereoselectivity, but the two *anti* aldols still could not be detected. The diastereofacial combinations of aldehyde and enolate leading to *syn* aldols are shown in Scheme 8.



Scheme 8.

In the presumed Zimmerman-Traxler transition states, the aziridine side-chains of **16** are expected to exert steric diastereofacial control effects similar to those proposed for the Evans oxazolidinone auxiliaries[8]. Assuming that the chair-like intermediates **A** and **B** resemble the transition states from which they are formed in a kinetically-controlled process, then the transition state leading to **B** should be destabilized because the R group is in an axial position. Thus "large" aldehydes should be expected to favour formation of **A**, while for less bulky aldehydes the chair-like transition state leading to **B** can compete.

The results with the isomeric naphthaldehydes were interesting in that the minor diastereomer was now an *anti* aldol. Presumably, the major product still arises from a chair-like transition state with the naphthyl groups equatorial, but inspection of molecular models implies increased steric repulsions between the incoming naphthalene unit and either the enolate methyl or the closest aziridine side-chain (depending on how the unsubstituted ring of the naphthyl group is oriented during the approach to the enolate). The alternative chair arrangement leading to **B** (axial naphthalene) should be very unfavourable, and a boat-like transition state[8,18] may now be able to compete. The stereochemical outcome can then be rationalized by consideration of the boat-like intermediates **C** and **D** shown in Scheme 9.



Scheme 9.

Once again, it is assumed that these intermediates resemble the transition states responsible for their formation. The transition state leading to **C** (and, ultimately, an *anti* aldol) should therefore be favoured, since the naphthyl moiety is in a pseudo-equatorial position (as compared to pseudo-axial in **D**).

The optically pure aldehydes used for entries 10 and 11 of Table 6 are obviously a "match" and "mismatch", respectively, for the enolate. The excellent *syn* selectivity obtained from the (*R*)-aldehyde can be compared to that obtained with other branched aldehydes (entries 5 and 6) but we have as yet no convincing explanation as to why the (*S*)-aldehyde produces only *anti* aldols with poor selectivity.

Entries 7 and 12 of Table 6 describe aldol products of the type used by Evans[19] in a total synthesis of the naturally occurring antibiotic Macbecin I. The aldols of entry 7 can be separated easily by flash chromatography, while in entry 12 a single *syn* aldol diastereoisomer is produced.

Removal of the auxiliary

The design of the aziridine auxiliaries was based, in part, on the expected relative ease of cleavage of aziridine amides. In our earlier paper we described an application of the Brown aldehyde synthesis[20] (reaction of an aziridine amide with 0.25 equiv. of $LiAlH_4$) for removal of our auxiliaries with very little epimerization. We have also found that the aziridine amides can be cleaved to the corresponding carboxylic acids under very mild conditions by means of the Evans LiOOH procedure[21]; again, little or no racemization occurs.

Concluding remarks

The C_2-symmetric aziridines described herein fulfil the requirements usually proposed for "good" chiral auxiliaries: (i) they are easily and relatively cheaply available in both enantiomeric forms (ii) they give good to excellent diastereoselectivity, usually in a predictable manner (iii) they are easily removed under mild conditions, with little or no racemization of the new chiral products. Further applications to other diastereoselective processes will be described elsewere.

EXPERIMENTAL

General

^1H and ^{13}C NMR spectra were run on a Varian XL 300 or UNITY 400 spectrometer using $CDCl_3$ as solvent and internal standard. IR spectra were run on a Perkin-Elmer FTIR spectrometer using $CDCl_3$ solutions or neat samples. Elemental analyses were performed by Analytische Laboratorien, Gummersbach, Germany. $[\alpha]_D$ values were measured on a Perkin-Elmer 241 polarimeter. Flash chromatography was performed using Merck silica gel. All reactions were run under nitrogen atmosphere in oven-dried glassware with dried solvents unless otherwise stated. Solvents were dried using standard procedures.

Synthesis of aziridines

Aziridine **1**. Both enantiomers of 1,4-bis-(benzyloxy)-2,3-epoxybutane are readily available from (+)- and (-)-tartaric acid respectively.[3]

(i) (*S,S*)-1,4-bis-(benzyloxy)-2,3-epoxybutane (1.00 g, 3.53 mmol) was dissolved in a 8/1 mixture of $MeCH_2CH_2OH/H_2O$ (15 ml). NaN_3 (0.916 g, 14.1 mmol) and NH_4Cl (0.301 g, 5.63 mmol) were added. After refluxing for 2h (TLC showed complete reaction) and cooling to RT the reaction mixture was poured into Et_2O and H_2O. The aqueous phase was extracted three times with Et_2O and the combined organics were washed twice with H_2O and once with sat. NaCl (aq.). The solution was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography (40% Et_2O/pentane) giving 1.09 g (94% yield) of azido-alcohol. ^1H NMR: δ 2.62 (1H, d, J=7,-O*H*); 3.61 and 3.70 (4H, m, 2×-CH_2OBn); 3.82 (2H, m, -CHN_3+ C*H*OH); 4.47 (4H, m, 2×-CH_2Ph); 7.31 (10H, m, -*Ar*). IR: 3447 cm^{-1} (b, OH); 2098 (s, azide).

(ii). The azido-alcohol (4.154 g, 12.7 mmol) was dissolved in CH_2Cl_2 (50 ml) and cooled to 0°C. MsCl (1.747 g, 15.3 mmol) and NEt_3 (1.670 g, 16.5 mmol) were added and the reaction mixture was stirred for 1.5h. After evaporation of the solvent and dilution with Et_2O the precipitated $Et_3N^+HCl^-$ was filtered off. Removal of the solvent and purification of the residue by flash chromatography (40% Et_2O/pentane) gave 4.504 g (88% yield) of azido-mesylate. ^1H NMR: 3.02 (3H, s, -S(O$_2$)CH_3); 3.62-3.78 (4H, m, 2×-CH_2OBn); 3.98 (1H, m, -CHN_3); 4.55 (4H, m, 2×-CH_2Ph); 4.85 (1H, m, C*H*OMs); 7.33 (10H, m, -*Ar*).

(iii). The azido-mesylate (4.504 g, 11.1 mmol) was dissolved in THF (50 ml) and cooled to 0°C. $LiAlH_4$ (1.067 g, 28.1 mmol) was added in small portions. When the addition was complete the ice-bath was removed and the reaction mixture was refluxed over night. The excess $LiAlH_4$ was quenched with wet THF and the solution was dried over $MgSO_4$. The mixture was filtered and the filter-cake was washed with Et_2O. The combined solvents were evaporated and flash chromatography (EtOAc) of the residue gave 2.323 g (74% yield) of the N-H-aziridine . $[\alpha]_D^{25}$=+32.9° (c=1.00, CH_2Cl_2). ^1H NMR: 0.91 (1H, br, -N*H*); 2.06 (2H, br s, 2×-C*H*N); 3.40 (2H, dd, J=10.5, 5, -CH_2OBn); 3.54 (2H, dd, J=10.5, 4, -CH_2OBn); 4.46 (4H, m, 2×-CH_2Ph); 7.28 (10H, m, -*Ar*). IR: 3300 cm^{-1} (s, NH).

(iv). The N-H-aziridine (0.847 g, 3.00 mmol) was dissolved in CH_2Cl_2 (50 ml). NEt_3 (0.750 ml, 5.40 mmol) was added followed by propionic anhydride (0.662 g, 5.09 mmol) and DMAP (cat.). The mixture was stirred at RT until TLC (50% Et_2O/pentane) showed complete reaction (2h). After dilution

with Et_2O the organic phase was washed twice with H_2O and once with sat. NaCl (aq.). The ethereal solution was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography (50% Et_2O/pentane) giving 0.901 g (89% yield) of aziridine **1**. $[\alpha]_D^{25}$= -10.6° (c= 0.96, CH_2Cl_2). ^1H NMR: 1.09 (3H, t, J=7, CH_3CH_2-); 2.41 (2H, dq, J=7, 4.2, CH_3CH_2-); 2.7 (2H, m, 2×C*H*N); 3.62 (2H, dd, J=10.5, 4, -CH_2OBn); 3.71 (2H, dd, J=10.5, 3, -CH_2OBn); 4.50 (4H, s, 2×PhCH_2-); 7.30 (10H, m, -*Ar*). IR: 1690 cm^{-1} (s, amide). Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31%; H, 7.42%; N, 4.13%. Found: C, 74.36%; H, 7.40%; N, 4.08%.

Aziridine **2**. Aziridine **2** was synthesized analogously to aziridine **1** with the only exception that MeI was used instead of BnBr in the alkylation of the diol derived from reduction of the tartrate. Overall yield = 10% (9 steps). $[\alpha]_D^{25}$=-17.1° (c=1.19, CH_2Cl_2). ^1H NMR: 1.12 (3H, t, J=7, CH_3CH_2-); 2.41 (2H, dq, J=7, 1.7, CH_3CH_2-); 2.72 (2H, m, 2×-C*H*N); 3.32 (6H, s, 2×-CH_3); 3.52 (2H, dd, J=11, 4.5, -CH_2OCH_3); 3.59 (2H, dd, J=11, 3.2, -CH_2OCH_3). IR: 1683 cm^{-1} (s, amide).

Aziridine **3**. A: Racemic material.

(i). *trans*-5-Decene (1.00 g, 7.13 mmol) was dissolved in CH_2Cl_2 and cooled to 0°C. mCPBA (1.92 g (80%), 8.91 mol) was added and the reaction mixture was stirred at RT for 5h. The precipitate was filtered off and the filtrate was washed twice with 10% $Na_2S_2O_5$, twice with 5% Na_2CO_3, once with H_2O and once with sat. NaCl (aq.). The organic phase was dried over $MgSO_4$ and the solvent evaporated. Flash chromatography (10% Et_2O/pentane) gave 0.621 g (56% yield) of the epoxide. ^1H NMR: 0.92 (6H, t, J=7, CH_3CH_2-); 1.30-1.59 (12H, m, ^{n}Bu-); 2.66 (2H, m, -C*H*OC*H*-).

(ii) The epoxide was ring opened with azide in the manner described for aziridine **1**. Isolated yield = 90%. ^1H NMR: 0.92 (6H, m, CH_3CH_2-); 1.23-1.60 (12H, m, ^{n}Bu-); 1.70 (1H, d, J=6, -O*H*); 3.34 (1H, m, -C*H*N_3); 3.66 (1H, m, -C*H*OH). IR: 3404 cm^{-1} (b, OH); 2099 (s, azide).

(iii) The azido-alcohol (1.153 g, 5.79 mmol) was dissolved in THF (25 ml). PPh_3 (1.824 g, 6.95 mmol) was added and the reaction mixture was refluxed for 1.5h. After evaporation of the THF the residue was dissolved in Et_2O and the precipitated $OPPh_3$ was filtered off. Removal of the solvent and flash chromatography (Et_2O) gave 0.626 g (70% yield, slightly volatile compound) of N-H-aziridine. ^1H NMR: 0.90 (6H, t, J=7, CH_3CH_2-); 1.39 (12H, m, ^{n}Bu-); 1.69 (2H, m, -C*H*NHC*H*-). IR: 3310 cm^{-1} (s, NH).

(iv). The N-H-aziridine was acylated according to the procedure described for aziridine **1**. Isolated yield = 73%. ^1H NMR: 0.90 (3H, t, J=7, $CH_3CH_2CH_2$-); 1.14 (3H, t, J=7.5, CH_3CH_2-); 1.16-1.77 (12H, m, 2×^{n}Bu-); 2.22 (2H, m, 2×-C*H*N); 2.35 (2H, dq, J=14, 7.5, CH_3CH_2-). IR: 1670 cm^{-1} (s, amide). Ana. Calcd. for $C_{13}H_{25}NO$: C, 73.88%; H, 11.92%; N, 6.63%. Found: C, 73.68%; H, 11.78%; N, 6.72%.

B: Optically pure material.

(i). ^{t}BuOH (35 ml), H_2O (35 ml), AD-mix-β (9.8 g) and $CH_3SO_3NH_2$ (0.665 g, 7.00 mmol) were mixed and cooled to 0°C. *trans*-5-Decene (0.980 g, 7.00 mmol) was added and the mixture was stirred at 0°C for 20h. The reaction was quenched with solid Na_2SO_3 (10.5 g) and was allowed to warm up to RT and stir for 45 minutes. The mixture was diluted with CH_2Cl_2 and the aqueous phase was extracted three times with CH_2Cl_2. The combined organics were washed twice with 2M KOH, once with sat. NaCl (aq.) and dried over $MgSO_4$. Flash chromatography (30% Et_2O/pentane) gave 1.131 g (93% yield) of the optically active *R,R*-diol. m.p.= 50-51°C. $[\alpha]^{24}_D$= +31.3° (c=0.995, $CHCl_3$) (lit. +29.2°).[4] ^1H NMR: 0.91 (6H, t, J=6.5, CH_3CH_2-); 1.29-1.56 (12H, m, ^{n}Bu-); 1.97 (2H, d, J=5, 2×O*H*); 3.41 (2H, m, -C*H*NHC*H*-).

(ii). The diol (0.88 g, 4.60 mmol) was dissolved in toluene (15 ml) and triethylorthoformate

(2.002 g, 13.8 mmol) and p-TsOH (cat.) were added. The reaction was refluxed for 1h while the EtOH formed was removed using a Dean-Stark receiver and condenser. The mixture was neutralised with conc. NH_3 (aq.) and dried over $MgSO_4$. Evaporation of the toluene gave 0.984 g (93% yield) of orthoformate pure enough to be used in the next step. ^{1}H NMR: 0.91 (6H, t, J=6.5, C*H*$_3$CH$_2$-); 1.22 (3H, t, J=7, C*H*$_3$CH$_2$O-); 1.27-1.71 (12H, m, ^{n}Bu-); 3.58 (2H, q, J=7, CH$_3$C*H*$_2$O-); 3.63 (1H, m, -C*H*O-); 3.82 (1H, m, -C*H*O-); 7.27 (1H, s, -OC*H*O-).

(iii). PCl_5 (1.150 g, 5.52 mmol) was dissolved in CH_2Cl_2 and cooled to 0°C. The orthoformate (0.984 g, 4.28 mmol) in CH_2Cl_2 was added and the reaction was stirred at RT for 3h. After quenching with sat. $NaHCO_3$ the aqueous phase was extracted three times with Et_2O. The combined organics were washed with sat. $NaHCO_3$, H_2O, sat. NaCl (aq.) and dried over $MgSO_4$. Removal of the solvent gave 0.970 g (96% yield) of the chloroformate, pure enough to be used in the next step. ^{1}H NMR: 0.91 (6H, m, C*H*$_3$CH$_2$-); 1.32-1.69 (12H, m, ^{n}Bu-); 3.99 (1H, dt, J=9, 4, -C*H*Cl); 5.12 (1H, dt, J=9, 4, -C*H*OCHO); 8.13 (1H, s, -OC*H*O).

(iv). The chloroformate (0.943 g, 4.28 mmol) was dissolved in dry MeOH (15 ml) and K_2CO_3 was added. The reaction was stirred at RT for 18h and was then diluted with Et_2O (50 ml). The mixture was washed once with sat. NaCl (aq.), twice with sat. NH_4Cl (aq.), and once with sat. NaCl (aq.) again and then dried over $MgSO_4$. The solvent was carefully evaporated since the epoxide is quite volatile. 0.594 g (89% yield). Data for the optically active epoxide: $[\alpha]^{25}_D$= +29.1° (c=1.005, CH_2Cl_2).

(v). The epoxide was then transformed to N-H-aziridine following the procedure for the racemic material. Data for the optically active N-H-aziridine: $[\alpha]^{25}_D$= -37.9° (c=1.065, CH_2Cl_2).

Aziridine **4**: Racemic aziridine **4** was prepared from *trans*-stilbene using the same procedure as for the *trans*-5-decene. 24% overall yield (4 steps).

Epoxide: ^{1}H NMR: 3.89 (2H, s, -C*H*OC*H*-); 7.38 (10H, m, -*Ar*).

Azido-alcohol: ^{1}H NMR: 2.19 (1H,br, O*H*); 4.69 (1H, d, J=7, -C*H*N$_3$); 4.84 (1H, d, J=7, -C*H*OH); 7.30 (10H, m, -*Ar*). IR: 3600 cm^{-1} (b, OH); 2107 (s, azide).

N-H-Aziridine: ^{1}H NMR: 1.37 (1H, br, -N*H*); 3.09 (2H, br s, -C*H*NHC*H*-); 7.29 (10H, m, -*Ar*).

4: ^{1}H NMR: 0.99 (3H, t, J=7.5, C*H*$_3$CH$_2$-); 1.92 (1H, dq, J=16.5, 7.5, CH$_3$C*H*H-); 2.32 (1H, dq, J=16.5, 7.5, CH$_3$CH*H*-); 3.78 (2H, s, 2×-C*H*N); 7.31 (10H, m, -*Ar*). IR: 1687 cm^{-1} (s, amide).

Aziridine **5**: Synthesis of 1,4-diphenyl-*trans*-2-butene: 1,4-diphenyl-*trans-trans*-1,3-butadiene (3.65 g, 17.7 mmol) was dissolved in EtOH (not completely soluble) and the mixture was heated to reflux. Na (2.04 g, 88.6 mmol) was added in small pieces. When all the Na had been added all of the diene was not dissolved and more Na was added until no solids were left in the solution. The reaction mixture was refluxed an extra fifteen minutes and was then allowed to cool to RT (crystals precipitated). The mixture was diluted with H_2O and the EtOH was evaporated. The aqueous phase was neutralised with conc. HCl and extracted twice with Et_2O. The organic phase was then washed with H_2O, dried over $MgSO_4$ and the solvent was evaporated. The crude product was recrystallized from MeOH. The unreacted diene was less soluble then the product and precipitated first and could be removed by filtration. Two recrystallizations gave 0.985 g (45% yield) of the *trans*-1,4-diphenyl-2-butene. mp= 43-46°C (lit. 43-45°C).[22] ^{1}H NMR: 3.39 (4H, m, 2×-C*H*$_2$Ph); 5.68 (2H, m, -C*H*:C*H*-); 7.27 (10H, m, -*Ar*).

(ii). 1,4-Diphenyl-*trans*-2-butene was transformed into the racemic azido-alcohol following the procedure for the *trans*-5-decene and to acylated aziridine **5** following the procedure for aziridine **1**. 63%

overall yield (4 steps).

Epoxide: ^{1}H NMR: 2.82 (2H, dd, J=14, 5, -C*H*$_2$Ph); 2.93 (2H, dd, J=14, 5, -C*H*$_2$Ph); 3.02 (2H, m, -C*H*OC*H*-); 7.23 (10H, m, -*Ar*).

Azido-alcohol: ^{1}H NMR: 1.82 (1H, d; J=4, -O*H*); 2.78 (1H, dd, J=14, 9,-C*H*$_2$Ph); 2.87 (1H, dd, J=14, 9-C*H*$_2$Ph); 3.02 (1H, dd, J=14, 3.5, -C*H*$_2$Ph); 3.08 (1H, dd, J=14, 4.2, -C*H*$_2$Ph); 3.68 (1H, m, -C*H*N$_3$); 3.89 (1H, m, -C*H*OH); 7.31 (10H, m, -*Ar*). IR: 3591 cm^{-1} (b, OH); 2108 (s, azide).

Azido-mesylate: ^{1}H NMR: 2.41 (3H, s, C*H*$_3$SO$_3$-); 2.86 (1H, dd, J=14, 9.8, -CH(N$_3$)C*H*HPh); 2.99 (1H, dd, J=14, 5, -CH(N$_3$)CH*H*Ph); 3.07 (2H, m, -CH(OMs)C*H*$_2$Ph); 4.03 (1H, m, -C*H*N$_3$); 4.83 (1H, m, -C*H*OMs); 7.31 (10H, m, -*Ar*).

N-H-Aziridine: ^{1}H NMR: 0.36 (1H, br, -N*H*); 2.03 (2H, m, -C*H*NHC*H*-); 2.70 (2H, dd, J=14, 5, -C*H*$_2$Ph); 2.86 (2H, dd, J=14, 4.5, -C*H*$_2$Ph); 7.21 (10H, m, -*Ar*). IR: 3290 cm^{-1} (s, NH).

5: ^{1}H NMR: δ.12 (3H, t, J=7.5, C*H*$_3$CH$_2$-); 2.25 (2H, m, CH$_3$C*H*$_2$-); 2.48 (2H, dd, J=14, 7.5, -C*H*$_2$Ph); 2.64 (2H, m, 2×-C*H*N); 3.17 (2H, dd, J=14, 4, -C*H*$_2$Ph); 7.17 (10H, m, -*Ar*). IR: 1677 cm^{-1} (s, amide).

Aziridine **6**: Racemic N-H-aziridine was prepared from *trans*-stilbene following the procedure for aziridine **4**. The N-H-aziridine was then acylated with PhCH$_2$OCH$_2$COCl (1.2 eq., no DMAP was needed) in the same manner as described for aziridine **1**. ^{1}H NMR: 3.77 (1H, d, J=16, CH$_3$C*H*H-); 3.84 (2H, s, 2×-C*H*N); 3.93 (1H, d, J=16, CH$_3$CH*H*-); 4.30 (1H, d, J=11.5 -CH*H*OBn); 4.46 (1H, d, J=11.5 -C*H*HOBn); 7.29 (10H, m, -*Ar*).

Aziridine **7**: Enantiomerically pure N-H-aziridine was prepared from (+)-tartaric acid following the procedure described for aziridine **1**. The N-H-aziridine was then acylated in the same manner as aziridine **6**. $[\alpha]_D^{25}$=-23.8° (c=1.03, CH_2Cl_2). ^{1}H NMR: 2.88 (2H, m, 2×-C*H*N); 3.71 (4H, m, 2×-C*H*$_2$OBn); 4.10 (1H, d, J=16, -CH*H*CON-); 4.20 (1H, d, J=16, -C*H*HCON-); 4.48 (4H, s, 2×PhC*H*$_2$-); 4.56 (2H, s, PhC*H*$_2$-); 7.31 (15H, m, -*Ar*). IR: 1688 cm^{-1} (s, amide).

Aziridine **8**: (i) NaH (1.40 g (80%), 48.0 mmol) was suspended in dry DMF and cooled to 0°C. (*S*)-(-)-glycidol (2.921 g, 40.0 mmol) was added and the mixture was stirred for thirty minutes. BnBr (8.885 g, 50.0 mmol) was added and the reaction was left at RT overnight. The reaction was quenched with phosphate buffer (pH=7) and poured into Et_2O and H_2O. The aqueous phase was extracted three times with Et_2O and the combined organics were washed twice with H_2O and once with sat. NaCl (aq.). After drying over $MgSO_4$ and evaporation of solvent, flash chromatography (20-30% Et_2O/pentane) gave 3.695 g (57% yield, volatile compound) of (*S*)-O-benzylglycidol. ^{1}H NMR: 2.63 (1H, dd, J=5, 2.5, -CH*H*O-); 2.81 (1H, dd, J=5, 4, -C*H*HO-); 3.20 (1H, m, -C*H*(O)CH$_2$OBn); 3.45 (1H, dd, J=11, 6, -CH*H*OBn); 3.78 (1H, dd, J=11, 3, -C*H*HOBn); 4.60 (2H, 2×d, J=12 and J=12, -C*H*$_2$Ph); 7.38 (5H, m, -*Ar*).

(ii). The (*S*)-O-benzylglycidol was ring opened to azido-alcohol using the earlier described method in 76% yield. ^{1}H NMR: 2.55 (1H, d, J=5, -O*H*); 3.38 (2H, m, C*H*$_2$N$_3$); 3.52 (2H, m, -C*H*$_2$OBn); 3.97 (1H, m, -C*H*OH); 4.59 (2H, s, -C*H*$_2$Ph); 7.36 (5H, m, -*Ar*). IR: 3453 cm^{-1} (b, OH); 2105 (s, azide).

(iii) The azido-alcohol (3.576 g, 17.3 mmol) was dissolved in pyridine (40 ml) and cooled to 0°C. MsCl (2.378 g, 20.7 mmol) was added. The ice-bath was removed and the reaction mixture was stirred at RT over night. The mixture was poured into Et_2O/$CuSO_4$ (aq.). The organic phase was washed several times with $CuSO_4$ (aq.) to remove the pyridine. The ethereal solution was dried over $MgSO_4$ and then evaporated to dryness. Flash chromatography (40% Et_2O/pentane) gave 4.233 g (86% yield) of

azido-mesylate. ^{1}H NMR: 3.08 (3H, s, CH_3SO_3-); 3.61 (2H, m, -CH_2N_3); 3.70 (2H, m, -CH_2OBn); 4.58 (2H, s, -CH_2Ph); 4.48 (1H, m, *CH*OMs); 7.33 (5H, m, *-Ar*).

(iv). The azido-mesylate was ring closed to the N-H-aziridine using the $LiAlH_4$ method described earlier. The reaction was almost quantitative but since the product is very volatile the isolated yield was only 27%. ^{1}H NMR: 0.40 (1H, br, -N*H*); 1.50 (1H, br s, -CH*H*NH-); 1.80 (1H, br d, J=5, -*CH*HNH-); 2.26 (1H, br m, -*CH*NH-); 3.39 (1H, dd, J=10, 6, -*CH*HOBn); 3.59 (1H, br dd, J=10, 4, -CH*H*OBn); 4.57 (2H, m, -CH_2Ph); 7.36 (5H, m, *-Ar*). IR: 3308 cm^{-1} (b, NH).

(v). The N-H-aziridine was acylated in the manner described for aziridine **1**. ^{1}H NMR: 1.18 (3H, t, J=7.5, CH_3CH_2-); 2.14 (1H, d, J=3.2, -CH*H*N-); 2.37 (1H, d, J=6, -*CH*HN-); 2.49 (2H, qd, J=7.5, 3.4, CH_3CH_2-); 2.71 (1H, m, -*CH*N-); 3.54 (1H, dd, J=10.5, 5.8, -CH*H*OBn); 3.65 (1H, dd, J=10.5, 4, -*CH*HOBn); 4.59 (2H, s, PhCH_2-); 7.35 (5H, m, *-Ar*).

Aziridine **9**: The enantiomerically pure N-H-aziridine (see aziridine **1**) was acylated with $CH_3(CH_2)_8$COCl in the manner described for aziridines **4** and **6**. $[\alpha]_D^{25}$=-12.8° (c=1.09, CH_2Cl_2). ^{1}H NMR: 0.88 (3H, t, J=6.5, CH_3CH_2-); 1.27 (12H, m, $CH_3C_6H_{12}$-); 1.62 (2H, m, $CH_3C_6H_{12}CH_2$-); 2.36 (2H, m, -CH_2CON-); 2.77 (2H, m, 2×-*CH*N); 3.62 (2H, dd, J=10.5, 4.5, -CH_2OBn); 3.71 (2H, dd, J=10.5, 3, -CH_2OBn); 4.51 (4H, s, 2×PhCH_2-); 7.31 (10H, m, *-Ar*). IR: 1693 cm^{-1} (s, amide).

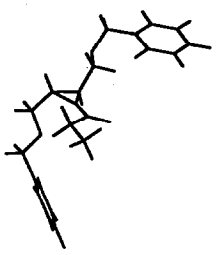
Aziridine **15**: Racemic aziridine **15** was prepared from 2,5-dimethyl-*trans*-3-hexene using the same procedure as for the *trans*-5-decene. 8% overall yield (4 steps). The epoxide and the N-H-aziridine were not isolated since they are very volatile.

Azido-alcohol: ^{1}H NMR: 0.92 (3H, d, J=2.5, CH_3-); 0.94 (3H, d, J=2.5, CH_3-); 1.01 (3H, d, J=7, CH_3-); 1.07 (3H, d, J=7, CH_3-); 1.48 (1H, d, J=5.8, -O*H*); 2.00 (1H, dqq, J=7, 5.8, 3.2, -CH(N_3)C*H*(CH_3)$_2$); 2.18 (1H, dqq, J=7, 5.8, 3.2, -CH(OH)C*H*(CH_3)$_2$); 3.24 (1H, dd, J=8.5, 3.2, -*CH*N_3); 3.42 (1H, ddd, J=8.5, 5.8 3.2, -*CH*OH). IR: 3445 cm^{-1} (b, OH); 2102 (s, azide).

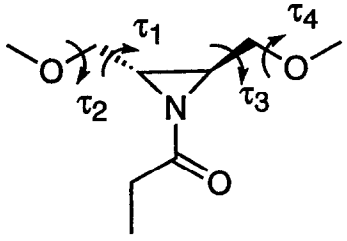
15: ^{1}H NMR: 0.91 (6H, d, J=7, 2×CH_3-); 1.11 (6H, d, J=6.5, 2×CH_3-); 1.13 (3H, t, J=7.5, CH_3CH_2-); 1.44 (2H, m, 2×C*H*(CH_3)$_2$); 2.08 (2H, m, 2×-*CH*N); 2.37 (2H, dq, J=7.5, 1.2, CH_3CH_2-). IR: 1677 cm^{-1} (s, amide).

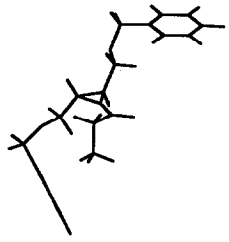
Molecular mechanics calculations on 1 and 2. Energy-minimized geometries were obtained by use of the MMX force field as included in the PCMODEL program (version PI 3.1, RM-486 computer). Boltzmann distributions were calculated for both 25°C and -78°C. Conformations were divided into groups characterized by the four dihedral angles shown below, which describe the relative positions of the two oxygen atoms, and each group contains at least 1% of the total number of conformations.

Parameters related to the orientation of the propanoyl moiety or (for **1**) the phenyl groups were not used in the classification, although some conformations of **1** appear to be stabilized by phenyl-phenyl interactions. The simpler compound **2** was treated first, and all possible staggered conformations were generated by a stepwise build-up strategy to span the conformational space. The MMX calculations produced 138 conformations with relative steric energies below 3 kcal mol^{-1}, and these were divided into the 15 groups given in the Table below.



Group 1





Group 8

Table. *Parameters defining groups of conformations of compounds 1 and 2 found in the MMX-calculations. Mean values of dihedral angles are given with standard deviations in parentheses. Also included are the Boltzmann distributions calculated at 25°C and -78°C.*

					Boltzmann distribution (%)			
	Conformational descriptor				1		2	
Group	τ_1	τ_2	τ_3	τ_4	25°	-78°	25°	-78°
1	48(2)	179(1)	38(1)	178(1)	12	15	11	17
2	49(3)	179(1)	177(1)	-63(1)			4	4
3	49(2)	179(1)	-96(1)	64(1)	4	3	3	3
4	49(2)	179(1)	-79(1)	179(1)	5	4	5	6
5	49(3)	179(1)	-68(2)	-64(1)	9	11	4	3
6	143(2)	66(1)	37(1)	178(1)	6	6	4	4
7	143(3)	68(1)	-80(1)	-179(1)	2	1	2	1
8	152(2)	179(1)	37(1)	178(1)	15	20	12	20
9	153(3)	179(1)	154(1)	179(1)	3	2	2	2
10	153(3)	179(1)	177(1)	-63(1)	3	3	6	6
11	153(3)	179(1)	-95(1)	64(1)	6	6	5	5
12	152(2)	179(1)	-81(1)	-179(1)	7	8	8	10
13	152(2)	179(1)	-70(1)	-64(1)	8	11	4	3
14	-97(1)	64(1)	39(1)	178(1)	4	3	3	2
15	-78(1)	179(1)	40(1)	178(1)	3	2	3	2

According to Boltzmann distributions at the temperatures indicated, these groups contain >75% and >89%, respectively, of the available conformations. The lowest-energy conformer belongs to group 8 and amounts to 6% (25°C) or 13% (-78°C) of the total conformational distribution. The conformations of **2** with steric energies <3 kcal mol^{-1} were used to generate conformations of **1** by successive replacement of each methyl hydrogen by phenyl. This produced 530 conformations with steric energies <3 kcal mol^{-1} (Table). The groups shown in the Table account for 88% (25°C) or 96% (-78°C) of the total number of conformers, and the lowest-energy conformer (group 8) is shown in Fig. 1.

General procedure for alkylation reactions.

The aziridine (1 eq.) was dissolved in THF and cooled with stirring to -78°C. LiHMDS (1.1 eq. of 1M THF solution) was added and the reaction mixture was stirred for ca. 45 minutes. The electrophile (1.2 eq.) was added and the temperature was allowed to rise slowly to RT or until TLC showed complete reaction. The reaction mixture was poured into Et_2O/sat. NH_4Cl (aq.). After separation of the layers the organic phase was washed twice with H_2O, once with sat. NaCl (aq.) dried over $MgSO_4$ and the solvent was evaporated. The diastereomeric ratio was determined by ^1H NMR on the crude product. The crude product was then purified by flash chromatography (Et_2O/pentane mixtures). Reactions with NaHMDS and KHMDS (Table 2) were carried out in exactly the same way.

Alkylation of aziridine **1** *(BnBr)*: ^1H NMR: 1.04 (3H, d, J=7.0, CH_3CH-); 2.62 (1H, dd, J=13, 8, PhCH*H*CH-); 2.77 (2H, m, 2×C*H*N); 2.89 (1H, ddq, J=8, 7, 6, CH_3CH-); 3.11 (1H, dd, J=13, 6, PhC*H*HCH-); 3.55 (2H, dd, J=10.5, 4.5, -CH_2OBn); 3.64 (2H, dd, J=10.5, 3, -CH_2OBn); 4.48 (4H, s, 2×-CH_2Ph); 7.10-7.36 (15H, m, *Ar*-). ^{13}C NMR: δ17.1, 38.8, 40.1, 43.0, 68.1, 73.0, 126.0, 127.6, 127.7, 128.2, 128.4, 129.2, 137.7, 139.9, 186.2. IR: 1666 cm^{-1} (s, amide).

Alkylation of aziridine **1** *(AllylBr), major diastereoisomer*: ^1H NMR: 1.06 (3H, d, J=7.0, CH_3CH-); 2.19 (1H, ddd, J=14, 7, 7, -C*H*HCH-); 2.46 (1H, ddd, J=14, 7, 7, -CH*H*CH-); 2.65 (1H, ddq, J=7, 7, 7, CH_3CH-); 2.79 (2H, m, 2×C*H*N); 3.62 (2H, dd, J=10.5, 4.5, -CH_2OBn); 3.71 (2H, dd, J=10.5, 3.5, -CH_2OBn); 4.50 (4H, s, 2×-CH_2Ph); 5.02 (2H, 2×d, J=17 and J=10, CH_2:CH-); 5.74 (1H, ddd, J=17, 10, 7, CH_2:C*H*-); 7.31 (10H, m, *Ar*-). ^{13}C NMR: 17.3, 38.5, 39.1, 40.9, 58.2, 73.2, 116.8, 127.9, 128.0, 128.4, 136.0, 137.9, 186.3. IR: 1680 cm^{-1} (s, amide).

Alkylation of aziridine **1** *(octyll) major diastereoisomer*: ^1H NMR: 0.88 (3H, t, J=7 CH_3CH_2-); 1.04 (3H, d, J=7, CH_3CH-); 1.20-1.68 (14H, m, -C_7H_{14}-); 2.61 (1H, m, CH_3CH-); 2.79 (2H, m, 2×C*H*N); 3.67 (4H, m, 2×-CH_2OBn); 4.51 (4H, m, 2×-CH_2Ph); 7.32 (10H, m, *Ar*-). ^{13}C NMR: 14.2, 17.6, 22.8, 27.2, 29.4, 29.6, 29.8, 32.0, 34.3, 38.8, 40.9, 68.1, 72.9, 127.7, 127.8, 128.4, 137.9, 187.2. IR: 1667 cm^{-1} (s, amide).

Alkylation of aziridine **2** *(BnBr)*: ^1H NMR: 1.12 (3H, d, J=7, CH_3CH-); 2.62 (1H, dd, J=13, 8, PhC*H*HCH-); 2.70 (2H, m, 2×C*H*N); 2.87 (1H, ddq, J=13, 8, 7, CH_3CH-); 3.29 (6H, s, 2×CH_3-); 3.47 (4H, m, 2×-CH_2OCH_3); 7.24 (5H, m, *Ar*-). ^{13}C NMR: 18.5, 38.9, 40.0, 43.2, 58.7, 70.6, 126.2, 128.4, 129.3, 140.1, 186.3. IR: 1690 cm^{-1} (s, amide).

Alkylation of aziridine **3** *(BnBr) major diastereoisomer*: ^1H NMR: 0.89 (6H, t, J=7, 2×CH_3CH_2-); 1.18 (3H, d, J=7, CH_3CH-); 1.10-1.50 (10H, m, ^{n}Bu-); 1.68 (2H, m, ^{n}Bu-);1.88 and 2.16 (2H, m, 2×C*H*N); 2.63 (1H, m, PhC*H*HCH-); 2.69 (1H, m, CH_3CH-); 3.06 (1H, dd J=13, 7, PhCH*H*CH-); 7.29 (5H, m, *Ar*-).

Alkylation of aziridine **4** *(BnBr) major diastereoisomer*: ^1H NMR: 1.20 (3H, d, J=7, CH_3CH-); 2.32 (1H, m, CH_3CH-); 2.48 (1H, m, PhCH*H*CH-); 2.68 (1H, m, PhC*H*HCH-); 3.59 (2H, s, 2×C*H*N);

7.25 (15H, m, *Ar*-).

Alkylation of aziridine **5** *(BnBr)*: The assignment of the ^{1}H NMR spectrum of the product was difficult because of overlap of the benzylic protons, but the diastereomeric ratio could be determined on the crude product from the integrals of the methyl doublets: δ1.11 and 1.14 IR: 1690 cm^{-1} (s, amide).

Alkylation of aziridine **6** *(MeI) major diastereoisomer*: ^{1}H NMR: 1.32 (3H, d, J=7, C*H*$_3$CH-); 3.82 (1H, q, J=7, CH$_3$C*H*-); 3.89 (2H, s, 2×C*H*N); 4.00 (1H, d, J=11.5, PhCH*H*O-); 4.49 (1H, d, J=11.5, PhC*H*HO-); 7.30 (15H, m, *Ar*-). ^{13}C NMR: 19.0, 47.5, 71.7, 126.3, 126.6, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.4, 128.7, 128.8, 135.6, 137.9, 182.2.

Alkylation of aziridine **7** *(MeI) major diastereoisomer*: ^{1}H NMR: 1.40 (3H, t, J=7 C*H*$_3$CH-); 2.88 (2H, m, 2×C*H*N); 3.70 (4H, m, 2×-C*H*$_2$OBn); 4.14 (1H, q, J=7, CH$_3$C*H*-); 4.47 (6H, m, 3×-C*H*$_2$Ph); 7.29 (15H, m, *Ar*-). ^{13}C NMR: 18.8, 38.9, 67.2, 67.9, 71.8, 73.0, 127.8, 127.9, 128.6, 137.9, 182.5. IR: 1682 cm^{-1} (s, amide).

Alkylation of aziridine **8** *(BnBr) major diastereoisomer*: ^{1}H NMR: 1.25 (3H, d, J=6.5, C*H*$_3$CH-); 1.95 (1H, m, -C*H*N-); 2.21 (1H, d, J=4, -CH*H*N-); 2.65 (1H, m, CH$_3$C*H*-); 2.94 (1H, m,-C*H*HN-); 3.06 (1H, m, PhCH*H*CH-); 3.36 (1H, dd, J=10.5, 7, -CH*H*OBn); 3.46 (1H, m, PhC*H*HCH-); 3.57 (1H, dd, J=10.5, 4.5, -C*H*HOBn); 4.51 (2H, s, -C*H*$_2$Ph); 7.25 (10H, m, *Ar*-). ^{13}C NMR: 18.6, 28.0, 34.8, 40.2, 42.6, 70.4, 73.2, 126.4, 127.7, 127.8, 128.5, 129.2, 138.0, 140.1, 188.4.

Generation of the enolate of **1** *for the NMR spectroscopic study.* Aziridine **1** (0.042g, 0.124 mmol) was dissolved under nitrogen atmosphere in THF-d$_8$ (0.5 ml) in an NMR tube and the solution was cooled to -78°C. 0.240 ml (0.136 mmol) of a 0.6M THF solution of LiHMDS was transferred to a dry, nitrogen flushed flask and the THF was pumped off. The dry residue was then dissolved in 0.3 ml of THF-d$_8$ and the resultant solution was added to the cooled NMR tube. The NMR experiments were run at -80°C and the enolate was stable for several hours at that temperature. The potassium enolate was prepared in a similar fashion (0.5M KHMDS in toluene).

General procedure for aldol reactions.

The aziridine (1 eq.) was dissolved in THF and cooled with stirring to -78°C. LiHMDS (1.1 eq. of 1M THF solution) was added and the reaction mixture was stirred for ca 45 minutes. The aldehyde (1.2 eq.) was added and when TLC (Et$_2$O/pentane mixtures) showed complete reaction (after 5-15 minutes) the reaction mixture was poured into Et$_2$O/sat. NH$_4$Cl (aq.). After separation of the layers the organic phase was washed twice with H$_2$O, once with sat. NaCl (aq.), dried over MgSO$_4$ and the solvent was evaporated. The diastereomeric ratio was determined by ^{1}H NMR on the crude product. The crude product was then purified by flash chromatography (Et$_2$O/pentane mixtures).

Aldol reaction of aziridine **1** *(PhCHO, compound* **10***)*: ^{1}H NMR: 0.92 (3H, d, J=7.0, C*H*$_3$CH-); 2.81 (2H, m, 2×C*H*N); 2.87 (1H, qd, J=7, 2.8, CH$_3$C*H*-); 3.55 (2H, dd, J=10.5, 4.8, -C*H*$_2$OBn); 3.70 (2H, dd, J=10.5, 2.9, -C*H*$_2$OBn); 3.82 (1H, d, J=1.9, *HO*-); 4.47 (4H, s, 2×-C*H*$_2$Ph); 5.08 (1H, dd, J=2.8, 1.9, PhC*H*(OH)-); 7.22 (15H, m, *Ar*-). ^{13}C NMR: 10.3, 38.7, 47.0, 67.7, 73.1, 125.8, 126.9, 127.7, 127.8, 128.0, 128.4, 137.2, 141.3, 187.3. IR: 3470 cm^{-1} (b, OH); 1664 (s, amide).

Aldol reaction of aziridine **1** *(CH$_3$CH$_2$CHO) major syn diastereoisomer*: ^{1}H NMR: 0.84 (3H, t, J=7, C*H*$_3$CH$_2$-); 1.17 (3H, d, J=7, C*H*$_3$CH-); 1.41 (2H, m, CH$_3$C*H*$_2$-); 2.65 (1H, m, CH$_3$C*H*-); 2.86 (2H, m, 2×C*H*N); 3.53 (1H, m, CH$_2$C*H*(OH)-); 3.68 (4H, m,2×-C*H*$_2$OBn); 4.52 (4H, m, 2×-C*H*$_2$Ph); 7.30 (10H, m, *Ar*-). Other signals not assigned due to strong overlap. IR: 3429 cm^{-1} (b, OH); 1659 (s, amide).

Aldol reaction of aziridine **2** *(PhCHO) major diastereoisomer*: ^{1}H NMR: 1.05 (3H, d, J=7.0,

CH_3CH-); 2.82 (2H, m, 2×C*H*N); 2.90 (1H, dq, J=7, 2.8, CH_3C*H*-); 3.37 (6H, s, 2×CH_3O-); 3.55 (2H, dd, J=10.5, 4.5, -CH_2OCH_3); 3.67 (2H, dd, J=10.5, 2.9, -CH_2OCH_3); 3.92 (1H, d, J=1.9, *H*O-); 5.14 (1H, dd, J=2.8, 1.9, PhC*H*(OH)-); 7.31 (5H, m, *Ar*-). IR: 3498 cm^{-1} (b, OH); 1678 (s, amide).

Aldol reaction of aziridine **16** *(PhCHO)*: ^{1}H NMR: 0.90 (6H, t, J=7 2×CH_3CH_2-); 1.11 (3H, d, J=7, CH_3CH-); 1.15-1.50 (10H, m, ^{n}Bu-); 1.81 (2H, m, ^{n}Bu-); 2.30 (2H, m, 2×C*H*N); 2.67 (1H, qd, J=7, 2.5, CH_3C*H*-); 4.08 (1H, d, J=1.5, *H*O-); 5.10 (1H, dd, J=2.5, 1.5,-CHC*H*(OH)-); 7.20-7.38 (5H, m, -Ar). IR: 3437 cm^{-1} (b, OH); 1648 (s, amide).

Aldol reaction of aziridine **16** *(CH_3CH_2CHO) major diastereoisomer*: ^{1}H NMR: 0.91 (6H, t, J=7, 2×$CH_3CH_2CH_2$-); 0.95 (3H, t,J=7, CH_3CH_2-); 1.20 (3H, d, J=7, CH_3CH-); 1.28-1.49 (10H, m, 2×^{n}Bu-); 1.54 (2H, m, CH_3CH_2-); 1.78 (2H, m, ^{n}Bu-); 2.29(2H, m, 2×C*H*N); 2.49 (1H, qd, J=7, 2.5, CH_3C*H*-); 3.58 (1H, d, J=2.5, *H*O-); 3.68 (1H, m, -CHC*H*(OH)-). IR: 3473 cm^{-1} (b, OH); 1650 (s, amide).

Aldol reaction of aziridine **16** *(CH_3CH:CHCHO) major diastereoisomer*: ^{1}H NMR: 0.90 (6H, t, J=7 2×CH_3CH_2-); 1.20 (3H, d, J=7, CH_3CH-); 1.11-1.51 (10H, m, 2×^{n}Bu-); 1.70 (3H, d, J=6.5, CH_3CH:CH-); 1.80 (2H, m, ^{n}Bu-); 2.29 (2H, m, 2×C*H*N); 2.50 (1H, qd, J=7, 3, CH_3C*H*-); 3.58 (1H, d, J=2.5, *H*O-); 4.34 (1H, m, -CHC*H*(OH)-); 5.48 (1H, ddd, J=15, 6, 1.5,-CH(OH)C*H*-); 5.73 (1H, dq, J=15, 6.5, CH_3C*H*:CH-). ^{13}C NMR: 11.8, 14.2, 18.0, 22.5, 29.5, 31.6, 43.8, 46.4, 73.0, 127.9, 130.4, 187.4. IR: 3462 cm^{-1} (b, OH); 1650 (s, amide).

Aldol reaction of aziridine **16** *($CH_3(CH_2)_4CHO$) major diastereoisomer*: ^{1}H NMR: 0.90 (9H, t, J=7 3×CH_3CH_2-); 1.20 (3H, d, J=7, CH_3CH-); 1.11-1.56 (18H, m, 3×^{n}Bu-); 1.79 (2H, m,^{n}Bu-); 2.28 (2H, m, 2×C*H*N); 2.45 (1H, qd, J=7, 2.5, CH_3C*H*-); 3.56 (1H, d, J=2.5, *H*O-); 3.86 (1H, m, -CHC*H*(OH)-). ^{13}C NMR: 11.2, 14.0, 14.1, 22.5, 22.6, 25.9, 29.8, 31.6, 32.0, 33.7, 43.8, 45.4, 71.5, 188.0. IR: 3472 cm^{-1} (b, OH); 1658 (s, amide).

Aldol reaction of aziridine **16** *($(CH_3)_2CHCHO$)*: ^{1}H NMR: 0.83 (3H, d, J=7, $CH_3CH(CH_3)$-); 0.90 (6H, t, J=7 2×CH_3CH_2-); 1.02 (3H, d, J=7, $CH_3CH(CH_3)$-); 1.19 (3H,d, J=7, CH_3CH-); 1.12-1.49 (10H, m, 2×^{n}Bu-); 1.71 (1H, m, -C*H*$(CH_3)_2$); 1.78 (2H, m,^{n}Bu-); 2.29 (2H, m, 2×C*H*N); 2.63 (1H, qd, J=7, 2.5, CH_3C*H*-); 3.44 (1H, ddd, J=9, 2.5, 1.8, -CHC*H*(OH)-); 3.77 (1H, d, J=1.8, *H*O-). ^{13}C NMR: 10.8, 14.0, 19.0, 19.7, 22.5, 29.4, 30.1, 31.8, 42.4, 43.9, 76.9, 188.3. IR: 3462 cm^{-1} (b, OH); 1650 (s, amide).

Aldol reaction of aziridine **16** *($(CH_3)_3CCHO$)*: ^{1}H NMR: 0.90 (6H, t, J=7 2×CH_3CH_2-); 0.98 (9H, s, 3×CH_3); 1.24 (3H,d, J=7, CH_3CH-); 1.09-1.50 (10H, m, 2×^{n}Bu-); 1.80 (2H, m,^{n}Bu-); 2.29 (2H, m, 2×C*H*N); 2.73 (1H, qd, J=7, 2, CH_3C*H*-); 3.34 (1H, d, J=2.3, *H*O-); 3.55 (1H, dd, J=2.3, 2, -CHC*H*(OH)-). ^{13}C NMR: 12.9, 14.0, 22.2, 27.5, 29.6, 31.6, 35.4, 42.3, 43.7, 78.0, 188.6. IR: 3425 cm^{-1} (b, OH); 1651 (s, amide).

Aldol reaction of aziridine **16** *(PhCH:CHCHO) major diastereoisomer*: ^{1}H NMR: 0.90 (6H, t, J=7 2×CH_3CH_2-); 1.26 (3H,d, J=7, CH_3CH-); 1.10-1.51 (10H, m, 2×^{n}Bu-); 1.82 (2H, m,^{n}Bu-); 2.30 (2H, m, 2×C*H*N); 2.62 (1H, qd, J=7, 2, CH_3C*H*-); 3.85 (1H, d, J=3, *H*O-); 4.61 (1H, m, -CHC*H*(OH)-); 6.19 (1H, dd, J=16, 5.5, -CH(OH)C*H*:CH-); 6.68 (1H, d, J=16, ArC*H*:CH-); 7.19-7.41 (5H, m, *Ar*-). ^{13}C NMR: 12.0, 14.0, 22.3, 29.5, 31.5, 43.7, 46.2, 72.6, 126.5, 127.7, 128.5, 129.1, 131.0, 136.9, 187.1.

Aldol reaction of aziridine **16** *(1-naphthaldehyde) major diastereoisomer (syn)*: ^{1}H NMR: 0.91 (6H, t, J=7 2×CH_3CH_2-); 1.08 (3H,d, J=7, CH_3CH-); 1.12-1.52 (10H, m, 2×^{n}Bu-); 1.87 (2H, m,^{n}Bu-); 2.32 (2H, m, 2×C*H*N); 2.91 (1H, qd, J=7, 2, CH_3C*H*-); 4.33 (1H, br s, *H*O-); 5.98 (1H, br s, -CHC*H*(OH)-); 7.49 (3H, m, *Ar*-); 7.84 (4H, m, *Ar*-). ^{13}C NMR: 11.0, 14.0, 22.3, 29.5, 31.5, 43.8, 45.8, 69.8, 122.3, 124.4, 125.5,125.6, 125.9, 127.8, 129.4, 129.7, 133.8, 136.1, 187.9. IR: 3463 cm^{-1} (b, OH);

1646 (s, amide).

Minor diastereoisomer (anti): J(CH_3CH-, -CHCH(OH)-)=7.

Aldol reaction of aziridine **16** *(2-naphthaldehyde) major diastereoisomer (syn)*: ^{1}H NMR: 0.92 (6H, t, J=7 2×CH_3CH_2-); 1.13 (3H,d, J=7, CH_3CH-); 1.12-1.53 (10H, m, 2×^{n}Bu-); 1.84 (2H, m,^{n}Bu-); 2.32 (2H, m, 2×CHN); 2.80 (1H, dq, J=7, 2.8, CH_3CH-); 4.25 (1H, d, J=1.5, HO-); 5.29 (1H, dd, J=2.8, 1.5, -CHCH(OH)-); 7.43 (3H, m, *Ar*-); 7.84 (4H, m, *Ar*-). ^{13}C NMR: 11.0, 14.0, 22.3, 29.7, 31.6, 43.9, 47.7, 73.2, 124.0, 124.9, 125.8, 126.0, 127.8, 127.9, 128.1, 133.0, 133.5, 139.0, 187.8. IR: 3454 cm^{-1} (b, OH); 1649 (s, amide).

Minor diastereoisomer (anti): J(CH_3CH-, -CHCH(OH)-)=7.

Aldol reaction of aziridine **16** *((R)-CH_3CH(OTBDMS)CHO)*: ^{1}H NMR: 0.08 (6H, s, 2×-SiCH_3); 0.89 (9H, s, -Si^t*Bu*); 0.91 (6H, t, J=7 2×CH_3CH_2-); 1.20 (3H,d, J=7, CH_3CH-); 1.21 (3H, d, J=6, CH_3CH(OSi)-); 1.07-1-50 (10H, m, 2×^{n}Bu-); 1.84 (2H, m,^{n}Bu-); 2.28 (2H, m, 2×CHN); 2.80 (1H, dq, J=7, 3.5, CH_3CH-); 3.50 (1H, d, J=1.5, HO-); 3.61 (1H, ddd, J=7, 3.5, 1.5, -CHCH(OH)-); 3.75 (1H, dd, J=7, 6, CH_3CH(OSi)-). IR: 3480 cm^{-1} (b, OH); 1654 (s, amide).

Aldol reaction of aziridine **16** *((S)-CH_3CH(OTBDMS)CHO) major diastereoisomer*: ^{1}H NMR: 0.07 (6H, s, 2×-SiCH_3); 0.89 (9H, s, -Si^t*Bu*); 0.91 (6H, t, J=7 2×CH_3CH_2-); 1.16 (3H, d, J=6, CH_3CH(OSi)-); 1.21 (3H,d, J=7, CH_3CH-); 1.06-1,51 (10H, m, 2×^{n}Bu-); 1.86 (2H, m,^{n}Bu-); 2.27 (2H, m, 2×CHN); 2.57 (1H, p, J=7, CH_3CH-); 2.70 (1H, d, J=6, HO-); 3.60 (1H, m, -CHCH(OH)-); 3.89 (1H, m, CH_3CH(OSi)-). IR: 3546 cm^{-1} (b, OH); 1655 (s, amide).

Aldol reaction of aziridine **16** *(2,5-dimethoxy-3-nitrobenzaldehyde)*: ^{1}H NMR: 0.93 (3H, t, J=6.5, CH_3CH_2-); 1.04 (3H, d, J=7, CH_3CH-); 1.20-1.91 (12H, m, 2×^{n}Bu-); 2.34 (2H, m, 2×CHN); 2.89 (1H, qd, J=7, 1.8, CH_3CH-); 3.80 (3H, s, CH_3O-); 3.85 (3H, s, CH_3O-); 4.76 (1H, d, J=1, HO-); 5.30 (1H, br s,(dd J=1.8, 1.0,) -CHCH(OH)-);7.30 (1H, d, J=3, -ArH); 7.46 (1H, d, J=3, -ArH). ^{13}C NMR: 11.1, 14.0, 22.4, 29.4, 31.2, 43.8, 44.4, 56.0, 62.3, 68.0, 108.8, 119.3, 138.4, 143.3, 143.6, 155.2, 188.7. IR: 3471 cm^{-1} (b, OH); 1665 (s, amide); 1458 (s, NO_2); 1352 (s, NO_2).

Aldol reaction of aziridine **4** *(PhCHO) major diastereoisomer*: ^{1}H NMR: 1.14 (3H, d, J=7.0, CH_3CH-); 2.21 (1H, qd, J=7, 2.0, CH_3CH-); 3.91 (2H, s, 2×CHN); 4.01 (1H, d, J=1.8, HO-); 4.63 (1H, dd, J=2.0, 1.8, PhCH(OH)-); 6.79 -7.30 (15H, m, *Ar*-). IR: 3492 cm^{-1} (b, OH); 1663 (s, amide).

Aldol reaction of aziridine **4** *(CH_3CH_2CHO) major diastereoisomer*: ^{1}H NMR: 0.98 (3H, t, J=7, CH_3CH_2-); 1.26 (3H, d, J=7, CH_3CH-); 1.98 (1H, dq, J=7, 1.5, CH_3CH-); 2.14-2.45 (2H, m, CH_3CH_2-); 3.34 (1H, m, CH_2CH(OH)-); 3.48 (1H, d, J=1.5, HO-); 3.86 (2H, s, 2×CHN); 7.31 (10H, m, *Ar*-). IR: 3492 cm^{-1} (b, OH); 1658 (s, amide).

Aldol reaction of aziridine **5** *(PhCHO) major diastereoisomer*: ^{1}H NMR: 1.01 (3H,d, J=7, CH_3CH-); 2.51 (2H, dd, J=14, 7, -CH_2Ph); 2.52 (1H, m, CH_3CH-); 2.71 (2H, m, 2×CHN); 3.12 (2H, dd, J=14, 4, -CH_2Ph); 3.80 (1H, br s, HO-); 5.07 (1H, apparent s, -CHCH(OH)-); 7.05-7.34 (15H, m, *Ar*-). IR: 3465 cm^{-1} (b, OH); 1653 (s, amide).

Aldol reaction of aziridine **5** *(CH_3CH_2CHO) major diastereoisomer*: ^{1}H NMR: 0.90 (3H, t, J=7, CH_3CH_2-); 1.10 (3H, d, J=7, CH_3CH-); 1.27 and 1.47 (1H each, m, CH_3CH_2-); 2.27 (1H, qd, J=7, 2.8, CH_3CH-); 2.54 (2H, dd, J=14, 7, -CH_2Ph); 2.72 (2H, m, 2×CHN); 3.14 (2H, dd, J=14, 4, -CH_2Ph); 3.39 (1H, d, J=1.5, HO-); 3.74 (1H, m, -CHCH(OH)-); IR: 3474 cm^{-1} (b, OH); 1664 (s, amide).

Aldol reaction of aziridine **15** *(CH_3CH_2CHO) major diastereoisomer*: ^{1}H NMR: 0.92 (6H, d, J=7, -CH(CH_3)$_2$); 0.95 (3H,d, J=7, CH_3CH_2-); 1.13 (6H, d, J=7, -CH(CH_3)$_2$); 1.17 (3H, d, J=7, CH_3CH-);

2.18 (2H, m, 2×C*H*N); 2.57 (1H, qd, J=7, 2.8, CH_3CH-); 3.57 (1H, d, J=2.0, *H*O-); 3.81 (1H, m, -CHC*H*(OH)-). IR: 3452 cm^{-1} (b, OH); 1652 (s, amide).

Typical procedures for removal of the aziridine

(i). With $LiAlH_4$: The alkylation product from aziridine **1** and BnBr (0.065 g, 0.152 mmol) was dissolved in Et_2O (5 ml) and cooled to 0°C. $LiAlH_4$ (0.0014 g, 0.038 mmol) was added and the reaction was stirred at RT. After 3h the reaction was quenched with H_2O. The phases were separated and the aqueous phase was extracted twice with Et_2O. The combined organics were washed three times with H_2O, once with brine and dried over $MgSO_4$. The solvent was evaporated and the aldehyde and the N-H-aziridine were separated by flash chromatography (40% Et_2O/pentane-EtOAc) giving 60 % yield of recovered N-H-aziridine and 40% yield of (*R*)-2-methyl-3-phenyl-propionaldehyde (volatile). $[\alpha]_D^{20}$=-4.75° (c=0.40, acetone) (Lit. for enantiomer $[\alpha]^{20}_D$=+4°, c=1.25, acetone)[23]. ^1H NMR: 1.03 (3H, d, J=7, CH_3CH-); 2.54 (1H, dd, J=13, 8, PhC*H*HCH-); 2.61 (1H, m, -C*H*CH_3); 3.04 (1H, dd, J=13, 6, PhCH*H*CH-); 7.19 (5H, m, *Ph*-); 9.68 (1H, s, -C*H*O). IR: 1721 cm^{-1} (s, aldehyde).

(ii). With LiOOH: The alkylation product from aziridine **1** and BnBr (0.150 g, 0.350 mmmol) was dissolved in a 3:1 mixture of THF:H_2O. H_2O_2 (30% in H_2O; 0.198 g, 1.75 mmol) and LiOH (0.0139 g, 0.699 mmol) were added and the reaction was stirred at RT for 5 days. The reaction mixture was cooled to 0°C and the excess LiOOH was quenched with Na_2SO_3. Saturated $NaHCO_3$ was added until pH=10. The THF was evaporated and the residue was diluted with H_2O and extracted three times with CH_2Cl_2. Drying over $MgSO_4$, evaporation of the solvent and purification of the residue by flash chromatography (EtOAc) gave 0.055 g (56% yield) of recovered N-H-aziridine. The aqueous phase was acidified with conc. HCl to pH=2 and extracted three times with EtOAc. Drying over $MgSO_4$, evaporation of the solvent and purification by flash chromatography gave 0.036g (63% yield) of (*R*)-2-methyl-3-phenyl-propionic acid. $[\alpha]_D^{22}$=-29.7° (c=0.90, CH_2Cl_2) (Optically pure material[6] showed $[\alpha]^{22}_D$=-31.1°, c=1.03, CH_2Cl_2). ^1H NMR: 1.18 (3H, d, J=7, CH_3CH-); 2.67 (1H, dd, J=13, 8, PhCH*H*CH-); 2.76 (1H, m, -C*H*CH_3); 3.08 (1H, dd, J=13, 6, PhC*H*HCH-); 7.22 (5H, m, -*Ph*).

This procedure could also be used for the aldol products. For example, hydrolysis of the product **10** from reaction of **1** and benzaldehyde yielded (2*R*,3*R*)-3-hydroxy-3-phenyl-2-methylpropanoic acid, $[\alpha]_D^{22}$=+28.3° (c=1.03, CH_2Cl_2) (Lit. for enantiomer $[\alpha]_D^{22}$=-26.4° (c=1.04, CH_2Cl_2).[24] Yield: 72%.

Other typical examples:

Hydrolysis of the product from reaction of **16** with benzaldehyde yielded (2*S*,3*S*)-3-hydroxy--3-phenyl-2-methylpropanoic acid, $[\alpha]_D^{22}$=-27.0° (c=0.70, CH_2Cl_2) (Lit. $[\alpha]_D^{22}$=-26.4° (c=1.04, CH_2Cl_2).[24] Yield: 80%.

Hydrolysis of the product from reaction of **16** with 2,2-dimethylpropionic aldehyde yielded (2*S*,3*S*)-3-hydroxy-2,4,4-trimethylpentanoic acid, $[\alpha]_D^{22}$=-16.0° (c=0.25, CH_2Cl_2) (Lit. $[\alpha]_D^{22}$=-17.0° (c=0.50, CH_2Cl_2).[25] Yield: 78%.

Hydrolysis of the product from reaction of **16** with propionic aldehyde yielded (2*S*,3*R*)-3-hydroxy-2-methylpentanoic acid, $[\alpha]_D^{23}$=+3.02° (c=1.72, CH_2Cl_2) (Lit. for enantiomer $[\alpha]_D^{23}$=-4.1° (c=1.72, CH_2Cl_2).[26] Yield: 74%.

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