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Chiral lithium amide base-mediated rearrangement of *meso*-cyclohexene oxides: asymmetric synthesis of amino- and aziridinocyclohexenols

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Two different chiral lithium amide base routes for the synthesis of amino- and aziridino-containing cyclohexenols have been explored. The first strategy involved the diastereoselective preparation of novel *meso*-aziridinocyclohexene oxides and their subsequent enantioselective rearrangement using chiral bases. In this approach, the diphenylphosphinoyl nitrogen protecting group proved optimal and aziridinocyclohexenols of 47–68% ee were obtained. Of particular note was the smooth rearrangement of the epoxide to an allylic alcohol in the presence of an aziridine: under optimised chiral base conditions, the aziridine remained essentially unaffected. A second more straightforward strategy for introduction of an amino functionality was also investigated: (1*S*,4*R*,5*S*)- and (1*R*,4*R*,5*S*)-4,5-bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enols, readily prepared in >95% ee using a chiral base approach, were subjected to Mitsunobu substitution using a sulfonamide and Overman rearrangement.

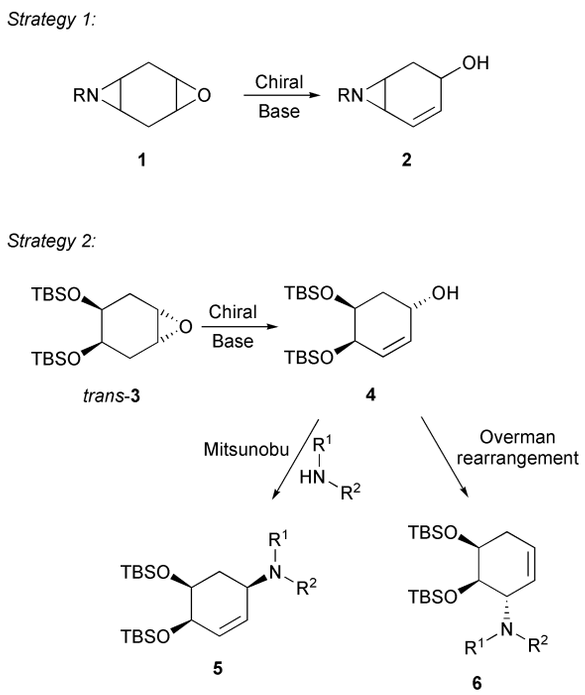
Introduction

The chiral lithium amide base-mediated rearrangement of *meso*-epoxides to the corresponding allylic alcohols is a widely studied and useful reaction in asymmetric synthesis.[1] Recent highlights in this area have involved the use of sub-stoichiometric amounts of chiral lithium amide bases in the presence of excess achiral (bulk) bases[2–4] and the extension of the reaction to functionalised epoxide substrates.[5,6] Our interest in epoxide rearrangement reactions, spanning the last six years, has focused on the development of a new norephedrine-derived chiral base[7,8] and on extending the reaction to new types of *meso*-epoxides. For example, we were the first group to report the enantioselective rearrangement of bis-protected *meso*-4,5-dihydroxycyclohexene oxides,[7–10] *meso*-4-amino substituted cyclopentene oxides[7,11] and *meso*-aziridinocyclohexene oxides.[12] In addition, we reported the first examples of diastereoselective epoxide rearrangements of chiral bis-protected 4,5-dihydroxycyclohexene oxides[13] and we have also developed epoxide rearrangement methodology suitable for use in synthesis.[14–16]

Since we had been successful in developing a general strategy for the diastereo- and enantiocontrolled preparation of polyhydroxylated cyclohexanes, exemplified by a synthesis of conduritol F,[15] we decided to investigate whether related chiral base methods could be used to synthesise amino conduritol analogues. Amino conduritols have proven to be popular targets in recent times[17] and two different strategies for introduction of the amino functionality were envisaged (Scheme 1).

In strategy 1, we proposed to investigate the chiral base-mediated rearrangement of *meso*-aziridino epoxides **1** to the corresponding aziridino allylic alcohols **2**. There were two key issues to address in this new approach to amino conduritol analogues: (i) methods for the diastereoselective synthesis of *cis*- and *trans*-aziridino epoxides **1** needed to be developed and (ii) conditions for the chiral base reactions which would rearrange the epoxide but leave the aziridine untouched needed to be found. Full details of our studies in these areas are described in this paper: in particular, by careful choice of protecting group, reaction conditions and chiral base, it proved possible to obtain diastereomerically pure aziridino allylic alcohols **2** in good enantiomeric excess (47–68% ee).[18]

A much simpler approach (strategy 2) involved use of allylic alcohol **4** (which can be prepared in >95% ee from epoxide *trans*-**3** by chiral base-mediated desymmetrisation[10]) and an investigation of ways of introducing the required nitrogen functionality. Of the methods available, we selected a direct Mitsunobu substitution with an appropriate amino source[19,20] to give allylic amines **5** and an Overman rearrangement approach[21] to give allylic amines **6**. As described in this paper, both of these methods also proved successful for introducing the required amino functionality.[18]



Scheme 1

Results and discussion

Strategy 1: synthesis and enantioselective rearrangement of *meso*-aziridinocyclohexene oxides

Prior to our work, aziridinocyclohexene oxides **1** were an unknown class of compound. However, since the corre-

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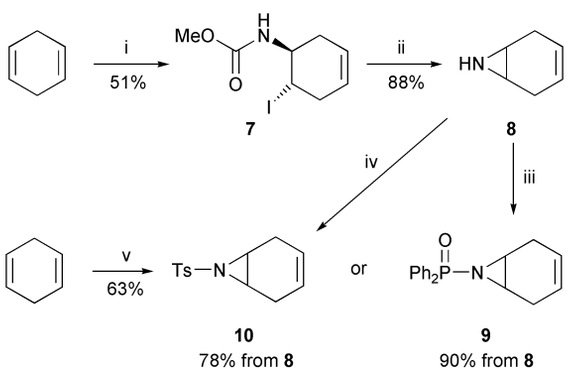
Table 1 Diastereoselective epoxidation of aziridinocyclohexenes **9** and **10**

Entry	R	Alkene	Epoxidation method	Epoxide	*trans*–*cis*[a]	Yield of *trans* (%)[b]	Yield of *cis* (%)[b]
1	Ph_2PO	**9**	MCPBA[c]	**11**	10 : 90	9	81
2	Ph_2PO	**9**	Dioxirane[d]	**11**	64 : 36	56	31
3	Ts	**10**	MCPBA[c]	**12**	42 : 58	40	55
4	Ts	**10**	Dioxirane[d]	**12**	91 : 9	83	9

[a] Ratio determined by ^{1}H NMR spectroscopy on the crude product mixtures. [b] Isolated yield of pure epoxide after chromatography. [c] MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 16 h. [d] Oxone®, trifluoroacetone, Na_2·EDTA, MeCN–water, $NaHCO_3$, 0 °C, 2.5 h.

sponding aziridinocyclohexenes had been prepared previously[22,23] and we had an ongoing interest in stereoselective epoxidation reactions,[24,25] we elected to investigate an epoxidation route to *meso*-epoxides **1**. By varying the nitrogen protecting group and the epoxidation conditions, we hoped to develop stereoselective syntheses of *cis*- and *trans*-diastereomeric epoxides **1**.

Our preferred approaches for the synthesis of the required *N*-protected aziridinocyclohexenes are summarised in Scheme 2. Using a method developed by Heathcock *et al.*,[26] and utilised



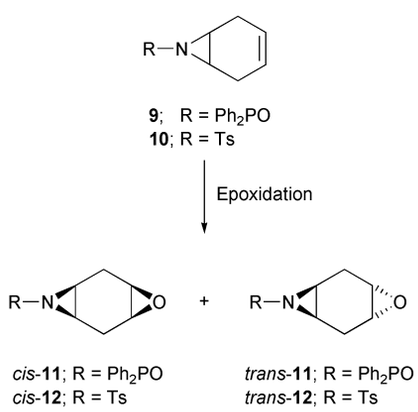
Scheme 2 *Reagents and conditions:* i, (a) I_2, AgOCN, THF, −20 °C, 6 h; (b) MeOH, reflux, 1.5 h; ii, KOH, water, reflux, 1 h; iii, $Ph_2P(O)Cl$, Et_3N, DMAP, CH_2Cl_2, rt, 50 h; iv, TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 20 h; v, Chloramine-T·$3H_2O$, 10 mol% $PhMe_3N^+Br_3^-$, MeCN, rt, 18 h.

by Paquette *et al.* in the synthesis of a range of aziridinocyclohexenes,[22] treatment of cyclohexa-1,4-diene with *in situ* formed iodine isocyanate followed by reaction with methanol generated iodocarbamate **7** (51% recrystallised yield on a multi-gram scale). Conversion of iodocarbamate **7** into the NH aziridine **8** (88% yield) was accomplished by reaction with aqueous potassium hydroxide at reflux. Aziridine **8** is a relatively volatile compound and must be carefully isolated by Kugelrohr distillation. A direct synthesis of aziridine **8** from cyclohexa-1,4-diene which did not require the intermediacy of iodocarbamate **7**, reported by Paquette *et al.*,[22] was not reproducible in our hands. The Heathcock methodology was a convenient way of preparing aziridine **8**. In general, we preferred to store stocks of iodocarbamate **7** and convert it into aziridine **8** immediately prior to *N*-protection.

Although we initially prepared aziridines with a wide range of *N*-protecting groups (N–Ph_2PO, N–Ts, N–CO_2Me, N–Cbz, N–Boc, N–Bz, N–Ac), it transpired that carbamate and amido protecting groups were useless for the present work (*vide infra*). Standard protection of aziridine **8** generated *N*-diphenylphosphinoyl and *N*-tosylaziridinocyclohexenes **9** and **10** in high yields (Scheme 2). The diphenylphosphinoyl *N*-protecting group was originally introduced by Ramage and coworkers[27] and has recently gained popularity as an aziridine protecting/activating group.[28] The alternative, direct synthesis of *N*-tosylaziridine from cyclohexa-1,4-diene by monoaziridination was briefly investigated: use of iodinane PhI=NTs in the presence of copper(II) triflate,† according to the method of Evans *et al.*,[29] gave a low 20% yield of *N*-tosylaziridine **10** of poor purity. In contrast, reaction of cyclohexa-1,4-diene with Chloramine-T (TsNCl·$3H_2O$) and phenyltrimethylammonium tribromide, Sharpless's conditions,[30] produced a good 63% yield of the monoaziridine **10**.

With *N*-protected aziridinocyclohexenes in hand, we were ready to investigate their epoxidation, with particular emphasis on the stereoselectivity. Surprisingly, we found that carbamate (*e.g.* N–CO_2Me, N–Cbz, N–Boc) and amide (N–Bz, N–Ac) protecting groups were of no use in the epoxidation reactions using either MCPBA or a dioxirane generated *in situ*:[31] ^{1}H NMR spectroscopy indicated the formation of several products, none of which appeared to be the desired epoxides and none of which could be isolated pure in acceptable yields. We are still unable to offer an explanation for the complete lack of success of these epoxidation reactions. In contrast, *N*-diphenylphosphinoyl-protected cyclohexene **9** and *N*-tosyl-protected cyclohexene **10** behaved in the expected fashion upon exposure to MCPBA.

The full results of the epoxidation of alkenes **9** and **10** using buffered MCPBA in dichloromethane and *in situ* generated methyl(trifluoromethyl)dioxirane (Yang's method[31]) are presented in Scheme 3 and Table 1. The stereoselectivity of each



Scheme 3

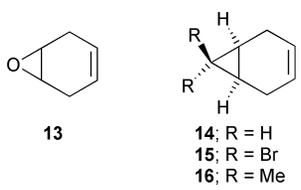
epoxidation reaction was determined by analysis of the ^{1}H NMR spectra of the crude product mixtures and the *cis*–*trans* diastereoisomers were identified by independent syntheses of aziridines *trans*-**11** and *trans*-**12** from a compound of known stereochemistry (*vide infra*). In each case, the diastereomeric *cis*- and *trans*-aziridino epoxides were easily separated by chromatography and high yields of epoxides were obtained. Although the MCPBA epoxidations could be carried out on a multi-gram scale, the dioxirane reactions were a lot less robust in terms of scale-up (>1 mmol of alkene). The dioxirane results in Table 1 were obtained on a 0.7–0.9 mmol scale.

It is possible to identify some trends from the epoxidation results presented in Table 1. Epoxidation of alkenes **9** and **10** is *cis*-selective using MCPBA in dichloromethane (Table 1, entries 1 and 3) and the degree of *cis*-selectivity (90 : 10) is significantly higher for the diphenylphosphinoyl protecting group (Table 1, entry 1). In contrast, epoxidation using a dioxirane is *trans*-selective (Table 1, entries 2 and 4) and a much higher degree of

† The IUPAC name for triflate is trifluoromethanesulfonate.

trans-selectivity (91 : 9) is obtained with a tosyl protecting group (Table 1, entry 4). Taken together, the epoxidation results indicate that by suitable choice of aziridine protecting group and reaction conditions, it is possible to selectively synthesise aziridino epoxides with *cis* or *trans* stereochemistry: an 81% isolated yield of epoxide *cis*-**11** (Table 1, entry 1) and an 83% yield of epoxide *trans*-**12** (Table 1, entry 4) were obtained. Thus, multi-gram quantities of epoxide *cis*-**11** could be generated easily but it must be stressed that the dioxirane reaction used for the preparation of epoxide *trans*-**12** could not be carried out effectively on a scale >1 mmol.

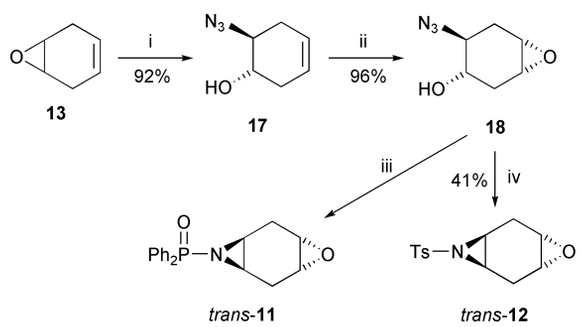
Much is known about diastereoselective epoxidation reactions in general[32] and the epoxidation of bicyclic-fused alkenes related to **9** and **10** has been described. For example, epoxidation of 4,5-epoxycyclohexene **13**[33] and norcar-3-enes **14**–**16**[34] using MCPBA are generally *trans*-selective. Although the exact conformation of these cyclohexenes is unknown, epoxidation *trans* to the three-membered ring appears to be the norm. This is supported by the fact that epoxidation of sterically hindered norcar-3-enes **15** and **16** are completely *trans*-selective whereas reaction of norcar-3-ene **14** gave a 62 : 38 mixture of *trans*- and *cis*-epoxides.[34]



13 **14**; R = H **15**; R = Br **16**; R = Me

Set against these literature results, it is surprising to note that MCPBA epoxidation of aziridinocyclohexenes **9** and **10** is *cis*-selective (Table 1, entries 1 and 3). We suspect that the *N*-diphenylphosphinoyl and *N*-tosyl groups hydrogen bond to the MCPBA leading to some degree of *cis*-direction. The *N*-diphenylphosphinoyl groups is clearly the better hydrogen bonding group (Table 1, entry 1) and this has some literature precedent.[35] Apparently, the *trans*-selective epoxidation of aziridinocyclohexenes **9** and **10** using a dioxirane reagent (Table 1, entries 2 and 4) are more in line with the literature precedent in related systems. As we have noted previously,[24,25] we believe that Yang's *in situ* generated methyl(trifluoromethyl)dioxirane (acetonitrile–water solvent system) overturns any *cis*-directing effects observed with MCPBA.

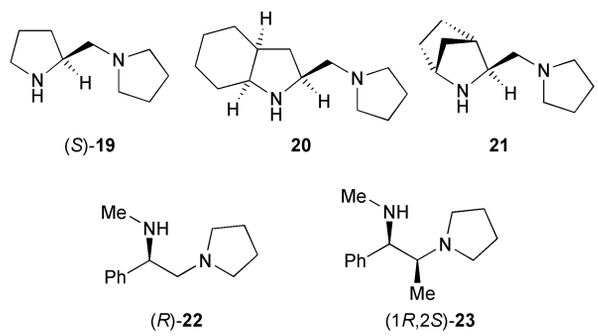
The relative stereochemistry of all the epoxides described in this paper was established as outlined in Scheme 4. Thus,



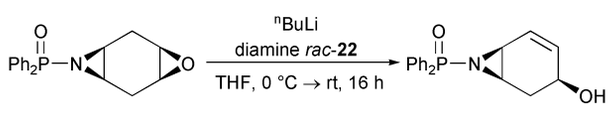
Scheme 4 *Reagents and conditions:* i, NaN_3, NH_4Cl, reflux, 8 : 1 $MeOCH_2CH_2OH$–water, 24 h; ii, ^tBuOOH, $Mo(CO)_6$, benzene, reflux, 2.5 h; iii, (a) Ph_3P, THF, reflux, 20 h; (b) $Ph_2P(O)Cl$, Et_3N, DMAP, CH_2Cl_2, rt, 20 h; (a) Ph_3P, THF, reflux, 20 h; (b) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 20 h.

known[23] azido alcohol **17** (prepared by reaction of the monoepoxide of cyclohexa-1,4-diene[36] with sodium azide) was subjected to a molybdenum-catalysed, hydroxy-directed epoxidation reaction[37,38] to generate epoxide **18** in 96% yield. Epoxide **18** was obtained as the sole diastereomeric product and as a result of the hydroxy direction, the azido group and the epoxy group are *trans* relative to each other. Hence, epoxide **18** furnished aziridino epoxides *trans*-**11** and *trans*-**12** after a Staudinger reaction[39] and subsequent *N*-protection. Comparison of ^1H and ^{13}C NMR spectroscopic data allowed assignment of the *cis*–*trans* stereochemistry in the aziridino epoxides generated from the previously described epoxidation reactions. We were unable to obtain a pure sample of epoxide *trans*-**11** *via* this sequence as it was always contaminated with triphenylphosphine oxide (even after careful chromatography).

Next, we initiated our study into the enantioselective rearrangement of both diastereomers of aziridino epoxides **11** and **12** to the corresponding allylic alcohols. Over the last few years, a range of chiral diamines has been developed and used for epoxide rearrangements. To date, the most useful chiral bases for rearranging epoxides are derived from diamines **19** and **20** (introduced by Asami[40,41]), diamine **21** (developed by Andersson[2,42]), diamine **22** (introduced by Singh[43]) and diamine **23** (developed independently by ourselves[7,8] and Ahlberg[3,44]). In the present study, we have utilised Singh's diamine **22** and our own norephedrine-derived diamine **23**. Diamines *rac*-**22**, (*R*)-**22** and (1*R*,2*S*)-**23** were prepared in multi-gram quantities using the procedures previously developed in our group.[8,45]



Our usual conditions for carrying out epoxide rearrangement reactions involve (i) generation of two equivalents of the chiral base (relative to the epoxide) from the diamine and *n*-butyllithium in THF at 0 °C; (ii) reaction of the chiral base with the epoxide at 0 °C for four hours and then at room temperature for a further 12 hours and (iii) aqueous work-up including washing with 2% hydrochloric acid in order to remove and recover the diamine. To establish whether these conditions were suitable for rearranging aziridino epoxides, initial optimisation studies were carried out with *N*-diphenylphosphinoyl protected epoxide *cis*-**11** as this was the easiest substrate to prepare on a large scale. Reaction of epoxide *cis*-**11** with the lithium amide base derived from diamine *rac*-**22** under the standard conditions did not lead to isolation of any of the desired allylic alcohol **24**. Instead, the only product obtained (25% recovery) was tentatively ascribed a structure in which ring opening of the allylic alcohol **24** with chloride had occurred. We presume that the hydrochloric acid in the work-up was the source of the chloride since omitting the hydrochloric acid from the work-up enabled quantities of racemic allylic alcohol **24** to be isolated (Scheme 5 and Table 2).



Scheme 5

Encouraged by the formation of allylic alcohol **24**, we varied the amount of lithium amide base used (Scheme 5, Table 2) and found that the highest yield was obtained with 1.2

Table 2 Optimisation of conditions for rearrangement of epoxide *cis*-**11**

Entry	*rac*-**22** (eq.)	BuLi (eq.)	Yield of *rac*-**24** (%)[a]
1	1.0	1.0	46[b]
2	1.2	1.2	62
3	1.3	1.3	46
4	1.5	1.5	32
5	2.0	2.0	42

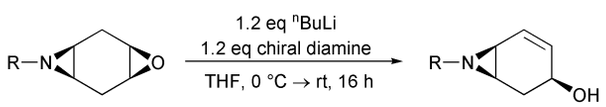
[a] Isolated yield of pure allylic alcohol *rac*-**24**. [b] 34% yield of recovered starting material also obtained.

equivalents of base (Table 2, entry 2): if 1.0 equivalents of lithium amide was used, the reaction did not go to completion (Table 2, entry 1, 34% recovered starting material) and if 2.0 equivalents (our generally preferred conditions) were used (Table 2, entry 5), we presume that the excess base destroys the aziridine in either the starting material or product, possibly *via* α-lithiation.

The modified conditions for the rearrangement of aziridino epoxide *cis*-**11** using the lithium amide base derived from diamine *rac*-**22** are: (i) use of 1.2 equivalents of the lithium amide under our usual conditions (THF, 0 °C for four hours and then room temperature for 12 hours) and (ii) quenching the reaction with aqueous ammonium chloride solution and separating the allylic alcohol from diamine using chromatography. Under these conditions, generally good yields of allylic alcohols were obtained. Crucially, the *N*-diphenylphosphinoyl protected aziridine remained unscathed during these lithium amide base conditions.

Attention was then turned to all of the aziridino epoxide substrates and the use of 1.2 equivalents of enantiomerically pure chiral lithium amide bases. The full results of all of our studies are presented in Scheme 6 and Table 3 (for *cis* aziridino epoxides) and in Scheme 7 and Table 4 (for *trans* aziridino epoxides).

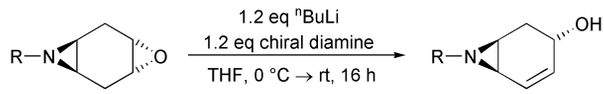
Rearrangement of *N*-diphenylphosphinoyl protected aziridino epoxide *cis*-**11** with chiral bases from diamines (*R*)-**22** and



cis-**11**; R = Ph_2PO
cis-**12**; R = Ts

24; R = Ph_2PO
25; R = Ts

Scheme 6



trans-**11**; R = Ph_2PO
trans-**12**; R = Ts

26; R = Ph_2PO
27; R = Ts

Scheme 7

(1*R*,2*S*)-**23** gave good yields of the enantioenriched allylic alcohol (1*R*,3*S*,6*S*)-**24** (Table 3, entries 2 and 3, 53% and 60% yields respectively). In each case, the enantiomeric excess was significantly lower than that obtained for cyclohexene oxide[43,44] which presumably reflects the conformational differences between cyclohexene oxide and aziridino epoxide *cis*-**11**. With epoxide *cis*-**11**, the less sterically encumbered diamine (*R*)-**22** gave the highest enantiomeric excess (45% ee) of allylic alcohol (1*R*,3*S*,6*S*)-**24** (Table 3, entry 2).

In contrast to the *N*-diphenylphosphinoyl protected aziridino epoxides, the corresponding *N*-tosyl protected epoxides *cis*-**12** and *trans*-**12** were much less robust as substrates and quite varied and non-reproducible results were obtained (Table 3, entries 4–6 and Table 4, entry 4). For example, diamine *rac*-**22** converted aziridino epoxide *cis*-**12** into allylic alcohol *rac*-**25** in 41% yield (Table 3, entry 4) but use of diamine (*R*)-**22** under otherwise identical conditions afforded allylic alcohol (1*R*,3*S*,6*S*)-**25** in only 14% yield (Table 3, entry 5). Although the enantioselective rearrangements of epoxide *cis*-**12** proceeded in low yields, the same trend as in the *N*-diphenylphosphinoyl protected examples was observed: higher enantioselectivity (allylic alcohol of 66% ee, Table 3, entry 5) was observed with diamine (*R*)-**22** compared to that with diamine (1*R*,2*S*)-**23** (allylic alcohol of 10% ee, Table 3, entry 6). Allylic alcohol *rac*-**27** was obtained from epoxide *trans*-**12** in only 26% yield (Table 4, entry 4) and no enantioselective rearrangements with epoxide *trans*-**12** were attempted due to the lack of availability of this epoxide.

Rearrangement of *N*-diphenylphosphinoyl protected aziridino epoxide *trans*-**11** was also well behaved (Table 4, entries 1–3). In this case, generally higher yields (up to 82%, Table 4, entry 3) and higher enantioselectivity (58–68% ee of allylic alcohol, Table 4, entries 2 and 3) was obtained for the reactions using diamines (*R*)-**22** and (1*R*,2*S*)-**23**. There was also less difference in the enantioselectivity obtained using diamines (*R*)-**22** and (1*R*,2*S*)-**23** since the aziridine is now on the opposite side of the ring to the epoxide functionality. With epoxide *trans*-**11**, diamine (1*R*,2*S*)-**23** gave allylic alcohol (1*R*,3*S*,6*R*)-**26** with the highest enantiomeric excess (68% ee, Table 4, entry 3); diamine

Table 3 Rearrangement of *cis*-aziridino epoxides

Entry	SM	Diamine	Product	Yield (%)[a]	ee (%)
1	*cis*-**11**	*rac*-**22**	*rac*-**24**	62	—
2	*cis*-**11**	(*R*)-**22**	(1*R*,3*S*,6*S*)-**24**	53	45[b]
3	*cis*-**11**	(1*R*,2*S*)-**23**	(1*R*,3*S*,6*S*)-**24**	60	25[b]
4	*cis*-**12**	*rac*-**22**	*rac*-**25**	41	—
5	*cis*-**12**	(*R*)-**22**	(1*R*,3*S*,6*S*)-**25**	14	66[c]
6	*cis*-**12**	(1*R*,2*S*)-**23**	(1*R*,3*S*,6*S*)-**25**	23	10[c]

[a] Isolated yield of pure allylic alcohol. [b] Enantiomeric excess determined by ^{1}H NMR spectroscopy in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. [c] Enantiomeric excess determined by chiral HPLC.

Table 4 Rearrangement of *trans* aziridino epoxides

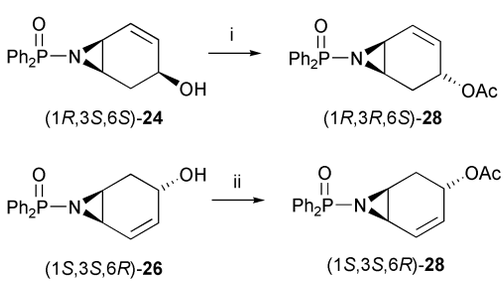
Entry	SM	Diamine	Product	Yield (%)[a]	ee (%)
1	*trans*-**11**	*rac*-**22**	*rac*-**26**	72	—
2	*trans*-**11**	(*R*)-**22**	(1*R*,3*S*,6*R*)-**26**	62	58[b]
3	*trans*-**11**	(1*R*,2*S*)-**23**	(1*R*,3*S*,6*R*)-**26**	82	68[b]
4	*trans*-**12**	*rac*-**22**	*rac*-**27**	26	—

[a] Isolated yield of pure allylic alcohol. [b] Enantiomeric excess determined by Mosher's ester formation.

(1*R*,2*S*)-**23** is often the base of choice with other epoxide substrates.[7,10,11]

There are some important observations from the results of rearranging aziridino epoxides using lithium amide bases. First of all, it is possible to rearrange epoxides to allylic alcohols in the presence of aziridines and to obtain good yields (up to 82%) of allylic alcohols. Of particular note is the fact that the aziridine survives these reactions. Indeed, recent results suggest that more forcing conditions (*e.g. sec*-butyllithium–(−)-sparteine[46] or superbases[47]) are required in order to convert aziridines into the corresponding allylic amines (presumably proceeding *via* α-lithiation and a carbene mechanism). Secondly, based on the isolated yields, we suggest that the *N*-tosyl protected aziridines are more susceptible to decomposition (*via* α-lithiation of the aziridine either in the starting aziridino epoxide or in the allylic alcohol product) than the corresponding *N*-diphenylphosphinoyl protected aziridines. In addition, cyclic vinyl aziridines, especially if activated by a *N*-tosyl substituent are relatively reactive[16,48] and it may be that the lower yields with *N*-tosyl aziridino epoxides *cis*- and *trans*-**12** is due to decomposition of the allylic alcohol product as it is also a vinylaziridine. Thirdly, the variation in yields obtained with racemic and enantiopure diamine **22** (*cf.* Table 3, entries 1 and 2; Table 3, entries 4 and 5; Table 4, entries 1 and 2) highlights the capricious nature of these reactions and that different extents of decomposition can occur under seemingly identical reaction conditions. Finally, good yields of allylic alcohols with moderate to good enantiomeric excess can be obtained using this chiral base route: use of diamine (*R*)-**22** with epoxide *cis*-**11** gave allylic alcohol (1*R*,3*S*,6*S*)-**24** in 53% yield and 45% ee (Table 3, entry 2) and use of diamine (*1R*,2*S*)-**23** with epoxide *trans*-**11** gave allylic alcohol (1*R*,3*S*,6*R*)-**26** in 82% yield and 68% ee (Table 4, entry 3). Both of these allylic alcohol products could prove to be useful building blocks for synthesis.

In all rearrangements of the cyclohexene oxide system reported to date in the literature, the chiral bases derived from diamines (*R*)-**22** and (1*R*,2*S*)-**23** generate an allylic alcohol chiral centre of (*S*)-configuration. A comparison of the chemical shifts of some of the resonances in the ^{1}H NMR spectra of the Mosher's esters[49] obtained from allylic alcohol **26** confirmed that this was the case for allylic alcohol **26**. Unfortunately, the same approach was not successful with allylic alcohol **24** since the Mosher's ester formation did not go to completion. Instead, synthesis (Scheme 8) coupled with a



Scheme 8 *Reagents and conditions:* i, Ph_3P, diisopropylazodicarboxylate (DIAD), AcOH, toluene, rt, 72 h; ii, AcCl, Et_3N, DMAP, CH_2Cl_2, rt, 72 h.

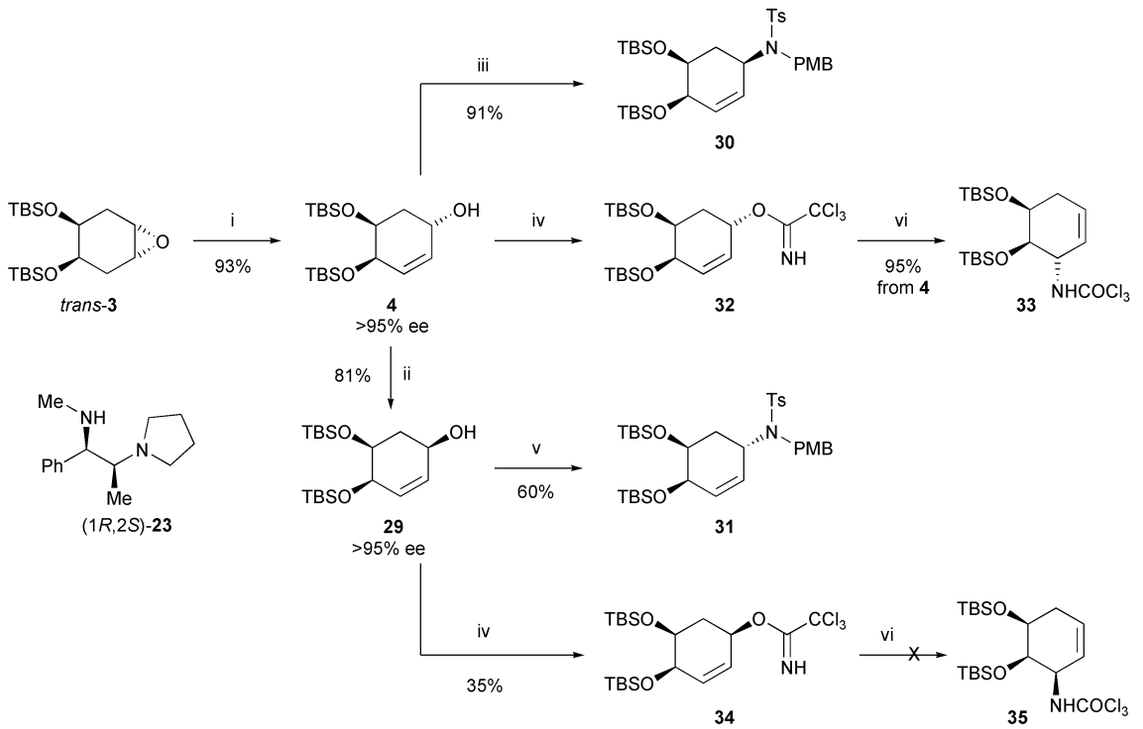
comparison of the sign of optical rotations was used to establish the absolute stereochemistry of allylic alcohol **24**. Thus, allylic alcohol (1*R*,3*S*,6*S*)-**24** of 45% ee was converted into allylic acetate (1*R*,3*R*,6S)-**28** by reaction with acetic acid under Mitsunobu conditions. Although this allylic acetate could not be obtained free from triphenylphosphine oxide (even after repeated chromatography), it had the opposite sign of optical rotation to its enantiomer, allylic acetate (1*S*,3*S*,6*R*)-**28**, prepared by simple acetylation of allylic alcohol (1*S*,3*S*,6*R*)-**24** (of 68% ee). These interconversions, together with analysis of the Mosher's esters obtained from allylic alcohol **26** established the absolute stereochemistry of all of the *N*-diphenylphosphinoyl protected allylic alcohols. The absolute stereochemistry of *N*-tosyl protected allylic alcohol (1*S*,3*S*,6*S*)-**25** was assigned by analogy but has not been established unequivocally.

Strategy 2: Mitsunobu and Overman approaches to aminodeoxyconduritols

An alternative approach to the synthesis of amino-containing cyclohexenols has been investigated. The plan was to make use of allylic alcohol **4** and its diastereomeric allylic alcohol **29** as we have already reported their preparation in >95% ee.[10] For example, chiral base-mediated rearrangement of epoxide *trans*-**3** using diamine (1*R*,2*S*)-**23** gave allylic alcohol **4** in 93% yield and >95% ee and simple oxidation–reduction of **4** generated allylic alcohol **29** (81% yield over the two steps) in >95% ee (Scheme 9). With straightforward access to multi-gram quantities of **4** and **29**, we envisaged converting them into allylic amines using direct Mitsunobu substitution[19,20] and/or Overman rearrangement.[21]

A range of amines has been developed for use under Mitsunobu reaction conditions.[19,20] The key to the success of these reagents is the pK_a of the amine proton which requires an appropriate electron withdrawing *N*-substituent. For the Mitsunobu substitution of allylic alcohol **4** with an amine, we screened a few of the commonly employed reagents[19,20] and found that the known,[50] Fukuyama-like[20] *N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (TsNHPMB) was optimal. The Mitsunobu reagent TsNHPMB was prepared by tosylation of *p*-methoxybenzylamine. Under typical Mitsunobu conditions, allylic alcohol **4** gave allylic amine **30** in 91% yield whilst allylic alcohol **29** gave allylic amine **31** in 60% yield (Scheme 9). Although the relative stereochemistry in **30** and **31** has not been proved by other means, the absence of the other diastereoisomer in each of the Mitsunobu reactions strongly suggests that the substitutions proceed with stereospecific inversion which is not always the case in cyclic allylic alcohols.[51] Thus, the Mitsunobu route was a simple and convenient way of preparing allylic amines.

Allylic alcohols **4** and **29** were also utilised in another synthetic sequence, the Overman rearrangement, which generates allylic amines with transposed amino functionality compared to that present in the previously prepared **30** and **31**. Thus, allylic alcohol **4** was converted into trichloroacetimidate **32** in essentially quantitative yield upon treatment with DBU and trichloroacetonitrile. Then, without isolation, the crude acetimidate **32** was heated overnight in xylene with potassium carbonate (Isobe's modification[52]) to give the rearranged allylic amine **33** in 95% yield (Scheme 9). However, carrying out exactly the same sequence with allylic alcohol **29** did not furnish any of the hoped-for allylic amine **35**. Instead, a 35% yield of trichloroacetimidate **34** was isolated (and *not* a 35% yield of **35**, as we had originally reported in our communication[15]). Two of the diagnostic signals in the ^{1}H NMR spectrum of the product confirm that trichloroacetimidate **34** has been isolated: δ_H(270 MHz; $CDCl_3$) 8.3 (1 H, br s, NH) and 5.4 (1 H, m, CHO). These signals clearly point to a trichloroacetimidate product when compared with those for isolated trichloroacetimidates reported by Overman[21] and Isobe *et al.*[52] In contrast, in allylic amine **33**, the NH resonance appears at δ_H 6.45–6.42 and the CHN resonance appears at δ_H 4.34, both of which are similar magnitudes to those of related allylic amines reported in the literature.[21,52] Thus, it was not possible to synthesise allylic amine **35** using the Overman rearrangement. Apparently, the silyloxy groups present too much steric bulk to allow the trichloroacetimidate to rearrange towards them in compound **34** which has all of the groups on the same face. The diastereomeric system **32** encounters no such problems and a high 95% yield of allylic amine **33** was obtained (Scheme 9).

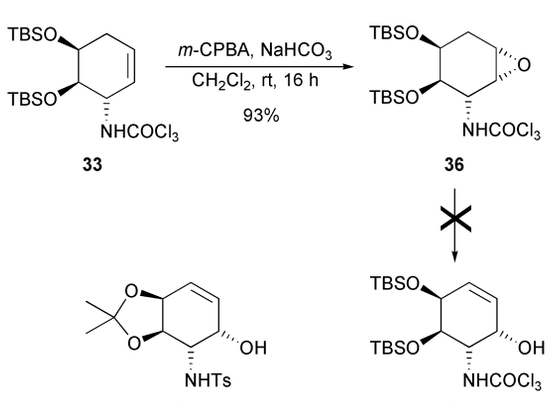


Scheme 9 *Reagents and conditions:* i, 2 eq. ^{n}BuLi, 2 eq. diamine (1*R*,2*S*)-**23**, THF, 0 °C ⟶ rt, 16 h; ii, (a) PCC, CH_2Cl_2, rt, 16 h; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 15 min; iii, 1. 5 eq. TsNHPMB, 3 eq. Ph_3P, 1 eq. DIAD, THF, rt, 16 h; iv DBU, CCl_3CN, −20 °C ⟶ rt, 20 h; v, 1.5 eq. TsNHPMB, 3 eq. Ph_3P, 2.5 eq. DIAD, THF, rt, 16 h; vi, K_2CO_3, xylene, reflux, 18 h.

Attempted elaboration of aziridinocyclohexenols and amino-cyclohexenols: use in synthesis

Having developed good synthetic routes to different amino- and aziridinocyclohexenols, it was our intention to use these compounds in synthesis. In particular, we attempted to ring open the aziridine in aziridinocyclohexenol *rac*-**24** using benzyl alcohol–boron trifluoride–diethyl ether,[53] sodium azide in refluxing ethanol–water[54] and lithium thiophenolate in THF.[55] However, in each case, decomposition occurred and we were never able to isolate any amounts of ring opened products. Due to this lack of success, it appears that much more work is required to discover suitable conditions/reagents for further elaboration of the aziridinocyclohexenols generated in this work.

We envisaged that allylic amine **33**, readily prepared in multigram quantities, would be a useful synthetic intermediate. One sequence that was attempted is summarised in Scheme 10.



Scheme 10

Epoxidation of the alkene in **33** should give **36** which could be converted into allylic alcohol **37**. Allylic alcohol **37** has the same regio- and stereochemical arrangement of functionality (different protecting groups) as compound **38** which Trost and Patterson used as a key intermediate in their synthesis of (−)-swainsonine.[56] Thus, conversion of **33** into **37** was investigated.

Treatment of allylic amine **33** with MCPBA under standard conditions afforded a 93% isolated yield of epoxide **36**. Epoxide **36** was the only diastereomer detected. Based on literature precedent,[32,57] we assume that the epoxidation is *cis*-directed due to hydrogen bonding between MCPBA and the amide (and this sense of epoxidation is *trans* to the bulky silyloxy groups). However, we have no proof of this. Nevertheless, we continued with our synthetic plan with the intention of establishing the relative stereochemistry in **36** at a later stage.

There are a number of methods available for the conversion of epoxides into allylic alcohols. Given our interest in lithium amide-mediated epoxide rearrangements, we attempted the reaction of epoxide **36** with 3 equivalents of LDA or the lithium amide from *rac*-**22** under typical conditions (THF, room temperature, 16–72 hours).[58] However, in all cases, decomposition of the starting epoxide **36** was observed and none of allylic alcohol **37** was obtained. Ring opening of the epoxide with lithium phenylselenide (with a view to a subsequent oxidation–elimination sequence for the generation of the allylic alcohol) was also unsuccessful.[59] Finally, the conversion of epoxides into silyl protected allylic alcohols using *tert*-butyldimethylsilyl trifluoromethanesulfonate and DBU has been reported.[60] Even using these conditions at reflux for prolonged times (up to 72 hours), we were unable to isolate any protected allylic alcohol from the reaction of epoxide **36**. Thus, we have been unable to satisfactorily utilise the amino- or aziridino-cyclohexenols in synthetic endeavours to date.

Conclusions

In summary, two different chiral lithium amide base routes for the synthesis of amino- and aziridino-containing cyclohexenols have been explored. The first strategy involved the diastereoselective synthesis of *meso*-aziridinocyclohexene oxides and their subsequent enantioselective rearrangement using chiral bases. Here, several interesting observations on the epoxidation

and rearrangement reactions were made. In particular, the *N*-diphenylphosphinoyl protecting group proved crucial and aziridinocyclohexenols of 47–68% ee were obtained. Thus, under optimised conditions, it was possible to rearrange the epoxide to an allylic alcohol in the presence of an aziridine: the aziridine remained essentially unaffected. Unfortunately, further synthetic elaboration of the aziridinocyclohexenols was not possible. A second more straightforward strategy for introduction of an amino functionality was also investigated. Allylic alcohols **4** and **29**, prepared in >95% ee by established methods, were converted into regioisomeric allylic amines *via* Mitsunobu substitution using a sulfonamide and Overman rearrangement. The Mitsunobu approach was more successful. Further work is required to make use of chiral building blocks such as **24**, **26**, **30**, **31**, **33** and **36** in total synthesis studies.

Experimental

General

General details have been described previously.[10] Et_2O was dried over sodium–benzophenone and distilled before use. Triethylamine was stored over potassium hydroxide pellets. MCPBA (approx. 70% pure) was used as supplied. *n*-Butyllithium was titrated against *N*-benzylbenzamide before use.[61] In the ^1H NMR spectra, the symbol * indicates that the signal disappears after a D_2O shake.

For Kugelrohr distillations, the temperatures quoted correspond to the oven temperatures. Microanalyses were carried out at the University of Newcastle on a Carlo Erba 1106 elemental analyser and weighed using a Mettler MT 5 microbalance. Analytical HPLC was carried out on a Chiralcel AS column and the compounds (detected at 215 nm) were eluted using a solution of 25% ^{i}PrOH in heptane as the mobile phase at a flow rate of 1.0 cm^3 min^{-1}. Optical rotations are given in 10^{-1} deg cm^2 g^{-1} and were recorded at 15–20 °C.

Toluene-*p*-sulfonyl chloride was purified before use. Anhydrous *tert*-butyl hydroperoxide was prepared using the literature procedure.[62] The preparation of diamines (*R*)-**22**[24] and (1*R*,2*S*)-**23**[8] as well as allylic alcohols (1*S*,4*R*,5*S*)-**4**[10] (>95% ee) and (1*R*,4*R*,5*S*)-**29**[10] (>95% ee) has been described previously.

General methods

Method A: epoxidation using MCPBA

Sodium hydrogen carbonate (2 equiv.) and MCPBA (2 equiv., approx. 70% pure material) were added in portions to a stirred solution of the alkene (0.8 mmol) in CH_2Cl_2 (10 cm^3) at room temperature under nitrogen. After stirring for 16 h at room temperature, 20% aqueous sodium sulfite solution (10 cm^3) was added and the mixture stirred for a further 20 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were washed with 20% aqueous sodium sulfite solution (20 cm^3), saturated aqueous sodium hydrogen carbonate solution (20 cm^3) and water (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

Method B: epoxidation using methyl(trifluoromethyl)-dioxirane

1,1,1-Trifluoroacetone (1.1 equiv.) was added *via* a precooled syringe to a stirred solution of alkene (0.68 mmol) and Na_2EDTA (0.002 equiv. of a 4 × 10^{-4} M aqueous solution) in acetonitrile (6 cm^3) at 0 °C. Then, a mixture of Oxone® (5.0 equiv.) and sodium hydrogen carbonate (8.0 equiv.) was added in portions over 1 h. After stirring at 0 °C for a further 1.5 h, the reaction mixture was poured into water (20 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

Method C: azido alcohol cyclisation and aziridine protection

Triphenylphosphine (1.0 equiv.) was added in one portion to a stirred solution of azido alcohol epoxide **18** (0.65 mmol) in THF (5 cm^3) at room temperature under nitrogen. The resulting solution was heated at reflux for 20 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give the crude product. To the crude product in CH_2Cl_2 (4 cm^3) at room temperature under nitrogen was added toluene-*p*-sulfonyl chloride or diphenylphosphinic chloride (1.2 equiv.), triethylamine (2.0 equiv.) and DMAP ("catalytic" amount). The resulting solution was stirred at room temperature for 20 h. Water (15 cm^3) and CH_2Cl_2 (15 cm^3) were added and the two layers were separated. The organic layer was washed with water (2 × 20 cm^3) and the combined aqueous washings were extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

Method D: enantioselective rearrangement of aziridino epoxides

n-Butyllithium (1.4–1.6 M solution in hexane, 1.2 equiv.) was added dropwise to a stirred solution of diamine (1.2 equiv.) in THF (2.5 cm^3) at room temperature under nitrogen. After stirring for 30 min at 0 °C, a solution of the epoxide (0.64 mmol) in THF (2.5 cm^3) was added dropwise *via* a cannula and the mixture was warmed to room temperature over 4 h. After stirring at room temperature for 12 h, saturated ammonium chloride solution (3 cm^3) was added followed by Et_2O (10 cm^3) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 cm^3) and the combined organic extracts were washed with water (15 cm^3) and saturated aqueous brine solution (15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

Method E: Mitsunobu substitution of allylic alcohols

Allylic alcohol (0.28 mmol) and then triphenylphosphine (1.5 equiv.) were added sequentially to a stirred solution of *N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (1.5 equiv.) in THF (5 cm^3) at room temperature under nitrogen. After stirring for 30 min, diisopropylazodicarboxylate (1.0 or 2.5 equiv.) was added dropwise and the resulting mixture was stirred at room temperature for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product.

Methyl 6-iodocyclohex-3-en-1-yl carbamate 7

Iodine (12.0 g, 47 mmol) was added to a stirred slurry of cyclohexa-1,4-diene (4.0 g, 50 mmol) and silver cyanate (9.5 g, 63 mmol) in THF (100 cm^3) at −20 °C under nitrogen. After stirring for 4 h at −20 °C, the salts were removed by filtration and the filtrate was evaporated under reduced pressure to a volume of approximately 20 cm^3. MeOH (100 cm^3) was added and the solution was heated at reflux for 1.5 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue dissolved in Et_2O (60 cm^3). The organic layer was washed with 20% aqueous sodium sulfite solution (20 cm^3) and the aqueous layer was then extracted with Et_2O (2 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Recrystallisation from 10 : 1 CH_2Cl_2–hexane (12 cm^3) gave iodocarbamate **7** (7.2 g, 51%) as a white powder, mp 96–98 °C (from 10 : 1 CH_2Cl_2–hexane)(lit.,[22] 99.5–100.5 °C); R_F(2 : 1 petrol–Et_2O) 0.4; data identical to those reported previously.[22]

7-Azabicyclo[4.1.0]hept-3-ene 8

Iodocarbamate **7** (2.45 g, 8.7 mmol) was added in one portion to a stirred solution of potassium hydroxide (10 g) in water (50 cm^3). The resulting solution was heated at reflux for 1 h. After cooling to room temperature, the aqueous layer was extracted with Et_2O (4 × 40 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated *at room*

temperature under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave aziridine **8** (730 mg, 88%) as a colourless oil, bp 60–80 °C/10 mmHg (lit.,[23] 60.5–61.5 °C/14 mmHg); data identical to those reported previously.[23] Aziridine **8** should be used immediately or stored under nitrogen in the refrigerator.

7-(Diphenylphosphoryl)-7-azabicyclo[4.1.0]hept-3-ene 9

Diphenylphosphinic chloride (0.96 cm^3, 5.0 mmol) was added dropwise to a stirred solution of aziridine **8** (400 mg, 4.2 mmol), triethylamine (1.17 cm^3, 8.4 mmol) and DMAP ("catalytic" amount) in CH_2Cl_2 (25 cm^3) at room temperature under nitrogen. The resulting mixture was stirred at room temperature for 50 h. Then, water (20 cm^3) was added and the two layers were separated and the organic layer was washed with water (2 × 20 cm^3). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with $CHCl_3$–MeOH (10 : 1) as eluent gave *N*-Ph_2PO aziridine **9** (1.10 g, 90%) as a white crystalline solid, mp 117–120 °C (from 1 : 1 petrol–EtOAc) (lit.,[22] 119–120.5 °C); R_F(10 : 1 $CHCl_3$–MeOH) 0.6; $\nu_{max}(CHCl_3)/cm^{-1}$ 2987, 2904, 1439 (P–Ph), 1216, 1186 (P=O), 1126, 1028, 970, 896, 800 and 729; δ_H(270 MHz; $CDCl_3$) 7.95–7.88 (4 H, m, *o*-Ph_2PO), 7.52–7.39 (6 H, m, *m*- and *p*-Ph_2PO), 5.53 (2 H, s, =CH), 3.01 (2 H, d, *J* 16.5, CHN) and 2.36 (4 H, s, CH_2); δ_C(67.9 MHz; $CDCl_3$) 133.5 (d, J_{CP} 127.0, *ipso*-Ph_2PO), 131.6, 131.5 (d, J_{CP} 8.0), 128.3 (d, J_{CP} 13.0), 121.9 (C=C), 33.5 (d, J_{CP} 5.5, CHN) and 24.4 (d, J_{CP} 5.5, CH_2); *m*/*z* (CI; NH_3) 296 [100%, $(M + H)^+$][Found: $(M + H)^+$, 296.1204. $C_{18}H_{18}NOP$ requires *M* + H, 296.1204]; Found: C, 73.0; H, 6.0; N, 4.7%; $C_{18}H_{18}NOP$ requires C, 73.2; H, 6.1; N, 4.7%.

7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]hept-3-ene 10

Toluene-*p*-sulfonyl chloride (1.00 g, 8.2 mmol) was added in one portion to a stirred solution of aziridine **8** (650 mg, 6.8 mmol), triethylamine (1.9 cm^3, 13.7 mmol) and DMAP ("catalytic" amount) in CH_2Cl_2 (25 cm^3) at room temperature under nitrogen. The resulting mixture was stirred at room temperature for 20 h. Then, water (20 cm^3) was added and the two layers were separated and the organic layer was washed with water (2 × 20 cm^3). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 20 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (1 : 1) as eluent gave *N*-tosylaziridine **10** (1.32 g, 78%) as a white crystalline solid, mp 111–113 °C (from 1 : 1 petrol–EtOAc)(lit.,[23] 112–113 °C); R_F(1 : 1 petrol–EtOAc) 0.5; $\nu_{max}(CHCl_3)/cm^{-1}$ 3033, 2902, 1600, 1408, 1320, 1232, 1157, 1092, 998, 947, 812 and 672; δ_H(270 MHz; $CDCl_3$) 7.83 (2 H, d, *J* 8.0, *o*-$C_6H_4SO_2$), 7.32 (2 H, d, *J* 8.0, *m*-$C_6H_4SO_2$), 5.44–5.43 (2 H, m, =CH), 3.11 (2 H, d, *J* 0.5, CHN), 2.44 (3 H, s, Me) and 2.37–2.36 (4 H, m, CH_2); δ_C(67.9 MHz; $CDCl_3$) 144.2 (*ipso*-$C_6H_4SO_2$), 135.8 (*ipso*-C_6H_4Me), 129.6, 127.7, 121.6 (C=C), 38.6 (CHN), 23.1 (CH_2) and 21.6 (Me); *m*/*z* (CI; NH_3) 250 [100%, $(M + H)^+$][Found: $(M + H)^+$, 250.0905. $C_{13}H_{15}NO_2S$ requires *M* + H, 250.0902]; Found: C, 62.8; H, 6.1; N, 5.6%; $C_{13}H_{15}NO_2S$ requires C, 62.6; H, 6.1; N, 5.6%.

7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]hept-3-ene 10

A solution of phenyl trimethylammonium tribromide (188 mg, 0.5 mmol) in acetonitrile (8 cm^3) was added dropwise to a stirred mixture of cyclohexa-1,4-diene (400 mg, 5.0 mmol) and Chloramine-T hydrate (1.55 g, 5.5 mmol) in acetonitrile (16 cm^3) at room temperature under nitrogen. The resulting yellow suspension was stirred vigorously for 18 h and then the solvent was evaporated under reduced pressure. Purification by filtration through a plug of silica with petrol–EtOAc (10 : 1) as eluent gave *N*-tosylaziridine **10** (783 mg, 63%) as a white crystalline solid, mp 109–110 °C (from 10 : 1 petrol–EtOAc) (lit.,[23] 112–113 °C); data identical to those reported above.

(1*R**,3*S**,5*R**,7*S**)-8-(Diphenylphosphoryl)-4-oxa-8-aza-tricyclo[5.1.0.0^{3,5}]octane *cis*-11

Using general method A, MCPBA (242 mg of 70% pure material, 0.98 mmol), sodium hydrogen carbonate (118 mg, 1.4 mmol) and alkene **9** (207 mg, 0.70 mmol) in CH_2Cl_2 (10 cm^3) gave the crude product which contained a 10 : 90 mixture of epoxides *trans*- and *cis*-**11** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave epoxide *trans*-**11** (9 mg, 9%) as an off-white solid identical to that obtained below and epoxide *cis*-**11** (170 mg, 81%) as a white crystalline solid, mp 164–166 °C (from 20 : 1 EtOAc–MeOH); R_F(20 : 1 EtOAc–MeOH) 0.2; $\nu_{max}(CHCl_3)/cm^{-1}$ 2989, 1439 (P–Ph), 1350, 1184 (P=O), 1126, 1093, 1017, 894, 739 and 668; δ_H(270 MHz; $CDCl_3$) 8.02–7.94 (4 H, m, *o*-Ph_2PO), 7.49–7.41 (6 H, m, *m*- and *p*-Ph_2PO), 3.14 (2 H, s, CHO), 2.81 (2 H, dd, *J* 2.5 and 17.0, CHN), 2.50 (2 H, d, *J* 16.5, CH_AH_B) and 2.20 (2 H, dd, *J* 2.5 and 16.5 (app. br d), CH_AH_B); δ_C(67.9 MHz; $CDCl_3$) 133.3 (d, J_{CP} 127.0, *ipso*-Ph_2PO), 131.7 (d, J_{CP} 9.5), 131.6, 128.3 (d, J_{CP} 12.5), 49.4 (CHO), 31.0 (d, J_{CP} 7.0, CHN) and 22.9 (d, J_{CP} 5.5, CH_2); *m*/*z* (CI; NH_3) 312 [100%, $(M + H)^+$][Found: $(M + H)^+$, 312.1150. $C_{18}H_{18}NO_2P$ requires *M* + H, 312.1153]; Found: C, 69.1; H, 5.5; N, 4.5%; $C_{18}H_{18}NO_2P$ requires C, 69.5; H, 5.8; N, 4.5%.

(1*R**,3*R**,5*S**,7*S**)-8-(Diphenylphosphoryl)-4-oxa-8-aza-tricyclo[5.1.0.0^{3,5}]octane *trans*-11

Using general method B, 1,1,1-trifluoroacetone (0.7 cm^3, 8.0 mmol), alkene **9** (200 mg, 0.68 mmol), Na_2EDTA (3.5 cm^3 of a 4 × 10^{-4} M aqueous solution, 0.0014 mmol), Oxone® (2.17 g, 3.5 mmol) and sodium hydrogen carbonate (460 mg, 5.4 mmol) in acetonitrile (6 cm^3) gave the crude product which contained a 64 : 36 mixture of epoxides *trans*- and *cis*-**11** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave epoxide *trans*-**11** (119 mg, 56%) as a white crystalline solid, mp 132–135 °C (from 20 : 1 EtOAc–MeOH); R_F(20 : 1 EtOAc–MeOH) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 2993, 1438 (P–Ph), 1337, 1239, 1189 (P=O), 1126, 1054, 981, 827, 751 and 666; δ_H(270 MHz; $CDCl_3$) 7.93–7.85 (4 H, m, *o*-Ph_2PO), 7.55–7.41 (6 H, m, *m*- and *p*-Ph_2PO), 3.15 (2 H, d, *J* 2.0, CHO), 2.81 (2 H, dd, *J* 3.0 and 16.5, CHN), 2.25 (2 H, dd, *J* 2.0 and 16.5, CH_AH_B) and 2.12 (2 H, dd, *J* 3.0 and 16.5, CH_AH_B); δ_C(67.9 MHz; $CDCl_3$) 132.9 (d, J_{CP} 127.0, *ipso*-Ph_2PO), 131.8 (d, J_{CP} 2.5), 131.4 (d, J_{CP} 8.0), 128.4 (d, J_{CP} 12.5), 49.2 (CHO), 31.3 (d, J_{CP} 7.0, CHN) and 23.3 (d, J_{CP} 5.5, CH_2); *m*/*z* (CI; NH_3) 312 [100%, $(M + H)^+$][Found: $(M + H)^+$, 312.1151. $C_{18}H_{18}NO_2P$ requires *M* + H, 312.1153]; Found: C, 69.2; H, 5.9; N, 4.5%; $C_{18}H_{18}NO_2P$ requires C, 69.5; H, 5.8; N, 4.5% and epoxide *cis*-**11** (66 mg, 31%) as a white crystalline solid identical to that obtained above.

(1*R**,3*S**,5*R**,7*S**)-8-[(4-Methylphenyl)sulfonyl]-4-oxa-8-aza-tricyclo[5.1.0.0^{3,5}]octane *cis*-12

Using general method A, MCPBA (300 mg of 70% pure material, 1.20 mmol), sodium hydrogen carbonate (100 mg, 1.28 mmol) and alkene **10** (200 mg, 0.80 mmol) in CH_2Cl_2 (10 cm^3) gave the crude product which contained a 42 : 58 mixture of epoxides *trans*- and *cis*-**12** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave epoxide *trans*-**12** (85 mg, 40%) as white needles identical to that obtained below and epoxide *cis*-**12** (116 mg, 55%) as a white crystalline solid, mp 109–112 °C (from EtOAc); R_F(1 : 1 petrol–EtOAc) 0.1;

$\nu_{max}(CHCl_3)/cm^{-1}$ 3032, 3013, 1598, 1496, 1321, 1247, 1158, 1093, 960, 775, 715 and 665; δ_H(270 MHz; $CDCl_3$) 7.83 (2 H, d, *J* 8.5, *o*-$C_6H_4SO_2$), 7.32 (2 H, d, *J* 8.5, *m*-$C_6H_4SO_2$), 3.04 (2 H, s, CHO), 2.94–2.83 (2 H, m, CHN), 2.53 (2 H, d, *J* 16.5, CH_AH_B), 2.44 (3 H, s, Me) and 2.23 (2 H, br d, *J* 16.5, CH_AH_B); δ_C(67.9 MHz; $CDCl_3$) 144.2 (*ipso*-$C_6H_4SO_2$), 135.6 (*ipso*-C_6H_4Me), 129.7, 127.7, 48.6 (CHO), 36.0 (CHN), 21.9 (Me) and 21.6 (CH_2); *m*/*z* (CI; NH_3) 266 [100%, $(M + H)^+$][Found: $(M + H)^+$, 266.0855. $C_{13}H_{15}NO_3S$ requires *M* + H, 266.0851]; Found: C, 58.7; H, 5.8; N, 5.1%; $C_{13}H_{15}NO_3S$ requires C, 58.9; H, 5.7; N, 5.3%.

(1*R**,3*R**,5*S**,7*S**)-8-[(4-Methylphenyl)sulfonyl]-4-oxa-8-azatricyclo[5.1.0.0^{3,5}]octane *trans*-12

Using general method B, 1,1,1-trifluoroacetone (0.9 cm^3, 10.0 mmol), alkene **10** (220 mg, 0.88 mmol), Na_2EDTA (4.6 cm^3 of a 4×10^{-4} M aqueous solution, 0.0018 mmol), Oxone® (2.82 g, 4.6 mmol) and sodium hydrogen carbonate (600 mg, 7.1 mmol) in acetonitrile (6 cm^3) gave the crude product which contained a 91 : 9 mixture of epoxides *trans*- and *cis*-**12** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) ⟶ EtOAc as eluent gave epoxide *trans*-**12** (194 mg, 83%) as white needles, mp 118–120 °C (from 1 : 1 EtOAc-petrol); R_F(1 : 1 petrol–EtOAc) 0.3; $\nu_{max}(CHCl_3)/cm^{-1}$ 3034, 3007, 1325, 1243, 1159, 1093, 1040, 763, 731 and 634; δ_H(270 MHz; $CDCl_3$) 7.81 (2 H, d, *J* 8.5, *o*-$C_6H_4SO_2$), 7.34 (2 H, d, *J* 8.5, *m*-$C_6H_4SO_2$), 3.05–3.03 (2 H, m, CHO), 2.89–2.87 (2 H, m, CHN), 2.46 (3 H, s, Me) and 2.29–2.09 (4 H, m, CH_2); δ_C(67.9 MHz; $CDCl_3$) 144.6 (*ipso*-$C_6H_4SO_2$), 135.1 (*ipso*-C_6H_4Me), 129.6, 127.7, 48.9 (CHO), 36.3 (CHN), 22.0 (Me) and 21.7 (CH_2); *m*/*z* (CI; NH_3) 283 [18%, $(M + NH_4)^+$] and 266 [100, $(M + H)^+$][Found: $(M + H)^+$, 266.0853. $C_{13}H_{15}NO_3S$ requires *M* + H, 266.0851]; Found: C, 58.9; H, 5.7; N, 5.1%; $C_{13}H_{15}NO_3S$ requires C, 58.9; H, 5.7; N, 5.3% and epoxide *cis*-**12** (20 mg, 9%) as a white crystalline solid identical to that obtained above.

(1*R**,6*R**)-6-Azidocyclohex-3-en-1-ol 17

Sodium azide (216 mg, 3.3 mmol) was added in portions over 10 min to a stirred solution of monoepoxide **13** (245 mg of epoxide which contained 20% CH_2Cl_2 by ^{1}H NMR spectroscopy, prepared according to a literature procedure,[35] 2.1 mmol) and ammonium chloride (178 mg, 3.3 mmol) in 8 : 1 2-methoxyethanol–water (18 cm^3) at room temperature. The resulting mixture was heated at reflux for 24 h. After cooling to room temperature, water (20 cm^3) was added and the aqueous layer was extracted with Et_2O (4 × 20 cm^3). The combined organic extracts were washed with saturated aqueous brine solution (8 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave azido alcohol **17** (265 mg, 92%) as a yellow oil, R_F(1 : 1 petrol–EtOAc) 0.5; data identical to those reported previously.[23]

(1*S**,3*R**,4*R**,6*R**)-4-Azido-7-oxabicyclo[4.1.0]heptan-3-ol 18

tert-Butyl hydroperoxide (0.96 cm^3 of a 3.0 M solution in toluene, 2.9 mmol) was added dropwise over 5 min to a stirred refluxing solution of azido alcohol **17** (200 mg, 1.4 mmol) and molybdenum hexacarbonyl (5 mg, 0.02 mmol) in benzene (20 cm^3) under nitrogen. The resulting solution was heated at reflux for 2.5 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give the crude product. Direct purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave a single diastereoisomer (by ^{1}H NMR spectroscopy) of azido alcohol epoxide **18** (214 mg, 96%) as a waxy solid (which decolourised on standing), R_F(1 : 1 petrol–EtOAc) 0.2; $\nu_{max}(CHCl_3)/cm^{-1}$ 3583 (OH), 3494 (OH), 3016, 2927, 2109, (N_3), 1434, 1246, 1068, 798, 779 and 764; δ_H(270 MHz; $CDCl_3$) 3.58–3.55 (2 H, m, C*H*OH and CHN_3), 3.26–3.21 (2 H, m, CHO), 2.63–2.33 (3 H, m) and 2.17–1.88 (2 H, m); δ_C(67.9 MHz; $CDCl_3$) 68.4, 59.5, 51.6 (CHO), 51.5 (CHO), 29.6 (CH_2) and 27.8 (CH_2); *m*/*z* (CI; NH_3) 173 [13%, $(M + NH_4)^+$] and 128 (100)[Found: $(M + NH_4)^+$, 173.1039. $C_6H_9N_3O_2$ requires *M* + NH_4, 173.1039].

(1*R**,3*R**,5*S**,7*S**)-8-(Diphenylphosphoryl)-4-oxa-8-azatricyclo-[5.1.0.0^{3,5}]octane *trans*-11

Using general method C, triphenylphosphine (170 mg, 0.65 mmol) and azido alcohol epoxide **18** (100 mg, 0.65 mmol) in THF (5 cm^3) followed by reaction with diphenylphosphinic chloride (0.15 cm^3, 0.77 mmol), triethylamine (0.18 cm^3, 1.28 mmol) and DMAP ("catalytic" amount) in CH_2Cl_2 (4 cm^3) gave the crude product. Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave an inseparable mixture of epoxide *trans*-**11** (identical to that obtained above) and triphenylphosphine oxide (342 mg) as a white foam.

(1*R**,3*R**,5*S**,7*S**)-8-[(4-Methylphenyl)sulfonyl]-4-oxa-8-azatricyclo[5.1.0.0^{3,5}]octane *trans*-12

Using general method C, triphenylphosphine (170 mg, 0.65 mmol) and azido alcohol epoxide **18** (100 mg, 0.65 mmol) in Et_2O (5 cm^3) followed by reaction with toluene-*p*-sulfonyl chloride (146 mg, 0.77 mmol), triethylamine (0.18 cm^3, 1.28 mmol) and DMAP ("catalytic" amount) in CH_2Cl_2 (4 cm^3) gave the crude product. Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave epoxide *trans*-**12** (70 mg, 41%) as an off-white solid identical to that obtained above.

(1*R**,3*S**,6*S**)-7-Diphenylphosphoryl-7-azabicyclo[4.1.0]hept-4-en-3-ol 24

Using general method D, *n*-butyllithium (0.51 cm^3 of a 1.5 M solution in hexane, 0.77 mmol), diamine *rac*-**22** (157 mg, 0.77 mmol) and epoxide *cis*-**11** (200 mg, 0.64 mmol) in THF (5 cm^3) gave the crude product. Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave allylic alcohol *rac*-**24** (123 mg, 62%) as a white solid, mp 160–162 °C (from 20 : 1 EtOAc–MeOH); R_F(20 : 1 EtOAc–MeOH) 0.3; $\nu_{max}(CHCl_3)/cm^{-1}$ 3683 (OH), 3020, 1523, 1423 (P–Ph), 1219 (P=O), 1034, 930, 756, 671 and 625; δ_H(270 MHz; $CDCl_3$) 7.87–7.77 (4 H, m, *o*-Ph_2PO), 7.57–7.41 (6 H, m, *m*- and *p*-Ph_2PO), 6.30 (1 H, ddd, *J* 1.0, 6.0 and 9.5, H^4), 6.21 (1 H, dd, *J* 4.5 and 9.5, H^5), 4.22–4.11 (1 H, m, H^3), 3.47 (1 H, qdd, *J* 2.0, 6.0 and 15.0, H^1), 3.36 (1 H, dddd, *J* 1.0, 4.5, 6.0 and 14.0, H^6), 3.09* (1 H, d, *J* 11.5, OH), 2.33 (1 H, br d, *J* 15.5, H^2) and 1.74 (1 H, tdd, *J* 2.0, 4.5 and 15.5, H^2); δ_C(67.9 MHz; $CDCl_3$) 134.4 (C^4), 132.1 (d, J_{CP} 125.5, *ipso*-Ph_2PO), 132.1, 131.8 (d, J_{CP} 125.5, *ipso*-Ph_2PO), 131.3 (d, J_{CP} 9.5), 131.1 (d, J_{CP} 9.5), 128.7 (d, J_{CP} 12.0), 128.6 (d, J_{CP} 12.0), 127.2 (d, J_{CP} 5.5, C^5), 63.0 (C^3), 37.5 (d, J_{CP} 7.0, C^1), 33.1 (d, J_{CP} 5.5,C^6) and 28.6 (d, J_{CP} 5.5, C^5); *m*/*z* (CI; NH_3) 312 [100%, $(M + H)^+$][Found: $(M + H)^+$, 312.1155. $C_{18}H_{18}NO_2P$ requires *M* + H, 312.1153]. The ^{1}H and ^{13}C NMR spectra were fully assigned using ^{1}H–^{1}H and ^{1}H–^{13}C COSY experiments.

(1*R*,3*S*,6*S*)-7-Diphenylphosphoryl-7-azabicyclo[4.1.0]hept-4-en-3-ol 24

Using general method D, *n*-butyllithium (0.38 cm^3 of a 1.5 M solution in hexane, 0.58 mmol), diamine (*R*)-**22** (118 mg, 0.58 mmol) and epoxide *cis*-**11** (150 mg, 0.48 mmol) in THF (5 cm^3) gave the crude product. Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave allylic alcohol (1*R*,3*S*,6*S*)-**24** (80 mg, 53%, 45% ee by ^{1}H NMR spectroscopy in the presence of 2 equiv. of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a white solid identical to that obtained above; $[a]_D$ +22.1 (*c* 1.0 in $CHCl_3$).

(1*R*,3*S*,6*S*)-7-Diphenylphosphoryl-7-azabicyclo[4.1.0]hept-4-en-3-ol 24

Using general method D, *n*-butyllithium (0.38 cm³ of a 1.5 M solution in hexane, 0.58 mmol), diamine (1*R*,2*S*)-**23** (126 mg, 0.58 mmol) and epoxide *cis*-**11** (150 mg, 0.48 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave allylic alcohol (1*R*,3*S*,6*S*)-**24** (90 mg, 60%, 25% ee by ^{1}H NMR spectroscopy in the presence of 2 equiv. of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a white solid identical to that obtained above; $[\alpha]_D$ +12.5 (*c* 1.0 in $CHCl_3$).

(1*R,3*S**,6*S**)-7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo-[4.1.0]hept-4-en-3-ol 25**

Using general method D, *n*-butyllithium (0.43 cm³ of a 1.6 M solution in hexane, 0.68 mmol), diamine *rac*-**22** (139 mg, 0.68 mmol) and epoxide *cis*-**12** (150 mg, 0.57 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave allylic alcohol *rac*-**25** (61 mg, 41%) as a white solid, mp 82–84 °C (from 1 : 1 EtOAc–petrol); R_F(1 : 1 EtOAc–petrol) 0.3; ν_{max}($CHCl_3$)/cm^{-1} 3360 (OH), 3030, 1408, 1335, 1158, 1064, 814 and 663; δ_H(270 MHz; $CDCl_3$) 7.74 (2 H, d, *J* 8.0, *o*-$C_6H_4SO_2$), 7.30 (2 H, d, *J* 8.0, *m*-$C_6H_4SO_2$), 6.06 (1 H, dd, *J* 4.0 and 9.5, H^5), 5.78–5.72 (1 H, m, H^4), 5.06* (1 H, d, *J* 10.5, OH), 3.99–3.91 (1 H, m, H^3), 3.60–3.57 (1 H, m, H^1), 3.35 (1 H, ddt, *J* 0.5, 1.5 and 4.0, H^6), 2.43 (3 H, s, Me), 2.31–2.25 (1 H, m, H^2) and 1.72 (1 H, dd, *J* 5.5 and 16.0, H^2); δ_C(67.9 MHz; $CDCl_3$) 143.1 (*ipso*-$C_6H_4SO_2$), 138.9 (*ipso*-C_6H_4Me), 132.3 (C^4), 129.7, 127.1 (C^5), 126.9, 55.2 (C^1), 47.0 (C^6), 45.9 (C^3), 28.3 (C^2) and 21.5 (Me); *m*/*z* (CI; NH_3) 283 [15%, $(M + NH_4)^+$], 266 [100, $(M + H)^+$] and 110 (15, *M* − Ts)[Found: $(M + H)^+$, 266.0854. $C_{13}H_{15}NO_3S$ requires *M* + H, 266.0851]. The ^{1}H and ^{13}C NMR spectra were fully assigned using ^{1}H–^{1}H and ^{1}H–^{13}C COSY experiments.

(1*R*,3*S*,6*S*)-7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]-hept-4-en-3-ol 25

Using general method D, *n*-butyllithium (0.57 cm³ of a 1.6 M solution in hexane, 0.91 mmol), diamine (*R*)-**22** (185 mg, 0.91 mmol) and epoxide *cis*-**11** (200 mg, 0.76 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave allylic alcohol (1*R*,3*S*,6*S*)-**25** (28 mg, 14%, 66% ee chiral HPLC) as a white solid identical to that obtained above; $[\alpha]_D$ +114.6 (*c* 1.0 in $CHCl_3$); HPLC: Chiralcel AS, 25% ^{i}PrOH in heptane, 1.0 cm³ min^{-1}, 215 nm, 22.2 min [(1*S*,3*R*,6*R*)-**25**], 24.9 min [(1*R*,3*S*,6*S*)-**25**].

(1*R*,3*S*,6*S*)-7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]-hept-4-en-3-ol 25

Using general method D, *n*-butyllithium (0.57 cm³ of a 1.6 M solution in hexane, 0.91 mmol), diamine (1*R*,2*S*)-**23** (197 mg, 0.91 mmol) and epoxide *cis*-**11** (200 mg, 0.76 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave allylic alcohol (1*R*,3*S*,6*S*)-**25** (45 mg, 23%, 10% ee chiral HPLC) as a white solid identical to that obtained above; $[\alpha]_D$ +18.5 (*c* 1.0 in $CHCl_3$); HPLC: Chiralcel AS, 25% ^{i}PrOH in heptane, 1.0 cm³ min^{-1}, 215 nm, 22.1 min [(1*S*,3*R*,6*R*)-**25**], 25.3 min [(1*R*,3*S*,6*S*)-**25**].

(1*R,3*S**,6*R**)-7-Diphenylphosphoryl-7-azabicyclo[4.1.0]hept-4-en-3-ol 26**

Using general method D, *n*-butyllithium (0.51 cm³ of a 1.5 M solution in hexane, 0.77 mmol), diamine *rac*-**22** (157 mg, 0.77 mmol) and epoxide *trans*-**11** (200 mg, 0.64 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave allylic alcohol *rac*-**26** (144 mg, 72%) as a white solid, mp 187–190 °C (from 20 : 1 EtOAc–MeOH); R_F(20 : 1 EtOAc–MeOH) 0.25; ν_{max}($CHCl_3$)/cm^{-1} 3604 (OH), 3328 (OH), 2998, 1439 (P–Ph), 1189 (P=O), 1126, 1015, 779, 738, 705 and 666; δ_H(270 MHz; $CDCl_3$) 7.89–7.80 (4 H, m, *o*-Ph_2PO), 7.54–7.38 (6 H, m, *m*- and *p*-Ph_2PO), 5.96–5.93 (2 H, m, H^4 and H^5), 4.59–4.48 (1 H, m, H^3), 3.21 (1 H, tdd, *J* 2.0, 6.0 and 15.5, H^1), 3.13 (1 H, tdd, *J* 3.0, 6.0 and 14.5, H^6), 2.52 (1 H, ddd, *J* 2.0, 7.5 and 14.0, H^2), 1.90* (1 H, d, *J* 6.5, OH) and 1.48 (1 H, tdd, *J* 2.0, 10.5 and 14.0, H^2); δ_C(67.9 MHz; $CDCl_3$) 137.7 (C^4), 132.8 (d, J_{CP} 127.5, *ipso*-Ph_2PO), 132.7 (d, J_{CP} 127.5, *ipso*-Ph_2PO), 131.9, 131.4 (d, J_{CP} 9.5), 131.3 (d, J_{CP} 9.5), 128.5 (d, J_{CP} 12.5), 128.4 (d, J_{CP} 12.5), 123.0 (d, J_{CP} 5.5, C^5), 64.0 (C^3), 33.6 (d, J_{CP} 7.0, C^1), 31.2 (d, J_{CP} 5.5,C^6) and 30.1 (d, J_{CP} 5.5, C^5); *m*/*z* (CI; NH_3) 312 [100%, $(M + H)^+$][Found: $(M + H)^+$, 312.1143. $C_{18}H_{18}NO_2P$ requires *M* + H, 312.1153]. The ^{1}H and ^{13}C NMR spectra were fully assigned using ^{1}H–^{1}H and ^{1}H–^{13}C COSY experiments.

(1*R*,3*S*,6*R*)-7-Diphenylphosphoryl-7-azabicyclo[4.1.0]hept-4-en-3-ol 26

Using general method D, *n*-butyllithium (0.36 cm³ of a 1.5 M solution in hexane, 0.58 mmol), diamine (*R*)-**22** (118 mg, 0.58 mmol) and epoxide *trans*-**11** (150 mg, 0.48 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave allylic alcohol (1*R*,3*S*,6*R*)-**26** (93 mg, 63%, 58% ee by Mosher's ester formation) as a white solid identical to that obtained above; $[\alpha]_D$ −81.0 (*c* 1.0 in $CHCl_3$).

(1*R*,3*S*,6*R*)-7-Diphenylphosphoryl-7-azabicyclo[4.1.0]hept-4-en-3-ol 26

Using general method D, *n*-butyllithium (0.36 cm³ of a 1.5 M solution in hexane, 0.58 mmol), diamine (1*R*,2*S*)-**23** (126 mg, 0.58 mmol) and epoxide *trans*-**11** (150 mg, 0.48 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–MeOH (20 : 1) as eluent gave allylic alcohol (1*R*,3*S*,6*R*)-**26** (123 mg, 82%, 68% ee by Mosher's ester formation) as a white solid identical to that obtained above; $[\alpha]_D$ −93.3 (*c* 1.0 in $CHCl_3$).

(1*R,3*S**,6*R**)-7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo-[4.1.0]hept-4-en-3-ol 27**

Using general method D, *n*-butyllithium (0.43 cm³ of a 1.6 M solution in hexane, 0.68 mmol), diamine *rac*-**22** (139 mg, 0.68 mmol) and epoxide *trans*-**12** (150 mg, 0.57 mmol) in THF (5 cm³) gave the crude product. Purification by flash column chromatography on silica with EtOAc–petrol (1 : 1) as eluent gave allylic alcohol *rac*-**27** (39 mg, 26%) as a white solid, mp 96–98 °C (from 1 : 1 EtOAc–petrol); R_F(1 : 1 EtOAc–petrol) 0.3; ν_{max}($CHCl_3$)/cm^{-1} 3380 (OH), 3030, 1599, 1414, 1335, 1160, 1081, 878, 764 and 663; δ_H(270 MHz; $CDCl_3$) 7.76 (2 H, d, *J* 8.0, *o*-$C_6H_4SO_2$), 7.31 (2 H, d, *J* 8.0, *m*-$C_6H_4SO_2$), 5.97 (1 H, ddd, *J* 3.0, 4.0 and 10.0, =CH), 5.58 (1 H, dd, *J* 1.0 and 10.0, =CH), 4.65* (1 H, d, *J* 9.5, OH), 3.93–3.81 (1 H, m, H^3), 3.42–3.40 (1 H, m, CHN), 3.23 (1 H, dt, *J* 2.0 and 4.0, CHN), 2.53 (ddd, *J* 2.0, 8.0 and 14.5, H^2), 2.44 (3 H, s, Me) and 1.42 (1 H, dd, *J* 11.5 and 14.5, H^2); δ_C(67.9 MHz; $CDCl_3$) 143.6 (*ipso*-$C_6H_4SO_2$), 137.4 (*ipso*-C_6H_4Me), 134.8 (=CH), 129.7, 127.1 (=CH), 125.2, 51.4 (CHN), 46.7 (CHN), 46.0 (C^3), 29.5 (C^2) and 21.5 (Me); *m*/*z* (CI; NH_3) 283 [30%, $(M + NH_4)^+$], 266 [100, $(M + H)^+$] and 110 (25, M − Ts)[Found: $(M + H)^+$, 266.0854. $C_{13}H_{15}NO_3S$ requires *M* + H, 266.0851].

***N*-((1*R*,4*R*,5*S*)-4,5-Bis{[*tert*-butyl(dimethyl)silyl]oxy}cyclohex-2-en-1-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide 30**

Using general method E, *N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (122 mg, 0.42 mmol), triphenylphosphine

(219 mg, 0.84 mmol), allylic alcohol (1*S*,4*R*,5*S*)-**4**[10] (100 mg, 0.28 mmol, >95% ee) and diisopropyl azodicarboxylate (50 μL, 0.28 mmol) in THF (3 cm^3) gave the crude product. Purification by flash column chromatography on silica with petrol–Et_2O (3 : 1) as eluent gave allylic amine (1*R*,4*R*,5*S*)-**30** (160 mg, 91%, >95% ee) as a white solid, mp 98–100 °C (from 3 : 1 petrol–Et_2O); R_F(3 : 1 petrol–Et_2O) 0.3; $[a]_D$ +25.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3034, 2957, 2632, 1513, 1338, 1251, 1162, 1119, 1037 and 837; δ_H(270 MHz; $CDCl_3$) 7.70 (2 H, d, *J* 8.5, *o*-$C_6H_4SO_2$), 7.32 (2 H, d, *J* 8.5, *m*-$C_6H_4SO_2$), 7.28 (2 H, d, *J* 8.5, *m*- C_6H_4OMe), 6.80 (2 H, d, *J* 8.5, *o*- C_6H_4OMe), 5.64 (1 H, ddd, *J* 2.5, 6.0 and 10.0, =CH), 5.13 (1 H, br d, *J* 10.0, =CH), 4.59–4.51 (1 H, m, CHN), 4.39 (1 H, d, *J* 15.5, NCH_AH_B), 4.20 (1 H, d, *J* 15.5, NCH_AH_B), 3.89–3.85 (1 H, m, CHO), 3.79 (3 H, s, OMe), 3.52–3.44 (1 H, m, CHO), 2.42 (3 H, s, Me), 2.07–1.94 (1 H, m, CH_AH_B), 1.36–1.25 (1 H, m, CH_AH_B), 0.86 (9 H, s, CMe_3), 0.82 (9 H, s, CMe_3), 0.02 (6 H, s, 2 × SiMe), −0.01 (3 H, s, SiMe) and −0.04 (3 H, s, SiMe); δ_C(67.9 MHz; $CDCl_3$) 158.7 (*ipso*-C_6H_4OMe), 143.1 (*ipso*-$C_6H_4SO_2$), 138.3 (*ipso*-C_6H_4Me), 130.7, 130.5, 129.7, 127.1, 113.4 (*o*-C_6H_4OMe), 69.7, 66.6, 55.7, 55.2 (OMe), 47.0 (NCH_2), 29.4 (CH_2), 26.0 (CMe_3), 25.8 (CMe_3), 21.5 (Me), 18.3 (CMe_3), 18.2 (CMe_3), −4.4 (SiMe), −4.5 (SiMe), −4.6 (SiMe) and −4.8 (SiMe) (two aromatic resonances not resolved); *m*/*z* (CI; NH_3) 574 (10%, *M* − CMe_3), 524 (10, *M* − *p*-$MeOC_6H_4$), 500 (100), 476 (35, *M* − Ts) and 121 (100). It was not possible to obtain HRMS data on this compound.

N-((1*S*,4*R*,5*S*)-4,5-Bis{[*tert*-butyl(dimethyl)silyl]oxy}cyclohex-2-en-1-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide 31

Using general method E, *N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (244 mg, 0.84 mmol), triphenylphosphine (438 mg, 1.68 mmol), allylic alcohol (1*R*4*R*,5*S*)-**29**[10] (200 mg, 0.56 mmol, >95% ee) and diisopropyl azodicarboxylate (250 μL, 1.4 mmol) in THF (6 cm^3) gave the crude product. Purification by flash column chromatography on silica with petrol–Et_2O (3 : 1) as eluent gave allylic amine (1*R*,4*R*,5*S*)-**31** (210 mg, 60%, >95% ee) as a white solid, mp 84–86 °C (from 3 : 1 petrol–Et_2O); R_F(3 : 1 petrol–Et_2O) 0.3; $[a]_D$ −44.8 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3032, 2957, 2632, 1513, 1339, 1253, 1160, 1096, 837 and 748; δ_H(270 MHz; $CDCl_3$) 7.70 (2 H, d, *J* 8.5, *o*-$C_6H_4SO_2$), 7.28 (4 H, d, *J* 8.5, *m*- $C_6H_4SO_2$ and *m*- C_6H_4-OMe), 6.84 (2 H, d, *J* 8.5, *o*- C_6H_4OMe), 5.44 (1 H, br d, *J* 10.0, =CH), 5.06 (1 H, br d, *J* 10.0, =CH), 4.75–4.67 (1 H, m, CHN), 4.58 (1 H, d, *J* 15.5, NCH_AH_B), 4.07 (1 H, d, *J* 15.5, NCH_AH_B), 4.00–3.96 (1 H, m, CHO), 3.91–3.86 (1 H, m, CHO), 3.80 (3 H, s, OMe), 2.42 (3 H, s, Me), 1.90–1.79 (1 H, m, CH_AH_B), 1.46–1.36 (1 H, m, CH_AH_B), 0.87 (18 H, s, 2 × CMe_3), 0.02 (6 H, s, 2 × SiMe), 0.01 (3 H, s, SiMe) and 0.00 (3 H, s, SiMe); δ_C(67.9 MHz; $CDCl_3$) 158.9 (*ipso*-C_6H_4OMe), 143.1 (*ipso*-$C_6H_4SO_2$), 137.9 (*ipso*-C_6H_4Me), 133.5, 130.7, 129.7, 129.2, 127.2, 127.1, 113.7 (*o*-C_6H_4OMe), 70.8, 69.4, 55.2, 53.0 (OMe), 47.7 (NCH_2), 35.7 (CH_2), 26.0 (CMe_3), 25.8 (CMe_3), 21.5 (Me), 18.3 (CMe_3), 18.2 (CMe_3), −4.4 (SiMe), −4.5 (SiMe), −4.8 (SiMe) and −5.0 (SiMe); *m*/*z* (CI; NH_3) 574 (10%, *M* − CMe_3), 500 (60), 476 (45, *M* − Ts) and 121 (100). It was not possible to obtain HRMS data on this compound.

N-((1*S*,5*S*,6*R*)-5,6-Bis{[*tert*-butyl(dimethyl)silyl]oxy}cyclohex-2-en-1-yl)-2,2,2-trichloroacetamide 33

DBU (0.5 cm^3, 3.3 mmol) and then trichloroacetonitrile (0.36 cm^3, 3.6 mmol) were added sequentially to a stirred solution of the allylic alcohol (1*S*,4*R*,5*S*)-**4**[10] (1.0 g, 2.8 mmol, >95% ee) in CH_2Cl_2 (30 cm^3) at −20 °C under nitrogen. After being allowed to warm to room temperature over 2 h, the resulting solution was stirred at room temperature for 18 h. Then, Et_2O (50 cm^3) was added and the organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Baseline impurities were removed from the residue by filtration through a plug of silica with petrol–Et_2O (3 : 1) as eluent. The solvent was evaporated under reduced pressure to give the crude product. To a stirred solution of the crude product in xylene (30 cm^3) was added potassium carbonate ("catalytic" amount). The resulting mixture was heated at reflux for 18 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–Et_2O (10 : 1) as eluent gave trichloroacetamide (1*S*,5*S*,6*R*)-**33** (1.32 g, 95%, >95% ee) as a white solid, mp 69–71 °C (from 10 : 1 petrol–Et_2O); R_F(10 : 1 petrol–Et_2O) 0.35; $[a]_D$ +65.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3246 (NH), 2930, 2857, 1713 (C=O), 1494, 1256 and 837; δ_H(270 MHz; $CDCl_3$) 6.45–6.42 (1 H, m, NH), 5.88 (1 H, br d, *J* 9.0, =CH), 5.54 (1 H, br d, *J* 9.0, =CH), 4.34 (1 H, br s, CHN), 3.89–3.86 (1 H, m, CHO), 3.80 (1 H, br s, CHO), 2.43–2.30 (1 H, m, CH_AH_B), 2.16 (1 H, br d, *J* 17.5, CH_AH_B), 0.89 (9 H, s, CMe_3), 0.88 (9 H, s, CMe_3), 0.17 (3 H, s, SiMe), 0.12 (3 H, s, SiMe), 0.07 (3 H, s, SiMe) and 0.05 (3 H, s, SiMe); δ_C(67.9 MHz; $CDCl_3$) 161.0 (C=O), 131.2 (=CH), 122.1 (=CH), 92.5 (CCl_3), 72.1, 68.5, 54.0, 30.8 (CH_2), 25.9 (CMe_3), 25.8 (CMe_3), 18.2 (CMe_3), 18.0 (CMe_3), −4.4 (SiMe), −4.5 (SiMe), −4.7 (SiMe) and −4.8 (SiMe); *m*/*z* (CI; NH_3) 521 [20%, ($^{35,35,37}M$ + NH_4)$^+$], 504 [55, ($^{35,35,37}M$ + H)$^+$], 432 (100), 398 (85), 372 (40), 300 (40) and 266[Found: (*M* + H)$^+$, 502.1524. $C_{20}H_{38}NO_3Si_2{}^{35,35,35}Cl_3$ requires *M* + H, 502.1534]; Found: C, 47.9; H, 7.8; N, 2.8%; $C_{20}H_{38}NO_3Si_2Cl_3$ requires C, 47.8; H, 7.6; N, 2.8%.

N-((1*R*,2*S*,3*R*,4*S*,6*S*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-7-oxabicyclo[4.1.0]hept-2-yl)-2,2,2-trichloroacetamide 36

Using general method A, MCPBA (700 mg of 70% pure material, 4.0 mmol), sodium hydrogen carbonate (350 mg, 4.0 mmol) and alkene **33** (1.0 g, 2.0 mmol, >95% ee) in CH_2Cl_2 (30 cm^3) gave the crude product. Purification by flash column chromatography on silica with petrol–Et_2O (10 : 1) as eluent gave epoxide **36** (960 mg, 93%, >95% ee) as a white solid, mp 65–67 °C (from 10 : 1 petrol–Et_2O); R_F(10 : 1 petrol–Et_2O) 0.3; $[a]_D$ +21.5 (*c* 1.0 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 6.98–6.95 (1 H, m, NH), 4.29 (1 H, br s, CHN), 3.73–3.67 (1 H, m, CHO), 3.65–3.62 (1 H, m, CHO), 3.45 (1 H, br s, CHO), 3.36–3.31 (1 H, m, CHO), 2.22–2.06 (2 H, m, CH_2), 0.91 (9 H, s, CMe_3), 0.88 (9 H, s, CMe_3), 0.17 (3 H, s, SiMe), 0.11 (3 H, s, SiMe) and 0.04 (6 H, s, SiMe); δ_C(67.9 MHz; $CDCl_3$) 161.5 (C=O), 92.3 (CCl_3), 70.9, 65.8, 56.9, 52.3, 50.4, 28.5 (CH_2), 25.8 (CMe_3), 25.7 (CMe_3), 18.1 (CMe_3), 18.0 (CMe_3), −4.5 (SiMe), −4.7 (SiMe), −4.8 (SiMe) and −4.9 (SiMe); *m*/*z* (CI; NH_3) 537 [100%, (^{35,35,37}M + NH_4)$^+$][Found: (M + NH_4)$^+$, 535.1747. $C_{20}H_{38}NO_4Si_2{}^{35,35,35}Cl_3$ requires *M* + NH_4, 535.1749]; Found: C, 46.4; H, 7.4; N, 2.6%; $C_{20}H_{38}NO_3Si_2Cl_3$ requires C, 46.6; H, 7.4; N, 2.7%.

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