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TETRAHEDRON:
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A convenient synthesis of activated enantiomerically pure 2-ethynylaziridines

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Abstract

2,3-*cis*- and 2,3-*trans*-*N*-Arylsulfonyl-2-ethynylaziridines with high enantiomeric purity have been synthesized. *N*-Protected amino aldehydes synthesized from natural α-amino acids were successively treated with $Ph_3P{=}C(Br)CO_2Me$, DIBAL, MsCl–Et_3N, NaH in DMSO, and *tert*-BuOK in THF to yield 2-ethynylaziridines in good to high yields. © 1998 Elsevier Science Ltd. All rights reserved.

Aziridines, the smallest of the azacycles, are known to undergo reaction with a wide variety of nucleophiles, and various methods for new bond formation via aziridine ring-opening have been developed utilizing this chemistry.[1,2] Although the synthesis and reaction of alkenylaziridines and their derivatives have attracted considerable interest over the past decade,[3] relatively little is known about the chiral alkynylaziridines. The alkynylaziridines contain synthetically exploitable and versatile ethynyl and aziridinyl moieties and hence should be amenable to a variety of important synthetic transformations.

Recently, Dai and co-workers have reported an interesting synthesis of alkynylaziridines.[4] The reported synthesis of aziridines bearing an alkynyl group either provides racemic material or necessitates the use of D-(+)-camphor-derived sulfonium salts providing alkynylaziridines with moderate enantiomeric purity.

In connection with a general programme directed towards the synthesis and reaction of chiral amino allenes, we required a reliable procedure for the synthesis of alkynylaziridines with high enantiomeric purity. It is generally accepted that ee or de values in excess of 90% are necessary. In this context, construction of chiral molecules using natural α-amino acids has assumed increasing importance.[5] In this communication, we report a new synthetic route to activated chiral ethynylaziridines from commercially available *S*-α-amino acids.

The requisite starting materials, mesylates of amino allylic alcohols **9–12**, for our initial study were prepared in a straightforward manner as depicted in Scheme 1. α-Bromo-α,β-unsaturated esters **1–4**, synthesized from the corresponding chiral amino aldehydes by treatment with $Ph_3P{=}C(Br)CO_2Me$,[6] were successively treated with DIBAL and methanesulfonyl chloride–Et_3N or pyridine to yield the allylic mesylates **9–12** in good to excellent overall yields.

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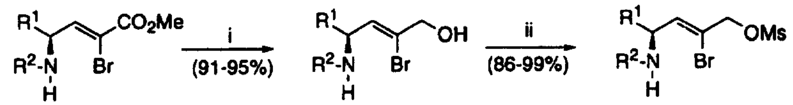


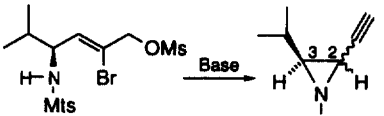
1 R^1 = Pr^i; R^2 = Mts
2 R^1 = Bu^i; R^2 = Ts
3 R^1 = Bn; R^2 = Mts
4 R^1 = Bn; R^2 = Mtr

5 R^1 = Pr^i; R^2 = Mts
6 R^1 = Bu^i; R^2 = Ts
7 R^1 = Bn; R^2 = Mts
8 R^1 = Bn; R^2 = Mtr

9 R^1 = Pr^i; R^2 = Mts
10 R^1 = Bu^i; R^2 = Ts
11 R^1 = Bn; R^2 = Mts
12 R^1 = Bn; R^2 = Mtr

Scheme 1. *Abbreviations*: Ts=4-methylbenzenesulfonyl; Mts=2,4,6-trimethylbenzenesulfonyl; Mtr=4-methoxy-2,3,6-trimethylbenzenesulfonyl. *Reagents*: i. DIBAL in toluene–$CHCl_3$; ii. MsCl–pyridine or Et_3N

Although conversion of the allylic mesylates such as **9** to ethynylaziridines **13** and **14** (Scheme 2) can be carried out in one pot by treating with *tert*-BuOK in DMSO, the yields of aziridines are considerably lower than those obtained from the two-step procedure described below.



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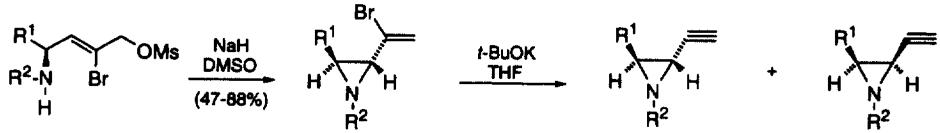
13 (2,3-*trans*)
14 (2,3-*cis*)

Scheme 2.

Based on our previous synthetic studies of alkenylaziridines from the corresponding allylic mesylates,[7] we anticipated that 3-alkyl-2-(1-bromovinyl)aziridines such as **15**–**18** could easily be prepared from the corresponding allylic mesylates **9**–**12** (Scheme 3). However, this was not to be the case. After considerable experimentation, we found that improved yields in the aziridine ring-forming reaction could be obtained by the use of sodium hydride in DMSO or mixed solvents containing DMSO. As illustrated in Table 1, except for entry 2, bromoaziridines **15**, **17** and **18** were obtained from the corresponding allylic mesylates **9**, **11** and **12** in both acceptable yields and high diastereoselectivities. Typically, the treatment of **9** with sodium hydride (1.2 equiv.) in DMSO at 30°C gave a mixture of bromoaziridine **15** and its 2,3-*cis*-isomer. Analysis by HPLC or ^1H NMR indicated a 97:3 ratio of diastereomers in favor of 2,3-*trans*-isomer **15** (Table 1, entry 1). Reaction in other solvents (e.g., THF and DMF) or in the absence of DMSO gave the expected products by slow reactions that often failed to proceed to completion.



9 R^1 = Pr^i; R^2 = Mts
10 R^1 = Bu^i; R^2 = Ts
11 R^1 = Bn; R^2 = Mts
12 R^1 = Bn; R^2 = Mtr

15 R^1 = Pr^i; R^2 = Mts
16 R^1 = Bu^i; R^2 = Ts
17 R^1 = Bn; R^2 = Mts
18 R^1 = Bn; R^2 = Mtr

13 R^1 = Pr^i; R^2 = Mts
19 R^1 = Bu^i; R^2 = Ts
20 R^1 = Bn; R^2 = Mts
21 R^1 = Bn; R^2 = Mtr

14 R^1 = Pr^i; R^2 = Mts
22 R^1 = Bu^i; R^2 = Ts
23 R^1 = Bn; R^2 = Mts
24 R^1 = Bn; R^2 = Mtr

Scheme 3.

Although 2,3-*trans*-bromoaziridines **16** and **17** could be separated, albeit with difficulty, from the corresponding 2,3-*cis*-isomers, other mixtures of the 2,3-*trans*- and 2,3-*cis*-isomers listed in Table 1 (entries 1 and 4) were inseparable by flash chromatographic techniques on various silica flash chromatographic columns. The predominant formation of 2,3-*trans*-bromoaziridines **15**–**18** could be rationalized by considering the 1,3-allylic strain of two aza-anionic intermediates **A** and **B** (Fig. 1). If the reaction conformers are as depicted in **A** and **B**, the higher diastereoselectivity is readily understood. Examination

Table 1
Aziridination reactions of bromo allylic mesylates **9**–**12** by treatment with sodium hydride[a]

entry	substrate	solvent	reaction time	products	ratio[b]	yield[c]
1	**9**	DMSO	1.0 h (30 °C)	**15** + its 2,3-*cis* -isomer	97:3	88%
2	**10**	DMF–DMSO	3.0 h (0 °C)	**16** + its 2,3-*cis*-isomer	95:5	47%
3	**11**	DMSO	2.5 h (30 °C)	**17** + its 2,3-*cis*-isomer	97:3	72%
4	**12**	DMSO	2.5 h (30 °C)	**18** + its 2,3-*cis*-isomer	97:3	65%

(a) All reactions were carried out using 1.2 equiv of NaH. (b) Ratios were determined by HPLC and/or ^{1}H–NMR.
(c) Combined isolated yields.

of the nonbonded interactions in the conformers **A** and **B** reveals that in conformer **A** a substantial nonbonded interaction does exist to destabilize this conformer. Thus, an aziridine ring-forming reaction would proceed preferentially from the more abundant conformer **B**.

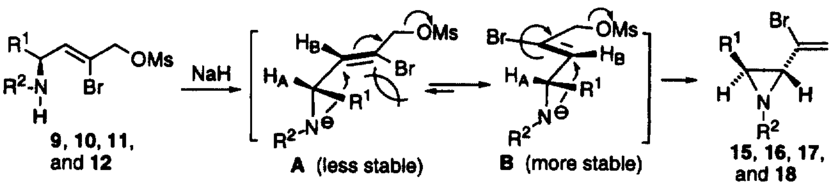


Figure 1.

Next, dehydrobromination reaction of the bromoaziridines **15**–**18** was investigated. Exposure of pure bromoaziridine **17** to *tert*-BuOK in THF unexpectedly gave a separable 65:35 mixture of 2,3-*trans*- and 2,3-*cis*-ethynylaziridines **20** and **23** in 80% combined yield. Consequently, without separating the mixtures of bromoaziridines, all the 2,3-*trans*- and *cis*-mixtures (2,3-*trans*:2,3-*cis*=95–97:5–3) were dehydrobrominated to yield the corresponding ethynylaziridines (2,3-*trans*:2,3-*cis*=63–77:35–23) in good to excellent yields. The results are listed in Table 2.[8] It should be clearly noted that, among various reaction conditions, only *tert*-BuOK in THF gave satisfactory results.

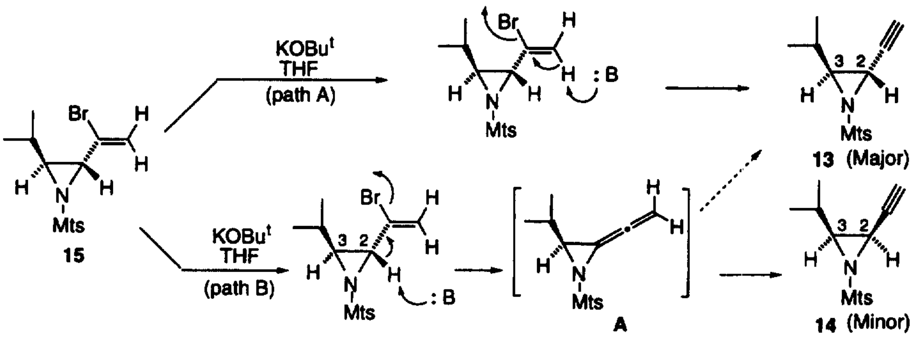
Interestingly, the reaction condition (*tert*-BuOK in THF) used for the dehydrobromination reaction did not cause any epimerization at the C-2 position of alkynylaziridine **13**. No sign of epimerization at the C-2 position of **13** was detected by ^{1}H NMR and HPLC after treatment with *tert*-BuOK (−78–0°C for 1 h).

Table 2
Synthesis of ethynylaziridines from 2-(1-bromovinyl)aziridines[a]

entry	substrate	reaction temp.	reaction time	product ratio[b] 2,3-*trans* : 2,3-*cis*	chemical yield[c]	enantiomeric purity (%ee)[d]
1	**15**	-78 ~ 0 °C	0.5 h	**13**:**14** = 74:26	99%	**13** (>99) **14** (>99)
2	**16**	-78 –-20 °C	1.0 h	**19**:**22** = 78:22	86%	**19** (>99) **22** (>99)
3	**17**	-78 –-20 °C	1.0 h	**20**:**23** = 65:35	80%	**20** (>99) **23** (>99)
4	**18**	-78 –-20 °C	1.0 h	**21**:**24** = 65:35	72%	**21** (>99) **24** (>99)

(a) Substrates containing 3–5% of 2,3-*cis*-isomers were employed. All reactions were carried out in THF using 2 equiv of *t*-BuOK. (b) Ratios were determined by isolation. (c) Combined isolated yields. (d) Determined by chiral HPLC on a CHIRALCEL OD and/or CHIRALCEL OJ (DAICEL).

Although the details of the dehydrobromination reactions have still not been elucidated, we are working under the assumption that both paths A and B are involved as depicted in Scheme 4. If the bromoaziridine **15** reacts with *tert*-BuOK only by path A, it will produce the 2,3-*trans*-ethynylaziridine **13** and if it proceeds only by path B, it will generate either only 2,3-*trans*-**13** or 2,3-*cis*-**14** or a mixture of both via an allenic intermediate **A**. The treatment of **13** with *tert*-BuOK in THF containing 5 equiv. of *tert*-BuOD gave a mixture of 2,3-*trans*- and 2,3-*cis*-alkynylaziridines as expected. Although no evidence was obtained of the incorporation of deuterium in the C-2 position of 2,3-*trans*-alkynylaziridine, it was found that ca. 10% of deuterium was incorporated at the C-2 position of 2,3-*cis*-ethynylaziridine. Taking together the above results, we propose the reaction of bromoaziridine **15** would proceed via two competitive paths **A** and **B** to yield 2,3-*trans*- and 2,3-*cis*-ethynylaziridines (**13** and **14**).



Scheme 4.

In summary, chiral 2,3-*trans*- and 2,3-*cis*-2-ethynylaziridines with high enantiomeric purity have been synthesized. Work on synthetic transformations of ethynylaziridines thus obtained is in progress and will be reported in due course.

Acknowledgements

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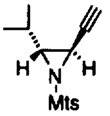
8. Enantiomeric purities of ethynylaziridines **13** and **14** have been determined by HPLC with a chiral stationary phase (Chiralcel OD and/or Chiralcel OJ) by comparison with their enantiomers (**25** and **26**) synthesized from D-valinol. Compounds **13** and **14** were found to be enantiomerically pure (ee >99%).



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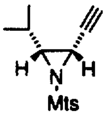

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