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NUCLEOPHILIC RING OPENING OF C_2-SYMMETRIC AZIRIDINES. SYNTHETIC EQUIVALENTS FOR THE β-CATION OF ASPARTIC ACID

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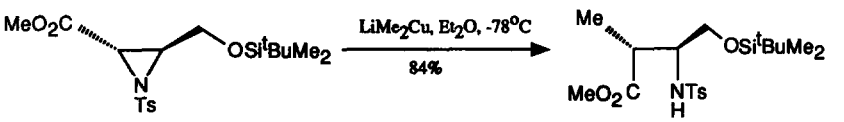
Abstract: The non-racemic C_2-symmetric aziridines **7** and **8**, easily available from (+)- and (-)-tartaric acid, respectively, undergo rapid nucleophilic attack to yield products formally derived from the β-cation of L- or D-aspartic acid.

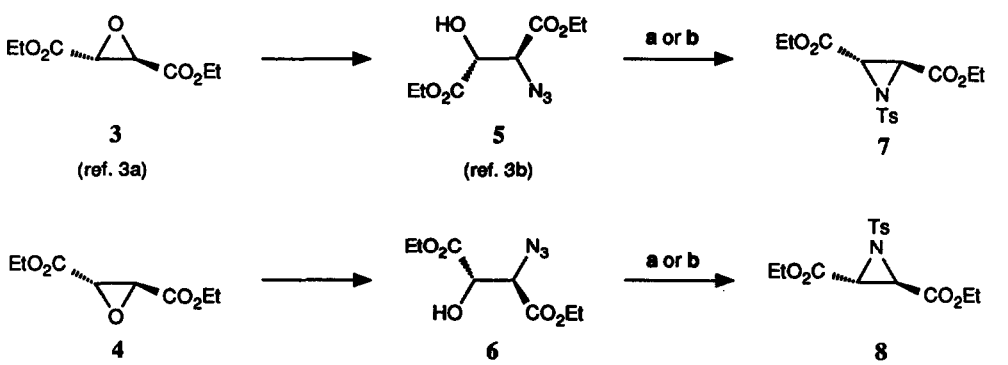
The synthesis of novel amino acids is currently a topic of great interest[1a-c] and both we[2a,b] and others[2c-g] have demonstrated the utility of suitably functionalized chiral aziridines as key synthetic intermediates. In the course of our work on the enantioselective synthesis of β-lactam antibiotics[2b] we recently attained complete regiocontrol in the ring opening of the aziridine shown in **Eq 1**.



(Eq 1)

1 **2**

The excellent regioselectivity shown above prompted us to synthesize the C_2-symmetric aziridines **7** and **8** (Scheme) for reaction with nucleophiles, in order to obtain products formally derived from the β-cation of either L- or D-aspartic acid.

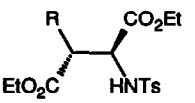


Scheme. (a): (i)PPh_3, C_6H_6, reflux → N-H aziridine (ii) pTsCl, pyridine, 73% overall.
(b): (i) PPh_3, C_6H_6, RT → amino-alcohol (ii) pTsCl, pyridine, -20°C →N-tosyl amino-alcohol (iii) DEAD, PPh_3, THF, RT, 61% overall.

In this Letter we present some of our results which complement those published in two recent papers by Baldwin[1c,2c]. In the first of these[1c] Baldwin showed that the β-anion of aspartic acid provides a useful entry to non-proteinogenic amino acids, while in the second paper[2c] he describes the ring opening of aziridine-2-carboxylate esters with organometallic reagents.

Our route to the chiral aziridines **7** and **8** is shown in the Scheme, key intermediates being the known[3a] epoxides **3** and **4** and the azido-alcohols[3b] **5** and **6**. The latter were transformed to the desired aziridines[3c] in two different ways, one of which involved an efficient intramolecular Mitsunobu reaction[4] to close the three-membered ring.

The C_2-symmetry of **7** and **8** removes the issue of regiochemistry from any discussion of ring opening, and nucleophilic attack on these species was expected to occur with clean inversion[2], thus conserving stereochemical and enantiomeric purity. Finally, the two ester groups and the tosyl moiety were expected to powerfully activate these aziridines towards nucleophiles. Our results are shown in the Table.

Table. Reaction: **7** ⟶ 

9a - e

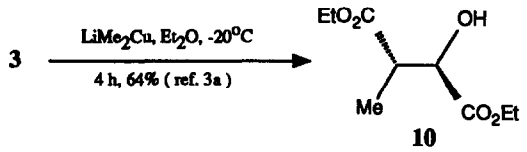
Entry	Nucleophile	Solvent	Temp.	Product	R	Isolated yield[a]
1	$LiMe_2Cu$ (2 eq.)	Et_2O	-78°C	**9a**[5a]	Me	68%
2	$LiBu_2Cu$ (2 eq.)	Et_2O	-78°C	**9b**	Bu	54%
3	Li_2Bu_2CuCN	Et_2O	-78°C			[b]
4	NaN_3 (2 eq.)	DMF	30°C	**9c**[5b]	N_3	81%
5	MgI_2 (3 eq.)	THF	0°C	**9d**	I	72%
6	$MgBr_2$ (3 eq.)	THF	0°C	**9e**	Br	76%

[a] After flash chromatography. [b] Decomposition.

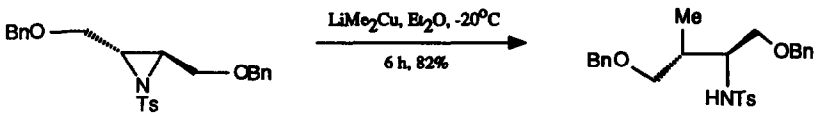
The first nucleophiles tested (entries 1 and 2) were the Gilman cuprates, and it was quickly found that **7** and $LiMe_2Cu$ reacted extremely rapidly (< 2 min) at -78°C in ethereal solution to furnish **9a** in acceptable isolated yield. The dibutyl cuprate gave somewhat poorer yields, partly due to the concomitant formation of the reduction product N-tosyl diethylaspartate[6]. Use of the Lipshutz higher-order cyanocuprates[7] (entry 3) was completely unrewarding. The facility with which **7** underwent ring-opening by the Gilman cuprates is remarkable, and stands in sharp contrast to the relatively sluggish behaviour of both its epoxide counterpart **3** (**Eq 2**) and the aziridine[8] congener **11** shown in **Eq 3**. For further comparison it may be noted that the reaction shown in **Eq 1** was complete after 3h at -78°C. The combined activating power of the ester groups and the N-tosyl moiety of **7** is thus clearly demonstrated.

A further contrast between aziridine **7** and epoxide **3** is provided by entry 4 in the **Table**, since **3** is essentially inert towards sodium azide under these reaction conditions (see also Ref. 3b). Iodide and

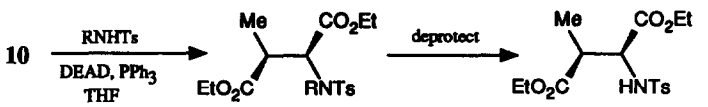
bromide (entries 5 and 6) also ring-opened **7** under mild conditions and in high yield. The relevant *enantiomeric* series of products is provided by analogous reactions of **8** (the optical antipode of **7**) and we are currently attempting to obtain *epimeric* materials by the type of sequence[4] shown in **Eq 4**.



10 (Eq 2)



11 **12** (Eq 3)



13 **14** (Eq 4)

In summary, we have demonstrated that the enantiomeric pair of C_2-symmetric[10] aziridines **7** and **8**, easily available in quantity from (+)- and (-)-tartaric acid, respectively, represent convenient synthetic equivalents for the β-*cation* of either L- or D-aspartic acid. Reactions of these aziridines with a wider range of nucleophiles are now being studied.

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References and Notes

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3. (a) Mori, K. and Iwasawa, H. *Tetrahedron* **1980**, *36*, 87. (b) Saito, S., Bunya, N., Inaba, M., Moriwake, T. and Torii, S. *Tetrahedron Lett.* **1985**, *26*,5309. (c) Selected data for **7**: $[\alpha]_D$ -49° (c=1, CH_2Cl_2);^{1}H NMR (300 MHz, $CDCl_3$,TMS): δ 1.30 (6H,t, J=7 Hz), 2.43 (3H,s), 3.79 (2H,s), 4.24 (4H,m), 7.32 and 7.85 (2x2H, *AA'BB'*, J_{AB}=8.5); IR: 1745(s), 1340(s), 1164(s) cm^{-1}; Anal.: Calcd. for $C_{15}H_{19}NO_6S$: C, 52.75;H, 5.61;N, 4.11. Found: C, 52.51;H, 5.57;N, 3.84%.

4. For recent related examples,see: Henry, J.R., Marcin, L.R., McIntosh, M.C., Scola, P.M., Harris, G.D.,Jr. and Weinreb, S.M. *Tetrahedron Lett.* **1989**, *30*, 5709.

5. (a) Selected data for **9a**: $[\alpha]_D$ +18.5° (c=0.53, CH_2Cl_2);^{1}H NMR ($CDCl_3$,TMS): δ 1.04 (3H,t, J=7), 1.22 (3H,t, J=7), 1.26 (3H,d, J=7), 2.40 (3H,s), 3.11 (1H,qd, J=7,4), 3.94 (2H,q, J=7), 4.05 (1H,dd, J=9.5,4), 4.09 (2H,m),5.49 (1H,d, J=9.5), 7.27 and 7.75 (2x2H, *AA'BB'*, J_{AB}=8.8).IR: 3285(b), 1736(s), 1341(s), 1165(s) cm^{-1}; (b) Selected data for **9c**: $[\alpha]_D$ +78.9° (c=0.8, CH_2Cl_2);^{1}H NMR ($CDCl_3$,TMS): δ 1.11 (3H,t, J=7), 1.30 (3H,t, J=7), 2.40 (3H,s), 4.05 (2H,m), 4.26 (2H,q, J=7), 4.43 (1H,d, J=3), 4.46 (1H,dd, J=7.5,3), 5.49 (1H,d, J=7.5), 7.30 and 7.76 (2x2H, *AA'BB'*, J_{AB}=8.9); IR: 3328(b), 2121(s), 1747(s), 1348(s), 1166(s) cm^{-1}.

6. See ref. 2c for a similar result.

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8. Aziridine **11** ($[\alpha]_D$ +1.57°, c= 0.98, CH_2Cl_2) was prepared from the relevant non-racemic epoxide[9] via the procedure outlined in refs. 2a and 2b.

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10. For an excellent review of the concept of "C_2 Symmetry and Asymmetric Induction", see: Whitesell, J.K. *Chem.Rev.* **1989**, *89*, 1581. See also: Isaksson, R., Wennerström, H. and Wennerström, O. *Tetrahedron* **1988**, *44*, 1697.

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