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Asymmetric Synthesis and Reactions of *cis*-*N*-(*p*-Toluenesulfinyl)aziridine-2-carboxylic Acids

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Summary: *cis*-Aziridine-2-carboxylic acids, **2**, precursors of the difficult to prepare *syn*-β-hydroxy-α-amino acid structural unit, are prepared in high diastereomeric purity by a Darzens-type reaction of the lithium enolate of methyl bromoacetate with enantiopure sulfinimines **1**.

The regio- and stereoselective ring-opening reactions of N-activated *cis*- and *trans*-aziridine-2-carboxylic acids play increasingly important roles in strategies for the synthesis of natural and unnatural amino acids.[1,2] While racemic aziridines are readily available, procedures for their synthesis in enantiomeric pure form are limited.[3] This is particularly true for *cis*-aziridine-2-carboxylic acids, precursors of the difficult to prepare *syn*-β-hydroxy-α-amino acid structural unit found in many bioactive materials.[4-6] Preparations of nonracemic *cis*-aziridine-2-carboxylic acids include (i) cyclization of synthetic[7] and naturally occurring β-hydroxy-α-amino acids,[8] (ii) the diastereoselective reaction of ammonia with nonracemic α-bromo-α,β-unsaturated esters,[9] (iii) the conversion of oxirane-2-carboxylic esters,[10] and (iv) enzymatic transesterification of *meso*-bis(acetoxymethyl)aziridines.[11] With the exception of the first method, limited by the availability of the naturally occurring β-hydroxy-α-amino acid, the others are lengthy, multistep procedures often requiring resolutions and/or separation of diastereoisomers. In this context we describe a simple one-pot, highly diastereoselective asymmetric synthesis of *cis*-*N*-(*p*-toluenesulfinyl)-2-carbomethoxyaziridines **2** via a Darzens-type reaction[12] of the lithium enolate of methyl bromoacetate with enantiopure sulfinimines (*S*)-(+)-**1** (Scheme 1). Applications of these aziridines to the enantioselective synthesis of α-amino- and *syn*-β-hydroxy-α-amino acids are also presented.

Typically, methyl 2-bromoacetate (2 mmol) was treated with an equivalent amount of lithium bis(trimethylsilyl-amide) in THF (10 mL) at −78 °C. After 30 min, a THF (10 mL) solution of 1.0 mmol of the appropriate sulfinimine (*S*)-(+)-**1a–c** or (*R*)-(−)-**1a** at −78 °C was slowly added to the enolate via cannula. After being stirred for 2.5 h the reaction mixture was quenched with H_2O at −78 °C and

• Abstract published in *Advance ACS Abstracts*, March 15, 1994.

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(3) (a) For leading references see: Legters, J.; Thija, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 1. (b) See also: Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.

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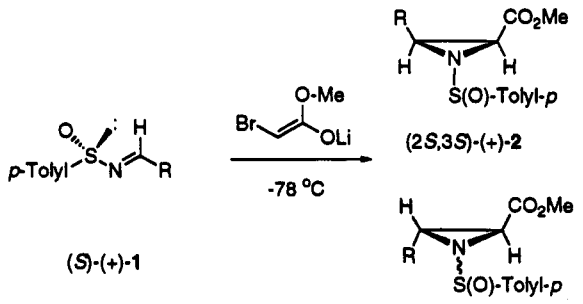
(11) Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Taga, T.; Miwa, Y. *Tetrahedron Lett.* **1990**, *31*, 6663.

(12) For Darzens-type synthesis of racemic aziridines see: Rosen, T. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 409. Cainelli, G.; Panunzio, M.; Giacomini, D. *Tetrahedron Lett.* **1991**, *32*, 121.

0022-3263/94/1959-3243$04.50/0

Scheme 1



R = a) Ph, b) *p*-MeOPh, c) Me_2CH-

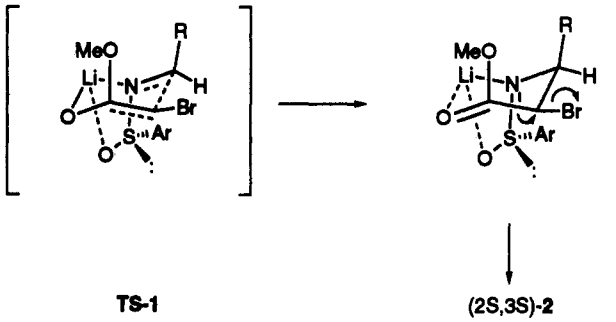
Table 1. Asymmetric Synthesis of *cis*-*N*-(*p*-Toluenesulfinyl)-2-carbomethoxyaziridines 2

entry	R[a]	*T* (°C)/ time (h)	ratio (2:3)[g]	(confign)[i]	$[\alpha]^{20}_D$ (*c*, $CHCl_3$)[i]	% yield[j]
1	**2a**, Ph	−78/2.5[b,c]	97:3	(2*S*,3*S*)	+51.4° (1.5)	65
2	Ph	−78 to rt/ 3[b,d]	90:10	(2*S*,3*S*)		77
3	Ph	−78/2.5[e,c]	88:12	(2*S*,3*S*)		60
4	Ph[f]	−78/2.5[b,c]	97:3	(2*R*,3*R*)	−50.8° (1.5)	70
5	**2b**, Ph-OMe-*p*	−78/2.5[b,c]	99:1[h]	(2*S*,3*S*)	+26.4° (1.7)	74
6	**2c**, Pr-*i*	−78/2.5[b,c]	99:1[h]	(2*S*,3*S*)	+110.7° (1.3)	64

[a] (*S*)-(+)-1 was used unless otherwise indicated. [b] The sulfinimine was cooled to −78 °C before addition to the enolate at −78 °C. [c] Reaction quenched at −78 °C. [d] Reaction quenched at rt. [e] A rt solution of the sulfinimine was added to the enolate at −78 °C. [f] (*R*)-(−)-1 was used. [g] Determined by NMR. [h] Minor isomer not detected. [i] Refers to the major isomer. [j] Isolated yield of major isomer.

diluted with EtOAc. Drying and removal of the solvent gave the crude *N*-(*p*-toluenesulfinyl)aziridines which were purified by silica gel flash chromatography (EtOAc:*n*-pentane) and isolated in good yield (Table 1).[13] The reaction works with both nonenzolizable (entries 1–5) and enolizable sulfinimines (entry 6), and the antipodal aziridines are readily available by choice of the enantiomeric sulfinimine; e.g., (*R*)-(−)-1 (entry 4). Enantiopure sulfinimines (*S*)-(+)-1 and (*R*)-(−)-1 were prepared as previously described from the corresponding aldehyde and menthyl (*S*)- or (*R*)-*p*-toluenesulfinate (Andersen reagent).[14]

In each case examined (2*S*,3*S*)-**2**, the *cis*-aziridine, was formed nearly exclusively. Only in the case of **1a** (R = Ph) was the *trans*-isomer (2*S*,3*R*)-**3a** detected (Table 1).[15] The stereochemical assignments are based on the large ring proton coupling constants observed for **2** vs **3**, (e.g., J = 7.0–7.4 Hz vs 4 Hz, respectively)[16] and their transformation into *syn*-β-hydroxy-α-amino acids described below. The high *cis*-selectivity is consistent with chairlike transition **TS-1** followed by intramolecular ring closure of the acyclic bromide intermediate which was not detected. In the transition state both the enolate and sulfinimine are required to have the *E* geometry. Sulfinimines, however, have relatively low barriers to inversion ($\Delta G^{\ddagger}$ = 13–14 kcal/mol),[17] but may be locked into the *E* geometry as a consequence of the metal cation of the enolate being coordinated with both nitrogen and oxygen atoms of the sulfinimine. Similar arguments were used to explain the high de's for the synthesis of β-amino acids from enolates and **1**.[18] While the orientation of the *N*-(*p*-toluenesulfinyl) group with respect to the ring substituents in **2** is unknown, the reasonable assumption is that it has the *syn*-orientation for steric reasons.[19] Barriers to nitrogen inversion in *N*-sulfenyl, *N*-sulfinyl, and *N*-sulfonylaziridines are low ($\Delta G^{\ddagger}$ = 10–14 kcal/mol), and at ordinary temperatures inversion in **2** may be rapid.[20]



Aziridine ring opening requires activation at nitrogen, and many activating groups have been studied.[1b] *N*-Tosyl activation often affords superior reactivity and regiospecificity. However, attempts to tosylate 1*H*-3-arylaziridine-2-carboxylic esters leads predominantly to ring-opened products.[1b] In contrast, our approach installs this key activating group prior to ring opening by oxidation of **2a** and **2c** with 1.5 equiv of *m*-CPBA (57%) in $CHCl_3$ affording **4a** [mp 86 °C; $[\alpha]^{20}_D$ +18.2° (*c* 2.75, $CHCl_3$)] and **4c** [mp 52–4 °C; $[\alpha]^{20}_D$ −34.3° (*c* 1.2, $CHCl_3$)] in 94 and 95% yield, respectively. Transfer hydrogenation[21] of **4a** for 3 h afforded the (*S*)-phenylalanine derivative **5a**,[3b] and acid-catalyzed hydrolysis at 100 °C (24 h) gave the phenylserine derivative **6a** (84:16) as a mixture of diastereoisomers.[3b] Under similar conditions, **2c** was unreactive but gave the formate ester **6c** [mp 114–5 °C; $[\alpha]^{20}_D$ +73.6° (*c* 1.3, $CHCl_3$)] as a single isomer on heating in 98% formic acid for 1.5 h at 100 °C. Ring opening of *cis*-aziridines **2a** and **2c** appears to be more difficult than the corresponding *trans*-isomers.[1b,3b]

Although Rapoport et al. have developed methodology for removal of the sulfonamide group in hydroxy amino acids the conditions are often harsh.[22] One of the advantages of the *N*-sulfinyl group is that it can be removed under comparatively mild conditions.[18] Thus, treatment of **2a** and **2c** with 5 equiv of TFA in 50% aqueous acetone for 15–20 min afforded 1*H*-aziridines **7a**[10] and **7c**[23] in 83 and 80% yield, respectively. The question remaining is whether the *N*-(*p*-toluenesulfinyl) group is activating enough for regiocontrolled ring opening to occur. Indeed,

(13) All new compounds gave satisfactory elemental analysis and had spectra consistent with their properties.

(14) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229.

(15) (2*S*,3*R*)-**3a** was isolated as an inseparable mixture of the *syn*- and *anti*-aziridines with respect to the carbomethoxy group which were oxidized with *m*-CPBA to the known (2*S*,3*R*)-*N*-(*p*-toluenesulfonyl)-2-carbomethoxy-3-phenylaziridine.[3b]

(16) The coupling constants for *cis*- and *trans*-2-(methoxycarbonyl)-3-phenylaziridines are 6.5 and 2.3 Hz, respectively.[9b] The ring proton coupling constant for the *N*-tosylaziridine corresponding to (2*S*,3*R*)-**3** is 4 Hz.[3b]

(17) Davis, F. A.; Kluger, E. W. *J. Am. Chem. Soc.* **1976**, *98*, 302.

(18) Davis, F. A.; Thimma Reddy, R.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.

(19) Methyl *N*-(phenylsulfinyl)-2-aziridinecarboxylate is reported to prefer the *trans*-configuration. Chervin, I. I.; Fomichev, A. A.; Moskalenko, A. S.; Zaichenko, N. L.; Aliev, A. E.; Prosyanik, A. V.; Voznesenskii, V. N.; Kostyanovskii, R. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, 1110; *Chem. Abstr.* **1989**, *110*, 56755g.

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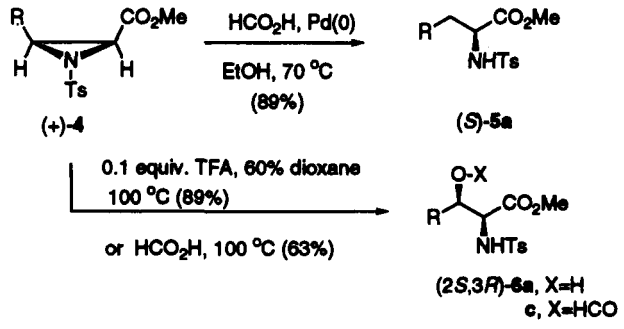
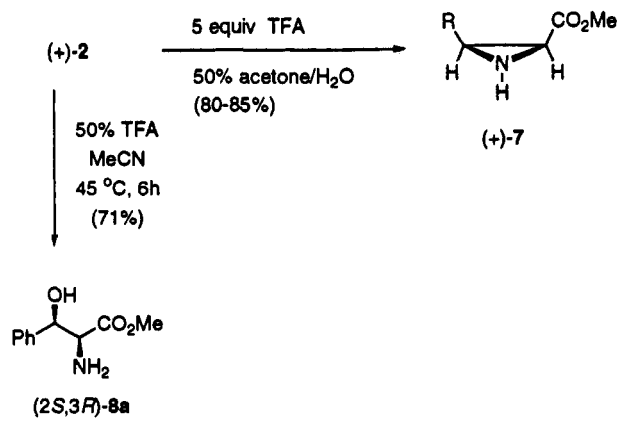
(23) Oil; $[\alpha]^{20}_D$ = +50.2° (*c* 2.9, $CHCl_3$).



heating **2a** at 45 °C for 6 h in 50% aqueous TFA afforded, after neutralization with concd NH_4OH and purification by flash chromatography, a 71% yield of *syn*-β-phenylserine derivative **8a**[24] as a 93:7 mixture of diastereoisomers. Ring opening of the less reactive aliphatic aziridine **2c**, however, proved to be more difficult, and under comparable conditions only the 1*H*-aziridine **7c** (85%) was isolated.

In summary, the Darzens-type reaction of the lithium enolate of methyl bromoacetate with enantiopure sulfinimines **1** represents a highly efficient method for the synthesis of enantiopure *cis*-aziridine-2-carboxylic acids derivatives **2**, precursors of the difficult to prepare *syn*-β-hydroxy-α-amino acid structural unit. In contrast to the usual aziridine N-activating group the *N*-(*p*-toluenesulfinyl) group is removed under comparatively mild conditions and is sufficiently activating for regioselective ring opening to occur for the 3-phenyl derivative **2a**. Work currently underway is aimed at the utilization of **2** in the asymmetric synthesis of bioactive materials.



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Supplementary Material Available: Experimental procedures and compound characterization data (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(24) Beulshausen, T.; Groth, U.; Schollkopf, U. *Liebigs Ann. Chem.* **1991**, 1207.