Chemistry of Aziridinecarboxylic Acids, 8[‡]

Asymmetric Synthesis of Enantiomerically Pure Aziridinecarboxylates from *N*-Boc-2,2-Dimethylserinal

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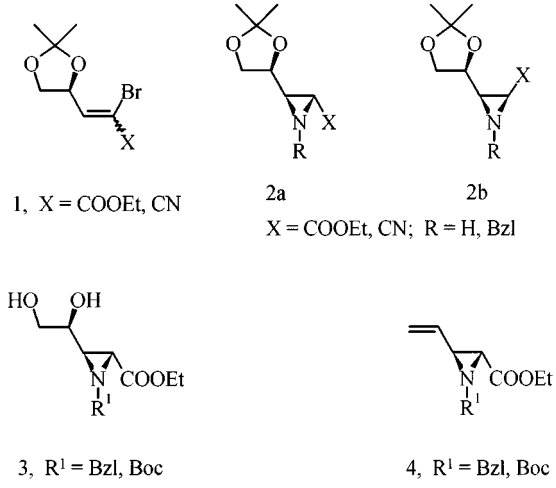
Enantiomerically pure *cis*- and *trans*-aziridinecarboxylic acid derivatives **7**–**10** have been prepared with high *syn* selectivity by asymmetric Michael-type addition of benzylamine to chiral acrylates **6**. The absolute configuration of (2*S*,3*S*,4*R*)-aziridine **10** was determined by X-ray analysis.

Introduction

Aziridine-2-carboxylates can be used as versatile building blocks in organic syntheses. Thanks to the high reactivity of the three-membered ring, they may be considered as precursors of a variety of functionalized α- and β-amino acids.[1−4]

Our research program is directed towards the development of effective methods for the preparation of enantiomerically pure aziridinecarboxylic acids from α-haloacrylic acid derivatives[5,6] and either amines or ammonia.

Previously, we were able to show that α-bromoacrylic acid derivatives **1**, easily accessible from glyceraldehyde acetonide, react with benzylamine or ammonia to form enantiomerically pure aziridines **2a** and **2b** (diastereomeric excess >99%, Scheme 1). Aziridine **2a** can be transformed into the dihydroxy derivative **3** or vinylaziridine **4**.[7]



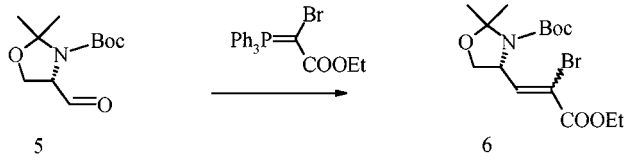
Scheme 1. Aziridinecarboxylic acid derivatives

The observed high *syn* selectivity of the reaction between amines and α-bromoacrylates may be explained in the context of a modified Felkin−Anh model. Thus, the nucleophile attacks the π system from the less hindered site antiperiplanar to the bulky oxygen substituent.

In this paper we describe the directing effect of a nitrogen-containing substituent at the stereogenic centre generated by the addition of the amine to the double bond. Enantiomerically pure 3-[hydroxy(amino)ethyl]aziridinecarboxylic acid derivatives thus formed possess a broad spectrum of applications as building blocks.

Results and Discussion

(4*S*)-3-*tert*-Butoxycarbonyl-4-formyl-2,2-dimethyloxazolidine **5** (Garner's aldehyde) was used as the starting compound. It gave the acrylic acid derivative **6** under Wittig conditions with ethyl bromo(phosphoranylidene)acetate (Scheme 2).



Scheme 2. Synthesis of starting compound **6** by Wittig reaction

HPLC and ^{1}H NMR examination showed that compound **6** was a mixture of (*E*) and (*Z*) isomers (19:81). Without separating the isomers, compound **6** was treated with an equimolar amount of benzylamine in the presence of triethylamine.

HPLC examination indicated that four stereoisomeric aziridines, **7**−**10** (Scheme 3), had been formed in an overall yield of 85%, the *syn* aziridines **7** and **8** predominating with an excess of 41 and 38%. The stereogenic centre in the ox-

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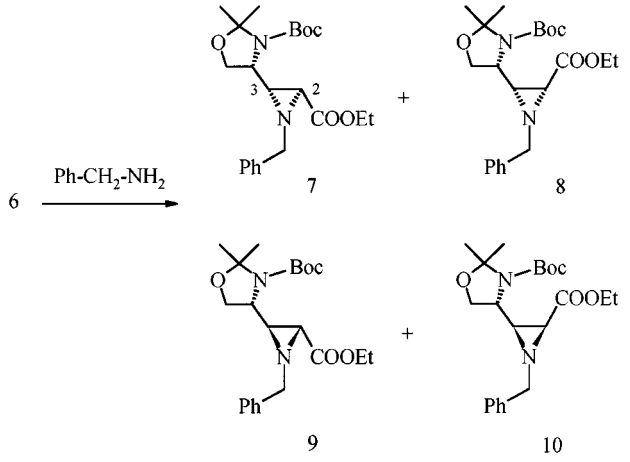
azolidine substituent of **6** had thus transferred its chiral characteristics to the C-3 atom of the aziridine ring formed. A high *syn* selectivity and a diastereomeric excess of 87% were observed. The enantiomerically pure aziridines **7**−**10** were separated by preparative column chromatography.



Scheme 3. Asymmetric synthesis of substituted aziridinecarboxylic ester derivatives **7**−**10**

A comparison of the NMR spectra at 25 °C and 100 °C showed that compounds **7**−**10** exist at room temperature as mixtures of invertomers.

The assignment of the absolute configuration was achieved by X-ray analysis. Crystalline aziridine **10**, formed in minor amounts, was identified as ethyl (2*S*,3*S*,4*R*)-1-benzyl-3-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)aziridine-2-carboxylate (see Figure 1). The coupling constant of the aziridine protons in the ^{1}H NMR spectrum (6.7 Hz) fits with the *cis* configuration.

On the assumption that aziridine **9** − the other minor product − must also have the (*S*) configuration at the C-3 atom of the aziridine ring, and hence that the two aziridines, **7** and **8**, formed as major products have the (*R*) configuration at the corresponding site, conclusive assignment of the configuration of the compounds can be made by determining the *cis* or *trans* relationships of the substituents on the aziridine rings. This is possible by measuring the coupling constants of the respective proton signals in the ^{1}H NMR spectrum.

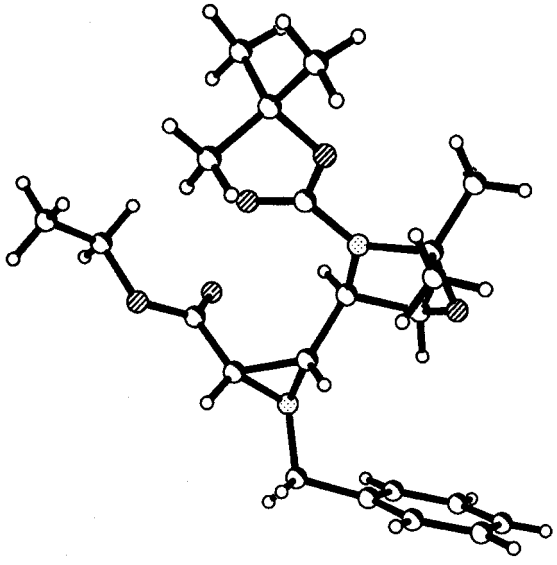
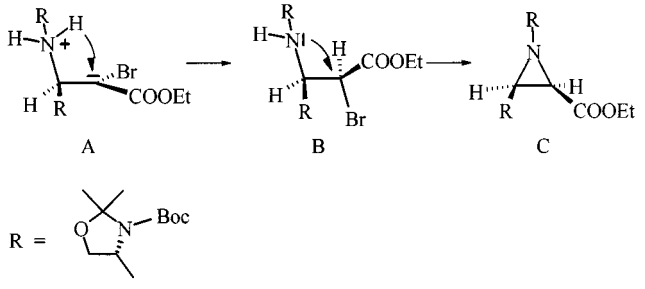


Figure 1. Crystal structure of *cis*-aziridine **10**

As expected, aziridine **9** showed a coupling constant of 2.8 Hz, indicating a *trans* configuration. Thus, **9** can be assigned the (2*R*,3*S*,4*R*) configuration.

For compound **8**, the *cis* configuration for the substituents at the aziridine ring was determined analogously (coupling constant 6.4 Hz). Thus, **8** has the (2*R*,3*R*,4*R*) configuration. After assigning the configurations of compounds **8**, **9**, and **10**, the (2*S*,3*R*,4*R*) configuration must follow, by elimination, for compound **7**. In this case, definite assignment of the *trans* configuration for the substituents of the aziridine ring turned out to be more difficult than for the other diastereomers, as the two aziridine ring proton signals appeared in deuterated tetrachloroethane as a common signal. A slight splitting of this signal was observed in deuterated benzene, but it was not sufficient for measurement of the coupling constant. Both signals were, however, sufficiently separated when measurement was performed in deuterated pyridine at 100 °C. A coupling constant of 3.0 Hz was found, which confirms the (2*S*,3*R*,4*R*) configuration for diastereomer **7**.

According to a suggested mechanism from the literature,[8,9] benzylamine attacks the prochiral centre at C-3 of the 2-bromoacrylate **6** regardless of (*E*) or (*Z*) configuration, affording the *syn*-product with high selectivity. This fact is in accordance with earlier observations[10−12] concerning the addition of ammonia and benzylamine to chiral α,β-unsaturated esters in the same manner, with formation of β-amino acids. The question of whether either the *cis* or the *trans* product is formed (configuration at C-2) depends on the solvent as well as the (*E*)/(*Z*) ratio. The decisive factor is whether, in an aprotic solvent, the protonation of the forming β-amino-α-bromo-carbanion **A** (Scheme 4) occurs by intramolecular proton transfer from the ammonium ion onto the C-2 carbanion on the same side (**A** to **B** in Scheme 4) as the introduced nitrogen, or, in protic solvents, the protonation of the carbanion **A** occurs non-selectively from both sides. An (*E*) product, for instance, would yield *cis* aziridines in the former case, and *cis*/*trans* mixtures in the latter.



Scheme 4. Aziridine ring-closure in aprotic solvents

Conclusion

In conclusion, a practical synthesis of enantiomerically pure aziridinecarboxylic acid derivatives **7**−**10** has been de-

veloped, based on a Michael-type addition of benzylamine to chiral acrylates **6**. The compounds are versatile building blocks for the synthesis of new, optically active amino acids, amino alcohols, or polyamines.

Experimental Section

General Remarks: Commercial chemicals were used without further purification if not otherwise stated. − Merck Kieselgel 60 silica gel (40−63 μm) was used for column chromatography. − Melting points are not corrected. − ^{1}H and ^{13}C NMR spectra: Varian UNITYplus 300 and 500, internal standard: HMDS. − MS: HP 5985 B. − Elemental analyses: Elemental analyzer 1406 (Carlo Erba). − Angles of rotation: Polarimeter Perkin−Elmer 241, cell length 1 dm. − X-ray analysis: Turbo CAD4-diffractometer (Enraf−Nonius) program SHELX-97,[13] for further details see ref.[14]

Ethyl (4*R*)-(−)-2-Bromo-3-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)acrylate (6): Ethyl bromo(triphenylphophoranylidene-)acetate (506 mg, 1.18 mmol) was added to a solution of (4*S*)-3-*tert*-butoxycarbonyl-4-formyl-2,2-dimethyloxazolidine (**5**) (240 mg, 1.05 mmol) in 5 mL of dry CH_2Cl_2. The mixture was left standing overnight. Compound **6** (200 mg, 55%) was obtained as a colorless oil after purification by column chromatography (heptane/*tert*-butyl methyl ether 20:3). (*E*)/(*Z*) = 19:81. − $[\alpha]_{20}^{D}$ = −7.8 (*c* = 0.79, $CHCl_3$). − ^{1}H NMR ($C_2D_2Cl_4$, 100 °C), (*E*)/(*Z*) isomer ratio 19:81: δ = 1.32 (t, ^3J = 6.7 Hz, 3 H, O−CH$_2$−C*H$_3$*), 1.43 [s, 9 H, O−C(*CH$_3$*)$_3$], 1.46−1.63 (m, 6 H, C*H$_3$* oxazolidine), 3.75−3.81 (m, 1 H, 5′-H), 4.10−4.20 (m, 1 H, 5′-H), 4.27 (q, ^3J = 6.7 Hz, 2 H, O−C*H$_2$*−CH$_3$), 4.70−4.80 (m, 0.81 H, 4′-H, *Z* isomer), 5.03−5.11 (m, 0.19 H, 4′-H, *E* isomer), 6.66 (d, 0.19 H, ^3J = 8.2 Hz, 3-H, *E* isomer), 7.21 (d, 0.81 H, ^3J = 7.5 Hz, 3-H, *Z* isomer). − ^{13}C NMR ($CDCl_3$, 25 °C): δ = 14.2* (O−CH$_2$−*C*H$_3$), 24.0*, 26.2*, (*C*H$_3$ oxazolidine, 28.4 [O−C(*C*H$_3$)$_3$], 58.7* (4′−C), 62.7* (O−*C*H$_2$−CH$_3$), 67.2* (5′-C), 80.5* [O−*C*(CH$_3$)$_3$], 94.8* (2′−C), 115.6* (2-C), 145.5* (*C*=O Boc), 149.8* (3-C), 161.9* (*C*O$_2$Et). [*: accompanied by a second, smaller *E* isomer peak] − MS: *m*/*z* = 378. − $C_{15}H_{24}BrNO_5$ (378.3): calcd. C 47.62, H 6.39, N 3.70; found C 47.64, H 6.37, N 3.74.

Ethyl 1-Benzyl-3-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)aziridine-2-carboxylates 7−10: Acrylic acid ester **6** (567 mg, 1.50 mmol) was dissolved in 5 mL of absolute ethanol. Triethylamine (152 mg, 1.50 mmol) and benzylamine (241 mg, 2.25 mmol) were added at room temperature. After standing for five days at room temperature, the solvent was removed under vacuum and the residue was separated by column chromatography into compounds **7−10** (heptane/ethyl acetate 20:1.5 to 20:2).

Ethyl (2*S*,3*R*,4*R*)-(−)-1-Benzyl-3-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)aziridine-2-carboxylate (7): Oil, yield 41.4%, $[\alpha]_{20}^{D}$ = −69.5 (*c* = 1.09, $CHCl_3$). − ^{1}H NMR ($C_2D_2Cl_4$, 100 °C): δ = 1.18 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$−C*H$_3$*), 1.44 [s, 9 H, O−C(C*H$_3$*)$_3$], 1.45 (s, 3 H, *CH$_3$* oxazolidine), 1.53 (s, 3 H, C*H$_3$* oxazolidine), 2.65 (s, 2 H, 2-H and 3-H), 3.69 (d, ^2J = 9.1 Hz, 1 H, 5′-H$_{4',5'\text{-}cis}$), 3.74 (dd, ^2J = 9.1 Hz, ^3J = 6.1, 1 H, 5′-H$_{4',5'\text{-}trans}$), 3.95 (d, ^2J = 14.0 Hz, 1 H, C*H$_2$*−Ph), 3.97 (d, ^2J = 14.0 Hz, 1 H, C*H$_2$*−Ph), 4.07−4.10 (m, 1 H, 4′-H), 4.13 (q, ^3J = 7.0 Hz, 2 H, O−C*H$_2$*−CH$_3$), 7.17−7.31 (m, 5 H, Ph). − ^{13}C NMR ($C_2D_2Cl_4$, 75 °C): δ = 14.2 (O−CH$_2$−*C*H$_3$), 24.1, 26.9, (*C*H$_3$, *C*H$_3$ oxazolidine), 28.5 [O−C(*C*H$_3$)$_3$], 37.8, 46.9 (C-3, C-2), 54.9 (−*C*H$_2$−Ph), 56.4 (4′-C), 61.1 (O−*C*H$_2$−CH$_3$), 63.6 (5′−C), 80.2 [O−*C*(CH$_3$)$_3$], 93.9 (2′−C), 126.9, 128.2, 128.3, 139.4 (Ph), 151.9 (*C*O$_2$-*t*Bu), 169.2 (*C*O$_2$Et). − MS − *m*/*z* (LSIMS, high resolution): 405.2389, $C_{22}H_{32}N_2O_5$.

Ethyl (2*R*,3*R*,4*R*)-(+)-1-Benzyl-3-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)aziridine-2-carboxylate (8): M.p. 53−56 °C, yield 37.9%, $[\alpha]_{20}^{D}$ = +0.76 (*c* = 0.65, $CHCl_3$). − ^{1}H NMR ($C_2D_2Cl_4$, 100 °C): δ = 1.22 (t, ^3J = 7.2 Hz, 3 H, O−CH$_2$−C*H$_3$*), 1.47 [s, 9 H, O−C(C*H$_3$*)$_3$], 1.47 (s, 3 H, C*H$_3$* oxazolidine), 1.56 (s, 3 H, C*H$_3$* oxazolidine), 2.07 (dd, ^3J = 7.6 Hz, ^3J = 6.4 Hz, 1 H, 3-H), 2.09 (d, ^3J = 6.4 Hz, 1 H, 2-H), 3.23 (d, ^2J = 13.9 Hz, 1 H, C*H$_2$*−Ph), 3.71 (dd, ^2J = 8.9 Hz, ^3J = 2.5 Hz, 1 H, 5′-H$_{4',5'\text{-}cis}$), 3.83 (dd, ^2J = 8.9 Hz, ^3J = 6.1 Hz, 1 H, 5′-H$_{4',5'\text{-}trans}$), 4.04 (d, ^2J = 13.9 Hz, 1 H, C*H$_2$*−Ph), 4.09−4.12 (m, 1 H, 4′-H), 4.13 (q, ^3J = 7.2 Hz, 2 H, O−C*H$_2$*−CH$_3$), 7.20−7.31 (m, 5 H, Ph). − ^{13}C NMR ($C_2D_2Cl_4$, 75 °C): δ = 14.3, 24.3, 27.3, 28.6, 41.1, 48.9, 57.5, 61.0, 63.0, 66.0, 80.0, 94.1, 127.3, 128.3, 128.4, 137.5, 152.2, 169.5 . − MS: *m*/*z* = 405.1. − $C_{22}H_{32}N_2O_5$ (404.5): calcd. C 65.32, H 7.97, N 6.93; found C 65.59, H 7.97, N 6.74.

Ethyl (2*R*,3*S*,4*R*)-(−)-1-Benzyl-3-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)aziridine-2-carboxylate (9): Oil, yield 1.15%, $[\alpha]_{20}^{D}$ = −16.7 (*c* = 0.31, $CHCl_3$). − ^{1}H NMR ($C_2D_2Cl_4$, 100 °C): δ = 1.20 (t, ^3J = 7.3 Hz, 3 H, O−CH$_2$−C*H$_3$*), 1.44 (s, 3 H, C*H$_3$* oxazolidine), 1.46 [s, 9 H, O−C(C*H$_3$*)$_3$], 1.53 (s, 3 H, C*H$_3$* oxazolidine), 2.47 (dd, ^3J = 7.6 Hz, ^3J = 2.8 Hz, 1 H, 3-H), 2.79 (d, ^3J = 2.8 Hz, 1 H, 2-H), 3.55 (dd, ^3J = 2.0 Hz, ^2J = 9.0 Hz, 1 H, 5′-H$_{4',5'\text{-}cis}$), 3.79 (dd, ^3J = 5.9 Hz, ^2J = 9.0 Hz, 1 H, 5′-H$_{4',5'\text{-}trans}$), 3.90 (s, 2 H, C*H$_2$*−Ph), 4.15 (m, 3 H, O−C*H$_2$*−CH$_3$ and 4′-H), 7.21−7.31 (m, 5 H, Ph). − ^{13}C NMR ($C_2D_2Cl_4$, 75 °C): δ = 14.2, 23.1, 26.9, 28.4, 42.0, 48.7, 55.0, 59.3, 61.1, 67.1, 80.2, 94.5, 127.4, 128.5, 128.7, 138.7, 151.9, 169.0. − MS − *m*/*z* (LSIMS, high resolution): 405.2389, $C_{22}H_{32}N_2O_5$.

Ethyl (2*S*,3*S*,4*R*)-(−)-1-Benzyl-3-(3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)aziridine-2-carboxylate (10): M.p. 126 °C, yield 4.4%, $[\alpha]_{20}^{D}$ = −21.7 (*c* = 1.05, $CHCl_3$). − ^{1}H NMR ($C_2D_2Cl_4$, 100 °C): δ = 1.26 (t, ^3J = 7.0 Hz, 3 H, O−CH$_2$−C*H$_3$*), 1.42 (s, 3 H, C*H$_3$* oxazolidine), 1.43 [s, 9 H, O−C(C*H$_3$*)$_3$], 1.49 (s, 3 H, C*H$_3$* oxazolidine), 2.04 (dd, ^3J = 6.7 Hz, ^3J = 6.1 Hz, 1 H, 3-H), 2.32 (d, ^3J = 6.7 Hz, 1 H, C-2), 3.44 (d, ^2J = 13.2 Hz, 1 H, C*H$_2$*−Ph), 3.67 (d, ^2J = 13.2 Hz, 1 H, C*H$_2$*−Ph), 3.78−3.85 (m, 2 H, 5′-H), 3.91−3.96 (m, 1 H, 4′-H), 4.18 (q, ^3J = 7.0 Hz, 2 H, O−C*H$_2$*−CH$_3$), 7.23−7.31 (m, 5 H, Ph). − ^{13}C NMR ($C_2D_2Cl_4$, 75 °C): δ = 14.0, 24.3, 27.2, 28.3, 43.1, 48.3, 54.2, 60.7, 63.9, 66.9, 79.7, 93.7, 127.4, 128.3, 128.4, 137.4, 151.8, 169.1 . − MS: *m*/*z* = 405.1. − $C_{22}H_{32}N_2O_5$ (404.5): calcd. C 65.32, H 7.97, N 6.93; found C 65.34, H 8.01, N 6.74.

Acknowledgments

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[14] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-140443. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44−1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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